A RESPONSE TO: “COST-EFFECTIVENESS OF ORAL SEMAGLUTIDE ADDED TO CURRENT ANTIHYPERGLYCEMIC TREATMENT FOR TYPE 2 DIABETES”

We read with interest the JMCP April 2021 article by Guzauskas et al, “Cost-effectiveness of oral semaglutide added to current antihyperglycemic treatment for type 2 diabetes.”¹ We commend the decision-analytic modeling in this study, but we have 2 major concerns that may undercut its findings. First, when applying standard practices for economic evaluations, the results from Guzauskas et al are clear—oral semaglutide is not cost-effective at current US prices. Second, a much greater reduction in the price of oral semaglutide than reported is required for it to be cost-effective vs empagliflozin.

Current reference case recommendations from the Institute for Clinical and Economic Review (which provided funding for the study) include presenting the incremental cost-effectiveness ratio (ICER) for an intervention relative to its comparators.² Because the “intervention” being studied was oral semaglutide, the results are presented as a series of pairwise comparisons to oral semaglutide, the most expensive treatment option considered (>\$6,000 per year).¹ Decision makers seeking to provide efficient health care may ask, “Why compare everything to the most expensive option?”

When comparing multiple mutually exclusive treatment options, health gains with less costly treatments must be considered to determine the cost-effectiveness of more costly treatments. ICERs are calculated relative to the next least costly option,³ and decision makers must decide if they are willing to pay for additional health gains. In the United States, the willingness-to-pay threshold is likely

around \$100,000 per quality-adjusted life-year (QALY) gained.⁴ Applying this approach to Guzauskas et al, the ICERs are as follows: sitagliptin vs background therapy approximately \$38,000 per QALY gained, empagliflozin vs sitagliptin approximately \$40,000 per QALY gained, and oral semaglutide vs empagliflozin approximately \$458,000 per QALY gained. Empagliflozin is thus the preferred treatment, since it gains the most QALYs with an acceptable ICER. This result is borne out in the probabilistic analysis. In [Supplementary Figure 4](#),¹ empagliflozin was the preferred treatment 79% of the time compared with 1% for oral semaglutide when willingness to pay was \$100,000 per QALY gained. This figure, however, is neither referenced in the manuscript nor listed in the supplementary table of contents.

Guzauskas et al also estimated that if oral semaglutide was priced at \$5,562 per year, an approximate \$550 reduction, it would be cost-effective vs empagliflozin at a willingness to pay of \$100,000 per QALY gained (Table 3).¹ We believe this price to be inconceivably high. Given the 0.08 QALY gain with oral semaglutide vs empagliflozin, the total incremental cost would need to be approximately \$8,000 to produce an ICER of \$100,000 per QALY gained. Nonmedication costs comprised approximately \$4,000 of the total incremental costs for oral semaglutide vs empagliflozin ([Supplementary Table 4](#)),¹ meaning that incremental medication costs must be less than \$4,000 over a lifetime. Incremental medication costs were more than \$31,000 when oral semaglutide was priced at \$6,103 per year. Furthermore, in one-way sensitivity analysis, total incremental costs were more than \$26,000 when oral semaglutide was priced at approximately \$4,900 per

year ([Supplementary Figure 1](#)).¹ A more realistic annual price for oral semaglutide to be cost-effective is likely approximately \$2,500.

As US health care costs continue to rise, health plans should prioritize efficient health care. The results of economic analyses should clearly state which treatment is the most cost-effective—that is, empagliflozin in Guzauskas et al.

Ciaran N Kohli-Lynch, PhD
Northwestern University
Center for Health Services
& Outcomes Research
Chicago, IL
ciar.n.kohli-lynch@northwestern.edu

Natalia Ruiz-Negrón, PharmD
University of Utah
Department of Pharmacotherapy
L. S. Skaggs Pharmacy Institute
Salt Lake City, UT

Amy Beal, PharmD
SelectHealth
Murray, UT

Brandon K Bellows, PharmD, MS
Columbia University
Department of Medicine
New York, NY

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THE AUTHORS RESPOND

We thank Kohli-Lynch et al for their letter (published in the *JMCP* August 2021 issue) and their interest in our study,¹ which estimated the incremental value of the novel oral semaglutide added to existing antihyperglycemic treatment for people with type 2 diabetes mellitus at increased risk for cardiovascular disease.

Our results demonstrated incremental benefits in major adverse cardiovascular events (MACE) avoided, along with greater quality-adjusted life-years (QALYs) compared with background antihyperglycemic treatment alone. Oral semaglutide use plus background treatment resulted in better outcomes than background treatment alone or sitagliptin plus background treatment, and similar outcomes to liraglutide plus background treatment or empagliflozin plus background treatment with overlapping 95% confidence ranges for QALYs. Oral semaglutide was estimated to be cost-effective compared with liraglutide plus background treatment and to have incremental cost-effectiveness ratios (ICERs) between \$100,000 and \$150,000 per QALY vs sitagliptin plus background treatment and background therapy alone, but was unlikely to meet these thresholds compared with empagliflozin plus background treatment.

We agree with Kohli-Lynch et al that extended dominance is an appropriate approach when evaluating the

full landscape of treatment options to identify the most cost-effective option within a class of drugs and/or for a particular indication. We also agree that empagliflozin would be the preferred add-on treatment in this analysis, since it gains comparable (though lower on average) QALYs with oral semaglutide at a lower (~\$35,500) lifetime cost.

However, this was not the aim of our analysis. We used pairwise comparisons of oral semaglutide vs each chosen comparator instead of calculating ICERs relative to the next least costly option because our overall goal was to separately evaluate the novel agent, oral semaglutide, compared with the 4 existing comparators. We did not perform an overall cross-class evaluation so as to determine the ordering of treatment value; rather, we sought to inform decision makers as they consider the place of oral semaglutide in the current treatment landscape.

Regarding the threshold cost, we thank Kohli-Lynch et al for bringing this to our attention. The calculated oral semaglutide price needed to reach a \$100,000 willingness-to-pay per QALY threshold was due to (a) the fact that empagliflozin had lower QALYs compared with oral semaglutide in 73% of simulations and (b) the micro-simulation modeling approach used to calculate each price threshold. Each threshold value was back-calculated from individual runs (15,000 total) of individual patient-level simulations per comparison. In the case of oral semaglutide vs empagliflozin, the 95% credible range for incremental QALYs spans zero, with 27% of the simulations having lower QALYs for oral semaglutide, whereas oral semaglutide had fully positive incremental QALY credible ranges vs the other comparators. Therefore, cost-effectiveness plane quadrant crossing unfortunately makes a threshold price

difficult to simply calculate from the overall costs and outcomes of the 2 treatments.

Gregory F Guzauskas MSPH, PhD
The Comparative Health Outcomes,
Policy, and Economics (CHOICE)
Institute
Department of Pharmacy,
University of Washington, Seattle

Ryan N Hansen, PharmD, PhD
The Comparative Health Outcomes,
Policy, and Economics (CHOICE)
Institute
Department of Pharmacy,
University of Washington, Seattle
rhansen@uw.edu

REFERENCE

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