MASSACHUSETTS
GENERAL HOSPITAL

The RSNA-QIBA SWS Profile: Current Status, Methods in Generating the Profile and a Discussion of Currently Open and Closed Issues

HARVARD
MEDICAL SCHOOL

Manish Dhyani, MD

QIBA – SWS Committee

- Duke University, Durham, NC
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- General Electric, Milwaukee, WI
- Hitach Aloka, Wallingford, CT
- HÔpitaux Universitaires, Paris-Sud, Paris, France
- Institut Langevin, Paris, France
- CIRS, Norfolk, VA
- Massachusetts General Hospital, Boston, MA
- Mayo Clinic, Rochester, MN
- Michigan Technological University, Houghton, MI
- Philips Ultrasound, Bothell, WA
- Rheolution, Inc, Montreal, Canada
- Royal Marsden Hospital, London, United Kingdom
- Samsung Medison, Seoul, South Korea
- Siemens Ultrasound, Issaquah, WA
- Southwoods Imaging Center, Youngstown, OH
- Supersonic Imagine (SSI), Aix-en-Provence, France
- Toshiba Medical Research Institute, USA
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- University of Michigan, Ann Arbor, MI
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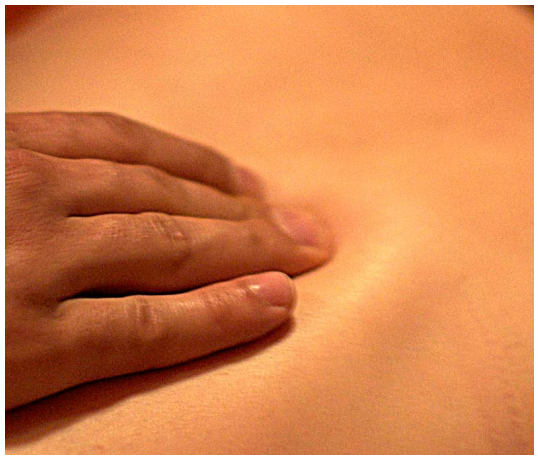
- University of Wisconsin, Madison, WI
- Food and Drug Administration, USA
- Veterans Affairs Medical Center, Washington DC
- Zonare, Mountain View, CA

Background

Underlying principle of the practice of “Palpation”

- Basic principle: To be palpable an object, it must be stiffer than the tissue around it



- Breast examination
- Digital rectal examination for prostate cancer screening
- Thyroid nodule palpation, Lymph node palpation

Palpation

From Wikipedia, the free encyclopedia

Not to be confused with palpitations.
"Palpable" is not to be confused with "palpebral".

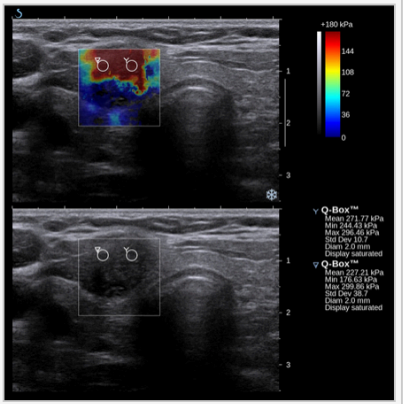
Palpation is the process of using one's hands to examine the body, especially while perceiving/diagnosing a disease or illness.[1] Usually performed by a health care practitioner, it is also the process of feeling an object in or on the body to determine its size, shape, firmness, or location (such as a veterinarian would check/feel the stomach of a pregnant animal to ensure good health and successful delivery).

Elastography [edit]

Main article: Elastography

Nowadays, the medical imaging modality of elastography can also be used to determine the stiffness of tissues. Manual palpation suffers from several important limitations: it is limited to tissues accessible to the physician's hand, it is distorted by any intervening tissue, and it is qualitative but not quantitative. Elastography is able to overcome many these challenges and improve on the benefits of palpation.

Elastography is a relatively new technology, and entered the clinic primarily in the last decade. The most prominent techniques use ultrasound or magnetic resonance imaging (MRI) to make both the stiffness map and an anatomical image for comparison.



Conventional ultrasonography (lower image) and elastography (supersonic shear imaging; upper image) of papillary thyroid carcinoma, a malignant cancer. The cancer (red) is much stiffer than the healthy tissue.

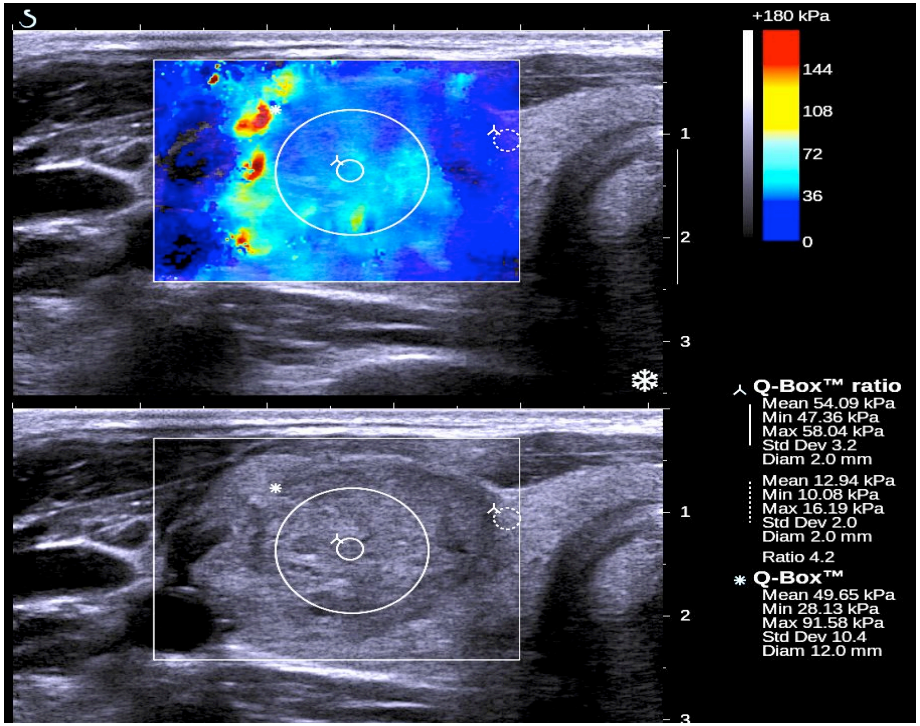
Computerized palpation [edit]

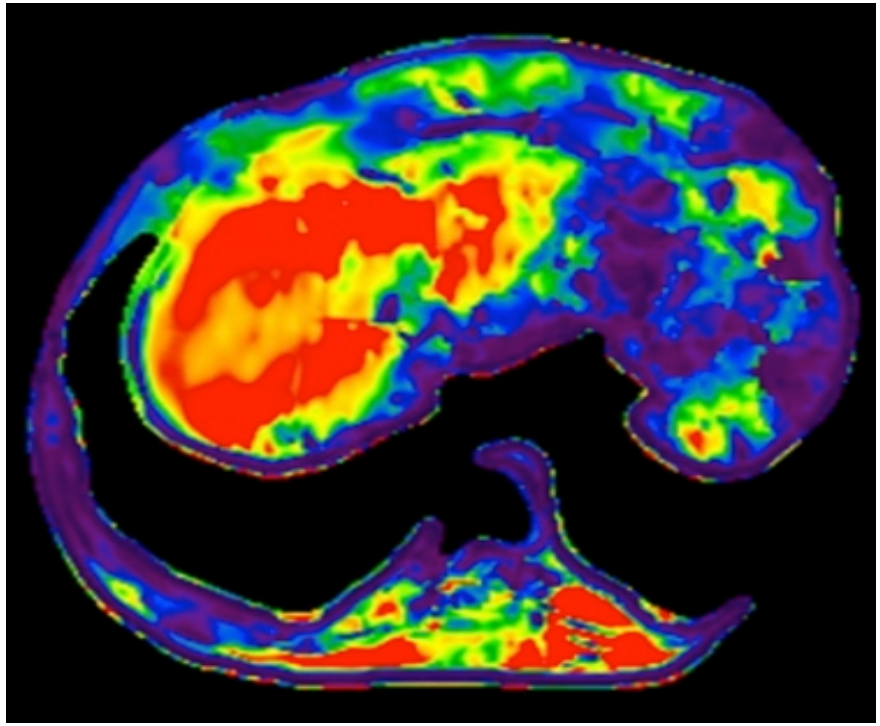
While not widespread amongst elastography methods, computerized palpation is of interest here because it essentially uses palpation to measure the stiffness, whereas other techniques will obtain data using other methods. Computerized palpation is also called "Tactile Imaging", "Mechanical imaging" or "Stress imaging", is a medical imaging modality that translates the sense of touch into a digital image. The tactile image is a function of P(x,y,z), where P is the pressure on soft tissue surface under applied deformation and x,y,z are coordinates where pressure P was measured. Tactile imaging closely mimics manual palpation, since the probe of the device with a pressure sensor array mounted on its face acts similar to human fingers during clinical examination, slightly deforming soft tissue by the probe and detecting resulting changes in the pressure pattern.

Physics

Types of Elastography

1. Sonoelastography
2. MR Elastography (MRE)





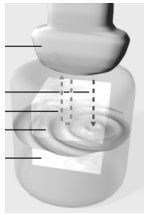
Ultrasound Elastography (USE)

1. Strain elastography

2. Transient Elastography (TE)

3. Shear Wave techniques

   a. Acoustic Radiation Force Imaging (ARFI)



   b. “Real time” shear wave sonoelastography (SWE)

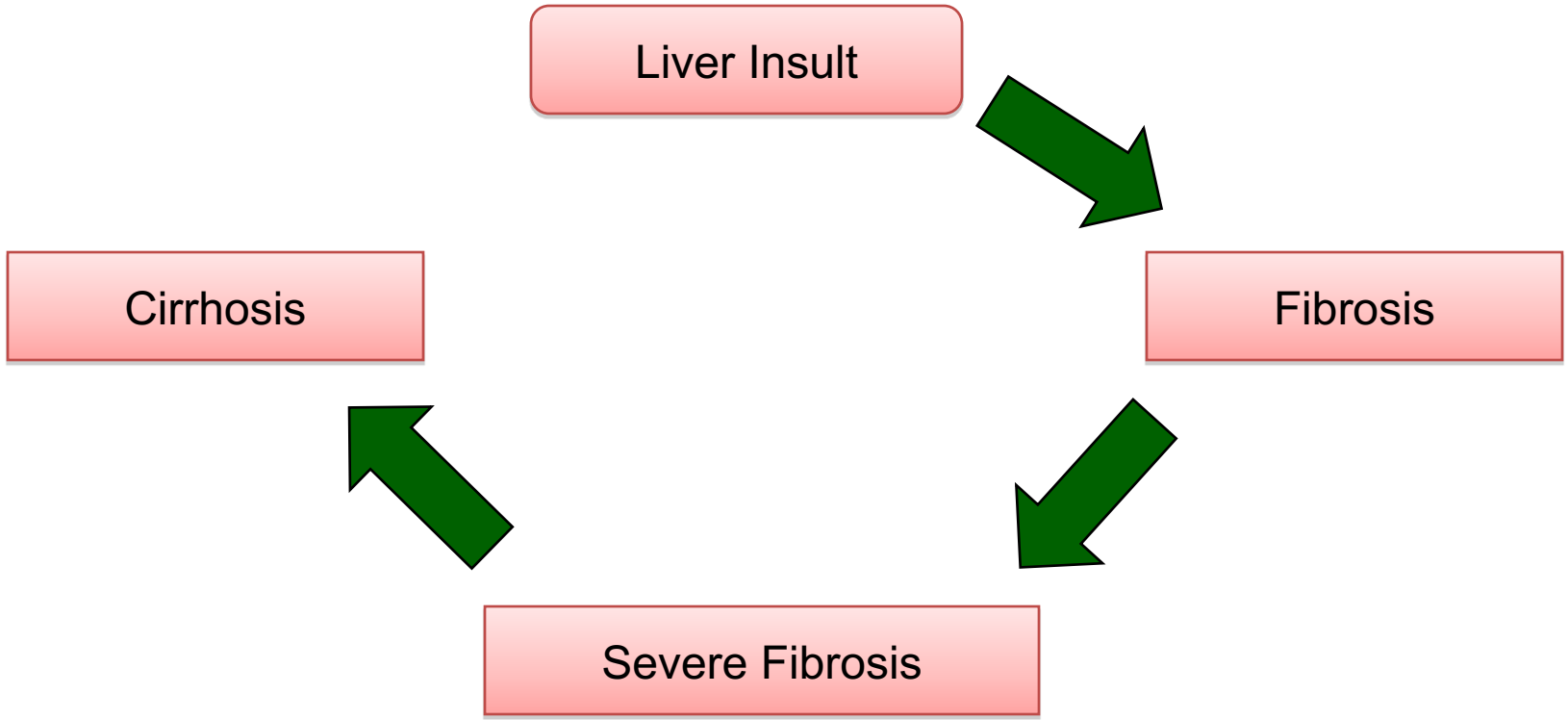
Why the Liver?

Prevalence: Chronic Liver Diseases

- **HCV:**
  - Worldwide prevalence of HCV infection is 170-200 M.
  - Prevalence of HCV in the USA is around 2-3 M.
- **HBV:**
  - Worldwide prevalence of HBV infection is around 2 billion.
  - Prevalence of HBV in the USA is around 730,000.
- **Nonalcoholic Fatty Liver Disease (NAFLD):**
  - The most common form of CLD in developed countries.
  - In the USA: Prevalence is estimated to be anywhere from 20-30% (~60-100 million people)

Background

- Liver Fibrosis is the final common pathway for many different liver insults
- In the context of diffuse liver disease, liver fibrosis staging is essential for prognostication and treatment selection.



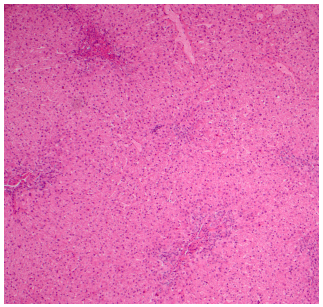
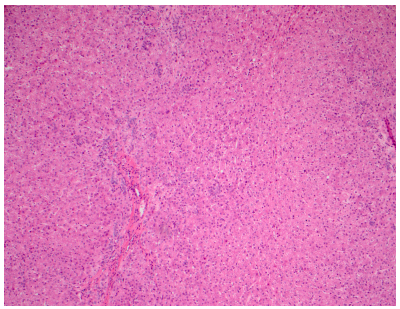
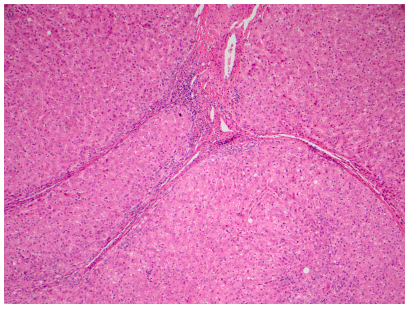
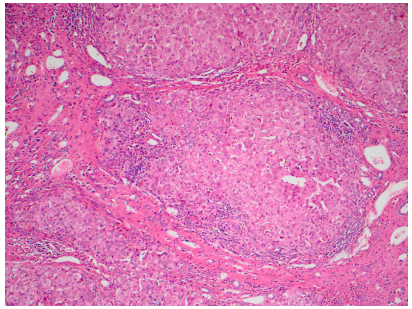
Goal of Management

HCV, HBV, NAFLD (Liver Insult)

Fibrosis | Severe Fibrosis | Cirrhosis

F0 → F1 → F2 → F3 → F4

No Fibrosis

Goal of Management

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Fibrosis

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Cirrhosis

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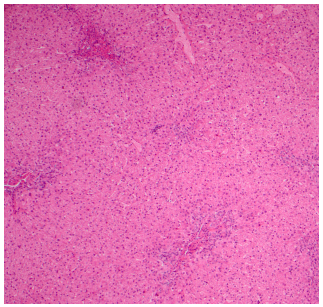
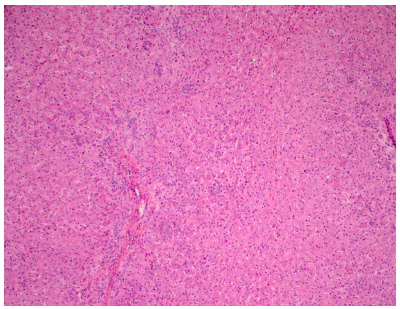
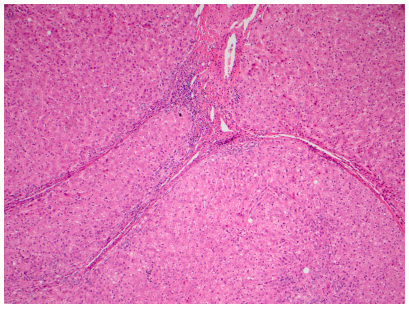
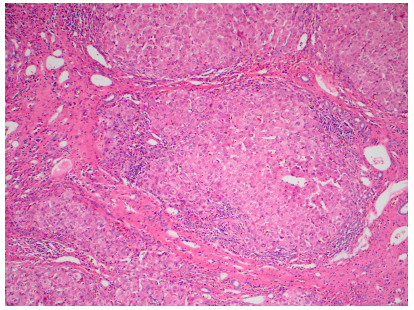


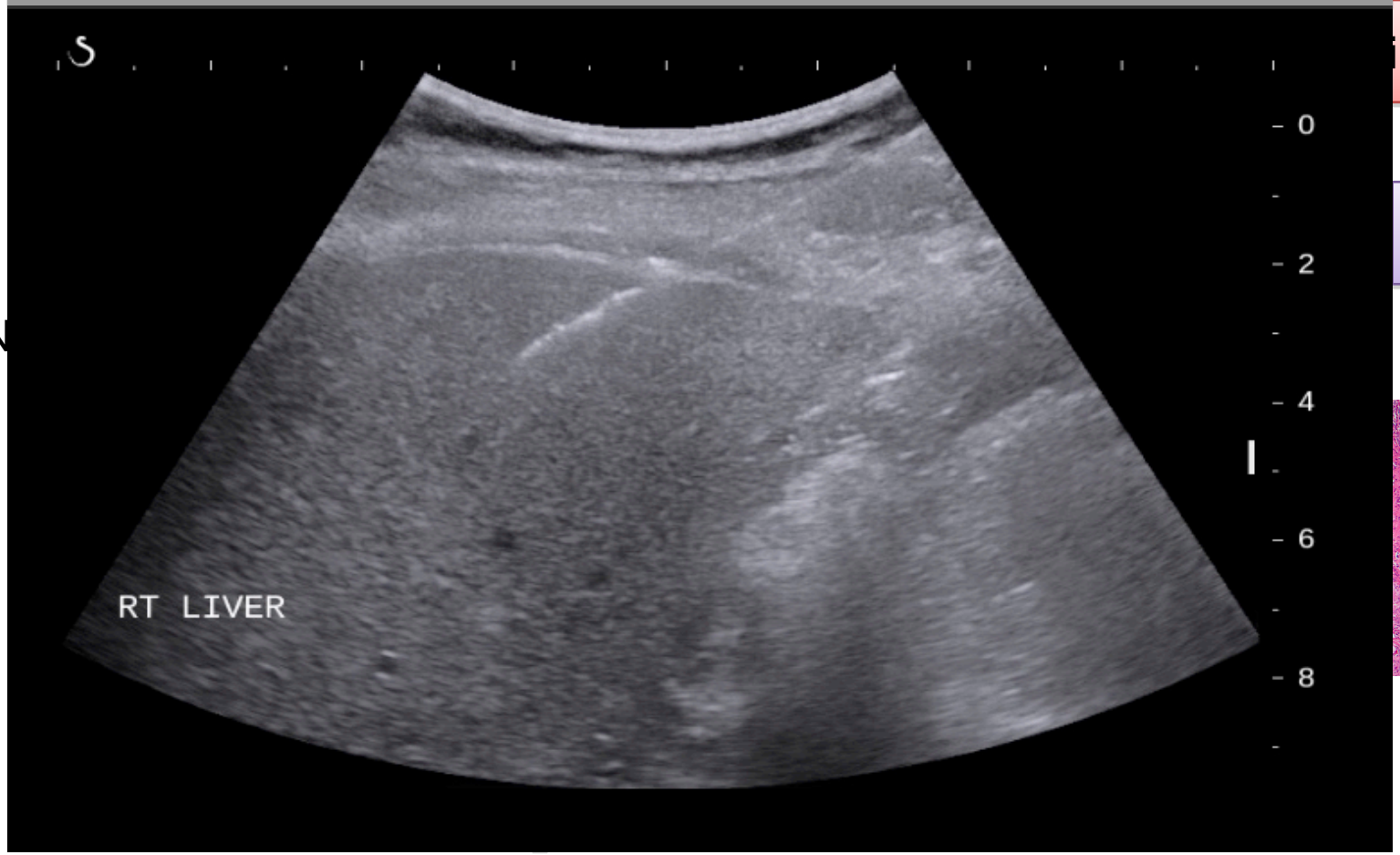






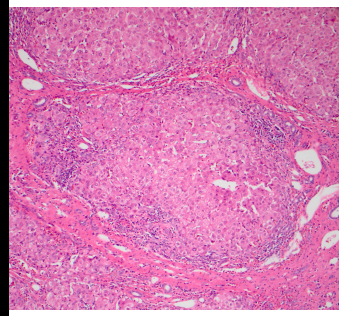
Current Gold Standard for Estimation of Fibrosis Grade

Liver Biopsy



irrhosis

F4



Diagnostic accuracy for F0-1 vs. F2-4

Modality	Study	Test	Study	Patients	AUROC
Serum Bio-marker	Halfon et al.	FibroTest	Meta-Analysis (38 studies)	7985	0.84
USE	Friedrich-Rust et al.	TE	Meta-Analysis (50 studies)	-	0.84
	Friedrich-Rust et al.	ARFI	Meta-Analysis (8 studies)	518	0.87
	Samir et al. (MGH)	SWE	Prospective study	136	0.83
	Ferraioli et al.	SWE	Prospective study	121	0.92
MRE	Wang et al.	MRE	Meta-Analysis	-	0.94

- *Halfon P, Munteanu M, Poynard T: FibroTest-ActiTest as a non- invasive marker of liver fibrosis. Gastroenterol Clin Biol 32:22-39, 2008*
- *Friedrich-Rust M, Ong MF, Martens S, et al: Performance of transient elastography for the staging of liver fibrosis: A meta- analysis. Gastroenterology 134:960-974, 2008*
- *Friedrich-Rust M, Nierhoff J, Lupsor M, et al: Performance of acoustic radiation force impulse imaging for the staging of liver fibrosis: A pooled meta-analysis. J Viral Hepat 19:e212-e219, 2012*
- *Wang QB, Zhu H, Liu HL, et al: Performance of magnetic resonance elastography and diffusion-weighted imaging for the staging of hepatic fibrosis: A meta-analysis. Hepatology 56:239-247, 2012*
- *Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C, et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology. 2012 Dec;56(6):2125–33.*

Hepatitis C

- Antiviral therapy – very expensive

Currently important to select the correct patients for antiviral therapy (the 20% that progress to cirrhosis).

THE WALL STREET JOURNAL. | PHARMALOT

WSJ Pharm

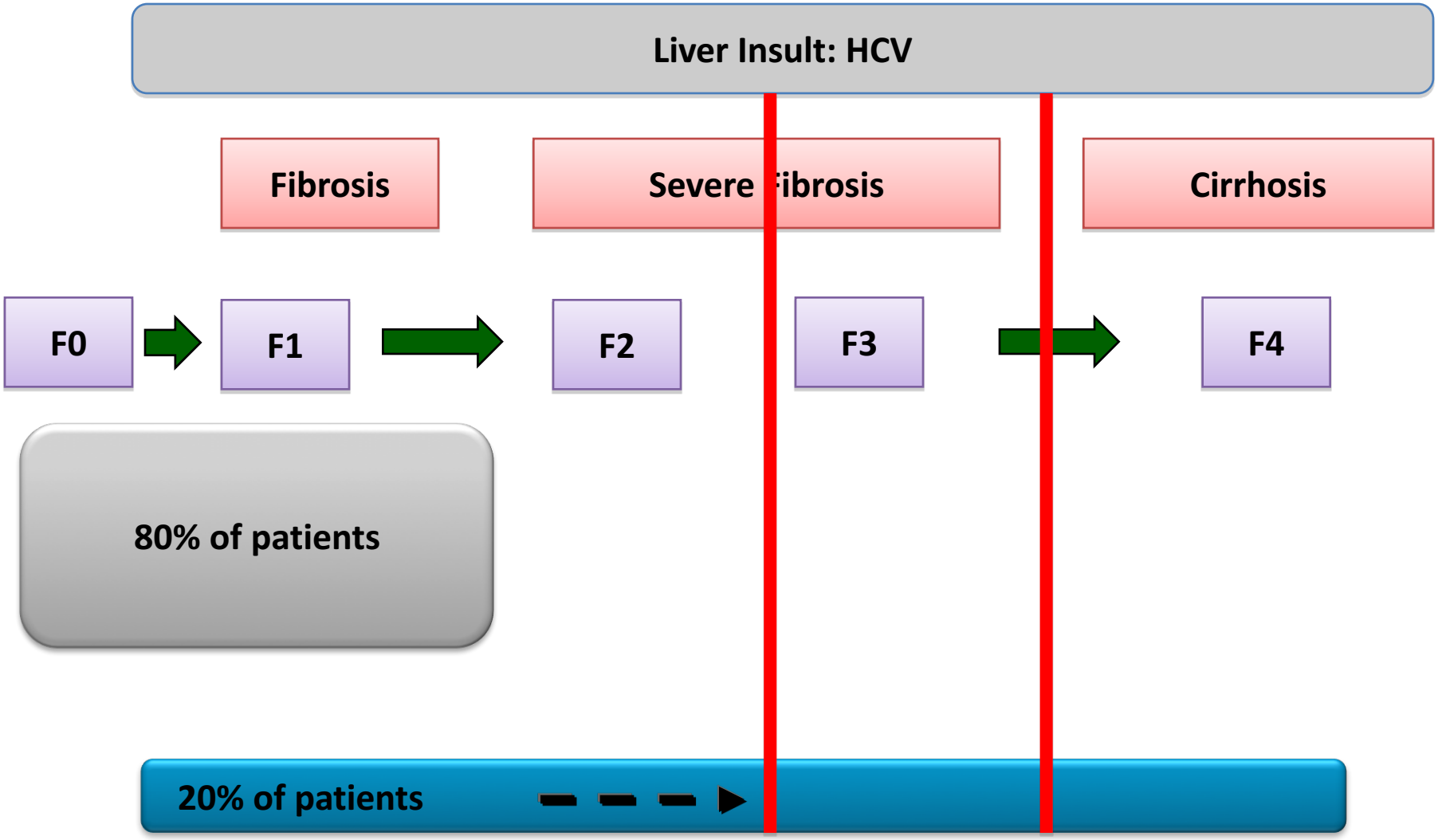
RESEARCH & DEVELOPMENT | FDA | LITIGATION | PRICING & PATIE

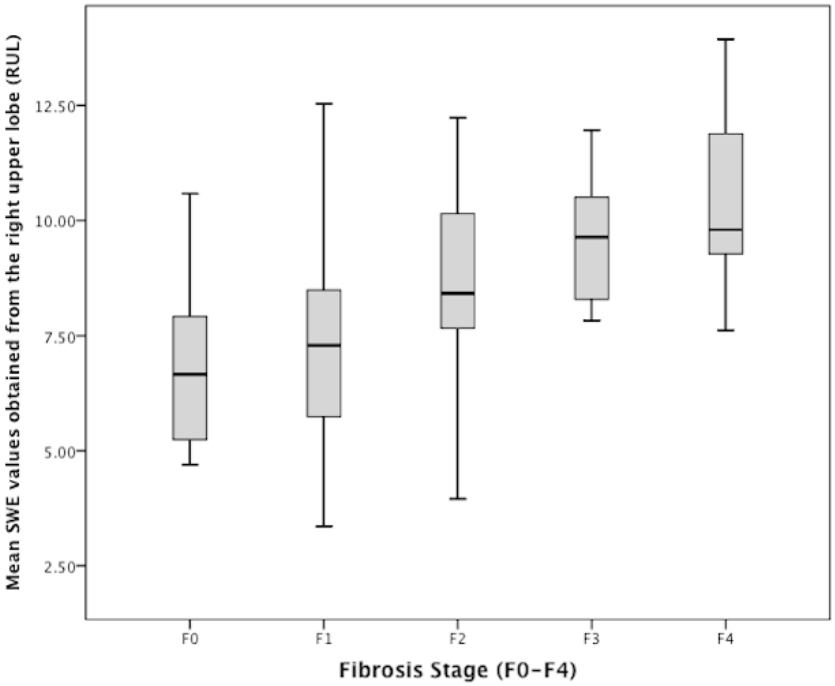
9:27 am ET
Mar 17, 2015 HEPATITIS C

Hepatitis C Drugs are Cost Effective, but Affordability is Another Matter

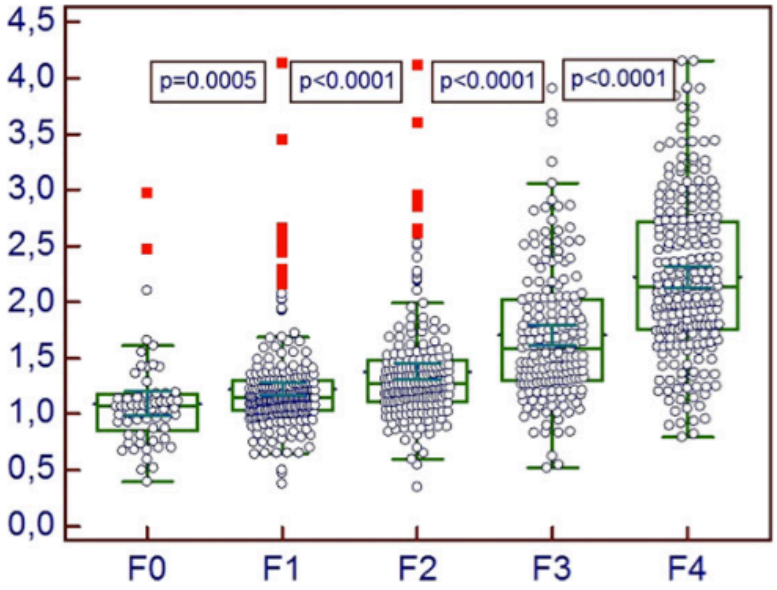
US Centers for Disease Control and Prevention, 2011 , http://wwwnc.cdc.gov/travel/pdf/yellowbook-2012-map-03-05-prevalence-chronic-hepatitis-c.pdf

Hepatitis C


Liver Insult: HCV
Fibrosis
Severe Fibrosis
Cirrhosis
F0
F1
F2
F3
F4
80% of patients
20% of patients

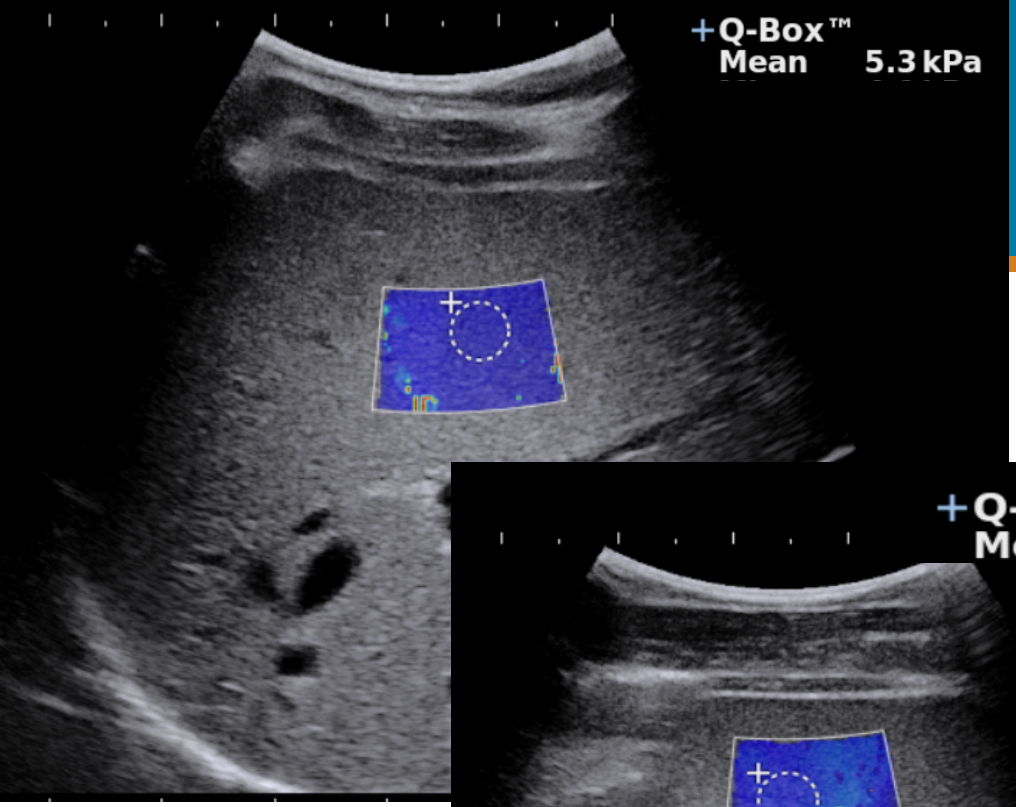


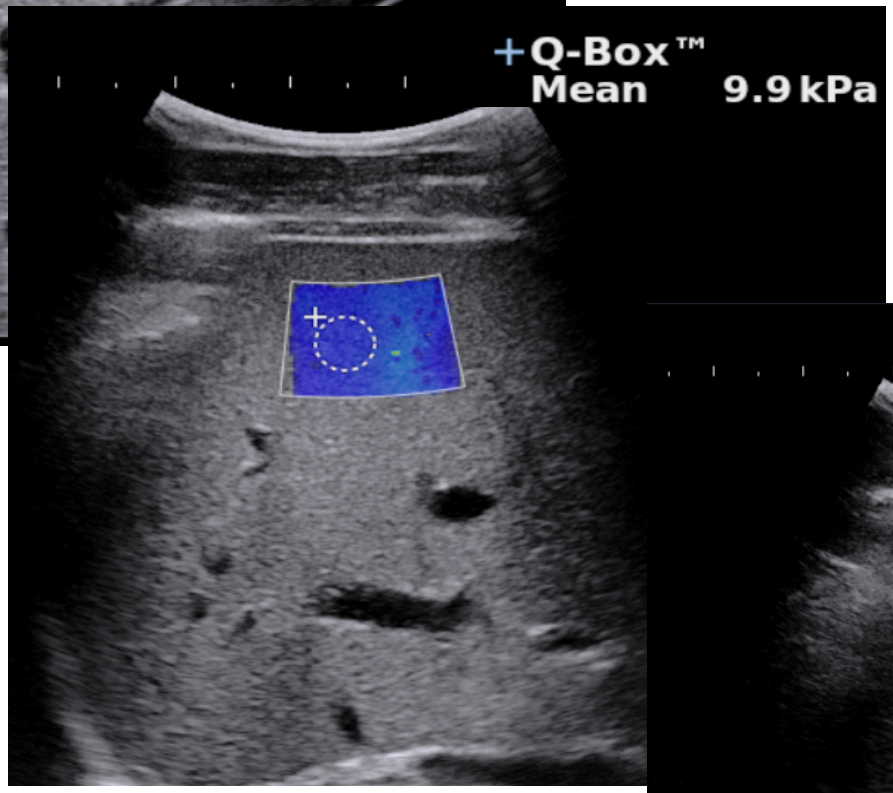
Samir AE, Dhyani M, Vij A, Bhan AK, Halpern EF, Mendez-navarro J, et al. Shear-wave Elastography for the Estimation of Liver Fibrosis in Chronic Liver Disease: Determining Accuracy and Ideal Site for Measurement. Radiology Nov 2014.

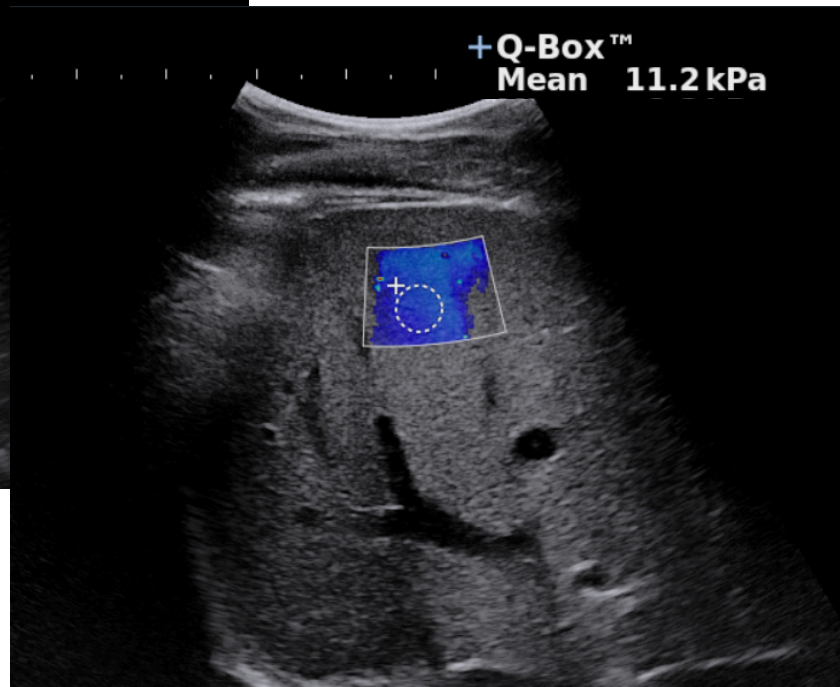


Sporea, I. et al., 2012. European journal of radiology, 81(12), pp.4112–4118.

24 year old Male, HCV







What is a QIBA Profile?

- A QIBA Profile
  - Makes claims about what is achievable.
  - What quantitative results can be achieved by following the Profile.
- Profile details serve two purposes:
  - Advise vendors what must be implemented in their product.
  - Communicate the necessary procedures to users.

SWS Biomarker Committee Profile

"Ultrasound Measurement of Shear Wave Speed for Estimation of Liver Fibrosis"

Profile Content

QIBA Profile:

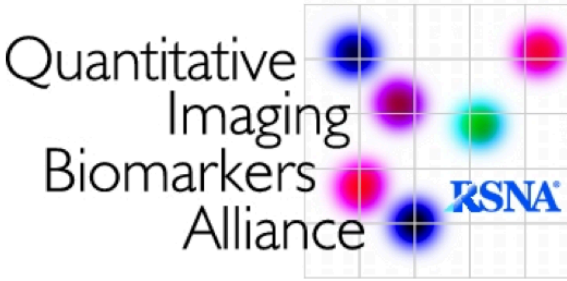
[Title of the Profile] ([Acronym])

Version x.x

[day month year]

Status: [current profile development stage]

QIBA Profile Template-09-10-2016



QIBA Profile:
Ultrasound Measurement of Shear Wave Speed for Estimation of Liver Fibrosis

Stage: A. Revised Draft prior to release for public comment

Profile Content

QIBA Profile Format 10APRIL2015

Open Issues:

The following open issues have been raised. They are provided here to capture the associated discussion, to focus the attention of reviewers on topics needing feedback, and to track them so they are ultimately resolved. In particular, comments on these issues are highly encouraged during the Public Comment stage

[List any issues known to still be open regarding the profile. though some issues may still be under consideration.]

Q. [issue (best stated as a concise question)]
A. [tentative resolution (or blank)]
[Discussion and details]
Q. [as many rows as needed]
A.

Closed Issues:

The following issues have been considered closed by the bi forestall discussion of issues that have already been raised rationale behind the resolution.

Q. [issue]
A. [decision (concise answer to the question, e.g. Yes o
[followed by any needed description of the rationale]

1. Executive Summary

[Summarize the applicability and utility of the Profile with respect to individual patient management and/or how it relates to clinical trial usage.]

The intended audiences include:

- Technical staffs of software developers and device manufacturers who create products for this purpose
- PIs of clinical trials and Clinical trial scientists
- Clinicians at healthcare institutions considering appropriate specifications for procuring new equipment
- Scientists involved in quantitative medical image analysis
- Anyone interested in the technical and clinical aspects of medical imaging

Note that specifications stated as "requirements" here are only requirements to achieve the claim, not "requirements on standard of care." Specifically, meeting the goals of the Profile is secondary to properly caring for the patient.

2. Clinical Context and Claims

Utilities and Endpoints for Clinical Trials

[Describe one or more clinical practice utilities or clinical trial endpoints this Imaging Profile could serve (e.g. to determine eligibility of potential subjects in a clinical trial; to triage eligible subjects into cohorts based on stage or severity of disease; to assess response to treatment; to establish the presence of progression of disease; to monitor for adverse events; to establish a database for the development, optimization, and validation of imaging biomarkers, etc.)]

Conformance with the activities of this Profile by relevant staff and equipment supports the following claim(s):

Profile Content

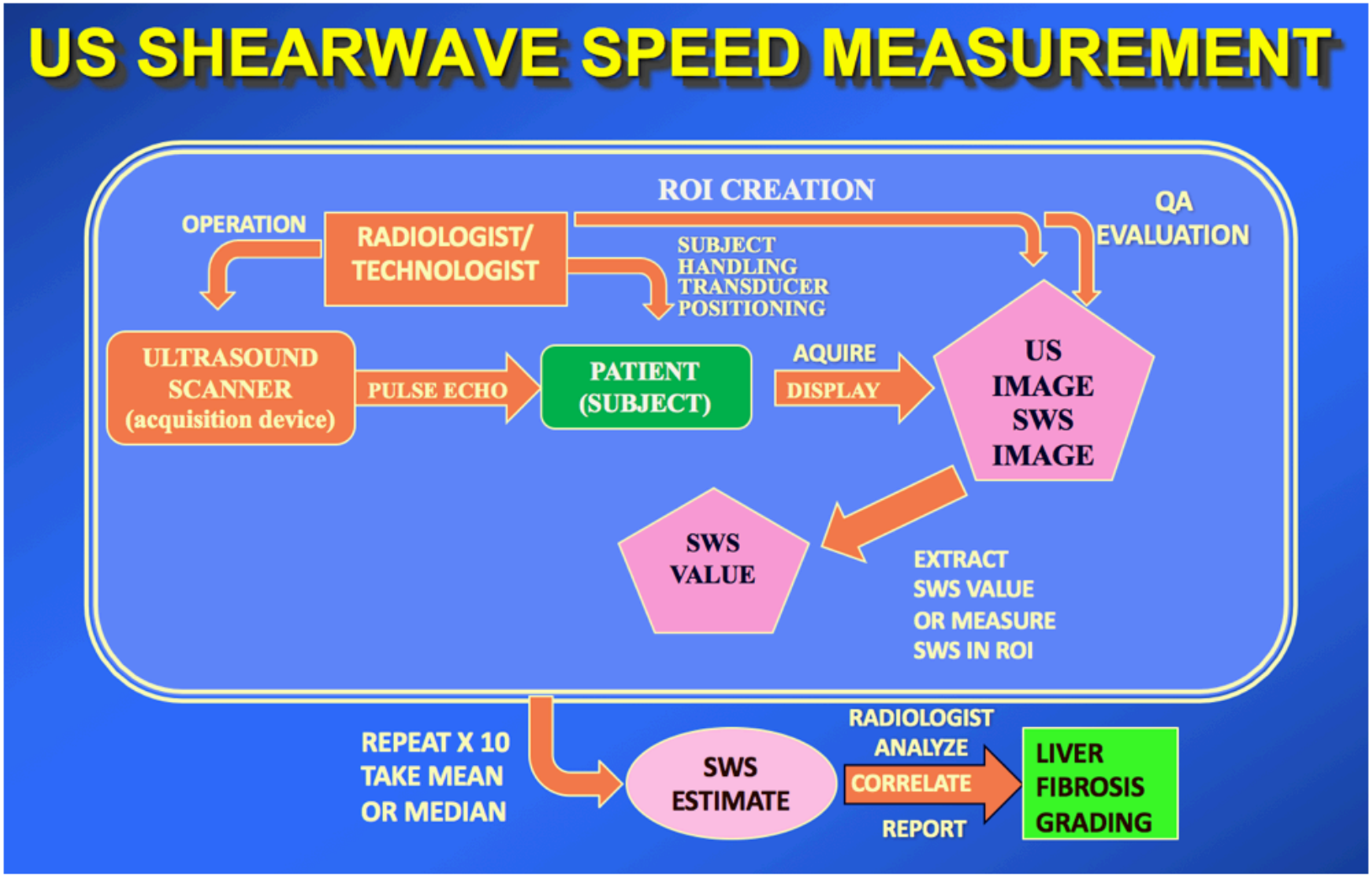


Figure 1: Ultrasound Measurement of Shear Wave Speed for Estimation of Liver Fibrosis - Activity Sequence

Profile Content

3. Profile Activities

The Profile is documented in terms of "Actors" performing "Activities".

Equipment, software, staff or sites may claim conformance to this Profile as one or more of the "A
the following table. Compliant Actors shall support the listed Activities by meeting all requireme
referenced Section. Failing to conform with a "shall" is a protocol deviation. Although deviations
the Profile Claim, such deviations may be reasonable and unavoidable as discussed below.

[Modify your list of Actors and Activities in the following table as appropriate.]

Table 1: Actors and Required Activities

Actor	Activity	Section
Acquisition Device	Subject Handling	3.1.
	Image Data Acquisition	3.2.
Technologist	Subject Handling	3.1.
	Image Data Acquisition	3.2.
	Image Data Reconstruction	3.3.
Radiologist	Subject Handling	3.1.
	Image Analysis	3.4.
Reconstruction Software	Image Data Reconstruction	3.3.
Image Analysis Tool	Image Analysis	3.4.

Pre-Delivery

Parameter	Actor	Requirement
Acoustic Output (SWS Mode)	MFR output testing	Within FDA recommended maximum acoustic output levels for diagnostic ultrasound devices. MFR specification and certification.
Phantom Testing	MFR QA	QIBA pre-specified homogeneous phantom* testing. 95%CI or CV [XX to YY%]. Bias: +-5% of nominal Xx. [place Phantom value using MRE at 140 Hz here]
Software verification	MFR	Software version equals version specified in QIBA profile (Manufacturer specific section – Appendix D).
Hardware and transducer Manufacturer specified parameters	MFR	Shall ensure the equipment intended for use is listed in Appendix D as a compliant combination of System, Software Revision and Transducer.

136 **3.1. Subject Handling**

137 [The subsections shown here may or may not be relevant to your profile. Feel free to populate them with
138 reference text such as "When the Profile is being used in the context of a clinical trial, refer to relevant
139 clinical trial protocol for further guidance or requirements on timing relative to index intervention activity.",
140 with null text such as "This document does not presume any timing relative to other activities." or remove
141 the subsection entirely.]

142 **3.1.1**

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195 # 4. Conformance Procedures

196 To conform with this Profile, participating staff and equipment ("Actors") shall support each
197 assigned to them in Table 1.
198
199 For each activity, the conformance requirements (sometimes referred to as the "shall langua
200 Actor are documented in Section 3.

201
202 Although most of the requirements described in Section 3 can be assessed for conformance
203 observation, some of the performance-oriented requirements cannot, in which case they wil
204 subsection here in Section 4. The following sub-sections elaborate on the meaning of perfor
205 oriented requirements and how they are intended to be correctly assessed.
206
207 Formal claims of conformance by the organization responsible for an Actor shall be in the for

136 **3.1. Subject Handling**

137 [The subsections shown here may or may not be relevant to your profile. Feel free to populate them with
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195 **4. Conformance Procedures**

196 To conform with this Profile, participating staff and equipment ("Actors") shall support each of the activities
197 assigned to them in Table 1.
198
199
200

213 **4.x. Performance Assessment: <Parameter X>**

214 [describe how the actor is required to go about assessing it's performance (w
215 which was specified in Section 3). For example, if Section 3 specified that the
216 achieve a tumor volume change repeatability metric/score of less than Q, the
217 about accessing an appropriate dataset, generating results and computing the
218 you deem necessary.]
219
220 [Refer to the work of the QIBA Metrology group (or recruit the group membe
221 these sections.]
222
223 [try to keep the text strictly to the performance of the procedure. Additional
224 material can be put in an Appendix and referenced if necessary.]
225
226 [it is possible that the same performance assessment procedure might be use
227 and the operator, or they might be separate procedures.]

228 **4.y. Performance Assessment: <Parameter Y>**

Open and Closed Issues

Closed Issues

- **Clinical**
  - What point in the respiratory cycle should acquisition occur?
    - Suspended tidal respiration.
  - Should the patients fast prior to acquisition?
    - At least 4 hours prior to acquisition.
  - Does steatosis effect assessment of liver fibrosis using elastography?
    - No

Closed Issues - Phantoms

- **Phantoms**
  - **What sort of phantom should be used for periodic QA and compliance (Section 3.3 of Profile)**
- Viscoelastic versus elastic phantom ?
  - Viscoelastic phantom to distinguish differences between different systems.
  - For a single machine, elastic phantoms will be affordable and practical.
- Complex versus simple?
  - Simple since the liver is relatively simple, unlike the breast.

Closed Issues - Phantoms

Phantom Specifications :

- Attenuation: 0.5 dB/cm/MHz
- Back Scatter: Approximately 10^{-4} – 10^{-3} $cm^{-1}Str^{-1}$ at 3 MHz or sufficient to create mean speckle brightness comparable to a human liver-mimicking phantom (± 3 dB)
- Speed of Sound: 1520-1540 m/sec
- Stiffness: 2 part phantom, Normal Liver Equivalent & Fibrotic F3 Liver equivalent
- Volume and Shape – Cylindrical, 20 cm tall, 12.5 cm in diameter - open issue

Closed Issues - Phantoms

Phantom Specifications :

- Temporal Stability
  - SWS: <5% change in both hard and soft components over 6 months .
  - Speed of Sound: <1% change over 6 months. [KW comments accepted]
- Testing of phantom as specified by the shorter of ACR/AIUM guidelines and system supplier's recommendations. [open issue – Which document? And link to document to be provided—if no AIUM or ACR guidelines for phantom testing does IEC have one?]

Closed Issues - Phantoms

Phantom Specifications :

- **QIBA testing to verify specifications and characterization of phantoms (paid for by phantom vendor ? QIBA? US manufacturers? Other societies? Combination of all?)**
  - For the time being – the specifications and characterization of the phantoms will be performed and verified by the QIBA committee. This will be relative to MRE and Mayo group will be performing characterization for the initial phantoms.
-

Closed Issues - Phantoms

Pass Fail Tolerances for Phantom Tests

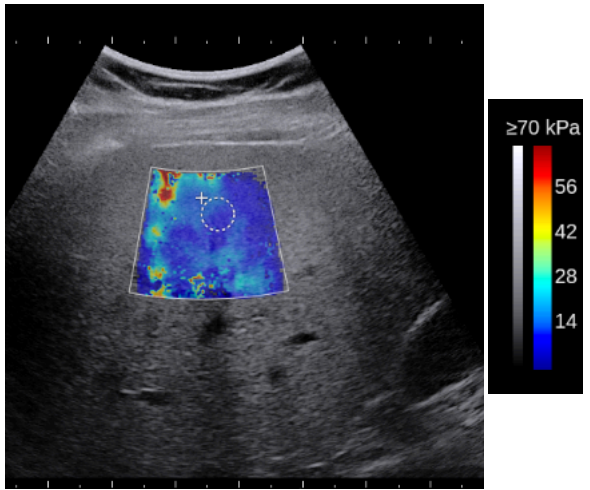
- **Testing to be performed at 21±1 ° C.**
- Attenuation: **± 5%:** 0.5 dB/cm/MHz
- Back Scatter: **± 5%**
  - Approximately 10^{-4} – 10^{-3} $cm^{-1}Str^{-1}$ at 3 MHz or sufficient to create mean speckle brightness comparable to a human liver-mimicking phantom (± 3 dB)
- Speed of Sound: **± 1%:** [1520-1540 m/sec]
- Stiffness: **± 5%**
  - 2-part phantom, Normal Liver Equivalent & Fibrotic F3 Liver equivalent

Closed Issue

- **Give stiffness in m/sec or kPa?**
- M/sec [Consensus from all]

Color Maps

- **Color Maps – Should these be QIBA specified ?**
  - Color scale and number of colors in the map .
  - **Red** = stiff & **Blue** = Soft
  - Black is stiff and White is soft.
  - Number of colors – Continuous scale (24-36 bit).
- Consensus has been achieved and this is now a closed issue.



Open Issues

Open Issue - Inflammation

- **What is the effect of inflammation on SWS and what is its magnitude?**
  - Inflammation stiffens the liver but the magnitude is not known precisely.
  - Retained as an open issue.

Open issues - Measurements

- **A. Number of measurements?**
  - The total number of measurements that are needed to make an SWS estimate per patient **(the claim refers to this value).**
  - ≥10 measurements: MFR – may specify a greater number than the minimum value of 10.
- **B.** Criteria for inclusion or exclusion for a given measurement?
- **C.** Repeatability versus reliability? [Decreasing variance may result in increased bias]

Comments – Number of measurements

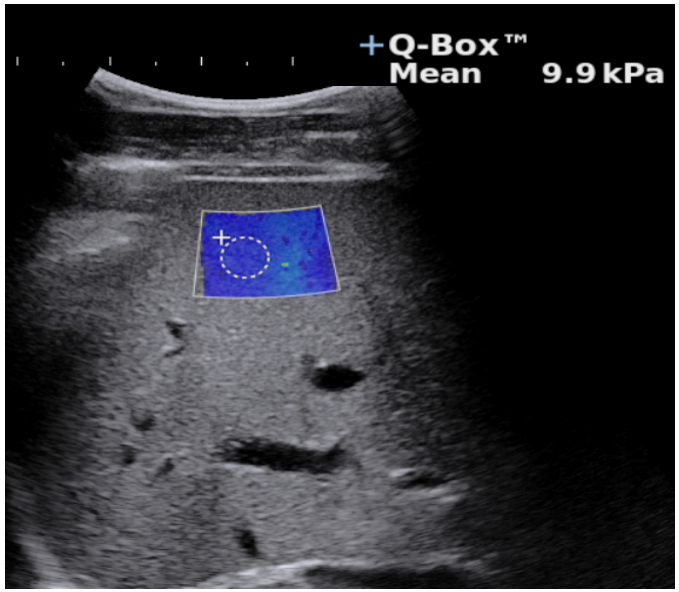
- We cannot agree to recommend a minimum number of measurements regardless of the technique used and the size of quantified ROI.
- The use of 10 measurements allows the use of IQR/M as a quality measure. Using smaller number of measurements may be acceptable, however this has not been proven and how to assess a quality measure with fewer measurements has not been determined. QIBA has a statistician why don't we ask her what is appropriate and how to prove it.
- Retained as an open issue pending statistical consideration and technical study confirmation.\
- The traditional 10 was set by Echosens (not sure in what basis) but many believe this is too much for image-based SWS estimates. I think Anthony is looking into this point.
- Echosens' IQR/mean is widely accepted
- This cannot be standardized between manufacturers who are providing a SWS map versus a single measurement. We have our own proprietary tool Stability Index) to identify measurements that should be excluded.

Open issue

- How does each MFR identify and display outliers in their images. Should QIBA specify a standard handling? [Section 3.7]
- [open issue – Feedback from manufacturers]

Open issues

- ROI Size - If user selected – how big? (size of homogenous region versus variance)
  - Each manufacturer should specify an optimal ROI size and make that a default for their system.
  - A minimum size of 10mm X 10mm or diameter of 10mm should be used?



Open issue

- **Number of values averaged for each pixel in the color image .**
  - Should vendors specify the number of values they average per pixel versus specifying average variance per pixel. [open issue]

Open issue

- Phantoms
  - Method to verify temperature of phantoms prior to testing.
    - Temperature measurement method: TBD [open issue]
  - Construction: A 2-part phantom.
    - Volume and Shape – open issue [open issue]

QIBA RSNA Profile

https://www.rsna.org/QIBA-Profiles-and-Protocols/

- Feedback once the document is released for public comment.

Thank you..!!

Dhyani.manish@mgh.harvard.edu