UT Southwestern Medical Center

Non-invasive Markers and Portal Hypertension

Lafaine Grant MD, FAASLD
Associate Professor of Internal Medicine
Division of Digestive and Liver Diseases
Hepatology and Liver Transplant
UT Southwestern Medical Center

Key Questions

- What are the non-invasive modalities available for the assessment of fibrosis in chronic liver disease?

- Which assessments of fibrosis might be most accurate?

- How to use these non-invasive tools to assess for portal hypertension, direct management and assess response.

Why measure fibrosis?

- **Assessment of disease**
  - Diagnosis
  - Prognosis
  - Treatment decisions
- **Monitoring disease**
  - Natural history
  - Treatment effects
  - Drug development

Cross-sectional

Dynamic change over time

Case presentation

HPI: 59y/o female who was first diagnosed with "fatty tissue around my liver" about 5 years ago. She was advised to eat healthy, exercise, avoid alcohol and Tylenol and "the fat around the liver would decline". Recently told of abnormal liver imaging was noted when she visited the ER for abdominal pain. Treated for constipation with resolution of symptoms.

MEDICATIONS: Reviewed as noted in the chart.
PMH: HTN, DM, hypothyroidism

SOCIAL HISTORY: Reviewed as noted in chart.
Retired teacher.
Tobacco - quit 2012; previously 1 pack/week
Alcohol – drank “a lot” since her 20’s. Slowed down in her 50’s and now only twice per year or the occasional family dinner.

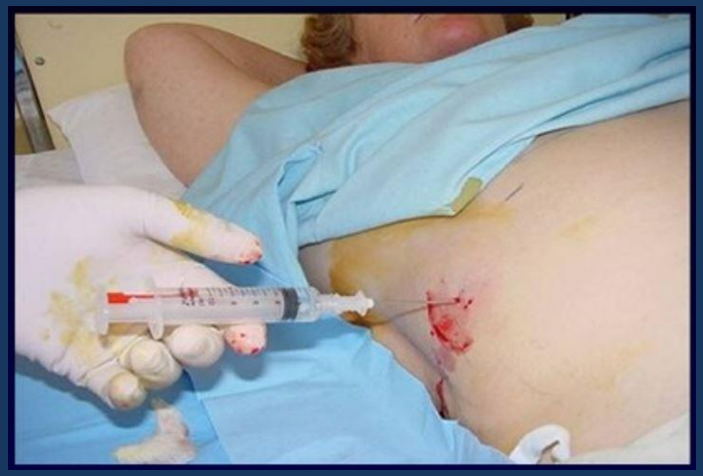
PHYSICAL EXAMINATION:
Appears well. No stigmata of chronic liver disease.

LABS: CLD panel negative. Alk phos 105, total bilirubin 1.2, AST 60, ALT 48, albumin 3.9, creatinine 0.48, WBC 5.4, Hemoglobin 12.3, platelets 186.

IMAGING:
US: Sonographic features suggesting chronic liver disease, not definitive for cirrhosis. Correlation with relevant risk factors and associated serum markers may be warranted. Ultrasound elastography may help assess for clinically significant fibrosis. No focal hepatic lesion identified. No cholelithiasis or biliary ductal dilatation. No evidence of portal hypertension.

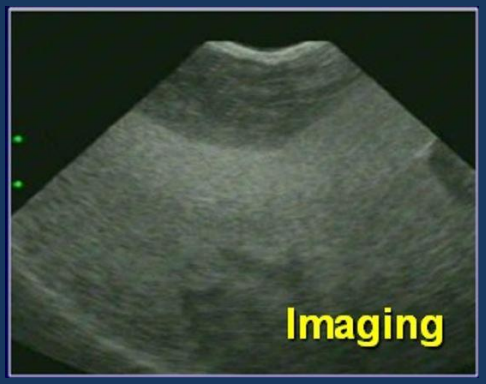
Next Steps…

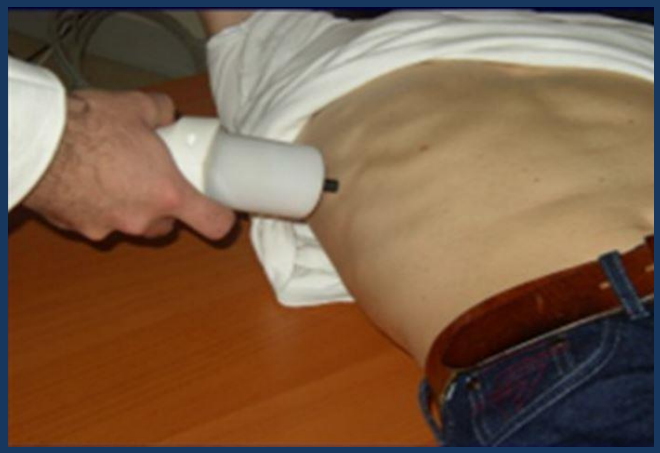
Current options for fibrosis assessment



Liver biopsy

Serum Biomarkers





Elastography

Limitations of liver biopsy

Sampling error

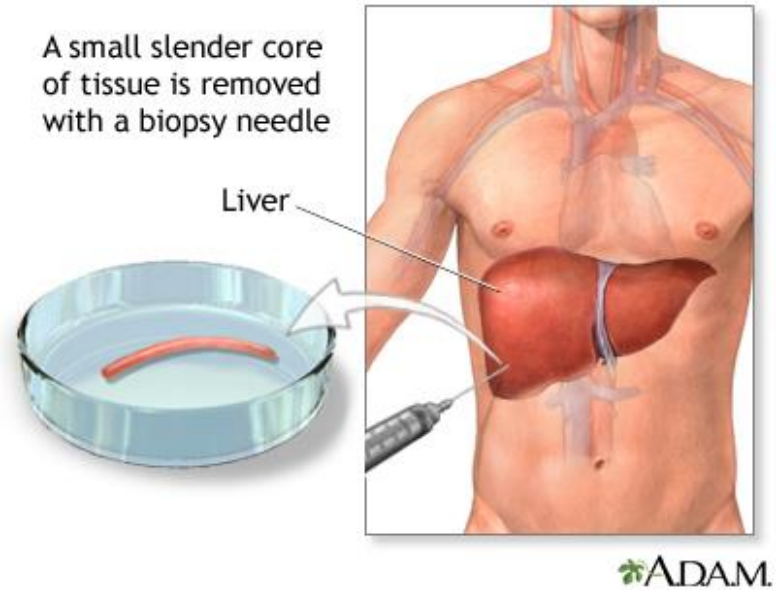
- 1/50,000 of the liver
- Uneven distribution findings

Intra & inter-observer variation

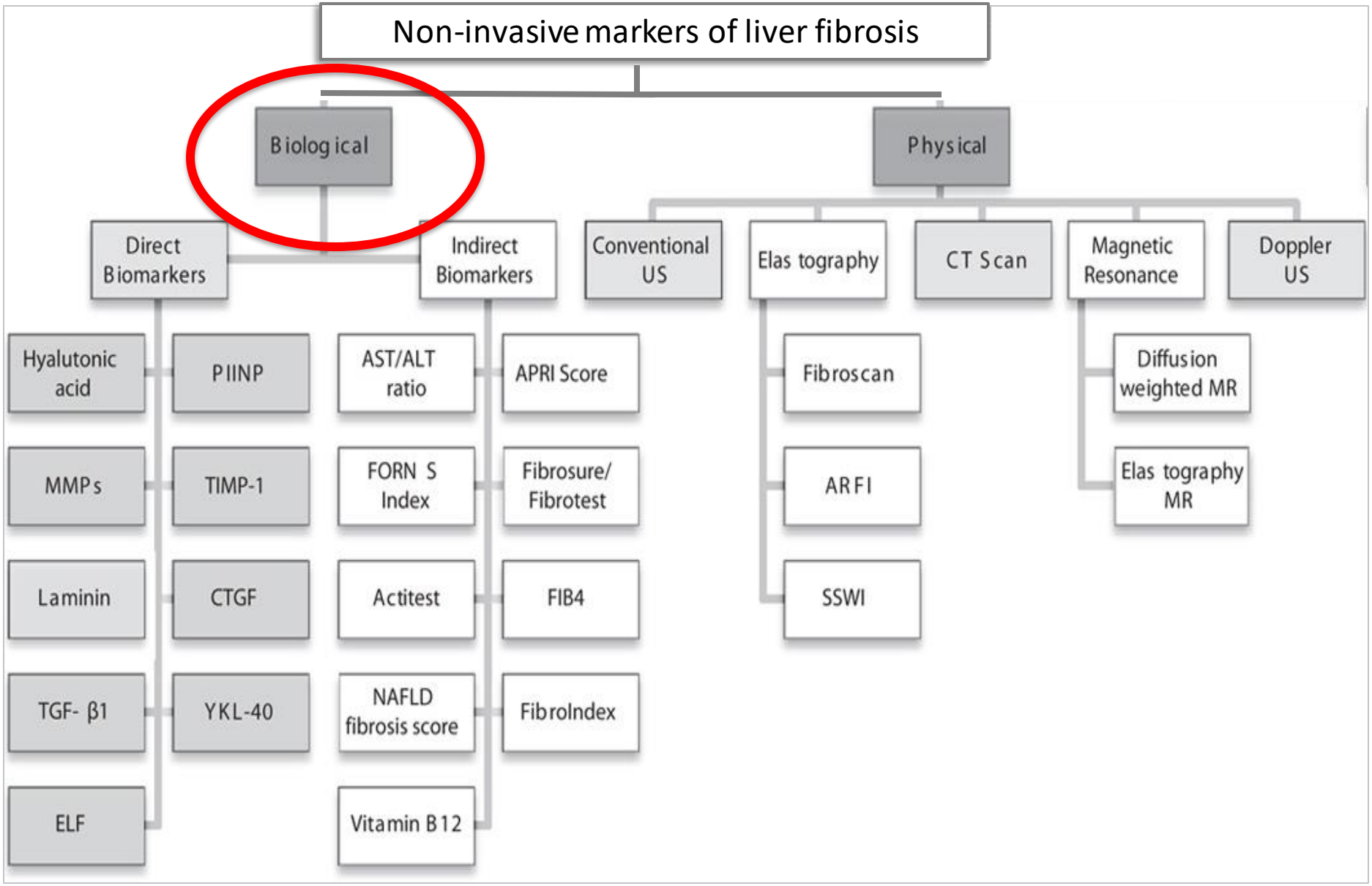
- 25% diagnostic errors

Complications

- Pain 80%
- Major complications 0.6 %
- Mortality 0.01 - 0.1%



Regev Am J Gastroenterology 2009. Rockey, Hepatology 2009. Bedossa,Hepatology 2003



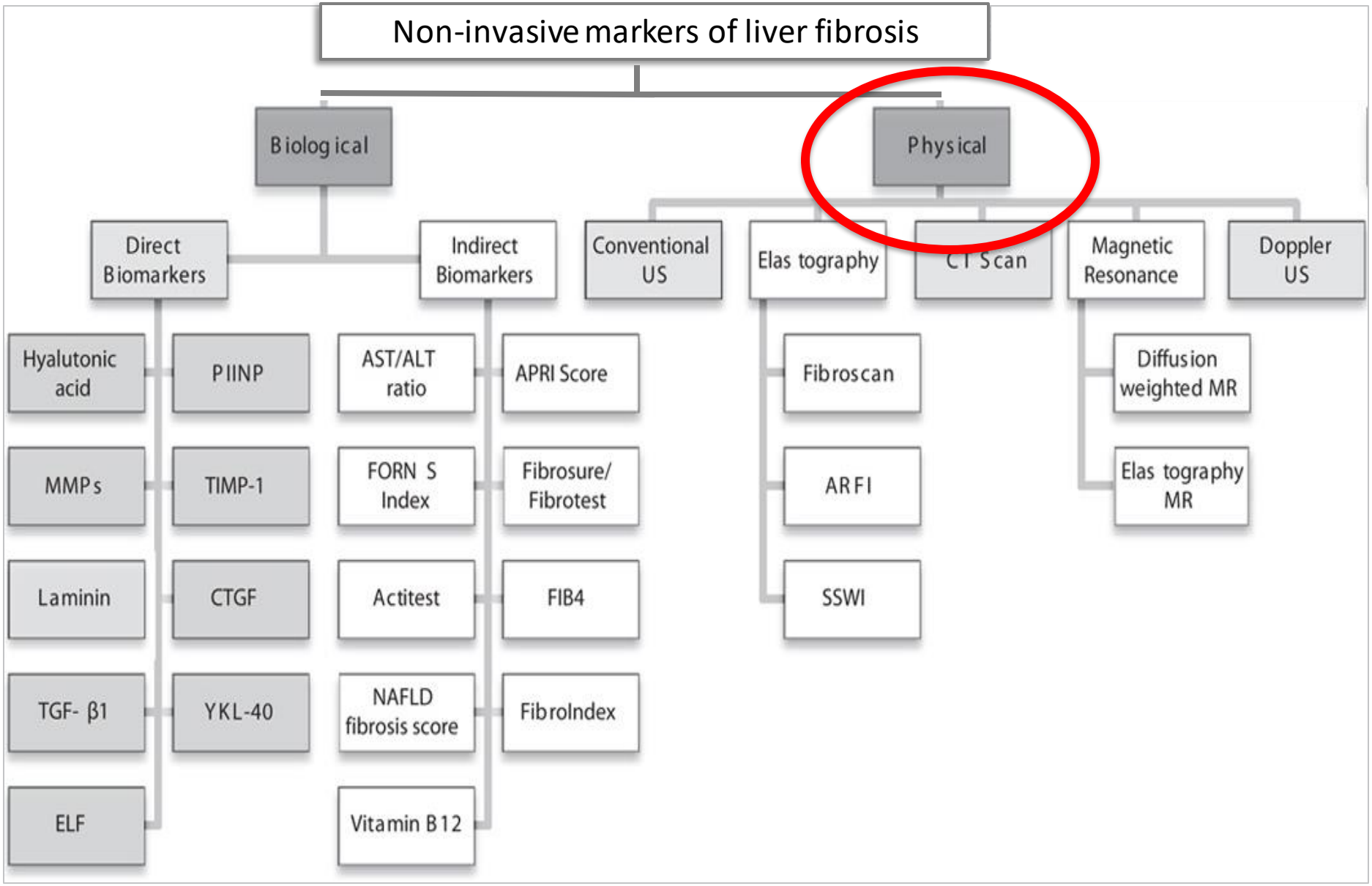
Czul et al. J Clin Gastroenterol 2016

Comparison of blood-based biomarkers of liver fibrosis

Biomarker	Components	Disease specificity	Validation	Accuracy*	Indeterminate cases†	Prognostic ability*
APRI	AST, platelets	CHC, NAFLD	+++	+/++	50%–60%	+
FIB-4	AST, ALT, platelets, age	CHC, NAFLD	+++	+++	20%–30%	++
NAFLD fibrosis score	Age, BMI, IFG/diabetes, AST, ALT, platelets, albumin	NAFLD	+++	+++	20%–35%	++
Fibrotest/fibrosure	Age, sex, bilirubin, GGT, α2M, haptoglobin, apo-A1	CHC, CHB, ALD, NAFLD	+++	+++‡	0%–35%	++++
Hepascore	Age, sex, bilirubin, GGT, α2M, HA.	CHC, CHB, ALD, NAFLD	+++	++++	0%–30%	++++
Fibrospect (CHC)	α2M, HA, TIMP-1	CHC	++	+++‡	0%	NA
Fibrospect (NASH)	α2M, HA, TIMP-1	NAFLD	+	++++	0%–40%	NA
FibroMeter^{V2G} (virus)	Age, sex, platelets, ALT, AST, GGT, PTI, urea, α2M,	CHC, CHB	++	+++	0%	++++
FibroMeter (SNAFFLED)	Age, sex, weight, platelets, ALT, AST, ferritin, glucose	NAFLD	++	++	0%–35%	NA
Enhanced liver fibrosis score	HA, TIMP-1, PNPIII	CHC, CHB, ALD, NAFLD, PSC	+++	++++/+++++	0%–40%	++++

+++++AUC ≥0.90, ++++AUC 0.85–0.89, +++AUC 0.80–0.84, ++AUC 0.75–0.79, +AUC <0.75

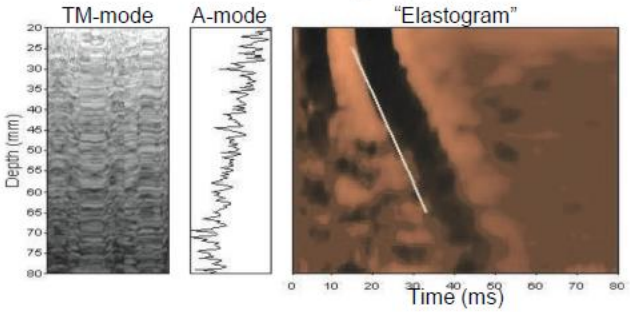
Loomba R,Adams LA. Gut. 2020;**69**:1343–1352



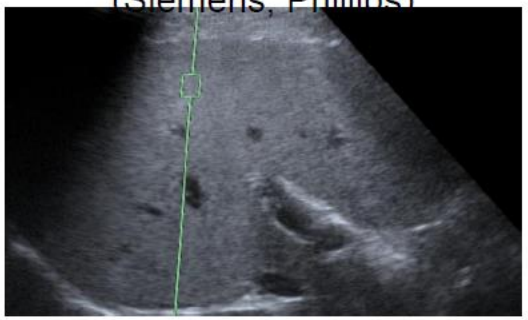
Czul et al. J Clin Gastroenterol 2016

Imaging tests that measure liver stiffness

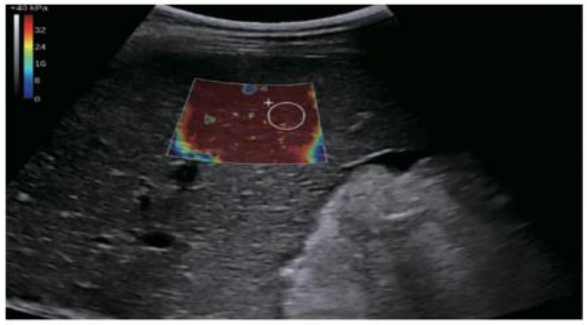
Transient Elastography (Echosens)



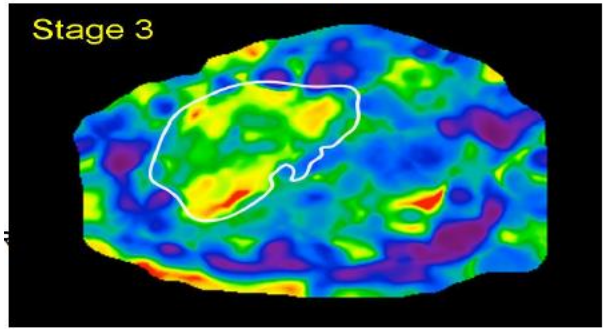
Point SWE ("ARFI quantification")
(Siemens, Phillips)



Shear Wave Elastography (Supersonic Imagine)



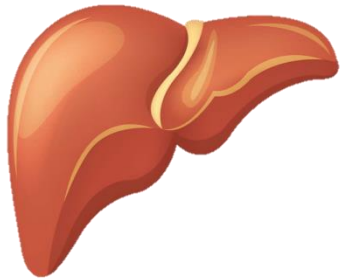
MR Elastography



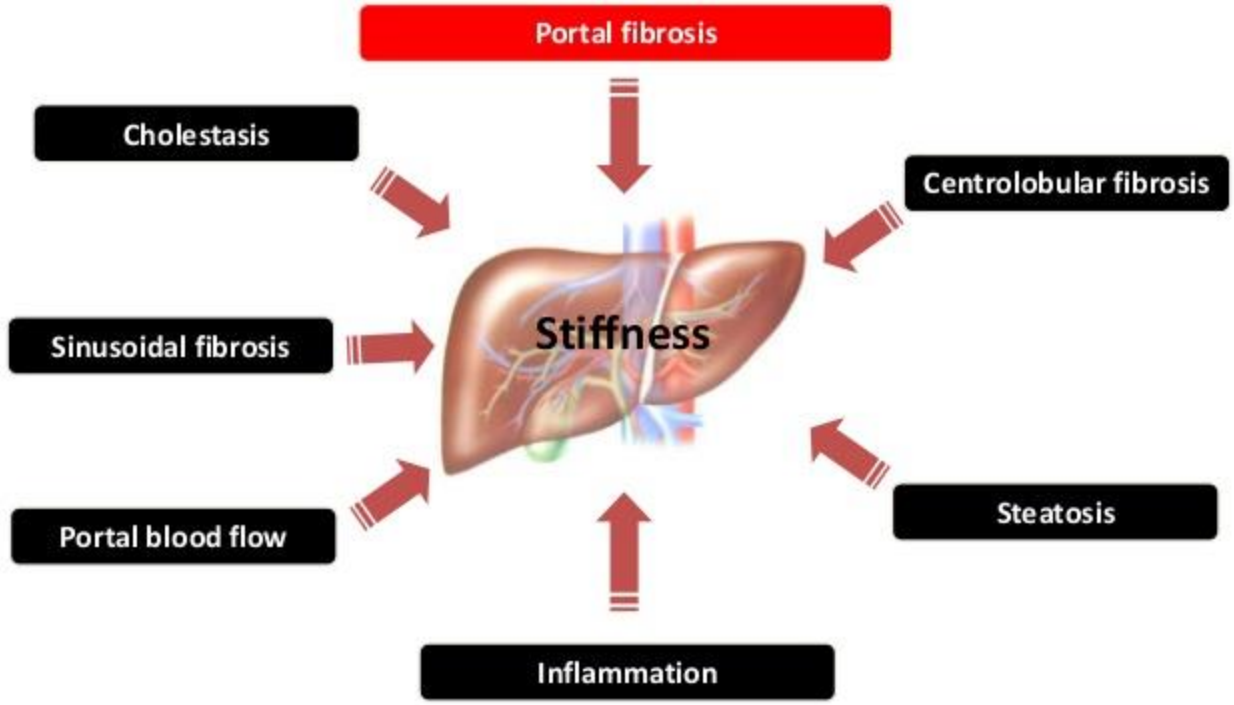
VCTE

Vibration
Controlled
Transient
Elastography

Fibroscan Operating Principle



Variables contributing to Liver Stiffness



Meal Restriction Recommendation

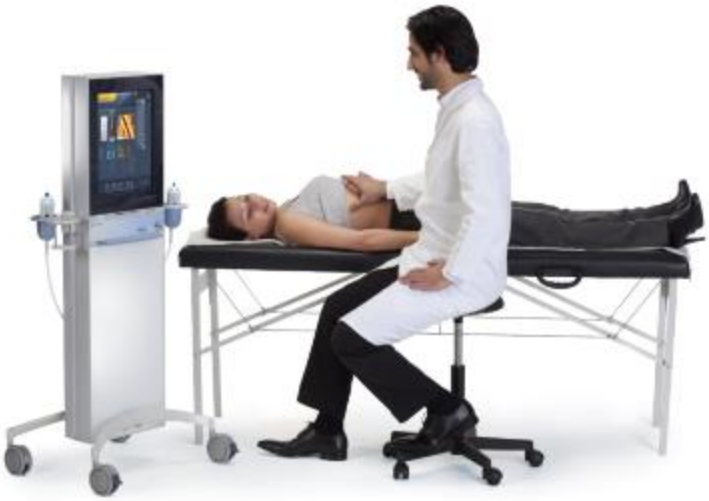
- Fast ≥ 3 hours prior to testing
- Drinking water is acceptable

Food intake increases liver stiffness in patients with chronic or resolved hepatitis C virus infection; Mederacke, I., et al; Liver International, 2009. 29(10): p. 1500-6.
Liver Stiffness Is Influenced by a Standardized Meal in Patients With Chronic Hepatitis C Virus at Different Stages of Fibrotic Evolution; Arena et al; Hepatology, Volume 58, No 1, 2013

FibroScan Technology

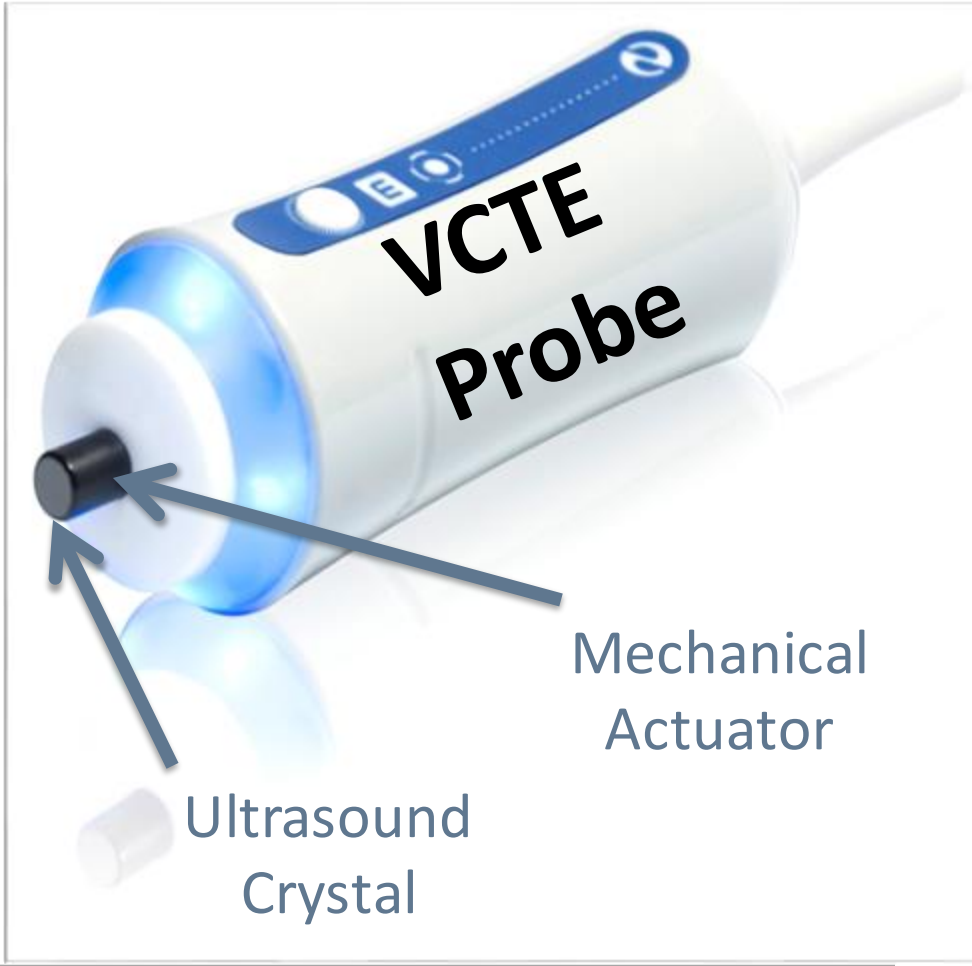
Dual Function Liver Testing

- Transient Elastography (VCTE)
- Ultrasound attenuation rate (CAP)



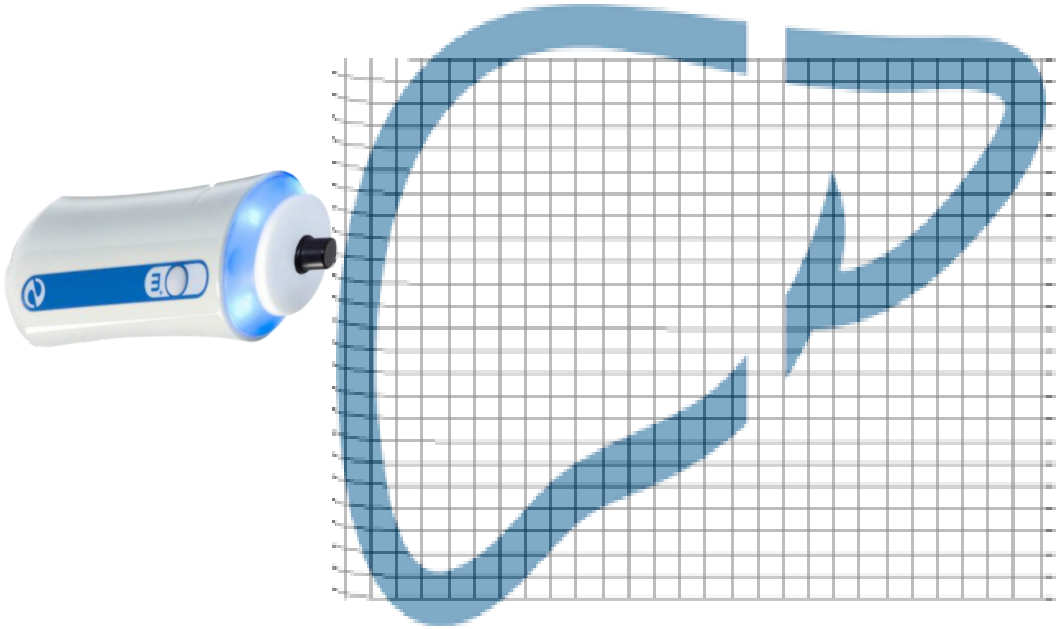
VCTE Measurement Steps

- Mechanically induce a shear wave
- Measure shear wave speed
- Calculate stiffness



Shear Wave Speed Correlates to Stiffness

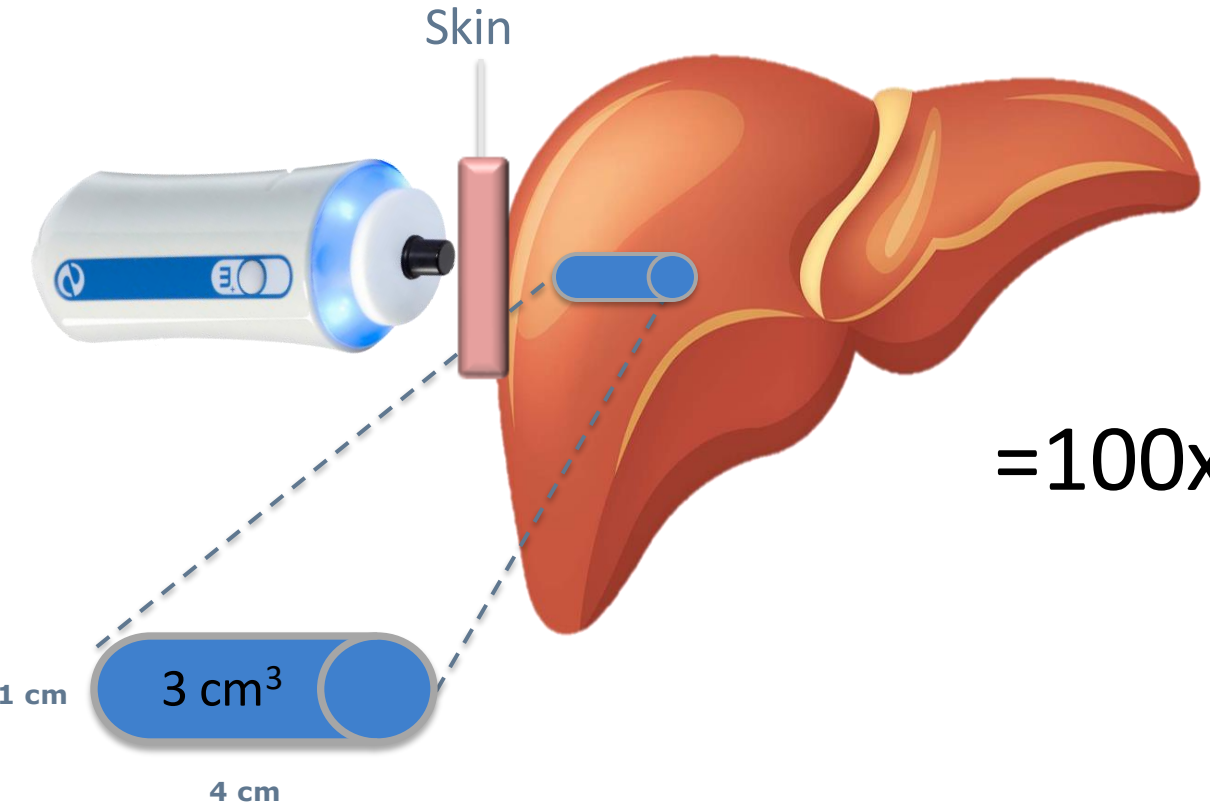
Hooke's Law



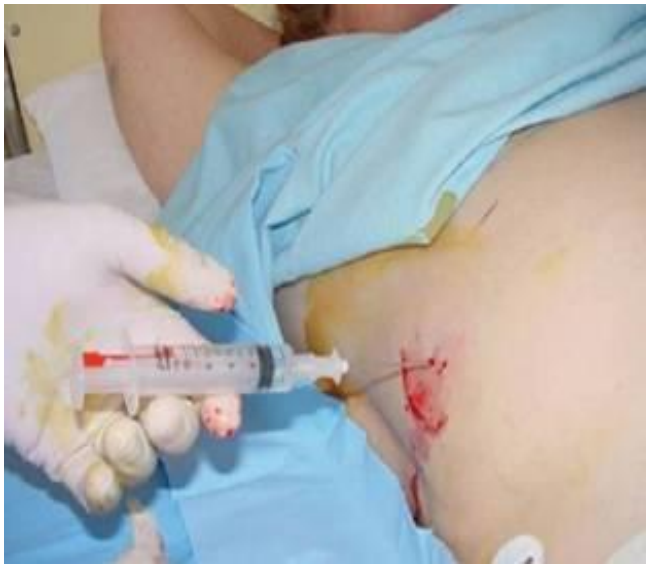
Low Speed = Low Stiffness

High Speed = High Stiffness

Controlled Exam Region



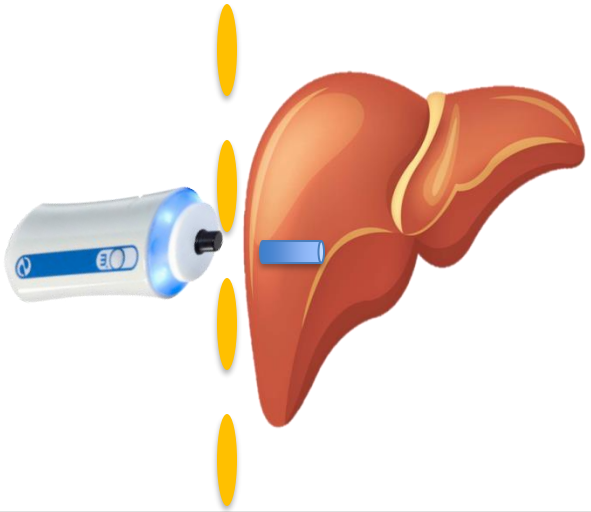
=100x



Roulot D, bet al.J Hepatol. 2008

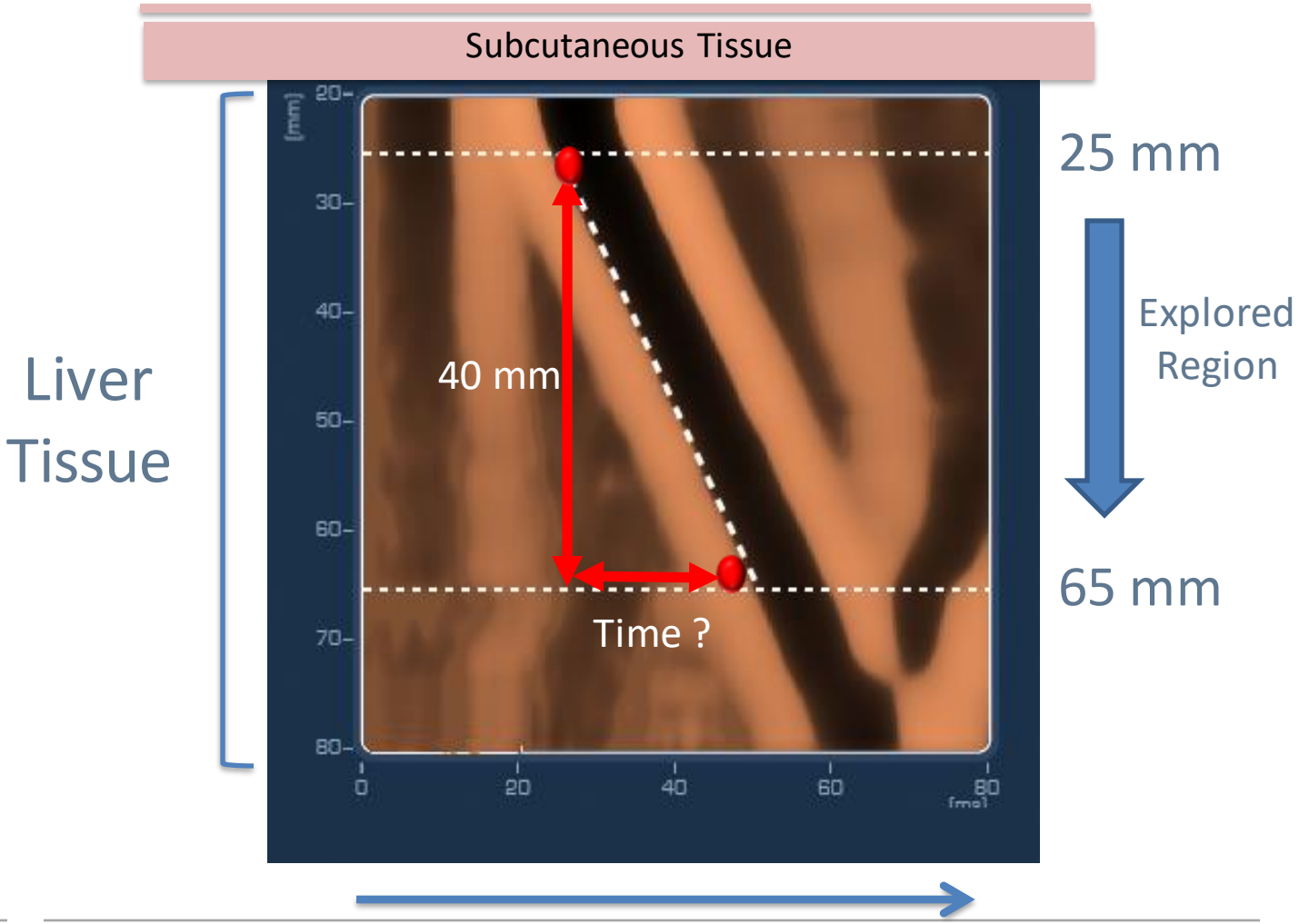
Data Acquisition Steps

- Position probe at center of liver
- Assess skin to liver distance / select probe for testing
- Acquire ≥ 10 measurements in same position
- Generate report
  - Median values
  - IQR/Med ratio
  - Measurement thumbnails

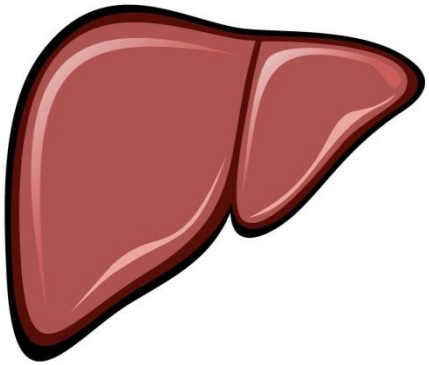


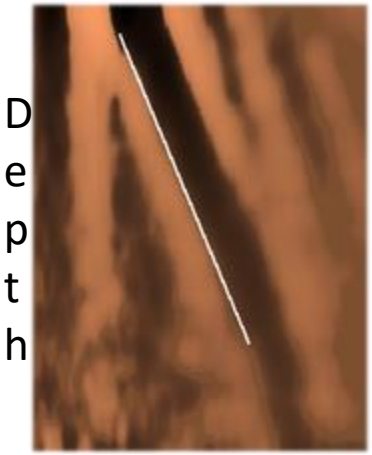
Propagation Map

Shear Wave Speed = D/T

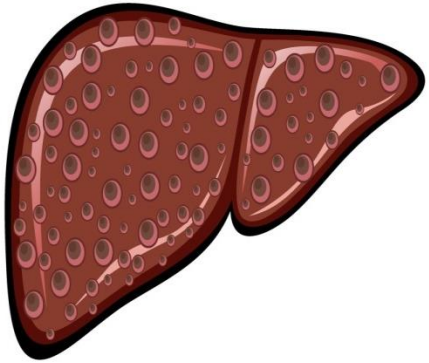


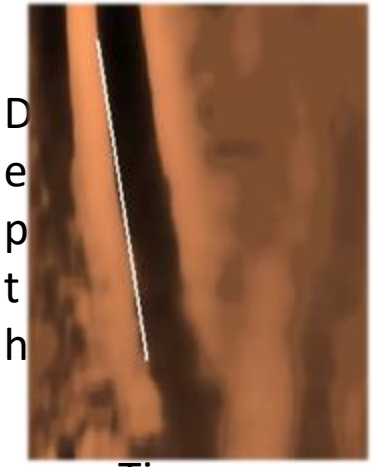
Shear Wave Speed Examples





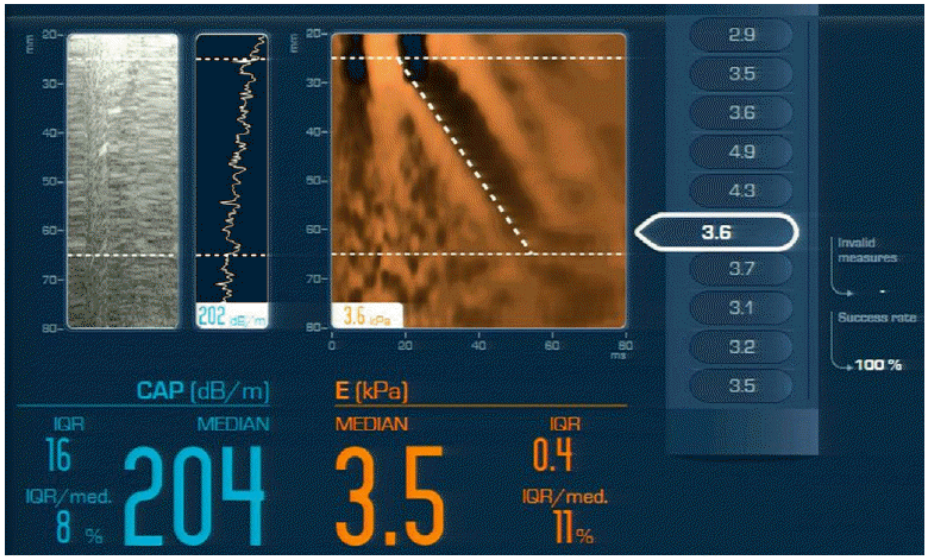
Slow



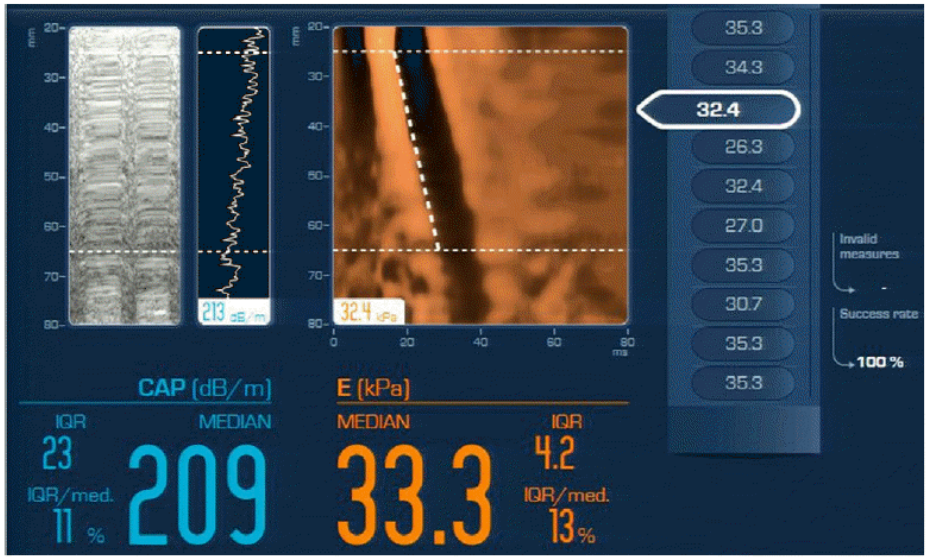


Fast

Fibroscan Result

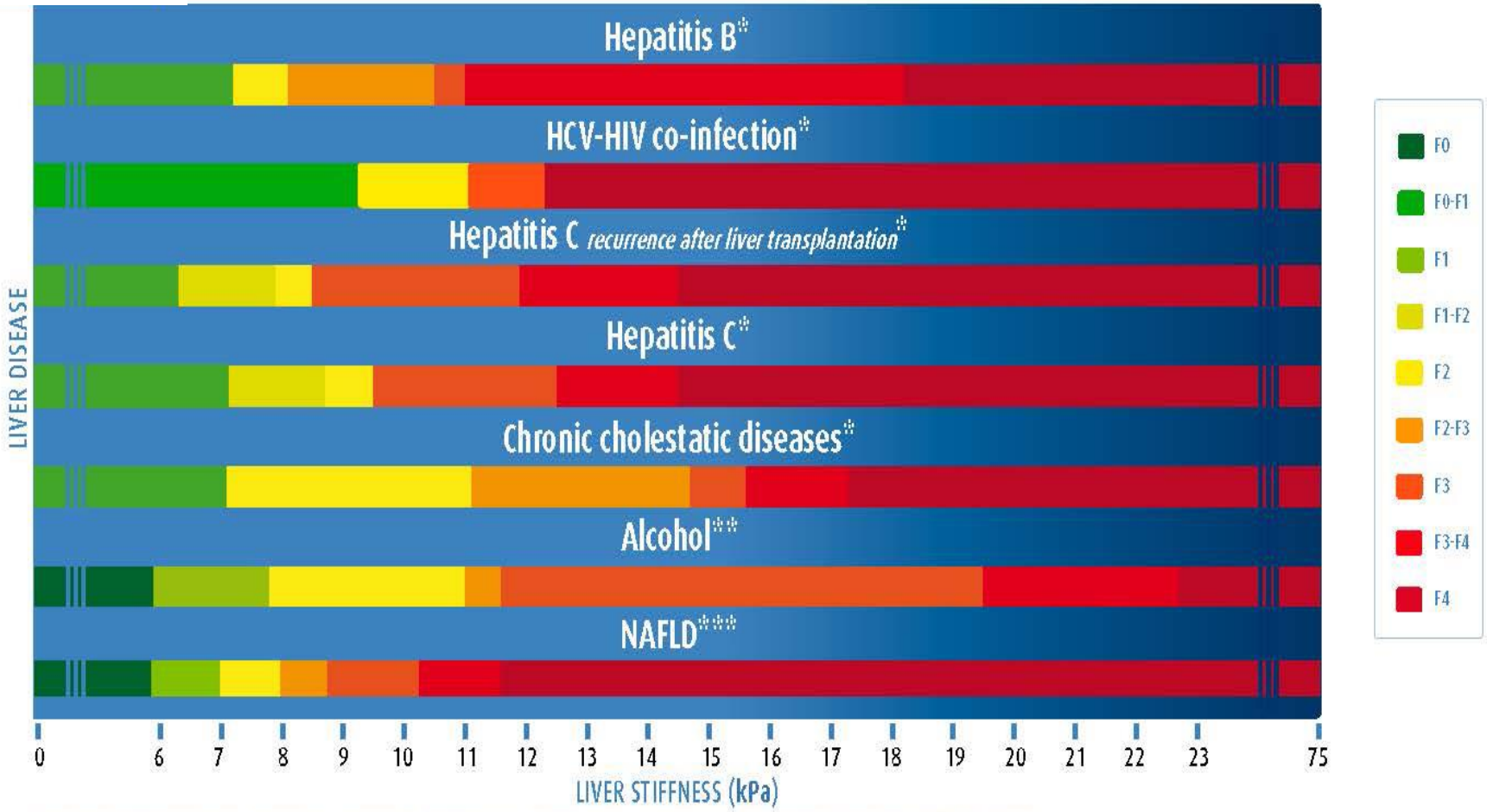


A



B

CORRELATION BETWEEN LIVER STIFFNESS (kPa) & FIBROSIS STAGE

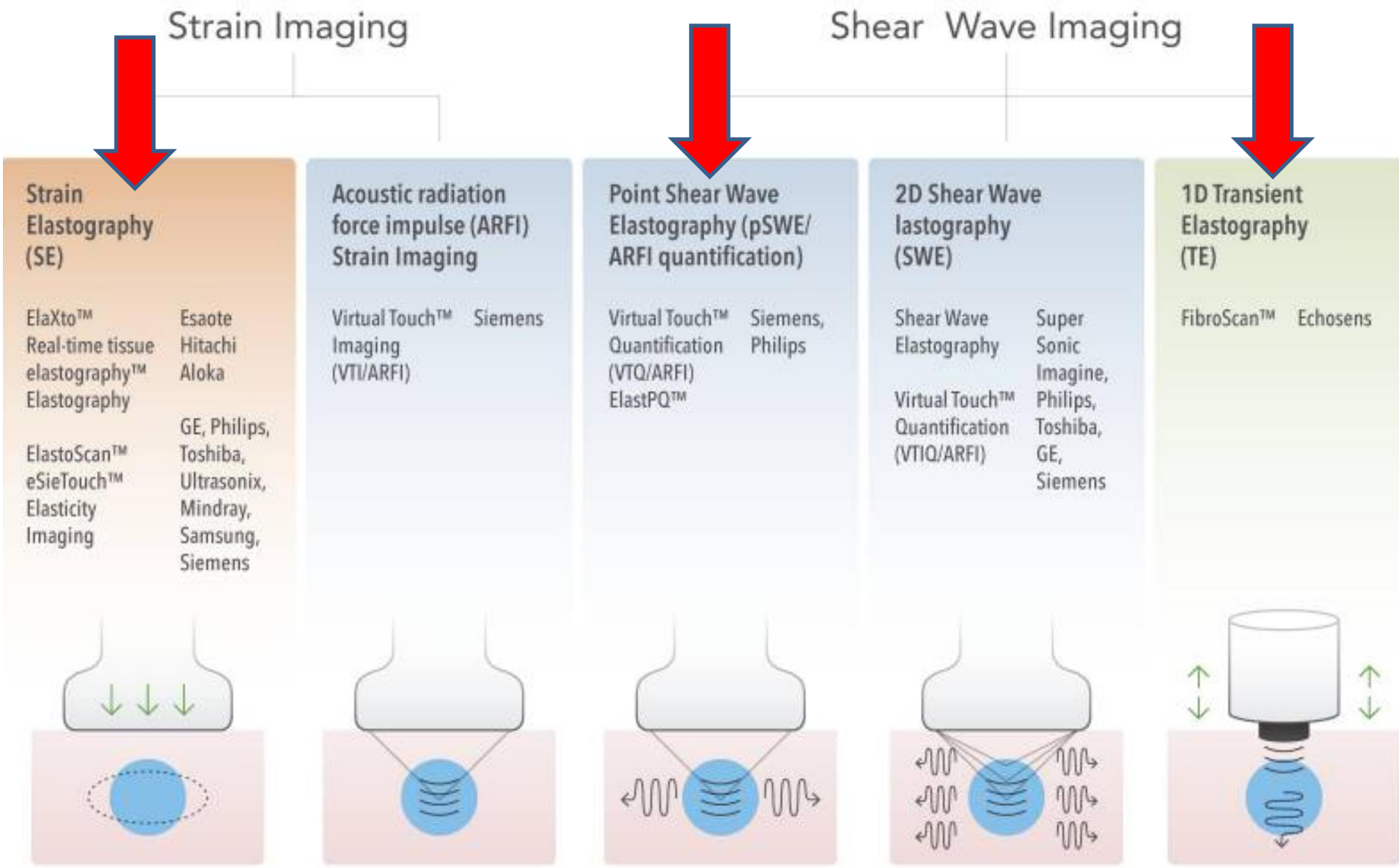


*According to Metavir score: Transient elastography (FibroScan): V. de Lédinghen, J. Vergniol, Gastroentérologie Clin Bio (2008) 32, 58-67

**According to Brunt score: Nahon et al. J Hepatol (2009) 49, 1062-68, Nguyen-Khac et al. , Aliment Pharmacol Ther (2008), 28, 1188-98

***According to Brunt score: Wong et al. Hepatology (2010) 51, 454-62Transient elastography (FibroScan®): V. de Lédinghen, J. Vergniol, Gastroentérologie Clin Bio (2008) 32, 58-67

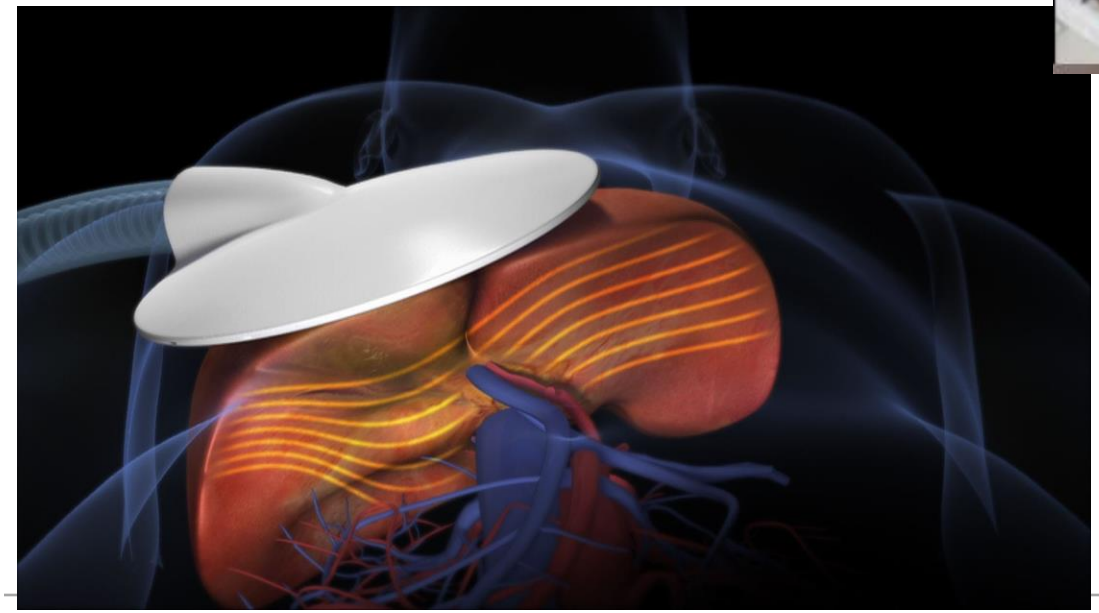
Other Sonographic Elastography Techniques



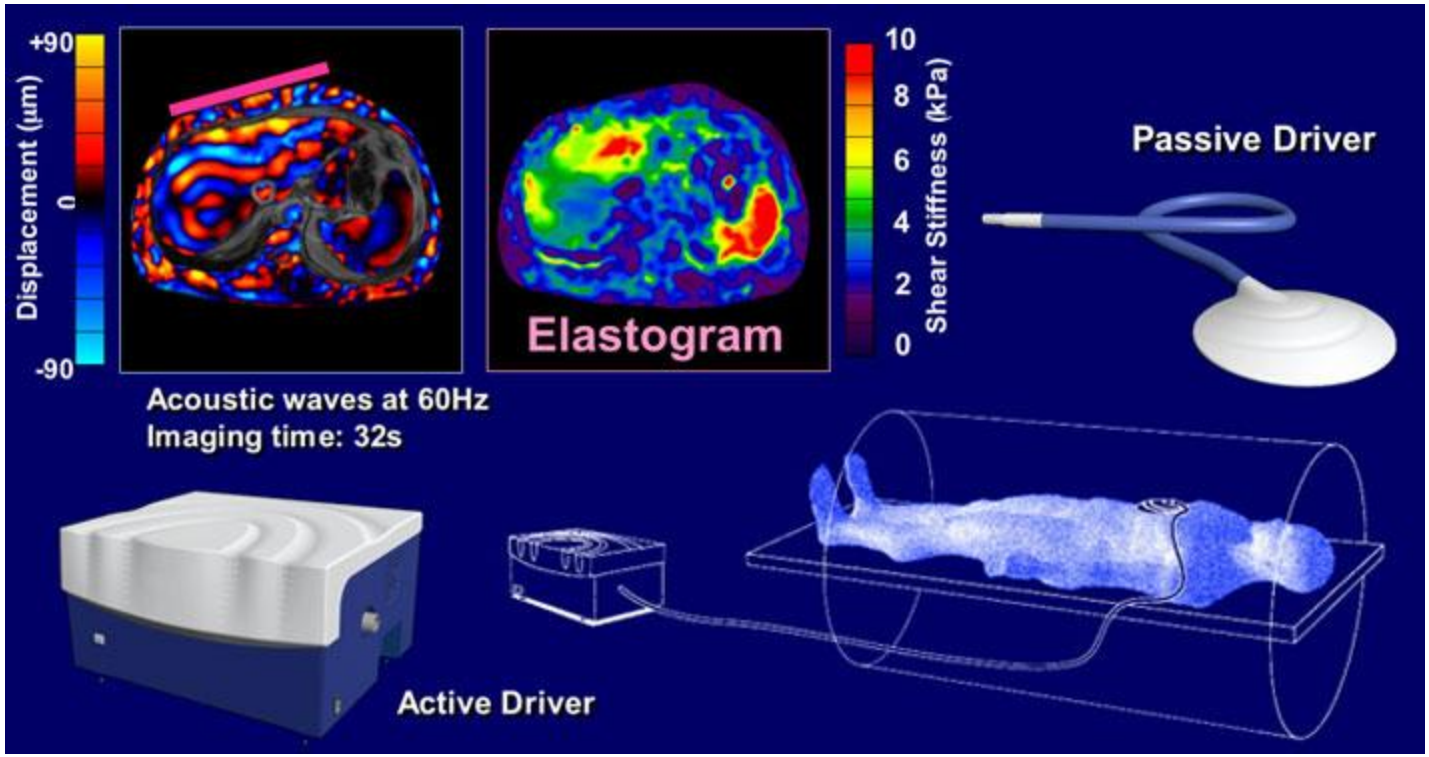
Rosa M.S. Sigrist et al. Theranostics. 2017; 7(5): 1303–1329.

Magnetic Resonance Elastography

- Uses a vibrating device to induce shear waves which are detected by the MRI machine

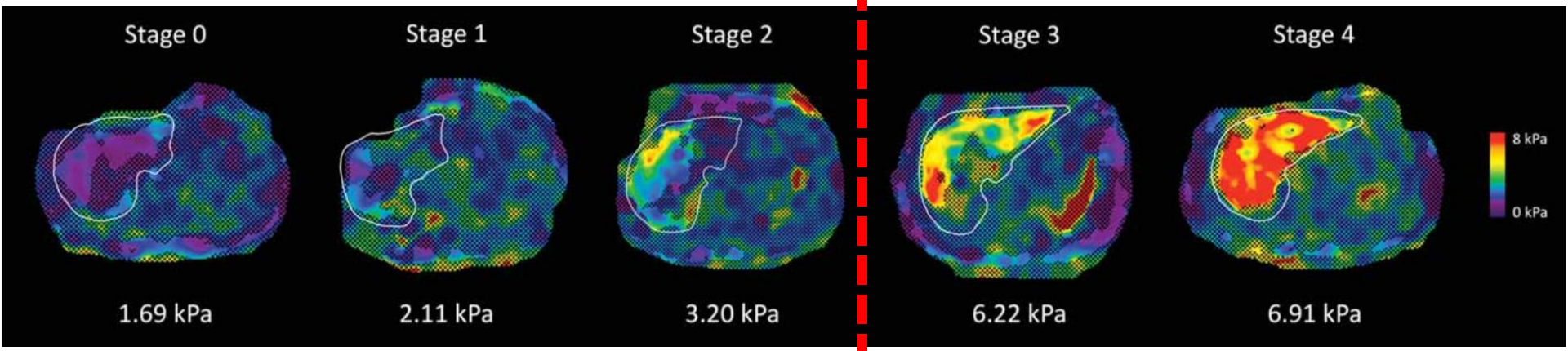


Magnetic Resonance Elastography



Muthupillai R et al. Science. 1995

Magnetic Resonance Elastography is accurate in diagnosing advanced fibrosis



"Stiffness" cutoff: 3.63 kPa
Sensitivity 0.86
Specificity 0.91

AUC for diagnosis of advanced fibrosis
0.924

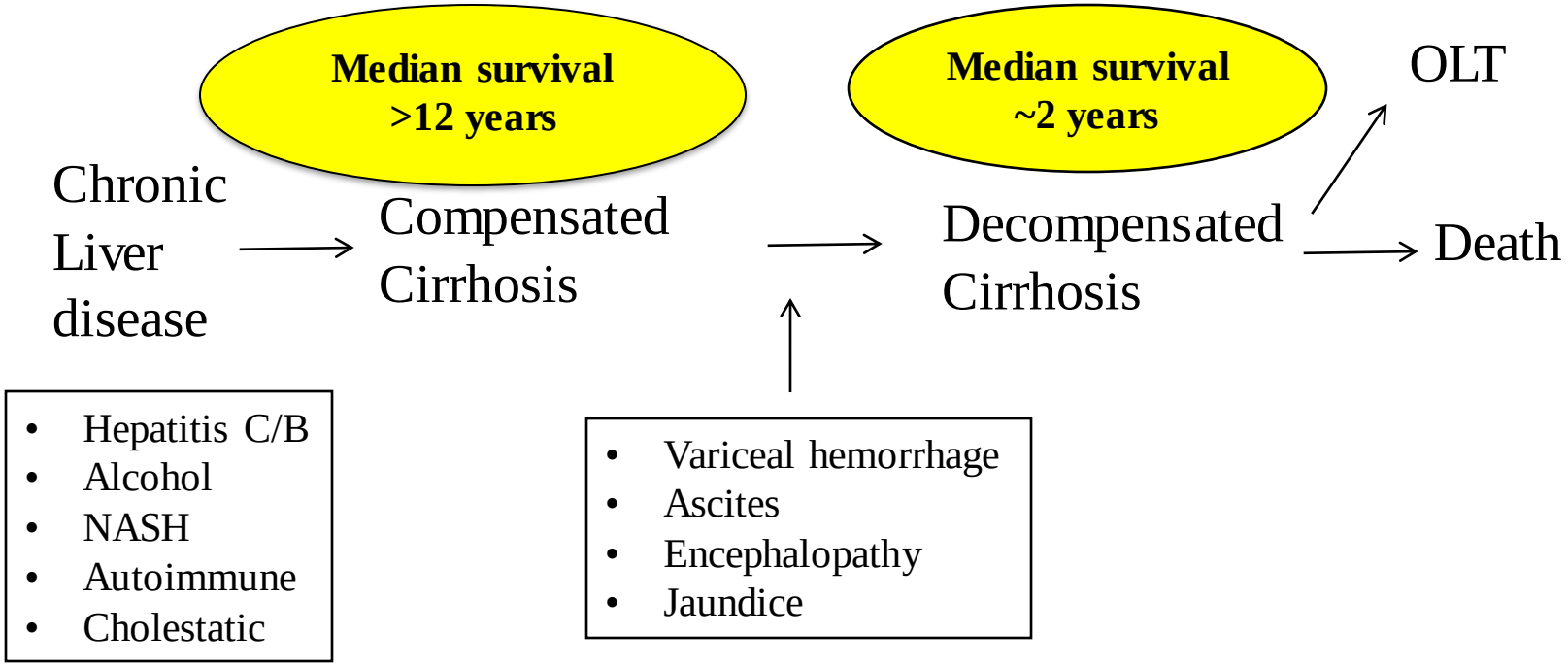
Loomba et al 2014.

Limitations of Non-invasive Tests

Fibrosis marker	Failure rate	Factors related to failure	Invalid/unreliable result rate	Confounders
Indirect blood-based biomarkers	Negligible	–	30% Indeterminate (FIB-4, NAFLD Fibrosis Score)	Acute hepatitis, cholestasis, systemic inflammation, Gilberts/hemolysis (scores with bilirubin)
Direct blood-based biomarkers	Negligible	–	?	Acute hepatitis, systemic inflammation
VCTE	3%–14%	Obesity (less with XL probe), ascites	1%–9%	Acute hepatitis, cholestasis, beta-blockers, food ingestion, obesity, cardiac congestion.
pSWE	0%–1%	Obesity	16%–24%	Acute hepatitis, food ingestion, obesity*
2D-SWE	1%–13%	Obesity	0%	Acute hepatitis, food ingestion*
2D-MRE	<5%	Claustraphobia, inability to fit in MRI or breath hold,	Negligible	Iron overload, acute hepatitis, massive ascites

Loomba R,Adams LA. Gut. 2020;**69**:1343–1352

Natural History of Chronic Liver Disease



D'Amico , Garcia-Tsao , Pagliaro. J Hepatol 2006;44:217-231.
D'Amico et al. dig Dis Sci 1986;31: 468-475.
D'Amico et al. Gastroenerology 2001;120:A2

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

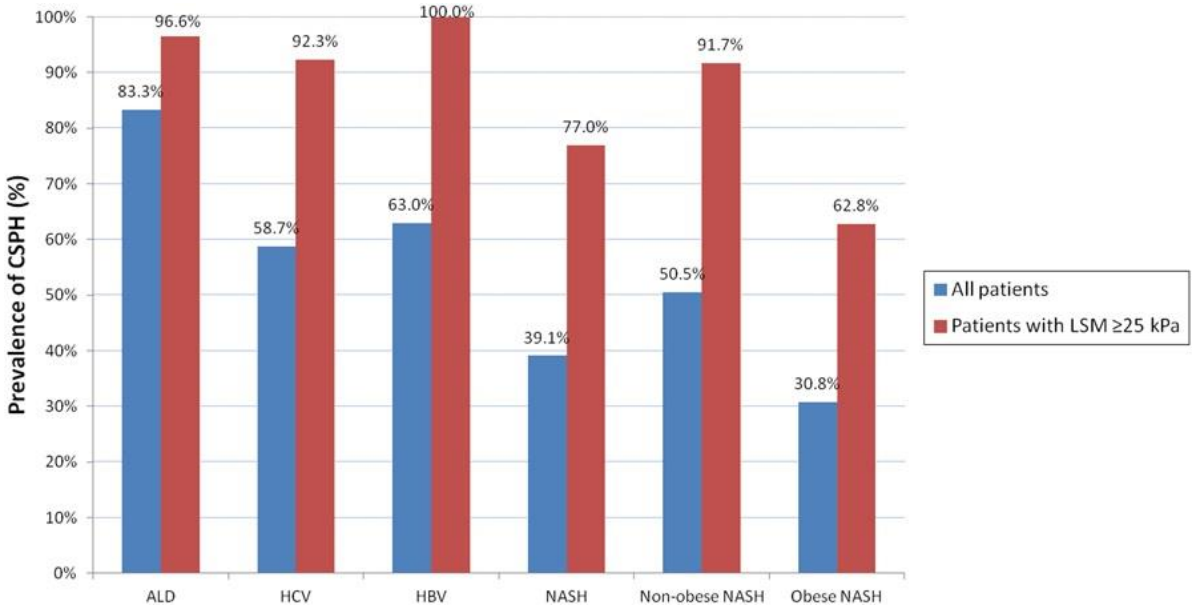
HEPATOLOGY, VOL. 64, NO. 6, 2016

Noninvasive Tools and Risk of Clinically Significant Portal Hypertension and Varices in Compensated Cirrhosis: The "Anticipate" Study

Juan G. Abraldes,[1] Christophe Bureau,[2] Horia Stefanescu,[3] Salvador Augustin,[4] Michael Ney,[1] Hélène Blasco,[2] Bogdan Procopet,[3,5] Jaime Bosch,[5,6] Joan Genesca,[4] and Annalisa Berzigotti,[5,6] for the Anticipate Investigators

In patients with compensated advanced chronic liver disease (cACLD), the presence of clinically significant portal hypertension (CSPH) and varices needing treatment (VNT) bears prognostic and therapeutic implications. Our aim was to develop noninvasive tests-based risk prediction models to provide a point-of-care risk assessment of cACLD patients. We analyzed 518 patients with cACLD from five centers in Europe/Canada with paired noninvasive tests (liver stiffness measurement [LSM] by transient elastography, platelet count, and spleen diameter with calculation of liver stiffness to spleen/platelet score [LSPS] score and platelet-spleen ratio [PSR]) and endoscopy/hepatic venous pressure gradient measurement. Risk of CSPH, varices, and VNT was modeled with logistic regression. All noninvasive tests reliably identified patients with high risk of CSPH, and LSPS had the highest discrimination. LSPS values above 2.65 were associated with risks of CSPH above 80%. None of the tests identified patients with very low risk of all-size varices, but both LSPS and a model combining TE and platelet count identified patients with very low risk (<5%) risk of VNT, suggesting that they could be used to triage patients requiring screening endoscopy. LSPS values of <1.33 were associated with a <5% risk of VNT, and 26% of patients had values below this threshold. LSM combined with platelet count predicted a risk <5% of VNT in 30% of the patients. Nomograms were developed to facilitate point-of-care risk assessment. *Conclusion:* A significant proportion of patients with a very high risk of CSPH, and a population with a very low risk of VNT can be identified with simple, noninvasive tests, suggesting that these can be used to individualize medical care. (HEPATOLOGY 2016;64:2173-2184).

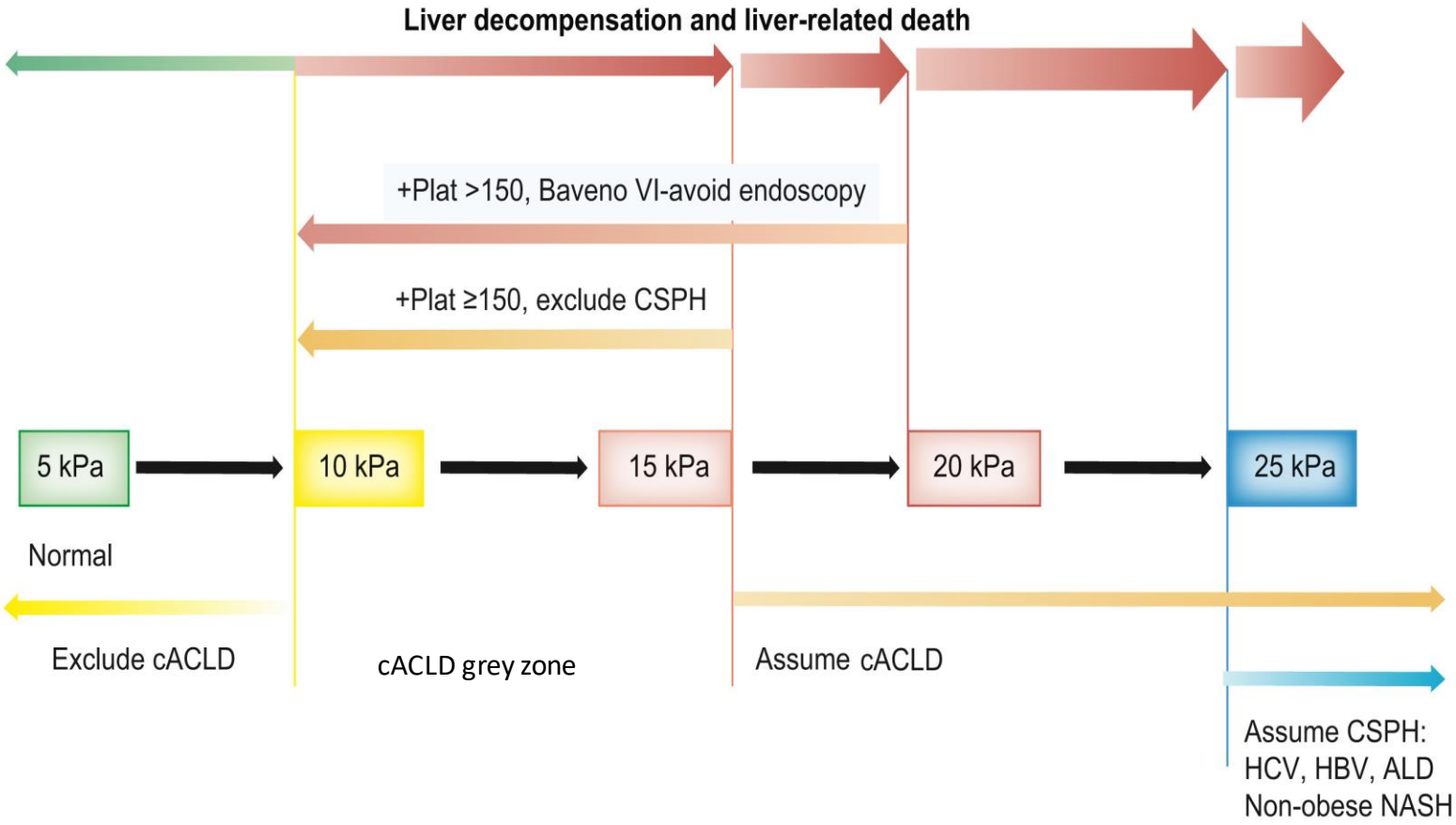
Prevalence of CSPH by Etiologies



Pons M et al, Am J Gastro 2021, 116 (4) 723-732

UTSouthwestern Medical Center

Algorithm for the non-invasive determination of cACLD and CSPH

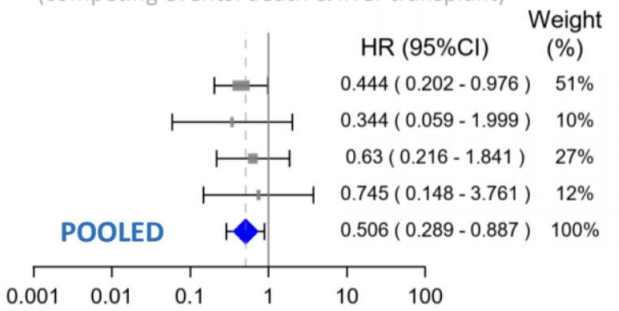


Journal of Hepatology 2022 vol. 76 j 959–974

Use NSBB in CSPH to Prevent Decompensation

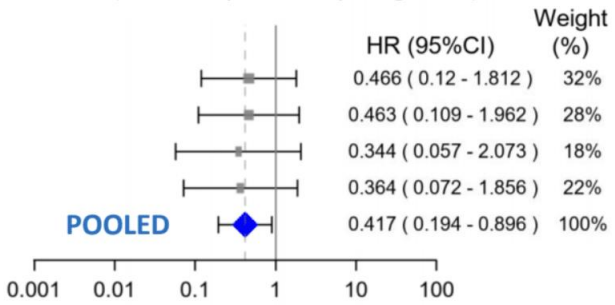
Carvedilol significantly decrease the risk of developing decompensation

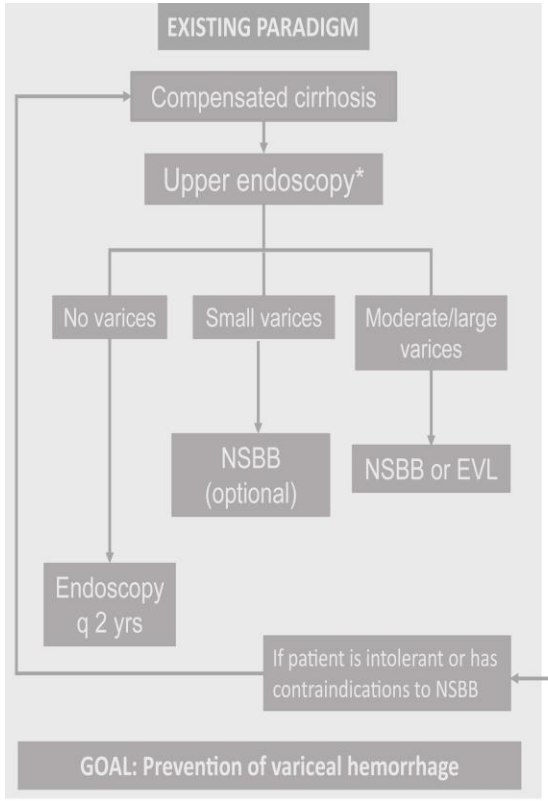
(competing events: death & liver transplant)

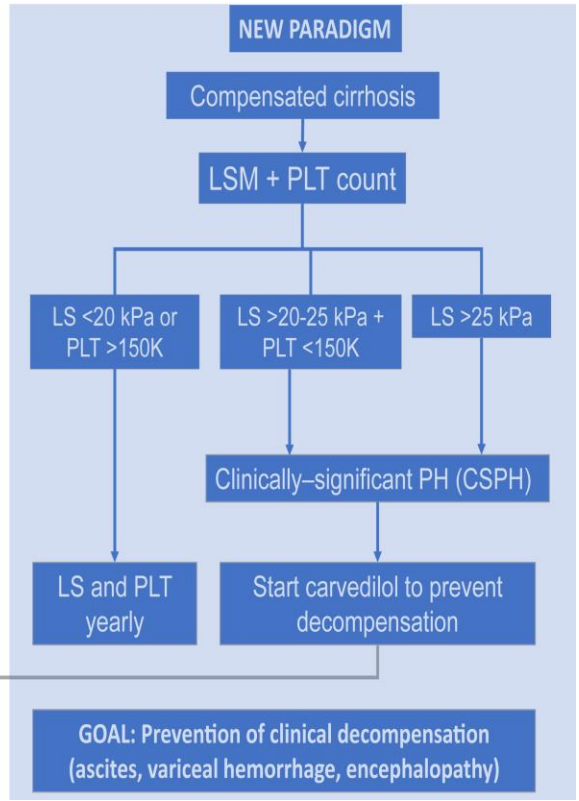


Carvedilol significantly improve survival

(liver transplant, competing event)







Villanueva, C et al. Journal of Hepatology 2022 vol. 77 j 1014–1025
Garcia-Tsao G and Abraldes JG. Gastro 161 (3); Sept 2021, 770-773

Take Away

Identify cACLD

- LSM < 10 kPa rules out cACLD, 10-15 are suggestive, >15 kPa highly suggestive of cACLD
- LSM <10 kPa <1% 3-year risk of decompensation and death

Outcome & Prognosis

- A rule of 5 for LSM by TE (10-15-20-25 kPa) should be used to denote progressively higher risk of decompensation and death

Monitor

- LSM 7-10 kPa monitored case-by-case basis for progression
- Consider adding serum marker of fibrosis (ex. ELF, Fibrotest)
- In cACLD, LSM could be repeated every 12 months to monitor changes
- ↓ LSM (≥ 20% or <10 kPa) is associated with decreased risk of decompensation and death.

Treatment response

- Pts with HCV-induced cACLD who achieve SVR and show consistent post-treatment improvements with LSM values of <12 kPa and PLT > 150x 10^9/L can be discharged from portal hypertension surveillance.
- Patients with cACLD on NSBB therapy with no evident CSPH(LSM <25 kPa) after removal/suppression of the primary etiological factor, should be considered for repeat endoscopy, preferably after 1–2 years. In the absence of varices, NSBB therapy can be discontinued.

Identify CSPH

- LS M by TE ≤ 15 kPa + Plt ≥150 x 10^9/L rules out CSPH in pts with cACLD (Sens/NPV >90%)
- *LSM by TE of ≥25 kPa rules in CSPH (Spe/PPV >90%)
- ANTICIPATE model for LSM <25 kPa, to predict risk of CSPH
- NASH cACLD, ANTICPATE-NASH model (LSM, Plt, BMI)may be used.

Varices/endoscopy

- Pts with compensated cirrhosis who cannot take NSBB, should have EGD if LSM by TE ≥ 20 kPa or Plts ≤ 150x 10^9/L
- Patients avoiding EGD, can be followed with yearly TE and platelet count.

Case presentation

HPI: 59y/o female who was first diagnosed with "fatty tissue around my liver" about 5 years ago. She was advised to eat healthy, exercise, avoid alcohol and Tylenol and "the fat around the liver would decline".
Recently told of abnormal liver imaging was noted when she visited the ER for abdominal pain. Treated for constipation with resolution of symptoms.

MEDICATIONS: Reviewed as noted in the chart.
PMH: HTN, DM, hypothyroidism

SOCIAL HISTORY: Reviewed as noted in chart.
Retired teacher.
Tobacco - quit 2012; previously 1 pack/week
Alcohol – drank "a lot" since her 20's. Slowed down in her 50's and now only twice per year or the occasional family dinner.

PHYSICAL EXAMINATION:
Appears well. No stigmata of chronic liver disease.

LABS: CLD panel negative. Alk phos 105, total bilirubin 1.2, AST 60, ALT 48, albumin 3.9, creatinine 0.48, WBC 5.4, Hemoglobin 12.3, platelets 186.

IMAGING:
US: Sonographic features suggesting chronic liver disease, not definitive for cirrhosis. Correlation with relevant risk factors and associated serum markers may be warranted. Ultrasound elastography may help assess for clinically significant fibrosis. No focal hepatic lesion identified. No cholelithiasis or biliary ductal dilatation. No evidence of portal hypertension.

Next Steps…

Liver biopsy: The liver shows micronodular formation consistent with established cirrhosis. Mild macro-vesicular steatosis with minimal steatohepatitis.
Fibroscan: Fibrosis: 17 kPa (F3-F4).CAP score: 210 (< 33% steatosis).IQR: 11%
cACLD: Can avoid endoscopy for variceal screening. Should have annual LSM to monitor changes and the need for NSBB.

It's **QUESTION TIME!!**