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Upon successful completion of this activity 1 contact hour will be awarded

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CONFLICT OF INTEREST

Dr. Jorge Mera is director of a program partially funded by Gilead.

Lisa Townshend-Bulson is a principal co-investigator on a grant that is partially funded by Gilead.

None of the other planners or presenters of this CE activity have any relevant financial relationships with any commercial entities pertaining to this activity.

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Acknowledgement

This presentation is funded in part by:

The Indian Health Service HIV Program
and
The Secretary's Minority AIDS Initiative Fund

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Addressing Transient Elastography (FibroScan): Integrating with HCV Care

YOUSSEF BARBOUR M.D

Agenda:

- 1- Fibrosis assessment in the liver
- 2- Non invasive assessment of liver fibrosis
- 3- Transient Elastography "FibroScan" role in Fibrosis assessment
- 4- FibroScan applications in liver disease
- 5- what is CAP

Questions.

- **1- which of the following statements is true about liver fibrosis:**
- A- Liver fibrosis can be estimated using an US
- B- Liver fibrosis can be estimated using Controlled Attenuation Parameter
- C- Liver cirrhosis is an early stage liver fibrosis
- D- Liver biopsy is the only way to assess liver fibrosis
- E- FibroScan is one of many non invasive tools to assess liver fibrosis

Questions

- **2-Which of the following statement is true about FibroScan**:
- A- Patients need to be fasting overnight for an accurate reading
- B- Patients don't need to be fasting before fibroscan.
- C- FibroScan can confirm the diagnosis of NASH
- D- Fibroscan assess a larger area in the liver for fibrosis than the liver biopsy does
- E- Fibroscan score interpretations are standardized across the whole spectrum of liver diseases

Questions

- **3- CAP can diagnose**:
- A- NASH
- B- NAFLD
- C- Fatty liver
- D- Cirrhosis

Liver Fibrosis assessment

Invasive assessment

- Liver Biopsy.

Non Invasive assessment

- Several tools, and continue to grow:
- 1- APRI
- 2- FIB4
- 3- Fibrospect/Fibrosure
- 4- Transient Elastography, or FibroScan
- 5- MRE

TE: non-invasive US-based method

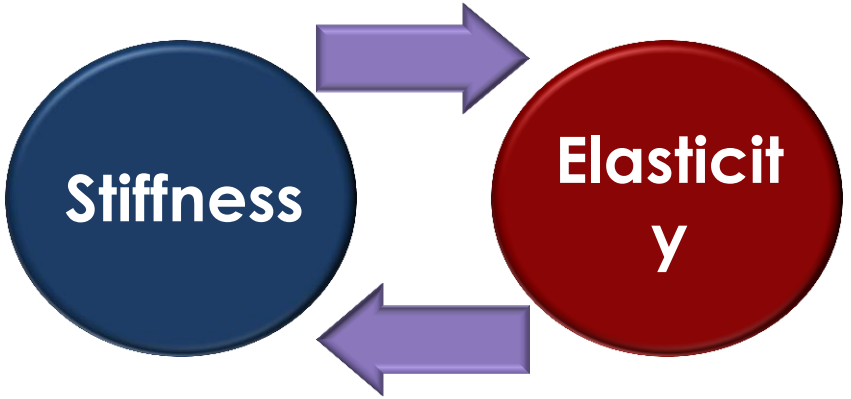
In contrast to sound waves, which are longitudinal, shear waves are transverse, thus the motion of the affected tissue is perpendicular to the direction of wave propagation.

The method was designed at the Langevin institute in 1995 and was initially implemented for quality control in the food industry

- Uses shear wave velocity to assess tissue (e.g. Liver) stiffness
- Shear (secondary or S-) waves were initially discovered in seismology as slow waves that follow the primary compressional wave, hence their name.
- They are the manifestation of elastic waves that travel through the body of an object, as opposed to the surface waves, which, as the name implies, travel on the surface.
- Shear waves move slowly (< 50 m/s) and are rapidly attenuated by liver parenchyma, depending on the elastic properties of the tissue, with the speed of shear waves inversely proportional to the tissue elasticity
- Applied in medical practice under the name FibroScan since 2001

Noninvasive Liver Stiffness Testing

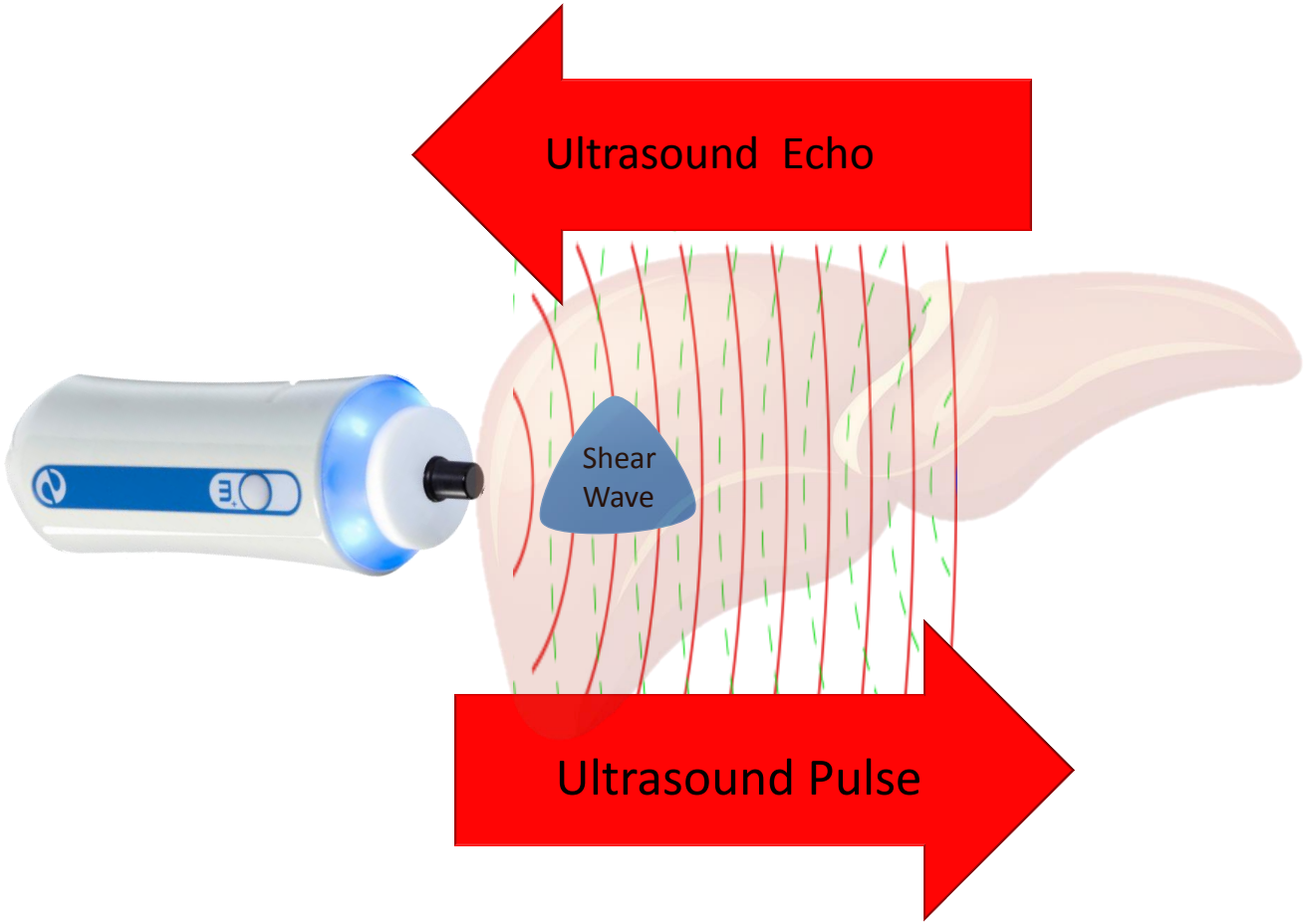
Understanding Elastography



Shear Waves in our body:

- Shear waves are affected by changes in the medium density, particularly in the presence of liquid medium; thus, the operator must avoid large vascular structures. To avoid this problem and ensure better results, the TE device is equipped with ultrasonographic display of the tissue that underlies the probe.
- The probe (piston) initially causes a slow-spreading low-frequency (50 Hz) shear wave, after which the fast ultrasound waves (emitted from the same probe) in a pulse-echo fashion are used to determine the position of the shear wave front in relation to time.

Measuring Shear Wave Speed



Pulse Echo Ultrasound

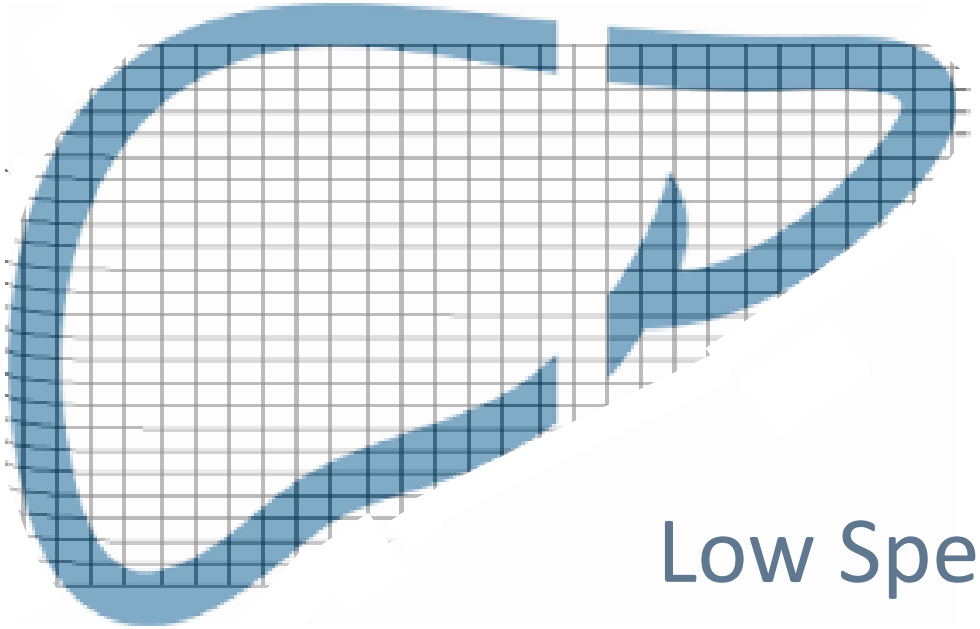
500X

Liver Stiffness Measurement LSM

- Measurement of liver stiffness is based on **Hook's law**, which states that the velocity of shear waves that travel through an elastic object is proportional to the object's stiffness (i.e., inversely proportional to the object's elasticity).
- Mathematical equation using **shear wave velocity (m/s)** and **tissue density (kg/m3)** to calculate E which represent **Young's modulus** which clinically corresponds to the **LSM (expressed in kPa).**
- Value range from 1.5 to 75 kPa

Shear Wave Speed Correlates to Stiffness

Hooke's Law

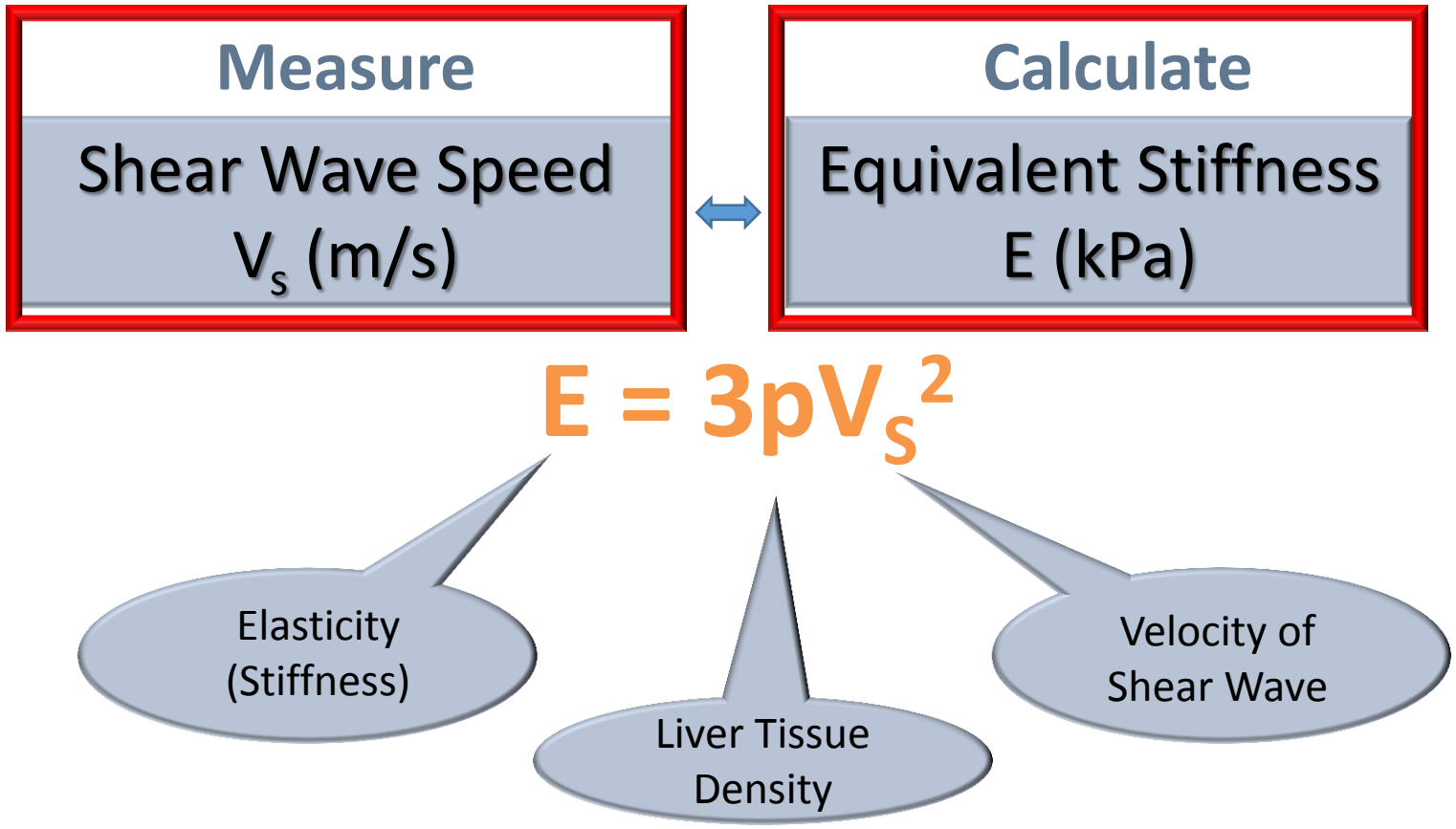


Low Speed = Low Stiffness

High Speed = High Stiffness

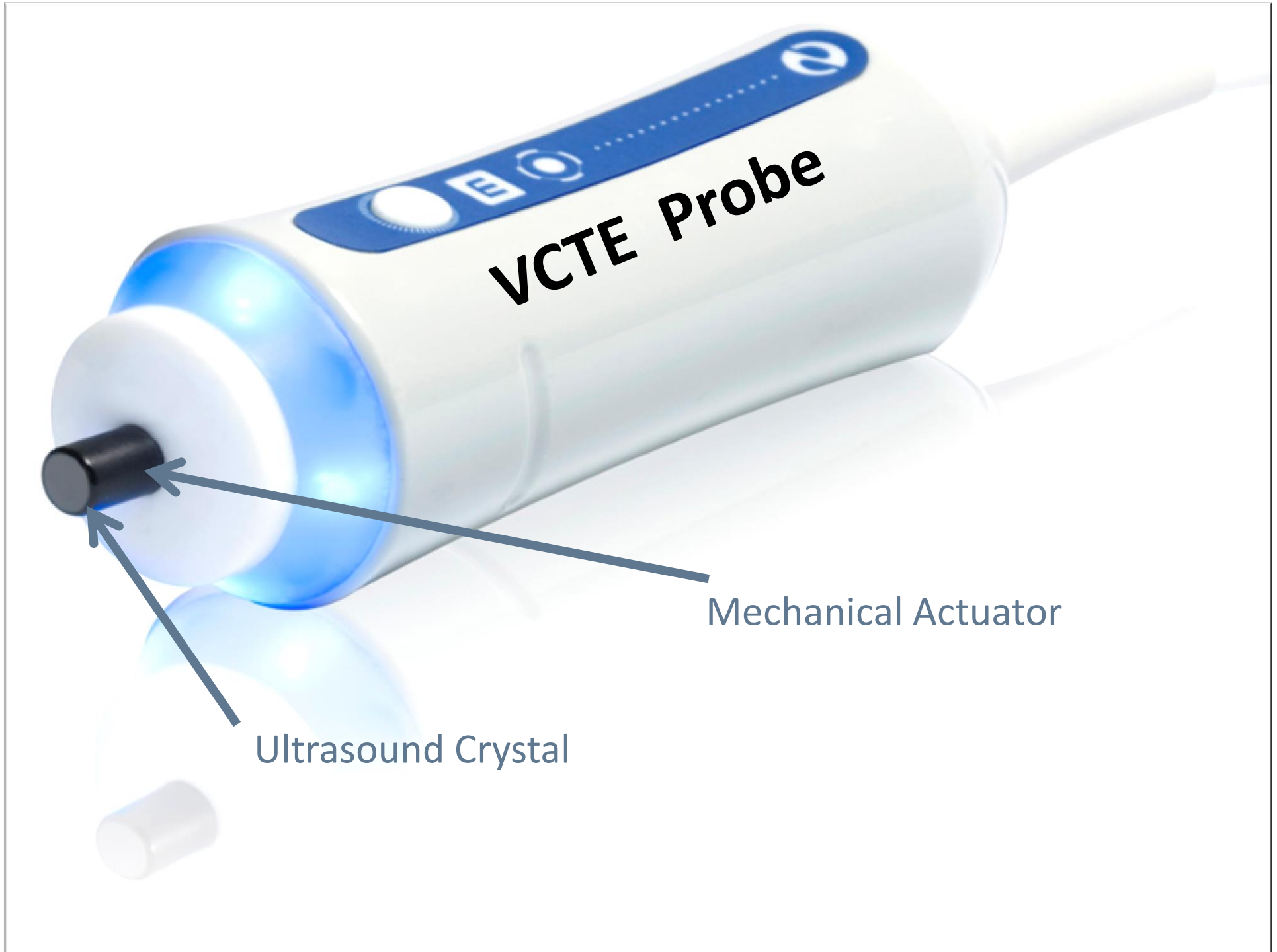
Stiffness Calculation Formula

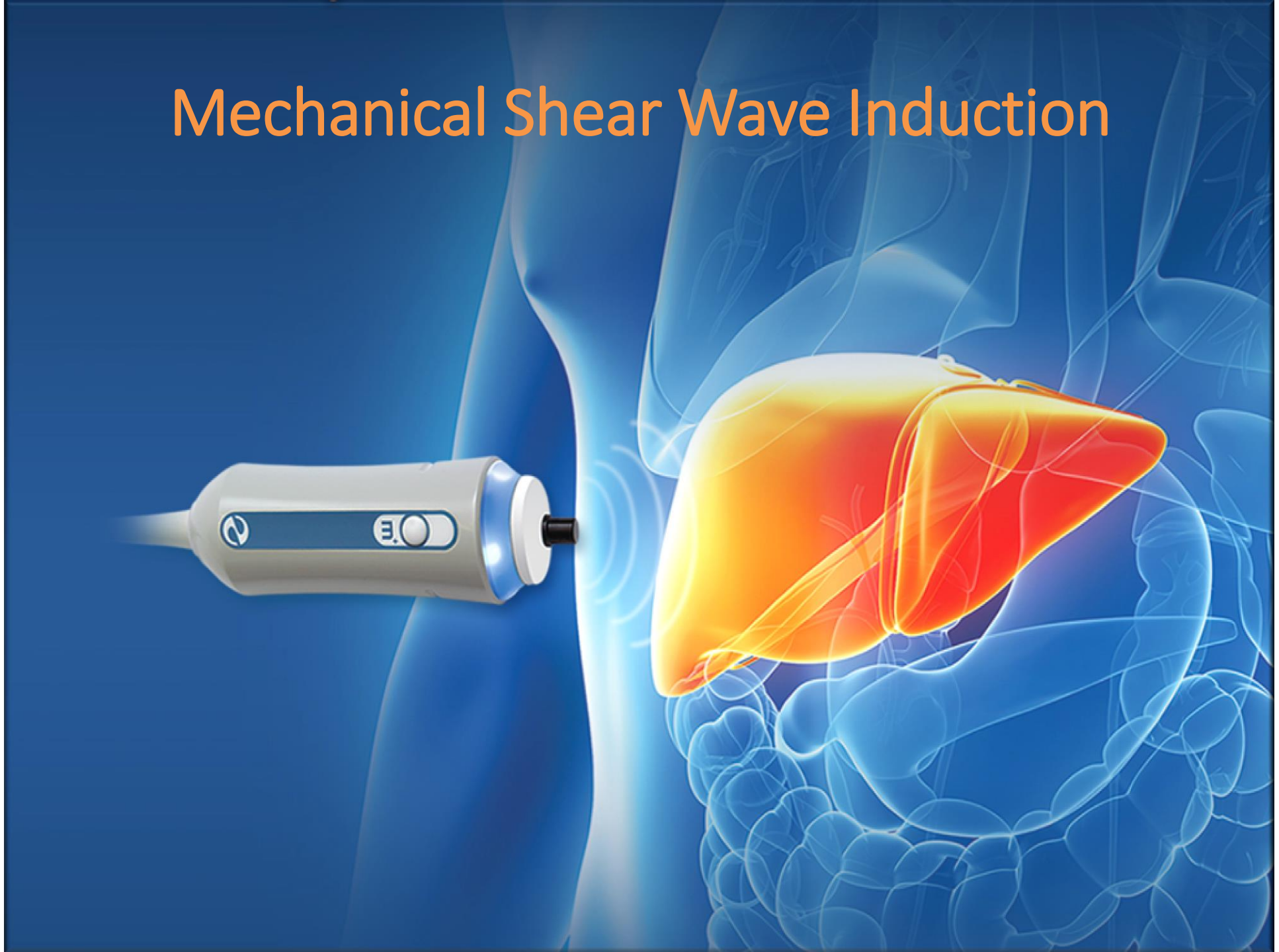
Young's Modulus



Vibration-controlled Transient Elastography VCTE

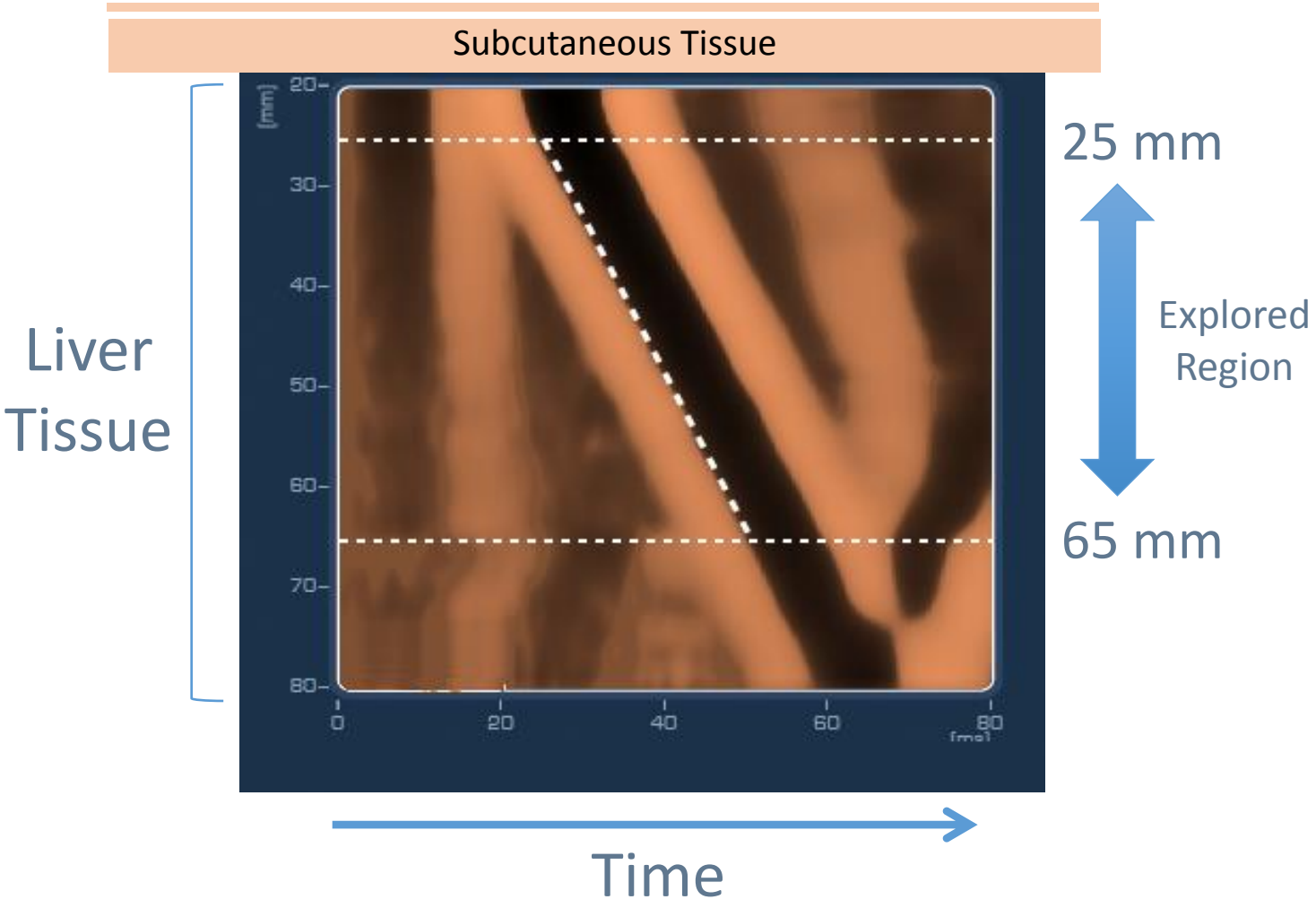
- The shear waves spread from the point of skin impact in a spherical manner, whereas the US waves are released in a straight line along the probe's axis, i.e., in one dimension.
- To ensure that the measurements are accurate and reproducible in the same patient and are comparable among different patients, the accompanying software modifies the shear wave characteristics by **maintaining the shear wave frequency and shape** while ***modifying the shear wave amplitude and energy output***. Thus the full name of the method is vibration-controlled 1D TE
- The resulting LSM is translated into an estimate of the liver fibrosis in a simple and straightforward manner. However, this estimation is possible only under the assumption that the liver is homogeneous and non-viscous, and its elasticity is predominantly affected by the level of fibrosis.


VCTE Probe
Mechanical Actuator
Ultrasound Crystal

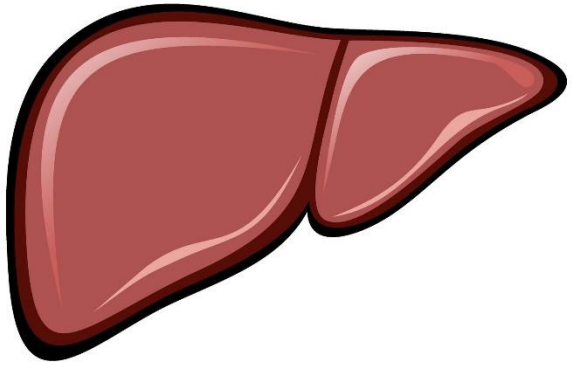

Mechanical Shear Wave Induction

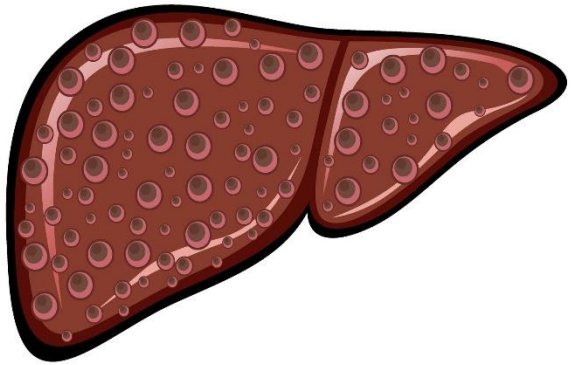
Propagation Map

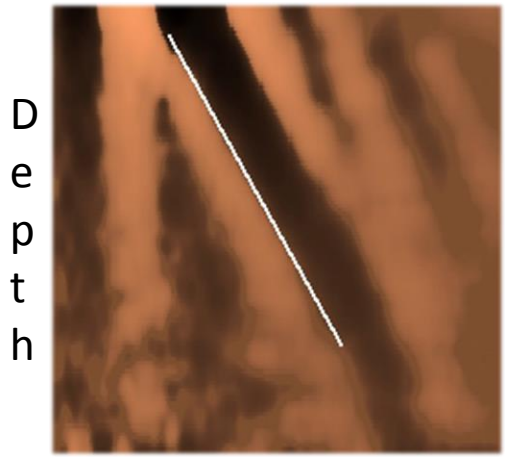
Mathematical Reconstruction of Shear Wave Propagation



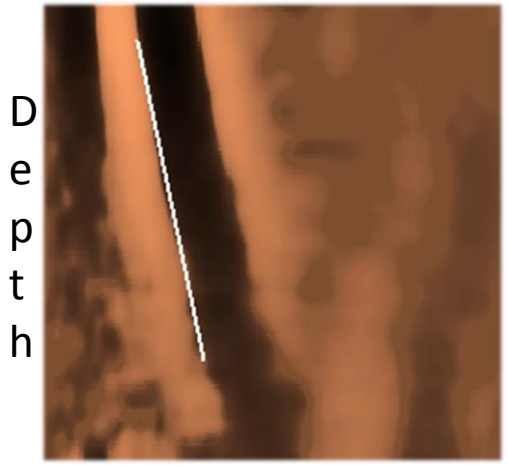
Shear Wave Speed Examples







Slow



Fast

Elastography Influencer Reference

Clinical Gastroenterology and Hepatology 2015;13:27–36

FibroScan (Vibration-Controlled Transient Elastography): Where Does It Stand in the United States Practice

Elliot B. Tapper,* Laurent Castera,‡ and Nezam H. Afdhal*

*Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; and ‡Department of Hepatology, Beaujon Hospital, Assistance Publique-Hôpitaux de Paris, INSERM U773, University of Paris-VII, Clichy, France

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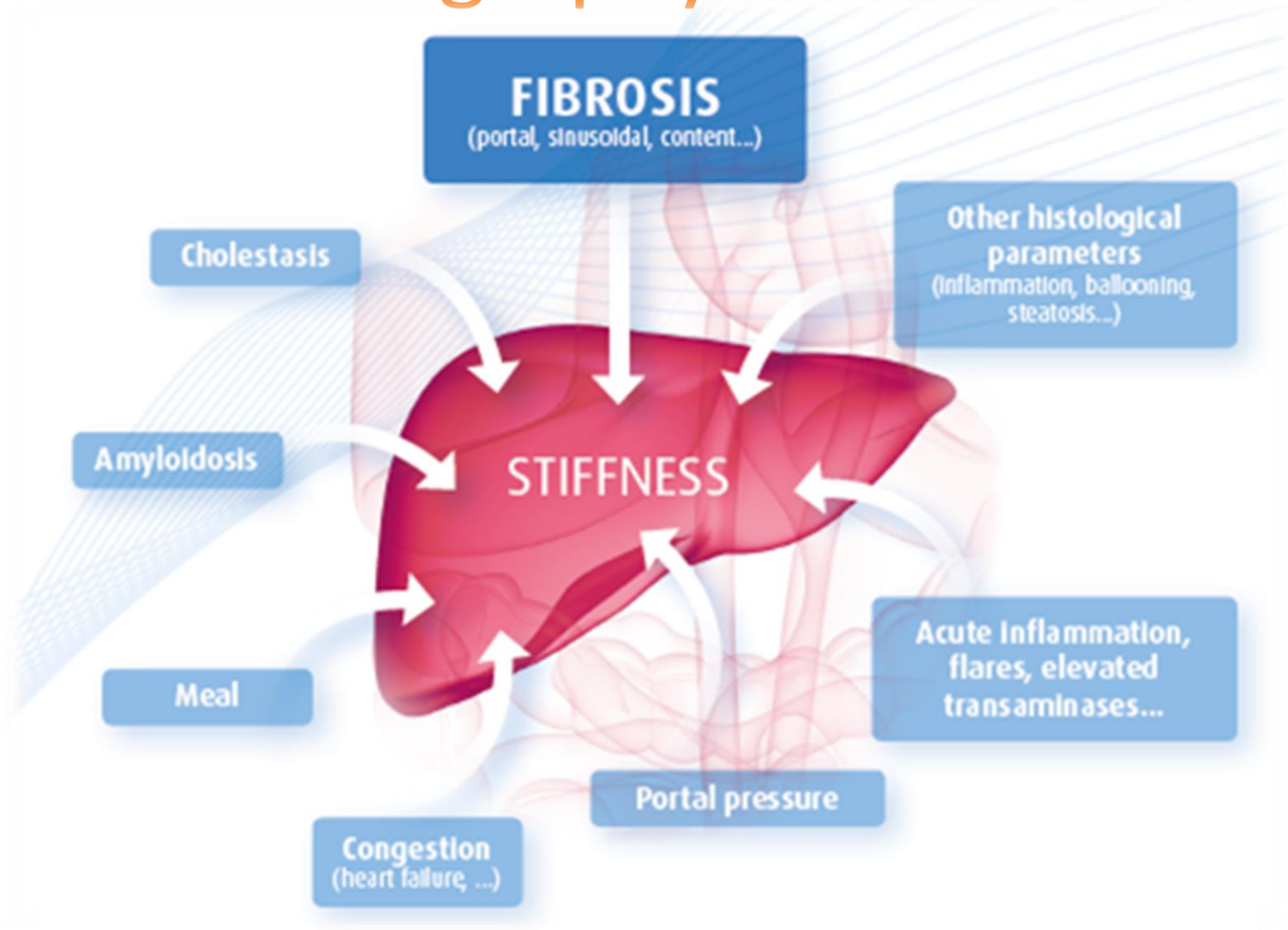
Elastography Influencers



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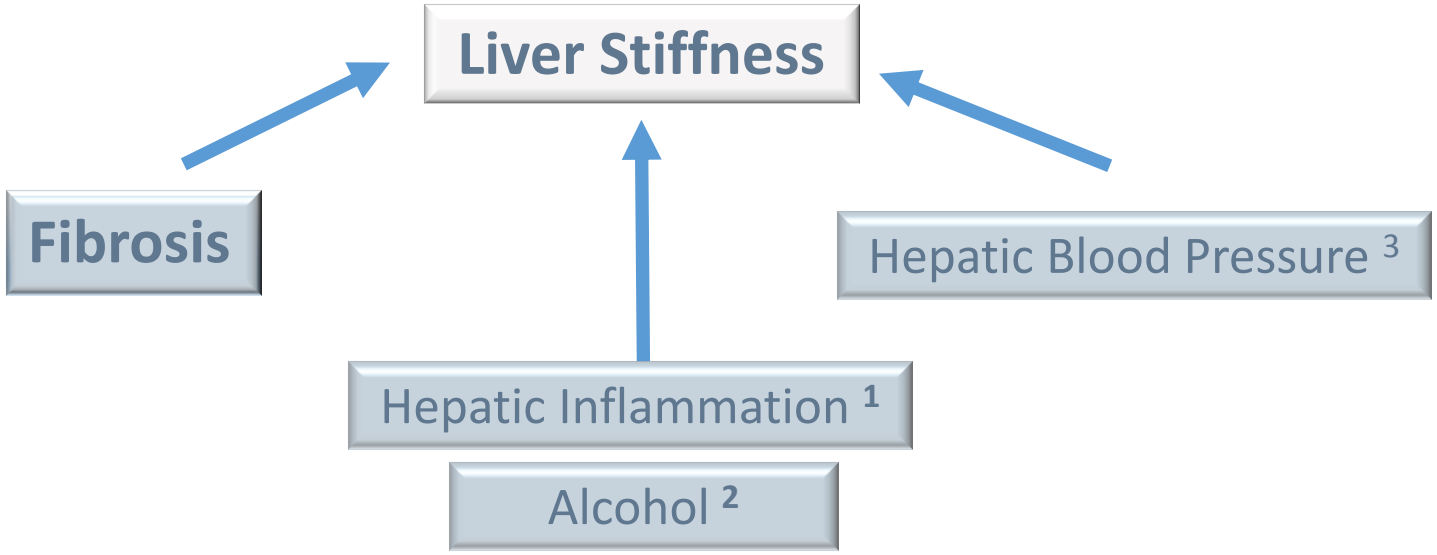
Elastography Influencers



FibroScan (VCTE): Where Does It Stand in The US Practice: Tapper et al, Clinical Gastroenterology & Hepatology, 2015 13:27-36

1. Alanine aminotransferase-based Algorithms of Liver Stiffness Measurement by Transient Elastography (FibroScan) for Liver Fibrosis in Chronic Hepatitis B; Chan et al; Journal of Viral Hepatitis, 2009, 16, 36–44
2. Effect of Alcohol on Liver Stiffness Measured by Transient Elastography; Bardou-Jacquet et al; World Journal of Gastroenterology, 2013 Jan 28, 19(4); 516-522
3. Effect of meal ingestion on liver stiffness in patients with cirrhosis and portal hypertension; Berzigotti, A., et al; PLOS One, 2013. 8(3): p. e58742

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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

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Testing Contraindications

- Pregnancy

- Implantable electronic devices

VCTE Testing Challenges

- Ascites
- Excessive skin to capsule distance
- Narrow intercostal spaces

95-98 % Success Rate[1]

1. Feasibility and Diagnostic Performance of the FibroScan XL Probe for Liver Stiffness Measurement in Overweight and Obese Patient; Myers et al; Hepatology, 2012 Jan;55(1):199-208

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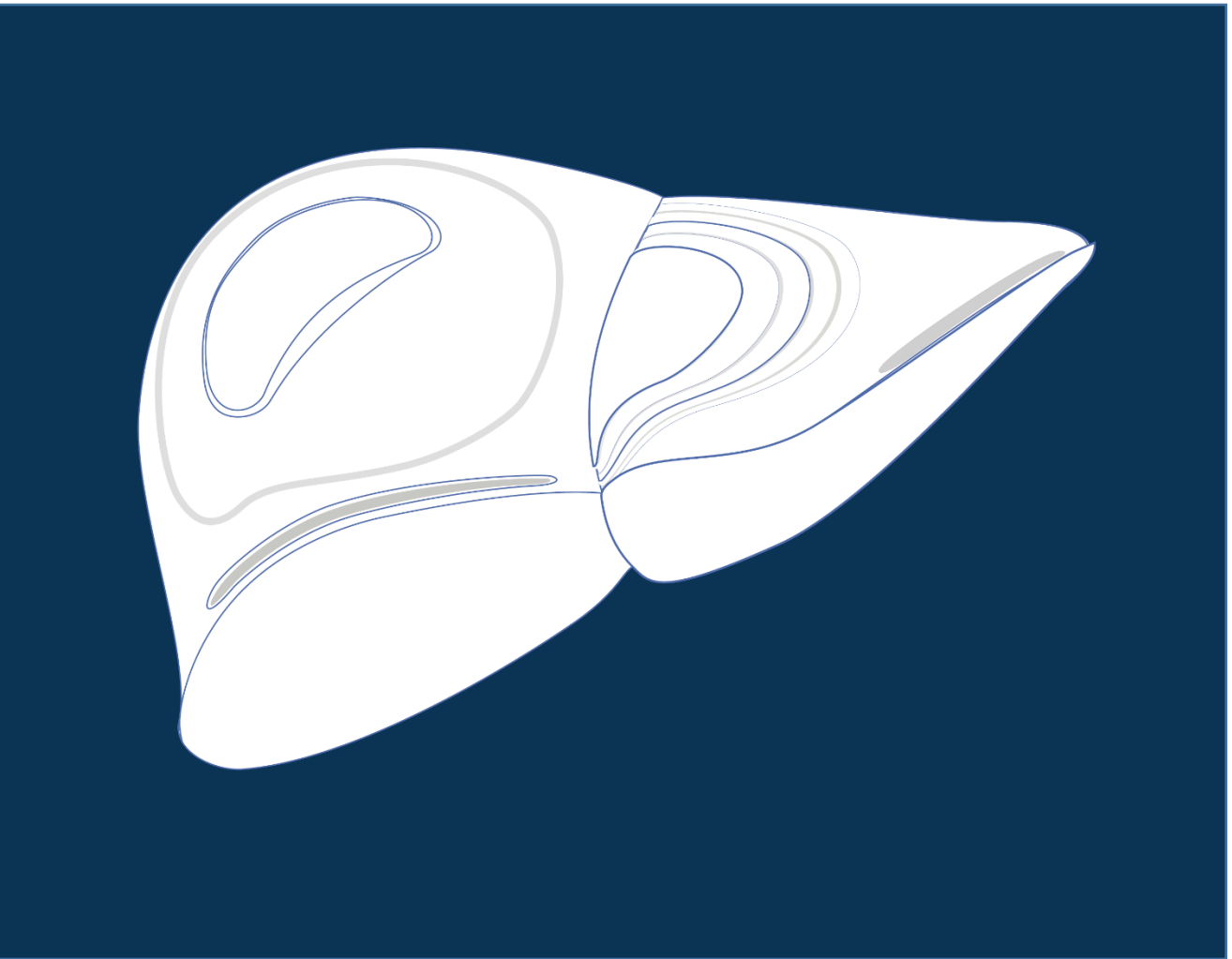
Scientific Validation



Peer Review Publications

- 1200 + peer review publications
- First line test in clinical practice guidelines

FibroScan®

Clinical Practice Guidelines

Guideline	Disease Etiology	Reference Citation
AASLD/IDSA	HCV	Recommendations for Testing, Managing and Treating Hepatitis C; When & In Whom to Initiate Antiviral Therapy, AASLD & IDSA Practice Guidelines; www.hcvguidelines.org
EASL	HCV	EASL Clinical Practice Guidelines : Noninvasive Tests for Evaluation of Liver Disease Severity and Prognosis; Journal of Hepatology 2015
EASL/EASD/EASO	NASH	Journal of Hepatology 2016 vol 64/1388-1402 http://www.journal-of-hepatology.eu/article/S0168-8278(15)00734-5/fulltext
WHO	HCV	WHO Guidelines for Screening, Care and Treatment of Persons with Hepatitis C Infection; ISBN 978 92 4 154875 5
WHO	HBV	Guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection. 2015 WHO Algorithm of WHO recommendations of the Management of Persons with Chronic Hepatitis B infection (Page xxvi)
WHO	HCV + HIV	Management of HCV & HIV co-infection WHO 2012 HIV/AID treatment. Clinical Protocol for the WHO European Region Chapter 6
Baveno VI	Portal Hypertension	Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individual care for portal hypertension; 2015 Journal of Hepatology 63, 3 (743-752)
NICE (UK)	HCV	Diagnosis and Management of Chronic Hepatitis B in Children, Young People & Adults; guidance.nice.org.uk/cg165

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Peer Review Cutoff Value Reference

Curr Gastroenterol Rep (2014) 16:372
DOI 10.1007/s11894-014-0372-6

LIVER (B BACON, SECTION EDITOR)

Utilization of FibroScan in Clinical Practice

Alan Bonder · Nezam Afdhal

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Peer Review Cutoff Value Reference

Disease	F0-F1	F2	F3 Significant Fibrosis	F4 Cirrhosis
HBV	≤ 6.0	> 6.0	≥ 9.0	≥ 12.0
HCV	≤ 7.0	> 7.0	≥ 9.5	≥ 12.0
HCV-HIV	≤ 7.0	≤ 10.0	≥ 11.0	≥ 14.0
Cholestatic	≤ 7.0	≥ 7.5	≥ 10.0	≥ 17.0
NAFLD/NASH	≤ 7.0	≥ 7.5	≥ 10.0	≥ 14.0

Utilization of FibroScan in Clinical Practice; Bonder et al, Current Gastroenterology Rep, 2014 16-372

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FibroScan Accuracy

Meta Analysis of VCTE vs Biopsy

Meta-analyses of transient elastography for liver fibrosis assessment

Reference	Diagnosis	Number of studies	Number of patients	AUROC (cut-off in kPa)		
				F≥2	F≥3	F4
Talwalkar *et al.*[24] (2007)	Mixed	9	2,083	0.87 (NA)	NA (NA)	0.96 (NA)
Stebbing *et al.*[23] (2010)	Mixed	22	4,760	0.84 (7.8)	0.89 (NA)	0.94 (15.6)
Friedrich-Rust *et al.*[22] (2008)	Mixed	50	8,206	0.84 (7.7)	0.89 (NA)	0.94 (13.0)
Tsochatzis *et al.*[62] (2011)	Mixed	40	7,723	NA (7.3)	NA (10.2)	NA (15.0)
Chon *et al.*[26] (2012)	HBV	18	2,772	0.86 (7.9)	0.89 (8.8)	0.93 (11.7)
		139	25,544			

Friedrich-Rust, M. *et al.* (2016) Critical Comparison of Elastography Methods to Assess Chronic Liver Disease *Nat. Rev. Gastroenterol. Hepatology* doi:10.1038/nrgastro.2016.86

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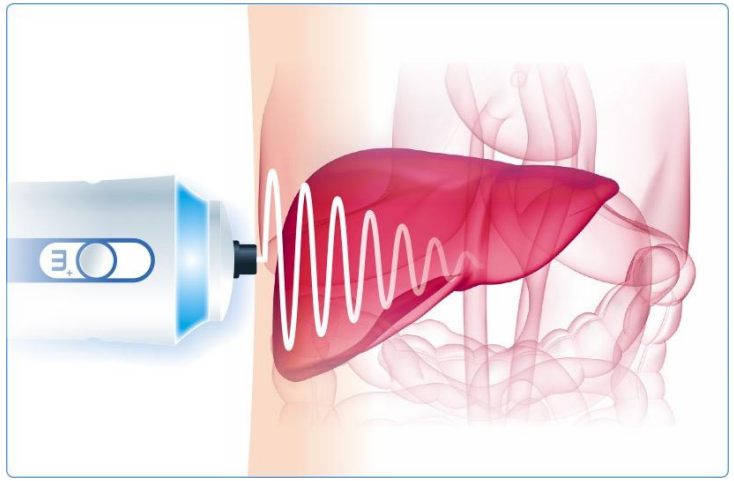
Controlled Attenuation Parameter/ CAP

- Conventional Ultrasonography has demonstrated that liver steatosis affects ultrasound waves by strongly attenuating their intensity. The changes in signal attenuation are followed by an increased reflection of incoming ultrasound waves (hyperechoic).
- The main problem with conventional ultrasonography are its subjective operator –dependent nature and multiple uncontrolled variables included in the examinations, which decrease the sensitivity of the examination in the detection of liver steatosis.
- CAP is based on a formula for intensity attenuation.
- The clinical application of CAP began 2011, 10 years after the introduction of LSM

What Does CAP Measure?

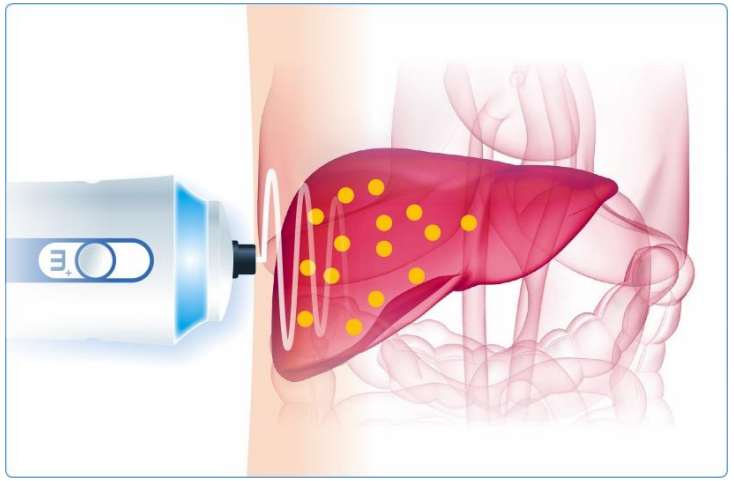
Ultrasound Attenuation Rate

Ultrasound Attenuation Rate
CAP



NORMAL LIVER WITHOUT STEATOSIS

- Low ultrasound attenuation rate
- Low CAP value (dB/m)



FATTY LIVER

- High ultrasound attenuation rate
- Elevated CAP value (dB/m)

Attenuation Rate Correlates to Steatosis

CAP

Low Attenuation Rate = Low Steatosis

High Attenuation Rate = High Steatosis

The controlled attenuation parameter (CAP): A novel tool for the non-invasive evaluation of steatosis using FibroScan; Sasso, Beaugrand, De Ledinghen et al;. Clin Res Hepatology Gastroenterol, 2012. 36(1): p. 13-20.

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CAP Performance By Steatosis Grade

11 Study Meta-Analysis / 2076 Subjects

Grade	CAP Cutoff dB/M	Sensitivity	Specificity	AUC
S0 vs S1-S3	**248**	0.69	0.82	0.82
S0-S1 vs S2-S3	**268**	0.77	0.81	0.86
S0-S2 vs S3	**280**	0.88	0.78	0.88

Steatosis Grade	Affected Hepatocytes
S1	**≤ 33 %**
S2	**≥ 33 – 66 %**
S3	**> 66 %**

Individual Patient Data Meta-Analysis of Controlled Attenuation Parameter (CAP) Technology for Determining Steatosis; Karlas et al, 2016

CAP Accuracy Meta-Analysis

Table 5 Performance of controlled attenuation parameter compared with liver biopsy for the detection of various steatosis grades

Study	Etiology of CLD	Probe	Cut-off (dB/m)	AUC	Sensitivity (%)	Specificity (%)	Number of patients with liver biopsy
Steatosis grade ⩾ 1							
Sasso *et al*[98] (2010)	CLD, ALD, NAFLD	M	238	0.91	91	81	115
de Lédinghen *et al*[100] (2012)	NAFLD, HCV, ALD, other	M	266	0.84	69	85	112
Shen *et al*[102] (2014)	NAFLD, HBV	M	253	0.92	88	83	189
Kumar *et al*[101] (2015)	HBV, HCV, NAFLD	M	214	0.68	64	64	317
Myers *et al*[99] (2012)	Hepatitis, NAFLD, other	M	289	0.79	68	88	153
Chan *et al*[103] (2014)	NAFLD, control	M	263	0.97	91	94	101
Imajo *et al*[83] (2016)	NAFLD, control	M	236	0.88	82.3	91	127
Lupșor-Platon *et al*[105]	HCV, HBV, NAFLD, other CLD	M	260	0.81	64.8	82.3	201
Steatosis grade ⩾ 2							
Sasso *et al*[98] (2010)	CLD, ALD, NAFLD	M	259	0.95	89	86	115
de Lédinghen *et al*[100] (2012)	NAFLD, HCV, ALD, other	M	311	0.86	57	94	112
Shen *et al*[102] (2014)	NAFLD, HBV	M	285	0.92	93	83	189
Kumar *et al*[101] (2015)	HBV, HCV, NAFLD	M	255	0.79	77	80	317
Myers *et al*[99] (2012)	Hepatitis, NAFLD, other	M	288	0.76	85	62	153
Chan *et al*[103] (2014)	NAFLD, control	M	263	0.86	96	67	101
Imajo *et al*[83] (2016)	NAFLD, control	M	270	0.73	64.3	73.6	127
Lupșor-Platon *et al*[105]	HCV, HBV, NAFLD, other CLD	M	285	0.82	69.7	85.1	201
Steatosis grade 3							
Sasso *et al*[98] (2010)	CLD, ALD, NAFLD	M	292	0.89	100	78	115
de Lédinghen *et al*[100] (2012)	NAFLD, HCV, ALD, other	M	318	0.93	87	91	112
Shen *et al*[102] (2014)	NAFLD, HBV	M	310	0.88	92	79	189
Kumar *et al*[101] (2015)	HBV, HCV, NAFLD	M	305	0.91	71	92	317
Myers *et al*[99] (2012)	Hepatitis, NAFLD, other	M	283	0.70	94	47	153
Chan *et al*[103] (2014)	NAFLD, control	M	281	0.75	100	53	101
Imajo *et al*[83] (2016)	NAFLD, control	M	302	0.70	64.3	73.6	127
Lupșor-Platon *et al*[105] (2015)	HCV, HBV, NAFLD, other CLD	M	294	0.83	83.3	82.5	201

Transient Elastography (FibroScan) with Controlled Attenuation Parameter in the Assessment of Liver Steatosis and Fibrosis in Patients with NAFLD; Mikolaseviv et al; World Journal Gastroenterology 2016 August 28;22(32):7236-7251

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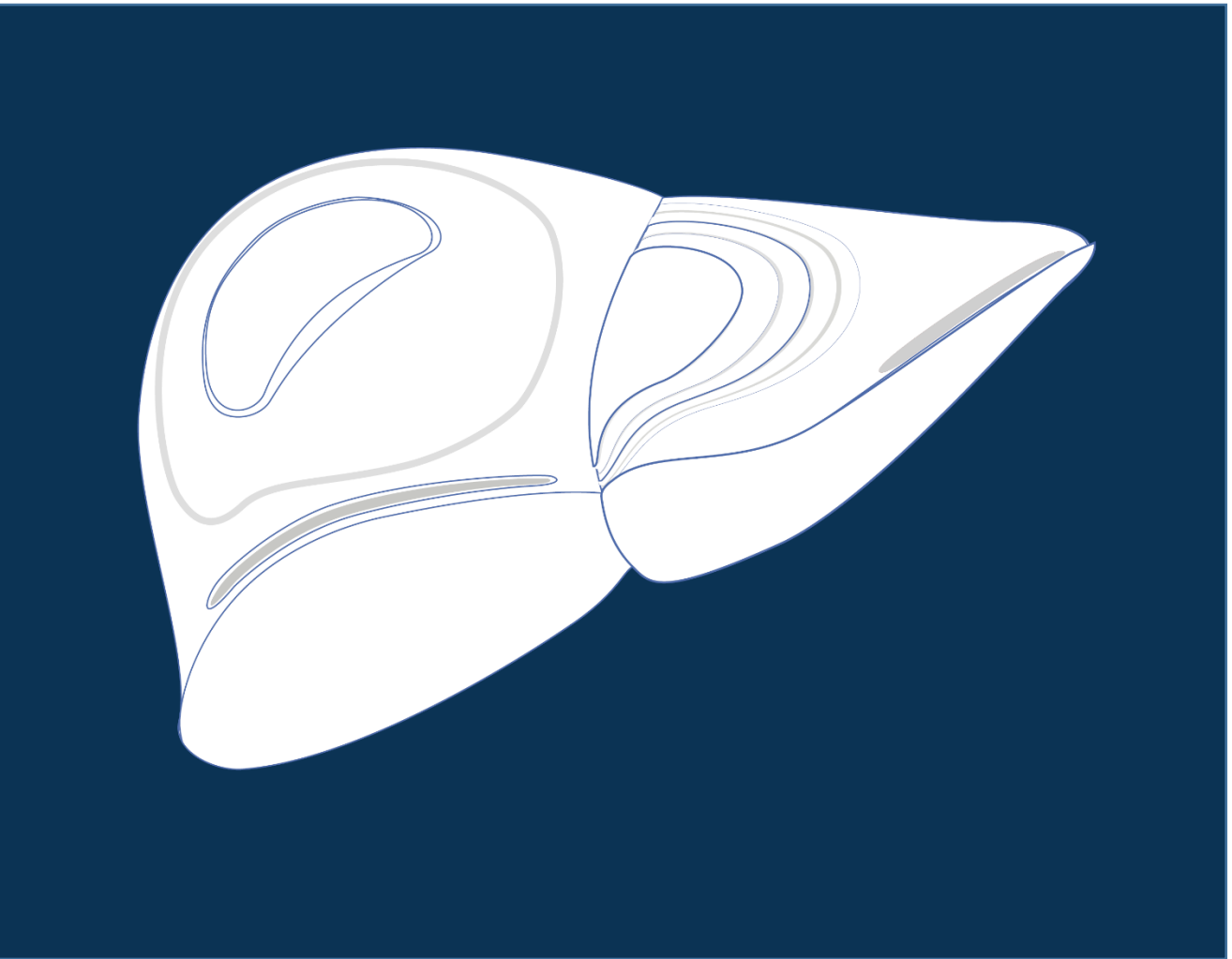
The Patient Examination



FibroScan Probe Selection

Pediatric

Adult

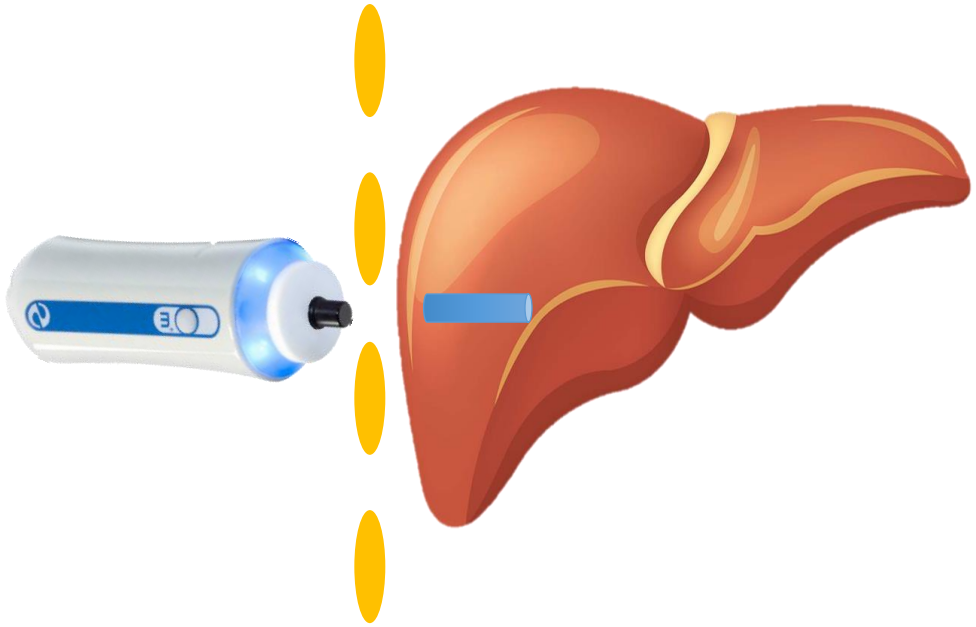
S

M

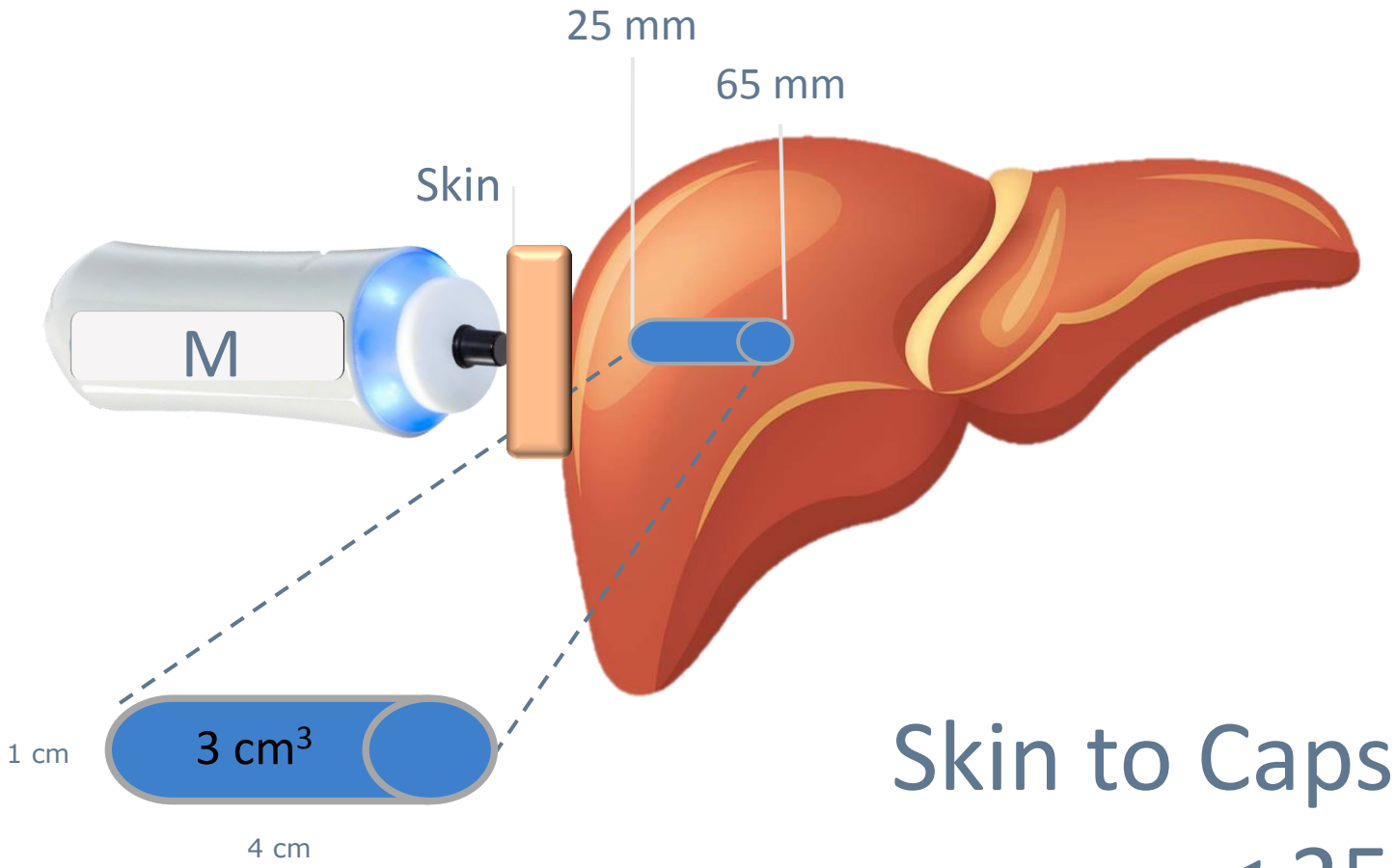
XL

Data Acquisition Steps

- Match the probe to the patient
- Center probe over liver
- Assure optimal signal quality
- Acquire 10 measurements



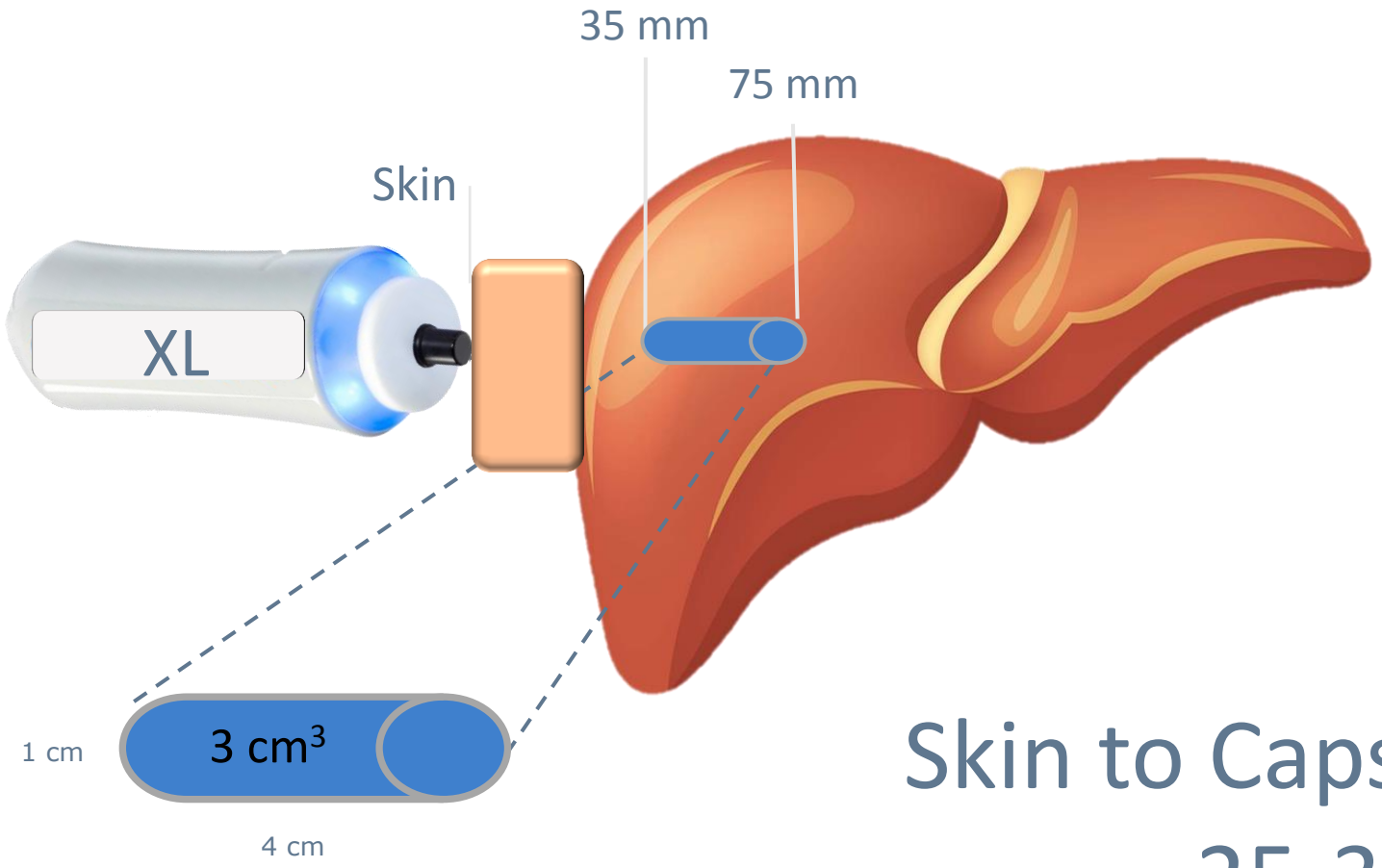
Measurement Parameters



Skin to Capsule Distance

≤ 25 mm

Measurement Parameters



Skin to Capsule Distance
25-35 mm

Holding The Probe Perpendicular

Perpendicular

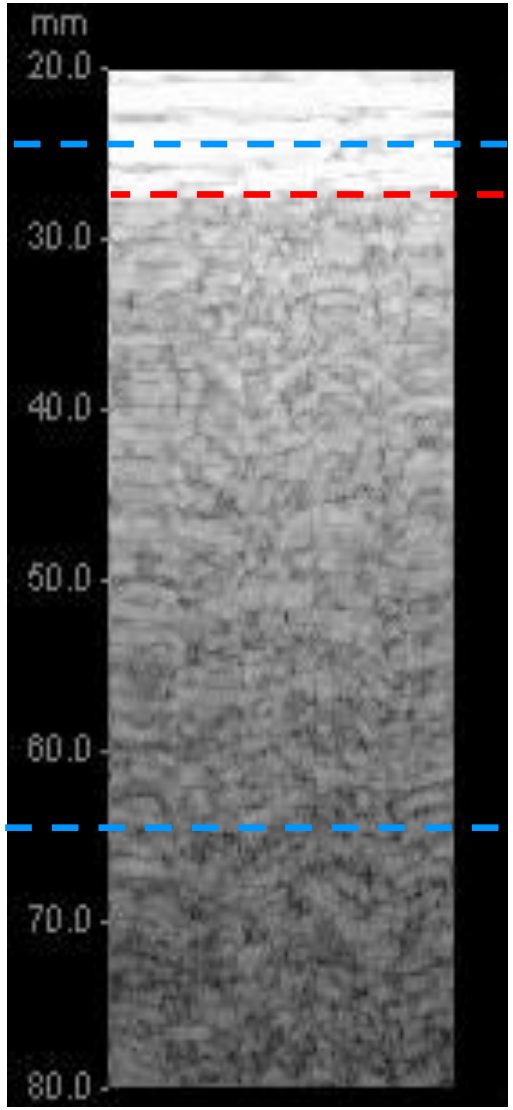
Not Perpendicular

Pre-Measurement Feedback Data

- Probe selection
- Probe position
- Signal quality

Probe Selection Guidance

TM Mode

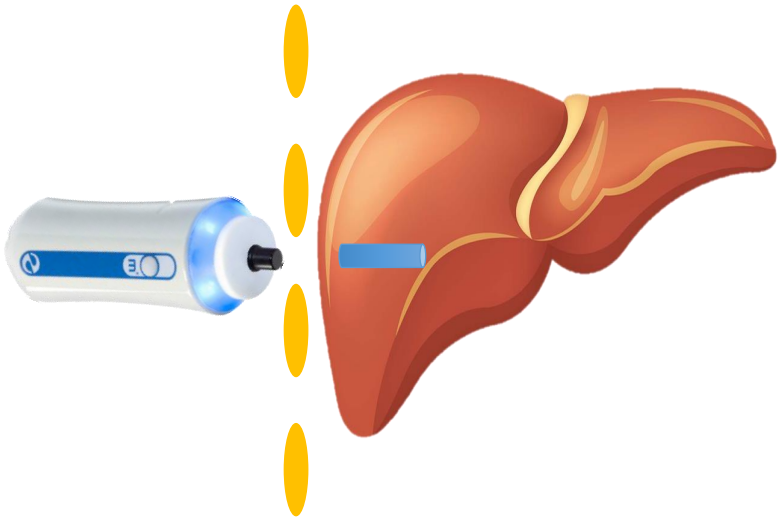


25 mm

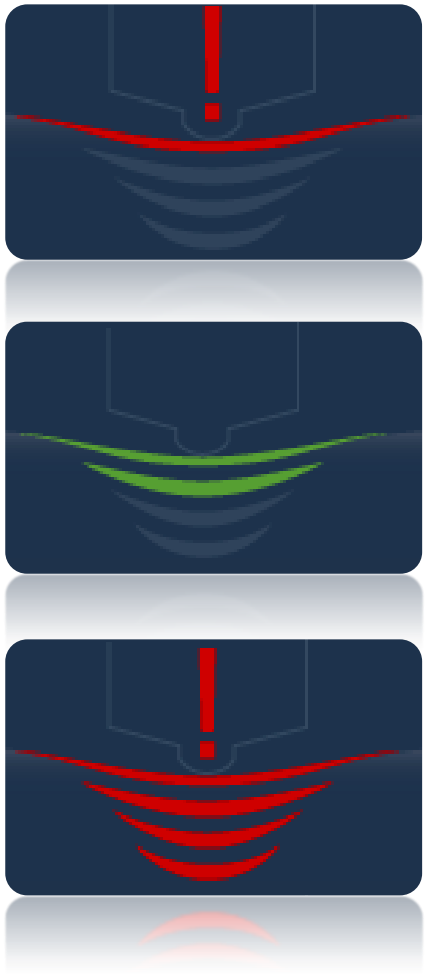
Tissue Change Point

65 mm

Probe Centered on Liver



Pressing The Probe to The Skin



One Red Line

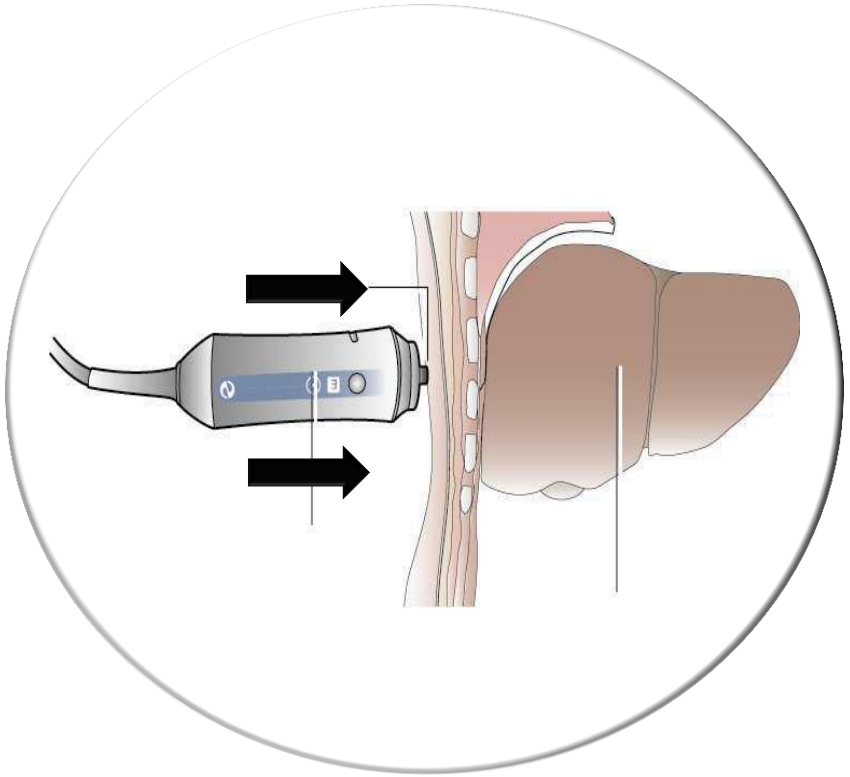
Low Pressure

Green Lines

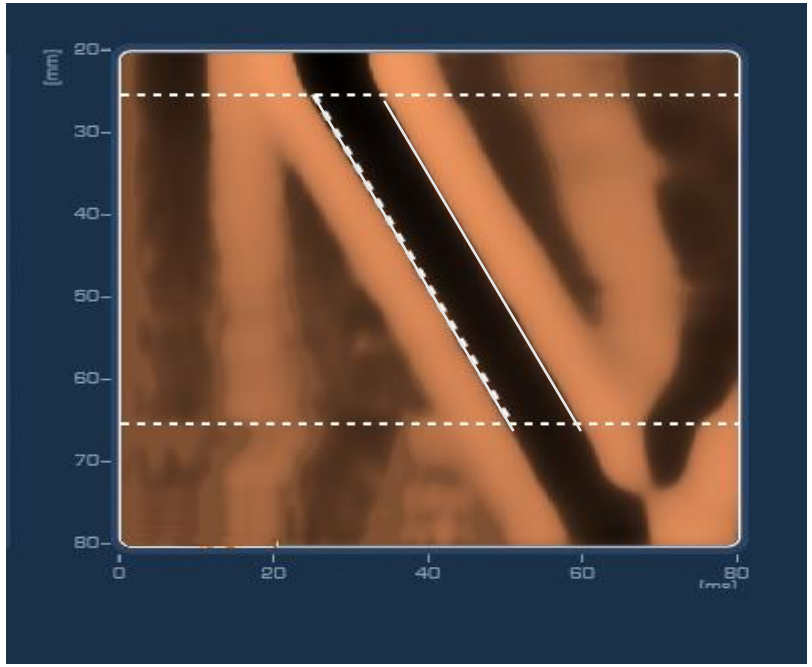
Correct Pressure

Multiple Red Lines

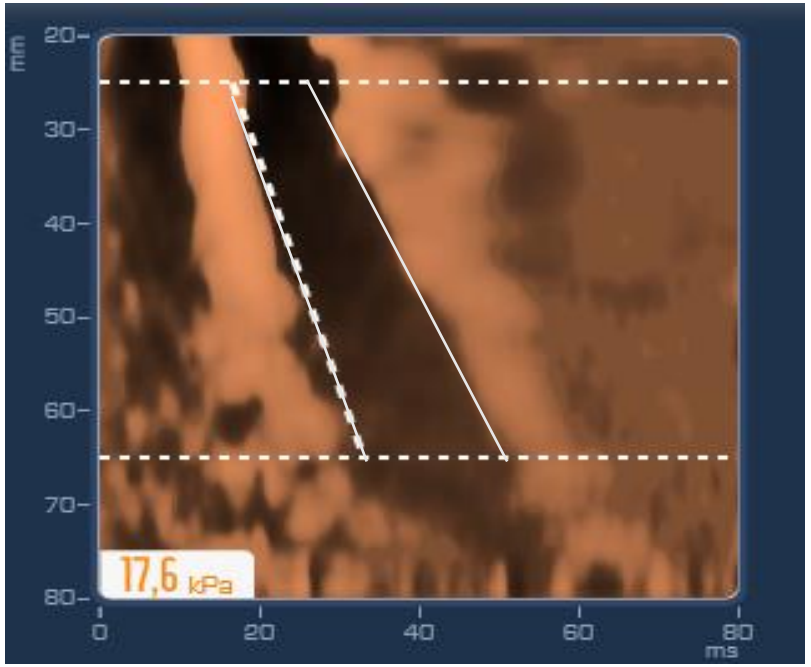
High Pressure



Propagation Map Assessment

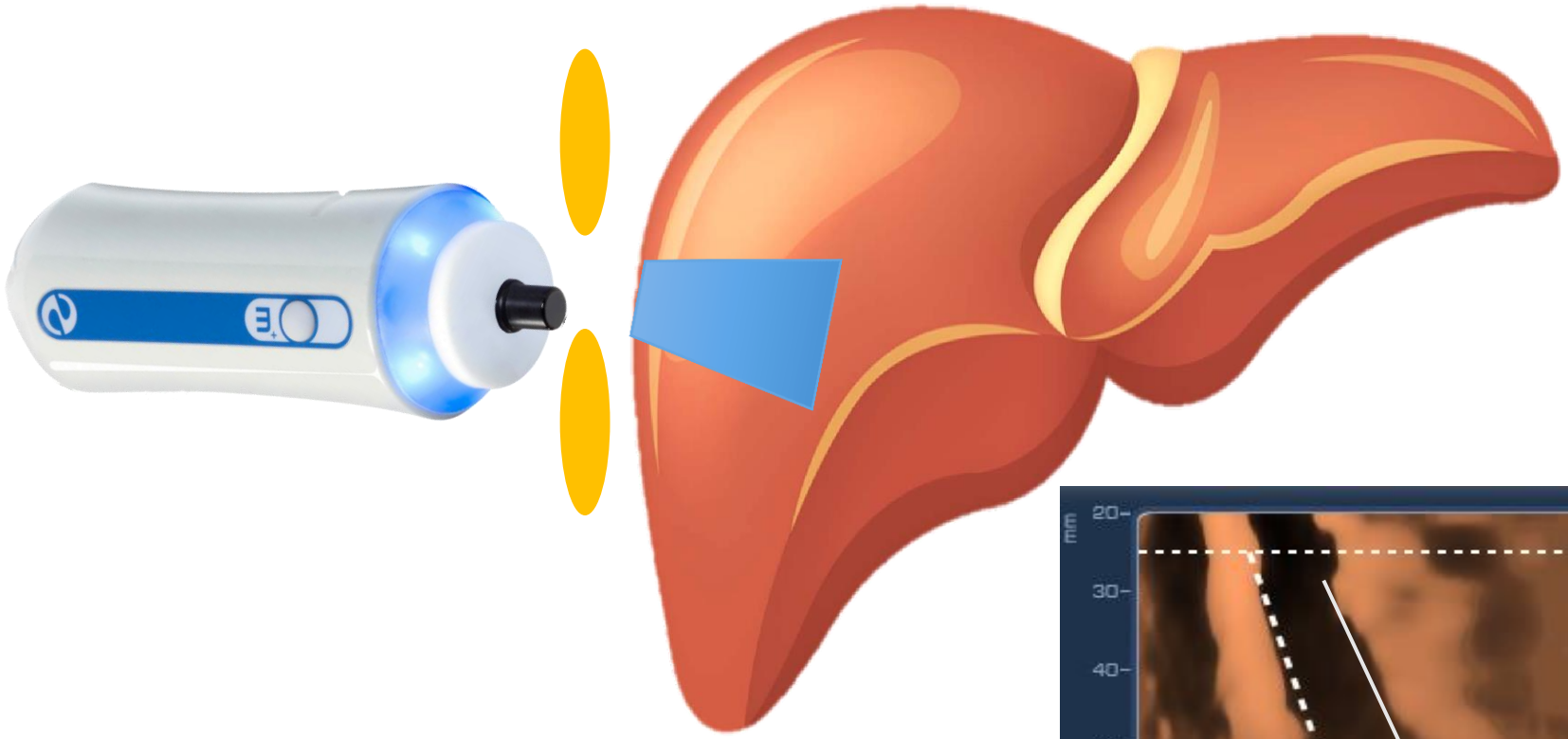


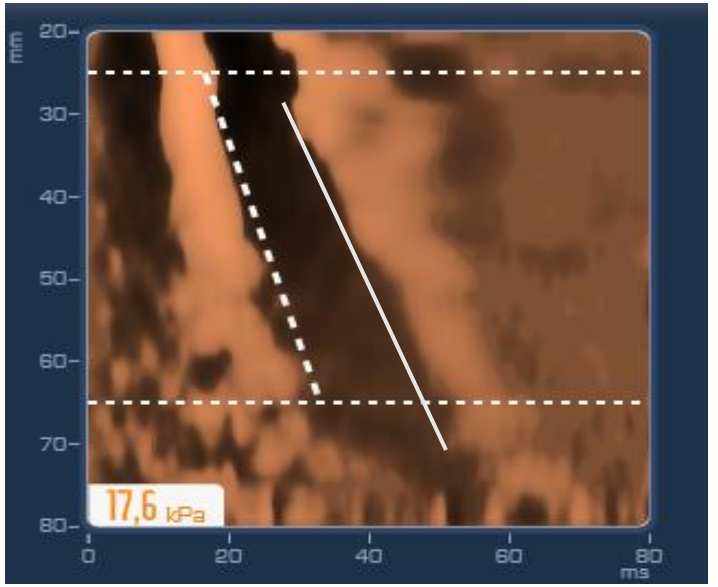
Parallel Shear Wave Margins



Non-Parallel Shear Wave Margins

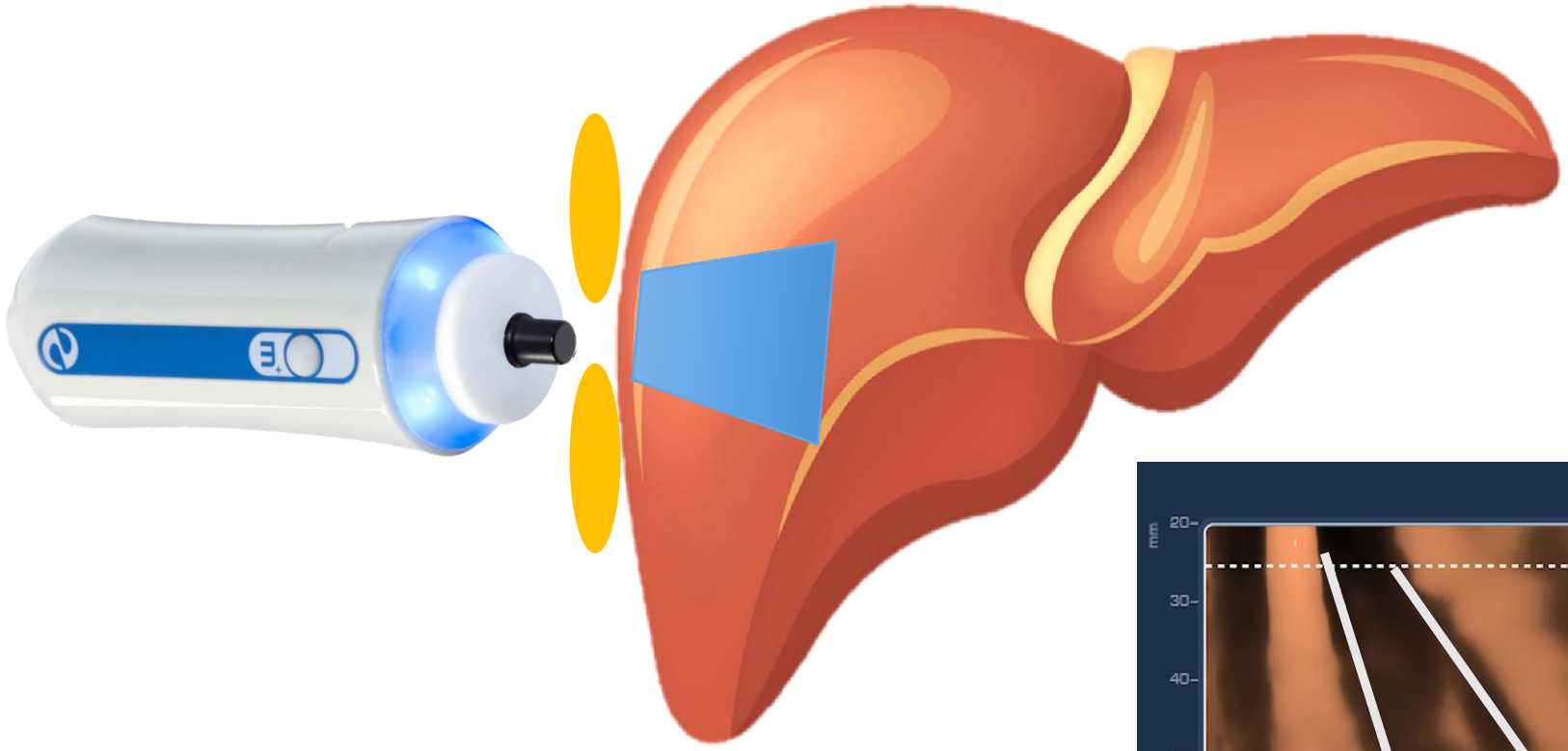
Rib Echo Generation



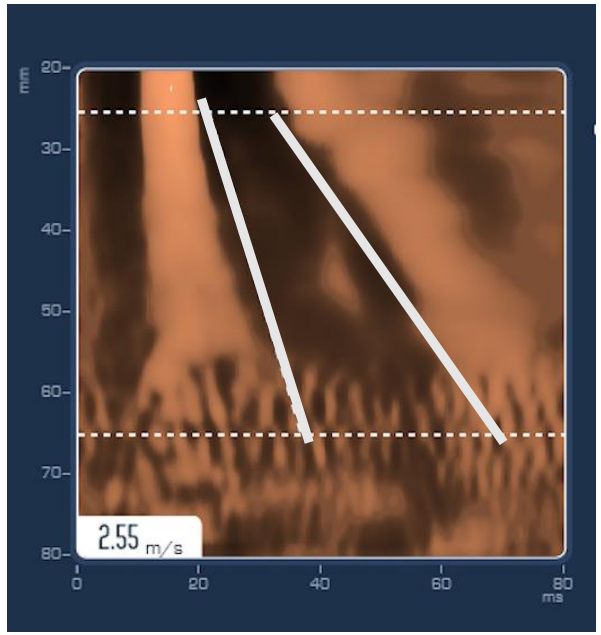


Poorly Centered in Intercostal Space

Narrow Intercostal Space - Rib Echo



Narrow Intercostal Space

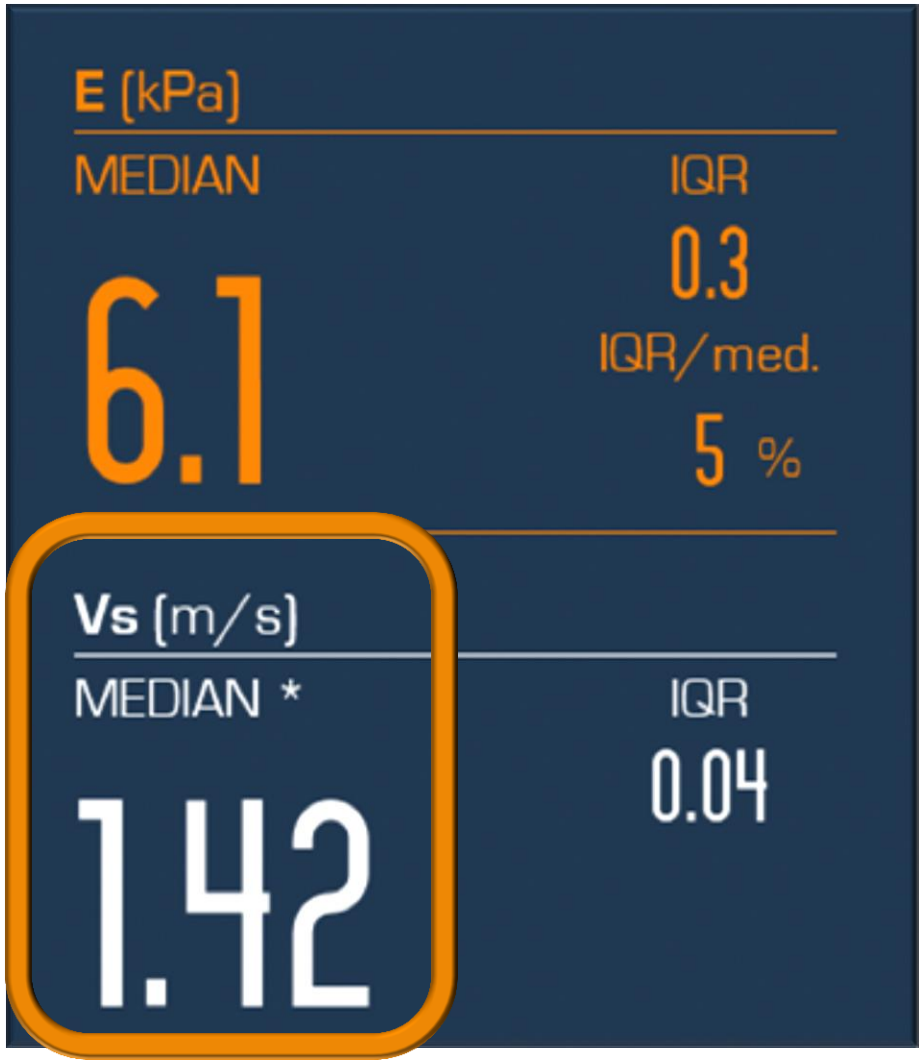


Post-Measurement Feedback Data

- Number measurements
- Data variability
- Shear wave quality
- Median test values

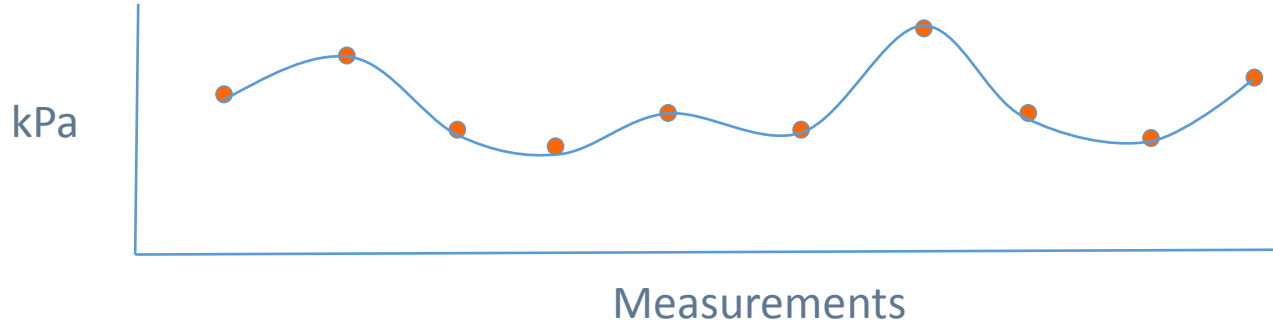
Shear Wave Speed

Speed

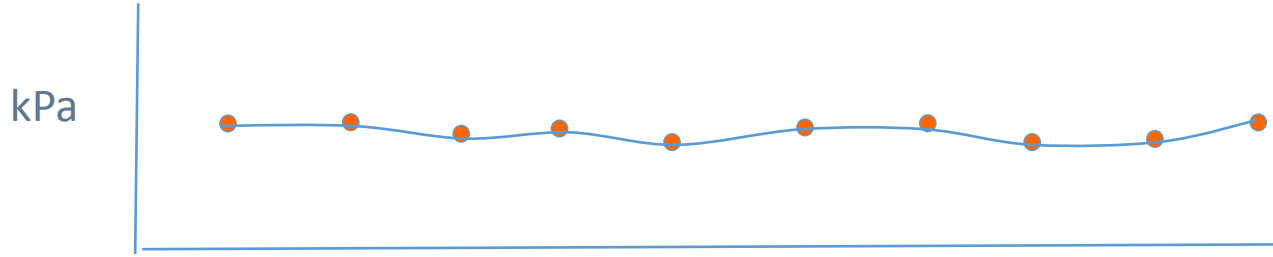


Interquartile Range

Data Variability Metric



High IQR %



Low IQR %

IQR/Med Percentage Must Be ≤ 30 %

Determination of Reliability Criteria for Liver Stiffness Evaluation by Transient Elastography; Boursier et al; Hepatology, Volume 57, No 3, 2013

FibroScan®

USA

2/11/2016

10:04:20 AM

SAMPLE

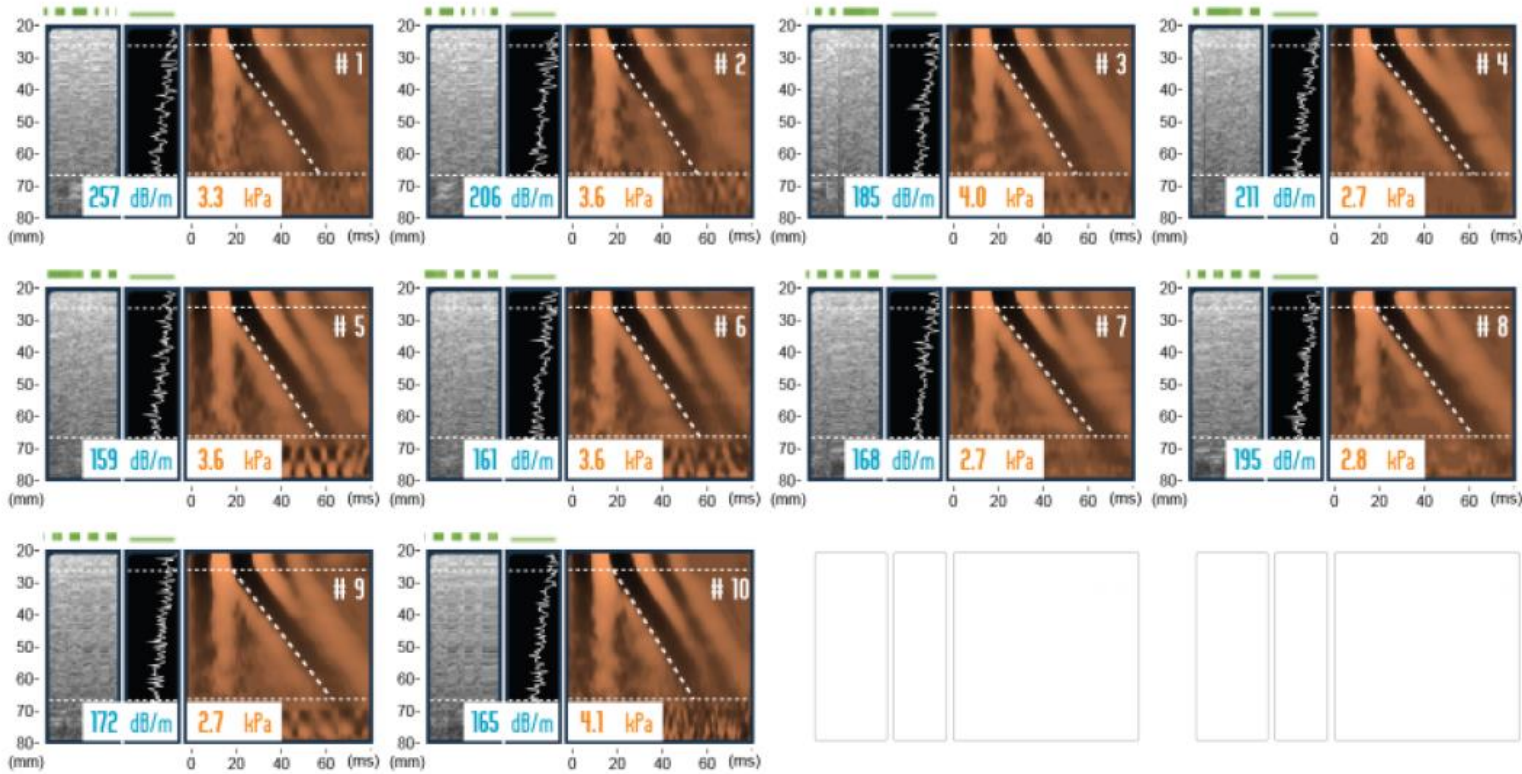
Normal

12345-67890

Admitting diagnosis : Volunteer

CAP (dB/m)		E (kPa)	
IQR	MEDIAN	MEDIAN	IQR
38	179	3.5	0.9
			IQR/med. 26 %

Exam M (Liver)
Operator : JEM
Valid measurements : 10
Total measurements : 10
SWS MEDIAN = 1.07 m/s
SWS IQR = 0.14 m/s



CAP
Performance By Steatosis Grade

Steatosis Grade	CAP Cutoff dB/M	Affected Hepatocytes
S0	≤ 247	
S1	248-267	≤ 33 %
S2	268-279	≥ 33 – 66 %
S3	≥ 280	> 66 %

11 Study Meta-Analysis / 2076 Subjects
Individual Patient Data Meta-Analysis of Controlled Attenuation Parameter (CAP) Technology for Determining Steatosis; Karlas et al, 2016

FibroScan
Peer Review Cutoff Value Reference

Disease	F0-F1	F2	F3	F4
HBV	≤ 6.0	> 6.0	≥ 9.0	≥ 12.0
HCV	≤ 7.0	> 7.0	≥ 9.5	≥ 12.0
HCV-HIV	≤ 7.0	≤ 10.0	≥ 11.0	≥ 14.0
Cholestatic	≤ 7.0	≥ 7.5	≥ 10.0	≥ 17.0
NAFLD/NASH	≤ 7.0	≥ 7.5	≥ 10.0	≥ 14.0

Utilization of FibroScan in Clinical Practice; Bonder et al, Current Gastroenterology Rep, 2014 16-372

Acoustic Radiation Force Impulse Imaging (ARFI)

- Is based on shear wave propagation, similar to TE.
- Compared with TE, inspected liver volume is smaller (1cm in length); however, ARFI can be used on modified commercial ultrasound machines. Thus, the point of interest can be pinpointed using ultrasound's B-mode.
- The downside of this method include a narrow range of results (0.5-4.4 m/s) with unclear cut-offs values for different fibrosis stage levels.

Thank you.

Evaluation and Certificates

- Please use the link or QR code below to complete the learner evaluation. This link will also be emailed to you within a few days. Please check your junk and spam email folders if you don't receive it.

http://sgiz.mobi/s3/August-NW-ECHO