THE ROLE OF EVIDENCE

Defining Markets, Demonstrating Value, Informing Product Lifecycles

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The increasing emphasis on evidence in international health care has profound implications for companies in the life sciences industries, informing their approach to market access and driving their strategies with regard to outcomes research, pricing, and reimbursement. Analysis Group consultants have contributed to wide-ranging discussions about evidence – from presenting on comparative effectiveness research at the annual meetings of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and other conferences, to addressing the role of evidence in pricing and reimbursement strategies in the pages of industry publications and peer-reviewed journals, including authoring articles for and editing a special issue of *PharmacoEconomics* (2010). In this issue of our ***Health Care Bulletin***, we focus on evidence from clinical, economic, and strategic perspectives.

Methods for Indirect Comparisons in Outcomes Research

by Eric Wu, Ph.D., and James Signorovitch, Ph.D.

Comparative effectiveness research (CER) has the potential to improve health outcomes while controlling costs. But a growing focus on CER has created practical challenges for pharmaceutical, biotechnology, and medical device makers aiming to demonstrate the value of their products. For example: How can growing customer expectations for comparative evidence be satisfied for new products with limited clinical trial data? And how can CER, which has traditionally focused on the average effects of health interventions across broad populations, inform care for individual patients?

CER aims to inform the choices of health care decision makers with the best possible information about potential treatments. With innovation increasing the number and diversity of effective therapies, the need for comparative evidence has never been greater. Yet the availability of reliable comparative evidence is often severely limited. (CONTINUED ON NEXT PAGE)

Indirect Comparisons (CONTINUED)

In the hierarchy of comparative evidence, head-to-head randomized trials are considered the gold standard. However, randomized trials are rarely available for all of the treatment comparisons that physicians and payers need to make decisions, especially as new treatments enter a market.

While studies comparing real-world treatment outcomes can fill this need over time, such studies, by their very nature, require long-duration real-world use and therefore are not immediately possible for new treatments. This systemic lag before CER evidence becomes available means that many of the critical post-launch decisions for a product, such as price, formulary position, and physician utilization, must be made without key information on the product's strengths and weaknesses.

An additional challenge for pharmaceutical firms has been identifying high-value patient populations for new treatments. There is growing recognition that developing blockbusters for large markets like hypertension or diabetes is becoming increasingly challenging as these markets become saturated with effective generics. Furthermore, payers often implement cost-containment measures to limit drug utilization, frequently to a smaller market than is supported by a drug's label. In this environment, identifying and supporting a possibly smaller market for a drug, but one in which its value proposition is enhanced for individual patients, becomes an attractive strategy.

Figure 1. Reweighting Patients Based on Gender Differences

Using robust statistical methodology, patients in Trial B can be reweighted to match the baseline characteristics of Trial A

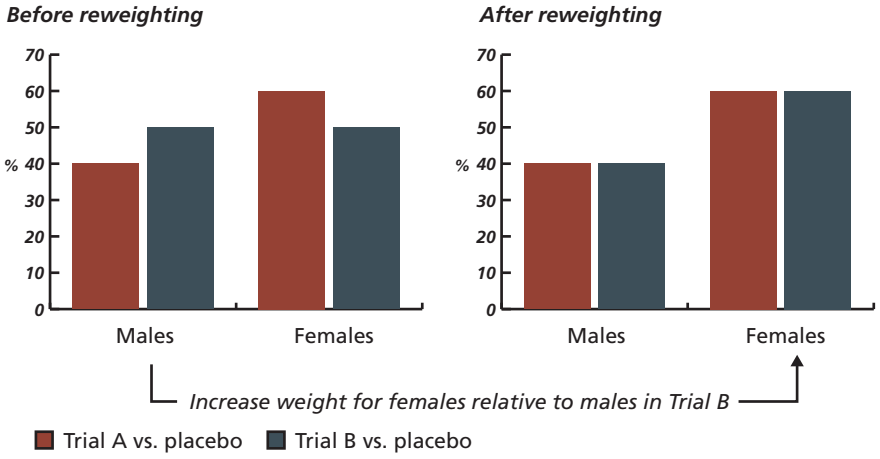
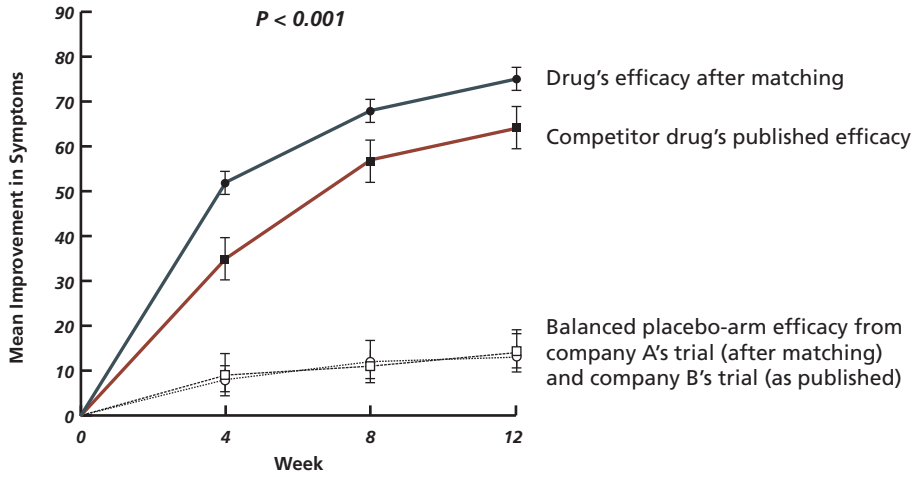


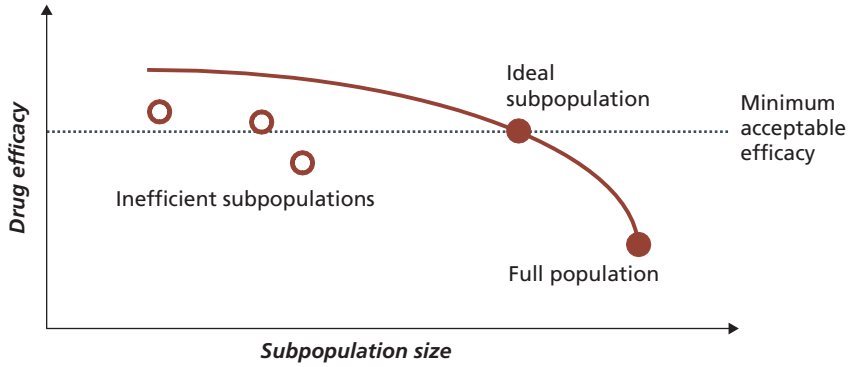
Figure 2. Comparison of Outcomes between Matched Trials



An Analysis Group team has been collaborating with the Harvard School of Public Health's Biostatistics Department to apply and develop methods for filling gaps in CER. [This work has been presented at a number of conferences and published in clinical and health economics journals, including a 2011 symposium on comparative effectiveness research methods sponsored by the Agency for Healthcare Research and Quality (AHRQ); the last three annual meetings of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR); and "Comparative Effectiveness Research without Head-to-Head Trials," *PharmacoEconomics*, Vol. 28, No. 10, 2010.]

Figure 3. The Tradeoff between Drug Efficacy and Subpopulation Size

The ideal subpopulation is the largest subpopulation with acceptable efficacy (or cost-effectiveness, or benefit-risk, etc.), and will lie on the efficiency frontier. Inefficient subpopulations limit the population size more than is needed and should be avoided.



Getting More CER Value from Existing Data

Over the past several years, comparisons of treatment outcomes across separate randomized trials have become an important tool for CER. Where there are no head-to-head trials of two treatments, these so-called indirect comparisons across separate trials may provide the only evidence for decision makers. However, an indirect comparison is only as reliable as the trials are similar. In particular, cross-trial differences in patient populations, such as greater disease severity in one trial versus another, can lead to incorrect comparisons of treatment outcomes. The differences between trial populations can limit the reliability of indirect comparisons and, therefore, their value for decision makers.

To address this limitation, we have developed a new method for matching patient populations across separate trials, in which we leverage the complete individual patient data from one trial (see Figure 1). With these complete data, we can then adjust the patient population on key dimensions (average age, disease severity, or prior treatment profile, for example) to match that of a published trial for which we have access only to summary results. After matching, the outcomes of different treatments can reliably be compared across the balanced trial populations (see Figure 2). Since publishing this methodology in 2010, we have used it to provide timely CER for new therapies in oncology, diabetes, and other treatment areas. Individual patient data from clinical trials have been a largely untapped resource for CER. With the advent of new research methodologies, we expect its use to grow in coming years.

Moving from Treating Diseases to Treating Individuals

At each stage of a therapeutic product's lifecycle, the preferred strategy is often to serve the largest possible patient population. However, in today's competitive and cost-conscious health care environment, a product's profile may not support this goal, due to limited average efficacy versus other effective therapies, or concerns about average cost-effectiveness or benefit-risk profiles. In these cases, it can be helpful to identify subpopulations of patients who receive the greatest value from a product.

To that end, working closely with Harvard biostatistician Professor Lee-Jen Wei, Analysis Group has applied new methodologies to identify the optimal treatment choice for each patient based on a large number of individual characteristics in addition to disease status. This approach has proved useful for identifying high-value subpopulations in early-phase trials that can be confirmed in later-phase trials.

Currently, when the cost-effectiveness of a drug is limited for the average patient, payers may restrict access or reimbursement to a targeted subpopulation. However, the subpopulation is usually not chosen based on a systematic evaluation of the costs and benefits. The individualized medicine approach developed by Professor Wei and Analysis Group addresses this shortcoming and has been used to identify the largest subpopulation in which a drug's efficacy and cost-effectiveness are acceptable to clinicians and payers (see Figure 3). For later-stage products, this approach has also been used to identify subpopulations that have a particularly poor benefit-risk profile with a traditional generic first-line agent, and who should have less restricted access to newer drugs as a first-line therapy. ■

Enhancing Product Value Propositions in the Pipeline

by Edward Tuttle, Anita Chawla, Ph.D., and William Leaf-Herrmann, Ph.D.

Many promising pharmaceutical products that survive the attrition inherent in scientific development and regulatory submission can expect to face another challenge – severe limitations on their commercial value due to payer concerns about cost and clinical effectiveness. Novartis, for example, opted not to market the EMA-approved drug Rasilamlo in Germany due to the authorities' assessment of its limited differentiation and consequent unwillingness to accept a premium price.

The lesson: not only are effective value propositions necessary for commercial success, but building them should be a strategic imperative during the development process. Companies and product teams need an understanding of what the market values and what evidence is necessary to support a price premium above that of the standard of care prior to late-stage development; otherwise, the evidence will not be available at launch. In addition, they need to consider up front how to structure payer contracts designed to share risk and to ensure favorable market access.

Using Value Analytics to Forecast Market Access Outcomes

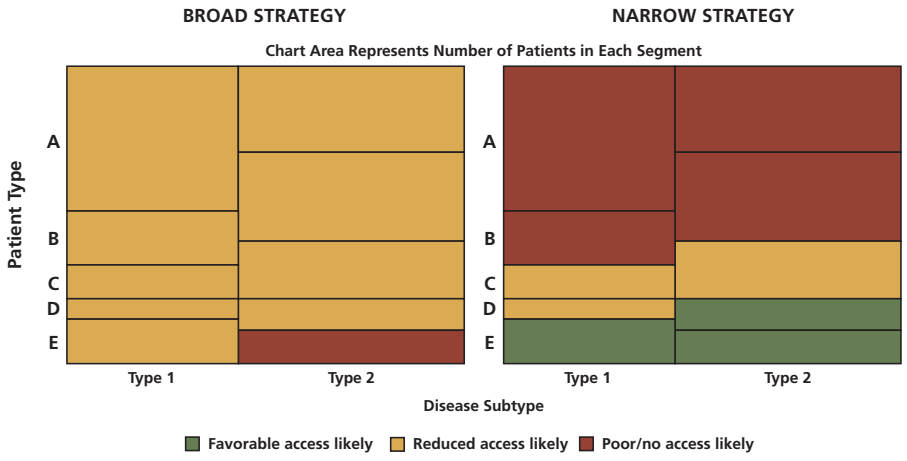
Companies can optimize product value propositions for their pipeline assets by applying multiple tools, including primary research, evidence review, and early-stage cost-effectiveness and budget impact analysis. The approach we have used incorporates the fundamental uncertainties in the product profile and the future competitive environment, paired with the key product development strategy decisions, to evaluate how well the product will perform against physician and patient expectations as well as those of the payer. We use economic modeling combined with primary and secondary research to forecast the likely market access outcome – that is, payer-imposed restrictions on utilization or cost burden on the patient – and the resulting implications for the product's market share and revenue forecast.

Recently, for example, a manufacturer's asset was entering Phase II development and appeared to have potential under two divergent clinical development strategies, one emphasizing side-effect mitigation, the other, efficacy maximization. The company had not previously drawn on a structured, data-driven method for making payer value proposition implications part of its strategy – but by developing an early-stage, scenario-based cost-effectiveness and budget impact estimation model, management was able to make early estimates of some of the key metrics that influence payer decision making.

With different potential target patient segments, varying value proposition criteria, and alternative strategies under consideration, the project team decided to develop a visual dashboard (Figure 1) combining modeled values for comparing likely value propositions given a strategy choice, patient segments, and market characteristics.

The analysis revealed that the side-effect mitigation strategy offered potential for very high differentiation and price premia, but only in a limited patient segment. The strategy emphasizing efficacy had broader market potential but greater competitive risk. In addition, a more optimistic hypothesis – that the side-effect mitigating

Figure 1. Strength of Value Proposition by Patient Segment and Disease Subtype
The narrow strategy delivers the best results but in a small population.



strategy could have broad market impact – was probably unrealistic. Bringing the value proposition into the clinical strategy dialogue earlier than before possible helped guide the development of evidence that will better align with payer requirements once the product comes to market.

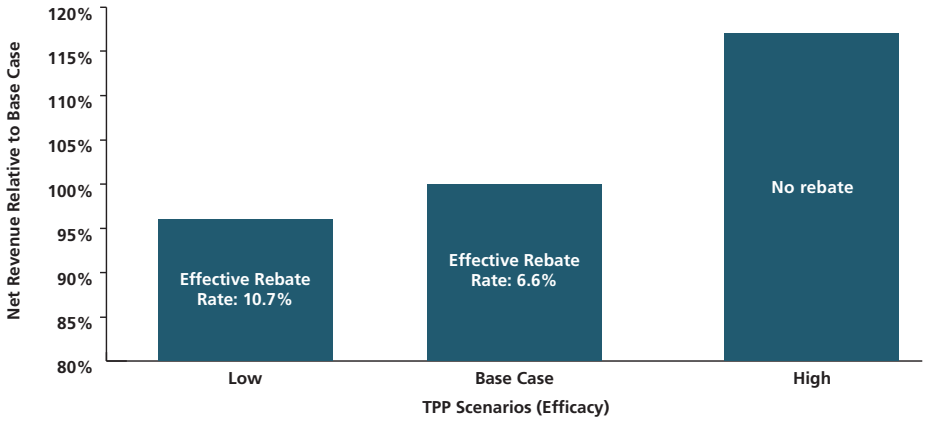
Risk Sharing in the Pipeline

Recently, Roche proposed a risk-sharing or pay-for-performance agreement for Avastin to German hospitals and insurers through which, it has been reported, Roche will refund the cost of the drug if patients experience disease progression within three to seven months after first-line treatment. While such contracts are not new – several have been proposed in the UK – the Roche proposal attracted attention because of the new German federal drug pricing law that permits this type of agreement and the potential for direct involvement of hospitals in risk-sharing arrangements.

If the Roche agreement represents a prototype for future contracts designed to ensure favorable market access, how might a manufacturer evaluate the tradeoffs associated with such an agreement, especially in very early phases of drug development when market access and pricing strategy are increasingly being considered in parallel with the clinical development plan? What is the impact of potential risk-sharing agreement(s) on the value of early-phase assets? Consider, for example, a novel oncology drug being developed for a potential metastatic breast cancer indication, where the target product profile includes expectations of 15.3 and 23.6 months for progression-free survival and overall survival, respectively. In markets where cost-effectiveness or budget impact criteria are used in coverage and reimbursement decisions, a rebate scheme may be introduced when the product is launched to achieve a cost-effectiveness ratio or budget impact consistent with conventional thresholds of acceptability as part of a global pricing and market access strategy.

Figure 2. Potential Net Revenue Impact of Risk Sharing under Varying Clinical Target Product Profile (TPP) Scenarios

Lower efficacy will require greater rebate amounts.



With an estimated survival curve based on target product profile assumptions about efficacy and pricing, the potential impact of a simple rebate scheme where the manufacturer provides a refund for the drug for patients who progress before a specified number of months can be explored. Figure 2 illustrates alternative efficacy scenarios for the hypothetical investigational drug and the resulting net revenue and effective rebate rate given a 10 percent price premium assumption and an expectation of maximum duration of therapy of 18 months.

The effective rebate rate, or the total amount refunded divided by the total revenue, varies depending on the relative efficacy of the investigational drug, which may have implications for clinical study design given a desired global pricing strategy. With the objective of a 10 percent price premium, given a cost-effectiveness threshold of acceptability, and overall market access objectives, these analyses provide quantitative information that highlights the imperative for pursuing efforts to increase the likelihood of a "best case" efficacy scenario. In addition, the analyses highlight the potential cost to the organization if this outcome is not achieved. There are significant opportunities to integrate market access strategy into product development decisions in early phases, and the case studies presented here illustrate the range of issues that may be addressed with data-driven analyses. ■

STEPHAN MCBRIDE CONTRIBUTED RESEARCH AND ANALYSIS TO THIS ARTICLE.

Health Care News and Events

Mei Sheng Duh Serves as Expert Panelist

Mei Sheng Duh, Managing Principal and chief epidemiologist, has been invited to join an expert panel to develop methodologies for studying drug-induced liver injuries on a national scale. The panel has been convened by the Observational Medical Outcomes Partnership and funded by the Foundation for the National Institutes of Health. Dr. Duh will assist in classifying drug-induced liver injury cases, conducting independent reviews of patient cases, and analyzing administrative claims and electronic health records.

China: New Focus on Data and Evidence

China's pharmaceutical market is growing more than 20% annually, compared to a 3–5% growth rate in the U.S. and 1–3% in the EU. By 2013, China is likely to become the world's third-largest pharmaceutical market. Researchers at Analysis Group have worked closely with Chinese government officials and leading academics on a number of health care studies. This research, which has utilized a range of data sources including national and regional claims data, patient survey data, clinical trial data, hospital purchase data, registry data, and emergency room data, is helping to build the health care data infrastructure in China and supporting future scientific research.

Eric Q. Wu, a managing principal of Analysis Group and adjunct professor at Nankai University who sits on the advisory boards of the Health Economic Evaluation Center of the Chinese Medical Doctor Association and China Health Economics and Policy Research Center, observes that one of the biggest challenges to continued development is the lack of reliable scientific data. Dr. Wu, who also serves on the review committee for China's formulary drug user guidelines, notes that as the focus on evidence increases, clinical experts and health economists will need scientific data to determine guidelines, policy, and formulary recommendations. "The ability to procure and apply data in studies involving comparative effectiveness, comparative safety, cost-effectiveness, and appropriate drug use is key," he says, "and will require collaboration among Chinese government agencies, pharmaceutical companies, and researchers."

VNS Study Lauded

"The Impact of Vagus Nerve Stimulation (VNS) Therapy on Healthcare Resource Use, Costs, and Adjunctive Anti-epileptic Drug Use in Medicaid Patients with Refractory Epilepsy" was judged to be in the top 5% of the scientific program at the American Academy of Neurology 2011 meeting. Coauthors include Managing Principal **Mei Sheng Duh**, Manager **Annie Guerin**, Associate **Sujata Sarda**, and Senior Analyst **Tom Samuelson**.

New Drug Importation Research

In "Commercial Importation of Prescription Drugs in the United States: Short-Run Implications" (*Journal of Health Politics, Policy and Law*, April 2011), Manager **Scott Johnson** and Managing Principal **Genia Long**, and Professors Patricia Danzon and Michael F. Furukawa, assessed the financial impact on U.S. payers/consumers and health care spending.

Overview of Generic Competition and Hatch-Waxman Published

Managing Principal **Genia Long**, Vice President **Richard Mortimer**, Manager **Noam Kirson**, and Professors **Henry Grabowski** and Margaret Kyle examined changes in pharmaceutical competition since passage of the Hatch-Waxman Act in "Evolving Brand-Name and Generic Drug Competition May Warrant a Revision of the Hatch-Waxman Act" (*Health Affairs* 2011, 30-11).

Value of New Telehealth Program Quantified

Principal **Howard Birnbaum** and Managers **Scott Johnson** and **Dendy Macaulay**, with affiliate **Laurence Baker**, found that a telehealth program cuts treatment expenses for chronically ill Medicare beneficiaries. "Integrated Telehealth and Care Management Program For Medicare Beneficiaries with Chronic Disease Linked to Savings" was published in *Health Affairs* 2011, 30(9).

See our website for recently presented research and an up-to-date list of health care publishing and events.

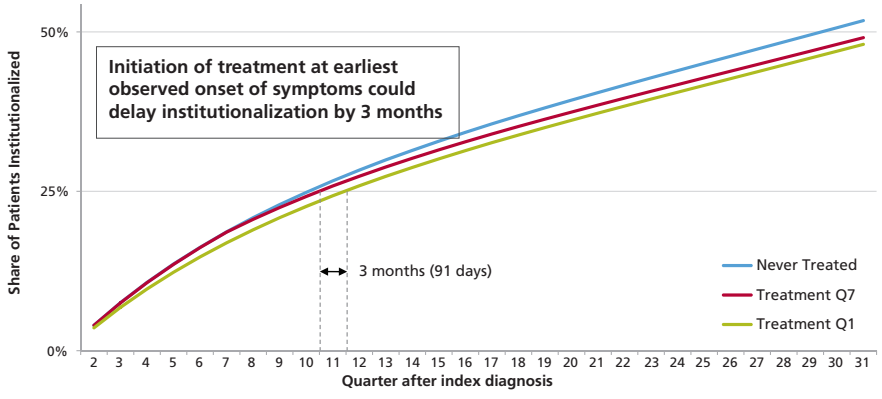
Highlights from ISPOR 2011

Analysis Group Consultants and Affiliates Present Award-Winning Research

Our consultants and affiliates delivered two workshops, a podium presentation, and 24 posters at the 16th annual meeting of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). The theme of the conference was "Health Care Reform and Comparative Effectiveness Research – Where Have We Been and Where Are We Going?" Our studies focused on quantifying the comparative costs and value of therapies used against a range of diseases including ADHD, arthritis, cystic fibrosis, depressive disorder, epilepsy, hypogonadism, kidney disease, prostate cancer, Parkinson's disease, and women's health concerns related to menstruation and menopause. "Our researchers value the opportunity to be active participants in the dialogue at ISPOR and at other prestigious venues," says Principal **Howard Birnbaum**. A complete list of the workshops, podium presentations, and posters presented at ISPOR (and at other health outcomes conferences) can be found on our website: bit.ly/hc_research.

With principal investigator Professor David Geldmacher (University of Alabama), Analysis Group Principal **Howard Birnbaum**, Managers **Noam Kirson** and **Sara Eapen**, Senior Analyst **Evan Kantor**, and Bayer HealthCare Pharmaceuticals' Vijay Joish coauthored a poster that earned a finalist award at the 14th Annual European Congress of ISPOR in Madrid (November 2011). In the "Effect of Treatment Timing on Risk of Institutionalization among Patients with Alzheimer's Disease," the authors examined some 5,600 New Jersey Medicaid patients diagnosed with Alzheimer's disease and assessed the relationship between when an Alzheimer's patient undergoes treatment and subsequent institutionalization. Using statistical models, they concluded that patients treated as soon as symptoms emerge could delay institutionalization by up to three months compared with median treatment timing.

Predicted Time to Institutionalization, by Treatment Timing



Several of Analysis Group's posters were awarded finalist ribbons:

"Comparison of Real-World Health Care Costs after the Initiation of Second-Line Duloxetine or Generic Selective Serotonin Reuptake Inhibitors in Patients with Major Depressive Disorder" (Principal Howard G. Birnbaum, Manager Jasmina Ivanova, and colleagues)

"Health Care Resource Utilization and Economic Burden of Metastatic and Recurrent Locally Advanced Head and Neck Cancer Patients" (Managing Principal Eric Q. Wu, Vice President Christian Frois, Manager Andrew Yu, Associates Hongbo Yang and Maryna Marynchenko, and colleagues)

"Does Route of Administration for Estrogen Hormone Therapy Impact Risk of Venous Thromboembolism: Estradiol Transdermal System vs. Oral Estrogen-Only Hormone Therapy" (Managing Principal Mei Sheng Duh, Vice President Patrick Lefebvre, Senior Economist François Laliberté, Economist Katherine Dea, and colleagues)

"Healthcare Resource Utilization and Costs in Females with Newly Diagnosed Heavy Menstrual Bleeding: An Employer's Perspective" (Dr. Duh, Mr. Lefebvre, Mr. Laliberté, Associate Sujata P. Sarda, and colleagues)

"Uncontrolled Epilepsy in a Medicaid Population" (Dr. Duh, Mr. Lefebvre, Senior Economists Pierre Emmanuel Paradis, Ludmila Rovba, Marie-Hélène Lafeuille, and Economists Natalia Mishagina, Hélène Parisé, and colleagues)

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