PIPC Partnership to Improve Patient Care

June 24, 2020

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 this opportunity to comment on the Institute for Clinical and Economic Review's (ICER) draft evidence report regarding treatments for Non-alcoholic Steatohepatitis (NASH). NASH is a severe form of non-alcoholic fatty liver disease (NAFLD) and is expected to become the leading cause of liver transplants in the United States by 2025.[1] Symptoms of NASH are often non-specific, making the condition difficult to diagnose. As a result, patients are frequently unaware they have NASH until later stages of the disease when the liver is damaged beyond repair and costly organ transplant surgeries are the only available treatment option. The cost of caring for patients with NASH is projected to increase 18% by 2035, with annual medical and societal costs associated with NAFLD estimated at $292 billion.[2] Additionally, since patients with NASH experience poor cardiometabolic function, these individuals are often at increased risk of death due to cardiovascular events. One study noted that up to 38% of deaths in patients with NASH were directly tied to cardiovascular events.[3] These characteristics make NASH a very threatening condition for patients and a costly condition for our healthcare system. Up to this point, there have been no FDA-approved treatments for NASH. This novel treatment is a breakthrough for patients, and it is critical that is it evaluated responsibly. With this in mind, PIPC asks ICER to consider the following comments:

ICER's model oversimplifies a complex condition

ICER's model groups the NASH patient populations into just two initial groups based on prior cardiovascular events and stage of fibrosis. Notably, the bulk of patients in fibrosis groups F1, F2 and F3 are combined into a single group. This generalization is problematic as there are significant differences in terms of severity of disease, co-morbidities, and associated risks of transition to worsening health states among patients in F1, F2, and F3 subgroups[4]. One study

[1] Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology*. 2015;148:547-555
[2] Perumpail BJ, Khan MA, Yoo ER, Cholankeril G, Kim D, Ahmed A. Clinical epidemiology and disease burden of nonalcoholic fatty liver disease. *World J Gastroenterol*. 2017;23(47):8263-8276.
[3] Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, associates with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2015;149(2):389-397.
[4] Ekstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, Hultcrantz R. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology. 2015 May;61(5):1547-54.

noted this heterogeneity and suggested that liver-related mortality increased exponentially as patients progress through worsening stages of fibrosis[5]. The simplification of a complex disease down to just a small number of health states is concerning as this type of dichotomization or over-categorization of outcomes has been shown to lead to underestimation of treatment effects[6,7]. Furthermore, this structure also suggests ICER's model does not account nor measure the value of reducing the probability of patients moving from stage F2 to F3, which can offer considerable health gains to patients.

ICER's model continues to rely on the discriminatory QALY, which is an inappropriate metric to accurately show health gains for NASH patients.

As PIPC has previously emphasized to ICER, the QALY is a discriminatory metric and has real limitations in measuring true health. The QALY is particularly problematic in measuring the effects of treatments for chronic diseases, which makes it inappropriate for use in evaluating treatments for NASH.

ICER's model exacerbates the shortcomings of the QALY by discounting the future health gains incorrectly. ICER constructed the model in a way which assumes that all life years 'gained' occur at the end of life. In reality, these gains are a result of a reduced mortality risk – and improved quality of life - in every single year of treatment from the first year of treatment to the final year of life or treatment. This is an important distinction as treatments improve a patient's quality of life consistently over time, allowing them to live more productive and symptom-free lives.

ICER's report makes incorrect assumptions about liver transplant procedures

ICER's model assumes when patients need a liver transplant, they get one. But in reality, the waiting list for liver transplants is always longer than the number of available livers in the United States. This means that only a fraction of patients who need a transplant get one.[8] Other studies, such as recent data from the United Network for Organ Sharing (UNOS), suggests this number to be as low as 20% depending on MELD score[9]. Patients with NASH experience additional barriers to receiving liver transplants. One study showed that NASH patients have both the lowest likelihood of receiving a liver transplant while having the highest mortality while on the

[5] Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, Sebastiani G, Ekstedt M, Hagstrom H, Nasr P, Stal P. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. Hepatology. 2017 May 1;65(5):1557-65.
[6] Altman DG, Royston P. The cost of dichotomising continuous variables. Bmj. 2006 May 4;332(7549):1080.
[7] Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Statistics in medicine. 2006 Jan 15;25(1):127-41.
[8] 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-.
[9] https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#

list,[10] as progression to end stage liver disease is significantly more severe for NASH patients than most patients on the liver transplant waiting list. By not accounting for these factors in the model, ICER is significantly underestimating the value of delaying or averting NASH patients' progression to later stages of disease.

ICER's models also ignore the public health value of reducing – or delaying – the demand for liver transplants in the NASH population. Since demand outstrips supply when it comes to livers available for transplant, each transplant averted has value not just to the individual patient but also to other patients who now see an increased probability of successfully receiving a liver. It is not uncommon to include holistic public health benefits when constructing value assessments. For example, it is typical when modeling the cost-effectiveness of vaccines to incorporate the benefits from the accrual of herd immunity. Following this blueprint, the public health value of reducing waiting lists for liver transplants should be incorporated into a model estimating the value of treating NASH, especially as it is fast becoming the largest cause of chronic liver disease in the United States.

ICER's base case should include societal costs of NASH

As mentioned previously, NASH is a devastating disease, as symptoms are non-specific and frequently silent. Patients often believe themselves to be healthy until they learn of their diagnosis, at which point the condition has already progressed to severe. The nonmedical costs associated with this diagnosis should be considered in ICER's review. NASH patients often must suddenly withdraw from the workforce due to cardiovascular events and other complications. This lost productivity has a huge impact on patients' lives and should be reflected accurately in the base case.

ICER incorrectly estimates cardiovascular risk

ICER's use of *prior cardiovascular event* as an overarching category for patients is an inappropriate oversimplification of its model. This generalization makes up a considerable proportion of patients suffering from NASH but hides considerable variation in both type of patients and level of risk for both future cardiovascular events and for other prominent comorbidities 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 significantly different from the risks associated with a previous myocardial infarction or stroke,[11] and this difference should be accounted for in ICER's model.

[10] 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.

[11] Rana JS, Liu JY, Moffet HH, Jaffe M, Karter AJ. Diabetes and prior coronary heart disease are not necessarily risk equivalent for future coronary heart disease events. Journal of general internal medicine. 2016 Apr 1;31(4):387-93.

Another concern is that ICER chose to source data from the Framingham Heart study to estimate cardiovascular risk, as opposed to leveraging real-world data sources. The Framingham risk model has been criticized numerous times as a poor source for real world modeling of outcomes in co-morbid populations[12,13] as it does not represent the true population of need in the United States. Several national and international clinical and research organizations, including ISPOR,[14] the Royal Society of Medicine[15], and, most recently, the Second Panel on Cost Effectiveness,[16] have endorsed the use of real world evidence for baseline risk in the evaluation of new technologies.

ICER's model does not accurately depict the financial impact of this treatment on patients and the healthcare system

NASH is a disease that not only puts a huge strain on patients, but as mentioned previously, is also very costly to the healthcare system. There are currently no FDA approved treatments for NASH, and the treatments and comorbidities that accompany the disease as it progresses are expensive to treat. The Global Liver Institute and American Gastroenterological Association highlighted this to ICER in their initial comments, stating, "The rise of NASH, its complications and comorbidities carry significant economic costs for health systems and society. The efficacy and side effects of [obeticholic acid] or any other pharmacologic intervention should be evaluated against the cost of disease progression and cost as well as efficacy of current standard of care (weight loss)." With this in mind, it is absolutely necessary that ICER's model should strive to accurately depict the economic value a treatment for NASH would have to the healthcare system.

In order to capture the accurate financial picture, ICER should have used dynamic pricing. The relevance of dynamic pricing is heightened where benefits are accrued over a longer time period, like lifetime models. The NASH model is a lifetime simulation model, where patients live up to another 15-20 years after initiating treatment. This means patients will continue to accrue benefits and the health system will save costs on other interventions they may have needed for this entire duration of time.

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[12] Abu-Assi E, Otero-Ravina F, Vidal GA, Méndez AC, Mosquera LV, Loureiro MS, Villar MC, Villaverde JF, Saavedra FM, González-Juanatey JR, Grupo Barbanza researchers. Comparison of the reliability and validity of four contemporary risk stratification schemes to predict thromboembolism in non-anticoagulated patients with atrial fibrillation. International journal of cardiology. 2013 Jun 5;166(1):205-9.

[13] 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.

[14] 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

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[16] 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.

Additionally, the uptake of new therapies happens slowly over time. Numerous studies have shown that while using static pricing may make sense for short-term cost-effectiveness modeling, it is not appropriate when developing lifetime models.[17,18,19] To assume that the cost of any treatment indicated for NASH will be the same in ten or twenty years from current prices, is highly unlikely. The price pattern for most drugs has seen significant decline after 5-7 years of relative stability, on average resulting in a price close to 10-20% of its launch price after ten years.[20] More accurate cost modeling must be considered in order to paint a true picture of a treatments impact on patients and society.

Conclusion

NASH is a complex condition, and it is important ICER holistically capture the complexity and the impact the disease has on individual patients and public health in its model.

Sincerely,

Tony Coelho
Chairman
Partnership to Improve Patient Care

[17] 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.
[18] Healy P, Pugatch M. Capturing value: Why dynamic efficiency should be considered in the pricing and reimbursement of medicines. Stockholm: Stockholm Network. 2012.
[19] Vondeling GT, Cao Q, Postma MJ, Rozenbaum MH. The impact of patent expiry on drug prices: a systematic literature review. Applied health economics and health policy. 2018 Oct 1;16(5):653-60.
[20] Lichtenberg, F. R., & Duflos, G. (2009). The effect of patent expiration on US drug prices, marketing, and utilization by the public. Manhattan Institute for Policy Research.