Gastroenterology 2017;152:1544–1577

American Gastroenterological Association Institute Technical Review on the Role of Elastography in Chronic Liver Diseases

Siddharth Singh,[1] Andrew J. Muir,[2] Douglas T. Dieterich,[3] and Yngve T. Falck-Ytter[4]

[1]Division of Gastroenterology, University of California San Diego, La Jolla, California; [2]Division of Gastroenterology, Duke University School of Medicine, Durham, North Carolina; [3]Division of Liver Disease, Icahn School of Medicine, New York, New York; and [4] Division of Gastroenterology and Hepatology, Cleveland VA Medical Center and University Hospitals, Case Western Reserve University, Cleveland, Ohio

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: ascertain the evidence on comparative diagnostic performance of different noninvasive imaging modalities for detection of cirrhosis, and performance of different vibration-controlled transient elastography-based liver stiffness cut-offs for detection of cirrhosis and clinically significant portal hypertension in patients with chronic liver diseases, in different clinical and practice settings.

Chronic liver diseases (CLDs), due to chronic hepatitis C; hepatitis B; nonalcoholic fatty liver diseases (NAFLD); and alcoholic liver disease, are a leading cause of morbidity and mortality globally. Early identification of patients with cirrhosis at high risk of progression to liver-related complications may facilitate timely care and improve outcomes. With risks and misclassification associated with invasive tests, such as liver biopsy, noninvasive imaging modalities for liver fibrosis assessment have gained popularity. Therefore, the American Gastroenterological Association prioritized clinical guidelines on the role of elastography in CLDs, focusing on vibration-controlled transient elastography (VCTE) and magnetic resonance elastography (MRE). To inform these clinical guidelines, the current technical review was developed in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for diagnostic accuracy studies. This technical review addresses focused questions related to: (1) comparative diagnostic performance of VCTE and MRE relative to nonproprietary, serum-based fibrosis markers for detection of cirrhosis in patients with hepatitis C virus (HCV), hepatitis B virus (HBV), NAFLD, and alcoholic liver diseases; (2) performance of specific VCTE-defined liver stiffness cutoffs as a test replacement strategy (to replace liver biopsy) in making key decisions in the management of patients with CLDs; and (3) performance of specific VCTE-defined liver stiffness cutoffs as a triage test to identify patients with low likelihood of harboring high-risk esophageal varices (EVs) or having clinically significant portal hypertension (for presurgical risk stratification). This technical review does not address performance of other noninvasive modalities for assessing fibrosis (eg, acoustic radiation force pulse imaging or shear wave elastography) or steatosis (controlled attenuation parameter or magnetic resonance imaging−estimated proton density fat fraction).

Keywords: Fibrosis; Noninvasive Imaging; Chronic Liver Diseases; Guidelines.

Globally >1.75 million deaths are attributed to chronic liver diseases (CLDs), which are an important source of health and economic burdens.[1] In the United States, nearly 150,000 people are diagnosed with CLDs annually (of which 20% are diagnosed with cirrhosis), and 36,000 patients die of CLDs, primarily attributable to complications of decompensated cirrhosis and/or hepatocellular cancer (HCC).[2,3] Annually, these generate approximately 5.9 million CLD-related ambulatory care visits and 759,000 CLD-related hospitalizations, with health care costs exceeding $1.5 billion.[3] HCC is the second leading cause of cancer-related death worldwide, and most patients with HCC will have underlying CLDs.[4] Globally, it is estimated that >185 million and 248 million people may be living with chronic HCV infection and chronic HBV infection, respectively; corresponding rates in the United States are approximately 4.7 million and 2 million, respectively.[5−7] NAFLD is a rapidly increasing cause of CLDs, with an estimated 13.5%−31.8% affected globally and 24.1% of adults in North America.[8] The burden of alcoholic liver disease is more difficult to determine, but one report estimated that alcohol-attributable liver cirrhosis was responsible for 493,300 deaths globally in 2010.[9]

Early identification of patients at high risk for progression to decompensated cirrhosis can help direct high-value care and decrease the morbidity and mortality attributed to CLDs.

Abbreviations used in this paper: **APRI, aspartate aminotransferase to platelet ratio index; AUROC, area under the receiver operating characteristic; CI, confidence interval; CLD, chronic liver disease; EGD, esophagogastroduodenoscopy; EVs, esophageal varices; FIB-4, fibrosis-4 index; FN, false negative; FP, false positive; HBV, hepatitis B virus; HCC, hepatocellular cancer; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IPD, individual participant data; kPa, kilopascal; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; PICO, patients; intervention, comparator and outcome; SVR, sustained virologic response; TN, true negative; TP, true positive; VCTE, vibration-controlled transient elastography.**

Most current article

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2017.03.016

AGA SECTION

One of the key determinants of progression to CLD-related complications is degree of liver fibrosis, and is often factored in making treatment and surveillance decisions (for HCC and/or esophageal variceal screening). Historically, liver biopsy has been the gold standard for diagnosis and staging of fibrosis, in addition to its role in identifying etiology of abnormal liver enzymes and assessing degree of inflammation. However, this procedure has several limitations. It is invasive and associated with an estimated morbidity (including severe pain) and mortality rate of 3% and 0.01%, respectively; in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis trial, serious adverse events occurred in 29 of the 2740 (1.1%) biopsies performed and included 16 (0.6%) bleeding cases.[10,11] Liver biopsy is prone to sampling error resulting in misclassification of fibrosis stage in up to 25% of cases, and there is also considerable intra- and inter-observer variability in interpretation of histology, especially at lower stages of fibrosis.[12]

To overcome these limitations and inconvenience of an invasive test, noninvasive serum- and imaging-based methods of staging fibrosis have been developed. Although several proprietary and nonproprietary serum-based markers have been developed, they are nonspecific for the liver and may have inferior performance characteristics to imaging-based tests.[13] Among imaging tests, ultrasound-based VCTE has been studied most extensively and validated with high intra- and inter-observer reproducibility, and can be performed quickly, potentially at point of care.[14] In this technique, a piston vibrator placed in the intercostal space generates a shear wave, and then the velocity is measured in a region 25−65 mm below the skin surface with the standard adult M-probe and 35−75 mm with the XL probe for larger patients. The unit of measurement is kilopascals (kPa), and the device readings range from 2.5 to 75 kPa.

With recent recommendations for universal screening for HCV, availability of highly effective but expensive newer direct-acting agents against HCV, and rising prevalence of NAFLD, an increasing number of patients are seeking evaluation for CLDs, and fibrosis staging through noninvasive means has become increasingly important and appealing for physicians.[15,16] Patients also have a strong preference for VCTE over liver biopsy. In a Canadian survey of 422 patients, of whom 205 had undergone liver biopsy, approximately 95% patients preferred VCTE over liver biopsy, with the majority reporting no discomfort (84%), no feelings of anxiety (78%), short test duration and short time to result.[17] In its recent guidelines, the European Association for the Study of Liver Diseases and the Latin American Association for the Study of the Liver have recommended VCTE as a validated noninvasive standard for assessment of liver fibrosis, in patients with HCV and HBV, with >90% negative predictive value in ruling out cirrhosis.[18] However, these guidelines offer limited guidance on the diagnostic performance of specific cutoffs of VCTE-identified liver stiffness, in clinical contexts of high- and low-risk populations of patients with CLD, and its potential impact on downstream patient-important outcomes. Identifying specific cutoffs for liver stiffness corresponding to cirrhosis and advanced fibrosis could guide management decisions, including treatment for HCV and HBV and triage for preventive cirrhosis care. Therefore, the American Gastroenterological Association prioritized this topic for generation of clinical guidelines.

Objectives of This Review

This technical review addresses focused clinical questions on the diagnostic performance of VCTE (and MRE) in patients with HCV, HBV, NAFLD, and alcoholic liver disease, focusing specifically on: (1) overall performance relative to nonproprietary, serum-based fibrosis markers and (2) implications of specific liver stiffness cutoffs on downstream patient-important outcomes. Additionally, in this review we sought to evaluate the performance of specific liver stiffness cutoffs to assess portal hypertension to triage patients with compensated cirrhosis with low likelihood of high-risk EVs, as well as its role in presurgical risk stratification of patients with CLD.[19] This review does not address the performance and utility of other noninvasive imaging modalities, such as acoustic radiation force pulse imaging or shear wave elastography. Based on feedback during the public comment period, the technical review was updated with 2 additional questions on the comparative performance of VCTE and MRE in detection of cirrhosis in patients with HCV and NAFLD.

Methods

Formulation of Clinical Questions

The participants (including SS, AJM, DTD, and YFY) for this technical review were selected by the American Gastroenterological Association Clinical Guidelines Committee based on their clinical content and guidelines methodological expertise and went through a thorough vetting process for potential conflicts of interest. Through an iterative process, the participants developed focused clinical questions deemed relevant for clinical practice that the guideline would address and that related to the diagnostic performance and utility of VCTE in 5 different populations: adults with HCV, HBV, NAFLD, chronic alcoholic liver disease, and CLD suspected to have portal hypertension. From these focused questions, well-defined statements in terms of patients, intervention, comparator, and outcome (PICO) were defined, and these formed the framework for formulating the study inclusion and exclusion criteria and guided the literature search. The American Gastroenterological Association Governing Board approved the final set of questions and statements. The focused and PICO questions are shown in Table 1. Two questions on the role of MRE on detection of cirrhosis were added after the public comment period.

There were 2 broad themes for our focused questions. The first set of questions for each population of interest (HCV, HBV, NAFLD, and alcoholic liver diseases) were centered around the overall diagnostic performance (across a broad range of cutoffs) of VCTE in relation to commonly used, nonproprietary, noninvasive serum biomarkers of fibrosis in these conditions (aspartate aminotransferase to platelet ratio index [APRI] and fibrosis-4 index [FIB-4]) (PICO #1, 4, and 6).[13,20] Although proprietary serum-based fibrosis markers may have slightly higher diagnostic accuracy compared with nonproprietary markers, the latter are inexpensive, easy to calculate, and widely available.[18] After the public comment period, 2 questions (PICO #11 and 12) on the comparative performance of VCTE and MRE on

Table 1. Focused Clinical Questions and Corresponding Questions in PICO (Patients, Intervention, Comparison, Outcomes) Format Addressed in This Technical Review

Question no.	Focused question	Patients	Intervention	Comparison	Outcomes
	Hepatitis C				
1	In adults with chronic HCV, is the overall diagnostic performance of VCTE superior to other noninvasive markers of liver fibrosis (APRI, FIB-4)?	Adults with chronic HCV	Transient elastography (VCTE)	APRI, FIB-4	Detection of cirrhosis Benefits: TP rate, TN rate Harms: FP rate, FN rate
2	In adults with chronic HCV undergoing VCTE, at what liver stiffness cutoff, can we accurately diagnose cirrhosis, obviating the need for liver biopsy?	Adults with chronic HCV undergoing VCTE	Liver stiffness, $\geq$12.5 kPa	Liver stiffness, $<$12.5 kPa	Beneficial: for detection of cirrhosis, TP rate, TN rate Harms: FN rate (maximal tolerable FN rate, 5%$-$10%), FP rate
3	In adults with HCV, can VCTE-defined liver stiffness cutoff $\leq$9.5 kPa accurately rule out advanced fibrosis, so patient may be discharged from a dedicated liver clinic?	Adults with chronic HCV, treated with anti-viral therapy, undergoing VCTE	Liver stiffness, $\leq$9.5 kPa	Liver stiffness, $>$9.5 kPa	Beneficial: For detection of advanced fibrosis, TP rate, TN rate Harms: FN rate (maximal tolerable FN rate, 1%$-$5%), FP rate
	Hepatitis B				
4	In adults with chronic HBV, is the overall diagnostic performance of VCTE superior to other non-invasive markers of liver fibrosis (APRI, FIB-4)?	Adults with chronic HBV	Transient elastography (VCTE)	APRI, FIB-4	Beneficial: For detection of cirrhosis, TP rate, TN rate Harms:FP rate, FN rate
5	In adults with chronic HBV undergoing VCTE, at what liver stiffness cutoff, can we accurately diagnose cirrhosis, obviating the need for liver biopsy?	Adults with chronic HBV undergoing VCTE	Liver stiffness, $\geq$11 kPa	Liver stiffness, $<$11 kPa	Beneficial: for detection of cirrhosis, TP rate, TN rate Harms: FN rate (maximal tolerable FN rate, 5%$-$10%), FP rate
	NAFLD				
6	In adults with NAFLD, is the overall diagnostic performance of VCTE superior to other noninvasive markers of liver fibrosis (APRI, FIB-4)?	Adults with chronic NAFLD	Transient elastography (VCTE)	APRI, FIB-4	Beneficial: for detection of cirrhosis, TP rate, TN rate Harms: FP rate, FN rate

Table 1. Continued

Question no.	Focused question	Patients	Intervention	Comparison	Outcomes
7	In adults with NAFLD undergoing VCTE, at what liver stiffness cutoff, can we accurately diagnose cirrhosis, obviating the need for liver biopsy?	Adults with NAFLD undergoing VCTE	Liver stiffness, ≥11 kPa	Liver stiffness, <11 kPa	Beneficial: For detection of cirrhosis, TP rate, TN rate Harms: FP rate, FN rate
	Alcoholic liver disease				
8	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?	Adults with chronic alcoholic liver disease undergoing VCTE	Liver stiffness, ≥12.5 kPa	Liver stiffness, <12.5 kPa	Beneficial: For detection of cirrhosis, TP rate, TN rate Harms: FN rate (maximal tolerable FN rate, 5%−10%), FP rate
	Portal hypertension				
9	In adults with CLDs suspected to have compensated cirrhosis, undergoing VCTE, at what liver stiffness cutoff, can we accurately rule out high-risk esophageal varices, obviating the need for routine upper endoscopy in all patients with cirrhosis?	Adults with CLDs suspected to have compensated cirrhosis, undergoing VCTE	Liver stiffness ≤19.5 kPa	Liver stiffness, >19.5 kPa	Beneficial: For detection of high-risk EVs, TP rate, TN rate Harms: FN rate (maximal tolerable FN rate, 1%−5%), FP rate
10	In adults with CLDs undergoing VCTE, at what liver stiffness cutoff, can we accurately rule out clinically significant portal hypertension for presurgical risk stratification, obviating the need for invasive testing before surgery?	Adults with CLDs suspected to have cirrhosis, undergoing VCTE	Liver stiffness ≤17 kPa	Liver stiffness, >17 kPa	Beneficial: For detection of any EVs, TP rate, TN rate Harms: FN rate (maximal tolerable FN rate, 1%−5%), FP rate
	MRE vs VCTE				
11	In adults with HCV, should MRE vs VCTE be used to diagnose cirrhosis in adults with chronic hepatitis C	Adults with HCV	MRE	VCTE	Beneficial: For detection of cirrhosis, TP rate, TN rate Harms: FP rate, FN rate
12	In adults with NAFLD, should MRE vs VCTE be used to diagnose cirrhosis in adults with NAFLD	Adults with NAFLD	MRE	VCTE	Beneficial: For detection of cirrhosis, TP rate, TN rate Harms: FP rate, FN rate

detection of cirrhosis in patients with HCV and NAFLD were added. The second set of focused questions were focused on identifying reliable VCTE-derived liver stiffness cutoffs to diagnose cirrhosis (PICO #2, 4, 6, and 8), or rule out advanced fibrosis (PICO #3) or rule out high-risk EVs (defined as any medium/large EV, or small varices with high-risk stigmata for bleeding) (PICO #9) or clinically significant portal hypertension (defined as presence of any EV) (PICO #10).

For PICO #1−8, VCTE was considered as a test replacement strategy for detection of cirrhosis, that is, in patients with valid results, VCTE would replace routine use of liver biopsy and limit its use to cases with inconclusive VCTE results or diagnostic equipoise. For PICO #9, VCTE was considered as a triage (screening) strategy for upper endoscopy for ruling out high-risk EVs, that is, in patients with liver stiffness below the VCTE-identified threshold, the likelihood of high-risk EVs is sufficiently low to avoid routine upper endoscopy; however, in patients with liver stiffness at or above VCTE-identified threshold, upper endoscopy is warranted to confirm diagnosis before treatment is considered. Likewise for PICO #10, VCTE was considered a triage strategy, that is, patients with liver stiffness below VCTE-identified threshold, clinically significant portal hypertension may be ruled out in risk stratification for elective, nonhepatic surgery; however, in patients with liver stiffness at or above VCTE-identified threshold, further testing (with upper endoscopy or hepatic venous pressure gradient) to evaluate clinically significant portal hypertension may be warranted before a patient is deemed high risk for elective surgery.

Search Strategy, Study Selection, Data Abstraction, and Quality Assessment

Details of the search strategy, study selection, data abstraction, and risk of bias assessment is reported in the Supplementary Material.

Outcomes of Interest

For the first set of PICO statements pertaining to overall diagnostic performance of VCTE compared with other commonly used, nonproprietary, noninvasive fibrosis biomarkers or MRE, primary outcome of interest was the overall diagnostic performance (true positives [TP], false positives [FP], true negatives [TN], and false negatives [FN] rates) for detection of cirrhosis in different illustrative clinical scenarios, corresponding to variable observed prevalence of cirrhosis depending on practice setting and population in which the test was applied.

For the second set of PICO statements pertaining to reliable VCTE-derived liver stiffness cutoffs to either diagnose (PICO #2, 4, 6, and 8), or rule out (PICO #3) cirrhosis or rule out high-risk EVs or any EVs (PICO #9 and 10), the preferred outcome was direct consequences on patient-important outcomes (ie, implications of TP, FP, TN, and FN results for patients, see the following section). However, none of the studies assessed these outcomes directly and, therefore, we used TP, FP, TN, and FN rates as surrogate outcomes and inferred downstream consequences on patient-important outcomes. For questions focusing on ruling out cirrhosis, high-risk or any EVs, our outcome was minimizing rates of FN (ie, patients incorrectly being labeled as not having the condition, when they actually have the condition) with reasonable rates of TP, FP, and TN. For questions focusing on diagnosing patients with cirrhosis, our outcome was a balance of FN and FP (ie, patients incorrectly labeled as having the condition, when they actually do not have the condition). This was also estimated in different clinical scenarios, as detailed here.

Consequences of Diagnostic Test Results on Patient-Important Outcomes

Corresponding to each possible outcome (TP, FP, TN, and FN), presumed downstream consequences on patient-important outcomes were considered. For example, for PICO #1−8 on detection of cirrhosis,

1. TP (patients correctly diagnosed as having cirrhosis) would be eligible to receive preventive cirrhosis care (such as HCC surveillance, screening for EVs), may receive treatment prioritization (HBV patients with compensated cirrhosis who may not have qualified for treatment), or different treatment regimen (HCV patients may receive 12-week therapy instead of 8-week therapy with direct antiviral agents), all of which may eventually decrease morbidity and mortality, without being subject to risks and invasive testing with liver biopsy.
2. FPs (patients incorrectly labeled as having cirrhosis based on VCTE, when actually they do not) may receive unnecessary testing (HCC surveillance, screening for EV) and treatment (longer treatment for HCV) and have avoidable anxiety, potential testing- or treatment-related complications, and excessive resource utilization.
3. TNs (patients correctly diagnosed as not having cirrhosis based on VCTE) would be reassured and obviate the need for invasive testing with liver biopsy, although they may need to undergo serial assessment of liver stiffness at periodic intervals.
4. FNs (patients incorrectly labeled as not having cirrhosis based on VCTE, when actually they have cirrhosis) would be falsely reassured, and may not receive appropriate preventive cirrhosis, may receive inappropriate treatment (shorter HCV treatment course), potentially leading to increased morbidity and mortality.

In using specific VCTE-derived liver stiffness cutoffs either as a test replacement or triage strategy, health care providers and patients need to be aware of test performance, and be comfortable with potential FN and FP rate with attending downstream consequences. Such downstream consequences of test results for each PICO statement and scenario have been discussed in detail in each evidence profile. For both test replacement and triage questions, the technical review team decided to focus on optimizing FN rate, with a reasonable FP tradeoff (depending on downstream consequences).

A premeeting questionnaire was administered to both the content experts in the technical review team and the guideline panel to determine their a priori maximal tolerable FN rate for each PICO (ie, what level of FN rate would they be willing to accept for a particular test, for their patient). As the maximally tolerable rates of FN tests for any diagnostic strategy is highly context sensitive, we devised different clinical scenarios with corresponding downstream consequences for each PICO to arrive at fully contextualized estimates of FN thresholds (see Supplementary Material).

Data Synthesis and Statistical Analysis

Details of data synthesis and statistical analysis are reported in the Supplementary Material. Specifically, for PICOs focusing on identifying reliable cutoffs, we a priori sought to identify VCTE cutoff maximizing sensitivity (to rule out cirrhosis, high-risk EVs or clinically significant portal hypertension), or maximizing specificity (to diagnose cirrhosis). However, during the data abstraction process, we recognized that variable cutoffs were not consistently reported in included studies; in addition, most studies did not prospectively study a particular cutoff, but rather retrospectively applied the cutoff corresponding to the area under the receiver operating characteristic (AUROC). Therefore, to identify reliable cutoffs, we used the most commonly reported cutoff in studies, confirmed their clinical use with content experts (and use in clinical trials which recruited patients with cirrhosis based on VCTE cutoffs), and calculated sensitivity, specificity, and positive and negative predictive values corresponding to these.

Quality of Evidence

We rated the quality of evidence using the GRADE approach for diagnostic tests and strategies.[21] In this approach, all evidence from randomized controlled trials (comparing different diagnostic tests or cutoffs of same test) and observational diagnostic accuracy studies start at high-quality, but can be rated down for any of the following factors:

1. Risk of bias in included studies (inferred based on QUADAS instrument),[22]
2. Indirectness (present if there are important differences in population studied and those for whom recommendation is being is intended; if cutoffs for VCTE for cirrhosis detection were not prespecified but obtained post-hoc corresponding to AUROC; and if TP, FP, TN, and FN rates are used as surrogates for presumed downstream consequences on patient-important outcomes),
3. Inconsistency (present if there were considerable differences in the accuracy estimates),
4. Imprecision (present if there were wide confidence intervals [CIs] for TP and FP and TN and FN rates), and
5. Publication bias.

In the absence of direct patient-important outcomes from observational diagnostic accuracy studies, surrogate outcomes including TP, FP, TN, and FN were all rated as critical outcomes, and included in evidence profiles.

Results

Appropriate Interpretation of Transient Elastography

For optimal interpretation of VCTE, the following are required: at least 10 validated measurements and an interquartile range (reflects variations among measurements) <30% of the median value is required.[13,14] In a prospective study of 13,369 VCTE examinations in Europe, liver stiffness measurement was unsuccessful (no valid shots could be obtained in 3% of patients), and in another 16% of patients, results were unreliable[23]; corresponding rates in an Asian population were 2.5% unsuccessful measurement and 0.9% with unreliable liver stiffness measurement.[24] Primary factors associated with unsuccessful or unreliable measurements are: obesity (body mass index >30 kg/m^2), in particular, increased waist circumference, ascites, narrow inter-rib spaces, advanced age, female sex, and operator inexperience (<500 examinations).[23–25] Besides fibrosis, factors that influence viscoelastic properties of the liver may also result in increased liver stiffness, such as the presence of severe hepatic inflammation, extrahepatic arteriovenous or biliary obstruction, and congestive heart failure. Therefore, caution should be exercised in interpreting VCTE results in patients with significant elevation in liver enzymes (aminotransferases >5× upper limit of normal) or excessive alcohol consumption.[26–30] Recent studies have identified that nonfasting state may also significantly influence liver stiffness and, therefore, VCTE should ideally be undertaken when the patient has been fasting for at least 2 hours.[31]

Illustrative Prevalence of Cirrhosis

The diagnostic accuracy of any test in terms of rates of TP, TN, FP, and FN depends on pretest probabilities and prevalence of condition, which in turn depends on practice setting (higher prevalence of cirrhosis in referral liver clinic compared to community primary care practice), patient-level characteristics (higher prevalence of cirrhosis in patients with concomitant viral infections like human immunodeficiency virus (HIV), obesity, diabetes, excessive alcohol use), and physician suspicion (which often encompasses practice setting and patient characteristics, including clinical history, physical examination, laboratory features). While we acknowledge that this baseline pretest probability of cirrhosis varies along a continuum of these factors, for ease of interpretation of data in day-to-day practice, we anchored the baseline prevalence of cirrhosis into 2 categories—low risk (5% prevalence of cirrhosis) and high risk (30% prevalence of cirrhosis). To illustrate this concept, patients with high risk for having prevalent cirrhosis may be asymptomatic patients with HCV, HBV, NAFLD, or alcoholic liver disease with associated obesity, diabetes mellitus, excessive alcohol use, and/or concomitant viral infections (eg, HIV), who are often seen in referral centers, and the estimated risk of cirrhosis in this population would be approximately 30%.[32–35] Patients with low risk of having prevalent cirrhosis would be those who are asymptomatic, seen by community primary care practitioners with HCV, HBV, NAFLD, or alcoholic liver disease, without clear factors associated with presence of cirrhosis, and the estimated risk of cirrhosis in this population would be approximately 5%. Using this illustrative prevalence of outcome, and sensitivity/specificity of liver stiffness cutoffs in different scenarios, positive and negative predictive value of each cutoff is summarized in Table 2.

Table 2. Performance Characteristics of Suggested Stiffness Cutoffs in Different Disease Conditions

PICO	Condition/outcome	Liver stiffness cutoff, *kPA*	Sensitivity, %	Specificity, %	Positive predictive value, estimate (and 95% CI)		Negative predictive value, estimate (and 95% CI)	
					Low prevalence[a]	High prevalence[b]	Low prevalence[a]	High prevalence[b]
2	Hepatitis C; cirrhosis	12.5 (±1)	86	91	33 (25–42)	80 (76–85)	99 (98–100)	94 (92–96)
3	Hepatitis C; advanced fibrosis or cirrhosis	9.5 (±1)	78	86	23 (17–30)	70 (65–75)	99 (98–99)	90 (88–92)
5	Hepatitis B; cirrhosis	11 (±1)	81	83	20 (15–27)	67 (62–72)	99 (98–99)	91 (89–93)
8	Alcoholic liver disease; cirrhosis	12.5 (±1)	95	71	15 (11–19)	100 (99–100)	58 (54–63)	97 (95–98)
9	Chronic liver disease; high-risk EVs[a]	19.5 (±2)	89	56	10 (7–13)	34 (30–38)	99 (98–100)	95 (93–97)
10	Suspected liver disease; any EVs	17.0 (±2)	83	52	Very low risk: 1 (0–2) low risk: 8 (6–11)	54 (50–58)	Very low risk: 100 (99–100) low risk: 98 (97–99)	82 (78–86)

NOTE. While identifying cutoffs we placed more emphasis on high negative predictive value.
[a]Low prevalence corresponds to an illustrative low-risk population with prevalence of outcome, 5%.
[b]High prevalence corresponds to an illustrative high-risk population with a prevalence of cirrhosis/advanced fibrosis (PICOs #2, 3, 5, and 8) of 30%, prevalence of high-risk EVs (PICO #9) of 20% and prevalence of any EVs (PICO #10) of 40%.

Question 1. In adults with chronic HCV, is the overall diagnostic performance of VCTE superior to other noninvasive markers of liver fibrosis (APRI, FIB-4) for detection of cirrhosis?

Key message. In adults with chronic HCV, VCTE has superior sensitivity and specificity, and lower FP and FN rates, suggesting better diagnostic performance compared with APRI and FIB-4 for detection of cirrhosis. (***Moderate quality of evidence***).

Effect estimates. We used an existing well-conducted systematic review on the diagnostic performance of noninvasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with CLDs published in January 2015.[36] This systematic review included 36 studies in patients with HCV that reported on the diagnostic performance of VCTE for detection of cirrhosis using liver biopsy as a reference standard. In these studies, the liver stiffness cutoff corresponding to AUROC ranged from 9.2 to 17.3 kPa. The summary sensitivity and specificity for detection of cirrhosis across this range of cutoffs were 0.89 (95% CI, 0.84−0.92) and 0.91 (95% CI, 0.89−0.93), respectively. The evidence profiles are summarized in Tables 3 and 4. Based on this, VCTE classified more patients correctly as having cirrhosis (TP) or not having cirrhosis (TN) compared with APRI (low cutoff), and had lower rates of misclassification (FP, FN), in both low- and high-prevalence populations; compared with FIB-4 (low cutoff), although rates of TP and FN were comparable, VCTE resulted in significantly lower FP rate.

Quality of evidence. All included studies were cross-sectional diagnostic accuracy studies, required <6-month interval between performance of diagnostic test (VCTE, APRI, or FIB-4) and gold standard (liver biopsy), minimizing disease progression bias, and were generally of fair quality and not at serious risk for bias (eg, spectrum bias, disease progression bias, partial or differential verification bias, adequate blinding of outcome assessors). For comparison of diagnostic performance of VCTE with other noninvasive, serum-based fibrosis markers, rates of TP, FP, TN, and FN were directly relevant outcomes in a comparable population, and although there were limited head-to-head comparisons of VCTE and other measures, the overall body of evidence was not rated down for indirectness. Considerable heterogeneity was observed in pooled sensitivity and specificity, and there was a wide range of "ideal" cutoffs for VCTE (corresponding to AUROC), rather than prespecified cutoffs for detection of cirrhosis and, therefore, evidence was rated down for inconsistency. There was no evidence of serious imprecision, and diagnostic performance of VCTE was superior to APRI and to FIB-4 in both low- and high-risk populations, even in worst-performance scenarios (using lower limit of 95% CI for diagnostic accuracy of VCTE, and upper limit of 95% CI of APRI or FIB-4). To summarize, using the GRADE approach for diagnostic accuracy studies, the quality of

Table 3. Grading of Recommendations Assessment, Development and Evaluation Evidence Profiles for Clinical Question #1 on the Comparative Diagnostic Performance of Transient Elastography vs Aspartate Aminotransferase to Platelet Ratio Index for the Diagnosis of Cirrhosis in Adults with Hepatitis C Virus

PICO 1A. Should TE vs APRI be used to diagnose cirrhosis in adults with chronic hepatitis C?
Population/setting: Adults with hepatitis C—high-risk population (HCV with excessive alcohol use, obesity, diabetes, co-infection with HIV/HBV) with estimated cirrhosis prevalence of 30%; low-risk population with estimated cirrhosis prevalence of 5%.
New test: TE–derived liver stiffness, cutoff range: 9.2–17.3 kPa (sensitivity, 0.89; 95% CI, 0.84–0.92; specificity, 0.91; 95% CI, 0.89–0.92).
Comparison test: APRI, low cutoff: 0.75–1.0 (sensitivity, 0.77; 95% CI, 0.73–0.81; specificity, 0.78; 95% CI, 0.74–0.81).
Reference test: Adequate liver biopsy specimen; ≥1.5 cm and ≥6 portal tracts.

	No. of results per 1000 patients tested (95% CI)						
	Low-risk (prevalence 5%)		High-risk (prevalence 30%)				
Test result	TE	APRI	TE	APRI	No. of studies	Quality of the evidence (GRADE)	Comments
TPs (patients with cirrhosis)	45 (42–46)	39 (37–41)	267 (252–276)	231 (219–243)	VCTE, 36 APRI, 24	⊕⊕⊕◯ Moderate[a] (inconsistency)	TE is superior to APRI for identifying patients who truly have cirrhosis. Detection of TP may lead to priority treatment allocation and preventive cirrhosis care (HCC surveillance, immunizations), and may reduce morbidity and mortality. TPs will have further testing, which may increase anxiety.
	6 more TP in TE (1 more to 9 more)		36 more TP in TE (9 more to 57 more)				
FNs (patients incorrectly classified as not having cirrhosis)	5 (4–8)	11 (9–13)	33 (24–48)	69 (57–81)			TE is superior to APRI, with lower rates of misclassifying patients with cirrhosis as not having cirrhosis. FN may be falsely reassured, receive inappropriate treatment (shorter course of anti-viral therapy), may not receive appropriate preventive cirrhosis care, and be at increased risk of progression to hepatic decompensation, and potentially increased morbidity and mortality.
	6 fewer FN in TE (1 fewer to 9 fewer)		36 fewer FN in TE (9 fewer to 57 fewer)				
TNs (patients without cirrhosis)	864 (845–884)	741 (703–770)	637 (623–651)	546 (518–567)		⊕⊕⊕◯ Moderate[a] (inconsistency)	TE is superior to APRI for identifying patients who truly do not have cirrhosis. TN may be reassured and obviate the need for invasive testing with liver biopsy, although they may need to undergo repeated assessment of liver stiffness at periodic intervals.
	123 more TN in TE (75 more to 181 more)		91 more TN in TE (56 more to 133 more)				
FPs (patients incorrectly classified as having cirrhosis)	86 (66–105)	209 (180–247)	63 (49–77)	154 (133–182)			TE is superior to APRI, with lower rates of misclassifying patients without cirrhosis as having cirrhosis. FP may receive unnecessary testing (HCC surveillance, immunization) and treatment (shorter course of antiviral therapy) and have avoidable anxiety, potential testing- or treatment-related complications, and excessive resource utilization.
	123 fewer FP in TE (75 fewer to 181 fewer)		91 fewer FP in TE (56 fewer to 133 fewer)				

TE, transient elastography.
[a]High heterogeneity, with wide range of liver stiffness cutoffs.

Table 4. Grading of Recommendations Assessment, Development and Evaluation Evidence Profiles for Clinical Question #1 on the Comparative Diagnostic Performance of Transient Elastography vs Fibrosis-4 Index for the Diagnosis of Cirrhosis in Adults with Hepatitis C Virus

PICO 1B. Should TE vs FIB-4 be used to diagnose cirrhosis in adults with chronic hepatitis C?
Population/setting: Adults with hepatitis C—high-risk population (HCV with excessive alcohol use, obesity, diabetes, co-infection with HIV/HBV) with estimated cirrhosis prevalence of 30%; low-risk population with estimated cirrhosis prevalence of 5%.
New test: TE-derived liver stiffness, cutoff range: 9.2−17.3 kPa (sensitivity: 0.89; 95% CI, 0.84−0.92; specificity, 0.91; 95% CI, 0.89−0.92).
Comparison test: FIB-4, low cutoff: 1.45 (sensitivity, 0.87; 95% CI, 0.74−0.94; specificity, 0.61; 95% CI, 0.53−0.69).
Reference test: Adequate liver biopsy specimen; ≥1.5 cm and ≥6 portal tracts.

	No. of results per 1000 patients tested (95% CI)						
	Low-risk (prevalence 5%)		High-risk (prevalence 30%)				
Test result	TE	FIB-4	TE	FIB-4	No. of studies	Quality of the evidence (GRADE)	Comments
TPs (patients with cirrhosis)	45 (42−46)	44 (37−47)	267 (252−276)	261 (222−282)	VCTE, 36 FIB-4, 2	⊕⊕◯◯ Low[a,b] (inconsistency, imprecision)	TE may be superior to FIB-4 for identifying patients who truly have cirrhosis. Detection of TP may lead to priority treatment allocation and preventive cirrhosis care (HCC surveillance, immunizations), and may reduce morbidity and mortality. TPs will have further testing, which may increase anxiety.
	1 more TP in TE (5 fewer to 9 more)		6 more TP in TE (30 fewer to 54 more)				
FNs (patients incorrectly classified as not having cirrhosis)	5 (4−8)	6 (3−13)	33 (24−48)	39 (18−78)			TE may be superior to FIB-4, with lower rates of misclassifying patients with cirrhosis as not having cirrhosis. FN may be falsely reassured, receive inappropriate treatment (shorter course of antiviral therapy), may not receive appropriate preventive cirrhosis care, and be at increased risk of progression to hepatic decompensation, and potentially increased morbidity and mortality.
	1 fewer FN in TE (5 more to 9 fewer)		6 fewer FN in TE (30 more to 54 fewer)				
TNs (patients without cirrhosis)	864 (845−874)	580 (503−656)	637 (623−644)	427 (371−483)		⊕⊕⊕◯ Moderate[a] (inconsistency)	TE is superior to FIB-4 for identifying patients who truly do not have cirrhosis. TN may be reassured and obviate the need for invasive testing with liver biopsy, although they may need to undergo repeated assessment of liver stiffness at periodic intervals.
	284 more TN in TE (189 more to 371 more)		210 more TN in TE (140 more to 273 more)				
FPs (patients incorrectly classified as having cirrhosis)	86 (76−105)	370 (294−447)	63 (56−77)	273 (217−329)			TE is superior to FIB-4, with lower rates of misclassifying patients without cirrhosis as having cirrhosis. FP may receive unnecessary testing (HCC surveillance, immunization) and treatment (longer course of anti-viral therapy) and have avoidable anxiety, potential testing- or treatment-related complications, and excessive resource utilization.
	284 fewer FP in TE (189 fewer to 371 fewer)		210 fewer FP in TE (140 fewer to 273 fewer)				

TE, transient elastography.
[a]High heterogeneity, with wide range of liver stiffness cutoffs.
[b]Overlapping confidence intervals for rates of TP and FN.

evidence supporting the use of VCTE over APRI or FIB-4 for detection of cirrhosis was rated as moderate quality.

Discussion. Pretreatment assessment of fibrosis stage is important to facilitate appropriate HCV treatment decisions and determine need for additional measures for managing cirrhosis, such as HCC surveillance.[37] While nonproprietary, inexpensive, serum-based fibrosis markers like APRI and FIB-4 are readily available, their diagnostic performance was suboptimal in both low- and high-prevalence scenarios, with high FP rates for detection of cirrhosis. This may result in avoidable patient anxiety and unnecessary testing and treatment. There was moderate certainty in the observation that VCTE has superior diagnostic performance in identifying cirrhosis in patients with HCV, with lower rates of misclassification of patients. We did not factor in cost-effectiveness of VCTE vs serum-based fibrosis markers, given rapidly changing prices of antiviral therapy, which may offset cost-to-benefit assessments.

Question 2. In adults with chronic HCV undergoing VCTE, at what liver stiffness cutoff, can we accurately diagnose cirrhosis (and initiate downstream management), obviating the need for liver biopsy?

Key message. In adults with chronic HCV, we can accurately diagnose cirrhosis (and initiate downstream management) with VCTE-defined liver stiffness of ≥12.5 (±1) kPa, with acceptable FP and FN rates. (***Low quality of evidence***).

Effect estimates. We updated an existing systematic review, to identify a range of liver stiffness cutoffs (9.2−26.5 kPa) corresponding to optimal sensitivity and specificity for diagnosis of cirrhosis in adults with HCV. From this, we identified a narrow range of liver stiffness cutoff, 12.5 (±1) kPa, which corresponded to the most commonly observed value in included studies (17 studies, 5812 patients), and corresponding to value most commonly applied in clinical trials and practice.[38−53] Supplementary Table 1 describes the characteristics of these included studies, and Supplementary Figures 1*A* and *B* report the sensitivity and specificity of this cutoff. The performance of this cutoff in low- and high-risk populations is shown in Table 5. In an illustrative low-risk population (5% prevalence of cirrhosis), for example, patients with HCV detected in primary care clinics during routine age-appropriate screening, using a cutoff of 12.5 (±1) kPa may misclassify 0.7% patients as not having cirrhosis (FN) and 8.6% patients as having cirrhosis (FP). In an illustrative high-risk population (30% prevalence of cirrhosis), for example, HCV patients with obesity, diabetes, excessive alcohol use, or co-infection with HIV or HBV, using a cutoff of 12.5 (±1) kPa may misclassify 4.2% as not having cirrhosis (FN) and 6.3% patients as having cirrhosis (FP).

Quality of evidence. The evidence supporting the use of this cutoff was derived from cross-sectional diagnostic accuracy studies, and there were no data on comparing different cutoffs and their effect on downstream patient-important outcomes related to impact of cirrhosis diagnosis (or misdiagnosis). Therefore, due to use of FP and FN as surrogates for presumed downstream consequences, and because the cutoff was largely obtained from post-hoc analysis corresponding to AUROC, the overall body of evidence was rated down for indirectness. Because we selectively included only studies that identified a cutoff of 12.5 (±1) kPa, and excluded studies in which the optimal cutoff was higher or lower (in which the diagnostic performance corresponding to a cutoff of 12.5 kPa was not reported and conceivably poorer), and because considerable heterogeneity was observed in the pooled sensitivity and specificity corresponding to the identified cutoff, we rated down further for inconsistency. The diagnostic accuracy studies were generally of fair quality, and there was no serious risk of bias. In addition, there was no evidence of serious imprecision and no evidence of publication bias detected. To summarize, using the GRADE approach for using diagnostic accuracy studies for patient management, the quality of evidence supporting the use of VCTE-defined liver stiffness of ≥12.5 (±1) kPa for diagnosis of cirrhosis in adults with HCV was rated as low quality.

Discussion. In the evaluation of patients with HCV, the stage of disease and the ability to detect cirrhosis is critical. While fibrosis stage at which antiviral therapy should be initiated is still in flux with the introduction of highly effective but expensive direct-acting antiviral agents, patients with advanced fibrosis/compensated cirrhosis definitely require antiviral treatment to prevent progression (and potential fibrosis regression); additionally, the presence of cirrhosis may extend treatment duration with some regimens.[37] Patients with cirrhosis will also need close surveillance for complications of portal hypertension and HCC even after cure of HCV cirrhosis.[54] As mentioned earlier, in using VCTE as strategy to replace liver biopsy, health care providers and patients need to be aware of test performance and be comfortable with potential FN and FP rates with attending downstream consequences. A priori, the maximal tolerable FN rate accepted by the Technical Review and Guideline Content Expert Panel was 5%−10%, that is, the test threshold would be acceptable if <10% of patients are misclassified as not having cirrhosis. With the use of this VCTE-defined liver stiffness cutoff of 12.5 (±1) kPa, we estimated that >85% of patients would be able to avoid liver biopsy with correct classification of either having or not having cirrhosis. Importantly, we observed that with this cutoff, <1% and <5% of low- and high-risk patients, respectively, may be falsely reassured (of not having cirrhosis; FN rate), potentially may not receive adequate duration of treatment course and be at-risk of treatment failure, may not receive supportive cirrhosis and consequently, and may be at increased risk of hepatic decompensation. Additionally, with this cutoff, <10% of patients without cirrhosis, in both low- and high-risk populations, may be falsely diagnosed as having cirrhosis, and receive unnecessary tests (like surveillance for HCC) and treatment (longer antiviral therapy), and have anxiety, testing-, and treatment-related complications, and lead to excessive

Table 5. Grading of Recommendations Assessment, Development and Evaluation Evidence Profiles for Clinical Question #2 on the Performance of Transient Elastography Threshold of 12.5 (±1) kPa for the Diagnosis of Cirrhosis and Anticipated Downstream Consequences in Patients with Hepatitis C Virus

PICO 2. In adults with HCV undergoing VCTE, at what liver stiffness cutoff, can we accurately diagnose cirrhosis, obviating the need for liver biopsy?
Population/setting: Adults with hepatitis C—high-risk population (HCV with excessive alcohol use, obesity, diabetes, co-infection with HIV/HBV) with estimated cirrhosis prevalence of 30%; low-risk population with estimated cirrhosis prevalence of 5%.
Pooled sensitivity VCTE with cutoff 12.5 (±1) kPa: 0.86 (95% CI, 0.83−0.88). Pooled specificity VCTE with cutoff 12.5 (±1) kPa: 0.91 (95% CI, 0.89-0.92).
Selection of VCTE cutoff: the VCTE cutoff was determined by eliciting a maximal tolerable FN rate through a clinically fully contextualized, prespecified survey (see Supplementary Material).
Reference test: Adequate liver biopsy specimen; ≥1.5 cm and ≥6 portal tracts.

Test result	No. of results per 1000 patients tested (95% CI)		No. of studies/ participants	Quality of the evidence (GRADE)	Comments
	Low-risk (prevalence 5%)	High-risk (prevalence 30%)			
TPs (patients with cirrhosis)	43 (42−44)	258 (249−264)	17/5812	⊕⊕◯◯ Low[a,b] (inconsistency, indirectness)	Detection of TP with VCTE may lead to priority treatment allocation and preventive cirrhosis care (HCC surveillance, immunizations), and may reduce morbidity and mortality. TPs will have further testing which may increase anxiety. By avoiding liver biopsy, these patients would avoid potential complications of liver biopsy, eg, pain, bleeding
FNs (patients incorrectly classified as not having cirrhosis)	7 (6−8)	42 (36−51)			FN may be falsely reassured, receive inappropriate treatment (shorter course of antiviral therapy), may not receive appropriate preventive cirrhosis care, and be at increased risk of progression to hepatic decompensation, and potentially increased morbidity and mortality. This potential underdiagnosis may have been avoided if all patients had undergone liver biopsy instead of VCTE, but that would put patients at risk for liver biopsy-related complications.
TNs (patients without cirrhosis)	864 (845−874)	637 (623−644)			TN may be reassured and obviate the need for invasive testing with liver biopsy (and potential complications related to it), although they may need to undergo repeated assessment of liver stiffness at periodic intervals.
FPs (patients incorrectly classified as having cirrhosis)	86 (76−105)	63 (56−77)			FP may receive unnecessary testing (HCC surveillance, immunization) and treatment (longer course of antiviral therapy) and have avoidable anxiety, potential testing- or treatment-related complications and excessive resource utilization. This potential overdiagnosis may have been avoided if all patients had undergone liver biopsy instead of VCTE, but that would put patients at risk for liver biopsy-related complications.

[a]High heterogeneity, selective inclusion of studies corresponding to cutoff of 12.5 (±1) kPa.
[b]Surrogate patient-important outcomes (FP, FN are surrogates for presumed downstream consequences on patient-important outcomes), no predetermined liver stiffness cutoff, which was determined post-hoc in individual studies, corresponding to AUROC.

burden on resource utilization. Due to the convenience of a noninvasive test, serial testing on a periodic basis may improve the classification of patients with HCV. Liver biopsy may be needed in case there is discrepancy between physician gestalt (based on clinical scenario, imaging such as computed tomography or ultrasound and biochemical markers) and VCTE findings.

Question 3. In adults with chronic 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 (F3 or F4) and consider discharging patients from a dedicated liver clinic?

Key message. In adults with chronic HCV who have achieved SVR with antiviral therapy, we can accurately rule out advanced fibrosis (F3 and F4) with post-treatment VCTE-defined liver stiffness of ≤9.5 (±1) kPa, with acceptable FN rates, and consider discharge from dedicated liver clinic, particularly those at lower risk. (***Very low quality of evidence***).

Effect estimates. We updated an existing systematic review to identify a narrow range of liver stiffness cutoffs, 9.5 (±1) kPa, which corresponded to the most commonly observed liver stiffness value for detection of advanced fibrosis or cirrhosis (13 studies, 4106 patients), and corresponding to the value most commonly applied in clinical practice.[39,42,48,50,51,53,55–61] Supplementary Table 2 describes the characteristics of these included studies, and Supplementary Figures 2*A* and *B* report the sensitivity and specificity of this cutoff. The performance of this cutoff in low- and high-risk populations is shown in Table 6. In an illustrative low-risk population (5% prevalence of advanced fibrosis), for example, patients with HCV who achieve SVR and have no ongoing risk factors for CLDs, using a cutoff of ≤9.5 (±1) kPa may misclassify 1.1% patients as not having advanced fibrosis (FN). Although the FP rate will be high with such a sensitive cutoff, the goal is to exclude significant fibrotic liver disease, and serial examinations over time may reduce this FP rate. In a high-risk population (30% prevalence of advanced fibrosis), for example, HCV patients who achieve SVR but either had cirrhosis (liver stiffness >12.5 kPa) before therapy or continue to have other risk factors for CLDs, such as obesity, diabetes, excessive alcohol use, or co-infection with HIV or HBV, using a cutoff of ≤9.5 (±1) kPa may misclassify 6.6% patients as not having advanced fibrosis (FN).

Quality of evidence. As with most evidence on diagnostic performance of different VCTE-derived liver stiffness cutoffs, the evidence supporting the use of this cutoff was derived from cross-sectional diagnostic accuracy studies in all patients with HCV, regardless of treatment, as opposed to studies specifically conducted in patients who achieve SVR after antiviral therapy. Additionally, there were no data on comparing different cutoffs (which were derived from post-hoc analysis corresponding to AUROC) and their effect on downstream patient-important outcomes related to impact of advanced fibrosis diagnosis (or misdiagnosis). Therefore, the overall body of evidence was rated down twice for very serious indirectness. Because we selectively included only studies that identified a cutoff of 9.5 (±1) kPa, and because considerable heterogeneity was observed in the pooled sensitivity and specificity corresponding to the identified cutoff, we rated down further for inconsistency. There was no evidence of serious risk of bias or serious imprecision, and no evidence of publication bias was observed. To summarize, using the GRADE approach for using diagnostic accuracy studies for patient management, the quality of evidence supporting the use of VCTE-defined liver stiffness of ≤9.5 (±1) kPa for ruling out advanced fibrosis in adults with HCV who have achieved SVR was rated as very low quality.

Discussion. With recommendations for universal screening for hepatitis C for persons born between 1945 and 1965, availability of effective antiviral therapies, tremendous numbers of patients are seeking care and being cured of HCV. For these cured patients, health care providers will need to decide whether or not they need ongoing care for their liver. This decision to discharge patients from hepatitis C care can be very meaningful to patients (who can put HCV behind them) and health care providers (to improve access to other patients to receive care for HCV). The American Association for the Study of Liver Diseases/Infectious Diseases Society of America guidance recommends ongoing care and surveillance for complications of portal hypertension and HCC in patients with advanced fibrosis (F3–4), and no further follow-up for patients for early fibrosis (F0–F2).[37] The technical review team decided that it may be appropriate to discharge patients from the liver clinic if there was no evidence of advanced fibrosis on liver biopsy after SVR. However, because repeat liver biopsy after achieving SVR is not feasible or universally acceptable, VCTE-defined liver stiffness may help make decisions regarding discharging patients after treatment for HCV. The maximal tolerable predefined FN rate accepted on by the Technical Review and Guideline Content Expert Panel was 1%–5%, that is, the test threshold would be acceptable if <5% of patients are misclassified as not having advanced fibrosis and are discharged from clinic. With a cutoff of ≤9.5 (±1) kPa, >80% and >60% of low-risk and high-risk patients, respectively, without advanced fibrosis may be considered for discharge from a dedicated liver clinic after achieving SVR with antiviral therapy, without increased risk of patient morbidity and mortality, and decreasing health care utilization and burden. Although approximately 1% of low-risk patients may be misclassified as not having advanced fibrosis using this cutoff, approximately 7% of high-risk patients (more than the maximal tolerable FN rate) may be falsely reassured and 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. However, despite this higher rate, it is expected that most misclassifications will occur by missing some patients with stage F3 fibrosis, but

Table 6. Grading of Recommendations Assessment, Development and Evaluation Evidence Profiles for Clinical Question #3 on the Performance of Transient Elastography Threshold of 9.5 (±1) kPa for the Diagnosis of Advanced Fibrosis and Anticipated Downstream Consequences in Patients with Hepatitis C Virus Who Achieve Sustained Virologic Response After Treatment

PICO 3. In adults with HCV, can VCTE-defined liver stiffness cutoff ≤9.5 kPa accurately rule out advanced fibrosis, so patient may be discharged from a dedicated liver clinic?
Population/setting: Adults with hepatitis C—high-risk population (HCV patients who have achieved SVR with antiviral therapy, with ongoing risk factors for liver disease, ie, excessive alcohol use, obesity, diabetes, co-infection with HIV/HBV) with estimated advanced fibrosis prevalence of 30%; low-risk population with estimated advanced fibrosis prevalence of 5%.
Pooled sensitivity VCTE with cutoff 9.5 (±1) kPa: 0.78 (95% CI, 0.75–0.81). Pooled specificity VCTE with cutoff 9.5 (±1) kPa: 0.86 (95% CI, 0.84–0.88).
Selection of VCTE cutoff: the VCTE cutoff was determined by eliciting a maximal tolerable FN rate through a clinically fully contextualized, prespecified survey (see Supplementary Material).
Reference test: Adequate liver biopsy specimen; ≥1.5 cm and ≥6 portal tracts.

Test result	No. of results per 1000 patients tested (95% CI)		No. of studies/ participants	Quality of the evidence (GRADE)	Comments
	Low-risk (prevalence 5%)	High-risk (prevalence 30%)			
TPs (patients with advanced fibrosis)	39 (38–41)	234 (225–243)	13/4106	⊕○○○ Very low[a,b] (inconsistency, very serious indirectness)	TP will have further follow-up in dedicated liver clinic. Detection of TP would lead to continuation of preventive cirrhosis care (HCC surveillance) and may reduce morbidity and mortality. TP may experience excessive resource utilization and anxiety.
FNs (patients incorrectly classified as not having advanced fibrosis)	11 (9–12)	66 (57–75)			FN may be falsely reassured and discharged from dedicated liver clinic, and may not receive appropriate preventive cirrhosis care, and be at increased risk of progression to hepatic decompensation, and potentially increased morbidity and mortality.
TNs (patients without advanced fibrosis)	817 (798–836)	602 (588–616)			TN would be discharged from dedicated liver clinic, and may not need ongoing preventive cirrhosis care. TN may still be at low risk for liver-related events.
FPs (patients incorrectly classified as having advanced fibrosis)	133 (114–152)	98 (84–112)			FP will receive continued care in dedicated liver clinic, receiving unnecessary testing (HCC surveillance) and have avoidable anxiety, potential testing-related complications and excessive resource utilization.

[a]High heterogeneity, selective inclusion of studies corresponding to cutoff of 9.5 (±1) kPa.
[b]Diagnostic performance inferred from studies in the general population with HCV with or without therapy, rather than studies in patients who achieved SVR; surrogate patient-important outcomes (FP, FN are surrogates for presumed downstream consequences on patient-important outcomes), no predetermined liver stiffness cutoff, which was determined post-hoc in individual studies, corresponding to AUROC.

likely very few or no patients with cirrhosis will be discharged. Any decision to discharge patients from a dedicated liver clinic would require consideration of other factors, such as co-existing liver diseases or ongoing abnormal liver tests. It is important to note that quality of evidence supporting this observation was very low and further research is needed in this area.

Question 4. In adults with chronic HBV, is the overall diagnostic performance of VCTE superior to other noninvasive markers of liver fibrosis (APRI, FIB-4) for detection of cirrhosis?

Key message. In adults with chronic HBV, VCTE has superior sensitivity and specificity, and lower FP and FN rates, suggesting superior diagnostic performance, as compared to APRI and FIB-4 for detection of cirrhosis. (***Low quality of evidence***).

Effect estimates. We used an existing well-conducted systematic reviews on the diagnostic performance of noninvasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with CLD.[36,62] This systematic review included 19 studies in patients with HBV, which reported on the diagnostic performance of VCTE for detection of cirrhosis using liver biopsy as a reference standard. In these studies, the liver stiffness cutoff corresponding to AUROC ranged from 9.4 to 16.0 kPa. The summary sensitivity and specificity for detection of cirrhosis across this range of cutoffs was 0.86 (95% CI, 0.79−0.91) and 0.85 (95% CI, 0.78−0.89), respectively. The evidence profiles are summarized in Tables 7 and 8. Based on this, VCTE classified more patients correctly as compared to APRI (low cutoff) with higher rates of TP and TN, and lower rates of FP and FN, although these estimates were imprecise in worst-performance scenarios. VCTE's diagnostic performance was comparable with FIB-4 (low cutoff) for diagnosing cirrhosis, but was superior to FIB-4 in ruling out cirrhosis.

Quality of evidence. Similar to studies on diagnostic performance of VCTE in HCV, studies were not deemed to be at serious risk of bias and there was no evidence of indirectness. Considerable heterogeneity was observed and there was a wide range "ideal" cutoffs for VCTE (corresponding to AUROC), rather than prespecified cutoffs for detection of cirrhosis and, therefore, evidence was rated down for inconsistency. In the comparison of VCTE vs APRI, there was evidence of serious imprecision for both ruling in and ruling cirrhosis, whereas in the comparison of VCTE vs FIB-4, there was evidence of serious imprecision for ruling in, but not ruling out, cirrhosis in worst-performance scenarios. To summarize, using the GRADE approach for diagnostic accuracy studies, the overall quality of evidence supporting the use of VCTE over APRI or FIB-4 for detection of cirrhosis, was rated as low quality.

Discussion. While several management decisions in patients with HBV are determined by host or virus-related characteristics, fibrosis assessment may be important for a subset of patients who do not meet criteria for antiviral treatment based on other characteristics.[63] However, given the risks and burden of liver biopsies, overall adherence to perform biopsy where indicated is low due to both physician- and patient-related factors[64]; noninvasive testing may help overcome this barrier. Among noninvasive tests, we identified that low-quality evidence supported the use of VCTE over other noninvasive serum-based fibrosis markers, with lower rates of false positivity (ie, risk of falsely classifying patients as having cirrhosis and initiating lifelong therapy), although rates of FN were comparable with FIB-4.

Question 5. In adults with chronic HBV undergoing VCTE, at what liver stiffness cutoff can we accurately diagnose cirrhosis (and initiate downstream management), obviating the need for liver biopsy?

Key message. In adults with chronic HBV, we can accurately diagnose cirrhosis (and initiate downstream management) with VCTE-defined liver stiffness of ≥11.0 (±1) kPa, with acceptable FP and FN rates. (***Low quality of evidence***).

Effect estimates. We updated an existing systematic review to identify a range of liver stiffness cutoffs (8.4−18.2 kPa) corresponding to optimal sensitivity and specificity for diagnosis of cirrhosis in adults with HBV. From this, we identified a narrow range of liver stiffness cutoffs, 11.0 (±1) kPa, which corresponded to the most commonly observed value in included studies (17 studies, 4864 patients).[39,57,65−79] Supplementary Table 3 describes the characteristics of these included studies, Supplementary Figures 3*A* and *B* report the sensitivity and specificity of this cutoff. The performance of this cutoff in low- and high-risk populations is shown in Table 9. In an illustrative low-risk population (5% prevalence of cirrhosis), for example, patients with HBV detected during routine screening with low HBV viral load, using a cutoff of ≥11.0 (±1) kPa may misclassify 0.9% patients as not having cirrhosis (FN), and 16.1% patients as having cirrhosis (FP). In an illustrative high-risk population (30% prevalence of cirrhosis), for example, HBV patients with obesity, diabetes, excessive alcohol use, or co-infection with HIV or HCV, using a cutoff of ≥11.0 (±1) kPa may misclassify 5.7% patients as not having cirrhosis (FN) and 11.9% patients as having cirrhosis (FP).

Quality of evidence. Similar to studies related to VCTE in HCV management, the evidence supporting the use of this cutoff was derived from cross-sectional diagnostic accuracy studies. FP and FN rates were used as surrogates for presumed patient-important downstream consequences, and cutoffs were largely obtained from post-hoc analysis corresponding to AUROC, and selective cutoff of ≥11.0 (±1) kPa was chosen as being most representative. For these reasons, evidence was rated down for imprecision and inconsistency. There was no evidence of serious risk of bias or serious imprecision, and no evidence of publication bias

Table 7. Grading of Recommendations Assessment, Development and Evaluation Evidence Profiles for Clinical Question #4 on the Comparative Diagnostic Performance of Transient Elastography vs Aspartate Aminotransferase to Platelet Ratio Index for the Diagnosis of Cirrhosis in Adults with Hepatitis B Virus

PICO 4A. Should TE vs APRI be used to diagnose cirrhosis in adults with chronic hepatitis B?
Population/setting: Adults with hepatitis B—high-risk population (HBV with excessive alcohol use, obesity, diabetes, co-infection with HIV/HCV) with estimated cirrhosis prevalence of 30%; low-risk population with estimated cirrhosis prevalence of 5%.
New test: TE-derived liver stiffness, cutoff range: 9.4−16.0 kPa (sensitivity, 0.86; 95% CI, 0.79−0.91; specificity, 0.85; 95% CI, 0.78−0.89).
Comparison test: APRI, low cutoff: 1.0 (sensitivity, 0.66; 95% CI, 0.47−0.85; specificity, 0.74; 95% CI, 0.56−0.84).
Reference test: Adequate liver biopsy specimen; ≥1.5 cm and ≥6 portal tracts.

	No. of results per 1000 patients tested (95% CI)						
	Low-risk (prevalence 5%)		High-risk (prevalence 30%)				
Test result	TE	APRI	TE	APRI	No. of studies	Quality of the evidence (GRADE)	Comments
TPs (patients with cirrhosis)	43 (40−46)	33 (24−43)	258 (237−273)	198 (141−255)	VCTE, 19 APRI, 5	⊕⊕○○ Low[a,b] (inconsistency, imprecision)	TE may be superior to APRI for identifying patients who truly have cirrhosis. Detection of TP may lead to treatment prioritization (in patients with compensated cirrhosis who do not meet other criteria for treatment) and preventive cirrhosis care (HCC surveillance for selected patients, immunizations), and may reduce morbidity and mortality. TPs will have further testing, which may increase anxiety.
	10 more TP in VCTE (3 fewer to 22 more)		60 more TP in VCTE (18 fewer to 132 more)				
FNs (patients incorrectly classified as not having cirrhosis)	7 (4−10)	17 (7−26)	42 (27−63)	102 (45−159)			TE may be superior to APRI, with lower rates of misclassifying patients with cirrhosis as not having cirrhosis. FN may be falsely reassured, may not receive appropriate preventive cirrhosis care, and be at increased risk of progression to hepatic decompensation, and potentially increased morbidity and mortality.
	10 fewer FN in VCTE (3 more to 22 fewer)		60 fewer FN in VCTE (18 more to 132 fewer)				
TNs (patients without cirrhosis)	808 (741−845)	703 (532−798)	595 (546−623)	518 (392−588)		⊕⊕○○ Low[a,b] (inconsistency, imprecision)	TE may be superior to APRI for identifying patients who truly do not have cirrhosis. TN may be reassured and obviate the need for invasive testing with liver biopsy, although they may need to undergo repeated assessment of liver stiffness at periodic intervals.
	105 more TN in VCTE (57 fewer−313 more)		77 more TN in VCTE (42 fewer−231 more)				
FPs (patients incorrectly classified as having cirrhosis)	142 (105−209)	247 (152−418)	105 (77−154)	182 (112−308)			TE may be superior to APRI, with lower rates of misclassifying patients without cirrhosis as having cirrhosis. FP may receive unnecessary testing (HCC surveillance, immunization) and treatment (HBV therapy) and have avoidable anxiety, potential testing- or treatment-related complications and excessive resource utilization.
	105 fewer FP in VCTE (57 more to 313 fewer)		77 fewer FP in VCTE (42 more to 231 fewer)				

TE, transient elastography.
[a]High heterogeneity, with wide range of liver stiffness cutoffs.
[b]Overlapping confidence intervals for rates of TP, FN, TN, and FP.

Table 8. Grading of Recommendations Assessment, Development and Evaluation Evidence Profiles for Clinical Question #4 on the Comparative Diagnostic Performance of Transient Elastography vs Fibrosis-4 Index for the Diagnosis of Cirrhosis in Adults with Hepatitis B Virus

PICO 4B. Should TE vs FIB-4 be used to diagnose cirrhosis in adults with chronic hepatitis B?
Population/setting: Adults with hepatitis B—high-risk population (HBV with excessive alcohol use, obesity, diabetes, co-infection with HIV/HCV) with estimated cirrhosis prevalence of 30%; low-risk population with estimated cirrhosis prevalence of 5%.
New test: TE-derived liver stiffness, cutoff range: 9.4−16.0 kPa (sensitivity, 0.86; 95% CI, 0.79−0.91; specificity, 0.85; 95% CI, 0.78−0.89).
Comparison test: FIB-4l, low cutoff: 0.84−1.05 (sensitivity, 0.87; 95% CI, 0.79−0.92; specificity, 0.65; 95% CI, 0.51−0.73).
Reference test: Adequate liver biopsy specimen; ≥1.5 cm and ≥6 portal tracts.

	No. of results per 1000 patients tested (95% CI)						
	Low-risk (prevalence 5%)		High-risk (prevalence 30%)				
Test result	TE	FIB-4	TE	FIB-4	No. of studies	Quality of the evidence (GRADE)	Comments
TPs (patients with cirrhosis)	43(40−46) 1 fewer TP in VCTE (6 fewer to 6 more)	44 (40−46)	258 (237−273) 3 fewer TP in VCTE (39 fewer to 36 more)	261 (237−276)	VCTE, 19 FIB-4, 4	⊕⊕◯◯ Low[a,b] (inconsistency, imprecision)	TE is comparable with FIB-4 for identifying patients who truly have cirrhosis. Detection of TP may lead to treatment prioritization (in patients with compensated cirrhosis who do not meet other criteria for treatment), preventive cirrhosis care (HCC surveillance for selected patients, immunizations), and may reduce morbidity and mortality. TPs will have further testing which may increase anxiety.
FNs (patients incorrectly classified as not having cirrhosis)	7 (4−10) 1 more FN in VCTE (6 more to 6 fewer)	6 (4−10)	42 (27−63) 3 more FN in VCTE (39 more to 36 fewer)	39 (24−63)			TE is comparable with FIB-4, with lower rates of misclassifying patients with cirrhosis as not having cirrhosis. FN may be falsely reassured, may not receive appropriate preventive cirrhosis care, and be at increased risk of progression to hepatic decompensation, and potentially increased morbidity and mortality.
TNs (patients without cirrhosis)	808 (741−845) 191 more TN in VCTE (47 more to 360 more)	617 (485−694)	595 (546−623) 140 more TN in VCTE (35 more to 266 more)	455 (357−511)		⊕⊕⊕◯ Moderate[a] (inconsistency)	TE is superior to FIB-4 for identifying patients who truly do not have cirrhosis. TN may be reassured and obviate the need for invasive testing with liver biopsy, although they may need to undergo repeated assessment of liver stiffness at periodic intervals.
FPs (patients incorrectly classified as having cirrhosis)	142 (105−209) 191 fewer FP in VCTE (47 fewer to 360 fewer)	333 (256−465)	105 (77−154) 140 fewer FP in VCTE (35 fewer to 266 fewer)	245 (189−343)			TE is superior to FIB-4, with lower rates of misclassifying patients without cirrhosis as having cirrhosis. FP may receive unnecessary testing (HCC surveillance, immunization) and treatment (HBV therapy) and have avoidable anxiety, potential testing- or treatment-related complications and excessive resource utilization.

TE, transient elastography.
[a]High heterogeneity, with wide range of liver stiffness cutoffs.
[b]Overlapping confidence intervals for rates of TP and FN.

Table 9. Grading of Recommendations Assessment, Development and Evaluation Evidence Profiles for Clinical Question #5 on the Performance of Transient Elastography Threshold of 11.0 (±1) kPa for the Diagnosis of Cirrhosis and Anticipated Downstream Consequences in Patients with Hepatitis B Virus

PICO 5. In adults with HBV undergoing VCTE, at what liver stiffness cutoff, can we accurately diagnose cirrhosis, obviating the need for liver biopsy?
Population/setting: Adults with hepatitis B—high-risk population (HBV with excessive alcohol use, obesity, diabetes, co-infection with HIV/HCV) with estimated cirrhosis prevalence of 30%; low-risk population with estimated cirrhosis prevalence of 5%.
Pooled sensitivity VCTE with cutoff 11.0 (±1) kPa: 0.81 (95% CI, 0.79−0.0.84). Pooled specificity VCTE with cutoff 11.0 (±1) kPa: 0.83 (95% CI, 0.82−0.84).
Selection of VCTE cutoff: the VCTE cutoff was determined by eliciting a maximal tolerable FN rate through a clinically fully contextualized, prespecified survey (see Supplementary Material).
Reference test: Adequate liver biopsy specimen; ≥1.5 cm and ≥6 portal tracts.

Test result	No. of results per 1000 patients tested (95% CI)		No. of studies/ participants	Quality of the evidence (GRADE)	Comments
	Low-risk (prevalence 5%)	High-risk (prevalence 30%)			
TPs (patients with cirrhosis)	41 (40−42)	243 (237−252)	17/4864	⊕⊕◯◯ Low[a,b] (inconsistency, Indirectness)	Detection of TP may lead to treatment prioritization (in patients with compensated cirrhosis who do not meet other criteria for treatment) and preventive cirrhosis care (HCC surveillance for selected patients, immunizations), and may reduce morbidity and mortality. TPs will have further testing which may increase anxiety. By avoiding liver biopsy, these patients would avoid potential complications of liver biopsy, eg pain, bleeding.
FNs (patients incorrectly classified as not having cirrhosis)	9 (8−10)	57 (48−63)			FN may be falsely reassured, may not receive appropriate preventive cirrhosis care, and be at increased risk of progression to hepatic decompensation, and potentially increased morbidity and mortality. This potential underdiagnosis may have been avoided if all patients had undergone liver biopsy instead of VCTE, but that would put patients at risk for liver biopsy-related complications.
TNs (patients without cirrhosis)	789 (779−798)	581 (574−588)			TN may be reassured and obviate the need for invasive testing with liver biopsy (and potential complications related to it), although they may need to undergo repeated assessment of liver stiffness at periodic intervals.
FPs (patients incorrectly classified as having cirrhosis)	161 (152−171)	119 (112−126)			FP may receive unnecessary testing (HCC surveillance, immunization) and treatment (HBV therapy) and have avoidable anxiety, potential testing- or treatment-related complications and excessive resource utilization. This potential overdiagnosis may have been avoided if all patients had undergone liver biopsy instead of VCTE, but that would put patients at risk for liver biopsy-related complications.

[a]High heterogeneity, selective inclusion of studies corresponding to cutoff of 11.0 (±1) kPa.
[b]Surrogate patient-important outcomes (FP, FN are surrogates for presumed downstream consequences on patient-important outcomes), no predetermined liver stiffness cutoff, which was determined post-hoc in individual studies, corresponding to AUROC.

was observed. Therefore, using the GRADE approach, the quality of evidence supporting the use of VCTE-defined liver stiffness of ≥11.0 (±1) kPa for diagnosis of cirrhosis in adults with HBV was rated as low quality.

Discussion. Liver stiffness threshold corresponding to cirrhosis seems to vary across the diseases, which could be truly related to differences in underlying disease processes, or may be an artifact of limited prospective research using predefined liver stiffness thresholds to define cirrhosis. While HCC surveillance is required for the majority of patients with HBV regardless of cirrhosis status, the diagnosis of compensated cirrhosis may be useful in identifying patients for antiviral therapy who would do not meet other criteria for receipt of therapy. A priori, the maximal tolerable FN rate accepted by the Technical Review and Guideline Content Expert Panel was 5%−10%, that is, the test threshold would be acceptable if <10% of patients are misclassified as not having cirrhosis. With a cutoff of ≥11.0 (±1) kPa, we estimated that >80% of patients would be able to avoid liver biopsy with correct classification of either having or not having cirrhosis. Approximately 1% and 5% of low- and high-risk patients, respectively, may be falsely reassured (of not having cirrhosis) and be ineligible to receive antiviral therapy, which can decrease risk of decompensation below the predefined maximal tolerable FN rate of 10%; hypothetically, in a setting where the prevalence of cirrhosis in HBV patients is >50%, the threshold FN rate of 10% would be exceeded. In contrast, this threshold carries an FP rate of 16% and 12% for low- and high-risk patients, respectively, wherein these patients without cirrhosis may be falsely diagnosed as having cirrhosis; receive unnecessary tests and treatment (HBV-related therapy, if there are no other indications for treatment); have anxiety, testing- and treatment-related complications; and lead to excessive burden on resource utilization. Due to the convenience of a noninvasive test, serial testing on a periodic basis may improve the classification of patients with HBV. Liver biopsy may be needed in case there is discrepancy between physician gestalt (based on clinical scenario, imaging such as computed tomography or ultrasound and biochemical markers) and VCTE findings.

Question 6. In adults with NAFLD, is the overall diagnostic performance of VCTE (M-mode) superior to other noninvasive markers of liver fibrosis (APRI, FIB-4) for detection of cirrhosis?

Key message. In adults with NAFLD, VCTE (M-mode) has superior sensitivity and specificity, and lower FP and FN rates, suggesting superior diagnostic performance, as compared to APRI and FIB-4 for detection of cirrhosis. (***Very low quality of evidence***).

Effect estimates

We updated an existing well-conducted systematic review on the diagnostic performance of noninvasive tests in patients with CLDs, and identified 11 studies on 1266 patients with NAFLD, which reported on the diagnostic performance of VCTE for detection of cirrhosis using liver biopsy as a reference standard (Supplementary Table 4).[48,80−89] In these studies, the liver stiffness cutoff corresponding to AUROC ranged from 10.3 to 22.3 kPa, and the corresponding summary sensitivity and specificity for detection of cirrhosis across this range of cutoffs was 0.90 (95% CI, 0.82−0.95) and 0.87 (95% CI, 0.85−0.89), respectively (Supplementary Figure 4*A* and *B*). VCTE was compared with performance of FIB-4 and APRI for detection of cirrhosis in NAFLD, derived from another recent systematic review.[90] This is summarized in Tables 10 and 11. Based on this, VCTE classified more patients correctly compared with APRI and FIB-4, with higher rates of TP and TN and lower rates of FP and FN, although these estimates were imprecise in worst-performance scenarios.

Quality of evidence. Studies on diagnostic performance of VCTE in NAFLD were at high risk of bias due to analysis of only patients with successful VCTE, and not an intention-to-diagnose analysis. Unsuccessful or unreliable liver stiffness measurement is high in patients with obesity, in particular those with central adiposity, a population at high-risk for NAFLD. Additionally, several studies on performance of VCTE in patients with suspected NAFLD either excluded obese patients (body mass index ≥30 kg/m^2), or performed only per-protocol diagnosis (excluding patients with unreliable VCTE) contributing to artificially high sensitivity and specificity. Similar to other VCTE studies in HCV and HBV, evidence was rated down for inconsistency. In the comparison of VCTE vs APRI, there was evidence of serious imprecision for both ruling in and ruling out cirrhosis, whereas in the comparison of VCTE vs FIB-4, there was evidence of serious imprecision for ruling in, but not ruling out, cirrhosis in worst-performance scenarios (using lower limit of 95% CI for diagnostic accuracy of VCTE and upper limit of 95% CI of APRI or FIB-4). Therefore, using the GRADE approach for diagnostic accuracy studies, the quality of evidence supporting the use of VCTE over APRI or FIB-4 for detection of cirrhosis was rated as very low quality.

Discussion. NAFLD is estimated to affect about 24% of Americans, and a small proportion of them can progress to cirrhosis.[8,91] Through a systematic review, we identified that although VCTE had superior diagnostic performance compared with APRI and FIB-4, there were limitations in the literature, particularly high rates of unsuccessful or unreliable VCTE readings with M-probe in obese patients and selection bias in studies, excluding obese patients at high risk for NAFLD. In a prospective study, XL probe was able to overcome some limitations of M-probe, with higher rates of successful (95% vs 81%) and reliable (90% vs 74%) liver stiffness measurement.[86] However, even with the XL probe, reliable liver stiffness measurements could be obtained in only 65% of obese patients. In another study of 169 patients with NAFLD, body mass index and waist circumference negatively impacted the diagnostic accuracy of VCTE; in their intention-to-diagnose analysis, the AUROC for diagnosis of advanced fibrosis or cirrhosis with VCTE was 0.65.[92] MRE also has superior diagnostic performance

Table 10. Grading of Recommendations Assessment, Development and Evaluation Evidence Profiles for Clinical Question #6 on the Comparative Diagnostic Performance of Transient Elastography vs Aspartate Aminotransferase to Platelet Ratio Index for the Diagnosis of Cirrhosis in Adults With Nonalcoholic Fatty Liver Disease

PICO 6A. Should TE vs APRI be used to diagnose cirrhosis in adults with NAFLD?
Population/setting: Adults with NAFLD—high-risk population (NAFLD with advanced age, obesity, particularly central adiposity, diabetes, alanine elevated >2× upper limit of normal) with estimated cirrhosis prevalence of 30%; low-risk population with estimated cirrhosis prevalence of 5%.
New test: TE-derived liver stiffness, cutoff range: 10.3–22.3 kPa (sensitivity, 0.90; 95% CI, 0.82–0.95; specificity, 0.87; 95% CI, 0.85–0.89).
Comparison test: APRI, cutoff: 0.50 (sensitivity, 0.78; 95% CI, 0.71–0.99; specificity, 0.71; 95% CI, 0.30–0.93).
Reference test: Adequate liver biopsy specimen; ≥1.5 cm and ≥6 portal tracts.

	No. of results per 1000 patients tested (95% CI)						
	Low-risk (prevalence 5%)		High-risk (prevalence 30%)				
Test result	TE	APRI	TE	APRI	No. of studies	Quality of the evidence (GRADE)	Comments
TPs (patients with cirrhosis)	45 (41–48) 6 more TP in TE (9 fewer to 12 more)	39 (36–50)	270 (246–285) 36 more TP in TE (51 fewer to 72 more)	234 (213–297)	VCTE, 9 APRI, 2	⊕○○○ Very low[a,b,c] (risk of bias, inconsistency, imprecision)	TE may be superior to APRI for identifying patients who truly have cirrhosis. Detection of TP may lead to preventive cirrhosis care (HCC surveillance, immunizations) and may reduce morbidity and mortality. TPs will have further testing which may increase anxiety.
FNs (patients incorrectly classified as not having cirrhosis)	5 (2–9) 6 fewer FN in TE (9 more to 12 fewer)	11 (0–14)	30 (15–54) 36 fewer FN in TE (51 more to 72 fewer)	66 (3–87)			TE may be superior to APRI, with lower rates of misclassifying patients with cirrhosis as not having cirrhosis. FN may be falsely reassured, may not receive appropriate preventive cirrhosis care, and be at increased risk of progression to hepatic decompensation, and potentially increased morbidity and mortality.
TNs (patients without cirrhosis)	827 (808–850) 152 more TN in TE (76 fewer to 365 more)	675 (285–884)	609 (595–627) 112 more TN in TE (56 fewer to 407 more)	497 (210–651)		⊕○○○ Very low[a,b,c] (risk of bias, inconsistency, imprecision)	TE may be superior to APRI for identifying patients who truly do not have cirrhosis. TN may be reassured and obviate the need for invasive testing with liver biopsy, although they may need to undergo repeated assessment of liver stiffness at periodic intervals.
FPs (patients incorrectly classified as having cirrhosis)	123 (100–142) 152 fewer FP in TE (76 more to 365 fewer)	275 (66–665)	91 (73–105) 112 fewer FP in TE (56 more to 407 fewer)	203 (49–490)			TE may be superior to APRI, with lower rates of misclassifying patients without cirrhosis as having cirrhosis. FP may receive unnecessary testing (HCC surveillance, immunization) and have avoidable anxiety, potential testing- or treatment-related complications and excessive resource utilization.

TE, transient elastography.
[a]Spectrum bias with diagnostic accuracy based on only patients with successful VCTE (recognizing high failure rate of VCTE due to high body mass index), rather than intention-to-diagnose analysis
[b]High heterogeneity, with wide range of liver stiffness cutoffs
[c]Overlapping confidence intervals for rates of TP, FN, TN, and FP.

Table 11. Grading of Recommendations Assessment, Development and Evaluation Evidence Profiles for Clinical Question #6 on the Comparative Diagnostic Performance Of Transient Elastography vs Fibrosis-4 Index for the Diagnosis of Cirrhosis in Adults With Nonalcoholic Fatty Liver Disease

PICO 6B. Should TE vs FIB-4 be used to diagnose cirrhosis in adults with NAFLD?
Population/setting: Adults with NAFLD—high-risk population (NAFLD with advanced age, obesity, particularly central adiposity, diabetes, alanine elevated >2× upper limit of normal) with estimated cirrhosis prevalence of 30%; low-risk population with estimated cirrhosis prevalence of 5%.
New test: TE-derived liver stiffness, cutoff range: 10.3–22.3 kPa (sensitivity, 0.90; 95% CI, 0.82–0.95; specificity, 0.87; 95% CI, 0.85–0.89).
Comparison test: FIB-4, cutoff: 1.92 (sensitivity, 0.74; 95% CI, 0.54–0.87; specificity, 0.71; 95% CI, 0.64–0.76).
Reference test: Adequate liver biopsy specimen; ≥1.5 cm and ≥6 portal tracts.

	No. of results per 1000 patients tested (95% CI)						
	Low-risk (prevalence 5%)		High-risk (prevalence 30%)				
Test result	TE	FIB-4	TE	FIB-4	No. of studies	Quality of the evidence (GRADE)	Comments
TPs (patients with cirrhosis)	45 (41–48)	37 (27–44)	270 (246–285)	222 (162–261)	VCTE, 9 FIB-4, 1	⊕○○○ Very low[a,b,c] (risk of bias, inconsistency, imprecision)	TE may be superior to FIB-4 for identifying patients who truly have cirrhosis. Detection of TP may lead to preventive cirrhosis care (HCC surveillance, immunizations) and may reduce morbidity and mortality. TPs will have further testing which may increase anxiety.
	8 more TP in TE (3 fewer to 21 more)		48 more TP in TE (15 fewer to 123 more)				
FNs (patients incorrectly classified as not having cirrhosis)	5 (2–9)	13 (6–23)	30 (15–54)	78 (39–138)			TE may be superior to FIB-4, with lower rates of misclassifying patients with cirrhosis as not having cirrhosis. FN may be falsely reassured, may not receive appropriate preventive cirrhosis care, and be at increased risk of progression to hepatic decompensation, and potentially increased morbidity and mortality.
	8 fewer FN in TE (3 more to 21 fewer)		48 fewer FN in TE (15 more to 123 fewer)				
TNs (patients without cirrhosis)	827 (808–845)	675 (608–722)	609 (595–623)	497 (448–532)		⊕⊕○○ Low[a,b] (risk of bias, inconsistency)	TE may be superior to FIB-4 for identifying patients who truly do not have cirrhosis. TN may be reassured and obviate the need for invasive testing with liver biopsy, although they may need to undergo repeated assessment of liver stiffness at periodic intervals.
	152 more TN in TE (86 more to 237 more)		112 more TN in TE (63 more to 175 more)				
FPs (patients incorrectly classified as having cirrhosis)	123 (105–142)	275 (228–342)	91 (77–105)	203 (168–252)			TE may be superior to FIB-4, with lower rates of misclassifying patients without cirrhosis as having cirrhosis. FP may receive unnecessary testing (HCC surveillance, immunization) and have avoidable anxiety, potential testing- or treatment-related complications and excessive resource utilization.
	152 fewer FP in TE (86 fewer to 237 fewer)		112 fewer FP in TE (63 fewer to 175 fewer)				

TE, transient elastography.
[a]Spectrum bias with diagnostic accuracy based on only patients with successful VCTE (recognizing high failure rate of VCTE due to high body mass index), rather than intention-to-diagnose analysis.
[b]High heterogeneity, with wide range of liver stiffness cutoffs.
[c]Overlapping CIs for rates of TP and FN.

compared with VCTE to detect fibrosis in patients with NAFLD.[81] With several novel pharmacologic therapies in development for patients with NAFLD, significant advances are required in noninvasive assessment of fibrosis in these patients to identify treatment candidates and assess response to therapy.

Question 7. In adults with NAFLD undergoing VCTE, at what liver stiffness cutoff can we accurately diagnose cirrhosis (and initiate downstream management), obviating the need for liver biopsy?

Key message. Given the inherent limitations of the literature on the use of VCTE for fibrosis assessment in patients with NAFLD, the guideline panel and the technical review team decided not to provide pooled estimates, as the evidence would not sufficiently support clinical decision making.

Question 8. In adults with chronic alcoholic liver disease undergoing VCTE, at what liver stiffness cutoff can we accurately diagnose cirrhosis (and initiate downstream management), obviating the need for liver biopsy?

Key message. In adults with chronic alcoholic liver disease, we can accurately diagnose cirrhosis (and initiate downstream management) with VCTE-defined liver stiffness of ≥12.5 (±1) kPa, with acceptable FP and FN rates. (***Low quality of evidence***)

Effect estimates

We updated an existing systematic review to identify a range of liver stiffness cutoffs (7.2−34.9 kPa) corresponding to optimal sensitivity and specificity for diagnosis of cirrhosis in adults with NAFLD based on 14 studies (834 patients).[93] From this, we identified a narrow range of liver stiffness cutoffs, ≥12.5 (±1) kPa, which corresponded to the most commonly observed value in included studies (7 studies, 330 patients).[94−100] Supplementary Table 5 describes the characteristics of these included studies, and Supplementary Figures 5*A* and *B* report the sensitivity and specificity of this cutoff. The performance of this cutoff in low- and high-risk populations is shown in Table 12. In an illustrative low-risk population (5% prevalence of cirrhosis), for example, patients with chronic excessive alcohol use without any other high-risk factors, using a cutoff of ≥12.5 (±1) kPa may misclassify 0.2% patients as not having cirrhosis (FN), and 27.5% patients as having cirrhosis (FP). In an illustrative high-risk population (30% prevalence of cirrhosis), for example, patients with alcoholic liver disease with advanced age, obesity, diabetes, and co-infection with HIV/HBV/HCV, using a cutoff of ≥12.5 (±1) kPa may misclassify 1.5% as not having cirrhosis (FN), and 20.3% patients as having cirrhosis (FP).

Quality of evidence. Similar to prior questions pertaining to VCTE cutoffs for diagnosis of cirrhosis in patients with HCV, the overall body of evidence was rated down for indirectness and inconsistency. Therefore, using the GRADE approach for using diagnostic accuracy studies for patient management, the quality of evidence supporting the use of VCTE-defined liver stiffness of ≥12.5 (±1) kPa for diagnosis of cirrhosis in adults with chronic alcoholic liver disease was rated as low quality.

Discussion. Nonproprietary, serum-based fibrosis markers like APRI and FIB-4 have limited utility in diagnosing cirrhosis in patients with chronic alcoholic liver disease. The number of studies is small, and among these, the performance of these markers was poor. Even for VCTE, timing of assessment of liver stiffness is very important—in the presence of acute alcoholic hepatitis, inflammation would increase liver stiffness and a false elevation in VCTE readings. For patients who have been treated for alcoholic hepatitis or have had a sustained period of sobriety with resulting reduction in inflammation, noninvasive assessment of cirrhosis would be helpful in counseling patients and facilitating appropriate cirrhosis supportive care. A priori, the maximal tolerable FN rate accepted by the Technical Review and Guideline Content Expert Panel was 5%−10%, that is, the test threshold would be acceptable if <10% of patients are misclassified as not having cirrhosis. With a cutoff of ≥12.5 (±1) kPa, we estimated that >70% of asymptomatic patients would be able to avoid liver biopsy with correct classification of either having or not having cirrhosis. Less than 2% of patients with cirrhosis, in both low- and high-risk populations, may be falsely reassured (of not having cirrhosis), and may not receive supportive cirrhosis care. Around 20%−30% of patients without cirrhosis, in both low- and high-risk populations, may be falsely diagnosed as having cirrhosis and receive unnecessary tests (like surveillance for HCC), and have anxiety and testing-related complications, and lead to excessive burden on resource utilization. In the absence of effective directed therapy against alcoholic liver disease, the detection of cirrhosis would not necessarily impact treatment decisions.

Question 9. In adults with suspected compensated cirrhosis undergoing VCTE, at what liver stiffness cutoff can we accurately rule out high-risk EVs, obviating the need for routine endoscopic screening?

Key message. In adults with suspected compensated cirrhosis due to any etiology, we can accurately rule out presence of high-risk EVs (at high risk of bleeding) with VCTE-defined liver stiffness of ≤19.5 (±2) kPa, with acceptable FN rates. (***Low quality of evidence***)

Effect estimates. From a range of liver stiffness cutoffs (14.6−47.2 kPa) reported in 15 studies corresponding to

Table 12. Grading of Recommendations Assessment, Development and Evaluation Evidence Profiles for Clinical Question #8 on the Performance of Transient Elastography Threshold of 12.5 (±1) kPa for the Diagnosis of Cirrhosis and Anticipated Downstream Consequences in Patients With Chronic Alcoholic Liver Disease

PICO 8. 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?
Population/setting: Adults with alcoholic liver disease—high-risk population (chronic alcoholic liver disease with advanced age, obesity, diabetes, co-infection with HIV/HBV/HCV) with estimated cirrhosis prevalence of 30%; low-risk population with estimated cirrhosis prevalence of 5%.
Pooled sensitivity VCTE with cutoff 12.5 kPa: 0.95 (95% CI, 0.87−0.98). Pooled specificity VCTE with cutoff 12.5 kPa: 0.71 (95% CI, 0.56−0.82).
Selection of VCTE cutoff: the VCTE cutoff was determined by eliciting a maximal tolerable FN rate through a clinically fully contextualized, prespecified survey (see Supplementary Material).
Reference test: Adequate liver biopsy specimen; ≥1.5 cm and ≥6 portal tracts.

Test result	No. of results per 1000 patients tested (95% CI)		No. of studies/ participants	Quality of the evidence (GRADE)	Comments
	Low-risk (prevalence 5%)	High-risk (prevalence 30%)			
TPs (patients with cirrhosis)	48 (44−49)	285 (261−294)	7/330	⊕⊕◯◯ Low[a,b] (inconsistency, indirectness)	Detection of TP may lead to preventive cirrhosis care (HCC surveillance, immunizations), potentially enhance motivation to abstain from alcohol and may reduce morbidity and mortality. TPs will have further testing which may increase anxiety. By avoiding liver biopsy, these patients would avoid potential complications of liver biopsy, eg, pain and bleeding.
FNs (patients incorrectly classified as not having cirrhosis)	2 (1−6)	15 (6−39)			FN may be falsely reassured and may not receive appropriate preventive cirrhosis care, and be at increased risk of progression to hepatic decompensation, and potentially increased morbidity and mortality. This potential underdiagnosis may have been avoided if all patients had undergone liver biopsy instead of VCTE, but that would put patients at risk for liver biopsy-related complications.
TNs (patients without cirrhosis)	675 (532−779)	497 (392−574)			TN may be reassured and obviate the need for invasive testing with liver biopsy (and potential complications related to it), although they may need to undergo repeated assessment of liver stiffness at periodic intervals.
FPs (patients incorrectly classified as having cirrhosis)	275 (171−418)	203 (126−308)			FP may receive unnecessary testing (HCC surveillance, immunization) and have avoidable anxiety, potential testing- or treatment-related complications and excessive resource utilization. This potential overdiagnosis may have been avoided if all patients had undergone liver biopsy instead of VCTE, but that would put patients at risk for liver biopsy-related complications.

[a]High heterogeneity, selective inclusion of studies corresponding to cutoff of 12.5 (±1) kPa.
[b]Surrogate patient-important outcomes (FP, FN are surrogates for presumed downstream consequences on patient-important outcomes), no predetermined liver stiffness cutoff, which was determined post-hoc in individual studies, corresponding to AUROC.

optimal sensitivity and specificity to detect high-risk EVs, we identified a narrow range of liver stiffness cutoffs, 19.5 (±2) kPa, which was the most commonly observed value to rule out high-risk EVs (8 studies, 964 patients),[101–108] and similar to cutoffs identified in the recent Baveno VI consensus conference.[109] Supplementary Table 6 describes the characteristics of these included studies, and Supplementary Figures 6*A* and *B* report the sensitivity and specificity of this cutoff. The performance of this cutoff in low- and high-risk populations is shown in Table 13. In an illustrative low-risk population (5% prevalence of high-risk EVs), for example, patients with newly diagnosed compensated cirrhosis based on imaging (liver nodularity on computed tomography, coarse echotexture on ultrasound, or based on VCTE), with platelet count >150,000/μL, using a cutoff of ≤19.5 (±2) kPa may misclassify 0.6% patients as not having high-risk EVs (FN), and 41.8% patients as having high-risk EVs (FP). In an illustrative high-risk population (20% prevalence of high-risk EVs), for example, patients with known compensated cirrhosis with platelet count <150,000/μL, using this cutoff may misclassify 2.2% patients as not having high-risk EVs (FN) and 35.2% patients as having high-risk EVs (FP).

Quality of evidence. The observed prevalence of high-risk EVs was much higher in included studies, which included the entire spectrum of patients with CLDs (including patients with decompensated cirrhosis) compared with values used as illustrative examples (restricted to patients with compensated cirrhosis). Due to use of FP and FN as surrogates for presumed downstream consequences, differences in patient population, post-hoc ascertainment of cutoff, selective use of studies (with reported a cutoff of 19.5 kPa), and considerable heterogeneity in estimates, evidence was rated down for imprecision and indirectness. Therefore, using the GRADE approach, the quality of evidence supporting the use of VCTE-defined liver stiffness of ≤19.5 (±2) kPa to rule out high-risk EVs in adults with compensated cirrhosis was rated as low quality.

Discussion. Current American Association for the Study of Liver Diseases guidelines recommend upper endoscopy in all patients with a new diagnosis of cirrhosis to evaluate for the presence of gastroesophageal varices.[110] While the risk of variceal bleeding is very low in patients with no or small varices, the risk increases significantly in patients with high-risk EVs, such that intervention (primary prophylaxis with nonselective β-blockers) is recommended in these patients. With this knowledge, triaging patients at low risk of harboring high-risk EVs through noninvasive liver stiffness measurement is very appealing, especially as the number of patients diagnosed with cirrhosis increases with rising prevalence of NAFLD, new diagnoses of HCV, and increasing uptake of VCTE to assess liver stiffness and classify patients as having cirrhosis or not. However, health care providers and patients need to be aware of test performance, and be comfortable with potential FN and FP rates with attending downstream consequences. A priori, the maximal tolerable FN rate accepted by the Technical Review and Guideline Content Expert Panel was 1%–5%, that is, the test threshold would be acceptable if <5% of patients are misclassified as not having high-risk EVs. With a cutoff of ≤19.5 (±2) kPa, we estimate that approximately 55% of low-risk patients and 45% of high-risk patients without high-risk EVs may be able to avoid invasive routine testing for high-risk EVs. With this cutoff, <1% of low-risk and <3% of high-risk patients with compensated cirrhosis may be falsely reassured (of not having high-risk EVs), leading to delayed diagnosis and increasing risk of variceal bleeding and associated morbidity and mortality; hypothetically, in a setting where the prevalence of high-risk EVs in patients with compensated cirrhosis is >45%, the maximal tolerable FN rate of 5% would be exceeded. Because VCTE is being proposed as a triage test (to minimize use of an invasive test like upper endoscopy) and not as a test-replacement strategy to esophagogastroduodenoscopy (EGD), patients with liver stiffness >19.5 kPa (both TP and FP) would undergo a confirmatory upper endoscopy to verify diagnosis of high-risk EVs. Therefore, a high FP rate of approximately 40% does not add any additional patient or provider burden or anxiety because routine EGD would have been recommended even if VCTE were not performed. It is important to note that these observations do not apply to patients with decompensated cirrhosis or known EVs and portal hypertension. It should also be mentioned that because patients with no varices or low-risk EVs progress to high-risk EVs gradually over time, serial VCTE assessment at periodic intervals for change in liver stiffness can improve the triage accuracy.

Question 10. In adults with suspected CLDs undergoing elective nonhepatic surgery, at what VCTE-identified liver stiffness cutoff can we accurately rule out clinically significant portal hypertension (identified here by presence of any EVs), potentially minimizing the risk of portal hypertension-related bleeding, obviating the need for routine invasive testing for portal hypertension?

Key message. In adults with suspected CLDs undergoing elective nonhepatic surgery, we can accurately rule out presence of clinically significant portal hypertension (absence of EVs) with VCTE-defined liver stiffness of ≤17.0 (±2) kPa with acceptable FN rates. (***Low quality of evidence***).

Effect estimates. From a range of liver stiffness cutoffs (12.0–27.3 kPa) reported in 17 studies corresponding to optimal sensitivity and specificity to detect any EVs, we identified a narrow range of liver stiffness cutoffs, 17.0 (±2) kPa, which was the most commonly observed value to rule out any EVs (8 studies, 895 patients).[101,106,111–116] Supplementary Table 7 describes the characteristics of these included studies, and Supplementary Figures 7*A* and *B* report the sensitivity and specificity of this cutoff. The performance of this cutoff in very-low-, low-, and high-risk populations is shown in Table 14. In an illustrative very-low-risk population (0.5% prevalence of any EVs), for

Table 13. Grading of Recommendations Assessment, Development and Evaluation Evidence Profiles for Clinical Question #9 on the Performance of Transient Elastography Threshold of 19.5 (±2) kPa for Triaging Patients Having High-Risk Esophageal Varices and Anticipated Downstream Consequences in Patients With Compensated Cirrhosis

PICO 9. In adults with suspected cirrhosis due to CLDs undergoing VCTE, at what liver stiffness cutoff, can we accurately rule out high-risk EVs, obviating the need for routine endoscopic screening?

Population/setting: Adults with CLDs suspected to have cirrhosis, without prior esophageal variceal bleeding—high pretest probability of having high-risk EVs (known compensated cirrhosis, platelet count <150,000/μL) with estimated prevalence of high-risk EVs of 20%; low pretest probability of having high-risk EVs (newly diagnosed compensated cirrhosis either based on cross-sectional imaging, with platelet count >150,000/μL) with estimated prevalence of high-risk EVs of 5%.

Pooled sensitivity VCTE with cutoff 19.5 (±2) kPa: 0.89 (95% CI, 0.84−0.92). Pooled specificity VCTE with cutoff 19.5(±2) kPa: 0.56 (95% CI, 0.52−0.59).

Selection of VCTE cutoff: the VCTE cutoff was determined by eliciting a maximal tolerable FN rate through a clinically fully contextualized, prespecified survey (see Supplementary Material).

Reference test: Upper endoscopy.

Test result	No. of results per 1000 patients tested (95% CI)		No. of studies/ participants	Quality of the evidence (GRADE)	Comments
	Low-risk (prevalence 5%)	High-risk (prevalence 20%)			
TPs (patients with high-risk EVs)	44 (42−46)	178 (168−185)	8/964	⊕⊕◯◯ Low[a,b] (inconsistency, indirectness)	TP may lead to preventive endoscopy for confirmation and initiation of therapy with β-blockers, potentially reducing mortality. TP will have further testing (EGD) and/or intervention, which may lead to side effects.
FNs (patients incorrectly classified as not having high-risk EVs)	6 (4−8)	22 (15−32)			FN may lead to increased risk of variceal bleeding with associated increased mortality due to delayed diagnosis.
TNs (patients without high-risk EVs)	532 (494−565)	448 (416−476)			TN will likely be reassured, avoid an invasive test but may still be retested with VCTE periodically
FPs (patients incorrectly classified as having high-risk EVs)	418 (385−456)	352 (324−384)			FP will likely have further testing (which they anyways would have with current standard of care) and will increase anxiety, complications and resources use.

[a]High heterogeneity, selective inclusion of studies corresponding to cutoff of 19.5 (±2 kPa).

[b]Surrogate patient-important outcomes (FP, FN are surrogates for presumed downstream consequences on patient-important outcomes); no predetermined liver stiffness cutoff, which was determined post-hoc in individual studies, corresponding to AUROC; observed prevalence of high-risk EVs in studies was much higher than that used in illustrative examples (median, 24.7%; range, 10.3%−37%).

Table 14. Grading of Recommendations Assessment, Development and Evaluation Evidence Profiles for Clinical Question #10 on the Performance of Transient Elastography Threshold of 17.0 (±2) kPa for Triaging Patients With Any Esophageal Varices and Anticipated Downstream Consequences in Patients With Suspected Chronic Liver Diseases Undergoing Elective, Nonhepatic Surgery

PICO 10. In adults with CLDs undergoing elective, extrahepatic surgery, at what VCTE-identified liver stiffness cutoff, can we accurately rule out clinically significant portal hypertension (defined as presence of any EVs), minimizing the risk of portal hypertensive bleeding and hepatic decompensation?
Population/setting: Adults with CLDs without decompensated cirrhosis being considered for elective surgery.[a,b,c]
Selection of VCTE cutoff: the VCTE cutoff was determined by eliciting a maximal tolerable FN rate through a clinically fully contextualized, prespecified survey (see Supplementary Material).
Reference test: Upper endoscopy.

	No. of results per 1000 patients tested (95% CI)					
Test result	Very low risk[a] (prevalence 0.5%)	Low-risk[b] (prevalence 5%)	High-risk[c] (prevalence 40%)	No. of studies/ participants	Quality of the evidence (GRADE)	Comments
TPs (patients with any EVs)	4(4−4)	42 (40−44)	332 (320−348)	8/895	⊕⊕◯◯ Low[d,e] (inconsistency, indirectness)	Detection of TP may help risk-stratify patients before elective surgery for shared decision-making, potentially decrease risk of postoperative hepatic decompensation and decrease avoidable mortality and morbidity
FNs (patients incorrectly classified as not having any EVs)	1 (1−1)	8 (6−10)	68 (52−80)			FN may falsely reassure patients and surgeons of safety of elective surgery, and in case they undergo surgery, will be at high risk of hepatic decompensation with attendant morbidity and mortality.
TNs (patients without any EVs)	517 (468−567)	494 (446−542)	312 (282−342)			TN will be reassured, and safely undergo elective surgery with reasonable surgical risk
FPs (patients incorrectly classified as having any EVs)	478 (428−527)	456 (408−504)	288 (258−318)			FP may falsely be considered to have high risk of hepatic decompensation, and be denied elective surgery due to fear of decompensation, leading to anxiety and distress; this may be avoided if confirmatory tests are conducted.

[a]Very-low-risk population (patients with very low risk of cirrhosis but have a recorded diagnosis of CLDs, such patients with prior noncirrhotic HCV who have achieved SVR, noncirrhotic hepatitis B in chronic inactive stage, fatty liver disease based on imaging with normal transaminases and absence of diabetes) with estimated prevalence of any EVs of 0.5%.
[b]Low-risk population (patients at risk for cirrhosis, but without any imaging/biochemical evidence supporting portal hypertension, such as patients with untreated hepatitis C or hepatitis B, excessive alcohol use) with estimated prevalence of any EVs of 5%.
[c]High-risk population (known or suspected compensated cirrhosis) with estimated prevalence of any EVs of 40%.
[d]High heterogeneity, selective inclusion of studies corresponding to cutoff of 17 (±2) kPa;
[e]Surrogate patient-important outcomes (FP, FN are surrogates for presumed downstream consequences on patient-important outcomes); no predetermined liver stiffness cutoff, which was determined post-hoc in individual studies, corresponding to AUROC; observed prevalence of any EVs in studies was much higher than that used in illustrative examples (median, 60%; range, 10%−78.3%).

example, in patients with very low risk of cirrhosis but with a recorded diagnosis of CLDs, patients with prior noncirrhotic HCV who have achieved SVR, noncirrhotic hepatitis B in chronic inactive stage, fatty liver disease based on imaging with normal transaminases, and absence of diabetes, using a cutoff of ≤17.0 (±2) kPa may misclassify 0.1% patients as not having any EVs (FN) and 47.8% patients as having any EVs (FP). In an illustrative low-risk population (5% prevalence of any EVs), for example, patients at risk for cirrhosis, but without any imaging/biochemical evidence supporting portal hypertension, such as patients with untreated hepatitis C or hepatitis B and excessive alcohol use, using a cutoff of ≤17.0 (±2) kPa may misclassify 0.8% patients as not having any EVs (FN) and 45.6% patients as having any EVs (FP). In an illustrative high-risk population (40% prevalence of any EVs), for example, patients with known or suspected compensated cirrhosis, using a cutoff of ≤17.0 (±2) kPa may misclassify 6.8% patients as not having any EVs (FN) and 28.8% patients as having any EVs (FP).

Quality of evidence. Similar to the PICO on liver stiffness cutoff for triaging high-risk EVs, the quality of evidence for this question was rated down for indirectness and inconsistency, and the overall evidence supporting the use of VCTE-defined liver stiffness of ≤17.0 (±2) kPa for triaging patients undergoing elective, extrahepatic surgery to minimize the risk of portal hypertensive bleeding was rated as low quality.

Discussion. Preoperative surgical risk stratification is a common consultation for hepatologists and gastroenterologists before elective, extrahepatic surgery. Besides Child-Pugh score and Model for End-Stage Liver Disease score (which have been validated in patients with known cirrhosis) and specific surgical risk stratification scores, presence or absence of portal hypertension also influences risk of bleeding and postoperative hepatic decompensation.[117,118] For patients and surgeons considering these procedures, the ability to rule out clinically significant portal hypertension is an important issue and, currently, upper endoscopy or measurement of the hepatic venous pressure gradient is considered. In this technical review, we identified a VCTE-defined liver stiffness threshold of 17.0 (±2) kPa corresponding to presence or absence of EVs. A priori, the maximal tolerable FN rate accepted by the Technical Review and Guideline Content Expert Panel was 1%−5%, that is, the test threshold would be acceptable if <5% of patients are misclassified as not having EVs before elective surgery. With this cutoff, 0.1% of very-low- and <1% of low-risk patients may be falsely reassured (of not having clinically significant portal hypertension), which can lead to increased risk of portal hypertensive bleeding and hepatic decompensation after elective surgery; in contrast, among high-risk patients (with known compensated cirrhosis), approximately 7% may be falsely reassured of not having clinically significant portal hypertension, which is above the maximal tolerable FN rate of 5% identified by the expert panel. Because VCTE is being proposed as a triage test (to minimize use of an invasive test like upper endoscopy or hepatic venous wedge pressure measurement) and not as a test-replacement strategy to EGD, patients with liver stiffness >17.0 kPa (both TP and FP) would undergo a confirmatory upper endoscopy to verify diagnosis of any EVs before being deemed high-risk candidates. Therefore, a high FP rate of approximately 30%−50% does not necessarily add any additional patient or provider burden or anxiety, because routine EGD would have been recommended even if VCTE were not performed. With such a high FP rate, Child-Pugh score, Model for End-Stage Liver Disease score, and other presurgical risk stratification scores may continue to be used as part of this clinical evaluation.

Question 11. In adults with chronic HCV, is the overall diagnostic performance of MRE superior to VCTE for detection of cirrhosis?

Key message. In adults with HCV, MRE has little to no increased diagnostic accuracy in identifying cirrhosis in patients who truly have cirrhosis over VCTE, but has lower diagnostic accuracy in ruling out cirrhosis in patients who do not have cirrhosis, over VCTE (***Very low quality of evidence***).

Effect estimates. We did not identify any head-to-head study comparing MRE vs VCTE in adults with HCV. Therefore, we indirectly compared the performance of MRE and VCTE based on well-conducted systematic reviews on the diagnostic performance of MRE and VCTE for assessment of liver fibrosis and cirrhosis in patients with CLDs.[36,119] In a recent pooled analysis of individual participant data (IPD) on the diagnostic performance of MRE, a cutoff of 4.71 had the highest accuracy for detecting cirrhosis in patients with HCV, with summary sensitivity and specificity of 0.94 (95% CI, 0.87−0.97) and 0.81 (95% CI, 0.61−0.98), respectively.[119] In another study-level systematic review of 36 studies of VCTE in patients with HCV, across a liver stiffness cutoff range from 9.2 to 17.3 kPa, the summary sensitivity and specificity for detection of cirrhosis were 0.89 (95% CI, 0.84−0.92) and 0.91 (95% CI, 0.89−0.93), respectively.[36] The evidence profile is summarized in Table 15. Based on this, there was little or no difference between MRE and VCTE in classifying patients correctly as having cirrhosis (TP), but MRE was inferior to VCTE in ruling out cirrhosis (TN) in both low- and high-prevalence populations.

Quality of evidence. All included studies were cross-sectional diagnostic accuracy studies, required <6 months between performance of diagnostic test and gold standard (liver biopsy) minimizing disease progression bias, and generally of fair quality and not at serious risk of bias (spectrum bias, disease progression bias, partial or differential verification bias, adequate blinding of outcome assessors). Evidence was rated down for indirectness, due to: absence of head-to-head comparisons between MRE and VCTE, and differences in study design for estimating diagnostic performance of MRE (pooled analysis of IPD) and VCTE (study-level meta-analysis). Considerable heterogeneity was observed in pooled sensitivity and specificity, and there was a wide range of "ideal" cutoffs for VCTE (corresponding to AUROC), rather than prespecified cutoffs for

Table 15. Grading of Recommendations Assessment, Development and Evaluation Evidence Profiles for Clinical Question #11 on the Comparative Diagnostic Performance of MRE vs VCTE for the Diagnosis of Cirrhosis in Adults With Hepatitis C virus

PICO 11. Should MRE vs VCTE be used to diagnose cirrhosis in adults with chronic hepatitis C?
Population/setting: Adults with hepatitis C—high-risk population (HCV with excessive alcohol use, obesity, diabetes, co-infection with HIV/HBV) with estimated cirrhosis prevalence of 30%; low-risk population with estimated cirrhosis prevalence of 5%.
New test: MRE, cutoff: 4.71 kPa (sensitivity, 0.94; 95% CI, 0.87−0.97; specificity, 0.81; 95% CI, 0.61−0.98).
Comparison test: TE-derived liver stiffness, cutoff range: 9.2−17.3 kPa (sensitivity, 0.89; 95% CI, 0.84−0.92; specificity, 0.91; 95% CI, 0.89−0.92).
Reference test: Adequate liver biopsy specimen; ≥1.5 cm and ≥6 portal tracts.

	No. of results per 1000 patients tested (95% CI)						
	Low-risk (prevalence 5%)		High-risk (prevalence 30%)				
Test result	MRE	TE	MRE	TE	No. of studies	Quality of the evidence (GRADE)	Comments
TPs (patients with cirrhosis)	47 (44−49) 2 more TP in MRE (2 fewer to 7 more)	45 (42−46)	281 (261−291) 14 more TP in MRE (15 fewer to 39 more)	267 (252−276)	MRE, 13 TE, 36	⊕○○○ Very low[a,b,c] (inconsistency, imprecision, indirectness)	MRE may be superior to TE for identifying patients who truly have cirrhosis. Detection of TP may lead to priority treatment allocation, preventive cirrhosis care (HCC surveillance, immunizations) and may reduce morbidity and mortality. TPs will have further testing which may increase anxiety.
FNs (patients incorrectly classified as not having cirrhosis)	3 (1−6) 2 fewer FN in MRE (7 fewer to 2 more)	5 (4−8)	19 (9−39) 14 fewer FN in MRE (39 fewer to 15 more)	33 (24−48)			MRE may be superior to TE, with lower rates of misclassifying patients with cirrhosis as not having cirrhosis. FN may be falsely reassured, receive inappropriate treatment (shorter course of antiviral therapy), may not receive appropriate preventive cirrhosis care, and be at increased risk of progression to hepatic decompensation, and potentially increased morbidity and mortality.
TNs (patients without cirrhosis)	770 (656−836) 94 fewer TN in MRE (218 fewer to 9 fewer)	864 (845−874)	567 (483−616) 70 fewer TN in MRE (161 fewer to 7 fewer)	637 (623−644)		⊕⊕○○ Low[a,c] (inconsistency, indirectness)	TE is superior to MRE for identifying patients who truly do not have cirrhosis. TN may be reassured and obviate the need for invasive testing with liver biopsy, although they may need to undergo repeated assessment of liver stiffness at periodic intervals.
FPs (patients incorrectly classified as having cirrhosis)	180 (114−294) 94 more FP in MRE (9 more to 118 more)	86 (76−105)	133 (84−217) 70 more FP in MRE (7 more to 161 more)	63 (56−77)			TE is superior to MRE, with lower rates of misclassifying patients without cirrhosis as having cirrhosis. FP may receive unnecessary testing (HCC surveillance, immunization) and treatment (shorter course of anti-viral therapy) and have avoidable anxiety, potential testing- or treatment-related complications and excessive resource utilization.

TE, transient elastography.
[a]High heterogeneity, with wide range of liver stiffness cutoffs.
[b]Overlapping CIs for rates of TP, FN, TN, and FP.
[c]No head-to-head comparisons, and diagnostic performance.

detection of cirrhosis, and hence, evidence was rated down for inconsistency. Evidence was also rated down for imprecision in ruling in cirrhosis since VCTE was superior to MRE in the worst-performance scenarios (using lower limit of 95% CI for diagnostic accuracy of MRE, and upper limit of 95% CI of VCTE). Therefore, using the GRADE approach for diagnostic accuracy studies, the overall quality of evidence supporting the use of MRE over VCTE for detection of cirrhosis, was rated as very low quality (very low certainty in the comparative evidence).

Discussion. Based on indirect comparisons, MRE had little to no increased diagnostic accuracy over VCTE in correctly identifying patients with HCV who truly have cirrhosis. In contrast, VCTE was superior to MRE in ruling out cirrhosis in these patients, with lower rates of misclassifying noncirrhotic patients as having cirrhosis, although there was low confidence in the comparative estimates. Study-level diagnostic accuracy meta-analysis of aggregate data tend to overestimate diagnostic performance due to spectrum bias, are more likely to have selective reporting bias, and are limited in ability to identify an optimal diagnostic threshold.[120] In contrast, pooled analysis of IPD is a more robust study design, overcoming several of these limitations and, traditionally, the diagnostic performance in IPD analysis is inferior to that observed in study-level meta-analyses; this may have biased estimates in favor of VCTE. It is important to note that most included studies derived diagnostic accuracy based on the "completer" population, and excluded patients who were unable to successfully undergo diagnostic tests (ie, did not perform intention-to-diagnose analyses). Although failure rate of MRE may be lower than that of VCTE in specific patient populations (eg, obese patients), patient preferences in choosing between MRE and VCTE are not well studied, and can differ—MRE is conducted in a specialist radiology center, whereas VCTE may be performed in the office at point of care; claustrophobia can also be a consideration. Although a formal cost-effectiveness analyses was not performed, it is highly unlikely that MRE would be more cost-effective than VCTE in detection of cirrhosis in patients with HCV, given marginal differences in diagnostic accuracy.

Question 12. In adults with NAFLD, is the overall diagnostic performance of MRE superior to VCTE for detection of cirrhosis?

Key message. In adults with NAFLD, MRE has little to no increased diagnostic accuracy in identifying cirrhosis in patients who truly have cirrhosis over VCTE, but has considerably higher diagnostic accuracy in ruling out cirrhosis in patients who do not have cirrhosis, over VCTE (***Very low quality of evidence***).

Effect estimates. Two head-to-head trials comparing the diagnostic performance of MRE vs VCTE in 246 patients with NAFLD (7.8% with cirrhosis) were identified.[81,121] On pooling these 2 studies, the summary sensitivity and specificity of MRE for detection of cirrhosis (cutoff, 3.4−6.7 kPa) was 0.84 (95% CI, 0.60−0.97) and 0.89 (95% CI, 0.84−0.93), respectively; the corresponding sensitivity and specificity for VCTE (cutoff, 6.9−14.0 kPa) was 0.83 (95% CI, 0.59−0.96) and 0.72 (95% CI, 0.65−0.78), respectively. The evidence profile is summarized in Table 16. Based on this, MRE was superior to VCTE in ruling out cirrhosis (TN) and was comparable with VCTE in classifying more patients correctly as having cirrhosis (TP). Using these estimates for MRE, in an illustrative low-risk population ($\leq$5% prevalence of cirrhosis), for example, patients incidentally noted to have fatty liver on imaging with normal or minimally elevated liver enzymes and typically seen in the primary care clinic, MRE may misclassify 0.8% patients as not having cirrhosis (FN) and 10.5% patients as having cirrhosis (FP); the positive predictive value of MRE would be 29%. In an illustrative high-risk population (30% prevalence of cirrhosis), for example, older NAFLD patients with obesity, particularly central adiposity, diabetes, alanine aminotransferase elevated $>2\times$ upper limit of normal, and typically seen in a referral liver clinic, MRE may misclassify 4.8% patients as not having cirrhosis (FN) and 7.7% patients as having cirrhosis (FP).

Quality of evidence. Both included studies were prospective cross-sectional diagnostic accuracy studies, but only analyzed patients who successfully completed VCTE and MRE; given high failure rate of VCTE in obese patients with NAFLD, evidence was deemed to be at risk of bias. Due to considerable differences in identified cutoffs and heterogeneity observed in sensitivity and specificity, evidence was also rated down for inconsistency. Evidence was also rated down for imprecision in ruling in cirrhosis given considerable overlap in diagnostic performance in the best- and worst-performance scenarios of diagnostic tests. Therefore, using the GRADE approach for diagnostic accuracy studies, the overall quality of evidence supporting the use of MRE over VCTE for detection of cirrhosis in patients with NAFLD was rated as very low quality (very low certainty in the comparative evidence).

Discussion. Based on head-to-head comparisons, MRE was superior to VCTE in ruling out cirrhosis in adults with NAFLD, but offered little to no increased diagnostic accuracy in detecting cirrhosis. Under conditions optimized to improve diagnostic accuracy (as seen in included studies), MRE has a modest positive predictive value, especially in a low prevalence setting; that is, in a setting with cirrhosis prevalence $\leq$5%, only 29% of patients with MRE "positive for cirrhosis" would truly have cirrhosis. This could result in a considerable proportion of patients with positive MRE being classified as having cirrhosis, and potentially cause harm in the form of anxiety and/or subject these patients to invasive testing with liver biopsy. In addition, because the cutoff for identifying cirrhosis with MRE is not well-defined, it can result in site-to-site variability. Unlike HCV, where fibrosis assessment is recommended at diagnosis to guide treatment, there is limited consensus on when fibrosis assessment should be performed in patients suspected of having NAFLD, regardless of modality. For example, current American Gastroenterological Association/American Association for the Study of Liver Diseases/

Table 16. Grading of Recommendations Assessment, Development and Evaluation Evidence Profiles for Clinical Question #12 on the Comparative Diagnostic Performance of MRE vs VCTE for the Diagnosis of Cirrhosis in Adults With Nonalcoholic Fatty Liver Disease

PICO 12. Should MRE vs TE be used to diagnose cirrhosis in adults with NAFLD?
Population/setting: Adults with NAFLD—high-risk population (NAFLD with advanced age, obesity, particularly central adiposity, diabetes, alanine elevated >2× upper limit of normal; typically seen in a referral liver clinic) with estimated cirrhosis prevalence of 30%; low-risk population with estimated cirrhosis prevalence of ≤5% (normal liver enzymes, steatosis on imaging; typically seen in primary care clinic).
New test: MRE-derived liver stiffness, cutoff range: 3.4−6.7 kPa (sensitivity, 0.84; 95% CI, 0.60−0.97; specificity, 0.89; 95% CI, 0.84−0.93).
Comparison test: TE-derived liver stiffness, cutoff range: 6.9−14.0 kPa (sensitivity, 0.83; 95% CI, 0.59−0.96; specificity, 0.72; 95% CI, 0.65−0.78).
Reference test: Adequate liver biopsy specimen; ≥1.5 cm and ≥6 portal tracts.

	No. of results per 1000 patients tested (95% CI)						
	Low-risk (prevalence 5%)		High-risk (prevalence 30%)				
Test result	MRE	TE	MRE	TE	No. of studies	Quality of the evidence (GRADE)	Comments
TPs (patients with cirrhosis)	42 (30−49) 0 fewer TP in MRE (18 fewer to 19 more)	42 (30−48)	252 (180−291) 3 more TP in MRE (108 fewer to 114 more)	249 (177−288)	MRE, 2 TE, 2 (only head-to-head comparative studies)	⊕○○○ Very low[a,b,c] (risk of bias, inconsistency, imprecision)	MRE is comparable with TE for identifying patients who truly have cirrhosis. Detection of TP may lead to preventive cirrhosis care (HCC surveillance, immunizations) and may reduce morbidity and mortality. There are currently no definitive therapies for NAFLD. TPs will have further testing, which may increase anxiety.
FNs (patients incorrectly classified as not having cirrhosis)	8 (1−20) 0 fewer FN in MRE (19 fewer to 18 more)	8 (2−20)	48 (9−120) 3 fewer FN in MRE (114 fewer to 108 more)	51 (12−123)			MRE is comparable with TE, with lower rates of misclassifying patients with cirrhosis as not having cirrhosis. FN may be falsely reassured, may not receive appropriate preventive cirrhosis care, and be at increased risk of progression to hepatic decompensation, and potentially increased morbidity and mortality. However, there are currently no definitive therapies for NAFLD that these patients may be at risk for missing.
TNs (patients without cirrhosis)	845 (798−884) 161 more TN in MRE (57 more to 267 more)	684 (617−741)	623 (588−651) 119 more TN in MRE (44 more to 196 more)	504 (455−546)		⊕⊕○○ Low[a,b] (risk of bias, inconsistency)	MRE may be superior to TE for identifying patients who truly do not have cirrhosis. TN may be reassured and obviate the need for invasive testing with liver biopsy, although they may need to undergo repeated assessment of liver stiffness at periodic intervals.
FPs (patients incorrectly classified as having cirrhosis)	105 (66−152) 161 fewer FP in MRE (267 fewer to 57 fewer)	266 (209−333)	77 (49−112) 119 fewer FP in MRE (196 fewer to 42 fewer)	196 (154−245)			MRE may be superior to TE, with lower rates of misclassifying patients without cirrhosis as having cirrhosis. FP may receive unnecessary testing (HCC surveillance, immunization) and have avoidable anxiety, potential testing- or treatment-related complications and excessive resource utilization.

TE, transient elastography.
[a]Spectrum bias with diagnostic accuracy based on only patients with successful TE or MRE (recognizing high failure rate of TE due to high body mass index), rather than intention-to-diagnose analysis.
[b]High heterogeneity, with wide range of liver stiffness cutoffs.
[c]Overlapping confidence intervals for rates of TP, FN, TN, and FP.

American College of Gastroenterology guidelines on NAFLD recommend against liver biopsy in asymptomatic patients with unsuspected hepatic steatosis with normal liver biochemistry; for these patients at very low risk of having cirrhosis, positive predictive value with MRE will be very low, resulting in significant misclassification.[122] To augment diagnostic performance and interpretability of MRE (and minimize rates of FN and FP), a more accurate risk stratification scheme to identify patients at high risk of progression to liver-related complications is warranted. Currently, treatment options that can favorably modify the natural history in patients with NAFLD are very limited; as effective therapies become available, thresholds for acceptable misclassification of cirrhosis with noninvasive imaging modalities may change.

Key Aspects in Interpreting the Technical Review

This technical review provides a somewhat different approach to analyzing VCTE performance in clinical practice when compared with narrative reviews in the field so far. Firstly, we do not provide a table that aligns the kPa values with fibrosis stage (F0 to F4). The reason is that by doing so, we would ignore that a specific kPa value/fibrosis stage pair is associated with defined FN and FP rates, and although lowering kPa thresholds decreases the FN rate, it will invariably increase the FP rates. Rather, clinical goals should guide the threshold-setting procedure.

Secondly, we provide thresholds for maximal tolerable FN rates in different patient-management scenarios, and these were based on predefined, best consensus judgment of clinical content experts. However, acceptable thresholds for maximal tolerable FN rates can vary from practitioner to practitioner when discussing diagnostic approaches with patients (some may have lower tolerance of FNs and others higher tolerance), depending on patients' values and preferences and subtle variations in clinical scenarios. Therefore, eliciting patient's values and preferences and tolerance for test inaccuracies is important and requires appropriate contextualization depending on clinical practice to enable best utilization of observations in this technical review.

Lastly, by rating our confidence in the evidence of downstream clinical consequences of true test positives and negatives, but also the potentially detriment of FNs (missing a diagnosis) and FPs (overdiagnosing), our goal was to increase transparency in the process and enable clinicians to provide optimal shared decision making.

Limitations of Current Evidence and Future Directions

This review of the literature for VCTE in patients with liver disease revealed a number of limitations. First, studies used a wide range of cutoffs for VCTE to define fibrosis stages in CLDs, mostly identified post-hoc corresponding to the AUROC, and this variability subsequently impacted the quality of evidence. Future studies need to evaluate the performance of standard predefined cutoffs for the different liver diseases. Second, the strength of the VCTE literature is in HCV but is generally limited to the initial assessment. Many patients with advanced fibrosis and cirrhosis have been or will soon be cured of their HCV, and there is hope that many will see improvement in their fibrosis in time. Their long-term care is currently expected to include surveillance for the complications of portal hypertension and liver cancer for many years. Studies are needed to establish ongoing assessment and determine whether fibrosis (or early cirrhosis) has regressed to the point where ongoing surveillance will no longer be required. However, this will likely require correlation with liver biopsies, as the decrease over time in kPa values alone may, or may not, be related to fibrosis regression, as other factors, such as degree of inflammation or fatty infiltration, may influence liver stiffness. Third, there is major dearth of high-quality evidence in patients with NAFLD. As more patients present for evaluation (including asymptomatic patients incidentally noted to have hepatic steatosis) and therapies are developed for the treatment of NAFLD, clinicians will require effective risk stratification and diagnostic tools to identify patients with progressive fibrosis at risk for complications. Fourth, due to limited data, prospective evaluation of the utility of VCTE as a triage test to evaluate for absence of high-risk EVs and ruling our clinically significant portal hypertension before elective surgery is warranted. Finally, although a variety of noninvasive imaging-based fibrosis assessment modalities have been developed, our review focused on VCTE and MRE only; a detailed synthesis of the performance and utility of other noninvasive imaging modalities, such as acoustic radiation force pulse imaging or shear wave elastography, in CLDs, particularly NAFLD, is warranted.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2017.03.016.

References

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117–171.
2. Asrani SK, Larson JJ, Yawn B, et al. Underestimation of liver-related mortality in the United States. Gastroenterology 2013;145:375–382 e1–e2.
3. Everhart JE, Ruhl CE. Burden of digestive diseases in the United States Part III: liver, biliary tract, and pancreas. Gastroenterology 2009;136:1134–1144.
4. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
5. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015;61:77–87.
6. Schweitzer A, Horn J, Mikolajczyk RT, et al. Estimations of worldwide prevalence of chronic hepatitis B virus

infection: a systematic review of data published between 1965 and 2013. Lancet 2015;386:1546–1555.
7. Ioannou GN. Hepatitis B virus in the United States: infection, exposure, and immunity rates in a nationally representative survey. Ann Intern Med 2011;154:319–328.
8. 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.
9. Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. J Hepatol 2013;59:160–168.
10. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001;344:495–500.
11. Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. Clin Gastroenterol Hepatol 2010;8:877–883.
12. Regev A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002; 97:2614–2618.
13. Castera L. Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology 2012; 142:1293–1302.e4.
14. Tapper EB, Castera L, Afdhal NH. FibroScan (vibration-controlled transient elastography): where does it stand in the United States practice. Clin Gastroenterol Hepatol 2015;13:27–36.
15. Smith BD, Morgan RL, Beckett GA, et al. Hepatitis C virus testing of persons born during 1945-1965: recommendations from the Centers for Disease Control and Prevention. Ann Intern Med 2012;157:817–822.
16. Sebastiani G, Ghali P, Wong P, et al. Physicians' practices for diagnosing liver fibrosis in chronic liver diseases: a nationwide, Canadian survey. Can J Gastroenterol Hepatol 2014;28:23–30.
17. Kan VY, Marquez Azalgara V, Ford JA, et al. Patient preference and willingness to pay for transient elastography versus liver biopsy: a perspective from British Columbia. Can J Gastroenterol Hepatol 2015;29:72–76.
18. European Association for Study of the Liver, Asociacion Latinoamericana para el Estudio del H. EASL-ALEH Clinical Practice Guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237–264.
19. Castera L, Pinzani M, Bosch J. Non invasive evaluation of portal hypertension using transient elastography. J Hepatol 2012;56:696–703.
20. Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. Hepatology 2006;43:S113–S120.
21. Schunemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ 2008;336: 1106–1110.
22. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–536.
23. Castera L, Foucher J, Bernard PH, et al. Pitfalls of liver stiffness measurement: A 5-year prospective study of 13,369 examinations. Hepatology 2010;51:828–835.
24. Ji D, Shao Q, Han P, et al. The frequency and determinants of liver stiffness measurement failure: a retrospective study of "real-life" 38,464 examinations. PLoS ONE 2014;9:e105183.
25. Sirli R, Sporea I, Bota S, et al. Factors influencing reliability of liver stiffness measurements using transient elastography (M-probe)-monocentric experience. Eur J Radiol 2013;82:e313–e316.
26. Arena U, Vizzutti F, Corti G, et al. Acute viral hepatitis increases liver stiffness values measured by transient elastography. Hepatology 2008;47:380–384.
27. Sagir A, Erhardt A, Schmitt M, et al. Transient elastography is unreliable for detection of cirrhosis in patients with acute liver damage. Hepatology 2008;47:592–595.
28. Millonig G, Reimann FM, Friedrich S, et al. Extrahepatic cholestasis increases liver stiffness (FibroScan) irrespective of fibrosis. Hepatology 2008;48:1718–1723.
29. Millonig G, Friedrich S, Adolf S, et al. Liver stiffness is directly influenced by central venous pressure. J Hepatol 2010;52:206–210.
30. Gianni E, Forte P, Galli V, et al. Prospective evaluation of liver stiffness using transient elastography in alcoholic patients following abstinence. Alcohol Alcohol 2017; 52:42–47.
31. Arena U, Platon ML, Stasi C, et al. Liver stiffness is influenced by a standardized meal in patients with chronic hepatitis C virus at different stages of fibrotic evolution. Hepatology 2013;58:65–72.
32. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA 2015;313:2263–2273.
33. Thein HH, Yi Q, Dore GJ, et al. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology 2008;48:418–431.
34. Yim HJ, Lok AS. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology 2006;43(Suppl 1):S173–S181.
35. Schwartz JM, Reinus JF. Prevalence and natural history of alcoholic liver disease. Clin Liver Dis 2012;16:659–666.
36. Crossan C, Tsochatzis EA, Longworth L, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: Systematic review and economic evaluation. Health Technol Assess 2015;19:1–458.
37. American Association for the Study of Liver Diseases-Infectious Diseases Society of American. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Published 2016. Accessed June 1, 2016.
38. Bota S, Sporea I, Peck-Radosavljevic M, et al. The influence of aminotransferase levels on liver stiffness assessed by acoustic radiation force impulse elastography: a retrospective multicentre study. Digest Liver Dis 2013;45:762–768.
39. Cardoso AC, Carvalho-Filho RJ, Stern C, et al. Direct comparison of diagnostic performance of transient elastography in patients with chronic hepatitis B and chronic hepatitis C. Liver Int 2012;32:612–621.
40. Castera L, Winnock M, Pambrun E, et al. Comparison of transient elastography (FibroScan), FibroTest, APRI and

two algorithms combining these non-invasive tests for liver fibrosis staging in HIV/HCV coinfected patients: ANRS CO13 HEPAVIH and FIBROSTIC collaboration. HIV Med 2014;15:30–39.
41. D'Ambrosio R, Aghemo A, Fraquelli M, et al. The diagnostic accuracy of Fibroscan for cirrhosis is influenced by liver morphometry in HCV patients with a sustained virological response. J Hepatol 2013;59:251–256.
42. Lupsor Platon M, Stefanescu H, Feier D, et al. Performance of unidimensional transient elastography in staging chronic hepatitis C. Results from a cohort of 1,202 biopsied patients from one single center. J Gastrointest Liver Dis 2013;22:157–166.
43. Verveer C, Zondervan PE, Ten Kate FJW, et al. Evaluation of transient elastography for fibrosis assessment compared with large biopsies in chronic hepatitis B and C. Liver Int 2012;32:622–628.
44. Carrion JA, Navasa M, Bosch J, et al. Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. Liver Transplant 2006;12:1791–1798.
45. Castera L. Transient elastography and other noninvasive tests to assess hepatic fibrosis in patients with viral hepatitis. J Viral Hepat 2009;16:300–314.
46. Degos F, Perez P, Roche B, et al. Diagnostic accuracy of FibroScan and comparison to liver fibrosis biomarkers in chronic viral hepatitis: a multicenter prospective study (the FIBROSTIC study). J Hepatol 2010;53:1013–1021.
47. De Ledinghen V, Douvin C, Kettaneh A, et al. Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/hepatitis C virus-coinfected patients. Journal of Acquir Immune Defic Syndr 2006;41:175–179.
48. Gaia S, Carenzi S, Barilli AL, et al. Reliability of transient elastography for the detection of fibrosis in non-alcoholic fatty liver disease and chronic viral hepatitis. J Hepatol 2011;54:64–71.
49. Gara N, Zhao X, Kleiner DE, et al. Discordance among transient elastography, aspartate aminotransferase to platelet ratio index, and histologic assessments of liver fibrosis in patients with chronic hepatitis C. Clin Gastroenterol Hepatol 2013;11:303–308.e1.
50. Liu CH, Liang CC, Huang KW, et al. Transient elastography to assess hepatic fibrosis in hemodialysis chronic hepatitis C patients. Clin J Am Soc Nephrol 2011;6:1057–1064.
51. Nitta Y, Kawabe N, Hashimoto S, et al. Liver stiffness measured by transient elastography correlates with fibrosis area in liver biopsy in patients with chronic hepatitis C. Hepatol Res 2009;39:675–684.
52. Patel K, Friedrich-Rust M, Lurie Y, et al. FibroSURE and FibroScan in relation to treatment response in chronic hepatitis C virus. World J Gastroenterol 2011;17:4581–4589.
53. Sporea I, Sirli R, Deleanu A, et al. Liver stiffness measurements in patients with HBV vs HCV chronic hepatitis: a comparative study. World J Gastroenterol 2010;16:4832–4837.
54. Aleman S, Rahbin N, Weiland O, et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. Clin Infect Dis 2013;57:230–236.
55. Cassinotto C, Lapuyade B, Mouries A, et al. Non-invasive assessment of liver fibrosis with impulse elastography: comparison of Supersonic Shear Imaging with ARFI and FibroScan. J Hepatol 2014;61:550–557.
56. Crisan D, Radu C, Grigorescu MD, et al. Prospective non-invasive follow-up of liver fibrosis in patients with chronic hepatitis C. J Gastrointest Liver Dis 2012;21:375–382.
57. Seo YS, Kim MY, Kim SU, et al. Accuracy of transient elastography in assessing liver fibrosis in chronic viral hepatitis: a multicentre, retrospective study. Liver Int 2015;35:2246–2255.
58. Castera L, Vergniol J, Foucher J, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343–350.
59. Cho HJ, Seo YS, Lee KG, et al. Serum aminotransferase levels instead of etiology affects the accuracy of transient elastography in chronic viral hepatitis patients. J Gastroenterol Hepatol 2011;26:492–500.
60. Obara N, Ueno Y, Fukushima K, et al. Transient elastography for measurement of liver stiffness measurement can detect early significant hepatic fibrosis in Japanese patients with viral and nonviral liver diseases. J Gastroenterol 2008;43:720–728.
61. Ziol M, Handra-Luca A, Kettaneh A, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005;41:48–54.
62. Xiao G, Yang J, Yan L. Comparison of diagnostic accuracy of aspartate aminotransferase to platelet ratio index and fibrosis-4 index for detecting liver fibrosis in adult patients with chronic hepatitis B virus infection: a systemic review and meta-analysis. Hepatology 2015;61:292–302.
63. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261–283.
64. Wu Y, Johnson KB, Roccaro G, et al. Poor adherence to AASLD guidelines for chronic hepatitis B Management and treatment in a large academic medical center. Am J Gastroenterol 2014;109:867–875.
65. Castera L, Bernard PH, Le Bail B, et al. Transient elastography and biomarkers for liver fibrosis assessment and follow-up of inactive hepatitis B carriers. Aliment Pharmacol Ther 2011;33:455–465.
66. Chan HLY, Wong GLH, Choi PCL, et al. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. J Viral Hepat 2009;16:36–44.
67. Chen YP, Liang XE, Dai L, et al. Improving transient elastography performance for detecting hepatitis B cirrhosis. Digest Liver Dis 2012;44:61–66.
68. Goyal R, Mallick SR, Mahanta M, et al. Fibroscan can avoid liver biopsy in Indian patients with chronic hepatitis B. J Gastroenterol Hepatol 2013;28:1738–1745.
69. Jia J, Hou J, Ding H, et al. Transient elastography compared to serum markers to predict liver fibrosis in a cohort of Chinese patients with chronic hepatitis B. J Gastroenterol Hepatol 2015;30:756–762.

70. Kongtawelert P, Chanmee T, Pothacharoen P, et al. Diagnostic accuracy of liver stiffness measurement and serum hyaluronic acid for detecting liver fibrosis in chronic hepatitis B with respect to ALT levels. Asian Biomed 2013;7:609–617.
71. Marcellin P, Ziol M, Bedossa P, et al. Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. Liver Int 2009;29: 242–247.
72. Kumar M, Rastogi A, Singh T, et al. Analysis of discordance between transient elastography and liver biopsy for assessing liver fibrosis in chronic hepatitis B virus infection. Hepatol Int 2013;7:134–143.
73. Lee HW, Kang W, Kim BK, et al. Red cell volume distribution width-to-platelet ratio in assessment of liver fibrosis in patients with chronic hepatitis B. Liver Int 2016;36:24–30.
74. Papatheodoridis GV, Manolakopoulos S, Margariti A, et al. The usefulness of transient elastography in the assessment of patients with HBeAg-negative chronic hepatitis B virus infection. J Viral Hepat 2014;21:517–524.
75. Trembling PM, Lampertico P, Parkes J, et al. Performance of Enhanced liver fibrosis test and comparison with transient elastography in the identification of liver fibrosis in patients with chronic hepatitis B infection. J Viral Hepat 2014;21:430–438.
76. Wong VWS, Lampertico P, de Ledinghen V, et al. Probability-based interpretation of liver stiffness measurement in untreated chronic hepatitis B patients. Digest Dis Sci 2015;60:1448–1456.
77. Zhang D, Chen M, Wang R, et al. Comparison of acoustic radiation force impulse imaging and transient elastography for non-invasive assessment of liver fibrosis in patients with chronic hepatitis B. Ultrasound Med Biol 2015;41:7–14.
78. Ogawa E, Furusyo N, Murata M, et al. Longitudinal assessment of liver stiffness by transient elastography for chronic hepatitis B patients treated with nucleoside analog. Hepatol Res 2011;41:1178–1188.
79. Wang JH, Changchien CS, Hung CH, et al. FibroScan and ultrasonography in the prediction of hepatic fibrosis in patients with chronic viral hepatitis. J Gastroenterol 2009;44:439–446.
80. Chan WK, Nik Mustapha NR, Mahadeva S. A novel 2-step approach combining the NAFLD fibrosis score and liver stiffness measurement for predicting advanced fibrosis. Hepatol Int 2015;9:594–602.
81. Imajo K, Kessoku T, Honda Y, et al. Magnetic resonance imaging more accurately classifies steatosis and fibrosis in patients with nonalcoholic fatty liver disease than transient elastography. Gastroenterology 2016;150:626–637 e7.
82. Myers RP, Elkashab M, Ma M, et al. Transient elastography for the noninvasive assessment of liver fibrosis: a multicentre Canadian study. Can J Gastroenterol 2010; 24:661–670.
83. Kumar R, Rastogi A, Sharma MK, et al. Liver stiffness measurements in patients with different stages of nonalcoholic fatty liver disease: diagnostic performance and clinicopathological correlation. Digest Dis Sci 2013; 58:265–274.
84. Mahadeva S, Mahfudz AS, Vijayanathan A, et al. Performance of transient elastography (TE) and factors associated with discordance in non-alcoholic fatty liver disease. J Digest Dis 2013;14:604–610.
85. Myers RP, Pomier-Layrargues G, Kirsch R, et al. Discordance in fibrosis staging between liver biopsy and transient elastography using the FibroScan XL probe. J Hepatol 2012;56:564–570.
86. Wong VWS, Vergniol J, Wong GLH, et al. Liver stiffness measurement using XL probe in patients with nonalcoholic fatty liver disease. Am J Gastroenterol 2012; 107:1862–1871.
87. Wong VWS, Vergniol J, Wong GLH, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology 2010; 51:454–462.
88. Yoneda M, Mawatari H, Fujita K, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with nonalcoholic fatty liver disease (NAFLD). Digest Liver Dis 2008;40:371–378.
89. Yoneda M, Suzuki K, Kato S, et al. Nonalcoholic fatty liver disease: US-based acoustic radiation force impulse elastography. Radiology 2010;256:640–647.
90. Sun W, Cui H, Li N, et al. Comparison of FIB-4 index, NAFLD fibrosis score and BARD score for prediction of advanced fibrosis in adult patients with non-alcoholic fatty liver disease: a meta-analysis study. Hepatol Res 2016;46:862–870.
91. Singh S, Allen AM, Wang Z, et al. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 2015;13:643–654 e1–e9; quiz e39–e40.
92. Petta S, Di Marco V, Camma C, et al. Reliability of liver stiffness measurement in non-alcoholic fatty liver disease: the effects of body mass index. Aliment Pharmacol Ther 2011;33:1350–1360.
93. Pavlov CS, Casazza G, Nikolova D, et al. Systematic review with meta-analysis: diagnostic accuracy of transient elastography for staging of fibrosis in people with alcoholic liver disease. Aliment Pharmacol Ther 2016;43:575–585.
94. Bardou-Jacquet E, Legros L, Soro D, et al. Effect of alcohol consumption on liver stiffness measured by transient elastography. World J Gastroenterol 2013; 19:516–522.
95. Boursier J, Vergniol J, Sawadogo A, et al. The combination of a blood test and Fibroscan improves the non-invasive diagnosis of liver fibrosis. Liver Int 2009; 29:1507–1515.
96. De Ledinghen V, Wong VWS, Vergniol J, et al. Diagnosis of liver fibrosis and cirrhosis using liver stiffness measurement: comparison between M and XL probe of FibroScan. J Hepatol 2012;56:833–839.
97. Dolman GE, Nieboer D, Steyerberg EW, et al. The performance of transient elastography compared to clinical acumen and routine tests—what is the incremental diagnostic value? Liver Int 2013;33:172–179.
98. Lannerstedt H, Konopski Z, Sandvik L, et al. Combining transient elastography with FIB4 enhances sensitivity in

detecting advanced fibrosis of the liver. Scand J Gastroenterol 2013;48:93–100.
99. Mueller S, Millonig G, Sarovska L, et al. Increased liver stiffness in alcoholic liver disease: differentiating fibrosis from steatohepatitis. World J Gastroenterol 2010; 16:966–972.
100. Kim SG, Kim YS, Jung SW, et al. [The usefulness of transient elastography to diagnose cirrhosis in patients with alcoholic liver disease]. Korean J Hepatol 2009; 15:42–51.
101. Calvaruso V, Bronte F, Conte E, et al. Modified spleen stiffness measurement by transient elastography is associated with presence of large oesophageal varices in patients with compensated hepatitis C virus cirrhosis. J Viral Hepat 2013;20:867–874.
102. Castera L, Bail BL, Roudot-Thoraval F, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. J Hepatol 2009;50:59–68.
103. Kazemi F, Kettaneh A, N'Kontchou G, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. J Hepatol 2006; 45:230–235.
104. Nguyen-Khac E, Saint-Leger P, Tramier B, et al. Noninvasive diagnosis of large esophageal varices by fibroscan: strong influence of the cirrhosis etiology. Alcoholism Clin Exp Res 2010;34:1146–1153.
105. Pineda JA, Recio E, Camacho A, et al. Liver stiffness as a predictor of esophageal varices requiring therapy in HIV/hepatitis C virus-coinfected patients with cirrhosis. J Acquir Immune Defic Syndr 2009;51:445–449.
106. Pritchett S, Cardenas A, Manning D, et al. The optimal cutoff for predicting large oesophageal varices using transient elastography is disease specific. J Viral Hepat 2011;18:e75–e80.
107. Vermehren J, Polta A, Zimmermann O, et al. Comparison of acoustic radiation force impulse imaging with transient elastography for the detection of complications in patients with cirrhosis. Liver Int 2012;32:852–858.
108. Wang HM, Lo GH, Chen WC, et al. Efficacy of transient elastography in screening for large esophageal varices in patients with suspicious or proven liver cirrhosis. J Digest Dis 2012;13:430–438.
109. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743–752.
110. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 2007;46:922–938.
111. Al-Dahshan M. Clinical application of transient elastography in prediction of portal hypertension related complication in patients with chronic liver diseases. J Egypt Soc Parasitol 2012;42:79–88.
112. Bintintan A, Chira RI, Bintintan VV, et al. Value of hepatic elastography and Doppler indexes for predictions of esophageal varices in liver cirrhosis. Med Ultrason 2015; 17:5–11.
113. Colecchia A, Montrone L, Scaioli E, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. Gastroenterology 2012;143:646–654.
114. Fraquelli M, Giunta M, Pozzi R, et al. Feasibility and reproducibility of spleen transient elastography and its role in combination with liver transient elastography for predicting the severity of chronic viral hepatitis. J Viral Hepat 2014;21:90–98.
115. Stefanescu H, Grigorescu M, Lupsor M, et al. Spleen stiffness measurement using fibroscan for the noninvasive assessment of esophageal varices in liver cirrhosis patients. J Gastroenterol Hepatol 2011;26:164–170.
116. Vizzutti F, Arena U, Romanelli RG, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology 2007; 45:1290–1297.
117. Telem DA, Schiano T, Goldstone R, et al. Factors that predict outcome of abdominal operations in patients with advanced cirrhosis. Clin Gastroenterol Hepatol 2010; 8:451–457, quiz e58.
118. Teh SH, Nagorney DM, Stevens SR, et al. Risk factors for mortality after surgery in patients with cirrhosis. Gastroenterology 2007;132:1261–1269.
119. Singh S, Venkatesh SK, Wang Z, et al. Diagnostic performance of magnetic resonance elastography in staging liver fibrosis: a systematic review and meta-analysis of individual participant data. Clin Gastroenterol Hepatol 2015;13:440–451.
120. Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet 1993;341:418–422.
121. Park CC, Nguyen P, Hernandez C, et al. Magnetic resonance elastography vs transient elastography in detection of fibrosis and noninvasive measurement of steatosis in patients with biopsy-proven nonalcoholic fatty liver disease. Gastroenterology 2017;152:598–607e2.
122. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 2012;142:1592–1609.

Reprint requests
Address requests for reprints to: Chair, Clinical Guidelines Committee, American Gastroenterological Association, National Office, 4930 Del Ray Avenue, Bethesda, Maryland 20814. E-mail: msiedler@gastro.org.

Acknowledgments
The authors sincerely thank Kellee Kaulback, Medical Information Officer, Health Quality Ontario, for helping in the literature search for this technical review.

Conflicts of interest
All the authors were vetted for potential conflicts of interest by the AGA. The authors disclose the following: Dr. Muir has served as a consultant for Abbvie, Bristol-Myers Squibb, Gilead, and Merck. Dr. Dieterich has presented lectures for Gilead and Merck products. The remaining authors disclosed no conflicts related to the content of this guideline.

Funding
Dr Singh is partly supported by the National Library of Medicine training grant T15LM011271.