PIPC Partnership to Improve Patient Care

March 16, 2023

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 nonalcoholic steatohepatitis (NASH). Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease. Of patients impacted by NAFLD, one in five will go on to develop NASH, which can progress to cirrhosis or liver cancer. Diagnosis and treatment of NASH is imperative to stem these more serious outcomes.[1] PIPC asks ICER to consider the following comments on its draft evidence report for NASH.

The assertions ICER makes in it evidence matrix are confusing and ignore the patient perspective.

The purpose of randomized controlled trials (RCTs) are to show a statistically significant difference in a clinically important primary outcome, which it clearly has in the case of *resmetirom*. It was shown in the MAESTRO-NASH trial to be better than the standard of care at achieving NASH resolution without worsening of fibrosis stage at 12 and 24 months with a p value of less than 0.0001, and with no statistically significant difference in terms of rate of adverse events.[2] Therefore, we would assert that this conforms to the definition of ICERs A grade, which equals a high certainty of a substantial benefit (moderate to large) net health benefit, or at a minimum, its B grade, which equals a high certainty of a small health benefit. The evidence rating ICER selects for *resmetirom* is C. This is confusing as ICER describes *resmetirom* in its evidence rating section as, "*resmetirom appears to reduce progression, promote regression of fibrosis, and lead to resolutions of NASH compared with placebo.*" ICER alludes to the fact that the reason it falls short in terms of evidence is due to its assertion that *long-term benefits are uncertain*, and the '*importance*' of these benefits are uncertain.

The reality is that if ICER continues to assess treatments at or before FDA approval, there will always remain a question as to long-term benefit. If ICER's evidence rating requires proof of long-term benefit beyond the duration of a clinical trial, then ICER must conduct its assessments later in the life-cycle of a treatment, when that evidence exists. If ICER is going to continue to conduct assessments at or before approval, ICER needs to reconsider how it weights its evidence matrix grades. The evidence matrix must have at least the possibility that any new technology can achieve a rating of A, which is currently not possible if it requires long-term evidence for treatments that have not yet been FDA approved. Another issue with this current paradigm is that ICER seems to imply that there is no cost to delaying the introduction of new therapies, but certainty and delay are a trade-off. Individuals living with

[1] https://globalliver.org/step-up-for-nash/
[2] Younossi ZM, Ratziu V, Loomba R, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet (London, England).* 2019;394(10215):2184-2196.

diseases now, as well as their providers, know that some level of risk is worth not having to wait 20-30 years for a definitive answer when there is a chance they could be benefiting today from treatment.[3]

The second point ICER makes regarding the 'importance' of the clinical effect is also confusing. Experts agree, which ICER acknowledges in its assessment, that slowing or halting the progression of fibrosis in NASH patients is important. ICER noted in its patient review that there is "*consensus among patients with NASH that the most important outcome is halting the progression of fibrosis.*" Yet, ICER states in regard to its evidence matrix rating that it is uncertain whether halting the progression of fibrosis is important, a statement that is not just contradictory to the goals of treating NASH, but also outright ignores the patient perspective acknowledged by ICER that halting or slowing fibrosis is not just important but *the most* important outcome.

ICER should work closely with NASH patients and providers to update its model.

ICER seems to mischaracterize certain aspects of NASH, which lead to an underestimation of the importance of treatment and a flawed model. ICER asserts that NASH is not a progressive disease and that NASH patients who are asymptomatic are not impacted by the disease. Neither of these assertions are accurate. Despite patients not experiencing symptoms, the cell damage that occurs with NASH, even while patients are asymptomatic, can ultimately lead to cirrhosis. Once a patient has progressed to cirrhosis, if not treated, cirrhosis can lead to liver failure.[4]

ICER should incorporate caregiver burden in its base case model.

A recent study of caregivers of patients with liver disease showed substantially lower quality of life than non-caregivers in categories.[5] A similar study comparing caregivers to a normal population showed lower level of quality of life as well as a higher level of anxiety. Answers from these caregivers on a questionnaire designed to measure depression also suggested that 34% of caregivers suffered from clinical depression.[6]

In instances, like NASH, where caregivers are known to have an outsized burden, it is becoming commonplace in health technology assessments to incorporate caregiver utility into base economic models. The National Institute for Health and Care Excellence (NICE), which ICER leans heavily on for its approach to value assessment, regularly includes caregiver utility in its base-case models for diseases where caregiver burden is known to be high.[7] Including caregiver utility is also the recommended

[3] Stevens W, Philipson T, Wu Y, Chen C, Lakdawalla D. A cost-benefit analysis of using evidence of effectiveness in terms of progression free survival in making reimbursement decisions on new cancer therapies. InForum for Health Economics and Policy 2014 Jan 1 (Vol. 17, No. 1, pp. 21-52).
[4] https://liverfoundation.org/liver-diseases/fatty-liver-disease/nonalcoholic-steatohepatitis-nash/nash-complications/
[5] Nguyen DL, Chao D, Ma G, Morgan T. Quality of life and factors predictive of burden among primary caregivers of chronic liver disease patients. Annals of gastroenterology: quarterly publication of the Hellenic Society of Gastroenterology. 2015 Jan;28(1):124.
[6] Hareendran A, Devadas K, Sreesh S, Tom Oommen T, Varghese J, Lubina S, Nahaz N, Krishna A, Mullali Mohamed Kunhi N. Quality of life, caregiver burden and mental health disorders in primary caregivers of patients with cirrhosis. Liver International. 2020 Dec;40(12):2939-49.
[7] Afentou N, Jarl J, Gerdtham UG, Saha S. Economic evaluation of interventions in Parkinson's disease: a systematic literature review. Movement disorders clinical practice. 2019 Apr;6(4):282-90.

perspective for cost-effectiveness models of the United States' Second Panel on Cost-Effectiveness[8], and the International Society for Pharmacoeconomics and Outcomes Research.[9] ICER should follow this example and include caregiver burden in its models.

ICER makes simplistic assumptions about disease progression and liver transplant.

ICER appears to make an assumption in the model that if someone needs a liver transplant, they get one. In reality, the number of patients on the waiting list for transplants is always longer than the number of available donor livers in the United States, which means that only a fraction of patients who need one, get one.[10] Most recent data from UNOS suggests between 20-60% of patients depending on MELD score.[11] A recent study showed that NASH patients have both the lowest likelihood of receiving a liver transplant while having the highest mortality while on the list.[12] Given this reality, progression to end stage liver disease is in fact significantly more severe for NASH patients than other patients on the liver transplant waiting list. Without factoring this into the model, any results will underestimate the value of delaying NASH patients' progression to later stages of disease.

ICER's model ignores the wide public health value of reduced demand for liver transplants.

In addition to its faulty assumptions about the availability of liver transplants, the model also ignores the public health value of reducing (or delaying) the demand for liver transplants in the NASH population. Since demand outstrips supply for liver transplants, each transplant averted has value not just to that patient but also to other patients who now see an increased probability of successfully receiving a donor liver. When modeling the cost-effectiveness of vaccines, the public health benefit is factored in by incorporating the benefits from the accrual of herd immunity. In the case of NASH, the public health benefit of fewer patients ultimately needing or delaying the need for liver transplants should be factored into the model.[13] This is especially true because NASH is quickly becoming the largest cause of end-stage liver disease in the United States.

ICER oversimplifies disease heterogeneity and complexity.

ICER's use of 'prior cardiovascular event' as an overarching category for patients is a simplification. The condition of prior cardiovascular event will likely make up a considerable proportion of patients suffering from NASH, but it will also hide a considerable variation in both type of patients and level of

[8] Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. Jama. 2016 Sep 13;316(10):1093-103.
[9] Garrison Jr LP, Mansley EC, Abbott III TA, Bresnahan BW, Hay JW, Smeeding J. Good research practices for measuring drug costs in cost-effectiveness analyses: a societal perspective: the ispor drug cost task force report—Part II. Value in Health. 2010 Jan;13(1):8-13.
[10] Wong RJ, Singal AK. Trends in Liver Disease Etiology Among Adults Awaiting Liver Transplantation in the United States, 2014-2019. JAMA Network Open. 2020 Feb 5;3(2):e1920294-.
[11] https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#
[12] Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, Ahmed A. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015 Mar 1;148(3):547-55.
[13] Jena AB, Stevens W, Gonzalez YS, Marx SE, Juday T, Lakdawalla DN, Philipson TJ. The wider public health value of HCV treatment accrued by liver transplant recipients. The American journal of managed care. 2016 May;22(6 Spec No.):SP212-9

risk for both future cardiovascular events and for other co-existing conditions excluded from the model. The risk of future cardiovascular events for a patient who has suffered a minor event, such as a transitory ischemic attack, is very different from the risks associated with a previous myocardial infarction or stroke.[14]

In addition to these simplified assumptions about the patient population, another issue is that the Framingham Heart study was used to estimate the risk of cardiovascular events rather than real world data sources. The Framingham risk model has been criticized as a source for real world modeling of outcomes in populations with co-existing conditions,[15,16] as it is far from representative of a true population of need in the United States as a whole. Several national and international clinical and research organizations, including ISPOR,[17] the Royal Society of Medicine[18], and, most recently, the Second Panel on Cost Effectiveness,[19] have endorsed the use of real-world evidence for baseline risk in the evaluation of new technologies.

Conclusion

PIPC urges ICER to go review its report alongside experts in the field of liver disease, including patients and providers to ensure that it is accurately representing NASH and its modeling choices can lead to an accurate representation of value to this community.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

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[16] Coleman RL, Stevens RJ, Retnakaran R, Holman RR. Framingham, SCORE, and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. Diabetes care. 2007 May 1;30(5):1292-3.
[17] Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices–Modeling Studies. Value Health 2003;6:9-17
[18] Rawlins M. De testimonio: on the evidence for decisions about the use of therapeutic interventions. Lancet 2008;372:2152-61
[19] Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. Jama. 2016 Sep 13;316(10):1093-103.