

Baffled by NAFLD: The Horse Might Be Out of the Barn but Should Not Take Us for a Ride

Zheng Che, MD; A. Mark Fendrick, MD; and Elliot B. Tapper, MD

Nonalcoholic fatty liver disease (NAFLD) is an increasingly common condition that often results in poor patient-centered outcomes and is becoming a driver of health care costs. Affecting roughly 85 million Americans,¹ NAFLD represents a spectrum of disease resulting from fatty infiltration of the liver, ranging from mild laboratory abnormalities with no other obvious clinical manifestations of disease to advanced stages with permanent liver damage. It carries an increased risk of cirrhosis, liver cancer, and cardiovascular mortality.¹ Obesity, diabetes, and dyslipidemia are the best-documented risk factors for NAFLD.^{1,2} Due to the lack of an evidence-based screening strategy and effective treatment, many affected individuals remain without a diagnosis, and patients with NAFLD often present at late clinical stages with cirrhosis or liver cancer.³

In contrast to infectious causes of liver disease, such as hepatitis B and C, no currently approved treatments exist for NAFLD outside of weight loss and other lifestyle modifications. Similarly, there is no consensus screening paradigm for NAFLD. Scoring systems such as the Fibrosis-4 (FIB-4) index and NAFLD fibrosis score (NFS) are validated methods to risk stratify using low-cost and routine laboratory tests with high negative predictive value for advanced liver fibrosis.³ For those individuals who require further work-up, vibration-controlled transient elastography (VCTE) can provide additional clinical information. VCTE is superior to routine liver ultrasound for the objective assessment of liver scarring and fatty infiltration. VCTE offers excellent negative predictive value and fair positive predictive value.⁴ Although it cannot discern histological stages of fibrosis, VCTE can classify patients as having a high risk of advanced fibrosis (or not) and whether they are at high risk of the complications of cirrhosis. This is often clinically sufficient because, among all histological features and fibrosis stages, only advanced fibrosis predicts the risk of future adverse clinical events.⁵ These noninvasive testing strategies are preferred by patients and are a lower-cost alternative to the more time-intensive and costly magnetic resonance elastography and the gold standard, liver biopsy, which has associated risks.⁶

“ IT IS ESSENTIAL TO DEVELOP AND IMPLEMENT A RIGOROUSLY DETERMINED APPROACH TO IDENTIFY PATIENTS WHO WILL, OR WILL NOT, BENEFIT FROM DIAGNOSTIC EVALUATION AS AWARENESS OF NAFLD RISES. ”

As is the case with many chronic conditions, such as diabetes and HIV, as well as treatable cancers, it is important to identify individuals at risk of adverse NAFLD outcomes as early as possible for effective intervention. Given past experience with the rapid and premature adoption of medical services prior to the development of a strong evidence base, it is essential to develop and implement a rigorously determined approach to identify patients who will, or will not, benefit from diagnostic evaluation as awareness of NAFLD rises. A multistep, evidence-based method such as that used by the United States Preventive Services Task Force to develop and refine risk-based screening for hepatitis C virus (populations recommended for screening have expanded over time)⁷ and *BRCA1/2* (recommended *only* for women with a personal or family history associated with potentially harmful mutations; explicitly recommended *against* for women without personal or family history associated with potentially harmful mutations)⁸ should guide the process.

In this issue of *The American Journal of Managed Care*[®], Nouredin et al evaluate the potential for population-wide screening using VCTE.⁹ The simulation estimates net savings for commercial and Medicare payers within 2 to 3 years. However, one important and yet unproven assumption—a 10% to 25% decrease in disease progression for patients diagnosed with early-stage NAFLD (for which currently there is no intervention beyond lifestyle change)—accounts for the majority of modeled economic savings. This optimistic postulation

should be accepted cautiously, especially when considering that these patients likely have coexisting metabolic derangements, including obesity and diabetes, for which lifestyle changes had been previously recommended.

Noureddin and colleagues make a compelling case for expanded use of VCTE as a tool to identify patients at risk for NAFLD complications. However, it is crucial to recognize that VCTE has inadequate positive predictive value,¹⁰ necessitating the consideration of the initial use of noninvasive serologic tests in an average-risk population.^{3,10} Serologic tests such as the FIB-4/NFS indices should be first utilized to exclude low-risk individuals from further evaluation. Subsequent referral for VCTE is appropriate for those determined to be at intermediate-high risk. Prior to the adoption of a population-based VCTE screening policy, similar modeling exercises should be undertaken to quantify the clinical and economic impacts of alternative screening strategies, such as one that incorporates a sequential serology/VCTE strategy.

In cases such as NAFLD diagnostic testing, where the evidence base is in a rapid state of flux, coverage with evidence development (CED) should be considered to permit access to innovative diagnostic methods while simultaneously collecting critical data to better inform coverage decisions. CED was developed by CMS in 2005 as an approach to policy coverage for drugs, devices, and procedures. It links provisional coverage of interventions with participation in a registry or clinical trial.¹¹ Importantly, it provides a framework for longitudinal prospective data collection, facilitating a better understanding of the risks, benefits, and costs of interventions. The coverage component of CED is conditional on further collection of population-level evidence in order to support continued, expanded, or withdrawal of coverage and is a method by which to examine medical necessity. The data generated are then used to determine future coverage once it is determined whether a service is reasonable and necessary for specific patient populations. It is particularly important for interventions for which the evidence is uncertain or limited, as is the case with NAFLD diagnostic testing. One of the first applications of the CED model was on lung volume reduction surgery; there was rapid early adoption of this procedure in the absence of well-designed trials. Under CED, a multicenter randomized trial demonstrated little clinical benefit to lung volume reduction surgery in many patient groups. Subsequently, coverage and utilization were substantially modified. A similar program could be implemented for NAFLD.

Clinicians, patients, and payers need to be aware of a paucity of population-based data guiding NAFLD decision-making. Recommendations for NAFLD testing are inconsistent and lack many clinical details, leaving concerns regarding both the underdiagnosis of those at risk for disease progression and overtesting of those at minimal risk for disease sequelae. Previous experience with the widespread use of other diagnostic tests with well-established benefits in specific populations, but of no clinical value—and potential harm—to others (eg, *BRCA1/2*, prostate-specific antigen) necessitates that the judicious proliferation of NAFLD testing be

accompanied by ongoing data collection assessing the clinical, quality-of-life, and economic impacts. As is often the case with “rapidly moving targets,” the threshold for NAFLD testing will likely change when effective treatments are identified, confirming the need for ongoing refinement of clinical and payment guidelines. In these increasingly common settings of uncertainty, CED is a favorable alternative to blunt “yes/no” coverage decisions, in that it allows access to innovative diagnostics and therapies coupled with systematic evaluation aiming to identify specific patient groups who would benefit from screening and additional diagnostic testing. ■

Author Affiliations: Department of Internal Medicine, University of Michigan School of Medicine (ZC, AMF, EBT), Ann Arbor, MI.

Source of Funding: None.

Author Disclosures: Dr Fendrick has been a consultant for AbbVie, Amgen, Centivo, Community Oncology Alliance, Covered California, EmblemHealth, Exact Sciences, Freedman Health, GRAIL, Harvard University, Health & Wellness Innovations, Health at Scale Technologies, MedZed, Merck, Montana Health Cooperative, Penguin Pay, Risalto, Sempre Health, State of Minnesota, US Department of Defense, Virginia Center for Health Innovation, Wellth, Yale–New Haven Health System, and Zansors; has performed research for the Agency for Healthcare Research and Quality, Arnold Ventures, Boehringer Ingelheim, Gary and Mary West Health Policy Center, National Pharmaceutical Council, Patient-Centered Outcomes Research Institute, PhRMA, Robert Wood Johnson Foundation, and State of Michigan/CMS; and holds outside positions as co-editor-in-chief of *The American Journal of Managed Care*[®], member of the Medicare Evidence Development & Coverage Advisory Committee, and partner in V-BID Health, LLC. Dr Tapper reports consultancies or paid advisory boards for Takeda and Mallinckrodt. Dr Che reports no relationship or financial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (ZC, AMF, EBT); acquisition of data (ZC, EBT); analysis and interpretation of data (ZC); drafting of the manuscript (ZC, AMF, EBT); critical revision of the manuscript for important intellectual content (ZC, AMF); and supervision (AMF).

Address Correspondence to: A. Mark Fendrick, MD, University of Michigan, 2800 Plymouth Rd, Bldg 16, Floor 4, 016-400S-25, Ann Arbor, MI 48109-2800. Email: amfen@med.umich.edu.

REFERENCES

1. Moon AM, Singal AG, Tapper EB. Contemporary epidemiology of chronic liver disease and cirrhosis. *Clin Gastroenterol Hepatol*. 2020;18(12):2650-2666. doi:10.1016/j.cgh.2019.07.060
2. Libman H, Jiang ZG, Tapper EB, Reynolds EE. How would you manage this patient with nonalcoholic fatty liver disease? *Ann Intern Med*. 2019;171(11):862. doi:10.7326/L19-0668
3. Petta S, Vanni E, Bugianesi E, et al. The combination of liver stiffness measurement and NAFLD fibrosis score improves the noninvasive diagnostic accuracy for severe liver fibrosis in patients with nonalcoholic fatty liver disease. *Liver Int*. 2015;35(5):1566-1573. doi:10.1111/liv.12584
4. Tapper EB, Castera L, Afdhal NH. FibroScan (vibration-controlled transient elastography): where does it stand in the United States practice. *Clin Gastroenterol Hepatol*. 2015;13(1):27-36. doi:10.1016/j.cgh.2014.04.039
5. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology*. 2015;149(2):389-397.e10. doi:10.1053/j.gastro.2015.04.043
6. Tapper EB, Lok ASF. Use of liver imaging and biopsy in clinical practice. *N Engl J Med*. 2017;377(23):2296-2297. doi:10.1056/NEJMc1712445
7. Owens DK, Davidson KW, Krist AH, et al; US Preventive Services Task Force. Screening for hepatitis C virus infection in adolescents and adults: US Preventive Services Task Force recommendation statement. *JAMA*. 2020;323(10):970-975. doi:10.1001/jama.2020.1123
8. Owens DK, Davidson KW, Krist AH, et al; US Preventive Services Task Force. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2019;322(7):652-665. doi:10.1001/jama.2019.10987
9. Noureddin M, Mackenzie A, Zhao E, Howell SC, Tunkelrott M, Duncan I. Population-based return on investment of deploying transient elastography. *Am J Manag Care*. 2021;27(9):376-381. doi:10.37765/ajmc.2021.88645
10. Tapper EB, Sengupta N, Hunink MGM, Afdhal NH, Lai M. Cost-effective evaluation of nonalcoholic fatty liver disease with NAFLD fibrosis score and vibration controlled transient elastography. *Am J Gastroenterol*. 2015;110(9):1298-1304. doi:10.1038/ajg.2015.241
11. Tunis SR, Pearson SD. Coverage options for promising technologies: Medicare's coverage with evidence development. *Health Aff (Millwood)*. 2006;25(5):1218-1230. doi:10.1377/hlthaff.25.5.1218

Visit ajmc.com/link/88671 to download PDF