U.S. NASH ACTION PLAN

NASH Council

GLI GLOBAL LIVER INSTITUTE

CONTENTS

EXECUTIVE SUMMARY

By most recent estimates, up to 444 million people worldwide and 40 million in the United States[1] are living with a progressive, chronic liver condition referred to as nonalcoholic steatohepatitis (NASH), the advanced form of fatty liver disease (NAFLD). On top of this is that an estimated 10% of children in the United States also currently have NASH.[2 3 4] NASH is closely associated with obesity, diabetes, chronic kidney disease, and cardiovascular disease (CVD) and is projected to rise in parallel to these diseases.[5]

As a patient-driven multi-stakeholder community for whom addressing this disease is a life-and-death issue, we strongly believe that 2021 is a crucial time to frame a set of specific action steps for the nation to begin taking to ensure that no more lives are lost unnecessarily from this disease. In 2015, it was estimated that there were 370,000 deaths among the NASH population; however, more than 90% of the deaths were classified as due to general background or excess cardiovascular.[6] Population-level NASH death rate data remains a critical issue that leads to difficulty in grasping the scope of the NASH crisis.

Global Liver Institute (GLI) created the NASH Council in 2017, defining a community around creating solutions for a liver condition, more broadly and inclusively than had ever been done previously. GLI and the NASH Council invited cardiology, endocrinology, and minority serving health organizations from the start to identify a framework for high-functioning disease state advocacy. There are currently more than 70 members of the NASH Council including the American Association for the Study of Liver Diseases (AASLD), the Endocrine Society, the Obesity Action Center (OAC), the American Cancer Society, the American Heart Association, the American Gastroenterological Association (AGA), the American College of Physicians, the American Nursing Association, Duke University School of Medicine, University of California San Francisco Medical Center, Massachusetts General Hospital/ Harvard Medical School: Fatty Liver Disease Clinic, Fatty Liver Foundation, NASH kNOWledge, the Liver Forum, and more.

In 2020, GLI and the NASH Council released the resource, The Language of NASH: A Narrative to Guide Communication on NASH. This core NASH messaging framework was designed to establish consistent and meaningful terminology and messaging to be used as a foundation for communication in all areas around NASH. GLI and the NASH Council now hope to build upon this messaging report by releasing a set of actionable recommendations for the NASH community in the form of this U.S. NASH Action Plan.

This U.S. NASH Action Plan is the logical next step in the work of the GLI NASH Council, setting an agenda and detailed roadmap with

1 Spengler EK, Loomba R. Recommendations for diagnosis, referral for liver biopsy, and treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Mayo Clinic Proceedings. 2015;90(9):1233–1246.

2 J Pediatr. 2013;162(3):496–500.e1 Welsh JA, Karpen S, Vos MB. Increasing prevalence of nonalcoholic fatty liver disease among United States adolescents, 1988-1994 to 2007-2010.

3 Pediatrics. 2006;118(4): 1388–1393 Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and Adolescents.

4 J Pediatr. 2018;200:174–180 Fernandes DM, Pantangi V, Azam M, et al. Pediatric nonalcoholic fatty liver disease in New York City: an autopsy study.

5 Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016; 64:73–84.

6 Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology. 2018;67(1):123-133. doi:10.1002/hep.29466

recommendation for meaningful activities for each relevant stakeholder group — patients/carepartners, clinicians, medical societies, patient advocacy organizations, industry, payors, health systems, regulators, and policymakers.

Our collaborative process has determined that four critical overriding issues must be addressed to save lives and stop the rise of this life-threatening disease:

1. Lack of awareness and education
2. Lack of agreement on how to diagnose
3. Lack of standardized patient management and treatment for NASH
4. Lack of NASH-specific policy initiatives leading to poor health system preparedness

BACKGROUND

The Impact of NASH on Patients and Families

NAFLD describes a spectrum of liver disease including NASH through to cirrhosis.[7] [8] NAFLD has commonly been described as fibrosis 0 – 4. The risk of adverse outcomes and mortality increases with fibrosis progression. Early stage NAFLD is when fat accumulates in the liver with little or no inflammation or liver cell damage. Left untreated, NAFLD can progress to NASH, which is characterized by the accumulation of fat in the liver, inflammation, and injury to the liver cells with or without scarring.

NASH is considered the most severe form of NAFLD, and patients with NASH experience a range of symptoms that negatively affect their quality of life, including major depressive disorder, generalized anxiety disorder, fatigue, feeling bloated, having discomfort or pain around the liver, sleeping problems, and lethargy.[9] The most prevalent impact of NASH on health-related quality of life is due to fatigue.[10] [11] [12] The rate of disease progression for NASH is not uniform; some people experience fast fibrosis progression while others follow a much slower course or may even experience regression.[13]

Due to the lack of public awareness of liver health and NASH in particular, patients with NASH find it difficult to differentiate between symptoms related to NASH and other health issues or comorbidities.[14] Patients also feel a lack of adequate educational support[15] from their physicians, and healthcare professionals may also not think to screen for NASH, even in patients with more than one high risk factor. [16] [17]

Studies have also found greater impairments in quality of life and work productivity in patients with

7 Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver diseaseMeta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016; 64:73–84.

8 Banini BA and Sanyal AJ. Nonalcoholic Fatty Liver Disease: Epidemiology, Pathogenesis, Natural History, Diagnosis, and Current Treatment Options. Clin Med Insights Ther. 2016; 8:75–84.

9 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

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

11 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

12 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

13 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

14 Hagström H, Nasr P, Ekstedt M, et al. 2017. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. Journal of Hepatology 67(6): 1265-73

15 Younossi ZM et al. Hepatology. 2016;64:73–84 4. Nascimbeni F, Pais R, Bellentani S, et al. 2013. From NAFLD in clinical practice to answers from guidelines. 59(4): 859-71

16 Hagström H, Nasr P, Ekstedt M, et al. 2017. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. Journal of Hepatology 67(6): 1265-73

17 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

advanced NASH.[18] Patients with a more severe disease stage mentioned taking frequent time off work due to medical appointments, ultimately leading to job changes.[19] Work absences are also an issue with caregivers, causing lost time, lost wages, and sometimes even job loss.

The Impact of NASH on Public Health

NASH is on the rise and is a concern for children and adults; men and women; and all racial and ethnic populations, especially Hispanics.[20] [21] [22] For children, the disease can be even more concerning because it can lead to serious consistent health consequences in adulthood.[23] In fact, people with NASH have an overall mortality rate of 7.9% within seven years of diagnosis — almost twice that of the general population.[24]

NASH has far-reaching public health effects that are not limited to the liver. The disease has shown significant comorbidities with a variety of other conditions ranging from obesity, type 2 diabetes, CVD, and chronic kidney disease.[25] [26]

Furthermore, NASH has a bidirectional relationship with type 2 diabetes. If NASH develops first, the patient is likely to develop type 2 diabetes. Conversely, in patients with type 2 diabetes initially, NASH is a common comorbid occurrence (37% of people with type 2 diabetes have NASH)[27]. Diabetes also contributes to a faster fibrosis progression of NASH and can accelerate the progression to cirrhosis and liver cancer.[28] Approximately 2% –12% of patients with NASH develop liver cancer annually.[29]

18 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

19 Hagström H, Nasr P, Ekstedt M, et al. 2017. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. Journal of Hepatology 67(6): 1265-73

20 Betancourt-Garcia M.M., Arguelles A., Montes J., Hernandez A., Singh M., Forse R.A. Pediatric Nonalcoholic Fatty Liver Disease: The Rise of a Lethal Disease among Mexican American Hispanic Children. Obes. Surg. 2017:1–9. doi: 10.1007/s11695-016-2440-5.

21 Pan JJ, Fallon MB. Gender and racial differences in nonalcoholic fatty liver disease. World J Hepatol. 2014;6(5):274-283. doi:10.4254/wjh.v6.i5.274

22 PEDIATRICS Volume 146, number 6, December 2020:e20200771 Incidence of Nonalcoholic Fatty Liver Disease in Children: 2009–2018.

23 Xanthakos SA, Kohli R. Pediatric nonalcoholic fatty liver disease: Prevalence, diagnosis, risk factors, and management. Clin Liver Dis (Hoboken). 2012 Sep 25;1(4):125-128. doi: 10.1002/cld.75. PMID: 31186868; PMCID: PMC6499281.

24 Anstee QM, Reeves HL, Kotsiliti E, et al. 2019. From NASH to HCC: current concepts and future challenges. Nature Reviews Gastroenterology & Hepatology: 1

25 Anstee QM, Targher G, Day CP. 2013. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nature Reviews Gastroenterology & Hepatology 10(6): 330

26 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

27 Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol. 2019; 71:793–801.

28 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

29 Anstee QM, Reeves HL, Kotsiliti E, et al. 2019. From NASH to HCC: current concepts and future challenges. Nature Reviews Gastroenterology & Hepatology: 1

Presence and degree of fibrosis are main factors in determining the disease outcome of NASH.[30] [31] [32] People with type 2 diabetes and other metabolic conditions appear more likely to have higher fibrosis stages and in turn more advanced NASH compared to people with few or no metabolic conditions. CVD is the most common cause of death, followed by cancer outside the liver and liver-related complications (due to cirrhosis and liver cancer).[33] [34] [35]

The Impact of NASH on the Economy

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.[36] Furthermore, comorbidities contribute not only to costs in healthcare spending but also to indirect costs, such as lost work productivity.[37]

As the severity of NASH and fibrosis increases, the cost associated with the disease increases as well. Estimates from 2017 suggest that the lifetime costs of all patients with non-advanced NASH in the U.S. was around $222.6 billion. Patients with advanced NASH, which is characterized by those who have reached fibrosis stage 3 or cirrhosis, have an estimated total cost of $95.4 billion.[38] In addition, comorbidity cost estimates have shown that the total cost of NASH for patients with type 2 diabetes is $667.9 billion.[39] This comorbidity cost estimate is especially high because when a patient has more than one chronic condition like NASH and type 2 diabetes, the conditions interact in such a way that the patient's healthcare costs are greater than the sum of the costs for the individual diseases.[40]

30 Angulo P, Kleiner DE, Dam-Larsen S, et al. 2015. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 149(2): 389-97.e10

31 Ekstedt M, Hagström H, Nasr P, et al. 2015. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology 61(5): 1547-54

32 Hagström H, Nasr P, Ekstedt M, et al. 2017. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. Journal of Hepatology 67(6): 1265-73

33 Anstee QM, Targher G, Day CP. 2013. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nature Reviews Gastroenterology & Hepatology 10(6): 330

34 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

35 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

36 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.

37 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

38 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

39 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

40 Cortaredona S, Ventelou B. The extra cost of comorbidity: multiple illnesses and the economic burden of non-communicable diseases. BMC Med. 2017 Dec 8;15(1):216. doi: 10.1186/s12916-017-0978-2. PMID: 29221453; PMCID: PMC5723100.

THE ISSUES

Lack of Awareness and Education

Currently, knowledge and awareness about this disease is minimal across all segments of the population including patients living with the disease and the medical community. Contributing to this issue is the reality that liver disease has a stigma due to an association with alcohol use and the injection of drugs. The rapid rise of NASH, a liver disease that develops as a result of causes other than alcohol, underlines this point.

Awareness and knowledge of NASH is also relatively poor among healthcare providers outside of the hepatology community. General practitioners reported in a survey that they often lack knowledge about NAFLD and how to care for it. In one survey, eight out of ten diabetologists, endocrinologists, and cardiologists reported the need for increased education on NASH management strategies and emerging therapies.[41]

Moving forward, we need clear agreement about what NASH is and straightforward, unified messaging. Towards this aim, Global Liver Institute and the NASH Council recently released, The Language of NASH: A Narrative to Guide Communication on NASH. In light of this need for consistent and meaningful terminology and messaging, this core NASH message framework can be utilized as a foundation for communication in all areas around NASH.

Outside of this specific messaging framework, to raise awareness, it is vital for patients with NASH to be supported and empowered with knowledge and have the opportunity to discuss lived experiences. Early intervention and education are critical; populations at higher risk should be encouraged to talk to their doctor about getting screened and implementing lifestyle interventions focused on adjusting diet and weight loss. Intervention efforts should be collaborative, patient-inclusive, motivational, and supportive. Also, awareness efforts must be targeted at health care providers. Providers must understand the treatment and management options that are available to them and how NASH is interconnected with a wide range of other diseases, like obesity, diabetes, and CVD. Awareness campaigns should also be available for children. A family-based education approach should be taken to help children avoid the upstream causes of NASH including, for example, nutrition within school lunches and food insecurity.

Lack of Agreement on How to Diagnose NASH

Routine screening for NASH as well as consensus around non-invasive diagnostics to assess NASH is lacking in primary care. General practitioners, nurses, and specialists outside of hepatology may not consider the overlap between NASH and metabolic risk factors and other comorbidities. Hence, physicians may overlook a high proportion of individuals who are at risk for NASH. Unfortunately, this lack of clinical guidelines can lead to missed early diagnosis which is when treatment would be most effective. It is vital that straightforward, patient-centric screening guidelines are developed that not only diagnose patients at risk but also promote a conversation between patients and their providers.

NASH is mainly diagnosed through assessment of family history and individual risk factors, eliminating other causes of liver disease, and a combination of physical examination, blood tests, and/or imaging tests such as an ultrasound. The current-but-concerning “gold standard” for NASH diagnosis, however, is liver biopsy.

41 Younossi ZM et al. Hepatology. 2016;64:73–84 4. Nascimbeni F, Pais R, Bellentani S, et al. 2013. From NAFLD in clinical practice to answers from guidelines. 59(4): 859-71

Historically, many medical society recommendations have referenced liver biopsy as the "gold standard," for definitive diagnosis of NASH. NASH continuing as a biopsy-defined disease does a disservice to the realities of current clinical practice, the pace of innovation in non-invasive diagnostics, and expanded needs for medical facilities to scale to meet the needs of millions of people to be appropriately identified, staged/segment, and linked to care. Liver biopsy is an invasive procedure that has higher risks than non-invasive diagnostics. It is also prone to sampling errors and inter and intra-interpreter variability; it should be a diagnostic test of last resort.[42] [43] [44] To conduct a liver biopsy, a needle is inserted into the patient's liver in order to extract a piece of the liver usually between 1 and 3 cm in length and between 1.2 mm to 2 mm in diameter.[45] This biopsy is usually only 1/50,000 of the total mass of the liver, which can lead to sampling variability. Each biopsy causes the patient pain and puts the already sick patient under greater stress.

Liver biopsy also plays a role in unnecessary high costs associated with the care for NAFLD independent of its metabolic comorbidities. 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.[46] The largest increases in health care utilization and costs in NAFLD are represented by liver biopsies and hospitalizations.[47] [48] Liver biopsy is rarely performed outside of a specialist setting, creating a barrier to access that leads to an extended wait time and contributes to misreporting and underdiagnosing NASH.[49] It is also not scalable and presents issues for broader diagnosis and screening as we look ahead and NASH becomes more commonly acknowledged and diagnosed.

Liver biopsy is not the only diagnostic option, though. Currently, acceptable and accurate non-invasive diagnostics to assess for liver fibrosis do exist.[50] [51] [52] Yet, disappointingly, the current federal guidelines for industry from the Food and Drug Administration (FDA) do not acknowledge this

42 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

43 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

44 Davison BA, Harrison SA, Cotter G, et al. Suboptimal reliability of liver biopsy evaluation has implications for randomized clinical trials [published online ahead of print, 2020 Jun 28]. J Hepatol. 2020;S0168-8278(20)30399-8. doi:10.1016/j.jhep.2020.06.025

45 Bravo, Arturo A., et al. "Liver Biopsy." New England Journal of Medicine, vol. 344, no. 7, 2001, pp. 495–500., doi:10.1056/nejm200102153440706.

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

47 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

48 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

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

50 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

51 Rinella ME, Sanyal AJ. 2016. Management of NAFLD: a stage-based approach. Nature Reviews Gastroenterology & Hepatology 13(4): 196

52 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): 130

point and still require liver biopsy for clinical trials. This is partly due to the reality that liver biopsies are the only diagnostic besides multiparametric magnetic resonance imaging (mpMRI) that have been used for grading of NASH and fibrosis. With that said, multiple non-invasive diagnostics can be performed in combination or sequence to reach the correct diagnosis. The dangers of tracking to a reference standard with as many drawbacks, limitations and flaws cannot be overstated, risking our understanding and description of disease and organ function anchored in the past rather than an innovative future.

Some of the non-invasive diagnostics that exist currently include:

- **Blood tests:** Different tests on the blood to calculate the amount of fat in the liver. They can be imprecise and not reflect the true degree of liver fibrosis. Specific blood tests include AST to Platelet Ratio Index (APRI), Fibrosis-4 Test (FIB-4), Enhanced Liver Fibrosis (ELF), and FibroTest.
- **Multiparametric Magnetic Resonance Imaging (LiverMultiScan):** Imaging technology that uses MRI to measure liver fat, iron, fibrosis and inflammation in a scan of up to 15 minutes.
- **Transient Elastography (Fibroscan):** Imaging device that uses ultrasound to measure liver stiffness.
- **Magnetic Resonance Elastography (MRE):** Imaging technology that combines MRI with sound waves to create a visual map (elastogram) to measure liver stiffness.
- **Shear Wave Elastography:** Imaging technology that uses ultrasound to measure liver stiffness.

Patient-centered value frameworks and value-based insurance design should both acknowledge that non-invasive diagnostics can act as a critical piece of the puzzle in the care of NASH, allowing for cost-effective community-based screening, treatment response, and periodic testing for disease progression. Community-based and at-risk population screening can facilitate earlier detection of NASH, thus potentially improving outcomes (i.e., prolonged survival) and enhancing the quality of life for patients. Patients with early-stage disease more frequently benefit from lower intensity interventions and have a chance of slowing or reversing disease progression.

The use of non-invasive diagnostics will also help patients understand what their options are and empower behavioral change and persistence in seeking and adherence to care.

Lack of Standardized Patient Management and Treatment for NASH

The aim of treatment for NASH, in the absence of a cure or an FDA-approved therapeutic, is to reduce the progression of the disease to cirrhosis or liver cancer and decrease fibrosis progression as well as NASH-related mortality.[53]

Due to a strong link between NASH and obesity, weight loss through the combination of diet and exercise is the most established approach to care.[54] The rate of disease progression, however, is not uniform; some people experience fast fibrosis progression while others follow a much slower course or may even experience regression. Symptoms of NASH are non-specific so they can often be misinterpreted as something else. This,

53 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

54 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

in turn, means that specialists and clinicians lack agreement on how to treat NASH, leading to NASH care looking markedly different depending on at what stage a patient is diagnosed and the unique complications experienced by each patient.

For example, while weight loss can show success at earlier stages, it is difficult to accomplish and sustain.[55] [56] 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.[57] [58] The patients that did show success achieving the necessary weight loss used intensive lifestyle modification programs, sometimes called intensive behavioral therapy (IBT), and many times still only were able to attain 7-10% weight loss at 6 months (usual peak for weight loss efforts) before regaining the weight back.

In response, bariatric surgery becomes the only consistent option to reduce weight and improve histology of the liver.[59] [60] [61] Bariatric surgery is an invasive procedure that is typically limited to those with severe obesity and has its own set of risks, costs, and significant barriers to access. Thus, its potential as a scalable widespread treatment for NASH may be limited, its current utilization stands at 1% of eligible patients, but should be reviewed for potential expansion.[62] [63]

For patients that have more advanced NASH, studies have found not only greater impairments in quality of life and work productivity[64] but also a need for liver transplantation as it is currently the only treatment option.[65] Chronic liver failure due to cirrhosis is the most common reason for liver transplantation and 20% of individuals with NASH progress to advanced fibrosis and cirrhosis caused by NASH.[66] A liver transplant is one of the single most expensive surgical operations in the U.S., costing, on average, between $600,000 and $1

55 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

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

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

58 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

59 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

60 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

61 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

62 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

63 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

64 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

65 European Association for the Study of the Liver. 2016. EASL Clinical Practice Guidelines: Liver transplantation. Journal of Hepatology 64(2): 433-85

66 Loomba R, Adams LA. The 20% Rule of NASH Progression: The Natural History of Advanced Fibrosis and Cirrhosis Caused by NASH. Hepatology. 2019 Dec;70(6):1885-1888. doi: 10.1002/hep.30946. PMID: 31520407; PMCID: PMC7504908.

million per patient.[67] The procedure requires six - twelve months of intensive aftercare, a supply of donated organs, highly trained and equipped medical teams and facilities. Furthermore, liver transplantation is not a cure for NASH, recurring in a number of patients post-transplant, and some individuals may not be eligible for transplantation due to comorbidities related to metabolic syndrome, such as obesity or coexistent CVD.[68] [69] Some find themselves not only too sick to donate, but in need of significant care or transplantation themselves.

A more standardized care pathway will allow treatment plans to be administered more consistently, which will help prevent NASH progression and lead to more predictable, evenly distributed positive outcomes. The establishment of integrated fatty liver disease clinics to provide co-located multi-specialty care have been essential to developing best practices and reducing the patient burden of attempting to piece together coordinated care from providers across health systems and disconnected by their different electronic health record systems. In the absence of such clinics, updated standard care pathways, practical guidelines anchored in accessible technology, the realities of clinical workflow, and patient lifeflow, connected to meaningful quality measures that apply across low and high resource settings would make a significant difference.

Lack of NASH Specific Policy Initiatives Leading to Poor Health System Preparedness

As it stands currently, our health system is poorly prepared to prevent and respond to NASH.

Gaps in surveillance, regulatory prioritization, community-based prevention efforts that ensure health equity, and reimbursement policies that resolve the effects of compounding access issues demonstrate a weak infrastructure for promoting liver health and NASH care across the country. Two initiatives that do stand out are the NASH Clinical Research Network (CRN) at the National Institutes of Health (NIH) and the Non-Invasive Biomarkers of Metabolic Liver Disease (NIMBLE) Consortium for biomarker validation through the Foundation for the National Institutes of Health (FNIH). It seems, though, that we have not learned the lesson of other disease states that research is insufficient without the health system and policy ecosystem to receive the products of research and bring the innovation to actual people.

Regulatory Policy

NASH is a serious, progressive, chronic disease. Regulators at the U.S. Food and Drug Administration (FDA) must understand the cost of not treating NASH. Use of breakthrough and expedited approval pathways are appropriate given the high unmet need and the lack of a treatment. It is necessary to prioritize the advancement of the development of medical products and support an integrated approach in the clinical evaluation of drugs, biologics, and devices for the treatment of NASH. To accomplish this, the regulatory processes of the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH), as well as other offices across FDA (e.g., Office of Pediatric Therapeutics) must be synchronized. Expertise from cardiology, endocrinology need to be well leveraged with that of the CDER Office of Immunology and Inflammation - Division of Hepatology and Nutrition (DHN)

67 2020. 2020 U.S. Organ And Tissue Transplants: Cost Estimates, Discussion And Emerging Issues. [ebook] Milliman Research Institute, p.3. Available at: <https://milliman-cdn.azureedge.net/-/media/milliman/pdfs/articles/2020-us-organ-tissue-transplants.ashx> [Accessed 19 November 2020].

68 Abrahamowicz M, Tamblyn R. Drug utilization patterns. Wiley StatsRef: Statistics Reference Online. 2014 Apr 14.

69 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

to be able to appropriately review and guide NASH treatment development.

Interactions with the agency need to be characterized by transparency, consistency, and a deep understanding of the patient perspective on issues such as disease burden and benefit-risk preference. This, in turn, leads to the consistent support of innovation resulting in the use of state-of-the-art approaches that provide new strategies for successful therapy.

Overall, to treat this life-threatening disease, transformative therapies must be promoted and used for the benefit of patients.

Legislative Policy

It is vital to consider ongoing legislative packages that should include NASH, especially packages that target the risk factors for NASH such as obesity, type 2 diabetes, metabolic syndrome, chronic kidney disease, and CVD.[70] [71] [72] Health disparities also must be considered. We know that NASH impacts all populations but disproportionately impacts certain racial and ethnic groups. For example, the prevalence of NASH in Hispanics is 19.4%.[73]

Most critically, NASH-specific policy initiatives must establish a national strategy that complements the previously mentioned efforts centered around building NASH awareness, establishing a set non-invasive diagnosis pathway, and developing treatment standards. These initiatives must elevate a multidisciplinary community of experts, promote collaborative research projects, increase education and awareness, support public health initiatives, and improve treatment reimbursement. It is also important to consider a national prevention program for people at higher risk of NASH, along with a national surveillance program and recommendations for the field.

Finally, liver health is public health. The liver supports more than 500 functions in the body. It is vital to elevate liver disease research and initiatives overall within relevant federal agencies like the NIH and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

70 Younossi Z, Anstee QM, Marietti M, et al. 2018. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nature Reviews Gastroenterology & Hepatology 15(1): 11

71 Anstee QM, Targher G, Day CP. 2013. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nature Reviews Gastroenterology & Hepatology 10(6): 330

72 Ratziu V, Bellentani S, Cortez-Pinto H, et al. 2010. A position statement on NAFLD/NASH based on the EASL 2009 special conference. Journal of Hepatology 53(2): 372-84

73 Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology. 2011;140(1):124- 131.

THE RECOMMENDATIONS

As described above, multiple issues are creating challenges and barriers to a NASH field that is characterized by: engaged and informed patients and carepartners with disease identified at early stages, linked seamlessly to care settings and clinical teams prepared to receive them and partner with them, providing interventions tailored to their stage of disease, preferences, values, and circumstances. With these issues and their impacts in mind, we make the following recommendations, segmented by stakeholder group and highlighted according to short, medium, and longer (often due to more collaboration needed to achieve) timeframes. We believe strongly that the success of achieving our aims for NASH, our vision for the field, is dependent on our interdependence, the acceptance of each stakeholder group of their role (internal initiatives) and our collaboration with (external advocacy) and accountability to each other. Following this section is a proposal to measure our progress in jointly filling these recommendations.

PATIENTS AND CAREGIVERS

Immediate/ Short Term

Medium Term (usually within a year)

Long Term (usually/expected more than a year)

Education	Diagnosis	Patient Management/ Treatment	Policy Effort/ Legislation
Internal Initiative: Seek information on your own personal risk (family history + individual medical history + lifestyle) for NASH so that you can self-identify and seek care	**Internal Initiative:** Learn the steps to diagnosis, how stages of disease are communicated, and your elevated risk at each stage	**Internal Initiative:** Be an active partner in your care, recording your symptoms (like fatigue), weight, blood glucose, and blood pressure at home and signing to to patient portals or asking for copies of your lab results and medical records between visits	**External Advocacy:** Consider becoming a patient advocate, join advocate training programs like the Advanced Advocacy Academy, and participate in policy advocacy events
External Advocacy: Ask your provider for NASH patient materials. If there are none available, share the GLI NASH materials in multiple languages. www.globalliver.org/resources#nash	**External Advocacy:** Ask your health care provider if noninvasive diagnostics can be substituted for biopsy	**External Advocacy:** Request referral to a liver specialist (hepatologist) if you are diagnosed or progress to advanced NASH	**External Advocacy:** Share your lived experiences; speak to the community impact, and educate Members of Congress about the burden of NASH
External Advocacy: Join NASH and liver-related support groups to receive and share experiences and resources	**External Advocacy:** Recognize the particular risk of type 2 diabetes and the need for screening. Insist on evaluation for NASH from endocrinology or primary care.	**External Advocacy:** Request consult with dietician, nutritionist, exercise specialist, or behavioral therapist to support meeting treatment plan goals	**External Advocacy:** Ensure patient perspectives are represented research design, regulatory processes, and value/ reimbursement decisions
		External Advocacy: Request or explore information about Participating in clinical trials to advance drug development NASH	**External Advocacy:** Participate in FDA Advisory Committees

Examples of Success Metrics:

- Increased patient knowledge on GLI Annual State of NASH Survey
- Increased patient activation on GLi Annual State of NASH Survey
- Increased enrollment of NASH patients in GLI Advanced Advocacy Academy (A3) and Advocacy Platform

CLINICIANS

Immediate/ Short Term

Medium Term (usually within a year)

Long Term (usually/expected more than a year)

Education	Diagnosis	Patient Management/ Treatment	Policy Effort/ Legislation
Internal Initiative: Expand knowledge of NASH, and participate in Continuing Medical Evaluation on NASH	**Internal Initiative:** Learn how and when to use non-invasive diagnostics to diagnose, stage, and monitor progress/response of patients.	**Internal Initiative:** Provide therapeutic options tailored to patient stage of disease, risk factors, preferences, capabilities, and circumstances	**External Advocacy:** Align with patient-driven advocacy agenda through collaborations like the GLI NASH Council
External Advocacy: Include your physician assistants (PAs) and nurses in NASH education opportunities	**External Advocacy:** Advocate for your clinic or health system to make the full range of non-invasive diagnostic tools available including EHR integration	**External Advocacy:** Provide coordinated team based care including dieticians, nutritions, exercise specialists, and bariatrics as appropriate (consider establishing integrated fatty liver disease clinic)	**External Advocacy:** Participate in advocacy opportunities to Educate Members of Congress about the burden of NASH
External Advocacy: Advocate for the issuance of updated guidelines for coordinated multi-disciplinary care for NAFLD and NASH patients	**Internal Initiative:** Learn to appropriately stratify and prioritize screening of at-risk groups such as patients with type 2 diabetes	**External Advocacy:** Make appropriate and timely referrals to specialists for patients with advanced NASH and with high-risk comorbidities such as type 2 diabetes	**External Advocacy:** Initiate or participate in health system research to inform policy in NASH
Internal Initiative: Participate in training on patient-provider communication to improve discussions of diagnosis, prognosis, risks, and treatment options at each stage of NASH	**External Advocacy:** Make timely referrals for evaluation for transplant and cancer		

Examples of Success Metrics:

- Increased awareness and knowledge on GLI Annual State of NASH Survey
- Increased uptake of NASH-related continuing medical education (CME)
- Increased use of non-invasive diagnostics
- Increased report of patients with concurrent/comorbid diseases being treated
- Increased participation on advocacy events, enrollment in GLI Advocacy Platform

MEDICAL SOCIETIES

Immediate/ Short Term

Medium Term (usually within a year)

Long Term (usually/expected more than a year)

Education	Diagnosis	Patient Management/ Treatment	Policy Effort/ Legislation
Internal/External: Develop and offer NASH-related medical school curricula	**External Advocacy:** Convene consensus conference to drive acceleration of adoption of non-invasive diagnostics and simplification/ streamlined version for integration into primary care and diverse (high-low resource) clinical settings	**Internal Initiative:** Develop and disseminate updated guidelines for best practice for management and treatment of NAFLD/NASH with a mechanism for updating in a timely manner	**Internal Initiative:** Prioritize NASH in public policy agenda - research, regulatory, national and state surveillance/ epidemiology, public health, clinical practice/ health system, and value assessment/ insurance coverage
Internal/External: Develop and offer NASH-related CME within and across specialties with priority on hepatology, endocrinology, and cardiology/lipids	**Internal Initiative:** Publish recommendations for Screening and Diagnosis NASH reflective of current best clinical practices prioritizing use of non-invasive diagnostics	**Internal/External:** Develop and/or collaborate/ support best practices of care/care pathways/ guidelines specifically for NAFLD/NASH with primary care/prevention, pediatrics/obstetrics, endocrinology/diabetes, and cardiology to support whole person care and management of patients with multiple risk factors/comorbidities	**External Advocacy:** Align with patient-driven collaborations like the GLI NASH Council to co-develop the national and international NASH agenda

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MEDICAL SOCIETIES CONTINUED

Immediate/ Short Term

Medium Term (usually within a year)

Long Term (usually/expected more than a year)

Education	Diagnosis	Patient Management/ Treatment	Policy Effort/ Legislation
Internal/External: Develop and offer CME on NASH prevention and diagnosis/care of pediatric patients (pediatric and primary care co-developed CME)		**External Advocacy:** Collaborate with health systems on development of meaningful quality measures for the diagnosis and management of NAFLD and NASH appropriate to each stage of disease	**External Advocacy:** Educate members of Congress on the unique perspective of the researcher and clinician experience in NASH, the urgency of addressing the issues for patients and communities with NASH and advocate to build support of NASH relevant legislative packages. See policymaker section. (NASH Care Act of 2020, LIVER Act of 2019 etc.)
Internal Initiative: Highlight NASH in annual conference, regional events, webinar, and e-learning themes			**External Advocacy:** Advocate for coverage/ reimbursement coding changes and raise awareness of recent NASH coding changes that have occurred (ICD-10 and CPT)

Examples of Success Metrics:

- Publication of updated NASH guidelines
- Increased NASH medical educational content related to treating specific at-risk populations
- Increased NASH medical educational content for non-hepatologists
- NASH prioritized on public policy agenda

PATIENT ADVOCACY ORGANIZATIONS

Immediate/ Short Term

Medium Term (usually within a year)

Long Term (usually/expected more than a year)

Education	Diagnosis	Patient Management/ Treatment	Policy Effort/ Legislation
Internal Initiative: Create mechanisms for provision of diverse NASH patient insights to inform programs and policy	**External Advocacy:** Highlight availability and use cases for noninvasive diagnostics to increase the number of patients appropriately diagnosed, at earlier stages of disease where less intense interventions may be effective, and link to care tailored to their stage of disease	**External Advocacy:** Engage in collaborations with medical societies, health systems, and payors on development of patient-centered care pathways, integrated care delivery models, guidelines and quality measures	**External Advocacy:** Coordinate and lead engagement of advocates across stakeholder groups in policy activities through collaborative efforts like the GLI NASH Council and Advanced Advocacy Academy
External Advocacy: Create partnerships with medical societies and patient advocacy organizations to develop and disseminate educational materials tailored to the needs of specific patient populations, particularly those at high risk such as type 2 diabetes and children	**Internal Initiative:** Participate in and support research in non-invasive diagnostics and biomarker validation initiatives	**External Advocacy:** Support the design of patient-centered clinical trials and patient participation in those trials	**External Advocacy:** Conduct FDA Patient Focused Drug Development meeting and other briefings to help regulators understand the urgency surrounding NASH and the need for a consistent, transparent therapy approval pathway

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PATIENT ADVOCACY ORGANIZATIONS CONTINUED

Immediate/ Short Term

Medium Term (usually within a year)

Long Term (usually/expected more than a year)

Education	Diagnosis	Patient Management/ Treatment	Policy Effort/ Legislation
Internal Initiative: Create educational materials with a goal to be accessible to multiple audiences in-culture, in-language, addressing visual, hearing, and learning differences across formats, platforms, or novel venues such as schools		**External Advocacy:** Support the development and dissemination of research on cost-effectiveness, patient-centered value, and methods to increase access to care to inform value assessors and payors	**External Advocacy:** Conduct briefings and other advocacy activities to ensure NASH patient and community perspectives are represented in relevant legislative packages: COVID-19, diabetes, obesity
External Advocacy: Collaborate with physician (medical school and continuing) education providers on materials including patient-provider communications in NASH		**External Advocacy:** Collaborate on the development of patient activation and engagement tools to support successful patient navigation of health system and treatment plan adherence	**External Advocacy:** Collaborate with other stakeholders to address NASH as prevention, pediatric, and public health policy
External Advocacy: Participate in conferences and educational fora to articulate patient experiences and expectations in NASH			**External Advocacy:** Collaborate with other stakeholders to build support for NASH relevant legislative packages. See policymaker section. (NASH Care Act of 2020, LIVER Act of 2019 etc.)

Examples of Success Metrics:

- Downloads, Views, Requests for Educational Materials
- Inclusion of NASH Language in legislation
- FDA participation in PFDD meeting
- Increased publications on value of NASH interventions and care models
- Enrollment in A3 and Advocacy Platform

INDUSTRY

Immediate/ Short Term

Medium Term (usually within a year)

Long Term (usually/expected more than a year)

Education	Diagnosis	Patient Management/ Treatment	Policy Effort/ Legislation
External Advocacy: Collaborate with the NASH community to ensure the creation and dissemination of synchronized unbranded patient and provider education. Ensure the community is unified on how NASH is defined.	**Internal Initiative:** Design clinical trials to include validation of non-invasive diagnostics	**Internal Initiative:** Design clinical trials that include diversity matching treatment populations, patient reported outcomes measures, and patient-centered design elements (e.g. decentralized)	**Internal Initiative:** Align with patient-informed advocacy agenda through collaborations like the GLI NASH Council
External Advocacy: Collaborate on development of patient-centered value framework models for future therapies to educate payors and value assessors	**External Advocacy:** Participate in biomarker validation consortia	**Internal Initiative:** Support pilots of innovative care pathways featuring non-invasive diagnostics and value-based insurance design	**External Advocacy:** Work collaboratively with regulators on design of research programs and meeting approval goals in a timely fashion
	Internal Initiative: Support community education, screening, and linkage to care programs	**External Advocacy:** Collaborate on the development of epidemiology and patient history analysis to identify patients prospectively; understand risk, progression to inform actionable tailored solutions for patients	

Examples of Success Metrics:

- Unbranded educational and awareness grants
- Support translational research
- Design patient-centric trials

HEALTH SYSTEMS

Immediate/ Short Term

Medium Term (usually within a year)

Long Term (usually/expected more than a year)

Education	Diagnosis	Patient Management/ Treatment	Policy Effort/ Legislation
Internal Initiative: Establish or expand internal NASH education and awareness efforts: • General NASH education/awareness on intranet • Clinician (MD, RN, NP, PA) education modules • Coding updates	**Internal Initiative:** Implement NASH to population management initiatives such as diabetes programs to screen at-risk patients	**Internal Initiative:** Clarify coordinated care pathways within existing resources for early and advanced stage NASH patients including access to services with primary care, specialists for concurrent/ comorbid conditions, hepatologists, and diet/ exercise/behavioral counseling	**External Advocacy:** Align with patient-driven advocacy agenda by participating in collaborations like the GLI NASH Council
External Advocacy: Establish or expand community education initiatives particularly for at-risk and medically underserved populations	**Internal Initiative:** Expand procurement, training, and accessibility of non-invasive diagnostics throughout each health system including the VA	**Internal Initiative:** Support and hire for establishment of integrated fatty liver disease clinics with appropriate co-located and satellite/community services based on your patient and provider population needs	**External Advocacy:** Support policies and goal setting/achievement of care targets within specialized health settings/public programs such as Veteran's Administration set goal of addressing the risk for cirrhosis, liver failure, liver cancer, and death among veterans
External Advocacy: Participation as International NASH Day site (live or virtual)	**Internal Initiative:** Screen health system employees for NASH	**Internal Initiative:** Add or integrate electronic health record (EHR) alerts and calculators to facilitate timely NAFLD and NASH screening, liver cancer screening, referral to specialists	

Examples of Success Metrics:

- Host Grand Rounds presentation on NASH
- Screen health system employees for NASH
- Increase number of integrated fatty liver disease clinics established

PAYORS

Immediate/ Short Term

Medium Term (usually within a year)

Long Term (usually/expected more than a year)

Education	Diagnosis	Patient Management/ Treatment	Policy Effort/ Legislation
External Advocacy: Engage patient advocates and patient advocacy organizations across the spectrum of NAFLD/NASH and with a diversity of common comorbidities to understand the impact and integrated care needs of patients	**Internal Initiative:** Reimburse for non-invasive diagnostics to make safer, cost-effective screening and treatment response methods accessible to more clinicians and patients	**Internal/External:** Collaborate with the NASH community to develop and study best practices in care and benefit design tailored to each stage of NASH and the patient comorbidities, preferences, values, capabilities, and circumstances	**External Advocacy:** Collaborate with medical societies to conduct a study within medical insured populations prior to setting budgets/ internal policies (research should include advanced fibrosis NASH epidemiology, urgency to treat, and noninvasive diagnostics)
Internal Initiative: Conduct research on your beneficiary population to understand the clinical, direct, and indirect costs of NASH on patients, carepartners, employers, and health systems	**Internal Initiative:** Collaborate with medical societies to understand the value of diagnosing, identifying, and preventing the progression of NASH	**Internal Initiative:** Reimburse (across plan types) for integrated, whole person care including evidence-based NAFLD/NASH-related services such as dieticians, exercise specialists, weight loss medications, and bariatric surgery	**External Advocacy:** Disseminate patient-centered value based care findings (consider disseminating within ISPOR and DIA meetings to inform practice and policy)
External Advocacy: Collaborate with the NASH community to understand the urgency of NASH and specific need to treat patient populations most at-risk of progression expensive life-threatening conditions such as cirrhosis, liver cancer, and liver failure/ need for transplant			

Examples of Success Metrics:

- Participation in Payor Summit with NASH patient advocates
- Design and launch of NASH study of beneficiaries
- Reimbursement of integrated NASH care pathway including non-invasive diagnostics

REGULATORS

Immediate/ Short Term

Medium Term (usually within a year)

Long Term (usually/expected more than a year)

Education	Diagnosis	Patient Management/ Treatment	Policy Effort/ Legislation
Internal Initiative: Conduct cross-center, multi-division briefing for FDA staff on needs in liver health and prioritization of NASH, rare liver, and liver cancer therapeutics (drug, device, diagnostic, and biologics)	**Internal Initiative:** Re-evaluate emphasis for insistence on biopsy in light of current evidence, clinical practice, and patient burden.	**Internal Initiative:** Update existing draft guidances, move to final guidances on NASH in timely fashion to bolster transparency and trust and foster culture of and mechanisms for accountability	**External Advocacy:** Recruit and train NASH patient representatives
External: Participate in PFDD on NASH	**External Advocacy:** Clearly and consistently communicate to NASH community threshold at which biopsies in certain trial settings will no longer be required and adhere to guidances communicated		**Internal Initiative:** Elevate priorities for liver drug approvals and ensure support and training are provided for appropriate expertise and time to be applied

Examples of Success Metrics:

- Partner on PFDD and demonstrate inclusion of patient perspectives in updated guidances
- Conduct cross-center briefing and demonstrate appreciate for urgency and prioritization of NASH drug approvals

POLICYMAKERS

Policy plays an integral role in the equation of NASH response. As highlighted above, we have provided clear actionable recommendations for a majority of the NASH community with one very clear omission, policymakers. While policy, and specific legislation is not a “cure all” in response to the NASH epidemic, it does deserve a unique section within this action plan. This point is only underlined when we acknowledge that many of the previously stated recommendations ask stakeholders to inform policymakers and advocate for legislative action.

In response, the following recommendations are still highlighted according to short, medium and longer timeframes. However, instead of being broken into internal initiatives, and external advocacy, they are seperated in general policy (or practice) that we hope each Congressional office embraces, and specific legislative asks that we believe must be enacted to respond to the growing NASH crisis. Most importantly, we ask that every policymaker recognize the value of collaboration and that investments in public health along with scientific discovery are crucial to improving the nation’s health, economy, and addressing NASH in both the near- and long-term. Also due to the prevalence of NASH, the health risks associated with, and the intrinsic link it shares with many other diseases, any response to NASH will surely lead to many other positive health outcomes for the United States.

Immediate/ Short Term

Medium Term (usually within a year)

Long Term (usually/expected more than a year)

Education	Diagnosis	Patient Management/ Treatment	Policy Effort/ Legislation
Direct Legislation: Appropriate for CDC Grants for NASH Community-Based Patient Education, Awareness campaigns, and Provider Training and Outreach	**Direct Legislation:** Establish CDC Noninvasive Diagnostic Awareness Initiatives for NASH	**General Policy/Direct** Legislation: Support NIH efforts to enable cutting-edge research that supports high-risk, high-reward exploratory projects into NASH therapies	**General Policy:** Understand the link between NASH and its most commonly associated risk factors and comorbidities; consider inclusion within other relevant legislation packages. Specifically within COVID-19, diabetes, and obesity, and nutrition legislation

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Education	Diagnosis	Patient Management/ Treatment	Policy Effort/ Legislation
General Policy: Collaborate with the liver advocacy community to educate and elevate liver health policy to its rightful place on the national public health agenda based on prevalence and impact	**Direct Legislation:** Develop a National Surveillance Program for NAFLD and NASH (a NASH report is needed to establish the scope of NASH epidemic)	**General Policy:** Prepare the U.S. health system for the future of NASH that includes an FDA-approved therapeutic and support a coverage and delivery system that makes the full range of appropriate solutions for patients with both early and advanced stage NASH accessible	**Direct Legislation:** Pass the NASH Care Act of 2020 (H.R. 8658)
Direct Legislation: Support the consistent increase in NIH and NIDDK funding to foster outstanding collaborative translational research projects in NASH	**General policy:** Consistently consider the value of timely, multi-stakeholder collaboration on identification and treatment of NASH and include in legislative strategy	**General Policy:** Think patient-centered value-based care. Work with CMS, Veterans Affairs, and CMMI to develop value-based care hepatology pilot programs: support development of models of care for excellence in treating NASH patients	**Direct Legislation:** Pass the The Liver Illness Visibility, Education, and Research Act of 2019 (S. 3074/H.R. 3016)
General Policy: Encourage CDC, FDA, CMS, and other relevant agencies to engage patient advocates, expand existing community-based programs, and promote patient education for both children and adults. Programs must aim to promote early detection, prevention, diagnosis and treatment for patients with NASH, while establishing new paradigms of care that will improve patient outcomes.	**General Policy:** Guide the U.S. Preventive Services Task Force to develop national screening guidelines	**General Policy:** Consider focusing policy efforts on developing national strategies targeting patient populations most at-risk for NASH and work to understand the urgency for a patient population without a consistent established care pathway	**Direct Legislation:** Pass the Treat and Reduce Obesity Act of 2019 (S. 595/H.R. 1530)

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Education	Diagnosis	Patient Management/ Treatment	Policy Effort/ Legislation
General Policy: Integrate the work of scientists, physicians, and administrators in policy agendas to advance knowledge in NASH and thereby improve clinical outcomes.			**Direct Legislation:** Pass the Medical Nutrition and Equity Act (S. 3657/H.R. 2501)
			Direct Legislation: Health Equity and Accountability Act of 2020 (H.R. 6637/S.4819)
			Direct Legislation: The CLINICAL TREATMENT Act (H.R. 913/S.4742)

Examples of Success Metrics:

- Passage of critical NASH or linked legislation
- Consistent representation of NASH within policy strategies
- Consistent support of NASH medical research, and public health program expansion

MEASURING PROGRESS

Annual State of NASH in the United States Report

The GLI NASH Council stands at 70 members in December 2020, convening members with experience in each of the stakeholder groups described in this U. S. NASH Action Plan.

Throughout 2021, GLI will work across our membership and throughout their networks to establish which recommended element(s) of the Action Plan different entities and organizations within each stakeholder group pledge to advance and set up a timeframe for achievement of that claimed element. Each pledge will be publicized and supported on or before International NASH Day on June 10, 2021.

Further, an Annual State of NASH in the United States Report will be published to recognize the individual and collective achievements of the NASH Council and the NASH community. The next edition of the Action Plan will be updated and issued based on our progress against the selected metrics and the evolved landscape, replacing achieved elements with new goals.

Measuring progress for some elements related to increased awareness, knowledge, and activation/ engagement is best done through a national survey of patients, carepartners, and clinicians. Other elements will be measured based on GLI-collected information from our website, social media analytics, and enrollment number for our Advanced Advocacy Academy (A3) and Advocacy platform.

CONCLUSION

NASH has been called a “ticking time bomb.” It is the most rapidly growing liver disease in the U.S. and the world. Symptoms of NASH are non-specific and often misinterpreted. Estimates of prevalence vary widely and are likely to be under-reported and inaccurate, making it difficult to quantify the scale of the problem. The rise of NASH, its complications, and its comorbidities carry significant economic and public health costs for health systems and our society.

Each critical recommended intervention within this plan will play a vital role in elevating NASH health policy to its rightful place on the national public health agenda commensurate with its prevalence and impact. While we do not have a “silver bullet” response to this life-threatening disease, we can positively shape the field for the future and save numerous lives if the healthcare community utilizes these recommendations to respond holistically to NASH.

Patients with NASH have been neglected for too long. It is critical to respond on a national scale in 2021 and beyond. As we move to implement the interventions suggested within this plan, we look forward to continuing to work together to prevent and address this life-threatening disease.

If you have any questions please don’t hesitate to reach out to Andrew Scott, GLI Policy Director, at ascott@globalliver.org.

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Global Liver Institute (GLI) is a 501(c)(3) tax-exempt not-for-profit organization, headquartered in Washington, D.C., United States, with offices in the U.S. and Europe. GLI's vision is for liver health to take its place on the global public health agenda commensurate with its prevalence and impact. GLI's mission is to improve the lives of individuals and families impacted by liver disease through promoting innovation, encouraging collaboration, and supporting the scaling of optimal approaches to help eradicate liver diseases.