GHAPP

Gastroenterology & Hepatology
Advanced Practice Providers

2021 Fourth Annual National Conference

September 9-11, 2021

Red Rock Hotel – Las Vegas, NV

Annenberg Center For Health Sciences at Eisenhower
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Fibroscan/Elastograpy

Ngoc Duong, MPAS, PA-C
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Arizona Liver Health
Phoenix, Az

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Disclosures

Ngoc Duong, MPAS, PA-C

No financial relationships to disclose.

Ann Moore, NP

Speakers Bureau: AbbVie, Clinical Area – HCV
Speakers Bureau: Gilead, Clinical Area – HCV
Speakers Bureau: Intercept, Clinical Area – PBC
Advisory Board: AbbVie, Clinical Area – HCV
Advisory Board: Gilead, Clinical Area – HCV
Advisory Board: Intercept, Clinical Area – PBC

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Fibroscan – 411

Ngoc Duong, MPAS, PA-C
Michael E. Debakey Veteran Affairs

Limitations in Liver Biopsy

- **Sampling error**
  - Major limitation
  - Small portion of liver (1/50,000)

→ 2-3 cm – 10 portal tracts

- **Intra/inter-observer variation**
  - G (**κ: 0.2–0.6**) – S (**κ: 0.5–0.9**)

→ Scoring system
Experienced pathologist

- **Invasive procedure**
  - Pain
  - Major complications
  - Mortality

→ US guided biopsy

G: grading – κ: kappa – S: staging.

AASLD position paper. Hepatology. 2009;49:107–1044.

For liver biopsy

The term “best standard” is more appropriate than “gold standard”

Bedossa P & Carrat F. *J Hepatology*. 2009;50:1–3.

Non-Invasive Markers of Fibrosis

- Serum Calculators
- Radiologic Tests

To Detect:

  - Significant Fibrosis: F2-F4
  - Advanced Fibrosis: F3-F4
  - Cirrhosis: F4

Fibrosis vs. Steatosis

- Measurement of Fibrosis
  - Vibration controlled Transient Elastography (VTCE) –
    - Fibroscan
    - MR Elastography
- Measurement of Steatosis
  - Controlled Attenuation Parameter (CAP)
  - Proton Density Fat Fraction (PDFF)

Non-Invasive Biomarkers

- Vibration Controlled Transient Elastography
- Magnetic Resonance Elastography

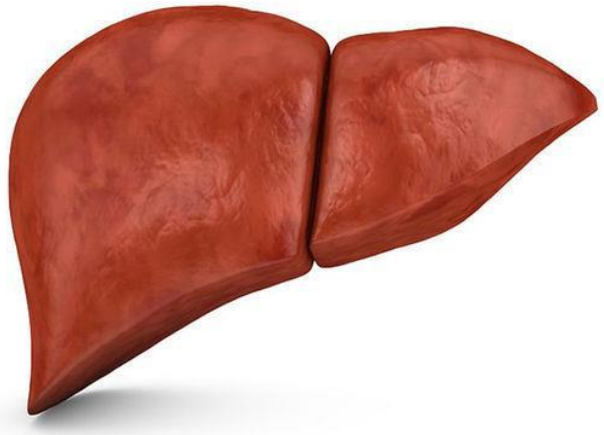
FibroScan Technology

Dual Function Liver Testing

- Liver stiffness (elastography)
- Fibrosis correlate

Ultrasound attenuation rate

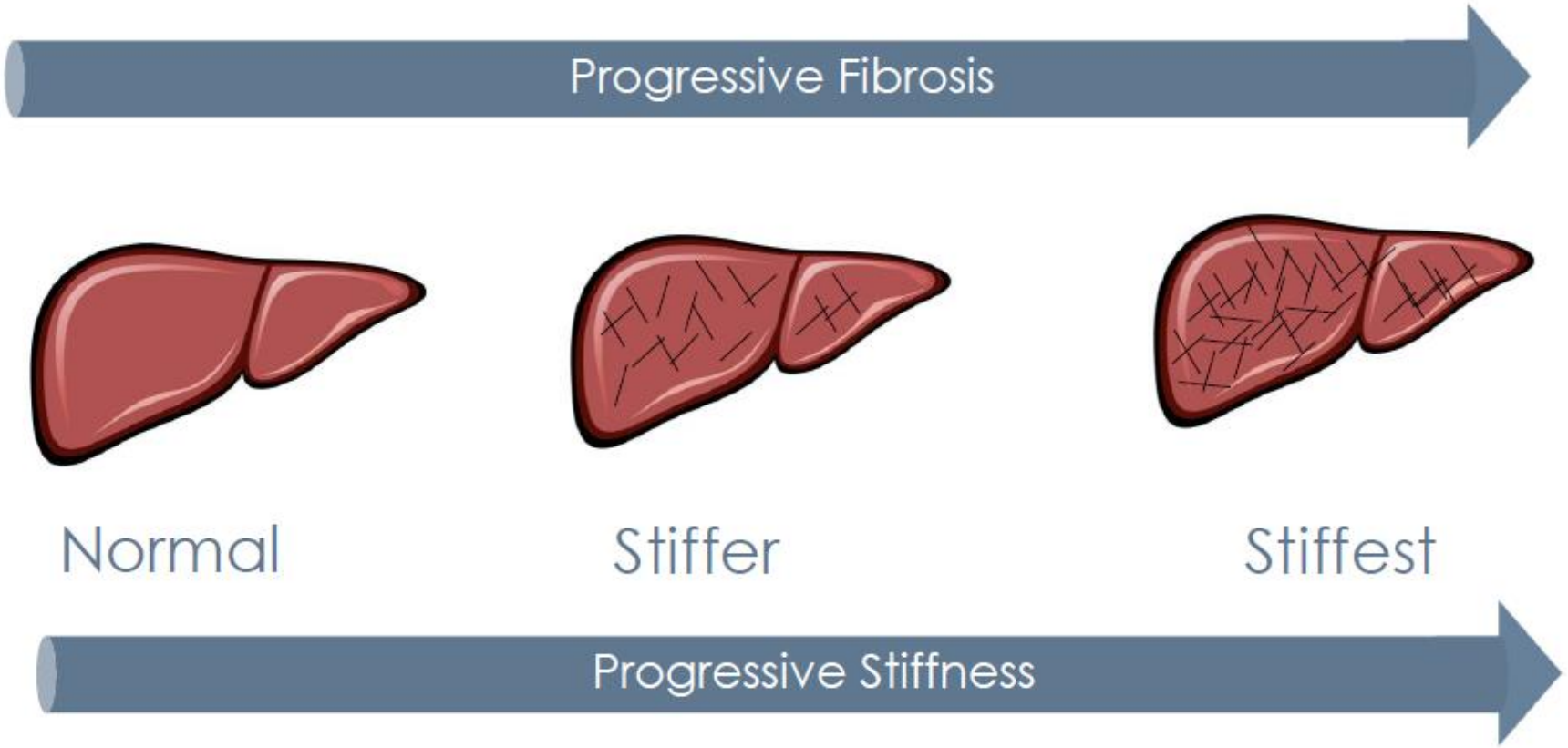
- Steatosis correlate



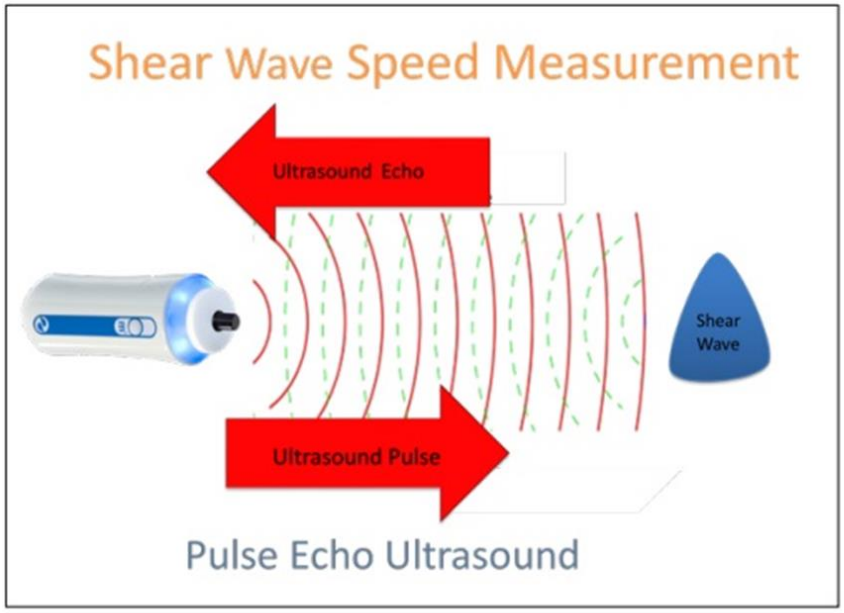
VCTE Measurement Steps

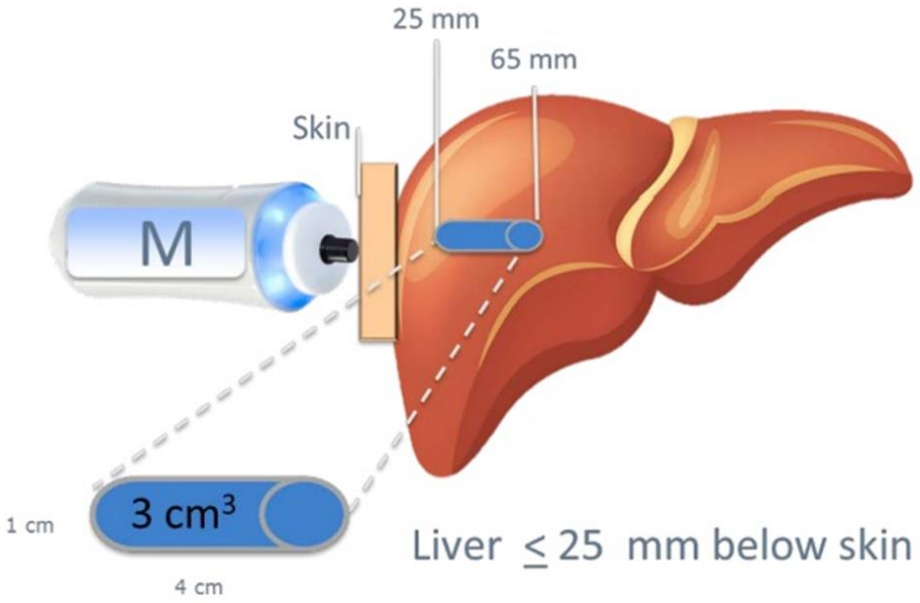
- Mechanically induce a shear wave in the liver
- Measure shear wave speed
- Calculate stiffness value

Elastography – Fibrosis Correlate

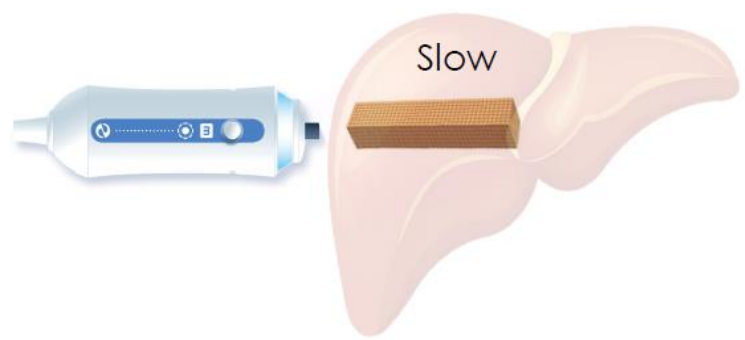


FibroScan

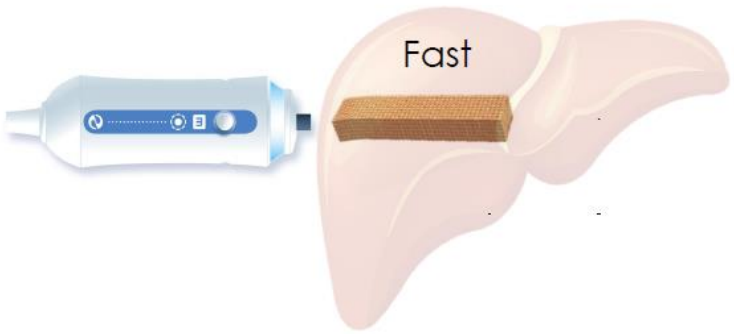

Shear Wave Speed Measurement
Ultrasound Echo
Shear Wave
Ultrasound Pulse
Pulse Echo Ultrasound

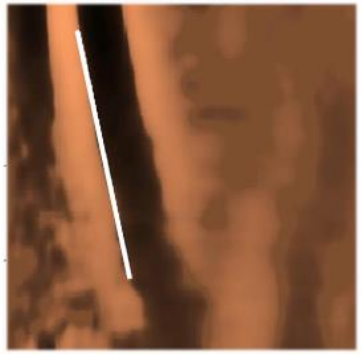

25 mm
65 mm
Skin
M
1 cm
3 cm³
4 cm
Liver ≤ 25 mm below skin

Liver Stiffness Correlates to Fibrosis Level



Healthy
- Low Stiffness





Fibrotic
- High Stiffness

VCTE Range: 2.5- 75 kPa

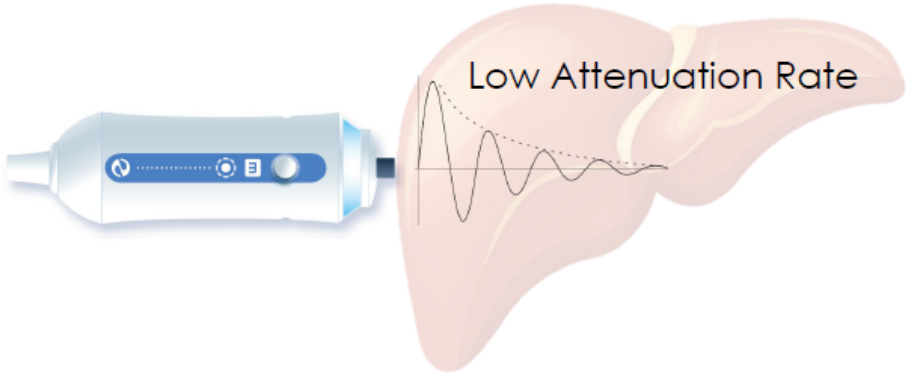
FibroScan CAP Operating Principle

Controlled

Attenuation **CAP™**

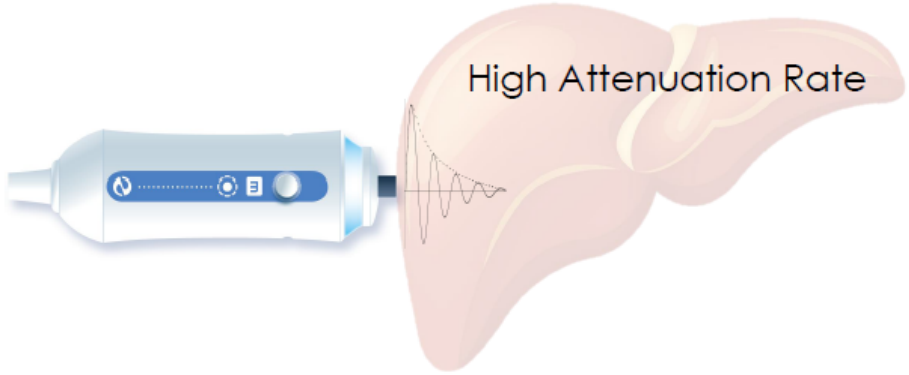
Parameter

Ultrasound Attenuation Rate Correlates to Steatosis Level



No Steatosis

- Low CAP Value



Elevated Steatosis

- High CAP Value

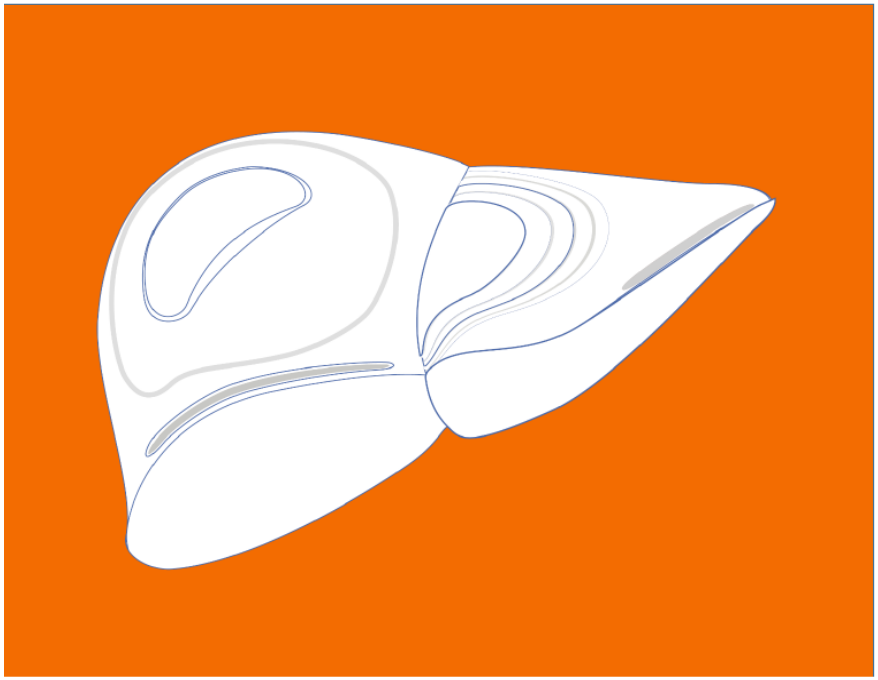
The Controlled Attenuation Parameter (CAP): A novel Tool for the Non-invasisve Evaluation of Steatosis Using FibroScan; Sasso, Beaugrand, De Ledinghen et al. *Clin Res Hepatology Gastroenterol*. 2012. 36(1): p.13-20.

FibroScan Test Protocol

Test Acquisition

- Center probe over liver
- Acquire 10 measurements
- Generate report
- Average time: 10 minutes

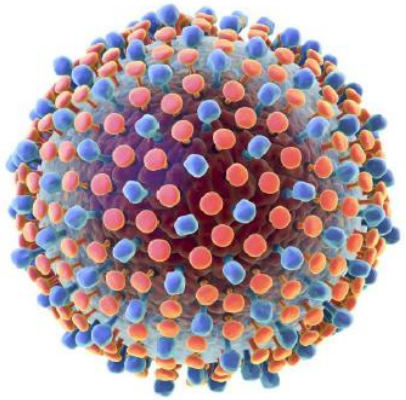
Clinical Application



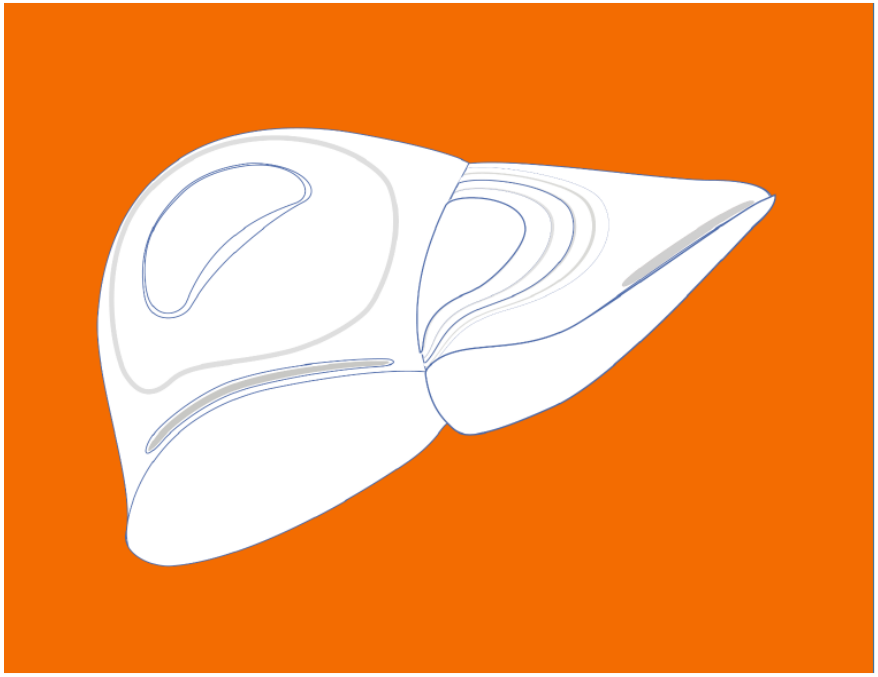
Viral Hepatitis

FibroScan Applications
Viral Hepatitis

- Antiviral treatment qualifier
  - Liver stiffness threshold based
- Fibrosis-based risk stratification
  - HCC surveillance
  - Esophageal varices surveillance
  - Portal hypertension – surgical risk



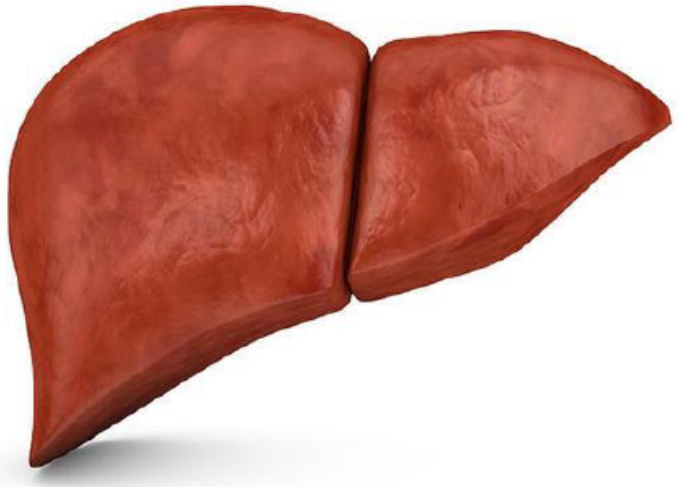
Clinical Application



NAFLD-NASH

FibroScan Clinical Applications
NAFLD

- Steatosis based risk assessment
  - CAP elevation
- Fibrosis based risk stratification
  - Disease management need
  - HCC & varices risk
- Serial monitoring
  - Disease progression
  - Therapeutic response



FibroScan Report Review

Test Review & Interpretation

- Review measurement thumbnails
- Select threshold value reference
- Compare test values to reference
- Average time: 1-2 minutes

Sample Report

Code 458887470

Birth date 1949-12-09

Gender Male

Admitting diagnosis ABNORMAL LFT

Referring physician DR.NATARAJAN

EXAMINATION

Date and time 2018-01-30 22:15:24

Operator NAOMI

Device Fibroscan 502TOUCH F60484

Probe XL 9 90488

Examination XL (Liver)

Number of valid measurements 15

Number of invalid measurements 0

Success rate 100%

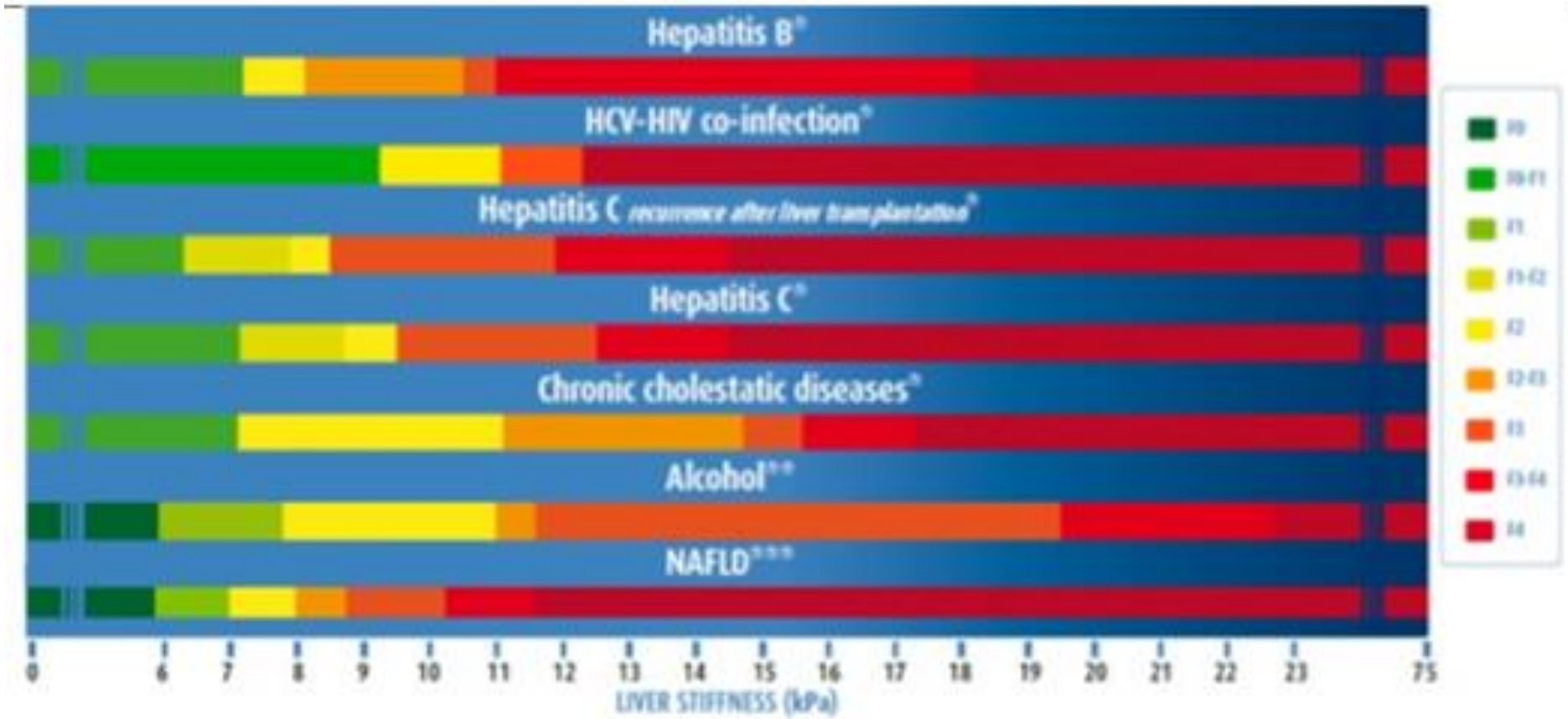
V (m/s)	
Median	1,55
IQR*	0,13

E (kPa)	
Median	7,2
IQR*	1,3
IQR*/med	18 %

Equivalent Liver stiffness is calculated using the formula $E = 3\rho Vs^2$ and assumes that liver tissue is isotropic, linear and purely elastic with a density (ρ) of 1000 kg/m3.
The values for shear wave speed and Young's modulus are relative indexes intended only for the purpose of comparison with other measurements performed using Fibroscan devices. Absolute values for these measurements may vary among measurement devices from different manufacturers.
SWS median is defined as the value which converts to the stiffness median.

*IQR: interquartile range

Interpretation



J Hepatol. 2009; 49:1062-68; *Aliment Pharmcol Ther*. 2008; 28:1188-98; *Hepatology*. 2010; 5:454-62.

Factors Affecting Liver Stiffness

- Meals
- Subcutaneous Adiposity
- Hepatic Congestion/Ascites
- Inflammation
- Infiltrative Diseases
  - Amyloid
  - Malignancy

Performance

	Sensitivity	Specificity
FibroScan	0.87	0.79
MRE	0.84	0.9

“In adults with NAFLD and a higher risk of cirrhosis, the AGA suggest using MRE, rather than VCTE, for detection of cirrhosis [High-risk populations are advanced age, obesity, particularly central adiposity, DM, ALT>2x ULN, estimated cirrhosis prevalence of 30%]

In adults with NAFLD and a lower risk of cirrhosis, the AGA makes no recommendation regarding the role of MRE or VCTE for detection of cirrhosis (usually primary care setting, prevalence cirrhosis < 5%)”

Interpretation of Liver US-Based Elastography
Guidelines of EFSUMB 2017*

- Past medical history
- Current complaints
- Physical examination: signs of chronic liver disease
- Liver biochemical & function tests
- Ultrasound of upper abdomen (B-mode & Doppler)

* EFSUMB: European Federation of Societies for Ultrasound in Medicine and Biology.
Dietrich CF et al. *Ultraschall Med*. 2017;38:e16-e47.

Cofounders of US-Based Elastography
Guidelines of EFSUMB 2017*

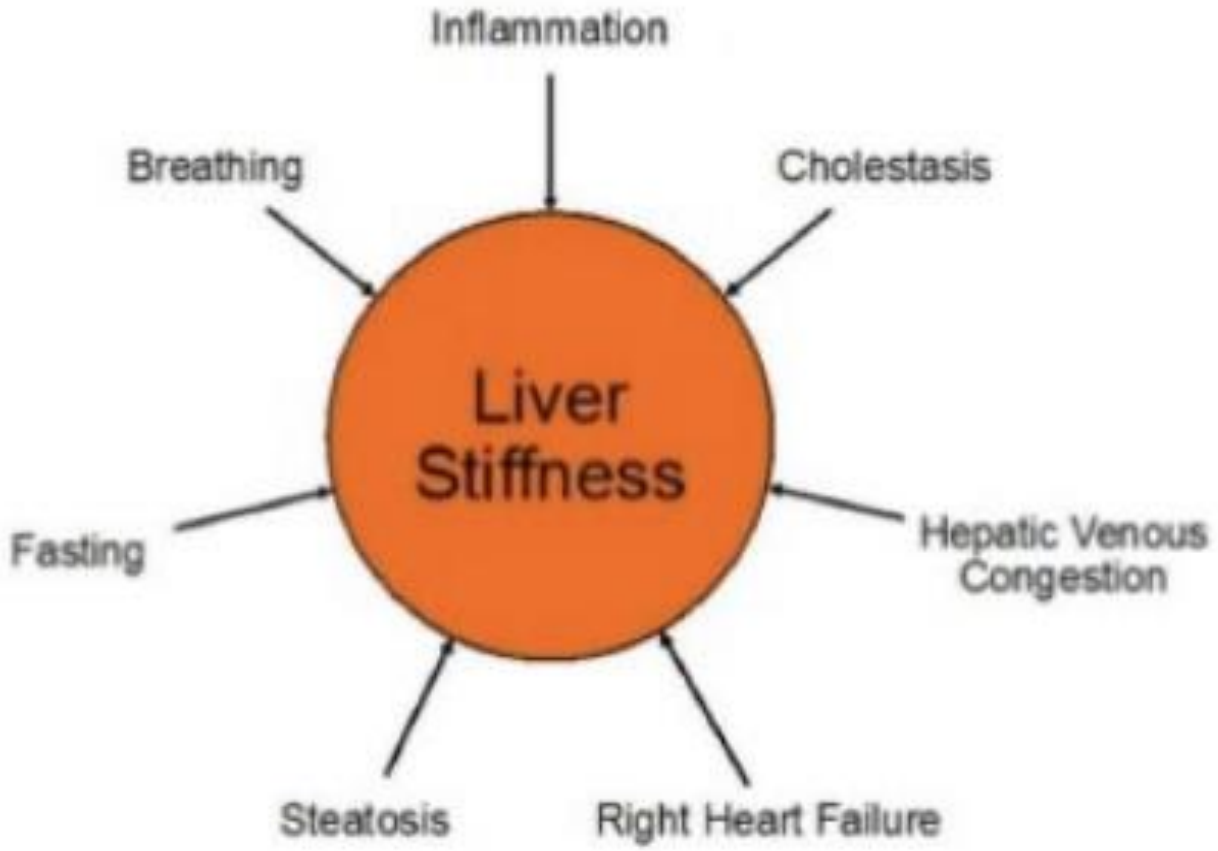
- Acute hepatitis
- Transaminases flares (ALT &/or AST > 5 ULN)
- Extra-hepatic cholestasis
- Congestive heart failure
- Infiltrative liver diseases: amyloidosis, lymphoma

Should be excluded before SWE to avoid **overestimation** and/or should be considered when interpreting results

ULN: upper limit of normal; * EFSUMB: European Federation of Societies for Ultrasound in Medicine and Biology.
Dietrich CF et al. *Ultraschall Med*. 2017;38:e16-e47.

Confounders of Liver Stiffness Measurements

Pathologic and normal physiologic processes



Sigrist RMS et al. *Theranostics*. 2017;7(5):1303–1329.

Techniques of US-Based Elastography

Technique	Manufacturer/Model	Version or Software
Transient elastography	Echosens/FibroScan®	430 mini, 502 touch, 530 compact, 630 expert
ARFI – point SWE	Acuson/S2000 & S3000 Esaote/My lab 9 Hitachi/Hi-Vision Medison/HS70 A, RS80 A Philips/Epiq series	VTQ® QElaXto® Shear wave measurement S-shearwave® ElastPQ®
ARFI – 2D SWE	Acuson/S3000 GE/Logic E9 Mindray/Resona series Philips/Epiq series Explorer/SuperSonic Imagine Toshiba/Aplio 500, i-series	VTIQ® – STE®, STQ® ElastQ® SSI® –
Strain elastography	Hitachi/EUB-8500, EUB-900	Hi-RTE®

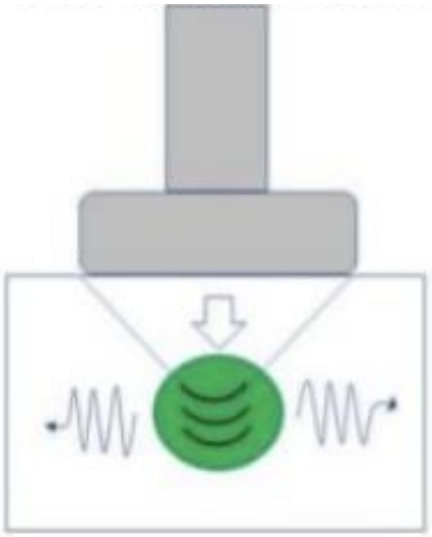
ARFI: acoustic radiation force impulse imaging – SWE: shear wave elastography.
Ferraioli G et al. *Ultrasound Med Biol*. 2018;44(12):2419–2440.

Principle of ARFI (pSWE and 2D SWE)

Operator-independent, quantitative, reproducible

pSWE

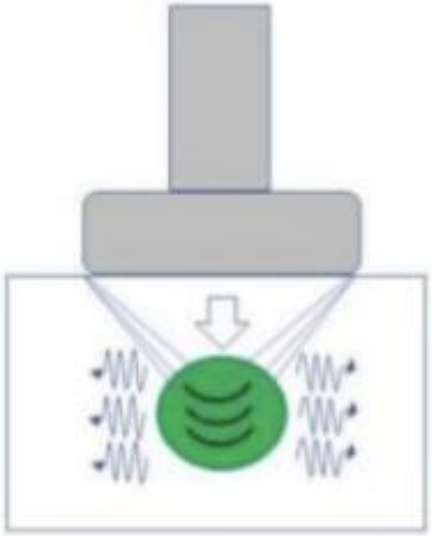
Point shear wave elastography



Mechanical excitation of target tissue in single location creating lateral shear wave

2D SWE

2 dimensions shear wave elastography



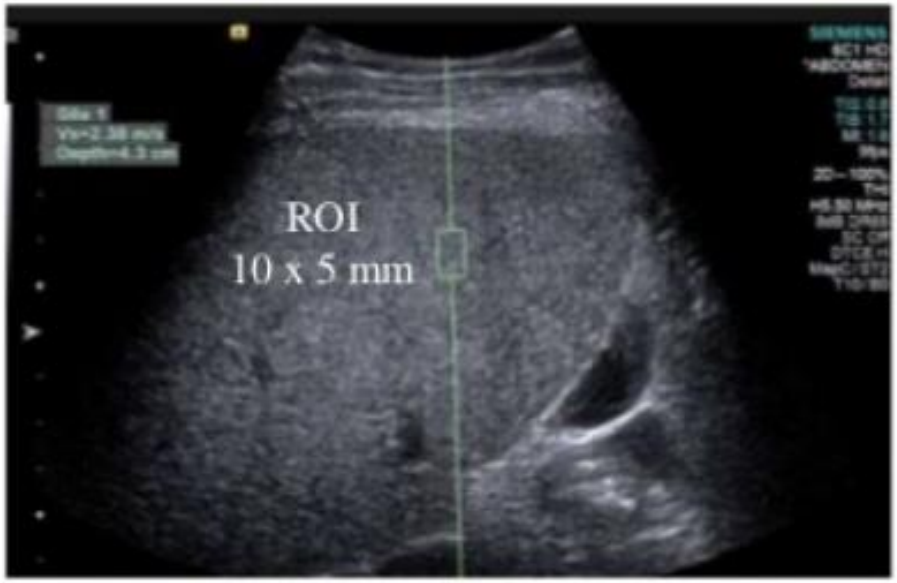
Generation of shear waves in full field of view

ARFI: acoustic radiation force impulse imaging.

Zhao CK et al. *Ultrasonography.* 2019;38(2):106–124.

ARFI – Point Shear Wave Elastography (pSWE)

Range: 0.5–4.4 m/sec



59-year-old woman with hepatitis C
Region of interest (green box) with 10 measurement in same location
Median value 2.38 m/sec (consistent with cirrhosis)
Metavir F4 confirmed at liver biopsy

ARFI: acoustic radiation force impulse imaging – SWE: shear wave elastography.
Barr RG et al. *Ultrasound Quarterly.* 2016; 32:94–107.

Reliable Results of Point SWE

- Number of valid shots ≥ 10
- Valid shots/total number of shots ≥ 60%
- Inter-quantile range/median ≤ 15–30%

SWE: shear wave elastography.
Ferraioli G et al. *Ultrasound Med Biol.* 2018; 44(12):2419–2440.

Fibrosis Staging in pSWE (Acuson S2000–S3000)

Normal value: 1.07–1.19 m/s

Cut-off values related to etiology of chronic liver disease

	F ≥ 2 significant fibrosis	F ≥ 3 severe fibrosis	F = 4 cirrhosis
HCV[1]	1.21 – 1.34	1.54 – 1.70	1.75 – 2
HBV[1]	≥ 1.35	≥ 1.55	≥ 1.87
NAFLD[1-2]	–	≥ 1.77	≥ 1.90
ALD[3]	1.63	1.84	1.94
AIH	–	–	–
PBC	–	–	–

WFUMB: World Federation of Ultrasound in Medicine & Biology.

[1]Sporea I et al. *Point SWE*. In: EFSUMB course book 2nd ed – Ed: Dietrich CF – 2018; [2]Cut-off value of > 1.10 m/s can discriminate between simple steatosis & NASH; [3]Kiani A et al. *World J Gastroenterol*. 2016;22(20):4926-35.

ARFI – 2D Shear Wave Elastography (2D SWE)

Normal values (GE: 6 ± 1.4 kPa – Explorer: 5.1 ± 1.3 kPa)

FDA Approved

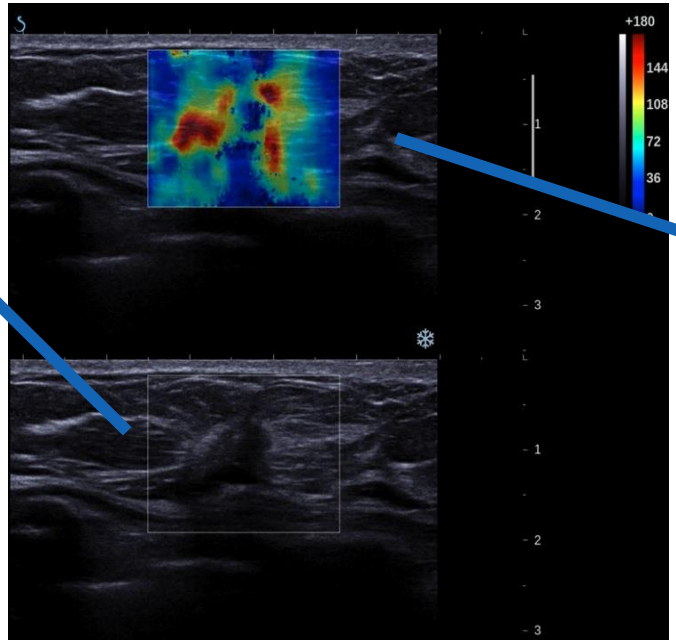
Field of view (FOV) where elastography will be obtained
Regions of interest (ROI) within FOV to obtain **3–5 measurements**

ARFI: acoustic radiation force impulse imaging.
Barr RG et al. *Ultrasound Quarterly*. 2016;32:94–107.

MultiWave™ Technology

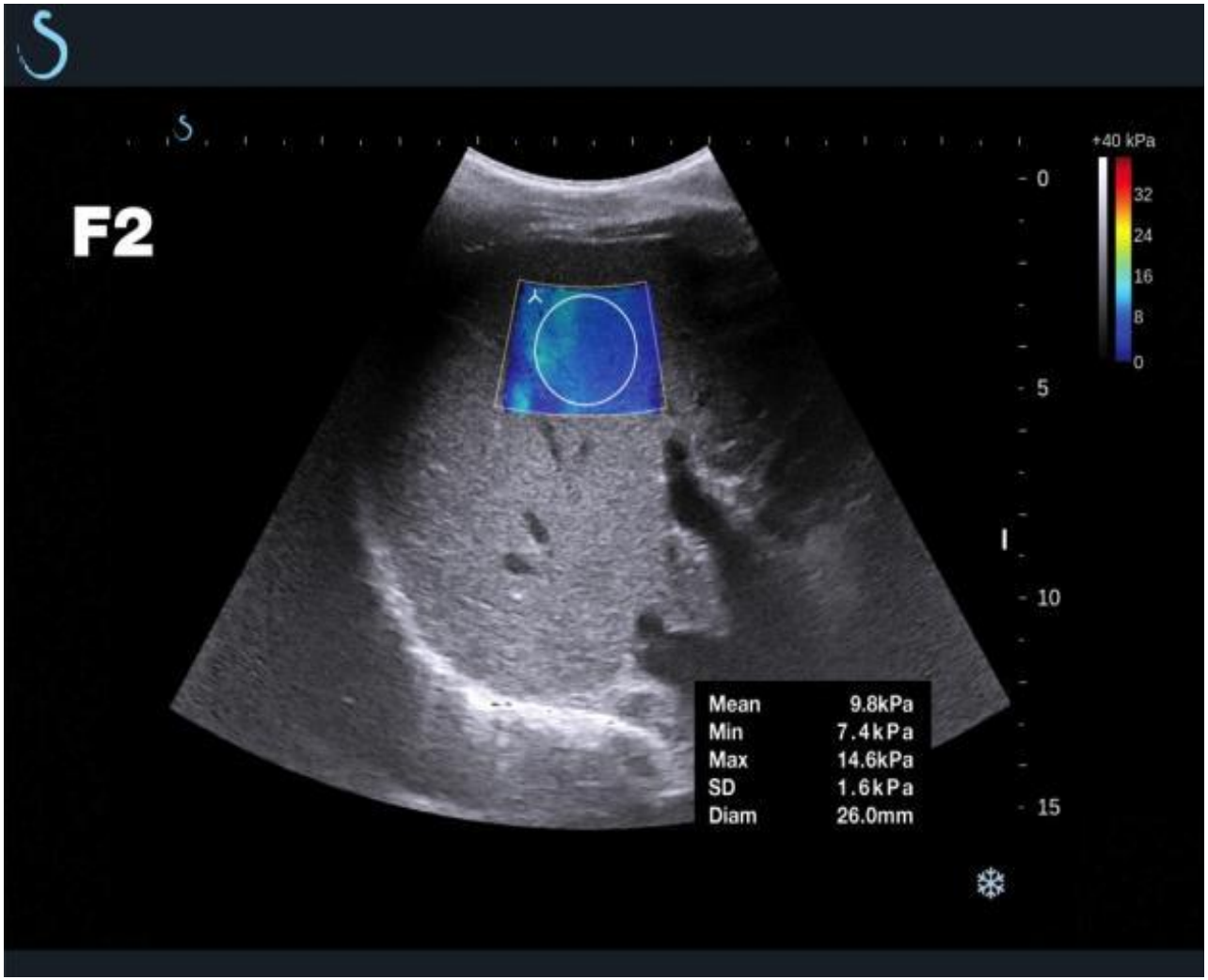
Two waves to better characterize tissue :

One Ultrasound Wave:
Impeccable image quality in B-mode

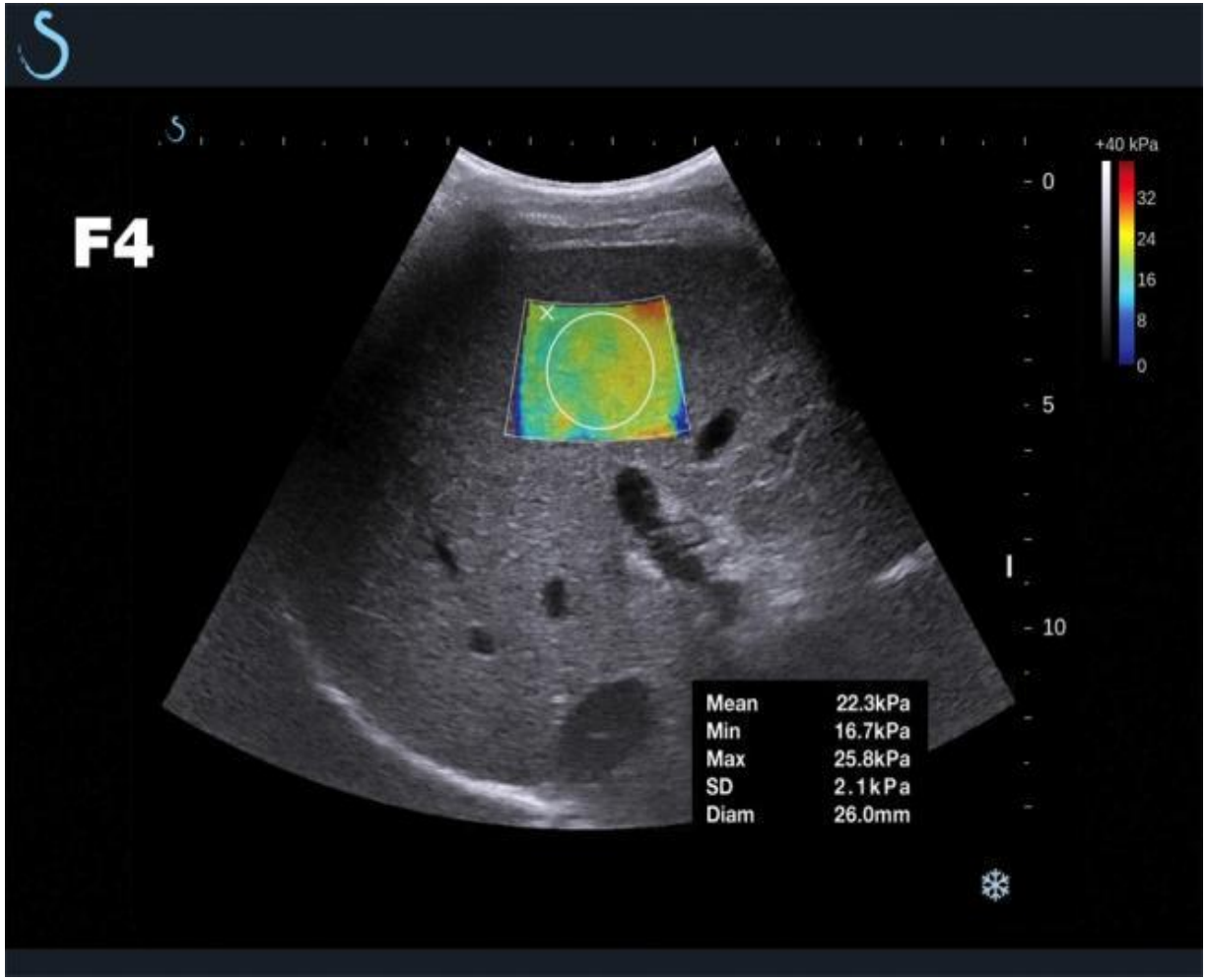


One Shear Wave :
Measures and displays, in real time, local tissue elasticity in kilopascals

Liver Fibrosis F2



Liver Fibrosis F4



Advantages & Limitations of ARFI

pSWE & 2D SWE

Advantages	Limitations
Integrated in ultrasound systems	Less published materials
More cost-effectiveness	No cutoff values for prognosis
No need for probe calibration	Acute liver injury (> 5 x ULN)
Not limited by obesity	Extra-hepatic cholestasis
Not limited by ascites	Increased central venous pressure
Safe in pregnant women	Narrow inter-costal spaces

ARFI: acoustic radiation force impulse imaging.
2D SWE: two dimensions shear wave elastography – pSWE: point shear wave elastography.

Comparison of Elastography Methods

- 21 chronic hepatitis C and 5 healthy individuals
  - Transient elastography (FibroScan®) as reference standard
  - pSWE: Acuson S2000, Philips EPIQ7, Hitachi Hi-Vision, MyLab
  - 2D SWE: SuperSonic Imagine, Toshiba
- Agreement of measurements with different systems good to excellent
  - Values follow same direction but absolute values not the same
  - Cutoff values not used interchangeably across different US systems
- Cutoffs are system specific & related to etiology of liver disease

pSWE: point shear wave elastography – 2D SWE: two dimensions shear wave elastography.
Ferraioli G et al. *Ultraschall Med.* 2019; 40(1):64–75.

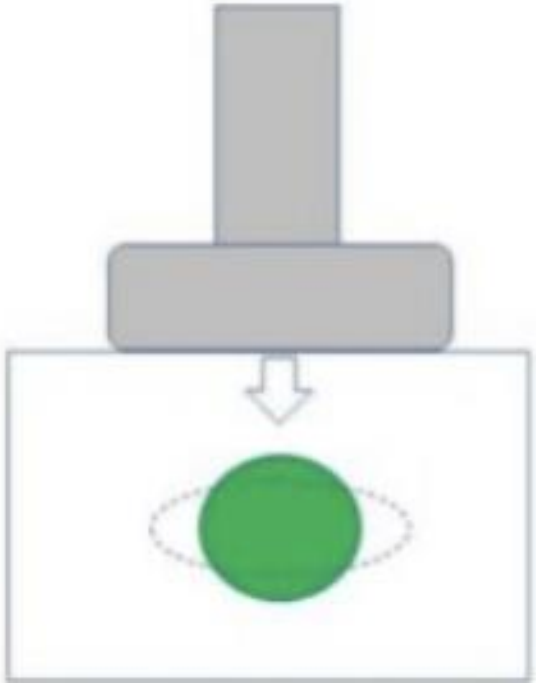
Techniques of US-Based Elastography

Technique	Manufacturer/Model	Version or Software
Transient elastography	Echosens/FibroScan®	430 mini, 502 touch, 530 compact, 630 expert
ARFI – point SWE	Acuson/S2000 & S3000 Esaote/My lab 9 Hitachi/Hi-Vision Medison/HS70 A, RS80 A Philips/Epiq series	VTQ® QElaXto® Shear wave measurement S-shearwave® ElastPQ®
ARFI – 2D SWE	Acuson/S3000 GE/Logic E9 Mindray/Resona series Philips/Epiq series Explorer/SuperSonic Imagine Toshiba/Aplio 500, i-series	VTIQ® – STE®, STQ® ElastQ® SSI® –
Strain elastography	Hitachi/EUB-8500, EUB-900	Hi-RTE®

ARFI: acoustic radiation force impulse imaging – SWE: shear wave elastography.
Ferraioli G et al. *Ultrasound Med Biol*. 2018;44(12):2419–2440.

Principle of Strain Elastography

Electronic palpation

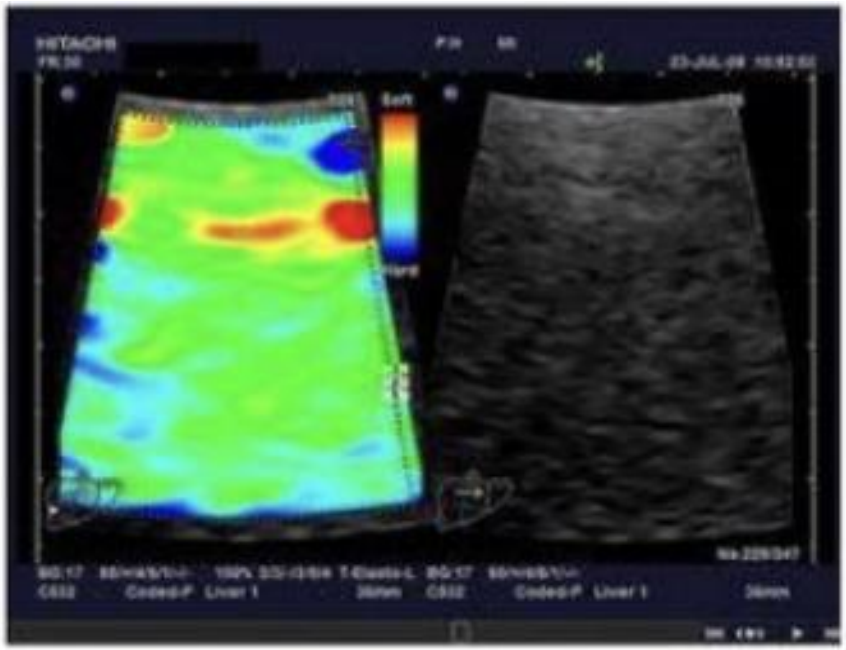


Elastographic image acquired through tissue displacement caused by free-hand compression with a transducer

Zhao CK et al. *Ultrasonography*. 2019;38(2)106–124.

Strain Elastography

Mainly in Japan – long learning curve



Scores: LF index, German elasticity score, Japanese elasticity score
Only **LF Index** recommended by the manufacturer
Positive results in Japanese series not confirmed in other series
Not recommended for clinical use in Europe

Dietrich CF et al. EFSUMB Guidelines. *Ultraschall in Med*. 2017;38:e16–e47.

Recommendations to Perform Liver Elastography

Adherence to a strict protocol

- Fasting for **4 hours** and rest for **10 min** before examination
- Supine/slight left lateral position & arm raised above head
- Choice of FibroScan® transducer based on SCD
- Transducer perpendicular to liver capsule
- Measurement **1.5–2.0 cm** below liver capsule in ARFI
- Region of interest avoids large vessels, bile duct & masses
- 10 measurements for TE & pSWE & **3–5** for 2D SWE
- IQR/median**: < 30%** for kPA – **< 15%** for m/s

kPA: kilopascal – SCD: skin to capsule distance – SWE: short wave elastography – TE: transient elastography – WFUMB: World Federation of Ultrasound in Medicine & Biology.

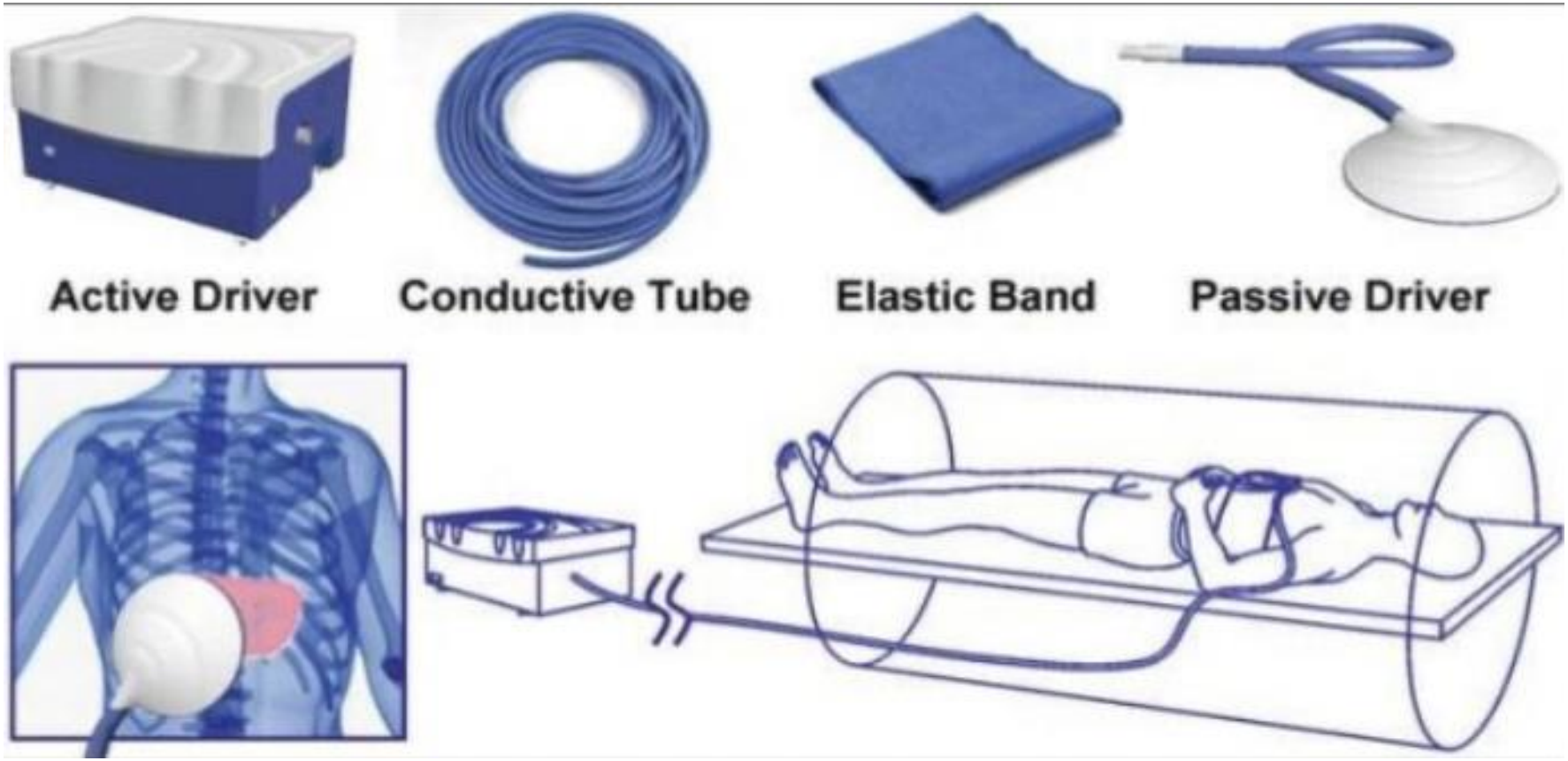
Ferraioli G et al. *Ultraschall Med.* 2018; 44(12):2419–2440.

MR Elastography obtains information about the stiffness of tissue by assessing the propagation of mechanical waves through the tissue with a special magnetic resonance imaging (MRI) technique.

The technique essentially involves three steps:

1. Generating shear waves in the tissue
2. Acquiring MR images depicting the propagation of the induced shear waves
3. Processing the image of the shear waves to generate quantitative maps of tissue stiffness, called Elastograms

MR Elastographic Technique



Correlation Between MR Elastographic Stiffness and the Stage of Fibrosis

MR Elastographic Stiffness (kPa)	Stage of Fibrosis
Less than 2.5	Normal
2.5–2.9	Normal or chronic inflammation
2.9–3.5	Stage 1–2
4.0–5.0	Stage 3–4

Normal liver stiffness is usually less than 2.5 kPa.
Most studies have reported normal liver stiffness within a range of 1.54 to 2.87 kPa.

MRE Accuracy

- Multiple published studies have concluded that MRE has a high diagnostic performance in detection and staging of liver fibrosis
- MRE can differentiate normal livers from fibrotic livers with an accuracy of ≥ 90% using a cut off of > 2.4 kPa
- MRE can also detect liver fibrosis when anatomical features of fibrosis and cirrhosis are absent
- The accuracy of MRE for detecting clinically significant fibrosis and cirrhosis are > 95% and 98% respectively
- The high performance of MRE has been demonstrated in chronic liver diseases of different etiologies

Diagnosis at Magnetic Resonance Based Techniques

Chemical shift gradient-echo (GRE) imaging with in-phase and opposed-phase acquisitions is the most widely used MR imaging technique for the assessment of fatty liver

Normal Liver	Fatty Liver
The signal intensity of the normal liver parenchyma is similar on in-phase and opposed-phase images	The signal intensity loss on opposed-phase images in comparison with in-phase images

MRI-derived proton density fat fraction (MRI-PDFF)

It uses MRI-visible protons that combine with fat in the liver to quantify steatosis by dividing all protons in the liver

MRI-PDFF is significantly associated with the histological steatosis grade

MRI-PDFF is superior to other imaging tools for the assessment of hepatic steatosis and its performance is not affected by obesity

H-MRS magnetic resonance spectroscopy

Detection of Hepatic Steatosis

- MRI-PDFF (proton density fat fraction) and MR Spectroscopy
  - Gold standard for fat quantification
  - Current noninvasive standard for screening for NAFLD in clinical studies, but costly
- Some studies suggest that degree of steatosis may predict severity of histologic features (ballooning and steatohepatitis) and incidence and prevalence of diabetes in pts with NAFLD
- AASLD guidelines: utility of noninvasively quantifying hepatic steatosis in NAFLD in routine clinical care is limited

Chalasani N et al. *J Hepatol*. 2008;48:829-834; Targher G et al. *Diabetes Metab*. 2016;42:142-156; Li X et al. *PLoS One*. 2013;8:e65210; Shah RV et al. *Atherosclerosis*. 2015;242:211-217; Chalasani N et al. AASLD Guidelines. *Hepatology*. 2018;67(1), 328-357; Noureddin M et al. *Hepatology*. 2013;58:1930-1940.

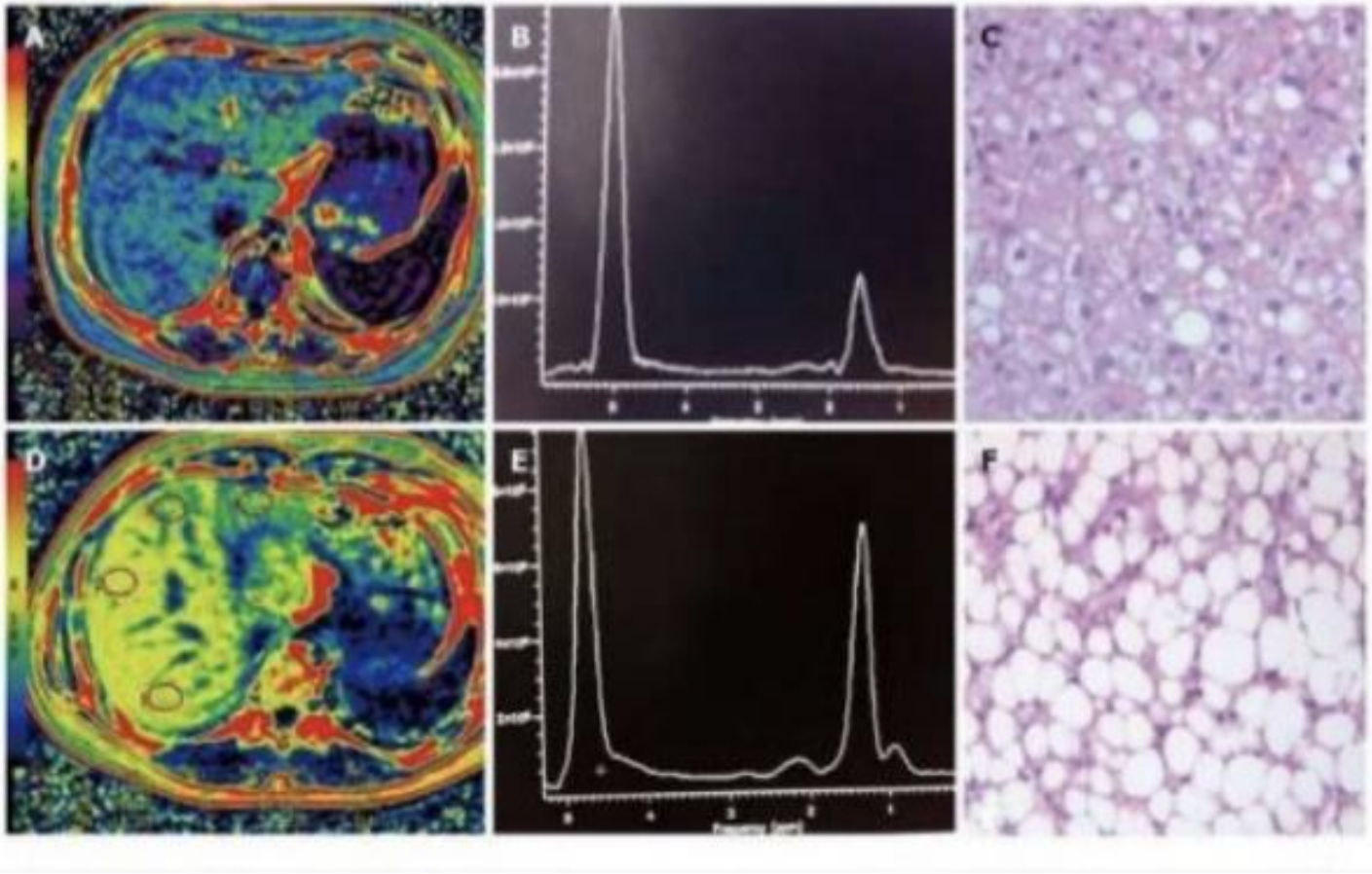


Figure 2. Mean lipid content for MR-Spectroscopy. A-C: MRI-PDFF reveals a hepatic fat fraction of 7%, MRS quantified 6.5% of liver steatosis and histological analysis 30% of liver steatosis; D-F: Severe hepatic steatosis in an 8-year-old girl: MRII-PDFF 25%, MRS 50% and histologic analysis 90% of liver steatosis respectively.

Conclusion

- Strict protocol necessary to obtain accurate measurements
- Elastography techniques used to distinguish 2 cutoff values:
  - No or minimal fibrosis (Metavir **F0 & F1**): no liver biopsy
  - Severe fibrosis or cirrhosis (Metavir **F3 & F4**): no liver biopsy
  - Middle group between these cutoff values requires more clinical evaluation/additional tests (blood tests, livery biopsy)
- Cutoffs are system specific & related to etiology of liver disease

Barr RG et al. *Ultrasound Quarterly*. 2016;32:94–107; Ferraioli G. *Ultrasound Med*. 2019;38:9–14.