Referral to liver specialist by other specialities

Advanced Liver Fibrosis Is Common in Patients With Type 2 Diabetes Followed in the Outpatient Setting: The Need for Systematic Screening

Lomonaco R, *et al.,* Diabetes Care 2021;44(2):399-406

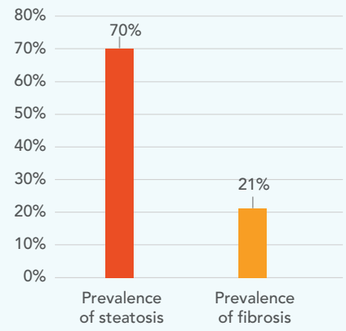
Objectives	• To assess the prevalence of steatosis & moderate-to-advanced fibrosis by transient elastography in unselected patients with type 2 diabetes mellitus (T2DM) attending a general internal medicine, family medicine, or endocrinology outpatient clinic
Method	**LSM by VCTE™ and CAP™ were performed with M or XL probe, according to automatic probe selection tool** **LSM by VCTE™ cut-off values [reference to Eddowes PJ., Gastroenterology 2019]** • F1; mild fibrosis; >= 7 - 8.1 kPa • F2; moderate fibrosis; >= 8.2 – 9.6 kPa • F3; advanced fibrosis; >= 9.7 kPa -13.5 kPa • F4; cirrhosis; >=13.6 kPa **CAP™ cut-off values** • S1; mild; 274 – 289 dB/m • S2; moderate; 290 – 301 dB/m • S3; severe; >= 302 dB/m **Patient with presence of liver fibrosis diagnosed by concordant non-invasive tests (VCTE™ & APRI and /or FIB-4) were proposed a liver biopsy**
Patients analyzed	• 561 patients with T2DM
Results	**Fibrosis & Steatosis Prevalence** • Prevalence of steatosis (CAP™>=274 dB/m) & fibrosis (LSM>=7.0 kPa) were 70% & 21%, respectively **(cf. Fig. 1)** • Moderate fibrosis (F≥2: LSM>=8.2 kPa) was present in 15% • Severe fibrosis or cirrhosis (F3-4; LSM>=9.7 kPa) was present in 9% • Elevated AST or ALT>=40 units/L was present in a minority of patients with steatosis (8% & 13% respectively) or with moderate-to-advanced fibrosis (18% & 28% respectively) ➜ this suggests that AST/ALT alone are insufficient as initial screening **Liver Biopsy** • Among those with LSM>=8.2, 21 has a liver biopsy • Liver fibrosis was confirmed by biopsy in 90% of cases.

VCTE™: Vibration Controlled Transient Elastography • LSM: Liver Stiffness Measurement • CAP™: Controlled Attenuation Parameter • APRI: AST/Platelet Ratio Index • FIB-4: Fibrosis-4 Index • T2DM: Type 2 Diabetes Mellitus • AST: Aspartate Aminotransferase • ALT: Alanine Aminotransferase

Key points

- Moderate-to-advanced fibrosis (F≥2) assessed by LSM by VCTE™, affects at least one out of six (15%) patients with T2DM
- Steatosis evaluated by CAP™ is present in almost 75% of patients
- Results are supporting the American Diabetes Association guidelines to screen for clinically significant fibrosis in patients with T2DM with steatosis or elevated ALT

FIGURE 1 **Proportion of patients with T2DM screened in the outpatient clinical setting having liver steatosis (measured by CAP™) & with liver fibrosis (measured by LSM by VCTE™)**



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Prevalence of Advanced Liver Fibrosis in Patients With Severe Psoriasis

Maybury CM, *et al.*, JAMA Dermatology 2019;155(9):1028-1032

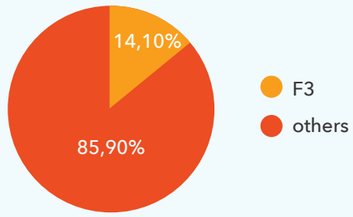
Objectives	• To describe the prevalence of and evaluate clinical factors associated with advanced fibrosis in people with severe psoriasis
Method	• **Enrollment criteria** **Subjects were recruited based on the diagnosis of severe chronic plaque psoriasis (PASI>=10) by a dermatologist, irrespective of their current psoriasis treatment (e.g., Methotrexate (MTX) & biologics)** • **FibroScan® examination** **LSM by VCTE™>=8.7 kPa was considered as advanced fibrosis (F≥F3)**
Patients analyzed	• 400 patients with psoriasis
Results	**Result of LSM by VCTE™** • 333/400 (83%) had an successful LSM by VCTE™ • 47/333 (14.1%) had advanced fibrosis based on LSM by VCTE™ **(cf. Fig. 1)** **Use of methotrexate (MTX)** • 85/400 (21%) were taking MTX, and 340/400 (85%) had been exposed to MTX • Mean MTX dosage was 15mg weekly • Median duration of MTX exposure was 0.6 years • As most individuals with advanced fibrosis were not taking MTX, MTX exposure was not associated with advanced liver fibrosis **Multivariate model predicting advanced fibrosis by LSM was a combination of below factors** • Increased central obesity • Increased insulin resistance • Increased psoriasis severity • Increased AST level • Increased platelet count • Reduced alcohol use

VCTE™: Vibration Controlled Transient Elastography • LSM: Liver Stiffness Measurement • PASI: Psoriasis Area Severity Index score • MTX: Methotrexate • AST: Aspartate Aminotransferase

Key points

- Advanced fibrosis assessed by LSM by VCTE™ is common in patients with severe psoriasis (7-fold increase when compared to the general population)
- Methotrexate treatment is unlikely to be the most important risk factor of advanced fibrosis
- People with severe psoriasis should be screened for advanced liver fibrosis irrespective of their treatment or medication

FIGURE 1 Result of LSM by VCTE™



Referral to liver specialist by other specialities

Transient elastography for the detection of hepatic fibrosis in HIV-monoinfected adults with elevated aminotransferases on antiretroviral therapy

Morse CG, *et al.*, AIDS 2015;29(17):2297-302

Objectives	• To evaluate the accuracy of liver stiffness (LSM) measured by VCTE™ for the detection of liver fibrosis in HIV-mono-infected adults
Method	• HIV -infected adults with elevated aminotransferase levels for at least 6 months while receiving antiretroviral therapy, and without known causes of chronic liver disease were recruited • Patients were prospectively evaluated by LSM by VCTE™, other noninvasive markers of fibrosis (FIB-4, APRI, NAFLD fibrosis Score), and percutaneous liver biopsy (fibrosis staged using the Ishak scoring system) • At least 10 measurements of LSM by VCTE™ were made using M probe, results were considered reliable if the success rate was at least 60% & IQR/median ratio was 0.3 or less
Patients analyzed	• 66 HIV mono-infected patients
Results	**Liver biopsy (n=66) (cf. Fig. 1)** • Bridging fibrosis (Ishak F3-4) was present in patients (21%) • Nonalcoholic steatohepatitis (NASH) in 38 patients (58%) **(cf. Fig. 1)** **LSM by VCTE™ (n=59)** • 89% of exams were deemed reliable • Median LSM was 5.9 kPa • LSM ≥ 7.1 kPa in 25 (42%) • LSM was elevated (>7.1 kPa) in 21/33 (64%) participants with steatohepatitis • AUROC 0.93 for detection of moderate fibrosis (Ishak F>=2) with an optimal cut-off value of 7.1 kPa **(cf. Fig. 2)** **Comparison with other noninvasive fibrosis markers (Table 1)** • LSM by VCTE™ had the best diagnostic performance (AUROC) vs other non-invasive tests evaluated • LSM by VCTE™ had high values for both sensitivity, specificity

VCTE™: Vibration Controlled Transient Elastography • LSM: Liver Stiffness Measurement • NAFLD: Non-alcoholic Fatty Liver Disease • NASH: Non-alcoholic Steatohepatitis • HIV: Human Immunodeficiency Virus • APRI: AST/Platelet Ratio Index • FIB-4: Fibrosis-4 Index • NFS/NAFLD-FS: NAFLD Fibrosis Score • AUROC: Area Under Receiving Operator Characteristics Curve

Key points

- LSM by VCTE™ was the best noninvasive predictor of significant fibrosis in HIV-monoinfected adults with biopsy-proven liver disease
- These results support the continued use of LSM by VCTE™ for fibrosis screening in HIV-monoinfected patients with elevated aminotransferases

FIGURE 1 Graphical presentation of histological assessment

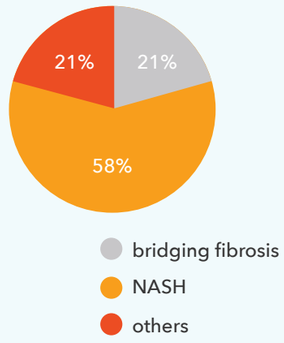


FIGURE 2 Receiver-operating curve of LSM by VCTE™ for the prediction of significant hepatic fibrosis (Ishak F≥2) in HIV-monoinfected adults

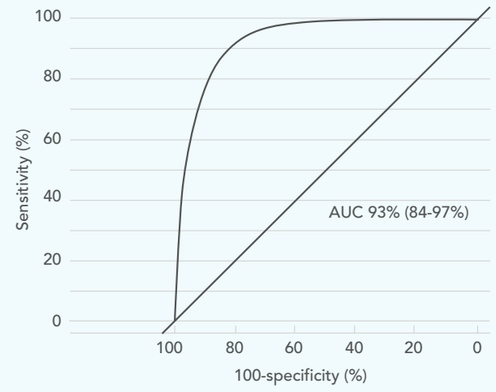


TABLE 1 Performance of LSM by VCTE™, APRI, FIB-4 & NFS for the detection of significant fibrosis (Ishak F≥2) in HIV-monoinfected adults with elevated aminotransferase & reliable LSM (n-59)

	VCTE™	APRI [12]	FIB-4 [19}	NAFLD-FS [14]
AUROC (%, 95% CI)	93 (86-99)	61 (46-77)	64 (49-79)	70 (55-85)
Cut-off (KPa)[a]	≥7.1	>1.5	>2.67	>0.676
Sensitivity (%)	93	21	21	14
Specificity (%)	73	82	89	96
Positive predictive value (%)	52	27	38	50
Negative predictive value (%)	97	77	78	78

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Non-invasive diagnosis of liver fibrosis in patients with alcohol-related liver disease by transient elastography: an individual patient data meta-analysis

Nguyen-Khac E, *et al.*, The Lancet Gastroenterology & Hepatology 2018;3(9):614-625

Objectives	• To determine specific diagnostic cut-off values for LSM by VCTE™ in alcohol-related fibrosis • To assess the effect of aminotransferase concentrations, bilirubin concentrations, and presence of asymptomatic and non-severe alcoholic hepatitis on LSM by VCTE™
Method	• **Search on PubMed led to identify 10 eligible studies that included patients with alcohol-related liver disease, liver biopsy, and LSM by VCTE™ results available** • **Specific diagnostic cut-offs were tested based on AST & bilirubin levels**
Patients analyzed	• 1026 patients with Alcoholic Liver Disease
Results	**Diagnostic performances of LSM by VCTE™ and optimal cut-offs (cf. Table 1)** **Performances and cut-offs as function of AST and bilirubin levels** • Both bilirubin and AST levels were signficantly correlated with LSM by VCTE™ • Bilirubin/AST-adjusted LSM cut-off values are proposed **(cf. Table 2)**

VCTE™: Vibration Controlled Transient Elastography • LSM: Liver Stiffness Measurement • AUROC: Area Under Receiving Operator Characteristics Curve • PPV: Positive Predictive Value • NPV: Negative Predictive Value • ALD: Alcohol-related Liver Disease • AST: Aspartate Aminotransferase

Key points

- Diagnostic performances of LSM by VCTE™ for advanced fibrosis and cirrhosis assessment in ALD are excellent
- LSM by VCTE™ can be used for the non-invasive diagnosis of liver fibrosis in patients with alcohol-related liver disease, but diagnostic cut-offs used should be adjusted to account for AST & bilirubin concentrations
- When AST & bilirubin levels are normal, diagnostic cut-offs are very similar to those used in chronic viral hepatitis C

TABLE 1 **Performance of LSM by VCTE™ vs histology for fibrosis assessment (with optimal LSM by VCTE™ cut-offs maximizing the sum of sensitivity & specificity)**

Fibrosis stage	Diagnostic Performance (AUROC)	Optimal LSM cut-offs	Sensitivity	Specificity	PPV	NPV
F>=1	0.83	7.0 kPa	0.79	0.71	0.94	0.38
F>=2	0.86	9.0 kPa	0.78	0.77	0.90	0.49
F>=3	0.90	12.1 kPa	0.81	0.83	0.85	0.72
F=4	0.91	18.6 kPa	0.84	0.85	0.74	0.87

TABLE 2 **Diagnostic performances & optimal cut-offs according to combined AST & bilirubin concentrations**

	AST<38.7 IU/L and bilirubin <9 µmol/L	AST 38.7-75 IU/L and bilirubin <9 µmol/L or AST<38.7 IU/L and bilirubin 9-16 µmol/L	AST 38.7-75 IU/L and bilirubin 9-16 µmol/L	AST >75 IU/L and bilirubin >16 µmol/L
≥F1				
Cut off (kPa)	**5.6**	**6.9**	**8.4**	**9.6**
AUROC	0.82	0.86	0.90	0.98
Sensitivity	0.83	0.85	0.83	0.89
Specificity	0.56	0.54	0.71	0.76
≥F2				
Cut off (kPa)	**6.9**	**8.1**	**8.8**	**11.6**
AUROC	0.87	0.88	0.90	0.89
Sensitivity	0.80	0.89	0.85	0.83
Specificity	0.77	0.64	0.82	0.79
≥F3				
Cut off (kPa)	**8.8**	**11.2**	**12.3**	**16.1**
AUROC	0.92	0.91	0.90	0.92
Sensitivity	0.80	0.80	0.83	0.83
Specificity	0.75	0.79	0.76	0.80
F4				
Cut off (kPa)	**12.1**	**15.4**	**19.9**	**25.9**
AUROC	0.92	0.93	0.92	0.96
Sensitivity	0.85	0.83	0.86	0.81
Specificity	0.84	0.82	0.86	0.80

Controlled Attenuation Parameter And Alcoholic Hepatic Steatosis: Diagnostic Accuracy and Role Of Alcohol Detoxification

Thiele M, *et al.*, Journal of Hepatology 2018;68(5):1025-1032

Objectives	• To validate CAP™ for assessment of alcoholic steatosis using liver biopsy as the reference • To study the effect of alcohol detoxification on CAP™
Method	**For diagnostic cohort** • Liver biopsy • Regular Ultrasound • CAP™ performed within 72 hours of liver biopsy, either during outpatient visit or at the beginning of hospitalization **For detoxification cohort** • Laboratory testing • Metabolic profiling • CAP™ (at baseline & at discharge from hospital) • Abdominal ultrasound
Patients analyzed	• 269 patients (diagnostic cohort) • 293 patients (detoxification cohort)
Results	• CAP™ is a good non-invasive marker of hepatic steatosis (cf. Fig. 1) • CAP™ decreases after short term alcoholl detoxification, except in obese patients (cf. Fig. 2)

CAP™: Controlled Attenuation Parameter

Key points

- CAP™ can be used to detect severe alcoholic steatosis >66% (CAP™ above 339 dB/m; 90% specificity; AUC 0.82) and to rule in steatosis ≥5% (CAP™ above 290 dB/m; specificity 88%; AUC 0.77)
- CAP™ decreased significantly (decrease of 32±47 dB/m, p<0.001) in non-obese (BMI<30 kg/m2) ALD patients after short-term alcohol withdrawal (median of 6.3 days)
- Time efficiency, cost and availability places CAP™ as the most convenient and reliable non-invasive marker of steatosis in patients with alcoholic liver disease

FIGURE 1 Box plot of CAP™ values as function of histological steatosis grade (%)

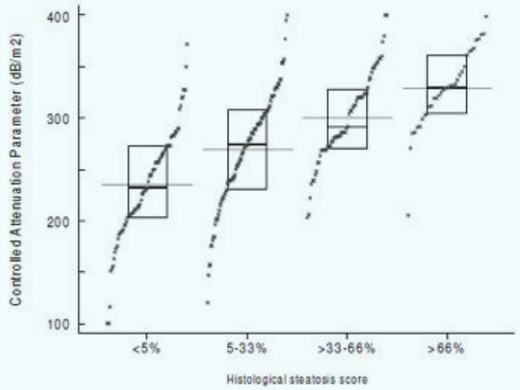
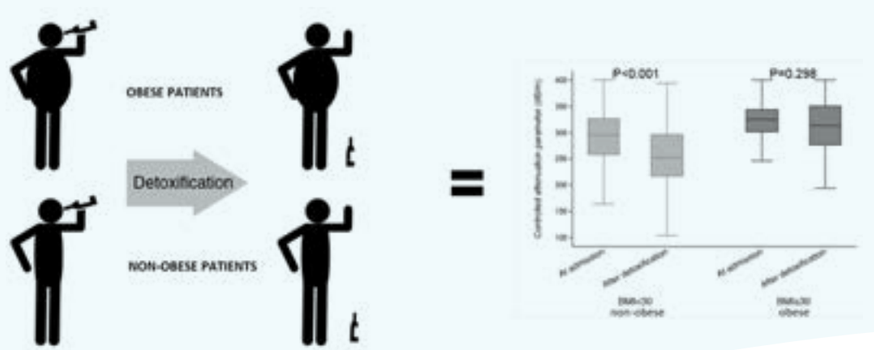


FIGURE 2 Decrease of CAP™ after alcohol detoxification as function of BMI



Referral to liver specialist by other specialities

FibroScan®Identifies Patients With Nonalcoholic Fatty Liver Disease and Cardiovascular Damage

Lombardi R, *et al.*, Clinical Gastroenterology & Hepatology 2020;18(2):517-519

Objectives	• To evaluate whether LSM by VCTE™ can detect CV damages
Method	• **Recruited NAFLD patients underwent liver biopsy within 6 months from Cardiovascular (CV) & FibroScan®assessment** • **Liver stiffness cut-off values for advanced fibrosis (F≥3)** - 8.7 kPa for M probe - 7.2 kPa for XL probe • **Carotid Atherosclerosis was defined according to mean carotid intima-media thickness (cIMT) and presence of carotid plaques** - cIMT values < 0.64 mm ➜ normal - cIMT values > 0.9 mm ➜ subclinical atherosclerosis - Focal thickening > 1.2 mm of the carotid artery ➜ carotid plaque • **Carotid arterial stiffness (pulse wave velocity, PWV) was measured by radiofrequency ultrasonography in 103 patients** • **Conventional echocardiographic parameters such as ejection fraction, left ventricular mass diastolic dysfunction (E/A ratio <1), and epicardial adipose tissue were also measured.**
Patients analyzed	• 472 NAFLD patients
Results	**CV risk profile** • Previous CV event occurred in 35 (8%) patients • Increased cIMT (>0.64mm) was present in 373 (79%) patients, subclinical atherosclerosis (cIMT>0.9mm) in 165 (35%) and carotid plaques in 212 (45%) • Mean PWV was 7.75±2.27 m/s **Liver damage & CV parameters** • High LSM values (n=198; 42%) confirmed by histology (>=F3) in 84% of cases • Carotid thickening & plaques, E/A ratio<1, increased PWV, and a past history of CV events were significantly more prevalent in patients with LSM> 8.7/7.2 kPa • On multivariate analysis, LSM> 8.7/7.2 kPa as significantly associated with carotid plaques in the overall series • In patients <50 years of age, LSM values >=8.7/7.2 kPa were also independently associated with increased PWV values

VCTE™: Vibration Controlled Transient Elastography • LSM: Liver Stiffness Measurement • NAFLD: Non-alcoholic Fatty Liver Disease • CV: Cardiovascular • E/A Ratio: Peak Early Diastolic and Peak Late Diastolic Ratio • cIMT: carotid Intima-Media Thickness • PWV: Pulse Wave Velocity

Key points

- LSM by VCTE™ is associated with Cardiovascular alterations in NAFLD patients
- LSM by VCTE™ is associated with the presence of carotid plaques in the overall series, identifying patients with a more advanced CV disease
- In patients <50 years of age, who have significantly lower prevalence of metabolic alterations, LSM by VCTE™ was independently associated with carotid stiffness, a very early marker of CV damage, previously associated with increased incidence of CV events and all-cause mortality

Validation of Transient Elastography Cut Points to Assess Advanced Liver Fibrosis in Children and Young Adults: The Boston Children's Hospital Experience

Lee CK, *et al.*, Journal of Pediatrics 2018;198:84-89.e2

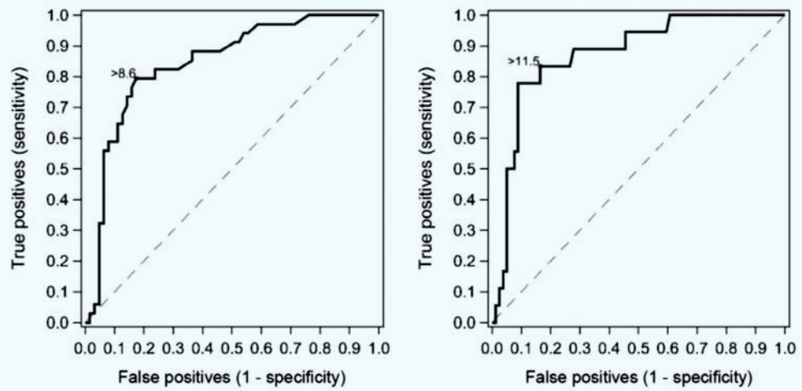
Objectives	• To derive an optimal liver stiffness measurement (LSM by VCTE™) cutoff point to discriminate METAVIR fibrosis stage F4 • To validate both METAVIR fibrosis stage F3-F4 & F4 cut-off points in a separate cohort
Method	• **Recruitment of children & young adults who underwent LSM by VCTE™, as well as liver biopsy** • **Probe selection of LSM by VCTE™ was based on the followings,** **- M probe was used if TP was >75cm** **- S probe was used if TP <=75cm**
Patients analyzed	• 267 patients of various etiologies, including autoimmune, viral, cholestasis, PSC, fatty liver & post transplantation
Results	**Optimal cut-off points to predict advanced fibrosis & cirrhosis were determined to be LSM>8.6 kPa & >11.5 kPa respectively, with diagnostic performances (AUROCs) of 0.85 & 0.87 (cf. Fig. 1)** **The diagnostic accuracy for predicting F3-F4 advanced fibrosis & F4 fibrosis in the calibration cohort was 81.4% & 83.5% respectively, compared with 67.1% & 75.3% in the validation cohort** **When analyzed on a subgroup of fasting patients, accuracy for the F3-F4 advanced fibrosis & F4 cirrhosis cut-off points were 72.7% & 79.5% respectively**

VCTE™: Vibration Controlled Transient Elastography • LSM: Liver Stiffness Measurement • TP: Thoracic Parameter • PSC: Primary Sclerosing Cholangitis • AUROC: Area Under Receiving Operator Characteristics Curve

Key points

- Validated LSM cut points of 8.6 kPa & 11.5 kPa to predict advanced fibrosis & cirrhosis in separate cohorts of children & young adults with liver disease
- VCTE™ may help identify children with greater risk of advanced fibrosis and those who need liver biopsy assessment and/or surveillance for the complications of cirrhosis in a variety of liver disorders

FIGURE 1 **ROC curves based on the calibration cohort. Optimal cut points for predicting A. METAVIR F3-F4 (advanced fibrosis) & B. F4 (cirrhosis)**



A. METAVIR F3-F4 (advanced fibrosis). Area under the curve = 0.85

B. METAVIR F4 (cirrhosis). Area under the curve = 0.87

Role of Noninvasive Tests in Clinical Gastroenterology Practices to Identify Patients With Nonalcoholic Steatohepatitis at High Risk of Adverse Outcomes: Expert Panel Recommendations

Younossi ZM, *et al.,* American Journal of Gastroenterology 2021;116(2):254-262

Objectives	• American College of Gastroenterology & Chronic Liver Disease Foundation jointly develop a practical decision tree/algorithm to risk stratify NAFLD/NASH
Method	• **A review of literatures on non-invasive tests for evaluating patients with NAFD, then summarized to create a practical, easy-to-use algorithm that can be used in clinical practice**
Patients analyzed	• NAFLD/NASH referrals from primary care & other specialists to liver specialists
Results	**To establish the diagnosis of NAFLD/NASH, clinicians need to decide the following** • Whether the patient has NAFLD by documentation of fatty liver & exclusion of excessive alcohol consumption • Whether there are other etiologies of chronic liver disease (e.g., viral hepatitis, autoimmune liver disease, medications) • Whether the patient is likely to have underlying NASH • Whether fibrosis is present • Whether fibrosis is at an advanced stage **Straightforward practical diagnosis & staging decision tree algorithm for NAFLD/NASH (cf. Fig. 1) recommended for use by gastroenterologists & hepatologists** • Once diagnosis of NAFLD/NASH is made, staging of fibrosis is indicated, especially for patients at risk of NASH & fibrosis • Fibrosis can be staged by using either of the following, - Serum biomarker •FIB-4 or NFS, confirmed high risk with LSM by VCTE™, MRE or ELF or liver biopsy •Second Non Invasive Test (NIT) can be performed to reduce the area of uncertainty - Imaging biomarker •LSM by VCTE™ LSM<8 kPa, especially those with <6kPa, considered as low risk LSM>=12 kPa, considered as high risk •For intermediate risk, recommend to receive another type of NIT

VCTE™: Vibration Controlled Transient Elastography • LSM: Liver Stiffness Measurement • NAFLD: Non-alcoholic Fatty Liver Disease • NASH: Non-alcoholic Steatohepatitis • FIB-4: Fibrosis-4 Index • NFS: NAFLD Fibrosis Score • MRE: Magnetic Resonance Elastography • ELF: Enhanced Liver Fibrosis • NIT: Non-invasive Test

Key points

- LSM by VCTE™ was recommended in this algorithm as the initial imaging biomarker for NASH staging
- The most important step is for clinicians to use NITs through an algorithm to risk stratify and identify patients with NASH who are at highest risk of adverse clinical outcomes
- This initial step can occur in the primary care or other specialty practice setting where patients at risk of NASH are seen (endocrinology, cardiology & gastroenterology)

FIGURE 1 **Algorithm to identify patients with NASH at high risk of adverse outcomes**