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Noninvasive Measurement of Fibrosis

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December 2017

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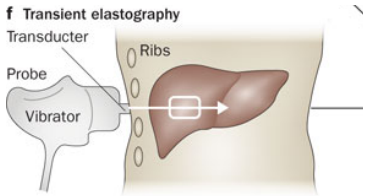
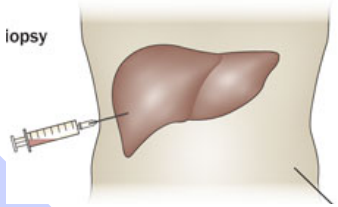
Noninvasive Measurement of Fibrosis

TOOLS TO DIAGNOSE CIRRHOSIS

Toolbox to diagnose cirrhosis (2017)





History and physical

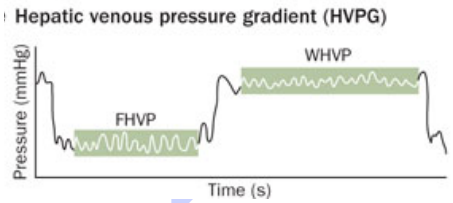
Serum biological

Imaging physical

HVPG

Biopsy

R.I.P
1700-1995

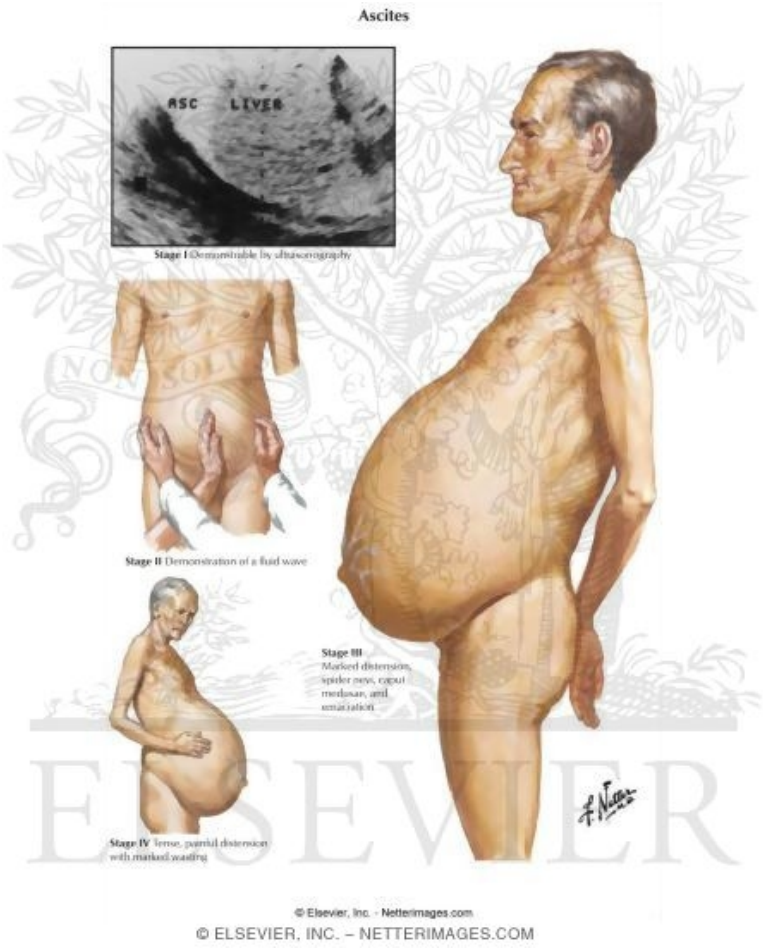


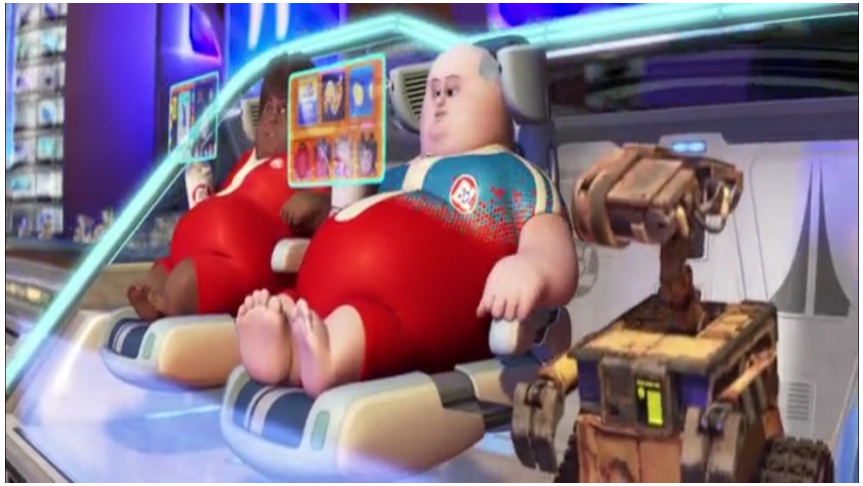
Invasive
Availability

Sampling?
Interobserver variability?
Gold standard?
Morbidity?

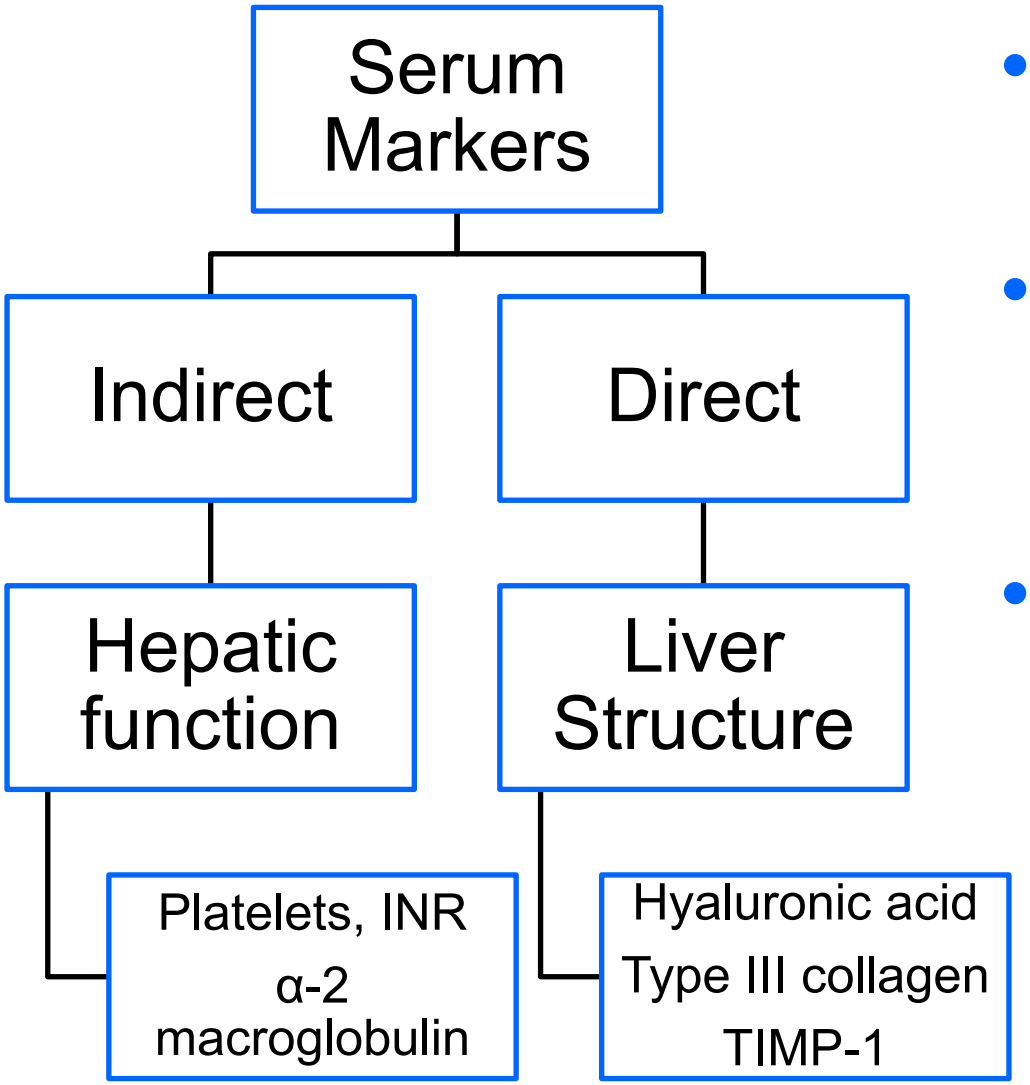
Friedman Nat. Rev. Gastroenterol. Hepatol 2010

The cirrhotic patient: A new face





Serum Markers



- **Scores**
  - E.g. APRI
- **Patented panels and modeling**
  - E.g. FibroTest
- **Combination of pt characteristics and markers**
  - E.g. FIB-4

Selected serum markers: Advanced Fibrosis in HCV

NON SPECIFIC	Components	AUROC
Indirect		
FIB-4	platelet, ast, alt, age	0.8
APRI	platelet, ast	0.85
FibroTest	age, sex, alpha-2 macroglobulin, alpha-2-globuin, gammaglobulin, apoA1, GGT, total bilirubin	0.81-0.9
Forns	7.811 - 3.131 x ln(platelet count) + 0.781 x ln (GGT) + 3.467 x ln (age) - 0.014 x (cholesterol)	0.8
Platelets		
Direct		
ELF	hyaluronic acid, TIMP-1, type III collagen	0.93

Clinical Application: Serum Markers

HCV: 61 y.o. man ast 120 and plt 50

- APRI (cutoff <0.5 and >1.5)

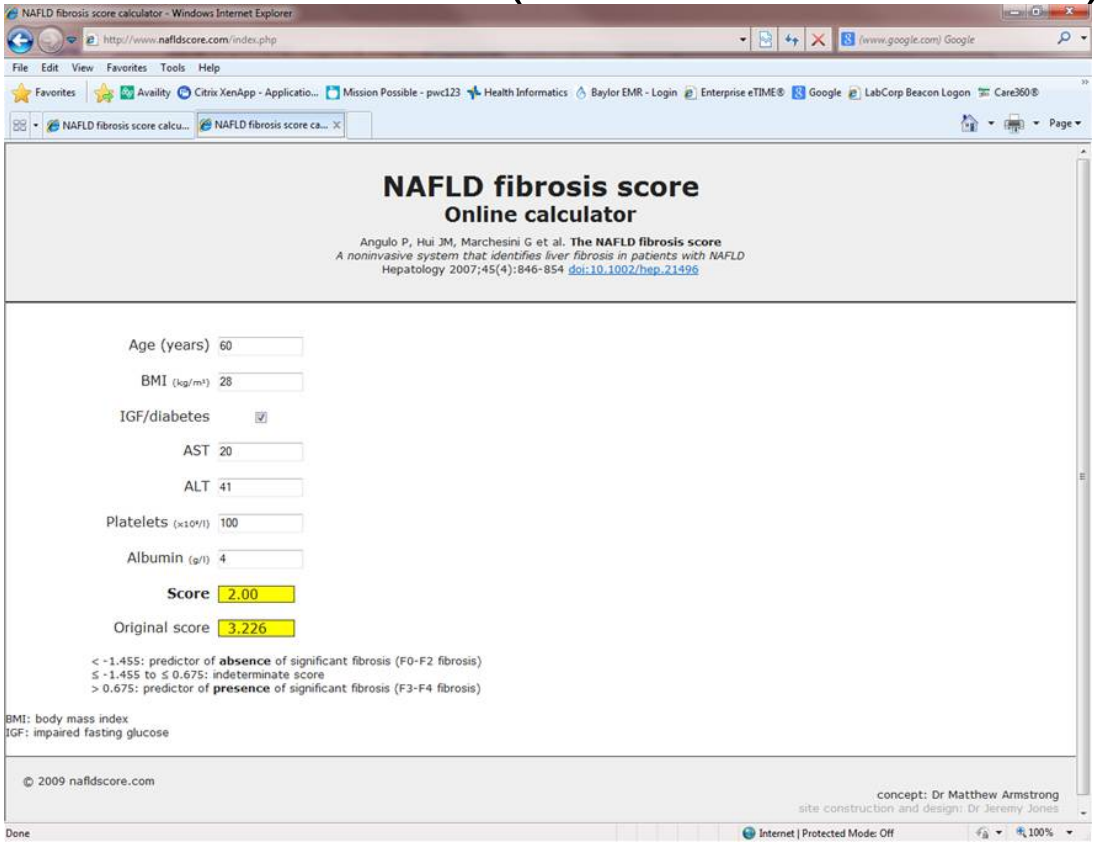
$$\frac{\text{AST/AST (ULN) x 100}}{\text{Plt}}$$

$$\frac{\text{120/40x 100}}{\text{50}} = 6$$

Clinical Application: Serum Markers

NAFLD

- NAFLD Fibrosis score (<-1.455 and >0.676)

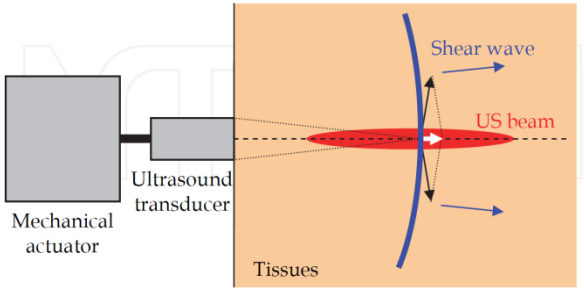


Serum Tests

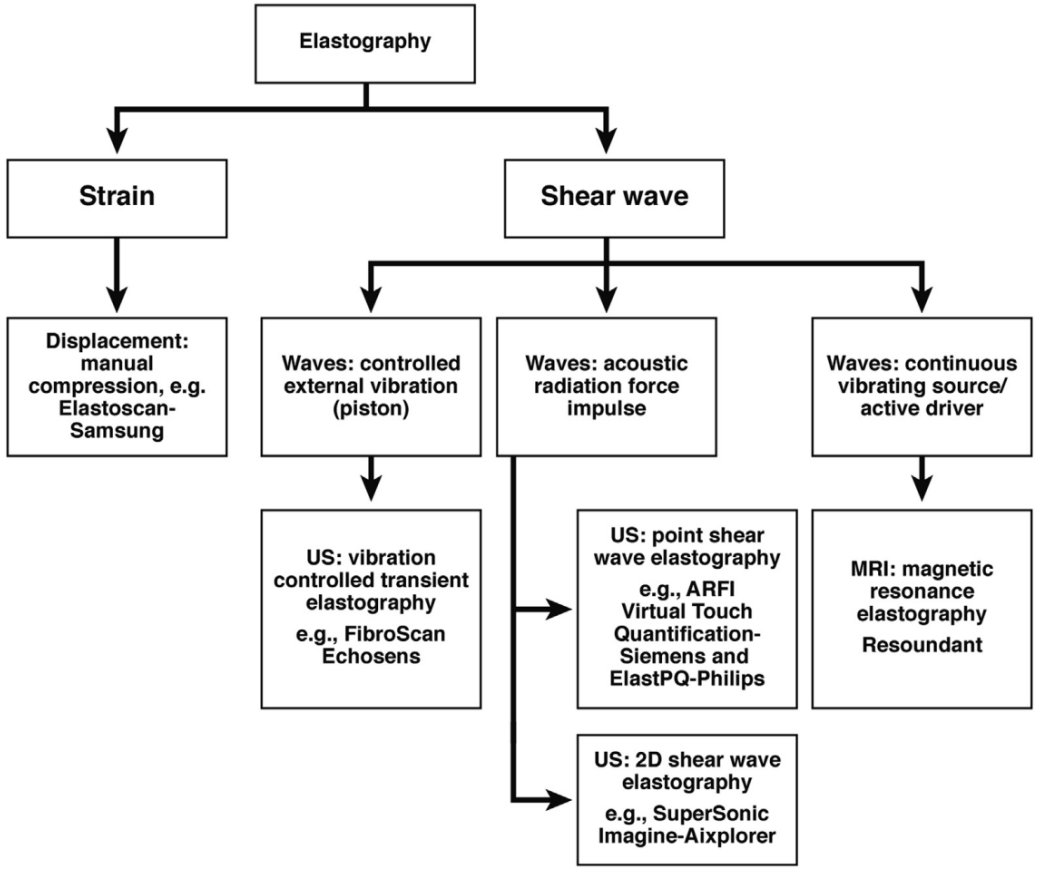
- AUROC F4: 0.74-0.87
- CC 35-82% (EASL guidelines)
- Usually high negative predictive value for relevant cutoffs
  - Identify who does NOT have advanced fibrosis
- No single test in isolation
- Benefits: repeat, noninvasive, accessible, combine with other modalities

Castera et al. Gastro 2005
Cassinotto et al. J Hep 2014

Elastography

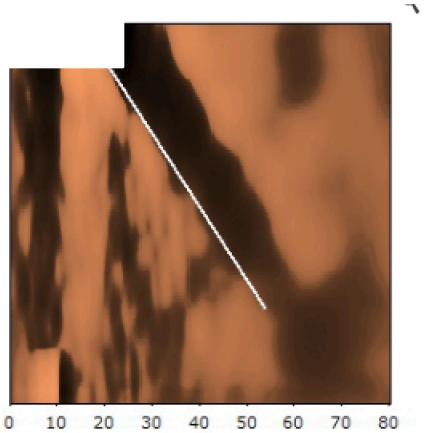


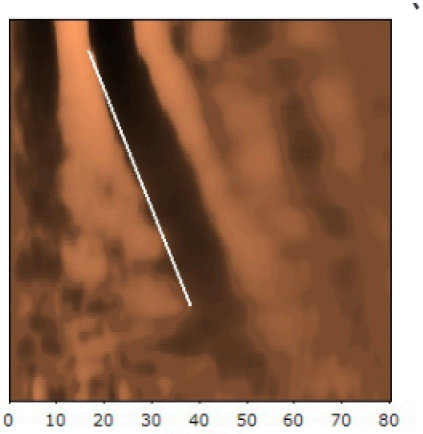
- Non-invasive measure of liver stiffness
- Physical property: between a rock and a soft place
- Velocity (m/s→kilopascals,kPa) of an elastic shear wave (picture) propagating through liver
  - stiffer the tissue the faster the progression

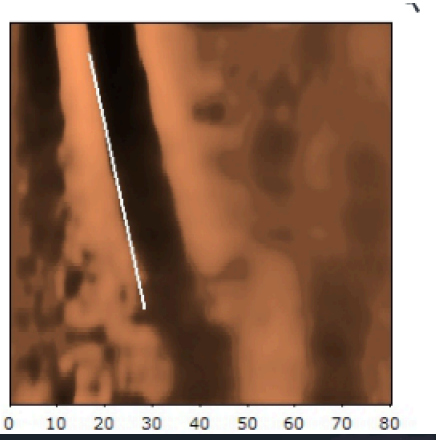


Asrani CGH 2015

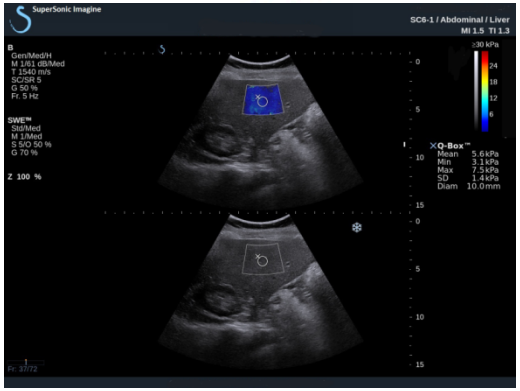
VCTE

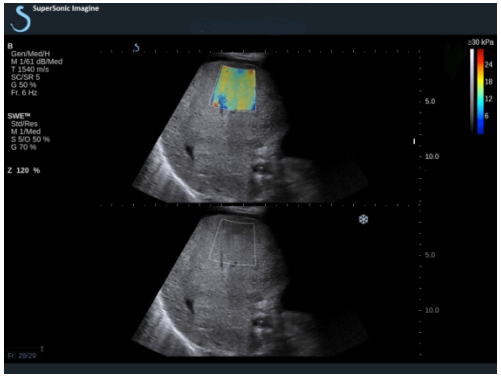


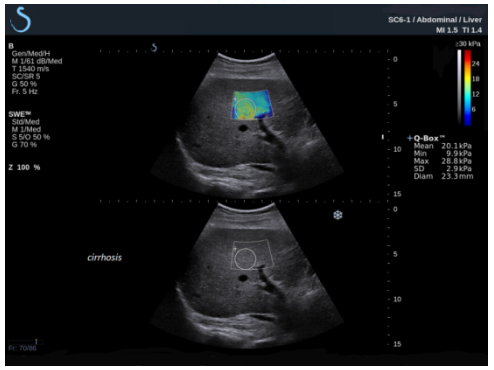




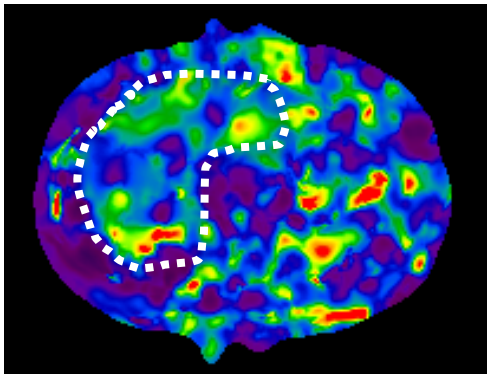
2D SWE

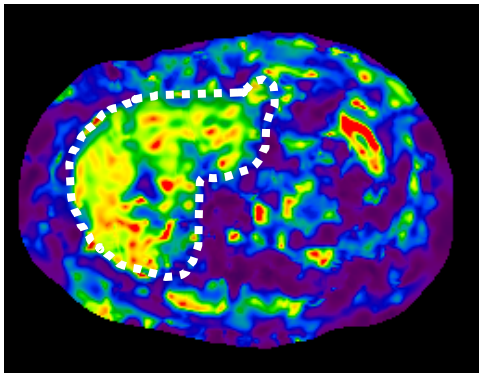


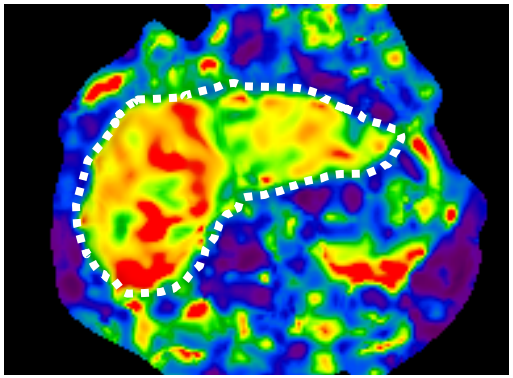




MRE





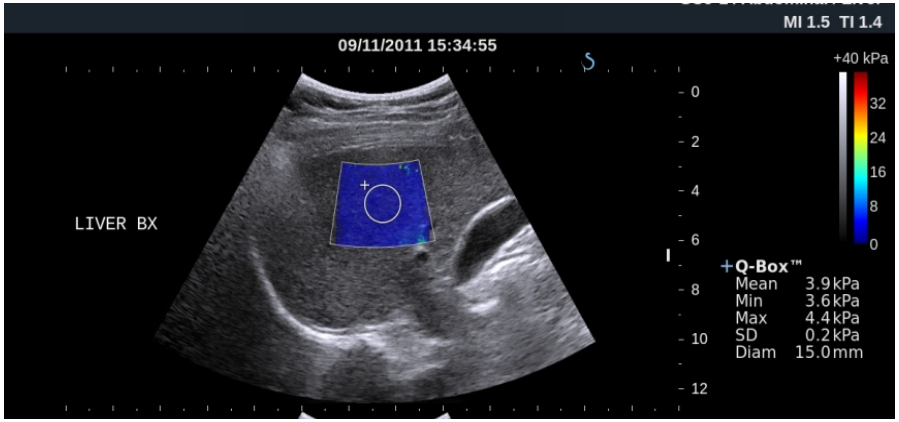


None/Minimal Fibrosis

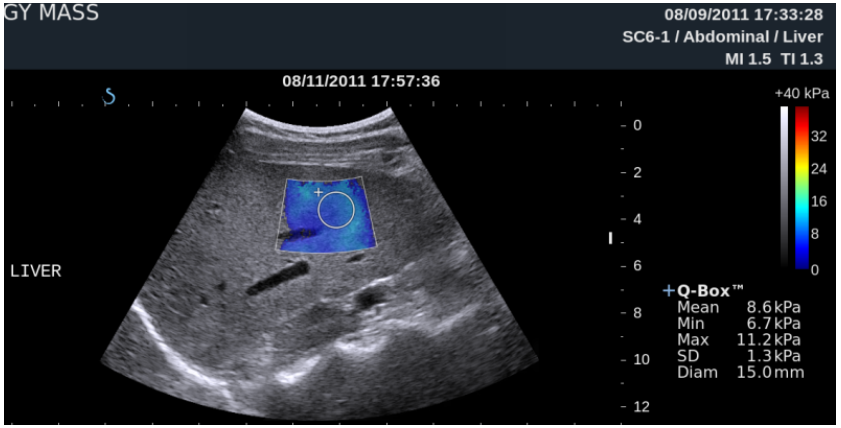
Advanced Fibrosis

Cirrhosis

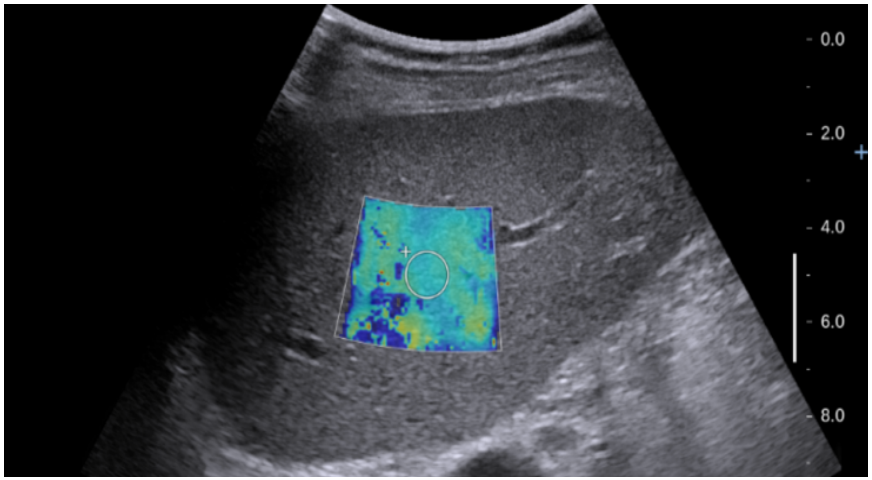
ShearWave



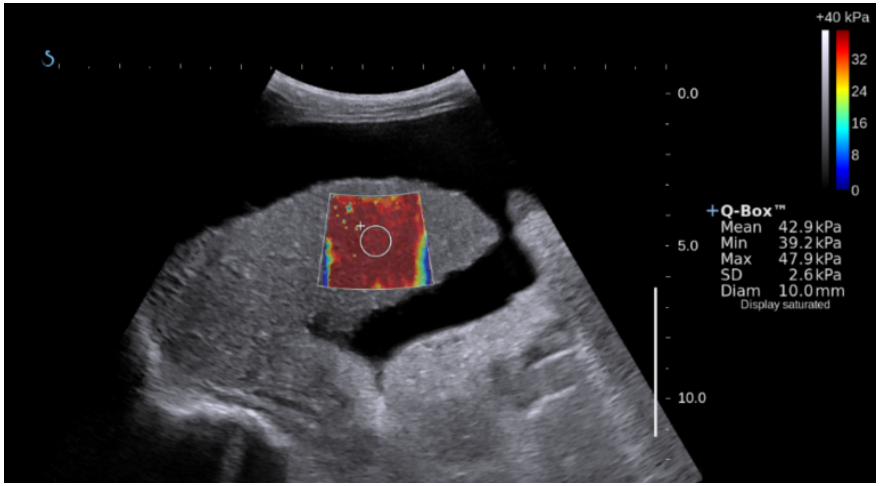
F0



F2



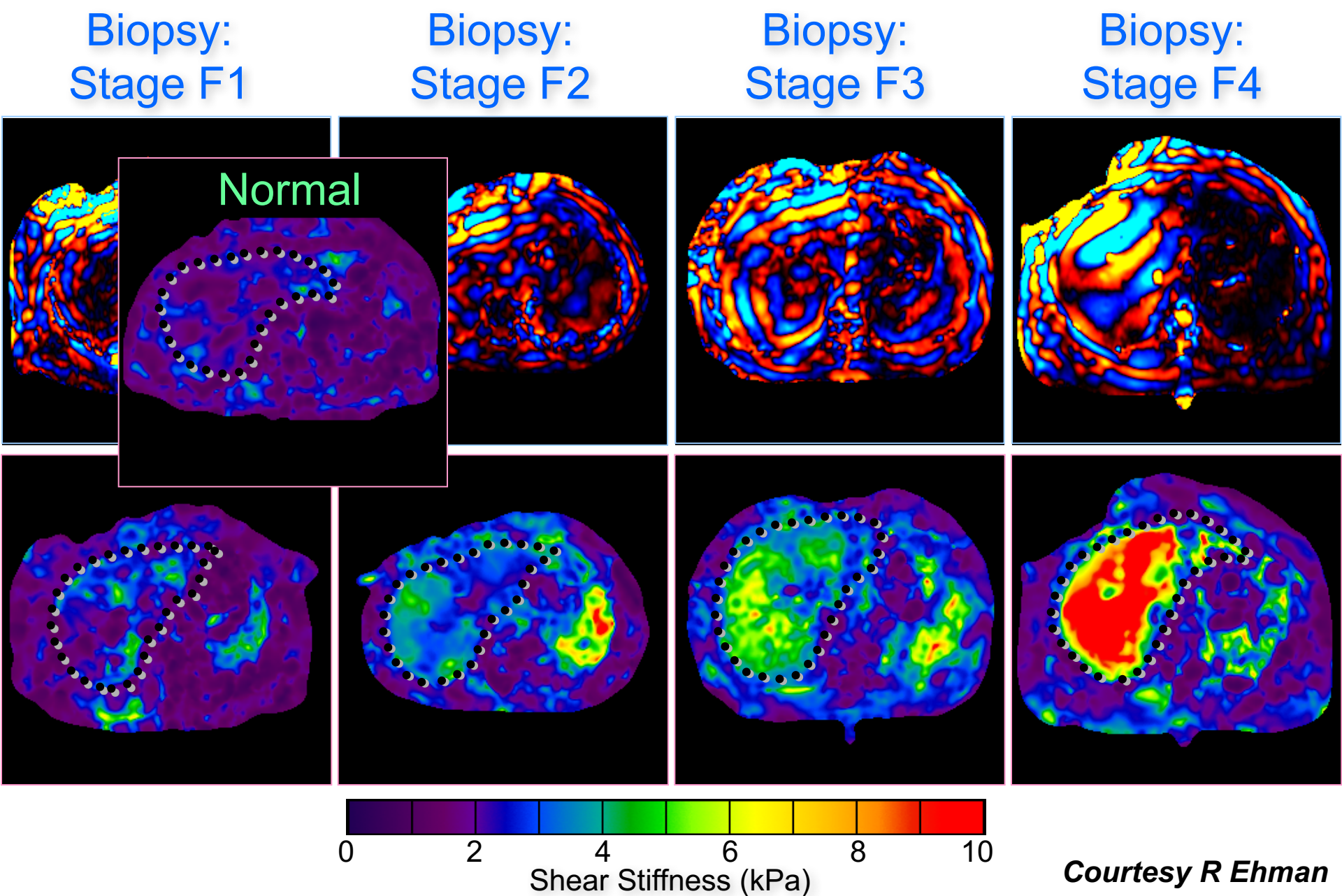
F3



F4

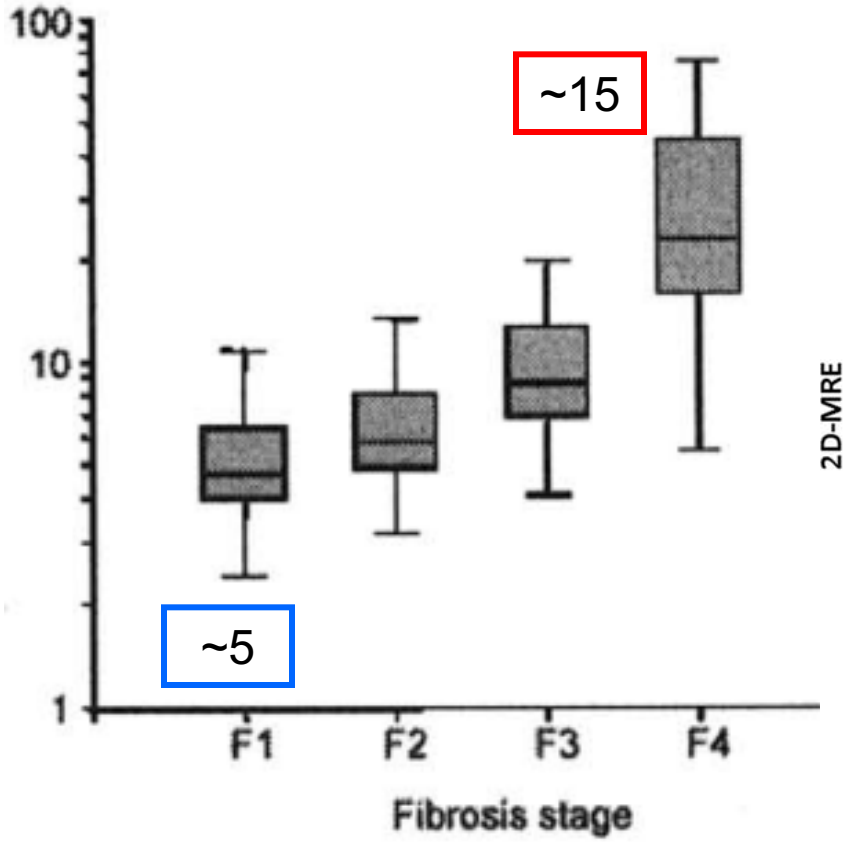
Trotter Liver Lab, Angela Solis

MAYO CLINIC

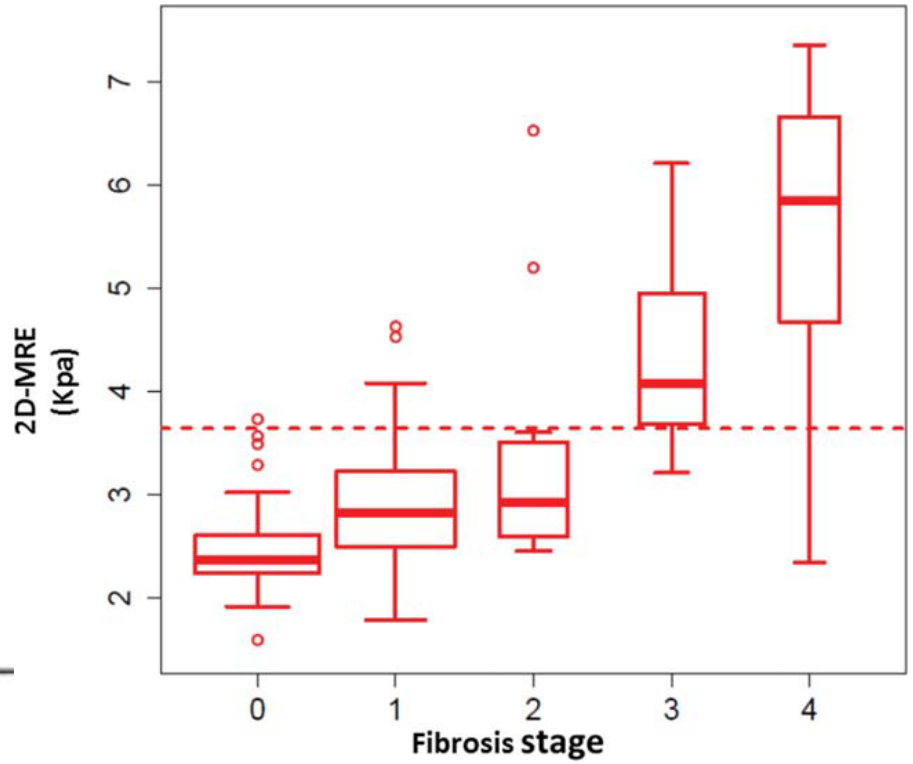


Courtesy R Ehman

Elastography and stage of fibrosis



TE/Fibroscan



MRE

Castera Gastroenterology 2005
Loomba et al. Hep 2014

Summary of Meta-analyses

	F4**		
	AUROC	**Sen**	**Spe**
TE	0.93	83-87 0.95#	87-89 0.71#
ARFI	0.92	88-89	83-87
MRE	0.92-0.97	91-93	92-96
SWE	0.93-0.95		

**variable cutoffs

Cochrane summary for ALD patients

Pavlov et al APT 2016
Tsotchatzis J Hep 2011
Wang Hepatology 2012
Bota Liver Int 2013
Nierhoff Eur Radiol2013
Guo Abd imaging 2014
Singh CGH 2015
Hermann et al Hepatology 2017

NAFLD

	Cutoff	Sens	Spec	PPV	NPV	AUC
Serum						
APRI	0.54-2	56	84	34	92	0.75
FIB-4	1.92-2.48	76	82	39	96	**0.85**
BARD	3	52	84	39	96	0.7
NFS	-0.014	80	81	43	96	**0.83**
Imaging						
VCTE M	13.4-22.3	78	91	60	95	**0.92**
VCTE XL	7.2-16	88	82	40	98	**0.94**
SWE	3.36	100	86	55	100	**0.97***
MRE	4.15-6.7	87	93	53	99	**0.92**

Prevalence across 64 studies for cirrhosis was 9.4% (General population: 1%?)

NFS and FIB-4 best

Xiao et al Hepatol 2017

Noninvasive Measurement of Fibrosis

HOW ACCURATE IS THE DIAGNOSIS OF CIRRHOSIS

Determinants of accurate diagnosis

- Gold standard
- Performance characteristics of test
- Context and population of interest
- Test related nuances

1: Liver biopsy as an imperfect gold standard

- Misclassification of stages
  - 25%
- Patchy fibrosis
- Interoberver variability
- Biopsy size matters

2: Bias, cutoffs and probabilities

- Spectrum bias: Variability in underlying prevalence of cirrhosis leads to variation in AUROC (1% versus 10%)
- Are there hard cutoffs?
  - Active NASH versus burnt out NASH
  - Alcohol versus non alcohol
- Pre test probability of cirrhosis
- How often are patients correctly classified?
- How many fall in intermediate ranges

Beyond AUROC/S/S: If the pre-test probability is 50%

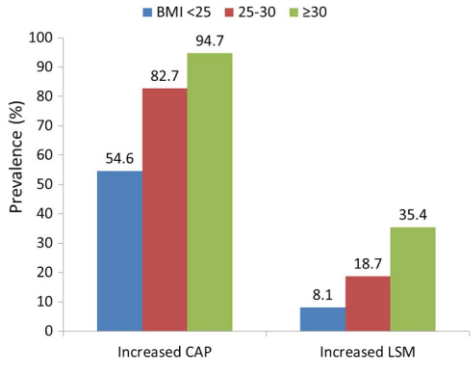
Test	Primary population	Post test Probability NEGATIVE test	Post test Probability POSITIVE TEST
Serum			
APRI	HCV	37%	84%
FIB-4	HBV HCV	39%	95%
Imaging			
VCTE	HBV HCV NAFLD Choles	5-15%	83-99%
MRE	NAFLD, All	9-24%	83-91%

3: Context matters

- Serum markers
  - Low platelets driven by something else
  - Active inflammation (alc hep)
  - Elevated Biluribin (Gilbert's)
- Imaging
  - Active inflammation
  - Skin to capsule distance

Drivers of elevated stiffness

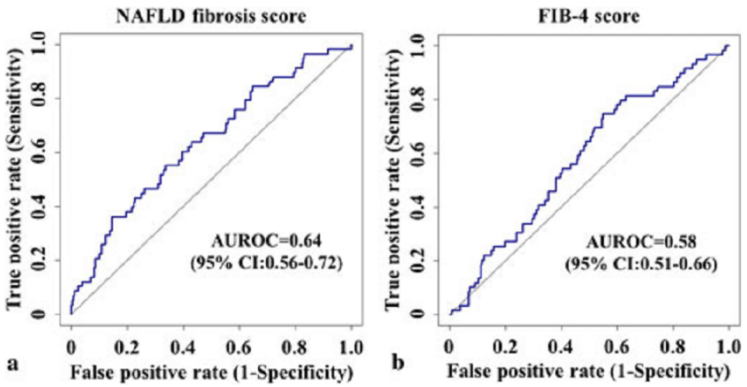
TE	Elevated Stiffness (OR)
Age/10yrs no DM	2.4
Spleen	1.2
Steatosis and DM	2-5.2
HBV/HCVAb	5.4
ALT/ 10	1.2
Smoking	1.8



Kwok et al Gut 2016
Koehler/Plompen et al. Hepatology 2016

Performance in other populations variable

- Prevalence of cirrhosis
- Patient comorbidities

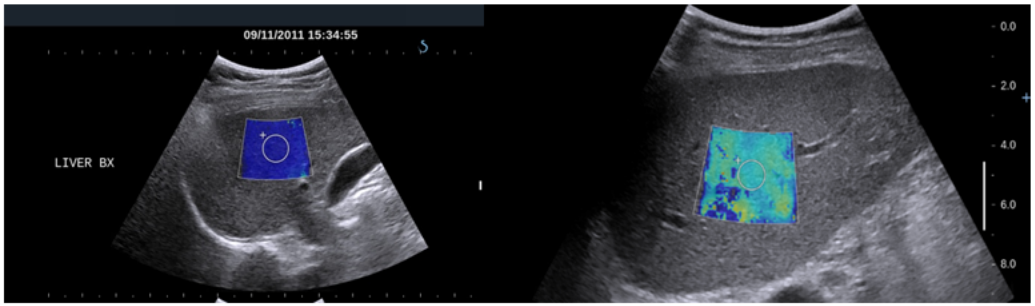


Accuracy in selected populations

- CHF
- Methotrexate
- Post transplant
- KTA in patients with liver disease

Patients with heart failure

- Initial LS was markedly elevated in patients with ADHF, median 15 kPa (9.5-47.1).



Normal Liver

Stiff Liver

Ledoux et al. HFSA 2017

Caveat: “Resolution of cirrhosis”

- What is a meaningful improvement
- Reduction in static or dynamic component
- High falase negative of non invasive testing, hence continue HCC surveillance

4. Diagnostic test matters

- Cutoffs
  - Probes and device
  - Patient population
  - m/s→ kPa
  - Location and interpretation
- Lack of standard definitions for reliability

Failure Rates and Unreliable examinations

Technique	Unreliable	Failure Rate
TE	12-18%	3-6%
ARFI	?	2%
2d SWE	?	4%
MRE	?	4.3%

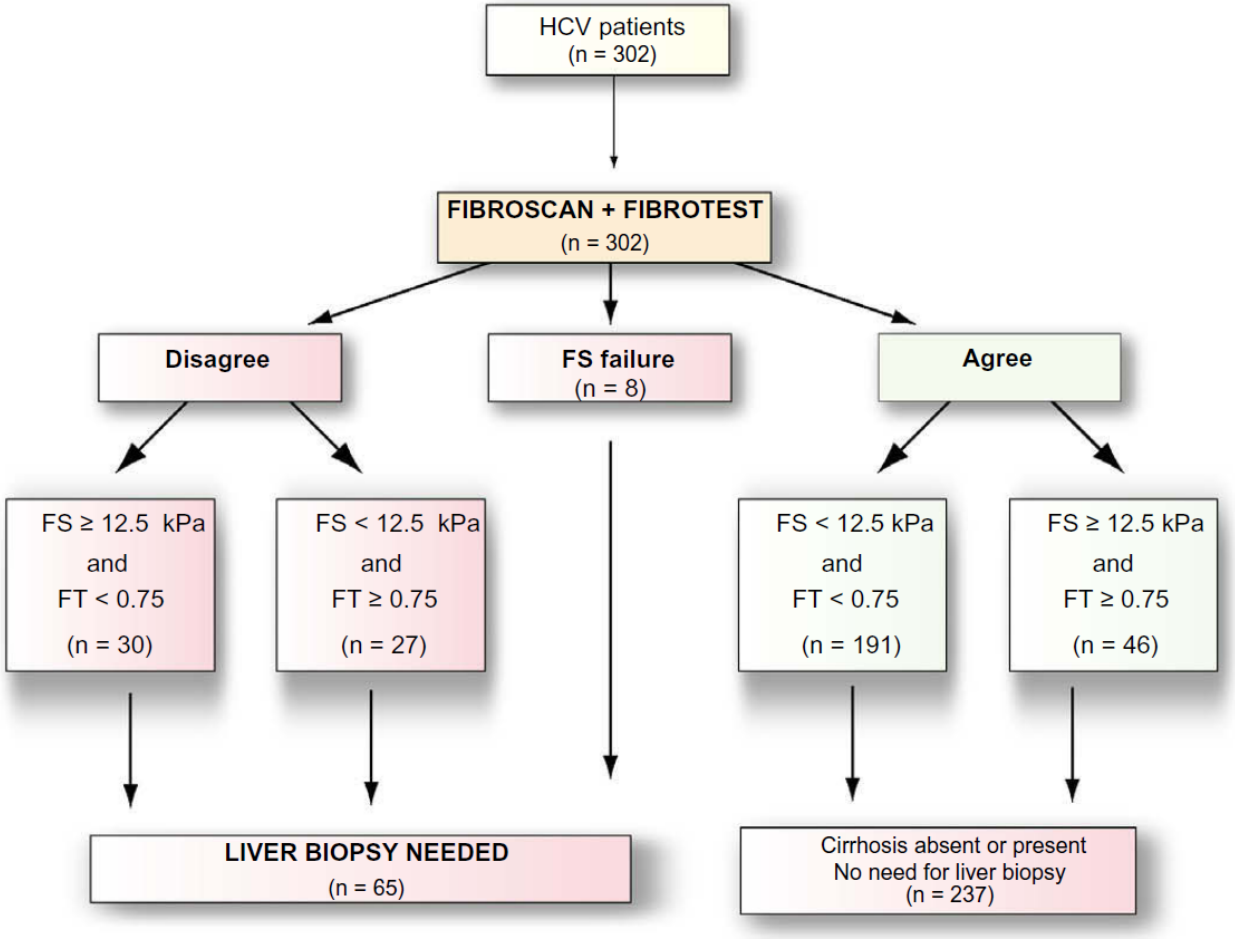
TE	Failure Rate (OR)
BMI>30	8.4
Operator experience	2.6
Age >52 yrs	2.2
DM	2.0
Time of exam	1.5

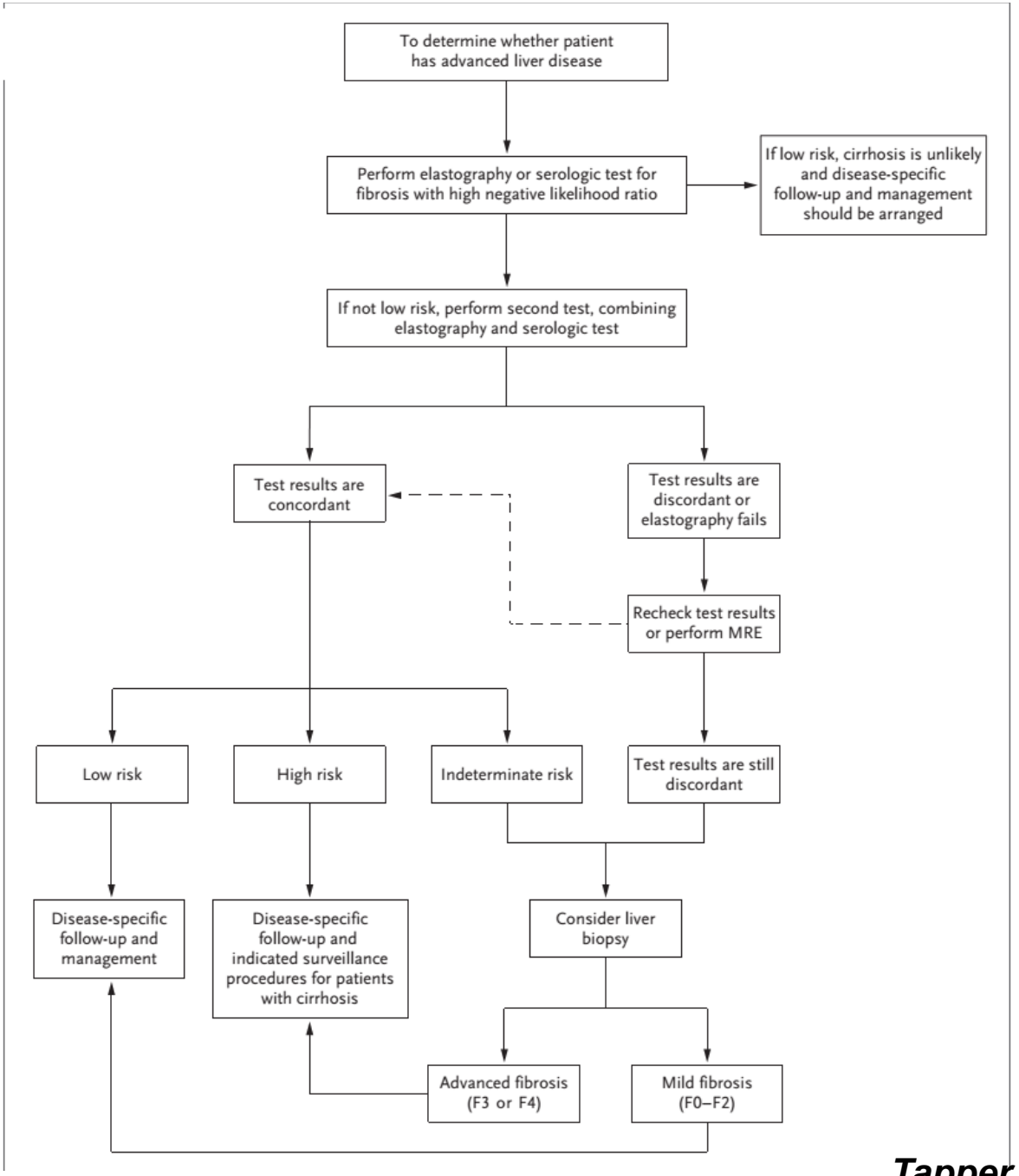
Bota Liver Int 2013
Castera et al hepatology 2010
Singh et al MRE
Rotterdam Study
Thiele 2016

Noninvasive Measurement of Fibrosis

INCREASING ACCURACY

Combining modalities: Castera algorithm: high accuracy, save biopsies in 78%



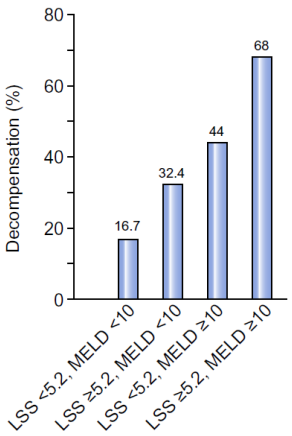


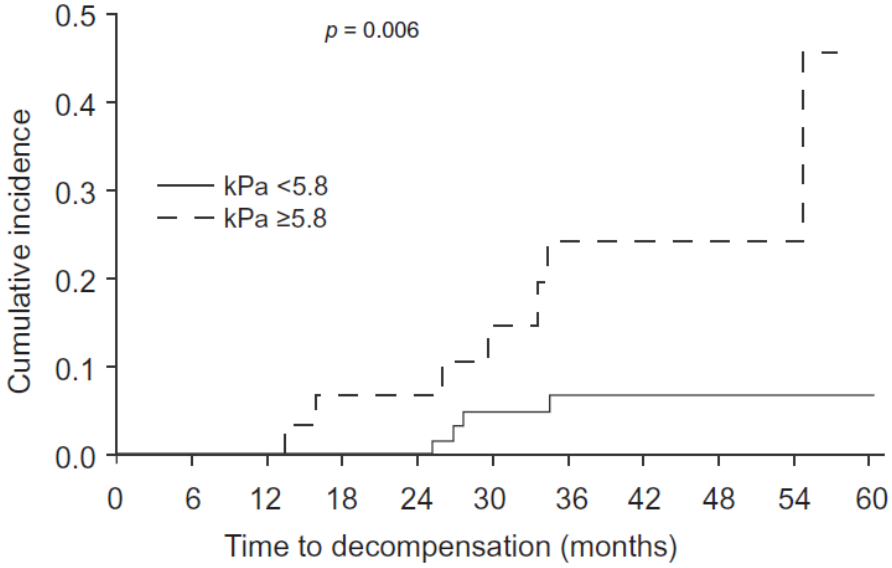
Tapper and Lok NEJM 2017

Noninvasive Measurement of Fibrosis

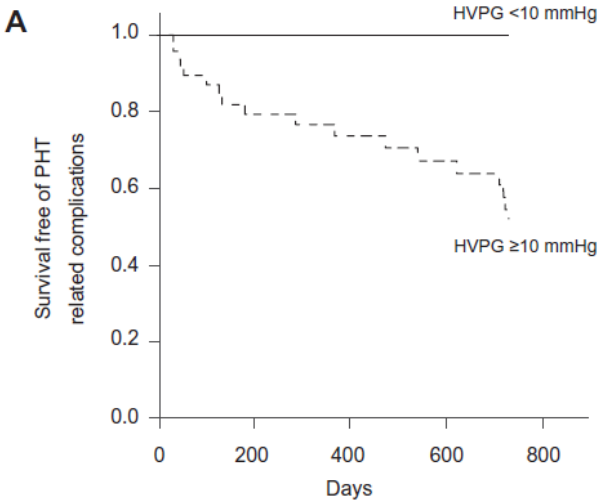
ELASTOGRAPHY AND PROGNOSIS

Elastography and decompensation

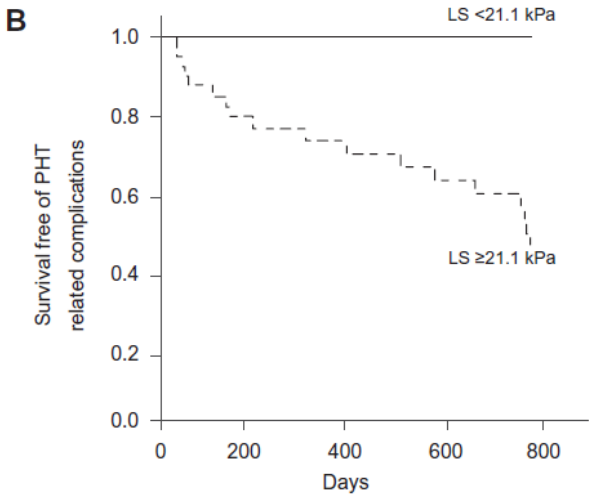




MRE

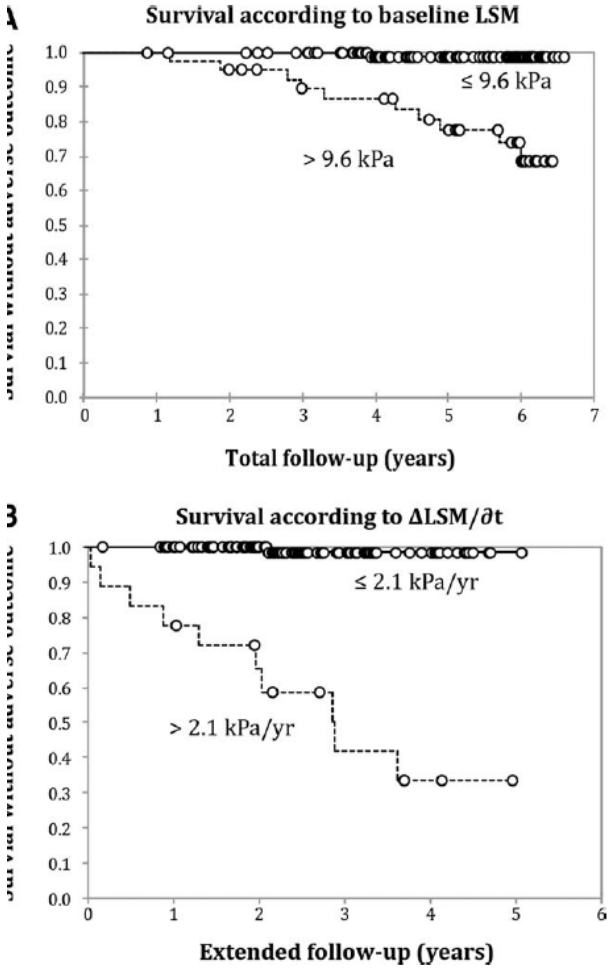


TE



Robic Hep 2011
Asrani J Hep 2014

Elastography and decompensation



	RR
Hepatic Decompensation	1.07
HCC	1.11
Mortality	1.22
Composite	1.32

Meta-analysis

Δ Liver Stiffness

Corpechot Hepatology 2012
Singh CGH 2013

Non invasive markers and cirrhosis

- Most tests perform well
  - AUROC ~0.9 (elasto) vs. ~0.8 (serum)
  - Consideration of other aspects of testing
- Accuracy is influenced by several factors
  - Clinical context matter: e.g. High ALT
  - Patient factors matter: e.g. high BMI
  - Diagnostic test nuances matter: eg. probe
- Increasing accuracy
  - Combining tests
  - Screen in enriched populations
  - Better if clinical context fits

Unmet needs: non invasive

- What is incomplete of unreliable rate
- What is a reliable test: standardizing
- Can we get the operator out of the picture?
- Performance in pediatrics
- What cutoffs to use given changes in probes
  - E.g. M versus XL
  - E.g. 2D versus 3D MRE, 40 vs. 60Hz

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