Are non-invasive markers of liver fibrosis reliable?

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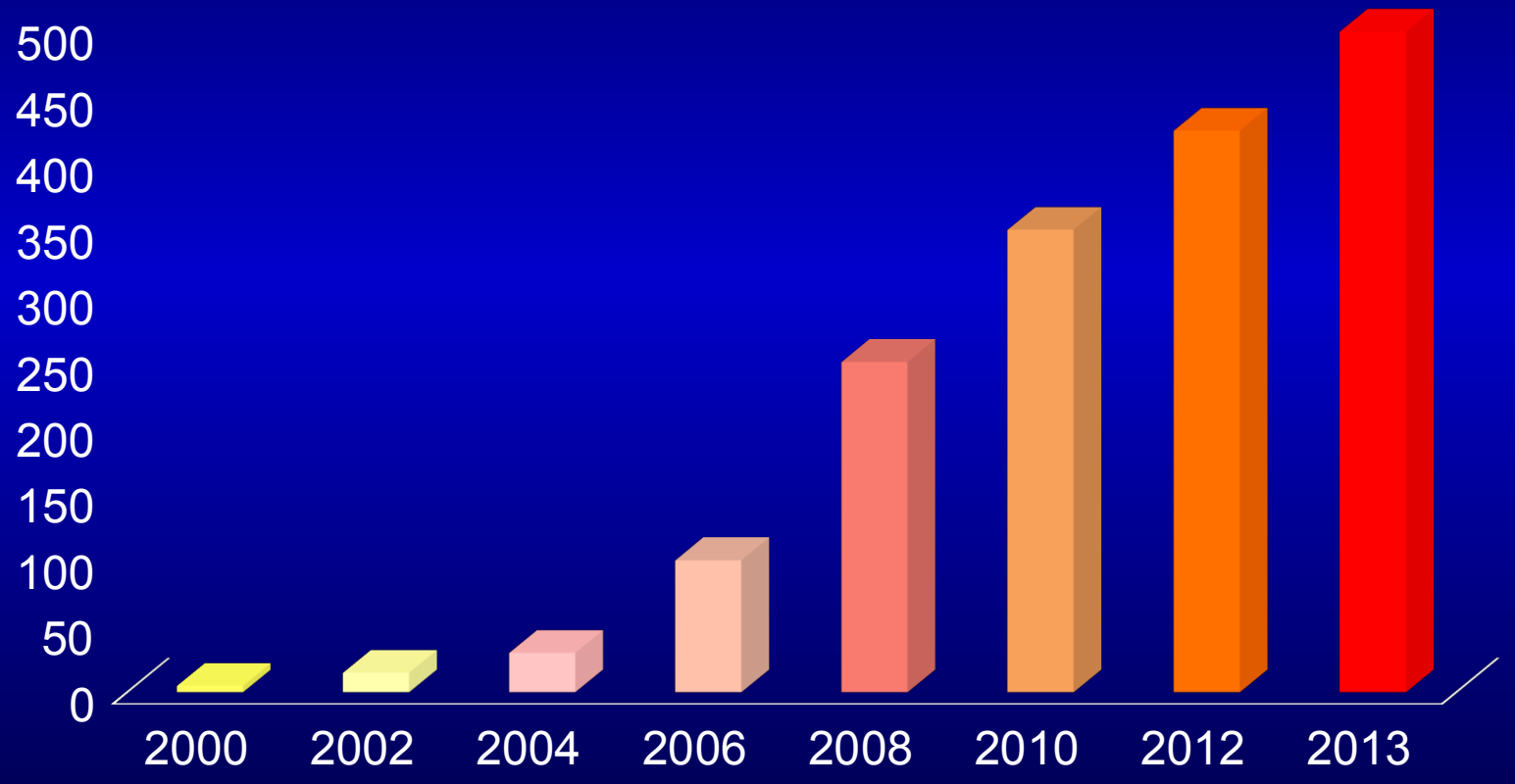
7th Paris Hepatitis Conference 2014

Non invasive methods:
An exponential increase in publications!



Source PubMed 2000-2013

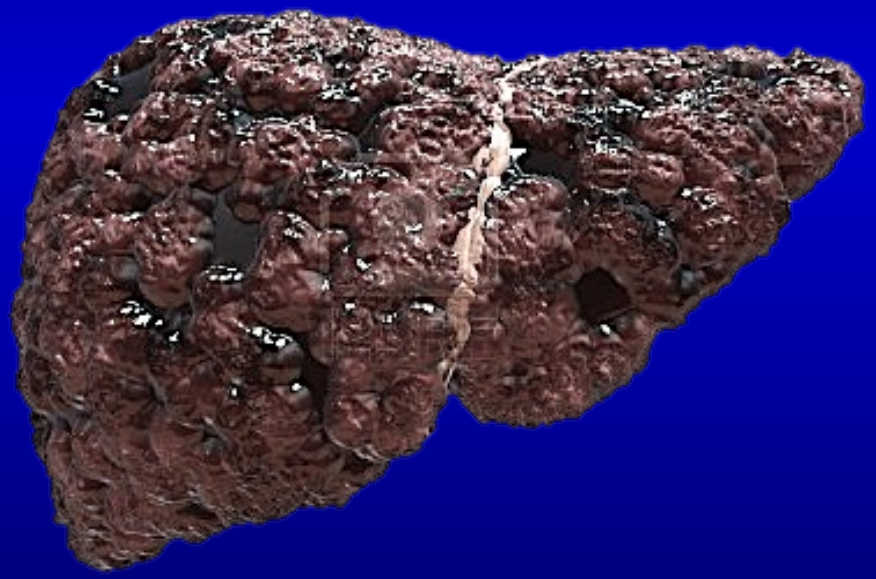
Available non-invasive methods

2 different but complementary approaches

« Biological » approach

Serum Biomarkers

« Physical » approach



Liver stiffness

Castera & Pinzani. Lancet 2010; 375: 419-20

Serum biomarkers

lon specific (HCV)

- APRI
- Forns Index
- FibroSpect II®
- ELF®
- FibroTest®
- Hepascore®
- FibroMeters®
- FIB-4

HBV specific

- Zeng score
- Hui Score

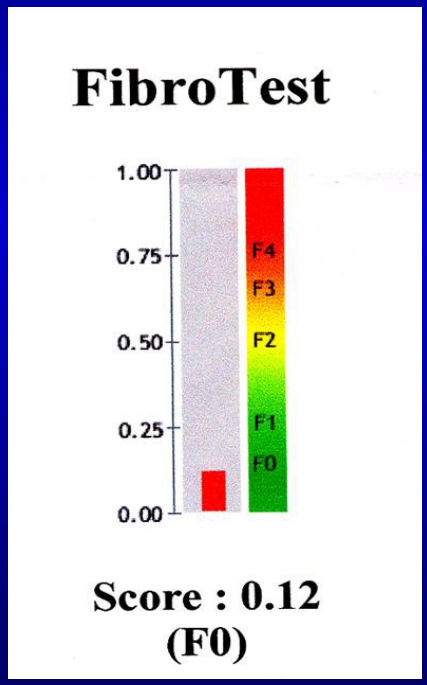
APRI and FibroTest® are the most validated

Non patented

$$\text{APRI} = \frac{\text{AST x 100}}{\text{Platelet}}$$

N=54 studies

Patented



N=25 studies

Chou & Wasson. Ann Intern Med 2013; 158: 807-20

Liver stiffness measurement

FibroScan ARFI SWE

The lessons from hepatitis C

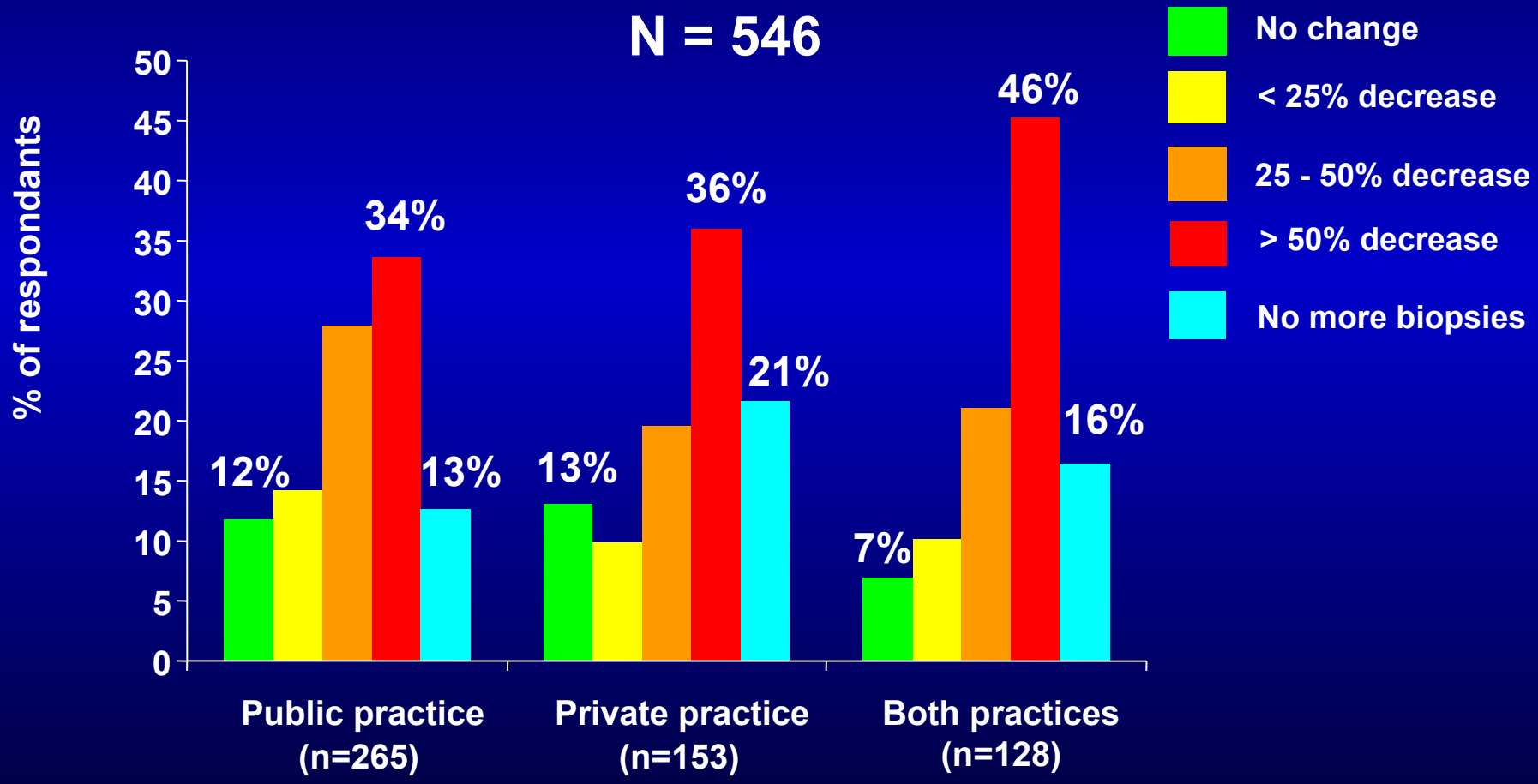
- Fibrosis stage can be assessed by non-invasive methods initially, with liver biopsy reserved for cases where there is uncertainty or potential additional etiologies (**recommendation B1**)

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER

EASL Clinical Practice Guidelines. J Hepatol 2011; 55: 245-64

EASL Clinical Practice Guidelines. J Hepatol 2014; in press

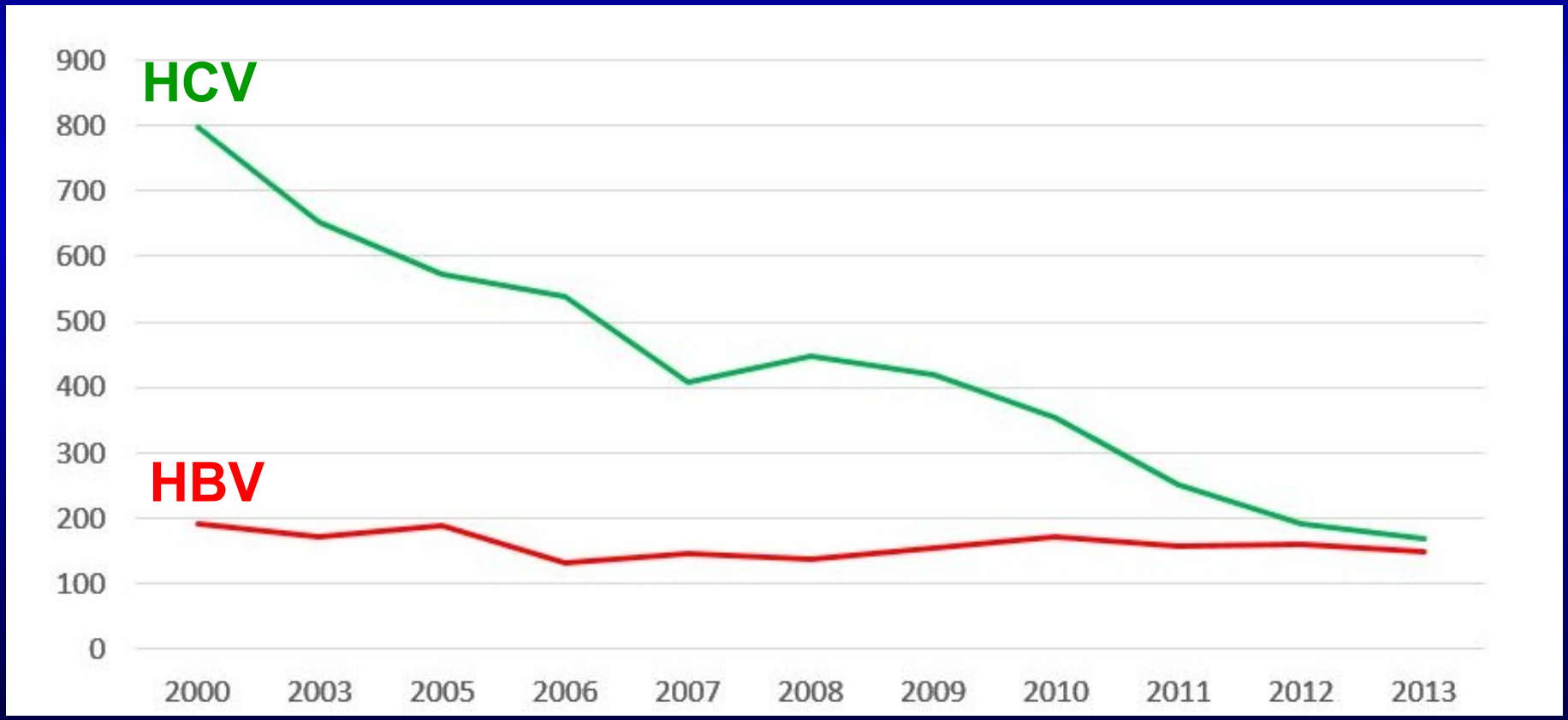
Impact of the use of non-invasive tests on the need for liver biopsy in hepatitis C in France



Castera et al. J Hepatol 2007; 46: 528-9

Trends in Liver biopsy practice: HCV *vs.* HBV

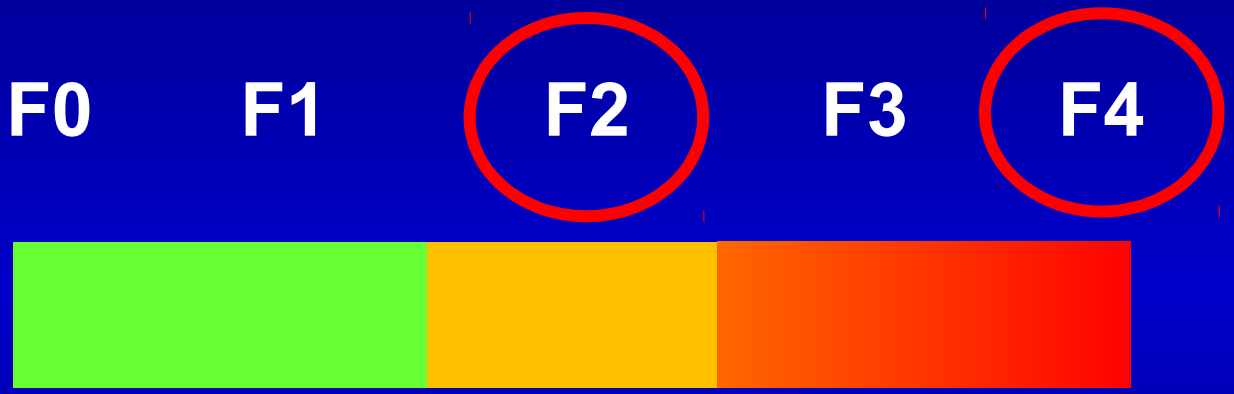
The Beaujon experience 2000-2013



Courtesy of Pierre Bedossa

Assessing the stage of liver disease

End points in viral hepatitis B



Indication for antiviral treatment

Screening for Eosophageal varices

Screening for Hepatocellular carcinoma

Serum biomarkers
Comparative performance

	Number of patients	Significant Fibrosis Cut-off	Significant Fibrosis AUC	Cirrhosis Cut-off	Cirrhosis AUC
Biomarkers[†‡]					
Fibrotest®	1197	0.48	0.78 (0.75-0.81)	0.74	0.82 (0.79-0.85)[†]
Fibrometre®	1204				
APRI	1272	0.5	0.72 (0.69-0.75)	2.0	0.77 (0.73-0.81)[†]
Hepascore	1238	0.5	0.78 (0.75-0.80)	0.84	0.86 (0.83-0.88)[‡]

P=NS

P=NS

N= 1307 patients; F2: 57%; F4: 14%

Degos et al. J Hepatol 2010; 53: 1013-21

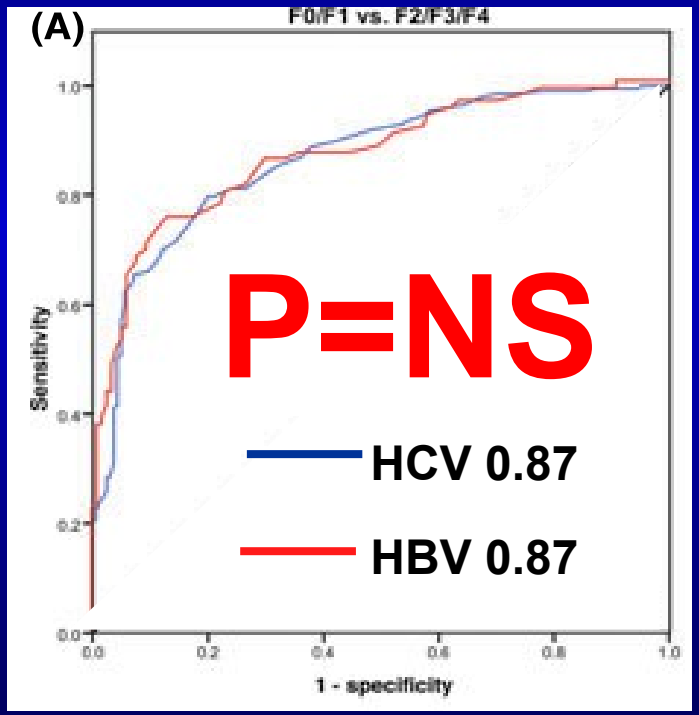
Applicability of serum biomarkers

FibroTest-ActiTest	
Interpretable	342,346 (99.03%; 99.00-99.06)
High risk False Positive/Negative (95% CI)	3349 (0.97%; 0.94-1.00)

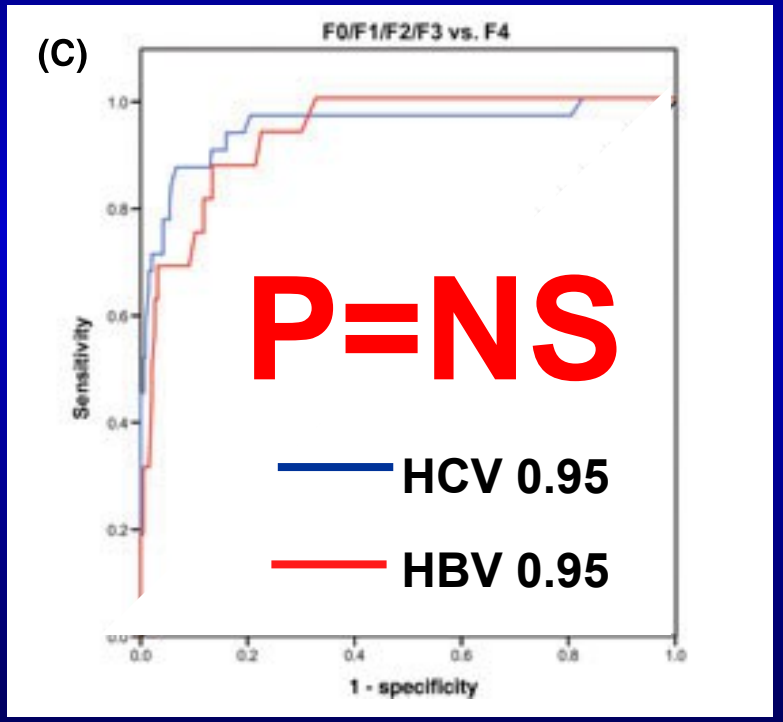
Poynard et al. BMC Gastroenterol 2011; 11; 39.

FibroScan
Hepatitis B *vs.* Hepatitis C

Significant fibrosis



Cirrhosis



N= 565 patients (202 HBV & 363 HCV)

Cardoso et al. Liver Int 2012; 32: 612-27

FibroScan:
meta-analyses

	Number of included studies	Number of included subjects for analysis	AUROC	
			≥ F2	F4
Talwalkar[15]	9	2,083	0.870	0.957
Stebbing[16]	22	4,760	0.84	0.94
Fredrich-rust et al[17]	50	8,206	0.84	0.94
Tsochatzis et al[18]	40	7,723	N/A	N/A
Chon et al	18	2,772	**0.859**	**0.929**

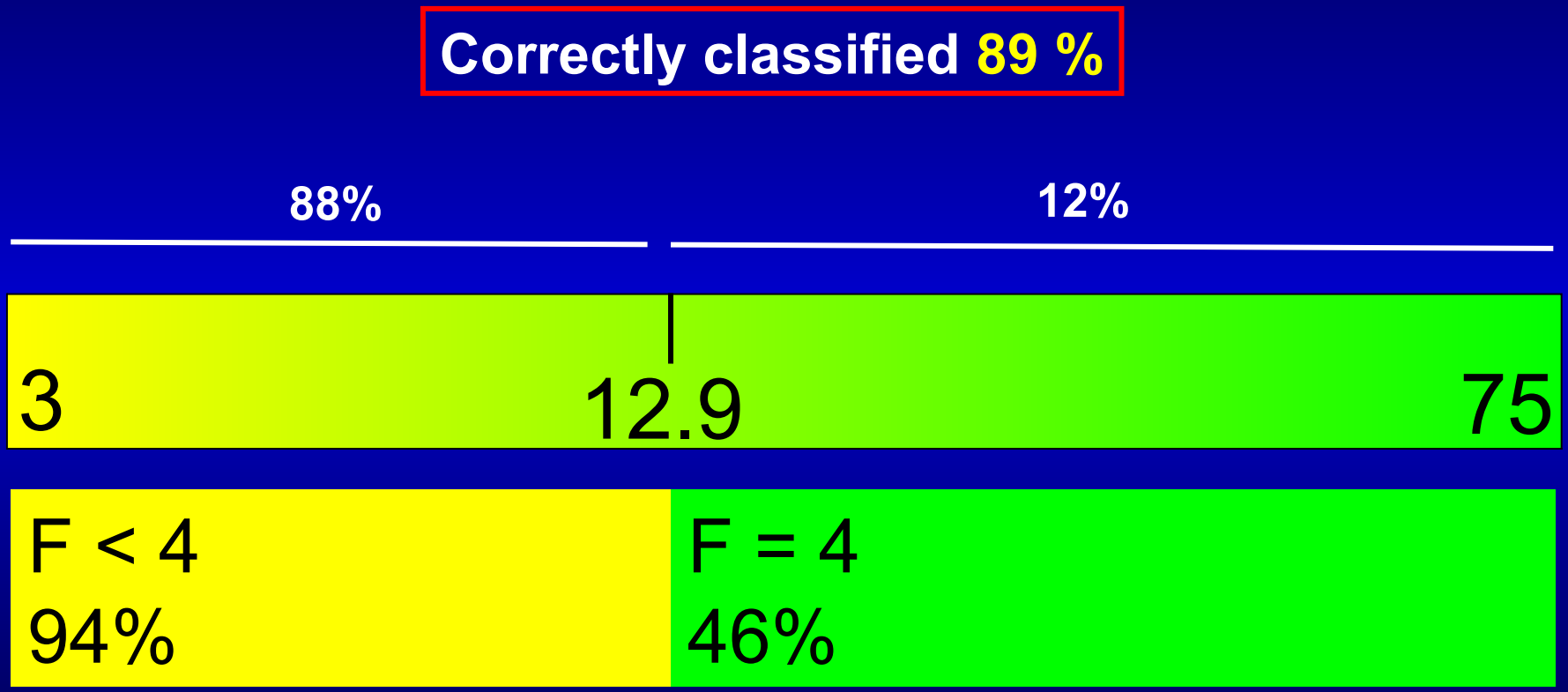
Chon et al. PLoS ONE 2012 7(9): e44930

Cut-offs
Hepatitis C *vs.* hepatitis B

Authors	Etiologies	Year	Patient (n)	F ≥2 (%)	F4 (%)	Cut-offs AUROC (*kPa*)		Se (%)	Sp (%)	CC (%)
Castera et al[66]	HCV	2005	183	74		7.1	0.83	67	89	73
					25	12.5	0.95	87	91	90
Ziol et al[67]	HCV	2005	251	65		8.6	0.79	56	91	68
					19	14.6	0.87	86	96	94
Arena et al[53]	HCV	2008	150	56		7.8	0.91	83	82	83
					19	14.8	0.98	94	92	92
Lupsor et al[68]	HCV	2008	324	65		7.4	0.86	76	84	79
					21	11.9	0.94	87	91	90
Degos et al[64]	HCV	2010	913	62		5.2	0.75	90	32	57
					14	12.9	0.90	72	89	87
Zarski et al[65]	HCV	2012	382	47		5.2	0.82	97	35	64
					14	12.9	0.93	77	90	88
Coco et al[69]	HBV (HCV)	2007	228	62		8.3	0.93	85	91	87
					50[a]	14.0	0.96	78	98	88
Oliveri et al[70]	HBV	2008	188	26		7.5	0.97	94	88	90
					20[a]	11.8	0.97	86	96	94
Marcellin et al[71]	HBV	2009	173	50		7.2	0.81	70	83	76
					8	11.0	0.93	93	87	94
Chan et al[72]	HBV	2009	161		25	12–13.4[b]	0.93	98	75	85
Degos et al[64]	HBV	2010	284	42		5.2	0.78	89	38	59
					10	12.9	0.85	52	93	89

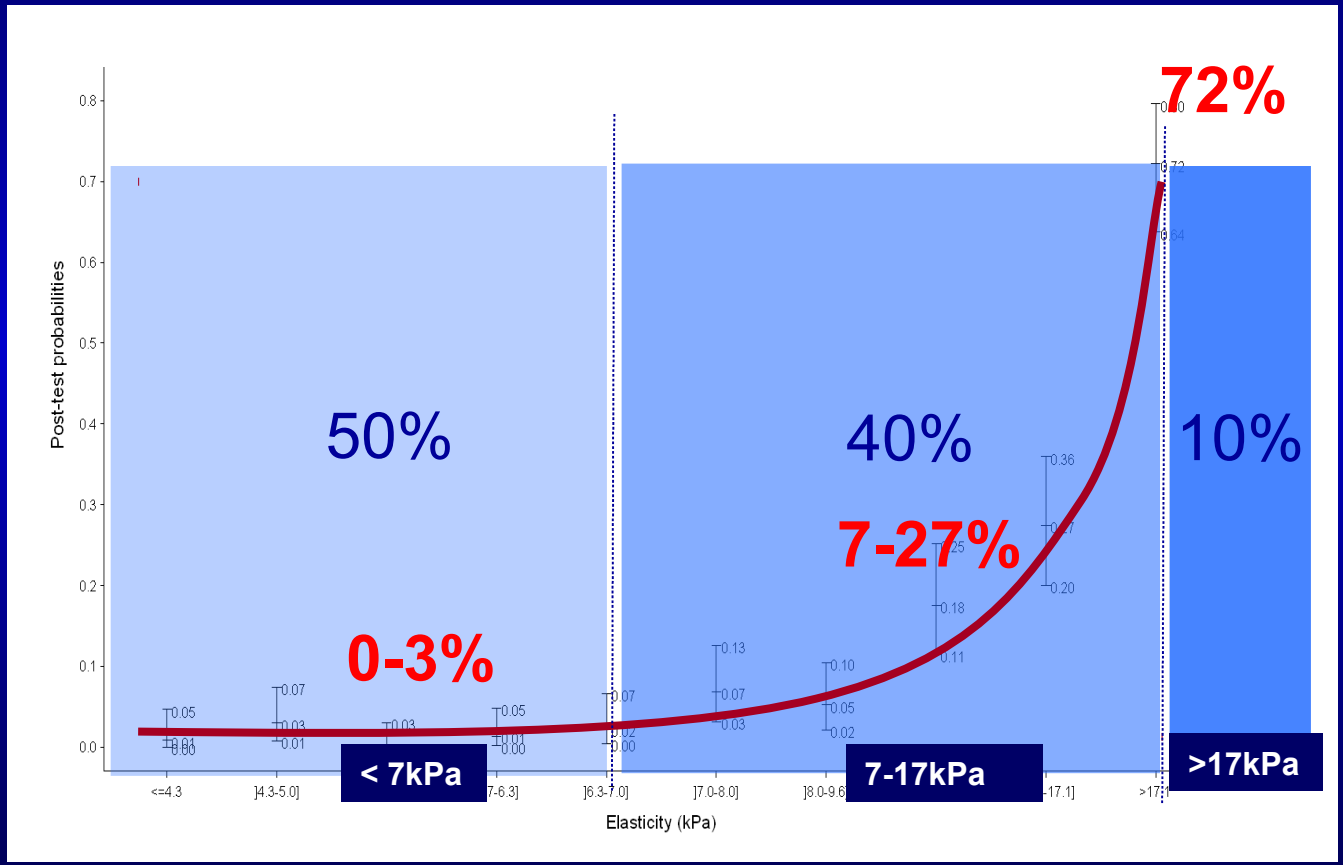
Castera L . Gastroenterology 2012; 142: 1293-302

Detection of cirrhosis
(n=284 HBV patients)



Degos et al. J Hepatol 2010; 53: 1013-21

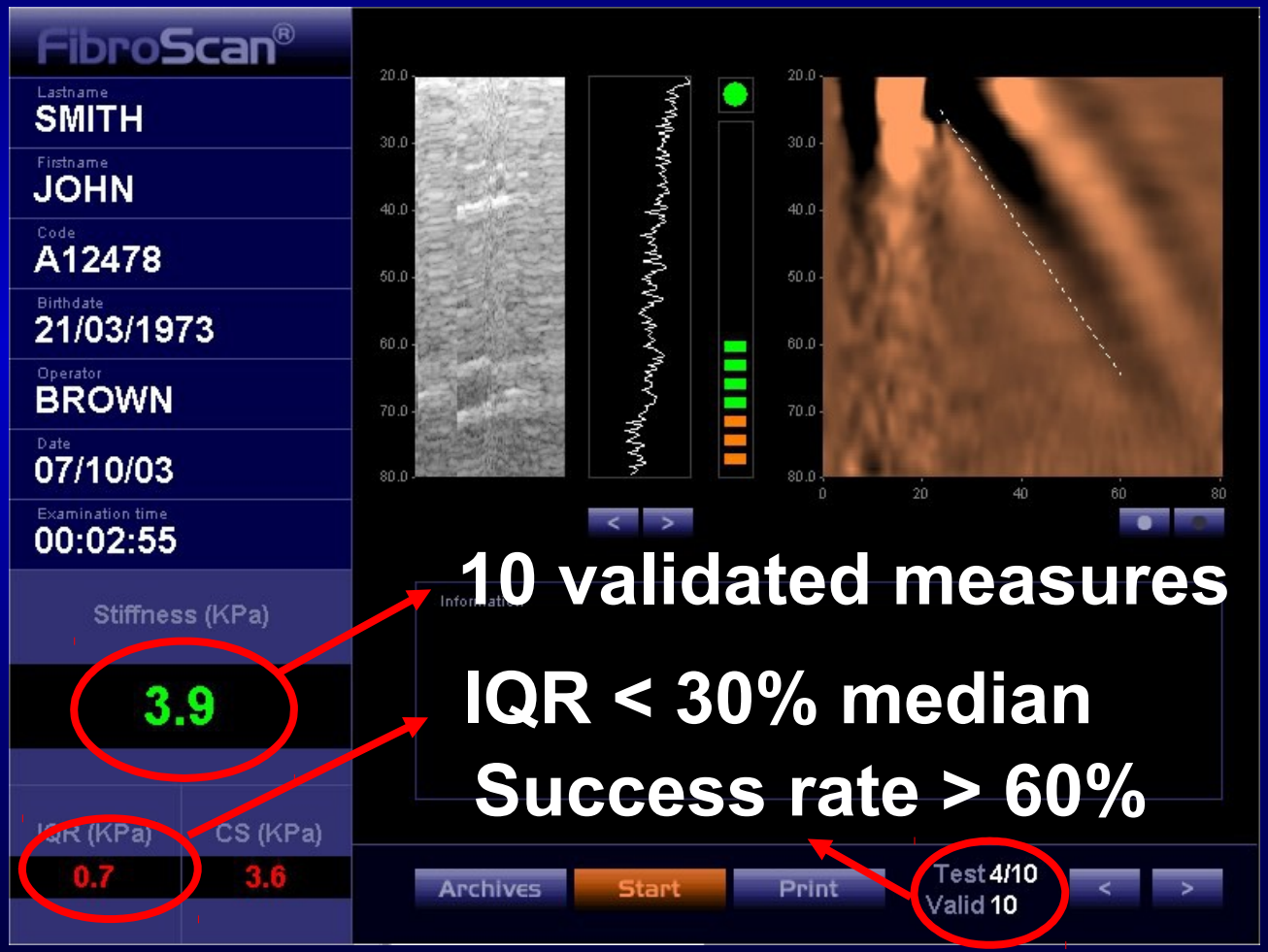
Cirrhosis: Post-test probabilities
(pre-test:14%)



N=1307 patients with viral hepatitis; 14% with cirrhosis

Degos et al. J Hepatol 2010; 53: 1013-21

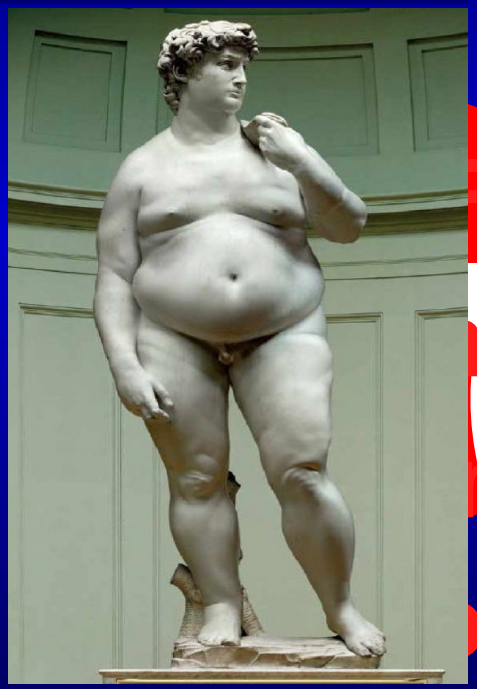
How to interpret FibroScan results
manufacturer's recommendations



Castera, Forns & Alberti. J Hepatol 2008; 48: 835-47

Applicability of transient elastography

Obesity



3.1%

Unreliab

60%

broScan

ot applicable

n 20%

f cases

IQR/LSM > 30%

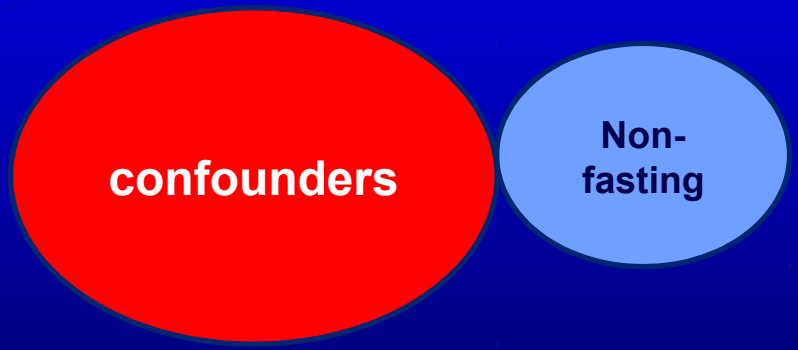
9.2%

Operator experience

N=13669 examinations

Castéra et al. Hepatology 2010; 51: 828-35

Confounders for liver stiffness



Tapper, Castera, Afdhal. Clin Gastroenterol Hepatol 2014; In press

Influence of food intake

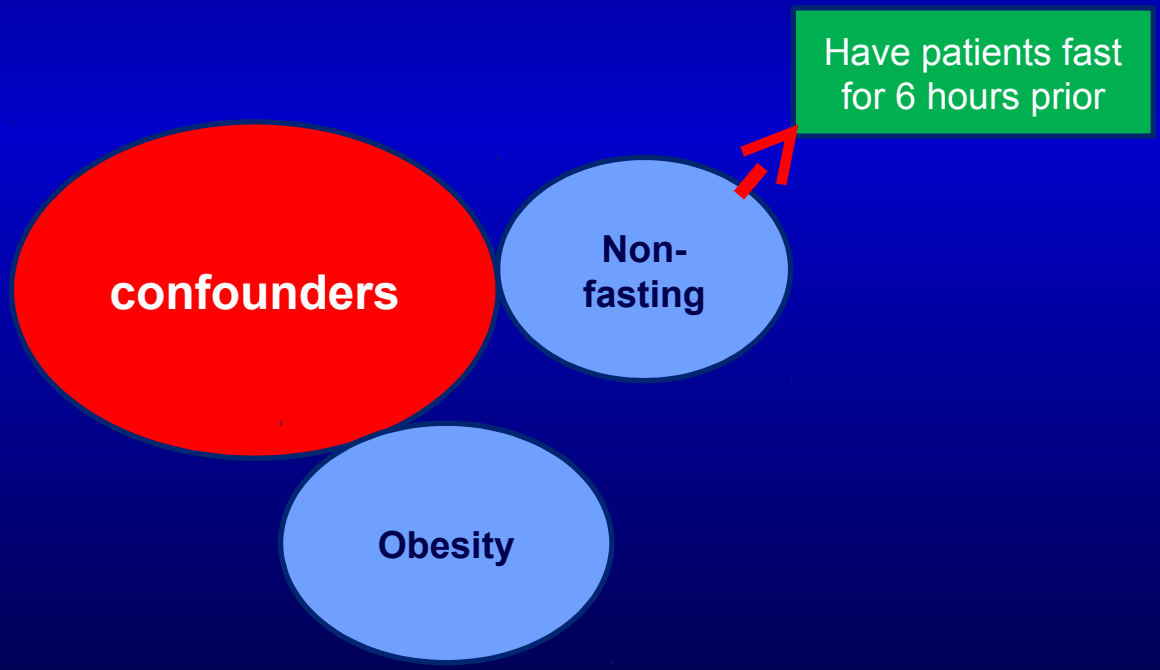
	F0-1 (n = 50) Median	IQR	F2-3 (n = 35) Median	IQR	F4 (n = 40) Median	IQR	JT test *P* Value
S_0 (kPa)	5.0	1.4	10.7	3.4	21.2	25.7	<0.001
S_{15} (kPa)	5.9	1.7	12.2	4.3	24.5	27.3	<0.001
S_{30} (							01
S_{45} (							01
S_{60} (							01
S_{min} (							01
S_{max} (kPa)	6.7	1.9	13.2	5.0	25.4	28.7	<0.001
S_{delta} (kPa)	1.9	0.9	2.7	0.8	4.7	2.8	<0.001
S_{delta} (%)	33.6	21.1	25.3	8.6	16.6	7.5	<0.001

TE should be performed in fasting patients

Mederacke et al. Liver Int 2009; 29: 1500-6

Arena et al. Hepatology 2013; 58: 65-72

Confounders for liver stiffness



Tapper, Castera, Afdhal. Clin Gastroenterol Hepatol 2014; In press

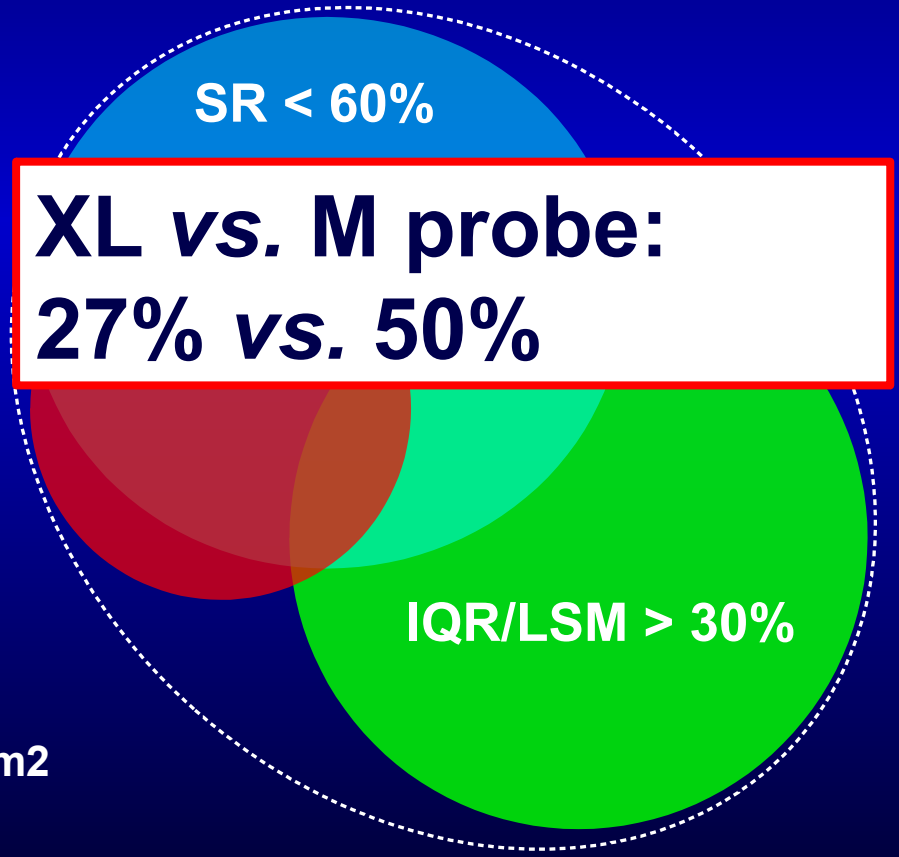
XL Probe:

Does it really overcome the limitations of M probe ?

Failure

XL *vs.* M probe:
1% *vs.* 16%

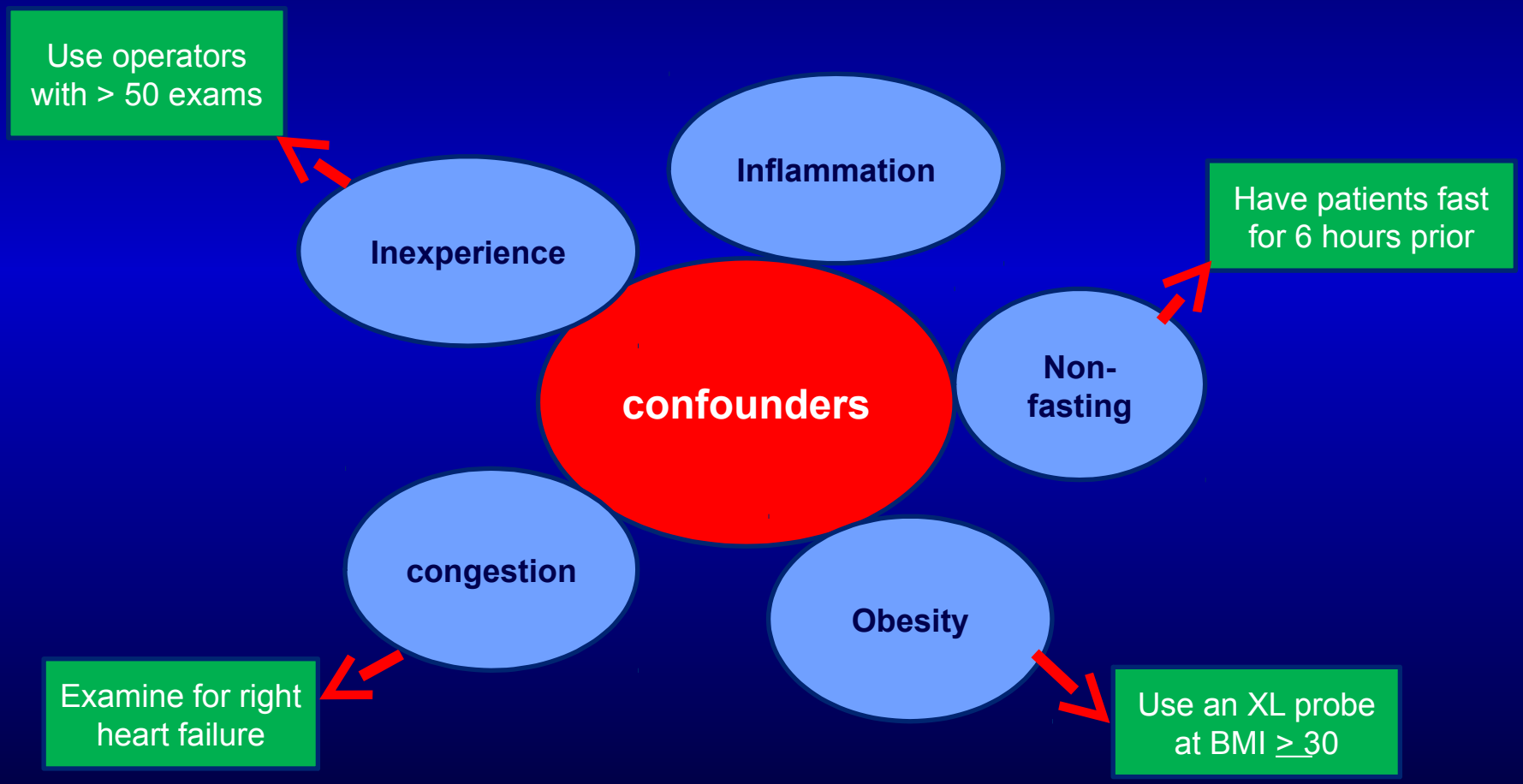
Unreliable



N= 276 patients with BMI > 28 kg/m2

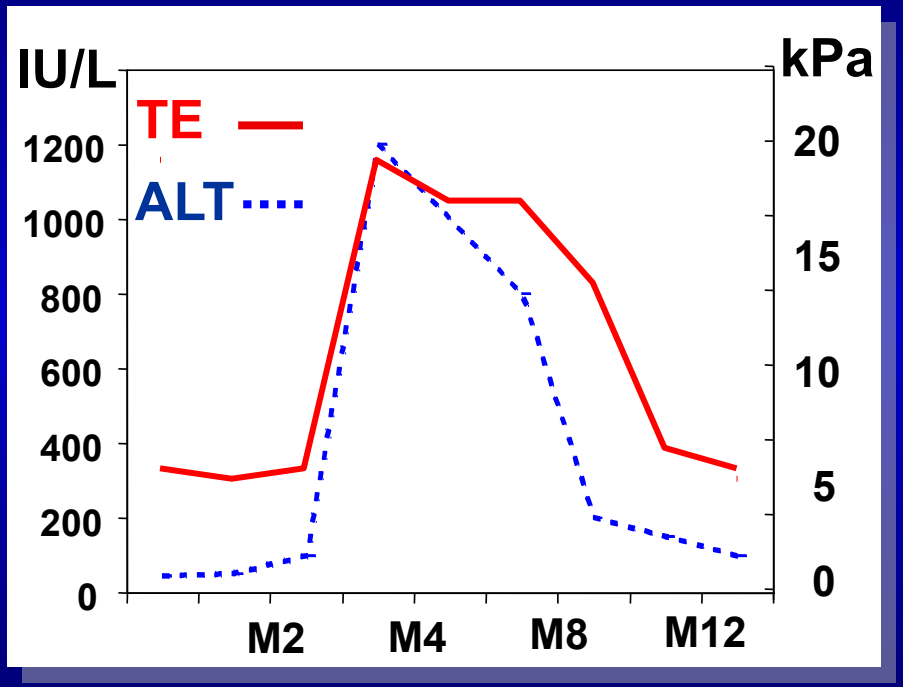
Myers et al. Hepatology 2012; 55:199-208.

Confounders for liver stiffness

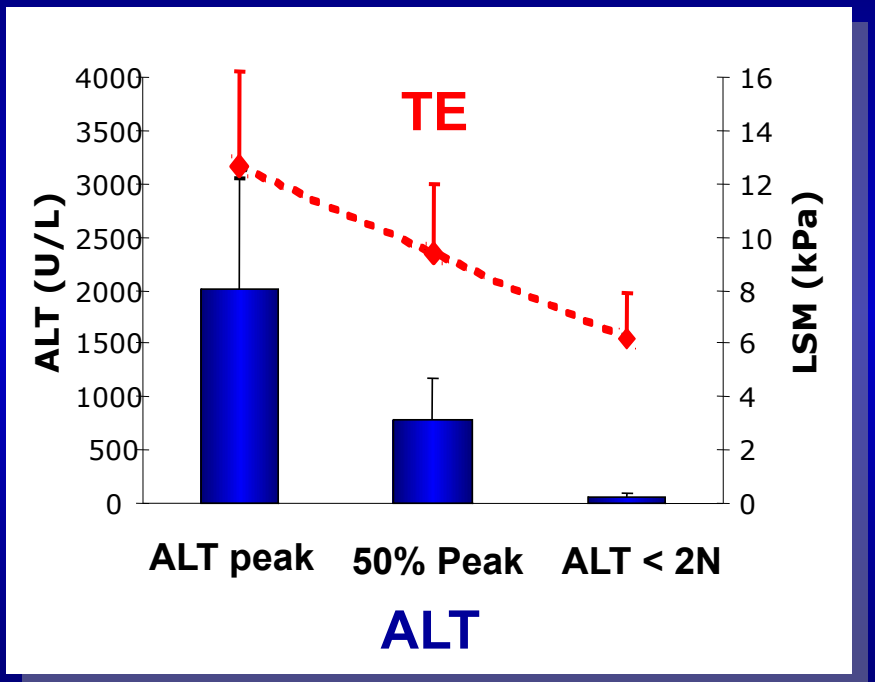


Tapper, Castera, Afdhal. Clin Gastroenterol Hepatol 2014; In press

Influence of inflammation



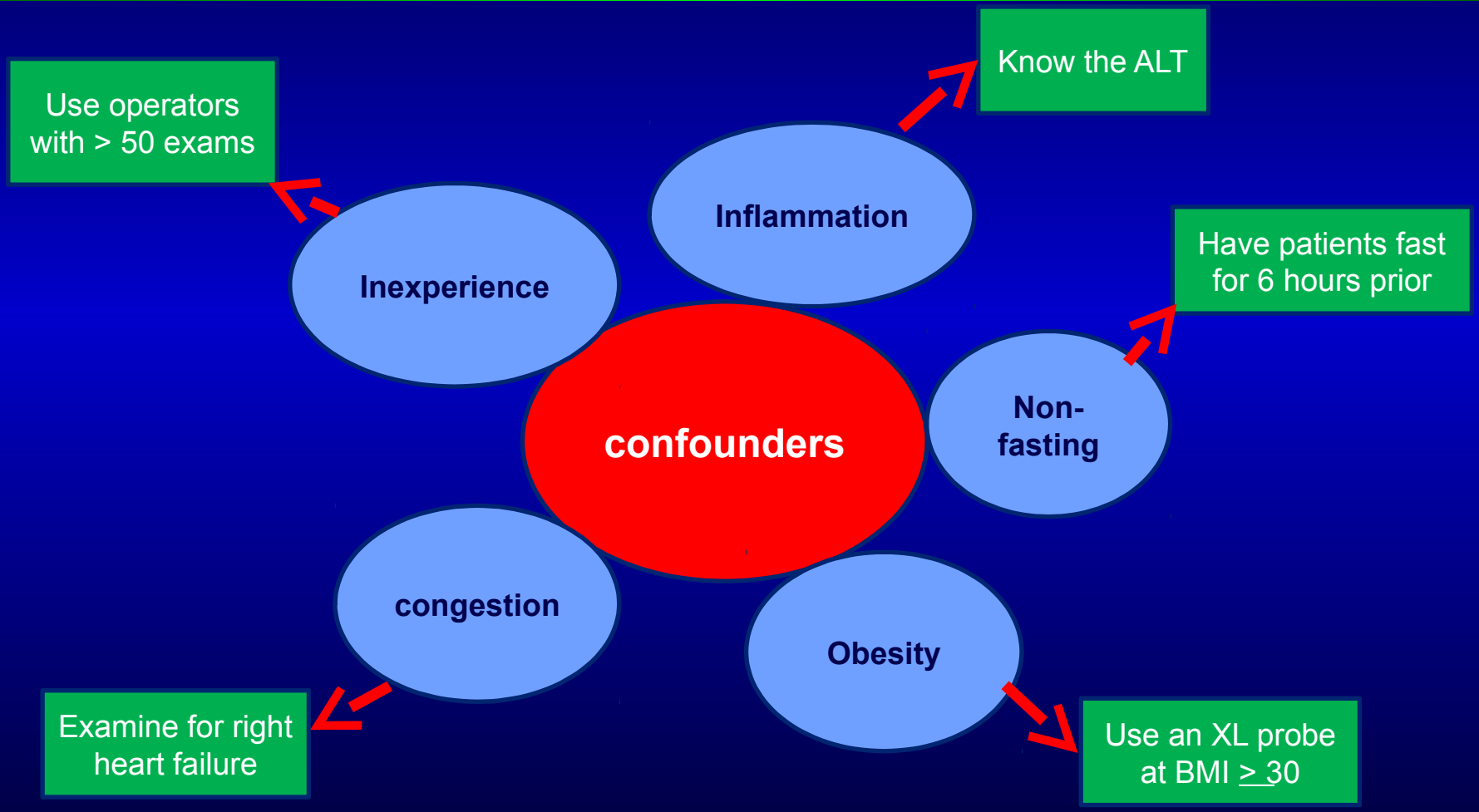
10 patients with ALT flares



18 patients with acute viral hepatitis

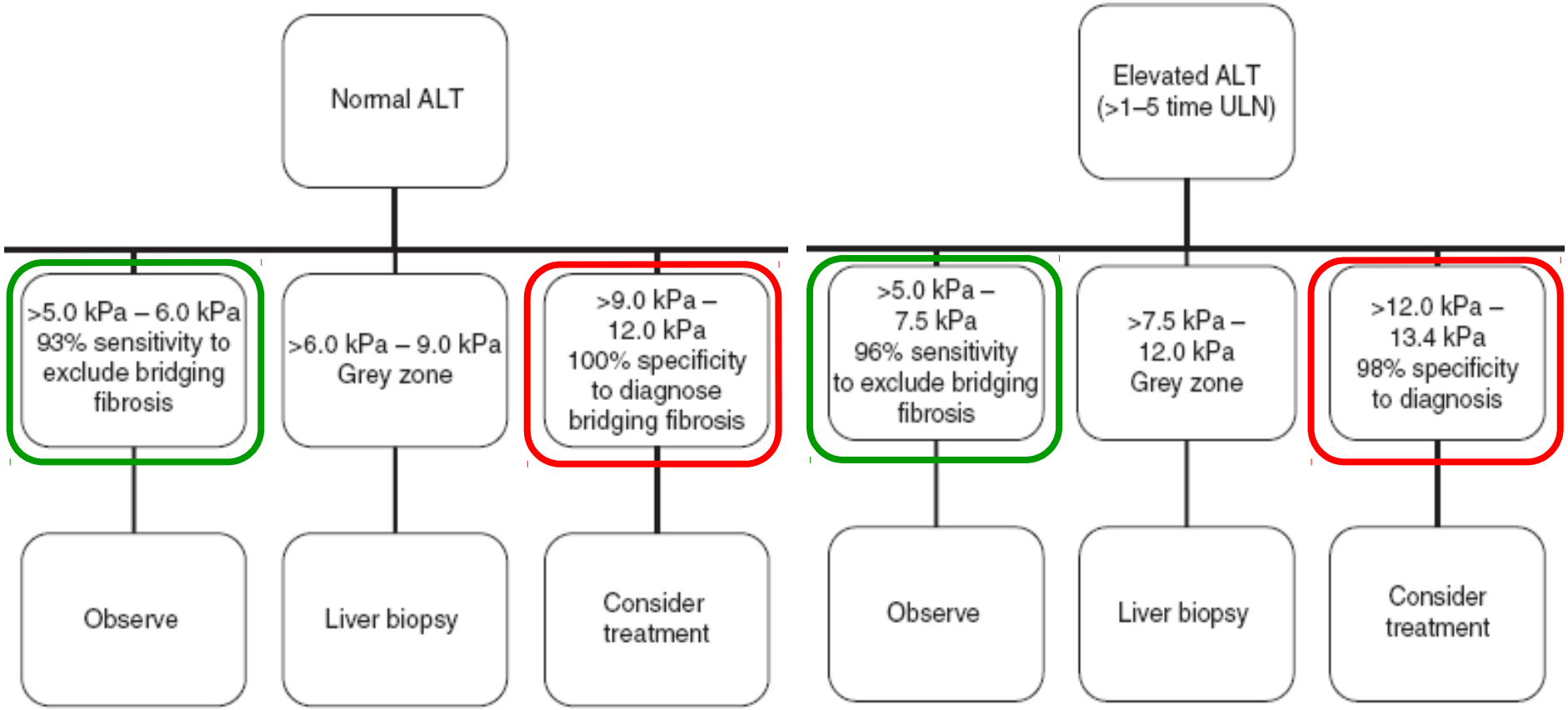
Coco et al. J Viral Hepat 2007; 14: 360-9
Arena et al. Hepatology 2008; 47: 380-4

Confounders of liver stiffness



Tapper, Castera, Afdhal. Clin Gastroenterol Hepatol 2014; In press

Adapt cut-offs according to ALT levels



Chan et al. J Viral Hepat 2009; 16: 36-44

Available non-invasive methods

2 different but complementary approaches

« Biological » approach

« Physical » approach

?

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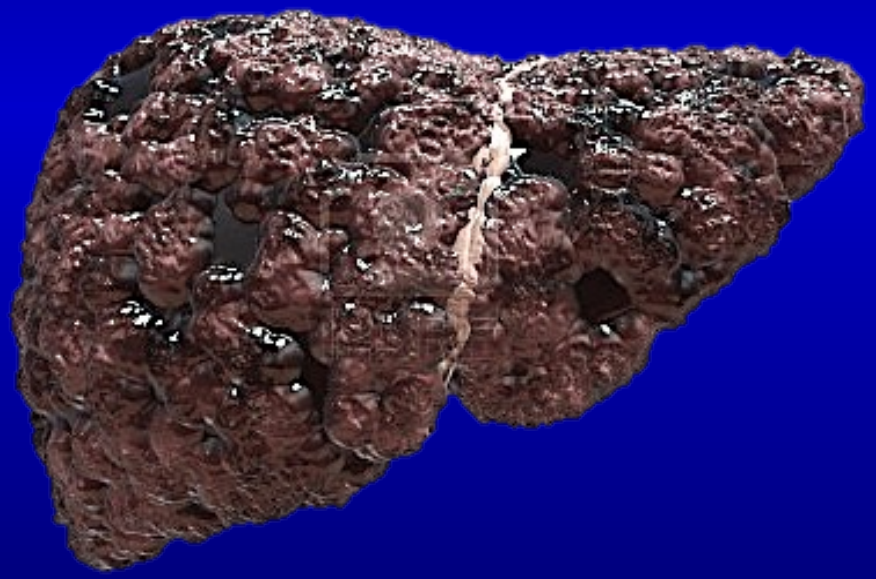


Serum Biomarkers

Liver stiffness

Castera & Pinzani. Lancet 2010; 375: 419-20

Comparative performance
significant fibrosis

	Number of patients	Prevalence	Cut-off	AUC
FibroScan®*	1307	57.1	7.1	0.76 (0.74-0.79)
Fibrotest®			0.48	0.78 (0.75-0.81)
Fibrometre®			0.41	0.79 (0.76-0.81)
APRI	1272	57.1	0.5	0.72 (0.69-0.75)
Hepascore	1238	57.1	0.5	0.78 (0.75-0.80)

P=NS

N= 1307 patients; F2: 56%

Degos et al. J Hepatol 2010; 53: 1013-21

Comparative performance
cirrhosis

	Number of patients	Prevalence	Cut-off	AUC
FibroScan®*	1307	13.8	12.5	0.90 (0.87-0.92)
Fibrotest®				0.82 (0.79-0.85)
Fibrometre®	1204	13.6	0.442	0.86 (0.83-0.89)
APRI	1272	13.9	2.0	0.77 (0.73-0.81)
Hepascore	1238	14.0	0.84	0.86 (0.83-0.88)

P<0.0001

N= 1307 patients; F4: 14%

Degos et al. J Hepatol 2010; 53: 1013-21

Biomarkers vs. FibroScan summary

Biomarkers

- **Advantages**
  - Good reproducibility
  - High applicability (95%)
  - Low cost & wide availability (non patented)
- **Disadvantages**
  - Non specific of the liver
  - Performance for cir
  - Cost & (patented)

FibroScan

- **Advantages**
  - Genuine property of the liver
  - High performance for cirrhosis
  - User-friendly
- **Disadvantages**
  - Low applicability (80%)
  - False positive (infl
  - Requires

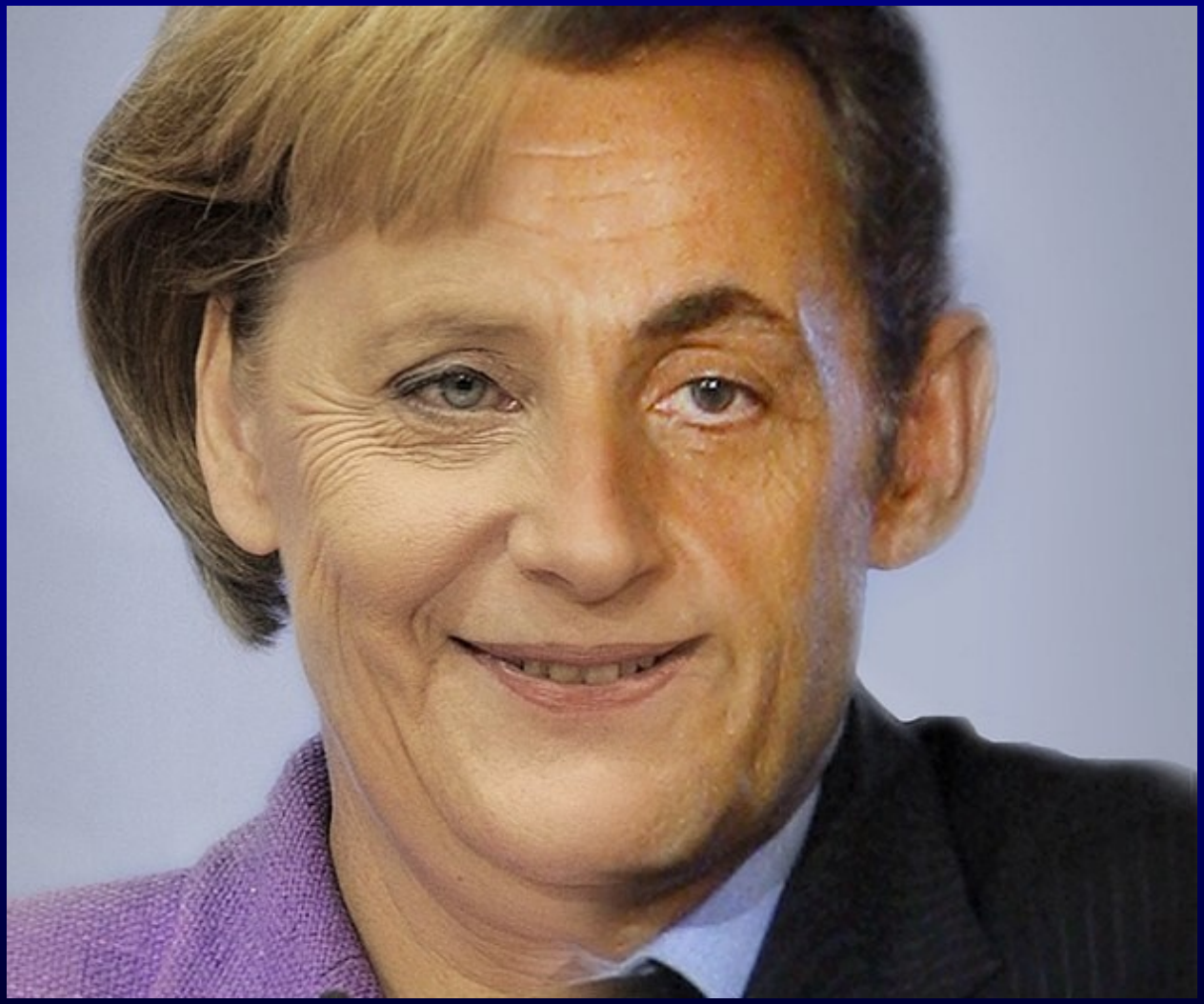
Castera L . Gastroenterology 2012; 142: 1293-302

What about combining both methods?

FibroScan

Biomarkers

Combining methods increases diagnostic accuracy



Combining methods increases diagnostic accuracy in hep C

Biomarkers

Correctly classified F≥2: 75%

Liver stiffness

Castera et al. Gastroenterology 2005; 128: 343-50.

Hepatitis B

Serum markers

?

Transient elastography

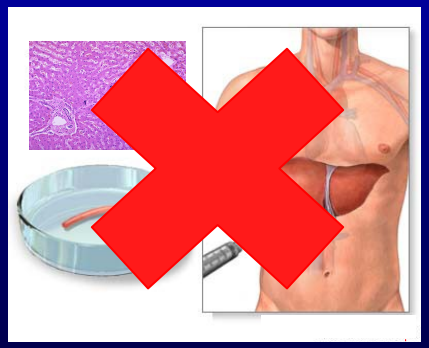
Use in clinical practice

Inactive carriers

HBe Ac +

ALT = N

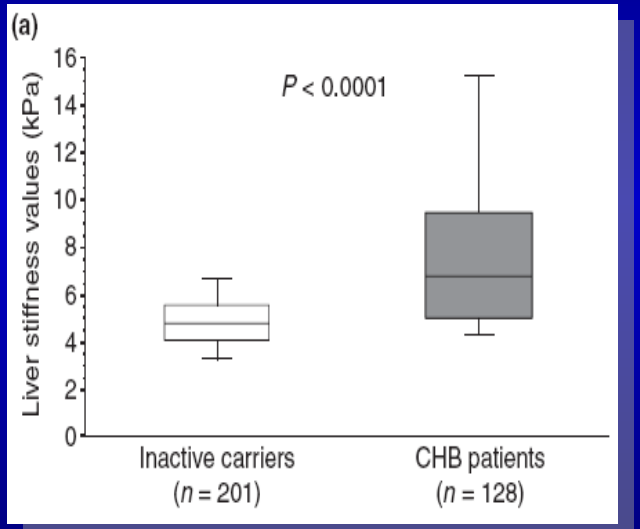
HBV DNA < 20000 UI/mL



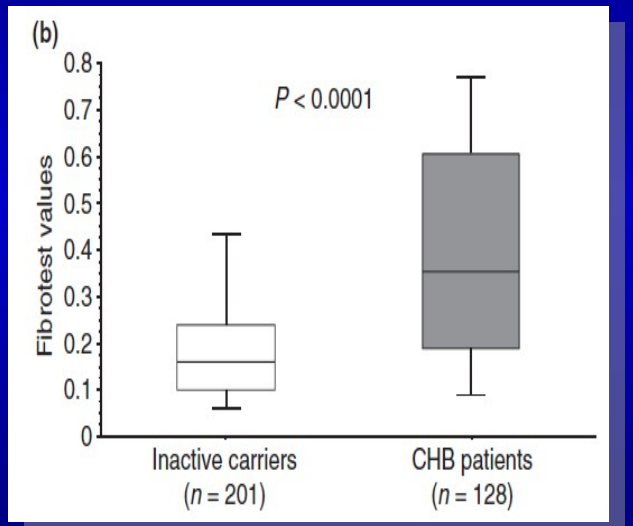
EASL CPG. J Hepatol 2012;57:167–185

HBV inactive carriers
FibroScan & biomarkers

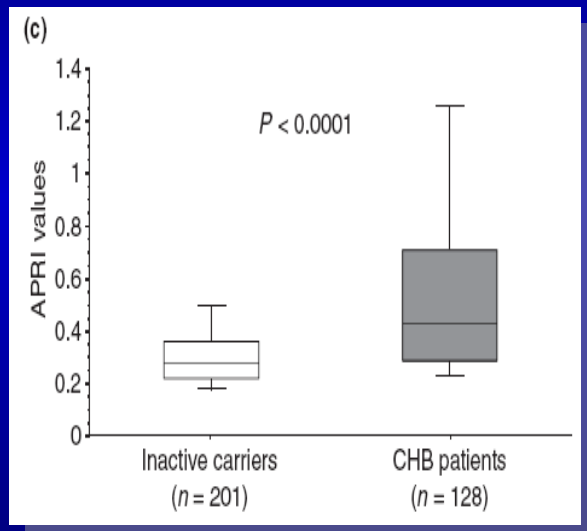
FibroScan



FibroTest



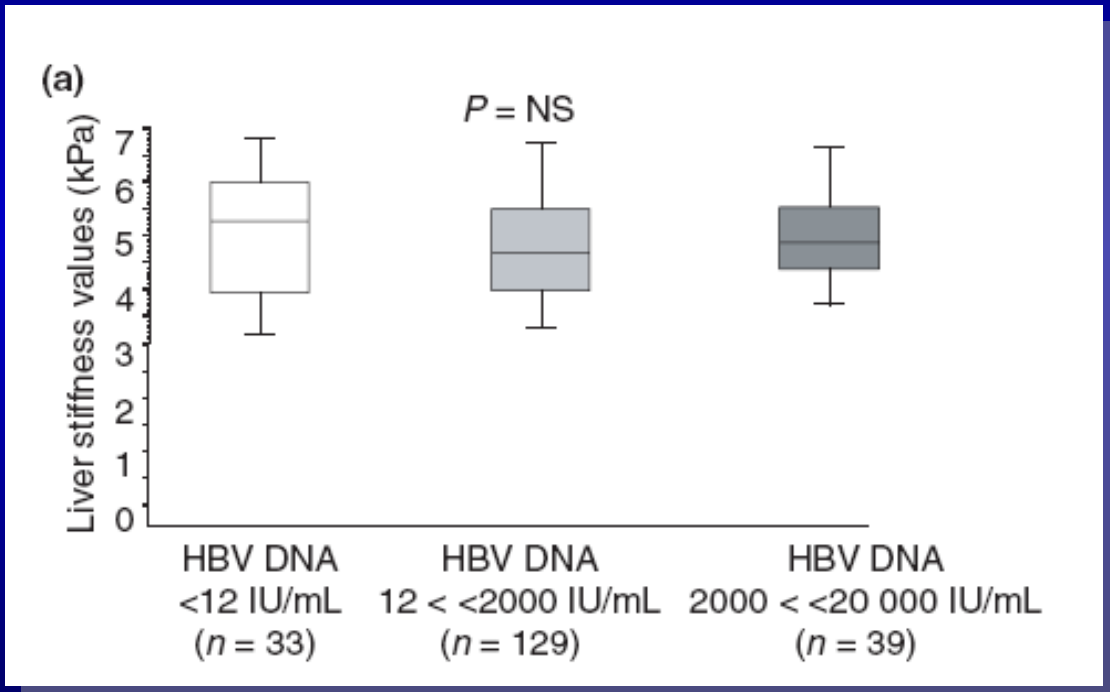
APRI



329 HBV HBeAg neg patients ; 201 inactive carriers

Castera et al. Aliment Pharmacol Ther 2011; 33: 455-65

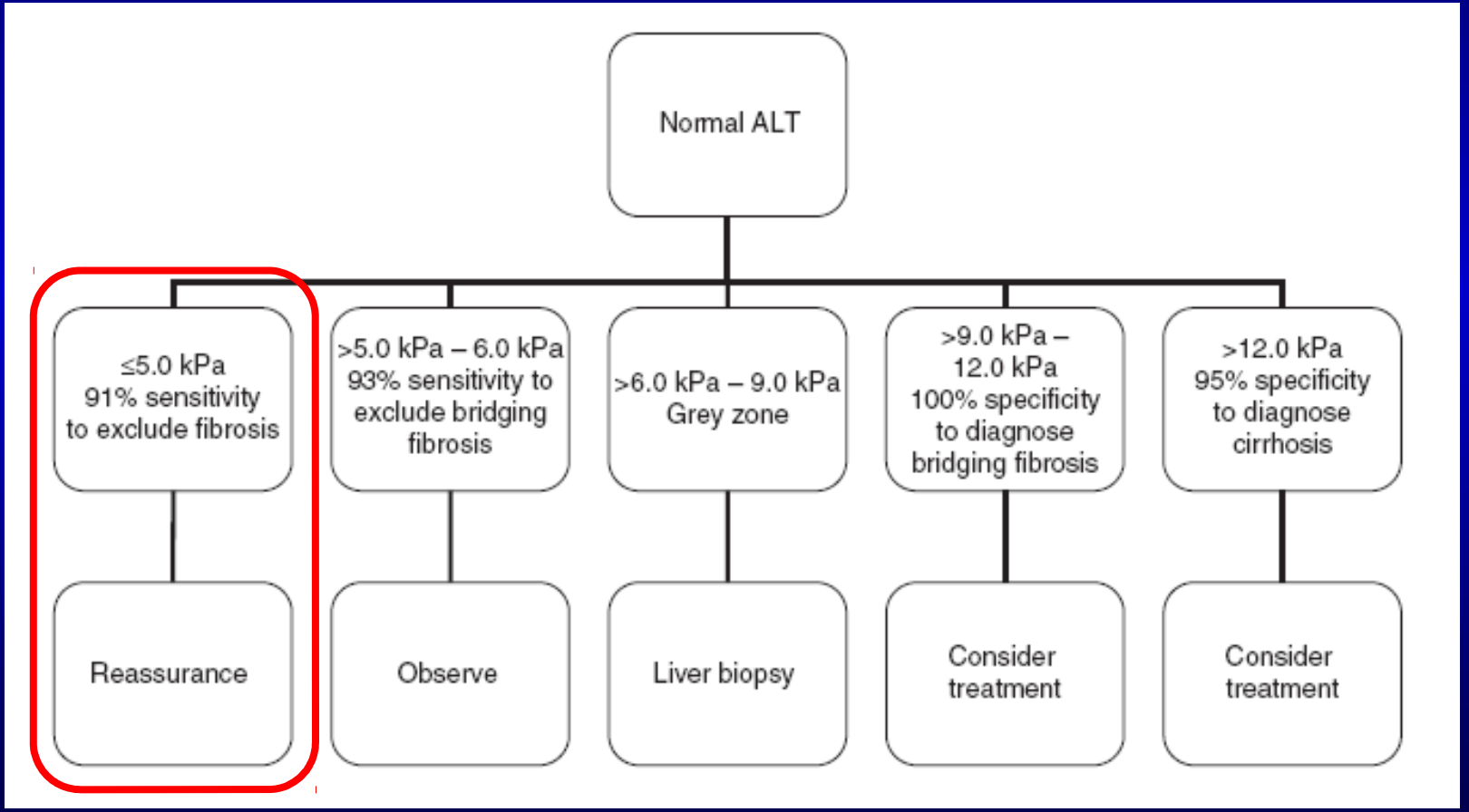
Inactive carriers
relationship with HBV DNA



329 HBV AgHBe neg patients ; 201 inactive carriers

Castera et al. Aliment Pharmacol Ther 2011; 33: 455-65

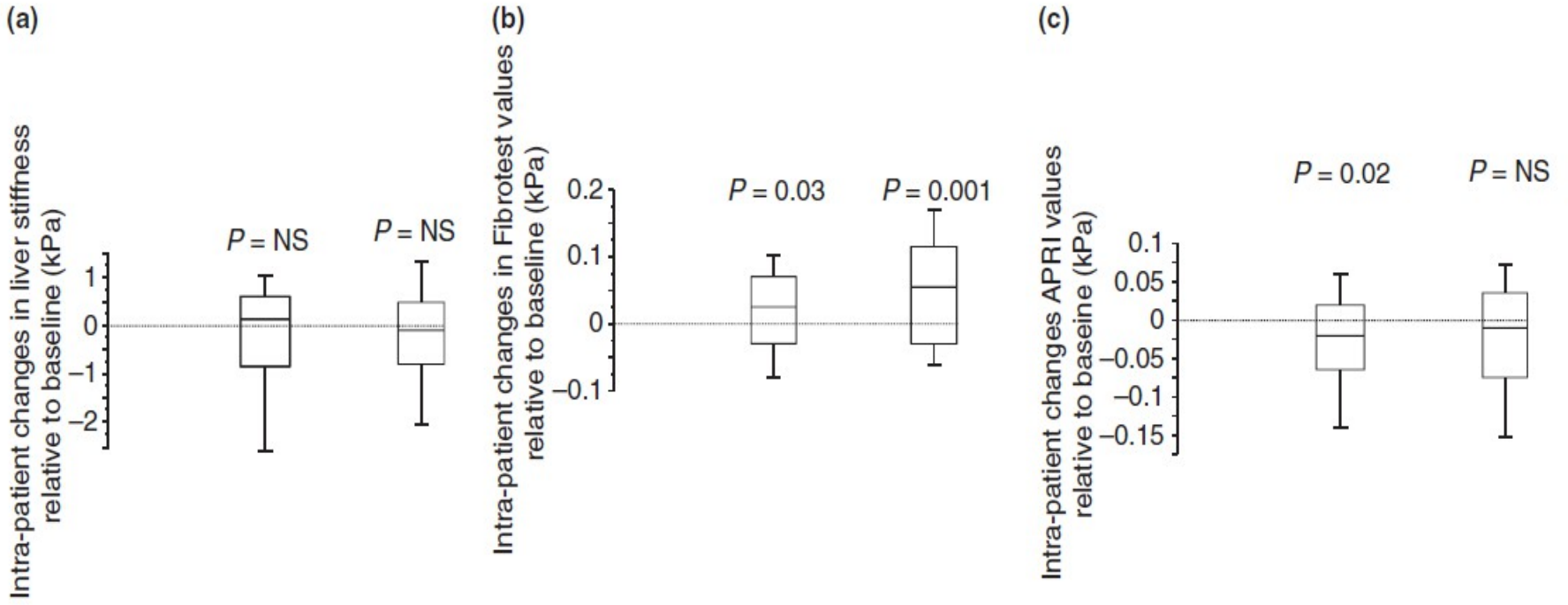
FibroScan
Performance in inactive carriers



Chan et al. J Viral Hepat 2009; 16: 36-44

Follow-up of HBV inactive carriers

FibroScan **FibroTest** **APRI**



N=82 inactive carriers follow-up (median: 21.7 months)

Castera et al. Aliment Pharmacol Ther 2011; 33: 455-65

Follow-up of HBV inactive carriers

Patients	Gender/age	BMI (kg/m^2)	ALT B-line (IU/L)	HBV DNA B-line (IU/mL)	LSM B-line (kPa)	Delay B-line and EOF (days)	LSM second (kPa)	LSM third (kPa)	LSM fourth (kPa)	ALT EOF (IU/L)	HBV DNA EOF (IU/mL)	LB
1	M/25	21.6	33	7536	7.4	460	7.3	6.5	7.8	35	7325	F2
2	F/25	19.7	24	<12	7.8	182	4.1	5.8	-	32	<12	No
3	M/49	27.1	35	<12	7.8	179	6.8	-	-	35	<12	No
4	M/31	20.5	18	315	7.9	253	5.9	-	-	23	<12	No
5	M/52	23.4	47	1600	8.0	236	5.4	4.8	-	34	973	No
6	M/18	21.8	24	662	8.2	395	9.8	9.5	12.7	21	372	F3
7	M/59	24.9	29	<12	8.6	247	6.3	-	-	20	<12	No
8	M/22	24.6	25	1782	8.8	100	5.9	-	-	29	1239	No
9	M/45	23.4	38	774	9.4	186	6.1	6.7	6.6	38	118	No
10	M/23	19.6	21	9380	9.5	416	6.9	6.8	-	9	9216	No
11	M/26	26.4	40	566	11.6	329	5.8	5.3	4.9	42	715	No

N=82 inactive carriers follow-up (median: 21.7 months)

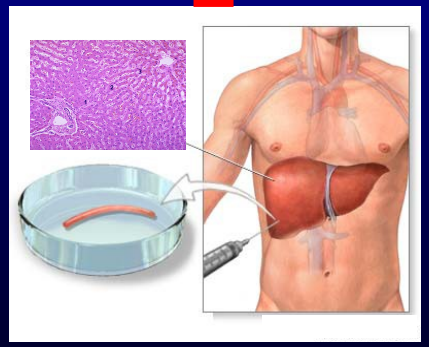
Castera et al. Aliment Pharmacol Ther 2011; 33: 455-65

Decision to treat: Hep C

HCV genotype

IL28B ?

Antiviral treatment



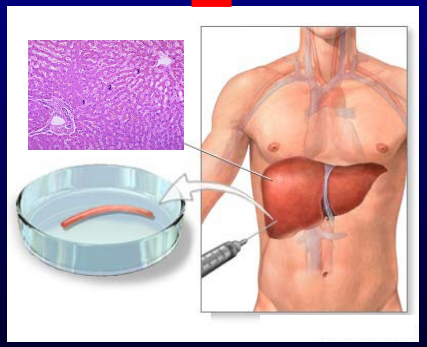
Decision to treat: Hep B

HBe Ag/Ab

HBV DNA

ALT/AST

Antiviral treatment



Antiviral treatment
Hep. C *vs.* Hep. B

Hepatitis C

- Curative treatment
- Finite duration (6-12 mths)
- Side-effects

≠

Hepatitis B

- Suppressive treatment
- Prolonged treatment
- Very few side effects
- Long-term side effects
- Inflammation im

Indication for antiviral treatment

HBe Ag +/-

ALT > ULN

HBV DNA > 2000 IU/mL

EASL CPG. J Hepatol 2012;57:167–185

Indication for antiviral treatment

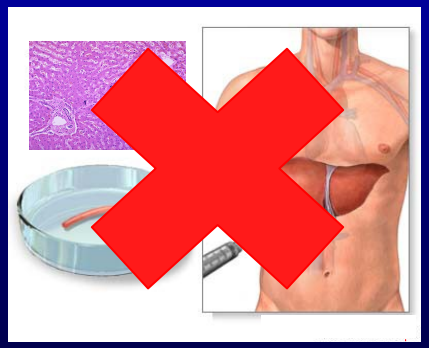
- If diagnosis of cirrhosis is clinically obvious or likely with FibroScan, liver biopsy is not needed.
- Antiviral treatment should be started and patients should be screened for eosophageal varices and HCC.

Indication for antiviral treatment

Ag HBe +/-

ALAT > 2 x N

ADN VHB > 20000 UI/mL



EASL CPG. J Hepatol 2012;57:167–185

Take Home messages

- Non invasive methods are reliable in Hepatitis B.
- Serum biomarkers have equivalent performance between patented and non patented and high applicability.
- TE is currently the most accurate method for detecting cirrhosis but cut-offs need to be adapted according to ALT levels and its applicability is limited in obesity.
- Strategy combining two unrelated methods (TE + serum markers) remains to be validated in hepatitis B.

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