

## ***Public Comment on ICER's Draft Evidence Report on Treatments for Obesity Management***

I thank ICER for this opportunity to submit a public comment on their draft evidence report on treatments for obesity management. As both a patient and a patient advocate, I believe it is vital that the patient voice is included in every step of the process of therapeutic development, including pos-market evaluations of efficacy and cost effectiveness.

I was a typically chubby child who lost the chubbiness when I hit a growth spurt in my teens, and remained at a relatively stable weight throughout middle and high school and college. At age 18, I was diagnosed with Polycystic Ovarian Syndrome (PCOS) when a cyst ruptured and made me severely ill enough that I was hospitalized briefly.

PCOS is an endocrine disorder impacting both the reproductive and metabolic systems. Throughout my twenties and thirties, my weight rose until I was significantly overweight and then obese. I finally found an endocrinologist who understood how to properly test for and diagnose the disease and its impact, and I showed signs of insulin resistance. I was successfully treated for the hormone imbalance associated with the reproductive issues, and have remained stable since then. I was also put on metformin to prevent me from becoming diabetic, and it worked. At age 49, I am still not diabetic. I am, however, still obese.

I have struggled for decades with my weight. I have tried several different dietary regimens, with little success. I tried phentermine, which gave me a headache constantly but did not result in any weight loss. In 2019, I had gall bladder removal surgery, and after surgery had an incident in which my blood sugar spiked. The next morning, my surgeon, who is smart *and* kind, came into my room and explained to me and my parents that my PCOS and insulin resistance would always cause my body to want to hold onto weight, and to crave the kinds of foods that I should not be eating. This was the first time anyone had explained to me in such plain terms the very simple fact that *my body was constantly at war with itself over weight*.

After he spoke to me, the surgeon sent in a dietitian to consult with me. I would like to note at this point that I had previously tried to get nutritional counseling services for weight loss, and

was told by my health insurance that I would need to be diabetic first in order for them to cover it, despite the fact that I was trying to prevent diabetes in the first place.

I spent 13 months following my surgery following a restrictive, 1,300 calorie-a-day diet where I ate the exact same thing every single day, and took up Pilates five days a week. I lost 40 pounds in 13 months, on a regimen that would cause ordinary people to lose 60-70 pounds in the same timeframe.

When the pandemic hit, as with so many others, my diet derailed and I ballooned up to my highest weight ever. My blood sugar and A1C crept up, my blood pressure crept up, and my knee was hurting. I recognized these as signals my body was sending that something had to give. By then, Wegovy had been approved six months prior and Ozempic had been on the market for several years, meaning there were several years of safety data on semaglutide. Because of this, I was comfortable asking my doctor to prescribe semaglutide, and he was happy to do so.

Health insurance will not cover weight loss programs and will not consider authorizing them unless someone has a serious comorbid disease already, such as diabetes. Naturally, Wegovy was not covered for me, but because I was already on metformin for insulin resistance and my numbers were changing, they are willing to cover Ozempic.

To put it simply, this drug has changed my life. My A1C is now 4.7 and my blood sugar is back at normal levels. My blood pressure hovers around 110/70, which is where it was for most of my life until the last couple of years. More importantly, I have been able to lose 36 pounds in less than 7 months. I no longer have insatiable cravings. I no longer feel hungry or not full. I eat normal amounts and can make healthy choices without feeling deprived.

**To put it simply, I now experience hunger and satiety in a way that I can only assume people with normal metabolism do.**

I am 49 years old and approaching the age where serious comorbidities associated with obesity begin to manifest. I no longer worry about bringing about my own demise with a fork and knife

because of misfiring hunger cues. I no longer worry about being an extraordinary burden on my family by making them care for a morbidly obese person as I get older and more infirm. My clothing is less expensive to purchase because I can buy in normal sizes again – *and I am not even at my goal weight yet*. And you'd better believe I have no intention of stopping.

I don't think you can put a price tag on this kind of help, but if we're really going to try, please take the following into consideration: right now, everyone is banking on the fact that people like me get sicker later in life, and the cost will be on Medicare. But the joke's on everyone making that assumption because America is getting heavier, younger, and those comorbidities that manifest in the fifties and sixties are now showing up in people in their teens and twenties. The cost of not bringing forward every available tool to fight obesity, is too great a cost to comprehend, for both the individual and for society.

Thank you.



As always, the Black Women's Health Imperative (BWHI) appreciates ICER's proactive inclusion of our organization in reviews that, like the pending obesity management review, focus on disease states that have a substantial and/or disproportionate impact on Black women and girls. We were pleased with the robust dialogue between BWHI and ICER's review team and submit the comments below to further contribute to ICER's analysis as it drafts and finalizes its Evidence Report.

BWHI was founded in 1989 and remains the only national organization dedicated to improving the health and wellness of this nation's 21 million Black women and girls. As a national thought leader for Black women's health, the Black Women's Health Imperative (BWHI) is committed to highlighting important issues, raising awareness about their impact on Black women, offering resources Black women can benefit from, and recommending policies that we believe can make a difference.

Systemic racism has impacted Black, Latinx, and other people of color with respect to (a) reliable access to health care, (b) income potential, and food and housing security; (c) inclusion within clinical trials; (d) prevalence of treatable, but inadequately addressed conditions such as obesity; and (e) poor health outcomes.

This review is a high priority for BWHI as the obesity epidemic is disproportionately decreasing life expectancy and quality of life for the nearly 60 percent of Black women with obesity. Black women, unlike their white and Latina counterparts, have high prevalence of obesity regardless of educational attainment or socioeconomic status. The ever-increasing rates of overweight and obesity in Black women reflect the lived experience of Black women and girls, including the tremendous burdens of psychological stress, sleep deprivation, psychological trauma, multi-generational caregiver burden and racial discrimination. These factors likely contribute to the high levels of cortisol – a “fight or flight” hormone that increases both obesity prevalence and persistence - observed in Black women.

In addition to increased obesity prevalence, Black patients are more likely to experience weight bias in health care encounters. For example, Black patients seeing white physicians had a 46% lower likelihood of receiving obesity behavioral interventions and/or counseling than White patients seen by White physicians. Black patients receiving behavioral interventions for obesity generally tend to lose approximately half the weight of their white counterparts. BWHI appreciates that ICER's review incorporates the growing body of scientific evidence underscoring that obesity is a chronic condition for which lifestyle modifications are essential but not always sufficient.

We urge ICER to approach its valuation of anti-obesity medications within the context of the scope of the obesity epidemic and the current under-utilization of this aspect of evidence-based obesity care. We remain concerned that an analysis that fails to fully consider the long-term impact that obesity has on the

health and lives of our communities, and the added value of pharmacotherapy in managing obesity for many patients, will further entrench health system reliance on behavioral interventions alone.

- Obesity rates have continued to rise despite data confirming its impact on health outcomes and health system costs, and population-level efforts to address both overweight and obesity.
- The increasing focus on addressing obesity through intensive behavioral interventions, counseling, diabetes prevention programs, and other lifestyle-focused interventions has neither disrupted the trajectory of obesity prevalence nor mitigated its associated personal, social, and economic costs. Some data suggest that reliance on these programs may actually widen health disparities (Ritchie 2018)
- Primary care clinicians remain inadequately trained in addressing obesity with the full range of tools available.
- Meaningful coverage for obesity interventions is limited.
  - Behavioral interventions have variable availability and effectiveness
  - Coverage for pharmacotherapy is extremely limited; Medicare Part D applies the coverage exclusion for “weight loss” treatments to anti-obesity medications
  - Access to bariatric surgery is limited by provider capacity in limited network plans. More importantly, coverage for surgical interventions routinely requires failure on medical treatment, including pharmacotherapy. Many payers, including Medicare, take a “step” approach despite noncoverage of the pharmacotherapy portion of the step protocol, creating a tiered, access landscape of “haves” and “have nots.” (Medicare NCD, Bariatric Surgery for Treatment of Morbid Obesity, NCD 100.1)
- Stigmatization of obesity as the natural consequence of a lack of willpower, enhanced by the racial bias Black women and other people of color experience, continues to permeate the health system and shape the care patients receive.
  - For example, Medicare’s national coverage decision on intensive behavioral therapy for obesity provides an initial 6-month service period and directs that “[f]or beneficiaries who do not achieve a weight loss of at least 3kg during the first six months of intensive therapy, a *reassessment of their readiness to change* and BMI is appropriate after an additional six month period.” (Medicare NCD 210.12)
- Despite the proven utility of anti-obesity medications in safely and effectively managing obesity, just 2% of US adults eligible for obesity pharmacotherapy receive it. (Velazquez 2018)



- Decisions on which drug to use for obesity management should be individualized and made through a shared decision-making process that accounts for patients' preferences, comorbidities, and out-of-pocket expenses.

***ICER should incorporate the disproportionate burden of type 2 diabetes (T2D) on communities of color into its analysis of obesity interventions.***

As ICER has previously noted, communities of color are disproportionately impacted by T2D – from prevalence of risk factors (e.g., obesity) to new T2D diagnoses, complications, progression to ESRD and/or limb amputations, and even death. Obesity is a primary driver of T2D and compromised health outcomes for Black women in prevalence and health outcomes. In fact, the greatest disparity in subpopulation T2D rates are between Black women and white women; and appear to be due to risk factors such as obesity. (NIH, Schneider, 2002) In addition, we urge ICER to ensure that its inputs reflect the lived experience of Black women and girls with respect to disparities and inequities in health outcomes throughout the T2D disease trajectory – from risk factors and disease prevalence through increased disease severity, complications, morbidity, and mortality.

- Black adults are 60 percent more likely than non-Hispanic white adults to be diagnosed with diabetes by a physician, twice as likely to die from T2D, and 3.2 times more likely to progress to ESRD when compared to their white counterparts.
- Black Medicare beneficiaries with diabetes are more likely to receive lower quality care<sup>i</sup> and have diabetes- related complications, such as end-stage renal disease, chronic kidney disease, and amputations. (Goodney 2013)
- Black patients are significantly overrepresented in the ESRD population, making up nearly one-third of the half-million US ESRD patients.<sup>ii</sup>
- Black women on dialysis are less likely to receive an adequate dialysis dose, have a fistula placed, and achieve target hemoglobin levels. These metrics are associated with decreased dialysis survival. (Kucirka 2011)
- Although kidney transplant is the standard of care for ESRD patients, Black patients are far less likely to have kidney transplant as an available option. Racial disparity in kidney transplant waitlisting persists even after adjusting for medical factors and social determinants of health.<sup>iii</sup>
- Black transplant recipients experience poorer outcomes, including higher rates of kidney rejection and patient death, than white transplant recipients.<sup>iv</sup>

***We urge ICER to ensure that its model reflects divergence among subgroups (sex, race, ethnicity) in obesity complications, including cardiovascular disease, and health outcomes. (Levy 2002; Gerber 2015)***





- Hypertension and diabetes play a greater role in the development of coronary artery disease in women than in men; thus, they also directly or indirectly play a significant role in the development of heart failure in women.
- Incidence rates of heart failure in Black women were more similar to those of men than of white women.
- Compared to men, women with heart failure have higher frequency rates of dyspnea on exertion, difficulty exercising, and edema. (Levy 2002; Gerber 2015)
- Despite controlling for age, ejection fraction, and New York Heart Association classification, women tend to have worse quality of life ratings than men for intermediate activities of daily living and social activity.
- Depression is more common in women with heart failure than in men.

***BWHI appreciates ICER's efforts to quantify the societal value of reducing health disparities within its value framework.***

ICER's recent evidence report in T2D included calculation of the Health Improvement Distribution Index for T2D. This index is intended to acknowledge and quantify increased subpopulation health gains in disease states that disproportionately impact identifiable subpopulations. BWHI appreciates that ICER seeks to incorporate a societal goal of reducing health disparities and inequities within its value framework. Use of the Health Improvement Distribution Index is a helpful tool toward that goal, but it does not fully capture the potential benefits of anti-obesity medications in Black women and other people of color. Ideally, ICER's framework would:

- Incorporate disparate prevalence among subpopulations as one factor in calculating potential health improvement. In obesity, disparities in health outcomes extend beyond cardiovascular consequences to include new T2D diagnoses, progression to ESRD, poorer prognosis. within ESRD, increased rates of limb amputations, vision loss, and higher mortality rates, increased breast cancer mortality, obesity impact on fertility and adverse pregnancy outcomes.
- Account for disparate health benefits within the base case and/or subpopulation scenarios to capture the potential that increased health gains can increase value from both the health system (payer) perspective and the societal perspective.
- Incorporate a treatment's potential to reduce health disparities within contextual considerations as an "added" benefit of a new treatment while also quantifying the potential health and productivity gains among subpopulations within the base case and societal perspective scenarios.



Despite the recommendations noted above, BWHI views ICER's efforts to address health disparities within its reviews as a clear step toward a value framework and methodology with potential to reduce, rather than perpetuate, the impacts of systemic racism on the health and lives of Black women and girls.

**BWHI continues to urge ICER to include outcomes, costs, and utility values that are important to women of childbearing potential.**

The increasing prevalence of overweight and obesity in younger populations combined with the challenges of excess maternal morbidity and mortality Black women face heightens the importance of ensuring access to all medical care with potential to improve outcomes. This includes, when possible, ensuring that patients have an opportunity to address obesity before becoming pregnant and are provided the full set of interventions needed to address pregnancy weight gain as appropriate. Obesity has implications for women's reproductive health that include:

- Overweight and obese women have higher levels of leptin, a hormone produced in fatty tissue that can disrupt hormonal balance and lead to reduced fertility.
- Women with a body mass index (BMI) above 27 are three times more likely than women in the normal weight range to be unable to conceive due to ovulation failure.
- Among women who ovulate, evidence indicates that each unit of BMI above 29 reduces the chance of achieving a pregnancy within 12 months by about 4%. For a woman with a BMI of 35, the likelihood of getting pregnant within a year is 26% lower, and for a woman with a BMI of 40 it is 43% lower compared with women with a BMI between 21 and 29. (Lake 1997)
- Elevated prepregnancy weight increases the risk of many adverse fetal and maternal outcomes including
  - o Spontaneous and recurrent miscarriages
  - o Suboptimal ultrasound screenings for fetal anomalies
  - o Heart and neural tube defects
  - o Post-partum maternal wound infections
  - o Maternal thromboembolic and anesthesia complications
  - o Gestational diabetes
  - o Pre-eclampsia (CDC 2015)

Reproductive health, fertility, and pregnancy-related complications are extremely important considerations for individuals of color capable of childbearing who, in comparison to white women: (1) face increased prevalence of obesity and experience overweight and obesity at younger ages, (2) are at disproportionate risk of pregnancy-related death and (3) for whom postponing pregnancy beyond age 30





is associated with a 4-5 times higher mortality risk. The maternal mortality risk disparity continues to widen with age and persists independent of socioeconomic factors.

Although data on fertility impact and reduced risk of poor outcomes with future pregnancy are not included in clinical trials of behavioral, pharmacologic, or surgical obesity interventions, women are encouraged to address overweight and obesity in advance of pregnancy. Ensuring access to anti-obesity medications in women of childbearing potential is an important incremental step toward reducing disparities in maternal morbidity and mortality.

BWHI remains eager to work with the ICER team toward more fully incorporating and more accurately quantifying disease and treatment impact on younger women in its reviews.

### ***Additional Recommendations***

- BWHI urges ICER to incorporate a “range” of health outcome impacts and costs beyond those associated with cardiovascular disease in its model and analysis. This should include obesity-related diseases and complications such as breast cancer (Picon-Ruiz 2017), non-alcoholic fatty liver disease (Sarwar 2018), and other obesity-related conditions (Milken 2020).
- We also urge ICER to fully incorporate the costs of lost productivity into its societal perspective, and to present that scenario as a co-base case. (Milken 2020)

### ***Conclusion***

As always, we appreciate the opportunity to engage with your team to collaborate on improving ICER’s ability to capture the value of emerging treatments on the lived experience of Black women impacted by life-limiting and life-threatening conditions. We remain available and eager to address any questions, concerns, or requests for additional information you might have with respect to our comments and recommendations.

Very truly yours,



Linda Goler Blount, MPH

President and CEO



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<sup>i</sup> Schneider, Eric C., Alan M. Zaslavsky, and Arnold M. Epstein. “Racial Disparities in the Quality of Care for Enrollees in Medicare Managed Care.” *Journal of the American Medical Association* 287, no. 10 (2002): 1288–1294.

<sup>ii</sup> Kucirka LM, Grams ME, Lessler J, et al. Association of race and age with survival among patients undergoing dialysis. *JAMA*. 2011;306(6):620-626. doi:10.1001/jama.2011.1127.

<sup>iii</sup> Ng YH, Pankratz VS, Leyva Y, Ford CG, Pleis JR, Kendall K, Croswell E, Dew MA, Shapiro R, Switzer GE, Unruh ML, Myaskovsky L. Does Racial Disparity in Kidney Transplant Waitlisting Persist After Accounting for Social Determinants of Health? *Transplantation*. 2020 Jul;104(7):1445-1455. doi: 10.1097/TP.0000000000003002. PMID: 31651719; PMCID: PMC7153978.

<sup>iv</sup> <https://www.myast.org/about-ast/presidents-blog/narrowing-racial-disparity-kidney-transplant-outcomes>

<https://www.nih.gov/news-events/nih-research-matters/factors-contributing-higher-incidence-diabetes-black-americans>

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[NCD - Bariatric Surgery for Treatment of Morbid Obesity \(100.1\) \(cms.gov\)](#)

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[American Obesity Crisis: The Health and Economic Costs \(milkeninstitute.org\)](http://milkeninstitute.org)



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Eli Lilly and Company  
Lilly Corporate Center  
Indianapolis, Indiana 46285 U.S.A.  
www.lilly.com

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August 8, 2022

**RE: Lilly's Public Comments for ICER's Draft Evidence Report for Obesity Management**

Eli Lilly and Company ("Lilly") appreciates the opportunity to provide public comments on the draft evidence report for the Institute for Clinical and Economic Review (ICER)'s assessment of obesity management ("Draft Report"). As Lilly stated to ICER directly in June 2022, Lilly does not feel it is appropriate to include "Drug X" (tirzepatide) in this review when it was not included as an intervention or comparator in the scope of this assessment, and Lilly has not been granted an equal opportunity to provide input as a key stakeholder to enable a more complete assessment of tirzepatide per ICER's process for manufacturer engagement.<sup>1</sup> To that end, we request that ICER remove the scenario analysis of "Drug X" in subsequent versions of this assessment for the reasons described below. In addition, we have outlined several important considerations, as well as references to support these considerations for an assessment of obesity. Lilly has actively engaged with ICER in prior assessments of our products, and we look forward to continued engagement as a key stakeholder in future assessments that involve our products.

**ICER should remove the scenario analysis of "Drug X," or tirzepatide, and all accompanying interpretations of this analysis. Lilly was not included as a key stakeholder in the ICER review process thereby preventing robust information exchange and a more comprehensive assessment of the value of tirzepatide.**

In the Draft Report, ICER includes a scenario analysis of tirzepatide as "Drug X" which assumes the weight loss effects of tirzepatide based on the SURMOUNT-1 trial (incorrectly noted as "SUPPORT 1" on Page 42), pricing of semaglutide, and effects on blood pressure and diabetes mellitus similar to semaglutide. Ergo, ICER completed an assessment of tirzepatide in this Draft Report. While ICER offers that the rationale for including tirzepatide data from SURMOUNT-1 is to 'provide context' (Section A3) or to 'address... uncertainties' (page 41), we are not clear on how the inclusion of "Drug X" provides any additional context or addresses any uncertainties in your assessment of the four interventions in scope. Further, ICER did not include tirzepatide efficacy data in the clinical effectiveness portion of ICER's network meta-analysis, and it is unclear how these data were included in the comparative value analysis despite ICER's summary of the SURMOUNT-1 results in the Appendix. In addition, these assumptions used for "Drug X" are not reflective of the potential value of tirzepatide in obesity given that the price of tirzepatide for obesity is currently unknown and the SURMOUNT trials are still ongoing. Despite the lack of transparency in ICER's analysis, ICER goes on to provide an incremental cost-effectiveness ratio of "Drug X" followed by further results (page 48 and 49, Table 4.10). ICER also states, "Decision on the order of cost-effectiveness will be subject to the cost of tirzepatide achieving larger quality-adjusted life-years (QALYs) gained with a significant decrease in body mass index (BMI) compared to the currently available weight management strategies" (page 52). ICER did not include tirzepatide in any prior scoping documents for this assessment and, therefore, making these assumptions, providing results, and drawing conclusions related to tirzepatide within this assessment is inappropriate.

It should be noted that ICER did not request any data or input from Lilly, as it typically does during its assessments. When ICER reached out to Lilly in June 2022 to inquire whether to include tirzepatide in the Draft

Report, Lilly advised that it should not be added halfway through an ongoing review. Lilly has been actively engaged with ICER in all stages of previous assessments involving our products. We value this engagement and would like to be afforded the opportunity to fully engage in all key milestones for an obesity management review, such as providing written input and participating in scoping calls with ICER. Research from the Center for the Evaluation of Value and Risk in Health underscores the importance of manufacturer engagement from the beginning of ICER’s assessment process by commenting on ICER’s draft scoping materials.<sup>2</sup> Therefore, ICER should remove the scenario analysis of “Drug X,” or tirzepatide, and all accompanying interpretations of this analysis as tirzepatide was not an intervention or comparator within the scope of this assessment. Lilly looks forward to engaging with ICER when additional data from our SURMOUNT clinical trial program is available, which includes four registration trials that thoroughly characterize tirzepatide for the treatment of obesity. Note that tirzepatide is also being investigated for additional benefits in obesity-related co-morbidities such as obstructive sleep apnea, heart failure with preserved ejection fraction and non-alcoholic steatohepatitis.

**ICER’s model structure is singularly focused on the impact of obesity on cardiovascular disease but does not capture additional outcomes and treatment benefits related to other comorbidities associated with obesity. ICER should acknowledge the risk and limitations of using a model structure that does not fully capture the complexity of obesity with associated comorbidities and the ensuing benefits of treatment.**

Obesity is a complex multifactorial disease with numerous complications and comorbidities. On Page 41, ICER states, “Although we did not include some conditions that are known to be associated with weight loss, the anticipated benefit of weight loss in reducing the onset of such conditions was implicitly captured.” ICER should explain how the model implicitly captures treatment benefits associated with other relevant comorbidities that are not captured by cardiovascular and diabetes complications, such as gastroesophageal reflux disease, back pain, gallbladder disease, liver disease, reproductive system disorders, gout, asthma, and cancer. Per the good research practices reported by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Modeling Good Research Practices Task Force,<sup>3</sup> ICER should choose a model structure that fully captures the complexity of obesity and all the conditions associated with treatment benefits. By choosing a simpler model approach, ICER’s model structure excludes outcomes required to appropriately model the full health and quality of life effects resulting from the complex comorbid health conditions patients with obesity may face.

On Page 51, ICER noted an additional scenario analysis was conducted to “test the potential impact of weight loss on cancer risk and chronic kidney disease using add-on ‘Comorbidity X’ Markov states,” but reported the incremental cost-effectiveness ratios were not significantly altered by the effects of these individual comorbidities. Further clarification of this conclusion is needed as the assumed impact of including both conditions would decrease the incremental cost-effectiveness ratios. Table E13 indicates *each* of these conditions reduces the cost-effectiveness ratio by about 10%. If ICER had included *both* these conditions in the base-case model, there may have been a reduction in the cost-effectiveness ratio by a significant percentage as modeling patients with multiple comorbidities has an additive effect on cost-effectiveness ratios. In addition, this scenario analysis only examines two comorbid conditions and does not examine all the possible relevant obesity-related complications that may impact weight loss. ICER should provide justification as to why these two conditions, along with other relevant comorbidities, were not included in the base-case model. ICER should also acknowledge the limitations of their model structure, which is unable to include multi-morbid states that could contribute to worse outcomes in patients and, therefore, underestimates the treatment benefits of anti-obesity medications in patients with multi-morbid conditions.

Comorbid conditions aside from cardiovascular disease have been included in other assessments of medications to capture treatment benefits for obesity management. In Section E7, ICER also references prior economic models including a cost-effectiveness model of medication-assisted weight loss treatment strategies compared

to lifestyle modification conducted by Kim et al.<sup>4</sup> ICER notes “the incremental cost-effectiveness ratio estimates were generally lower than observed in our model and the structure, inputs, and assumptions of this model were considerably different from our model.” Comorbidities included in the referenced model were post-myocardial infarction (MI), type 2 diabetes, post-stroke, obstructive sleep apnea, and cancer. Also, in the 2022 NICE appraisal of semaglutide for managing overweight and obesity, comorbidities such as non-diabetic hyperglycemia, type 2 diabetes, obstructive sleep apnea, acute coronary syndrome, stroke, and osteoarthritis were included to determine the cost-effectiveness of semaglutide.<sup>5</sup> By excluding such conditions, ICER’s model may not be fully capturing treatment benefits for obesity. We advise that ICER report the differences in assumptions in these models and address the limitations of omitting relevant obesity-related comorbidities in the model structure. Further, ICER should acknowledge that they are not fully capturing the potential value of anti-obesity medications in the cost-effectiveness results of this assessment.

**ICER should provide more clarity on the primary risk equation used in the model of this report and conduct sensitivity analyses that demonstrate the impact alternative risk equations may have on the model outcomes.**

On Page 40, ICER states, “The annual risk of developing cardiovascular conditions at the beginning of each cycle was calculated using a published risk equation model based on BMI, presence of diabetes mellitus, population demographics, and clinical characteristics. Specifically, the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline risk equation was used to calculate the 10-year risk of non-heart-failure cardiovascular conditions.” This 2013 guideline on cardiovascular risk reviews risk factors and includes an update of the Framingham risk equation by D’Agostino et al (Pooled Cohort Risk Equations, Appendix 7, Table A) which does not include BMI as a risk factor.<sup>6</sup> However, the 2008 Framingham risk equation by D’Agostino et al includes office-based measures that appear to align with what ICER claims to have used in their risk equation model and includes BMI as a risk factor.<sup>7</sup> ICER should therefore provide more specific details around the risk equation source, parameters, and variables used in their model to allow stakeholders to clearly follow how risk is being calculated.

ICER should explain the approach used to select the primary risk equation in the model and conduct scenario analyses using different risk equations. There are several potential risk equations that could be used, each with its own advantages and limitations. For example, the QRISK2 risk equation includes BMI and has been shown to better predict cardiovascular risk compared to the 2008 Framingham risk equation, but is based on UK data and may not reflect a US patient population with obesity.<sup>8</sup> The 2008 Framingham risk equation is widely used and was used in the 2022 National Institute for Health Care and Excellence (NICE) appraisal of semaglutide as a scenario analysis (NICE used the QRISK3 as the base-case primary risk equation),<sup>5</sup> but may reflect an outdated population that may not be representative of the patient population with obesity today, does not account for changes in treatment patterns, treatment landscape, and prevalence of risk factors related to obesity, and utilizes limited office-based measures. The decision of which risk equation to use has the potential to significantly alter the results of the model, including the estimate of cardiovascular risk. ICER should therefore provide an explanation for their selected primary risk equation, share details on its limitations, and conduct scenario analyses to show the impact different risk equations have on the model outcomes.

**ICER should evaluate several plausible time horizons including two, five, ten, and lifetime treatment durations to reflect varied clinical assumptions and uncertainties around utilization and benefit of anti-obesity medications over time.**

On Page 50 of the draft evidence report, ICER cites research from the Government Accountability Office reporting medication durations of 91 days or less in nearly 80% of patients with first treatment episode, but expert input indicated lifetime treatment duration is the “preferred approach” in obesity. While clinically advisable, ICER’s use of a lifetime duration for the base-case analysis does not reflect real-world utilization.<sup>9,10</sup> In comparison, NICE assumes a maximum treatment duration of two years in the base-case of their 2022



appraisal for semaglutide.<sup>5</sup> NICE notes they recognize that obesity is a lifelong condition but there is a lack of evidence on long-term use and benefits. Results of cardiovascular outcomes trials for oral semaglutide 14 mg, 0.5 mg/1.0 mg semaglutide, and 1.8 mg liraglutide in type 2 diabetes indicate significant mean differences in cardiovascular benefits between the GLP1s and placebo were seen around five years.<sup>11-13</sup> Therefore, a proxy of five years could be used to simulate the impact of anti-obesity medications on long-term use and benefits in weight management.

On Page 15 of ICER's model analysis plan, ICER stated they will include a weight regain scenario, in which "patients will be assumed to discontinue weight management intervention after the second year, which will be followed by weight regain over time" and will simulate the "lifetime benefits and cost-effectiveness of the short-term weight management." However, the results of this scenario analysis are not included in the draft evidence report, and ICER should provide explanation for their omission. It is critical that ICER addresses the uncertainties around weight regain trajectory and optimal treatment durations, such as the lack of data surrounding the long-term use and outcomes of anti-obesity medications, and exercise due diligence by conducting additional scenario analyses that align with the good research practices reported by the ISPOR Modeling Good Research Practices Task Force.<sup>3</sup> Therefore, Lilly recommends assessing several plausible time horizons to simulate treatment durations of two years, five years, ten years, and lifetime to reflect varied clinical assumptions and uncertainties around utilization and benefit of anti-obesity medications.

**In addition to the above recommendations, some additional information/data is needed to interpret the results of the cost-effectiveness model, including:**

- In general, for this report and any revised draft evidence reports, ICER should clearly state the corrections and changes made in order to provide full transparency to stakeholders.
- Explanation of which input values and sources were utilized to model the caregiver and productivity costs used to calculate the indirect costs included in the scenario analysis from a societal perspective.
- Inclusion of full disaggregated results with non-drug costs and cumulative incidence of the different types of cardiovascular events, including heart failure, and diabetes for all model arms across the full model time horizon would help assess what is occurring in the model. This would align with modeling best practices.
  - For example, on Page 50, ICER states the model estimated the cumulative incidence of cardiovascular conditions at 59.5% in patients receiving lifestyle management. Lilly recommends ICER provide cumulative incidence rates of cardiovascular disease over time for all treatment arms in a figure to allow users to assess and validate the model.
- Clarification on why the draft report and appendix do not present the scenarios and corresponding results that model a patient cohort with an average BMI of 50 kg/m<sup>2</sup>, a real-world population (50% females, 50% males), pre-diabetes cohort, discontinuation, weight regain, and inputs comparable to a recent cost-effectiveness analysis with lifetime and two-year treatment duration. Stating that an analysis was completed, without providing the results, is not sufficient to help the reader understand the impact or results of the analysis.
- ICER assumed that MI was a prerequisite to developing heart failure because of the strong causal association between obesity and heart failure mediated by myocardial changes. However, this assumption may underestimate the incidence of heart failure and implicated costs. ICER should further explain the underlying evidence for this assumption as it implies that rates of heart failure are lower than MI, when there are several studies that suggest rates of heart failure are higher than rates of MI in patients with obesity or that MI is only one of several different pathways in which obesity leads to heart failure.<sup>14-19</sup>

- ICER captures the increased risk of secondary cardiovascular events through the annual probabilities of recurrent MI and stroke in Table E4, but it is unclear if ICER used secondary risk equations or applied an additional risk of MI and stroke to patients who have already had an event. ICER should provide additional clarification on how the increased risk of secondary events is included in the model.
- In the ICER model analysis plan, ICER indicated they will validate the incidence of heart failure, but these figures are not reported in the draft evidence report.
- In Table 4.2, ICER provides the comorbidity annual cost inputs for post-stroke and post-MI states. ICER should provide more detail on how the post-MI state was utilized in the model as no post-stroke or post-MI states are described or shown in the model diagram (Figure 4.1). ICER also reports annual cost of heart failure as \$15,605, but a systematic review estimated median annual heart failure costs as \$24,383 in the US.<sup>20</sup>

**Furthermore, there are several areas that lack sufficient information to evaluate and replicate ICER's cost-effectiveness model. ICER should include clear details in the report on the following areas:**

- How is treatment effect durability applied throughout the model?
- How is progression from pre-diabetes to diabetes accounted for in the model? On Page 44, in Table 4.2, the inputs used to estimate the effect of HbA1c and BMI on the annual incidence of diabetes mellitus are based on an exponential regression of data from Edelman et al. ICER should provide additional details and clearly explain how these inputs were derived from the reference and utilized in the model to estimate the incidence of diabetes.
- Why is the 15 mg/92 mg dose of Qsymia utilized in the model despite the 7.5 mg/46 mg dose being recommended in the prescribing information for Qsymia? (Dose escalation to the 15 mg/92 mg dose is recommended if  $\geq 3\%$  weight loss is not achieved.)

**ICER should allow stakeholders the opportunity to review and provide input on results and analyses not presented within the Draft Report as a part of their commitment to open and transparent engagement with stakeholders in their reviews.**

Lilly has identified some inconsistencies and data input errors, which are listed in the Appendix, that ICER should correct.

We appreciate the opportunity to provide public comments on the draft evidence report and believe that the points made in this letter will support a scientifically sound evaluation for treatments in obesity.

Sincerely,



Christian Nguyen, PharmD, MBA, MS  
 Vice President, Value, Evidence, and Outcomes (VEO)  
 Eli Lilly and Company  
[nguyen\\_christian\\_t@lilly.com](mailto:nguyen_christian_t@lilly.com)

## Appendix: Additional Comments, Clarifications, and Corrections

Based on our detailed review, Lilly identified the following clarifications or inaccuracies in the draft evidence report that we would like ICER to address as they incorporate changes to the revised evidence report:

1. ICER should clearly distinguish the scenarios that will be examined in the clinical section versus those that will be examined in the modeling section if they expect those to differ.
2. On **Page E3**, ICER states the target population had HbA1c of 5.5% at model entry; this is at odds with the 5.7% figure on Page 39.
3. On **Page E11, Table E8**, ICER should clarify if the incremental cost-effectiveness ratios presented are for the undiscounted results as the section heading suggests. The results appear to be identical to the discounted results presented in Table 4.6.

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# Comments on Draft Evidence Report on Treatments for Obesity Management

Regarding the draft report on Obesity Management, I have some concerns regarding the QALYs and evLYs calculated for lifestyle modification. Your report shows that Lifestyle Modification leads to 16.95 QALYs. This does not pass even a basic sanity check given that it is well established in the literature that Diets [1, 2, 3] and Exercise [4, 5, 6, 7] do not result in weight loss in the long term. Indeed, the control group for the STEP trials judging Wegovy's effectiveness used "Lifestyle Changes" as the control group. The STEP trials found that Wegovy significantly outperformed the control group when it came to weight loss. Your own draft report notes that Wegovy received a B+ rating due to the, "demonstration of substantial short-term weight loss from multiple high-quality studies with few serious harms."

How is it possible, then, that "Lifestyle Modification" (presumably diet and exercise) can result in 16.95 QALYs, when it is well established that "Lifestyle Modification" does not result in long term weight loss? How is it possible that Wegovy, which results in substantially more weight loss than "Lifestyle Modification" only results in 0.9 more QALYs than "Lifestyle Modification?" Whatever methodology was used to generate these values is clearly suspect.

Quite frankly, based on the overwhelming evidence that "Lifestyle Modification" does not lead to any meaningful weight loss over the long-term, the QALYs gained from it should be 0. Any other value should be highly suspect.

In addition, "Bupropion/Naltrexone" has only a "C+" rating in your report. Yet it has a benefit of 0.33 QALYs as compared to Wegovy's net benefit of 0.9 QALYs. This also does not appear to pass the smell test. One of these has a likelihood of having a small net benefit while Wegovy has a "moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit." Surely moderate certainty of substantial net benefit should lead to substantially more QALYs than "moderate certainty of a comparable or small net health benefit."

The results of the draft report appear to be so obviously defective, the entire report should be scrapped and redone. In addition, a thorough review of the current analysis should be done to figure out how, exactly, "Lifestyle Modification" could have received any meaningful amount of QALYs at all and the lessons learned should be applied to the follow-up report to ensure that the same mistake is not repeated.

Obesity is one of the greatest public health threats of the last 50 years given that 70% of Americans are overweight or obese. It is critical, therefore, that this ICER report gets the analysis

right. If the QALY values of the draft report do not pass the smell test, it is vital we double check. If we still receive the same outcome, it is vital that we dig in and fully understand how we generated these values and fully explain to the public how “Lifestyle Modification” can lead to about equivalent QALY gains as medication that actually lead to substantial weight loss. Getting this report right is vital to both the public health and to the credibility of institutions like ICER.

Sincerely,

Matthew James Wiecek

Citations:

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2. <https://pubmed.ncbi.nlm.nih.gov/32238384/>
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Institute for Clinical and Economic Review (ICER)

14 Beacon Street, Suite 800

Boston, MA 02108, USA

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Novo Nordisk (henceforth referred to as “NN”) is a global healthcare company committed to helping improve the lives of people with obesity by changing how the world sees, prevents, and treats obesity including development of effective medications for chronic weight management. As the manufacturer of Wegovy® (semaglutide) injection 2.4 mg and Saxenda® (liraglutide) injection 3 mg, NN values the opportunity to provide comments to ICER regarding the *Medications for Obesity Management: Effectiveness and Value Draft Evidence Report* document.

As acknowledged by ICER, obesity is a serious, chronic, and progressive disease with a substantial economic burden to the US healthcare system. NN shares ICER’s commitment to improving the quality and effectiveness of care for all patients and appreciates the evidence-driven approach for this evaluation.

We have carefully reviewed the Draft Evidence Report (DER), and wish to offer the following comments and suggestions to refine the comparative clinical value and long-term cost-effectiveness evaluation of the medications for obesity management considered in this report.

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### **1) Limited capture of impact of BMI-related mortality**

The base-case cost-effectiveness analysis reported in the DER only considers the impact of weight loss on mortality through reductions in fatal cardiovascular (CV) events. We wanted to highlight that such an assumption would be inconsistent with evidence demonstrating an increased risk of all-cause mortality associated with obesity, and the benefits of weight loss in reducing all-cause mortality.

**Recommendation:** We would stress that the ICER team consider incorporating the risks of obesity and the benefits of weight loss on all-cause mortality into the base-case cost-effectiveness analysis.

The Global BMI Mortality Collaboration published a meta-analysis of data from 239 prospective studies with over 10 million participants and found that among patients who survived for at least 5 years, all-cause mortality risk increased steadily for patients who are overweight and obese (see Table 1 in the appendix).<sup>1</sup> Three other studies support this general trend of higher risk of all-cause mortality as BMI increases above normal for a variety of different population subgroups.<sup>2-4</sup> Furthermore, increasing risks of cause-specific mortality as BMI increases above the normal range were also demonstrated in a database study of the UK Clinical Practice Research Datalink<sup>2</sup> (see Figure 1 in the appendix).

Evidence also indicates that weight-loss interventions reduce the risk of all-cause mortality. Ma et al. (2017)<sup>5</sup> conducted a systematic literature review and meta-analyses of the effects of non-pharmaceutical weight loss interventions (diet and exercise programs) on mortality in

randomized controlled trials. The study found high quality evidence (34 trials, 21,699 participants, 685 events) that weight loss interventions reduced the risk of all-cause mortality (risk ratio 0.82; 95% CI: 0.71 to 0.95). In contrast, they found moderate quality evidence (8 trials, 134 events) that weight loss interventions reduce CV mortality (risk ratio 0.93; 95% CI 0.67 to 1.31).<sup>5</sup>

## **2) Limited inclusion of obesity-related comorbidities**

As described in the DER, the base-case cost-effectiveness analysis includes only type 2 diabetes (T2D) and CV comorbidities in the model. The justifications provided in the DER include uncertainty in the causation of weight on additional comorbidities and the assumption that the comorbidities will have little impact on outcomes. The DER includes scenario analyses that consider the addition of cancer and chronic kidney disease in separate scenarios, and the analyses do not account for the impact of these comorbidities on health-related quality of life. As the CDC notes that 40% of cancers diagnosed in the US are associated with overweight and obesity,<sup>6</sup> these scenario analyses are critical and based on our experience supporting research in obesity, a model without due consideration to the several obesity-related comorbidities may not capture the clinical presentation of such a complex disease as obesity comprehensively.

**Recommendation:** Based on available evidence as well as NN's experience in developing economic models for anti-obesity medications (AOMs), we encourage ICER to include the costs and utilities of a comprehensive list of comorbidities associated with obesity in the base-case cost-effectiveness analysis, including obstructive sleep apnea (OSA), chronic kidney disease (CKD), osteoarthritis, asthma, and non-alcoholic fatty liver disease (NAFLD) & non-alcoholic steatohepatitis (NASH).

Multiple studies document significant associations between BMI and numerous comorbidities, including OSA, CKD, osteoarthritis, and asthma, in addition to T2D and cardiovascular disease (CVD). A 2009 meta-analysis by Guh<sup>7</sup> identified 89 studies from the US and northern Europe that documented 18 comorbidities associated with obesity and overweight. A 2015 study of medical records in the US documented the prevalence and healthcare costs of 21 established obesity-related comorbidities.<sup>8</sup> And, a recent 2020 multi-cohort observational study based on 114,657 adults in Finland and replicated using data from 449,357 adults in the UK demonstrated association of obesity and 21 non-overlapping comorbidities.<sup>9</sup>

Weight loss can lead to improvements in certain comorbidities. A US publication by Ryan et al. synthesized the published studies to demonstrate the impact of weight loss on several comorbidities.<sup>10</sup> A recent set of studies presented by Khunti et al. 2022a<sup>11</sup> and b<sup>12</sup> demonstrate a strong correlation between weight loss and reductions in risk of multiple comorbidities based on a retrospective analysis of a database of anonymized electronic health records from a network of primary care practices across the UK that included 260,617 adults. Figure 2 in the appendix shows reductions in risk associated with lower BMI for multiple comorbidities, including OSA, CKD, osteoarthritis, and asthma in addition to type 2 diabetes, hypertension, and dyslipidemia. Refer to hazard ratios across a range of baselines for four weight loss/gain categories (Figure 3).

These comorbidities associated with obesity, beyond CV diseases, can contribute significantly to overall costs and negatively impact quality of life. Even in cases where per event costs are relatively low, high prevalence and/or large disutilities can significantly impact cost-effectiveness. Additionally, a 2015 US claims analysis based on 50,017 adults with obesity showed that the costs of comorbidities are compounded by the presence of multiple comorbidities.<sup>13</sup>

The available evidence also suggests that the disutility per BMI unit used in the cost-effectiveness analysis underestimates the HRQoL burden of obesity-related comorbidities. Several studies have estimated the effects of obesity on utility scores, controlling for patient characteristics and comorbidities.<sup>14–17</sup> Please see Table 2 through Table 6 in the appendix for a summary of the disutilities per BMI unit reported in literature, ranging from –0.0028 to –0.0043. These estimates, adjusted for patient characteristics and comorbidities, are similar in aggregate to the disutility of –0.0033 per BMI unit reported in the DER, but miss capturing the independent disutilities per comorbidity. Two of the studies reporting significant independent effects of comorbidities on utility scores are summarized in see Table 7 and Table 8 in the appendix.<sup>14,16</sup> Table 9 summarizes the costs and utilities associated with a subset of obesity-related comorbidities used by Kim et al.<sup>50</sup>

### **Obstructive sleep apnea**

OSA was included by Kim et al. and was part of the NICE evaluation of semaglutide for weight management in the UK.<sup>50</sup> Table 10 in the appendix presents the prevalence of OSA by BMI based on data from the Sleep Heart Health Study.<sup>18</sup> Li et al. assigned a cost of \$1,047.05 per year for OSA.<sup>8</sup>

Studies of pre-treatment and post-treatment utility scores report a large utility gain associated with OSA treatment as measured by a standard gamble approach [0.23 in Tousignant 1994 (N=19)<sup>19</sup> and 0.24 in Chakravorty 2002 (N=71)<sup>20</sup>], but a small utility gain (0.03 in Chakravorty 2002<sup>20</sup>) as measured by the EuroQol (see Table 11 in the appendix). A US cost-effectiveness model of upper respiratory airway stimulation for treatment of OSA derived utility weights from these sources of 0.84 for untreated OSA and 0.93 for treated OSA for a difference of 0.09 (see Table 12 in the appendix).<sup>21</sup>

### **Chronic kidney disease**

A recent study published a risk equation model that links body weight to the development of incident CKD.<sup>22</sup> An online risk calculator of this study is provided at the website <https://ckdpcrisk.org/ckdrisk/>.

While NN understands that accounting for costs from diabetes and hypertension might offset some cost of CKD due to diabetes and hypertension, the Pearson-Stuttard poster presented at the ECO/IFSO-EC 2022 Congress<sup>23</sup> shows the costs of CKD are higher than those of any other complication in the analysis, including diabetes (Figure 4). High annual costs of CKD increasing with stage have similarly been documented in other studies.<sup>24</sup>

To avoid double counting, ICER could perhaps consider only including costs for CKD that are not part of the costs for diabetes and other comorbidities by using a source that disaggregates the

costs of CKD, such as the cost-effectiveness analysis published by Kalantar-Zadeh (see Figure 5 in the appendix).<sup>25</sup> The Kalantar-Zadeh publication also has health-state utilities by CKD stage that may be incorporated into the analysis (see Figure 6 in the appendix).

### **Osteoarthritis**

Osteoarthritis can lead to knee replacements which are expensive. Kim et al. estimated the incidence of knee replacement based on the association of BMI with total knee replacements in a case-control study by Wendelboe.<sup>26,50</sup> Population-based incidence of knee replacement served as the baseline risk to which odds ratios (OR) per BMI category and gender were applied. Relative risks and calculated incidence by BMI category are presented in Table 13 and Table 14 in the appendix. A publication from the Blue Cross Blue Shield organization assigned a cost of \$31,979.29 for a knee replacement.<sup>27</sup>

### **Asthma**

Asthma is associated with continuing costs for medications that would not be included in the other comorbidities. A 2007 meta-analysis of prospective epidemiologic studies quantified dose-response effect of elevated BMI on asthma in adults.<sup>28</sup> A 2018 study by the Milken institute estimated the over 5 million cases for asthma and COPD were attributable to overweight and obesity in the United States in 2016.<sup>29</sup> A 2021 review provides a summary of recent studies on the links between obesity and asthma and concludes that weight loss appears to be effective in improving asthma among patients with obesity.<sup>30</sup> A 2018 study on the economic burden of asthma estimated the annual per-person incremental direct medical cost of asthma was \$3,266 (2015 USD).<sup>31</sup> Asthma can also be associated with low quality of life<sup>32</sup> and increased indirect costs due to loss of work productivity.<sup>33</sup>

### **Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis**

Obesity is strongly associated with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).<sup>34,35</sup> A systematic review and meta-analysis of population-based observational studies of NAFLD found that obesity was associated with an increased risk of severe liver disease outcomes (adjusted HR 1.20, 95% CI 1.12–1.28).<sup>36</sup> American Gastroenterological Association best practice advice recommends that weight loss  $\geq 7\%$  of total body weight can lead to NASH resolution, and weight loss  $\geq 10\%$  of total body weight can lead to fibrosis regression or stability.<sup>37</sup> NASH is also associated with substantial costs and quality of life burden, as documented in systematic reviews of cost-of-illness studies<sup>38</sup> and health economic models.<sup>39</sup>

### **3) Heart failure not-related to myocardial infarction is not represented in the model**

The assumption that myocardial infarction (MI) is a prerequisite to developing heart failure (HF) may be reasonable for heart failure with reduced ejection fraction (HFrEF), however, not for heart failure with preserved ejection fraction (HFpEF). HFpEF has strong associations with obesity, other comorbidities, and systemic inflammation, and one phenotype of HFpEF includes obesity-related HFpEF. The incidence of HFpEF has been increasing (and now accounts for approximately 50% of heart failure cases), while the incidence of HFrEF has been decreasing. Many patients with obesity who develop HF may have HFpEF in the absence of MI.

**Recommendation:** Our opinion, based on literature and clinical expertise, is that the model should account for a portion of HF not associated with MI and should include the impact of obesity on HFpEF. If this is not possible, we recommend that this be noted as a limitation.

#### 4) No analyses by obesity class subgroups may under-represent patient population

The model analysis plan stated that the cost effectiveness of AOMs in patients with BMI  $\geq 40$  kg/m<sup>2</sup> (Obesity Class III) would be evaluated in a scenario analysis. No such scenario analysis is presented in the DER. In addition, the Obesity Class III subgroup alone represents a small proportion (~15%) of the obesity population (Figure 7).

**Recommendation:** To ensure that the model developed by ICER not miss capturing the impact of interventions for persons living with obesity and overweight who may benefit from therapeutic interventions, we strongly recommend that ICER include subgroup analyses for each obesity class and not limited only to patients with BMI  $\geq 40$  kg/m<sup>2</sup> (Obesity Class III).. A study by Evans and colleagues not only reported that healthcare costs differ across obesity classes, but that patients incurred greater healthcare costs even after spending 8 years in the same obesity class.<sup>40</sup> NN has provided pertinent information to ICER about semaglutide and liraglutide by obesity classes during the data request phase. We believe that thorough subgroup analyses of all obesity classes will provide useful information for payers in determining coverage policies for AOMs.

#### 5) Year 2 weight loss model inputs needing references

The DER states that “percent weight change ... from baseline at year one and maximum percent weight change by the end of the second year were incorporated into the [cost-effectiveness] model” (p. 43). However, it does not report how those estimates are sourced, nor does it clarify the approach used for Contrave<sup>®</sup>, for which 2-year data are not available.

**Recommendation:** Kindly clarify the sources and estimates for maximum percent weight change by the end of the second year. We recommend using actual weight loss observed in high-quality studies that have been carried out for this duration, where those data are available: Wegovy<sup>®</sup> (STEP 5<sup>41</sup>), Saxenda<sup>®</sup> (SCALE Obesity and Prediabetes<sup>42</sup>), and Qsymia<sup>®</sup> (SEQUEL<sup>43</sup>). Gaps in the available evidence (e.g., Contrave<sup>®</sup>) should also be noted as a limitation of the analysis.

#### Closing Statement

We appreciate the opportunity to provide input on the draft evidence report, the active engagement with the ICER team throughout the course of this review, look forward to ongoing collaboration to help drive better outcomes for people living with obesity.

On behalf of the NN working group,

Neeraj N. Iyer, PhD

Senior Director & Head, Evidence Synthesis & Value Assessment

[nriy@novonordisk.com](mailto:nriy@novonordisk.com)

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## Appendix

**Table 1: Mortality hazard ratios by BMI**

<b>BMI kg/m<sup>2</sup></b>	<b>HR for all-cause mortality</b>
15.0-<18.5	1.51
18.5-<20.0	1.09
20.0-<22.5	1.01
22.5-<25.0	reference
25.0-<27.5	1.06
27.5-<30.0 (overweight)	1.17
30.0-<35.0 (Obesity Class I)	1.39
35.0-<40.0 (Obesity Class II)	1.93
40.0-<60.0 (Obesity Class III)	2.58

Source: Table 3 of The Global BMI Mortality Collaboration, 2016<sup>1</sup>

**Figure 1: Cause-specific mortality hazard ratios by BMI**



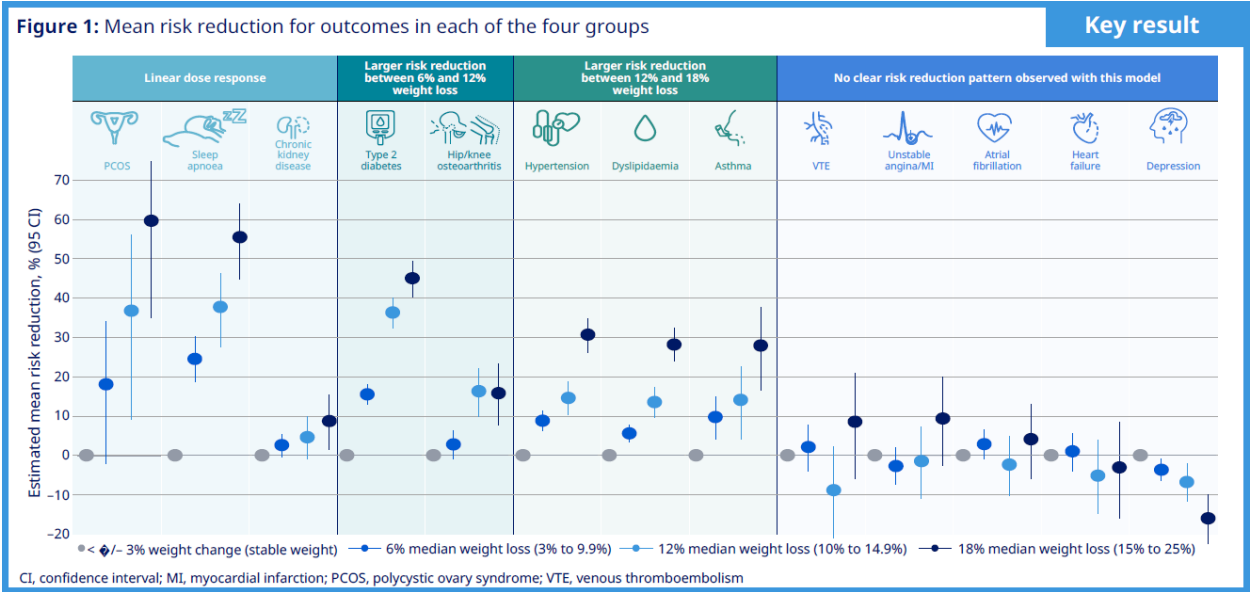
**Figure 2: Association between BMI and Level 2 and Level 3 cause-specific mortality outcomes among never-smokers (organised by ICD-10 code)**

We used a three-level hierarchical classification of causes of death as used by the Global Burden of Diseases, Injuries, and Risk Factors Study.<sup>16</sup> We studied all Level 2 non-communicable disease outcomes and selected Level 3 outcomes that were either common causes of death in the UK or were a priori expected to have important associations with BMI. 5-year exclusion period applied for person-time and events after a BMI record; estimates adjusted for age, deprivation, calendar year, diabetes, alcohol status (all as defined at date of BMI measure) and stratified by sex. HR=hazard ratio. ICD-10=International Classification of Diseases, 10th revision.

Source: Figure 2 of Bhaskaran, 2018<sup>2</sup>

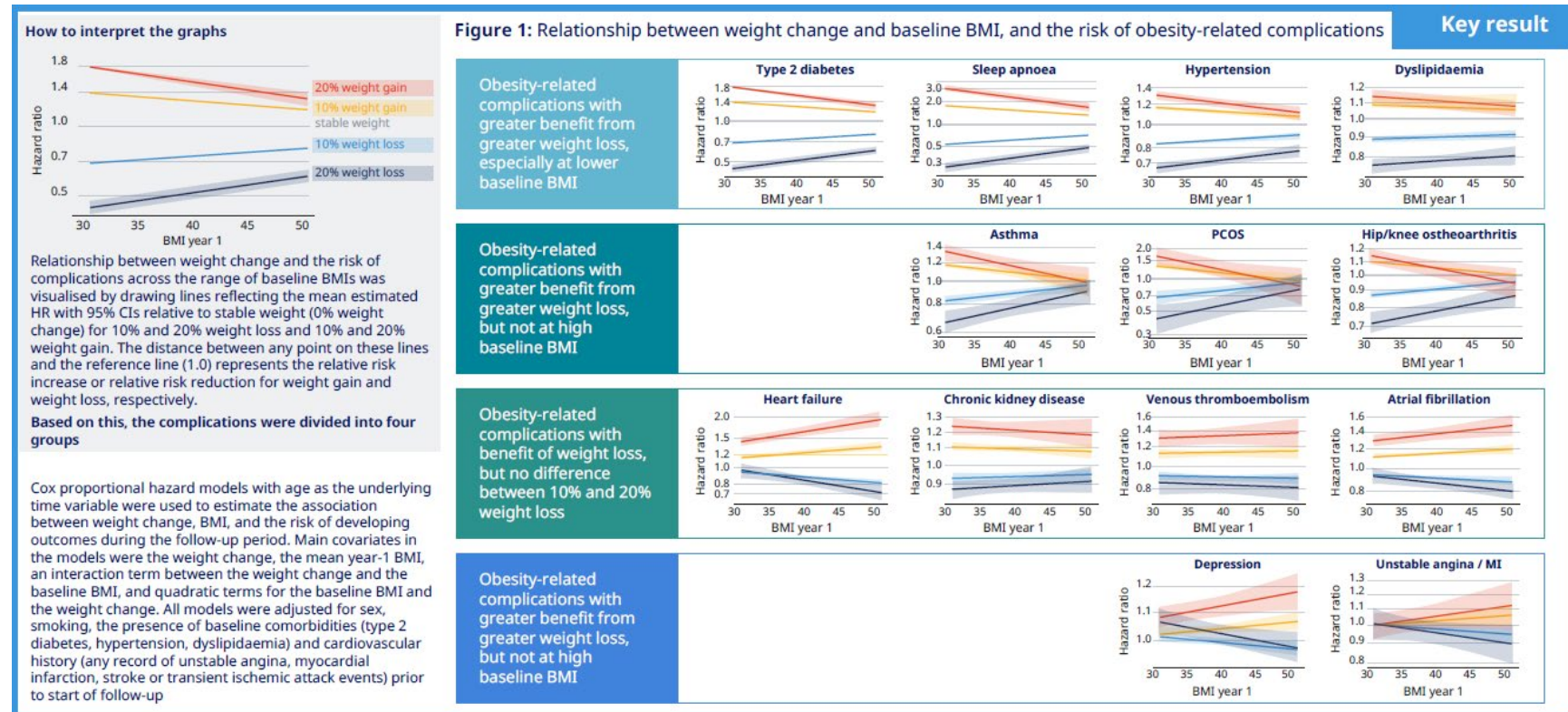


Figure 2: Mean risk reduction for obesity related comorbidities with lower BMI from analysis of electronic health records in the UK



Source: Figure 1 from Khunti, 2022a<sup>11</sup>

**Figure 3: Relationship between weight change and baseline BMI, and risk of obesity-related comorbidities**



Source: Figure 1 from Khunti, 2022b<sup>12</sup>

**Table 2: Estimates of the disutility per unit BMI in obese patients, adjusted for patient characteristics and comorbidities, derived from population studies**

Source Study	HRQoL	Subgroup	Disutility per unit BMI <sup>a</sup>
Jia and Lubetkin 2005 <sup>14</sup> (N=13,646)	EQ-5D	Moderate obesity (BMI 30–34.9)	–0.0030
		Severe obesity (BMI ≥35)	–0.0039
Stephenson et al. 2021 <sup>15</sup> (N=64,631)	EQ-5D	Obese (30–<40)	–0.0036
		Morbidly obese (BMI ≥40)	–0.0040
Søltoft et al. 2009 <sup>16</sup> (N=14,416)	EQ-5D	Men	–0.0030
		Women	–0.0043
Sach et al. 2007 <sup>17</sup> (N=1,730)	EQ-5D	Obese (BMI ≥30)	–0.0030
	SF-6D	Obese (BMI ≥30)	–0.0028

<sup>a</sup> Estimates of the disutility per unit BMI were derived by linear interpolation from the multiple regression results adjusted for patient characteristics and comorbidities reported in each study (see Table 3 through Table 6 for details).

Abbreviations: BMI, body mass index.

**Table 3: Disutility of obesity in the 2000 Medical Expenditure Panel Survey (Jia and Lubetkin 2005)<sup>14</sup>**

Parameter	Normal weight (18.5–24.9 kg/m <sup>2</sup> )	Moderate obesity (30–34.9 kg/m <sup>2</sup> )	Severe obesity (≥35 kg/m <sup>2</sup> )
N	4437	1907	1064
EQ-5D index score	Not reported	Not reported	Not reported
vs. Normal weight <sup>a</sup>		–0.033	–0.073
per BMI unit increase <sup>b</sup>		–0.0030	–0.0039

<sup>a</sup> Incremental utility scores vs. normal weight represent regression coefficients in a multiple regression analysis controlling for sociodemographic variables (age, sex, race/ethnicity, income), smoking, physical activity, and comorbidities including asthma, hypertension, diabetes, heart disease, stroke, emphysema (Table 2 in the source).

<sup>b</sup> Derived estimates of the incremental utility per BMI unit increase are linearly interpolated, assuming average BMIs of 21.5 kg/m<sup>2</sup> for normal weight, 32.5 kg/m<sup>2</sup> for moderate obesity, and 40 kg/m<sup>2</sup> for severe obesity. For example, the estimate for moderate obesity is calculated as:  $-0.033/(32.5-21.5) = -0.0030$ .

Abbreviations: BMI, body mass index.

**Table 4: Disutility of obesity in the 2010-2015 Yorkshire Health Study (Stephenson et al. 2021)<sup>15</sup>**

Parameter	Normal weight (18 to <25 kg/m <sup>2</sup> )	Obese (30 to <40 kg/m <sup>2</sup> )	Morbidly obese (≥40 kg/m <sup>2</sup> )
n	27,488	12,676	1,678
EQ-5D index score			
Mean	0.848	0.733	0.619
vs. Normal weight			
Unadjusted <sup>a</sup>		-0.115	-0.229
Adjusted <sup>b</sup>		-0.049	-0.113
per BMI unit increase <sup>c</sup>			
Unadjusted		-0.0085	-0.0080
Adjusted		-0.0036	-0.0040

<sup>a</sup> Unadjusted effect sizes vs. normal weight represent coefficient estimates in a univariable regression analysis (Table 4 in the source).

<sup>b</sup> Adjusted effect sizes vs. normal weight represent coefficient estimates in a multivariable regression analysis controlling for age, ≥3 vs. <3 mental health conditions (tiredness/fatigue, insomnia, anxiety/nervousness, depression, memory problems), ≥3 vs. <3 physical health conditions (diabetes, breathing problems, hypertension, heart disease, osteoarthritis, stroke, cancer), the level of contact with health professionals in 3 months, the number of outpatient hospital visits in 3 months, and the number of hours per week spent walking (Table 5 in the source).

<sup>c</sup> Derived estimates of the incremental utility per BMI unit are linearly interpolated, assuming average BMIs of 21.5 kg/m<sup>2</sup> for the normal category, 35 kg/m<sup>2</sup> for the obese category, and 50 kg/m<sup>2</sup> for the morbidly obese category. For example, the unadjusted estimate for the obese category is calculated as:  $-0.115/(35-21.5) = -0.0085$ .

Abbreviations: BMI, body mass index.

**Table 5: Disutility of obesity in the 2003 Health Survey for England (Søltøft et al. 2009)<sup>16</sup>**

Men (N=6,408)		Women (N=8,008)	
BMI (kg/m <sup>2</sup> )	EQ-5D index score	BMI (kg/m <sup>2</sup> )	EQ-5D index score
25.37390209	0.973739211	25.37390209	0.976164225
25.96318054	0.973822571	25.93286786	0.975536949
26.61356935	0.973031511	26.58155916	0.974163925
27.21448787	0.972451764	27.19993778	0.972791603
27.94781216	0.972185821	27.77466615	0.971495736
28.56764579	0.970625930	28.37849468	0.969336968
29.15813675	0.968974030	28.93746046	0.967507963
29.76075278	0.967036236	29.57402669	0.964777212
30.36336881	0.964758940	30.17664272	0.962499916
30.96598484	0.962645108	30.77925874	0.959619060
31.65226386	0.959895243	31.38308728	0.956463342
32.24154231	0.957730345	31.98449080	0.953593293

32.85870842	0.955195122	32.59074435	0.950033350
33.46132445	0.952905251	33.18123531	0.946888718
34.10637823	0.950413213	33.78385134	0.943668361
34.73688192	0.948144971	34.38646737	0.940183947
35.31161029	0.946424457	34.98908340	0.936661810
35.61716208	0.945662935	35.54077413	0.933668967
Slope <sup>a</sup>	-0.0030	Slope <sup>a</sup>	-0.0043

Data represent the estimated relationship between utility and BMI (Figure 1 in the source) from multiple regression models controlling for sociodemographic characteristics (age, age when left school, non-manual vs. manual work), psychosocial well-being, and diagnosed morbidities including type 2 diabetes, heart and circulatory problems, respiratory problems, musculoskeletal problems, and cancer. Data were digitized from the figure in the source using Web Plot Digitizer (<https://apps.automeris.io/wpd/>).

<sup>a</sup> Derived estimates of the incremental utility per BMI unit increase represent the slopes of linear regression models fitted to the digitized data over the range of BMI values between 25 and 35 kg/m<sup>2</sup>.

**Table 6: Disutility of obesity in a UK primary care study (Sach et al. 2007)<sup>17</sup>**

<b>Parameter</b>	<b>Normal BMI (18.5 to &lt;25 kg/m<sup>2</sup>)</b>	<b>Obese (≥30 kg/m<sup>2</sup>)</b>
EQ-5D utility score		
n	782	267
Mean	0.803	0.695
vs. Normal BMI		
Unadjusted <sup>a</sup>		-0.108
Adjusted <sup>b</sup>		-0.040
per BMI unit increase <sup>c</sup>		
Unadjusted		-0.0080
Adjusted		-0.0030
SF-6D utility score		
n	726	248
Mean	0.781	0.708
vs. Normal weight		
Unadjusted <sup>a</sup>		-0.073
Adjusted <sup>b</sup>		-0.038
per BMI unit increase <sup>c</sup>		
Unadjusted		-0.0054
Adjusted		-0.0028

<sup>a</sup> Unadjusted effects vs. normal BMI represent parameter estimates of a one-way analysis of variance (Table 2 in the source).

<sup>b</sup> Adjusted effects vs. normal BMI represent parameter estimates of a multiple linear regression analysis controlling for the effects of age, sex, smoking status, back pain, hip pain, knee pain, heart disease, stroke, asthma, cancer, diabetes, rheumatoid arthritis, and osteoarthritis (Table 3 in the source).

<sup>c</sup> Derived estimates of the incremental utility per BMI unit increase are linearly interpolated, assuming average BMIs of 21.5 kg/m<sup>2</sup> for the normal category and 35 kg/m<sup>2</sup> for the obese category. For example, the unadjusted estimate for EQ-5D scores is calculated as:

$$-0.108/(35-21.5) = -0.0080.$$

Abbreviations: BMI, body mass index.

**Table 7: Disutility of obesity-related comorbidities in the 2000 Medical Expenditure Panel Survey (Jia and Lubetkin 2005)<sup>14</sup>**

<b>Comorbidity</b>	<b>EQ-5D Index<sup>a</sup></b>	
	<b>Coefficient</b>	<b>p-value</b>
Asthma	-0.045	<.0001
Hypertension	-0.053	<.0001
Diabetes	-0.042	0.0002
Heart disease	-0.083	<.0001
Stroke	-0.080	<.0001
Emphysema	-0.120	<.0001

<sup>a</sup> Disutilities represent regression coefficients in a multiple regression analysis of EQ-5D index scores as function of BMI, controlling for sociodemographic variables (age, sex, race/ethnicity, income), smoking, physical activity, and the comorbidities shown (Table 2 in the source). Abbreviations: BMI, body mass index.

**Table 8: Disutility of obesity-related comorbidities in the 2003 Health Survey for England (Søltøft et al. 2009)<sup>16</sup>**

Comorbidity	Men		Women	
	Coefficient	Robust SE	Coefficient	Robust SE
Type 2 diabetes	-0.0528 <sup>†</sup>	0.0145	-0.0325	0.0183
Heart problems	-0.0486 <sup>†</sup>	0.0084	-0.0278 <sup>‡</sup>	0.0085
Respiratory problems	-0.0242 <sup>‡</sup>	0.0084	-0.0430 <sup>†</sup>	0.0097
Musculoskeletal problems	-0.1721 <sup>†</sup>	0.0078	-0.2014 <sup>†</sup>	0.0074
Cancer	-0.0946 <sup>†</sup>	0.0237	-0.0724 <sup>†</sup>	0.0184

Note: Data represent coefficients in multiple regression models of the effects of BMI on EQ-5D index scores controlling for sociodemographic characteristics (age, age when left school, non-manual vs. manual work), psychosocial well-being, and the comorbidities shown.

<sup>†</sup> P < 0.001; <sup>‡</sup> P < 0.01

Abbreviations: BMI, body mass index; SE, standard error.

**Table 9: Disutilities and costs of obesity related comorbidities**

Parameter	Input value	Source
<b><i>Disutilities/health state utilities</i></b>		
Obstructive sleep apnea	-0.24	Pietzsch 2015 <sup>21</sup> ; Tousignant 1994 <sup>19</sup>
CKD		
CKD, Stage 3 (health utility index)	0.67	Kalantar-Zadeh 2020 <sup>25</sup>
CKD, Stage 4-5 (health utility index)	0.55	Kalantar-Zadeh 2020 <sup>25</sup>
End-stage renal disease (health utility index)	0.54	Kalantar-Zadeh 2020 <sup>25</sup>
Cancer	-0.0735	Gough 2009 <sup>44</sup>
<b><i>Acute event disutilities</i></b>		
Musculoskeletal	-0.18046	Shah et al., 2020 <sup>45</sup>
<b><i>Health-state costs (2021 USD)</i></b>		
Obstructive sleep apnea	\$1,047	Li et al., 2015 <sup>8</sup>
CKD costs:		
Drug costs	\$17,274	Kalantar-Zadeh 2020 <sup>25</sup>
CKD, Stage 3	\$23,635	Kalantar-Zadeh 2020 <sup>25</sup>
CKD, Stage 4-5	\$35,405	Kalantar-Zadeh 2020 <sup>25</sup>
End-stage renal disease	\$102,648	Kalantar-Zadeh 2020 <sup>25</sup>
Asthma	\$3,858	Nurmagambetov 2018 <sup>31</sup>
Colorectal cancer, 1st year	\$83,243	Mariotto 2011 <sup>46</sup>
Post-menopausal breast cancer, 1st year	\$37,336	Mariotto 2011 <sup>46</sup>

Post-menopausal endometrial cancer, 1st year	\$43,316	Mariotto 2011 <sup>46</sup>
Cancer treatment follow-up years	\$5,714	Mariotto 2011 <sup>46</sup>
<b>Acute event costs</b>		
Knee surgery	\$31,979	Weiner 2013 <sup>47</sup>

Note: Costs were inflated from cited sources to 2021 USD using the Medical Care component of the Consumer Price Index.

**Table 10. Sleep apnea prevalence by BMI level<sup>18</sup>**

<i>BMI level (kg/m<sup>2</sup>)</i>	<i>Sleep apnea Prevalence</i>	<i>BMI level (kg/m<sup>2</sup>)</i>	<i>Sleep apnea Prevalence</i>	<i>BMI level (kg/m<sup>2</sup>)</i>	<i>Sleep apnea Prevalence</i>
24	0.0%	32	22.2%	40	47.5%
25	11.4%	33	24.4%	41	52.3%
26	12.5%	34	26.8%	42	57.5%
27	13.8%	35	29.5%	43	63.3%
28	15.2%	36	32.5%	44	69.6%
29	16.7%	37	35.7%	45	76.5%
30	18.3%	38	39.3%	46	84.2%
31	20.2%	39	43.2%	47	92.6%

**Abbreviation:** BMI, body mass index.

**Table 11: Utility gain of treating OSA**

<b>Parameter</b>	<b>Tousignant 1994<sup>19</sup> (N=19)</b>	<b>Chakravorty 2002<sup>20</sup> (N=71)</b>	
	<b>Standard gamble</b>	<b>Standard gamble</b>	<b>Euroqol</b>
Utility score			
Pre-treatment	0.63	0.32	0.73
Post-treatment	0.87	0.55	0.77
Utility gain with treatment	0.24	0.23	0.03

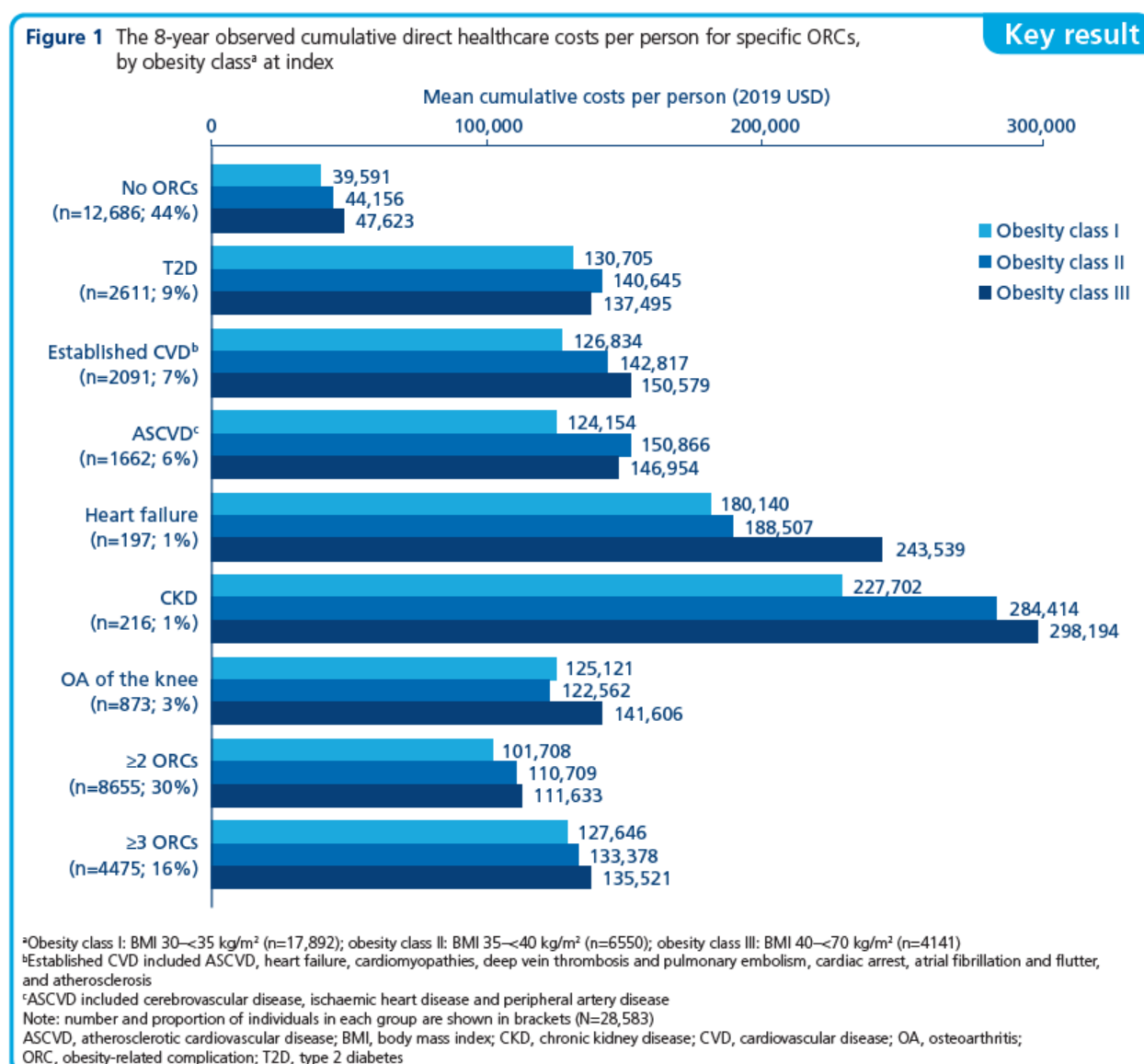
**Table 12: Health state utility weights in a US cost-effectiveness analysis of OSA treatment<sup>21</sup>**

<b>Health state</b>	<b>Utility weight</b>	<b>Range</b>	<b>PSA distribution</b>	<b>Reference</b>
Well	1.00	N/A	N/A	
Untreated OSA	0.84	0.80–0.93	Beta, a = 126.0, b = 24.0	19,20
Treated OSA	0.93	0.84–0.98	Beta, a = 37.2, b = 2.8	19,20

Abbreviations: N/A, not applicable; OSA, obstructive sleep apnea



**Figure 4: Comparison of 8-year cumulative costs of obesity related comorbidities**



Source: Figure 1 from Pearson-Stuttard, 2022<sup>23</sup>

**Figure 5: Disaggregated cost inputs associated with CKD and resulting economic outcomes showing significant costs of CKD in addition to cardiovascular event costs from a CKD cost-effectiveness model**

Table 4. Drug and clinical event costs.		
Cost category	Cost (2017 USD)	Source
ERC WAC gross annual cost, label dosing	\$11,136	10
Paricalcitol WAC gross annual cost, label dosing	\$4,684	18
CKD stage III	\$21,440	29
CKD stage IV–V	\$32,116	29
ESRD	\$93,113	30
Any CV event	\$26,454	28
Hip fracture	\$28,227	28
Abbreviations. CKD, chronic kidney disease; CV, cardiovascular; ERC, extended-release calcifediol; ESRD, end-stage renal disease; USD, United States dollars; WAC, wholesale acquisition cost.		

Table 6. Total costs and QALYs for ERC and paricalcitol, 1,000 patients, 5 years.				
	Extended-release calcifediol	Paricalcitol	Difference	95% CI*
<i>Treatment Efficacy</i>				
Change in serum 25(OH)D (ng/mL)	47.4	−6.7	—	
Change in iPTH (pg/mL)	−31.9	−104	—	
<i>Clinical Outcomes</i>				
CV events, Disc.	2,211	2,356	−145	(−489, 78)
Fractures events, Disc.	50	57	−7	(−10, −4)
Number of patient-years in Stage 5	856	1,280	−423	(−617, −208)
Life years	4,288	3,974	315	(142, 516)
Deaths averted/patients alive at end of analysis	739	647	92	(47, 142)
<i>Economic outcomes</i>				
Total costs	\$230,666,856	\$245,470,802	(\$14,803,946)	(−\$45,224,269, \$10,021,090)
Drug costs	\$19,525,819	\$7,414,227	\$12,111,592	
CKD progression costs	\$150,967,687	\$173,735,113	(\$22,767,426)	
Fracture costs	\$1,422,036	\$1,605,690	(\$183,654)	
CV event costs	\$58,485,330	\$62,317,219	(\$3,831,889)	
Total QALYs	2,960	2,620	340	(200, 496)
Incremental cost-effectiveness ratio	—	ERC is dominant	—	
Per patient total costs	\$230,667	\$245,471	(\$14,804)	(−\$45,224, \$10,021)
Per patient QALYs	2.96	2.62	+0.34	(0.20, 0.50)
Abbreviations. CKD, chronic kidney disease; CV, cardiovascular; Disc., discounted; ERC, extended-release calcifediol; QALY, quality-adjusted life year.				
*95% CIs estimated from probabilistic sensitivity analysis.				

Source: Tables 4 and 6 from Kalantar-Zadeh, 2020<sup>25</sup>

**Figure 6. Utilities used in CKD cost-effectiveness model of Kalantar-Zadeh**

Table 5. Utility values by CKD stage.			
	Time trade-off (SE)	HUI-3 global utility (SE)	Source
Utility level for Stage III patients	0.87 (0.24)	0.67 (0.31)	34
Utility level for Stage IV patients	0.85 (0.23)	0.55 (0.34)	34
Utility level for Stage V/ESRD patients	0.72 (0.37)	0.54 (0.31)	35
Disutility for CV event*	−0.14 (0.21)		35
Disutility for fracture†	−0.09 (0.16)		35
Abbreviations. ESRD, end-stage renal disease; HUI, Health Utilities Index; SE, standard error.			
*Average disutility of CV events, including MI, angina, heart failure, and stroke.			
†Average disutility of arm and hip fracture.			

Source: Table 5 from Kalantar-Zadeh, 2020<sup>25</sup>

**Table 13. Incidence rate of total knee replacement procedures**

Age	Incidence knee replacement procedure
55–64 yrs	0.0005352
65–74 yrs	0.0012022

Source: Table from NN model showing data from Wendelboe, 2003<sup>26,50</sup>

**Table 14. Risk of knee replacement**

BMI Range	Males				Females					
	N	OR	(95% CI)	Incidence age 55–64	Incidence age 65–74	N	OR	(95% CI)	Incidence age 55–64	Incidence age 65–74
<20	7	2.06	(0.35–12.10)	0.0011	0.0025	56	0.71	(0.26–1.99)	0.0004	0.0009
20–22.49 (ref.)	68	1	187	0.0005	0.0012	1			0.0005	0.0012
22.5 - 24.99	153	1.43	(0.67–3.03)	0.0008	0.0017	323	1.16	(0.68–1.97)	0.0006	0.0014
25.00 - 27.49	259	2.14	(1.06–4.31)	0.0011	0.0026	338	2.07	(1.25–3.44)	0.0011	0.0025
27.50 - 29.99	192	2.98	(1.47–6.06)	0.0016	0.0036	269	4.62	(2.81–7.59)	0.0025	0.0056
30.00 - 32.49	100	3.61	(1.69–7.75)	0.0019	0.0043	215	6.42	(3.86–10.69)	0.0034	0.0077
32.5 - 34.99	74	5.88	(2.64–13.13)	0.0031	0.0071	147	7.52	(4.37–12.96)	0.0040	0.0090
35.00 - 37.49	40	8.62	(3.35–22.20)	0.0046	0.0104	89	11.88	(6.41–22.03)	0.0064	0.0143
37.50 - 39.99	25	16.4	(5.19–51.86)	0.0088*	0.0197*	59	8.72	(4.42–17.21)	0.0047*	0.0105*
≥ 40	19	14.89	(4.24–52.32)	0.0080*	0.0179*	84	19.05	(9.79–37.08)	0.0102	0.0229

**Abbreviations:** BMI, body mass index; CI, confidence interval; N, number; OR, odds ratio.

\*Excluded from regression; small sample size.

Source: Table from NN model showing data from Wendelboe, 2003<sup>26,50</sup>

**Figure 7. Prevalence of obesity by BMI Class**



Source: CDC QuickStats<sup>48,49</sup>

Dr S D Pearson  
President  
Institute for Clinical and Economic Review  
Two Liberty Square, 9<sup>th</sup> Floor  
BOSTON MA 02109

28 July 2022

My dear Dr Pearson

## **PUBLIC COMMENT: MEDICATIONS FOR OBESITY MANAGEMENT, EFFECTIVENESS AND VALUE**

I refer to your recently released draft evidence report for *Medications for Obesity Management: Effectiveness and Value* <sup>1</sup>

As you will no doubt recall, you are aware of my concerns that the ICER reference case framework for value assessment, the creation of assumption driven imaginary claims fails to meet the standards of normal science <sup>2</sup>. That is, given the standards for credibility of claims, empirical evaluation and replication, that distinguish science from pseudoscience, you persist in creating these cost-effectiveness models when it is quite clear that they have no validity. Your reports for modeled claims, many of which are produced by expert academic groups, lack credibility in the claims made for the value of products; they cannot be evaluated empirically nor can the claims be replicated. Your models also violate the fundamental axioms of modern measurement theory in confusing ordinal scales with interval and ratio scales. While you might view these reports and the application of lifetime incremental cost-per-QALY calculations and the application of cost-per-QALY thresholds as the state of the art in health technology assessment, the problem is that the entire exercise is essentially a waste of time. This has been detailed in a recent publication in *F1000Research* which has addressed the manifest deficiencies in the CHEERS 22 guidance for constructing imaginary worlds, described as the ISPOR/ICER meme or belief system for inventing (non-evaluable by design) value claims for cost-effectiveness <sup>3 4</sup>.

The focus of this comment on your report is the use of utilities and concerns I have that it is far from clear how they should be interpreted. This is not, as I have mentioned in previous comments to point out, once again, that the multiattribute utilities or preference scores are composite ordinal measures. This is now accepted by those familiar with the standards of fundamental measurement. While you might claim that these are, in fact ratio measures in disguise this argument has no merit as you cannot demonstrate that the utility has a true zero (the algorithms yield negative scores) or, implicit in a ratio score, interval or invariance properties.

My concern is more fundamental: a concern that you, or your academic consultant model builders, have brought together utilities from different instruments/techniques and, in effect, claimed that that are interchangeable. If this is case then this will invalidate your modelling.

Let me start by referencing the leading textbook by Drummond et al <sup>5</sup>, on the assumption driven simulation meme to create non-evaluable cost-effectiveness claims (Ch. 5 Section 5.5.6):

*Having decided to use a preference based multi-attribute health status system in a study the researcher must decide which one to use .... We can give some guidance for considerations*

*First, the decision does matter. These systems are far from identical. They differ in the dimensions of health they cover, in the number of levels defined on each dimension, the description of these levels, and the severity of the most severe level. In addition, they differ in the populations surveyed and in the instruments used to determine the preference-based scoring. Finally, they differ in the theoretical approach taken to modelling the preference data into a scoring formula .....Because of these various differences, it is not surprising that comparative studies show that the same patient groups can score differently depending upon the instrument used.*

The message is quite clear: you cannot combine utility scores from different instruments to define health state utilities in the same modelled study. My concern is that this standard has been put aside in the model that you present. This is doubly concerning as these disparate utilities are the foundation for your QALYs and your subsequent claims (imaginary though they are) for incremental cost-per-QALY and threshold values. If this is the case then your model should either make this clear or be withdrawn.

Let me refer you to Table 4.2 (Quality of Life Inputs) of your draft report and your referenced sources for the utilities and accompanying discussion. You reference four sources (the reference for Matza is not given but I have provided it): these are (i) Sullivan 2006; (ii) Kim 2022; (iii) Pi-Sunyer 2019 and (iv) Matza 2015 <sup>6 7 8 9</sup>. Let's consider these in turn:

- Sullivan 2006: application of the multivariate EQ-5D-3L instrument and utility scores
- Kim 2022: utilities reported are from a diversity of sources. The base case BMI source was Pi-Sunyer with the SF-36 and four studies reporting the EQ-5D-3l (one rescaled) for comorbidity disutilities and adverse event disutilities
- Pi-Sunyer 2019: application of SF-36 for overall quality of life together with the Kolotkin Impact of Weight on Quality of Life Measure and the TRIM-weight quality of life measure
- Matza2015: Time trade off for six specific cardiovascular health states

It is not clear from the discussion provided how these various sources were utilized to create the utilities for the parameters identified in Table 4.1. We are told (there is no additional information in the appendix) that the starting utility is from Sullivan utilizing the EQ-5D-3L for hypothetical patient characteristics and that the linear association between utility is from Pi-Sunyer where we have the SF-36 and two other instruments. These are far from informative descriptions. Perhaps more details can be provided to allay concerns? It is no good just citing references, giving no

further details and expecting the reader to follow up on the trail of references with different instruments cited. Perhaps your consultants mapped from the SF-36 to the EQ-5D-3L?

In the case of comorbidities associated with higher BMI we are referenced to Matza for acute stroke disutility and chronic post-event health states. Health states were valued in a time trade off (TTO) valuation (which is ordinal). Three cardiovascular acute conditions were represented in the health states (stroke, acute coronary syndrome, heart failure) each of which are multiattribute composite TTOs which fail standards for fundamental measurement (value claims for single attributes). They admit states worse than death but try to create bounded negative values without recognizing the need for a true zero. Three TTO health states were 'valued' for chronic conditions. The six health states are all multiattribute ordinal TTO scores and as such are not compatible with EQ-5D-3L and SF-36 scores. This means that the model includes values which are inappropriate when combined.

All your expert group say (Pg. 45) is that: *For comorbidities associated with higher BMI, we used consistent health state utility values across all evaluated treatments*” with the health state disutilities derived from systematic reviews, prior studies and manufacturer submitted data with a *multiplicative approach ...used to apply health utility value changes for each of the Markov states*. This far from clear with no mention made that the utilities come from different instruments/techniques. Perhaps you might care to clarify these points for each of the utilities including how you apply multiplicative techniques to different ordinal utility scores. To claim your health states have consistent utility values is incorrect.

An issue that is overlooked by Drummond *et al* in their characterization of the various multiattribute utility measures is the requirement that the utility score should have bounded ratio properties (a true zero and an invariance of comparisons) with normally distributed scores if they are to be summarized in terms of means and standard deviations. These are strict requirements which none of the instruments meet. The presence, by design, of health states with negative values means there is no true zero and the scores are ordinal. The question of normality is never raised, at least in all of the models your expert groups have produced over the years. If normality and bounded ratio properties cannot be demonstrated then the application of means and standard deviations is disallowed. The reason is simple: the impact of extreme values which produces extremely wide standard deviations. You have no basis for correctly supporting claims for response to therapy (or creating QALYs). All you can do with your ordinal scores is to produce medians and interquartile ranges.

Given the need for normality and a bounded ratio scale, perhaps your expert modeling group could confirm that is the case for all the utilities in the obesity model?

In addition, given your application of different utility measures (as I am not the only one with these concerns) perhaps your academic consultant group could allay these use of alternative utility concerns by an unequivocal statement that the utilities listed in Table 4.2 are all from the same instrument; that they are equivalent in terms of the criteria identified by Drummond *et al*. If the response is positive, it would be useful to detail for each of the utilities listed how this transformation from apparently diverse ordinal instrument sources was achieved?

Of course, it may be that utility data were so limited that your consultants were forced to capture what they could from a diverse array of sources and for the purpose of the model assume they are equivalent without going into too much detail. If so, this merely points to the inadvisability of assumption driven simulations.

As a final point: I am sure that this issue could be raised in respect of previous modelled claims. Is it possible for each of these to lay their concerns to rest for the choice of utility scores and make the same affirmations?

Perhaps this time you might respond to my comments instead of just thanking me for them.

Keep well

Yours sincerely

Paul C. Langley, Ph.D.  
Adjunct Professor  
College of Pharmacy  
University of Minnesota  
MINNEAPOLIS MN  
Email: [langley@maimonresearch.com](mailto:langley@maimonresearch.com)

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<sup>2</sup> Langley P. Nonsense on Stilts – Part 1: The ICER 2020-2023 value assessment framework for constructing imaginary worlds. *InovPharm*. 2020;11(1): No. 12  
<https://pubs.lib.umn.edu/index.php/innovations/article/view/2444/2348>

<sup>3</sup> Langley P. Nothing to Cheer About: Endorsing Imaginary Economic Evaluations and Value Claims with CHEERS 22 [version 1; peer review: 2 approved]. *F1000Research* 2022, **11**:248  
(<https://doi.org/10.12688/f1000research.109389.1>)

<sup>4</sup> Husereau D, Drummond M, Augustovski F et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 22) Statement: Updated reporting guidance for health economic evaluations. *ValueHealth*. 2022;25(1):3-9

<sup>5</sup> Drummond M, Sculpher M, Claxton K et al. Methods for the Economic Evaluation of Health Care Programmes (4<sup>th</sup> Ed.). New York: Oxford University Press, 2015

<sup>6</sup> Sullivan PW, Ghushchyan V. Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med Decis Making*. 2006;26(4):410-420. 98.



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<sup>7</sup> Kim N, Wang J, Burudpakdee C, et al. Cost-effectiveness analysis of semaglutide 2.4 mg for the treatment of adult patients with overweight and obesity in the United States. *J Man Specialty Pharmacy*. 2022;28(7):740-752.

<sup>8</sup> Pi-Sunyer X, Astrup A, Fujioka K, et al. A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management. *NEJM*. 2015;373(1):11-22.

<sup>9</sup> Matza L, Stewart K, Gandra S et al. Acute and chronic impact of cardiovascular events on health state utilities. *BMC Health Ser Res*. 2015;15:173

August 8, 2022

Dr. Steven D. Pearson  
President  
Institute for Clinical and Economic Review  
Two Liberty Square, Ninth Floor  
Boston, MA 02109

Dear Dr. Pearson:

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to provide feedback on ICER's assessment of treatments for obesity management. Obesity is a complex disease that increases the risk for other diseases and conditions. The prevalence of obesity in the United States is growing, and it is important that appropriate interventions are available to individuals that address obesity and limit risk of associated diseases. PIPC asks ICER to consider the following comments.

**ICER's model assumes the burden of obesity is limited solely to cardiovascular disease (CVD) risk, which likely underestimates the overall benefit of intervention.**

Obesity is a complex disease that can lead to and impact the severity of many diseases. It can also have an independent impact on an individual's physical and social functioning and quality of life. Given this reality, any model designed to assess benefit of treatments for obesity must reflect this complexity, not treat obesity solely as a risk factor for cardiovascular disease (CVD).

There is widespread evidence that many conditions are impacted by obesity such as non-alcoholic fatty liver disease (NAFLD),<sup>1</sup> gallbladder disease,<sup>2</sup> sleep apnea,<sup>3</sup> and fatigue.<sup>4</sup> The global burden of disease study highlights that obesity is a significant driver of population-attributable risk in the mortality and morbidity burden of many diseases including osteoarthritis, chronic back pain, chronic kidney disease, chronic liver disease, Alzheimer's, asthma, colorectal, esophageal, pancreatic, liver and uterine cancers.<sup>5</sup> It has been estimated that obesity is the cause of up to 15% of all-cause mortality in the US.<sup>6</sup> The need for hip and knee replacement are also accelerated by 10-15 years in people with obesity,<sup>7</sup> which leads to increased medical costs and physical burden on patients.

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<sup>1</sup> Koutoukidis DA, Koshiaris C, Henry JA, Noreik M, Morris E, Manoharan I, Tudor K, Bodenham E, Dunnigan A, Jebb SA, Aveyard P. The effect of the magnitude of weight loss on non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Metabolism*. 2021 Feb 1;115:154455.

<sup>2</sup> Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *Jama*. 1999 Oct 27;282(16):1523-9.

<sup>3</sup> Jehan S, Zizi F, Pandi-Perumal SR, Wall S, Auguste E, Myers AK, Jean-Louis G, McFarlane SI. Obstructive sleep apnea and obesity: implications for public health. *Sleep medicine and disorders: international journal*. 2017;1(4).

<sup>4</sup> Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *The Journal of Clinical Endocrinology & Metabolism*. 2000 Mar 1;85(3):1151-8.

<sup>5</sup> <https://www.healthdata.org/data-visualization/gbd-compare>

<sup>6</sup> Flegal KM, Panagiotou OA, Graubard BI. Estimating population attributable fractions to quantify the health burden of obesity. *Annals of epidemiology*. 2015 Mar 1;25(3):201-7.

<sup>7</sup> Changulani M, Kalairajah Y, Peel T, Field RE. The relationship between obesity and the age at which hip and knee replacement is undertaken. *The Journal of Bone and Joint Surgery. British Volume*. 2008 Mar;90(3):360-3.

With obesity having such a broad range of health ramifications, representing the burden of obesity as a risk factor for CVD and CVD events is over-simplistic and likely to underestimate the net health gain from appropriate treatment.

**ICER's model ignores the benefits of treatment on physical function, which can have a significant impact on a patient's quality of life.**

Trials for semaglutide showed a 10-point improvement in physical function scores for patients from a baseline of around 50.<sup>8</sup> This is a 20% improvement in quality of life related to physical functioning. That is likely worth 2-3 additional points in respect to health utility gains over and above any gains from reduction in CVD risk, but this value is not incorporated into the model. Given that the model assumes an overall mean QALY gain over a lifetime of just 0.25-0.89 QALYs, an additional 0.03 could be a significant addition. This benefit should be incorporated to capture a full picture of a patient's improvement with treatment.

Similarly, liraglutide shows a 5-point improvement in physical function score compared to placebo, as well as a statistically significant improvement in mood and self-esteem. These are benefits also excluded from a model that is based solely on CVD risk.

**The model's assumption about how long patients will receive treatment for obesity is unrealistic, which leads to an overestimation of treatment costs over a lifetime.**

The model assumes that patients will be on the drug under evaluation for 20 years. Though clinical guidelines indicate lifetime treatment, real world observation studies have suggested that patients are unlikely to continue treatment beyond 2 years.<sup>9</sup> Other models similarly structured around estimating the benefits of obesity medications limited to reductions in relative risk of CVD events have tended to make this very assumption,<sup>10</sup> and have produced different results, even though they have assumed weight gain once patients stop treatment happens at a faster rate than natural weight gain.<sup>11</sup>

**ICER's model uses data from randomized controlled trials. Real world data would be more appropriate in this scenario.**

Baseline cohort characteristics that act as the patient archetype in ICER's model are derived from randomized controlled trials (RCTs), not from real world populations diagnosed with obesity. RCTs tend to have strict inclusion and exclusion criteria, meaning they tend to be healthier populations than real-world populations with co-existing conditions and higher health needs. Using this group to derive

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<sup>8</sup> Wilding JP, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MT, Wadden TA, Wharton S. Once-weekly semaglutide in adults with overweight or obesity. *New England Journal of Medicine*. 2021 Feb 10.

<sup>9</sup> Ganguly R, Tian Y, Kong SX, Hersloev M, Hobbs T, Smolarz BG, Ramasamy A, Haase CL, Weng W. Persistence of newer anti-obesity medications in a real-world setting. *Diabetes research and clinical practice*. 2018 Sep 1;143:348-56.

<sup>10</sup> Kim, Nina, Jessie Wang, Chakkarin Burudpakdee, Yan Song, Abhilasha Ramasamy, Yanwen Xie, Rochelle Sun, Neela Kumar, Eric Q. Wu, and Sean D. Sullivan. "Cost-effectiveness analysis of semaglutide 2.4 mg for the treatment of adult patients with overweight and obesity in the United States." *Journal of Managed Care & Specialty Pharmacy* 28, no. 7 (2022): 740-752.

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baseline data may underestimate the burden of disease on people with obesity and ultimately underestimate the value of the treatments being evaluated.

**ICER continues to rely on the Quality-Adjusted Life Year, which is known to be discriminatory.**

Multiple studies have shown that cost-effectiveness models that use the quality-adjusted life year (QALY) discriminate against patients with chronic conditions<sup>12</sup> and people with disabilities.<sup>13</sup> There is widespread recognition that the use of the QALY is discriminatory. The National Council on Disability (NCD), an independent federal agency, concluded in a 2019 report that QALYs discriminate by placing a lower value on treatments which extend the lives of people with chronic illnesses and disabilities. NCD recommended that policymakers and insurers reject QALYs as a method of measuring value for medical treatments.<sup>14</sup> PIPC encourages ICER to heed this advice and work to develop and use better, non-discriminatory metrics.

**ICER uses Framingham risk equations, which are known to underestimate risk in populations of lower socio-economic status.**

A recent study<sup>15</sup> evaluating the Framingham risk equations in groups of differing socio-economic status showed that the ratio of predicted-to-observed cardiovascular mortality for men and women with complete risk factor information was 0.56 a relative underestimation of 44%. CVD mortality was also underestimated by 48% in manual participants compared to 31% in the non-manual participants. Underestimation was also worse in participants from lower income areas. The likely consequence is that treatments are estimated being less effective than they would be for those with the fewest resources. This finding has been confirmed in other studies.<sup>16</sup> PIPC would suggest that ICER carefully consider this and look to alternate sources, as use of tools that do not accurately capture benefit to those in lower socio-economic classes will perpetuate existing health inequities.

**To accurately capture the heterogeneity of patient populations, ICER should be producing ranges, not averages.**

ICER's model estimates cost-effectiveness based on average treatment effect (ATE), not incremental effect of treatment for individuals.<sup>17</sup> It is well established that generating and reporting of differential value estimates across subgroups leads to substantial health gains, both through treatment selection and

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<sup>12</sup> Paulden M. Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable?. Expert review of pharmacoeconomics & outcomes research. 2017 May 4;17(3):239-42.

<sup>13</sup> Nord E, Pinto JL, Richardson J, Menzel P, Ubel P. Incorporating societal concerns for fairness in numerical valuations of health programmes. Health economics. 1999 Feb;8(1):25-39.

<sup>14</sup> [https://www.ncd.gov/sites/default/files/NCD\\_Quality\\_Adjusted\\_Life\\_Report\\_508.pdf](https://www.ncd.gov/sites/default/files/NCD_Quality_Adjusted_Life_Report_508.pdf)

<sup>15</sup> Brindle PM, McConnachie A, Upton MN, Hart CL, Smith GD, Watt GC. The accuracy of the Framingham risk-score in different socioeconomic groups: a prospective study. British Journal of General Practice. 2005 Nov 1;55(520):838-45.

<sup>16</sup> Ramsay, S.E., Morris, R.W., Whincup, P.H., Papacosta, A.O., Thomas, M.C. and Wannamethee, S.G., 2011. Prediction of coronary heart disease risk by Framingham and SCORE risk assessments varies by socioeconomic position: results from a study in British men. *European Journal of Preventive Cardiology*, 18(2), pp.186-193.

<sup>17</sup> Stevens W, Normand C. Optimisation versus certainty: understanding the issue of heterogeneity in economic evaluation. Social science & medicine. 2004 Jan 1;58(2):315-20.

coverage.<sup>18,19</sup> PIPC encourages ICER to move away from the assumption that all patients are the same, and that the value to each can be determined by the estimation of an average value only.

## Conclusion

PIPC encourages ICER to make changes in its model to ensure it is representative of a real-world population, including using real world evidence where possible and recognizing the broad implications of obesity beyond risk of CVD.

Sincerely,



Tony Coelho  
Chairman  
Partnership to Improve Patient Care

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<sup>18</sup> Basu A. Economics of individualization in comparative effectiveness research and a basis for a patient-centered health care. *Journal of health economics*. 2011 May 1;30(3):549-59.

<sup>19</sup> Espinoza MA, Manca A, Claxton K, Sculpher MJ. The value of heterogeneity for cost-effectiveness subgroup analysis: conceptual framework and application. *Medical Decision Making*. 2014 Nov;34(8):951-64.



August 08, 2022

Steven D. Pearson, M.D., M.Sc  
President  
Institute for Clinical and Economic Review  
2 Liberty Square, 9<sup>th</sup> Floor  
Boston, MA 02109

Maggie O'Grady  
Program Manager  
Institute for Clinical and Economic Review  
2 Liberty Square, 9<sup>th</sup> Floor  
Boston, MA 02109

Dear Mr. Pearson and Ms. O'Grady:

The Southern Christian Leadership Conference (SCLC) appreciates the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) review of obesity management treatments. SCLC has been fighting for justice and to address racial inequities since its founding in connection with the Montgomery Bus Boycott, which began in 1955 after Rosa Parks was arrested for refusing to give up her seat to a white man on the bus. The boycott lasted for 381 days and ended on December 21, 1956, with **change** -- the desegregation of the Montgomery bus system.

The boycott also launched the modern civil rights movement and led to the formation of the SCLC, led by Dr. Martin Luther King, Jr., Dr. Ralph Abernathy and others. SCLC is a nation-wide organization with chapters and affiliates all over the country committed to addressing America's inequities to ensure that all American's -- including people of color and other marginalized communities -- can achieve the American Dream. Healthcare (along with economic and educational) inequities continue to be a substantial barrier to this goal.

Obesity, the subject of ICER's current review, is especially important to this mission due to: (1) its growing prevalence in America; (2) its link to many other co-morbidities that decrease quality of life and life expectancy; and (3) the **disproportionate burden obesity and related co-morbidities place on people of color**. ICER's obesity review is currently the front line in our health care system's opportunity to change the high disease burden of obesity, which is exacerbated by under-utilization of proven, effective treatments and together put people of color at substantial risk of disparately poor health outcomes.

SCLC joined a number of other organizations with shared commitment to eliminate the inequities in health care that drive poor health outcomes in people of color and other underserved communities ("the Diversity

Stakeholders”) in a letter to ICER regarding this review, which discusses in detail that the status quo of restricted coverage for anti-obesity medications widens health disparities and disproportionately harms individuals of color. SCLC wishes to associate itself with those comments.

We understand that ICER’s role in the health care system has been growing and that payors use ICER’s reviews to inform and guide their decisions that determine whether patient’s can access therapies. While SCLC and ICER share the same broad goals – to improve health outcomes through affordable and valuable health care -- we have serious concerns that ICER’s “value” analyses fail to consider, systemically or sufficiently, the real world lived experiences of patients, especially people of color. We understand that ICER’s analysis often fails to consider properly significant differences between white and non-white patients – which may lead to unhelpful actions that risk perpetuating or exacerbating health disparities, considering the role ICER plays in the access related decisions of payors.

**ICER’s model does not include (or count) the significant harms of obesity in patients under age 45, including failing to count complications for women of childbearing age.**

ICER focused its model on patients over 45 years of age. Accordingly, the long-term benefits of obesity treatments in younger adults, including women of childbearing age, were not counted in the review. We associate ourselves with the detailed comments (including citations) in the Diversity Stakeholders letter on this issue.

The recent Supreme Court reversal of *Roe v Wade* has led many states to adopt highly restrictive state abortion laws, especially those with some of the highest obesity prevalence and maternal morbidity/mortality rates. Obesity will certainly complicate health outcomes for women in these states who will be forced to carry unplanned pregnancies to term.

**SCLC urges ICER to retool its analysis to account properly for all likely benefits of anti-obesity medications, including healthcare costs avoided by successful treatment, in its final Evidence Report.**

We acknowledge that the relationship between obesity and other chronic conditions is complex, and it is difficult to assign monetary costs to all potential obesity related complications and comorbidities; but, ICER should incorporate an estimated range when supported by science and logic.

Also, there are meaningful differences in subpopulation prevalence, outcomes, and response to alternative treatments. As such, a value assessment aggregating data into a single value calculation will tend to under-value interventions that have higher value in those subpopulations. For the purposes of the obesity review, People of color and other underserved populations are under-studied and under-represented in clinical trials. Accordingly, ICER would improve the accuracy of its reviews if it either performed subpopulation scenarios or extrapolated disparate data to simulate the impacted population, disease burden, and treatment response. SCLC associates itself with the examples of key inputs to which the Diversity Stakeholders letter refers.

Moreover, the model does not consider ongoing weight gain in patients failing behavioral interventions and not receiving anti-obesity medication or reduced effectiveness of behavioral interventions in individuals of color. Economic models typically assign utility increments/decrements for incremental decreases/increases in BMI. So, a range of decrements should be assigned to the base case calculations for behavioral interventions alone.

Finally, the Draft Evidence Report did not include 2021 evidence demonstrating that Semaglutide’s effectiveness is similar across races and that it is actually more effective in individuals on the lower-BMI levels of obesity and in female patients.

The decisions ICER makes can either help eliminate -- or continue to perpetuate -- health inequities. SCLC goal -- to ensure ICER incorporates, systemically and sufficiently, the lived experiences of non-white patients into the value assessments that payors use to define the contours of access -- is not easy. We understand that systemic change takes time, commitment, creativity and understanding. We urge ICER to acknowledge that lives are impacted when payors use its reviews to guide access to care. We ask that any review of disease states in which health inequities exist be published by ICER only after ICER has incorporated the health and lives of black and brown patients into the core of its model and analysis. SCLC urges the voting panel to consider carefully the lived experience of people of color battling obesity and related co-morbidities as it assesses the value of obesity treatments and to find ways to account for such experience in its model and assessment.

Sincerely

Dr. Charles Steele, Jr  
President / CEO

Charles Brooks, Esq  
General Counsel

Kevin Kimble, Esq  
D.C. Bureau Chief



Icer public comments as to evidence report on treatments for obesity management.

From

Thomas Kaye RPh., MBA, FASHP

K-Groups strategies LLC

Tomkaye@rxman.com

Relating to the recent report on the use of therapeutic medications to reduce obesity offered by ICER, I find the report appropriate for those patients who have morbid obesity that complexes with comorbid issues ( Class I,II,III)<sup>1</sup>, and a BMI greater than 35.

*(The prevalence of obesity in the U.S. population has increased steadily since the 1960s—from 3.4 percent of adults in 1962 to 39.8 percent in 2016, the year of the most recent Centers for Disease Control and Prevention data. In all, 180.5 million people—or 60.7 percent of the population ages 2 and over—were either obese or overweight)<sup>2</sup>* As the scope of the

demographics is very large, the pharma manufacturers are seeking a bonanza in profiteering for a often self-anointed medical condition that is self-imposed. As noted in the draft document the GPL-1 are generally very costly, some injectables may offer a patient concern as to needle aversion and the oral tablets offer an alternative dose form. All the medications listed in the context of the draft publications offer side effects from mild to serious in outcomes for those patients that may seek such therapy. In some instances, the drug package inserts carry a black box warning to be heeded. Thus, is the risk of a serious and possible life threatening side effect worth the treatment for a self-imposed syndrome? Secondly, when is the right time to initiate such obesity treatment; additional data analysis will need to be formulated to fully evaluate a sociological benefit in reductions healthcare costs. Some may point to impending pre-diabetes potential and frank diabetes that has followed the increase in obesity; possible complicated cardiovascular efficacy, hypertension and cancer being promoted by the medications from side effects. This alone may also stimulate costs due to unintended consequences at attempting to help. The point being that the progression of wishful desires by the manufacturers in cost avoidance dialog with reduction of future disease costs remains high in question. Its needs to be recognized that this position is not tenatable based on the cost to be incurred or increasing the dwell time for disease advancement which may be slowed with simple lifestyle changes.

Prevention of disease is not always salient in deployment. The dwell time to development of disease may exceed the membership duration of the patient. Benefits are offer the member based on medical necessity, not hopeful changes. Most of the obesity seen is derived based on self-anointed-lifestyles and self-image as envisioned by the patient as to body image, not medical necessity. When the obesity reaches a point of medical complexity and known avoidance of higher costs if so used, and there is a clear view for therapy advantage as to patient cost this should implemented based on the class of obesity of I,II or III <sup>3</sup>.

(Medicare and Medicaid) have explicit non-coverage, non-payment regulations for obesity treatments as listed. Exclusions are also to prevent payments for “morbid” obesity as described as class (I,II,III obesity)as defined by the CDC reference. This being said payer plans do evaluate patients who are morbidly obese ( greater than 32+ BMI) and may apply non-reimbursed costs for care in means of known cost avoidance of more serious disease progression with co-morbid patients. This is especially true for pediatric patients and payment stemming from (EPSDT, Early and Periodic Screening, Diagnostic, and Treatment )<sup>4</sup>. This regulation is also implemented often to the commercial benefit member uniformly in policy.

It remains that opening the door to obesity therapy would be a very significant expense to payers of the benefits without current cost offsets for future disease prevention. Until a validated financial analysis can be provided as to cost effectiveness and cost reductions in the future, the use of obesity drug should remain excluded for all but those morbid obese patients. It needs to be understood the patient is not being denied such opportunity for the drug use, but restriction as to payment for a non-covered benefit. The patient may if desired purchase the drug with a prescribers prescription with his or her personal money without payer plan sponsorship payment. Our healthcare system presently is the highest cost venue in the world, opening this therapy up offers little healthcare gain other than possible vanity for many but with a significant cost burden on stakeholders of healthcare.

- (1) <https://www.cdc.gov/obesity/basics/adult-defining.html>
- (2) [https://milkeninstitute.org/sites/default/files/reports-pdf/Mi-Americas-Obesity-Crisis-WEB\\_2.pdf](https://milkeninstitute.org/sites/default/files/reports-pdf/Mi-Americas-Obesity-Crisis-WEB_2.pdf)<https://www.cms.gov/files/document/excluded-drug-reference-file-faq.pdf>
- (3) <https://www.cms.gov/files/document/excluded-drug-reference-file-faq.pdf>
- (4) <https://www.medicaid.gov/medicaid/benefits/early-and-periodic-screening-diagnostic-and-treatment/index.html>



August 8, 2022

**RE: Draft Evidence Report - Medications for Obesity Management: Effectiveness and Value**

The Black Women's Health Imperative (BWHI), together with the undersigned health equity stakeholders, appreciates the opportunity to contribute to ICER's review of obesity management treatments. We are committed to eliminating the disparities and inequities in health care that drive poor health outcomes and impede individuals of color, and other underserved communities, from living to their full potential. BWHI submitted a set of recommendations for ICER's consideration following its discussion of the Model and Model Analysis Plan with ICER's review team. Those comments are attached. We also attach a brief description of each organization contributing to the set of recommendations and concerns set forth below.

ICER's review presents an opportunity to disrupt the trajectory of high obesity disease burden combined with under-utilization of proven, effective treatments that disproportionately places Black women and other people of color at high risk of poor health outcomes. Conversely, under-valuing anti-obesity medications generally or justifying restricted access to emerging treatments will likely further entrench payer policies of exclusive reliance on behavioral interventions. Noncoverage policies and restrictive benefit designs excluding obesity pharmacotherapy are grounded in stigma, ignore clinical guidelines, and reflect an anti-science judgment that individuals can, with sufficient will-power, make "good" lifestyle choices and overcome obesity.

The patient, payer and societal impacts of the obesity care gap were summed up in a recent call-to-action for the Latinx community – "insurance coverage for obesity-related treatment doesn't kick in until a person is diagnosed with obesity-related comorbidities, like type 2 diabetes. The system waits until you have a preventable disease, then covers your treatment rather than preventing it in the first place" (Benavides, Rios, Cruz, Univision 2021). As you are likely aware, for most Americans, coverage drives access. The status quo of noncoverage and restricted coverage for anti-obesity medications widens health disparities and disproportionately harms individuals of color who experience approximately half the weight loss from behavioral interventions as their white counterparts (Richie 2018).

- It is projected that half of the US population will have obesity by 2030. (CDC, 2015; Ward, 2019).
- The obesity epidemic is disproportionately decreasing life expectancy and quality of life for individuals of color (see attached CDC state-level data on obesity prevalence).
- Black women have the highest prevalence of obesity and are 2.3 times more likely to have overweight as compared to white women.
- Complications of overweight and obesity are prevalent in the Asian and Pacific Islander communities. In a 2014, an estimated 12.8% of Native Hawaiians, 10.0% of Chinese, 13.0% of Filipinos, 13.6% of Japanese, and 14.9% of Other Pacific Islanders were diagnosed with diabetes compared with 5.0% of white residents of Hawaii (Hawai'i Health Data Warehouse 2018).
- If present trends in obesity continue, it is estimated that 1 in 3 Americans will have diabetes by 2050 (Gao 2018). The projections are even more jarring for women of color
  - 52.5% of Latinas and 49% of Black women are likely to develop diabetes in their lifetime, compared with 31% of white women (Crawford 2015; Narayan 2003).

- Obesity may be the most under-treated chronic disease in the US – just 2% of US adults eligible for obesity pharmacotherapy receive it (Velazquez 2018).

**ICER’s model excluded the considerable harms associated with obesity in patients under age 45, including women of childbearing age.**

ICER focused its model on patients over 45 years of age. This means that the long-term benefits of obesity treatments in younger adults, including women of childbearing age were not considered.

- Gestational diabetes is linked to obesity.
  - U.S. Hispanics/Latinas are at two- to fourfold higher risk for gestational diabetes compared with non-Latina whites (Ferrara 2007; Fujimoto et al. 2013).
  - Black women are generally less likely to suffer from gestational diabetes, but those who do are more likely to be obese and far more likely to subsequently develop Type 2 diabetes.
- Cardiologists and gynecologists recommend that women address obesity before becoming pregnant. In 2019, over half of the young women (20-44 years of age) giving birth had at least one cardiovascular risk factor.
- Overweight and obese women are more likely to suffer from infertility. This can have a life-changing impact on women of color who do not enjoy the same level of access to fertility treatments as their white counterparts (Lake 1997).
- Prepregnancy obesity is associated with increased risk of poor fetal and maternal outcomes including miscarriage, pre-eclampsia, surgical complications, and heart and neural tube defects.
- Obesity may interfere with the pharmacokinetics of emergency contraception (“Plan B”), reducing its effectiveness in women with a BMI over 30 (Edelman, 2016).

The recent Supreme Court decision reversing *Roe v Wade* has driven adoption of very restrictive state abortion laws, particularly in states with high obesity prevalence and maternal morbidity/mortality rates approaching those of developing nations. While it is not possible to predict the likely cost in terms of women’s lives, it is nearly certain that obesity will complicate health outcomes for women forced to carry an unplanned pregnancy to term. We are similarly confronted with the chilling effect of criminal abortion penalties on health care for pregnant women with existing and emergent comorbidities. These laws will not only impact the treatment options available to pregnant women; they will require providers to decide whether a woman’s impending death is sufficiently certain and immediate to justify the provider’s risk of loss of license and/or imprisonment. Women of color, and particularly those with obesity, will likely bear the disproportionate burden of these laws with their future health and even their lives. The impact of obesity on women of childbearing age is of greater urgency now than it was when ICER started its review; it should be included in the model within the base case and societal perspective as well as in the set of contextual considerations.

**ICER should ensure that all avoided costs and likely benefits of anti-obesity medications are factored into the final Evidence Report.**

We recognize that the relationship between obesity and other chronic conditions is complex and that assigning monetary costs to the full range of potential obesity outcomes, complications and comorbidities with precision and certainty would be nearly impossible. We continue to believe that ICER should incorporate an estimated range when science and its logical interpolations/extrapolations make the uncertainty of a particular outcome or finding a matter of increments or degrees.

Similarly, there are meaningful differences in subpopulation prevalence, outcomes, and/or response to alternative treatments; a value assessment aggregating data into a single value calculation will tend to under-value interventions that have higher value in those subpopulations. Black and Latinx patients and other underserved populations are under-studied and under-represented in clinical trials and, unfortunately, most likely to suffer compromised health outcomes from treatment delays and/or denials. ICER would improve the accuracy of its reviews if it either performed subpopulation scenarios or extrapolated existing data to simulate the real world with respect to impacted population, disease burden, and treatment response. The attached “references” list identifies data sources for inputs that are particularly important in obesity, including:

- ICER does not appear to fully consider the association between obesity and heart failure. It appears that myocardial infarction (MI) risk is the driver for heart failure inputs in ICER’s model despite the connection between obesity and non-MI-associated heart failure.
  - o Heart failure with preserved ejection fraction (HFpEF) cases make up between 30% and 75% of heart failure cases worldwide (Harper 2018).
  - o For patients with or at risk for HFpEF, addressing and resolving obesity should be a priority (Aneesh 2022).
  - o Obesity is the primary driver of HFpEF; the obese-diabetic phenotype of HFpEF is both common and tied to worse outcomes (Aneesh 2022).
- ICER limits its inputs related to Type 2 diabetes (T2D) to insulin costs and cardiovascular outcomes. Individuals of color have disproportionate prevalence and compromised outcomes associated with T2D that are ignored by ICER’s model. Given the clear link between obesity and T2D, as well as the heightened risk associated with obesity for patients with T2D, ICER should include the range of T2D outcomes, as well as their associated costs and impact on quality of life, in its obesity review.
  - o the greatest disparity in subpopulation T2D rates is between Black women and white women; and appear to be due to risk factors such as obesity. (NIH, Schneider, 2002)
  - o Black adults are 60 percent more likely than non-Hispanic white adults to be diagnosed with diabetes by a physician, twice as likely to die from T2D, and 3.2 times more likely to progress to ESRD when compared to their white counterparts.
  - o Black and Latinx Medicare beneficiaries with diabetes are more likely to receive lower quality care<sup>i</sup> and have diabetes- related complications, such as end-stage renal disease, chronic kidney disease, and amputations. (Goodney 2013) Black patients make up nearly a third of the US ESRD population (Kucirka 2011).
  - o Black women and other individuals of color with ESRD are more likely to suffer poor health outcomes, including death (Kucirka 2011)
  - o Black transplant candidates have fewer transplant opportunities, and when they receive a kidney transplant, they have higher rates of kidney rejection and death. recipients experience poorer outcomes, including higher rates of kidney rejection and patient death, than white transplant recipients (Purnell 2016)<sup>ii</sup>
- ICER’s model does not reflect the increase in all-cause mortality associated with obesity. Studies suggest that obesity reduces life expectancy by 9 years (Flegel 2013; Greenberg 2013) and that patients resolving their obesity can mitigate their long-term health risks (Ma 2017).
- The model does not consider ongoing weight gain in patients failing behavioral interventions and not receiving anti-obesity medication or reduced effectiveness of behavioral interventions in individuals of color.
  - Economic models generally assign utility increments and decrements for incremental decreases and increases in BMI – a range of decrements should be assigned to the base case calculations for behavioral interventions alone.

- Many cancers impacting women are estrogenic (breast cancer, endometrial cancer, ovarian cancer); excess adiposity increases risk associated with these cancers. Obesity has consistently been found to be associated with breast cancer among women, increasing the prevalence by 30 to 50 percent.
  - o In addition, among women who have breast cancer, those who are overweight or obese have shorter survival times and worse prognoses.
  - o Women with obesity are at increased risk of ovarian cancer compared (1.53 for women who are overweight and 3.22 for women with obesity).
  - o There appears to be a linear relationship between endometrial cancer risk and BMI.
- Several studies have shown a link between obesity in men and the likelihood of developing advanced prostate cancer. Men with obesity are more likely to develop advanced symptoms and die, and to have recurrence after radical prostatectomy.
- There is significant subpopulation variability in cardiovascular outcomes associated with obesity.
  - o Hypertension and diabetes are more likely to lead to coronary artery disease and heart failure in women than in men
  - o Compared to men, women with heart failure have higher frequency rates of dyspnea on exertion, difficulty exercising, and edema. (Levy 2002; Gerber 2015)
  - o Women with cardiovascular disease tend to have worse quality of life ratings than men for intermediate activities of daily living and social activity.
  - o Depression is more common in women with heart failure than in men.
- The Draft Evidence Report did not include 2021 evidence demonstrating that Semaglutide's effectiveness is similar across races and that it is especially effective in individuals on the lower-BMI levels of obesity and in female patients.
- The review appears to assume that ALL patients on medication will remain on drug throughout their lives. The prevailing standard of care is to continue medication ONLY in patients losing at least 5% of body weight in the initial 12 weeks (some recommendations suggest 6 months) of treatment. Including non-responders in the "averaging" is appropriate in clinical trials but not in modeling costs and benefits to mirror real-world use. We suggest that nonresponders "exit" the model at 3 or 6 months.
- CDC and CMS have cited to a report compiled by The Milken Group," finding that in 2016, obesity-associated chronic conditions accounted for \$480.7 billion in direct health care costs in the US, and an added \$1.24 trillion in indirect costs. ICER's figures for the same year set direct medical costs at \$260 billion. Moreover, the report noted that obesity is the greatest contributing risk factor to the burden of chronic diseases, accounting for \$47.1% of total US chronic disease costs. While we do not assert that all those costs would be eliminated through clinically meaningful weight loss, an estimated range of avoided costs and/or improved outcomes would improve the accuracy of ICER's base case and scenario calculations and alert readers to the inherent uncertainties associated with calculating and comparing value in obesity interventions.
- Clinical guidelines include cautionary statements on use of the various treatments that should be included in ICER's final evidence review, including
  - o Phentermine should be avoided in patients with diabetes mellitus and uncontrolled hypertension or a history of heart disease (Endocrine Society, European Society of Endocrinology, Obesity Society Guidelines), a history of nephrolithiasis (AACE guidelines) or anxiety disorders
  - o Naltrexone/bupropion, lorcaserin, and phentermine/topiramate ER are not recommended in patients with severe renal impairment (<30 mL/min) (AACE guidelines)

- Medications other than naltrexone/bupropion should be used in patients with high blood pressure. Naltrexone/bupropion should be avoided in patients with chronic pain requiring opioid medications.

**We appreciate ICER's previous efforts to quantify the societal value of reducing health disparities within its value framework and recommend that the Health Improvement Distribution Index (HIDI) include disparities in both prevalence and health outcomes.**

ICER has previously calculated a Health Improvement Distribution Index to acknowledge and quantify increased subpopulation health gains in disease states that disproportionately affect identifiable subpopulations. We believe that inclusion of a HIDI in ICER reviews highlights ICER's goal of reducing health disparities and inequities within its value framework. The HIDI can be a helpful tool toward that goal, particularly if ICER refines its methodology to:

- Incorporate disparate prevalence among subpopulations as one factor in calculating potential health improvement.
- Include consideration of greater disease burden beyond prevalence to include poorer health outcomes, higher risk of comorbidities, variability in disease progression and treatment response, differential age of onset, and other factors that contribute to health disparities and inequities.

## **Conclusion**

We appreciate ICER's continuing efforts to include input from stakeholders as it finalizes its reports. We urge ICER to ensure that the final Evidence Review for anti-obesity medications prioritizes access to treatments that are desperately needed in our communities. Now, just 2% of individuals potentially benefiting from anti-obesity medications are able to receive them. We expect that it will take years, or longer, for the medical community to translate the scientific consensus on obesity as a chronic disease into clinical practice reflecting the standard of care. ICER, therefore, will have time and multiple opportunities to make recommendations to reduce the budgetary impact of these treatments if and when anti-obesity medication use reflects the treatment needs of the US population. For this report, we urge that ICER focus its cautions toward ensuring that the full benefits of the reviewed medications are considered in the base case and available to prescribers, patients, and payers.

We appreciate the opportunity to provide our recommendations and concerns and look forward to continuing our participation in ICER's review.

Very truly yours,

Black Women's Health Imperative  
National Hispanic Council on Aging  
Healthy Women  
National Black Nurses Association  
Association of Black Cardiologist  
National Hispanic Medical Association  
National Minority Quality Forum  
National Black Leadership Commission on Health (Black Health)  
Southern Christian Leadership Conference – Global Policy Initiative

## Attachment 1: Health Equity Stakeholder Organizations



**BLACK WOMEN'S**  
HEALTH IMPERATIVE

BWHI is the first and only national non-profit solely dedicated to achieving health equity for Black women in America. Founded in 1983 by Byllye Y. Avery as the National Black Women's Health Project at a conference on the campus of Spelman College, BWHI has evolved into a nationally recognized organization leading health policy, education, research, knowledge and leadership development and communications designed to improve the healthy outcomes of Black women. BWHI continues to be dedicated to promoting the physical, mental and spiritual health and well-being of the nation's 21 million African American women and girls.



The National Hispanic Council on Aging (NHCOA) was conceived in 1969 by Hispanic researchers, educators, and services providers to enhance Hispanic older adults' quality of life by identifying and addressing their unique needs and the issues of most critical impact. NHCOA has recently completed half a century of existence, and has established groundbreaking programs targeting older adults and their families, health care providers, media, local health departments and other public agencies, and academic institutions, among others. As we face a pandemic, NHCOA is pivoting to use innovative ways to continue meeting the needs of Hispanic older adults, their families and caregivers.

NHCOA not only works to improve the quality of life for Hispanic seniors—it focuses on bringing out the best in the Hispanic community to empower older adults and their families, ensuring all are able to age in dignity and with good health.



HealthyWomen is on a mission to educate women ages 35 to 64 to make informed health choices. We achieve our mission of educating women to make informed health choices by connecting with women through fact-based, expert-sourced content, and creative evidence-based programming. We keep women's health part of the national dialogue by raising awareness to decision makers about the impact health policy



has on women and families. And we work collaboratively with partner organizations and alliances to reach more women.



THE NATIONAL BLACK NURSES ASSOCIATION, INC. is a non-profit organization that was organized in 1971 under the leadership of Dr. Lauranne Sams, former Dean and Professor of Nursing, School of Nursing, Tuskegee University, Tuskegee, Alabama.

NBNA represents approximately 200,000 African American nurses from the USA, Canada, Eastern Caribbean and Africa, with 115 chartered chapters nationwide. Our mission is to provide a forum for collective action by African American nurses to advocate for and implement strategies to ensure access to the highest quality of healthcare for persons of color. NBNA collaborates with private and public agencies/organizations that share common concerns for improving the health status of all people, particularly African Americans and other minority consumers.



Founded in 1974, the Association of Black Cardiologists, Inc., (ABC) is a nonprofit organization with an international membership of over 2,000 health professionals, lay members of the community (Community Health Advocates), corporate members, and institutional members. The ABC is dedicated to eliminating the disparities related to cardiovascular disease in all people of color. Today, the ABC's public and private partnerships continue to increase our impact in communities across the nation.

ABC adheres to the vision that all people regardless of race, ethnicity or gender should benefit equally from reduction in the frequency, duration and impact of diseases of the heart and blood vessels. Our mission is to promote the prevention and treatment of cardiovascular disease, including stroke, in blacks and other minorities and to achieve health equity for all through the elimination of disparities.



Established in 1994 in Washington, DC, the National Hispanic Medical Association is a non-profit association representing the interests of 50,000 licensed Hispanic physicians in the United States. NHMA is dedicated to empowering Hispanic physicians to be leaders who will help eliminate health disparities and improve the health of Hispanics.

NHMA has developed a set of unique programs to address the major barriers and needs of the Hispanic community and other underserved populations. Our programs serve to provide platforms, resources, and

coordination among our network of physicians and key contacts with a special emphasis on work with major public and private sector stakeholders in public health and healthcare policies.



The National Minority Quality Forum is a nonprofit, nonpartisan research and educational organization dedicated to ensuring that high-risk racial and ethnic populations and communities receive optimal health care. The Forum was founded in 1998 to address the critical need for strengthening national and local efforts to use evidence-based, data-driven initiatives to guide programs to eliminate the disproportionate burden of premature death and preventable illness for racial and ethnic minorities and other special populations.

Our partnerships and collaborations are wide-ranging. The Forum works with key stakeholders (including health-care providers and professionals, administrators, policy makers, payers, industry, and community and faith-based organizations) to improve the delivery of optimal care to diverse populations.



The National Black Leadership Commission on AIDS, Inc. (NBLCA) was founded in 1987 by Debra Frazer-Howze, who led the organization for 21 years as President and CEO. Building on the strong foundation of NBLCA – the nation’s oldest nonprofit organization of its kind, dedicated to educating, mobilizing and empowering Black leaders to meet the challenge of fighting HIV/AIDS – Black Health has evolved to become a comprehensive advocacy, policy and action organization that addresses multiple health disparities affecting Blacks/African Americans.



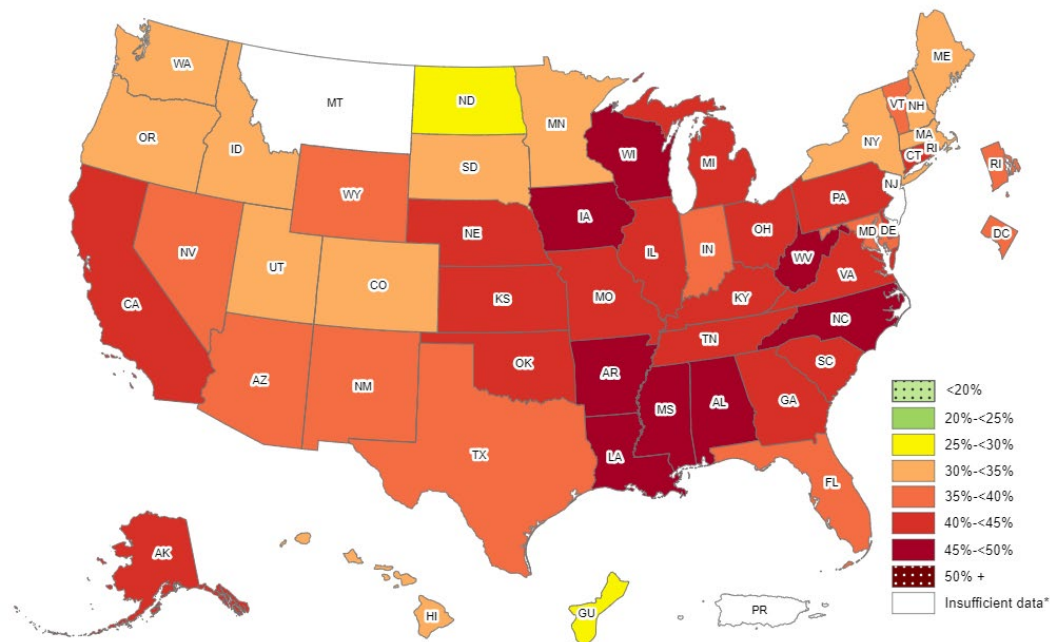
The Southern Christian Leadership Conference is a nonprofit, non-sectarian, inter-faith, advocacy organization that is committed to nonviolent action to achieve social, economic, and political justice. SCLC’s focus is to educate youth and adults in the areas of personal responsibility, leadership potential, and community service; to ensure economic justice and civil rights and to eradicate racism wherever it exists.

SCL Global Policy Initiative researches specific social justice issues to identify correctable problems, design innovative policies to address these problems, and build coalitions to advocate for a policy strategy supporting a better standard of living for all communities.

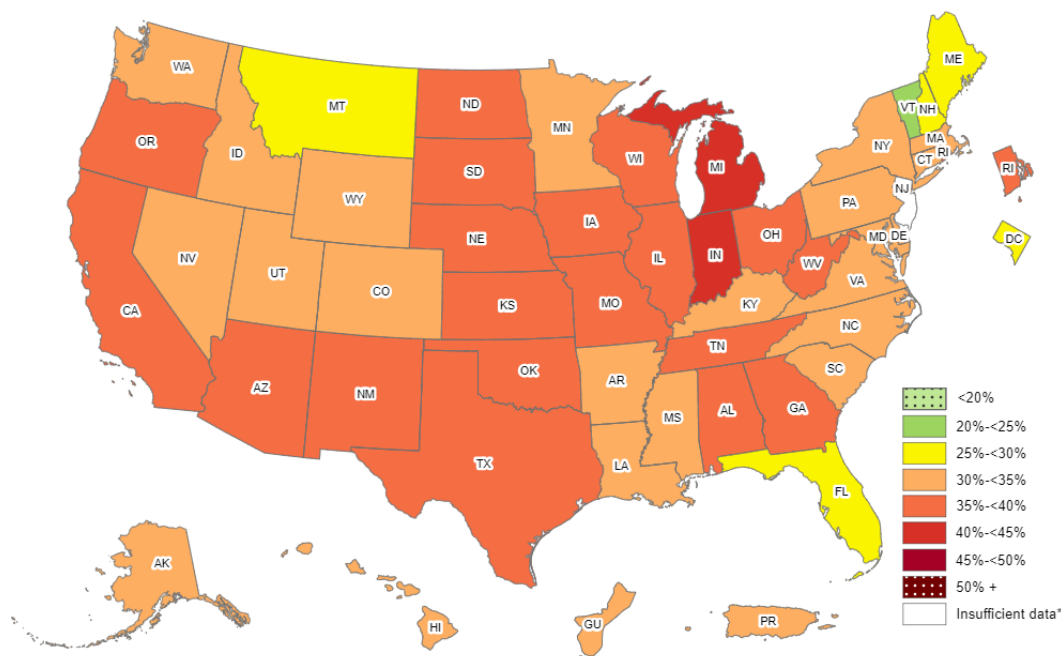


**Attachment 2 CDC Adult Obesity Prevalence Maps - [Adult Obesity Prevalence Maps | Overweight & Obesity | CDC](#)**

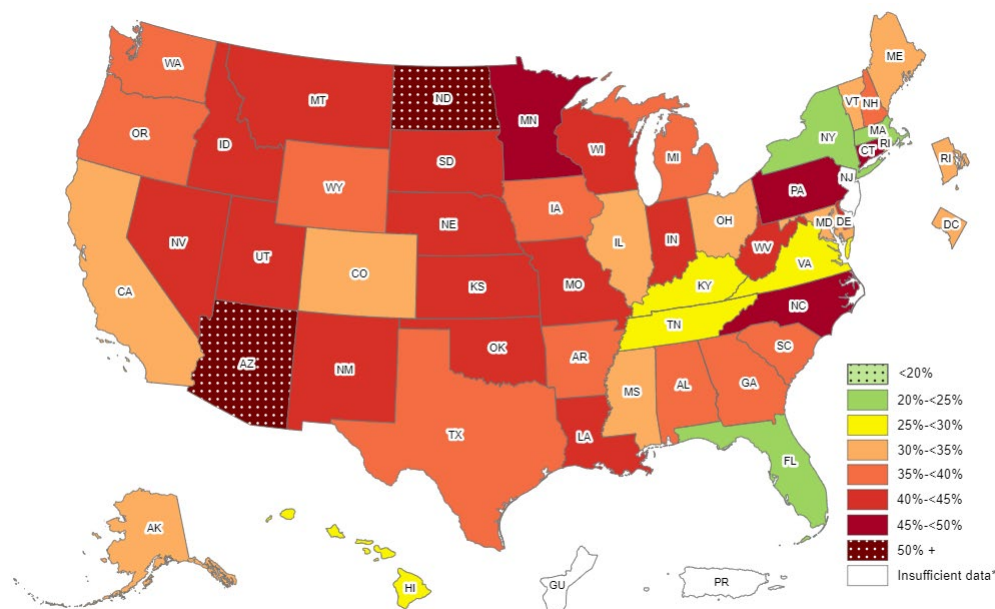
***Prevalence of Self-Reported Obesity Among Non-Hispanic Black Adults, by State and Territory, BRFSS, 2018–2020***



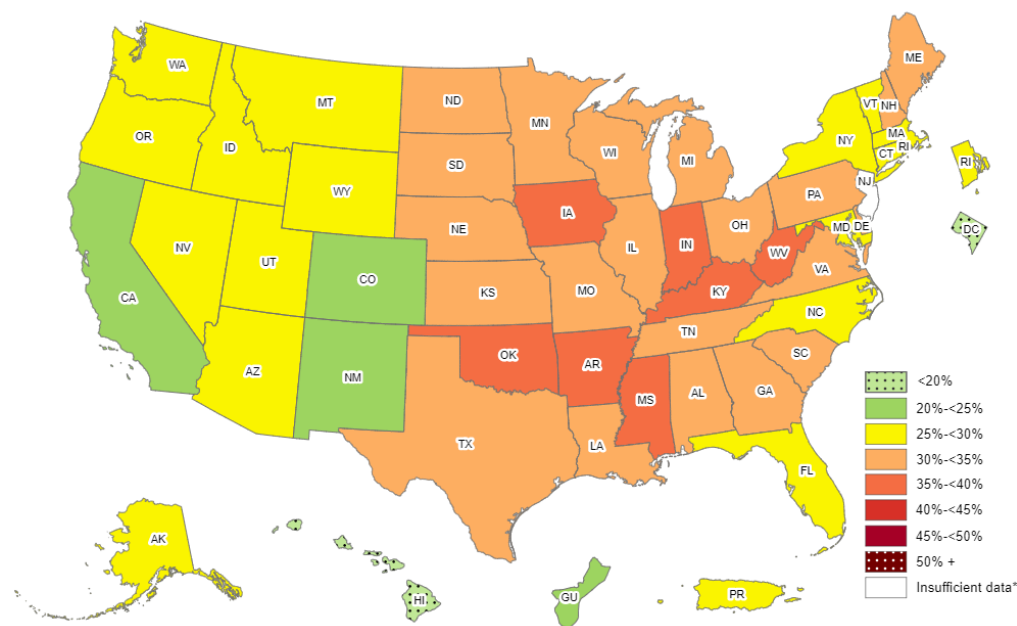
***Prevalence of Self-Reported Obesity Among Hispanic Adults, by State and Territory, BRFSS, 2018–2020***



***Prevalence of Self-Reported Obesity Among Non-Hispanic American Indian or Alaska Native Adults, by State and Territory, BRFSS, 2018–2020***



***Prevalence of Self-Reported Obesity Among Non-Hispanic White Adults, by State and Territory, BRFSS, 2018–2020***



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