

AGA SECTION

American Gastroenterological Association Institute Guideline on the Role of Elastography in the Evaluation of Liver Fibrosis



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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e19. Learning Objective: Upon completion of this CME activity successful learners will be able to: (1) describe the role of vibration-controlled transient elastography (VCTE) in the diagnosis of cirrhosis in adults with chronic hepatitis C, chronic hepatitis B, nonalcoholic fatty liver disease, and chronic alcoholic liver disease; (2) determine appropriate liver stiffness thresholds for the diagnosis of cirrhosis and clinically significant portal hypertension; (3) describe the role of magnetic resonance elastography (MRE) compared with vibration controlled transient elastography (VCTE) in the diagnosis of cirrhosis in adults with chronic hepatitis C and non-alcoholic fatty liver disease; and (4) understand the limitations of VCTE and MRE relevant to its application to clinical practice.

This document represents the official recommendations of the American Gastroenterological Association (AGA) on the role of vibration-controlled transient elastography (VCTE) in the evaluation of liver fibrosis. The guideline was developed by the Clinical Guidelines Committee and approved by the AGA Governing Board. The guideline was developed utilizing a process outlined elsewhere.¹ Briefly, the AGA process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology,² as outlined by the Institute of Medicine.³

GRADE methodology was utilized to prepare the background information for the technical review and guideline. Optimal understanding and application of this guideline will be improved by reading applicable portions of the technical review. Four members of the guideline panel and AGA support staff met in person with the authors of the technical review on May 20, 2016. The information in the technical review was discussed in a systematic manner facilitating subsequent creation of guideline recommendations addressing each focused question. The strength of each recommendation rated as either strong or conditional.⁴

The assessment of liver fibrosis represents a critical component in the evaluation of chronic liver disorders. Liver biopsy represents the gold standard diagnostic tool for liver fibrosis assessment,⁵ although noninvasive techniques are commonly used as a surrogate to the liver biopsy. Since the first description of the percutaneous liver biopsy in 1923,⁶ histologic assessment of the liver has been used in the diagnosis and staging of liver disorders such as hepatitis C, hepatitis B, fatty liver disease, autoimmune hepatitis, primary biliary cirrhosis, and hemochromatosis.^{7–12} However, liver biopsy has intrinsic limitations that dampen the enthusiasm of patients and clinicians for their routine incorporation in clinical practice. Although generally safe, liver biopsy is invasive, associated with significant pain in up to 30% of patients,⁶ severe bleeding in <1% of

patients,¹³ requires hospitalization in 2%–3% of patients,¹⁴ and has a mortality rate of up to 0.33%.¹⁵ Furthermore, liver biopsy is subject to sampling error and both intra-observer and inter-observer variability in interpretation,¹⁶ and is difficult to repeat for serial assessments over several points in time. In this context, the role of noninvasive tests for the assessment of liver fibrosis has increased in the United States and worldwide, and has been incorporated into clinical practice guidelines in Europe and Latin America.¹⁷ A wide spectrum of fibrosis assessment tools has emerged, including direct and indirect serum markers of liver fibrosis, and several imaging-based methods, such as transient elastography, 2-dimensional shear wave elastography, acoustic radiation force impulse imaging or point shear wave elastography, and magnetic resonance elastography (MRE).

Vibration-controlled transient elastography (VCTE) is the most commonly used imaging-based fibrosis assessment method in the United States. It can be performed at bedside in an ambulatory office setting, is rapid to perform, has a wide range of scores (2.5–75 kPa), is associated with acceptable intra-observer and inter-observer reproducibility, and has been validated in large cohorts worldwide in a spectrum of liver diseases, including hepatitis B, hepatitis C, fatty liver disease, and autoimmune liver disorders, among others. By applying a probe to the intercostal skin in

Abbreviations used in this paper: AGA, American Gastroenterological Association; APRI, aspartate aminotransferase to platelet ratio index; CI, confidence interval; FIB-4, fibrosis-4 index; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; SVR, hepatocellular carcinoma; VCTE, vibration-controlled transient elastography.

Most current article

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the 9th to 11th intercostal space in a region 25–65 mm (M-probe) or 35–75 mm (XL-probe) below the skin surface, a minimum of 10 valid liver stiffness measurements are obtained to derive a composite score used to estimate stage of liver fibrosis, which is determined to be of adequate quality if there are at least 10 validated measurements and the interquartile range/median value of liver stiffness is $\leq 30\%$.¹⁸ VCTE has several limitations, including technical limits for performance (diameter of intercostal space, obesity), variable diagnostic performance across liver conditions with differing cutoffs to establish significant or advanced liver fibrosis or cirrhosis, inaccurate readings in patients with acute hepatitis, alcohol abuse, food intake within 2–3 hours, congestive heart failure, and extrahepatic cholestasis.

The current technical review and guideline were developed to provide clinicians with evidence-based guidance on the specific role of VCTE in clinical practice, and addressed focused clinically relevant questions reviewed by the Technical Review Committee.

Question 1. Should VCTE vs aspartate aminotransferase to platelet ratio index (APRI) be used to diagnose cirrhosis in adults with chronic hepatitis C?

Question 2. Should VCTE vs fibrosis-4 index (FIB-4) be used to diagnose cirrhosis in adults with chronic hepatitis C?

The pooled effect estimates of test characteristics for the diagnosis of cirrhosis in patients with chronic hepatitis C were obtained from 36 studies evaluating VCTE, 24 studies evaluating APRI, and 2 studies evaluating FIB-4. The test characteristics for these noninvasive fibrosis assessment tools were as follows: VCTE: sensitivity, 0.89; 95% confidence interval [CI], 0.84–0.92; specificity, 0.91; 95% CI, 0.89–0.92; APRI: sensitivity, 0.77; 95% CI, 0.73–0.81; specificity, 0.78; 95% CI, 0.74–0.81; and FIB-4: sensitivity, 0.87; 95% CI, 0.74–0.94; specificity, 0.91; 95% CI, 0.89–0.92. In adults with chronic hepatitis C, VCTE demonstrated superior sensitivity and specificity compared with FIB-4 and APRI for the diagnosis of cirrhosis. The AGA did not review the utility of other proprietary serum fibrosis assays for the diagnosis of cirrhosis, although available evidence does not support a significant advantage of these assays over nonproprietary tests (ie, APRI and FIB-4). Furthermore, other imaging-based fibrosis assessment tools were not evaluated within this review. The identification of cirrhosis remains a vital step in the pretreatment assessment of patients with chronic hepatitis C infection, and directly impacts treatment choice, duration, and potential need for ribavirin, as well as the requirement for variceal and hepatocellular carcinoma surveillance. VCTE is superior to noninvasive serum tests in the detection of cirrhosis, although caution should be exercised in the reliance of any one fibrosis assessment tool in ruling in or ruling out cirrhosis, which should incorporate all available clinical information.

Recommendation: In patients with chronic hepatitis C, the AGA recommends VCTE, if available, rather than other nonproprietary, noninvasive serum tests (APRI, FIB-4) to detect cirrhosis. GRADE: Strong recommendation, moderate quality evidence.

Question 3. In adults with hepatitis C virus (HCV) undergoing VCTE, at what liver stiffness cutoff can we accurately diagnose cirrhosis (and initiate downstream management), obviating the need for liver biopsy?

In assessing the diagnostic performance of particular cutoffs for assessing liver stiffness, the context (or pretest probability) in which these are applied is important to define. For this question, 2 illustrative scenarios were chosen: one of a low prevalence of cirrhosis (5%, as can be seen in patients with HCV detected in primary care clinics during routine age-appropriate screening) and another of a high prevalence of cirrhosis (30%, as can be seen in patients with HCV with comorbid obesity, diabetes, excessive alcohol use, or co-infection with human immunodeficiency virus or chronic hepatitis B infection). The pooled effect estimates of test characteristics of a liver stiffness cutoff of 12.5 (± 1) kPa for the diagnosis of cirrhosis in patients with HCV were obtained from 17 studies with 5812 patients. Using a cutoff for cirrhosis of 12.5 (± 1) kPa, which is optimized to keep the rate of missing cirrhosis low, the pooled sensitivity was 0.86 (95% CI, 0.83–0.88) and pooled specificity was 0.91 (95% CI, 0.89–0.92). Using these values, it can be estimated that a cutoff of 12.5 kPa may misclassify $<5\%$ of patients as not having cirrhosis (when they indeed have cirrhosis), and $<10\%$ of patients as having cirrhosis (when they do not have cirrhosis). The evidence base to support the use of a liver stiffness cutoff of 12.5 kPa for the detection of liver cirrhosis was derived from cross-sectional diagnostic accuracy studies, as opposed to studies comparing different cutoffs and their effect on downstream patient-important outcomes related to impact of cirrhosis diagnosis (or misdiagnosis); therefore, false-positive and false-negative rates were considered surrogate measures of downstream patient important outcomes, and evidence was rated down for indirectness. Considerable heterogeneity was observed in pooled estimates of sensitivity and specificity, and studies reporting performance of a cutoff of 12.5 (± 1) kPa were selectively chosen. On this basis, caution should be exercised in solely utilizing a cutoff of 12.5 kPa to diagnose cirrhosis, and the result of VCTE should be considered in context of other clinical information to guide management.

In summary, by selecting a cutoff of 12.5 kPa, the guideline panel made a conscious decision to minimize false-negative tests, thus making a judgment that the harm of missing cirrhosis is greater than the harms of overdiagnosis. However, although this strategy will result in a significant number of patients falsely labeled at high risk for

cirrhosis (particularly in the low-prevalence setting), there is likely less harm with this strategy as the clinical implication in the hepatitis C population is mitigated for the following reasons:

1. Repeating elastography after achieving viral cure will frequently result in a reduction of liver stiffness readings, thus reducing the number of patients falsely classified as having cirrhosis over time. (See Question 4. In adults with HCV who have achieved SVR with antiviral therapy undergoing VCTE, at what liver stiffness cutoff can we accurately rule out advanced fibrosis and consider discharging patients from a dedicated liver clinic?)
2. The downstream decisions leading to invasive tests (eg, upper endoscopy to screen for varices) should not be solely based on this cutoff (12.5 kPa). (See Question 11. In adults with suspected compensated cirrhosis undergoing VCTE, at what liver stiffness cutoff can we accurately rule out high-risk esophageal varices, obviating the need for routine endoscopic screening?)
3. Other downstream consequences, such as screening for hepatocellular carcinoma (HCC) with noninvasive tests (eg, with liver ultrasound) should ideally not only include hepatitis C patients with cirrhosis, but also advanced fibrosis. However, patients falsely labeled as having cirrhosis frequently have advanced fibrosis (F3) and can still benefit from screening.

Recommendation: In patients with chronic hepatitis C, the AGA suggests a VCTE cutoff of 12.5 kPa to detect cirrhosis.
GRADE: Conditional recommendation, low-quality evidence.

Question 4. In adults with HCV who have achieved sustained virologic response (SVR) with antiviral therapy undergoing VCTE, at what liver stiffness cutoff can we accurately rule out advanced fibrosis and consider discharging patients from a dedicated liver clinic?

Criteria for discharging patients after successful HCV treatment has not been well defined and post-treatment VCTE can provide additional guidance to decide who is unlikely to benefit from continued follow-up. The diagnostic performance of a prespecified cutoff of 9.5 (± 1) kPa to rule out advanced fibrosis (F3 and F4) was interpreted in 2 illustrative scenarios—one of a low prevalence of advanced fibrosis (5%, as can be seen in patients with HCV who achieve SVR and have no ongoing risk factors for chronic liver diseases) and another of a high prevalence of advanced fibrosis (30%, as can be seen in patients with HCV patients who achieve SVR, but either had suspected advanced fibrotic liver disease before therapy or continue to have other risk factors for chronic liver diseases, such as obesity, diabetes, excessive alcohol use, or co-infection with human immunodeficiency virus or hepatitis B or C virus).

The pooled effect estimates of test characteristics for the exclusion of F3–F4 fibrosis was obtained from 13 studies in 4106 patients. Using a cutoff for advanced fibrosis/cirrhosis of 9.5 (± 1) kPa, the pooled sensitivity was 0.78 (95% CI, 0.75–0.81) and pooled specificity was 0.86 (95% CI, 0.84–0.88). Using these values, it can be estimated that using a cutoff of 9.5 kPa to rule out advanced fibrosis after achieving SVR can misclassify 1% of low-risk patients and approximately 7% of high-risk patients as not having advanced fibrosis, who then might be falsely reassured, be discharged from a dedicated liver clinic, and not receive appropriate post-treatment supportive care, putting them at increased risk of hepatic morbidity and mortality. The evidence base to support the use of a single cutoff for the detection of advanced fibrosis was largely derived from post-hoc analysis of cross-sectional diagnostic accuracy studies, and no studies were specifically performed in patients who achieved SVR. Therefore, evidence was rated down for indirectness. Only studies using a cutoff of 9.5 (± 1) kPa were included in the technical review, and significant heterogeneity was observed in these test characteristics. Due to evidence gap, additional research is needed to further define the role of single or serial VCTE testing, as well as appropriate liver stiffness threshold, in the management of patients with chronic hepatitis C post-SVR.

Recommendation: In noncirrhotic patients with HCV who have achieved SVR after antiviral therapy, the AGA suggests a post-treatment vibration controlled transient elastography cutoff of 9.5 kPa to rule out advanced liver fibrosis.

GRADE: Conditional recommendation, very-low-quality evidence.

Comment: Noncirrhotic patients with VCTE <9.5 kPa who place a low value on the inconvenience and risks of continued laboratory and fibrosis testing, and a high value on avoiding the small risk of developing HCC, may reasonably select to continue specialty care rather than being discharged from the specialty clinic.

Question 5. Should VCTE vs APRI be used to diagnose cirrhosis in adults with chronic hepatitis B?

Question 6. Should VCTE vs FIB-4 be used to diagnose cirrhosis in adults with chronic hepatitis B?

The pooled effect estimates of test characteristics for the diagnosis of cirrhosis in patients with chronic hepatitis B were obtained from 19 studies evaluating VCTE, 5 studies evaluating APRI, and 4 studies evaluating FIB-4. The test characteristics for these noninvasive fibrosis assessment tools were as follows: VCTE: sensitivity, 0.86; 95% CI, 0.79–0.91; specificity, 0.85; 95% CI, 0.78–0.89; APRI: sensitivity, 0.66; 95% CI, 0.47–0.85; specificity, 0.74; 95% CI, 0.56–0.84; and FIB-4: sensitivity, 0.87; 95% CI, 0.79–0.92; specificity, 0.65; 95% CI, 0.51–0.73. In adults

with chronic hepatitis B, VCTE demonstrated superior diagnostic performance compared with FIB-4 and APRI for the diagnosis of cirrhosis. The AGA did not review the utility of other proprietary serum fibrosis assays or imaging-based fibrosis assessment tools for the diagnosis of cirrhosis. Routine liver biopsy or fibrosis assessment is less common in the care of patients with chronic hepatitis B infection (compared with patients with chronic hepatitis C), and is not uniformly required by practice guidelines before initiation of antiviral therapy. However, the identification of cirrhosis directly impacts the treatment decision, as well as the indication/frequency of hepatocellular carcinoma surveillance. Although transient elastography is superior to noninvasive serum tests in the detection of cirrhosis, the overall diagnostic performance was similar; specifically, VCTE's performance was comparable with FIB-4 for ruling in cirrhosis, but superior to FIB-4 in excluding cirrhosis. Caution should be exercised in the interpretation of VCTE findings in the context of other available clinical information to diagnose cirrhosis.

Recommendation: In patients with chronic hepatitis B, the AGA suggests VCTE rather than other nonproprietary noninvasive serum tests (ie, APRI and FIB-4) to detect cirrhosis.
GRADE: Conditional recommendation, low-quality evidence.

Question 7. In adults with HBV undergoing VCTE, at what liver stiffness cutoff can we accurately diagnose cirrhosis, obviating the need for liver biopsy?

In 17 studies evaluating 4864 patients, and using a VCTE cutoff of 11.0 (± 1) kPa, the pooled sensitivity of VCTE for diagnosing cirrhosis was 0.81 (95% CI, 0.79–0.84) and the pooled specificity for diagnosing cirrhosis was 0.83 (95% CI, 0.82–0.84). In adults with chronic hepatitis B, a VCTE median liver stiffness cutoff of 11.0 (± 1) kPa demonstrated acceptable sensitivity and specificity for the detection of cirrhosis. Using these values, it can be estimated that a cutoff of 11.0 kPa may misclassify <1% of low-risk, and approximately 5% of high-risk patients as not having cirrhosis (when they indeed have cirrhosis), and approximately 10%–15% of patients as having cirrhosis (when they do not have cirrhosis). The evidence base to support the use of a single cutoff for the detection of cirrhosis was derived from post-hoc analysis of cross-sectional diagnostic accuracy studies and, therefore, of lower quality due to indirectness. Only studies using a cutoff of 11.0 (± 1) kPa were included in the technical review, and significant heterogeneity was observed in these test characteristics. Patients with chronic hepatitis B infection who place a high value on certainty in the assessment of liver fibrosis to guide management, and a low value on risks and inconvenience of fibrosis testing, may reasonably choose to obtain additional confirmatory studies, such as liver biopsy to clarify stage of liver disease.

In summary, by selecting a cutoff of 11.0 kPa the guideline panel made a conscious decision to minimize false-negative tests, thus making a judgment that the harm of missing cirrhosis is greater than the harm of overdiagnosis. However, although this strategy will result in a significant number of patients falsely labeled at high risk for cirrhosis (particularly in the low-prevalence setting), there is likely less harm with this strategy, as the clinical implication in the hepatitis B population is mitigated for several reasons:

1. Repeating elastography after successfully achieving viral suppression will often result in a reduction of liver stiffness readings over time, thus reducing the number of patients falsely classified as having cirrhosis.
4. The downstream decisions leading to invasive tests (eg, upper endoscopy to screen for varices) should not be solely based on this cutoff (11.0 kPa). (See Question 11. In adults with suspected compensated cirrhosis undergoing VCTE, at what liver stiffness cutoff can we accurately rule out high-risk esophageal varices, obviating the need for routine endoscopic screening?)
2. Because many patients with hepatitis B should be screened for HCC regardless of extent of liver fibrosis, overcalling cirrhosis in this population will not adversely affect screening practices.

Recommendation: In patients with chronic hepatitis B, the AGA suggests a VCTE cutoff of 11.0 kPa to detect cirrhosis.
GRADE: Conditional recommendation, low-quality evidence.

Question 8. Should VCTE vs APRI be used to diagnose cirrhosis in adults with nonalcoholic fatty liver disease (NAFLD)?

Question 9. Should VCTE vs FIB-4 be used to diagnosed cirrhosis in adults with NAFLD?

Although the diagnosis of NAFLD may be established on the basis of liver imaging, identification of nonalcoholic steatohepatitis and associated liver fibrosis or cirrhosis typically requires histologic confirmation by liver biopsy. Due to intrinsic risks and limitations of liver biopsy, and its poor acceptance by patients, noninvasive diagnosis of liver cirrhosis in patients with NAFLD with serum fibrosis assays or liver elastography would be desirable. The pooled effect estimates of test characteristics for the diagnosis of cirrhosis in patients with NAFLD were obtained from 9 studies evaluating VCTE, 2 studies evaluating APRI, and 1 study evaluating FIB-4. The test characteristics for these noninvasive fibrosis assessment tools were as follows: VCTE (sensitivity, 0.90; 95% CI, 0.82–0.95; specificity, 0.87; 95% CI, 0.85–0.89), APRI (sensitivity, 0.78; 95% CI, 0.71–0.99; specificity, 0.71; 95% CI, 0.30–0.93), and FIB-4 (sensitivity, 0.74; 95% CI, 0.54–0.87; specificity, 0.71; 95% CI, 0.64–0.76). Pooled

estimates of test performance of VCTE and noninvasive serum tests in the diagnosis of cirrhosis in patients with NAFLD were determined to be subject to unacceptable bias due to intrinsic limitations of available studies, including exclusion of obese patients (body mass index ≥ 30 kg/m²); exclusion of unsuccessful or inadequate liver stiffness measurements, which are more common among patients with NAFLD; and use of per-protocol rather than intention-to-diagnose analyses. Significant imprecision was identified for both the identification and exclusion of cirrhosis. Liver biopsy remains the gold standard test for the diagnosis and staging of nonalcoholic steatohepatitis. Future studies are needed to further examine the role of noninvasive serum and imaging-based fibrosis assessment tools in the diagnosis of advanced liver fibrosis and cirrhosis.

Recommendation: The AGA makes no recommendation regarding the role of VCTE in the diagnosis of cirrhosis in adults with NAFLD.
GRADE: no recommendation—knowledge gap.

Question 10. In adults with chronic alcoholic liver disease undergoing VCTE, at what liver stiffness cutoff can we accurately diagnose cirrhosis, obviating the need for liver biopsy?

The pooled effect estimates of test characteristics for the diagnosis of cirrhosis in patients with alcoholic liver disease were obtained from 7 studies evaluating 330 patients with chronic alcoholic liver disease. Using a median liver stiffness cutoff of 12.5 (± 1) kPa to diagnose cirrhosis, the pooled sensitivity was 0.95 (95% CI, 0.87–0.98) and the pooled specificity was 0.71 (95% CI, 0.56–0.82). In a low-risk cohort (prevalence 5% advanced fibrosis), only 0.2% of patients would be misclassified as not having cirrhosis (false negative) and 27.5% of patients would be misclassified as having cirrhosis (false positive). In a high-risk cohort (prevalence 30% advanced fibrosis), including those with ongoing risk factors for liver injury (eg, obesity, fatty liver, co-infection with human immunodeficiency virus or hepatitis B virus), approximately 1.5% of patients may be misclassified as not having cirrhosis, and 20.3% of patients may be misclassified as having cirrhosis. The evidence base to support the use of a single cutoff for the detection of cirrhosis was derived from post-hoc analysis of cross-sectional diagnostic accuracy studies and, therefore, of lower quality due to indirectness. Only studies using a cutoff of 12.5 (± 1) kPa were included in the technical review, and significant heterogeneity was observed in these test characteristics. Patients with chronic alcoholic liver disease who place a high value on certainty in the assessment of liver cirrhosis to guide management, and a low value on risks and inconvenience of fibrosis testing, may reasonably choose to obtain additional confirmatory studies, such as liver biopsy to clarify stage of liver disease. These estimates were derived in patients with chronic alcoholic liver

disease, and should not be applied to patients with acute alcoholic hepatitis.

In summary, by selecting a cutoff of 12.5 kPa, the guideline panel made a conscious decision to minimize false-negative tests, thus making a judgment that the harm of missing cirrhosis is greater than the harms of over diagnosis. However, although this strategy will result in a significant number of patients falsely labeled at high risk for cirrhosis in the low prevalence setting, there is likely less harm with this strategy as the clinical implication in patients with alcoholic cirrhosis is mitigated for a number of reasons:

1. The downstream decisions leading to invasive tests (eg, upper endoscopy to screen for varices) should not be solely based on this cutoff (12.5 kPa). (See Question 11 regarding at what liver stiffness cutoff can high-risk esophageal varices be ruled out.)
2. Other downstream consequences, such as screening for HCC with noninvasive tests, such as liver ultrasound, should ideally not only include patients with established cirrhosis but also advanced fibrosis. However, patients falsely labeled as having cirrhosis frequently have advanced fibrosis (F3) and can still benefit from screening.

Recommendation: In patients with chronic alcoholic liver disease, the AGA suggests a VCTE cutoff of 12.5 kPa to detect cirrhosis.
GRADE: Conditional recommendation, low-quality evidence.

Question 11. In adults with suspected compensated cirrhosis undergoing VCTE, at what liver stiffness cutoff can we accurately rule out high-risk esophageal varices, obviating the need for routine endoscopic screening?

In this context, VCTE was evaluated as an add-on triage test to better define which patients with suspected cirrhosis may benefit from further investigation of high risk esophageal varices. The diagnostic performance of a pre-specified cutoff of 19.5 (± 2) kPa to rule out high-risk esophageal varices was interpreted in 2 illustrative scenarios—one of a low-risk population (5% prevalence of high-risk varices, such as patients with newly diagnosed compensated cirrhosis with platelet count $>150,000/\mu\text{L}$ without overt features of portal hypertension), and another of a high-risk population (20% prevalence of high-risk varices, such as patients with compensated cirrhosis with platelet count $<150,000/\mu\text{L}$ and without overt features of portal hypertension). The pooled effect estimates of test characteristics for the exclusion of high-risk esophageal varices was obtained from 8 studies in 964 patients. Using a cutoff for advanced fibrosis/cirrhosis of 19.5 (± 2) kPa, the pooled sensitivity was 0.89 (95% CI, 0.84–0.92) and pooled specificity was 0.56 (95% CI, 0.52–0.59). Using these values, it can be estimated that using a cutoff of 19.5

kPa to rule out high-risk esophageal varices, may misclassify 0.6% of low-risk patients and approximately 2.2% of high-risk patients, as not having high-risk esophageal varices, who then may be falsely reassured, and not receive appropriate prophylactic interventions such as nonselective β -blocker or band ligation, placing them at increased risk of acute variceal hemorrhage and associated morbidity and mortality. The evidence base to support the use of a single cutoff for the detection of advanced fibrosis was largely derived from post-hoc analysis of cross-sectional diagnostic accuracy studies. Therefore, evidence was rated down for indirectness. Only studies using a cutoff of 19.5 (± 2) kPa were included in the technical review, and significant heterogeneity was observed in these test characteristics. Additional research is needed to further define the role of single or serial transient elastography testing, as well as appropriate liver stiffness threshold, in the evaluation of compensated cirrhotic patients with high-risk esophageal varices. Importantly, patients with decompensated cirrhosis, as well as patients with compensated cirrhosis with known esophageal varices or portal hypertension, were not considered in this analysis and, therefore, endoscopic evaluation should be pursued in these patients as per standard clinical practice without consideration of a VCTE cutoff of 19.5 kPa. Guidelines of the Baveno VI Consensus Workshop further support risk stratification based on a VCTE cutoff of <20 kPa and platelet count $>150,000/\mu\text{L}$.¹⁹

Recommendation: In patients with suspected compensated cirrhosis, the AGA suggests a vibration controlled transient elastography cutoff of 19.5 kPa to assess the need for esophagogastroduodenoscopy to identify high risk esophageal varices.

GRADE: Conditional recommendation, low-quality evidence.

Comment: Patients, particularly those at higher risk, with VCTE <19.5 kPa who place a low value on the inconvenience and risks of endoscopy, and a high value on avoiding the small risk of acute variceal hemorrhage associated with VCTE values of <19.5 kPa, may reasonably select to undergo screening endoscopy.

Question 12. In adults with suspected chronic liver disease undergoing elective nonhepatic surgery, at what VCTE-identified liver stiffness cutoff can we accurately rule out clinically significant portal hypertension (identified as presence of any esophageal varices), potentially minimizing the need for routine invasive testing for portal hypertension (endoscopy, hepatic venous pressure gradient measurement)?

In this context, VCTE was evaluated as an add-on triage test to better define which patients may benefit from further investigation of clinically significant portal hypertension. The diagnostic performance of a prespecified cutoff of 17.0 (± 2) kPa to rule out clinically significant portal hypertension was

interpreted in 3 illustrative scenarios—a very low-risk population (0.5% prevalence of any varices, such as patients with a diagnosis of chronic liver disease but very low risk of cirrhosis, such as patients with prior noncirrhotic HCV who have achieved a SVR); a low-risk population (5% prevalence of any varices, such as patients with chronic liver disease at risk for cirrhosis, but without any clinical evidence for portal hypertension); and a high-risk population (40% prevalence of any varices, such as patients with known or suspected compensated cirrhosis). The pooled effect estimates of test characteristics for the exclusion of high-risk esophageal varices was obtained from 8 studies in 895 patients. Using a cutoff for clinically significant portal hypertension of 17.0 (± 2) kPa, the pooled sensitivity was 0.83 (95% CI, 0.80–0.87) and pooled specificity was 0.52 (95% CI, 0.47–0.57). Using these values, it can be estimated that using a cutoff of 17.0 kPa to rule out clinically significant portal hypertension, may misclassify 0.1% of very low-risk patients, 0.8% of low-risk patients, and approximately 6.8% of high-risk patients, as not having clinically significant portal hypertension, who then may be falsely reassured, and undergo nonhepatic surgery, which may be associated with increased morbidity and mortality. The evidence base to support the use of a single cutoff for the detection of clinically significant portal hypertension was largely derived from post-hoc analysis of cross-sectional diagnostic accuracy studies. Therefore, evidence was rated down for indirectness. Only studies using a cutoff of 17.0 (± 2) kPa were included in the technical review, and significant heterogeneity was observed in these test characteristics. Importantly, patients with decompensated cirrhosis, as well as patients with compensated cirrhosis with known esophageal varices or portal hypertension, were not considered in this analysis and, therefore, standard clinical practice should be pursued in the care of these patients.

Recommendation: In patients with suspected chronic liver disease undergoing elective nonhepatic surgery, the AGA suggests a VCTE cutoff of 17.0 kPa to detect clinically significant portal hypertension to inform preoperative care.

GRADE: Conditional recommendation, low-quality evidence.

Comment: Patients, particularly those at higher risk, with VCTE <17.0 kPa who place a low value on the inconvenience and risks of interventions (endoscopy, hepatic venous pressure gradient measurement) to detect clinically significant portal hypertension, and a high value on avoiding the small risk of operative morbidity and mortality associated with elective nonhepatic surgery, may reasonably select to undergo screening endoscopy.

Question 13. Should MRE vs VCTE be used to diagnose cirrhosis in adults with chronic hepatitis C?

The pooled effect estimates of test characteristics for the diagnosis of cirrhosis in patients with chronic hepatitis C were obtained from 13 studies evaluating MRE and 36

studies evaluating VCTE. The test characteristics for these noninvasive fibrosis assessment tools were as follows: MRE (sensitivity, 0.94; 95% CI, 0.87–0.97; specificity, 0.81; 95% CI, 0.61–0.98); and VCTE (sensitivity, 0.89; 95% CI, 0.84–0.92; specificity, 0.91; 95% CI, 0.89–0.92). In adults with chronic hepatitis C, MRE showed little or no difference in accuracy over transient elastography in identifying patients who truly have cirrhosis with comparable rates of misclassifying patients with cirrhosis as not having cirrhosis (false negatives). However, VCTE demonstrated superior specificity over MRE in identifying patients who truly do not have cirrhosis with lower rates of misclassifying non-cirrhotic patients as having cirrhosis. Overall, in adults with chronic hepatitis C, MRE appears to have little to no increase in identifying cirrhosis over VCTE, but poorer specificity with higher false-positive rates, suggesting poorer diagnostic performance. In addition, lower cost and the availability of VCTE at the point of care makes this an attractive solution compared with MRE. The identification of cirrhosis remains an essential component of the pretreatment assessment and, therefore, the decision to pursue either fibrosis assessment tool requires consideration of availability and cost, as well as individual patient characteristics, which can influence technical success, or limit eligibility for either modality.

Recommendation: In adult patients with chronic hepatitis C, the AGA suggests using VCTE rather than MRE for detection of cirrhosis.
GRADE: Conditional recommendation, very-low-quality evidence.

Question 14: Should MRE vs VCTE be used to diagnose cirrhosis in adults with NAFLD?

The diagnostic performance of MRE and VCTE was interpreted in 2 illustrative scenarios—one of a high-risk population (30% prevalence of cirrhosis: eg, NAFLD with advanced age, obesity, particularly central adiposity, diabetes mellitus, elevated liver enzymes, typically seen in a specialty referral setting), and another of a low-risk population ($\leq 5\%$ prevalence of cirrhosis, such as patients with signs of fatty liver on imaging only, typically seen in a primary care setting, lacking high risk features). The pooled effect estimates of test characteristics for the diagnosis of cirrhosis in patients with NAFLD were obtained from 2 head-to-head studies comparing the diagnostic performance of MRE and VCTE. The test characteristics for these noninvasive fibrosis assessment tools were as follows: MRE: sensitivity, 0.84; 95% CI, 0.60–0.97; specificity, 0.89; 95% CI, 0.84–0.93 and VCTE: sensitivity, 0.83; 95% CI, 0.59–0.96; specificity, 0.72; 95% CI, 0.65–0.78. Applying these accuracy estimates to a high-prevalence setting showed little or no difference between MRE and VCTE in the rate of false negatives (incorrectly classifying as not having cirrhosis where in fact cirrhosis is present), but the use of MRE would result in 119 in 1000 fewer patients incorrectly classified as having cirrhosis (false positives) compared with VCTE, who otherwise would undergo unnecessary

further invasive testing (eg, liver biopsy). In a low prevalence setting, both MRE and VCTE performed poorly with 2.5 (MRE) to 6 (VCTE) times as many false-positive tests compared with true positives. When either additional noninvasive tests are unavailable (ie, it is likely that a large number of false-positive tests will lead to liver biopsy) and/or downstream clinical consequences of false-positive tests may cause harm (more aggressive treatment of NAFLD, such as bariatric surgery), indiscriminant application of such tests are likely to cause substantially more harms than benefits. Additional research is needed to further define the role of VCTE and MRE in identifying noncirrhotic liver fibrosis in adult patients with NAFLD, from the perspective of replacement or triage for liver biopsy, which remains the gold standard tool for the diagnosis and staging of nonalcoholic steatohepatitis with or without fibrosis.

Recommendation: In adults with NAFLD and a higher risk of cirrhosis, the AGA suggest using MRE, rather than VCTE, for detection of cirrhosis
GRADE: Conditional recommendation, low quality evidence.

In adults with NAFLD and a lower risk of cirrhosis, the AGA makes no recommendation regarding the role of MRE or VCTE for detection of cirrhosis.

GRADE: no recommendation – knowledge gap.

Comment: High-risk populations are NAFLD with advanced age, obesity, particularly central adiposity, diabetes, alanine elevated $>2\times$ upper limit of normal with an estimated cirrhosis prevalence of 30% (typically seen in a referral setting); low-risk population are those with NAFLD and signs of fatty liver on imaging only and an estimated cirrhosis prevalence of $\leq 5\%$ (typically seen in a primary care setting).

Summary

The assessment of liver fibrosis in patients with chronic liver disease remains an important component of clinical management, and requires careful review and synthesis of a combination of medical history, physical examination, laboratory, and imaging findings, which may signal the presence or absence of advanced liver disease. Although liver biopsy continues to have a vital role in the care of patients with both acute and chronic liver disorders, additional evidence-based recommendations are needed to guide clinicians in the incorporation of emerging noninvasive serum and imaging-based fibrosis assessment tools into routine clinical practice. Pooled analyses of diagnostic performance studies suggest that VCTE can be used to accurately diagnose cirrhosis at an acceptable rate of false negatives and false positives in patients with chronic liver disease, particularly those with chronic hepatitis B or C infection.⁴ MRE appears to have somewhat higher accuracy in NAFLD. This systematic review and guideline were focused on routine clinical management issues, and did not address comparisons with proprietary serum fibrosis assays, other emerging imaging-based fibrosis assessment techniques, or combinations of more than one noninvasive fibrosis test, and assessments of

VCTE cutoff were limited to a single threshold (optimized to minimize false negatives) rather than a range of thresholds. Additional studies are needed to further define the role of VCTE, MRE, and emerging diagnostic studies in the assessment of liver fibrosis, for which a significant unmet medical need remains, particularly in conditions such as NAFLD/nonalcoholic steatohepatitis. In particular, defining the implications for serial liver stiffness measurements over time on management decisions is of great interest. Recognizing these and other limitations, the recommendations included here represent a rigorous, evidence-based summary of available literature. Review of this technical review and guideline may facilitate effective shared decision making with patients who desire liver fibrosis assessment.

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Conflicts of interest

All members were required to complete disclosure a statement. These statements are maintained at the American Gastroenterological Association Institute (AGA) headquarters in Bethesda, Maryland. The authors disclose the following: Dr. Lim has served as a consultant for Bristol Myers-Squibb, Gilead, Merck, and Boehringer-Ingelheim. Dr. Flamm has served as a consultant or received research support from Gilead, Bristol Myers-Squibb, Abbvie, Salix, and Intercept. The rest of the authors disclosed no conflicts related to the content of this guideline.