SuperSonic Imagine's Innovative Solutions for Clinical Liver Disease

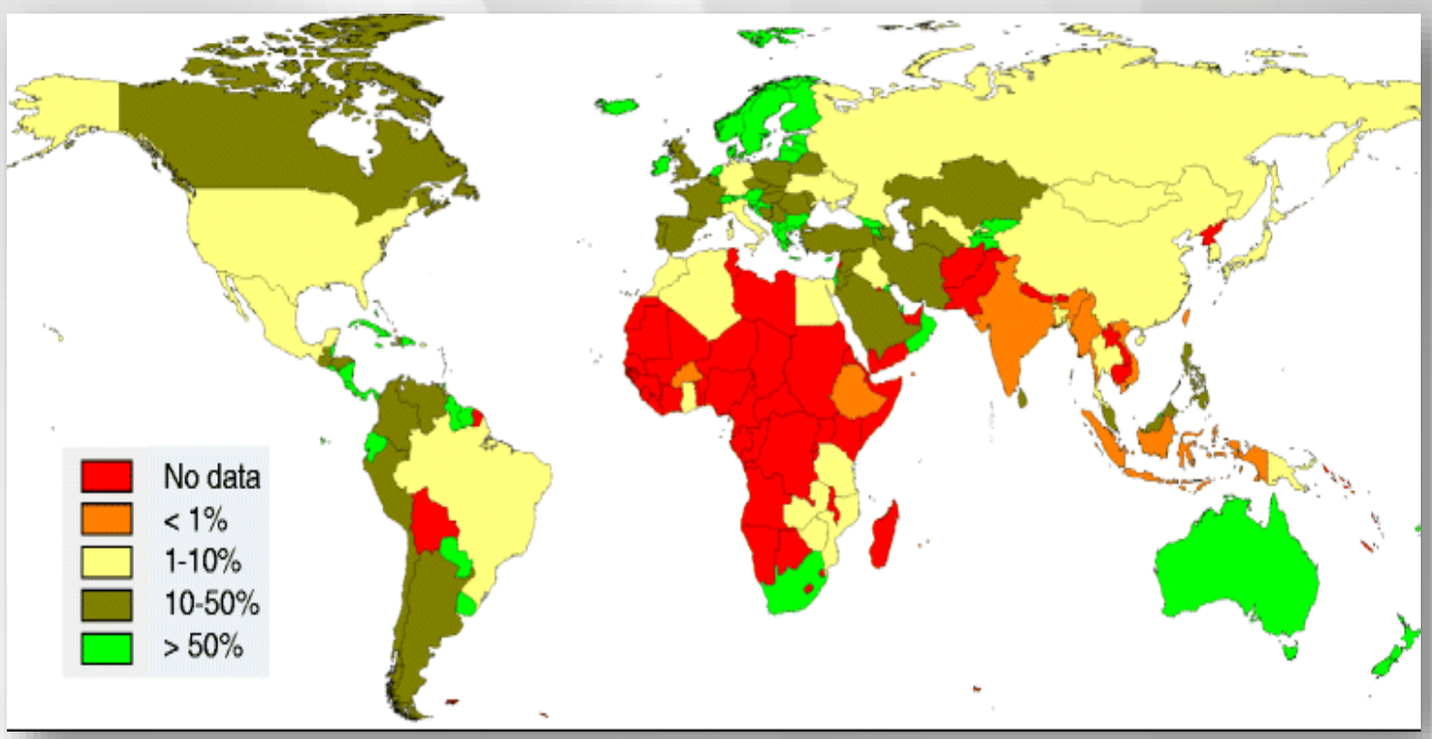
Global Product Marketing & Education
October 2016

Liver Disease is a Growing Global Problem

The Facts:

- Liver fibrosis is a GLOBAL problem impacting 300-700 million people (5-10% of the world's population).
- The most common causes are:

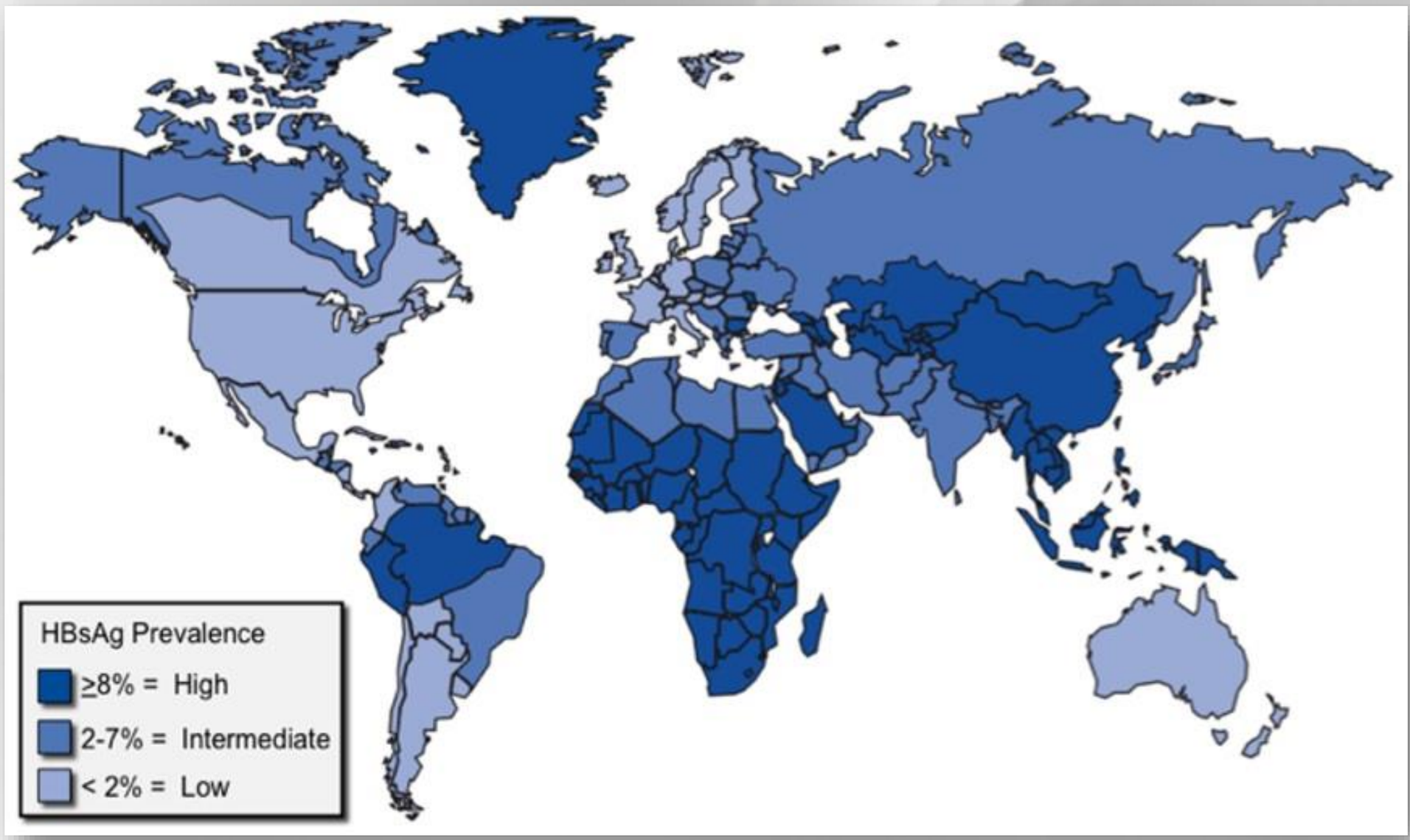
  Hepatitis B virus (HBV), **Hepatitis C** (HBV), **Alcohol** and **Non-alcoholic Fatty Liver Disease** (NAFLD) including **Non-alcoholic Steatohepatitis** (NASH).



Reference: The global impact of hepatic fibrosis and end-stage liver disease.
Lim YS1, Kim WR. Clin Liver Dis. 2008 Nov;12(4):733-46, vii. doi: 10.1016/j.cld.2008.07.007.

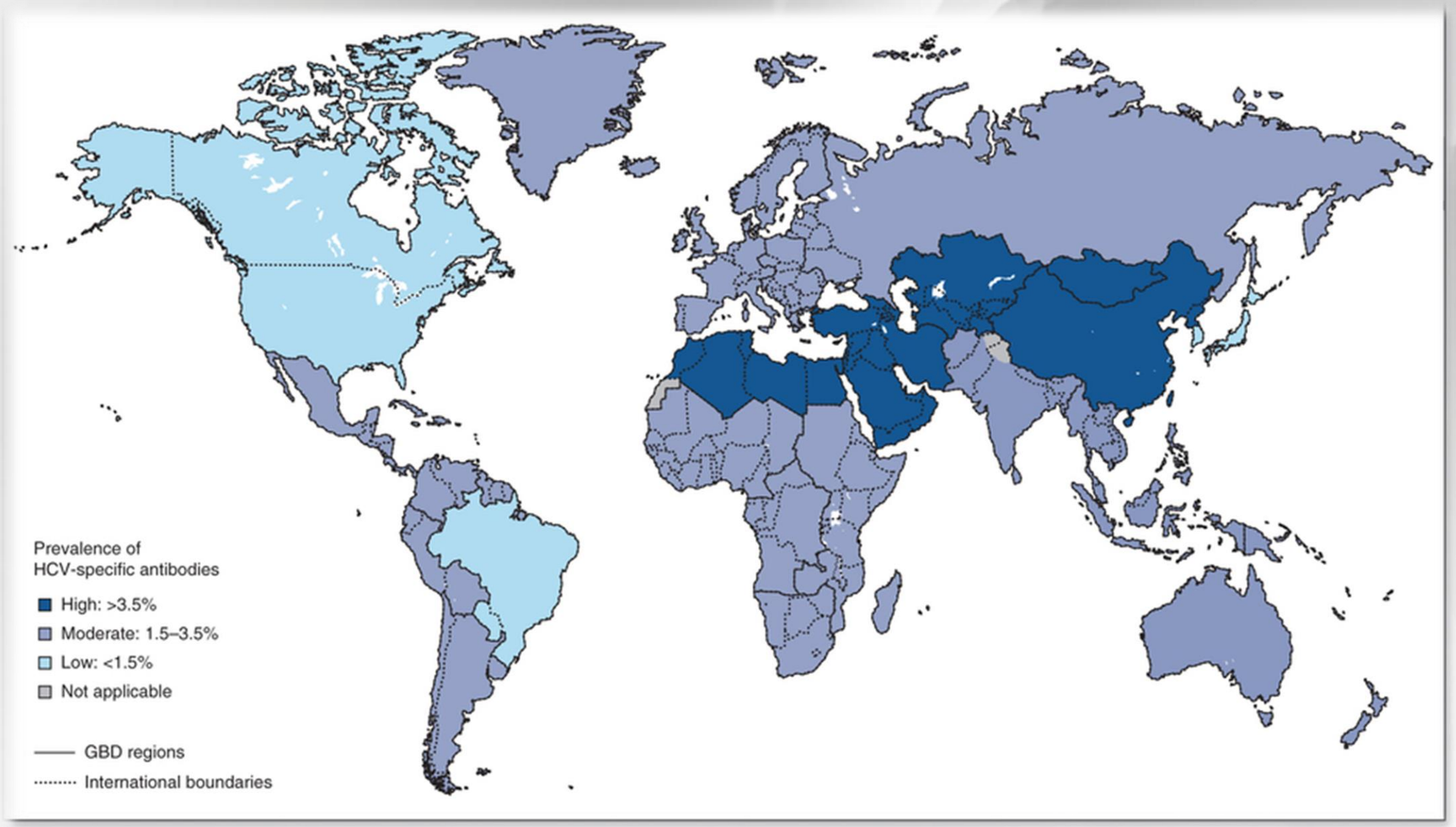
Image: The global burden of liver disease: a challenge for methods and for public health
Peter Byass, BMC Medicine 2014 12:159.

Global Prevalence of HBV



240 million people worldwide

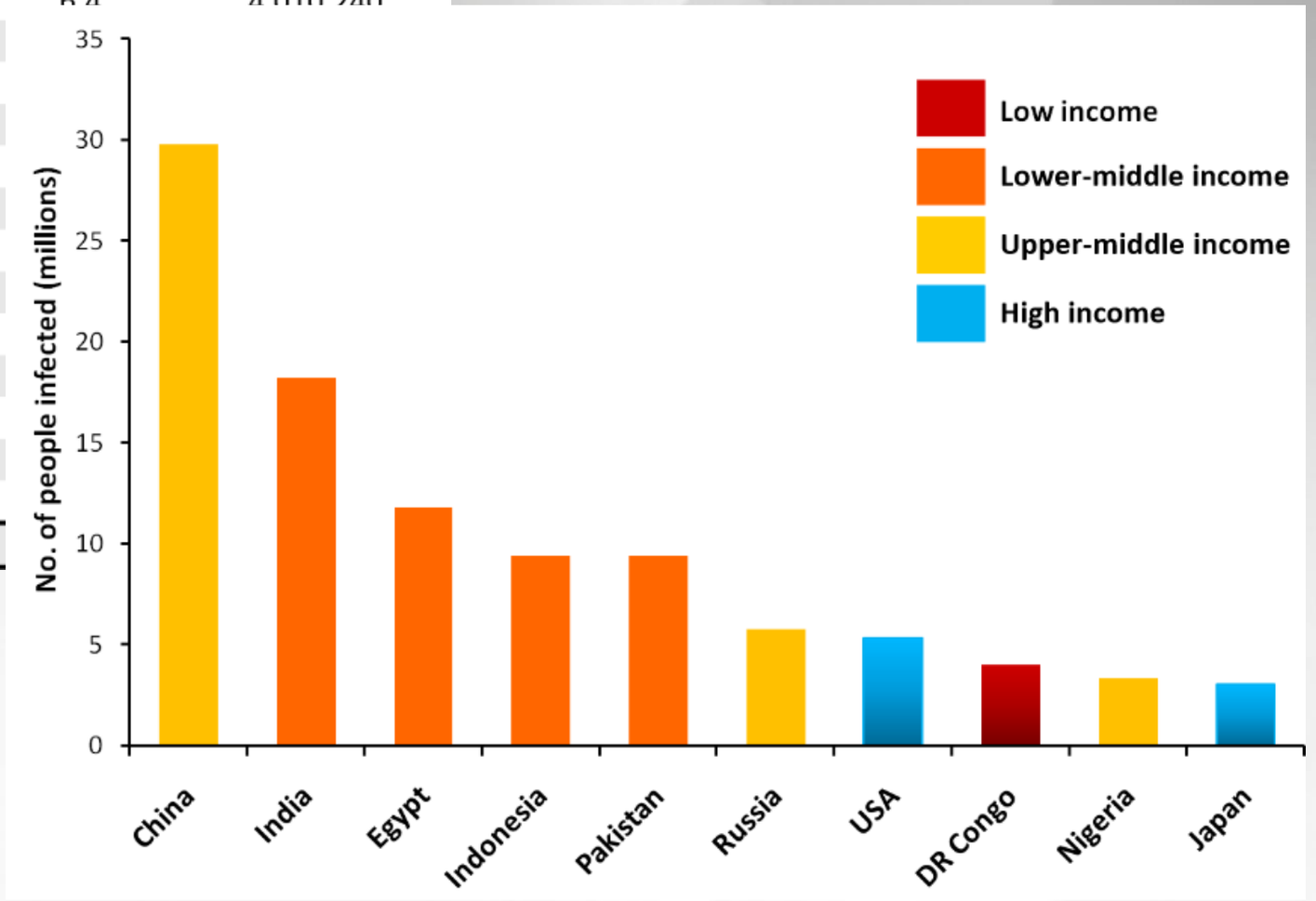
Global Prevalence of HCV



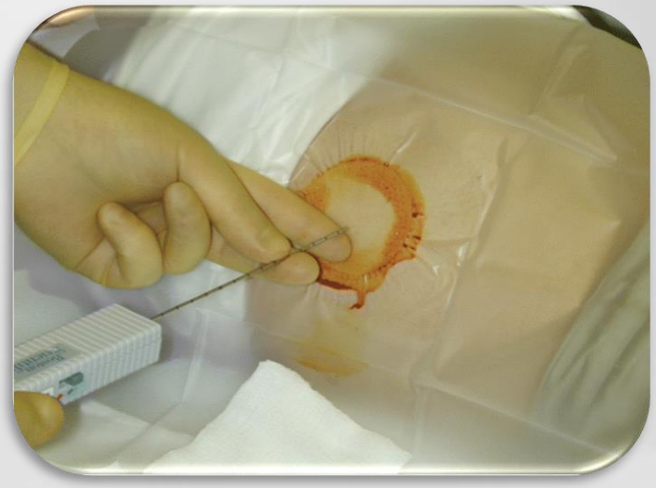
180 million people worldwide

Prevalence of HCV per Country

Country	Income classification	Most prevalent genotypes	Anti-HCV (%)	No. infected
China	Upper-middle	1,2,6	2.2	29,791,212
India	Lower-middle	1,3	1.5	18,216,960
Egypt	Lower-middle	4	14	11,826,360
Indonesia	Lower-middle	1,2	3.9	9,436,986
Pakistan	Lower-middle	3	5.9	9,422,403
Russia	Upper-middle	1,3	4.1	5,796,498
USA	High	1,2,3	1.8	5,367,834
Democratic Republic of Congo	Low	4	6.4	4,010,240
Nigeria	Lower-middle	1,2		
Japan	High	1,2		
Cameroon	Lower-middle	1,2,4		
Brazil	Upper-middle	1,3		
Uganda	Low	1,4		
Philippines	Lower-middle	1		
Italy	High	1,2		
Ukraine	Lower-middle	1		
Uzbekistan	Lower-middle	1,3		
Turkey	Upper-middle	1		
Ethiopia	Low	1,2,4		
Thailand	Upper-middle	1,3,6		
World's Population				

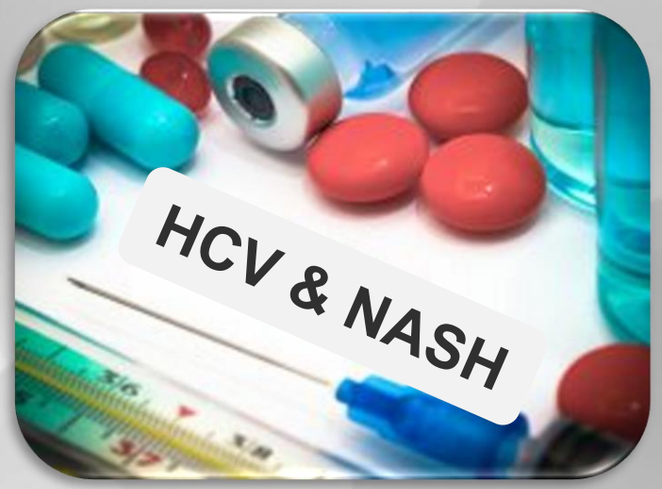


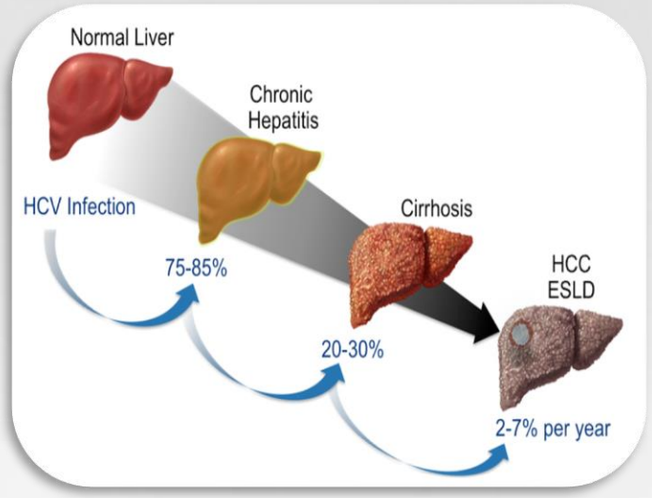
The Clinical Challenge: What do clinicians want?



A faster, easier, safer and non-invasive alternative to liver biopsy.

A method which allows for repeated serial evaluations. This is critical for monitoring new anti-viral HCV drugs and NAFLD-NASH.





A validated tool to screen for liver fibrosis/cirrhosis, AND the ability to stage fibrosis with a score.

A method which is low cost for the patient, AND provides a good reimbursement and return on investment.

- Current costs: Up to $300,000 over a patients lifetime

There is global consensus that a non-invasive, accurate, validated, and economical test for early detection and staging is needed.

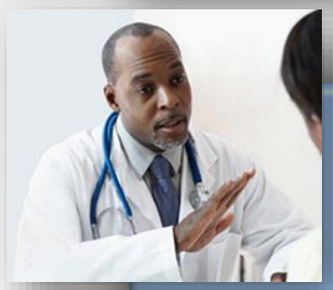
Our Solution:
The Aixplorer® ultrasound system for Liver Fibrosis

Aixplorer's Key Pillars

"One Probe Solution"
Unique ShearWave Technology

"60 Second Exam"
Faster Workflow

"Clinically Proven"
Superior Performance and Accuracy



"Higher Reimbursement"
4 times Transient Elastography

Now there is a Solution

Aixplorer® with ShearWave™ Elastography

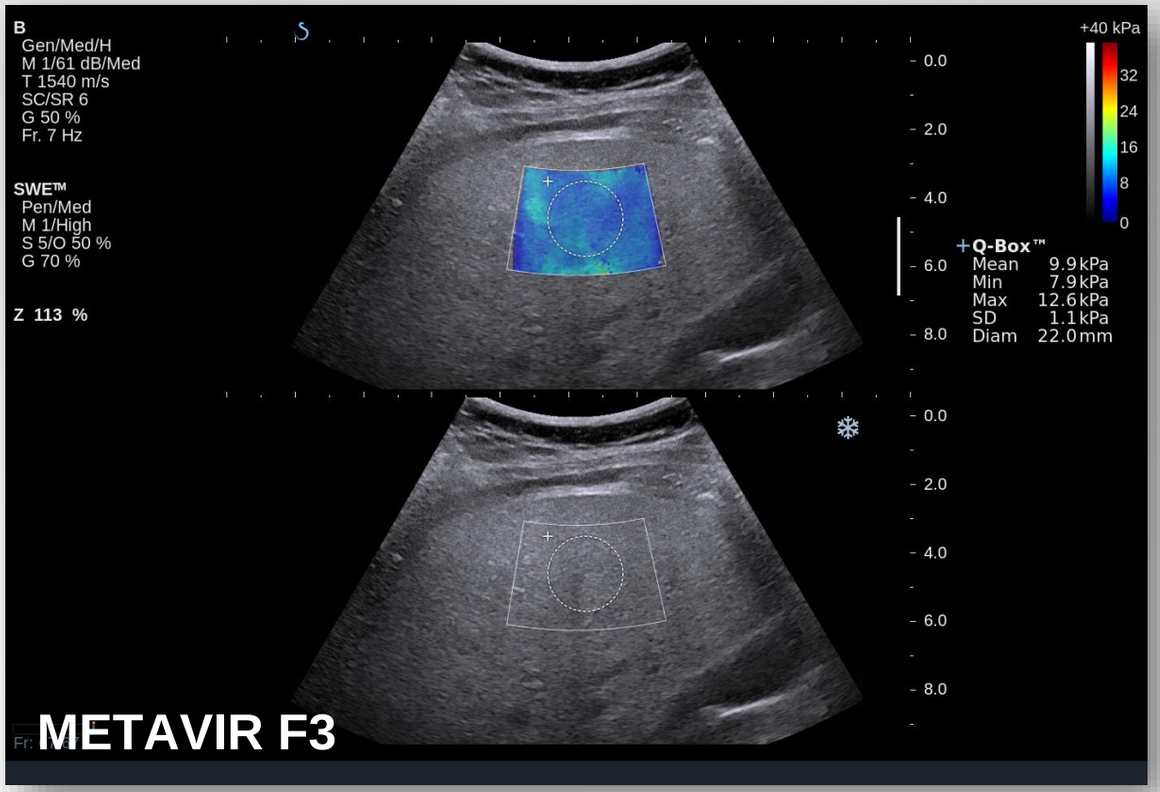
Our Solution:

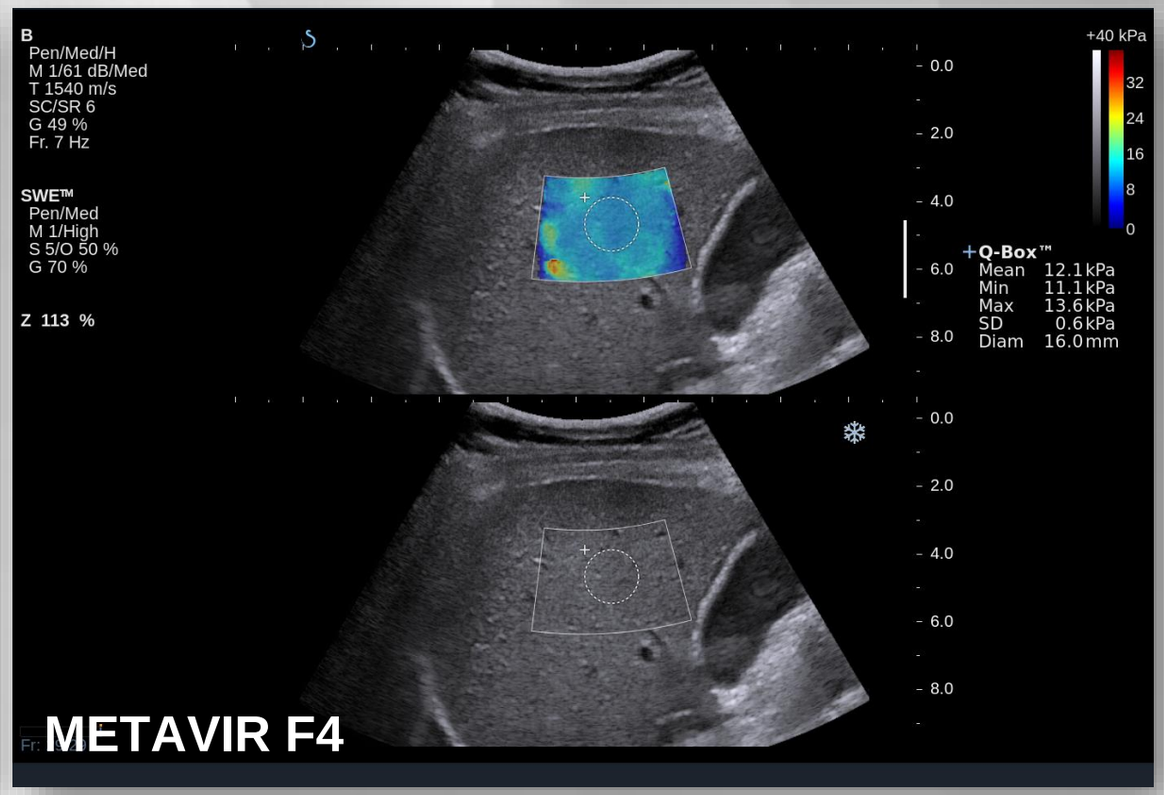
- **SuperSonic Imagine's** unique technology can provide liver fibrosis **screening, staging and monitoring.**
- The 60 second ShearWave™ Elastography exam – **fast**, **easy**, **clinically proven** and **cost effective**:
  - Simple 1 image acquisition and 3 measurement workflow
  - Quick Q-Box™ Analysis Tools with Stability Index to assure quality
  - Clear and concise Liver Report package

One Probe Solution

XC6-1 Single Crystal Curved Array Transducer

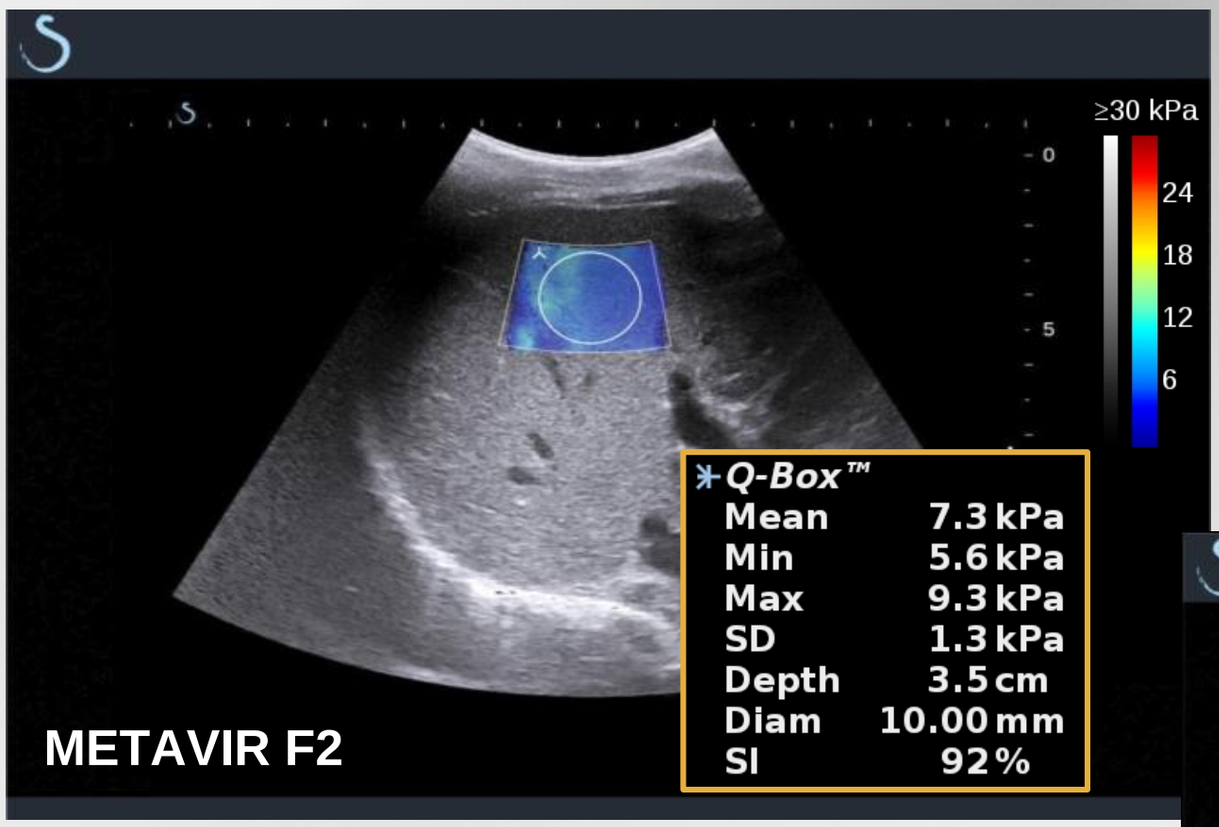
- "One Probe Solution" for All Patient Types:
  - Reliable – One probe lasts a lifetime. No need for annual recalibration.
  - Excellent SWE™ penetration down to 10 cm in obese patients. Maximum imaging to depths beyond 30 cm!
  - No failures due to ascites.
  - Single crystal technology for maximum sensitivity and image clarity.
  - Lightweight, ergonomic design.



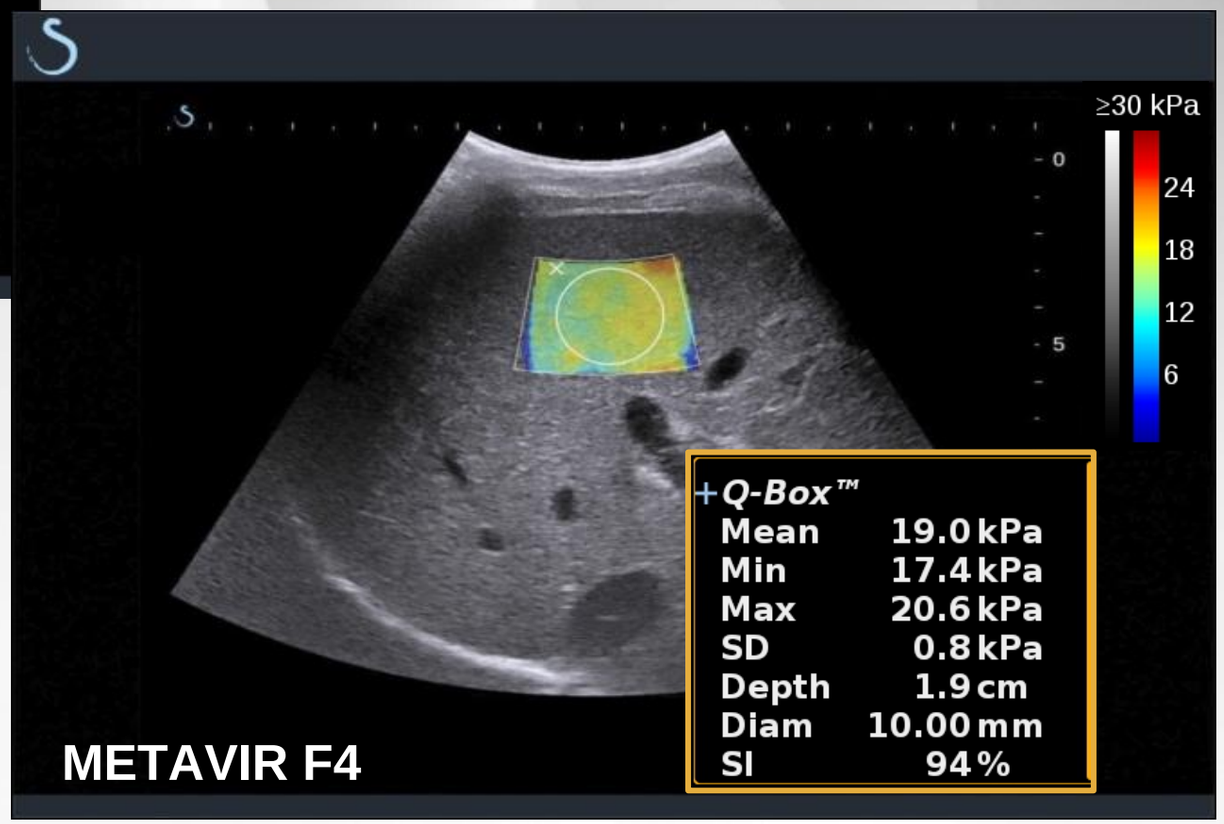


60 Second Exam

Non-Invasive & Quantitative Liver Fibrosis Assessment



- Large color-coded ShearWave™ area for easy visualization of the heterogeneity and extent of liver fibrosis.
- Simple blue to red color scale for easy qualitative interpretation of stiffness.



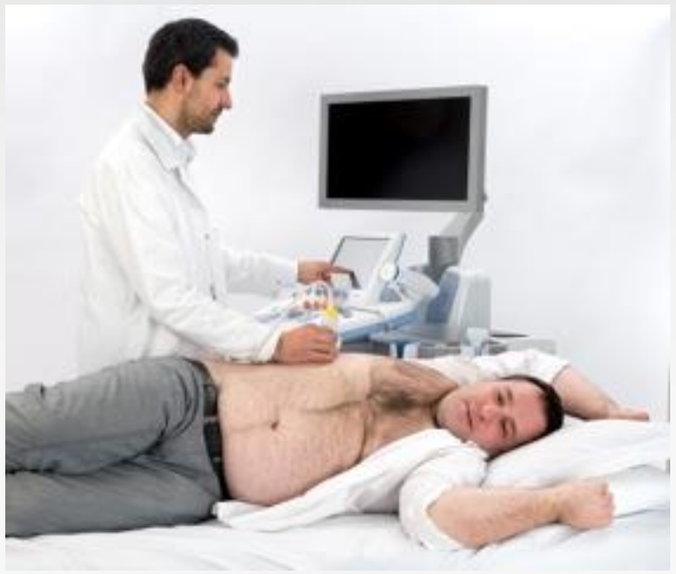
- Q-Box™ quantitative tools allow rapid quantitative measurement of tissue stiffness.
- Stability Index for accurate and confident quantitative results.

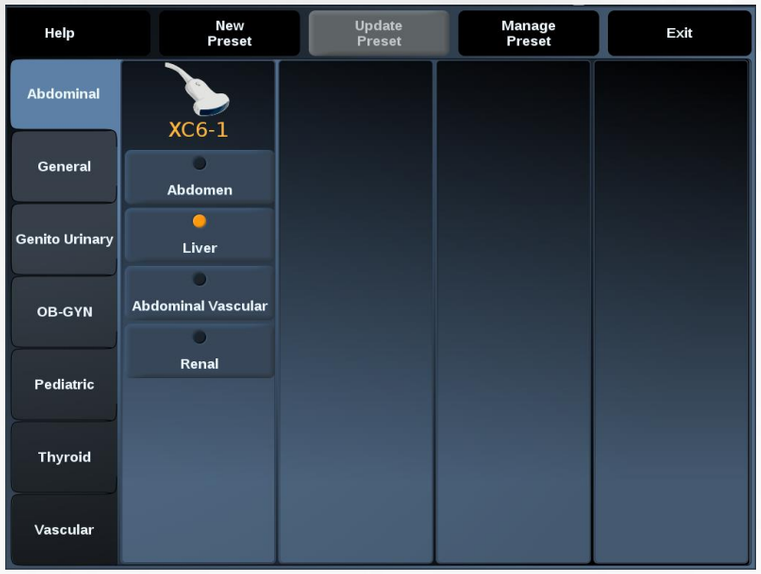
60 Second Exam

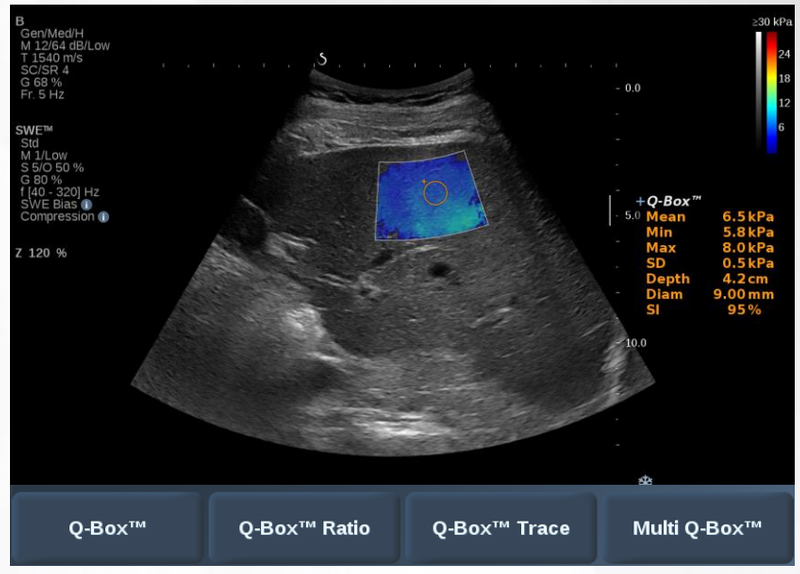
4 Easy Steps

1. Position the patient in a supine or slight left oblique position, hand above head, and activate the XC6-1 probe.
2. Firmly press the probe to enlarge the intercostal space. When a clear B-mode image of the liver is seen up to 8 cm of depth, activate SWE™ and ask the patient to pause breathing.
3. Acquire 5-10 seconds of real-time SWE images. Press Freeze.
4. Choose an image with clear parenchyma free of vessels. Press Q-Box™. Position the ROI in an area where the Stability Index (SI) reads 90% or higher. Press Save.

Repeat this procedure 3 times to acquire 3 valid, independent SWE™ images of the same scanning view.







The Aixplorer®:
Clinically Proven for Liver Fibrosis

Clinically Proven

Liver Fibrosis Assessment with SWE™

Liver stiffness values measured with SWE in Hepatitis C patients

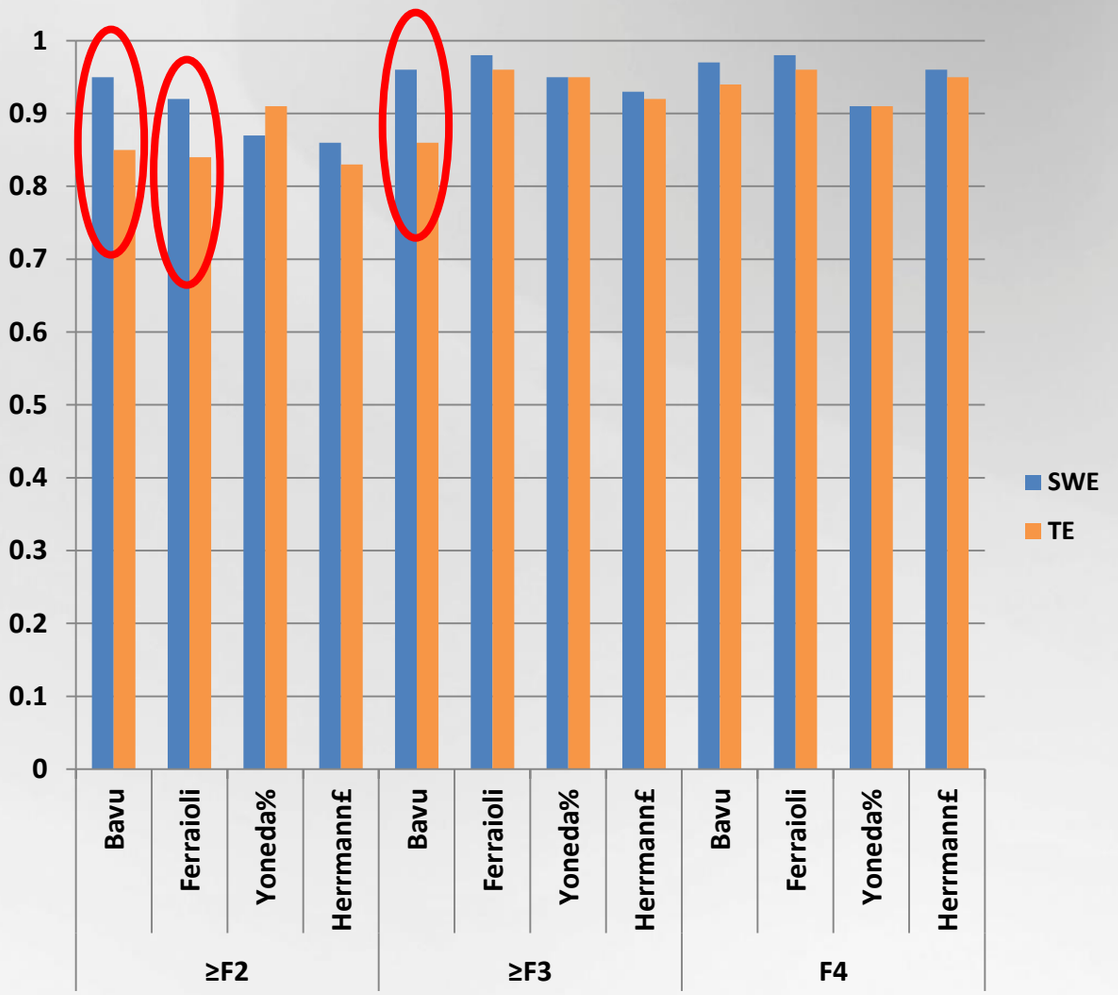
METAVIR Scores	Stiffness values (IQR)	Fibrosis assessment (METAVIR)	Cut-off values
F0-F1	5.1-6.8		
F2	7.2-8.3	F≥2	7.1
F3	9.2-10.1	F≥3	8.7
F4	12.8-18.8	F=4	10.4

Values taken from “Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C; Liver Fibrosis Study Group. Hepatology. 2012 Dec;56(6):2125-33.”

Clinically Proven

Liver Fibrosis Assessment with SWE™

HCV Patients



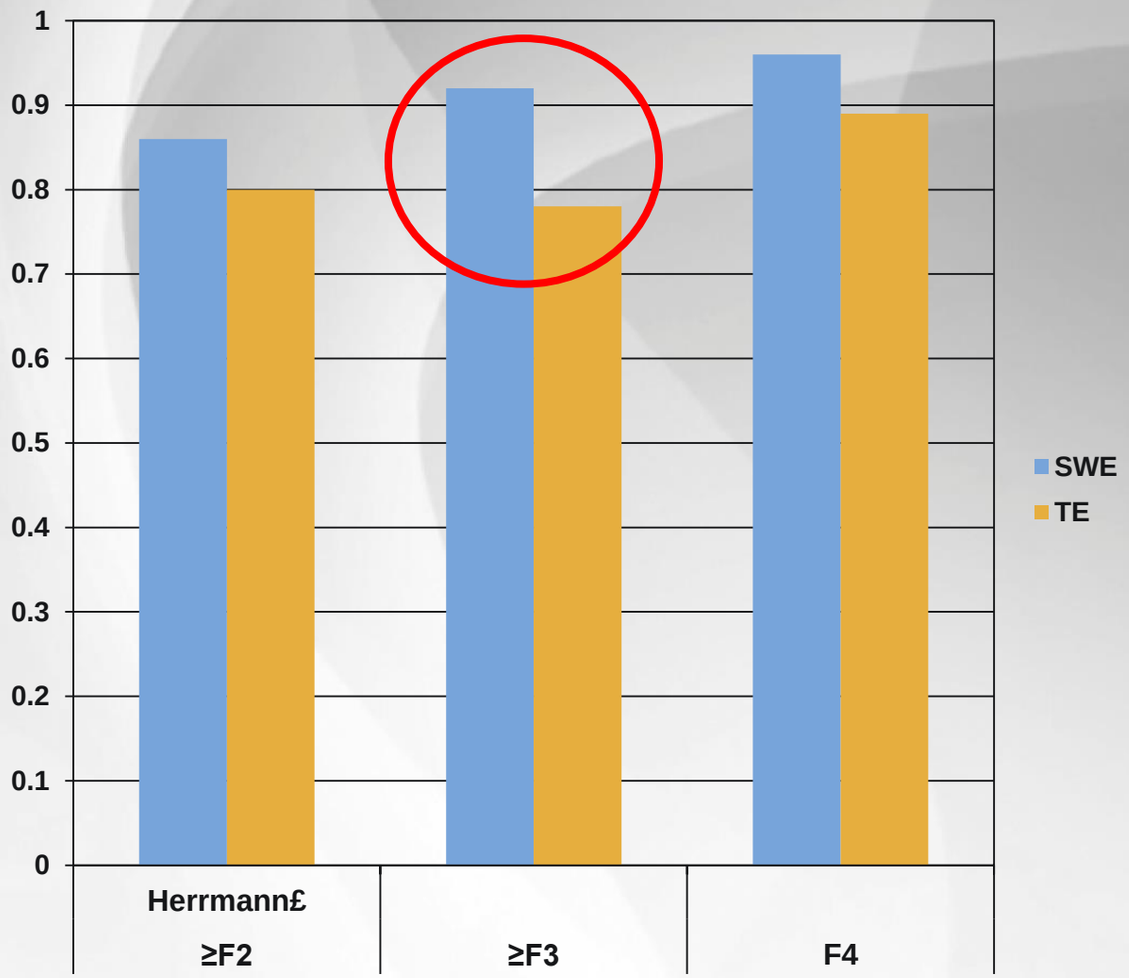
Bavu E et al. Ultrasound Med Biol. 2011 Sep;37(9):1361-73.

Ferraioli G et al. Hepatology. 2012 Dec;56(6):2125-33.

Yoneda M et al. Clin Gastroenterol Hepatol. 2015 Aug;13(8):1502-9.
(% Patients with BMI > 25 kg/m²)

Herrmann et al. J Hepatol 2015 Apr;62:S187–S212. (£ Oral presentation at EASL 2015)

NAFLD Patients



Herrmann et al. J Hepatol 2015 Apr;62:S187–S212. (£ Oral presentation at EASL 2015)

Clinically Proven

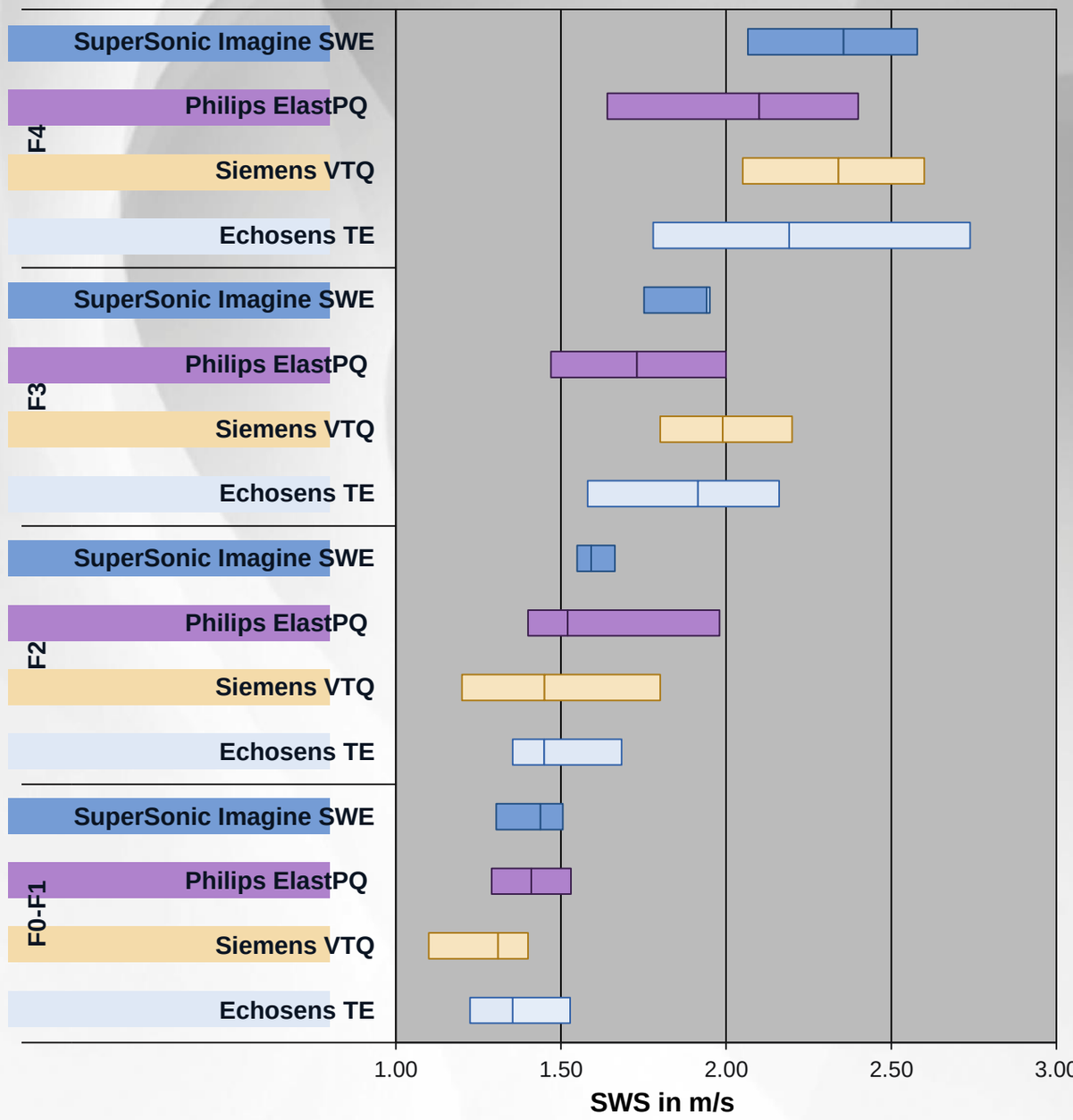
Liver Fibrosis Assessment with SWE™

- Correlation coefficient between liver stiffness measured non-invasively and liver fibrosis scoring

	SWE™	TE	ARFI VTTQ
Ferraioli[1]	**0.83**	**0.74**	
Cassinotto[2]	**0.79**	**0.70**	**0.64**
Gerber[3]	**0.71**	**0.73**	**0.75**
Samir[4]	**0.41**		
Dhyani[5]	**0.58**		
Franchi[6]	**0.83**		

1 Ferraioli G et al. Hepatology. 2012 Dec;56(6):2125-33.
2 Cassinotto C et al. J Hepatol. 2014 Sep;61(3):550-7.
3 Gerber L et al. Ultrasound Med Biol. 2015 Sep;41(9):2350-9.
4 Samir A et al. Radiology. 2015 Mar;274(3):888-96.
5 Dhyani M et al. J Med Imaging Radiat Oncol. 2015 Dec;59(6):687-94.
6 Franchi-Abella S et al. Radiology. 2016 Feb;278(2):554-62.

SSI SWE: No overlap between IQRs



Clinically Proven

SWE™ Multicenter Retrospective Study

First Results of the Multicenter Retrospective Study on Liver Fibrosis Assessment with SWE™

15 International Sites / 1340 patients

ShearWave™ Elastography delivers **excellent** results in managing chronic liver disease patients

In HBV patients, SWE™ delivers **increased sensitivity** in the assessment of significant fibrosis and cirrhosis (≤F1 vs. ≥F2)

In HCV patients, SWE delivers **excellent sensitivity** in the evaluation of cirrhosis (≥F4)

The Results Are IN!

RS-3186

Non-Invasive markers of liver fibrosis

2D-SHEAR WAVE ELASTOGRAPHY IS EQUIVALENT OR SUPERIOR TO TRANSIENT ELASTOGRAPHY FOR LIVER FIBROSIS ASSESSMENT:
RESULTS FROM AN INDIVIDUAL PATIENT DATA BASED META-ANALYSIS

Eva Herrmann[*1], Victor de Lédinghen[2], Christophe Cassinotto[3], Winnie C.-W. Chu[4], Vivian Y.-F. Leung[5], Giovanna Ferraioli[6], Carlo Filice[6], Laurent Castera[7], Valérie Vilgrain[8], Maxime Ronot[8], Jérôme Dumortier[9], Aymeric Guibal[10], Stanislas Pol[11], Jonel Trebicka[12], Christian Jansen[12], Christian Strassburg[12], Rongqin Zheng[13], Jian Zheng[13], Sven [illegible] Vonghia[14], Emanuel K. Manesis[15], Pavlos Zoumpoulis[16], Ioan Sporea[17], Friedrich-Rust[18]

[illegible] Hepato-Gastroenterolog[illegible], [3] [illegible] Imaging, Centre Hospitalier Universitaire du Haut-Lévèque, Bordeaux, [illegible] Imaging and Interventional Radiology, Prince of Wales Hospital, [illegible] Ultrasound Unit, [illegible] University of Pavia, Pavia, Italy, [7]Department of Hepatology, [8]Department of [illegible] Department of Hepatology, Assistance Publique de Hôpitaux de Paris, Hôpital [illegible] [13] Department of Ultrasound Imaging, 3rd Hospital of Sun Yat-Sen University, Guangzhou, China, [14]Division of Gastroenterology and Hepatology, Antwerp University Hospital, Edegem, Belgium, [15]Department of Internal Medicine, [16] Department of Radiology, Athens University School of Medicine, Athens, Greece, [17]Department of Gastroenterology and Hepatology, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania, [18]Research Unit for Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark, [19]Department of Internal Medicine, Goethe University Hospital Frankfurt, Frankfurt, Germany

Corresponding author's email: herrmann@med.uni-frankfurt.de

Do you want to apply for a Young Investigator Bursary?: No

Background and Aims: 2D shear wave elastography (2D-SWE) based on supersonic shear imaging (SSI) has proven to be efficie[illegible] several small to moderate size trials. We aimed at running a lar[illegible]r scale analysis [illegible]
Methods [illegible] collected retrospe[illegible]tively from 13 [illegible] [illegible]raphy (TE) were available in a subsample of [illegible]72 patients. [illegible] at each site. The database was cleared by the French National Commis[illegible] [illegible] The da[illegible] were analysed [illegible] [illegible] AUROC.
Results: [illegible] (HCV, n=370), hepatitis B (HBV, n=420), non-alcoholic fatty li[illegible]er disease [illegible] [illegible] between sites for liver d[illegible]isease etiologie[illegible] [illegible] had minimal or no fibrosis, 19.3% had significant fibrosis, 1[illegible].0% had severe fi[illegible]
Overall p[illegible] [illegible]%, 85.9% for diagnosing significant fibrosis and 96.1%, 97.1% and 95.5% for diagnosing cirrhosis, respectively. Optimal cut-offs were 7.1 kPa for diagnosing significant fibrosis in all patients (75.7% correctly classified), 13.5 kPa for diagnosing cirrhosis in HCV and NAFLD patients, and 11.5 kPa for diagnosing cirrhosis in HBV patients (87% correctly classified). Differences in AUROC were borderline significant for diagnosing significant fibrosis (95%>CI for AUROC-2D-SWE minus AUROC-TE: [0.0004, 0.055], p=0.047) and AUROC was significantly higher for 2D-SWE when diagnosing cirrhosis (95%>CI for AUROC-2D-SWE minus AUROC-TE: [0.006, 0.036], p=0.0058). 2D-SWE was superior for diagnosing

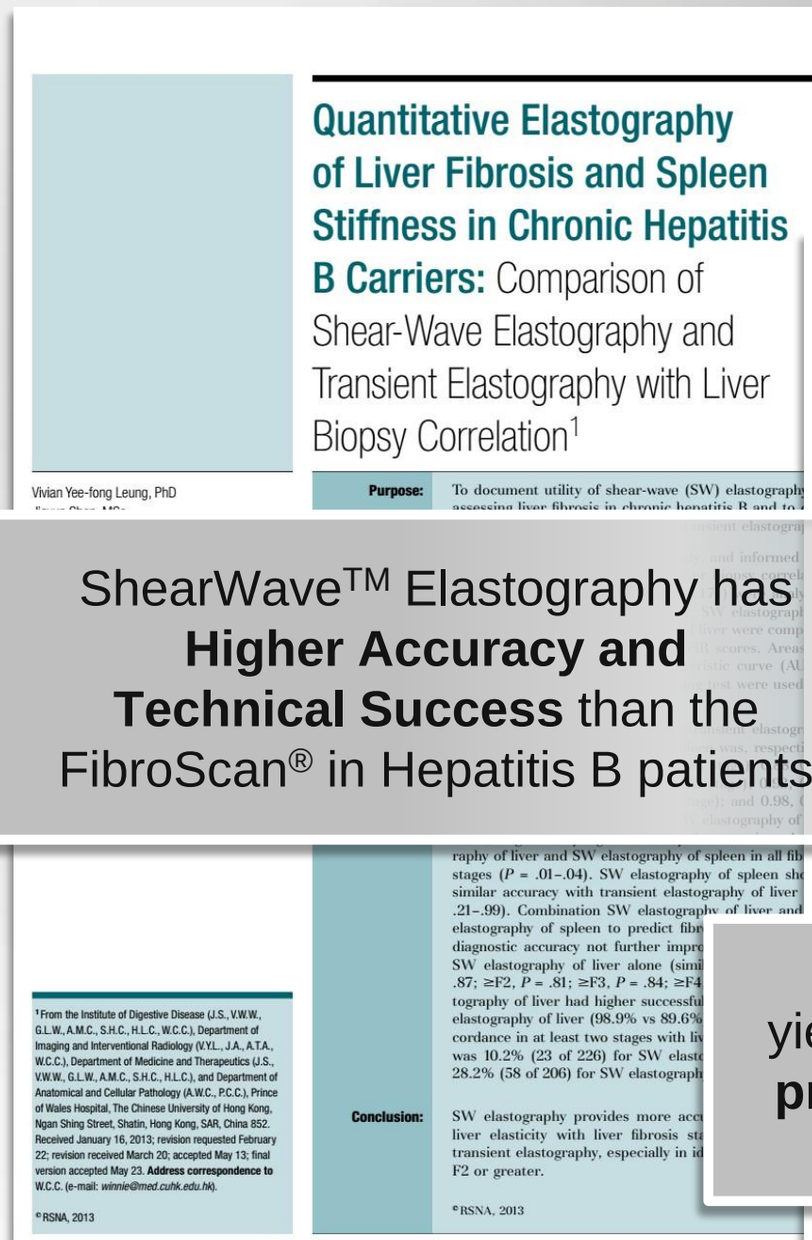
ShearWave™ Elastography delivers **excellent** diagnostic assessment of all fibrosis stages

NAFLD and NASH patient assessment **superior** in severe fibrosis (≤F2 vs. ≥F3)

Clinically Proven

Liver Fibrosis Assessment with SWE™ vs. FibroScan®

SUPERSONIC imagine



Radiology

Quantitative Elastography of Liver Fibrosis and Spleen Stiffness in Chronic Hepatitis B Carriers: Comparison of Shear-Wave Elastography and Transient Elastography with Liver Biopsy Correlation[1]

Vivian Yee-fong Leung, PhD

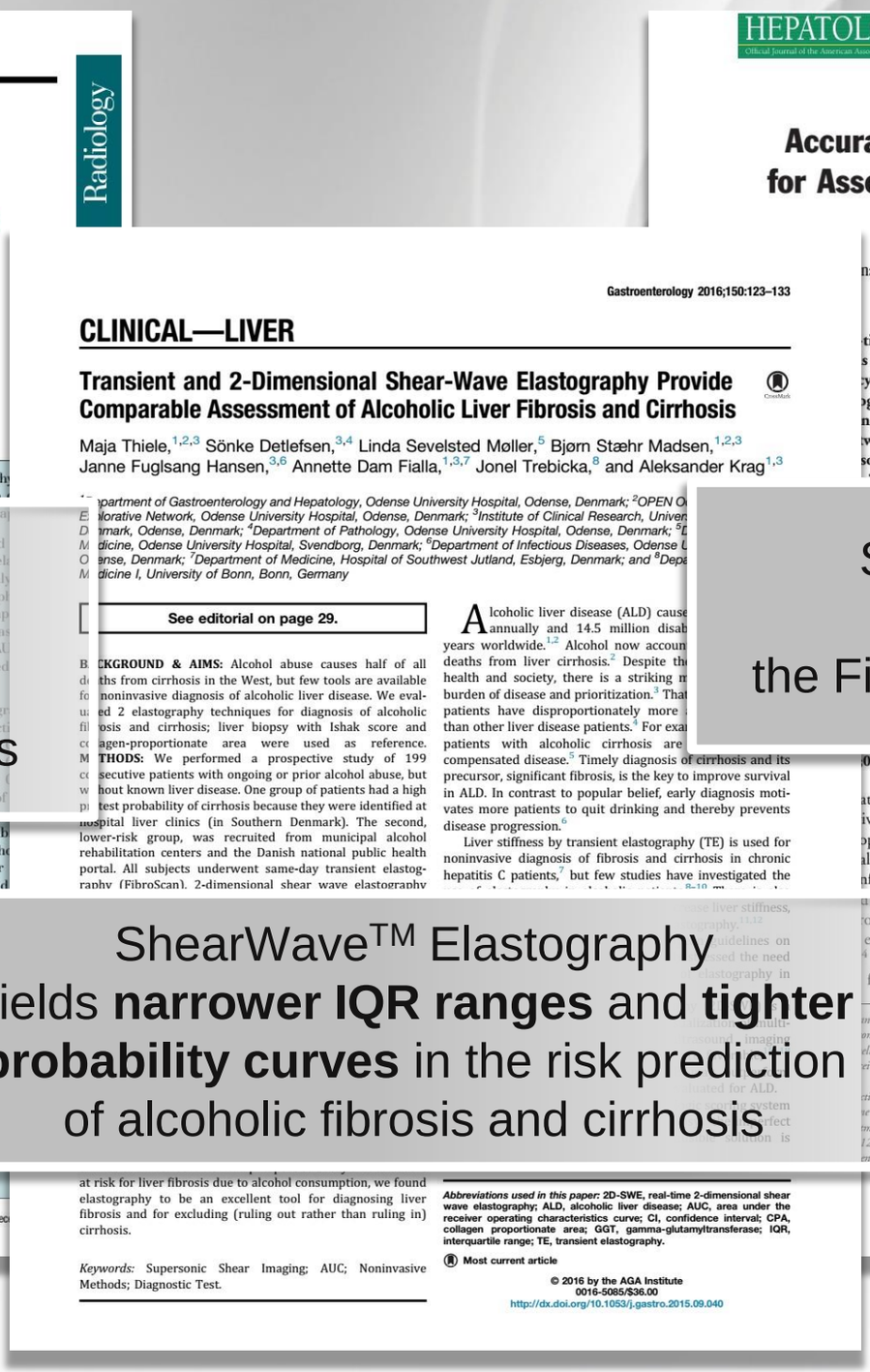
Purpose: To document utility of shear-wave (SW) elastography assessing liver fibrosis in chronic hepatitis B and to

raphy of liver and SW elastography of spleen in all fib stages (P = .01–.04). SW elastography of spleen sh similar accuracy with transient elastography of liver .21–.99). Combination SW elastography of liver and elastography of spleen to predict fibr diagnostic accuracy not further impro SW elastography of liver alone (simi .87; ≥F2, P = .81; ≥F3, P = .84; ≥F4 tography of liver had higher successfu elastography of liver (98.9% vs 89.6% cordance in at least two stages with li was 10.2% (23 of 226) for SW elast 28.2% (58 of 206) for SW elastograph

Conclusion: SW elastography provides more acc liver elasticity with liver fibrosis st transient elastography, especially in id F2 or greater.

[1]From the Institute of Digestive Disease (J.S., V.W.W., G.L.W., A.M.C., S.H.C., H.L.C., W.C.C.), Department of Imaging and Interventional Radiology (V.Y.L., J.A., A.T.A., W.C.C.), Department of Medicine and Therapeutics (J.S., V.W.W., G.L.W., A.M.C., S.H.C., H.L.C.), and Department of Anatomical and Cellular Pathology (A.W.C., P.C.C.), Prince of Wales Hospital, The Chinese University of Hong Kong, Ngan Shing Street, Shatin, Hong Kong, SAR, China 852. Received January 16, 2013; revision requested February 22; revision received March 20; accepted May 13; final version accepted May 23. **Address correspondence to** W.C.C. (e-mail: *winnie@med.cuhk.edu.hk*).

ShearWave™ Elastography has **Higher Accuracy and Technical Success** than the FibroScan® in Hepatitis B patients



Gastroenterology 2016;150:123–133

CLINICAL—LIVER

Transient and 2-Dimensional Shear-Wave Elastography Provide Comparable Assessment of Alcoholic Liver Fibrosis and Cirrhosis

Maja Thiele,[1,2,3] Sönke Detlefsen,[3,4] Linda Sevelsted Møller,[5] Bjørn Stæhr Madsen,[1,2,3] Janne Fuglsang Hansen,[3,6] Annette Dam Fialla,[1,3,7] Jonel Trebicka,[8] and Aleksander Krag[1,3]

[1]Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark; [2]OPEN Collaborative Network, Odense University Hospital, Odense, Denmark; [3]Institute of Clinical Research, University of Southern Denmark, Odense, Denmark; [4]Department of Pathology, Odense University Hospital, Odense, Denmark; [5]Department of Medicine, Odense University Hospital, Svendborg, Denmark; [6]Department of Infectious Diseases, Odense University Hospital, Odense, Denmark; [7]Department of Medicine, Hospital of Southwest Jutland, Esbjerg, Denmark; and [8]Department of Medicine I, University of Bonn, Bonn, Germany

See editorial on page 29.

BACKGROUND & AIMS: Alcohol abuse causes half of all deaths from cirrhosis in the West, but few tools are available for noninvasive diagnosis of alcoholic liver disease. We evaluated 2 elastography techniques for diagnosis of alcoholic fibrosis and cirrhosis; liver biopsy with Ishak score and collagen-proportionate area were used as reference. **METHODS:** We performed a prospective study of 199 consecutive patients with ongoing or prior alcohol abuse, but without known liver disease. One group of patients had a high pretest probability of cirrhosis because they were identified at hospital liver clinics (in Southern Denmark). The second, lower-risk group, was recruited from municipal alcohol rehabilitation centers and the Danish national public health portal. All subjects underwent same-day transient elastography (FibroScan), 2-dimensional shear wave elastography

at risk for liver fibrosis due to alcohol consumption, we found elastography to be an excellent tool for diagnosing liver fibrosis and for excluding (ruling out rather than ruling in) cirrhosis.

Keywords: Supersonic Shear Imaging; AUC; Noninvasive Methods; Diagnostic Test.

Alcoholic liver disease (ALD) causes annually and 14.5 million disab years worldwide.[1,2] Alcohol now accoun deaths from liver cirrhosis.[2] Despite th health and society, there is a striking n burden of disease and prioritization.[3] That patients have disproportionately more than other liver disease patients.[4] For exa patients with alcoholic cirrhosis are compensated disease.[5] Timely diagnosis of cirrhosis and its precursor, significant fibrosis, is the key to improve survival in ALD. In contrast to popular belief, early diagnosis motivates more patients to quit drinking and thereby prevents disease progression.[6]

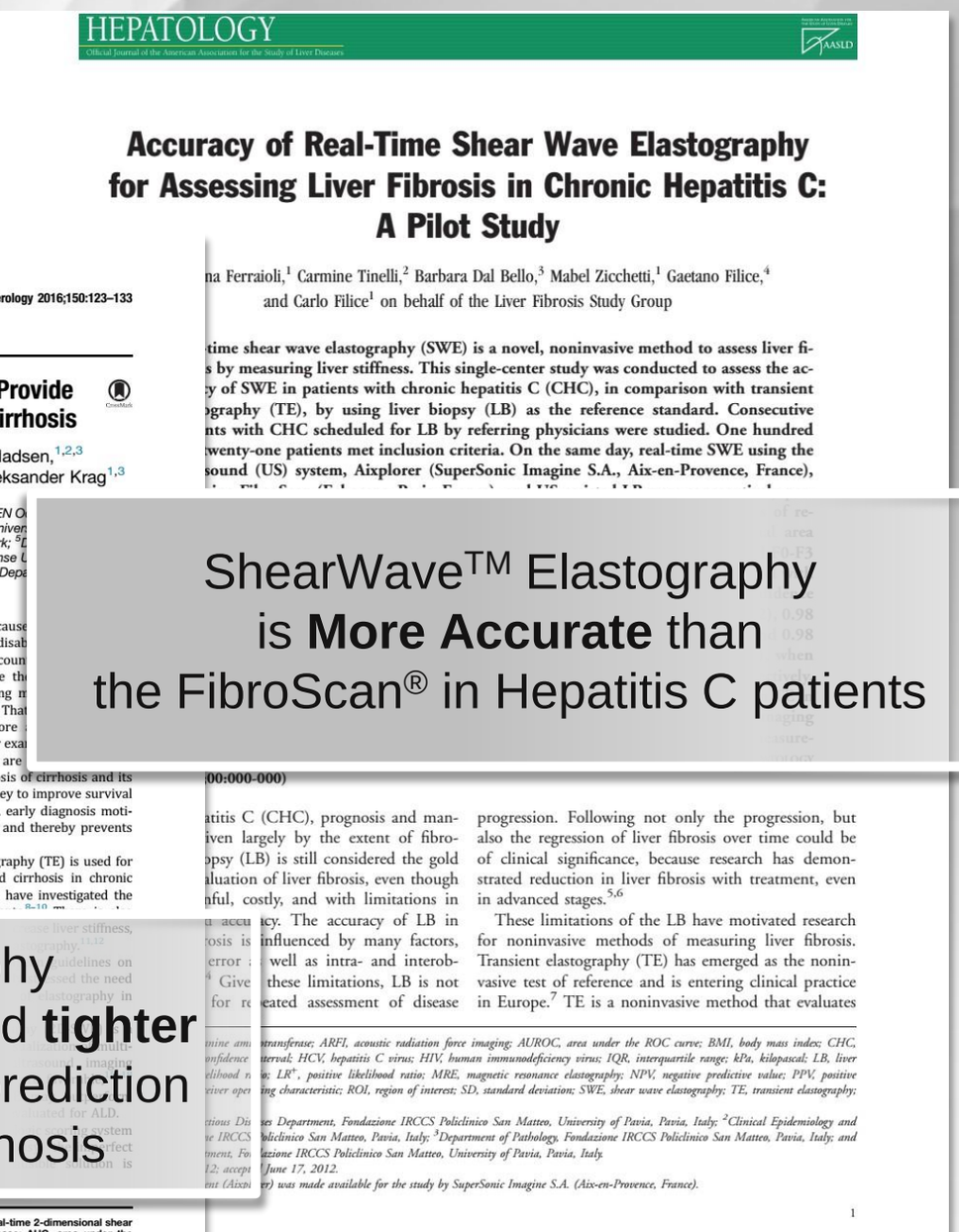
Liver stiffness by transient elastography (TE) is used for noninvasive diagnosis of fibrosis and cirrhosis in chronic hepatitis C patients,[7] but few studies have investigated the

ShearWave™ Elastography yields **narrower IQR ranges** and **tighter probability curves** in the risk prediction of alcoholic fibrosis and cirrhosis

Abbreviations used in this paper: 2D-SWE, real-time 2-dimensional shear wave elastography; ALD, alcoholic liver disease; AUC, area under the receiver operating characteristics curve; CI, confidence interval; CPA, collagen proportionate area; GGT, gamma-glutamyltransferase; IQR, interquartile range; TE, transient elastography.

Most current article

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2015.09.040



HEPATOLOGY

Official Journal of the American Association for the Study of Liver Diseases

AASLD

Accuracy of Real-Time Shear Wave Elastography for Assessing Liver Fibrosis in Chronic Hepatitis C: A Pilot Study

na Ferraioli,[1] Carmine Tinelli,[2] Barbara Dal Bello,[3] Mabel Zicchetti,[1] Gaetano Filice,[4] and Carlo Filice[1] on behalf of the Liver Fibrosis Study Group

time shear wave elastography (SWE) is a novel, noninvasive method to assess liver fi- by measuring liver stiffness. This single-center study was conducted to assess the ac- of SWE in patients with chronic hepatitis C (CHC), in comparison with transient graphy (TE), by using liver biopsy (LB) as the reference standard. Consecutive nts with CHC scheduled for LB by referring physicians were studied. One hundred wenty-one patients met inclusion criteria. On the same day, real-time SWE using the sound (US) system, Aixplorer (SuperSonic Imagine S.A., Aix-en-Provence, France),

00:000-000)

titis C (CHC), prognosis and man- iven largely by the extent of fibro- opsy (LB) is still considered the gold aluation of liver fibrosis, even though nful, costly, and with limitations in acy. The accuracy of LB in osis is influenced by many factors, error well as intra- and interob- Give these limitations, LB is not for re eated assessment of disease progression. Following not only the progression, but also the regression of liver fibrosis over time could be of clinical significance, because research has demonstrated reduction in liver fibrosis with treatment, even in advanced stages.[5,6]

These limitations of the LB have motivated research for noninvasive methods of measuring liver fibrosis. Transient elastography (TE) has emerged as the noninvasive test of reference and is entering clinical practice in Europe.[7] TE is a noninvasive method that evaluates

mine am transferase; ARFI, acoustic radiation force imaging; AUROC, area under the ROC curve; BMI, body mass index; CHC, onfidence terval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; kPa, kilopascal; LB, liver elihood r o; LR+, positive likelihood ratio; MRE, magnetic resonance elastography; NPV, negative predictive value; PPV, positive iver ope ing characteristic; ROI, region of interest; SD, standard deviation; SWE, shear wave elastography; TE, transient elastography;

tious Di es Department, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy; [2]Clinical Epidemiology and e IRCCS oliclinico San Matteo, Pavia, Italy; [3]Department of Pathology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; and tment, Fo dazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy.

12; accep June 17, 2012.

nt (Aixp er) was made available for the study by SuperSonic Imagine S.A. (Aix-en-Provence, France).

1

ShearWave™ Elastography is **More Accurate** than the FibroScan® in Hepatitis C patients

Clinically Proven

Liver Fibrosis Assessment with SWE™ vs. FibroScan®

SUPERSONIC imagine

Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Cirrhosis

Non-invasive assessment of liver fibrosis with impulse elastography: Comparison of Supersonic Shear Imaging with ARFI and FibroScan®

Christophe Cassinotto[1,2,*], Bruno Lapuyade[1], Amaury Mouries[1], Jean-Baptiste Hiriart[3], Julien Vergniol[3], Delphine Gaye[1], Claire Castain[4], Brigitte Le Bail[2,4], Faiza Chermak[3], Juliette Foucher[3], François Laurent[5], Michel Montaudon[5], Victor De Ledinghen[2,3]

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Background & Aims: Non-invasive assessment of liver fibrosis by elastography is a rapidly developing field with frequent technological innovations. The aim of this study was to assess the diagnostic performances of Supersonic Shear Imaging (SSI) for the diagnosis of liver fibrosis in chronic liver disease.

Methods: A total of 349 consecutive patients with chronic liver diseases who underwent liver biopsy from November 2011 to October 2013 were prospectively enrolled. For each patient, liver stiffness was assessed by SSI, ARFI, FibroScan® (M probe for patients with BMI <30 kg/m², and XL probe for patients with

than ARFI for the diagnosis of significant fibrosis (≥F2) ($p = 0.0003$). No significant difference was observed for the diagnosis of mild fibrosis and cirrhosis.

Conclusions: SSI is an efficient method for the assessment of liver fibrosis in chronic liver diseases, comparing favourably to FibroScan® and ARFI.

nine AminoTransferase; ALP, Alkaline Phosphatase; APRI, Aspartate-to-Platelet Ratio Index; AST/ALT, aspartate aminotransferase/alanine aminotransferase ratio index; kPa, kilopascal; IQR, Interquartile Range; AUROC, Area Under the Receiver Operating Characteristic curve; CI, confidence interval; NASH, Non-Alcoholic Steato-Hepatitis.

the measurement of the velocity of a local shear wave through soft tissues. As ARFI and conversely to FibroScan®, this method is built on an ultrasound device (Aixplorer, Supersonic Imagine, Aix-en-Provence, France), and requires no external vibrator to

ELSEVIER

Journal of Hepatology **2014** vol. 61 | 550–557

Clinical Gastroenterology and Hepatology 2015;13:1502–1509

Supersonic Shear Imaging and Transient Elastography With the XL Probe Accurately Detect Fibrosis in Overweight or Obese Patients With Chronic Liver Disease

Masato Yoneda, Emmanuel Thomas, Seth N. Sclair, Tiffannia T. Grant, and Eugene R. S

Schiff Center for Liver Diseases, University of Miami Miller School of Medicine, Miami, Florida

BACKGROUND & AIMS: **Assessment of the severity of liver fibrosis is an important step in evaluating patien chronic liver disease and determining their prognosis. We compared liver stiffness m ments (LSMs) made by supersonic shear imaging (SSI) with those of transient elasto (TE)-XL for their ability to determine the degree of liver fibrosis in overweight or obese p with chronic liver disease.**

the 102 biopsy-proven patients with chronic HCV infection.

CONCLUSIONS: **SSI and the TE-XL probe each accurately quantify liver fibrosis in overweight or obese p with chronic liver disease, including those with HCV infection, when compared with d tained from histologic analysis. SSI data obtained from the right lobe and the TE- be used to evaluate fibrosis with similar accuracy.**

Keywords: Viral Hepatitis; Cirrhosis; Fibrosis Stage; Obesity.

See editorial on page 1510.

Staging of liver fibrosis is essential in determining the prognosis and optimal treatment for patients with chronic liver disease and also to guide surveillance for the development of hepatocellular carcinoma.[1] Liver biopsy is recommended as the reference standard method for the diagnosis and staging of fibrosis in chronic liver disease.[2] This procedure, however, is invasive with associated risks of complications, is costly, and is time consuming both for providers and patients.[3] In addition, despite being the gold standard test for assessing liver fibrosis, liver biopsy is limited further by sampling error and intra-observ observer variability.[4,5] Therefore, there is for rapid, quantitative, and noninvasive

Abbreviations used in this paper: AAR, aspartate amin alanine aminotransferase ratio; APRI, aspartate amin platelet ratio index; AST, aspartate aminotransferase; AU the receiver-operating characteristic; BMI, body mass in stage 3; F4, fibrosis stage 4; FIB-4, Fibrosis-4 score; HC rus; LSM, liver stiffness measurement; SSI, supersonic SSI-Lt, supersonic shear imaging from the left lobe; SS shear imaging from the right lobe; TE, transient elastogr

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2015.03.01

Radiology

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rançois Durand, MD
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idier Lebrec, MD
alérie Vilgrain, MD, PhD
aurent Castéra, MD

Prospective Comparison of Spleen and Liver Stiffness by Using Shear-Wave and Transient Elastography for Detection of Portal Hypertension in Cirrhosis[1]

Purpose: To prospectively compare the technical success rate and accuracy of shear-wave elastography (SWE) and transient elastography (TE) for the detection of clinically significant portal hypertension (PH) in patients with advanced cirrhosis who are undergoing hepatic vein pressure gradient (HVPG) measurements.

Materials and Methods: The institutional ethics committee approved the study, and written informed consent was obtained. Seventy-nine consecutive patients with cirrhosis who were undergoing SWE and TE at the time of HVPG measurement were studied. The technical success rate of SWE and TE was compared with the diagnostic value of liver stiffness (LS) and spleen stiffness (SS) measurements and composite scores (LS spleen-diameter-to-platelet-ratio score [LSPS] and PH risk score) by using SWE and TE to detect clinically significant PH (HVPG ≥ 10 mm Hg) and esophageal varices at high risk of bleeding. Areas under the receiver operating characteristic curve and the DeLong test were

ShearWave™ Elastography is **Comparable to Biopsy** and **Superior to FibroScan®** in Obese patients

ShearWave™ Elastography **Clinically Outperforms** the FibroScan® in Chronic Liver Disease Patients

ShearWave™ Elastography is more **Technically Successful** and has **Better Performance** than the FibroScan® in the Detection of Portal Hypertension in Cirrhosis

Clinically Proven

What the experts are saying

"I can reduce my biopsy numbers by 90% during initial fibrosis staging when I use the Aixplorer's® real-time, quantitative ShearWave™ Elastography from SuperSonic Imagine"

"This is especially helpful for my patients who are eligible to receive the new antiviral treatments for HCV. This quick, non-invasive exam improves the overall patient experience."

Dr. James Trotter
Medical Director of Liver Transplantation
Baylor University Medical Center
Dallas, Texas

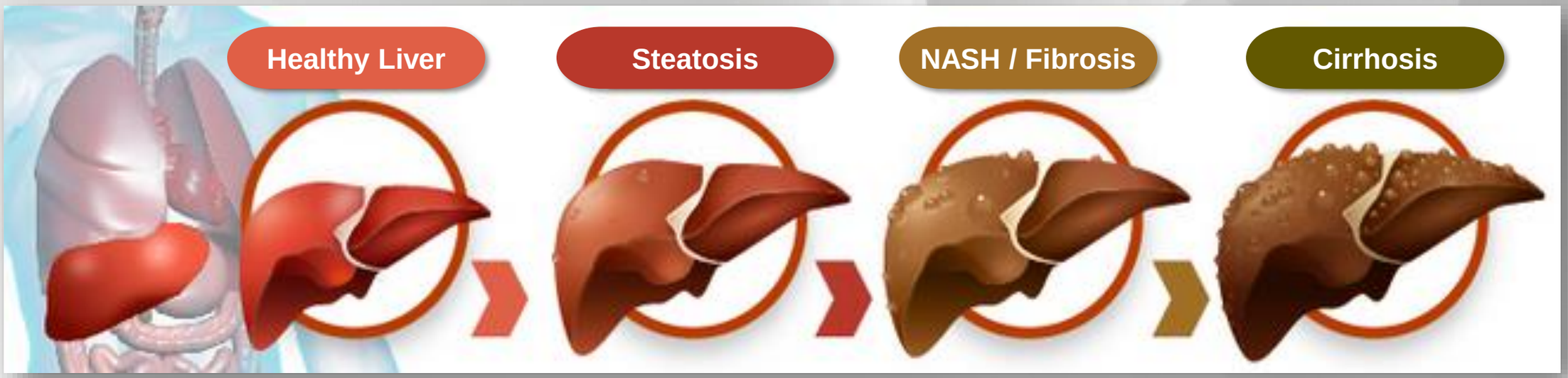
"The advent of ShearWave™ Elastography, has ushered in an era of fewer liver biopsies for the Hepatitis C patient, while allowing the clinician to evaluate, monitor and effectively treat these patients without the risks of an invasive biopsy."

Dr. Ravi Ravinuthala
Ohio Gastroenterology & Liver Institute
Cincinnati, Ohio

The Clinical Challenge:
Liver Steatosis

The Clinical Challenge
Assessment of Liver Steatosis

- What is Steatosis?
  - Steatosis, or fatty liver, describes the accumulation of excess fat in the liver, usually above 5%.
  - Steatosis is the hallmark of most prevalent liver diseases, including alcoholic and nonalcoholic fatty liver disease (NAFLD).



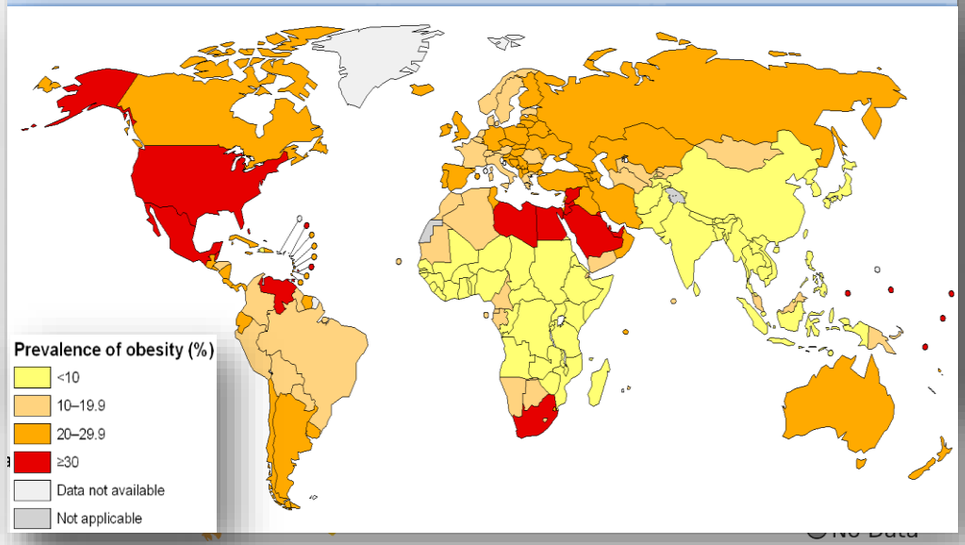
- Steatosis / NAFLD > 5% may progress to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis and liver cancer.
- Steatosis also reduces the viral response in hepatitis C treatment, complicates liver surgery, and raises overall risk to cardiovascular events.

The Clinical Challenge
Obesity and Steatosis

The Facts:

- NAFLD and NASH, and their progression was relatively unknown in etiology until 10 years ago.
- Today, more than 25% of the world's population is at risk with NAFLD, 3% with NASH.
- NAFLD/NASH has very high prevalence in the Americas, Asia-Pacific, the Middle East and Europe.
- Approximately 10%-25% of patients with NAFLD will develop NASH. 5%-8% of those will develop liver cirrhosis within 5 years. Furthermore, 12.8% of patients with liver cirrhosis will develop hepatocellular carcinoma (HCC) within 3 years.
- NAFLD/NASH is a silent killer, growing at an epidemic rate in proportion to obesity. From 1980-2013 obesity increased by 10% in adults and by 47% in children.

Region	Population studied	Prevalence of NAFLD in these populations (%)
USA	Pediatric population	13–14
	General population	27–34
	Morbid obesity	75–92
	European-Americans	33
	Hispanic-Americans	45
	African-Americans	24
Europe	Pediatric population	2.6–10
	General population	20–30
Western countries	General population	20–40
	Obesity or diabetes	75
	Morbid obesity	90–95
Worldwide	Obese population	40–90
Middle East	General population	20–30
Far East	General population	15
Pakistan	General population	18

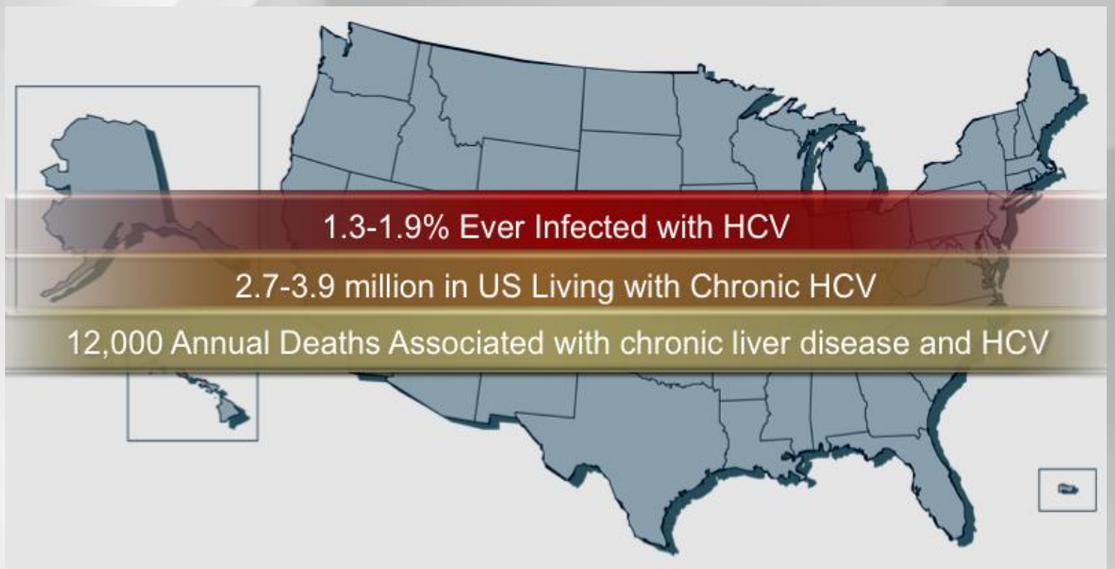


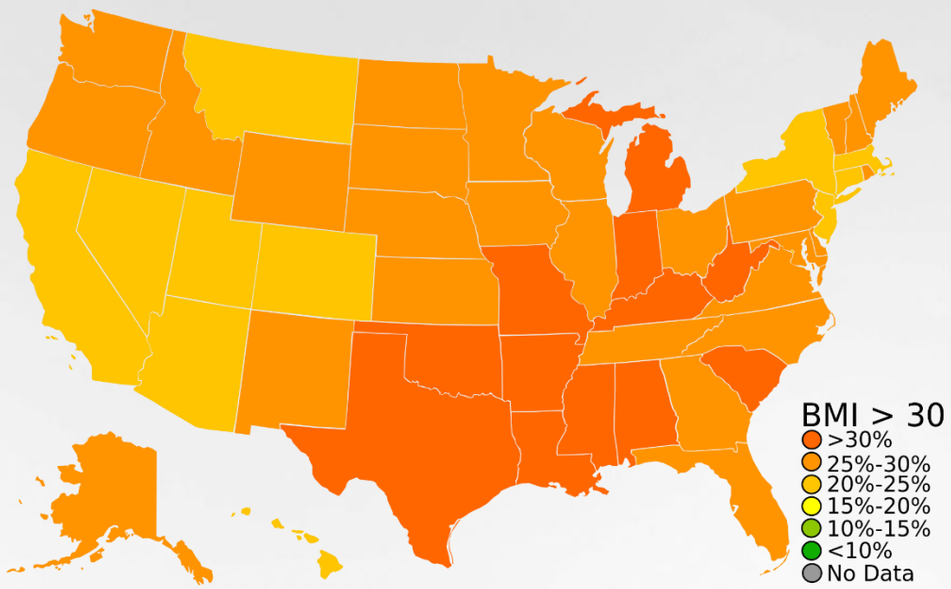
Non-alcoholic fatty liver disease and obesity: Biochemical, metabolic and clinical presentations. Milić S. World Journal of Gastroenterology : WJG. 2014;20(28):9330-9337. doi:10.3748/wjg.v20.i28.9330.

USA Predilection for Liver Fibrosis

USA Statistics:

- 700,000-1.4 million persons are estimated to be infected with the HBV virus
- 3.2 million persons are chronically HCV-infected
- 27-34% of all Americans are estimated to have NAFLD





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	Morbid obesity	75–92
	European-Americans	33
	Hispanic-Americans	45
	African-Americans	24

USA Data: http://www.cdc.gov/hepatitis/statistics/2013surveillance/commentary.htm

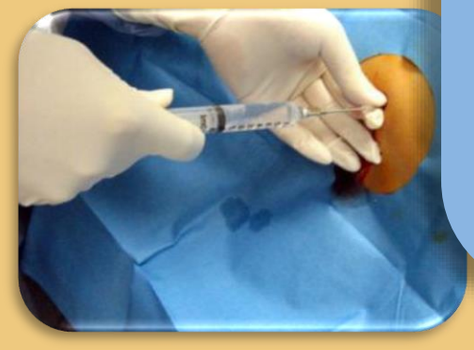
The Clinical Challenge
Obesity and Steatosis

A Global Effort to Address the Epidemic of Fatty Liver Disease
William F. Balistreri. Medscape. September 24, 2014

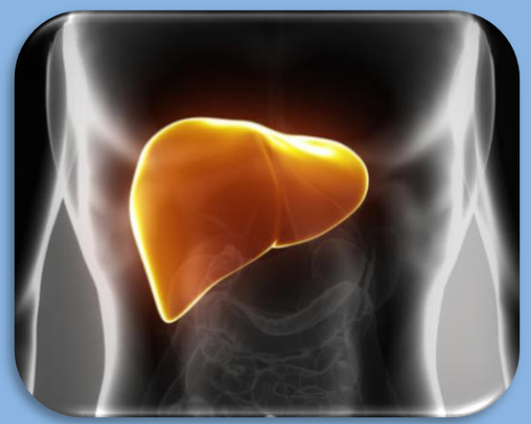
> ***"Left unchecked, obesity will make the current generation of children the first in human history to have a life span shorter than that of their parents."***
>
> ***David Satcher, MD, PhD***
> ***US Surgeon General (1998-2002)***

The Clinical Challenge
Assessment of Liver Steatosis

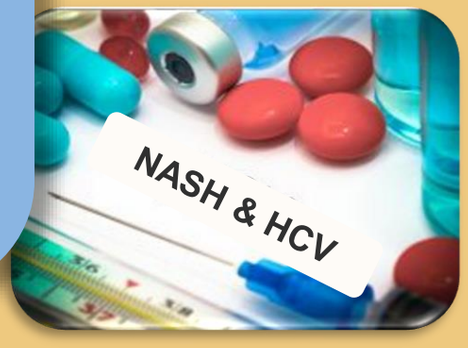
Low cost.



Non-invasive.
Safe.
Well tolerated.



Early detection of steatosis at the 5% level.



Serial assessment during treatment and beyond.

Globally available.

A non-invasive, accurate, validated, and economical test to detect, assess and monitor steatosis is needed.

Our Solution:
The Aixplorer® ultrasound system for Liver Steatosis

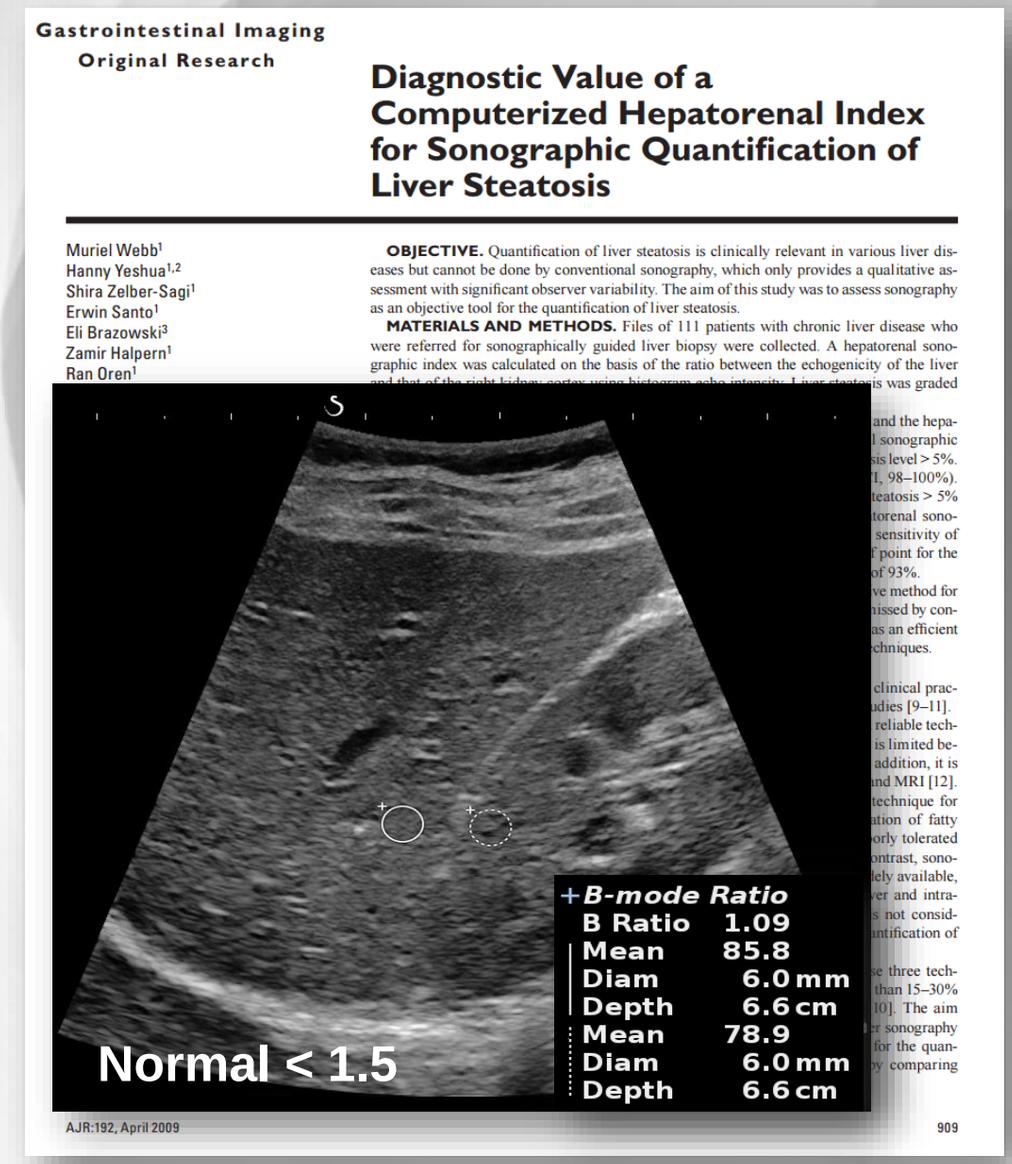
60 Second Exam

Steatosis Assessment with B-mode Ratio Tool

- Hepatorenal Ratio for Steatosis Assessment: B-Mode Ratio Tool
  - Quantifies brightness of the liver with renal cortex.
  - Significantly improves the assessment of fatty liver compared to traditional “guess-timation”.
  - Fast and easy to use. Requires only B-mode.

- Clinically Proven
  - Ultrasound Hepatic-Renal Ratio was found to be an excellent predictor of liver fat content.
  - Able to discriminate between levels of steatosis with high sensitivity and specificity.[1]
  - The addition of ultrasound attenuation parameter (e.g. CAP) only improved the accuracy by 1.8%.[2]
  - Can be done on DICOM images.[3]

- No additional cost
  - Compare to FibroScan CAP tool at +$22k.



[1] Diagnostic value of a computerized hepatorenal index for sonographic quantification of liver steatosis. Webb M et al. AJR Am J Roentgenol. 2009 Apr;192(4):909-14.

[2] Standardized Ultrasound Hepatic/Renal Ratio and Hepatic attenuation Rate to Quantify Liver Fat Content: an Improvement Method. Xia, et. al. Obesity (2011) 20, 444–452.

[3] Improved method for calculating hepatic steatosis using the hepatorenal index. Shiralkar K et al. J Ultrasound Med. 2015 Jun;34(6):1051-9.

The Aixplorer®:
Clinically Proven for Liver Steatosis

Clinically Proven

Ultrasound Meta-Analysis for the Detection of Steatosis

Diagnostic Accuracy and Reliability of Ultrasonography for the Detection of Fatty Liver: A Meta-Analysis

49 Publications / 4720 patients

Ultrasonography allows for
reliable and accurate detection
of moderate-severe fatty liver,
compared to histology.

The Hepato-Renal brightness (HRI)
performed best
with a sensitivity of 98% and specificity of 93%.

Other measures of ultrasound brightness
e.g. hepatic or portal vessel walls
significantly outperformed
ultrasound beam attenuation (CAP),
sensitivity 59%, specificity 95%.

HEPATOLOGY, Vol. 54, No. 3, 2011

Diagnostic Accuracy and Reliability of Ultrasonography for the Detection of Fatty Liver: A Meta-Analysis

Ruben Hernaez,[1,2,3]* Mariana Lazo,[1]* Susanne Bonekamp,[4] Ihab Kamel,[4] Frederick L. Brancati,[1,3,5] Eliseo Guallar,[3,5,6] and Jeanne M. Clark[1,3,5]

Ultrasonography is a widely accessible imaging technique for the detection of fatty liver, but the reported accuracy and reliability have been inconsistent across studies. We aimed to perform a systematic review and meta-analysis of the diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver. We used MEDLINE and Embase from October 1967 to March 2010. Studies that provided cross-tabulations of ultrasonography versus histology or standard imaging techniques, or that provided reliability data for ultrasonography, were included. Study variables were independently abstracted by three reviewers and double checked by one reviewer. Forty-nine (4720 participants) studies were included for the meta-analysis of diagnostic accuracy. The overall sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of ultrasound for the detection of moderate-severe fatty liver, compared to histology (gold standard), were 84.8% (95% confidence interval: 79.5-88.9), 93.6% (87.2-97.0), 13.3 (6.4-27.6), and 0.16 (0.12-0.22), respectively. The area under the summary receiving operating characteristics curve was 0.93 (0.91-0.95). Reliability of ultrasound for the detection of fatty liver showed kappa statistics ranging from 0.54 to 0.92 for intrarater reliability and from 0.44 to 1.00 for interrater reliability. Sensitivity and specificity of ultrasound was similar to that of other imaging techniques (i.e., computed tomography or magnetic resonance imaging). Statistical heterogeneity was present even after stratification for multiple clinically relevant characteristics. *Conclusion:* Ultrasonography allows for reliable and accurate detection of moderate-severe fatty liver, compared to histology. Because of its low cost, safety, and accessibility, ultrasound is likely the imaging technique of choice for screening for fatty liver in clinical and population settings. (HEPATOLOGY 2011;54:1082-1090)

Fa y liver is the accumulation of fat (i.e., macro- vesicular steatosis) within the hepatic parenchyma. Nonalcoholic fatty liver disease (NAFL]), the presence of fat infiltration in the liver in the bsence of excessive alcohol consumption and other c uses of liver disease, is the most common cause of fatty liver, with a prevalence as high as 30% in many populations.[1] NAFLD may lead to fibrosis,[2] cirrhosis,[3] liver cancer,[4,5] liver failure requiring liver transplant,[6] and mortality[7], and it is associated with type 2 diabetes, metabolic syndrome, and other cardiovascular risk factors.[8,9] Although NAFLD represents a

Abbreviations: CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFLD, nonalcoholic fatty liver disease; NIR, not reported; OR, odds ratio; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; ROC, receiver operating characteristics; STARD, STAndards for the Reporting of Diagnostic accuracy studies.

From the [1]Department of Medicine The Johns Hopkins School of Medicine, Baltimore, MD; [2]Department of Medicine, Washington Hospital Center, Washington, DC; [3]Department of Epidemiology, The Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [4]Department of Radiology, The Johns Hopkins University School of Medicine, Baltimore, MD; [5]Welch Center for Prevention, Epidemiology, and Clinical Research, The Johns Hopkins University, Baltimore, MD; [6]Department of Cardiovascular Epidemiology and Population Genetics, National Center for Cardiovascular Research (CNIC), Madrid, Spain

This study was supported by the American Diabetes Association Mentor-Based Postdoctoral Fellowship Program (7-07-MN-08; to R.H. and M.L.), National Institute of Diabetes and Digestive and Kidney Diseases grant 1RO1DK083393-01A1 (to J.M.C.), and K24-DK62222 P60 DK079637 (to F.L.B.).

**These authors contributed equally to this work*

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DOI 10.1002/hep.24452

Potential conflict of interest: Nothing to report.

Additional Supporting Information may be found in the online version of this article.

Clinically Proven

Liver Steatosis Assessment with Hepatorenal Ratio

SUPERSONIC imagine

Significant correlation
was found between HRR and histologic steatosis (r=0.80).
The cutoff for predicting steatosis was 1.24
(sensitivity 92.7%; specificity 92.5%).

An HRI > 1.28
has **100% sensitivity** for predicting a >5% level of fat.

The Hepatic Renal Ratio is the strongest predictor of liver fat content.

Clinically Proven

What the experts are saying

> ***"The hepatorenal index is a simple, reliable, and cost-effective screening tool for identifying patients who should not undergo liver biopsy for evaluation of steatosis."***

Dr. Richard H. Marshall
Assistant Professor of Clinical Radiology
LSU School of Medicine
New Orleans, Louisiana

> ***"The use of the hepatorenal sonographic index facilitates quantification of liver steatosis, even in small degrees, and is not affected by fibrosis or steatohepatitis. It is reproducible and operator-independent and easily can be made available and applicable in routine clinical practice."***

Dr. Muriel Webb
Department of Gastroenterology
Sourasky Medical Center
Tel Aviv, Israel

Advantages of Aixplorer®
Comparison to Fibroscan®

Aixplorer®	FibroScan®	Aixplorer Advantage
One Probe Solution XC6-1 probe works in a broad range of patients	Fails under common conditions of obesity and ascites[1] Requires 3 probes with annual recalibration/replacement[1]	**Superior Workflow** **Fewer Failed Exams**
60 Second Exam Real-time Imaging over a large 2D area As few as 3 acquisitions Qualitative and Quantitative ShearWave™ Analysis Steatosis Assessment with B-mode Ratio Fully validated connectivity options	5-10 Minutes per case Requires minimum of 10 acquisitions Higher technical failure rate due to blind positioning and small target area CAP tool adds add'l $26k cost Limited connectivity	**Higher Patient Throughput** **Lower Cost**
Clinically Proven In HBV, HCV, NAFLD and General Liver Disease and Cirrhosis	Higher Technical Failure Rates Proven lower accuracy	**Clinically Superior Performance and Accuracy**
Higher Reimbursement	Low Reimbursement Annual Calibration Costs	**Increased Return on Investment**

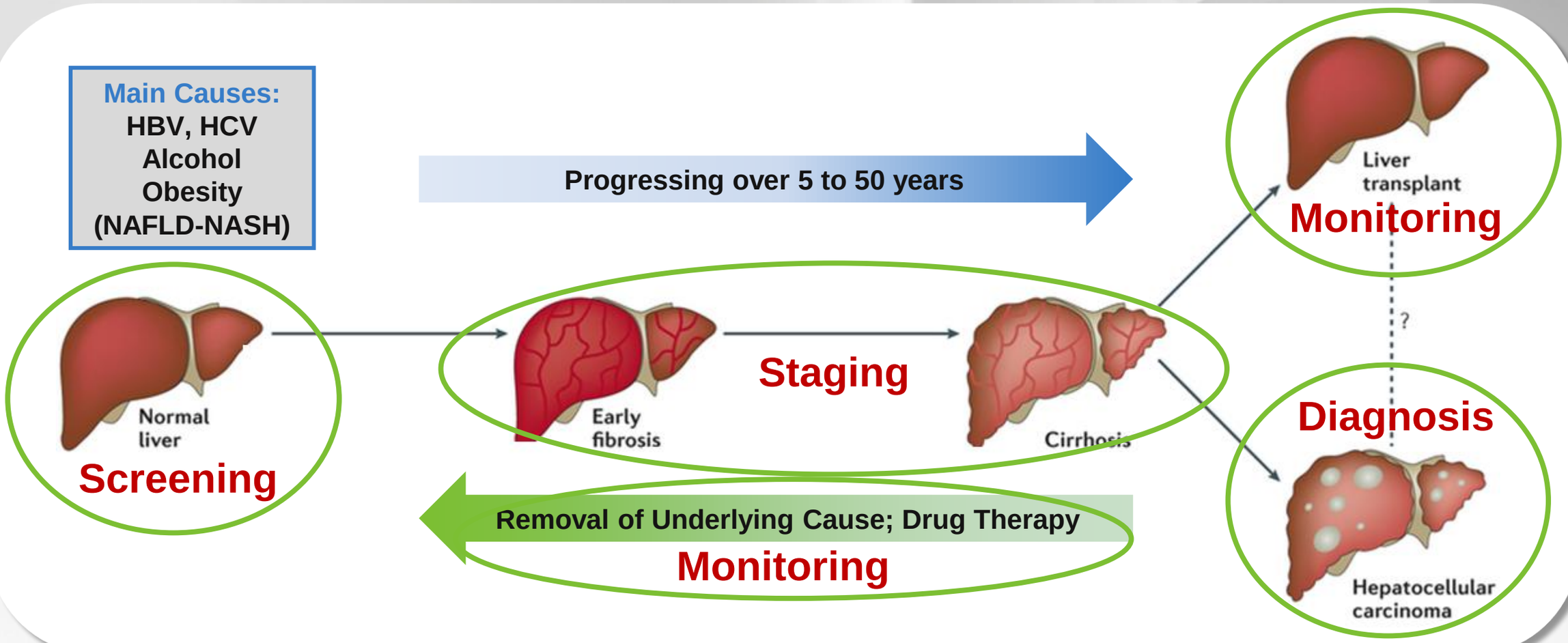
1 Elastography Assessment of Liver Fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement. Radiology: Volume 276: Number 3—September 2015

Clinically Proven
SWE™ - A Solution For All Stages

SuperSonic Imagine's ShearWave™ Elastography provides solutions at ALL stages of liver disease.

Main Causes:
HBV, HCV
Alcohol
Obesity
(NAFLD-NASH)

Progressing over 5 to 50 years



Removal of Underlying Cause; Drug Therapy

Monitoring

Thank you!