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VIA Electronic Delivery

RE: Draft Evidence Report: Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis with Fibrosis

Request for Comments

Dear Sir or Madam:

Global Liver Institute (GLI) and GLI's NASH Council appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) draft evidence report entitled "Obeticholic Acid for the Treatment of Nonalcoholic Steatohepatitis with Fibrosis."

The NASH Council coalesces an expanded set of stakeholders around the urgency of developing mechanisms for quantifying and addressing nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). We appreciate the institute's transparency and recognition of the need to include the NASH community voice throughout your assessment of the comparative clinical effectiveness and value of Obeticholic Acid (Intercept) for the treatment of this life-threatening disease.

As we read through the draft evidence report, we have found a few core issues that should be considered and addressed as you advance towards a final draft:

1. Lack of Patient Inclusive Language and Impact on Quality of Life
2. Model Assumption: NASH Standard of Care
3. Model Assumption: "Gold" Standard Diagnostic
4. Model Assumption: Length of Treatment
5. Solution at Every Stage
6. The Cost of Not Treating NASH

Lack of Patient Inclusive Language and Impact on Quality of Life

Throughout the report there is a lack of patient inclusive or people first language, and acknowledgment of the NASH impact on quality of life. It is critical for ICER to put patients at the center of all of their assessments, and this should be abundantly through their choice of language and recognition of how a disease can impact daily life.

Firstly, communication is one of the foundational aspects of patient care that impacts patient satisfaction, morale, and builds rapport between physicians, researchers, and patients. Person-first language is a style of communication in which the person is listed first followed by descriptive terms, which avoids defining a person by his or her disease state, reduces stigma and places the emphasis on the person rather than the disease or disability. Multiple agencies and organizations including Center for Disease Control and Prevention (CDC), American Psychological Association, and American Society of Addiction Medicine encourage person-first language. The American Medical Association (AMA) also recommends the use of person-first language in the AMA Code of Styles. In many instances throughout the draft evidence report the choice of classifying patients as obese or as a diabetic instead of patients with obesity or diabetes, portrays a judgmental tone that is counterproductive to ICER's goals.

Secondly, patients with NASH experience a range of symptoms that negatively affect their quality of life with the most prevalent being fatigue, but also including major depressive disorder, generalized anxiety disorder, feeling bloated, having discomfort or pain around the liver, sleeping problems and lethargy.[1] [2] [3] [4] Studies have also found greater impairments in quality of life and work productivity in patients with advanced NASH.[1] [5] Work absences are also an issue with caregivers, causing lost time, lost wages and sometimes even job loss. It is important for any assessment of NASH treatment to consider holistically the impact on quality of life.

Model Assumption: NASH Standard of Care

Standard of or "usual" care is a faulty comparator, as it does not truly exist for NASH. The ultimate aim of treatment for NASH is to reduce progression to cirrhosis or liver cancer and decrease fibrosis progression as well as NASH related mortality.[6] ICER defines usual care as, "usual care includes lifestyle interventions as well as usual care for associated metabolic comorbidities, and may include vitamin E."

There is a lack of unified approach in early detection and management of NASH. The rate of disease progression is not uniform; some people experience fast fibrosis progression while others follow a much slower course or may even experience regression.[7] Symptoms of NASH, which may include fatigue, lethargy, abdominal pain and sleeping problems, are non-specific so they can often be misinterpreted.[8] [9] Most often patients will present with fatigue alone and are ignored. NASH is typically only detected once it has progressed to cirrhosis or liver cancer,[10] therefore most people live with the disease for years without being aware of the damage accumulating in their liver. Currently there is a lack of guidelines for regular follow up that providers use. In many ways the current NASH standard of care can be compared to previously outdated standards for one of its comorbidities, prediabetes and diabetes. For decades prediabetes was ignored as well.

With this said, we ask for the clarification of a few critical points when discussing "usual care" in the final report. First, 7-10% weight loss is truly rare and only achieved by a small portion of patients. Second, while Vitamin E has shown some success as a treatment for early stages of NASH, it has limited to no effect on reversing advanced stages of fibrosis and cirrhosis.[11] Finally, the use of Pioglitazone as an adequate comparator does not accurately account for the variability in effectiveness and lack of agreement between experts in the field.

Due to NASH's strong link to obesity, weight loss, through the combination of diet and exercise, is the most established approach to care.[12] Weight loss also addresses associated comorbidities such as Type 2 diabetes.[7] However, weight loss is difficult to accomplish and sustain.[13] [14] A study found that 85% of people with NAFLD could not achieve and maintain a weight loss of 7-10% or more, which is the threshold to induce the highest rates of NASH resolution and fibrosis

regression.[8] [15] The patients that did show success achieving the necessary weight loss utilized "intensive lifestyle modification" programs (sometimes called Intensive Behavioral Therapy (IBT), and many times still only were able to attain 7-10% at 6 months (usual peak for weight loss efforts) before regaining the weight back. In response, bariatric surgery becomes one of the only consistent options to reduce weight and improve histology of the liver. [16] [17] [18] Bariatric Surgery is an invasive procedure that is typically limited to those with severe obesity with its own set of risks costs and significant barriers to access; thus its potential as a widespread treatment for NASH may be limited as is demonstrated by its overall low overall utilization (less than 1% of people eligible utilize surgery).[19] [20]

We also understand that for a cost effectiveness model to operate as intended there needs to be a base comparator. In this case, we understand why Pioglitazone has been chosen. Pioglitazone is a drug approved for Type 2 diabetes that has also shown positive improvement of NASH in some patients. [21] [22] However, Pioglitazone may only be worthwhile for leaner populations where weight gain is not a factor. Multiple studies have found that patients with type 2 diabetes experienced some negative side effects of weight gain, issues with water retention, edema, and risk of fracture.[23] [24] [25] [26] For patients with NASH who also have type 2 diabetes and obesity, the use of Pioglitazone could be problematic, and can lead to questions about the risk-benefit ratio.[27] This point is highlighted when we understand that in people with obesity and type 2 diabetes, NAFLD prevalence is approximately 50-70% and NASH prevalence is approximately 56%.[28] [29] There are also cardiovascular concerns for this patient population when anywhere from 20-80% of patients with NASH currently have hyperlipidemia.[25] This is especially alarming for patients with preexisting cardiac dysfunction where Pioglitazone has been shown to increase the risk of congestive heart failure.

NASH care can look markedly different depending on when a patient is diagnosed, and the unique complications experienced by each patient. Currently the model utilizes methods that do not adequately account for the variability in care for NASH. There is a lack of specialist and clinician agreement on how to treat NASH. Due to this lack of standardized care, treatment plans administered often vary drastically depending on the unique characteristics of each patient. This must all be factored in to and acknowledged in any cost model analysis for NASH.

Model Assumption: "Gold" Standard Diagnostic

In this draft evidence report ICER has chosen to reference liver biopsy as the "gold standard" for diagnosing NASH. We have a few serious concerns with this classification. First, liver biopsy is a risky, invasive procedure that can be subject to sampling variability; and is increasingly only used after many other diagnostic and non-invasive tests (NIT) have been exhausted.[30] [31] We understand that the American Association for the Study of Liver Diseases (AASLD) currently refers to liver biopsy as the strongest diagnostic option however, we have come to understand that they plan to revise and modernize this recommendation in the near future. Second, liver biopsy plays a role in unnecessary high costs associated with the care for NAFLD independent of its metabolic comorbidities. Third, liver biopsy is rarely performed outside of a specialist setting, creating an access barrier and in some cases an extended wait time, contributing to misreporting and underdiagnosing of NASH.[9]

Liver biopsy can artificially inflate the cost of care for NASH, and unnecessarily lengthen treatments. This is especially important to understand when trial data for OCA (25 mg) suggests that 38% of patients with NASH experience improved fibrosis.[32] On average liver biopsies cost more than $7,000 per patient, and the lengthy conventional diagnosis pathway in total can run up

to more than $10,000 per patient.* The largest increases in health care utilization and costs in NAFLD are represented by liver biopsies and hospitalizations.[33] [34]

Liver biopsy is not the only diagnostic option. Currently, there does exist acceptable and accurate NIT to assess for liver fibrosis.[35] [36] [37] NITs lead to fewer patient visits, quicker diagnosis, and are more cost-effective with no surgical risks. We understand that there currently is no consensus around a single NIT to diagnose NASH and replace liver biopsy.[35] [38] [39] However, we already see many gastroenterologists and hepatologists frequently diverge from published practice guidelines that previously classified liver biopsy as the "gold" standard for NASH diagnosis. It has been found that less than 25% of clinicians routinely require it to make the diagnosis of NASH.[40] From initial diagnosis to monitoring treatment change and deciding length of treatment, NITs can play a valuable role throughout the entire NASH care pathway. NITs should be prioritized within this ICER cost effectiveness model.

Model Assumption: Length of Treatment

The current ICER model makes the assumption that patients will be using OCA treatment under optimal prescribing conditions "for life as long as they continue to respond to treatment." This is highly unrealistic.[41] It is typical in drugs taken for chronic conditions for patients to take treatment holidays, often when the treatment is effective, and at times when it is ineffective, as agreed by their physicians.[42] It is also true that drug use, especially of specialized drugs, falls away later in life when pain relief and symptom management become more common. In addition, the model assumes that the price of these treatments will remain the same for the next 20 years, which is very unlikely.[43] What is more likely is that generic substitutes will enter the market, driving down prices. If you factor in this steep drop in price after 10-15 years, along with other potential savings from reducing the incidence of expensive hospital care, end stage liver diseases like liver cancer, and potentially using NITs, the model's cost estimates would drop dramatically.

Solution at Every Stage

It is important to understand and factor in the reality that NASH must have a different solution and response at each stage of the disease. While weight loss can show success at earlier stages, it is less effective at more advanced stages. As the disease progresses to more advanced stages studies have also found greater impairments in quality of life and work productivity.[44] Currently, at more advanced stages liver transplantation is the only possibility.[45] A liver transplant is one of the single most expensive surgical operations in the United States. It costs on average between $600,000 and $1 million per patient. The procedure requires nearly a year of intensive aftercare, but a lifetime of follow up, a steady supply of organs, high-tech operating rooms and massive quantities of blood for transfusion. Furthermore, liver transplantation is not a cure for NASH, and some individuals may not be eligible for transplantation due to comorbidities related to metabolic syndrome, such as obesity or coexistent CVD.[45] [46]

Liver cancer is a factor at all stages of NASH. [47] The costs associated with an outcome of liver cancer must be considered, even when the mechanisms associating NALFD and NASH and the development of liver cancer need further investigation. Estimates vary between studies but suggest that of people with cirrhosis due to NASH, approximately 2–12% develop liver cancer per year.[48] Recent evidence also suggests that people with lean NAFLD are at higher risk of developing severe liver disease compared to patients with NAFLD who also have obesity.[49]

* Data from Mayo Clinic, FL, Values taken from market feedback from clinical practice and are estimates based on total cost without health insurance

There is no "silver bullet" response to NASH. While prevention and weight loss management can be effective earlier, it is difficult, and less effective at later stages. Treatment options for advanced NASH should also not be forced upon earlier, less advanced patients with NASH. Patients at different stages of the disease carry different costs as well. This truth about NASH care must be made clear in the report.

The Cost of Not Treating NASH

In any cost-effective analysis of a disease, it is important to pose the question of, what if we chose not to treat the disease? With NASH there is both an immense public health and economic burden that must be accounted for.

First, NASH and NAFLD have far-reaching public health effects that are not just limited to the liver. People with NASH have an overall mortality rate of 7.9% within seven years of diagnosis- almost twice that of the general population.[50] NASH and NAFLD have shown significant comorbidities with a variety of other conditions ranging from obesity, Type 2 diabetes, cardiovascular disease, and chronic kidney disease.[51] [52] [53] Cardiovascular disease is the most common cause of death for patients with NASH.[54] Furthermore, NASH has a bidirectional relationship with Type 2 diabetes. If NASH develops first, the patient is likely to develop Type 2 diabetes or conversely, in patients with Type 2 diabetes initially, NASH is a common comorbid occurrence. Diabetes also contributes to greater fibrosis progression of NASH and can accelerate the progression to cirrhosis and liver cancer.[39]

Second, the rise in prevalence of NASH, its complications, and its comorbidities carry significant economic costs. Costs associated with NASH include inpatient, outpatient, professional services, emergency department and drug costs.[55] As severity of NASH and fibrosis increases, the cost associated with the disease increases as well. Furthermore, comorbidities also contribute to cost not only in healthcare spending but also in indirect costs, such as lost work productivity.[56] Estimates of other cost models have suggested that the rise of NAFLD will be similar to the rise of obesity prevalence. The estimated total cost of NAFLD in the next 10 years in the United States could be $1.005 trillion dollars.[44] Another model suggested that lifetime costs of all non-advanced patients with NASH in the United States in the year, 2017, was around $222.6 billion. For advanced patients with NASH, which was characterized by those who have reached fibrosis stage 3 or cirrhosis have an estimated total cost of $95.4 billion.[44] Furthermore, comorbidity cost estimates have shown that the total cost of NASH with Type 2 diabetes is $667.9 billion.[52]

We must be cognizant of the unique issues and costs at each stage of NASH. The standard of care, the impact on quality of life, the truth about liver biopsy, the need for a solution at every stage of the disease, the length of treatment, and the outcome of not treating this life threatening disease, are all crucial factors that must be considered when painting the cost picture for NASH and when considering potential other benefits offered by the intervention.

As a community for whom access to treatment to this disease is literally a life-and-death issue, we are appreciative of the opportunity to work together towards correctly capturing the costs associated with this disease. If you have any questions please don't hesitate to reach out to our Director of Policy, Andrew Scott, at ascott@globabliver.org or 831-246-1586.

With appreciation and respect,

Global Liver Institute

[1] Cook NS, Nagar SH, Jain A, et al. 2019. Understanding patient preferences and unmet needs in nonalcoholic steatohepatitis (NASH): Insights from a qualitative online bulletin board study. Advances in Therapy 36(2): 478-91

[2] Younossi ZM, Henry L. 2015. Economic and quality-of-life implications of non-alcoholic fatty liver disease. Pharmacoeconomics 33(12): 1245-53

[3] Newton JL, Jones DE, Henderson E, et al. 2008. Fatigue in non-alcoholic fatty liver disease (NAFLD) is significant and associates with inactivity and excessive daytime sleepiness but not with liver disease severity or insulin resistance. Gut 57(6): 807-13

[4] Huber Y, Boyle M, Hallsworth K, et al. 2018. Health-related quality of life in non-alcoholic fatty liver disease associates with hepatic inflammation. Clinical Gastroenterology and Hepatology: 10.1016/j. cgh.2018.12.016

[5] Younossi ZM, Stepanova M, Anstee QM, et al. 2019. Reduced patient-reported outcome scores associate with level of fibrosis in patients with nonalcoholic steatohepatitis. Clinical Gastroenterology and Hepatology: 10.1016/j.cgh.2019.02.024

[6] European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. 2016. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Journal of Hepatology 9(2): 65-90

[7] McPherson S, Hardy T, Henderson E, et al. 2015. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. Journal of Hepatology 62(5): 1148-55

[8] Rinella ME. 2015. Nonalcoholic fatty liver disease: a systematic review. Journal of the American Medicinal Association 313(22): 2263-73

[9] Nascimbeni F, Pais R, Bellentani S, *et al.* 2013. From NAFLD in clinical practice to answers from guidelines. 59(4): 859-71

[10] Ratziu V, Cadranel J-F, Serfaty L, *et al.* 2012. A survey of patterns of practice and perception of NAFLD in a large sample of practicing gastroenterologists in France. *Journal of Hepatology* 57(2): 376-83

14. Castera L, Friedrich-Rust M, Loomba R. 2019. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology 156(5): 1264–81.e4

[11] Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *New England Journal of Medicine*. 2010;362(18):1675–1685.

[12] Vilar-Gomez E, Athinarayanan SJ, Adams RN, et al. 2019. Post hoc analyses of surrogate markers of non-alcoholic fatty liver disease (NAFLD) and liver fibrosis in patients with type 2 diabetes in a digitally supported continuous care intervention: an open-label, non-randomised controlled study. BMJ Open 9(2): e023597

[13] Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. 2015. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 149(2): 367-78.e5

[14] The NASH Education Program. Infographics and Leaflets. Available from: https://www.the-nasheducation-program.com/news-medias/infographics/ [Accessed 08/05/2019]

[15] Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. 2015. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 149(2): 367-78.e5

[16] Schauer PR, Bhatt DL, Kirwan JP, et al. 2014. Bariatric surgery versus intensive medical therapy for diabetes — 3-year outcomes. New England Journal of Medicine 370(21): 2002-13

[17] Lassailly G, Caiazzo R, Buob D, et al. 2015. Bariatric surgery reduces features of nonalcoholic steatohepatitis in morbidly obese patients. Gastroenterology 149(2): 379-88

[18] Taitano AA, Markow M, Finan JE, et al. 2015. Bariatric surgery improves histological features of nonalcoholic fatty liver disease and liver fibrosis. Journal of Gastrointestinal Surgery 19(3): 429-37

[19] Ofosu A, Ramai D, Reddy M. 2018. Non-alcoholic fatty liver disease: controlling an emerging epidemic, challenges, and future directions. Annals of Gastroenterology 31(3): 288-95

[20] Campos, Guilherme M. MD, PhD; Khoraki, Jad MD; Browning, Matthew G. PhD; Pessoa, Bernardo M. MD; Mazzini, Guilherme S. MD, PhD; Wolfe, Luke MS Changes in Utilization of Bariatric Surgery in the United States From 1993 to 2016, Annals of Surgery: February 2020 - Volume 271 - Issue 2 - p 201-209 doi: 10.1097/SLA.0000000000003554

[21] Ahmed A, Wong RJ, Harrison SA. NAFLD review: diagnosis, treatment and outcomes. *Clinical Gastroenterology and Hepatology.* 2015;13(12):2062–2070.
[22] Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology.* 2012;55(6):2005–2023.
[23] Basu R, Basu A, Chandramouli V, et al. Effects of pioglitazone and metformin on NEFA-induced insulin resistance in type 2 diabetes. *Diabetologia*. 2008;51(11):2031–2040. doi:10.1007/s00125-008-1138-1
[24] Rita Basu, Pankaj Shah, Ananda Basu, Barbara Norby, Betty Dicke, Visvanathan Chandramouli, Ohad Cohen, Bernard R. Landau, Robert A. Rizza. Comparison of the effects of pioglitazone and metformin on hepatic and extra-hepatic insulin action in people with type 2 diabetes. Diabetes. 2008 Jan; 57(1): 24–31. Published online 2007 Oct 3. doi: 10.2337/db07-0827
[25] Bundhun PK, Janoo G, Teeluck AR, Huang F. Adverse drug effects observed with vildagliptin versus pioglitazone or rosiglitazone in the treatment of patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *BMC Pharmacol Toxicol*. 2017;18(1):66. Published 2017 Oct 23. doi:10.1186/s40360-017-0175-0
[26] Berlie HD, Kalus JS, Jaber LA. Thiazolidinediones and the risk of edema: a meta-analysis. 2007. In: Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]. York (UK): Centre for Reviews and Dissemination (UK); 1995-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK74161/
[27] Schernthaner G, Currie CJ, Schernthaner GH. Do we still need pioglitazone for the treatment of type 2 diabetes? A risk-benefit critique in 2013. *Diabetes Care*. 2013;36 Suppl 2(Suppl 2):S155–S161. doi:10.2337/dcS13-2031
[28] Portillo-Sanchez P, Bril F, Maximos M, et al. 2015. High prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and normal plasma aminotransferase levels. The Journal of Clinical Endocrinology & Metabolism 100(6): 2231-38
[29] Kwok R, Choi KC, Wong GL-H, et al. 2015. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut 65(8): 1359-68
[30] Castera L, Friedrich-Rust M, Loomba R. 2019. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology 156(5): 1264–81.e4
[31] Cook NS, Nagar SH, Jain A, et al. 2019. Understanding patient preferences and unmet needs in nonalcoholic steatohepatitis (NASH): Insights from a aualitative online bulletin board study. Advances in Therapy 36(2): 478-91
[32] Younossi, Z. M., MD, Ratziu, V., MD, Loomba, R., MD, Rinella, M., MD, Anstee, Q. M., MD, & Goodman, Z., MD. (2019). Obeticholic acid for the treatment of non-alcoholic steatohepatitis: Interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial. *The Lancet, 394*(10215), 2184-2196. doi:https://doi.org/10.1016/S0140-6736(19)33041-7
[33] Ratziu V, Cadranel J-F, Serfaty L, *et al.* 2012. A survey of patterns of practice and perception of NAFLD in a large sample of practicing gastroenterologists in France. *Journal of Hepatology* 57(2): 376-83
[34] Alina M. Allen, Holly K. Van Houten, Lindsey R. Sangaralingham, Jayant A. Talwalkar, and Rozalina G. McCoy. Healthcare Cost and Utilization in Nonalcoholic Fatty Liver Disease: Real-World Data From a Large U.S. Claims Database. Hepatology. American Association for the Study of Liver Diseases. Hepatology, VOL. 68, NO. 6, 2018
[35] Younossi ZM, Koenig AB, Abdelatif D, et al. 2016. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. Journal of Hepatology 64(1): 73-84
[36] Rinella ME, Sanyal AJ. 2016. Management of NAFLD: a stage-based approach. Nature Reviews Gastroenterology & Hepatology 13(4): 196
[37] Alexander M, Loomis AK, Fairburn-Beech J, et al. 2018. Real-world data reveal a diagnostic gap in nonalcoholic fatty liver
disease. BMC medicine 16(1)
[39] European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. 2016. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Journal of Hepatology 9(2): 65-90

[40] Rinella ME, Lominadze Z, Loomba R, et al. Practice patterns in NAFLD and NASH: real life differs from published guidelines. *Therap Adv Gastroenterol*. 2016;9(1):4–12. doi:10.1177/1756283X15611581
[41] Abrahamowicz M, Tamblyn R. Drug utilization patterns. Wiley StatsRef: Statistics Reference Online. 2014 Apr 14.
[42] Alpert A. The anticipatory effects of Medicare Part D on drug utilization. Journal of health economics. 2016 Sep 1;49:28-45
[43] Lichtenberg FR, Duflos G. The effect of patent expiration on US drug prices, marketing, and utilization by the public. Manhattan Institute for Policy Research. 2009.
[44] Younossi ZM, Stepanova M, Anstee QM, et al. 2019. Reduced patient-reported outcome scores associate with level of fibrosis in patients with nonalcoholic steatohepatitis. Clinical Gastroenterology and Hepatology: 10.1016/j.cgh.2019.02.024
[45] European Association for the Study of the Liver. 2016. EASL Clinical Practice Guidelines: Liver transplantation. Journal of Hepatology 64(2): 433-85
[46] Pais R, Barritt 4th AS, Calmus Y, et al. 2016. NAFLD and liver transplantation: current burden and expected challenges. Journal of Hepatology 65(6): 1245-57
[47] Tarkan L. Being overweight increases risk of liver cancer. EndocrineWeb website. endocrineweb.com/news/obesity/55627-being-overweightincreases-risk-liver-cancer. Updated October 28, 2016. Accessed August 22, 2019.
[48] Anstee QM, Reeves HL, Kotsiliti E, et al. 2019. From NASH to HCC: current concepts and future challenges. Nature Reviews Gastroenterology & Hepatology: 1
[49] Hagström H, Nasr P, Ekstedt M, et al. 2018. Risk for development of severe liver disease in lean patients with nonalcoholic fatty liver disease: A long-term follow-up study. Hepatology Communications 2(1): 48-57
[50] Anstee QM, Reeves HL, Kotsiliti E, et al. 2019. From NASH to HCC: current concepts and future challenges. Nature Reviews Gastroenterology & Hepatology: 1
[51] Anstee QM, Targher G, Day CP. 2013. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nature Reviews Gastroenterology & Hepatology 10(6): 330
[52] Younossi ZM, Koenig AB, Abdelatif D, et al. 2016. Global epidemiology of nonalcoholic fatty liver disease— meta-analytic assessment of prevalence, incidence, and outcomes. Journal of Hepatology 64(1): 73-84
[53] Adams LA, Anstee QM, Tilg H, et al. 2017. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut 66(6): 1138-53
[54] Targher G, Day CP, Bonora E. 2010. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. New England Journal of Medicine 363(14): 1341-50
[55] Younossi, Zobair M., et al. "Burden of Illness and Economic Model for Patients With Nonalcoholic Steatohepatitis in the United States." *Hepatology*, vol. 69, no. 2, 2019, pp. 564–572., doi:10.1002/hep.30254.
[56] Younossi ZM, Blissett D, Blissett R, et al. 2016. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Journal of Hepatology 64(5): 1577-86