MAYO CLINIC

CHALLENGES WITH IMPLEMENTING LIVER SHEAR WAVE ELASTOGRAPHY IN A LARGE CLINICAL PRACTICE

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AAPM Annual Meeting
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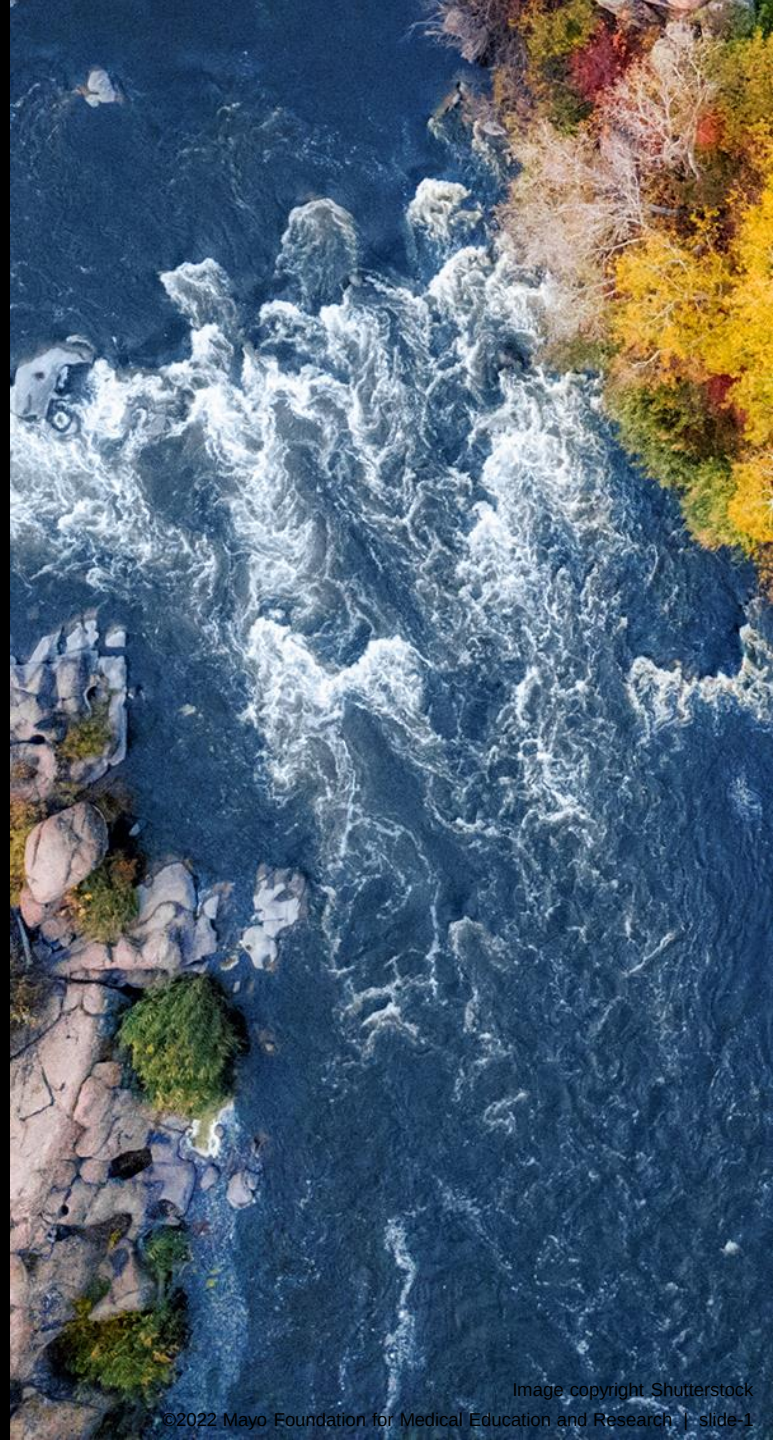
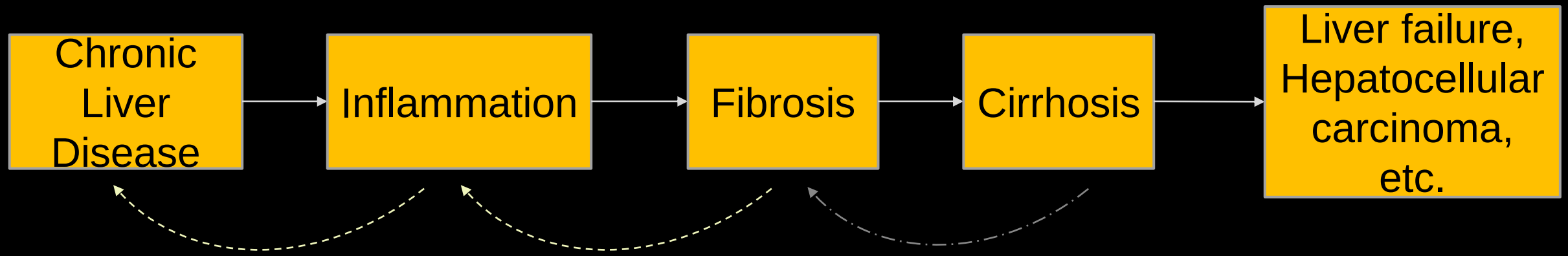


MOTIVATION

- Chronic liver disease has been estimated to affect >1 billion people worldwide and account for 2 million deaths each year [1]

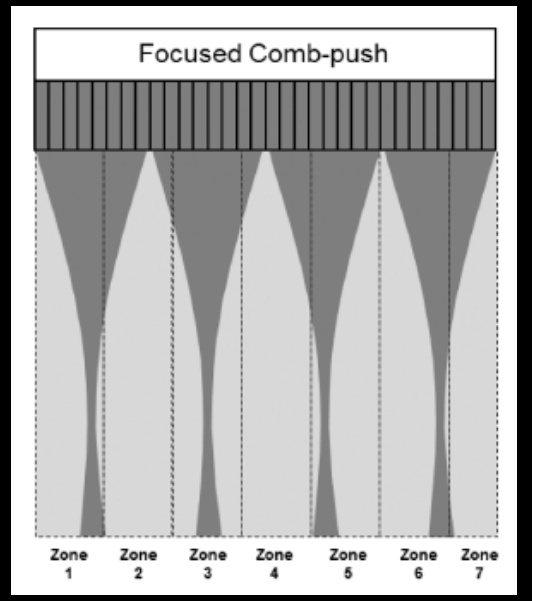


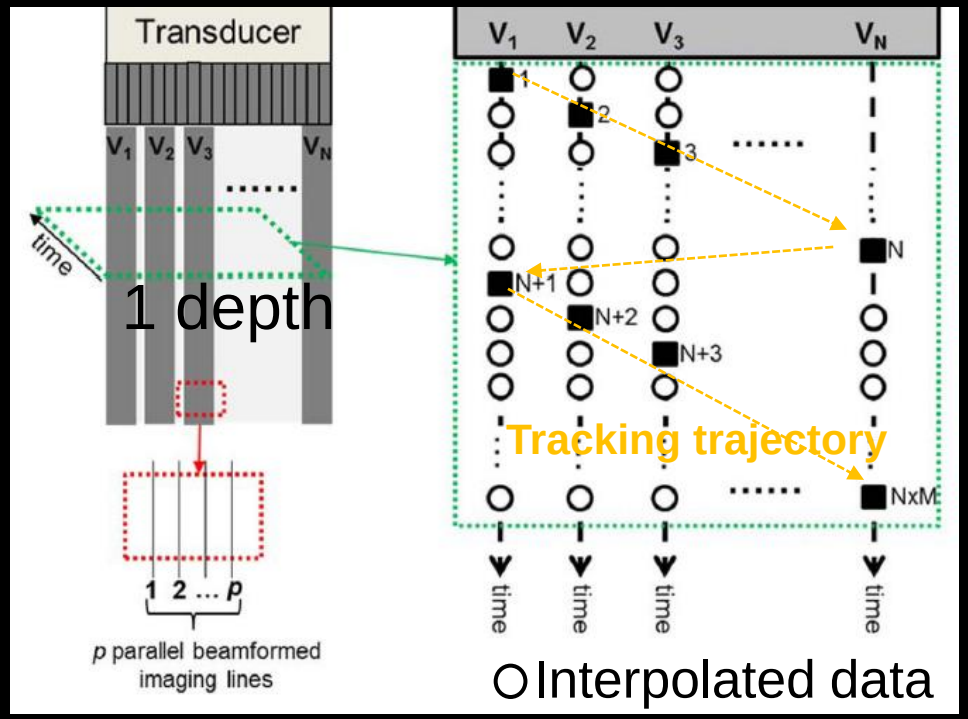
- Biopsy: reference standard for assessing fibrosis and inflammation, but is subject to sampling error, and inter-observer variability
- Well-accepted non-invasive technologies estimating elasticity
  - Transient elastography (FibroScan, Echosens) no-imaging guidance
  - MR elastography (MRE) less available

1. Cheemerla and Balakrishnan. Clin Liver Dis 2021;17(5):365-70;

ULTRASOUND SHEAR WAVE ELASTOGRAPHY (SWE)

- New GE LOGIQ E9 scanners in our practice in 2015-2016
  - High-end scanner with conventional hardware beamformer
  - Realized SWE through a combination of comb-push excitation, and time aligned sequential tracking, with directional filter [1-2]
- A team of radiologists, physicists, and education sonographers for liver SWE implementation

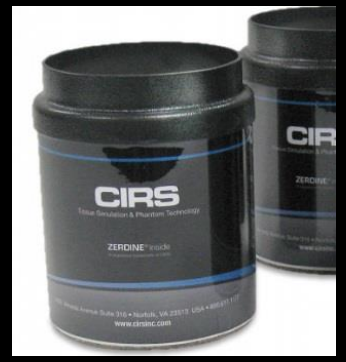




1. Song et al. IEEE Trans Med Imaging 2012 ; 2. Song et al. IEEE Trans Ultrason Ferroelectr Freq Control 2015;

ACCEPTANCE TESTING OF SWE AND BEYOND

- AT of 10 scanners with C1-6 for liver SWE [1]
  - Two depths, two operators, salt water or gel as coupling medium
- Statistically significant difference observed in measurements from different depths
- No statistically significant difference using gel as coupling medium



CIRS 039 shear wave liver fibrosis phantom

Shear wave speed (m/s)	"Soft" Phantom (3 kPa, 0.985 m/s)		"Stiff" Phantom (45 kPa, 3.816 m/s)	
	3 cm depth	7 cm depth	3 cm depth	7 cm depth
Mean ± standard deviation (SD)	0.97 ± 0.01	1.00 ± 0.01	3.74 ± 0.03	3.83 ± 0.10
Maximum deviation from group mean	1.2%	1.6%	1.4%	5.3%

Close to estimated ground truth

Close to each other

1. Long et al. JACMP 2018;19:3:336-42;

REVIEW OF GUIDELINES

- European Federation for Ultrasound in Medicine and Biology (EFSUMB) 2013
- World Federation of Ultrasound in Medicine and Biology (WFUMB) 2015
- Society of Radiologists in Ultrasound (SRU) 2015

EFSUMB Guidelines and Recommendations on the Clinical Use of Ultrasound Elastography. Part 1: Basic Principles and Technology

Authors J. Bamber[1], D. Cosgrove[2], C. F. Dietrich[3], J. Fromageau[1], J. Bojunga[4], F. Calliada[5], V. Cantisani[6], J.-M. Correas[7], M. D'Onofrio[8], E. E. Drakonaki[9], M. Fink[10], M. Friedrich-Rust[11], O. H. Gilja[12], R. F. Havre[13], C. Jenssen[14], A. S. Klauser[15], R. Ohlinger[16], A. Saftoiu[17], F. Schaefer[18], I. Sporea[19], F. Piscaglia[20]

ELSEVIER CrossMark
Ultrasound in Med. & Biol., Vol. 41, No. 5, pp. 1161–1179, 2015

0301-5629/$ - see front matter
http://dx.doi.org/10.1016/j.ultrasmedbio.2015.03.007

WFUMB GUIDELINES AND RECOMMENDATIONS FOR CLINICAL USE OF ULTRASOUND ELASTOGRAPHY: PART 3: LIVER

Giovanna Ferraioli, MD,[1] Carlo Filice, MD,[1] Laurent Castera, MD, PhD,[2] Byung Ihn Choi, MD,[3] Ioan Sporea, MD,[4] Stephanie R. Wilson, MD,[5] David Cosgrove, MD,[6] Christoph F. Dietrich, MD,[7] Dominique Amy, MD,[8] Jeffrey C. Bamber, PhD,[9] Richard Barr, MD, PhD,[10] Yi-Hong Chou, MD,[11] Hong Ding, MD,[12] Andre Farrokh, MD,[13] Mireen Friedrich-Rust, MD,[14] Timothy J. Hall, PhD,[15] Kazutaka Nakashima,[16] Kathryn R. Nightingale, PhD,[17] Mark L. Palmeri, MD, PhD,[17] Fritz Schafer, MD,[18] Tsuyoshi Shiina, PhD,[19] Shinichi Suzuki, MD,[20] and Masatoshi Kudo, MD, PhD[21]

Radiology

Richard G. Barr, MD, PhD
Giovanna Ferraioli, MD
Mark L. Palmeri, MD, PhD
Zachary D. Goodman, MD, PhD
Guadalupe Garcia-Tsao, MD
Jonathan Rubin, MD, PhD
Brian Garra, MD
Robert P. Myers, MD, MSc
Stephanie R. Wilson, MD
Deborah Rubens, MD
Deborah Levine, MD

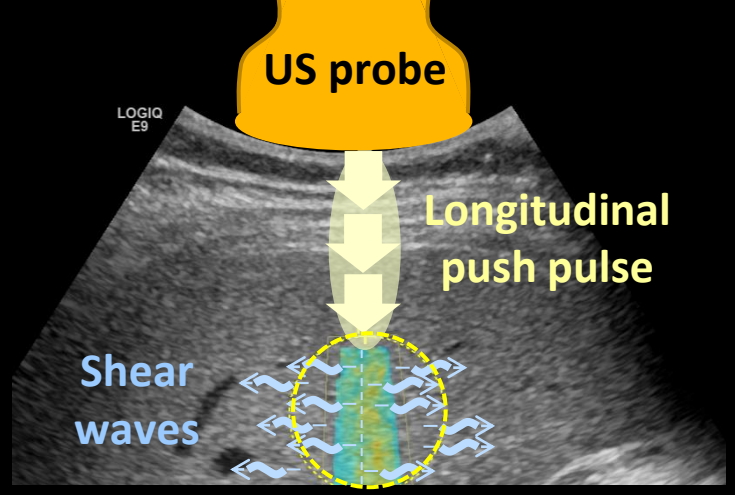
Elastography Assessment of Liver Fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement[1]

Consistent explanations & recommendations on patient preparation, imaging protocol & confounding factors;
Vendor specific thresholds (m/s or kPa) indicated;

1. Bamber et al. Ultraschall in Med 2013;34:169-84; 2. Ferraioli et al. Ultrasound in Med & Biol 2015;41(5):1161-79;
3. Barr et al. Radiology 2015;276:845-61;

PROTOCOL AND EDUCATION

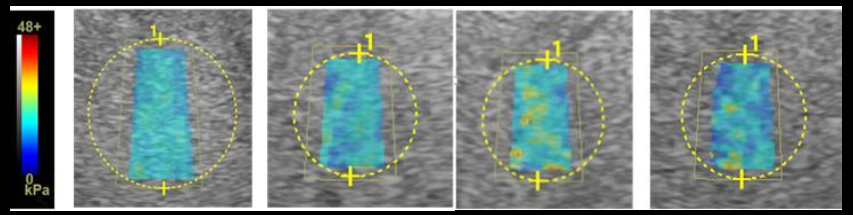
- Imaging protocol, radiologist reporting template, and education
- Sonographer hands-on practice
  - Right lobe of liver, intercostal
  - Optimize grayscale imaging!
  - Push pulse perpendicular to liver capsule
  - SWE box placement
  - Visual quality check and artifact recognition before circular ROI measurement



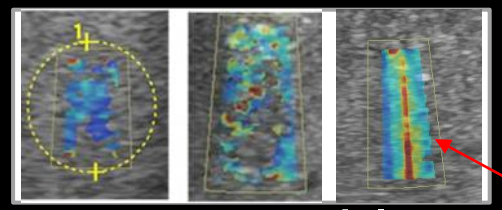
Liver Shear Wave Elastography (SWE)

Mayo Rochester Protocol

1. **Patient**
   a. Must be clear-liquids-only fasting for at least 4 hours
   b. Supine (LPO w/wedge if needed for better window)
   c. Right arm above head
2. **LE9 SWE mode**
   a. ABD tab/Abd model
   b. Elasto button (operator panel above keyboard)
   c. Penetration mode (touch screen) if not defaulted
3. **Transducer position**
   a. Best right intercostal window available
   b. Parallel to ribs
   c. Liver capsule/surface horizontal in the FOV (perpendicular to the push pulse)
4. **Placement of SWE Acquisition ROI**
   a. Adjust <u>only</u> ROI depth position
   b. Place shallow margin of ROI 1.5 – 2.0 cm deep and perpendicular to liver capsule
   c. Ideally the ROI center will be 5-6 cm from the skin
   d. The deep margin of ROI should not be deeper than 8.0 cm
   e. Avoid large vessels, GB, liver edge, etc.,within the ROI; Stay at least 1cm away from liver margin
   f. Avoid rib shadow; ROI should be at least 1.5cm from rib shadow
5. **Stiffness map acquisition**
   a. Monitor tidal breathing motion in the image and ask the patient to stop breathing at end expiration
      i. *IMPORTANT*: Explain that they should not take in a breath; do not say "hold your breath"; do not have them forcibly exhale
   b. When the liver becomes stationary in the image press the Start button
      i. Be patient – several moments may pass before the liver is truly motionless
      ii. Be aware of transducer motion



acceptable

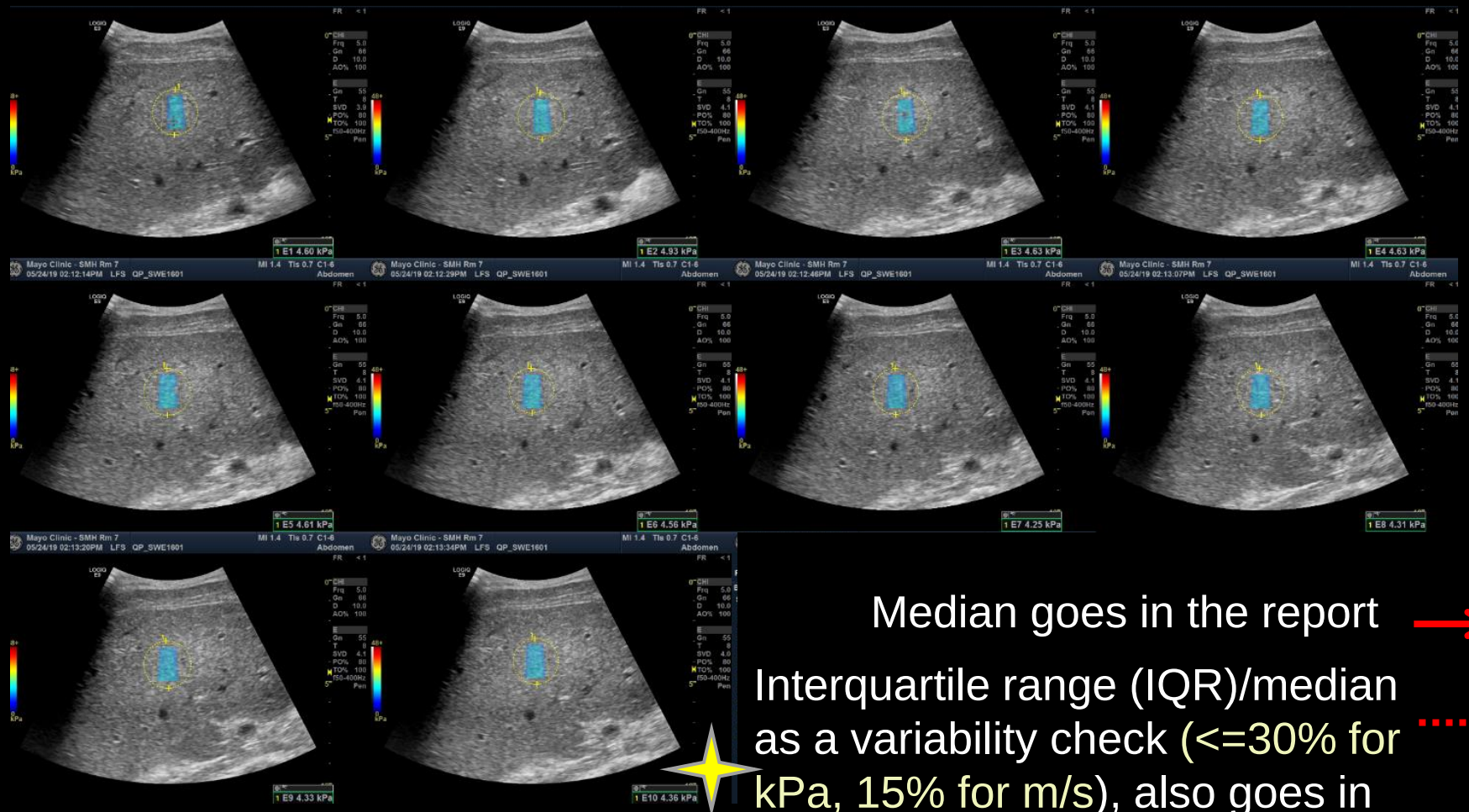


motion

unacceptable

PROTOCOL AND EDUCATION

- 10 acceptable measurements



Parameter	Value
B Mode Measurements	
ShearStiffnessSequence	
E1	4.60 kPa
E2	4.93 kPa
E3	4.63 kPa
E4	4.63 kPa
E5	4.61 kPa
E6	4.56 kPa
E7	4.25 kPa
E8	4.31 kPa
E9	4.33 kPa
E10	4.36 kPa
E Median	4.58 kPa
E IQR	0.29 kPa
E IQR/Median	6.3 %

Median goes in the report

Interquartile range (IQR)/median as a variability check (<=30% for kPa, 15% for m/s), also goes in the report

IQR: diff btw 1st and 3rd quartile

REPORTING TEMPLATE

Liver shear wave elastography (2D-SWE, GE, C1-6, [supine LPO position] with [right arm overhead]) was performed with patient in suspended respiration. [Patient was fasting for at least 4 hours prior to the exam.] Representative images were obtained.

Subjective study quality: [Good/TechnicallyChallenging/Poor]

Median liver stiffness of [...] kPa
Interquartile Range/Median (IQR/M): [...]% (quality metric; < / = 30% suggests acceptable variability).

Interpretation of US 2D SWE results:

<8.3 kPa = normal or minimal risk for clinically significant fibrosis (normal or mild fibrosis)

8.3-11.9 kPa = moderate risk of having clinically significant fibrosis (moderate to severe fibrosis), additional testing may be appropriate

>11.9 kPa = high risk of having clinically significant fibrosis and/or cirrhosis (severe fibrosis and cirrhosis)

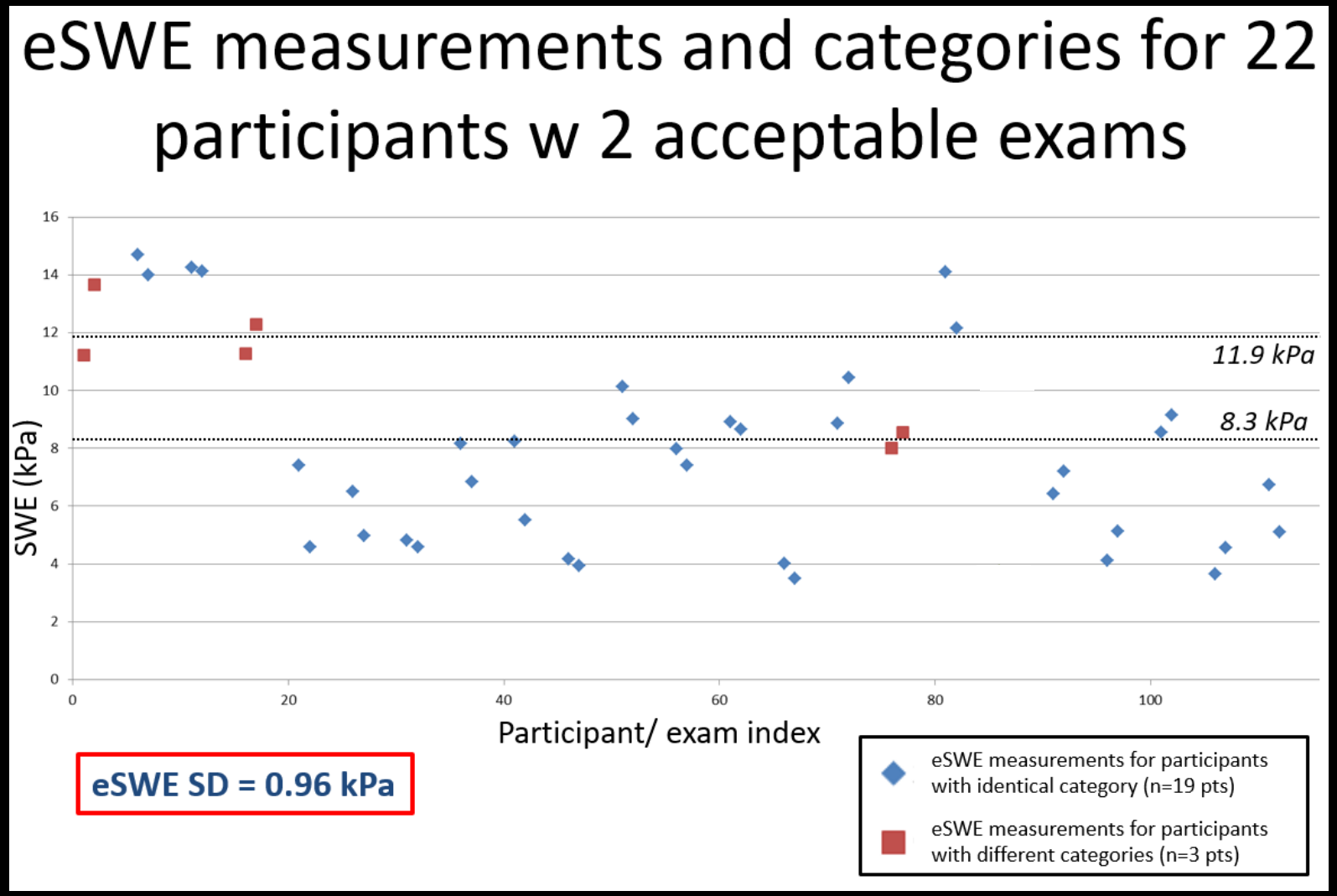
Liver Fibrosis Staging

Liver Fibrosis Staging	Metavir Score	kPa	m/s
Normal – Mild	F1	5.48 kPa – 8.29 kPa	1.35 m/s – 1.66 m/s
Mild – Moderate	F2	8.29 kPa – 9.40 kPa	1.66 m/s – 1.77 m/s
Moderate – Severe	F3	9.40 kPa – 11.9 kPa	1.77 m/s – 1.99 m/s
Cirrhosis	F4	> 11.9 kPa	> 1.99 m/s

1. GE LOGIQ E9 Shear Wave Elastography whitepaper, 2015;

REPRODUCIBILITY STUDY

- Two sonographers performed liver SWE on patients under IRB

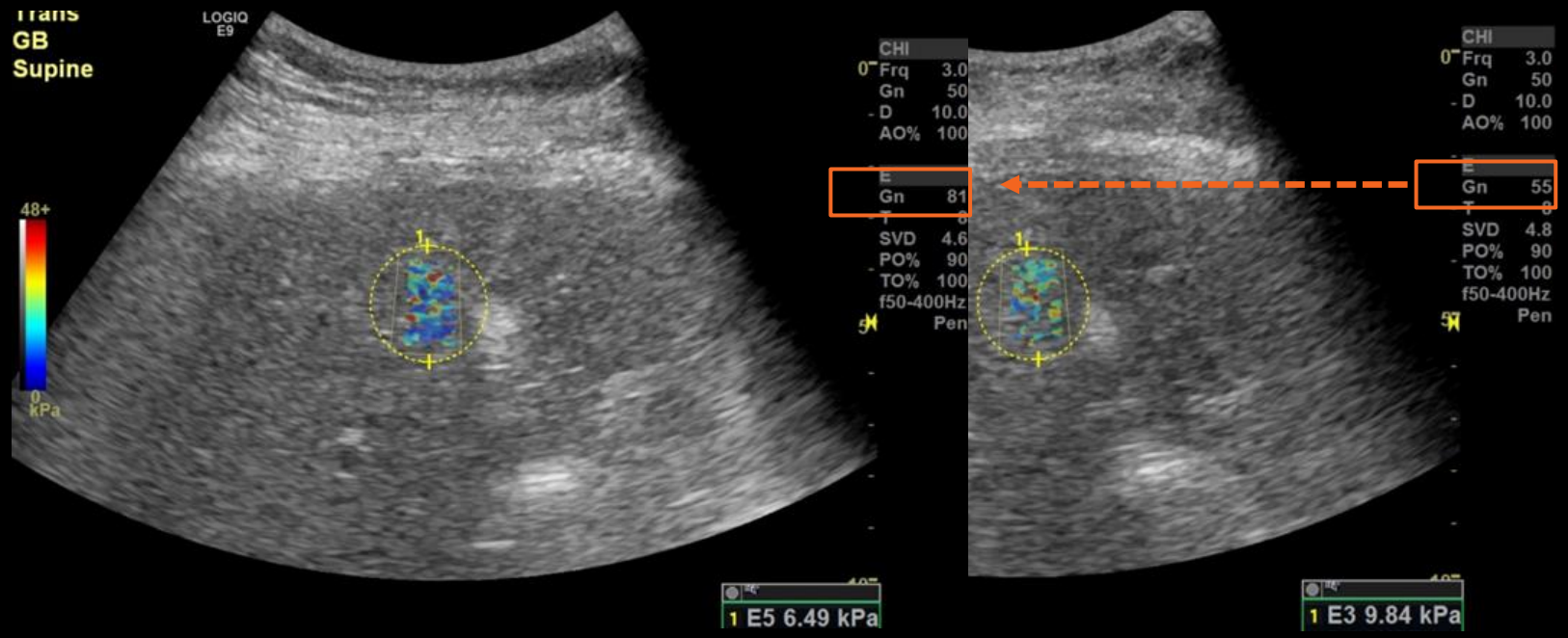


blinded to each other's measurements

Hangiandreou et al. 2019 AAPM Annual Meeting

WHAT WENT WRONG?

- Earlier acquisition-related errors/changes
  - Poor quality/color filling – should not measure
  - Changed SWE gain (from default of 55 on LOGIQ E9) – change quantification!
  - Others: SWE box too deep, too close to rib shadows or interface laterally, oblique angle relative to liver capsule



New study showed using intercostal probe pressure improved SWE success rate without impacting quantification [1]

1., Byenfeldt et al. Ultrasound Med Biol 2019;

WHAT WENT WRONG?

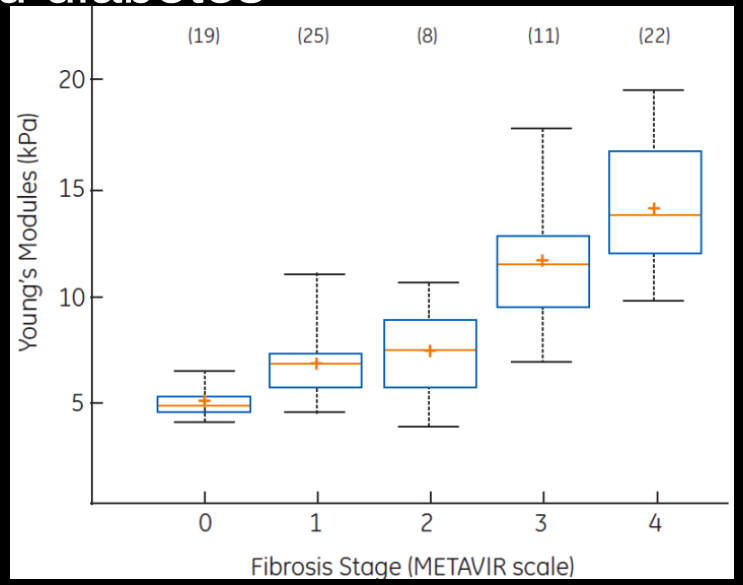
- 450 patients reviewed ~late 2019, acquired by 64 sonographers
  - 13.3% failed due to sparse color fill, i.e., low signal to noise ratio
    - Sample volume depth had a median of 5.6cm and was significantly deeper than the general group (median of 4.3cm, $p<0.01$)
  - Spearman correlation coefficient was 0.525 between SWE and MRE ($p<0.01$)
    - 36 patients, data from one MRE and six SWE excluded due to poor quality or increased elastography gain
  - Seven cases with >=stage 2 fibrosis on MRE measured lower than 8.3kPa in Young's modulus on SWE (normal or minimal risk for significant fibrosis)

Long et al., 2020 AIUM Annual Meeting

MAIN ISSUE: CUT-OFF VALUES AND OVERLAPPING

- ROC analysis derived from 85 subjects in Italy (18 healthy and 67 w/ biopsy-proven chronic liver disease)
  - A mixture of viral hepatitis (B and C, 72% of patients), autoimmune hepatitis, nonalcoholic steatohepatitis, alcoholic steatohepatitis, cryptogenic cirrhosis, primary biliary cirrhosis, newly diagnosed diabetes

	F>0	F>1	F>2	F>3
Cutoff (m/s)	1.35	1.66	1.77	1.99
Cutoff (kPa)	5.48	8.29	9.40	11.9
AUROC	0.87	0.94	0.98	0.94



Cut-off values using ROC analysis to maximize sensitivity and specificity, and typically have not been applied to a validation cohort. Despite high area under the curve, there is a small failure rate.

1. GE LOGIQ E9 Shear Wave Elastography whitepaper, 2015

ETIOLOGY DEPENDENCE AND OVERLAPPING ISSUE

Singh et al.
IOSR-JDMS
2018;17:42-7.

FibroScan

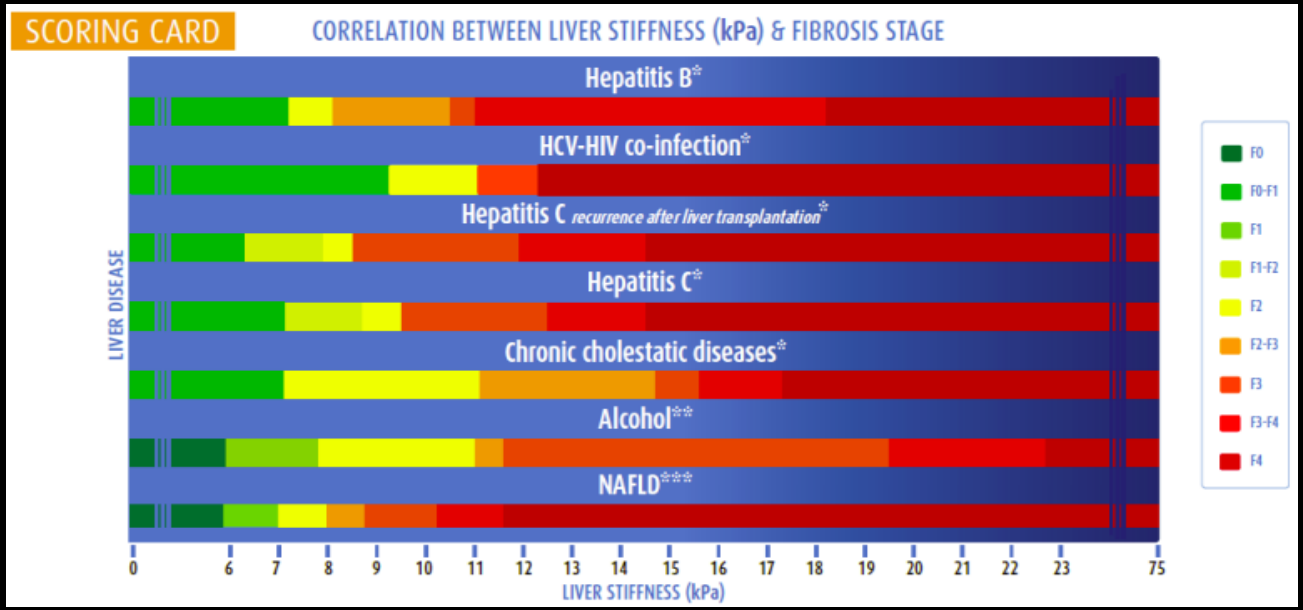


Table 2: Recommendation for Interpretation of Liver Stiffness Values Obtained with ARFI Techniques in Patients with Viral Hepatitis and NAFLD

Liver Stiffness Value	Recommendation
≤5 kPa (1.3 m/sec)	High probability of being normal
<9 kPa (1.7 m/sec)	In the absence of other known clinical signs, rules out cACLD. If there are known clinical signs, may need further test for confirmation
9–13 kPa (1.7–2.1 m/sec)	Suggestive of cACLD but need further test for confirmation
>13 kPa (2.1 m/sec)	Rules in cACLD
>17 kPa (2.4 m/sec)	Suggestive of CSPH

Note.—ARFI = acoustic radiation force impulse, cACLD = compensated advanced chronic liver disease, CSPH = clinically significant portal hypertension, NAFLD = non-alcoholic fatty liver disease.

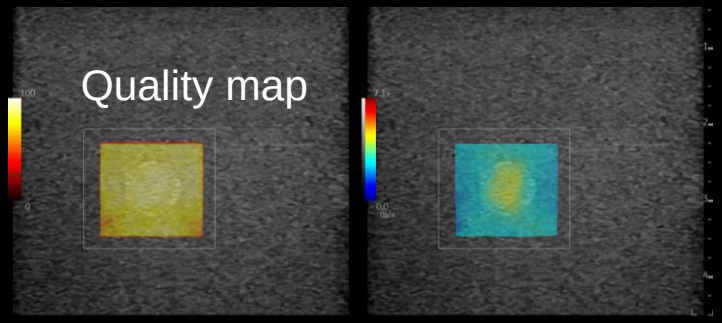
Vendor neutral

New SRU consensus

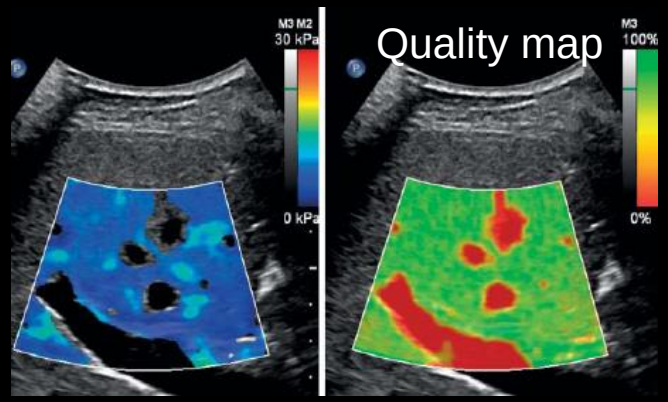
Barr et al.
Radiology
2020;296:263-74;

QUALITY MAP OR INDICATOR

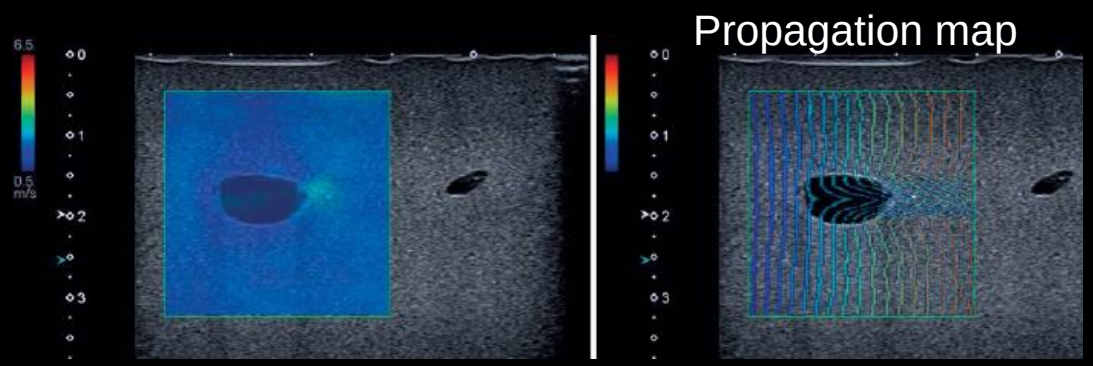
- Most vendors have 2D SWE quality map currently, but may not on all models, and still subject to operator assessment



GE LOGIQ E10, needs to be turned on prospectively



Philips EPIQ

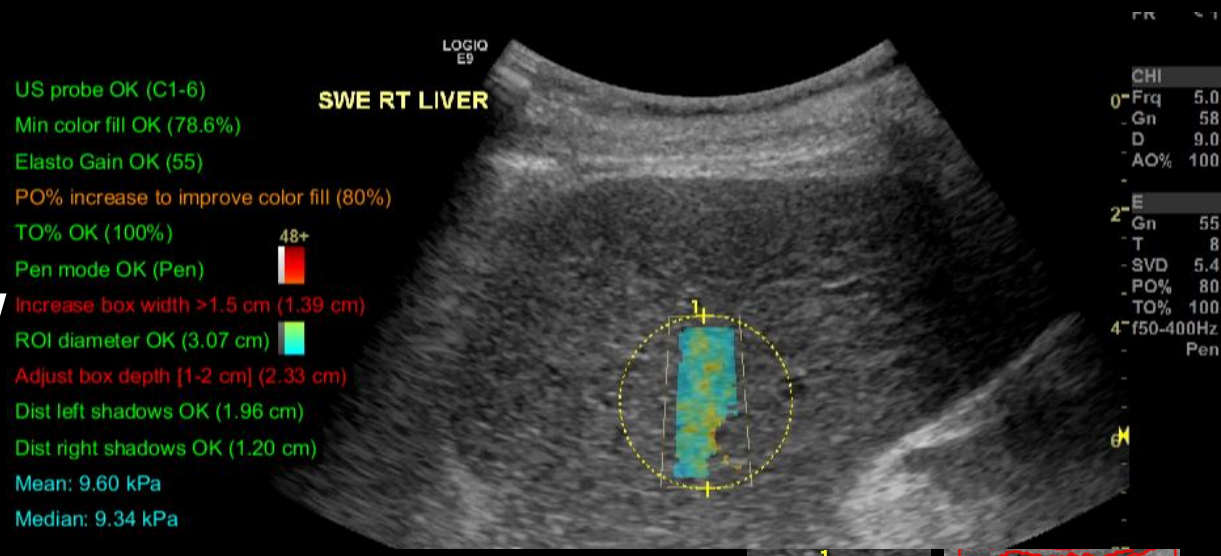


Canon Aplio

1. Dietrich CF et al. Ultraschall Med. 2017;38(4):e16-e47.

CURRENT STATUS

- Re-rolling out liver SWE with new interpretation strategy
- Custom automated QA tool



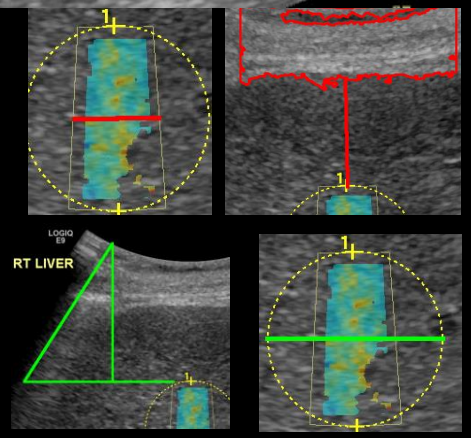
- **Transducer model:** Is different than (C1-6D) → **Fail**.
- **Overall quality of Elastography acquisition:**
  - Color fill < 50% → **Fail**.
- **Elastography acquisition settings:**
  - Elastography "gain", or threshold for cross-correlation, different than 55 → **Fail**.
  - Push beam output < 80% → **Fail**.

    ... or not high enough to ensure color fill > 80% → **Warning**.
  - Track beam output different than 100% → **Fail**.
  - Penetration mode OFF → **Fail**.
- **SWE acquisition box:**
  - Width < 1.5 cm → **Warning**.
  - Depth from liver capsule to box < 1.0cm or > 2.0cm → **Warning**.
  - Distance to lateral shadow artifacts (if any), from the sides of the box < 1.5cm → **Warning**.
- **Elasticity measurement:** Diameter of the elastography measurement ROI <1.0 cm -> **Warning**.

Information extracted from image-based analysis

Information extracted from RAW header

Information extracted from image-based analysis



Gomez-Cardona et al. 2021 AAPM Annual Meeting

BIASES AND OPEN QUESTIONS

- Simple assumptions to derive Young's modulus (isotropic, linear, elastic, incompressible, density); viscoelastic property, frequency bandwidth and differences between vendors; boundary condition, etc.
- True automated quality check and quantification?
- Liver fibrosis heterogeneity - sample more locations?
- Realistic use of cut-off values or probability for various etiology?
- Reproducibility on patients, especially cross sites and potentially vendors/scanners?
- Multi-center, systematic and comprehensive evaluation with shear wave speed, shear wave dispersion, and attenuation, to capture the disease progress?
- ……

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THANK YOU!

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