Non-Invasive Assessment of Liver Fibrosis

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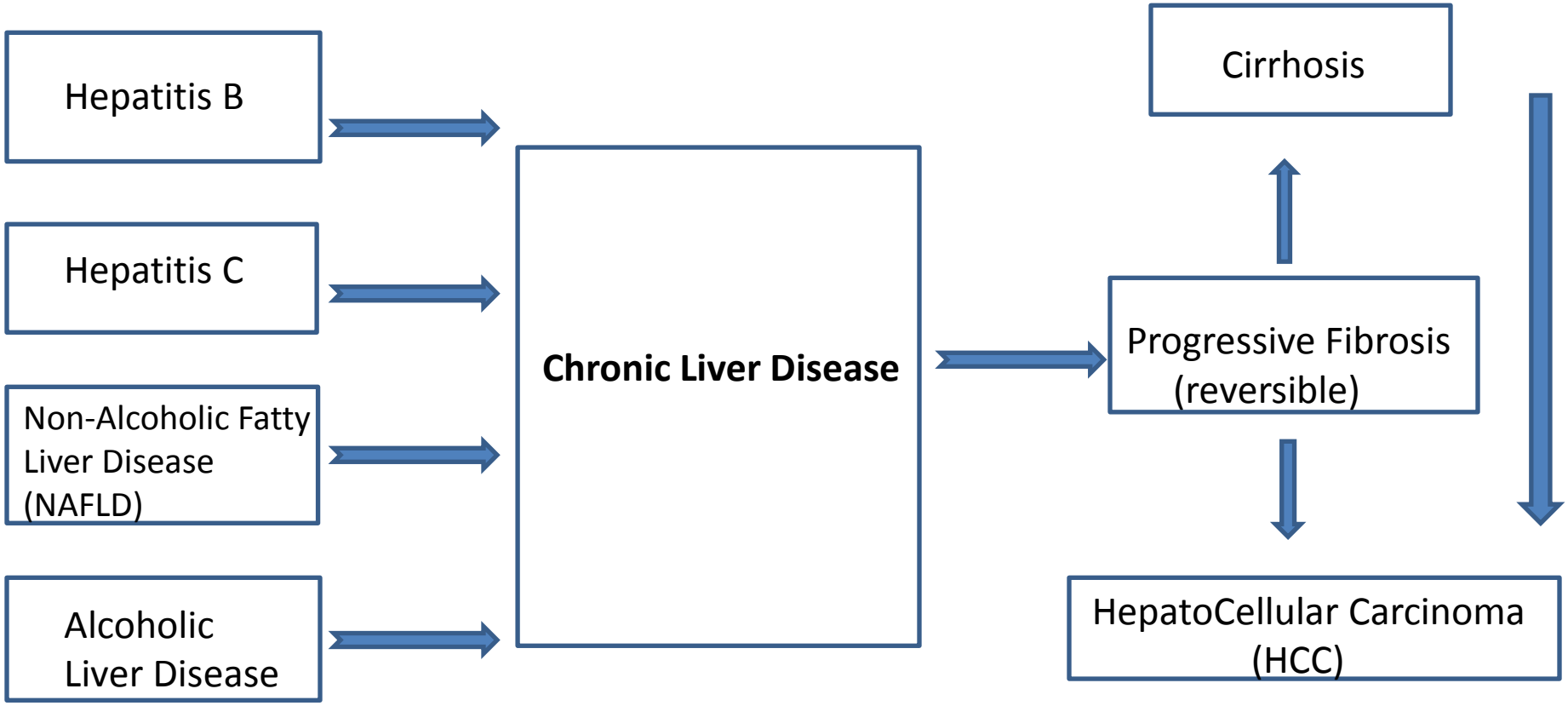
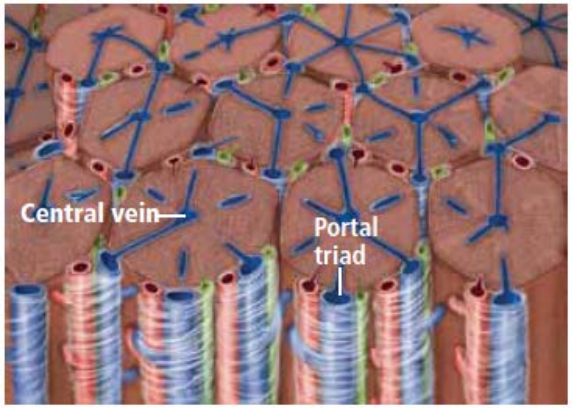
Disclosure

- Patricia Slev has no relevant financial relationships to disclose.

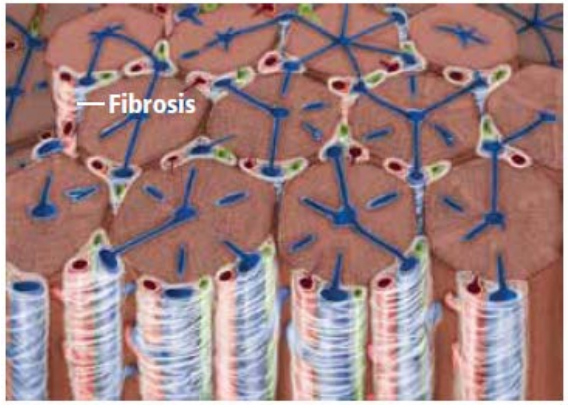
Chronic Liver Disease



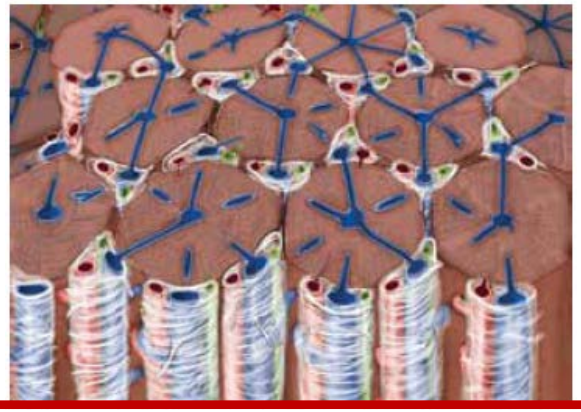
Stages of Fibrosis



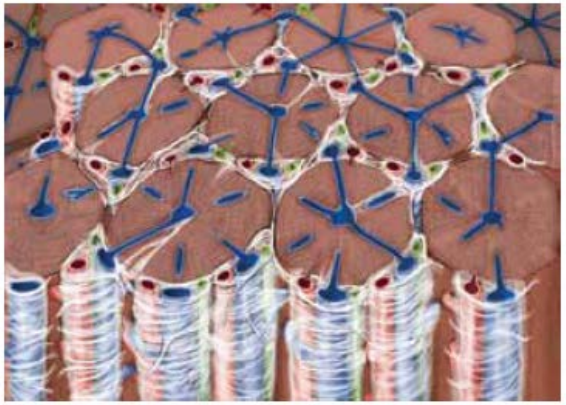
Stage 0 (normal): No fibrosis surrounding portal triads.



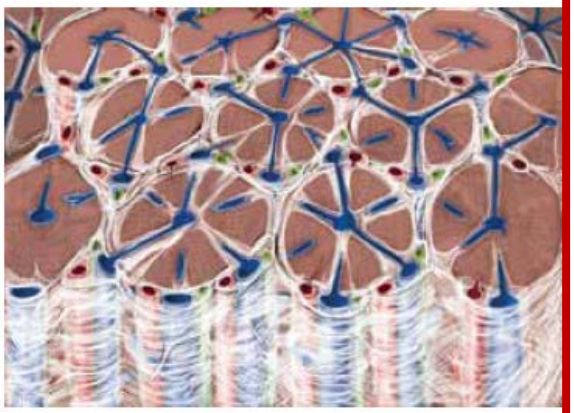
Stage 1 (portal fibrosis): Fibrous connective tissue surrounds portal triads but is limited to those areas.



Stage 2 (periportal fibrosis): Fibers begin to extend into the periportal space but do not connect any portal area to any other.



Stage 3 (septal fibrosis): Fibrous connective tissue now links neighboring portal triads and begins to extend to the central veins and to distort the shape of the lobules.



Stage 4 (cirrhosis): Most portal areas connected by fibrous tissue and some portal areas and central veins connected. Hepatocyte clusters surrounded by fibrous tissue producing sclerotic nodules.

Cleve Clin J Med 2010 77(8):519–527

Liver Biopsy – "The Gold Standard"?

- Invasive
  - Risks include pain, hypotension, bleeding, pneumothorax, infection
  - Contraindicated in certain patient populations

- Sample variation
  - Needle biopsy produces small tissue sample (1/50,000 of liver)
  - Grading/staging accuracy influenced by sample size and location

Differences Between Right and Left Lobes	Number of Patients	% of Total
Identical grade	94	75.8
Different grade (total)	30	24.2
Difference of one grade	28	22.6
Difference of two grades	2	1.6
Grade 1–2 in one lobe *vs* 3–4 in the other	5	4.0

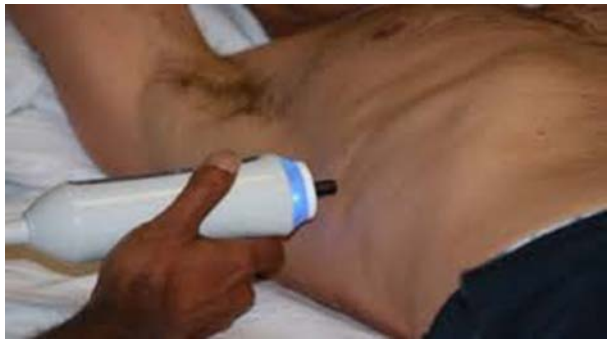
Differences Between Right and Left Lobes	Number of Patients	% of Total
Identical stage	83	66.9
Different stage (total)	41	33.1
Difference of one stage	38	30.6
Difference of two stages	3	2.4
Stage 0–2 in one lobe *vs* 3–4 in the other	12	9.7

Am J Gastroenterol 2002 97(10):2614–2618

- Intraobserver variation
  - Accuracy of biopsy interpretation influenced by pathologist experience

Non-Invasive Tests for Assessment

- Useful in patients who cannot undergo biopsy
- Can limit the number of biopsies performed
- Can be used to serially monitor disease progression
- Imaging
  - Ultrasonography
  - Computed tomography
  - Transient elastography



- Non-invasive markers (NIMs)

direct - fragments of liver matrix components produced by hepatic stellate cells during remodeling

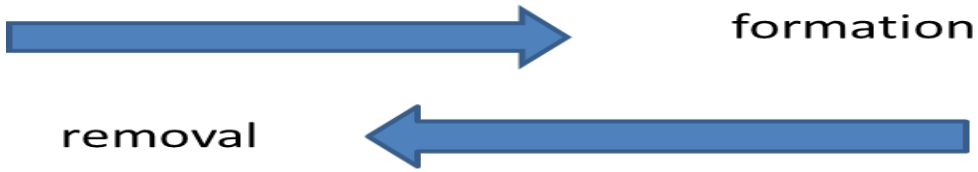
indirect – markers present in increased concentration due to inflammation or impaired liver function

Biopsy vs. Non-invasive Test Comparison

	Liver biopsy	Non-invasive test
Advantages	Direct; semi-quantitative; evaluation of co-existing pathologies	Measurement of global fibrosis; suitable for serial observations
Limitations	Sampling error; intra-observer variability; possible hospitalization	Indirect
Risks	Pain; bleeding; pneumothorax; hemothorax; infection	None
Cost	Expensive	Varies but usually less than biopsy
Contraindications	Uncooperative patient; severe coagulopathy; extrahepatic biliary obstruction; ascites; morbid obesity	Non-hepatic influences on biomarkers (hemolysis, Gilbert's syndrome; thrombocytopenia, etc.)

Direct Tests

- Tests not routinely performed in clinical lab



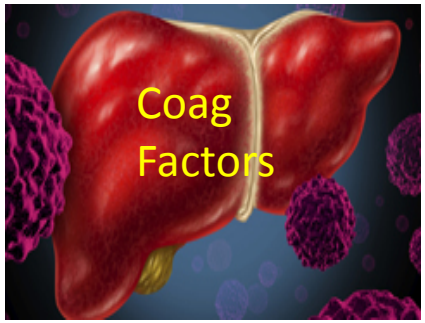
ECM Remodeling

Category	Examples
ECM enzymes	• Prolyl-hydroxylase • Lysyl-oxidase • Collagen peptidase
Fragments of collagen degradation	• Procollagen type I, type III , IV and VI
Glycoproteins & MMPs	• Laminin • MMP-2 • Vitronectin • ICAM • VCAM • TIMP-1 and TIMP-2
Glycosaminoglycans	• Hyaluronic acid
Cytokines	• TGF-β

Indirect Tests

- Markers that reflect the functional alterations of the liver
  - impairment
  - inflamation
- Tests commonly performed in clinical lab (some exceptions)

Test name	Constituents	
FibroSure/FibroTest (HCV/ASH/NASH)	• GGT • ALT • α2 macroglobulin • Bilirubin	• Haptoglobin • Apo A1
FibroMeter (viral/ALD/NAFLD)	• GGT • ALT • α2 macroglobulin • Platelet count • PT index • AST	• Hyaluronic acid • Ferritin • Glucose • Urea



Fibrosure & Fibrometer Components

FibroSure Test	Age	Gender	Height	Weight	α2-macroglobulin	Haptoglobin	Apo A1	Bilirubin	GGT	ALT	AST	Cholesterol	Triglyceride	Glucose
HCV	✔	✔			✔	✔	✔	✔	✔	✔				
ASH & NASH	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

FibroMeter	Age	Gender	Weight	α2 macro	Hyaluronic acid	PT Index	Platelets	AST	Urea	GGT	ALT	Ferritin	Glucose
Viral	✔	✔		✔		✔	✔	✔	✔	✔	✔		
ALD	✔	✔		✔	✔	✔							
NAFLD	✔	✔	✔				✔	✔			✔	✔	✔

Fibrometer

- Fibrometer is comparable to Fibrosure and provides a fibrosis/cirrhosis score, and a necroinflammatory activity score, and the Metavir classification F0-F4 for fibrosis/cirrhosis and activity grade A0-A3

- Developed at the University of Angers (France) and first described in 1997
  - 2nd generation test in 2005
  - 3rd generation test in 2010

- Available only in Europe and now in the US
  - Lab performs the tests and send results to Echosens for score calculation

- Results evaluated by an "expert system" to detect discordant results of component tests
  - Eliminates analyte from algorithm to correct possible false-positive/negative results

Example Chart

Liver Fibrosis, Chronic Viral Hepatitis (Echosens FibroMeter)

ARUP Accession number: [redacted]
Patient: Fibrometer, Male50years
Date of birth: 01/01/1964
Age: 50
Gender: M

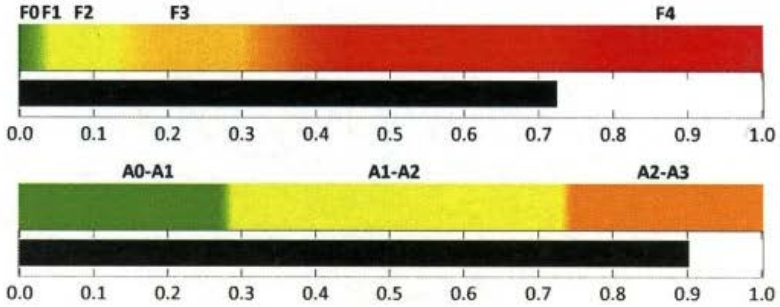
Collection date: 04/23/2014
Received in lab: 04/23/2014
Completion date: 04/23/2014

ARUP Test Code: 2005661

Physician: ARUP
Client ID: 4070
Client:
ARUP Physician Services
321 TESTING ANSR EXTRACT
Salt Lake City, NY 84108

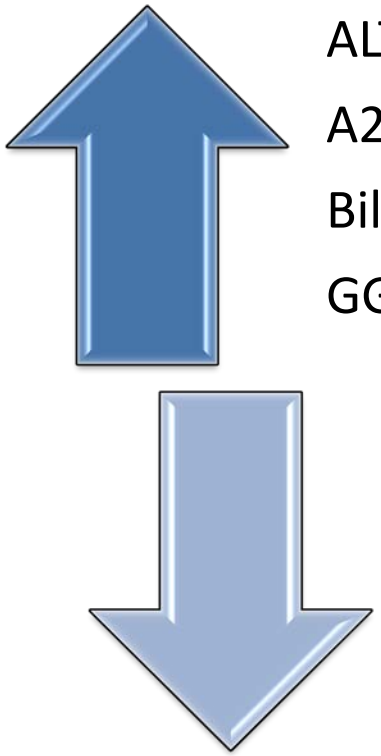
	Patient Score (Range 0 -1)	Metavir Classification[1]
FibroMeter (fibrosis score)	**0.98***	**F4[F3-F4]**
	Predominance of F4, but F3 is possible	
CirrhoMeter (cirrhosis score)	**0.72***	**F4[F3-F4]**
	Predominance of F4, but F3 is possible	
InflaMeter (activity score)	**0.90**	**A2/A3**
	Equal probability between A2 and A3	

FibroMeter scale not displayed since CirrhoMeter is the most accurate fibrosis stage score for this individual.



* FibroMeter and CirrhoMeter scores modified by the rules-based algorithm.

Fibrosure Limitations



ALT

A2-macroglobulin

Bilirubin

GGT

Apo A1

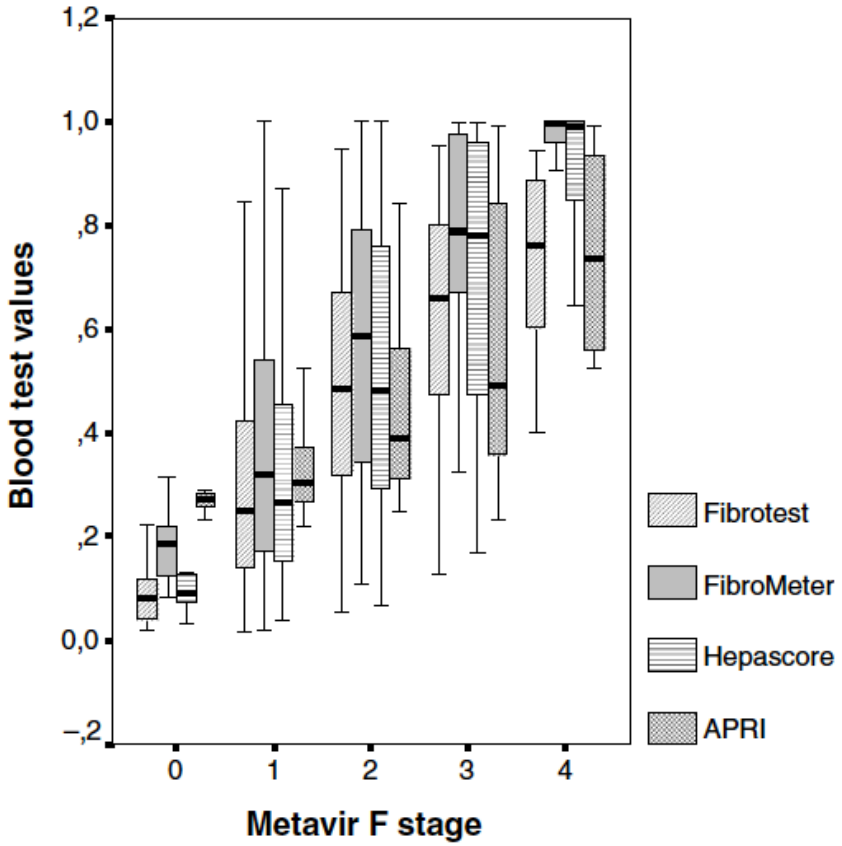
Haptoglobin

- False positive results
  - Hemolysis
    - Decreased haptoglobin
    - Ribavirin therapy for HCV
  - Extrahepatic cholestasis; Gilbert's syndrome
    - Increased bilirubin
  - Inflammation
    - Increased α2-macroglobulin
  - Acute hepatitis
- False negative results
  - Inflammation
    - Increased haptoglobin

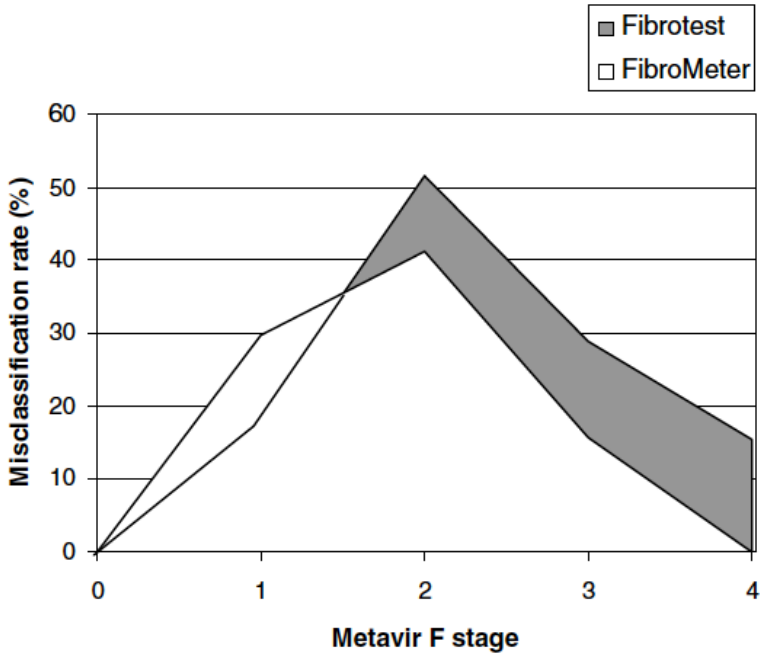
Fibrometer & Fibrosure Comparison

	Fibrometer	Fibrosure
AUROC		
≥F2	0.85-0.89	0.74-0.87
F4	0.91	0.71-0.87
Sensitivity (%)		
F≥2	80.5-89.0	65-77
F4	94.1	50-87
Specificity (%)		
≥F2	84.1-89.9	72-91
F4	87.6	70-92.9
Positive Predictive Value (%)		
≥F2	82-86.3	76-80
F4	68	57.9-93
Negative Predictive Value (%)		
≥F2	77.6-82.5	66.71-81
F4	94.7	44-90.5

Fibrometer vs Fibrotest(sure)



- Tests that include HA (FM and HS) had highest likelihood ratios and narrower score ranges for stages F3 and F4

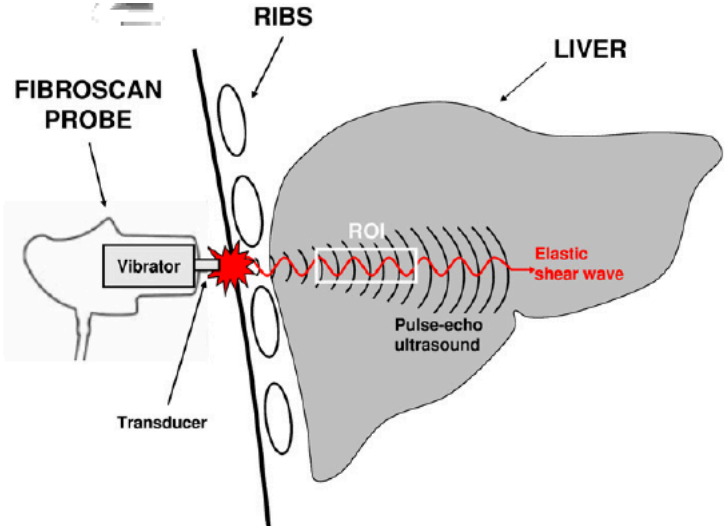


- FT better than FM at stage F1 (19 vs. 30% misclassification rate)
- FM better than FT at all other stages, particularly F4

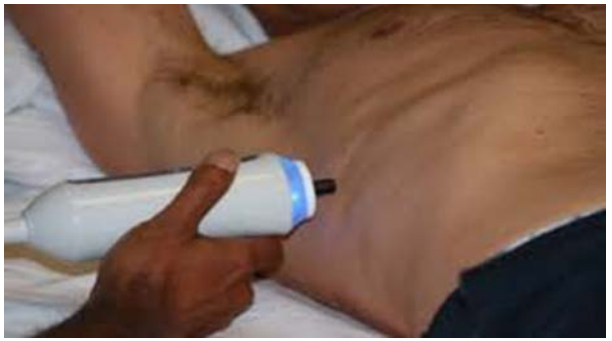
J Hepatol 2007 46(3):395-402

Transient Elastography

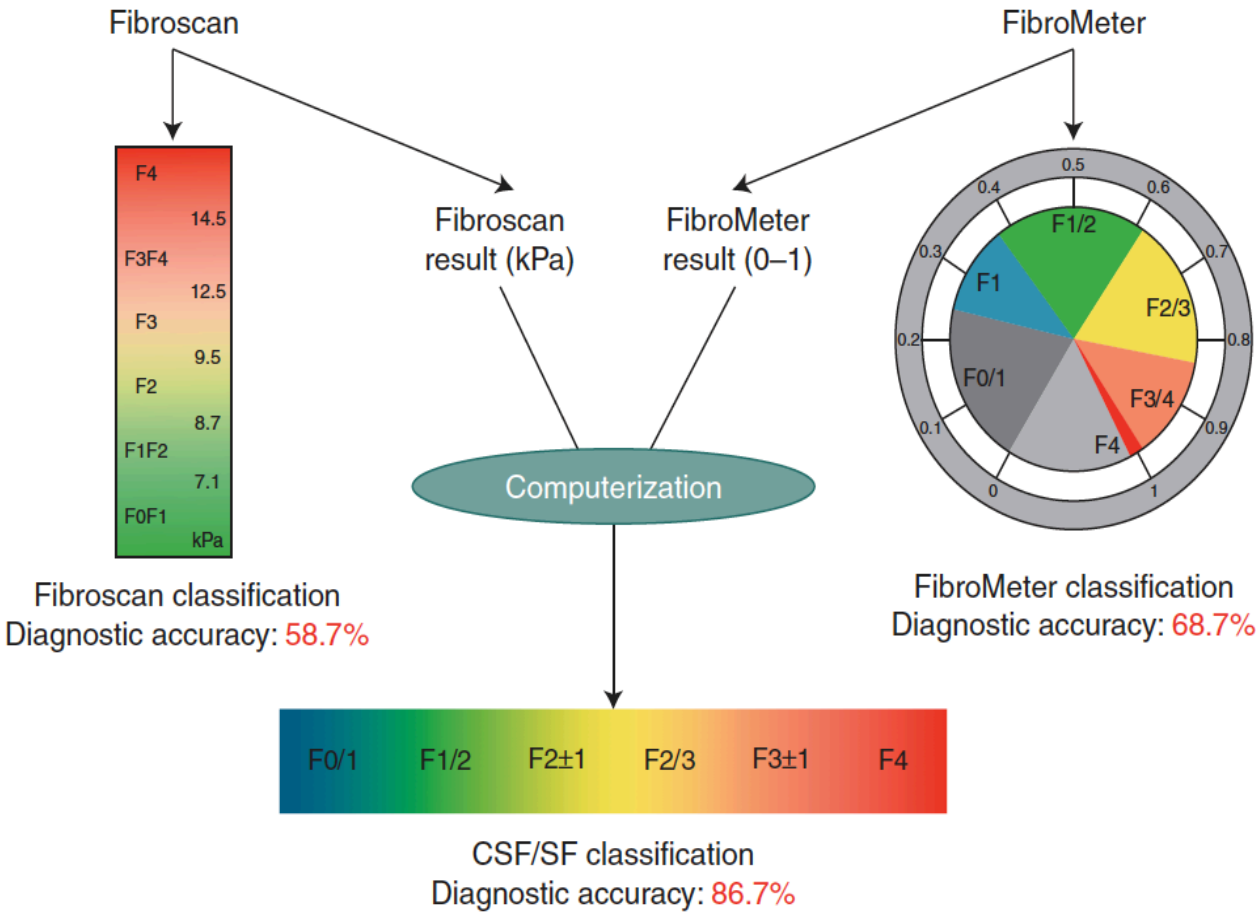
- Ultrasound-based measurement of liver stiffness
- Transducer probe mounted on axis of a vibrator
- Vibrator induces an elastic shear wave that propagates through underlying tissue



- Pulse-echo ultrasound measures velocity of shear wave which is directly related to tissue stiffness
- The stiffer the tissue, the faster the shear wave propagates
- Patented device marketed as FibroScan (Echosens, Paris, France)
- FDA-cleared
- Best for diagnosis of cirrhosis
- Difficult in obese patients



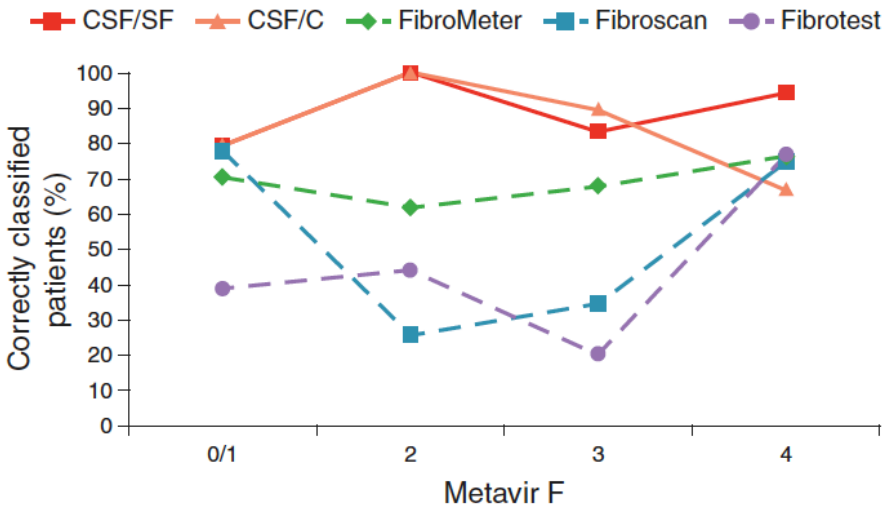
Combining Non-Invasive Tests for Improved Accuracy



Am J Gastroenterol 2011 106(7):1255-1263

Combining Non-Invasive Tests for Improved Accuracy

Diagnosis	Test	AUROC
Significant fibrosis (≥F2)	FibroScan	0.791
	FibroMeter	0.813
	CSF-index	0.846
Severe fibrosis (≥F3)	FibroScan	0.847
	FibroMeter	0.829
	SF-index	0.875
Cirrhosis (F4)	FibroScan	0.905
	FibroMeter	0.861
	C-index	0.921



- Combined tests (indexes) performed better than individual components

Am J Gastroenterol 2011 106(7):1255-1263

HCV Management Guidelines

- AASLD/IDSA guidance[1]
  - Most efficient strategy combines serum biomarkers and transient liver elastography[2]
  - Consider biopsy for any patient with discordant results between 2 testing methods if the information will affect clinical decisions

1. AASLD/IDSA HCV Management Guidance. October 2014.
2. Boursier J, et al. Hepatology. 2012;55:58-67.

Summary

- Liver biopsy is the cornerstone of managing patients with chronic liver disease and remains the reference method for assessing liver fibrosis
- Non-invasive biomarker panels do not have sufficient accuracy to replace biopsy
- Non-invasive biomarker assays combined with transient elastography provides increased accuracy
- Algorithms that combine two or more serum biomarker assays or biomarker assay and transient elastography can be used to provide enough accuracy for staging liver fibrosis and significantly reduce the number of biopsies needed

Acknowledgements

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