

April 9, 2021

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VIA Electronic Delivery

RE: USPSTF Draft Recommendation Statement on Screening for Prediabetes and Type 2 Diabetes

Screen people ages 35 to 70 who are overweight or obese for prediabetes and diabetes

Dear Acting Director Meyers and Chairperson Davidson,

As advocacy organizations, medical societies, and individual patient advocates committed to improving the lives of all people impacted by prediabetes, diabetes, and liver disease, we appreciate the recently released United States Preventive Services Task Force (USPSTF) Draft Recommendation Screening Statement for screening for prediabetes and Type 2 Diabetes Mellitus. We are disappointed, however, that the statement does not mention the strong link between type 2 diabetes (T2D) and chronic liver disease, especially nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). NAFLD can progress to NASH silently, and if left untreated it can continue progressing into other conditions such as cirrhosis, liver cancer, or result in death.^{1 2 3}

We welcome the task force's interest in providing clear recommendations for the community. This is why we urge the USPSTF to make two critical adjustments. First, the Recommendation Statement must highlight the risks for patients with or at risk of T2D of NAFLD and NASH. Second, USPSTF must consider the use of patient-inclusive or people-first language throughout the Recommendation Statement.

The Risks For Patients With T2D of NAFLD and NASH

It is common for patients to have NAFLD, or its more severe form, NASH, and diabetes. For individuals with T2D, the prevalence of NAFLD affects 70% of adults in the U.S. with an estimated 30% having NASH and about 20% having liver fibrosis.^{4 5 6 7} In a large study in India, 56.5% of patients overall with T2D between the ages of 25 and 84 had NAFLD; in the northern Indian states alone, NAFLD was prevalent in 72.4%.^{8 9} Notably, researchers in Romania examined patients with T2D who were mostly Caucasian and older and found that having a

higher body mass index (obesity) increases the risk of developing severe steatosis and fibrosis.¹⁰

On top of this is the impact of NAFLD and NASH as a risk factor for T2D. NAFLD is associated with a two- to three-fold increased risk of developing T2D; this risk may be even higher in patients with more severe liver disease.¹¹ Patients with diabetes are also at high risk of disease progression from NAFLD to NASH.¹² T2D and diabetes risk are closely associated with the severity of NAFLD, progression to NASH, advanced fibrosis, and the development of hepatocellular carcinoma (HCC)^{13 14} or primary liver cancer, independent of liver enzymes¹⁵.

This omission within the Recommendation Statement is even more glaring when we acknowledge that the Centers for Disease Control and Prevention (CDC) Division of Diabetes Translation highlights the connection between T2D and fatty liver disease within the division's educational resources. Furthermore, a robust list of sourced research is included within the review, *Screening for Prediabetes and Type 2 Diabetes Mellitus: An Evidence Review for the U.S. Preventive Services Task Force*, underlining the connection between fatty liver disease, NASH and T2D.

The Use Of Patient-Inclusive Or People-First Language

It is important to refer to “patients with diabetes, patients with fatty liver disease or patients affected by obesity” instead of “diabetics, fatty liver disease patients or obese.” By doing this, we avoid defining a person by their disease, reduce stigma and emphasize the person rather than their disease or disability. Multiple agencies and organizations including the CDC, American Psychological Association and American Society of Addiction Medicine encourage person-first language. The American Medical Association (AMA) also recommends the use of person-first language in the AMA Code of Styles. In many instances throughout the Recommendation Statement, the choice of classifying patients as “diabetic” or “obese” fails to recognize the patient first which is counterproductive to USPSTF's goals.

Conclusion

It is of the utmost importance that patients with or at risk of T2D are aware of their increased risk for liver disease, and that a conversation takes place between providers and patients about this risk to avoid progressing to a potentially life-threatening diagnosis such as HCC or primary liver cancer. Patients with both T2D and NASH have a higher risk of liver-related and non-liver related illness and premature death than those without liver disease.¹⁶ Liver cancer is the second deadliest cancer worldwide, in large part due to a lack of knowledge among the most at-risk populations concerning their risk. This point is underlined when we take into consideration that, according to the American Cancer Society, 70% of liver cancer cases could be prevented.

In his February 2020 article *Time to Include Nonalcoholic Steatohepatitis in the Management of Patients With Type 2 Diabetes*, Dr. Ken Cusi, a leading expert on NASH and diabetes, directly makes the case for patients with diabetes to be screened for NAFLD/NASH. He shares, “The above results call on endocrinologists to view NASH as a frequent and serious complication of T2D and to be proactive in the early identification of patients at risk for liver fibrosis.”

With this understanding, we respectfully ask for an update to the recently released draft Recommendation Statement to acknowledge the direct connection between liver diseases such as NAFLD/NASH and diabetes. By including this link between T2D and NAFLD/NASH within the

Recommendation Statement we can raise awareness among primary care providers and patients of this devastating disease.

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.

Sincerely,

Global Liver Institute (GLI)

American Association for the Study of Liver Diseases (AASLD)

American Gastroenterological Association (AGA)

Community Liver Alliance

Digestive Disease National Coalition (DDNC)

Endocrine Society

Fatty Liver Foundation (FLF)

Liver Coalition of San Diego

Liver Wellness Foundation: Greater Los Angeles, Northern California, Nevada, Washington, Oregon, Hawaii

NASH kNOWLEDge

Obesity Action Coalition (OAC)

¹ Estes C, Razavi H, Loomba R, et al. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology*. 2018; 67:123–133.

² 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

³ Tesfay M, Goldkamp WJ and Neuschwander-Tetri BA. NASH: The Emerging Most Common Form of Chronic Liver Disease. *Mo Med*. 2018; 115:225–229.

⁴ Portillo-Sanchez, P., Bril, F., Maximos, M., Lomonaco, R., Biernacki, D., Orsak, B., Subbarayan, S., Webb, A., Hecht, J., & Cusi, K. (2015). High Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Type 2 Diabetes Mellitus and Normal Plasma Aminotransferase Levels. *The Journal of clinical endocrinology and metabolism*, 100(6), 2231–2238. <https://doi.org/10.1210/jc.2015-1966>

⁵ Lomonaco, R., Godinez Leiva, E., Bril, F., Shrestha, S., Mansour, L., Budd, J., Portillo Romero, J., Schmidt, S., Chang, K. L., Samraj, G., Malaty, J., Huber, K., Bedossa, P., Kalavalapalli, S., Marte, J., Barb, D., Poulton, D., Fanous, N., & Cusi, K. (2021). Advanced Liver Fibrosis Is Common in Patients With Type 2 Diabetes Followed in the Outpatient Setting: The Need for Systematic Screening. *Diabetes care*, 44(2), 399–406. <https://doi.org/10.2337/dc20-1997>

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- ⁶ Ciardullo, S., Monti, T., & Perseghin, G. (2021). High Prevalence of Advanced Liver Fibrosis Assessed by Transient Elastography Among U.S. Adults With Type 2 Diabetes. *Diabetes care*, *44*(2), 519–525. <https://doi.org/10.2337/dc20-1778>
- ⁷ Younossi, Z. M., Golabi, P., de Avila, L., Paik, J. M., Srishord, M., Fukui, N., Qiu, Y., Burns, L., Afendy, A., & Nader, F. (2019). The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. *Journal of hepatology*, *71*(4), 793–801. <https://doi.org/10.1016/j.jhep.2019.06.021>
- ⁸ Kalra, S., Vithalani, M., Gulati, G., Kulkarni, C. M., Kadam, Y., Pallivathukkal, J., Das, B., Sahay, R., & Modi, K. D. (2013). Study of prevalence of nonalcoholic fatty liver disease (NAFLD) in type 2 diabetes patients in India (SPRINT). *The Journal of the Association of Physicians of India*, *61*(7), 448–453.
- ⁹ Premnath M. (2014). Study of prevalence of nonalcoholic fatty liver disease (NAFLD) in type 2 diabetes patients in India (SPRINT). *The Journal of the Association of Physicians of India*, *62*(7), 651–652.
- ¹⁰ Sporea, I., Mare, R., Popescu, A., Nistorescu, S., Baldea, V., Sirlu, R., Braha, A., Sima, A., Timar, R., & Lupusoru, R. (2020). Screening for Liver Fibrosis and Steatosis in a Large Cohort of Patients with Type 2 Diabetes Using Vibration Controlled Transient Elastography and Controlled Attenuation Parameter in a Single-Center Real-Life Experience. *Journal of clinical medicine*, *9*(4), 1032. <https://doi.org/10.3390/jcm9041032>
- ¹¹ Gastaldelli, A., & Cusi, K. (2019). From NASH to diabetes and from diabetes to NASH: Mechanisms and treatment options. *JHEP reports : innovation in hepatology*, *1*(4), 312–328. <https://doi.org/10.1016/j.jhepr.2019.07.002>
- ¹² European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), & European Association for the Study of Obesity (EASO) (2016). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *Journal of hepatology*, *64*(6), 1388–1402. <https://doi.org/10.1016/j.jhep.2015.11.004>
- ¹³ Vernon, G., Baranova, A., & Younossi, Z. M. (2011). Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Alimentary pharmacology & therapeutics*, *34*(3), 274–285. <https://doi.org/10.1111/j.1365-2036.2011.04724.x>
- ¹⁴ Loomba, R., Abraham, M., Unalp, A., Wilson, L., Lavine, J., Doo, E., Bass, N. M., & Nonalcoholic Steatohepatitis Clinical Research Network (2012). Association between diabetes, family history of diabetes, and risk of nonalcoholic steatohepatitis and fibrosis. *Hepatology (Baltimore, Md.)*, *56*(3), 943–951. <https://doi.org/10.1002/hep.25772>
- ¹⁵ Fracanzani, A. L., Valenti, L., Bugianesi, E., Andreoletti, M., Colli, A., Vanni, E., Bertelli, C., Fatta, E., Bignamini, D., Marchesini, G., & Fargion, S. (2008). Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. *Hepatology (Baltimore, Md.)*, *48*(3), 792–798. <https://doi.org/10.1002/hep.22429>
- ¹⁶ Cusi, K. (2020, February). Time to Include Nonalcoholic Steatohepatitis in the Management of Patients With Type 2 Diabetes. *Diabetes Care*, *43*(2): 275-279. <https://doi.org/10.2337/dci19-0064>