

JULY/AUGUST 2019 VOL. 5, NO. 4

# VALUE & OUTCOMES SPOTLIGHT

*An ISPOR publication for the global HEOR community*

## Precision Medicine Based on Whole Genome Sequencing

ALSO:

Historical Development of Precision Medicine

Interview with Joanne M. Hackett of Genomics England



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# VALUE & OUTCOMES SPOTLIGHT

JULY/AUGUST 2019  
VOL. 5, NO. 4

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



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## FROM THE EDITOR

It has long been recognized that for a variety of reasons average treatment effects reported from clinical trials are of limited relevance to individual patients presenting in clinical practice. Even the adage, “the average treatment effect is only applicable to the average patient” doesn’t really hold from a statistical standpoint. Treatment outcomes will always be subject to some degree of unpredictability, and this makes it challenging to ensure that each individual patient receives the most suitable treatment regimen.

Getting the right medicine to the right patient at the right time is the stated goal of a treatment approach originally called “personalized medicine,” but now also referred to as “precision medicine.” It is still common to see the two terms used interchangeably, so is this simply a ‘you say to-mā-to, I say to-mah-to’ kind of thing? Maybe, but the National Research Council in the United States has specifically urged adoption of the term precision medicine to convey “... the tailoring of medical treatment to the individual characteristics of each patient.” This contrasts to personalized medicine, which they acknowledge “... is also used to convey this meaning, [but] is sometimes misinterpreted as implying that unique treatments can be designed for each individual.” In other words, stratifying patients into clinically distinct segments is a realistic objective, but ‘N-of-one’ segmentation of each individual patient is not.

Precision medicine is the theme of this issue of *Value & Outcomes Spotlight*. Our feature article presents some of the challenges surrounding precision medicines and companion diagnostics, including reimbursement hurdles, real-world evidentiary needs, and ISPOR’s role in supporting the widening acceptance of these products. We also include an interview with a representative of Genomics England, a company set up by the United Kingdom’s National Health Service (NHS) to administer the 100,000 Genomes Project, an ambitious attempt to sequence the genomes of that many NHS patients—and which, as of last December, had reached its target. We also have a By-the-Numbers infographic page on various aspects of precision medicine and, to cap things off, our Q&A section features Kathryn Phillips, PhD, of University of California, San Francisco.

In addition to the precision medicine themed content, we include a variety of material of relevance to our Society. We have three articles with wide-ranging interest, one framing the growing tension between digital health and patient privacy, the second discussing the importance of model validation for reimbursement dossiers, and the third describing opportunities and challenges for use of multi-criteria decision analysis in European health technology assessment submissions.

Our ISPOR Central section features the incoming presidential address from Nancy Devlin, who deserves congratulations for being ISPOR’s first president from down under! Upcoming conferences are highlighted as well, including the ISPOR Latin America 2019 conference in Bogotá. For those of you thinking of traveling to Colombia for the meeting, we include an article summarizing ISPOR’s activities in the Latin America region.

See you there!



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



## ISPOR SPEAKS

## Important Opportunities and Challenges

Nancy J. Devlin, PhD, Director, Centre for Health Policy, University of Melbourne, Melbourne, Victoria, Australia

Kia Ora!

I am delighted to have this opportunity to be ISPOR President for the 2019-2020 term. Past-president Professor Federico Augustovski was ISPOR's first president from Latin America and its first president from outside North America and Europe. My presidency continues to reinforce ISPOR's truly global nature: I will be ISPOR's first president from Australasia (partly because I shifted to the University of Melbourne this year, but also because I am a very proud New Zealander!). The representation in ISPOR's leadership from different regions is important, as different people bring different perspectives. And seeing the world differently (literally...as shown by this map!) can bring new insights.



(Image courtesy of MapCo NZ Ltd.)

I am somewhat in awe of the achievements of our past presidents, whose work and service to ISPOR I greatly admire (and some of whom—such as Professor Mike Drummond—are my personal heroes) and welcome the challenge of living up to their combined legacy of leadership.

As I look ahead to the coming year, I am mindful that ISPOR presents

both important opportunities and some interesting challenges for a new president. I touch on these here because I hope these comments may be of interest to those considering leadership roles in ISPOR and may encourage still others to consider putting themselves forward.

The organization is exceptionally well run and actively managed by its mainly US-based professional staff, led by CEO Nancy Berg. This means that the support which is provided to those serving as president is outstanding. It does also mean, as a new president, carefully navigating and clarifying the dividing line between governance and management roles which, in the context of a US-based organization, can sometimes

feel culturally a little different than Board roles in Europe and elsewhere.

The role of ISPOR president also differs from leadership roles I have previously held in other organizations in that it is for 1 year only. The presidential term is preceded by a 1-year run-in as president-elect, during which time the objective for the president-elect is to learn as much as possible

and to understand, 'from the inside,' the workings of what is a large and very complex global membership organization. And, within that period, the additional challenge is to find the best way to prioritize efforts to make a difference within the limited time span of the presidency, and to achieve things that improve ISPOR's services to its members and its wider impact on health economics and outcomes research (HEOR).



As I pick up the presidential gavel (and yes, there is an *actual* gavel!) for the first time at our Board of Directors meeting in San Diego in late July, I am extremely grateful to ISPOR's immediate past presidents, Professor Federico Augustovski and Professor Shelby Reed. They have been generous in their support over the past year, as they have gently passed the baton to me, and are excellent role models. I know I can count on their continued guidance during the coming year. In turn, one of my objectives will be to welcome and support Jens Greuger as president-elect to ensure that his presidential term is as successful as possible.



### WHAT DO I HOPE TO ACHIEVE DURING 2019-2020?

It seems like a long time ago that I wrote my vision statement (<https://www.ispor.org/about/our-leaders/nancy-devlin>) for the ISPOR elections—and that's because it is: I wrote it at the start of 2017. My >

understanding of ISPOR has improved since then and I am sure I will continue to learn over the coming year, but the things I highlighted in that statement continue to be a good reflection of my priorities.

- To ensure that we continue to grow not just the scale of our activities, but also the stature, relevance, and impact of ISPOR as an organization.

As a not-for-profit organization, ISPOR's mission—to promote health economics and outcomes research excellence to improve decision making for health globally—lies at the heart of all that we do. ISPOR's success should ultimately be judged by its impact in improving science and improving decision making. We will continue to strengthen efforts to show, both to members and to potential members, that resources generated from income-earning activities (such as our conferences) are directed to the achievement of those ends. Strengthening the future of the science of HEOR and being proactive as well as responsive in doing that is of key importance.

- ISPOR has been very successful in

to the achievement of ISPOR's mission to improve health globally.

- To continue efforts to ensure that ISPOR conference plenaries and panels are representative of our membership, and that ISPOR conferences serve as opportunities to highlight and develop emerging talent and research leaders.

I delivered my address to the ISPOR 2019 conference in New Orleans partly in te reo (the language of the indigenous people of New Zealand), including in it a well-known Māori Whakataukī (proverb) shown below. I think this phrase nicely captures the fact that people, and our treatment of people, is central to ISPOR as a membership association.

My first act as president has been to respond<sup>1</sup> to an article by ISPOR members<sup>2</sup> highlighting the issue of 'all male panels' at ISPOR conferences. ISPOR is very diverse in some ways that other organizations would envy (for example, see the composition of our Board of Directors). But in other ways, particularly regarding the diversity of speakers at our conferences, ISPOR needs to improve. Actions have

2019/2020: unusually, and as a product of the cycle of Board elections, I will be chairing a board comprising 10 members who are continuing from the previous year and who are 'hitting the ground running.'

Finally, I am interested in hearing your ideas and thoughts, as its members and its stakeholders, about ISPOR's direction. During 2019, I will have the privilege of speaking at and participating in the ISPOR Europe 2019 conference in Copenhagen, meeting local members of ISPOR chapters in Mexico, Australia, China, and New Zealand, and plan to visit further chapters in 2020. I look forward to meeting as many of you as possible during the next 365 days. •

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**Ki mai ki ahau, he aha te mea nui o te Ao?**

*If you were to ask me, what is the most important thing in the world?*

**He tāngata, he tāngata, he tāngata**

*It is people, it is people, it is people.*

bringing together health technology assessment organizations, the pharmaceutical industry, patients, academics researchers and regulators, and is truly unique in the extent to which it has created an effective dialogue between these groups. This model should be expanded to further engage healthcare budget holders, policy makers and healthcare system leaders in ISPOR's work, as their concerns and HEOR needs are crucial

already been taken over the past year (including a formal diversity policy and the establishment of Women in HEOR), but there is still a long way to go. As I concluded in my article, our aim is to reflect ISPOR's diverse membership in its conferences and other activities and, ambitiously, I would like ISPOR to become a beacon of good practice in this respect. This will require efforts from *all* ISPOR members—men and women. I anticipate a highly productive Board for

## HEOR NEWS



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

### 1 New Study Finds 45,000 Deaths Annually In the United States Linked to Lack of Health Coverage *(Harvard Gazette)*

According to a study in the *American Journal of Public Health*, 45,000 deaths a year can be attributed to lack of health coverage, with uninsured, working Americans facing a 40% higher death risk than their privately insured counterparts. Previous estimates from the Institutes of Medicine (IOM) and others had put that figure near 18,000.

<https://tinyurl.com/y3kmh26j>

### 2 Cost-Effectiveness of Multigene Panel Sequencing for Patients With Advanced Non-Small-Cell Lung Cancer

*(JCO Clinical Cancer Informatics)*

The results of the first economic modeling study to estimate the cost-effectiveness of multigene panel sequencing (MGPS) as compared to standard-of-care, single-gene tests for patients with advanced non-small-cell lung cancer (aNSCLC) show that the MGPS tests are moderately cost-effective but could deliver more value if patients with test results identifying actionable genetic mutations consistently received genetically guided treatments. The study was commissioned by the Personalized Medicine Coalition (PMC).

<https://tinyurl.com/y2sgjuwq>

### 3 The Values in Value Frameworks *(Med Ad News)*

Pharma companies may not like their products being the subject of Institute for Clinical and Economic Review (ICER) reports, but they can provide a jumping-off point for manufacturers to expand the conversation of the value of new medicines in the rare-disease area. Even as manufacturers hotly dispute ICER's findings, and private payers have different budgeting goals that ICER's methods do not consider, experts believe that manufacturers are going to have to better address the questions the organization raises.

<https://tinyurl.com/yylp72v2>

### 4 Out-of-Pocket Costs Rising Even as Patients Transition to Lower-Cost Settings of Care *(TransUnion Healthcare)*

A new TransUnion Healthcare analysis found that most patients likely felt a bigger pinch to their wallets as out-of-pocket costs across all settings of care increased in 2018. The analysis reveals that patients experienced annual increases of up to 12% in their out-of-pocket responsibilities for inpatient, outpatient, and emergency department care in 2018, paying on average between \$500-\$1000 in out-of-pocket costs during healthcare visits.

<https://tinyurl.com/y6qc3uft>

### 5 Can ICER Bring Cost-Effectiveness to Drug Prices? *(Managed Care magazine)*

The Institute for Clinical and Economic Review (ICER), a small band of economists and health services researchers in Boston, is emerging as the nation's go-to source for cost-effectiveness calculations and as a voice of reason on what the price of a drug should be, not simply what the market will bear. Health insurers are paying attention, and drug manufacturers are afraid to look away.

<https://tinyurl.com/y3d9e9dc>

### 6 Anticholinergic Drug Exposure and the Risk of Dementia *(JAMA)*

In this nested case-control study of 58,769 patients with a diagnosis of dementia and 225,574 matched controls, the authors of the study say there were statistically significant associations of dementia risk with exposure to anticholinergic antidepressants, antiparkinson drugs, antipsychotic drugs, bladder antimuscarinics, and antiepileptic drugs after adjusting for confounding variables. "The associations observed for specific types of anticholinergic medication suggest that these drugs should be prescribed with caution in middle-aged and older adults," the experts conclude.

<https://tinyurl.com/y3vz4z69>

### 7 The High Price of Hospital Care *(Center for American Progress)*

Across America's acute care hospitals, total revenues exceeded expenses by more than \$64 billion in 2016, according to an analysis by the Center for American Progress, a left-leaning think tank. The analysis says experiences among individual hospitals vary, however, and about one-quarter of both for-profit and not-for-profit hospitals lost money in 2016.

<https://tinyurl.com/y5lzh74>

### 8 Cost-Effectiveness Analysis of Multigene Expression Profiling Assays to Guide Adjuvant Therapy Decisions in Women with Invasive Early Stage Breast Cancer

*(The Pharmacogenomics Journal)*

A study that looked at gene expression profiling testing to aid in chemotherapy decision-making —when traditional clinicopathological predictors are insufficient to accurately determine recurrence risk in women with axillary lymph node-negative, hormone receptor-positive, and human epidermal growth factor-receptor 2-negative early stage breast cancer— found that using any of the 3 recurrence score assays available on the market "is likely clinically and economically attractive." The total expected value of perfect information about GEP assays' utility was \$10.4 million/year.

<https://tinyurl.com/y3jnpcqd>



# ISPOR in Latin America

## Supporting the HEOR and HTA Community

Robert Selby, MBA, Director, Global Networks—Asia Pacific and Latin America, ISPOR

The Latin American healthcare landscape is in a dynamic time, with many countries in the region undergoing key reforms in their healthcare systems' management and decision-making processes to better meet the diverse needs of their citizens.<sup>1</sup> A major trend is the noted expansion of healthcare coverage and increased healthcare spending across many countries, which has led to expanded patient access to key therapies and services. But significant challenges remain in the areas of affordability for patients and sustainability for healthcare systems. Rising healthcare expenditures due to aging populations, shifting disease burdens, introduction of novel high-cost health technologies, and persistent inefficiencies in health systems are inhibiting policymakers' ability to improve overall health outcomes and control costs.<sup>2</sup> Health economics and outcomes research (HEOR) and health technology assessment (HTA) have been long recognized as powerful tools to help achieve these ends, but local population needs require experts in the region to understand how to adapt the global methodologies to be appropriate for Latin American jurisdictions.<sup>3,4</sup>

As the leading global HEOR society with an extensive presence in Latin America, ISPOR is an important resource for knowledge and support for the region. It is true that ISPOR's global community of HEOR experts are leading the way in best practices methodology. But ISPOR also has a large community of members that belong to the Latin America region and are the leading voices in that region for HEOR. Indeed, the organization has taken great pride in the fact that ISPOR's Past President, Dr Federico Augustovski—a key opinion leader for HEOR in Latin America—was the first ISPOR president to come from the region.<sup>5</sup> Dr. Augustovski not only brought matters of import for the global regions to the forefront of the organization and the ISPOR Board of Directors, but he also advocated for what ISPOR has been doing already to support the science's development in Latin America and globally.

ISPOR's commitment to the region has come through the robust activity of its numerous global and regional groups, as well as capacity-building initiatives and research initiatives. Some of these key groups include the ISPOR Latin America Consortium, which has over 500 members; 10 regional chapters with over 1400 members; and 5 student chapters. These groups provide an invaluable information-sharing platform for those in the HEOR community who are interested in developing the science in Latin America. These groups are incredibly dynamic and conduct important initiatives such as research projects, seminars, workshops, and even conferences. Additionally,

ISPOR groups have contributed to translating key HEOR distance-learning modules and good practices reports for outcomes research into local languages; provided updates into their healthcare systems roadmaps, and pharmaco-economic guidelines; and regularly provided timely health policy updates to ISPOR newsletters and consortia meetings.

**As the leading global HEOR society with an extensive presence in Latin America, ISPOR is an important resource for knowledge and support for the region.**

Through ISPOR's global groups and regional chapters, these expert members influence policy and bring vital knowledge about HEOR best practices and needs from the Latin America region to the global community. This interchange of knowledge is what makes ISPOR so valuable. Moreover, ISPOR has invested heavily in the region's lower-middle-income countries through travel grants, fee-waived memberships, and educational grants for chapters.<sup>6</sup> ISPOR also has engaged in important capacity-building initiatives through HTA training, webinars, short courses and roundtables.

ISPOR is indeed proud of its extensive involvement in Latin America, but it is arguably the regional biennial conference that is the most prominent initiative. This is the largest HEOR conference in the region, bringing together more than 1000 global participants from over 20 countries. As has been the case in past years, the upcoming ISPOR Latin America 2019 Conference on 12-14 September 2019 promises to be a very valuable experience for all involved. The captivating city of Bogotá, Colombia will host this year's conference, home to rich cultural heritage and beautiful sights and sounds. The program will be equally interesting and will tackle the theme "Data and Value in Healthcare: 2020 and Beyond." There will be numerous sessions featured that cover important topics for HEOR in Latin America and key issues and opportunities facing the region, including the proliferation of new fields of technologies such as machine learning and digital health, the growing role of data in health systems' management and decision making, new methodologies for measuring the value of healthcare interventions, and current policy trends. There are also numerous short courses on core HEOR disciplines, as well as educational symposia and poster presentations addressing the



## CONFERENCES &amp; EDUCATION



Through ISPOR's global groups and regional chapters, these expert members influence policy and bring vital knowledge about HEOR best practices and needs from the Latin America region to the global community.

latest approaches in methodology and innovation. The ISPOR Latin America Conference also provides a unique opportunity for ISPOR groups to meet and even present forums and spotlight sessions. We are especially pleased that the conference will host the first ISPOR student and new professional event in Latin America titled, "Career Advice Across the Globe: How to Advance in Your Chosen Career Path." So outside of the traditional presentations and breakout sessions, many interesting small group gatherings will take place over the course of the event.

Apart from the vast amount of information to learn, the conference is also a wonderful opportunity for different stakeholders to come together to share perspectives and learn from one another on best practices, particularly for policymakers, payers, assessors and regulators. Several different platforms that enable this take place alongside the conference, including the ISPOR HTA roundtable–Latin America, ISPOR Patient Representatives Roundtable, and ISPOR Latin America Regional Health Policy Summit. These events are invitational meetings that convene key healthcare stakeholders to debate health policy issues and challenges in Latin America. These events are important ways that ISPOR is engaging with local decision makers and stakeholders in the region to foster dialogue, all the while providing an opportunity for them to participate in the broader conference.

Considering these revelations, I am sure you are asking, "How can I get involved?" Actually, there are many ways you can get involved in what ISPOR is doing in Latin America:

1. **Participate** in the ISPOR Latin America Conference—submit an abstract or be a reviewer (too late for this one but there is always 2021), register, or be a conference sponsor or supporting institution
2. **Join ISPOR groups**—join ISPOR, ISPOR Latin America Consortium (open to all interested in Latin America HEOR), or an ISPOR regional chapter in the region
3. **Be a reviewer** or submit manuscripts to ISPOR journals
4. **Submit your news** to *News Across Latin America*
5. **Contribute** through Consortium meetings and activities

For more information, contact us at [laconsortium@ispor.org](mailto:laconsortium@ispor.org).

The future is bright for HEOR and ISPOR in Latin America.  
¡Nos vemos en Bogotá este septiembre!

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# ISPOR Latin America 2019

## *Data and Value in Healthcare: 2020 and Beyond*

12-14 September 2019

Ágora Bogotá International Convention Centre, Bogotá, Colombia

### Exploring the key issues for healthcare in Latin America

Join us in the beautiful city of Bogotá this 12-14 September for ISPOR Latin America 2019! The leading HEOR Conference in the region, ISPOR Latin America 2019 will draw more than 1000 from the regional global healthcare community to explore the key issues facing the healthcare community in the region surrounding the theme of *Data and Value in Healthcare: 2020 and Beyond*. The Conference Program will be very robust, including 2 plenaries, educational symposia, and over 450 scientific presentations covering this and many more important topics. We anticipate the participation of key healthcare decision-makers at the conference and during our HTA and patient roundtables and Health Policy Summit.



#### FIRST PLENARY SESSION — OVERVIEW

##### The Role of Data Supporting an Effective Decision-Making Process

Real-world data extends the usefulness of randomized controlled trials by its ability to include timely data, large sample sizes that enable analysis of subpopulations and less common effects, and real-world practice and behaviors in applied research studies. The plenary will explore how the management of these “data” impact real-life healthcare decisions and resource allocation in Latin America.

**Moderator:** Manuel Antonio Espinoza, MD, MSc, PhD, Pontificia Universidad Católica, Chile

**Speakers:** William Crown, MA, PhD, OptumLabs, USA; Rafael Alfonso, MD, MSc, PhD, GSK R&D, USA; Oscar Espinosa, MSc, Institute of Technology Assessment in Health, Colombia; Edson Amaro Jr, MD, PhD, Hospital Israelita Albert Einstein, Brazil

#### SECOND PLENARY SESSION — OVERVIEW

##### Value Measurement in 2020: Moving Forward in Low- to Middle-Income Countries

Based on the delivery model of value-based healthcare, “value” is determined by measuring health outcomes against the cost of delivering the outcomes. However, value measurement in health involves some important decisions about what to measure and how. The plenary will present different approaches to increase efficiency in health systems and improve access to patients.

**Moderator:** Mariana Barraza Llorens, MSc, Blutitude Healthcare Intelligency, Mexico

**Speakers:** Hector Castro, MD, MSc, PhD, Management Sciences for Health, USA; Alejandro Gaviria, PhD, Former Ministry of Health Colombia, Colombia; Cristina Gutiérrez Delgado, PhD, Economic Evaluation Unit, Health Secretariat, Mexico; Analia Lopez, MD, MSc, Chief of Cabinet, Health Secretariat, Ministry of Health and Social Development, Argentina

#### SPOTLIGHT SESSIONS

The following spotlight sessions will be focused on the assessment of value from both international stakeholders and patient perspectives:

- Defining Value in Medical Device – “The Stakeholder Matters”
- Value Assessment Frameworks in Latin America – Are We There Yet?
- Recent Social Valuation Studies in Latin America. Methods, Results, Lessons Learned



#### 3 NEW SHORT COURSES INTRODUCED

Sharpen your skills with short courses at ISPOR Latin America 2019. Join us for 10 essential HEOR courses, including 3 new courses: *Evaluation of Medical Devices: How to Manage HTAs*; *Introduction to Real-World Evidence: Between Epidemiology and Digital Tools*; and *Introduction to Machine Learning*. Led by global experts, ISPOR's hands-on courses are offered in Spanish and English. In-demand courses sell out, register today! Come for the courses; stay for the conference!

For full information on the Program visit: [www.ispor.org/LatinAmerica2019program](http://www.ispor.org/LatinAmerica2019program)

#### New Regional Health Policy Summit to Draw Payers, Government, and HTA Groups to ISPOR Latin America 2019

A new, exclusive, invitational regional health policy summit will also be held up against the Latin America conference, convening representatives from payers, government, and HTA groups. Partnership opportunities are available. For more information, please email [polycysummit@ispor.org](mailto:polycysummit@ispor.org)

#### Exhibitor and Sponsorship Opportunities

Showcase your business and products as an exhibitor or sponsor. Put your company in front of the regional global healthcare community. Learn more at [www.ispor.org/LatinAmerica2019sponsorship](http://www.ispor.org/LatinAmerica2019sponsorship)

JOIN THE CONVERSATION ON TWITTER #ISPORLA

## CONFERENCES &amp; EDUCATION



# ISPOR Summit 2019

**Mark your calendar!**

**8:00 am – 4:00 pm**

**October 11, 2019**

**Baltimore Marriott Inner Harbor at Camden Yards**

**Baltimore, MD, USA**

*ISPOR'S Real-World Evidence Transparency Initiative*



## Building Trust in RWE – The Role of Study Registration

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

This Summit will be a forum for discussion of the work of the Real-World Transparency Partnership, led by ISPOR, ISPE, Duke-Margolis, and NPC, and involving a number of other organizations and stakeholders. It will focus on the key elements needed for the creation of a common registration site for these real-world studies that will be oriented for regular use by researchers and seen as a credible registry by decision-makers. The work already completed in this effort will be presented and the future steps envisioned will be discussed with Summit attendees.

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Section Editors: Agnes Benedict and Soraya Azmi

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

### **Value in Health Regional Issues May 2019**

#### **ECONOMIC EVALUATION**

#### **Assessing the Burden of Type 2 Diabetes in China Considering the Current Status Quo Management and Implications of Improved Management Using a Modeling Approach**

Volker Foos, Ke Wang, Phil McEwan, Yanlei Zhang, Ping Xin, Xiaohua Jiang, Shuli Qu, Tengbin Xiong, Raf De Moor, Mafalda Ramos, Mark Lamotte, Linong Ji

Patterns of diabetes in the world have changed over the past few decades. While it used to be mainly a “disease of affluence,” diabetes is now increasing among the poor.<sup>1</sup> Today, at a global level, 4 out of 5 people with diabetes now live in low- and middle-income countries, and the highest prevalence rates (>20%) appear to be in island nations such as the Marshall Islands and Tuvalu, followed by such countries as Saudi Arabia, Egypt, and Malaysia with age-adjusted prevalence rates in the mid-to high teens.<sup>2</sup>

Other middle-income developing countries with a burgeoning middle class are in a close race to catch up to the leading nations in this category. Like other countries experiencing rapid economic growth in recent decades, such as Mexico and India, China has a surprisingly high age-adjusted prevalence rate of 9.7%. To

provide some context, the age-adjusted prevalence rates in developed countries are 10.8% in the United States, 8.3% in Germany, and 4.8% in France.<sup>3,4</sup> Studying and predicting the impact of diabetes in any developing country is formidable due to still-limited health data resources. Bearing in mind that China is geographically vast with variations in healthcare administration systems in each jurisdiction, access to consistent and detailed data would be challenging. This study by Foos et al set out with the objective to estimate the economic burden of diabetes in China to reflect the status quo (SQ) of diabetes management. And secondarily, to estimate changes in cost if hypothetical enhancements in management were made to optimize type 2 diabetes (T2D) management.

The authors utilized the IQVIA CORE Diabetes Model as a basis for the study while data to populate the model were collected through pragmatic literature reviews using Pubmed as well as Chinese literature databases. Data that were not adequate to inform the model were supplemented by interviews with local experts. Data were collected on population characteristics (based cohort divided into 3 age categories: aged ≤45 years, between 46- 64 years, and >65 years), healthcare costs to treat diabetes and its complications, treatment modalities regarding choice of glucose-lowering agents, long-term progression of HbA1c, and current standards of T2D management to determine the status quo. Direct medical costs were considered by the authors as the sum of costs of complications and treatment. Because there would be a proportion of undiagnosed patients, the authors assumed that access to healthcare and costs were the same as those in the diagnosed population. Costs of complications were based on applying current and follow-up costs depending on the medical event occurring during model simulation. Treatment costs were calculated by summation of glucose-lowering medication and cardiovascular (CV) medication costs. These were on the

basis of unit cost of the most commonly prescribed pack type and daily dose. As to indirect costs, productivity losses were also obtained from literature.

The authors considered 4 different treatment paradigms to create the cost burden of the current status quo and then subsequently imposed 15 different improvement scenarios where the current management regime is improved upon. The 4 treatment paradigms relevant to the treatment of diabetes used in the study were based on a national survey of physicians as well as a patient survey. These 4 paradigms were delay in treatment onset, HbA1c threshold at which treatment is escalated, adherence rate, and cardiovascular risk factor management.

The results of the study showed that the estimated cost of diabetes with status quo management was RMB 621 billion (approximately USD 90 billion). In comparison, if various steps were put in place as modelled by the 15 different scenarios in univariate analysis, this could result in net savings varying from between RMB 19 billion to RMB 106 billion. The annual unchanged cost related to the population that remains undiagnosed and untreated was estimated at RMB 1,122 billion. In terms of indirect costs related to productivity losses, status quo was estimated to cost RMB 173 billion while the best-case scenario would reduce this to RMB 149 billion. As an aside, it is important to recall here that indirect costs are what would be borne by society in general, ie, patients, their families, and communities. In terms of life expectancy, the best-case scenario compared to status quo found life expectancy increased by 3.21 years in the total population. The authors acknowledge that the net savings even at its maximal estimate seem modest (RMB 160 billion), and this is essentially due to the costs of better diabetes disease management. Modest savings notwithstanding, the study results help to reinforce and support decision makers in implementing policies and practices that result in optimized care.

There were several study limitations. Among these were the use of expert opinion due to lack of data (for instance, to identify the treatment escalation threshold of 9%) and the use of equations from the UKPDS to assess the risk of CV complications. Expert opinion was also used for baseline population characteristics in diabetes complication rates. However, it is worth bearing in mind that the study's primary objective was to estimate the economic burden of diabetes in China. Hence, despite the study limitations, the study was commendable in its effort to attempt to quantify economic cost where no direct financial data is available.

The reader may wonder, why should I care about the modelled cost or cost savings of better treatment in China? In response, consider that diabetes is a devastating chronic disease that, if not

managed well, can wreak havoc on any healthcare system and change the way it substantially has to budget and plan for the future. This is important to bear in mind in any place where diabetes is still new but on the rise due to increase due to changing lifestyles and diet. On the individual level, it can impact patients' lives both personally and financially, which in turn impacts personal well-being. While diabetes prevalence rates in China are still in the low-to-medium range (compared to several other countries), these could continue to climb if not kept in check. Understanding the impact on cost and future budgets can spur better planning for preventive and management strategies. There are many other low- to middle-income countries faced with increasing diabetes where cost data are lacking. Therefore, ascertaining the national cost of diabetes, or cost for a region or state,

can seem an insurmountable challenge to researchers in places with such limited data availability. This study provides a helpful path forward for decision makers or researchers to obtain similar estimates of cost burden and savings in their jurisdictions. •

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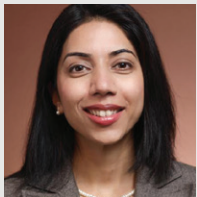
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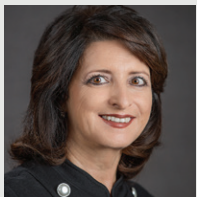
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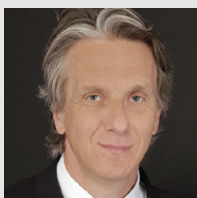
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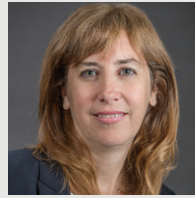
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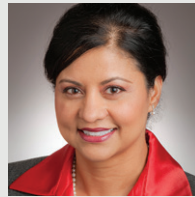
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# A Review of Precision Medicine, Companion Diagnostics, and the Challenges Surrounding Targeted Therapy

In the era of a fully mapped genome, continued personalization of pharmaceutical and diagnostics development can only accelerate. Personalized/precision medicine's aim is tailored treatments – the right treatment, for the right patient, at the right time. However, the high cost of developing therapies for small populations, coupled with the costs of developing the companion diagnostic tests forces manufacturers to recoup development costs through increased prices across smaller volumes. Balancing affordability and access may jeopardize precision medicine's promising future. This article examines these issues while asking – can we ensure access to these therapies while also sustaining innovation?

By Michele Cleary



## INTRODUCTION

With the arrival of a fully mapped genome, precision medicines are entering the global market at an ever-increasing rate. These tailored therapies promise more efficient use of healthcare resources by targeting those patients most likely to respond to therapy. However, challenges abound due largely to their very high price.

Precision medicine treatments serve a very narrow population, making research and development investments enormous. For instance, recruiting enough numbers of trial participants within these narrow populations is often an arduous process. In addition, these products require companion diagnostic tests to target the responder population.

Clearly, these products can provide enormous benefits. However, the question of affordability is inescapable. Can regulatory and reimbursement structures sustain access and innovation? How personalized is too personalized?

This article examines some of the challenges surrounding precision medicines: the development of companion diagnostics, reimbursement structures, real-world data (RWD) needs, and future trends. The article closes by reviewing how ISPOR is supporting the widening acceptance of these products.

## PRECISION, PERSONALIZED, INDIVIDUALIZED

Precision medicine identifies biological information (genes, RNA/DNA, proteins) to stratify patients, targeting those patients most likely to respond to a specific treatment. In precision medicine, diagnosis and treatment are intrinsically linked. While this field has evolved under different names (targeted treatment, individualized care, stratified treatments), the current preferred term is “precision medicine.”

Precision medicine represents a significant departure from the trial-and-error processes endemic to empirical medicine. Under these traditional processes, prescribers select a product and dosage with limited biologic information, monitor treatment effects, and adjust treatment accordingly. For example, a provider may prescribe a broad-spectrum antibiotic until more precise culture data are received on the causal organism, and a more targeted antibiotic can be prescribed.

This approach is often characterized by high rates of ineffective therapies. One study found drug therapies were ineffective in 38% of patients on antidepressants, 40% on asthma drugs, 43% on diabetes drugs, 50% taking arthritis medication, 70% of patients with Alzheimer’s disease, and 75% taking cancer drugs.<sup>1</sup> Even if these therapies are lower cost relative to precision medicine therapies, ineffective treatments are tremendously costly—racking up additional costs for adverse events, ongoing testing, and disease progression due to forgone more effective treatment.

## BENEFITS OF PRECISION MEDICINE

With whole genomic data sequencing, new disease pathways are being discovered, new therapeutic targets revealed, adverse drug effects evaluated, and ideal treatment populations identified. Precision medicine treatment targets only responders,

meaning tolerability and treatment adherence increases. This, in turn, leads to improved health outcomes and, ultimately, more efficient use of limited health services. Shifting treatment emphasis from reactive to targeted, precision medicine can help control the cost of healthcare.

Precision medicine has revolutionized oncology care. Next-generation sequencing (NGS), sometimes associated with sequential single-gene testing, is used to identify multiple specific mutations in a tumor and inform the selection of targeted therapy. NGS identifies those patients most likely to respond to a given precision medicine treatment, thereby improving patient survival by avoiding fewer effective treatments.

While most precision medicine therapies have been within the field of oncology, precision medicine research is successfully expanding into other disease classes. Genomic-based research has made significant progress in tackling diseases of the cardiovascular system, central nervous system, and immune system, as well as tackling metabolic, respiratory, and viral diseases.

Various models suggest that these products will alter healthcare utilization patterns significantly. For instance, a Genomic Health study estimated a 34% reduction in chemotherapy use would occur if women with breast cancer received genetic tests of their tumors prior to treatment.<sup>2</sup> Annual healthcare cost savings have been estimated to total \$604B if patients with metastatic colorectal cancer received genetic tests for the KRAS gene and then were treated appropriately.<sup>3</sup>

## REGULATORY SUCCESS

These benefits may be realized soon as more precision medicine products gain regulatory approval. Last year, precision medicine products made up 40% of all new products approved by the FDA. The first new class of precision drugs—small interfering ribonucleic acid (siRNA) treatments—was also approved in 2018.

In addition, the FDA approved the first pharmacogenetic and cancer risk-related genetic tests for the consumer market. One, a limited BRCA variant test, measures breast and ovarian cancer risks. The second, a personal pharmacogenetic test, provides information about 33 genetic variants that may be associated with a patient’s ability to metabolize some medications.

## GROWING GLOBAL SUPPORT

Precision medicine has garnered significant legislative support globally, reducing roadblocks to patient-centered drug development. In the United States, the Precision Medicine Institute was launched in 2015 to support precision medicine research and patient engagement. The 21st Century Cures Act of 2016 gave the FDA the tools needed to accelerate precision medicine therapies by reducing regulatory requirements, recognizing new trial designs (adaptive, innovative platform), and facilitating the use of real-world evidence.

In the United Kingdom, precision medicine received endorsements at the highest political levels for more than a decade (eg, 2009’s House of Lords Genomic Medicine Report), leading to a national strategic vision presented by the Human

Genomics Strategy Group supporting the National Health Service's adoption of precision medicine. Australia has taken bold steps to integrate genomics into the Australian health system outlined in the National Health Genomics Policy Framework and the Canadian Institute of Health Research included precision medicine within its 2015-2019 strategic plans.

## THE CRITICAL IMPORTANCE OF COMPANION DIAGNOSTICS

Despite these achievements, the promise of personalized medicine—the right treatment, for the right patient, at the right time—will remain unfulfilled without strong support for companion diagnostic testing. Companion diagnostic tests detect specific genetic mutations and biomarkers in those patients who are most likely to respond to precision medicine treatment, thus reducing the number of patients treated.

Eric Faulkner, MPH, vice president and executive director of Real-World Medicine at Evidera and a recognized global thought leader in personalized medicine, noted that “it is the actual diagnostic-drug knowledge confirmation that makes it precision medicine.” Providers need to act on test results—prescribe the indicated treatment (or not, if the test does not indicate suitability)—in order to garner the benefit of the added information or clinical utility. However, genomic markers often have limited ability to predict treatment response. Says Faulkner, “We are addressing precision medicine like a rifle (accurate and precise). When diseases [often] have more of a shotgun issue going on—multiple biomarkers that may cause a preponderance of the actual disease effect.”

Some targeted therapies may ameliorate the disease but fall short of being curative. Many genetic disorders, even so-called monogenetic diseases, often have multiple variants that cause the disease. Even so-called monogenetic diseases often have multiple variances that cause the disease sequelae.

Faulkner continued, “In the early days of precision medicine, we were targeting individual markers— EGFR, ALK, HER2, etc. And that's still the preponderance of what's on the market. But where we are going, and we are getting closer and closer, is hitting a tipping point.”

He predicts larger-panel tests are entering the market—first in oncology and then expanding to other disease areas. “Where we are headed though is for a test to be administered at the time the patient is being worked up for diagnosis where we could test hundreds of different biomarkers. Those tests will redefine what good looks like in precision medicine once they gain full acceptability.

Next-generation testing (NGT)—larger-panel tests including dozens of common biomarkers are now more readily available, testing smaller samples for a wide array of markers in one panel. Faulkner sees NGT as the next frontier of precision medicine,

stating, “It's reconciling our ability to know more biomarker information and then how to pull it through to a patient's treatment approach.”

John Watkins, PharmD, who leads Premera's Biotechnology Initiative and serves on ISPOR's Personalized Medicine Core group, shared Premera's successful experiences with gene-expression panel testing in early stage breast cancer. He noted that tests identify women who do not need chemotherapy along with their surgery, as the cancer is predicted unlikely to return. “That gets us a much better picture than the older methods of evaluating risks potential. We now can identify a number of women who don't need chemotherapy.” He added, “We can also identify groups of women that previously would have been told they probably shouldn't get chemotherapy, but the tests results find genetic variants that predict higher risks. So that test enabled that considerable improvement in terms of fine-tuning our treatment of those patients.”

**The concern obviously, is that we are working with complex things that we understand only a small part of. That always carries risk. But that doesn't mean you don't go there; it just means that you just go with appropriate caution and be prepared for the results not to be quite what you expected.**

Maarten IJzerman, PhD, chair of Cancer Health Services Research at the University of Melbourne, shared his experiences with NGS panels in distinguishing cancer subtypes

and identifying appropriate treatments for a patient. “Finding new molecular operations that can influence treatment decision, I consider to be the value of that whole gene sequence,” he shared.

But will payers cover such testing approaches? Watkins warned, “Payers tend to resist testing a whole bunch of stuff that is not as easily actionable.” IJzerman echoed this concern, stating that “It's very rigid if you only reimburse a specific test or just the single gene panel that can be very restrictive into what actually is going on in clinical practice.”

## BUT CAN HEALTH SYSTEMS AFFORD THESE THERAPIES?

As stated earlier, precision medicine has the potential to make health systems more efficient by targeting treatments to only those who will benefit. Despite these potential efficiencies, reimbursement remains a challenge. While regulatory bodies are open to precision medicine (eg, 21st Century Cures Act), reimbursement bodies are less accepting. For example, Centers for Medicare & Medicaid Services (CMS) requires step therapy to get to newer targeted therapy in Part B drugs or decreased payments for many precision medicine diagnostic tests.

Lou Garrison and Adrian Towse shared their foundational thoughts on value assessment for precision medicine, stating, “A broader concept of value is needed in the context of personalized healthcare. ... The potential barrier posed by inflexible or cost-based reimbursement systems, especially for biomarker-based predictive tests. These personalized technologies have global public goods characteristics that require global value-based differential pricing to achieve dynamic efficiency in terms of the optimal rate of innovation and adoption.”<sup>4</sup> >

Value assessment frameworks (VAFs) are evolving to better quantify the value of precision medicine treatments. Faulkner recommends 9 core components that should be considered regarding value frameworks aimed at precision medicine:

1. Incorporating diagnostic performance
2. Aligning evidence and reimbursement for the test component
3. Clarifying acceptable study designs and evidentiary expectations for the test component
4. Clarifying evidence expectations for different diagnostic applications
5. Incorporating value of “ruling out” treatment options
6. Addressing next generation testing special considerations
7. Addressing adaptive trial designs
8. Addressing the potential to target multiple pathways
9. Integrating precision medicine with artificial intelligence (AI), machine learning, and decision support

The American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO), the Institute for Clinical Effectiveness and Research (ICER), and the National Institute of Clinical Excellence (NICE) all have developed VAFs to better serve the needs and interests of their stakeholders. These VAFs were shared during ISPOR's 2018 Summit.<sup>5</sup>

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**Real-world evidence is changing what good looks like in the precision medicine space**

Contrary to the reimbursement strategies for precision medicine treatment, reimbursement for diagnostics remains largely focused on costs rather than value. However, without sound reimbursement policies for precision medicine, access to these diagnostic tests could be threatened, increasing the likelihood of disease progression and side effects stemming from suboptimal treatments. Further discussion is needed regarding reimbursement approaches for these companion and complementary diagnostics.

### RWE MAY HELP ADDRESS THESE ISSUES

The future of precision medicine—from product development to reimbursement strategies—is heavily reliant upon RWD. These data can reduce clinical and health economic uncertainty on an individual patient level and clearly show the promise of the diagnosis-targeted treatment tandem. Real-world registry data should inform trial design, including adaptive trials, where added information about benefit can help target the right populations as more data accrue.

Technology has unlocked large biological data sets—DNA/RNA sequencing, proteomics, metabolomics—combining with electronic medical record/electronic health record (EMR/EHR) data to enrich our understanding of disease states and biomarkers. Clinical trial simulations, biomarker discovery and validation, cost models—will all require large volumes of RWD linked to both clinical and laboratory information, particularly due to the smaller patient populations. Finally, evaluating the

impact of WGS requires both randomized clinical trial (RCT) data and RWD, as there is increasing evidence that health outcomes reported in clinical trials usually overestimate clinical outcomes achieved in the real world.

Faulkner reflected on the convergence of genomic data with real world evidence, noting a common criticism is insufficient information about the epidemiology of biomarkers—how it connects to what’s happening with the population. “Real-world evidence is changing what good looks like in the precision medicine space,” said Faulkner. “We are having a convergence of acceptance of real-world evidence, changing study designs, knowledge of biomarkers, the evolution of analytical data sources, including AI machine learning. A lot of this stuff is starting to converge.”

Ijzerman added, “The longer-term objective here is to track patients to reduce practice variation and maximize outcomes across care pathways. That requires a much more conclusive dataset of patient-reported data, but also remote, long-term tools that can incorporate in the registry data.” He said that the goal is to “... really see all the services that they receive throughout their cancer care. And that’s a longer-term goal. And that takes a bit of time to build those registries.”

### NEW GENOMIC DATA SOURCES

Real-world data sets are helping populate clinical trials when clinical trial data are insufficient to inform outcomes for rare conditions. Genomic data can be strengthened by linking real-world, patient-level data to other data so that trends can be analyzed and incorporated into research and development, tracking outcomes over time to understand the real-world benefit of these treatments. Adjustments to regulatory indications and coverage decisions can be made in real time as more information accrues.

Some of the critical real-world data sources include genomic databases. In the United States, the All of Us Research Program collects genetic data, biological samples, and other health information from more than 192,000 people from all 50 states. The United Kingdom initiated the 100,000 Genomes Project to promote precision medicine research. Similar registries are being assembled in Australia and the Netherlands, some including tissue storage for future study.

### REAL-WORLD DATA AND CLINICAL UTILITY

Watkins outlined a critical need for RWD in demonstrating clinical utility surrounding variants of unknown significance. “Usually, getting to clinical validity is relatively easy. Demonstrating clinical utility is very hard.”

Clinical utility refers to the systematic assessment of a test’s usefulness—the ability of a diagnostic test to prevent adverse health outcomes by informing better clinical decision making—balancing the benefits to risks. Data are needed to demonstrate both the benefits and risks accruing from positive and negative test results.

Per Watkins, “I am hoping that machine learning systems or artificial intelligence will enable us to identify correlations that

will be predictive of treatment outcomes.” However, he warned that we are a long way from being there at this point. “We need to be able to collect large databases in order to apply machine learning algorithms to be able to draw useful conclusions from that. And when you consider the number of different types of cancer, there are literally hundreds of variants that have been identified that they test for, some of which we don’t fully know the significance of.”

Usually, getting to clinical validity is relatively easy.  
Demonstrating clinical utility is very hard.

### ISPOR CONTRIBUTIONS

ISPOR has been actively supporting the ongoing development and acceptance of precision medicine. ISPOR’s Precision/Personalized Medicine Special Interest Group has been highly active in evaluating research best practices, decision standards, and value assessment processes.

In its 2012 report, *Challenges in the Development and Reimbursement of Personalized Medicine—Payer and Manufacturer Perspectives and Implications for Health Economics and Outcomes Research: A Report of the ISPOR Personalized Medicine Special Interest Group*, the ISPOR Precision/Personalized Medicine Special Interest Group published its report evaluating key development and reimbursement considerations from the payer and manufacturer perspectives.<sup>6</sup>

In 2016, ISPOR hosted a forum, “Generating Evidence of the Added Value of ‘Precision’ Medicine,” presented by the ISPOR Precision Medicine: Assessing the Value Working Group of the Precision/Personalized Medicine Special Interest Group.<sup>7</sup> This forum introduced many core concepts surrounding precision medicine, its value in predictive analyses, best practices, practical challenges, and research priorities.

During ISPOR’s 2017 Annual International Meeting, the ISPOR Precision Medicine: Assessing the Value Working Group of the Precision/Personalized Medicine Special Interest Group hosted a workshop, “Are Payers Equipped to Assess the Unique Value of Precision and Personalized Medicine (PPM)? Analyzing Current Value Frameworks and Their Application Within the PPM Context.”<sup>8</sup> In addition to introducing the members and goals of the working group, the workshop provided an overview of the field of various value assessment frameworks currently considered.

In 2018, ISPOR hosted 2 events concerning precision medicine—the 2018 Summit on VAFs mentioned earlier and a session during the ISPOR Europe 2018 conference. During this latter session, the ISPOR Precision/Personalized Medicine Special Interest Group hosted a session, “Diagnostics Evidentiary Dinosaur Evolution: Conventional Health Economics and Market Access Approaches Vs. Advanced Analytics as the New Norm?”<sup>9</sup> which reviewed companion diagnostics and future challenges that these products may face regarding evidence expectations.

ISPOR retains a virtual collection of related *Value in Health* articles on its website.<sup>9</sup> This ISPOR Precision/Personalized Medicine Special Interest Group, together with the whole ISPOR organization, will continue to share their thoughts, concerns, findings, and challenges as this field evolves.

### CONCLUSION

Precision medicine is now transitioning to wider acceptance. As this field matures, considerable challenges surrounding clinical research, regulatory approval processes, and reimbursement must be addressed carefully to ensure patient access and sustainable innovation.

Progress may be slow. But as Watkins summarized the current state of the field, “The concern obviously, is that we are working with complex things that we understand only a small part of. That always carries risk. But that doesn’t mean you don’t go there; it just means that you just go with appropriate caution and be prepared for the results not to be quite what you expected.”

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### ABOUT THE AUTHOR

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

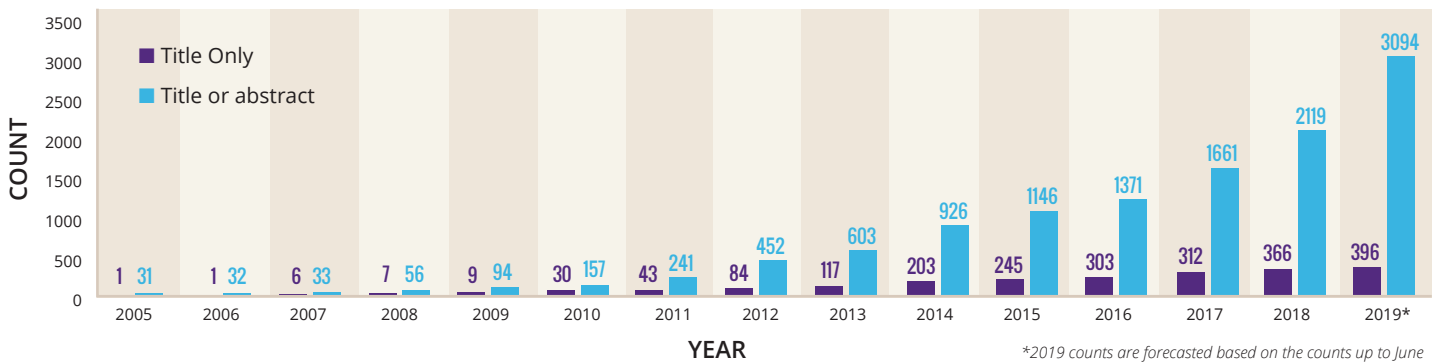
# By the Numbers: Personalized Medicine Based on Whole Genome Sequencing

Section Editor: The ISPOR Student Network

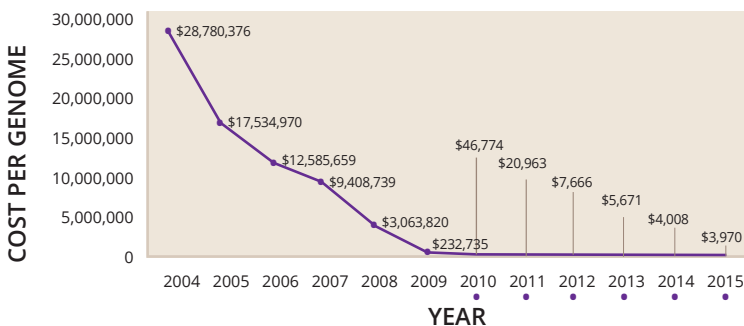
## Milestones in Personalized Medicine

- 1869** The discovery of DNA by the Swiss chemist Friedrich Miescher sets the stage for future studies in molecular medicine<sup>1</sup>
- 1953** Double helix structure of DNA proposed by James D. Watson and Francis H.C. Crick<sup>2</sup>
- 1977** First DNA sequencing method developed by Frederick Sanger<sup>3</sup>
- 1990** Work begins on the Human Genome Project, a 13-year project coordinated by the U.S. Department of Energy and the National Institutes of Health<sup>4</sup>
- 1998** FDA approves Herceptin, a pioneer drug in personalized medicine for the treatment of HER2-positive metastatic breast cancer<sup>5</sup>
- 2012** Icelandic company DeCODE Genetics, which proposed the world's first population-wide genetic biobank in the late 1990s is acquired by Amgen for \$415 million<sup>6</sup>
- 2015** Former United States President Barack Obama signs and launches the bipartisan \$215 million 'Precision Medicine Initiative'<sup>7</sup>

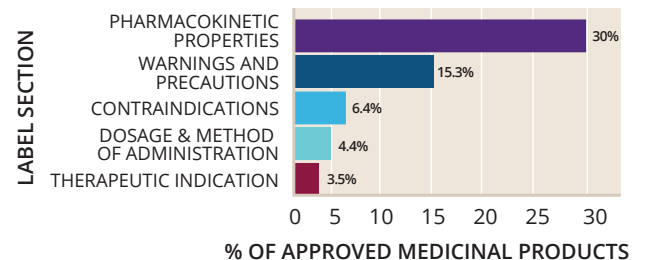
## Number of PubMed Publications with the Term "Whole Genome Sequencing" in their Title and/or Abstract (2005 – 2019)



## Costs for Whole Genome Sequencing (2004-2015)<sup>8</sup>



## % of European Medicines Agency (EMA) authorized medicinal products with any pharmacogenomic information in their labels by product characteristics: 1995-2014



Contributors: Koen Degeling, University of Twente, Netherlands; Christy Choi, University of Minnesota, USA; Shannon Vaffis, University of Arizona, USA; Judith John, Kerala University of Health Sciences, India; Jayesh Patel, West Virginia University, USA; Aakash Bipin Gandhi, University of Maryland, USA *Acknowledgement: We would like to thank Dr. Zeba Khan for her review of the material*

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## Insights on How an Experienced CCO Delivers Novel Ideas to the World of Genomics

### An Interview with Joanne M. Hackett

*Value & Outcomes Spotlight* was fortunate enough to sit down with Joanne M. Hackett, Chief Commercial Officer at Genomics England, to talk about the impact the field of genomics is having on personalized medicine. Joanne began her career as a clinical scientist, before coming to the United Kingdom to be one of the main driving forces in the commercialization of precision medicine. In her current role at Genomics England, Joanne focuses on developing and managing strategic relationships with industry. With an international career in and out of the lab, across start-ups and Fortune 500 companies, Joanne has accumulated keen insights on personalized medicine.



**VOS: Can you present for our readers some of the likely applications of genome sequencing for the realization of personalized medicine? What are the public health implications?**

**Joanne M. Hackett:** The development of next-generation sequencing (NGS) has drastically reduced the time and cost of sequencing a genome. This has had 2 important knock-on effects: first, it is now relatively simple to convert biological information into digital data; and second, the scale at which we can sequence whole genomes has turned this into a big data field. This is significant for understanding why there is so much hype around genomics. Because we are so data rich, there are several technology fields converging—meaning the potential applications are limited only by our own imaginations.

Before we talk about applications, it's important to understand the science. Being able to sequence a genome is not the same as understanding a genome. A tremendous amount of research goes into identifying not only gene variants, but also the traits they are associated with and the molecular pathways they influence. That is the research that underpins everything else that follows. There is still much we don't know when it comes to understanding the genome.

In a healthcare context, gene variants are proving to be useful biomarkers

for predicting disease susceptibility and diagnosis, drug response, and adverse drug reactions. This is helping to transform the ways we deliver healthcare through faster and more cost-effective disease diagnoses and also make better-informed treatment decisions. Getting the right drug to the right patient is central to personalized medicine. Identifying those genetic biomarkers is at the heart of what we do here at Genomics England—we sequence a patient's DNA, analyze it for known clinically actionable variants, and return the results back to the clinicians who can then decide on the best course of treatment.

And that leads us nicely to the application area that excites me the most—the treatment. Diagnosing patients is only part of the mission. We can find the right patients, but we still need to have the right drugs available to treat them.

There's an argument as to whether the cost of personalized medicine is justifiable in relation to the positive impact that same funding could have on broader public health initiatives. It's hard to argue against when you consider how many hospital admissions are brought on by smoking or alcohol consumption. But personalized medicine is just an application of research. That same research can be applied to public health initiatives by giving greater insights into the genetic predispositions of a

population. Identifying high-risk subsets of a population can give you a better chance of understanding behaviors and drivers that could be addressed to improve population health and reduce the strain on healthcare systems. In that regard, we should not treat this as an "either/or" scenario. The important thing is to encourage the research that will continue to present more opportunities to improve health wherever there is need.

**We now have 16 years from the first full sequence of human genome publication. What is the research bringing over the next 5 years?**

I think we'll see the biggest changes in pharma. I'm sure you have heard a lot of people talk about the need to "fail earlier" in drug development. I think we'll see that mindset shift to "succeed earlier." It's a subtle difference. The focus on failing earlier is looking at the way science is evaluated in a commercial pipeline and placing the emphasis on scientific rigor. In 5 years' time we'll know a lot more about the molecular mechanisms of disease progression and how to target them. This is where the relationship between genomic and real-world data will start to shine through reverse translation. This should make it easier to find the "winners" in a drug development pipeline and to run powerful, precision clinical studies designed around the principle of getting the right drug to the right patient. >

In 5 years' time we'll also be talking about new classes of drugs on the horizon. Cell and gene therapies are starting to change things already, and we know that gene editing will come sooner or later. These techniques will continue to develop alongside our increased understanding of our molecular biology. Of course, this will need to be supported by strong legal and ethical frameworks to make sure they are regulated responsibly.

### **Can you provide examples of how personalized medicine is helping patients with the diagnosis and treatment of rare diseases?**

Through the 100,000 Genomes Project we've been fortunate enough to witness firsthand the strength and determination of families affected by rare diseases. Patients with rare diseases are often subjected to a seemingly never-ending rotation of specialists, tests, and a devastating lack of answers. By analyzing the whole genome, we are now able to start providing some answers. The diagnosis alone can be a tremendous relief to patients and their families, helping to narrow down the focus and bringing a sense of much-needed closure.

Again, this all goes back to the research that helps us understand the mechanisms underpinning conditions. For example, one of our participants in the 100,000 Genomes Project is a young girl named Jessica. She was enrolled in the project with her parents, due to the frequent epileptic fits she was suffering. As you can imagine, this was extremely distressing for the family, especially not knowing what was causing the fits. Jessica's genome was analyzed and compared with those of her parents. This produced a few potential variants of interest, one of which was identified by our open-source PanelApp. This tool has information on thousands of genes that may be linked to rare diseases, as reported by doctors and researchers. The variant was identified in a gene called SLC2A1. Without the fully functioning gene, a particular type of sugar wasn't being transported to her brain, resulting in the fits. We were able to diagnose this as Glut1

deficiency syndrome. Fortunately for Jessica and her parents, adjusting to a low-carbohydrate, ketogenic diet is able to provide an alternative energy source to her brain and significantly reduce the number of seizures she experiences.

While this isn't the case for every patient with a rare disease, it does show the value a diagnosis can have. For others it may be a case of being able to recommend a particular treatment or referring them to a relevant clinical trial.

### **For readers of *Value & Outcomes Spotlight*, there is particular interest in health technology assessment (HTA)—how are NICE and other HTA agencies responsible for population-wide decision making coming to grips with personalized medicine applications?**

In first instances, it's understanding the technology. We're fortunate in the United Kingdom that notified bodies and regulators are very proactive in facilitating the responsible adoption of new technologies. The key is in understanding what new technologies can do, how they do it, what the need is, and what the risk is.

If we look at something like whole genome sequencing (WGS), this raises some interesting questions around the clinical and cost-effectiveness and broader impact of healthcare treatments and tests. As much as NGS has made WGS cheaper, it is still relatively expensive. A lot of work is going into demonstrating clinical utility, health economics, and understanding the risks and ethical considerations. Organizations like NIHR, NICE, and MHRA all enable new technologies and protect the interest of the population. It's that last bit that people tend to forget sometimes. The population are the main stakeholders and the taxpayers for all of this.

At Genomics England, we involve participants of the 100,000 Genomes Project actively in our decision making. This is extremely useful for us, as it grounds us in real-world needs of patients and helps build trust around emerging technologies. •

#### **ADDITIONAL INFORMATION**

*To learn more about personalized medicine, go to ISPOR Personalized/Precision Medicine Special Interest Group at [www.ispor.org/specialinterestgroups](http://www.ispor.org/specialinterestgroups).*



## Digital Health versus Patient Privacy (General Data Protection Regulation): Is the Future Here to Stay?

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**For digital health to move forward in a sustainable way, the process for limiting the use of data needs to be transparent. Data security and privacy issues need to be adhered to before assessing the personal preferences and behavior of individual customers.**

Healthcare system stakeholders are constantly trying to look for ways and means to reduce inefficiencies and redundancies, improve healthcare quality and patient access, and personalize care while still attempting to reduce healthcare expenditures. There is a staggering amount of data emerging from the “digital universe.” The introduction of digital data in the healthcare sector could be used in myriad ways to enable this process. Currently, there are a great deal of opportunities to utilize digital data to assist the decision-making process in the healthcare sector.<sup>1</sup>

data of EU residents, regardless of where they reside. The GDPR is a one-stop shop. It provides enhancements in the form of enhanced rights, additional obligations, new rules on consent, access rights, profiling, impact assessments, data transfers, and more. In terms of how the GDPR will impact the healthcare industry, it mandates that breaches be reported within 72 hours. This will serve as an incentive to organizations responsible for data collection and analytics to secure the data they are responsible for since fines will be levied against them if they do not ensure data security.

**The highest risks of the implementation of the GDPR include the inability of the healthcare provider to ensure the continued confidentiality, integrity, availability, and resilience of treatment systems and services.**

### CARE OF DATA

On May 25, 2018, the General Data Protection Regulation (GDPR) was implemented in Europe to ensure that patients’ data are protected. The GDPR was intended to harmonize and unify the legal regulation across the European Union (EU). The key objective of the GDPR is to support innovation while at the same time enforcing the privacy rights of individuals.<sup>2</sup> The GDPR provides a set of regulations intended to provide EU citizens with increased control over their personal data and harmonization across EU jurisdictions,<sup>3</sup> including giving patients the right to erase their full personal medical records. Stakeholders in other geographic regions are watching the example provided by the GDPR and in the future, may even follow the European lead in one form or another. GDPR replaces Data Protection Directive 95/46/EC, which previously focused on the physical, physiological, mental, economic, cultural, or social identity of the patient.

The GDPR has a worldwide territorial scope, meaning that it will apply to data controllers that possess the personal

Owing to the obligation of explicit consent, GDPR has the potential to challenge the ability of companies and healthcare systems to engage with their customers in a new business model built on the premise of partnership. It is very much based on the patient-centric approach in healthcare. Still, it will not be without its challenges as each individual has a right to be forgotten and request erasure of his/her data at any time. Given the recent concerns of how social media companies utilize personal information (eg, Facebook and Cambridge Analytica) and global incidences of data breaches, the GDPR offers the opportunity to build trusting relationships among companies, staff, customers, and patients.

In the first 8 months since the implementation of GDPR, there have been 95,180 individual complaints and 41,502 data breach notifications to the local DPA, with Germany accounting for one third of all the breaches.<sup>5</sup> This suggests that the GDPR may have caused barriers to data sharing and added obstacles without significant benefit. On the other hand, at the time of writing this article, it was >

still too early to tell the results of this challenging effort.

The highest risks of the implementation of the GDPR include the inability of the healthcare provider to ensure the continued confidentiality, integrity, availability, and resilience of treatment systems and services. Also of great concern is the nonimplementation of the technical and organizational measures to ensure an adequate level of security, including a process of regularly testing, assessing, and evaluating the technical and organizational measures to ensure the security of the processing. Within the European Union, national Data Protection Authorities (DPA) have already started imposing fines on primary care providers.<sup>4</sup>

One important factor that will affect the decisions by individuals about data access is the trust they place in the organizations gaining access to their data. Will these organizations use the data responsibly and to improve their health outcomes? Or will they abuse or misuse that access? At least one study from the United States suggests that Americans do not place much trust in healthcare organizations compared to other countries, including European countries.<sup>6</sup> The lack of trust will threaten the opportunities that GDPR offers.<sup>7,8</sup>

Another factor that can affect data access is privacy. Many people in EU countries like The Netherlands value their privacy so much that they may opt to withhold data access.<sup>9</sup> This may prove to be an obstacle in some parts of the European Union.

### SUMMARY

To support and improve decision making in the healthcare sector, one needs to preserve data that provide knowledge concerning a patient's health status while concurrently paying heed to data protection principles to ensure that patients and all stakeholders benefit. Difficult challenges will undoubtedly emerge in the future, and these will only be resolved properly if we respect the individual's right to the privacy of their data.

GDPR represents an effort to govern data-processing transparency through

legislation. It builds patient knowledge, confidence, and trust into their personal data collection, organization, structuring, storage, alteration, consultation, use, communication, combination, restriction, erasure or destruction.<sup>10</sup> As such, digital health stakeholders have to conform to new rules in order to successfully recruit patients to allow for data processing, in order to avoid data erasure or destruction initiated by the same patient, which will cause missing data and inconsistencies affecting digital data analytics, thus stifling innovation. •

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### ADDITIONAL INFORMATION

*The preceding article was based on an issue panel presented at ISPOR Europe 2018. Presentations from this meeting can be found at [www.ispor.org/conferences](http://www.ispor.org/conferences).*

# Standardization of Model Validation in Reimbursement Dossiers and Research Dissemination

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Despite its acknowledged importance, validation practice and reporting are not standardized for reimbursement dossiers and research dissemination.

## INTRODUCTION

In many countries, health economic (HE) decision models have become an important part of the healthcare policy decision process.<sup>1</sup> Since the outcomes of these models can have significant consequences for reimbursement, payment, or resource allocation decisions, it is important that these models are valid — that is, these models are in accordance with the current knowledge about the medical intervention and economic effects, and suitable to serve as a solid basis for decision making.<sup>2</sup> Although there is widespread support for the idea of model validation, the validity of HE models remains elusive. For example, a study towards the quality of models used in Australian policy making reported important flaws in 203 of the 247 reviewed models.<sup>3</sup> A lack of validation presents a potential loss of invested resources and a risk to the decision-making process.

Several widely accepted tools discuss validation in some form or another, such as the CHEERS guidelines on reporting,<sup>4</sup> the guidelines by Philips et al,<sup>5</sup> the questionnaire by Caro et al,<sup>6</sup> and the model validation assessment tool, AdViSHE, which is designed solely for model validation.<sup>7</sup> However, despite the availability of these tools, validation practice and reporting are not standardized in the HE processes. Some standardized validation seems desirable, as it is likely that it will improve the transparency for other model builders and users, increase the possibilities for comparing models, and reduce the loss of invested resources and the risk to the decision-making process. The objective of this article is to discuss factors that will hinder or incentivize the standardization of model validation efforts and its reporting, identified by modelling experts. We look at two important application areas which involve HE models, namely dossiers sent to the

(national) decision maker when applying for drug reimbursement, and research dissemination. The factors discussed were identified using expert interviews.

## INTERVIEWS

This article was based on 6 interviews,<sup>8-13</sup> which addressed the following questions. First, how can model validation tools in general — and the model validation assessment tool AdViSHE (Assessment of the Validation Status of Health-Economic decision models) in particular — be useful in daily practice? And secondly, are there any barriers and facilitators to implementation of a standardized model validation tool? Three interviews were conducted with 4 people with many years of experience in building reimbursement dossiers. They either had a history of working in consultancy or worked directly for pharmaceutical companies.<sup>8-10</sup> The other 3 interviews were held with editors of academic journals that publish HE modelling studies.<sup>11-13</sup>

## MODEL VALIDATION IN DAILY PRACTICE

Fortunately, the importance of model validation seems to be understood by many model builders. For example, the consultancy firm MAPI has an internal validation process, which includes sending a model to another office in another country, where the model is validated by going over their internal checklist. Validation efforts were mentioned in publications, although not in detail.<sup>8</sup> At BMS, a pharmaceutical company, a chapter on model validation is included in reimbursement dossiers.<sup>9</sup> At Roche, a base model was developed for oncological models, which is considered well-known, well-validated and therefore accepted.<sup>9</sup> Finally, AstraZeneca always validates their models, in detail.<sup>10</sup> Private companies have developed their own tools<sup>8</sup>, and there are some tools without any official status (eg., published in gray literature, educational textbooks).<sup>11</sup> >

With the importance of model validation so widely accepted, it is surprising that it is not always reported extensively (see for example, reference 14) or in a transparent and consistent way. Because of this, model validation — and model quality — are very different between reimbursement submissions.<sup>9</sup> Model users such as decision makers, or journal readers, have 3 options to address model validation when presented with a model result. Since the cost of model validation can be significant,<sup>15</sup> a user could assume that the model was already validated by the modelers and rely on its outcomes without further examination. However, this requires a lot of confidence in the model and its makers. For example, for some applications core models are used and translated to local settings, but these core models often have errors in them.<sup>8</sup> A loss of confidence happens faster when the modelling team has an economic interest in the outcomes.<sup>6</sup> The second and opposing option is for model users to validate the model themselves. This increases the confidence in the model but may also lead to spending scarce time and money on work that the modelling team has already performed.

A third, middle-ground option is for model users to request a standardized report of the model validation efforts that were performed, with the following questions in mind:

- 1) How have the validation techniques been applied?
- 2) Can and should we replicate (some of) the reported results?
- 3) What is missing?

A standardized tool would be very helpful in standardizing validation, but also in saving time for agencies,<sup>9</sup> while leading to improved confidence in models.<sup>12</sup>

### STANDARDIZED REPORTING OF MODEL VALIDATION AS PART OF THE REIMBURSEMENT PROCESS

Reimbursement decisions based on models with incorrect outcomes may incorrectly limit access to new drugs or allocate budget to interventions that are not cost-effective. Because of these far-reaching consequences of a wrong decision, not only is academic credibility important in validating HE models (“Is the model logically and scientifically sound?”), but also salience (“Is the model applicable within this context?”) and legitimacy (“Are stakeholder concerns, values, and views included in a proper way?”).<sup>15</sup>

One facilitating factor for standardizing model validation is a growing perception of this being needed or useful. A validation report would give a standard, making it possible to compare between models: how good models are, how much effort was undertaken.<sup>8</sup> For example, in both the Dutch and Australian pharmacoeconomic guidelines, reporting validation efforts systematically is obligatory, with AdViSHE being named as an example tool.<sup>16,17</sup> In addition, as discussed earlier, recent publications stress the problems with the current situation and the need for more and better structured model validation reporting.

A second facilitating factor would be whether a standardized tool for validation is embraced by local trade organizations, such as the Dutch VIG (*Vereniging Innovatieve Geneesmiddelen*, Association

Innovative Medicines) or the French LEEM (*Les Entreprises du Médicament*, Pharmaceutical Companies Association). This will be beneficial for the support for such a tool from pharmaceutical companies.<sup>9</sup>

Another facilitating factor is the perceived level of HE expertise of model users, in this case, the employees at the local reimbursement bodies. Although this expertise has improved remarkably in the last few years,<sup>9</sup> the experience with HE of regional payers is limited,<sup>10</sup> with big variation between assessors.<sup>9</sup> This leads to a discussion of (the interpretation of) results.<sup>9,10</sup> If tools are structured for uniform validation, this may improve the quality of dossiers.<sup>9</sup> Especially for smaller jurisdictions with less market power and possibly less resources for extensive validation, standardized validation may help to increase the quality of dossiers and hence, the quality of reimbursement decisions.

**A standardized tool would be very helpful in standardizing validation, but also in saving time for agencies, while leading to improved confidence in models.**

The main limiting factor seems to be that models are often provided by — and validated at — a global office while implementation of standardized validation often starts locally, through local guidelines.<sup>9,10</sup> Because of this, there is a risk that each jurisdiction will have its own way of standardizing validation. From the point of view of the local authorities, validation may be standardized over all submissions but may lead to different methodologies from the modeller’s point of view. If this is the case, standardized validation may be just another hurdle.<sup>9</sup> It was therefore preferred if standardized validation is implemented in several countries, at the same time, and in the same manner.<sup>9,10</sup> If a certain validation method is accepted more broadly, it can then be standardized on a global level. Since local changes are likely only for data, not for the model structure,<sup>10</sup> only a short report might then be needed at a local level. If it’s a set of extra rules, for one or a few jurisdictions, it will only add work, which will make it difficult to get implemented by model developers at international firms.<sup>9,10</sup>

Countries look at each other and learn from each other.<sup>9</sup> Five EU countries (the United Kingdom, Germany, France, Spain, and Italy) are considered leading in this respect.<sup>9,12</sup> Because the Nordic countries are considered to have strict guidelines, they are good countries on which to focus.<sup>9</sup> In addition, decision makers look at the scientific community. For national bodies to accept it, it is expected that the scientific field should accept it first.<sup>10</sup> It first must be a matter of course, integrated in the good modelling practice.<sup>13</sup> Previous guidelines on model reporting in general have been widely adopted,<sup>4,6</sup> suggesting that there is likely support for standardized validation.

### STANDARDIZED REPORTING OF MODEL VALIDATION IN RESEARCH DISSEMINATION

In clinical publications, data sharing is something everybody wants, but it still seems to be a long way off in health

economics.<sup>12</sup> On the one hand, readers, editors, and reviewers of academic papers require transparency. On the other hand, model developers have concerns about sharing their model. Even though *Value in Health* has a system in place where a reviewer signs for confidentiality, generally there is a lot of hesitancy on this from authors. The same is true for pharmacoeconomics. Agencies want to protect their intellectual content against cloning, or confidential pricing information.<sup>12,13</sup>

Standardization of model validation seems to be an acceptable middle ground, which is a major facilitating factor. As stated before, most current HE studies report only limited or no information about validation.<sup>12</sup> Reviewers have reported in the past that they don't have enough information to make the assessment whether a model is valid.<sup>13</sup> Word limits can make it hard to explain what a model is doing well enough that the reader has confidence, persuading the reader it is legitimate. Technical appendices help, but since most readers don't read the appendix, they need to be persuaded by the information in the main article.<sup>11</sup> A standardized validation report will provide an inside view of the model validation process, without having the model code exposed.<sup>12</sup>

Even if a tool is useful, the question remains whether it can be made obligatory for research dissemination purposes. For example, after the CHEERS checklist was published in 13 journals at the same time, *Pharmacoeconomics* decided to adopt CHEERS, considering it good practice that contains basic items.<sup>12</sup> In contrast, *Value in Health*, one of the other journals that published CHEERS, thought that requiring CHEERS would be an extra barrier to publication,<sup>13</sup> especially since the submission process is already time-consuming. Other examples were the probabilistic sensitivity analysis or a conflict of interest statement. Before these were a requirement, they were part of the standard modelling process.<sup>13</sup>

Working the other way around, adding a tool as a requirement will not automatically mean that the scientific community will follow. The Netherlands are considered to have guidelines with items that are not always supported by the community.<sup>9</sup> This runs the risk of losing support from submitters.<sup>9,10</sup> If a technique is easy to work with and accepted by the scientific population, modellers will start to use it automatically — not because it's the guideline, but because they believe in it.<sup>9,10</sup>

With the large number of tools already available, a legitimate question could be whether it is possible to do a meta-analysis of reporting tools.<sup>11</sup> Such a tool would do away with all overlap and synthesize everything into a single tool. It is an interesting suggestion for further research and a way to standardize over the different available journals.<sup>11</sup>

## CONCLUDING THOUGHTS

It was pointed out that a tension exists between reimbursement decision makers and pharmaceutical companies in model transparency. Decision makers, supported by the ISPOR/SMDM guidelines and ongoing discussions in the academic field,<sup>18</sup> often ask for the software code of models — to make changes themselves and for validation, — but pharmaceutical companies cannot always provide that, either because they don't own the

code and the builders don't want to make sharing available,<sup>9</sup> or the model contains sensitive information they are unwilling to share. This is currently solved by being as transparent as possible. Standardizing validation reporting may reduce this tension by further increasing transparency.

Any tool developed to standardize model validation reporting to aid model users will never fully replace the need of validation by model users or other methods like code sharing. Validation will still have to be performed, one way or another. In a reimbursement situation, for example, it may not be possible, or even desirable, to fully prevent the duplication of effort because you want somebody with the reimbursers' interest trying the model out, as well as someone from the point of view of the producer of the intervention.<sup>11</sup> These 2 different, and maybe even conflicting, points of view are both legitimate, as both model builders and users come from a different context. It is a matter of salience: is the model applicable in either or both contexts?

Although there are clear barriers, there are also clear facilitating factors in the implementation of tools to standardize model validation. Major facilitating factors are the growing perception of a need for systematic validation, and the discussion about HE model transparency. Standardization of the reporting of validation efforts in both an academic and applied context, may lead to a higher quality of models, better model-supported decisions in medical decision making, and a better acceptance of these decisions by various stakeholders. •

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# The Potential and Pitfalls of Using Multi-criteria Decision Analysis to Support Health Technology Assessment in Europe

Janine van Til, PhD, University of Twente, Enschede, The Netherlands; Susanne Schmitz, PhD, Luxembourg Institute of Health, Strassen, Luxembourg; Michele Tringali, PhD, MD, Regione Lombardia, Milan, Italy; and Rob Baltussen, PhD, Radboudumc-Department for Health Evidence, Humlebæk, Denmark

**Multi-criteria decision analysis (MCDA) has the potential to improve the structure, transparency, consistency, accountability, and validity of deliberative decision-making processes.**

In most European countries, decisions to reimburse innovations in health care are made after a long and complex process of problem analysis, evidence gathering, and assessment. In most countries, evidence gathering and assessment are followed by deliberative sessions with experts from different backgrounds within and outside health care who appraise the evidence, share their perspective, and discuss the need for reimbursement of an innovation from a societal perspective. This decision process is influenced by multiple criteria. Sometimes the assessment criteria are stated explicitly by the agency; sometimes none or only a subset of criteria is made explicit. For instance, cost-effectiveness of the intervention is an important criterion in most European countries. Moreover, the severity of the disease, the safety and tolerability of the innovation, the quality of the evidence, and budget impact of reimbursement might also affect decisions in Europe.

With the growing costs of health care and the need for budget management, decision panels are increasingly asked to justify their decisions. Multi-criteria decision analysis (MCDA) is often proposed as a way to support reimbursement decision processes. MCDA is “an umbrella term to describe a collection of formal approaches, which seek to take explicit account of multiple criteria in helping individuals or groups explore decisions that matter” (Belton and Steward, 2003).<sup>1</sup> From a theoretical perspective, it seems very promising to use MCDA to support reimbursement decisions, as it is developed to support complex decisions driven by multiple and possibly conflicting arguments, multiple stakeholders, and in which there is no obvious “right” decision.

This article will explore the potential and pitfalls of MCDA to increase structure, transparency, consistency, and validity of deliberative decision processes, based on our experiences in Europe with introducing MCDA to health technology assessment (HTA) decision making.

The Potential of MCDA to Support HTA Although MCDA consists of a wide range of techniques, the common denominator is that all methods follow a stepwise approach to decision making.<sup>2,3</sup> By following this stepwise approach, the promise of MCDA lies in improving the structure, transparency, consistency, validity, and accountability of the decisions that are made. The structure of decisions refers to the extent to which the organizational body has formalized the reimbursement decision-making process. Its transparency is the extent to which the arguments and motivation for decisions are clearly communicated to all stakeholders, including the public. Consistency refers to the extent to which repeated decisions have a similar process and outcomes. The validity of a decision is the extent to which the appraisal committee recommendations reflect the priorities within the society. All these contribute to accountability, which is the extent to which the organizational body can justify the decisions they take.

Our experiences in Europe have shown that explicitly stating, defining, and operationalizing the criteria that are used for assessment contributes to both the structure and transparency of the process. In Lombardy, the EVIDEM framework was adapted to local processes and decision procedures and benefits or shortfalls of several medical devices and procedures were identified and discussed through a performance-scoring exercise in 2 steps (personal then group discussion) against each criterion.<sup>4</sup> In this case, having a pre-emptive list of explicit criteria to assist the performance assessment was a great improvement to the previously unstructured deliberative decision process. By doing so, arguments and motivations for decisions also can be clearly communicated to all stakeholders, including the public.

In the Netherlands, an example of how MCDA can increase structure and transparency of a decision process was the absence of an explicit comparator >

for performance assessment. It was identified in the project “A roadmap for uncertainty analysis in MCDA.”<sup>5</sup> While evidence gathering and assessment in the Netherlands includes explicit comparison of costs and effects for the innovation compared to “current care,” for the other criteria, evidence on the relative performance is not always available. For instance, the budget impact of implementation (or de-implementation of current care) is difficult to estimate, and performance estimates had to be based on the committee members’ expert judgements. Lack of evidence to support decisions is recognized in the current decision-making process and reflected in the qualitative recommendations of the National Health Care Institute in the Netherlands. Criteria weighting and performance scoring in an MCDA model are complicated by the lack of a comparator and are likely reflected in higher uncertainty in weights and performance valuations of committee members. In MCDA, the impact of being uncertain about some of the inputs on the output of the model can be estimated in the final step of MCDA, and the validity of the decision can be appraised.<sup>6</sup>

**If MCDA were to be implemented, it should be integrated with strong deliberative components to combine the benefits of the quantitative analysis with the benefits of a strong, value-based deliberation process, thus resulting in a sum that is better than its parts.**

Unstructured qualitative decision processes can result in disproportionate time being spent on minor issues or undue attention to the opinions of more dominant panel members. When MCDA is used, the relative priorities and values of all committee members are elicited. In our opinion, this can focus the discussion on the most important issues and the most divergent opinions in the panel. In the discussion, each of the committee’s members is required to explicitly state the reasons and arguments to support their judgments, which benefits transparency and validity of the decision process (“Are our explicit priorities in line with how we feel about the importance of this issue, if not, why is this the case?”). Once the overall value of the alternative compared to current care is calculated via formal MCDA, it is of paramount importance to discuss the reimbursement recommendation deliberatively. If there is a feeling of unease with the proposed decision, arguments to deviate from the proposed decision are probably not part of the core set of criteria, and should be discussed (“What are the reasons, not considered in the analysis so far, that would influence our judgment? Would they increase or decrease the value of the innovation that is being discussed?”). When applied and well documented, this can bring validity (and in a broader perspective: accountability) to the decision process.

One would expect that by improving the structure, transparency, and validity of the decision process, the decisions that follow become more consistent. However, varying priorities between assessments reduce consistency of subsequent decisions. While these are difficult to recognize in qualitative discussion, quantitative weight elicitation can highlight inconsistency in importance of criteria. Once potential inconsistency is identified,

it can be a topic of discussion. The most extreme manner in which to increase consistency of repeated decisions within an MCDA framework is to use a fixed criteria set and equal criteria weights over decisions — performance scales that would be able to capture the value of a wide range of innovations and a direct link between overall value of an innovation and the decision to reimburse. For instance, by introducing cut-off points above which reimbursement of health innovations is recommended. However, the major pitfall of this approach is that it could reduce HTA to an algorithmic approach, and the specific aim of having decision committees, which is to appraise the evidence from a public perspective and incorporating societal values, would be lost.<sup>7</sup>

### POTENTIAL PITFALLS TO USING MCDA TO SUPPORT HTA

Our experiences in Europe taught us that building a valid MCDA model to assist reimbursement decision making is a difficult but worthwhile process.<sup>4,5</sup> First, it is questionable whether one MCDA decision model will fit all decisions made by HTA organizations. Some criteria (like disease severity) might not be relevant to consider if multiple innovations for one disease are considered, but are very important for prioritization of reimbursement on a higher level<sup>8</sup>. Second, preferential independence of criteria, which is one of the requirements for MCDA, is difficult to ensure in the model, as many commonly considered criteria are related in their current definition. For instance, cost-effectiveness, budget impact, and effectiveness are related. Third, if MCDA is used to support HTA, a balance has to be struck between explicitly formalizing all conceivable criteria, and keeping the set manageable for the larger organisation, for instance, with regard to evidence gathering and assessment. In addition, the explicit technology performance scoring and weighting of criteria in themselves add an additional layer of complexity to the decision process. The time requirements of doing so have to be considered. Fourth, for some criteria, a performance scale is not easily defined and developing scales takes much time. For instance, in recent years, the GRADE methodology was developed to measure the overall quality of clinical evidence [9]. However, quality of the evidence itself is influenced by multiple criteria, for instance, the number of studies available, their research methodology, the number of respondents per study, and of course, their findings. Further study is required to determine whether using GRADE to assess evidence will suffice or whether meta-analysis or more complicated modelling techniques are required to determine the quality of the clinical evidence as a whole. Fifth, with regard to data aggregation, a simple additive value function may not be able to capture non-compensatory criteria, which are employed by agencies, and more complex analysis methods might be required. Although this is technically possible within MCDA, models that are more complex are more difficult to understand by laypeople, who are the main audience to which HTA decisions have to be justified. Finally, and most importantly, although having an explicit list of criteria is important, we do not expect that all arguments in favor or against reimbursement during appraisal can be fully captured in a “one-size-fits-all” set of criteria. We envisage such a set, along with criteria weight elicitation and performance valuation as a starting point for appraisal, not the result.

When introducing MCDA to a European HTA decision process, a sensitive balance has to be struck between having the benefit of



increased structure and transparency by having clear steps and questions in the decision process, while maintaining the high quality, in-depth discussion on societal priorities and the ability to deviate from criteria as needed and based on well-motivated argumentations. If the latter were lost, the benefit of having an appraisal panel would be lost. Reimbursement decision making is an ethical problem for which the goal should not be to provide a mathematical solution. However, MCDA can be used as a way of more systematic thinking about reimbursement decisions and thereby fulfill its promise of adding transparency and validity to the current process. If MCDA were to be implemented, it should be integrated with strong deliberative components to combine the benefits of the quantitative analysis with the benefits of a strong, value-based deliberation process, thus resulting in a sum that is better than its parts.<sup>7</sup> •

#### ADDITIONAL INFORMATION

*This preceding article is based on an issues panel given at the ISPOR 19th Annual European Congress.*

*To learn more about the ISPOR MCDA Task Force, go to <https://www.ispor.org/Multi-Criteria-Decision-Analysis-guideline.asp>*

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# Q&A

## Getting “Personal” With Personalized Medicine: An Interview With Kathryn A. Phillips, PhD

*Value & Outcomes Spotlight* had the opportunity to sit down with Kathryn A. Phillips, PhD, to discuss personalized medicine and its role in today's world of health economics and outcomes research (HEOR). Kathryn is a professor at the University of California at San Francisco, where she is a health services researcher and health economist and leader in the application of new technologies to improve healthcare, and is the founding director of the Center for Translational and Policy Research on Personalized Medicine (TRANSPERS) in the School of Pharmacy at the University of California, San Francisco (UCSF). She is also a professor of health economics and health services research in the Department of Clinical Pharmacy at UCSF, with additional appointments in the UCSF Philip R. Lee Institute for Health Policy Studies and UCSF

Helen Diller Family Comprehensive Cancer Center. Kathryn is an active member of ISPOR; she is a current member of the Society's Personalized/Precision Medicine Special Interest Group and a member of the Value in Health Editorial Advisory Board, in which she has served as guest editor on ViH's themed section on Value to Decision Makers of Evaluations of Personalized/Precision Medicine: Applications to Other Emerging Technologies in January 2017, which assessed the value and implications of personalized/precision medicine and the “lessons learned” for other emerging technologies. In 2018, she served as a guest editor on the themed section on Measuring the Economic Value of Multigene Tests and Clinical Sequencing. She currently is serving as a guest editor on a themed section on implementation of evaluation approaches.

**Value & Outcomes Spotlight: Is personalized/precision medicine still a “hot” topic that has important implications for HEOR?**



*Phillips:* Yes absolutely! Although some have noted that progress in implementing precision medicine has not been as fast as predicted, its importance and impact continue to grow. Precision medicine has been referred to as “medicine's Wild West”, given that 10 new genetic tests enter the market each day in the United States.<sup>1</sup> Expenditures on genetic testing are also growing, with the highest expenditures for prenatal tests among commercial payers.<sup>1</sup> And much of the growth is for multigene tests.

We are seeing similar growth globally, so it is not only limited to the United States. The global clinical next-generation sequencing market was \$2.2 billion in 2015 and is forecast to reach \$7.7 billion by 2020, which is a compound annual growth rate of 28%.<sup>2</sup>

The continuing interest and excitement about precision medicine, however, must be tempered by the realization that genetics is only one contributor to disease and disease risk. We learn about new genetic associations every day, but it is going to take a long time to understand the role of genetics more completely and how that compares to other etiological factors. We should all keep eating healthy and exercising!

**What are the biggest challenges to appropriate implementation of precision medicine, and where are we in terms of finding solutions?**

It has been said, “The biggest challenge to implementation for precision medicine now is not the science but the economics.” It has also been said, “The three biggest barriers to precision medicine are reimbursement, reimbursement, reimbursement.”

There's a big role for HEOR!

I founded the UCSF Center for Translational and Policy Research on Personalized Medicine (TRANSPERS) in 2008 to develop objective evidence on the appropriate and efficient implementation of precision medicine. At the time, there was excitement about these new technologies but very little focus on their translation into clinical care and health policy. I am happy to say that there are now other centers and initiatives underway.

One ongoing initiative that I'm very excited about is the Global Economics and Evaluation of Clinical Sequencing Working Group (GEECS), which consists of leading global economists who are working together to develop economic evaluation frameworks and approaches for assessing next-generation sequencing. GEECS published a special theme section in the September 2018 issue of *Value in Health* that focused on assessing the value of NGS-based clinical testing.<sup>3-8</sup> This series of expert articles pushed the envelope by highlighting the challenges and by suggesting innovative solutions to move the value assessment process forward for precision medicine. The papers incorporate a wide range of perspectives and topics and use both systematic reviews and case studies—but they all focus on the overarching issue of proposing new methodologies to assess the value of NGS-based technologies in clinical care. GEECS is now developing additional papers that delve more deeply into the challenges of implementing appropriate evaluation methods and approaches.

I also continue to be excited by our work on understanding payer coverage policies. Since 2007, we have led a Payer Advisory Council that includes senior executives from the largest private health plans as well as other thought leaders, which enables us to have a deep understanding of payers' decision making for coverage policies. For example, we are finishing analyses of 14 in-depth interviews with payers on how they view coverage of whole exome sequencing in the prenatal and pediatric settings.

So stay tuned!

### What are some important developments in this field that are relevant to HEOR?

There are many! One important topic is the increasing use of real-world evidence and the challenges faced by payers in using such evidence for coverage policies. Our group just completed a study that developed 14 recommendations for how to facilitate the ability of payers to use real-world evidence rather than only randomized clinical trials (RCTs) for coverage decisions, which is critical given that precision medicine is often not appropriately studied by RCTs.

Another fascinating development is the evolution of the lab industry. We recently published a paper in *JAMA* on the growth of "hybrid labs" that provide low-cost testing with medical-grade results, which we believe is changing how genetic testing is and will be done in the United States.<sup>9</sup> We also have a paper under review on the growth of lab benefit managers (LBMs), which has substantial implications for precision medicine—particularly that some payers are now contracting with LBMs to develop and write their coverage policies and thus, the focus can no longer just be on payers as the coverage decision makers.

Lastly, HEOR needs to prepare for the next frontiers of "precision health" and artificial intelligence. There are many definitions and permutations of these topics, but there is no doubt that the integration of data to facilitate overall individual well-being and the use of big data and machine learning will have important impacts on economics and implementation. •

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### ADDITIONAL INFORMATION

*ISPOR has a Personalized/Precision Medicine Special Interest Group focusing on topics such as leveraging RWE to address uncertainty in cell and gene therapy, and, in cross collaboration with the Medical Device and Diagnostic Special Interest Group, exploring unique methodological and value demonstration considerations associated with next generation testing.*

*For more information on these topics, go to <http://www.ispor.org/member-groups/special-interest-groups>.*

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