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December 18, 2020

The Honorable Joseph R. Biden, Jr.
President-elect
1401 Constitution Ave. NW
Washington, DC 20230

RE: Liver Health Is Public Health: 2021 Liver Health Policy Priorities

Dear President-elect Biden,

Global Liver Institute (GLI) is a nonpartisan nonprofit patient advocacy organization committed to improving the lives of individuals and families impacted by liver disease by promoting innovation, encouraging collaboration, and scaling optimal approaches to help eradicate liver diseases. As the only global liver patient advocacy organization, we applaud the steps you and your team have already taken to seek and then follow recommendations from the scientific community during the deadly COVID-19 pandemic. We also appreciate your choices of leadership for vital federal health agencies. Your early choices and actions clearly recognize the value of collaboration and that investments in public health along with scientific discovery are crucial to improving the nation's health and economy in both the near- and long-term.

2020 will be remembered as the year of the dual crises: the COVID-19 pandemic and the heightening of health inequities. Both of these have shaken every healthcare, economic, and social system at their core. Both of these crises also rightfully deserve a majority of our nation's attention and directly impact the liver health community.

With this in mind, over the last year we have seen a continued rise of liver disease prevalence and mortality both directly and indirectly connected to the impact of COVID-19 on our healthcare system. The harsh reality of systemic racism and health disparities has also played a role in this continued growth of liver disease and the negative health outcomes.

In response, we write to you to urge your attention on the following six liver health policy/regulatory priorities within three critical categories (COVID-19 response, health disparities, and liver health policy/regulations). Each of these actions would most significantly impact the lives of patients with liver disease in the United States.

1. **COVID-19 Response:** Fund public health programs serving those with underlying liver disease and other underlying medical

conditions that are at increased risk for severe illness from the virus that causes COVID-19.

2. **COVID-19 Response:** Fund research on how COVID-19 impacts both adult and pediatric patients with liver disease and provide funding to restart NIH-funded liver disease research.

3. **Health Disparities:** Implement strategies targeting liver disease health disparities, especially the excess liver cancer mortality of black men in America.

4. **Health Disparities:** Urgently respond to the inequities that impact organ transplantation.

5. **Liver Health Policy:** Support the GLI NASH Council national strategy to address the rapidly rising chronic liver disease, nonalcoholic steatohepatitis (NASH).

6. **Liver Health Regulations:** Prioritize regulatory processes to approve therapies for liver diseases, particularly rare liver diseases.

Liver Health Policy Background:

Liver health is public health.

Over the past several decades, liver diseases have relentlessly risen to become one of the leading causes of death and illness worldwide. According to the Global Burden of Disease project released in 2012, in 2010 more than two million deaths were due to major liver diseases including acute hepatitis, cirrhosis, and liver cancer, which accounted for approximately 4% of all deaths worldwide.[1] Despite the development of vaccines and antiviral agents, the global burden of liver disease is poised to swell yet further due to health-modulating factors such as the extension of life expectancy, increasingly sedentary lifestyles, and over-nutrition. This expected ballooning of liver disease was already occurring before we were hit by the single greatest modern public health emergency, COVID-19.

In most developed countries, the incidence of viral hepatitis is still concerning but waning as a result of modern advances in disease prevention, diagnosis, and therapies. In contrast, with the improvement in living standards, the prevalence of metabolic liver diseases, including nonalcoholic fatty liver disease and alcohol-related liver disease, is set to rise, ultimately leading to more cases of end-stage liver diseases (liver failure, cirrhosis, and liver cancer). For example,

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[1] Byass P. The global burden of liver disease: a challenge for methods and for public health. *BMC Med.* 2014; 12: 159

the prevalence of NASH, the most severe form of nonalcoholic fatty liver disease (NAFLD), is estimated to increase by 63% by 2030.[2] [3]

Disease Category	**United States Prevalence (%)**
Cirrhosis	633 thousand (0.27)
Liver Cancer	42 thousand (0.01)
Hepatitis B Virus (HBV)	2.2 million (0.71)
Hepatitis C Virus (HCV)	3.5 million (1.13)
Nonalcoholic Fatty Liver Disease (NAFLD)	76 million (24.13)
Nonalcoholic Steatohepatitis (NASH)	4.9 million - 19 million (1.50 - 6.20)
Alcoholic Liver Disease (ALD)	19 million (6.20)

Steps must be taken to protect the lives of patients with liver disease. National strategies must be implemented to prevent, treat, and raise awareness about these diseases. Liver dysfunction as a whole has a wide-ranging impact in a patient's body so any future prevention effort that improves liver status overall will almost certainly have secondary impacts of value. It is also critical for our healthcare system to be prepared for the growing burden of patients who already have a liver disease.

Priority 1: Fund public health programs serving those with underlying liver disease and other underlying medical conditions that are at increased risk for severe illness from the virus that causes COVID-19.

Whether directly from COVID-19 or as a consequence of the burden of the pandemic on our healthcare systems, lives are at risk. As it stands currently, and as was abundantly apparent during this global public health crisis, our healthcare system is poorly prepared to prevent, document, and respond to public health emergencies.

Recent research has also found increased mortality rates from COVID-19 among people with chronic liver disease and cirrhosis.[4] Many, including Admiral Brett P. Giroir, M.D., Assistant Secretary for Health at the U.S. Department of Health and Human Services (HHS), have also called for patients with worsening liver function to be treated first. The Centers for Disease Control and Prevention (CDC) underlined the same point and released resources addressing concerns related to COVID-19 and liver disease.[5] The CDC highlighted what people living with chronic liver disease, liver cancer, fatty liver disease, and hepatitis B and/or hepatitis C infection

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[2] Informa (2019) Non-alcoholic steatohepatitis (NASH). Epidemiology. July 2019. [Online] [Accessed 16 Oct. 2019] https://service.datamonitorhealthcare.com

[3] Estes, C. et al., Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology, 2018. 67(1): p. 123-133.

[4] https://www.journal-of-hepatology.eu/article/S0168-8278(20)30305-6/fulltext#%20

[5] https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/liver-disease.html

can do to protect themselves and maintain their health. They also acknowledged the same startling information that COVID-19 has been found to cause increased levels of liver enzymes and liver damage and that outcomes from COVID-19 can be worse for people who already have liver fibrosis/cirrhosis. On top of this, the CDC recently found that over 40% of adults have delayed or forgone medical treatment during the pandemic.

The CDC plays a vital role in studying disease prevalence, examining what interventions work best, and distributing money to states and localities for prevention efforts. The CDC is also the federal agency in charge of surveillance and prevention. Even amid a pandemic, our public health infrastructure needs to remain operational and effective; therefore, it's paramount the federal government continues to invest in public health and value evidence-based science above all else.

This is even more critical as we begin to move past the COVID-19 pandemic. According to the World Health Organization (WHO), non-communicable diseases (NCDs) accounted for seven of the top ten causes of death before the coronavirus pandemic. The next national health crisis of NCDs/chronic diseases like chronic liver disease is not some far off concern—it is about to boil over. Continued greater support of the CDC's ability to respond to these quickly rising concerns is necessary, and the expansion of the agency's ability to provide expansive preventative public health programs is vital. This is why we greatly applaud your pick of Dr. Rochelle Walensky, the Chief of Infectious Diseases at Massachusetts General Hospital, to run the CDC. Selecting an expert like Dr. Walensky to lead this critical division shows your willingness to prioritize and listen to evidence-based science and medical professionals.

Going forward it is critical for the CDC to respond to the rising concerns of NCDs like chronic liver disease. The liver has more than 500 functions in the body, and many chronic liver diseases share an intrinsic link with other chronic diseases like diabetes and obesity. Prioritizing public health programs that are collaborative across CDC divisions and consider liver health holistically, due to the integral role the liver plays, could positively improve health outcomes for a wide range of diseases quickly and efficiently saving thousands of lives.

Priority 2: Fund research on how COVID-19 impacts both adult and pediatric patients with liver disease and provide funding to restart NIH-funded liver disease research.

Many research projects have been severely impacted by the COVID-19 pandemic. It is critical that, as we continue to respond to COVID-19, all governments also prioritize funding to restart and support research that has either had to shut down or be scaled back due to the pandemic.

The federal agencies supporting liver disease and liver cancer research and liver public health programs are leading to better health and well-being for people across the nation. These agencies include the National Institutes of Health (NIH), National Cancer Institute (NCI), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Congressionally Directed Medical Research Programs (CDMRP) at the Department of Defense (DoD), Department of Veterans Affairs (VA), and CDC.

Without additional funding these agencies will not have the capacity to continue existing research projects and undertake new research on COVID-related comorbidities that will be critical both for disease mitigation and the development of effective treatments and vaccines. In general, there is already limited funding to support research on liver disease, and additional funds will be needed to cover the cost of restarting research and not impede critical research progress.

This is why we proudly support both the Liver Illness Visibility, Education, and Research (LIVER) Act of 2019, H.R. 3016 and S. 3074, and the Nonalcoholic Steatohepatitis (NASH) Care Act of 2020, H.R. 8658. Both of these vital bipartisan pieces of legislation move the needle on a wide range of critical liver health policy issues and, most importantly, elevate liver health research overall within NIH and NIDDK. Both bills would create a liver disease division and add "Liver" to the name of NIDDK, thus organizing and syncing the wide range of liver disease research projects.

Over the last few years, Congress has ensured that our nation honors the longstanding commitment to improve and save lives through federal support and research. Thanks to their commitment, federal research has led to several significant breakthroughs and achievements, contributing to the health and welfare of all Americans. A continued emphasis on federal funding will only build on these successes.

Outside of specific research initiatives, medical research has also been an important economic driver. A recent report showed that the $30.82 billion that NIH awarded for research grants in FY2019 supported 475,905 jobs and $81.22 billion in national economic activity. This funding is going to continue to be essential not only to the patients who are counting on the treatments and early detection tools that will be developed as a result but also to reboot the economy as part of a larger plan after the pandemic.

As we continue to fight through this global public health emergency, it is vital to maintain continuity in investment in these important research programs to ensure that our nation responds properly to the current crisis while also being prepared for any other public health challenges, like the rise of liver disease, that threaten our population.

Priority 3: Implement strategies targeting liver disease health disparities, especially the excess liver cancer mortality of black men in America.

Race, ethnicity, gender, and sexuality are societal constructs that have a significant impact on American lives, particularly regarding health. Many different social structures place burdens, prejudices, and discriminations on many different groups of people which have severe negative consequences on health outcomes. This can be seen in the high incidence, prevalence, and mortality rate of a countless number of diseases, many of which have established treatments. Minorities and people of color are often in an oppressive cycle of low education, poor working conditions, and low income which results in poor health outcomes. The history and current state of discrimination can limit the equitable access that people of color have to health care including clinical trials, treatments, and follow-up appointments. It is essential that the public health community address the barriers that prevent people of color from accessing essential care.

From viral hepatitis to NAFLD and NASH, minority populations are disproportionately impacted by liver disease. Many Hispanics in the U.S. possess the PNPLA3 gene variation, which has been associated with a heightened risk of NAFLD and NASH. It is especially concerning, however, to see the stark disparities in disease outcome by race for liver cancer.

Unlike most cancers in the U.S., new cases of and deaths due to primary liver cancer — hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (iCCA) — have increased steadily since the early 1980s. The five-year survival rate for liver cancer is 18 percent. The most common risk factors for liver cancer are cirrhosis, chronic infection with viral hepatitis, alcohol related cirrhosis, NASH, and exposure to certain toxins.

Unfortunately, liver cancer disproportionately impacts communities of color. Native American and indigenous Alaskans have the highest rates of liver cancer followed by Asian/Pacific Islanders, Hispanics, and African Americans. Not only are communities of color at a much higher risk for developing liver cancer, but they are less frequently enrolled in clinical trials because of myriad barriers, including access, knowledge, multiple comorbid conditions, and limited financial resources.

The disparities do not just follow racial lines but also translate into gender inequalities in healthcare outcomes and the prevalence of liver cancer as seen in the table below.

Liver Cancer Incidence Rates* by Sex and Race 2012-2016

Race/Ethnicity	Both Sexes	Female	Male
Non-Hispanic Black	10.9	5.4	17.9
All races	8.3	4.4	12.7
Non-Hispanic White	6.9	3.7	10.5

**American Cancer Society*

Excess liver cancer incidence and liver cancer mortality are clearly highest among non-Hispanic Black males. Adding the COVID-19 crisis to this equation, however, has only amplified these startling statistics.

The CDC published data on hospitalizations for COVID-19 across 14 states from March 1-30 in its Morbidity and Mortality Weekly Report. It documented that African Americans accounted for 33% of the hospitalizations but only 18% of the total population in the 14 states. Many states have reported an even higher percentage. African Americans accounted for 40% of COVID-19 deaths in Michigan and 43% in Illinois despite making up only 14% of the population in both states. What's worse is that only 13.2% of those tested are Black, suggesting that African Americans are being drastically underserved by the effort to control the spread of the disease.

With that said, this pandemic has only brought an ongoing issue back into the national spotlight. Over the last 20 years, as all other cancer mortality has decreased, liver cancer mortality has increased 43%. And yet, the American Cancer Society estimates that up to 70% of new liver cancer cases could be prevented with clinical interventions, such as vaccination for hepatitis B virus, treatment for hepatitis C virus, and behavioral interventions to decrease the impact of NASH. This is why we must act quickly to put research, as well as policies, to work to eliminate health disparities.

Providing racial data is essential to mitigating the spread of disease in communities that are disproportionately impacted. Race data must be more thoroughly reported by counties, states, and the federal government. It is also critical to ensure the continuity and consistency of the development of educational materials across patient populations. Outreach efforts must encompass all patient populations, from those that are geographically to culturally diverse. Relevant agencies must look to partner with disease specific advocacy groups that understand the burden of the patient population they represent best.

Most importantly, a more systematic, culturally appropriate strategy is needed to urge more African Americans to get tested, screened for liver cancer, and to get treated. Of course, barriers to testing and treatment must also be removed, including the appropriate placement of testing sites and cost. We also strongly suggest following through on the recommendation of some panelists at the FDA-American Association for Cancer Research workshop who suggested that a “diversity score” be attached to trials to incentivize sponsors into improving diversity. Connected to this point is the need to restart the “Minority Snapshot” to better understand the composition of different clinical trials.

Issues of health equity are complex and, as is manifest in our nation’s history, not easily solved. Black men stand out for the disparity of their liver cancer mortality, which occurs as a result of late-stage diagnosis when treatment options are limited, if available, to this population. COVID-19 has presented us with an opportunity to reimagine our healthcare systems for the future. Each diverse patient population is the only community who can accurately provide essential insight into how living with any one condition impacts their life.

Priority 4: Urgently responding to the inequities that impact organ transplantation

The U.S. organ donation system is broken. This problem is not new; in fact, it’s been well-documented for over 20 years by everyone from government agencies to academic institutions to patient groups to private contractors. It is no more evident than its impact on patients and donor families of color through every phase of the process – from getting on the waitlist, to finding a match, to becoming a donor.[6] Both donor families and patients of color who need an organ experience different treatments and a system deeply rooted in inequity.[7]

Asian Americans are four times more likely to have HCC,[8] one of the most common indications for liver transplant. The need for liver transplantation is also rising. For example, NASH which is estimated to affect 148 million to 444 million people worldwide, and for which there are currently no approved treatments available,[9] [10] has become the fastest growing reason for liver

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[6] This article follows a Black patient’s journey from listing to transplant. “Good for Harvest, Bad for Planting,” Health Affairs, 2007.

[7] “Comparison of black and white families’ experiences and perceptions regarding organ donation requests,” Crit Care Med, 2003

[8] “Role of Ethnicity in Risk for Hepatocellular Carcinoma in Patients With Chronic Hepatitis C and Cirrhosis,” CGH Journal, 2004.

[9] Estes, C., Razavi, H., Loomba, R., Younossi, Z., and Sanyal, A.J. (2018). “Modeling the Epidemic of Nonalcoholic Fatty Liver Disease Demonstrates an Exponential Increase in Burden of Disease.” Hepatology, 68(1), 123-133. Doi: 10.1002/hep.2946

[10] Ratziu V, Goodman Z, Sanyal AJJoh. 2015. Current efforts and trends in the treatment of NASH. 62(1): S65-S75

transplantation. NASH impacts all populations but disproportionately impacts certain minority communities. The prevalence of NASH in the Hispanic community, for instance, is 19.4%.[11] Liver transplantation is the only recourse for people with end-stage liver disease and/or NASH-related liver cancer.[12]

Even with this reality, more than 28,000 viable organs are wasted. Currently, 13,192 patients with liver disease are waiting for transplants, a majority of which are people of color. And yet, ethnic minorities comprise approximately 30% of all adult liver transplantations performed annually.[13]

To respond to the health disparities in the organ transplant system we must focus on strategies that address: racial obstacles to getting on the waitlist, fewer medically suitable organs available for patients of color, potential donors of color being less likely to be referred, Organ Procurement Organizations (OPO) not showing up to talk to donor families of color, failing to get proper authorization, and finding a correct donor/organ match.

A vital first step towards accomplishing this goal is Congressional oversight and Administration action. This is why, in July of 2019, we could not have been more excited to see a positive bipartisan step in Congress and through the Administration focused on modernizing this system, namely, the Trump Administration's Executive Order on Advancing American Kidney Health.

This movement of the community has culminated in the Centers for Medicare & Medicaid Services (CMS) just recently finalizing a rule that reforms the quality measures that OPOs must meet in order to receive Medicare and Medicaid payment.

This rule is a critical provision within the executive order and increases accountability by setting new, objective, transparent, reliable, and enforceable outcome measures and metrics for OPOs. It ensures safe, high-quality care that puts patients first by: supporting higher donation rates; reducing discarded but viable organs; and modernizing organ recovery and transplantation. Most importantly, this measure incentivizes OPOs to invest in serving their entire community, which includes hiring more diverse staff and investing more time and resources to develop relationships with underserved populations and the hospitals that serve them.

OPOs have the power to rapidly improve outcomes for patients of color. This bipartisan rule positively shortens waiting lists and saves lives by incentivizing OPOs to increase the number of safe, timely transplants. It should be implemented and enforced as quickly as possible allowing us to focus our efforts on other critical health disparity issues within the organ donation system.

Priority 5: Support the GLI NASH Council U.S. NASH Action Plan

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[11] 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.

[12] Wong RJ, Cheung R, Ahmed A. 2014. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. 59(6): 2188-95

[13] Kemmer N. (2011). Ethnic disparities in liver transplantation. *Gastroenterology & hepatology*, *7*(5), 302–307.

Sharing an intrinsic link with diabetes, obesity, metabolic syndrome, chronic kidney disease and cardiovascular disease (CVD), NASH impacts anywhere from 148 million to 444 million people worldwide. NASH has far-reaching 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.[14] Even with this harsh reality, the U.S. continues to lack a federal response strategy to this life-threatening, widespread liver disease.

Currently, 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. Symptoms of NASH, which may include fatigue, lethargy, abdominal pain and sleeping problems, are non-specific so they can often be misinterpreted as something else. 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; therefore, most people live with the disease for years without being aware of the damage accumulating in their liver. Currently, providers lack guidelines for regular follow-up. For patients who are diagnosed with NASH, there are no FDA-approved treatments available.

We need a national plan in place to raise awareness about NAFLD and NASH. We need to improve data collection to achieve a better understanding of NASH prevalence, economic costs, and impact on quality of life. We need to develop clear care pathways to encourage more effective diagnosis and high-quality care. The U.S. NASH Action Plan developed by GLI and the GLI NASH Council touches on many of these points and includes many detailed specific recommendations for the field.

Thankfully, leaders in Congress, Congressman Dan Crenshaw (R-TX) and Congressman Raul Ruiz (D-CA), have recently acted on this national concern and introduced a bipartisan initiative entitled the “Nonalcoholic Steatohepatitis (NASH) Care Act of 2020,” H.R. 8658. This bill would establish a national strategy for preventing, diagnosing, and treating NASH.

Over the years, GLI and many in the NASH community have advocated for a greater national priority on NASH. We have seen the amount of impacted people continue to grow with minimal to no acknowledgement. This piece of legislation acts as a positive first step, opening the door for many other vital initiatives recommended by the field to respond urgently to this life-threatening disease. It is critical to act now not only for the patients who already live with the immense burden of this disease but for the numerous future patients with NASH.

Priority 6: Prioritize regulatory processes to approve therapies for liver diseases, particularly rare liver diseases.

Rare liver diseases are not so rare if they affect you or someone you love. There are more than 100 different types of liver disease, and many deserve greater prioritization. Primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), and autoimmune hepatitis (AIH) for example, are all rare liver diseases that deserve more attention.

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

The 21st Century Cures Act provided legislative authority for FDA Centers of Excellence (COE). This was a departure from FDA's traditional orientation towards centers that focus on specific products; instead supporting an integrated approach to the clinical evaluation of products. The first COE (Oncology) was established in 2017. The Oncology COE has been viewed as a success, resulting in the approval of dozens of new drug and biologic applications.

First, it is critical to consider the creation of a Center of Excellence for Rare Diseases (Rare Disease COE). This Rare Disease COE would leverage the combined skills of regulatory scientists and reviewers with experience in rare diseases in drugs, biologics, and medical devices, including diagnostics. It would be tasked with helping expedite the development of medical products and support an integrated approach in clinical evaluation of drugs, biologics, and devices for the treatment of rare diseases. The COE would be made responsible for: harmonization of rare disease-specific regulatory approaches; coordination of rare disease-specific regulatory science initiatives and outreach; implementation of cross-center rare disease-focused meetings; and stakeholder engagement to the external community and international regulatory agencies on rare disease product development.

Second, it is critical to implement verifiable standards/metrics of success for the new Rare Disease COE. While the Oncology COE overall has been viewed as a success, it is still important to ensure transparency, and accountability for the new Rare Disease COE. To this end, we suggest that the COE produces an annual report compiling data, ensuring consistent action, and accountability. Not only must there be a center for rare disease therapy development, but the center must also consistently release transparent results for the community.

Conclusion

As we continue to respond to the dual crises of COVID-19 pandemic, and health inequality, it is important to acknowledge the impact of these crises on at risk populations. We must consider the impact on liver health research, public health programs, and the direct connection between liver disease and COVID-19. It is also critical to urgently address liver disease health disparities especially in the organ donation system and liver cancer health outcomes. Finally, we must consider the populations impacted by liver diseases that have been ignored for too long.

Liver health truly is public health, and patients with liver disease deserve to be prioritized. We respectfully ask for you to consider these six liver health policy priorities and to elevate liver health policy to its rightful place on the national public health agenda commensurate with the prevalence of liver disease. We also look forward to being a resource for you and your new Administration so that we can address the rising concerns of these life-threatening diseases.

If you have any questions please don't hesitate to reach out to our Director of Policy, Andrew Scott, at ascott@globalliver.org or 831-246-1586.

Donna R Cryer

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