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The Honorable Diana DeGette
U.S. House of Representatives
Washington, DC 20515

The Honorable Fred Upton
U.S. House of Representatives
Washington, DC 20515

RE: ARPA-H Request for Information

Prioritizing Liver Disease and Liver Health

Dear Representatives DeGette and Upton:

As a global 501(c)3 nonpartisan nonprofit liver health organization, we are 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. We applaud the steps that you are taking to seek and then follow recommendations from the health community in the development of ARPA-H. Your early 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.

Today, we are writing in response to your request for stakeholder input on the development of a new Advanced Research Projects Agency for Health (ARPA-H). Overall, we enthusiastically support the creation of ARPA-H as it has the potential to provide a vital bridge between the lack of tools and resources currently available to patients impacted by liver diseases, and the improved survival rates that are so desperately needed.

Collectively, liver diseases impact more than 120 million Americans. Research shows that cirrhosis impacts 633 thousand people, liver cancer impacts 42 thousand, Hepatitis B Virus (HBV) impacts 2.2 million, Hepatitis C Virus impacts 3.5 million. The prevalence of viral hepatitis remains high, while drug-induced liver injury continues to increase as a major cause of acute hepatitis. Approximately one out of every three adults have obesity, 34.2 million people of all ages had diabetes; both of which are risk factors for nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and hepatocellular carcinoma. An estimated 76 million are impacted by NAFLD and 4.9 million - 19 million already have NASH (37% of people with type 2

diabetes also have NASH).[1] These metabolic conditions drive NASH (especially type 2 diabetes) and NASH drives these conditions. 69.5 percent of adults reported that they drank in the past year, and 19 million people are impacted by alcohol-associated liver disease. Liver transplantation is the second most common solid organ transplantation, yet 13,000 liver patients in the U.S. are waiting for a lifesaving transplant every year, and, sadly, three people die everyday while waiting.[2]

Between 1999 and 2016, deaths from cirrhosis increased by 65 percent, and deaths from liver cancer doubled. In the United States, liver cancer is the fastest-growing cause of cancer death and among the leading causes of cancer deaths.[3] [4] Despite the development of vaccines and antiviral agents, the 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. On top of this, over the last year, this burden has only intensified due to the impact of COVID-19 on overall liver health as well as our healthcare system.[5] [6]

Despite these facts, liver disease is under recognized, under diagnosed, and undertreated. The liver is not a significant focus of routine medical evaluations. 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.

Federal agencies like the National Cancer Institute (NCI), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Centers for Disease Control and Prevention (CDC) have made progress on developing new approaches and resources, and public health prevention programs, but there is clearly still much work that needs to be done. We welcome the potential that ARPA has in spurring new and innovative approaches in prevention, early detection, and treatment of the variety of liver diseases.

In calling for the creation of ARPA-H, President Biden has cited the success of the Defense Advanced Research Projects Agency (DARPA) and expressed his belief that ARPA-H should be similar. Please provide specific details on which aspects of DARPA ARPA-H should replicate and why this would lead to similar success.

While the NIH process is critical in developing new tools for liver diseases, it traditionally favors incremental, hypothesis-driven research. As the Office of Science & Technology Policy noted in their ARPA-H concept paper, NIH proposals are typically "curiosity-driven". We are particularly intrigued by the DARPA approach to focus on "use-driven" research that is directed at solving a practical problem. We believe that approaching medical issues from both ends of the spectrum – curiosity-driven and use-driven – will speed progress toward developing the tools our patients desperately need.

We also support using the DARPA principle of embracing failure in a newly created ARPA-H. The hallmark of this program should be a focus on bold projects that would be transformative to

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[1] https://www.globalliver.org/news/2020/9/28/the-language-of-nash-a-foundational-nash-messaging-framework-for-communication-about-nash-and-nafld

[2] Organ Procurement Transplantation Network, U.S. Department of Health and Human Services

[3] https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21402

[4] https://www.cancer.org/cancer/liver-cancer/about/what-is-key-statistics.html#:~:text=In%20many%20of%20these%20countries,than%20700%2C000%20deaths%20each%20year

[5] https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30432-6/fulltext

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

patient care. While NIH paylines tend to necessitate a focus on funding projects that are likely to succeed, it is critical that ARPA-H embrace true innovation and out-of-the-box thinking. Risk-taking should therefore be a fundamental principle in determining areas of focus and funded-projects. In that regard, we agree with the statement made by White House Office of Science and Technology Policy (OSTP) Director Dr. Eric Lander, NIH Director Francis Collins and others that "patients ARPA-H should expect that a sizable fraction of its efforts will fail; if not, the organization is being too risk-averse. The best approach is to fail early in the process, by addressing key risks upfront."[7]

To ensure it has the biggest impact, what activities or areas should ARPA-H focus on? What activities or areas should ARPA-H avoid?

We were pleased to note that both in your concept paper and in President Biden's budget, the stated purpose of ARPA-H is to focus on bold projects that would be transformative to patient care. We strongly believe that this focus on fundamentally changing patient outcomes is critical to ARPA-H's success and urge you to hold fast to this principle as you are developing the legislative language authorizing the program. While we understand that "quick hits" would be helpful in demonstrating the potential success of a new ARPA-H, we urge you to focus instead on projects that aim to enable clear change in disease from that which is recalcitrant to manageable and curable.

Currently, knowledge and awareness about liver health is minimal across all segments of the general population including patients living with the disease and the medical community. Due to the lack of public awareness of liver health, patients find it difficult to differentiate between symptoms related to a liver disease and other health issues or comorbidities. Patients also feel a lack of adequate educational support from their physicians, and healthcare professionals may also not think to screen for a liver disease, even in patients with more than one high risk factor.

Most importantly, there are a variety of barriers that prevent providers from addressing liver health early. Patients remain unaware of their liver health status until diseases are relatively advanced or difficult to treat. Patients and the medical community are also many times unaware of the steps they can and must take to preserve the health of the liver.

This is why liver diseases exemplify areas where medical practice would be dramatically changed through the technologies and platforms that could be developed under ARPA-H. For these reasons, we urge you to ensure that ARPA-H focuses on the hardest problems and areas where medical practice will be dramatically changed, including liver diseases, as you develop authorizing language. Specifically, we urge you to ensure that the principles that ARPA-H uses to prioritize funding decisions incorporates a definition of "need" that includes mortality rates and areas where tools are particularly lacking instead of just focusing on incidence.

Some assert ARPA-H's ability to operate independently and transparently will be essential to its success. Do you agree? If so, what is the best way to design ARPA-H in order to accomplish this?

[7] https://www.whitehouse.gov/ostp/news-updates/2021/06/22/science-magazine-arpa-h-accelerating-biomedical-breakthroughs/ Accessed July 9, 2021.

Federal research has led to several significant breakthroughs and achievements, contributing to the health and welfare of all Americans. Global Liver Institute steadfastly supports the critical research funded through the NIH.

With that said, our hope is that ARPA-H is authorized in such a way to speed cures in a different fashion – by focusing on specific problems that have eluded us to date. To achieve these goals, ARPA-H will need to be able to make funding decisions independent of NIH's current processes and culture.

Some examples of the types of projects we believe should be funded through ARPA-H are:

- Innovative non-invasive diagnostics - Currently, liver biopsy is considered the "gold standard" for diagnosing a variety of liver diseases, especially NAFLD and NASH. This 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/segmented, 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.[8] [9] [10]
- Leverage the power of patient experience through technology - The rise of Real World Evidence as a potential source of data in prospective FDA-regulated clinical trials is also creating new opportunities for remote monitoring of patients through the use of wearable and other mobile technology. ARPA-H, based on experience from technology innovation from DARPA, could propel this field forward through a focused initiative on producing affordable, regulatory-grade, standardized patient- and caregiver-reported (symptom, sign, function) assessment tools. Validation and adoption of patient-reported outcomes measures would significantly improve the patient-centeredness of drug development and also help reveal clinical benefit in addition to survival.

Given ARPA-H's lofty goals and the diverse patient population it aims to serve, transparency in making funding decisions will also be critical. Patient advocates and researchers need to be able to understand the rationale that is being used. Further, and perhaps most important, we must also have transparency into projects that have failed so that we can learn from them.

What is the best way to ensure ARPA-H has a mission, culture, organizational leadership, mode of operation, expectations, and success metrics that are different than the status quo?

A key pillar of GLI's advocacy efforts is centered around the idea of patient value. ARPA-H must give consideration to two interconnected and equally important perspectives. First, there is the value to patients, and second there is the value of patients. From access to treatments and clinical trials, to interaction with regulatory agencies and NGOs both of these perspectives must remain equally represented.

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[8] 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

[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] 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

Fundamentally, ARPA-H must adopt a culture and operational processes that are distinct from NIH and which are driven by patient centered transparency and an urgency to improve patient outcomes. The agency must be empowered to, and embrace, collaborations with any and all stakeholders that can advance breakthroughs for patients including other federal agencies and public-private partnerships with industry. Further, the agency should have full transactional authority, as well as the ability to conduct all phases of research, product development and regulatory approval.

Transparency must be a hallmark of ARPA-H, particularly with respect to the selection criteria and decision-making process for its broad strategic investment goals and selection of individual research projects. Patient centered research and initiatives that utilize patient reported outcomes and experiences will ensure that the patient voice is represented and heard. Further, we feel strongly that identification of unmet needs within disease areas should be conducted through a formal multi-stakeholder process that includes patient advocacy groups focused on that particular disease. It is important to understand that the liver has more than 500 functions in the body. It is of utmost importance that we think of whole-person care, and consider the centrality of the liver to overall good health, but also the interconnection with liver disease and a wide range of diseases. Stakeholders representing all aspects of the liver health community should be involved in the stakeholder process.

What is the appropriate funding level for ARPA-H? How do we ensure ARPA-H funding does not come at the expense of traditional funding for the National Institutes of Health?

We believe that funding for ARPA-H must be both sufficiently substantial and sustainable over time to truly transform the biomedical ecosystem. In addition, ARPA-H funding should neither subtract from existing NIH funding nor prevent robust, annual increases—no less than the rate of biomedical inflation--for the NCI, NIDDK, and other core NIH research programs.

We greatly appreciate your leadership on this issue and the opportunity to provide input on the formation of ARPA-H. Thank you for your persistence in getting real answers, and your attention to the voices and experiences of patients impacted by liver diseases.

We look forward to working with you as you develop legislative language authorizing the program. If you have any questions, please don't hesitate to reach out to Global Liver Institute's Policy Director, Andrew Scott, at ascott@globalliver.org or 831-246-1586.

With appreciation and respect,

Donna R. Cryer, JD
President & CEO
Global Liver Institute