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A Discourse on Value™

OCTOBER 2016

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OCTOBER 2016

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Evidera Joins PPD
Creating the Global Leader in Real-World Research

David Simmons, Chairman and CEO, PPD

David Simmons serves as Chairman and Chief Executive Officer of PPD, a leading global contract research organization (CRO). Simmons establishes the strategic direction of PPD and leads its global workforce of more than 17,000 employees, with offices in 46 countries, in the design, implementation and execution of drug development programs on behalf of its biopharmaceutical clients. Simmons joined PPD in 2012 following 15 years with Pfizer Inc., where, in his most recent position, he was President and General Manager of the emerging markets and established products business units, reporting directly to the CEO of Pfizer. Simmons began his career as a software engineer in the steel industry, where he spent 10 years advancing his career to management positions before transitioning to the pharmaceutical industry. He earned a bachelor's degree in applied mathematics and industrial management from Carnegie Mellon University.

Perhaps you've heard the exciting news: Evidera is joining PPD. As Chairman and CEO of PPD, I'm enthusiastic about bringing together our best-in-class companies to provide transformational services enabling our clients to better succeed in the fast-changing drug development and market access landscape.

Our value proposition is clear: By leveraging our combined strengths, we will provide our clients comprehensive development strategies to achieve regulatory approval, while simultaneously generating the evidence needed for optimized market access for new products. We will provide broader access to real-world data, accompanied by deeper disease modeling and analytical skills, all of which can inform and be applied at all stages of drug development. We believe our capabilities and expertise will provide a clear advantage in helping to address the complexities of drug development and achieving market access in today's challenging environment.

Both PPD and Evidera share a deep commitment to the highest quality standards of research, service delivery, and customer focus. For more than 30 years, PPD has been dedicated to the success of our clients and their important research programs, having worked with 48

David Simmons

of the top 50 pharmaceutical companies last year and more than 750 biotechnology companies. PPD's team of more than 17,000 dedicated professionals and offices in 46 countries provide global scope for our comprehensive, integrated drug development, laboratory, and lifecycle management services. Evidera is the clear industry leader in evidence-based solutions demonstrating the real-world effectiveness and value of biopharmaceutical products. By combining our respective industry-leading capabilities under one umbrella, we look forward to continuing to deliver the highest level of service to our customers across a broader spectrum of offerings.

Operating as a standalone subsidiary of PPD, Evidera will serve as the real-world research and market access consulting business of PPD, leveraging PPD's medical affairs operational capabilities for study delivery. This strategic approach, unique in the industry, will maintain and nurture Evidera's culture and focus on scientific excellence and thought leadership.

That I'm writing in this issue of *The Evidence Forum*, with its focus on oncology, is fitting. Oncology is an important focus area and strength for both PPD and Evidera. As biopharmaceutical investments in oncology continue to increase, and the need for evidence to support market access grows concurrently, we will be ideally positioned to help our clients design and implement programs to drive success. Hematology and oncology form one of the leading therapeutic areas for PPD. In fact, we have provided clinical support for 40 percent of the new drug applications (NDA) and supplemental new drug applications (sNDA) approvals over the last three years. We have conducted more than 500 hematology and oncology studies in the past five years alone, at more than 17,000 sites and with more than 67,000 patients. We have more than 2,100 trained staff in this therapeutic area and a global network of more than 9,500 hematology and oncology investigators. Evidera has a similarly strong track record, having conducted more than 400 research projects and contributed to over 100 product submissions across nearly all cancer types since 2013.

In the coming weeks and months, the PPD and Evidera teams will continue to explore opportunities to collaborate and bring our teams closer together. Ultimately, our commitment is to continue to invest in the best science, drive innovation and create a dynamic offering recognized as the industry leader. Please join us on this exciting journey. We look forward to speaking with you about the opportunities ahead.

Evidera and PPD – Looking Forward...

Jon Williams, President, Evidera

Jon Williams

In this first issue of *The Evidence Forum* since Evidera joined PPD, I would like to share my experience thus far in becoming part of the PPD family, and, more importantly, share with you why I'm so excited about this news. From my first discussions with PPD it was obvious to me that they are not just another CRO, and that this was not just another acquisition. As I met with their leadership and extended team, and as I learned more about their organization as a whole, I realized PPD and Evidera shared much in common. PPD is much larger, and they play in an adjacent space, but their mission and culture are similar to ours. Their commitment to the success of their clients, to high quality and high impact research, to the progress of their field, and to the overall improvement of patient outcomes is what drives them, similar to Evidera. I knew almost immediately that these shared values would be the foundation for something unique and special.

As a subsidiary of PPD, we will work together to provide evidence of value that will help bring novel therapeutics to market more efficiently, thereby improving the lives of patients. Together, we want to continue to push the limits of what is possible in our field. In three short years as Evidera, we have built upon the expertise and experience of our talented staff and our predecessor organizations to develop numerous new methods and approaches. We have expanded our capabilities, our geographic reach, and our contribution to science. We have won awards; we have published hundreds of articles; we have been a thought leader in advancing our field; and we have even been named a Vault top ranked company, something unprecedented for an organization in its first year of consideration. Now with PPD, we have a partner with the same high quality, and the same drive for progress and innovation. And, in addition, we have the global reach, regulatory expertise, and operational capabilities that will allow us to better serve the needs of our clients and, by extension, bring novel therapeutics to patients more quickly and efficiently.

The demand for evidence of value continues to rise and we are already working with our new PPD colleagues to develop and deliver innovative solutions to meet this demand, but we also hope to work with you. We would like to learn more about the challenges you face so we can be a more effective partner. Please let us know what we can do to better meet your needs, both now and in the future.

We look forward to collaborating with you, our colleagues in this journey to improve value-based healthcare. In the words of the always inspiring Helen Keller: "Alone we can do so little; together we can do so much."

As President, Jon oversees Evidera's global team of scientists, consultants, and software programmers, providing strategic direction for the company in this rapidly changing healthcare environment. Jon joined UBC in 2010 and oversaw the building of Evidera as an independent company in 2013. He was previously Senior Vice President of Strategy and Business Development at Medco-UBC, where he was responsible for business strategy, organic business development, and establishing partnerships with life sciences and other healthcare organizations. Prior to joining Medco-UBC, Jon was a Senior Principal in the Los Angeles office of the Boston Consulting Group. He has more than 15 years of consulting experience in the healthcare industry, where he has worked extensively with pharmaceutical, biotech, and medical device companies. Jon holds an MBA from the UCLA Anderson School of Management and an undergraduate degree in molecular biology from Brigham Young University.

Oncology
An Exciting Time of New Hope and New Challenges

Noemi Muszbek, MA, MSc
Senior Research Scientist, Modeling and Simulation, Evidera

Noemi Muszbek

The number of trials ongoing (25% of all medicines in clinical trials in 2013[1]) and the amount spent on oncology within healthcare budgets has led to increasing attention on cancer care. The excitement in cancer care is palpable not only in the medical community, but also in the media. The availability of multiple new treatments and treatment sequences, the move towards a potential cure in some cancer indications with the help of immuno-oncology treatments, such as checkpoint inhibitors, the increasing understanding of the underlying disease biology, research into identifying patients who will benefit from the different treatments with the help of biomarkers, and the faster routes to registration based on earlier data from clinical trials are all contributing to this excitement. However, these developments bring their own set of challenges for all stakeholders, including concerns of the increasing economic burden of the cost of cancer treatments and the challenges emphasized or brought about by the focus on immuno-oncology.

Development in immuno-oncology

One of the most visible differences in immuno-oncology compared to chemotherapies that we have come to expect in some indications is the substantial overall survival (OS) benefit shown by the new checkpoint inhibitors, and the now characteristic plateau in the OS curve. This suggests the potential of some patients being cured of their disease (but, of course, still subject to other mortality). However, the unusual survival curve and the hazard ratio (HR) that seems to increase over time do not lend themselves to the conventionally used methods for extrapolation, therefore requiring new approaches and assumptions on what happens after the end of the follow-up period. In addition, there is limited follow-up with immunotherapies for clinicians to provide guidance on long-term mortality, and historical OS curves with chemotherapies and targeted therapies will likely have very different mortality patterns.

Questions have also emerged regarding the appropriateness of progression-free survival (PFS) as an outcome. PFS is usually based on Response Evaluation Criteria in Solid Tumors (RECIST) or the World Health Organization (WHO) criteria that are commonly reported. The different response patterns seen in immunotherapy agents has led to the development of the immune-related response criteria (irRC).[2-4] However, while irRC may capture benefits more accurately, they are less likely to be accepted by regulatory bodies given their newness. Use of irRC would also impair the use of conventional network meta-analyses (NMA) to establish the relative efficacy of immunotherapies versus chemotherapies or targeted therapies.

Accelerated approval by the U.S. Food and Drug Administration (FDA) and early access programs available in Europe, such as adaptive licensing or Medicines

Adaptive Pathways to Patients (MAPPs), and the early access to medicines scheme (EAMS) in the UK[5, 6] which provided access to ipilimumab, nivolumab and pembrolizumab, enhances these challenges. Evidence initially is often based on single-arm trials increasing the difficulty and uncertainty of projecting and comparing clinical outcomes.

With developing clinical knowledge of the disease biology and the development of biomarkers, the patient population is becoming more fragmented, leading to challenges in the comparative assessment of new therapies relative to older ones.

Focus of the cost of cancer treatments

With the development of new therapies comes the focus on drug costs. Recently, not only payers, but also clinicians, started to look at methods to help in selecting treatments offering the best value. In Europe the use of the current health technology assessment (HTA) frameworks are increasing their focus on assessing efficiency with the help of cost-effectiveness analyses (CEAs).

From the payer side, the role of economic criteria has been increasing in the decision making process for innovative drugs. In the UK, starting in April 2016, all new cancer drugs and significant new licensed indications for cancer drugs are to be referred for health technology appraisal, including CEA, to the National Institute for Health and Care Excellence (NICE), as opposed to just a selection of cancer drugs and indications.[7] In Latin America and Asia, the number of formal agencies has been growing. In the U.S., the Institute for Clinical and Economic Review (ICER) has been providing recommendation on drug prices based mainly on cost-effectiveness and budget impact.[8]

From the clinical side, recent years have seen the publication of different value frameworks, including the Medical Oncology Magnitude of Clinical Benefit Scale[9] (ESMO-MCBS) from the European society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO) Value Framework,[10] the National Comprehensive Cancer Network (NCCN) Evidence Blocks,[11] and the DrugAbacus from the Memorial Sloan Kettering Cancer Center.[12] These have been constantly evolving, with ASCO publishing an update in May 2016; ESMO is currently working on a newer version including structural, technical, and immunotherapy triggered revisions;[13] NCCN releasing assessments of treatments in 22 indications; and, DrugAbacus extending the markets included (U.S. Medicare, U.S. Veterans Administration, UK, Ireland, Belgium, and Canada).

The challenges in these assessment include:

- The definition of value, including the criteria according to which value is measured. In the current frameworks, although not identical, the criteria go beyond efficacy and safety and include unmet need, the severity of the disease, innovation, and the patient's voice.
- The determination of value, currently determined in a variety of ways, for example with the use of quality-adjusted life years (QALYs), the determination of a Care Value (for ICER), scoring systems (ASCO and ESMO) or visually (NCCN).
- The assessment of this value using different tools, including CEAs, budget impact analyses, and a form of multi-criteria decision analyses (MCDA).
- The assessment and determination of decision making rules, such as thresholds, the debate around which has been ongoing for decades among health economists, and has recently seen multiple publications.[14-17]

Meeting these challenges requires combined efforts from the different stakeholders, including payers, clinicians, and patients; the development of the methodology that has both a sound theoretical background and is practical for decision making; and the availability of sufficient data to allow the assessments.

The recent clinical developments in oncology offer hope for patients who have not dared to hope before. As with all new developments, these also bring challenges in assessment of the new therapies and, due to the limited resources, the determination of what offers "value for money." These challenges, however, also provide opportunities for the payers, health economics and outcomes researchers, the clinical community, and patients to work together and start discussions to identify new, better solutions and methods that take into account the different aspects of healthcare.

For more information, please contact Noemi.Muszbek@evidera.com.

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An Interview with
Dr. Clifford A. Hudis
CEO of ASCO and the Conquer Cancer Foundation

Dr. Clifford A. Hudis

Clifford A. Hudis, MD, FASCO, *is the Chief Executive Officer of the American Society of Clinical Oncology (ASCO). Previously he served for nearly two decades as the Chief of the Breast Medicine Service and Attending Physician at Memorial Sloan Kettering Cancer Center (MSKCC) in New York City where he was also a Professor of Medicine at the Weill Medical College of Cornell University. He was Co-chair of the Breast Committee of the Alliance for Clinical Trials in Oncology (formerly Cancer and Leukemia Group), Chair of the Scientific Advisory Committee of the Breast Cancer Research Foundation, a former Associate Editor of the Journal of Clinical Oncology, and the President of ASCO during its 50th anniversary year, 2013-2014.*

For almost 30 years he worked to develop more effective treatment and prevention for breast cancer. His early work focused on translating the kinetic predictions of the Norton-Simon model into more effective dose-dense adjuvant chemotherapy programs. For the past decade he has studied the interplay of inflammation, obesity, and cancer, and his group described low-grade, chronic white adipose inflammation in most overweight and obese women. Similar observations have been made in other malignancies and risk groups and these insights have been used to inform intervention studies and public policy initiatives at an international level.

This interview was conducted by Sonja V. Sorensen, MPH, Senior Director and Senior Research Scientist, Modeling and Simulation, Evidera.

Founded in 1964, ASCO is the world's leading professional organization for physicians and oncology professionals caring for people with cancer.

Its mission is conquering cancer through research, education, and promotion of the highest quality patient care.

ASCO is supported by its affiliate organization, the Conquer Cancer Foundation, which funds groundbreaking research and programs that make a tangible difference in the lives of people with cancer.

Before becoming CEO of ASCO, you spent 18 years at Memorial Sloan Kettering Cancer Center as Chief of the Breast Medicine Service and served on their faculty for 10 years prior to that. During your time there, how did real-world evidence and big data change your practice, and what did you learn about real-world data that has helped you in working with ASCO?

As a clinical investigator I had the opportunity to participate in a variety of research projects, including some that anticipated the modern era of "big data" such as the worldwide overviews of adjuvant therapy organized at Oxford University and the real-world data collection efforts by the National Comprehensive Cancer Network (NCCN). In different ways, these projects provided me with an early opportunity to see the promise and possibility of big data. The Oxford Overview[1], for example, allowed us to see the numerically modest but clinically important and life-saving potential of widely available post-operative systemic therapies for breast cancer. Recognizing and confirming these small effects in large populations allowed collaborators around the world to establish life-saving standards of care globally.

You were a member of ASCO's Board of Directors when it developed a vision for Cancer Care in 2030. As the new CEO, what do you hope to bring to ASCO to further this vision for evolving oncology through big data, cancer panomics, and value-based decision-making?

It is becoming clearer with every passing week that we have to begin to leverage the investment and day-to-day effort we put into assembling electronic health records to accelerate insights and the development of new knowledge. As we do this, it will be key to enable empathic caregivers to continue to exercise informed judgment for each individual patient. This is the promise of CancerLinQ[2], ASCO's dynamic learning health system connecting members' electronic health records – it will add layers and depths of insight where we lacked informative data in the past.

What other stakeholders in the industry are important to advancing the ASCO mission, and how are you looking to engage them?

Every stakeholder has a role in this effort and we want to enable more people to make faster progress controlling and curing cancer. It is that simple. Of course, this effort is ongoing, but with CancerLinQ we see that it may be possible to accelerate everyone's work by providing access to more and better data than has been available in the past. The progress we envision requires patients, healthcare providers, payers, the pharmaceutical industry, biotechnology, informaticists, and essentially everyone who contributes to care and progress in any form or fashion. Our engagement will have to be tailored and flexible to allow each to identify where they can contribute the most and provide the greatest support. Within CancerLinQ, this means we are developing opportunities for data sharing, collaboration, governance, and guidance from all quarters.

The Cancer Moonshot being led by the Vice President of the United States, Joe Biden, seems to align with many of the goals of ASCO and its members, such as improving access to treatments, early detection, and prevention. Do you see a way to contribute to this effort to achieve some of these overlapping goals?

Absolutely! Every part of currently available care can be improved by measuring and providing feedback to clinicians on what they do now. Indeed, one of the key benefits that CancerLinQ can provide is to enable our communities of caregivers around the world to deliver the optimal evidence-based care that we already know to be effective. Then we can build on that as we make technical advances in the years ahead. While we provide CancerLinQ to assist clinicians in providing today's state-of-the-art care, we are simultaneously collaborating on pilot research projects to develop even better care tomorrow.

ASCO clearly signals big data as a driver of change that will have an impact on cancer treatment in the coming decades. How do you see real-world data impacting cancer research, and do you think it will have an impact on clinical treatment beyond advancing research?

One of the most immediate benefits of the real-world data collected by CancerLinQ is the opportunity to see if treatments work as well in "real" patients outside of

"...one of the key benefits that CancerLinQ can provide is to enable our communities of caregivers around the world to deliver the optimal evidence-based care that we already know to be effective."

the carefully assembled cohorts enrolled in prospective clinical trials. These trials are critical to testing and developing treatments but they don't tell us everything there is to know. For example, how does a drug, given at a particular dose and schedule in otherwise healthy 40-year-olds, really perform when administered to patients in their 70s with several common comorbidities like diabetes or hypertension? How does that data allow us to refine treatment recommendations and identify new unmet needs? At the same time it is obvious that we can't study every treatment in every conceivable subgroup and population. So, how will we go from knowing little to knowing something more, and more importantly, useful? Real-world data offers that possibility. Looked at it from another perspective, the lack of prospective controlled trials does not stop us from collecting and using data across many areas of activities outside of medicine. With the right controls and cautions it should prove to be useful in cancer care as well.

"My aspiration is that our CancerLinQ team assembles and builds a resource that becomes a central "must-have" tool facilitating markedly more efficient and effective care while enabling faster development of ever improving treatment options."

What are you hearing from ASCO members regarding their data needs?

The needs for data are as broad as our membership and its activities. Everything from scientific analytics to benchmarking to practice management to knowledge assessments and clinical decision support. Essentially, we are looking for tools within cancer care that match those we have grown used to seeing elsewhere in our day-to-day digital lives!

What do you think are the biggest short-term obstacles for greater use of real-world data? Do you foresee any problems with greater reliance on real-world data?

The challenges are substantial and should not be minimized. Our data is only as good as it is accurate. We need to re-imagine how we support recording of data at the source by caregivers so that their workflows are improved and easier instead of interrupted and illogical. We need to make it easy to record data in an interoperable way and to reward everyone in this system for the substantial work this represents. We will also always have to maintain a healthy skepticism with regard to cause and effect as opposed to associations in the results we see from real-world data.

How can ASCO and other organizations help to promote the collection and use of data from a variety of sources, and what are your aspirations for CancerLinQ?

Here again, there is tremendous opportunity but also significant work ahead. We need to think carefully about the kind of data we need, how it is recorded and structured, who puts the data there, and how we can remove the obstacles to its use.

My aspiration is that our CancerLinQ team assembles and builds a resource that becomes a central "must-have" tool facilitating markedly more efficient and effective care while enabling faster development of ever improving treatment options.

The clinical trial landscape is changing, with earlier phase trials going to the FDA and so-called "basket trials" focusing on biomarkers rather than target organs, so what should life science companies consider when gathering evidence?

We treat cancer to achieve cures where possible and longer and better lives when a cure is not possible. This is easy to say but perhaps harder to measure than many people realize. As we divide what used to be common cancers into subtypes defined by molecular tests and treat them with more and more narrowly targeted drugs, we will need to think carefully about which surrogate endpoints are most reproducible and comparable across trials. We will have to develop tools that allow us to make indirect comparisons across studies. We will need to share toxicity and adverse event data in more efficient ways. All of this can be supported by improved interoperability of electronic records and greater data sharing.

ASCO also envisions that the value delivered by treatments, rather than their efficacy, will become the driver for oncology practices. How can life science companies support this goal?

Value and quality of care are completely intertwined. High quality care will generally be valuable and low quality care, while expensive, will not be valuable. It is critical not to lose sight of the ultimate goal: the cure and control of cancer. As we reach for that, we will have to

invest. We will have more and less expensive treatment options, and together with our patients, we will have to make decisions among many options. Value is certainly one criteria to consider in all of this but we should never lose sight of its tight link to overall quality.

How does the ASCO Value Framework[3] affect practicing clinicians as they balance cost and value considerations along with traditional safety and effectiveness considerations?

ASCO's Value Framework is a tool to enable more informed decision making at all levels of drug development and clinical care. It is meant to facilitate and inform discussions that occur and touch on challenging domains such as personal autonomy, the role of third party payers, hope for extraordinary benefit, and personal financial responsibility, among many others. It is a new and evolving tool meant to help all of society begin to grapple with a difficult and emotional issue.

Where do you see the role of patient-reported outcomes (PROs) in decision making regarding cancer treatments?

Across all of care, the patient's experience is central to determining the optimal treatment option. This is not only true when palliating a patient with an advanced and incurable disease but also when delivering curative therapy. To get this right we need much better data than has been available in the past. PROs offer the possibility of far more granular determinations of the day-to-day benefits and subjective and objective toxicities of treatment. We see the integration of PROs as critical to CancerLinQ and the drug approval and monitoring process in the years ahead.

"ASCO's Value Framework is a tool to enable more informed decision making at all levels of drug development and clinical care. ... It is a new and evolving tool meant to help all of society begin to grapple with a difficult and emotional issue."

ASCO's vision statement predicts big changes in oncology treatment over the next 15 years. What can we expect in the next five years?

Recently, I was reminded of a description of technology change attributed to a founding father of the modern information era which said something like "technology changes less in one or two years than you expect, but much more than you expect in five or ten." I am sure I have failed to capture the phrase accurately but the concept resonates. Day by day, we see a new drug, a new biological understanding, a new technology, and we think we are seeing the small incremental steps we expect. But when we look back at five years or ten, we suddenly realize how far we have come. We saw this happen with childhood leukemia, with breast cancer and other diseases with widely available conventional treatments. More recently we have seen it happening at an accelerating pace in chronic myelogenous leukemia, multiple myeloma, melanoma, non-small cell lung cancer, and many other diseases. Each advance, in its own right, may seem to be modest or routine. But a revolution in cancer care is already underway and we will see more and more of the changes predicted for 15 years as time goes by.

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An Interview with Jola Gore-Booth
Chief Executive Officer, EuropaColon

Jola Gore-Booth

Jola Gore-Booth founded EuropaColon, the first Pan European Not for Profit organisation dedicated to preventing deaths and improving the quality of life for those with colorectal cancer, in 2004. Jola's vision for EuropaColon has grown from long-standing experience and deep understanding of the needs and challenges faced by people with colorectal cancer. Previously, between 1997 and 2005, she was Chief Executive of Colon Cancer Concern (CCC), a leading UK colorectal cancer charity (now known as Bowel Cancer UK). Whilst there, Jola launched Bowel Cancer Awareness Month and the Bowel Cancer Forum – a collaboration of key stakeholders working together for the good of colorectal cancer patients and the general public. In addition, she has served on various advisory boards, steering committees, and achieved notable success with NICE on patient access to treatments. Jola saw the importance of collaboration and patient advocacy which drove her to create a colorectal cancer community by coordinating the development of patient advocacy groups across Europe. EuropaColon is an umbrella organization, represented by 43 groups across 32 European countries.

This interview was conducted by Agnes Benedict, MA, MSc, Senior Research Scientist, Modeling and Simulation, Evidera.

EuropaColon has four main goals; 1) to reduce the number of European citizens affected by colorectal cancer; 2) to identify colorectal cancer at an early stage; 3) to ensure access to the best treatment and care to all European patients; and, 4) to support novel and innovative colorectal cancer research. This interview focuses on the last two of these goals, which are most relevant to our readers.

Increasingly in healthcare we are seeing more involvement from patients, patient advocacy organizations, and disease foundations in the drug development process, as well as market access and reimbursement. Has EuropaColon been involved in activities related to drug development and/or market access?

The role of patients in drug development is an important topic and has been around for a long time, without much resolution. Should patients be involved in the development of clinical trials? I am often asked this question. Yes, of course, we think that patients should be involved in trial development, but it is a difficult challenge since manufacturers, clinicians, and patients often have different perspectives and goals that are not always easy

to reconcile. So the issue is at what point should patients get involved, and I don't have an answer for that. I feel that all stakeholders should, however, have this discussion sooner rather than later.

We are involved in guideline development. In 2012-2013, we participated in EURECCA's (European Registration of Cancer Care) first benchmark project on colon cancer. EURECCA's goal was to define core treatment strategies and develop a European audit structure in order to improve the quality of care for all patients with colon and rectal cancer through the analysis of data from national registries.

EuropaColon is also part of the new EU Joint Action on Comprehensive Cancer Control (CanCon), designed to facilitate the international cooperation and exchange of best practice between EU countries and to identify and define key elements to ensure optimal, comprehensive cancer care. We are providing the patient perspective.

We were also recently asked to provide input on a new Informed Consent document for patients entering into clinical trials. We referred this to our Expert Patient Advisory Group (EPAG), who reviewed the document and offered their opinions for consideration.

We are seeing a growing interest in patients and advocacy groups contributing to market access and reimbursement issues. Where does EuropaColon stand on that front?

In terms of market access, we are talking health technology assessment (HTA). Given that there is no pan-European HTA right now, it is at the national level where our groups can get involved. Bowel Cancer UK is a regular participant of National Institute for Health and Care Excellence (NICE) reviews. Barbara Moss, the Chair of our Expert Patient Advisory Group, has previously been involved with NICE appraisals and with the European Medical Agency (EMA), but that is the extent to our participation in that area.

You already mentioned your Expert Patient Advisory Group (EPAG). How many members serve on this group and how were those individuals selected?

We consider the EPAG an incredible strength of EuropaColon. There are currently nine members of this group who were recruited from our Associate and Affiliate Members. This is a very active group with true commitment and the members have already helped EuropaColon on a number of different topics.

"Over the years, it has become accepted that EuropaColon is the voice of colorectal cancer patients at the European level."

What kind of activities has this group participated in, and how can organizations contact this group if they would like to obtain their input on specific issues related to colorectal cancer?

Amongst others, they developed a patient leaflet on RAS (predictive biomarker) testing in colorectal cancer. They created a patients' diary enabling patients to highlight important questions to ask when visiting their oncologist or surgeon. The group is also involved in helping draft the program for our next Master Class. I can only anticipate the value of their contribution increasing even more with time.

Any approach to EPAG should come through the EuropaColon Head Office and we will discuss the project with the Chair, who is also a member of the Board of EuropaColon.

As a patient organization, your aim is bringing together key stakeholders in the fight against colorectal cancer. How does EuropaColon interface with key stakeholders (regulatory, pharma, clinicians)? Who do you work with exactly? Do you negotiate directly with national and European Union stakeholders, or do you leave it to your Member Groups to work at a national level?

That is an interesting question. Over the years, it has become accepted that EuropaColon is the voice of colorectal cancer patients at the European level. We have done various events in the EU Parliament, building relationships with Members of the European Parliament (MEPs), and working with our champions over the years. Politically it is hard work, but we aim to have a constant presence in Brussels and we do a lot of networking to support our goals. At a national level we support our Member Groups to develop and build their own relationships with their Health Ministry, MEP's, and Members of Parliament (MPs). Together we are making a difference.

We also work closely with many medical organizations. These include the European Cancer Organization (ECCO), the European Society for Medical Oncology (ESMO),

and the European Society of Digestive Oncology (ESDO) amongst others, and more recently with the European Society for Surgical Oncology (ESSO).

What is your relationship with biopharmaceutical and medical device and diagnostics companies? Do you feel you can have a role in working with industry to advance your cause?

We also sit on the European Federation of Pharmaceutical Industries and Associations (EFPIA) Think Tank made up of pharma and patient organizations to ensure patients have a voice in healthcare. This is a forum where very diverse issues of mutual interest are discussed and aired in a safe place.

We have long-standing working relationships with many in the pharma industry. As you can imagine, funding is always a challenge, so having support from industry companies is very important. We are transparent, however, and have clear contracts that outline what is expected of both parties when a company agrees to be a sponsor.

I would imagine that having good relationships with clinicians is also very important in moving your goals forward. How does EuropaColon engage with clinicians and what type of input do they offer to enhance your activities?

Honestly, the biggest challenge we have faced has been engaging with clinicians. First, clinicians are extremely busy and if you want to work with the best in the field it is a challenge to get their time. The younger ones, up and coming, are very focused on building their careers and concentrating on their practices and have less time to participate in outside activities. Many doctors also are less interested in the political part of healthcare; they want to focus on their patients and not necessarily get involved in advocacy. I can say, however, that progress is happening. Whereas the attitude used to be that patient advocacy groups were something clinicians had to "put up with," now there seems to be a better appreciation of what we are trying to accomplish. Over the years, advocacy groups have become more professional as well with well thought-out business plans, measurements of success, reporting of activities, etc., which brings another layer of respect to our community and makes us more credible at all levels.

How do you determine what research projects EuropaColon will get involved with, and how does that process work as far as stakeholders engaging your participation?

I would first like to say that this is a very early initiative for us, and to start, our focus will be on the small projects with truly innovative ideas. We are currently establishing a Scientific Committee that will be comprised of senior European clinicians. This committee will evaluate relevant requests for support and EuropaColon will help raise funds for those we feel hold promise.

We are also slowly expanding our remit into other digestive cancers as this is an area where patients are needing more support. Initially we will focus on pancreatic cancer and then gastric cancer.

In conclusion, what do you feel your biggest contribution has been in starting EuropaColon?

One of the biggest contributions and most rewarding has been the growth of our organisation across Europe. Together with our 43 groups we are making a difference in patients' lives through improved access to best treatments and care. At the same time, we are raising awareness of colorectal cancer - and the risks, signs, and symptoms of the disease - within the populations of Europe, and working towards achieving earlier diagnosis which will lead to more lives being saved. In the 12 years we have been established, our groups have developed into a very strong, committed, and vocal colorectal cancer community working together for the common good of all colorectal cancer patients and European citizens.

Medical Specialty Societies
An Emerging Source of Real-World Evidence

Vernon F. Schabert, PhD
Senior Research Scientist, Real-World Evidence, Evidera

Vernon F. Schabert

For many conditions requiring specialty clinical care, the era of obtaining real-world evidence (RWE) insights from insurance claims is drawing to a close. Life sciences companies are developing treatments for increasingly smaller subsets of disease populations, increasing the information demands to define populations and characterize their course of illness. The data elements required to establish these patient populations, and demonstrate that new treatments improve those patients' outcomes relative to usual care, are rarely needed to substantiate payment for services in any current reimbursement model. Among the 14 oncology drugs approved by the FDA in 2015, patients indicated for nine drugs (alectinib, cobimetinib, daratumumab, dinutuximab, necitumumab, osimertinib, palbociclib, trabectedin, trifluridine/tipiracil) are impossible to identify solely from the use of insurance claims. Tumor biomarkers, histology, and the level of response observed from prior therapies are all missing from insurance claims and are needed to verify these medicines' treatment indications.

"The declining value of insurance claims for many RWE questions has exerted several forms of pressure on evidence for market access."

Even when treatment-eligible patients can be identified from insurance claims, insights regarding clinical judgments and treatment outcomes are still missing from those claims. Mortality can only be crudely inferred by events preceding a patient's disenrollment, or by the infrequent case of in-hospital death. Progression is often inferred from insurance claims by the administration of a new line of therapy, but these data cannot discriminate between progression, toxicity, and patient preference as reasons for therapy discontinuation. New data sources are also required to analyze prognostic scores, performance status, and tumor attributes that imply specific treatment pathways.

The declining value of insurance claims for many RWE questions has exerted several forms of pressure on evidence for market access. It has prompted innovation in the ways that life sciences companies use randomized trial data (e.g., new simulation technologies, indirect and mixed treatment comparisons). It has also increased readiness to invest in observational studies that depend on primary data collection. But notably, it has also maintained pressure on locating healthcare data from other sources, such as electronic medical records (EMR), that may hold the level of clinical detail required for evaluation of today's treatments. The cost, flexibility, and repeated use benefits of healthcare databases such as EMRs hold continued appeal to those managing

constrained evidence generation budgets. Described below are the factors leading to increased availability of EMRs, incentives to improve EMR data quality, and the emerging role of medical specialty societies in aggregating EMR databases for RWE.

Expanded Adoption of Electronic Medical Records

EMR data sources have been available for RWE purposes in some European countries since the 1990s. The predecessor to the Clinical Practice Research Datalink has been publicly available since 1994, and practice registers have been available in the Netherlands through the PHARMO Institute since 1999. However, research-ready access to EMRs varies widely among European countries, and it remains heavily biased towards general practitioner records. Life sciences companies interested in exploring the benefits and risks of specialty care products have seen limited value from European EMR databases.

The availability of EMR records in the U.S. has increased dramatically due to business concerns and regulatory developments. The initial transition from practice management systems to EMRs was prompted by fears that the "Y2K" problem, the hard-coding of two-digit years in FORTRAN- and COBOL-programmed billing systems, would create fatal errors in providers' ability to invoice for services.

Some U.S. EMR companies aggregated data from their new customers for research purposes. Aggregated databases from general purpose EMR vendors such as Allscripts, Cerner, and General Electric have been used for peer-reviewed research in the life sciences. The collective experiences of using such databases have been mixed. While they provide access to content not typically available from other healthcare databases, many data elements were missing or unpopulated. EMR companies could sell systems to physician practices, but had little influence on the quality or completeness of data entry in those systems. Researchers increasingly sought information that was stored in unstructured documents, such as dictated clinician notes or laboratory reports. EMR vendors, however, lacked the incentive, authority, or technical capabilities to strip identifiers that could compromise patient privacy from those documents.

"...research-ready access to EMRs varies widely among European countries, and it remains heavily biased towards general practitioner records. Life sciences companies interested in exploring the benefits and risks of specialty care products have seen limited value from European EMR databases."

In addition to general purpose EMR systems, some EMRs were developed for the needs of specific medical specialties. Among those, the EMRs for oncology practices were most likely to have their data aggregated for research purposes. Oncology databases sourced from Varian and Impac became available for research use, but bore many of the same challenges as those from general-purpose EMR databases. Some specialty EMR database providers made an effort to improve data entry quality, for their own business benefit as well as the benefit of researchers. McKesson's iKnowMed EMR system, originally developed by U.S. Oncology, enforced data entry checks and quality systems as a condition for getting access to group purchasing and drug ordering benefits. Most recently, Flatiron Health has committed to automated and manual enhancement of data for several different EMR brands to improve feedback for physician customers and to enhance the value of data for life science research.

Incentives for Improved EMR Data Quality

U.S. companies marketed EMRs not just as solutions to fixing Y2K problems, but also for improving population-based care. This marketing push, and perhaps some effective lobbying, inspired the U.S. government to incentivize their adoption in exchange for greater accountability for quality care. The 2009 American Reinvestment and Recovery Act contained provisions referred to as the Health Information Technology for Economic and Clinical Health Act (HITECH). HITECH offered payment incentives for EMR adoption as long as providers demonstrated "meaningful use" of non-billing features to assure high quality care processes in their practice.[1] The Centers for Medicare and Medicaid Services (CMS) gained authority in 2006, under the Tax Relief and Health Care Act (TRHCA), to reward voluntary physician quality reporting with increased physician reimbursements.[2] That program, now called the Physicians Quality Reporting System (PQRS), has gradually shifted its range of reporting options to favor use of EMR data. PQRS received additional support when the 2010 Affordable Care Act (ACA) authorized Medicare reimbursement penalties for those not participating in PQRS by 2015. The Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) streamlined HITECH's EMR adoption incentives and TRHCA's PQRS reporting incentives into a Merit-Based Incentive Payment System (MIPS), which will begin in 2017.[3]

The legislative incentives for EMR use and quality reporting apply to physicians across medical specialties. This has increased the likelihood that data on real-world specialty care exist within the EMR databases of U.S. physician practices. However, obtaining ethical access to well-powered cohorts from these EMRs requires aggregation from their distributed locations, and also sufficient data processing to assure patient privacy and research validity.

Medical Specialty Societies Offer Support

Physicians can meet PQRS reporting requirements through participation in registries; CMS has established two models by which entities can form registries for submitting physicians' PQRS results. One of these models, called the Qualified Clinical Data Registry (QCDR), has gained favor among numerous medical specialty societies. U.S. medical specialty societies have increasingly taken on the challenge of aggregating specialty EMR records and applying for certification as QCDRs. The Council of Medical Specialty Societies (CMSS) has fostered this interest, sharing best practices through conferences and the publication of a registry primer.[4] The current list of QCDRs includes EMR-based registries affiliated with more than a dozen U.S. medical specialty societies.[5]

Given that PQRS reporting influences physicians' reimbursement rates under Medicare, medical societies can provide a substantial membership benefit by assisting practicing physicians with their EMR-based quality reporting. Most medical societies do not have the technical capabilities to extract or aggregate EMR records from distributed physician practices; these societies have outsourced extraction and aggregation tasks to technology vendors. Unlike the EMR databases aggregated by individual EMR companies, the task of aggregating EMRs for medical specialty societies requires merging data from multiple brands with dissimilar data models. PQRS measures are based on a Quality Data Model (QDM), first developed by the National Quality Forum and now jointly maintained by CMS and the Office of the National Coordinator for Health Information Technology.[6] While the QDM provides a target list of data elements that should be standardized, it provides little guidance to data aggregators on the database structure in which to arrange these elements from disparate EMR systems.

Aggregation vendors' technical support is often funded directly by the sponsoring medical society. A review of public information on the QCDR list and specialty society websites suggests that member physicians currently pay minimal or no fees for participation in their society's QCDR. The sponsorship and financial underwriting of the medical societies are substantial incentives for physicians to contribute EMR data into aggregated registries. A synopsis of several medical specialties, and their current state of research readiness, appear below.

The **American College of Cardiology (ACC)** has developed an increasing number of registries under the National Cardiovascular Data Registry® (NCDR) brand.[7] ACC maintains numerous hospital-based registries that depend on data collection forms. Their first outpatient registry, – Practice INNovation And Clinical Excellence (PINNACLE™) began in 2008, with its first PQRS reporting conducted in 2009.[8] Initial data collection was also performed using data collection forms, but ACC has incentivized EMR-based reporting through partnerships with a data extraction vendor and certification of export functions from EMR vendors. A functioning EMR has been a participation requirement since 2010, although the registry still extracts only a portion of participants' full EMR data.

"Unlike the EMR databases aggregated by individual EMR companies, the task of aggregating EMRs for medical specialty societies requires merging data from multiple brands with dissimilar data models."

PINNACLE is the most research-ready of the medical specialty registries. ACC maintains a governance process to approve research applications. Approved applications are executed by a limited set of approved analytic centers, not by the research requestor. ACC publishes the PINNACLE data dictionary, a printed version of its data collection form, and a list of abstracts, manuscripts, and unpublished reports on studies that have used PINNACLE. The first peer-reviewed manuscript using PINNACLE data was published in 2010.[9]

The **American Academy of Ophthalmology (AAO)** began development of the Intelligent Research In Sight Registry (IRIS®) in 2014. IRIS was certified as a QCDR for PQRS reporting in 2016. Unlike ACC's PINNACLE, IRIS was conceptualized as an EMR aggregation registry from its inception. AAO states clear intentions to use the data for research purposes in its promotional materials. A case study of IRIS in the CMSS registry primer mentions pilot study contracts between AAO and external researchers.[4] AAO acknowledges in this same case study that broader support for external research depends on their development of a review infrastructure, slated for 2017. AAO has not yet published a data dictionary or other

"Supplementing database studies with prospective data collection, or more precisely targeting recruitment for clinical trials, might become feasible uses of specialty society EMR databases in ways that commercial databases could not support."

support materials that would inform potential applicants of the IRIS Registry's value for particular research questions.

The **American Academy of Neurology (AAN)** announced the formation of its Axon Registry™ in 2015.[10] By 2016, AAN announced that the Axon Registry had already been approved as a QCDR.[11] Like AAO's IRIS Registry, the Axon Registry was established as an EMR-sourced registry from its inception. AAN has established a Registry Committee and a Data Governance Committee with responsibilities for the Axon Registry, but has not published specific intentions to release data for external research, nor has it published supporting materials that could inform researchers of the Axon Registry's potential value.

The **American Society of Clinical Oncology (ASCO)** established CancerLinQ™ in 2012. ASCO developed a prototype CancerLinQ database in 2013, based on breast cancer patients from several cancer centers.[12] Development accelerated in 2015, when the enterprise was incorporated as a wholly owned subsidiary and a new executive team was hired to expand enrollment. The current model involves data extraction through participating practice EMRs, as with the other registries previously described.

CancerLinQ has been the most explicit of medical specialty society registries in terms of identifying its participating practices, which could inform how representative participating practices are of oncology practices as a whole.[13] CancerLinQ has also published its governance structure and its authority for re-use of data.[14,15] Although neither ASCO nor CancerLinQ have published details regarding current external research use of registry data, these publications provide more specific details about the potential for future data use than are available from other medical specialty registries. First, the current CancerLinQ framework maintains personal health identifiers (PHI) from contributing practices. CancerLinQ proposes separate database instances, some retaining PHI for use in CancerLinQ's role as a Business Associate for participants, and others stripped of identifiers for use as Limited Data Sets or De-Identified Data Sets as defined under the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Second, the scope of elements collected within CancerLinQ includes unstructured documents, with intention to use those documents for future analysis activities. CancerLinQ consulted an Institutional Review Board, which deemed that the scope of activities proposed for CancerLinQ participants was exempt under the healthcare operations clause of the HIPAA Privacy Rule. It is possible that future data uses may be considered beyond the scope of healthcare operations and may require ethics review.

Potential Advantages of Medical Specialty EMR Databases

As previously discussed, aggregated EMR databases in the U.S. have previously been accessed through commercial entities. Accessing similar records from a medical specialty society has several potential advantages to the commercial access model. First, commercial enterprises have usually obtained access to EMR records through purchasing or barter agreements. The cost or effort required to obtain these data must be passed along to researchers through data access or license fees. Medical specialty societies collecting EMR records for registries are also, in effect, bartering for data access. However, the magnitude of pass-through cost is likely to be much lower for medical societies than for commercial entities, as long as those societies are able to obtain data without payments to individual practices.

Second, the purpose of medical society EMR registries includes a built-in feedback loop that holds potential for improving the quality of data entry and consistency. QCDRs can show physicians which patients fail performance measures in ways not likely visible within the practice's EMR interface. Because better performance on PQRS measures leads to improved reimbursement, physicians have incentive to correct data entry for poorly-documented patients. Medical specialty societies are more directly involved in the development of PQRS measures than are commercial entities. The potential benefit is that EMR databases aggregated by those societies naturally lead to improved data entry quality. The Business Associate relationship that permits this feedback loop also depends on specialty societies' access to patient identifiers, which are usually stripped or encrypted prior to sharing of EMR data with commercial entities. Possession of identifiers increases the opportunity to link patient records with those in other care settings, potentially overcoming the disadvantages of researching patients in a single practice setting.

Finally, medical specialty societies maintain a stronger professional relationship with their physician members

than would commercial entities. The benefits of this relationship can be observed in the registry examples discussed above. Practices appear willing to contribute patient identifiers and content such as unstructured documents to these registries, which would be unlikely for commercially aggregated EMR databases. It is likely that member physicians would be more open to appeals from a specialty society to expand the level of engagement in externally sponsored research. Supplementing database studies with prospective data collection, or more precisely targeting recruitment for clinical trials, might become feasible uses of specialty society EMR databases in ways that commercial databases could not support.

Criteria for Viable Specialty Society EMR Databases

While EMR registries from medical specialty societies possess potential advantages, that potential must be realized before these registries hold value for external researchers. At present, the volume of research supported by these databases is small, limited to few medical specialties, and a subset of EMR data elements within those specialties. Several success factors will determine whether these EMR registries become useful RWE resources for the life sciences industry.

First, medical societies are in the business of serving their clinician members. They are not experienced at developing financial and operating models for the production of research-ready data. The registry examples previously described all appear to depend on external technology vendors to accomplish the initial steps of data extraction and aggregation. Additional functions of data curation, database documentation, inquiry support, and fulfillment must all be developed if specialty societies hope to support external research at any scale. The potential for unintended privacy exposure or processing errors that undermine data validity also require a robust set of quality management procedures. Such procedures are also not a core capability of medical societies. External interest in such data will be directly proportional to the quality, scale, and speed of access that result from a well-organized data production enterprise. Medical societies will most likely require external support to design and implement such operations.

Second, medical specialty societies who undertake EMR registries will face tension between their membership mission and the range of research interests from external parties. Governance structures must clearly identify the range of potential uses for registry data, so that participating practices maintain confidence in their continued participation. Beyond concerns about maintaining privacy, participating practices may not yet be prepared for uses of registry data that compare quality performance across practices, use financial information such as contracted rates or staffing costs, link patient records to care rendered outside the practice, or represent intrusions in the form of patient recruitment activities. The boards of medical specialty societies, populated with physician members, will need to demonstrate leadership in defining mutually acceptable uses that balance the interests of participants and research sponsors.

Finally, the incentives that have prompted societies to establish EMR registries must either remain in place, or be replaced by equally attractive incentives. As with most healthcare databases, research access to medical specialty registries is secondary to other business or regulatory functions. Should government incentives for EMR use be repealed or decreased, U.S. medical specialty societies would require additional reasons to underwrite registries, and members would need additional reasons to continue participating. Funding from external research sponsors can provide one such incentive for continuing registries, but benefits of that funding may be perceived differently by medical societies and their members. Efforts that inspire participants to a higher purpose, such as the Cancer Moonshot Initiative's urging to break down barriers to research collaboration in oncology, will likely need to be paired with incentives that meet the continued financial and business interests of participating specialty practices. However, under current incentives, medical specialty EMR registries hold increasing promise for obtaining real-world insights on specialty care.

For more information, please contact Vernon.Schabert@evidera.com.

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Is Oncology Market Access Indeed Special?

Susanne Michel, MD
Vice President and Practice Lead, Payer Strategy, Evidera
Frances MacDonald, PhD
Vice President, Real World Outcomes, PPD

Susanne Michel

Frances MacDonald

In September 2016, the Evidera and PPD team consulted the Pricing and Reimbursement Policy Council (PRPC) composed of one current or former payer each from Italy, Spain, England, France and Germany and two current or former payers from the U.S. The council is consulted by Evidera on a regular basis to obtain updates on current policy trends in market access and to debate how manufacturers can best address changing environments and payer demands.

At the September meeting, our interest was to gain the council's perspective on how oncology medicines will be handled by payer organizations in future years. Some countries, such as Germany, assess oncology medicines with the same methodology and thresholds as any other, with oncology orphan medicines also following the same route as other orphans. Other markets have historically given orphan oncology medicines a degree of special status. England's National Health Service (NHS) instituted a specific Cancer Drugs Fund (CDF) for those medicines found not to be cost-effective by the National Institute for Health and Care Excellence (NICE). U.S. payers have found it challenging to value medicines in this sensitive area, and many states mandate coverage for virtually all oncology medicines. Our key question to the PRPC, therefore, was will past trends continue in those countries that treat oncology medicines as a 'special case' (i.e., will they continue to be less subject to health technology assessment (HTA) and price pressures)? If not, how do council members foresee the way in which the balance between high need, innovation, and budget impact will be handled?

"Some clear trends and commonalities emerged from the PRPC, suggesting that payers are increasingly aware of the cost impact of oncology medicines and the difficulty demonstrating additional clinical value as opposed to innovation."

Some clear trends and commonalities emerged from the PRPC, suggesting that payers are increasingly aware of the cost impact of oncology medicines and the difficulty demonstrating additional clinical value as opposed to innovation. Those consulted all indicated that considerations were being given to how this could be better managed.

Quote from a U.S. payer: **"We have concerns and beliefs that many of the new agents offer only small improvements over existing treatments, and not enough to justify the huge cost increases."**

As a clear example of a shift in payer perspective, England's CDF was revised in July 2016, introducing a managed entry period, with the expectation that positive guidance will only be available if final cost-effectiveness figures are within the conventional £20-30K per QALY range. Previously, this range was not applied. This is a highly material change.

Equally in Germany, where oncology treatments never enjoyed a 'special status,' the latest proposed changes to the law to strengthen the supply with medications (Entwurf eines Gesetzes zur Stärkung der Arzneimittelversorgung in der GKV, July 2016, BMG) may

"Most PRPC council members commented on the imminent and expected arrival of biosimilars into the oncology market, and their expectation that these will enter the market at significantly lower prices, exerting broad downward pressure on prices within the relevant market segment."

challenge the access of oncology treatments by objecting to the reimbursement of populations that have not demonstrated an incremental benefit.

Quote from the Spanish PRPC council member: **"I guess part of the contracting will go down DRG type of reimbursement."**

Quote from a U.S. payer: **"In crowded specialty categories like rheumatoid arthritis and multiple sclerosis, we contract for preferred agents and this type of approach could cross over into oncology."**

The fact that some segments of the oncology market are becoming relatively competitive (i.e., with choices now available) gives leverage to payers in many countries when discussing reimbursement prices. In these busier segments, payers are beginning to move into contracting discussions in a similar manner to other therapy areas, without significant hurdles.

Most PRPC council members commented on the imminent and expected arrival of biosimilars into the oncology market, and their expectation that these will enter the market at significantly lower prices, exerting broad downward pressure on prices within the relevant market segment. Pharmaceutical companies need to be aware of this expectation and manage it appropriately to ensure there is no mismatch in expectations. Are the differences between generic products and biosimilars fully understood?

Again learning from past experience in other therapy areas, there is a clear move in most countries towards introducing clearer value frameworks within oncology contracting. Payers from many countries (Italy, U.S., England, France) all mentioned the potential for some type of financial and/or outcome-based risk sharing agreements, and in many countries these agreements are already in place. Italy has had such schemes in place since 2006, and NICE in England and the Scottish Medicines Consortium (SMC) in Scotland have been expecting and accepting such proposals for several years, primarily since they were included as an option within the 2009 UK Pharmaceutical Price Regulation Scheme (PPRS). It appears that the U.S. is also looking at this option.

Quote from a U.S. council member: **"Value-based contracts are in early development, but I think it is unlikely that we will see meaningful value-based contracts with oncology drug manufacturers in the next two to three years due to the complexities of implementing these types of contracts. However, we are seeing the growth of full or partial risk sharing by physician groups."**

The challenges in managing outcome-based schemes are very real (i.e., tracking the relevant outcome over time and over multiple healthcare providers), and ensuring that the consequence if the target outcome is not attained triggers the relevant action is not simple, especially if there are multiple such schemes. If a rebate is then due, ensuring that it can be provided to the relevant payer is also often not simple. Most healthcare systems are not designed to track information in this way, in particular if the patient can move between providers. Consequently, most payers prefer financial-based schemes such as an upfront discount (generally confidential, to maintain the list price) or a price-volume discount arrangement.

With the proposed latest changes in Germany, the ultimate end to free pricing in Germany will be assured. If the proposed change to the law is accepted by the Parliament, companies will face the need for very tough price calculations in the first year of being on the market, and with having to accept the agreed price from the month the revenue will exceed €250M. Equally, the ability to evaluate treatments launched before AMNOG (Arzneimittelmarkt-Neuordnungsgesetz - The Act on the Reform of the Market for Medical Products) in 2014 permanently excluded from any G-BA (Gemeinsamer Bundesausschuss – Federal Joint Committee) evaluations, may be evaluated henceforth if these treatments seek an extension into another indication or line of treatment. This is likely to hit oncology treatments hard.

Pharmaceutical companies need to be aware of these payer considerations and adapt to global and local trends as they develop their launch or lifecycle strategy for each market.

And looking further ahead, payers expressed some concerns regarding the impact of EU adaptive pathways on the ability to maintain any value-based frameworks.

Quote from the Italian payer: **"Adaptive licensing could give a blow to evidence-based medicine."**

Maybe a topic for a future discussion!

Years ago oncology was a uniquely attractive therapy area for drug development. There is still high need, therefore it is still attractive, but it needs significant management.

Historically, oncology has been viewed as a health priority with an elevated social importance that is widely acknowledged by payers and reflected in political initiatives including National Cancer Plans and development research facilities.

Payers have been apprehensive to place downward pressure on prices of oncology drugs to manage budgets, so the strategy has generally been to focus on market access.

Source: www.who.int; www.nhs.gov.uk; www.e-cancer.fr

Given evolving payer trends in oncology and the robustness of manufacturers' oncology pipelines, it is essential for manufacturers to incorporate market access implications into its development and commercialization strategies.

By incorporating the payer perspective into commercialization strategies, manufacturers will be able to help shape future outcomes for pipeline products and achieve optimal pricing and market access (P&MA) opportunities.

The trend that payers across the U.S. and EU5 are creating an increasingly restrictive environment for oncologics will continue and will present a challenge which must be managed proactively, in portfolio and lifecycle management.

"COPD and heart disease are worse ways to die but these don't get a look compared to cancer!"
*– UK payer, 2010**

"Cancer is a priority in France. Our President has said that it is a priority."
*– French payer, 2010**

"Oncology is an area to do with life threatening illnesses affecting all ages, so it will always have a special status."
*– German payer, 2010**

"It's very, very unlikely that cancer will lose its protected status."
– UK KOL, 2010#*

*Entwurf eines Gesetzes zur Stärkung der Arzneimittelversorgung in der GKV, July 2016, BMG

Evidera Payer Research 2010

Table 1: Pricing and Reimbursement Council Feedback on Evolving Trends in Market Access – September 2016

Evolving Landscape		Oncology Management				
		Contracting in oncology	New pricing strategies	Adjusting assessment frameworks	New funding and pricing schemes (i.e. DRG pricing or indication pricing)	Biosimilar preference
U.S.	Hoping that value frameworks will supply the means to manage oncology products better	✓		✓	✓	
ENG	Working within the newly defined Cancer Drug Fund, including a Managed Entry scheme if relevant	✓	F	F	✓	F
GER	Free pricing to be abolished for drugs that exceed €250MEuros in any months during the first 12 months and excluding sub- populations from reimbursement rated "no incremental benefit"*	✓	F	F	F	
FR	The pricing committee considers since March 2016 contracting as a substantial part of pricing	✓	F	F	F	F
IT	AIFA pushes for Biosimilar use and encourages the investigation into switching	✓	F		F	✓
SP	Consideration to pricing aligned to DRG coding	✓	✓	✓	F	

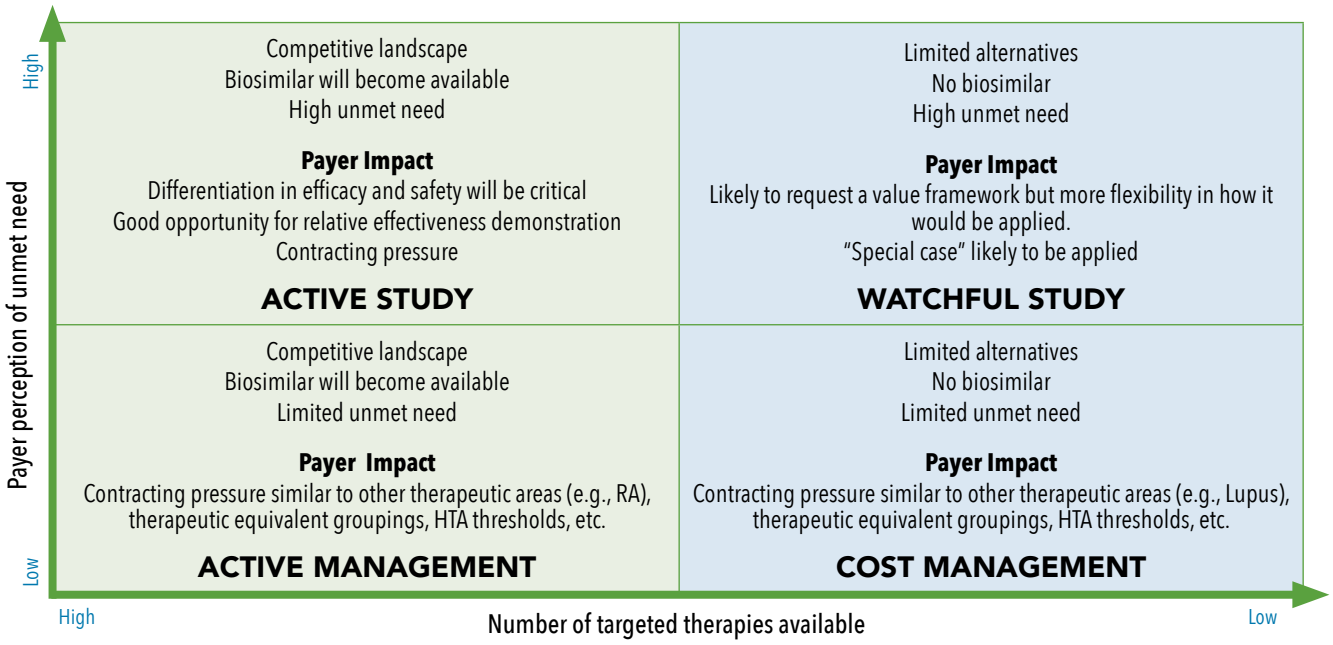
✓ - In place F – Likely future consideration

Contracting: financial, volume, target or clinical outcome schemes agreed with funding or pricing agencies valid over a defined period or time or until value review of the molecule.

Biosimilar preference: Preference in treatment initiation or switching to biosimilar use. Italy: http://www.agenziafarmaco.gov.it/sites/default/files/Secondo_Concept_Paper_AIFA_BIOSIMILARI.pdf

*Entwurf eines Gesetzes zur Stärkung der Arzneimittelversorgung in der GKV, July 2016, BMG

Oncology should not be viewed as one environment: Understanding payer views by tumor and specific indication gives insight into their approach to pricing and management



Limited unmet need according to payer perception – current treatments have achieved benefits

Table 2: Concluding Key Trends in the Evolving P&MA Oncology Landscape

Issue	Key Trends
Evolving P&MA Trends	1. Specific oncology indications may remain for the time being "special" to payers (i.e., less focus on price and HTA assessment) depending on the need in the specific indication given current treatments and achieved survival benefits versus economic considerations such as price of competitors, number of alternative treatments, and biosimilar availability.
	2. We are already seeing downward pressure on price levels achievable for new oncology agents. Payers will assess their ability to pursue contracting, optimize biosimilar availability and uptake, and improve their means to assess value. 3. New pricing and funding schemes at national/regional and local levels are likely to evolve over the next five to seven years and may hit oncology.
Client Learnings	1. By fully understanding how payers view a specific tumour/indication, manufacturers can develop more successful strategies. • Can a high-need sub-group be identified (e.g., with biomarkers)? • Has the most appropriate comparator in pre- or post-authorization trials been ensured? • What clinical data and real-world evidence (RWE) package is required for contracting? • How can any contracting agreement be operationalized to the uptake management by payers and how will contracting and operationalization be monitored? 2.Transfer learnings from other indications. • Payers are likely to use control and management solutions which have worked well in other high-tech disease areas. 3. Prepare to address funding early in clinical development and when preparing for HTA submission. 4. Be prepared for new stakeholders in price determination – such as on regional and local levels.

For more information, please contact Susanne.Michel@evidera.com.

The Importance of Real-World Evidence Generation in Oncology

Applications of Retrospective Chart Review Methodology

Dara Stein, MSc
Research Scientist and Lead, Multi-National Chart Review Studies, Real-World Evidence, Evidera

Linda Ross, MPH
Director, Late Phase Clinical Operations Real-World Evidence, Evidera

Krista Payne, MEd
Vice President and Senior Research Scientist Late Phase Studies, Real-World Evidence, Evidera

Dara Stein

Linda Ross

Krista Payne

Background

The burden of cancer remains high, with an estimated worldwide incidence of 14.1 million new cases and 8.2 million deaths in 2012.[1] By 2025, the predicted global cancer burden is expected to exceed 20 million new cancer cases annually.[2] As technologies for early cancer detection improve, and effective and novel treatments emerge (e.g., immunotherapy, targeted therapy), progression-free survival rates and durations are anticipated to improve.[3] Though the number of cancer survivors will increase, these important advances in cancer care will continue to place significant economic burden on healthcare systems. The generation of real-world evidence that reflects the complexity of usual care patterns of oncology care, as well as clinical and economic outcomes, is foundational to successful market access and value demonstration.

While clinical trials are designed to demonstrate efficacy and safety under experimental and controlled circumstances,[4] payers and regulators require marketing authorization holders to undertake non-interventional observational studies to generate evidence of burden of illness, treatment patterns, drug effectiveness, cost, and safety in usual care practice to demonstrate effectiveness, safety, and value *in the real-world setting.*

If in the context of a robust real-world data strategy,[5] it is determined that suitable secondary data, such as administrative/claims databases and electronic health records, are not available to fulfill evidence needs, a retrospective chart review methodology is a viable alternative solution as either a sole source of evidence or to resolve specific data gaps. Though more complex to operationalize than database studies, chart studies can be employed to build fit-for-purpose, patient-level databases that can be harvested to support a broad array of research objectives and questions. Retrospective chart review studies, like database studies, allow for the collection of naturalistic data free of the Hawthorne effect — the phenomenon whereby study subjects (in this case, healthcare professionals) inadvertently modify their behavior as a result of their awareness of being observed.

Chart Review Studies in Oncology

Why so Common Given the Availability of "Big" Healthcare Data?

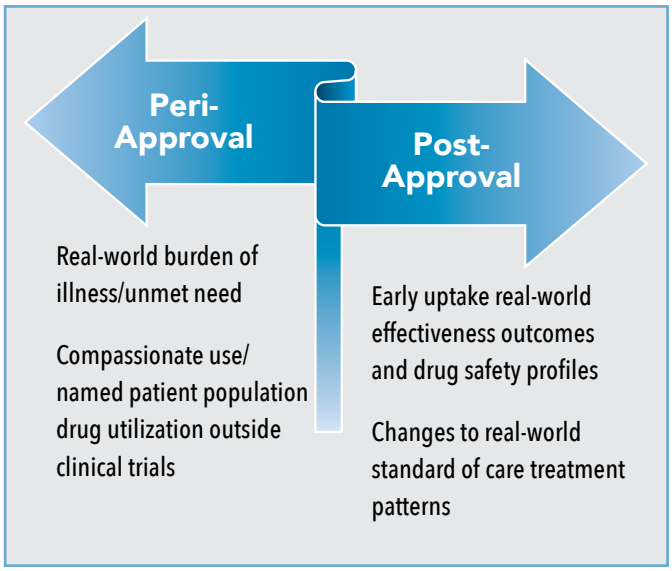
Although some oncology-focused databases exist in the United States to facilitate real-world evidence (RWE) generation, existing databases in Europe are more frequently administrative in nature, and only a few (e.g., CPRD[A] in the United Kingdom and SIDIAP[B] in Spain) are linked to electronic medical records.[6] Such **databases typically lack two key components necessary for robust and fit-for-purpose oncology RWE generation:** *1) clinical indicators* such as stage of disease, histology, or performance status; and, *2) hospital drug administration* information inclusive of treatment type, duration, and/or sequencing. These data are important when researchers characterize the patient population and try to understand why certain treatments were administered, whether specific populations may have better treatment outcomes, or why some patients had better or worse overall survival. Most oncology treatments are administered in hospitals, and the diagnosis-related group (DRG) systems used in hospitals do not allow for the identification of these treatments, even though they are essential data elements when research objectives include the evaluation of treatment patterns. Chart review studies permit the collection of a full range of patient-level data pertaining to cancer treatments; obtaining this data can allow an understanding of treatment sequencing, types of regimens being used, treatment duration, reasons for discontinuation, and treatment response.

Timing Is Everything

Prior to market launch, chart review studies can be used to generate RWE related to the burden of disease, and can effectively highlight important areas of unmet need in standard practice. Understanding contemporary treatment patterns, such as the sequencing of therapies in usual care, can illuminate where in a treatment pathway a new product can be most impactful. A detailed delineation of real-world resource utilization is a foundation for estimating direct costs of care, which can then be used for input into health economic evaluations and market access submissions.

Peri-approval, compassionate use (or named patient programs), which provide access to medications for patients with no other treatment options, can also provide a rich source of data on treatment effectiveness and safety of investigational products outside the clinical trial setting. Retrospective chart reviews in these patient populations may inform hypotheses related to their future real-world use and associated outcomes.[7-10]

Figure 1. Peri- and Post- Approval Chart Review Study Real-World Evidence Generation



Post-market approval, chart review studies can also be used to better understand emerging patterns of early drug uptake before available databases can compile and release their data. For example, if trial data are released only annually for commercial use, existing databases will experience a delay in providing that newer data. Chart review studies can be used to generate interim data that may improve the quality and extent of analyses when more data are ultimately available over time. For example, early data can also be fundamental for the characterization of patients considered "warehouse" patients — those patients for whom the standard of care treatment has not been effective and who await novel therapies.

Real-World Patient Characteristics, Health Outcomes, Treatment Pathways, and Costs of Care Data are Foundational for Successful Market Access

Patients can be characterized by chart data in terms of demographics, disease characteristics, medical history, and treatment history, at different points in time such as at first-ever diagnosis, diagnosis of advanced/metastatic disease, and initiation of first and subsequent lines of therapy. Typical core study variables collected to

[A] The Clinical Practice Research Datalink (CPRD) is a governmental, non-profit research service that provides anonymized primary care records for public health research.

[B] The Information System for the Improvement of Research in Primary Care (SIDIAP) generates research databases from computerized medical records of the primary health care setting within the Catalan Institute of Health.

characterize patients include, but are not limited to, the following:

- Demographics: age, sex, race/ethnicity, height, weight
- Disease characteristics: primary tumor type and location, histology, stage, mutation status
- Medical history: family and personal history of cancer, comorbidities
- Treatment history: adjuvant/neo-adjuvant therapy, diagnostics, surgical removal of primary tumor, radiotherapy

Chart review studies can effectively evaluate and document the therapy sequences and regimen combinations being used in the usual care environment. Treatment patterns can be described for oncology patients who receive treatment and/or supportive care at different stages of disease. Chart data can help researchers understand which regimen types are being used in the neo-adjuvant/adjuvant setting, including time from diagnosis to initiation, duration of therapy, types of agents, reasons for discontinuation, and dosing. The delineation of lines of therapy can be challenging to decipher from a database, but indication(s) of changes in therapy and therapy line sequencing can be gleaned more easily from chart data. The use of radiation in combination with systemic therapy and/or between regimens, as well as information on surgical procedures, can be identified by reviewing the chart notes

Health outcomes and their associations with oncology treatments may also be determined from medical chart data. For example, while Response Evaluation Criteria In Solid Tumors (RECIST)[C] criteria are not generally followed outside of clinical trials, healthcare professionals do frequently assess disease status and treatment response (complete or partial response, stable or progressive disease) by combining imaging and clinical judgment and documenting those results in patient medical charts, thus allowing the estimation of progression-free survival (PFS) or best overall response (OR). PFS can be measured from initiation of a treatment line to the earliest date of disease progression or death; best OR can be measured using the best documented response from initiation of treatment line until the initiation of any other regimens.

Performance status (Eastern Cooperative Oncology Group [ECOG][D] and/or Karnofsky scales[E]) can be ascertained at diagnosis, at treatment initiation, and throughout treatment. Death status can be obtained to estimate overall survival, which can be measured from initiation of a treatment line to date of death.

Safety profiles for different usual care regimens can be evaluated by collecting data which may include: type of event, dates of onset/resolution, seriousness, severity (CTCAE criteria[F]), outcome of event, action taken with treatment (treatment modification/discontinuation), and documented relationship to treatment.

Detailed information pertaining to healthcare professional visits, emergency room visits, inpatient hospitalizations, surgical and non-surgical procedures, transfusions/infusions, and laboratory tests related or unrelated to oncology care can all be collected throughout the cancer care trajectory to estimate direct costs of care via post-hoc application of unit costs and analysis.

Key Design Considerations

Patient Identification

Despite protocol-driven selection criteria, the *process* by which sites can logistically identify and select a patient cohort from medical records will differ markedly. Understanding variations in medical chart access, storage, and retrieval infrastructure across study sites will facilitate the development of a flexible yet systematic and robust patient sampling frame. Sites may find it difficult to identify patients with advanced/metastatic disease who had an initial diagnosis of early stage cancer compared to patients with their initial diagnosis being advanced/metastatic disease. Ensuring clear procedures for the identification of either or both of these groups (where applicable) will reduce the risk of selection bias.

Core Protocol and Case Report Form in Support of Multi-national Patient-level Data Repositories

In the context of strategic multi-national evidence generation, a common core protocol and core minimum dataset are essential to ultimately achieve a standardized database structure as well as a robust repository of

[C] Response Evaluation Criteria In Solid Tumors (RECIST) is a set of published rules that define when tumors in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.

[D] Eastern Cooperative Oncology Group (ECOG) Performance Status are scales and criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

[E] The Karnofsky Performance Scale Index is an assessment tool for functional impairment. It can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients.

[F] Common Terminology Criteria for Adverse Events (CTCAE) is a standard classification and severity grading scale for adverse events in cancer therapy clinical trials and other oncology settings, from the National Cancer Institute.

real-world evidence that can be pooled or compared across countries as appropriate.

Key Operational Considerations

Ethical Requirements and Data Protection

Ethics requirements differ by country and are constantly changing. It is important to consult with a regulatory expert knowledgeable about the ethics and regulatory requirements landscape for each country, region, and site included in the study to determine the requirements for ethics committee dossier submission. The sequencing of submissions and/or notifications to ethics committees and other health authorities may sometimes occur sequentially vs. concurrently; this will affect start-up and data collection timelines. National or regional ethics committees, for example, in European countries, review dossiers on their own schedules, which may be more or less frequent than other countries in the study. These variations in timing will affect when a study protocol may receive approval and ultimately study initiation.

It is also critical to ensure that all versions of a dossier, the master and all subsequent versions, are prepared in accordance with retrospective chart review regulations. The regulatory expert must be knowledgeable about retrospective data collection and the processes by which chart review studies are conducted, to ensure clear communications with the ethics committee and regulatory authorities. For example, these experts must convey that no personal health information (PHI) will be collected during the chart review study.

Data protection is critically important in these studies, so only de-identified data, void of PHI, is collected. If assurance of data privacy can be shown to an ethics committee, frequently a waiver of informed consent can be obtained. This is ideal as the data collection process remains unbiased (e.g., data for subjects who refuse consent or are deceased does not have to be excluded), and ensures more generalizable data inclusive of the patient sampling criteria. Recently, however, certain European countries' ethics committees have been requiring informed consent for any patient alive at the time the chart abstraction begins. To note, due to the strong and supportive relationships oncology practices have with their patients, the consent rate we have observed is typically ≥95% for these studies.

Site Engagement

When collecting data in chart review studies, we rely on the site staff (e.g., investigator, study coordinator/nurse) to participate in study start-up activities – training, patient identification, data collection, and query resolution. Utilizing site staff is ideal; they are employed by or under contract with the study sites and therefore have signed confidentiality agreements to keep patient privacy, they are usually experts in oncology, have relationships with the patients, and understand medical chart documentation. However, site staff do tend to have multiple and competing priorities from regular patient care to other studies/trials, making their time rather limited. It is important to ensure the aims of the study are clear, the data collection effort is streamlined, and the benefits to the site staff and their future patients are clear. Payment to study sites must also follow fair market values and compensate for their direct efforts needed to complete the study (as required by the Anti-Kickback Statute developed by the U.S. Department of Health & Human Services Office of Inspector General and the European Federation of Pharmaceutical Industries and Associations 2014 Code) by estimating total time for training, identifying patient populations, screening charts for enrollment, abstracting data, and responding to queries.

Summary

Retrospective chart review studies are effective methodologies to generate robust patient-level repositories of data to facilitate overall and country-specific analyses as stand-alone studies, or as inputs into economic models/value dossiers. Chart review studies can support many client objectives and data needs.

Peri-approval, chart review studies can inform contemporary treatment patterns, healthcare resource utilization, and costs of care, thereby characterizing the burden of illness and/or unmet need.

Chart review studies in compassionate use/named patient program populations allow an early look at treatment effectiveness and clinical and safety outcomes outside trial settings, thereby informing future potential real-world use.

Post-market approval, chart review studies can be used to continue to generate evidence of a product's effectiveness and value.

Like database studies, chart reviews are not without their limitations, including issues with missing and/or poor quality data, representativeness, and generalizability. However, understanding the potential pitfalls of chart review studies and how best to employ them as part of a broader real-world evidence strategy[5] can contribute significantly to market access success.

For more information, please contact Dara.Stein@evidera.com, Linda.Ross@evidera.com, or Krista.Payne@evidera.com.

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Challenges in Network Meta-Analyses of Oncology

Yingxin Xu, PharmD, PhD
Research Scientist, Meta Research, Evidera

Ajibade Ashaye, MD, MPH
Research Scientist, Meta Research, Evidera

Kyle Fahrbach, PhD
Principal Statistician, Meta Research, Evidera

Yingxin Xu

Ajibade Ashaye

Kyle Fahrbach

Network Meta-Analyses (NMA) in Oncology

- Timing is key for pharmaceutical companies seeking global market access for immunotherapy agents.
- Phase II or early phase program for Breakthrough Therapy Designations Approval would have insufficient data to support generation of relative effectiveness evidence.
- Immunotherapy poses new challenges for comparable endpoints required for an NMA.

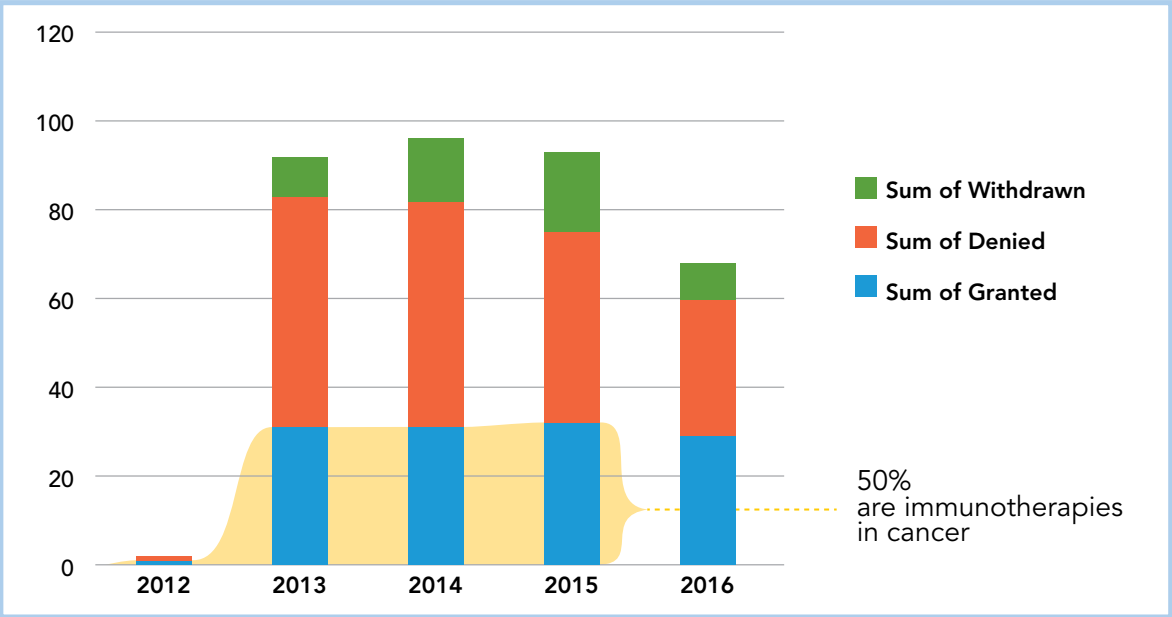
Introduction

The era of the Tens has brought exciting and promising news for many patients with cancer. At the forefront is the growing possibility that "curing cancer," rather than just "treating or managing cancer" may not be merely a dream — at least for some cancers and patient subtypes, if not for all. Part of the reason for this optimism is the growth of immunotherapy and immunochemotherapy, as these treatments have shown great promise in multiple clinical trials.

Research into immunotherapy has attracted a great deal of investment across the world. Since July 2012, when the U.S. Food and Drug Administration (FDA) created the Breakthrough Therapy Designation (BTD) as part of the FDA Safety and Innovation Act, they have received nearly 100 applications per year, and they have approved approximately one third of those.[1] As of June 30, 2016, 70% of the treatments approved as breakthrough therapies are immunotherapy or biologic agents to be applied in cancer treatment.[2] As at December 2015, 19 out of 38 BTD approvals were immunotherapy agents in cancer-related indications. Given these successes, timing is key for pharmaceutical companies seeking global market access for these newly approved molecules. Since demonstrating their relative effectiveness is still an important part of the evidence required by many reimbursement or health technology assessment authorities, the need for indirect treatment comparisons (ITC) or network meta-analyses (NMAs) has increased.

Standard evidence generation through NMA is complex in its own right. The rapid evolution of these breakthrough immunotherapy agents presents new challenges in preparing for and conducting such analyses. These include maturity of data; definition of relevant comparators; comparability of outcome measures with those used with earlier, conventional chemotherapies; and non-standard patterns of survival data.

Figure 1. Trend of Breakthrough Therapy Approvals by the FDA (July 2012 through June 2016)



* 2016 data include requests that are still pending a decision and are included in the total request received column; data in 2012 started from July 9, 2012.

Maturity of Data Available for NMA

The rapid evolution in evidence related to immunotherapy means that many molecules have been evaluated in only Phase II or even Phase Ib trials when they receive their breakthrough designation. Data from Phase I or II trials are often not suitable for use in an NMA for various reasons, including low sample size, looser inclusion/exclusion criteria, and less stringent primary endpoints (e.g., response rather than survival). To proceed with an NMA, randomized controlled trials are required and are considered to be the gold-standard evidence for several countries or regions that require indirect treatment comparisons, such as Germany, France, the United Kingdom, and the European Union.

The evidence generation process involves conducting a systematic literature review; this includes identifying published evidence for all relevant comparators via public databases (e.g., PubMed, EMBASE, and conference proceedings). While the treatment (applicant) data are maturing, the comparator (competitor) data are also maturing. The comparator may have no results available in the public domain, thus precluding the feasibility of conducting an NMA, or perhaps only interim results may have been released, without sufficient follow-up on patient numbers or trial duration to support adequate comparisons. Often, interim data are available only in conference proceedings; these do not always require rigorous peer review processes, and often differ from the final results or expect to be updated/finalized at a later date. The quality of the data may be poor, and relevant information on trial design, implementation, and outcome measurements are lacking. These issues prevent an adequate assessment of potential methodological variation and clinical differences; such deficiencies might preclude an NMA or seriously undermine the validity of some of its findings.

Defining Relevant Comparators

Different immunotherapy agents could be effective for the same cancer, and the same immunotherapy agent may be effective for multiple cancer indications. The different mechanisms of action for these immunotherapy agents often further complicate the questions an NMA is designed to address. Would the control arm in the treatment (applicant) trial be the standard of care? Would that be sufficient to provide relative effectiveness for the application? If not, what are the appropriate, common, and relevant comparators to be considered in the NMA? Answers to those questions drive the approach of the systematic literature review (SLR) and thus the NMA.

"To proceed with an NMA, randomized controlled trials are required and are considered to be the gold-standard evidence for several countries or regions that require indirect treatment comparisons. . ."

"Without immune-specific measures, it can be challenging for NMAs to accurately reflect the benefits of immunotherapy."

The commercialization strategy for immunotherapy agents will vary from company to company. A particular agent may be filed for approval for the same cancer indication at different therapeutic lines at a different time, while another agent could be submitted for the cancer indications, but at a different time for the same line of therapy. These permutations further complicate the process of defining the relevant comparators at each stage.

Comparability of Outcome Measures

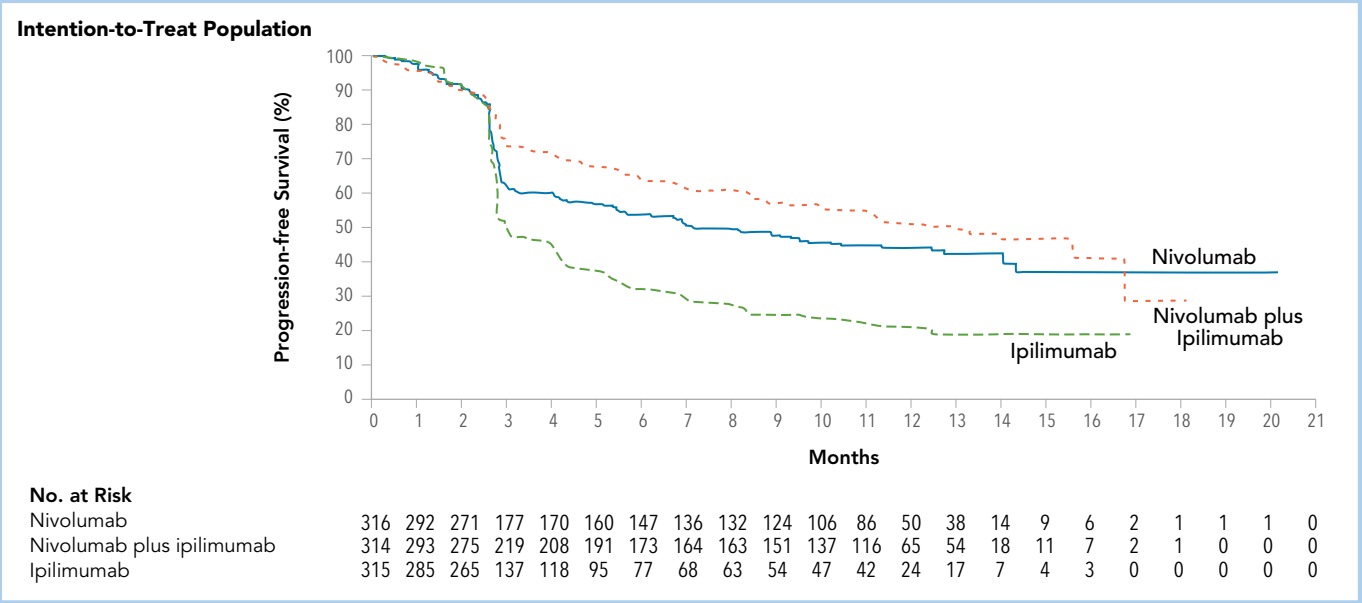
Immunotherapies often have a slower onset of action but then show more durable responses and prolonged survival compared to conventional chemotherapy. This difference in the mechanisms of action between classical chemotherapy and the novel immunotherapies is now driving the ongoing evolution of outcomes measurement. The outcomes measurement processes are actively changing, and new trials for immunotherapy agents find new and different ways to examine and define treatment success. However, the problem remains: how to compare these new outcomes measures to the existing data from outcomes defined in older trials for conventional chemotherapy agents. Without immune-specific measures, it can be challenging for NMAs to accurately reflect the benefits of immunotherapy.

Survival Outcome and the Assumption of Proportion Hazards

It is common in oncology to measure relative treatment efficacy through the consideration of hazard ratios for progression-free and overall survival. A typical NMA makes a proportional hazards assumption hold across all the RCTs included in the network. However, since the "plateau of survival curve" in melanoma was first noted at the 2015 ASCO (American Society of Clinical Oncology) Annual Meeting, the plateauing mortality in immunotherapy has been recognized in various cancer indications.[3]

It also phrases a new challenge to the assumption required in the conventional NMA on survival outcomes: does a single hazard ratio (HR) capture the true benefit of immunotherapy? When an NMA involves both immunotherapy and classical chemotherapy, is it necessary to model survival in the NMA in a more sophisticated fashion, and are there any risks in doing so? It seems clear that in some instances, alternative approaches must be considered, such as applying analyses at different time points (i.e., before vs. after plateau as seen in Figure 2), or using more advanced techniques that attempt to model the time-dependent HRs or time-to-event distributions of treatment arms, e.g., a fractional polynomial approach. The implementations of these advanced methodologies are often threatened

Figure 2. First Immunotherapy Plateau Survival Curve*



* Adapted from Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med.* 2015 July 2;373(1):23-34. doi: 10.1056/NEJMoa1504030.[3]

by gaps in the aggregated data on relevant comparators that has been derived from the literature. In some instances alternative approaches, such as matching adjusted indirect comparisons (MAIC) or simulated treatment comparisons (STC), can be employed as these techniques also offer the flexibility of directly estimating time-dependent effects.

Conclusion

Most NMAs come with methodological challenges for which there are no right answers, or, more accurately, several possible right answers. The growing promise of immunological therapy comes with a need to address these challenges both accurately and swiftly in order to meet what can be accelerated timetables.

For more information, please contact Yingxin.Xu@evidera.com, Ajibade.Ashaye@evidera.com, *or* Kyle.Fahrbach@evidera.com.

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Oncology Treatments, Health-Related Quality of Life, and Value Assessments

Dennis A. Revicki, PhD
Senior Vice President, Outcomes Research, Evidera

Dennis Revicki

New oncology treatments are intended to increase survival without compromising health-related quality of life (HRQL) due to adverse effects and disease progression. HRQL outcomes are important and relevant for patients and their clinicians in order to better understand the effects of treatment on functioning and well-being.[1] Survival benefits and decreases in disease progression of new chemotherapies often come at some cost in terms of toxicity and HRQL, and patients and their families need information on these effects to make more informed decisions about their cancer care.[2] For the past 35 years,[1,3] clinical trials comparing oncology treatments have included measures of health-related quality of life outcomes to evaluate the impact of treatment on patient-reported functioning and well-being. Clinical trials comparing cancer treatments continue to incorporate symptom assessments and HRQL endpoints and provide information that is useful for understanding the overall effects of these interventions.

"...to date, it is uncertain how these HRQL data are being incorporated into the valuation process for new oncology treatments. In many cases, there is little formal evaluation of HRQL outcome data, and published clinical trial data may have limited reporting of HRQL endpoints."

While there are exciting developments in the discovery and evaluation of new cancer therapies, some of these new treatments may be costly for the healthcare system. Increasingly, organizations are developing methods for the evaluation of treatment value for a healthcare system based on analyses of effectiveness, benefits and risks, and healthcare costs.[4] Several of the existing treatment valuation approaches include some mention of HRQL.[4,5] However, to date, it is uncertain how these HRQL data are being incorporated into the valuation process for new oncology treatments. In many cases, there is little formal evaluation of HRQL outcome data, and published clinical trial data may have limited reporting of HRQL endpoints.

Chandra and colleagues completed a recent review and comparison of valuation frameworks, with many of these frameworks mostly focusing on oncology products.[4] Treatment effectiveness for these frameworks mostly focus on survival and progression-free survival and indicators of toxicity. How does data on health-related quality of life effects fit into the treatment valuation process? For some models, such as the European

Society for Medical Oncology (ESMO), the National Comprehensive Cancer network, and the Institute for Clinical and Economic Review (ICER), there is some mention of HRQL outcomes. For example, in the ESMO approach, HRQL effects are assumed based on survival or delayed disease progression, and although the ICER methods consider HRQL outcomes, it is unclear exactly how these data are taken into account when determining the value of the oncology treatment for the healthcare system. Even when clinical trials with symptom and HRQL assessments are included in the evidence base, many oncology clinical trials incompletely report these patient-reported outcomes.[2]

Given the range of cancer-specific HRQL measures incorporated into clinical trials comparing new oncology interventions, consideration of these HRQL outcomes may be problematic. For example, the Functional Assessment in Chronic Illness Therapy (FACIT) and the European Organization for Research and Treatment of Cancer (EORTC) families of instruments include generic cancer-specific HRQL instruments[6,7] and a number of cancer-specific modules (see www.facit.org; www.eortc.org). These HRQL instrument scores are not measured on common metrics, making it difficult to synthesize results of HRQL analyses based on different instruments across clinical trials. These differences in score metrics make it challenging to evaluate the HRQL findings from clinical trials for a particular oncology treatment, and, if different HRQL measures are used, across different treatments for a specific cancer (e.g., non-small cell lung cancer). In addition, many registration clinical trials recruit samples of patients that may not necessarily be generalizable to the cancer population.

Many of the valuation frameworks for cancer treatments quantify effectiveness based on estimated quality-adjusted life years (QALYs). QALYs combine the impact of survival and HRQL, and may provide an acceptable indicator of treatment benefit. However, there are challenges associated with methods for estimating preferences for cancer-related health states, in the underlying assumptions for calculating QALYs, and there is continued debate as to whether patients or the general public should provide the preference valuations.

Methods other than quality-adjusted life years may be needed to evaluate treatments for cancers and other diseases so that effectiveness, adverse effects, and survival are incorporated. For example, quality-adjusted time without symptoms or toxicity (Q-TWiST) methods[8-11] may be effectively applied to evaluate the overall effectiveness of treatments for cancer, where apart from progression-free survival and overall survival, there may be treatment-related toxicity of varying severity that can also be evaluated. The Q-TWiST method involves the partitioning of survival duration into clinically relevant health states (e.g., treatment toxicity, disease progression, progression free), assigning preference weights (or utilities) to these health states, and calculating quality of life-adjusted weighted sums of the mean duration of each health state to create the overall Q-TWiST scores. The utilities for each health state may be generated by physicians, patients, or the clinical investigators, and range from 0 (representing dead) to 1.0 (representing complete health).

"Methods other than quality-adjusted life years may be needed to evaluate treatments for cancers and other diseases so that effectiveness, adverse effects, and survival are incorporated."

The Q-TWiST method, however, may not be applicable to the evaluation of all disease conditions and treatments. More comprehensive approaches to evaluating treatment effectiveness in oncology should be identified and assessed. All of the HRQL and other outcomes that are relevant to patients may not be included in the available evidence package at the time of the valuation assessment, but understanding which relevant (to patients and clinicians) outcomes are absent and their importance may provide for a more complete understanding of the limitations of the evaluation of the targeted treatment in comparison with alternative treatments. This will be most challenging for some cancer diagnoses where there are few approved, effective treatment options, and where only limited effectiveness evidence may be available.

In summary, patient-reported symptom and HRQL outcomes are critical for a more complete understanding of the effects of oncology treatments on patient functioning and well-being. The patient perspective is important in quantifying the risks and benefits of new cancer interventions. Increasingly, efforts are underway to increase patient engagement in identifying relevant effectiveness outcomes and in the objectives and design of clinical trials and comparative effectiveness studies.[12,13] Improvements can and should be made in the methods for quantifying the benefits and harms of new oncology treatments, whether QALYs or other approaches are utilized. The incorporation of important and relevant effectiveness and toxicity indicators, from the patient's perspective, can only improve the valuation of new oncology treatments for the healthcare system.

For more information, please contact Dennis.Revicki@evidera.com.

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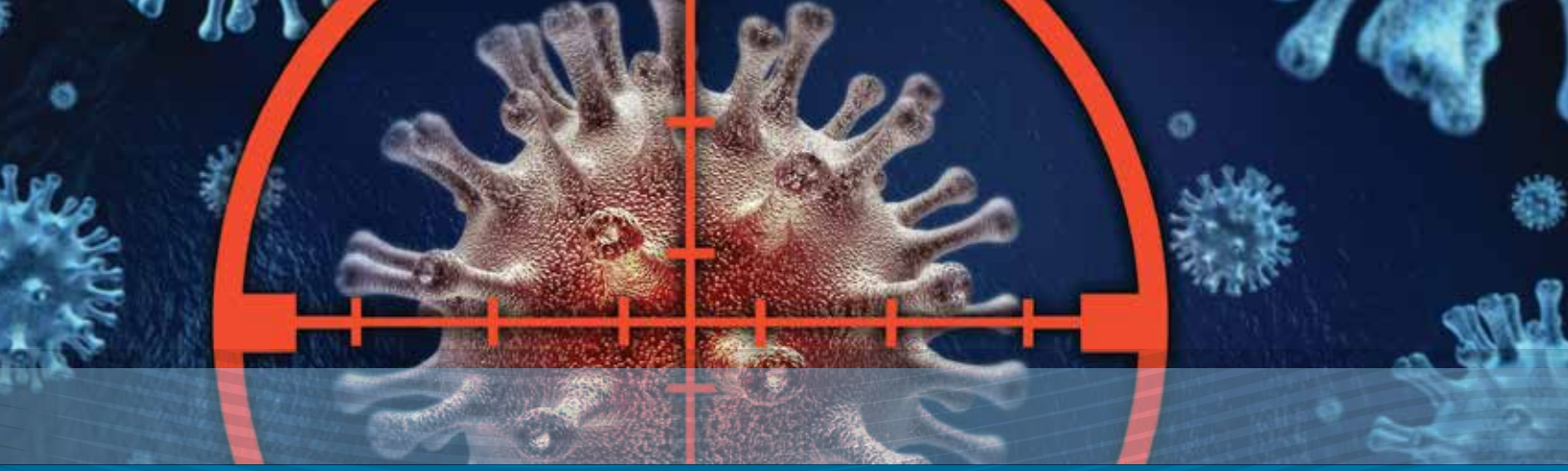

Projecting Overall Survival with Immuno-Oncology Treatments

K. Jack Ishak, PhD
Senior Research Leader, Modeling and Simulation; Executive Director, Center of Excellence for Statistics, Evidera

Irina Proskorovsky, MSc
Director, Principal Statistician, Modeling and Simulation, Evidera

Noemi Muszbek, MA, MS,
Senior Research Scientist, Modeling and Simulation, Evidera

K. Jack Ishak

Irina Proskorovsky

Noemi Muszbek

Introduction

On February 4, 2016, the American Society of Clinical Oncology (ASCO) announced immunotherapy as the top cancer advance of the year.[1] As an alternative to traditional chemotherapies and targeted therapies, scientists and doctors are increasingly suggesting immunotherapies, including checkpoint inhibitors, transforming the clinical landscape and patients' lives. Differing substantially from traditional chemotherapies, immunotherapies induce the patient's immune system to produce an anti-tumor response. Checkpoint inhibitors block certain T-cell receptors, such as CTLA-4 (e.g., ipilimumab), PD-1 (e.g., pembrolizumab, nivolumab) and PD-L1 (e.g., atezolizumab, avelumab, and durvalumab), which act as "checkpoints" regulating T-cell activation. Inhibiting the action of these receptors promotes T-cell activation and anti-tumor response, possibly even tumor rejection.[2]

As experience with immunotherapies in other oncology areas is growing, questions have emerged regarding challenges in the assessment of the value of these therapies. The most visible challenge is in extrapolating overall survival (OS). In some indications, the new checkpoint inhibitors, either as monotherapy or as combination therapy, provide substantial survival benefits, and the OS curve appears to plateau for an important proportion of patients (20-25% in previous trials for PD1 and PDL 1 inhibitors).[3,4] This suggests that many patients could potentially be cured of their disease (but of course, still subject to other mortality). This presents several difficulties, as the shape of the OS Kaplan-Meier curve often does not conform to the conventionally used distributions[5,6] and the proportional hazard assumptions required for conventional network meta-analyses (NMAs) do not hold. In addition, the follow-up in the trials is relatively short and there is no long-term experience with these therapies (the first checkpoint inhibitor, ipilimumab was approved in 2011 by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) in advanced melanoma. Thus extrapolation of OS presents new challenges.

This article reviews different methods for the projection of OS, covering both standard approaches and extensions to deal with the expected challenges to model survival with immunotherapies.

Standard Statistical Methods

Parametric survival analysis methods are the standard approach for modeling and projecting time-to-event outcomes. This involves testing various statistical distributions, such as the exponential, Weibull, Gompertz, Gamma, Log-Logistic, and Log-Normal distributions, and assessing their suitability for projection based on fit statistics and contextual/clinical considerations. For instance, a suitable fit may be chosen based on whether the predicted curve obtained from the parametric models align with the observed curve over the observation window and if the long-term shape and properties (e.g., longest survival, expected event time) align with clinical opinion.

Parametric modeling can work in a broad range of scenarios, but may not produce an adequate projection in cases where the underlying risk functions are complex. The case of survival with immuno-oncology treatments may be such a case due to the shape of mortality curves. For instance, in a trial of ipilimumab in patients with advanced melanoma,[7] the OS curve dropped rapidly in the first 12 months, reaching the median at 11.4 months and plateauing at 3 years with 22% still alive. Follow-up continued to year 7 with the curve only dropping down to 17%. A similar pattern can be seen in the OS observed in the nivolumab arm of the CHECKMATE-017 trial[8] in advanced squamous non-small-cell lung cancer (NSCLC); the OS curve dropped quickly in the first 9 to 12 months and then started to plateau. Capturing both high early mortality and gradual deceleration to a steady rate can be difficult to fit with a single parametric function.

Piecewise parametric fitting is a more flexible alternative and may improve fit. This consists of fitting the OS curves in segments by dividing the time axis to allow the distribution being fitted to have different parameter values in each part. In the NICE appraisal of nivolumab for previously treated locally advanced or metastatic squamous NSCLC[9], 2-knot spline analysis was conducted to fit distributions to the OS curve since none of the standard distributions provided a good fit. While this can help in fitting the observed pattern more closely, the shape of the long term projection may remain implausible. That is, projecting a flat mortality pattern over a long term may yield life-expectancy estimates that are implausible. Thus, economic models using such projections may have to limit the period over which the fitted curve is applied and revert to alternate means of predicting beyond this window, which may be difficult without additional data or assumptions.

"Parametric modeling can work in a broad range of scenarios, but may not produce an adequate projection in cases where the underlying risk functions are complex."

Other strategies may help overcome these challenges. We discuss some of these in the following sections.

Alternative Strategies

Modeling OS as Sum of TTP and PPS

While the OS curve may be difficult to fit due to long-term survivors, it is possible that patients who have progressed are at greater risk of death. Thus, the post-progression survival (PPS) may be easier to fit with standard distributions. The projection model can incorporate progression time and other patient characteristics so that predicted PPS times are consistent with patients' characteristics.

To derive projected OS with this approach, a projection is also needed for time-to-progression (TTP) so that survival can be predicted for patients not observed to have progressed during the trial. This would also be done using standard parametric modeling. The TTP and PPS projections can be used together to generate individual TTP and PPS predictions, and deriving OS from these.

It is possible, however, that TTP itself may be difficult to project as some patients receiving immuno-oncology treatments may achieve long-term remission, manifesting as a plateau in the curve. Predicting survival for these patients in economic models would require different considerations; for instance, one possibility is to use life tables to model their survival, which would assume these patients are effectively cured. Alternately, some adjustment could be applied to life tables to reflect the impact of disease on survival using additional data from historical controls, for instance.

Landmark Analysis

In landmark analyses, patients are grouped based on patients' status on a marker of their condition at some fixed time point. For instance, the grouping event may be response to treatment. Outcomes like survival can then be assessed in these landmark groupings, after omitting patients who have the outcome prior to the landmark point. This avoids grouping patients at baseline based on a future status, which introduces bias.

Landmark analyses typically aim to estimate treatment effects and assess the impact of the grouping variable on

the effects. This approach can be leveraged for projection of OS by stratifying the population by response status at an appropriate time point following start of treatment (e.g., three months) and fitting parametric models within each of these groups. This modeling would be done directly on OS and would represent projection of conditional survival among those who are alive at the landmark point. The full OS curve can then be reconstructed by combining the projection with the mortality rate prior to the landmark.

While this approach can improve fit for some of the landmark groups, survival in other groups may remain difficult to fit. In particular, some responders may have sustained remission leading to some of the same challenges noted above.

Dynamic Modeling of Response, Progression and Survival

In this approach, a reference group would be identified in which OS can be projected adequately with parametric distributions. For instance, patients who have failed to achieve response may be such a group. A parametric model produces a projected OS for this reference group, but cannot be applied for projections more broadly. To allow for this, the projected curve must be adjusted to the complement of the population (e.g., responders). This requires quantifying the relative OS between the reference group and its complement. A Cox regression model can be used for this, as it allows including both baseline and time-dependent factors (like response), and can incorporate the effect of other relevant events that may impact survival (like progression).

As with the TTP/PPS method, the dynamic modeling approach also requires predicting the intermediate events like response and progression. OS would be reconstructed by combining the reference curves, Cox regression, and projections of the intermediate events.

Parametric Mixture Cure Models

Parametric mixture cure models[10] assume that a fraction of the population may be cured, or at least achieve long-term sustained response, and as a result, have a different mortality risk distribution from others. Outcomes in the cured and non-cured patients are allowed to arise from different underlying models. Thus, the statistical procedure aims to determine which patients will achieve cure, and allows a different parametric function in the two population strata. Thus, projections for patients that are not cured is more likely to produce plausible projections, while projections for patients who are cured may require external data, for instance, general mortality rates, possibly adjusted to reflect that patients have cancer. The key assumption in this approach is the plausibility of a cure in the context being modeled; this can be verified in the data based on the observed pattern of the outcome (long-term flattening of the curve) and a high rate of censoring.

"Immuno-oncology treatments can offer significant long-term response and survival. Modeling these outcomes for economic evaluations introduces challenges with the projection of outcomes for economic modeling."

Discussion

Immuno-oncology treatments can offer significant long-term response and survival. Modeling these outcomes for economic evaluations introduces challenges with the projection of outcomes for economic modeling. Different strategies are possible to help improve fit to ensure cost-effectiveness assessments are accurate. The common feature in the approaches described above is the attempt to enhance fit by separating the population or the time-axis into subsets that may be easier to model. With piecewise fitting, the subsetting is done directly on the time axis without explicitly characterizing which patients are followed through each period. With the TTP/PPS approach, the progression event is used to separate OS into two parts, with the hope of making each of these easier to fit with standard approaches. The landmark analyses group patients based on response, while the dynamic modeling strategy attempts a finer breakdown by incorporating both response and progression, and attempts to model the effects of these events. The parametric mixture cure model subsets the population based on whether they are cured, which in this setting would be interpreted as long-term remission; in addition to projecting survival, the approach can also help understand the profile of long-term survivors. In all cases, challenges can remain in projecting survival in one or more of the subsets created in the analyses – those achieving long-term remission. Additional data, clinical insight, and assumptions may be required to be able to project for the entire population. It is advisable to attempt various approaches and assess the sensitivity of conclusions from economic analyses.

For more information, please contact Jack.Ishak@evidera.com, Irina.Proskorovsky@evidera.com, or Noemi.Muszbek@evidera.com.

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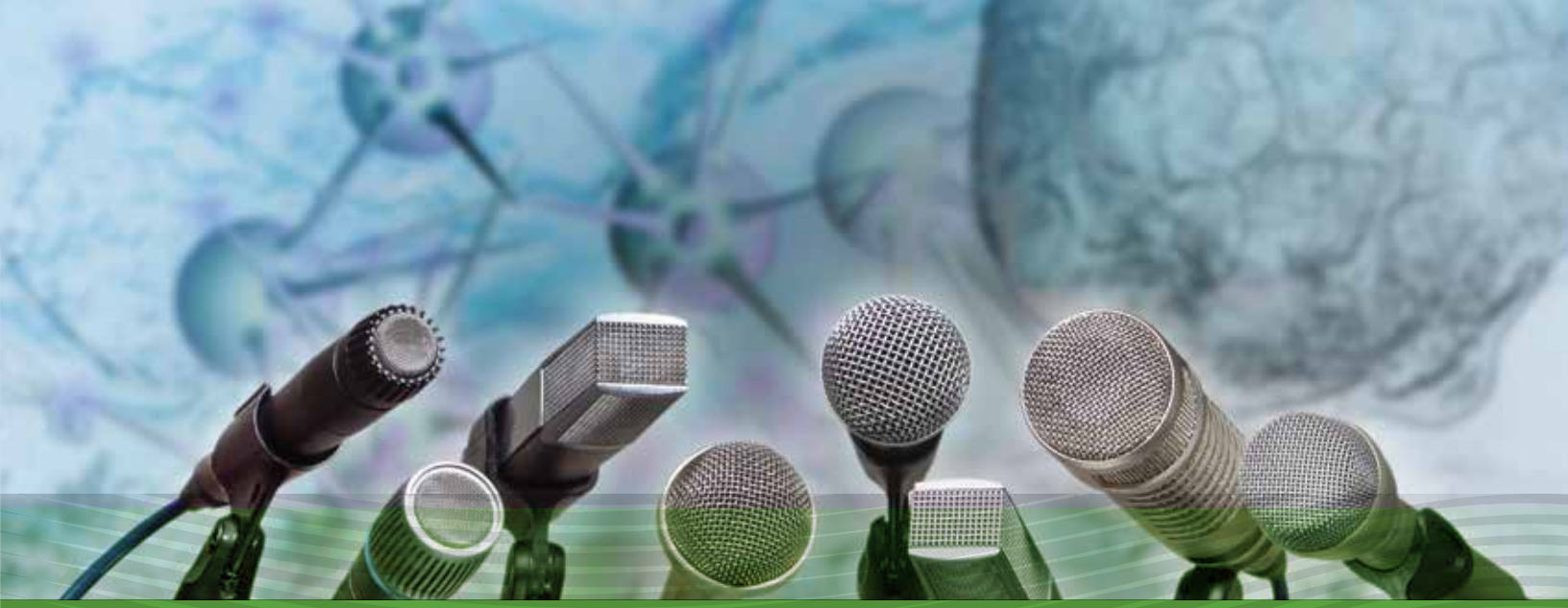
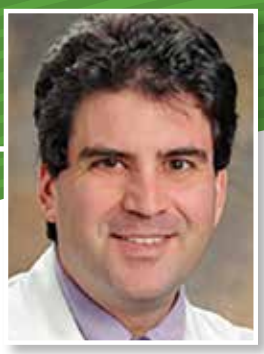


Interview with Dr. Kevin Knopf
Medical Oncologist and Hematologist



Kevin Knopf

Kevin Knopf, MD, MPH, is a Staff Oncologist and a Visiting Senior Research Scientist with Evidera and is a practicing oncologist in San Francisco, California. He is the Director of the Hematology and Oncology Clinic at St. Luke's Hospital, Associate Clinical Professor at Dartmouth Medical School, and the Medical Director, Cancer Commons. Dr. Knopf is the Co-Editor of the Journal of Community and Supportive Oncology and on the editorial boards of Value Based Cancer Care and the Journal of Managed Care Pharmacy, in addition to an Ad Hoc Reviewer for the Journal of Clinical Oncology and the Journal of Clinical Genitourinary Cancer. Dr. Knopf received his medical degree from the University of California – San Francisco School of Medicine, and his oncology training was completed at the National Cancer Institute in Bethesda, Maryland. He also has a background in epidemiology and health economic modeling.

This interview was conducted by Noemi Muszbek, MA, MSc, Senior Research Scientist, Modeling and Simulation, Evidera.

There have been many advances in oncology in the last few years, including immunotherapies such as checkpoint inhibitors and biomarkers. How do you see the immune-oncology products affecting the treatment landscape?

From my perspective as a clinician, it is always the art of picking the therapy that is most likely to work for each patient. For both immunotherapy and targeted therapies, we are trying to find biological targets that will predict a priori how the therapies are going to work. For example, we know that smokers are more likely to respond to immunotherapy in lung cancer than nonsmokers. Previously, before we had the EGFR assay to predict response to tyrosine kinase inhibitors (TKIs), we knew nonsmokers would be more likely to respond to specific drugs than smokers. So, we are looking for markers or predictors, whether it is mutational status or mutational burden or other measurable indicators, and in a clinical setting, it then becomes the art of discovering which predictive markers are the most reliable in deciding a treatment path for each individual patient.

Right now, immunotherapy is being given to many patients and we are only seeing some of them respond. For those who do, it is wonderful and we are seeing durable responses where we were not previously, such as in metastatic melanoma. But there is a lot of information coming at the individual clinician and processing all of that information to figure out the best predictive markers for any one given patient from large trials is a challenge which clinicians face.

Clearly, the development of these immunotherapies are very promising to certain groups of patients. What role do you think chemotherapies and TKIs will play?

I think everybody is very excited about immunotherapy because it's a new class of agent, and we're seeing responses where we hadn't before, but it does not work for everyone. Chemotherapy, therefore, still plays a very important role in treating many types of cancer. Right now there are maybe five or six major histologies that we see day-to-day that do not have any immunotherapy indication for them. Targeted therapies are also extremely important for many types of cancers. For example, currently we have different treatment options for both renal cell cancer and kidney cancer, so sequencing the therapies, when and when not to use immunotherapy is a challenge for the average clinician to figure out. For example, in lung cancer, immunotherapy has a very big role in squamous cell cancer and adenocarcinoma, but in the adenocarcinomas found in nonsmokers, we're much more likely to be using TKIs, first line and second line, before we get to immunotherapy.

"One important aspect of these value frameworks being successful will be more dialogue between the different stakeholders in the healthcare system."

As advances are made, there are more options for patients, but with more information becoming available all the time, choosing the right therapy for each patient is more challenging for clinicians. Biomarkers, companion diagnostics, precision genomics - these are all much more important in day-to-day clinic work than they used to be. This makes it more important than ever for clinicians to continue educating themselves on the latest information. The amount of information the average clinician needs to know to practice effectively is increasing year by year.

Biomarker research, then, is key?

Yes. In the U.S., one issue that we are facing more and more is balancing the cost of therapy versus the efficacy. The therapies can be very expensive, and so we are looking for ways to make sure that we can get the right therapy to the right patient, and get it paid for by the insurance companies. At the same time, there is concern about total cost of cancer care.

The development of value frameworks, which help assess different therapies in different populations, could be a valuable tool to clinicians, in addition to payers, in making treatment decisions. Do you see this as a benefit to clinicians?

Yes, to a degree, but this is different in the U.S. than in Europe where we have to deal with six or seven different payers, each with their own set of rules and developing their own value frameworks. I would say nine out of ten clinicians are not thinking too much about the cost of the therapy but rather focusing on choosing the right therapy for their patient. Some physician groups are forming larger groups and becoming part of accountable care organizations, which will take on risk like cost of medicines, diagnostic imaging, therapeutic imaging, etc., that will then need to be part of a framework. Then, someone within each organization will need to understand this framework very well so that the organization can be financially solvent, while ensuring clinicians can continue to provide optimal care to their patients. So, I think that the value framework is going to have an increasingly important role for anybody practicing in any part of oncology - medical radiation, surgery, pathology, diagnostic imaging – and we will see a lot of opportunities and challenges facing us in the next couple of years within the value framework.

One important aspect of these value frameworks being successful will be more dialogue between the different stakeholders in the healthcare system. Right now clinicians seem to be in one part of an organization and administration is in another part. Everybody needs to have a seat at the table, with open and honest dialogue about what the trade-offs are going to be. We are all potential patients, so that triumvirate of clinicians, administration, and patients is a good place to start. Many physicians are not used to thinking about economic trade-offs, so it's important to have economists involved, as well as pharma because they want to be able to cover the cost of innovating for new drugs. To make these future frameworks effective, there needs to be more cross-talk and cross-pollination of ideas.

So, I think there are more challenges and pressure on the clinicians right now, but the positive thing is that we have much more dialogue about these things than we did a decade ago.

How do you think individual clinicians or the larger clinician organizations should balance the cost and value of the different treatments?

It's very challenging, especially when you have large fully capitated healthcare systems, academic medical centers, large multi-specialty group organizations, and individual physician practices in the mix. I think from a patient and societal perspective, the balance is between how you spend the healthcare dollar and what you get for that dollar. So, in economic terms, we want to eliminate options where cost minimizations clearly show you should not pursue a treatment. The challenge will be in the cost-effective domains where trade-offs need to be made between side effects versus cost, quality of life, and/or length of life. These decisions have to be made fairly high up in healthcare organizations, but there have to be many people at the table, including clinicians, patients, and finance people to decide how to make the right decisions. In the U.S., Medicare will probably force the issue for the private payers as they switch away from fee-for-service oncology and average sales price methodology to MACRA (Medicare Access and CHIP Reauthorization Act) and other newer methodologies. I think the patient has to always come first, and we always have to do the right thing for the patient, but as we lay out what the exact right thing for the patient is from the clinician and patient's perspective, we'll have to align the financial incentives so that we can still keep delivering optimal healthcare.

Many of the value frameworks would like to incorporate more than just cost effectiveness, efficacy, and safety and also look at need, severity of the disease, and the patients' perspective. From a practicing clinician perspective, what would you find most useful for value frameworks to take into consideration?

I think clinicians in the U.S. are most comfortable talking about quality of life, because we know toxicities and we know which of the therapies have which side effects. So, whenever we have a patient/physician interaction, part of the interaction is assessing the patient's quality of life. We have economic ways of turning quality of life into cost utility functions, but I think it is crucial to understand and appreciate that quality of life is extremely important to patients. In my field, medical oncology, we have three goals: cure, prolong survival with quality of life, and palliate. Patients, especially those with incurable cancers, are not just concerned with how long they live, but also what their quality of life will be. I think there is more of a focus on quality of life, and I think that will continue.

"Patients, especially those with incurable cancers, are not just concerned with how long they live, but also what their quality of life will be."

Cost will always be a big part of the equation though.

Definitely, and part of that is because now in the U.S. there is a lot more press about the cost of some therapies and of how much things cost in general in healthcare. It is more in the public eye, and oncology is a perfect place to start to have more dialogue about this, because we are always making those trade-offs between quality of life and quantity of life for patients who have an incurable cancer.

What would increase the acceptance of the economic argument or the economic issues for clinicians?

I'm not really sure. Some physicians do not want to think that way, and others, with some economic or social policy experience, are very interested. I expect there will be some doctors within every health organization who have an interest in this and will be the stewards for the others in the group. I imagine some oncologists will become experts in the value of cancer care and will form working groups to talk about how value propositions can be implemented in clinical care. There is a movement happening already. The number of articles about cost effectiveness has risen dramatically in the past five years compared to the five previous years. We just want it to happen in the right way and that patients get the right treatment at the right time in a cost-effective way.

You are the director of Cancer Commons, a non-profit network of patients, physicians, and scientists focused on knowledge sharing to get the best possible outcomes. How do you see the relationship between patients and clinicians changing in the future, especially with the increase of available information?

Cancer Commons (www.cancercommons.org) is a completely not-for-profit organization in Silicon Valley. There is a patient-facing side where patients can ask how

"Patients will be better informed about their treatment options, and clinicians will have to be better prepared to respond."

they should treat their cancer and a doctor-facing side where doctors can collaborate around complex clinical issues. One of the changes I see in the next five years is that patients in states with electronic health records will have access to their health information in ways they never have before. The patient will be much more involved in their care, asking the doctors more questions, and seeking out the best treatment for their cancer in different ways. Organizations like Cancer Commons are in response to that, allowing patients a resource to get their questions answered as best as possible from knowledgeable sources. Patients will be better informed about their treatment options, and clinicians will have to be better prepared to respond.

There is a growing effort to collect, combine, and analyze data, such as ASCO's CancerLinQ. Do you see real-world evidence helping clinicians in your decision making?

Real-world evidence is great because we're prescribing drugs based on clinical trials that were done with certain types of patients, and then in the real world, we have to figure out if our patient matches the patient in the clinical trial. There is a scarcity of real-world evidence trials, so having retrospective data sets to analyze or a series of real-world trials with economic and quality of life endpoints might help fill that gap. We know that we do not always get the same results in the real world compared to clinical trials, but we don't know why some patients in the clinical trials and some of our patients are outstanding responders to certain agents. Data will help answer that question, as will the movement in precision oncology. I think both of these things are very promising to improve quality of care.

What advantages and risks do you see in the use of real-world evidence?

The advantages are that it is real and most patients are treated in community settings, not in rarified settings. Most patients have real-world comorbidities or other issues not accounted for in clinical trials. Clinical trials can underrepresent patient populations. For example, a large proportion of our patients are over the age of 70, but they are underrepresented in clinical trials. Having real-world evidence would help us treat specific patient populations and select the best therapies. The risks are the same as in any sort of analytic framework - does what you're getting from the analysis match the person before you? I also think the risk of overfitting data is there, so results of analyses from real-world data will have to be interpreted with the same caveats as those from clinical trials. Overall, there is a lot of good that comes from real-world evidence, and potentially a little harm.

Lastly, why do you think oncology drugs in particular are singled out of all the expenditures in healthcare?

I think oncology is an interesting use case because we have had a lot more drugs approved in the past 10 years than prior. We have made a lot of progress in oncology in large part because the molecular biology revolution of the 1970s allowed us to understand much more about how cancer behaves, so we have a lot more targets than we did before. There are a lot more drugs available, and this brings the economic issues to the forefront. Also, with the speed of new drug options becoming available, it is harder to find the value proposition compared to other therapeutic areas where new options come more slowly. There is also a lot more media coverage about the cost of oncology treatments than ever before, which increases public awareness.

Hopefully, the establishment of value frameworks and the new developments we just discussed, such as big data, precision oncology, etc., will provide help in the assessment of value. I see a lot of opportunity in the area of oncology coming our way in the next several years.

Pricing and Reimbursement Policy Trends in Europe

Susanne Michel, MD
Vice President and Practice Lead, Payer Strategy, Evidera

Market access is the ultimate goal for healthcare treatments, however, priorities and decision processes can vary from country to country and can change quite often. To gain insight into what factors affect a product's access in various markets, Evidera has established a Pricing and Reimbursement Policy Council (PRPC) composed of current and former payers from six countries, including Germany, Italy, Spain, England, France, and the U.S. This council meets on a quarterly basis, in addition to debates and discussions via blog throughout the year, to identify changes in policy trends across the markets that may affect and influence changes in pricing and reimbursement (P&R).

Below is an overview of the trends affecting Europe as identified by the PRPC at their September 2016 meeting. (Note the U.S. payers are not included in this update.)

POLICY TRENDS	IMPLICATIONS FOR MARKET ACCESS

Key Trends in Germany

A change to the current law proposed on 22 July 2016 is under consultation.[1] Ratification of the law is expected by the end of 2016/beginning of 2017 invoking several changes to Germany's pharmaceutical market.

- Limited reimbursement for patient groups with no additional benefits
- Price freezes will continue until 2022
- Introduction of a turnover threshold for new drugs with an annual threshold of 250M Euros – if this threshold is reached in any month of the first 13 months on the market, the agreed price with the GKV (statutory health insurance funds) will be applied retroactively from the month the threshold was met.
- Details of pricing and drug rebates will not be made public
- Benefit assessment for drugs launched pre-AMNOG. Drugs that launched before 2011 cannot (since 2014) be considered for G-BA (Gemeinsamer Bundesausschuss – The Federal Joint Committee) assessment. However, in the future and in exceptional cases, an assessment may be possible if the active ingredient, launched before 2011, is intending to extend its use and launch in a different line of therapy or indication.

The storm ahead: German reform proposals will allow limits on reimbursement and potentially limits on free pricing.

New restrictions and hurdles

In the past, G-BA was not in a position to exclude sub-populations with no "incremental benefit" from reimbursement, hence all populations went forward to price negotiations and reimbursement. This is likely to change and G-BA may recommend to exclude "no incremental benefit populations" from reimbursement.

This would provide an opportunity for manufacturers to obtain a high price (at lower volume). This requires careful preparation of the GKV dossier only after the G-BA makes its final incremental value verdict.

Protect your price

The reform presents an opportunity to assess medications launched prior to 2011 for their incremental value.

It can well be expected that price negotiations will follow the benefit assessment and will be used to negotiate price, though for drugs launched prior to 2011 free pricing applies. This requires careful consideration in launching a line or indication extension in Germany and what effect this may have on the price of the molecule.

POLICY TRENDS	IMPLICATIONS FOR MARKET ACCESS
Key Trends in Germany (continued) • Evidence Transfer. For patient groups or part-indications that are included in a label, but no separate evidence and studies were submitted to the G-BA, the G-BA can consider an incremental benefit assessment if "evidence transfer" would allow this. What will constitute an "evidence transfer" will need to be defined by the G-BA. This clause was mainly included to allow innovative drugs to be used in paediatric setting (note: label inclusion is required).	**Protect your price (continued)** While GKV negotiations and any additional rebates were not actively published, in the future the price, any rebates, or contracts beyond legal rebates will be treated as strictly confidential. This is likely to protect price referencing and will push international referencing to the published German list price. In addition, price freezes will continue. The introduction of the turnover threshold limits the "free pricing" period during the first 12 months on the German market. Hence careful assessment of use/demand/volume/time and expected negotiated price (or fixed price reference group price) is needed to determine when the threshold may be reached.

POLICY TRENDS	IMPLICATIONS FOR MARKET ACCESS
Key Trends in Spain • The Ministry of Health (MOH) set the Informe de Posicionamento Terapeutico, i.e. Therapeutic Positioning Report (IPT), in 2013 with the aim to allow for restrictions and potential non-reimbursement on national listings if a new product is more expensive than therapeutic alternatives and does not provide an incremental benefit (Inform Posicionamiento Terapeutico – Therapeutic Positioning Report: http://www.aemps.gob.es/medicamentosUsoHumano/ informesPublicos/home.htm). • Hospital-initiated specialist drugs can have continued prescribing and dispensing in ambulatory setting and community pharmacy. http://www.diariomedico.com/2016/09/07/area-profesional/sanidad/sanidad-farmacos-de-diagnostico-hospitalario-pueden-deben-ir-a-la-farmacia. • Stronger biosimilars promotion at national and autonomous community level is anticipated. • DRG (diagnosis related group) payments in Cataluña are being deferred to hospitals negotiating directly with manufacturers over pricing – leading to DRG aligned pricing. This will be initially initiated for auto-immune conditions; oncology was initially included but withdrawn for implementation.	**Align price of new pharmaceuticals to available budgets** Excluding reimbursement if price exceeds therapeutic alternative The effect, and if the MOH would be committed to exclude national reimbursement listing, remains to be seen. The implication may be that access is via autonomous regions. A space to watch. Aligning DRGS to price- and indication-based pricing Indication-based pricing is a concept in which payers in many markets are interested. It is important to evaluate the first DRG aligned prices. However some indications may be more sensitive to price disadvantages depending on budgets in the current DRGs. For the pilot project in Cataluña, we certainly will watch the group of auto-immune conditions.

POLICY TRENDS	IMPLICATIONS FOR MARKET ACCESS

Key Trends in France

- In August 2016, the Government released new policy guidelines[2] to the CEPS (Comité économique des produits de santé) providing general guidance on the increased support for the use of budget impact and stronger use of price/volume or outcomes-related pricing and contracting.
- Beyond traditional price volume agreements, the French government is supporting CEPS to explore new types of agreements. While the guidance is vague, it includes indication-based pricing and control of budgets by indication.
- The increased emphasis to outcomes-based contracting includes, in particular, the intention to use real-world evidence.
- Incentivising competition between biosimilars and branded products is especially highlighted within the guidance document.

Getting tough on pricing – opening the doors to indication-based pricing

Some of the suggested measures are already known to manufactures, such as volume-based contracting. Other aspects, such as considering budget impact in price negotiations, need to be made more explicit (e.g., to what degree will budget impact be considered in pricing).

However, the French government also provides the CEPS with the mandate to consider completely new schemes, such as indication-based pricing. This is an opportunity for manufactures to collaborate with the CEPs and shape the approach of a new pricing and access model.

Key Trends in Italy

The push for biosimilar switching is a first in the EU. Other measures are aimed to allow increased contracting and tendering.

- Pharmaceutical governance for Italy likely to change in the 2017 budget, but no drafts have been released yet.
- As part of that process, in April 2016, the regions proposed to promote increased volume/discount agreements. These agreements should potentially include portfolio pricing and discounts and duration of treatment with a specific drug.
- In addition, regions propose a) to extend the therapeutic equivalence among different drugs belonging to the same therapeutic class in order to favour tendering; and, b) to promote the competition between biologics and their biosimilars by supporting switching patients from branded to biosimilars.[3]

Oncology pricing and reimbursement

- The Italian association of oncology (Associazione Italiana di Oncologia Medica - AIOM) has proposed to establish a national fund dedicated to innovative cancer drugs independent from the National Health Fund (Fondo Sanitario Nazionale, FSN). This proposal has been officially endorsed by the AIFA (Agenxia Italiana del Farmaco – Italian Medicines Agency).

Moreover, the AIOM has made the following proposal: a) promoting price-volume agreements; b) establishing treatment cost per patient independently from its length (parity price); and, c) improving the implementation of registries and managed entry agreements (MEAs).

First mover in Europe to give wide support to biosimilars switching

Very likely that the abilities of regions to administer new contracts and tendering will vary significantly. Hence budget control and compliance to new contracting measures is unlikely to be homogenous across Italy – and requires even more attention to local requirements of Health Regions.

However, the move to recommend switching patients from branded to biosimilars is a daring one and may require further endorsement. Monitoring is needed as the current decision is carefully phrased, but nevertheless requires planning ahead and considerations on how to maintain market share, such as by additional service offerings or local service contracts with Health Regions, to protect market share.

POLICY TRENDS	IMPLICATIONS FOR MARKET ACCESS

Key Trends in the UK

- All cancer drugs/indications expecting to receive a marketing authorisation (license) will now be appraised by National Institute for Health and Care Excellence (NICE).
- Early funding option available, through new interim funding arrangements, for those drugs given either a NICE draft recommendation for routine commissioning use, or a NICE draft recommendation for use within the Cancer Drugs Fund (CDF).
- Clear entry and exit points for drugs in the CDF.
- Managed Access Agreements between National Health Service (NHS) England and pharmaceutical companies, setting out the terms of a drug's entry into the CDF and the means by which data will be collected to resolve any uncertainty relating to a drug's clinical and cost-effectiveness.
- All eligible patients to receive CDF drugs, not just the number of patients needed to resolve uncertainty.
- Expenditure control mechanism to reduce risk of overspend and ensure the fund never needs to close to new entrants.
- A new, joint NHS England/NICE CDF Investment Group to manage the overall CDF budget.
- Similar opportunities for off-label drugs to gain access to CDF funds, if deemed to show clinical promise.

A new fast-track system, including an accelerated NICE appraisal process

- Earlier funding, from the point of marketing authorisation, for the most promising drugs through new interim funding arrangements.
- A managed access approach to rapidly support and resolve any areas of uncertainty for drugs showing clinical promise.
- Each drug/indication looked at on an individual basis with bespoke data collection and **commercial access arrangements** – no "one size fits all" approach - managed by a joint NHS England/NICE CDF Investment Group.
- **Investment Group** will oversee budget management (expected to be fixed £340M budget in year one); expenditure control mechanism to reduce the risk of overspend; closer working with the pharmaceutical industry to encourage the responsible pricing of cancer drugs, driving stronger value for money in drug expenditure.

If you have questions or would like to share the trends you have identified (confidentially), please contact marketaccess@evidera.com. Questions and comments are encouraged and welcomed and updates will continue to be made available in future issues of this newsletter.

REFERENCES

[1] Referentenentwurf, des Bundesministeriums für Gesundheit Stand: 22. Juli 2016, Entwurf eines Gesetzes zur Stärkung der Arzneimittelversorgung in der GKV; (GKV-Arzneimittelversorgungsstärkungsgesetz – AM-VSG)

[2] http://social-sante.gouv.fr/IMG/pdf/la_lettre_d_orientation_des_ministres_du_17_aout_2016-2.pdf

[3] http://www.agenziafarmaco.gov.it/sites/default/files/Secondo_Concept_Paper_AIFA_BIOSIMILARI.pdf

Evidera Presents at ISPOR's 19TH Annual European Congress

29 OCTOBER - 2 NOVEMBER, 2016 – VIENNA, AUSTRIA

SHORT COURSE

Sun., 30 Oct., 8:00–12:00

Using DICE Simulation for Health Economic Analyses

Instructors: Caro JJ, Moller J

WORKSHOPS

SESSION II
Mon., 31 Oct., 14:15–15:15

W5: New Approaches to Survival Modeling in Oncology

Discussion Leaders: Ishak J, Felizzi F, Gauthier A, Federico V

SESSION IV
Mon., 31 Oct., 17:00–18:00

W8: The Importance of Relevance in Health Economic Evaluations: Challenges and Ways Forward

Discussion Leaders: Rolden HJA, **Caro JJ**, Joore MA, Grutters JPC

SESSION X
Wed., 2 Nov., 10:00–11:00

W27: Guidelines for Analyzing Published Summary Time to Event Data

Discussion Leaders: Ishak J, Hoyle M, **Altincatal A**

ISSUE PANELS

SESSION I
Mon., 31 Oct., 11:15–12:15

IP1: Patient Centered Decision Making with Multi-Criteria Decision Analysis: Should We Be Trying to Quantify the Patient Voice for Use in Health Technology Assessment?

Moderator: Caro JJ

Panelists: Sandman L, Kolminsky PL, Hamed A

SESSION XI
Wed., 2 Nov., 13:45–14:45

IP18: Patient Preferences in Drug Evaluation: Which Method Should We Use?

Moderator: Gelhorn H

Panelists: Tervonen T, Muhlbacher A, Postmus D

ISPOR FORUMS

SESSION I
Mon., 31 Oct., 18:15–19:15

F3: Generating Evidence of the Added Value of "Precision" Medicine

Moderator: Payne K

Speakers: Faulkner E, Siebert U, Holtorf AP, Sandhu G

SESSION II
Tues., 1 Nov., 17:45–18:45

F10: Health Economic Modeling in Oncology

Moderator: Muszbek N

Speakers: Wolowacz S, **Benedict A**

PODIUM PRESENTATION

SESSION III
CARDIOVASCULAR OUTCOMES RESEARCH STUDIES
Mon., 31 Oct., 15:45–16:45

CV1: Comparison of Oral Anti-Coagulants for Stroke Prevention in Non-Valvular Atrial Fibrillation: Two Multi-Criteria Decision Analyses

Tervonen T, Ustyugova A, Lip GYH, Verdecchia P, **Sri Bhashyam S**, Heinrich-Nols J, Gropper S, Kwan R, **Marsh K**

POSTERS

SESSION I
INFECTION
Mon., 31 Oct., 08:45–14:15

PIN65: Health State Utilities Associated with Post-Surgical Staphylococcus Aureus Infection

Matza LS, Kim KJ, Yu H, Belden K, Chen AF, Kurd M, Lee BY, Webb J

SESSION I
NEUROLOGICAL DISORDERS
Mon., 31 Oct., 08:45–14:15

PND7: Differences in Long-Term Patient Outcomes with Disease-Modifying versus Symptomatic Treatments for Alzheimer's Disease (AD)

Kansal A, Dos Santos R, **Tafazzoli A**

PND49: Cost-Effectiveness of Daclizumab versus Fingolimod in the Treatment of Patients with Relapsing-Remitting Multiple Sclerosis in Norway

Toro-Diaz H, Cele C, Hernandez L, Haines P, Liu Y, Bjornstad BM, Haukaas FS

SESSION I
RESEARCH ON METHODS
Mon., 31 Oct., 08:45–14:15

PRM93: Potential Efficacy of Lomitapide, A MTP (Microsomal Triglyceride Transfer Protein) Inhibitor, on Survival in Homozygous Familial Hypercholesterolaemia (HOFH): Results of an Event Modelling Analysis

Leipold R, Raal F, **Ishak J**, Phillips H, Deanfield J

PRM144: Development of a Responder Definition for the Migraine Physical Function Impact Diary (MPFID)

Kawata AK, Hsieh R, Sapra S, Desai P, Ortmeier B, **Poon JL**, Tepper SJ, Stewart WF, Dodick DW, **Hareendran A**

PRM154: Psychometric Validation of the Pulmonary Arterial Hypertension Symptoms and Impact (PAH-SYMPACT) Questionnaire

Gomberg-Maitland M, Channick R, Chin K, Fischer A, Frantz R, **Roberts L**, Miller C, Hunsche E, Zamanian R, Zastrow M, Badesch D

PRM155: An Anchor-Based Approach to Define an Impaired Day in Migraine Patients Utilizing the Migraine Physical Function Impact Diary

Kawata AK, Hsieh R, Sapra S, Desai P, Ortmeier B, **Gleeson S, Revicki D**, Lipton RB, Bayliss M, **Hareendran A**

PRM168: Qualitative Research Approaches in Rare Diseases: Acid Sphingomyelinase Deficiency (ASMD) Symptoms and Impact as Reported by Patients and Caregivers

Avetisyan R, **Hareendran A, Stringer S**, Tan S, Sanson BJ, Hass S

PRM171: Content Validation of the Pulmonary Arterial Hypertension Symptoms and Impact (PAH-SYMPACT) Questionnaire

Gomberg-Maitland M, Channick R, Chin K, Fischer A, Frantz R, **Roberts L**, Miller C, Hunsche E, Zamanian R, Badesch D

PRM230: Value and Cost Conundrum in Advanced Oncology: Integration of Value Frameworks into Cost-Effectiveness Analyses

Ambavane A, Benedict A, Lanitis T, Kongnakorn T

KEY: Oncology-related sessions

SESSION II
HEALTH CARE USE & POLICY STUDIES
Mon., 31 Oct., 15:45–19:45

PHP175: Simulating Patient-Level Profiles to Capture Patient Heterogeneity in Health-Economic Applications

Rael M, Ishak J

PHP270: Attributes Defining Patient Engagement and Centeredness in Health Care Research and Practice: A Framework Developed by the ISPOR Patient-Centered Special Interest Group

Hanna ML, Oehrlein EM, Perfetto EM, Astratinei V, Berner T, Burke LB, Camp R, **Hareendran A**, Harrington R, Houyez F, Patrick DL, Scott A, von Gizycki R, Wheeler R

PHP302: Systematic Review and Network Meta-Analysis (NMA) in Reimbursement Submission: What NICE Says Versus What NICE Wants

Sarri G, Rizzo M, Iheanacho I

SESSION III
MENTAL HEALTH
Tues., 1 Nov., 08:45–13:45

PMH45: Examining the Relationship between Suicidal Ideation, Depression and Selected Chronic Diseases Using the NHANES Dataset

Shalhoub H, Rafael Albertorio-Diaz J, Reaney M

SESSION III
SENSORY SYSTEMS DISORDERS
Tues., 1 Nov., 08:45–13:45

PSS56: Reliability and Convergent Validity of the NEI VFQ-25 with and without Near and Distance Activity Appendix Items in Patients with Geographic Atrophy (GA) Secondary to Age Related Macular Degeneration (AMD)

Kapre A, Tschosik E, **Kimel M**, Chabi A, Dolan C, Sivaprasad S, Bressler N, Varma R

SESSION III
SYSTEMIC DISORDERS/CONDITIONS
Tues., 1 Nov., 08:45–13:45

PSY68: A Cost-Consequence Analysis of Parecoxib Plus Opioids versus Opioids Alone in the Management of Postoperative Pain in China

Barra M, Remak E, Liu DD, Xie L, Abraham L, Sadosky A

PSY121: Comparison of Methods to Assess the Relative Importance of Criteria in Multi-Criteria Decision Analysis: an Evaluation of Orphan Drugs in Russia

Fedyaeva VK, Omelyanovskiy V, Rebrova O, **Marsh K**

SESSION IV
DIABETES/ENDOCRINE DISORDERS
Tues., 1 Nov., 15:15–19:15

PDB22: Impact of Empagliflozin (Jardiance) to the NHS: Estimation of Budget and Event Impact Based on EMPA-REG Outcome Data

Daacke I, Kandaswamy P, Tebboth A, **Kansal A, Reifsnider O**

PDB46: Cost-Effectiveness of Empagliflozin (Jardiance) in the Treatment of Patients with Type 2 Diabetes Mellitus (T2DM) in the UK Based on EMPA-REG Outcome Data

Daacke I, Kandaswamy P, Tebboth A, **Kansal A, Reifsnider O**

PDB52: Cost-Effectiveness of Empagliflozin in Patients with T2DM and High CV Risk in Canada

Mettam SR, Bajaj H, **Kansal AR**, Kandaswamy P

SESSION V
CANCER
Wed., 2 Nov., 08:45–13:45

PCN20: Sunitinib Dosing Schedules in the Management of Metastatic Renal Cell Carcinoma: A Meta-Analysis

Abogunrin S, Ashaye AO, Fahrbach K, Cappelleri JC, Sandin R, Ramaswamy K

PCN137: Modeling Treatments and Outcomes in Metastatic Castration-Resistant Prostate Cancer: A Case Study of Discrete Event Simulation and the Challenges for a UK NICE Evaluation

Sorensen S, Hall F, **Reifsnider O, Proskorovsky I**, Dearden L, Girod I, Lee J

PCN252: Real-World Treatment Patterns Among Patients with Ovarian Cancer: An Analysis of a Large US Electronic Health Records Database

Karve S, Walker G, **Wang R**, Lawrence D, Horsfield A

PCN269: The Cancer Drugs Fund: The Evolving Assessment Process

Carroll M, **Satherley A**, Miller PS

KEY: Oncology-related sessions

Upcoming Presentations

ACoP7 - American Conference on Pharmacometrics

Oct. 23-26, 2016; Bellevue, WA, USA

ORAL PRESENTATION

DICE Simulation: A Shotgun Marriage or Wedded Bliss for Pharmacometrics and Pharmacoeconomics?

Caro JJ

IDWeek 2016

Oct. 26-30, 2016; New Orleans, LA, USA

POSTERS

Association between Carbapenem Resistance and Mortality among Adults Hospitalized with Serious Infections due to an Enterobacteriaceae spp: Results of a Systematic Literature Review and Meta-Analysis

Martin A, Fahrbach K, Zhao Q, Lodise TP

Caregiver Impact of Respiratory Syncytial Virus Hospitalizations among US Preterm Infants 29-35 Weeks' Gestational Age

Pokrzywinski RM, Swett LL, Yi J, Kumar VR, McLaurin KK, **Leidy NK**

Clinical and Economic Burden of Multi-drug Resistant Pseudomonas sp. (MDRP) among Patients with Serious Infections in US Hospitals

Lodise TP, **Wang R, Bhagnani T**, Zhao Q, Ye M, **Berger A**

ORAL PRESENTATION

Does Timing of Receipt of Appropriate Antimicrobial Therapy Make a Difference among Patients with Serious Infections due to Resistant Gram-negative Pathogens?

Berger A, Bhagnani T, Wang R, Zhao Q, Ye M, Lodise TP

2016 Annual Fall Scientific Meeting of SMSNA

Nov. 3-6, 2016; Scottsdale, AZ, USA

POSTER

Conversations with Women about Female Sexual Dysfunction (FSD) and Treatment with Bremelanotide

Koochaki PE, Althof S, Kingsberg SA, Perelman MA, Lucas J, Jordan R, **Revicki DA**

MISSED ANY OF OUR RECENT WEBINARS?

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- Post-Authorization Safety Studies: PASS the Word Around
- Medication Adherence and Outcomes Research: 21st Century Insight
- FDA Post-Marketing Safety Studies: When a Retrospective Design May be the Ideal
- How are Patient Preferences Used to Support Decisions? Examples from Industry
- Which Method to Use for Capturing Patient Preferences in Benefit-Risk Assessment
- Incorporating Patient Preferences into Product Development and Value Communication
- Real-World Data Strategy and Programs of Research: A Roadmap for Late Phase Success
- Network Meta-Analyses and Indirect Treatment Comparisons – Not Just for Reimbursement
- What Relevance Does PCORI have for the International Life-Sciences Industry

Recent Presentations

ISOQOL 2016

Oct. 19-22, 2016; Copenhagen, Denmark

WORKSHOPS

An Introduction to Health-Related Quality of Life Assessment

Gelhorn H, Wyrwich K

Concept Elicitation for the Development of Clinical Outcome Assessments (COAs) – Qualitative Methodological Approaches for Data Collection, Analyses and Reporting

Skalicky A, Hareendran A, Magasi S

SHORT COURSE

Introduction to Quality of Life and Other Patient Reported Outcomes: Theory, Measurement and Applications

Valderas JC, **Lenderking WR**

ORAL PRESENTATIONS

Evaluating Options for Presenting Health States from PROMIS Item Banks

Hanmer J, Feeny D, Fischhoff B, Hays R, Hess R, Pilkonis P, **Revicki D**, Roberts M, Tsevat J, Yu L

Psychometric Properties of the Migraine Physical Function Impact Diary (MPFID)

Kawata AK, Hsieh R, Hareendran A, Bender R, Shaffer S, Sapra S, Desai P, Widnell K, Bayliss M, Buse DC, **Revicki D**

Translation and Linguistic Validation of the Migraine Physical Function Impact Diary (MPFID) for Use in 25 Countries

Oko-osi H, Arnold B, Savic L, Desai P, **Hareendran A, Mannix S**, Sapra S, Eremenco S

POSTERS

A New Symptom-Specific Patient-Reported Outcome Measure for Patients with Soft Tissue Sarcoma

Rentz A, Skalicky A, Ghate S, Chawla SP, Conley AP, Villalobos VM, Perez JR

An Adaptation of the Profile of Mood States (POMS) for Use in Adults with Phenylketonuria (PKU): Development of the PKU-POMS

Bacci ED, Wyrwich KW, Bender R, Gries K, Chen Y, Jain R, Konkol L, Merilainen MJ, Weng H

Assessing the Content Validity of the Investigator-Rated ADHD Rating Scale Version IV (I-ADHD RS-IV) Instrument for Use in Adults with Phenylketonuria (PKU)

Wyrwich KW, Gries K, Al-Jassar G, **Bacci ED**, Chen Y, Jain R, Konkol L, Merilainen MJ, Weng H

Psychometric Evaluation of the ANMS Gastroparesis Cardinal Symptom Index-Daily Diary

Revicki D, Parkman H

Psychometric Properties of the FAACT Additional Concerns Subscale (A/CS) for Measurement of Anorexia in Patients with Non-Small Cell Lung Cancer

Gelhorn HL, Gries KS, Duus EM, Bourne RK, Friend JE, **Speck RM, Leidy NK**, Cella D

2016 ASHG Meeting

Oct. 18-22, 2016; Vancouver, BC, Canada

POSTER

Disease Symptoms and Impacts as Reported by Patients with Acid Sphingomyelinase Deficiency (ASMD) and Caregivers

Avetisyan R, **Hareendran A, Stringer S**, Tan S, Sanson BJ, Hass S

World CDx 2016

Oct. 18-21, 2016; Boston, MA, USA

ISSUE PANEL

How to Improve the Integration of Precision Medicine and Multi-Biomarker Diagnostic Tests in Healthcare Systems

Whelan J, Pezalla E, Roth D, Mills Shaw K, Fiore L, **Faulkner E**

UEG Week 2016

Oct. 15-19, 2016; Vienna, Austria

POSTER

Patterns of Dose Escalation among Patients with Ulcerative Colitis or Crohn's Disease Treated with Vedolizumab vs. Infliximab in the US

Raluy-Callado M, Li Q, Luo M, Lasch K, Khalid JM

Hospitalisations and Treatment Discontinuation among Patients with Ulcerative Colitis and Crohn's Disease Treated with Vedolizumab Compared with Infliximab

Raluy-Callado M, Alam N, Wang R, Khalid JM

ACT 2016

Oct. 14-19, 2016; Las Vegas, NV, USA

POSTERS

Hospitalisations and Treatment Discontinuation among Patients with Ulcerative Colitis and Crohn's Disease Treated with Vedolizumab Compared with Infliximab

Raluy-Callado M, Alam N, Wang R, Khalid JM

Patterns of Dose Escalation among Patients with Ulcerative Colitis or Crohn's Disease Treated with Vedolizumab vs. Infliximab in the United States

Raluy-Callado M, Li Q, Luo M, Lasch K, Khalid JM

Congres de la Societe Francaise d'Endocrinologie

Oct. 5-8, 2016; Bordeaux, France

POSTER

Preferences des Patients Selon Leur Age pour les Differentes Caracteristiques des Agonistes du Recepteur du Glucagon-like Peptide-1 (GLP-1RA) dans le Traitement du Eiabete au Royaume-uni : Un Modele de Choix Discret

Adetunji O, **Poon J**, Davies E, Paczkowski R, Curtis S, Gentilella R, Boye K, **Gelhorn H**

AMCP Nexus 2016

Oct. 3-6, 2016; National Harbor, MD, USA

POSTERS

Budget Impact Analysis of Eliglustat for Treatment of Gaucher Disease Type 1 in the United States (US)

Sugarman R, Ward A, Richmond W, Wilson R, Nalysnyk L

The Economic Implications of Different Rheumatoid Arthritis Drug Treatment Pathways

Lee J, Pelkey R, Gubitosa J, Henrick MF, **Ganz ML**

KEY: Oncology-related sessions

Work Productivity and Caregiver Impact of Respiratory Syncytial Virus Hospitalizations Among US Preterm Infants 29–35 Weeks' Gestational Age

Swett LL, Pokrzywinski RM, Leidy NK, Pannaraj PS, Yi J, Pavilack MS, Kumar VR, McLaurin KK

Positive Predictive Value of an Algorithm to Identify Moderate-to-Severe Psoriasis in a Claims Database

Malatestinic W, **Nordstrom B,** Wu JJ, Goldblum O, Solotkin K, Lin CY, **Kistler K, Fraeman K,** Johnston J, Hawley L, Sicignano N, Araujo A

2016 ASA Biopharmaceutical Section Regulatory-Industry Statistics Workshop

Sept. 28-30, 2016; Washington, DC, USA

ISSUE PANEL

Developing PRO Instruments in Clinical Trials: Issues, Considerations and Solutions

Chen WH, Coon C, Johnson LL, Kammerman L, **Revicki D**

OHDSI Symposium 2016

Sept. 23-24, 2016; Washington, DC, USA

ISSUE PANEL

The State of CDM Adoption, My Perspectives: Research vs Practice

Reisinger S

POSTER

Highly Scalable Patient-At-A-Time Transformation of Observational Databases into OMOP CDM v5 Format Using Cloud-Based Open Source Tools

O'Hara D, Lyman S, Golbaz M, Reisinger S

Findacure - Intro to Rare Disease Patient Registries

Sept. 16, 2016; London, UK

ORAL PRESENTATION

Opportunities for Patient (Group) Engagement in Real World Rare Disease Registries

Hareendran A, Payne K

EHMTIC 2016

Sept. 15-18, 2016; Glasgow, UK

POSTERS

The Migraine Physical Function Impact Diary (MPFID): Usability Testing of an Electronic Patient Assessment Tool

Shaffer S, Eremenco S, Hwang S, Evans C, Dallabrida S, Savalia M, **Hareendran A**, Sapra S, Desai P

The Migraine Physical Function Impact Diary: Content Validity of a New Instrument to Evaluate the Benefit of Preventive Migraine Treatments

Mannix S, Oko-Osi H, Gleeson S, Skalicky AM, Desai P, Sapra S, Bayliss M, Buse DC, **Hareendran A**

EASD 2016

Sept. 12-16, 2016; Munich, Germany

POSTER

Delays in Treatment Intensification with Oral Anti-Diabetes Drugs Impact the Risk of Microvascular and Macrovascular Events: An Individual Patient Simulation Study

Mukherjee J, **Folse H, Ward A, Pelkey R**, Dinh T, Sheehan J, Qin L, Hunt P, Kim J

DukeNUS Medical School

Sept. 6, 2016; Singapore

SESSION SPEAKER

Changing the Paradigm: Discretely Integrated Condition Event (DICE) Simulation for HTA

Caro JJ

Educational Workshop Organized by Saw Swee Hock School of Public Health & ISPOR Singapore Regional Chapter

Sept. 6, 2016; Singapore

WORKSHOP

Changing the Paradigm: Discretely Integrated Condition Event (DICE) Simulation for HTA

Caro JJ

PAINWeek 2016

Sept. 6-10, 2016; Las Vegas, NV, USA

POSTERS

Discriminating Between Neuropathic Pain and Sensory Hypersensitivity Using the Chronic Pain Questions (CPQ)

Coyne K, Currie B, Cappelleri J, Hegeman-Dingle R, Alexander A, Abraham L, Sadosky A, Brodsky M

The Burden of Opioid-Induced Constipation in Younger Patients with Chronic Pain

Gupta A, **Coyne KS**, Datto C, Venuti C

The Impact of Nausea on Pain and its Relief

Bender R, Schachtel B, **Revicki D, Rentz A**, Kwong J, Marrett E

ERS International Congress 2016

Sept. 3-7, 2016; London, UK

POSTER

Item Performance of the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) Questionnaire: Results from the SYMPHONY Study with Macitentan

Chin K, Channick R, Fischer A, Frantz R, Gomberg-Maitland M, **Kleinman L**, Miller C, Hunsche E, Zamanian R, Badesch D

ISPOR 7TH Asia-Pacific Conference – 2016

Sept. 3-6, 2016; Singapore

SHORT COURSE

Budget Impact and Cost Analysis

Caro JJ, Lai A

POSTERS

A Systematic Review Comparing Studies of Cardiovascular Event Utilities by Geographic Region

Blieden M, Szatkowski A, Cheng LI, Gandra SR

A Systematic Review of Cardiovascular Event Utilities in Asia

Blieden M, Szatkowski A, Cheng LI, Gandra SR

Cost-Minimization Analysis in Postoperative Pain Management after Non-Cardiac Major Surgeries in China: Parecoxib vs Nonselective Nonsteroidal Anti-Inflammatory Drugs and Tramadol

Barra M, Remak E, Liu DD, Xie L, Abraham L, Sadosky A, **Kongnakorn T**

KEY: Oncology-related sessions

DICE Simulation: A New Method That Facilitates Decision-Analytic Modeling

Caro JJ, Moller J

Differences in Cost-Effectiveness Estimates for Chronic Hepatitis C Treatment among Cohort Markov Model, Microsimulation and Discrete Event Simulation

Zhou HJ, Zhao YJ, Chrosny WAL, Lin L, **Caro JJ, Moller J**, Dan YY, Lim BP

Improvement of Long Term Risks of Cardiovascular Events Associated with Community Based Disease Management in Chinese Patients of the Xin Jiang Autonomous Region of China

Yang L, Cai M, Ma M, Huang X, Liu L, Wang B, Zhu M, Zhu W, Zhe W, Guan Y, **Kongnakorn T, Xiao Y, Peng S**, Hach T

Preferences for Treatment Attributes of Dulaglutide and Liraglutide among Patients with Type 2 Diabetes Mellitus and their Willingness to Self-Inject Diabetes Medication: A Comparison between Japan and the United Kingdom

Gelhorn HL, Bacci ED, Poon JL, Boye KS, Suzuki S, Babineaux SM

35TH Annual Meeting of the European Bone & Joint Infection Society – 2016

Sept. 1-3, 2016; Oxford, UK

POSTER

The Burden of Illness, Impact and Costs Associated with Post-Operative Infections: The Patient Perspective

Gelhorn HL, Anand SB, Parvizi J, Morrison T, Yu H, **Pokrzywinski R**, Al-Jassar G, Chen AF

ESC Congress 2016

Aug. 27-31, 2016; Rome, Italy

POSTER

Comparison of Oral Anti-Coagulants for Stroke Prevention in Non-Valvular Atrial Fibrillation: a Multi-Criteria Decision Analysis

Lip GYH, Verdecchia P, **Tervonen T**, Ustyugova A, Heinrich-Nols J, Gropper S, Kwan R, **Sri Bhashyam S, Marsh K**

32nd ICPE

Aug. 25-28, 2016; Dublin, Ireland

WORKSHOP

What's in a Code? Algorithm Validation in Drug Safety Studies

Nordstrom BL, Lanes S, Wang C. Weiss S

SYMPOSIUM

Who To Ask and How? Preference-Based Methods for Benefit-Risk Assessment

Marsh K, Hillege HL, Ataher Q, **Tervonen T**

SHORT COURSE

Selection of Databases for Pharmacoepidemiology Research

Reynolds M

POSTERS

An Analysis of Characteristics of Post-Authorization Safety Studies Registered on ENCePP

Ramagopalan SV, Wasiak R, Lambrelli D

Decrease in Rate of Multiple Sclerosis-Related Hospitalizations in Portugal

Pereira M, **Lambrelli D, Ramagopalan SV**

Prevalence of Bone Metastases in Patients with Prostate Cancer: A Systematic Review and Meta-Analysis

Fahrbach K, Amelio J, **Xu Y, Abogunrin S**, Talbot S, Booth E, Niepel D, Body JJ

Risk Factors for Major Bleeding Events in Rivaroxaban Users with Atrial Fibrillation: A Nested Case-Control Study

Simeone JC, Tamayo SG, **Nordstrom BL**, Patel MR, Yuan Z, Sicignano NM, Peacock WF

Social Media Mining to Investigate Multiple Sclerosis Treatment Patterns and Adverse Effects

Cooper S, **Wasiak R, Ramagopalan SV**

ORAL PRESENTATION

Development and Validation of an Algorithm for Identifying Pediatric Patients with Type 2 Diabetes in Claims Data

Teltsch DY, Swain RS, Farsani SF, Brodovicz KG, Kaspers S, **Huse S**, Sicignano N, Cristaldi C, **Nordstrom BL**, Bartels DB

ISPOR IV Congreso Colombia 2016

Aug. 24-26, 2016; Bogota, Colombia

PLENARY SESSION

Definicion de Precios Basados en Valor (Definition of Value Based Pricing)

Caro JJ

AAIC 2016

July 24-28, 2016; Toronto, Canada

ORAL PRESENTATION

Simulation Study on Early Treatment with a Hypothetical Disease Modifying Therapy (DMT) on Need for Institutional Care

Tafazzoli A, Dos Santos R, **Krotneva M, Ishak J, Kansal A**

Health Policy Seminar at Tufts Medical Center

July 21, 2016; Boston, MA, USA

FEATURED SPEAKER

Changing the Paradigm: Discretely Integrated Condition Event (DICE) Simulation for HTA

Caro JJ

SMDM 16TH Biennial European Conference

June 12-14, 2016; London, UK

ORAL PRESENTATION

Statin Benefit-Risk Profiles in Individuals at Intermediate Risk for Cardiovascular Disease

Tervonen T, van Valkenhoef G, Naci H, Postmus D, Hillege H

POSTER

Structuring Benefit-Risk Models in Presence of Numerous Adverse Events: A Case Study of Multiple Sclerosis

Sri Bhashyam S, Gelhorn H, Gries K, Marsh K, Poon JL, Rentz A, Tervonen T

KEY: Oncology-related sessions

American Diabetes Association 76TH Scientific Session

June 10-14, 2016; New Orleans, LA, USA

POSTER

Long-term Economic Outcomes of Empagliflozin (Jardiance) Treatment in Type 2 Diabetes Mellitus (T2DM) based on the EMPA-REG OUTCOME Trial

Kansal A, Zheng Y, **Proskorovsky I, Reifsnider O**, Kandaswamy P, Ruffolo A

AHS 2016

June 9-12, 2016; San Diego, CA, USA

POSTERS

Methods for Addressing Challenges for Evaluating Patient-Reported Outcomes in Clinical Trials of Prophylactic Treatments for Migraines

Roberts L, Oko-Osi H, Hareendran A, Mannix S, Desai P, Sapra S

Reflecting Patients' Perspectives in Measuring Migraine-related Impacts on Functioning: A Qualitative Study with Migraine Patients

Skalicky A, Mannix S, Hareendran A, Corey-Lisle P, Widnell K, Buse DC, Desai P, Sapra S

EHA21 Congress

June 9-12, 2016; Copenhagen, Denmark

POSTERS

A Frailty Scale Predicts Outcomes in Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma Treated with Continuous Lenalidomide Plus Low-Dose Dexamethasone in the First (MM-020) Trial

Facon T, Hulin C, Dimopoulos MA, Belch A, Meuleman N, Mohty M, Chen WM, Kim K, Zamagni E, Rodriguez-Otero P, Renwick W, Rose C, Tempescul A, Boyle E, Palumbo A, **Guo S**, Monsini MS, Sturniolo M, Ervin-Haynes A, Fermand JP

Economic Evaluation of Carfilzomib + Lenalidomide + Dexamethasone (KRD) vs. Lenalidomide + Dexamethasone (RD) in Relapsed or Refractory Multiple Myeloma (R/RMM)

Fonseca R, Panjabi S, Campioni M, Giannopoulou A, **Benedict A, Houisse I**, Aggarwal S, Jakubowiak A

ASCO Annual Meeting 2016

June 3-7, 2016; Chicago, IL, USA

POSTERS

Economic Evaluation of Carfilzomib + Lenalidomide + Dexamethasone (KRd) vs. Lenalidomide + Dexamethasone (RD) in Relapsed or Refractory Multiple Myeloma (R/RMM)

Jakubowiak AJ, **Benedict A**, Panjabi S, **Houisse I**, Campioni M, Giannopoulou A, Aggarwal S, Fonseca R

Health-Related Quality of Life over Time in Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma Treated with Lenalidomide and Dexamethasone until Progression

Vogl DT, Delforge M, Song K, **Guo S**, Gibson CJ, Ervin-Haynes A, Facon T

59TH Annual Meeting of the Japan Diabetes Society

May 19-21, 2016; Kyoto, Japan

POSTER

A Discrete Choice Experiment to Evaluate Diabetes Patients' Preferences for Profiles of GLP-1 Treatments in Japan

Suzuki S, **Bacci ED, Poon JL**, Boye KS, Babineaux SM, **Gelhorn HL**

ATS International Conference 2016

May 13-18, 2016; San Francisco, CA, USA

POSTERS

Gender Differences by Age in St. George's Respiratory Questionnaire Total Scores and Self-reported Overall Health among Subjects with and without COPD in the COPDGene Cohort

DeMeo DL, Han MK, Regan EA, Yadao A, Kavati A, Vegesna A, Keininger D, **Wilcox TK, Ramagopalan S**, Pereira M, Make BJ, for the COPDGene Investigators

Gender Differences by Age in Symptoms, Airflow Limitations, Exacerbation Risk and GOLD Combined Assessment among Subjects with COPD in COPDGene Cohort

DeMeo DL, Han MK, Regan EA, Yadao A, Kavati A, Vegesna A, Keininger DL, **Wilcox TK, Ramagopalan S**, Pereira M, Make BJ, for the COPDGene Investigators

How 'Stable' is Stable COPD? Daily Symptom Variability of Subjects Enrolled in the SPIROMICS Exacerbation Sub-Study

Ancy KM, Oromendia CI, Ballman KV, **Leidy NK, Malley KG**, Anderson WH, et al.

Respiratory Symptom Patterns Over One Year in Patients with COPD: Results from the Acute Exacerbation and Respiratory Infections (AERIS) Study

Sung R, Allinder M, Aris E, Bourne S, Devaster J, Kim V, **Leidy NK**, Locantor N, Mannino F, Ostridge K, Peeters M, Tal-Singer R, Welch L, Weynants V, Williams N, Miller B, Wilkinson T

2ND Congress of the SEUD

May 12-14, 2016; Barcelona, Spain

POSTER

Assessing the Patient-Reported Symptoms and Impacts of Uterine Fibroids: Development of the Uterine Fibroid Daily Symptom Scale (UF-DSD) and Uterine Fibroid Impact Scale (UFIS)

Mattera M, Wichmann K, Filonenko A, Seitz C, Schaefers M, Goldstein J, Gerlinger C, **Wiklund I**

HTAi 2016 Annual Meeting

May 10-14, 2016; Tokyo, Japan

ISSUE PANEL

Patient Centered Decision Making: How Multi-Criteria Decision Analysis Can Help Capture the Patient Voice

Caro JJ, Hamed A, Wibulpolprasert S, **Marsh K**, Youngkong S

26TH Congresso Nazionale SID

May 4-7, 2016; Rimini, Italy

POSTER

Age-Related Differences in Patients' Preferences for Profiles of Glucagon-like Peptide-1 Receptor Agonist (GLP-1RA) Diabetes Treatments in the United Kingdom: A Discrete Choice Experiment

Adetunji O, **Poon JL**, Davies EW, Paczkowski R, Curtis SE, Gentilella R, Boye KS, **Gelhorn HL**

KEY: Oncology-related sessions

Publications

Alberti A, Lacoin L, Morais E, Lefevre C, **Abogunrin S, Iheanacho I**. A Literature Review of the Distribution of Hepatitis C Virus Genotypes across Europe. *J Med Virol*. 2016 May 12. doi: 10.1002/jmv.24573. [Epub ahead of print]

Askew RL, Cook KF, Keefe FJ, Nowinski CJ, Cella D, **Revicki DA**, Morgan DeWitt EM, Michaud K, Trence DL, Amtmann D. A PROMIS Measure of Neuropathic Pain Quality. *Value Health*. 2016 Jul-Aug;19(5):623-30. doi: 10.1016/j.jval.2016.02.009.

Askew RL, Cook KF, **Revicki DA**, Cella D, Amtmann D. Evidence from Diverse Clinical Populations Supports Clinical Validity of PROMIS Pain Interference and Pain Behavior. *J Clin Epidemiol*. 2016 May;73:103-11. doi: 10.1016/j.jclinepi.2015.08.035.

Azimi M, Schmaus K, Greger V, Neitzel D, Rochelle R, Dinh T. Carrier Screening by Next-Generation Sequencing: Health Benefits and Cost Effectiveness. *Mol Genet Genomic Med*. 2016 Jan 29;4(3):292-302. doi: 10.1002/mgg3.204. eCollection 2016.

Bacci ED, Staniewska D, **Coyne K**, Boyer S, White LA, Zach N, Cedarbaum JM, the Pooled Resource Open-Access ALS Clinical Trials Consortium. Item Response Theory Analysis of the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised in the Pooled Resource Open-Access ALS Clinical Trials Database. *Amyotroph Lateral Scler Frontotemporal Degener*. 2016 Apr-May;17(3-4):157-67.

Bacci ED, Wyrwich KW, Gries KS, Chen Y, Jain R, Konkol L, Merilainen MJ, Weng HH. An Adaptation of the Profile of Mood States for Use in Adults with Phenylketonuria. *Journal of Inborn Errors of Metabolism & Screening*. [In Press]

Bajaj JS, Frederick RT, Bass NM, Ghabril M, **Coyne K**, Margolis MK, Santoro M, Coakley DF, Mokhtarani M, Jurek M, Scharschmidt BF. Overt Hepatic Encephalopathy: Development of a Novel Clinician Reported Outcome Tool and Electronic Caregiver Diary. *Metab Brain Dis*. 2016 Oct;31(5):1081-93. doi: 10.1007/s11011-016-9851-9.

Ben-Joseph R, Bell JA, Brixner D, **Kansal A**, Paramore C, Chitnis A, Holly P, S Burgoyne D. Opioid Treatment Patterns Following Prescription of Immediate-Release Hydrocodone. *J Manag Care Spec Pharm*. 2016 Apr;22(4):358-66. doi: 10.18553/jmcp.2016.22.4.358.

Ben-Joseph R, Bell JA, Chitnis A, **Kansal A**, Holly P, Paramore C, Wild H. Characterizing Downstream Healthcare Resource Utilization and Costs Based on Prior Utilization Patterns of Immediate-Release Hydrocodone. *J Med Econ*. 2016 Feb;19(2):169-80. doi: 10.3111/13696998.2015.1105810.

Borer JS, **Kansal AR, Dorman ED, Krotneva S,** Zheng Y, Patel HK, Tavazzi L, Komajda M, Ford I, Bohm M, Kielhorn A. Budget Impact of Adding Ivabradine to Standard of Care in Patients with Chronic Systolic Heart Failure in the United States. *J Manag Care Spec Pharm*. 2016 Sep;22(9):1068-1075.

Bourbeau J, Lavoie KL, Sedeno M, De Sousa D, Erzen D, Hamilton A, Maltais F, Troosters T, **Leidy N**. Behaviour-Change Intervention in a Multicentre, Randomised, Placebo-Controlled COPD Study: Methodological Considerations and Implementation. *BMJ Open*. 2016 Apr 4;6(4):e010109. doi: 10.1136/bmjopen-2015-010109.

Browne C, Muszbek N, Chapman R, Marsh K, Gould IM, Seaton RA, Allen M. Comparative Healthcare-associated Costs of Methicillin-resistant Staphylococcus Aureus Bacteraemia-infective Endocarditis Treated with Either Daptomycin or Vancomycin. *Int J Antimicrob Agents*. 2016 May;47(5):357-61. doi: 10.1016/j.ijantimicag.2016.02.006.

Caro JJ. Discretely Integrated Condition Event (DICE) Simulation for Pharmacoeconomics. *Pharmacoeconomics*. 2016 Jul;34(7):665-72. doi: 10.1007/s40273-016-0394-z.

Caro JJ. Response to Letter to the Editor Regarding Discretely Integrated Condition Event Simulation for Pharmacoeconomics. *Pharmacoeconomics*. 2016 Sep 12. [Epub ahead of print]

Caro JJ, Moller J. Advantages and Disadvantages of Discrete-event Simulation for Health Economic Analyses. *Expert Rev Pharmacoecon Outcomes Res*. 2016 Jun;16(3):327-9. doi: 10.1586/14737167.2016.1165608. Epub 2016 Mar 25.

Celli B, Tetzlaff K, Criner G, Polkey MI, Sciurba F, Casaburi R, Tal-Singer R, **Kawata A**, Merrill D, Rennard S; COPD Biomarker Qualification Consortium. The 6-minute Walk Test as a COPD Stratification Tool: Insights from the COPD Biomarker Qualification Consortium. *Am J Respir Crit Care Med*. 2016 Jun 22. [Epub ahead of print]

Cid Ruzafa J, Merinopoulou E, Baggaley RF, **Leighton P**, Werther W, Felici D, **Cox A**. Patient Population with Multiple Myeloma and Transitions Across Different Lines of Therapy in the USA: an Epidemiologic Model. *Pharmacoepidemiol Drug Saf*. 2016 Aug;25(8):871-9. doi: 10.1002/pds.3927.

Ciomek K, Kadzinski M, **Tervonen T**. Heuristics for Prioritizing Pair-Wise Elicitation Questions with Additive Multi-Attribute Value Models. *Omega (Westport)*. [In Press]

Cox A, Raluy-Callado M, Wang M, Bakheit AM, Moore AP, Dinet J. Predictive Analysis for Identifying Potentially Undiagnosed Post-stroke Spasticity Patients in the United Kingdom. *J Biomed Inform*. 2016 Apr;60:328-33. doi: 10.1016/j.jbi.2016.02.012.

Coyne KS, Currie BM, Donevan S, Brodsky M, Asmus MJ, Krichbaum DW, Cappelleri JC, Hegeman-Dingle R, Sadosky A, Whipple SZ, Burbridge C, Mulhem E, Hillenberg JB. Psychometric Validation of the Electronic Chronic Pain Questions (eCPQ) in a Primary Care Setting. *Curr Med Res Opin*. [In Press]

Coyne KS, Sexton C, LoCasale RJ, King FR, Margolis MK, Ahmedzai SH. Opioid-Induced Constipation among a Convenience Sample of Patients with Cancer Pain. *Front Oncol*. 2016 June; doi.org/10.3389/fonc.2016.00131.

Datto CJ, LoCasale RJ, Margolis MK, **Thompson CL, Coyne KS**. Laxative Utilization over Time in Chronic Pain Patients with Opioid-Induced Constipation. *Pain Manag*. 2016 Aug 1. [Epub ahead of print]

Desai K, Gupta SB, Dubberke ER, Prabhu VS, **Browne C**, Mast TC. Epidemiological and Economic Burden of Clostridium Difficile in the United States: Estimates from a Modeling Approach. *BMC Infect Dis*. 2016 Jun 18;16(1):303.

Etemadifar M, Mehrabi B, Kiani-Peykani R, Abtahi SH, Nekouie-Isfahani K, **Ramagopalan SV**, Fereidan-Esfahani M. Soil Heavy Metals are Associated with the Distribution of Multiple Sclerosis in Isfahan, Iran. *Acta Neurol Scand*. 2016 Oct;134(4):292-9. doi: 10.1111/ane.12543.

Ganz ML, Liu J, Zou KH, **Bhagnani T**, Luo X. Real-World Characteristics of Elderly Patients with Overactive Bladder in the United States. *Curr Med Res Opin*. 2016 Sep 20:1-9. [Epub ahead of print]

Ganz ML, Sugarman R, Wang R, Hansen BB, Hakan-Bloch J. The Economic and Health-Related Impact of Crohn's Disease in the United States: Evidence from a Nationally Representative Survey. *Inflamm Bowel Dis*. 2016 May;22(5):1032-41. doi: 10.1097/MIB.0000000000000742.

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KEY: Oncology-related publications

PPD Completes Acquisition of Evidera
Establishes Global Leader in Real-World Research

WILMINGTON, N.C., September 6, 2016 — Pharmaceutical Product Development, LLC (PPD), a leading global contract research organization (CRO), today announced the completion of its acquisition of Evidera, a leading provider of evidence-based solutions to demonstrate the real-world effectiveness and value of biopharmaceutical products.

The acquisition unites two best-in-class research companies, creating transformative opportunities for clients of PPD and Evidera to generate evidence of product value that helps optimize market access for new health technologies. The companies will create a set of seamless services across the drug development continuum that will enhance biopharmaceutical companies' ability to deliver life-changing therapies to patients.

Operating as a wholly owned subsidiary of PPD, Evidera will continue to be led by its current management team and a seasoned staff of highly credentialed scientific and consulting professionals. Evalytica also will continue to operate as a wholly owned subsidiary of Evidera, providing both Evidera and PPD clients with an innovative, technology-enabled analytic platform for rapid and transparent analysis of diverse data sources.

"By leveraging Evidera's scientific research and consulting capabilities and PPD's operational excellence in global clinical research, our clients can greatly enhance their ability to navigate today's complex and fast-evolving R&D and reimbursement landscape," said David Simmons, Chairman and CEO of PPD. "For biopharma companies, our considerable joint expertise will benefit clients in executing comprehensive development strategies for regulatory success, while in parallel collecting the necessary evidence to support discussions with payers and health authorities on pricing and reimbursement. These combined strengths will further support clients in bringing innovative therapies to patients in need."

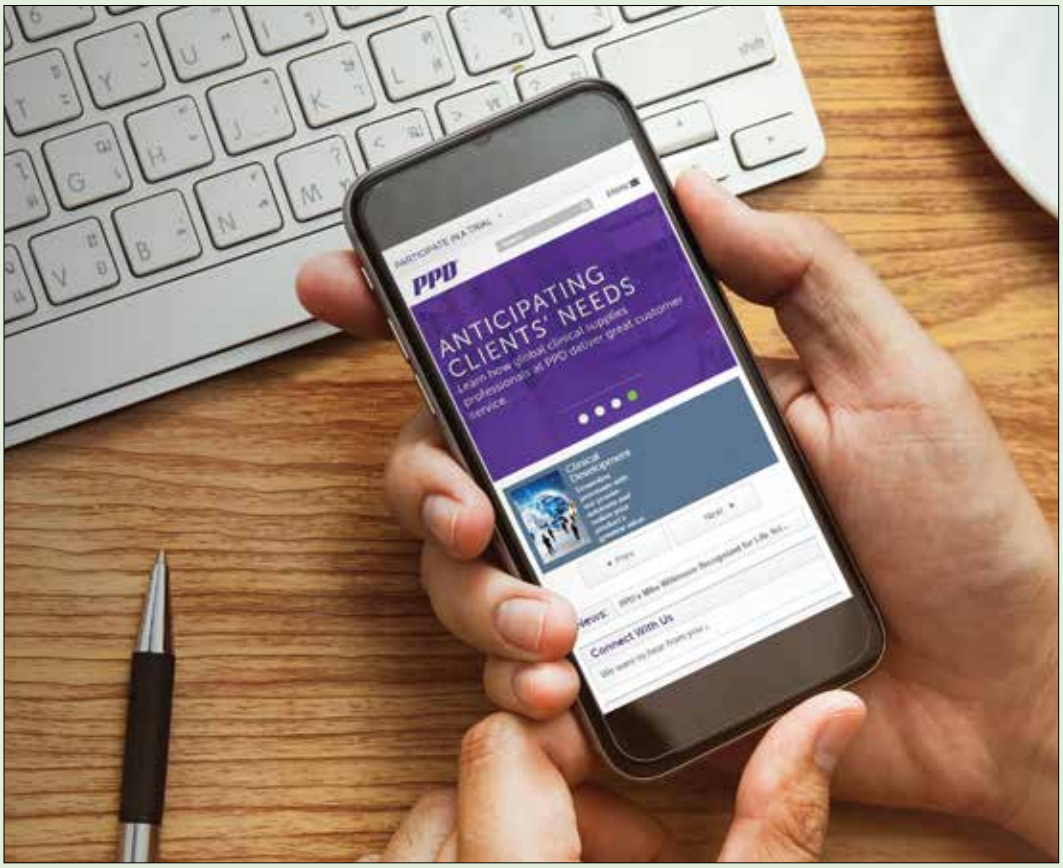
Jon Williams, President of Evidera, said: "Demonstrating product value and effectiveness in real-world settings is increasingly critical for the biopharma industry to justify access and reimbursement. Evidence-based value demonstration must be well integrated with, and begin early in, the clinical development process, as payers, health authorities and providers increasingly have set this as a condition for market access. Until today, biopharma companies had limited options for partners with the required expertise. But by marrying a best-in-class CRO with a best-in-class real-world research and market access company, we are providing transformative opportunities for our clients to demonstrate the value of their products."

Evidera was created as a market-leading independent company under the ownership of Symphony Technology Group (STG) following the acquisition of long-standing health economics, outcomes research, market access, epidemiology, and data analytics practices.

Since it was formed in 2013, Evidera has worked with all of the top biopharma companies, and is a preferred provider for most of the top 50. Evidera scientists and consultants have published more than 2,200 peer-reviewed articles and have more than 1,100 studies in progress across all major therapeutic areas. Evidera will continue to operate its office locations in North America and Europe and grow its network of experts in major markets around the world.

PPD's acquisition of Evidera closed Sept. 1.

The above press release was distributed by PPD and can be viewed in its entirety at http://ppdi.com/News-And-Events/News/2016/Evidera-Joins-PPDI or http://www.evidera.com/company/news-room



Evidera Among the Top 50 Consulting Firms to Work For in Vault's 2017 Ranking

Evidera was ranked among the best consulting firms to work for in the 2017 Vault Consulting 50, capturing the #46 spot among larger consulting firms such as Deloitte, Bain, McKinsey, and BCG. Evidera also ranked among Vault's 2017 Top 25 Best Boutique Consulting Firms.

Vault surveyed more than 17,000 practicing consultants worldwide to create their 2017 Top 50 Consulting firm list, and evaluated the firms across several factors, including relationships with supervisors (Evidera ranked #8), international opportunities (Evidera ranked #14) and innovation (Evidera ranked #15).

Survey respondents had some very positive feedback for Evidera:

> *"Working with smart, motivated people on some of the most challenging problems in life sciences."*
>
> *"It's an environment that emphasizes excellence while recognizing work-life balance."*
>
> *"If you want a health economic model to submit to NICE, they may be your guys."*

To view Evidera's complete profile on Vault, visit http://www.vault.com/company-profiles/health-care-and-pharmaceutical-consulting/evidera,-inc/company-overview.aspx.

Evidera Congratulates the COPD Foundation on the Inclusion of the SGRQ in the New FDA COPD Draft Guidance

Evidera would like to extend an enthusiastic congratulations to the COPD Foundation and their Chronic Obstructive Pulmonary Disease (COPD) Biomarker Qualification Consortium (CBQC). Thanks to their efforts over the past five years, the FDA's updated draft guidance for COPD drug development, "Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment," released May 19, 2016, includes information on the use of the St. George's Respiratory Questionnaire (SGRQ) as a co-primary or secondary endpoint supporting evidence of efficacy in clinical trials.

The CBQC SGRQ Working Group developed the empirical evidence needed to support the recognition and acceptance of the SGRQ as a key endpoint in drug development trials. The Group included scientists from Evidera, academic clinical research, and industry (AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Novartis, and Pfizer). Dr. Heather Gelhorn led the Evidera team, assisted by Dr. Hilary Wilson and other members of Evidera's scientific and support staff. Evidera was pleased to work with the COPD Foundation and CBQC on this important endeavor, developing and analyzing an aggregated database of 21 studies and over 35,000 patients with COPD and participating in the interpretation and dissemination of results.

Evidera Welcomes New Senior Staff

Colleen A. McHorney, PhD

is a Senior Research Leader in Evidera's Outcomes Research group and is an internationally-recognized thought leader in the fields of health outcomes assessment and medication adherence. Dr. McHorney will be leading clinical outcome assessment as well as medication adherence projects for our clients.

Dr. McHorney's 30-year career has focused on integrating the patient voice into health research and has spanned the methodology gamut, from qualitative research to advanced classical and modern psychometric techniques. A trained psychometrician and health services researcher, Dr. McHorney has conceptualized and developed numerous patient-centered quality-of-life and quality-of-care measures, both generic and disease-specific. She has published more than 80 peer-reviewed articles, 6 book chapters, has made over 115 presentations at professional conferences, and has been cited more than 11,000 times, making her one of the most highly cited health services researchers in the world.

Dr. McHorney began her career at The Health Institute, New England Medical Center, and the Harvard School of Public Health. At The Health Institute, she was the co-architect, with John E. Ware, Jr., of the early psychometric work published on the MOS SF-36 Health Survey. Dr. McHorney held tenured positions at the Indiana University School of Medicine, the University of Kentucky, and the University of Wisconsin-Madison School of Medicine; was a Senior Scientist at the Regenstrief Institute; and a Research Career Scientist in the VA Health Services Research program.

Prior to joining Evidera, Dr. McHorney was a Senior Scientist at ERT where she led the development and validation of patient-reported outcome (PRO) measures for pharmaceutical clients as well as regulatory support for PRO label claims. Dr. McHorney also led Covance's market access scientific research on patient-reported outcomes (development, validation, and regulatory support) and Merck's outcomes research on osteoporosis and scientific work on medication adherence from which she conceptualized, developed, and validated the Adherence Estimator®.

Moira Ringo, PhD, MBA

is Senior Consultant, Precision and Transformative Technology Solutions, covering value demonstration, market access, and commercial at Evidera. Dr. Ringo brings over 15 years' experience in the healthcare industry developing new products from both the scientific and commercial side. At Evidera, she assists with health technologies with significant disruptive potential such as personalized medicine, diagnostics, orphan drugs, combination products, e- technologies, cell therapy and regenerative medicine, immuno-oncology and vaccines, and e-connectivity technologies.

Dr. Ringo is experienced in enhancing value propositions for emerging healthcare technologies. Prior to Evidera, she developed patient, physician and payer strategies for a specialty pharmaceutical manufacturer applying novel drug delivery technology to neurology and orphan disease indications. She has formulated stakeholder value demonstration and business strategies for innovative pipeline biopharma products in the U.S., Europe, and emerging markets as Design to Value Lead at GlaxoSmithKline. She is an expert at understanding and addressing patient adherence from a cultural, psychological, and product design perspective. Dr. Ringo also has corporate strategy and financial valuation experience in developing of academic, commercial, and social venture partnerships for commercial and R&D innovation groups.

Prior to these roles, she managed a scientific team at GlaxoSmithKline R&D and helped develop over 10 pharmaceutical products spanning pre-clinical to post-approval. Her scientific contributions resulted in five approved drug products in the U.S., Europe, and Japan spanning neurology, oncology, and urology.

Dr. Ringo is a graduate of the Duke Fuqua School of Business, with an MBA in health sector management. She also holds a PhD from the University of Michigan in chemistry.

Dara Stein, MSc, is a Research Scientist in the Real-World Evidence group at Evidera and is based in Toronto, Canada. Ms. Stein brings almost 10 years of observational, non-interventional study experience to Evidera, including over six years in industry and two in academia, and she is a recognized industry expert in chart review study methodology and implementation. Ms. Stein offers applied experience in various therapeutic areas including oncology, hematology, neurology, cardiology, intensive care, infectious diseases, gastroenterology and acute bleeding events. Her research portfolio includes evaluations of drug utilization, safety, burden of illness, treatment patterns and resource utilization (including direct and indirect cost of healthcare), and the collection of data from several compassionate use patient populations in North America

and Europe. Ms. Stein has considerable experience working on FDA- and EMA-mandated and non-mandated chart review applications of post-authorization safety studies (PASS) in North America and Europe and is familiar with ENCePP requirements.

Prior to joining Evidera, Ms. Stein worked as a Senior Research Scientist at UBC: An Express Scripts Company and as a Research Associate in the division of clinical epidemiology at McGill University Health Centre's Research Institute.

Ms. Stein holds a BSc in human kinetics from the University of Ottawa, and an MSc in human nutrition from McGill University. The results of Ms. Stein's work have been published in peer-reviewed journals and presented at various scientific meetings.

Denise Zou, MA, is a Research Scientist with Evidera's Modeling and Simulation group in San Francisco, California. Ms. Zou has more than 10 years' experience in decision analytical modeling, cost-effectiveness analysis, budget impact analysis, burden of illness modeling, and micro-costing analysis. Her main focus is the application of rigorous statistical and modeling methods in developing global models for new drug therapies to be used for country adaptations; and, adaptations of models to the use by multiple countries in consideration of local requirements.

Before joining Evidera, Ms. Zou was a Senior Health Economist at ICON (formerly Oxford Outcomes, based in Vancouver, Canada), where she has worked on a number of economic evaluations and prepared economic dossiers for drug submissions in different countries. She has led projects in a wide range of disease areas including oncology, multiple sclerosis, rheumatoid arthritis, human immunodeficiency virus, pertussis, asthma, chronic obstructive pulmonary disease, and respiratory syncytial virus. Before joining ICON in 2006, Ms. Zou held a health economics research position at the University of Calgary, Canada. She was responsible for data collection and analysis, communication with clinical experts, and writing reports and manuscripts.

Ms. Zou holds an MA in economics from the University of Alberta.

Elizabeth Donahue, BS, is an Associate Project Director in the Real-World Evidence Data Collection Group at Evidera, based in Waltham, Massachusetts. Ms. Donahue brings over 10 years clinical research experience to her position at Evidera. Her primary therapeutic area experience includes oncology, pulmonology, women's health, central nervous system disorders and medical devices. Throughout her experience, Ms. Donahue has

had the opportunity to manage numerous late-phase/post-market observational and registry projects as well as retrospective chart reviews, expanded access studies, time and motion studies, and Phase 3 clinical trials in North America and Europe. Prior to joining Evidera, Ms. Donahue held a Senior Project Manager position at United BioSource Corporation. Ms. Donahue earned her BS in marine biology from Roger Williams University.

We're Hiring!

Due to Evidera's exceptional growth trajectory, we are interested in hearing from experienced healthcare/life science consulting candidates with expertise at all levels in the following content areas: meta research, health economics, real-world evidence, modeling, clinical outcomes assessments, project leadership, client engagement, and pricing and reimbursement. We generally prefer candidates who are able to work in one of our offices – Boston, Budapest, London, Montreal, San Francisco, or Washington, D.C. However, we will consider all qualified candidates. If you don't see an appropriate opening posted at this time, please email your resume and a cover letter of interest to careers@evidera.com.

Evidera's success begins with our people, which is why we are committed to attracting, developing, and retaining the industry's most talented scientists and life sciences professionals.

We are actively recruiting for the following positions in our US and UK offices:

- Associate Director/Principal Market Access Writer - Payer Communications
- Principal - Payer Strategy
- Japan Market Access Lead - Payer Strategy
- Senior Research Scientist - Real-World Evidence
- Research Scientist - Meta Research
- Research Scientist - Modeling & Simulation
- Research Scientist - Outcomes Research
- Senior Statistician - Modeling & Simulation

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SPOTLIGHT POSITIONS

Associate Director/ Principal Market Access Writer

We are looking for a Market Access Writer to join our growing Payer Communications team in our London office. This role will work as part of a team of writers on market access projects for global pharmaceutical clients that include value dossiers and value stories to support the case for new products; literature reviews to inform clinical trial and economic model design; analyses of the pricing, reimbursement and competitive landscapes; and, reports from payer advisory boards.

Principal – Payer Strategy

We are looking for a Principal in our Waltham, Massachusetts, office for our Payer Strategy team. This role is expected to lead delivery of client projects; provide leadership, coaching and direct supervision to Waltham-based project staff; build/nurture client relationships to meet assigned financial targets; and, lead/participate in process improvement and innovation efforts.

Japan Market Access Lead – Payer Strategy

We are looking for a Japan Market Access Lead in our Waltham, Massachusetts, or London offices. This individual will need to have Japanese language skills and knowledge of the Japanese pharmaceutical market. This role acts as a key project contributor and, increasingly over time, overall project manager in collaboration with the senior team. The Japan Market Access Lead undertakes multiple (4-5 at a time) global pricing, reimbursement, and market access consulting projects.

Senior Research Scientist – Real-World Evidence

We are looking for a Senior Research Scientist to join our Real-World Evidence (RWE) team in our London office. The Senior Research Scientist will act as the Subject Matter Expert within the Real-World Evidence division, providing senior level direction in the development and delivery of RWE proposals and client deliverables. They will contribute to thought leadership while promoting sound methodological expertise and ensuring high levels of quality. The Senior Research Scientist serves as a Principal Investigator for complex projects through expertise in the areas of health data capture and prospective observational research.

Research Scientist – Meta Research

We are looking for a Research Scientist for our Meta Research team to join our London office. A key component of this role will be to ensure that the team's thinking and approach is grounded in leading research and best scientific and consulting practice for this methodology. In addition to such team-wide interests and priorities, you will be the independent Principal Investigator/ Consultant of projects and oversee all aspects of project delivery, including delegating project-management tasks to junior staff. This role will also involve scientific responsibility for project completion, strategic consultation, and for use of best methods to address research needs. Specifically, this will include design and implementation of selected studies; conceptualization of advanced study designs; and development of study protocols.

Research Scientist - Modeling & Simulation

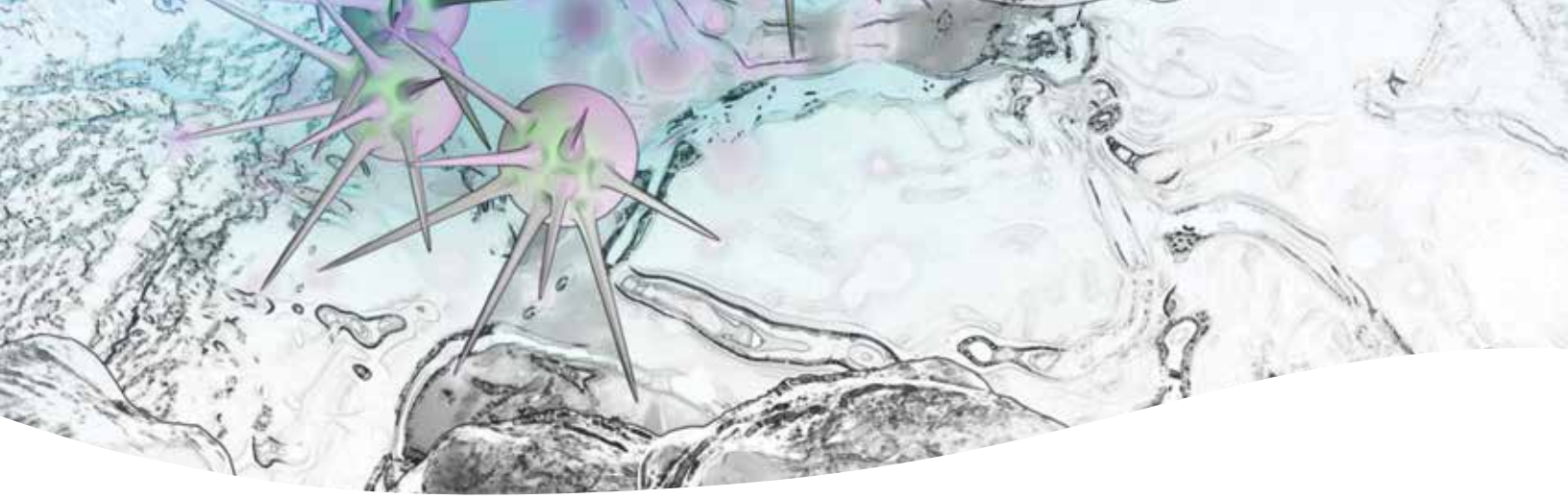
We are looking for a Research Scientist or Senior Research Scientist to join our Modeling & Simulation team in our Bethesda, Maryland, or Waltham, Massachusetts, office. This role is an independent Principal Investigator of projects responsible for overseeing all aspects of project delivery; delegates project management tasks to mid-level and junior staff. Takes scientific responsibility for project completion; responsible for strategic consultation and for use of best methods to address research needs. Oversees and participates in a large project portfolio. Innovates scientifically and produces output of high scientific quality. Assumes significant responsibilities for sales targets and client development.

Research Scientist – Outcomes Research

We are looking for a Research Scientist in our Bethesda, Maryland, office. The Research Scientist is the independent Principal Investigator of projects responsible for overseeing all aspects of project delivery and delegates project management tasks to more junior scientific staff. This role takes scientific responsibility for project completion, are able to oversee and participate in a large project portfolio, and assumes significant responsibilities for sales targets and client development. We are looking for someone who innovates scientifically and produces output of high scientific quality.

Senior Statistician

We are looking for a Senior Statistician in our Bethesda, Maryland, office to support studies in health economics, including analytic support for economic models, meta-analysis, network meta-analysis or mixed treatment comparisons, trial simulation, and exploratory analysis of data.



Evidera

CORPORATE HEADQUARTERS
7101 Wisconsin Avenue, Suite 1400
Bethesda, MD 20814

contact Susan Potter Couch
phone +1 301 654 9729
email info@evidera.com

WWW.EVIDERA.COM

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