Journal of Medical Economics in review: the best of 2021

Ivo Abraham\textsuperscript{a}, Kenneth K. C. Lee\textsuperscript{b} and Mike Gregg\textsuperscript{c}

\textsuperscript{a}Professor of Pharmacy, Medicine, and Clinical Translational Sciences, University of Arizona, Tucson, AZ; \textsuperscript{b}Professor of Pharmacy, School of Pharmacy, Monash University, Subang Jaya, Malaysia; \textsuperscript{c}Executive Editor, Journal of Medical Economics, Taylor & Francis, London, UK

The (western) New Year is a popular time to do “best of the year” reviews. The Editors of Journal of Medical Economics (JME) have succumbed to that temptation as well – knowing full well the risk of subjectivity and the flood of protest Letters to the Editor that may be unleashed (that is, letters to us about us). We tried to embed a quantitative component but admit that what follows is not a probabilistic model and even fails the essentials of a deterministic model. At least we refrained from using self-serving inputs, contorted outputs, graphs with manipulated axes, and a two-line conclusion that the analyses confirmed what we wanted to show anyway.

Much more positively (and seriously), though, is the evolution in methodological and analytical quality, clinical relevance and validity, and innovation of the papers submitted to JME. This evolution is in parallel to the journal’s continued commitment to standard economic evaluations that drive the adoption of both novel and established treatments and, more generally, patient care.

We have ranked the top five papers for 2021 and have tried to be somewhat quantitative in doing this by considering the citations of the articles. The selected papers do a fantastic job of tackling the economics of some significant challenges in healthcare. In addition to these, Professor Ken Lee (Editor in Chief) and Professor Ivo Abraham (Deputy Editor in Chief) each identified three remarkable papers published in 2021.

Also presented in this review is a recap of the Special Issue that was published in December 2021.

Top five most cited articles in 2021

Click the article titles to view them in full.

1. Health outcomes and economic burden of hospitalized COVID-19 patients in the United States

Perhaps unsurprisingly so, the most read papers in 2021 pertained to COVID-19. However, what a surprise this paper is: it lays a quantitatively solid foundation to support future health economic evaluations related to severe and critical COVID-19 disease. Using the Premier Healthcare Database, which covers approximately 20% of US hospital admissions, the authors identified 173,942 COVID-19 patients hospitalized between 1 April and 31 October 2020, the 7-month period of the first, second, and third surges. The paper provides a plethora of demographic and clinical data on these patients, stratifying them also by whether they were admitted to the intensive care unit (ICU) and/or required invasive mechanical ventilation (IMV): ICU with IMV; without ICU with IMV; with ICU without IMV; without ICU or IMV. Perhaps most helpful to future economic evaluations were overall and stratified estimates of hospital length of stay, in-hospital mortality, hospital charges, and hospital costs. This paper should become the standard reference for healthcare utilization and cost inputs in economic studies of severe and critical COVID-19 disease.

2. Benefits of fracture liaison services (FLS) in four Latin American countries: Brazil, Mexico, Colombia, and Argentina

Fracture liaison services (FLS) refer to a multidisciplinary approach to reduce the risk of subsequent osteoporotic fractures in patients who suffered such fracture. Fractures are associated with increased rates of hospitalizations and admission to long-term care facilities, impaired quality-of-life, and a significant economic burden. A prior meta-analysis demonstrated the efficacy of FLS in preventing subsequent fractures. With FLS remaining an underutilized treatment model in Latin America, this paper by Aziziyeh and colleagues estimated the number of fractures averted, bed days avoided, and costs saved if FLS were implemented in the four largest Latin American countries (aggregate population approximately 435 million; similar to the EU but well above the US). The model predicted that universal adoption of FLS would prevent 31,400 fractures, avoid 292,281 bed days, and yield cost savings of 58.4 million USD. In addition to the numbers being important, this
study concerns middle income countries that spend between 5.4% and 9.7% of GDP on healthcare (compared to 16.9% for the US; 2018 data) and are relatively “young” (age 65 and above between 8% and 11% versus 17% for the US; 2020 data). This paper sensitizes the Latin-American region to the problem of recurrent osteoporotic fractures and, importantly, offers the region an effective and cost-saving approach to decrease recurrence and the associated healthcare resource utilization.

3. **A budget impact analysis of gilteritinib for the treatment of relapsed or refractory FLT3mut+ acute myeloid leukemia in a US health plan**

Despite significant progress in the treatment of acute myeloid leukemia (AML), a cluster of hematological malignancies caused by genetic mutations, most patients will relapse or become refractory (R/R). Prognosis is particularly poor for the 30% of AML patients with one or more FMS-like tyrosine kinase 3 gene mutations. Gilteritinib, a novel oral inhibitor of FLT3, is the only therapy indicated specifically for R/R FLT3mut+ AML. The Pandya et al. paper reports on a manufacturer-sponsored budget impact analysis of adding gilteritinib to the extant treatment mix of 11 treatment regimens for R/R FLT3mut+ AML in a hypothetical health plan of 1 million members (20.9 incident cases annually). With a drug cost of $22,050/cycle and requiring five cycles, total costs for gilteritinib therapy came in well above the costs of the treatment alternatives. The per-member-per-month (PMPM) costs ranged from 0.055 to 0.091 over the 3-year period, which the authors contend is at the lower end of (PMPM) costs in oncology in general. Interesting in this study was that incremental treatment costs were offset by savings in blood and platelet transfusion, post-progression, and monitoring costs.

4. **Budget impact of capmatinib for adults with metastatic non-small cell lung cancer harboring a MET exon 14 skipping mutation in the United States**

A major consequence of the advances in our understanding of the “omics” in oncology and hematology is that general cancer categories are being substratified into what, in the end, makes many of them a rare disease with a highly specific treatment option. In turn, this presents challenges for economic evaluation in that treatment development and manufacturing costs may be high relative to the incident population. This translates into a high price and the belief that expensive treatments may not be affordable for small indications. In a manufacturer-sponsored analysis, Cai et al. evaluated the budget impact of oral kinase inhibitor capmatinib ($17,950 per 28-day supply) as a treatment option for metastatic NSCLC with a MET exon 14 skipping mutation in hypothetical 1-million-member commercial (eight cases over 3 years) and Medicare (117 cases over 3 years) plans. PMPM estimates were between $0.0008 to $0.0056 for the commercial plan and $0.0118 to $0.0821 for the Medicare plan. This study is also interesting in that it shows that budget impact is not only a matter of costs being added on. The incremental drug costs were partially offset by savings related to adverse events and lower progression-related and terminal care costs. Novel interventions may indeed impact budgets in different ways in terms of effectiveness (better clinical benefits decreasing disease costs) and safety (better safety benefits decreasing disease costs).

5. **Cost-effectiveness of valbenazine compared with deutetrabenazine for the treatment of tardive dyskinesia**

Treatment innovations in schizophrenia and affective disorders have been scant over the past few decades. The majority of patients with these conditions are being treated with dopamine receptor-blocking agents (DRBA). Long-term use of DRBAs is associated with tardive dyskinesia, a persistent movement disorder characterized by repetitive movements of the face, trunk, and/or extremities (and long referred to as “Parkinsonism”). Supportive care studies with various agents have failed to show a clear benefit in terms of involuntary movement control, with the exception of the vesicular monoamine transporter 2 (VMAT2) inhibitors valbenazine and deutetrabenazine approved in 2017. Ganz and colleagues conducted a cost-effectiveness analysis sponsored by the manufacturer of valbenazine comparing both agents. Using an indirect treatment comparison as the base, the authors conducted separate cost-utility analyses based on scores on the Abnormal Involuntary Movement Scale (AIMS) and scores on the Clinical Global Impression of Change (CGIC). The incremental cost-utility ratio (ICUR) based on AIMS was $9,951 per QALY gained. Using the CGIC, valbenazine dominated deutetrabenazine as valbenazine patients accumulated more QALYs, however, at lower lifetime costs. The encouraging news from this study is that the limited progress in treatments for schizophrenia and affective disorders is offset by the cost-effective clinical progress in pharmacotherapy to counter tardive dyskinesia and that these supportive care options are relatively affordable.

**Top three papers in 2021: Editor-in-Chief’s choice**

Embarking on the task of selecting my top three choices of articles published in 2021 represents one of the most challenging duties in my 15-plus years as Editor-in-Chief of the journal. Identifying these three articles out of hundreds of world class publications was profoundly difficult. I must point out that the selection of these three articles in no way reflects that other articles are less superior. It is purely based on their potential impact on the overall healthcare system. It should also be emphasized that the order of these three does not suggest that there is any difference in their quality.

I hope my choices of articles will increase your research and reading interests.

**Click the article titles to view them in full.**

1. **The Global South political economy of health financing and spending landscape – history and presence**

Healthcare financing is persistently a global issue. In this article, the authors have delineated the history of
development of the Global South nations and pointed out that in order to develop relevant healthcare policy, understanding of the past remains essential for the development of successful health strategies for the present and future. While these nations represent one of the largest economies in the world, a number of factors, including political stability, capacity building in evaluation of health technologies, and traditional approach in financing healthcare will decide the pace of their developing into modern health systems.

2. **A pragmatic methodology for the evaluation of digital care management in the context of multimorbidity**

Digital health has been increasingly used in patients with non-communicable diseases due to multimorbidity. This article describes a novel and pragmatic methodology for the evaluation of digital care management that is generalizable to any longitudinal intervention for multimorbidity, irrespective of its mode of delivery. This methodology implements propensity matching with bootstrapping to address some of the major challenges in evaluation. It was applied at a US payor setting and demonstrated favorable outcomes in emergency room utilization, inpatient admissions, and utilization of preventive medicine services. The findings of this study allow national health systems, payors, and risk bearing providers who are responsible for managing multimorbidity to do so in an effective and efficient manner.

3. **Evaluation of COVID-19 vaccine breakthrough infections among immunocompromised patients fully vaccinated with BNT162b2**

While there is still doubt on the actual benefits of receiving the booster dose of COVID-19 vaccine, this article provides real-world evidence of COVID-19 vaccine breakthrough infections among immunocompromised (IC) individuals. In total, 1,277,747 individuals vaccinated with BNT162b2 were selected from a US database (10 December 2020 to 8 July 2021). The most prevalent IC conditions were solid malignancy, kidney disease, and rheumatologic/inflammatory conditions. IC conditions were identified through diagnosis codes and immunosuppressive medication usage. The proportion with breakthrough infections was 3-times higher in the IC cohort compared to the non-IC cohort. The findings from this large study support the FDA authorization and CDC recommendations to offer a 3rd vaccine dose to increase protection among IC individuals. The result of this study also advances the understanding of post-vaccination outcomes in a real-world setting and may help healthcare providers in the decision-making process when vaccinating and treating patients at high-risk for COVID-19.

**Top three papers in 2021: Deputy Editor-in-Chief’s choices**

To manage this incredibly difficult task, I decided to pick a top article for three key areas of JME content: economic evaluation, methodological innovation (or methodologically innovative papers), and perspective and synthesis in support of economic evaluations.

**Click the article titles to view them in full.**

**Economic evaluation**

1. **Economic value of vaccines to address the COVID-19 pandemic: a US cost-effectiveness and budget impact analysis**

The start of 2021 coincided with vaccination programs ramping up following the December 2020 emergency use authorization of the first COVID-19 vaccine. While at times it has felt that the anti-vaxxers were getting more airtime than the scientists and the policymakers, the individual and public health benefits of the COVID-19 vaccines are beyond doubt. Whether, and under what conditions, they are cost-effective and affordable, was evaluated in a study by Padula et al. that compared vaccination to “do nothing”. This study faced many of the challenges inherent to economic evaluations of vaccines, in particular the dynamics, at the population level and captured in a Markov model, of susceptibility, exposure, infection (asymptomatic vs. degrees of symptomatic), and recovery or death. Unsurprisingly, vaccination was found to be cost-effective: per-subject savings of $16 coupled with 0.02 QALY differential dominated the “do nothing” alternative. On the affordability end, for a population of 330 million, the cost to the healthcare sector associated with vaccination was estimated to be about $13 billion. In contrast, the “do nothing” cost totaled $34 billion, mainly due to 6.3 million hospital days and over 283,000 deaths. The per-person impact of “do nothing” was calculated to be $102/person compared to $40/person with vaccination. In addition, the labor sector was projected to incur an additional $32 billion in productivity losses. Likely, these numbers will change, yet this paper provides the field with a model to replicate and an initial order of magnitude of cost-effectiveness and affordability.

**Methodological innovation**

2. **A comparison of mixture cure fraction models to traditional parametric survival models in estimation of cost-effectiveness of nivolumab for relapsed small cell lung cancer**

In this report on a cost-effectiveness analysis of nivolumab in relapsed small cell lung cancer, Roth and colleagues compared mixture cure modeling (MCM) with parametric modeling of long-term survival. MCM is indicated in situations where a fraction of patients show a durable response, as for instance shown in a flattening survival curve that eventually shows a plateau. As the authors point out, “failure to account for such heterogeneity in survival outcomes could result in biased estimates of expected survival over a lifetime horizon, as well as undervaluing the effect” of a treatment in terms of such metrics as the cost per (quality-adjusted) life year.
[(QA)LY]. Applying this to the case of nivolumab vs. usual care (CheckMate 032 trial), the authors found that mixture cure fraction models and parametric models, both with exponential fit, yielded, respectively, 0.43 vs. 0.38 more life years and 0.34 vs. 0.30 more QALYs at incremental costs of $69,308 vs. $61,336. This resulted in mean costs of $161,263 per LY gained and $204,386 per QALY gained. Despite some acknowledged limitations – in particular the small 12.9% nivolumab cure fraction – this study supports that MCM is an appropriate approach to estimate survival outcomes in situations where a cure fraction can be identified.

**Perspective and synthesis**

3. **Setting and maintaining standards for patient-reported outcome measures: can we rely on the COSMIN checklists?**

In an incisive and controversial review, McKenna and Heaney challenge the checklists and tools of the COSMIN group. They argue that guidelines like COSMIN are not helpful if so many of the patient-reported outcomes measures (PROMs) in the literature are of poor quality and that, consequently, reviews of PROMs end up being reviews of poor health outcome measures. They point out that the COSMIN checklist is based mainly on opinion rather than evidence; and this with an implicit focus on health-related quality-of-life PROMs at the expense of PROMs for other outcomes. The authors then identify several important issues that should be included in systematic reviews of PROMs – and therefore should be stated in guidelines like COSMIN: the construct theory (conceptual model) supporting a PROM; the measurement theory applied during instrument development; whether a scale is unidimensional with each item measuring an aspect of a given construct, multidimensional, or uses composite scores; and the limitations of Classical Test Theory (CTT) and the benefits of Item Response Theory (IRT) and Rasch Measurement Theory (RMT). McKenna and Heaney also cite several COSMIN-based reviews that yielded contradictory results and therefore question the reliability and validity of the COSMIN checklists. They also doubt that many authors of systematic reviews of PROMs have the necessary expertise in instrument development and clinimetrics to assure quality reviews.

In a Letter to the Editor (Reply to the concerns raised by McKenna and Heaney about COSMIN), Mokkink and colleagues, developers of the COSMIN methodology, challenge McKenna and Heaney’s paper. They provide some technical details related to construct theory, the use of conceptual models, the issue of unidimensionality vs. multidimensionality of scales, and the evidence base for the COSMIN methodology and checklists. With regards to IRT and RMT, they point out that these are mainly methods for developing PROMs, while also asserting that these methods and CTT complement each other in the evaluation of instruments.

In reply (COSMIN reviews: the need to consider measurement theory, modern measurement and a prospective rather than retrospective approach to evaluating patient-based measures), McKenna and Heaney offer rebuttals to the technical issues raised. They also re-assert that, given the poor quality of many PROMs, systematic reviews of such PROMs will be inherently flawed, while also pointing out that many such PROMs tend to be rated as good by the reviewers. They re-emphasize the importance of unidimensionality and interval level measurement, and the need to build on measurement theory and apply modern measurement techniques in the development of PROMs. McKenna and Heaney conclude that, with most PROMs outdated and invalid, retrospective reviews are not the best way forward and that efforts should be re-channeled prospectively to the development of high-quality outcome measures.

This debate seems to hinge on two different premises. The COSMIN group emphasizes the need for guidelines and supporting materials for conducting and reporting systematic reviews of PROMs, with some consideration of minimum quality requirements. On the other hand, McKenna and Heaney seem concerned about the presumed poor quality of the PROMs, question the usefulness of systematic reviews of poor PROMs, and advocate the development of PROMs that are grounded in contemporary rather than classical methods of instrument development. Stated differently, McKenna and Heaney imply that the field should stop considering (and reviewing) extant PROMs, as such a retrospective approach is not warranted due to the low quality of the current corpus of PROMs.

**Journal of Medical Economics special issue**

Finally the Journal of Medical Economics was delighted to release a special issue for 2021 titled Therapeutic Innovations: The Future of HEOR, which complemented the theme of Virtual ISPOR Europe 2021: Emerging Frontiers and Opportunities: Special Populations and Technologies. The issue provided an important insight into the hot topics of contemporary health economics and outcomes research with articles from a variety of key authors in the field. Click the titles below for full access to the articles.

- Asia-Pacific innovation in pharmaceutical and medical device industry – beyond tomorrow
- Comparing jurisdiction-specific pharma-economic evaluations using medical purchasing power parities
- Economic evaluation of polatuzumab-bendamustine-rituximab vs. tafasitamab-lenalidomide in transplant-ineligible R/R DLBCL
- Economic evaluation using dynamic transition modeling of ebola virus vaccination in lower-and-middle-income countries
- Economic evaluations of exome and genome sequencing in pediatric genetics: considerations towards a consensus strategy
- Epidemiology, healthcare resource utilization and healthcare costs for spinal muscular atrophy in Alberta, Canada
The Global South political economy of health financing and spending landscape – history and presence

Therapeutic innovations: the future of health economics and outcomes research – increasing role of the Asia-Pacific

Trilaciclib and the economic value of multilineage myelo-protection from chemotherapy-induced myelosuppression among patients with extensive-stage small cell lung cancer treated with first-line chemotherapy

The authors have created plain language summaries and video interviews for their articles to enhance the reader’s experience. These are available to view on the Special Issue’s landing page.

Conclusion

We hope you enjoy reading the articles that we have collated for this recap of 2021 and find them as interesting as we did. 2022 promises to be another year of growth for the journal having co-published the 2022 CHEERS statement on 11th January and already benefiting from a healthy editorial pipeline.

As editors, we are always keen to receive more high-quality articles for the journal, and we welcome papers in the following areas: articles on how much a disease or treatment costs, whether a treatment is worth its cost (or savings), and whether a treatment is affordable. Just as much, we hope for growth in the areas of methodological innovation, synthesis, and perspective.

As our understandings of health and disease have evolved and our treatments have advanced from general to increasingly targeted, JME would like to lead the field in the dissemination of new, adapted, or revised methods and analytics.

The journal is broad in the types of articles it considers in terms of knowledge synthesis; we refer in the first instance to narrative or systematic reviews as well as meta-analyses. These syntheses may be about economic evaluations of treatments. They may also focus on clinical treatments and provide estimates of efficacy/effectiveness and safety across a number of clinical studies that can subsequently be used as inputs in economic evaluations. In addition, we consider perspective papers as speculative, forward-looking, even visionary – balancing opinion, expertise, and evidence. These papers are also an opportunity to present reasoned criticism or address controversy.

A final comment concerns the journal’s global responsibility. As editors, we would like to disseminate more economic evaluations from low- and middle-income countries. We are also looking for ways that the findings of jurisdiction-specific studies can be extrapolated to jurisdictions that are comparable in how healthcare is organized, delivered, and financed.

In closing, as the journal enters its 25th year volume, we encourage our readers to contact us with ideas or questions.

Transparency

Declaration of funding

No funding was received to produce this article

Declaration of financial/other relationships

KKCL is the Editor in Chief of Journal of Medical Economics. IA is the Deputy Editor in Chief of Journal of Medical Economics. MG is the Executive Editor of Journal of Medical Economics. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgements

None stated