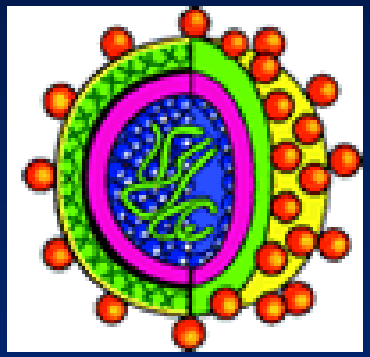
PARENCHYMATEUSES

CHOLESTATIQUES

VHB(0.7%), VHC(1%) Alcool(10 %) Ob/Db(20%)



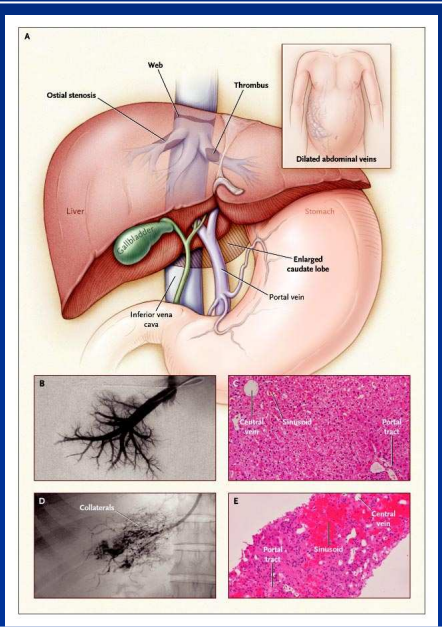
CBP I et II

Chol. sclérosante

+ médicaments, autol, hémochromat., wilson

Hépatites chroniques cirrhogènes

VASCULAIRES



Budd-Chiari

Foie cardiaque

MVO

HNR

Médicts : vit A …

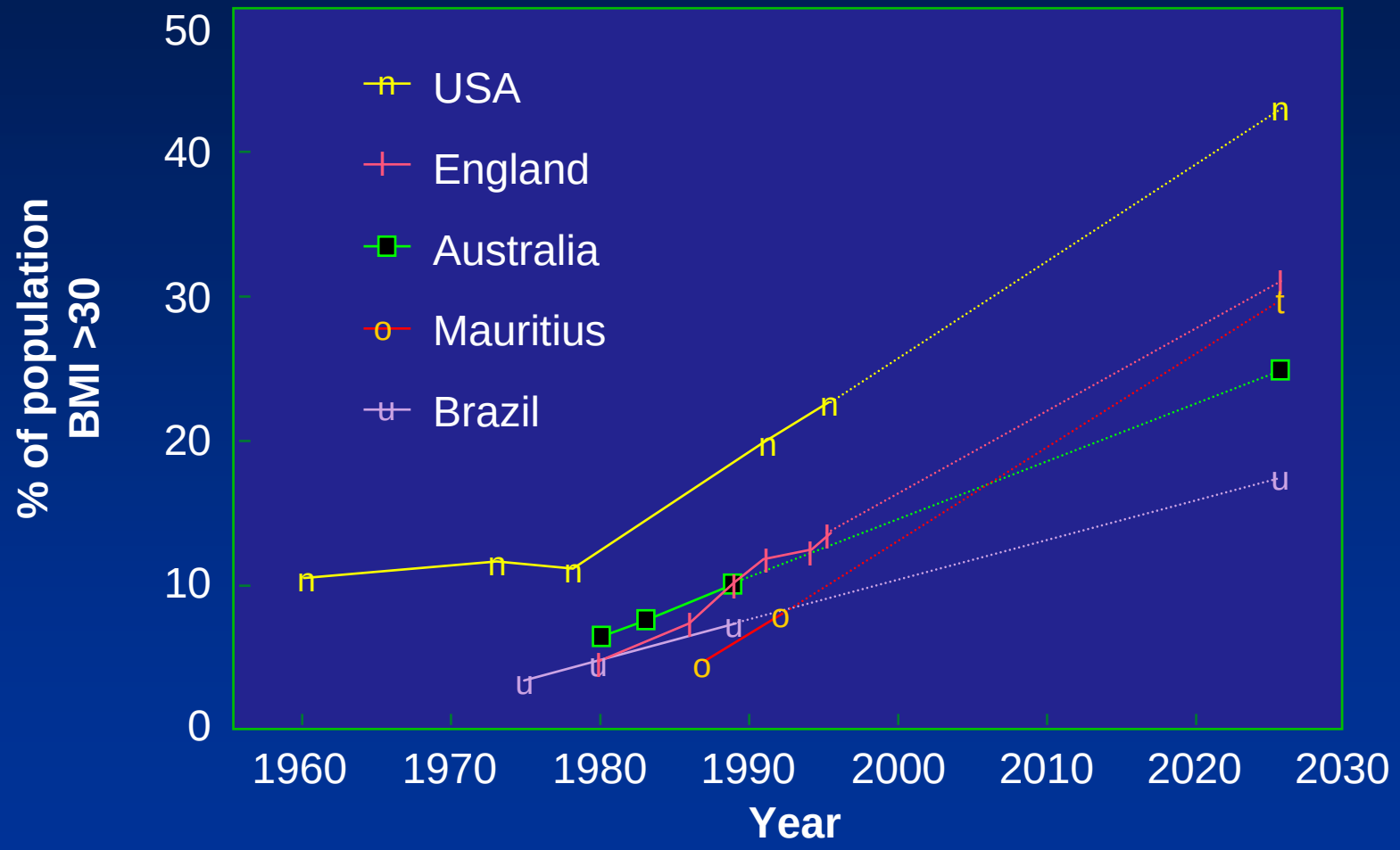
STEATOHEPATOPATHIES DYSMETABOLIQUES

SHNA/NAFLD vs NASH

Fatty liver hepatitis and cirrhosis in obese patients.

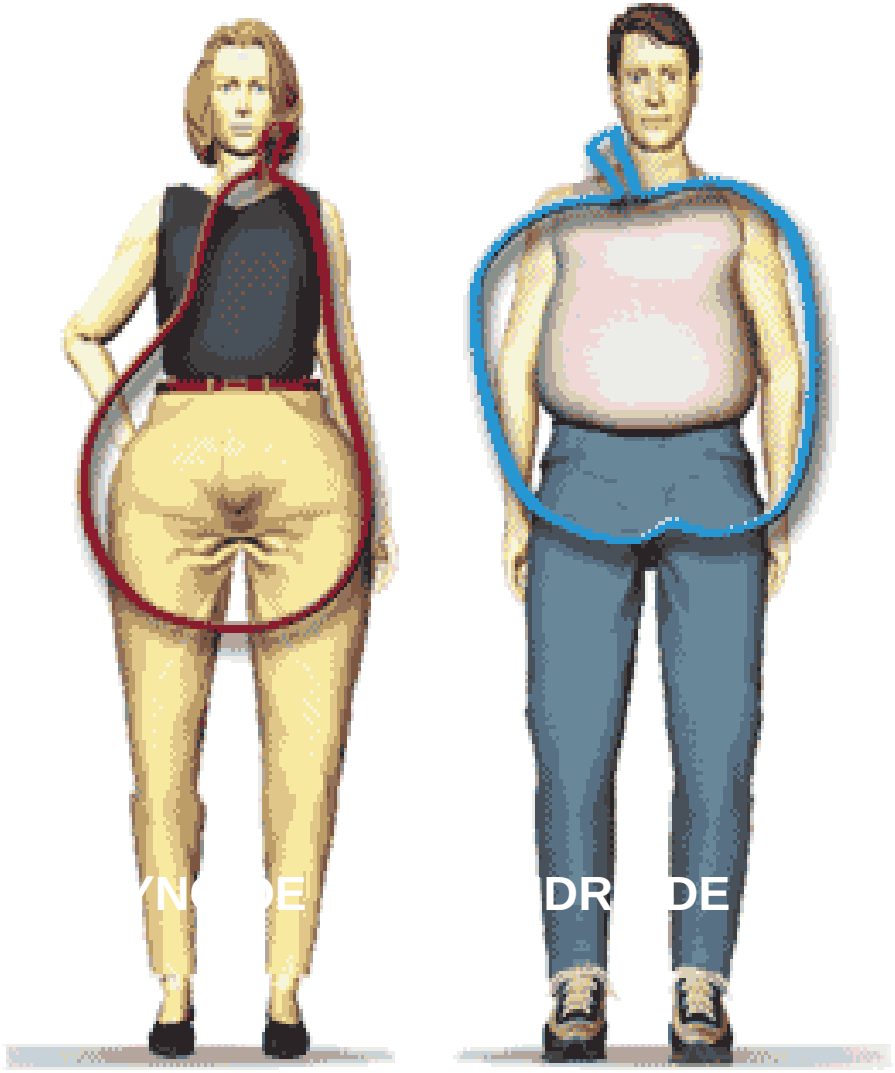
Adler M, Schaffner F. Am J Med. 1979

OBESITY RATES COULD DOUBLE IN 30 YEARS



Adapted from International Obesity Task Force Web site. Available at: http://www.rri.sari.ac.uk/iotf/slides/graph12.gif.Accessed August 11, 1998.

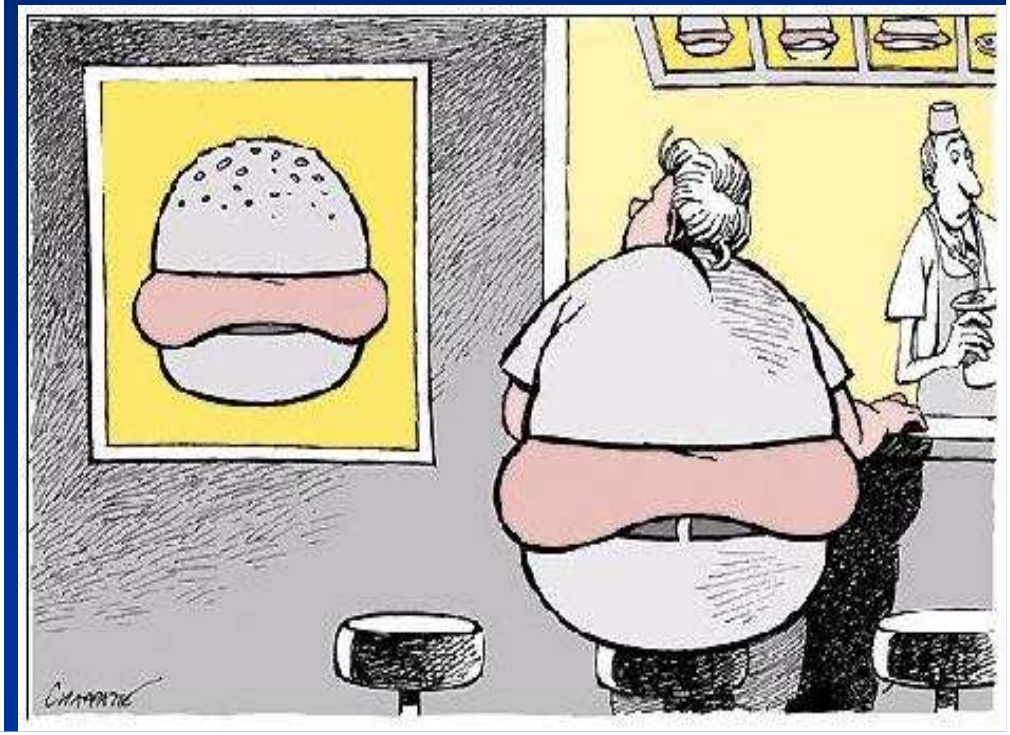
L’OBESITE =MALADIE DU SIECLE



Conséquence de la mal bouffe,

↘ Activité physique,

facteurs génétiques ??



OBESITE CHEZ L'ENFANT

>20 % UK*

Surpoids > 85th percentile

Obésité > 95 th percentile

PREVENTION AVANT TOUT !!!!!.....

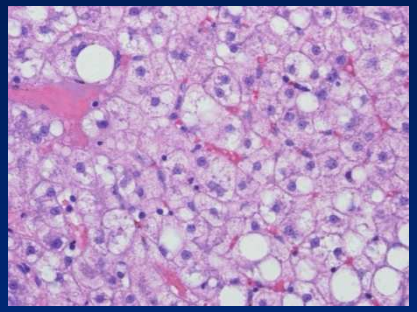
DE BRUYNE 2010*

Spectre de la NAFLD

Stéatose hépatique

POP.GENERALE

15--30 %

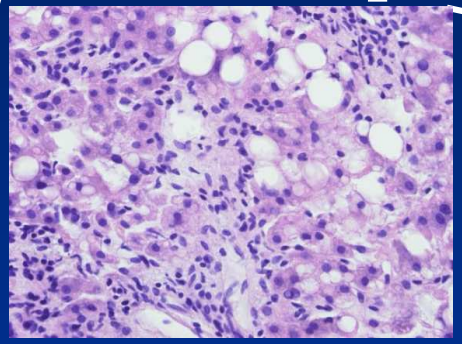


OBESITE

80 %

Stéatohépatite(NASH)

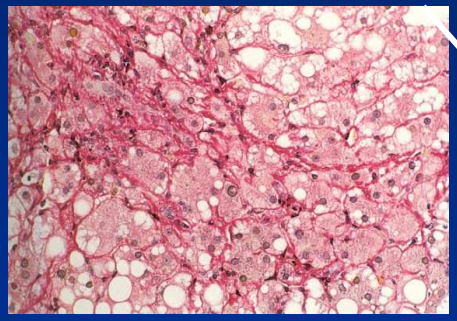
5 %



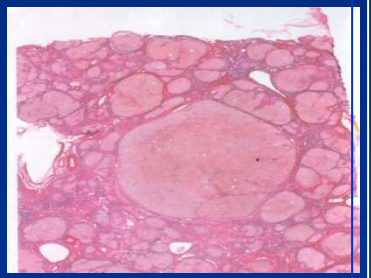
20 %

Fibrose

1 %



Cirrhose



4 -10 %

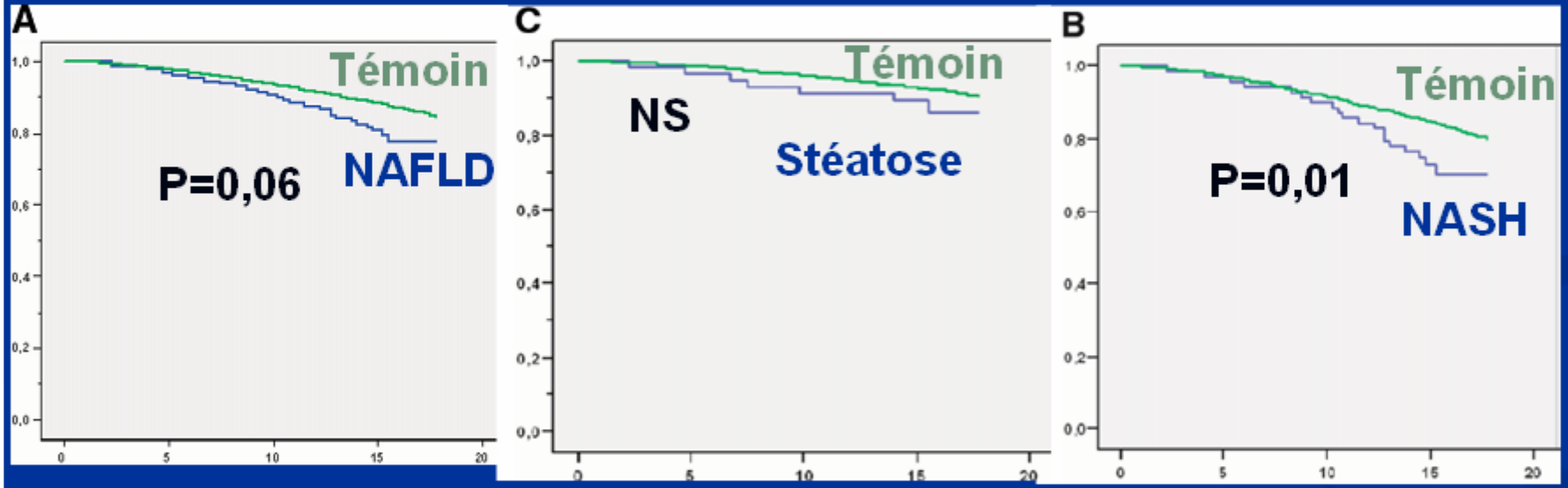
HepatoK

Pas de complications hépatiques en l'absence de fibrose

129 patients avec NAFLD + ALAT augmentées

Suivi moyen 13,7 ans; étude de la survie

Etude de la survie par rapport à une population témoin



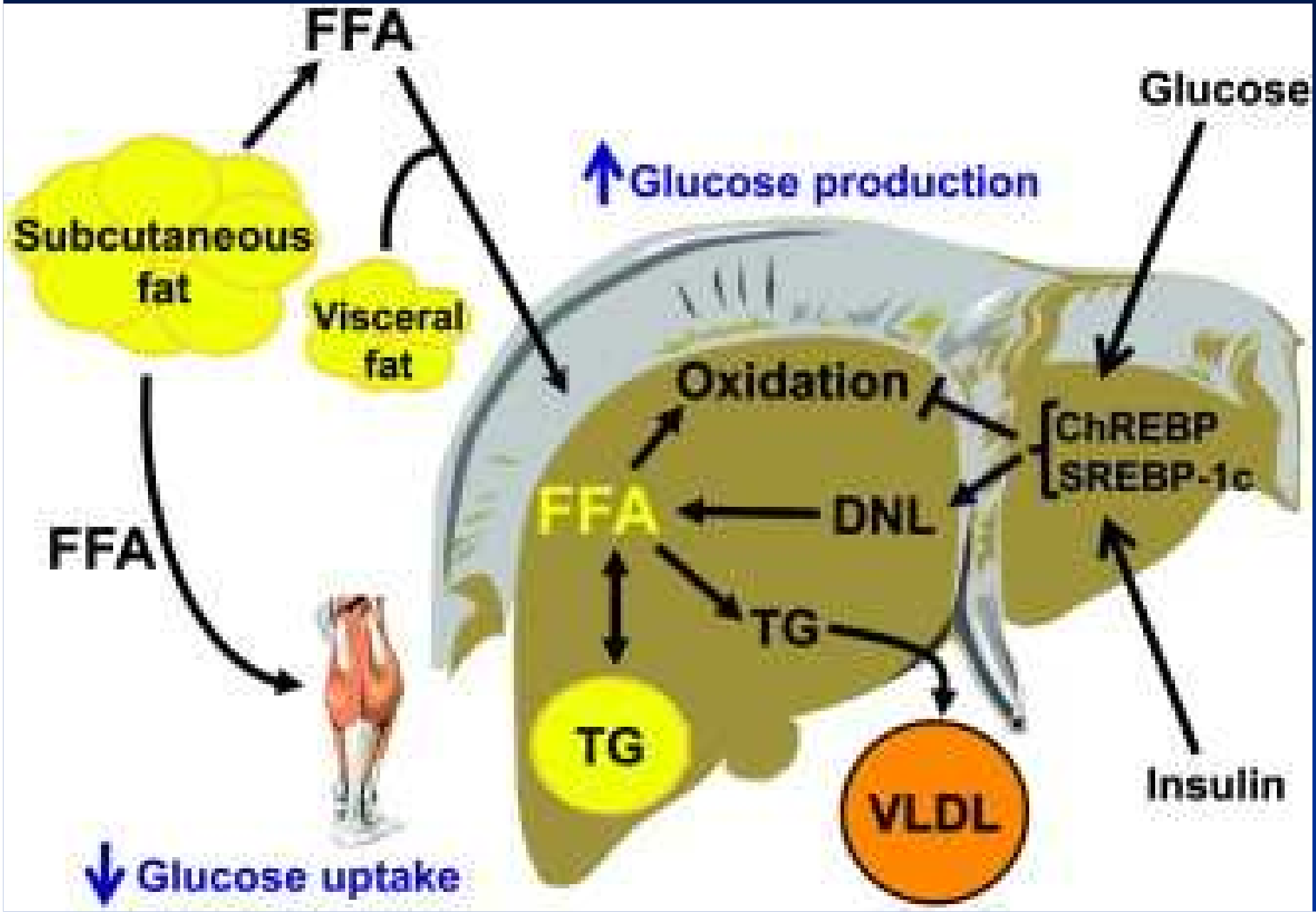
Absence de fibrose : VPN de complication hépatique 100 %

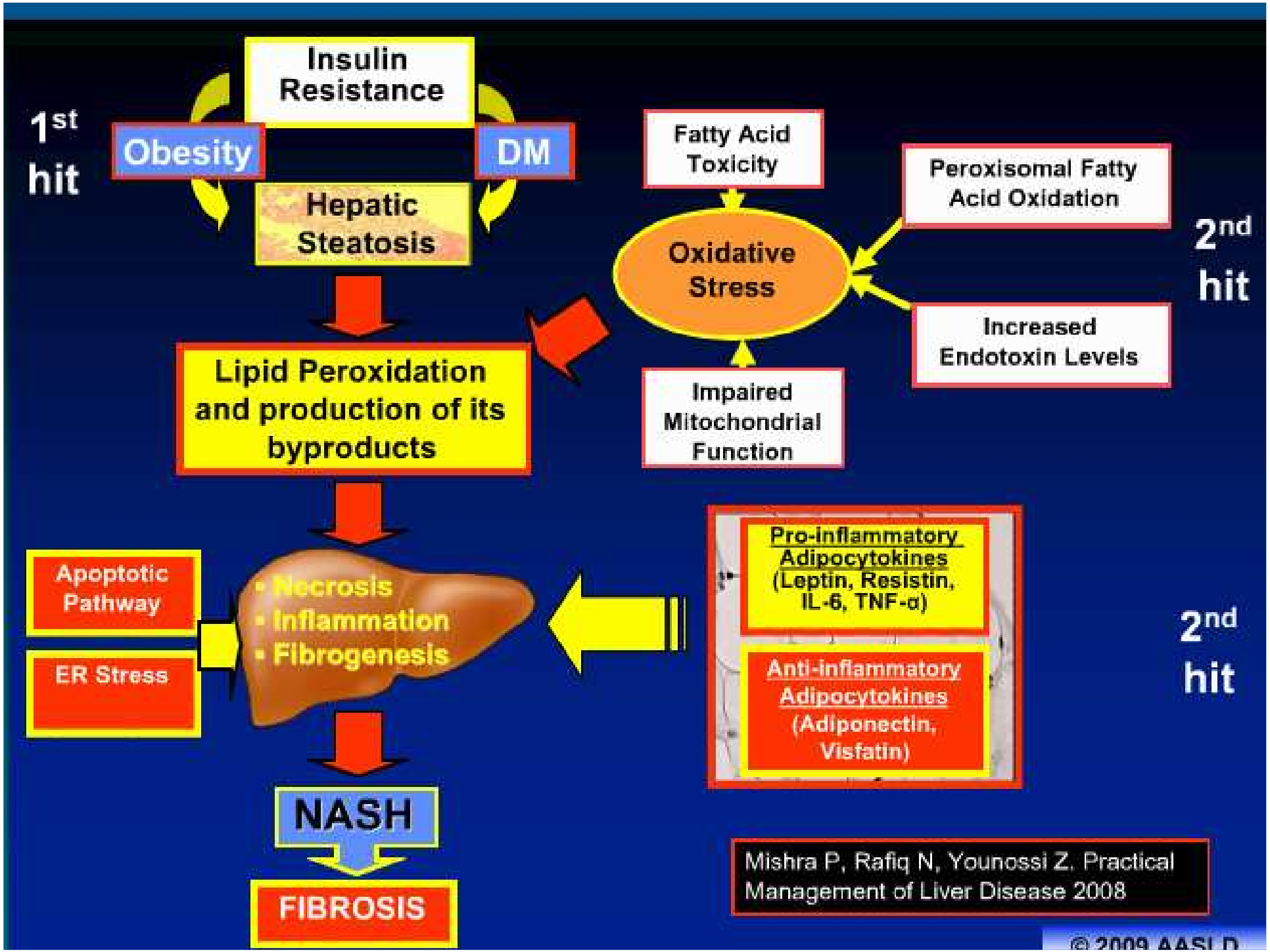
Mortalité

- cardio-vasculaire : 15,5 %
- néoplasie : 5,6 %
- hépatique : 2,8 % (vs 0,2 % population de référence)

Ekstedt *Hepatology* 20

PATHOGENIE DE LA NAFLD /NASH/FIBROSE 1ere ETAPE




1st hit
Insulin Resistance
Obesity
DM
Hepatic Steatosis
Lipid Peroxidation and production of its byproducts
Apoptotic Pathway
ER Stress
• Necrosis
• Inflammation
• Fibrogenesis
NASH
FIBROSIS
Fatty Acid Toxicity
Peroxisomal Fatty Acid Oxidation
Oxidative Stress
Increased Endotoxin Levels
Impaired Mitochondrial Function
2nd hit
Pro-inflammatory Adipocytokines (Leptin, Resistin, IL-6, TNF-α)
Anti-inflammatory Adipocytokines (Adiponectin, Visfatin)
2nd hit
Mishra P, Rafiq N, Younossi Z. Practical Management of Liver Disease 2008
© 2009 AASLD

Pathologies hépatiques alcooliques

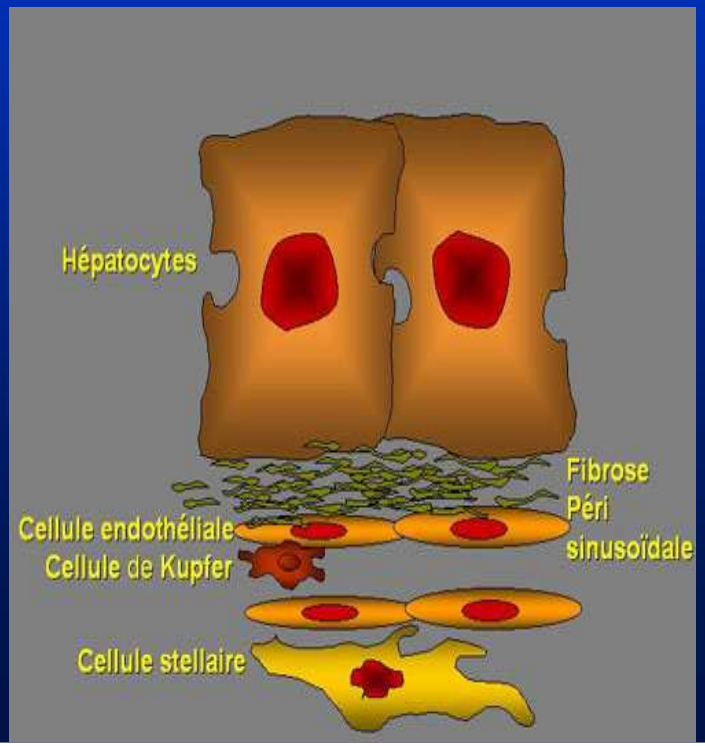
> 20 g/j F

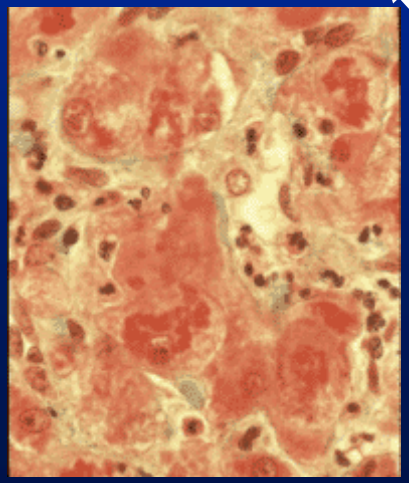
> 40 g/j H

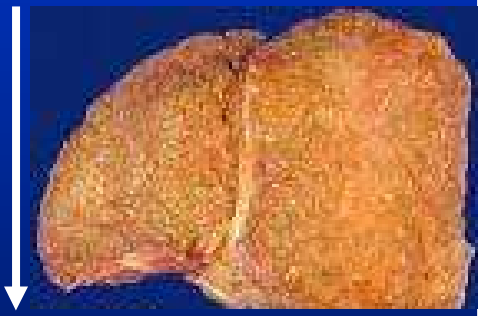
Foie normal → (90 %) **Stéatose** → (40-60 % > 25 ans) **STEATOFIBROSE**

Stéatose → **HAA**

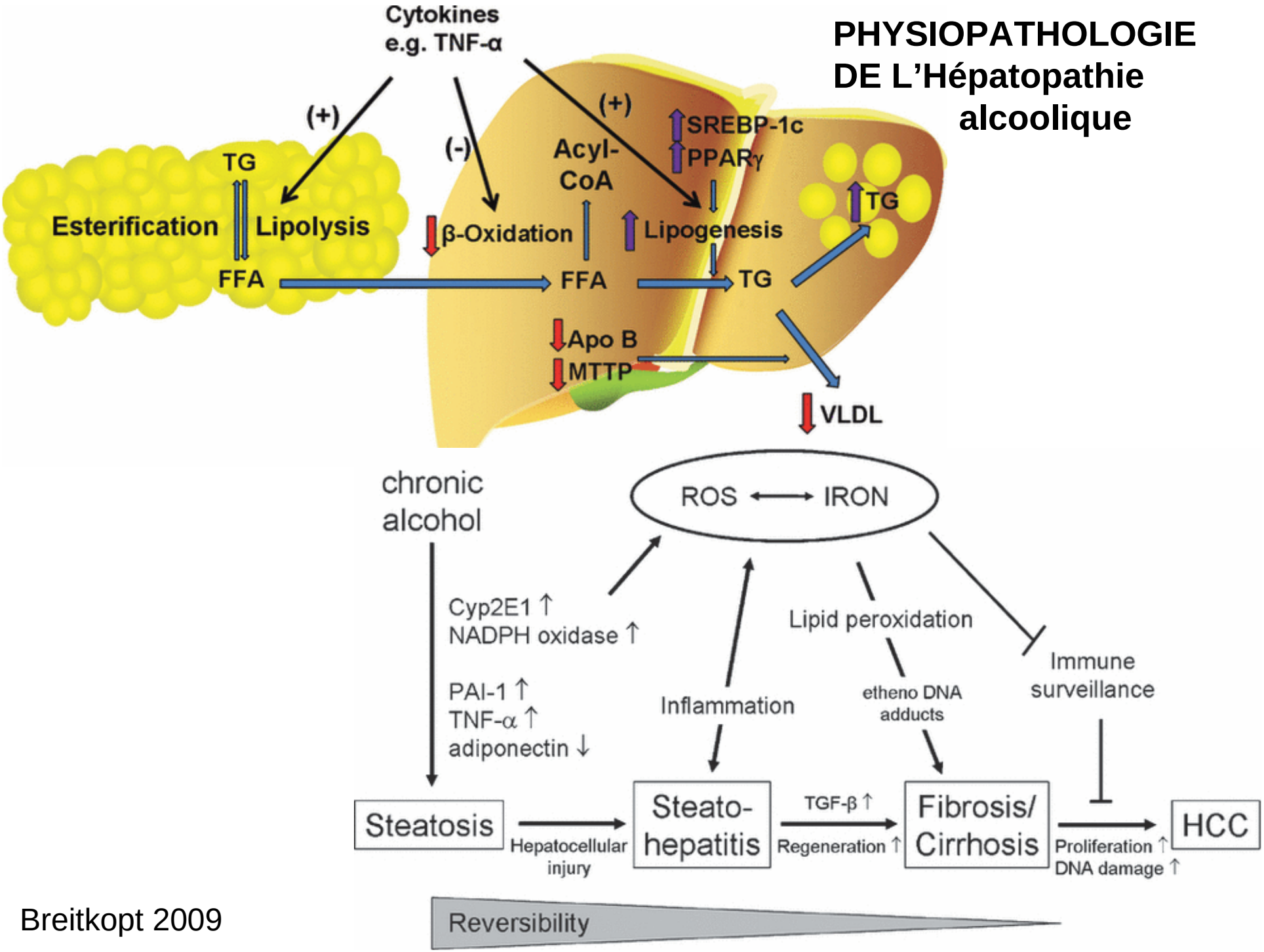
HAA → **Cirrhose** (30 %) → **HEPATOME**







PHYSIOPATHOLOGIE DE L'Hépatopathie alcoolique

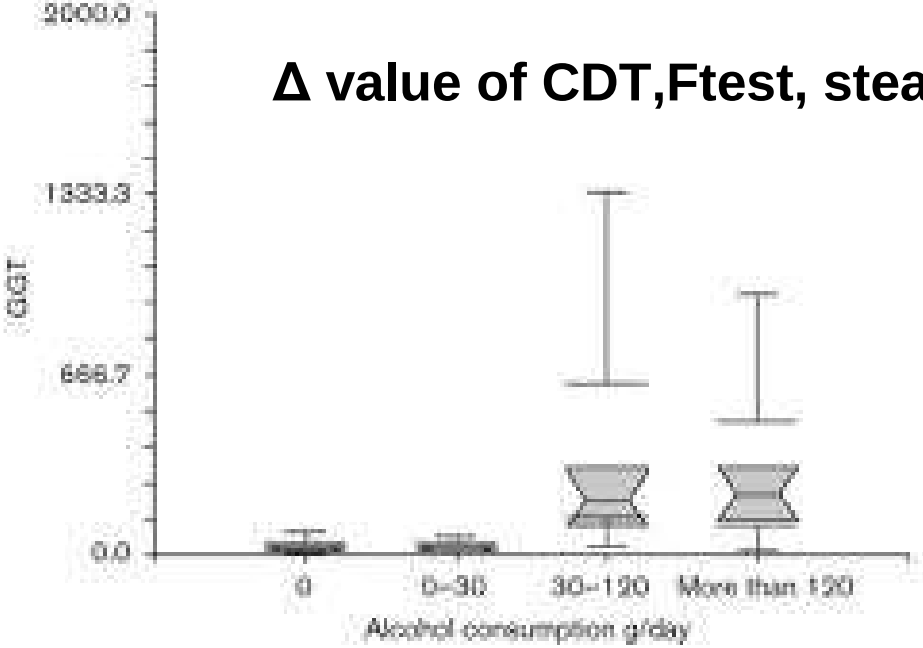


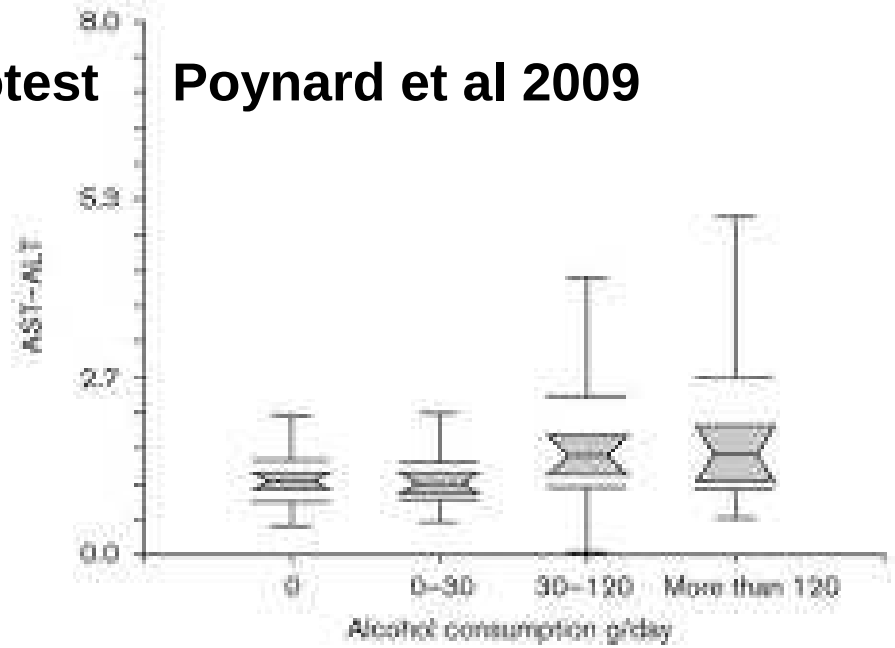
Breitkopt 2009

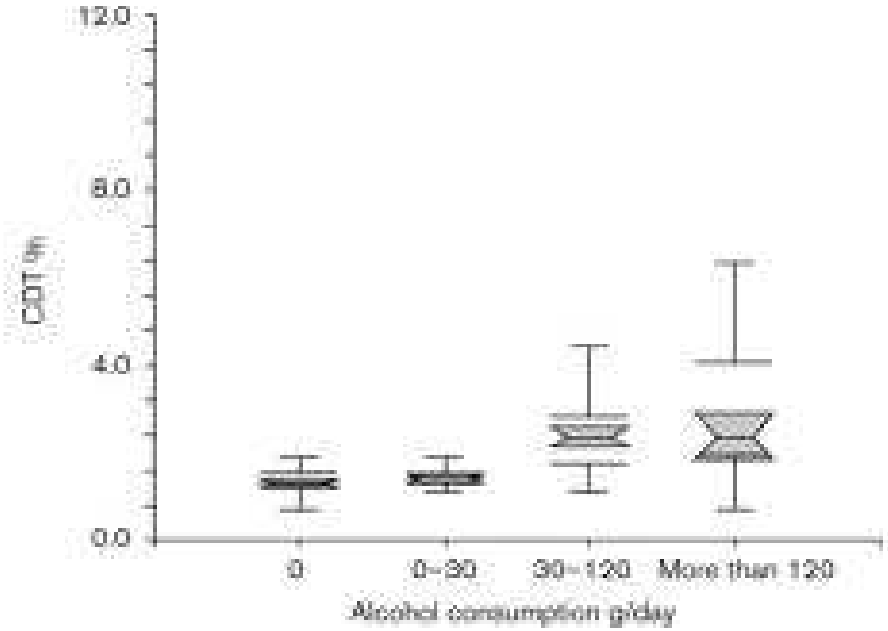
CDT et excès d’alcool

Δ value of CDT,Ftest, steatotest

Poynard et al 2009







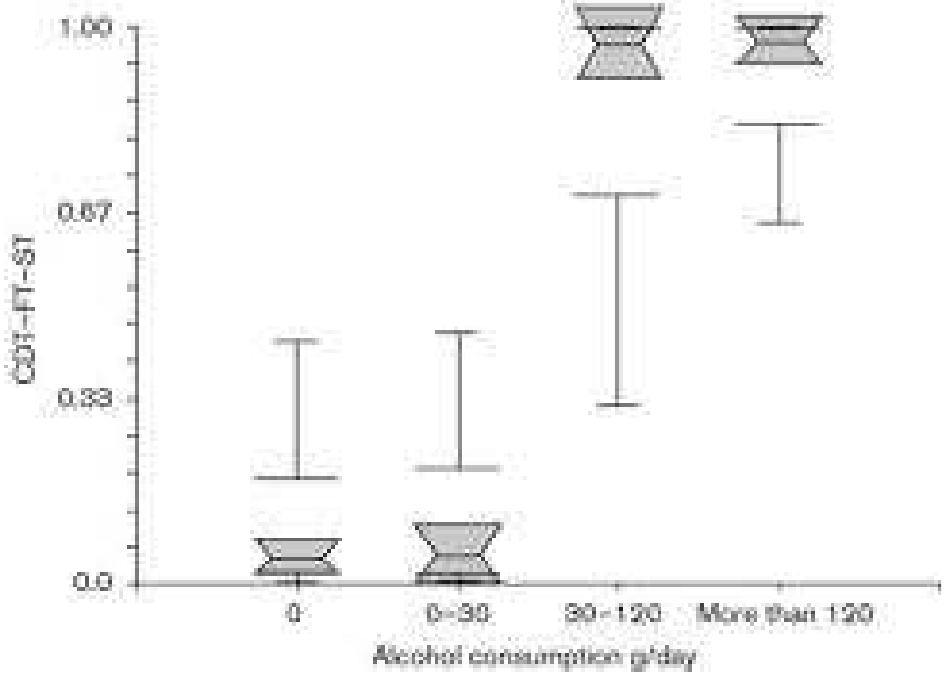
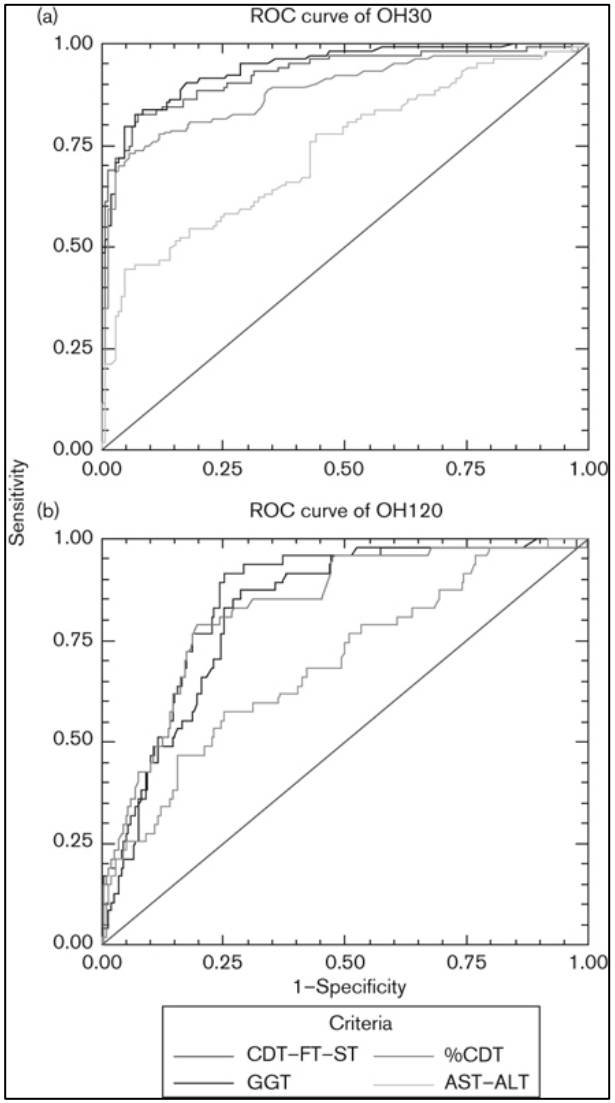


Fig. 2



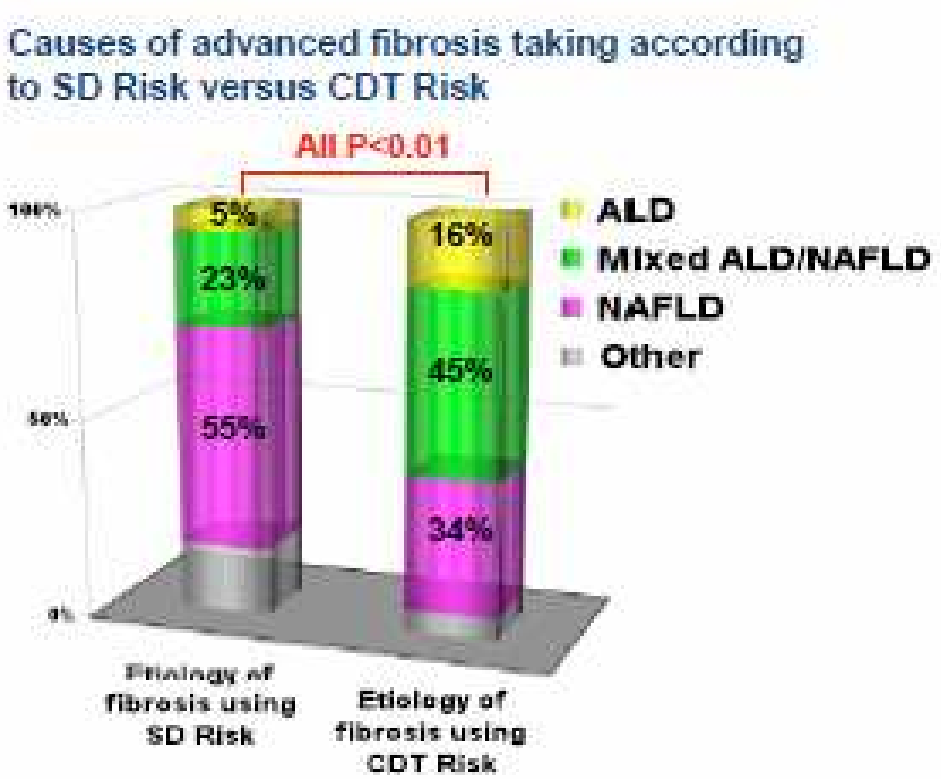
The diagnostic value of combining carbohydrate-deficient transferrin, fibrosis, and steatosis biomarkers for the prediction of excessive alcohol consumption.
Imbert-Bismut, Francoise; Naveau, Sylvie; Morra, Rachel; Munteanu, Mona; Ratziu, Vlad; Abella, Annie; Messous, Djamila; Thabut, Dominique; Benhamou, Yves; Poynard, Thierry

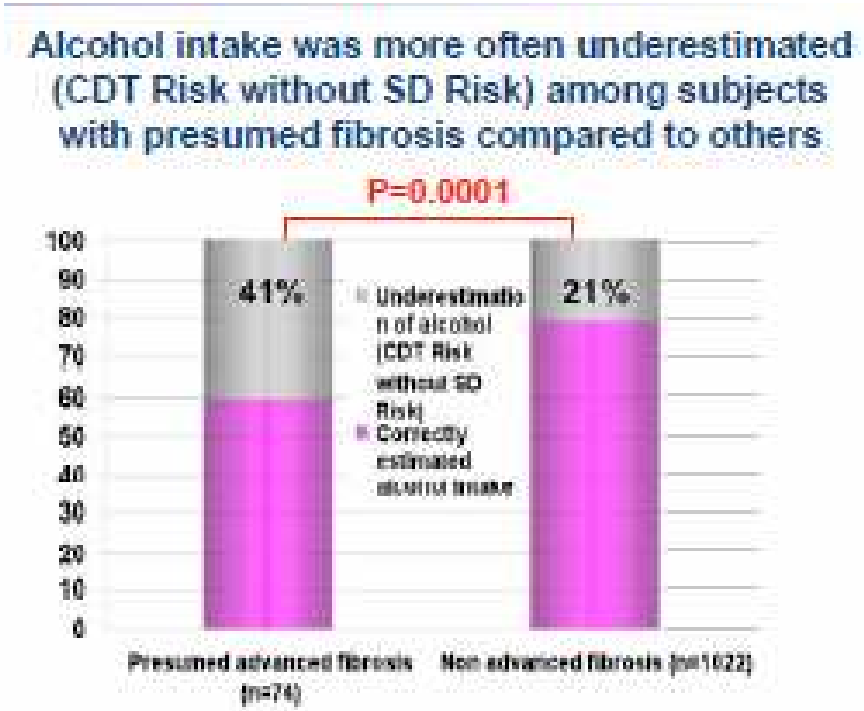
European Journal of Gastroenterology & Hepatology. 21(1):18-27, January 2009.
DOI: 10.1097/MEG.0b013e32830a4f4c

Fig. 2 Receiver operating characteristic (ROC) curves of biomarkers for the detection of excessive alcohol consumption of 30 g or more per day (a) and of 120 g or more per day (b). The diagonal line represents that achieved by chance alone [area under the receiver operating characteristic curve (AUROC) 0.50]; the ideal AUROC is 1.00. For the primary outcome, the detection of 30 g/day, the area under the curve of carbohydrate-deficient transferrin (CDT)-FibroTest (FT)- SteatoTest (ST) was 0.92 (95% confidence interval: 0.88-0.95), CDT% 0.88 (0.83-0.92) (P=0.004 vs. %CDT), [gamma]-glutamyl-transpeptidase (GGT) 0.94 (0.90-0.96), and 0.74 (0.66-0.79) for aspartate aminotransferase/alanine aminotransferase (AST/ALT), all highly significant versus 0.50 (PP=0.14 vs. %CDT), GGT 0.82 (0.75-0.87), and AST/ALT 0.69 (0.59-0.77), all highly significant versus 0.50 (P<0.0001).

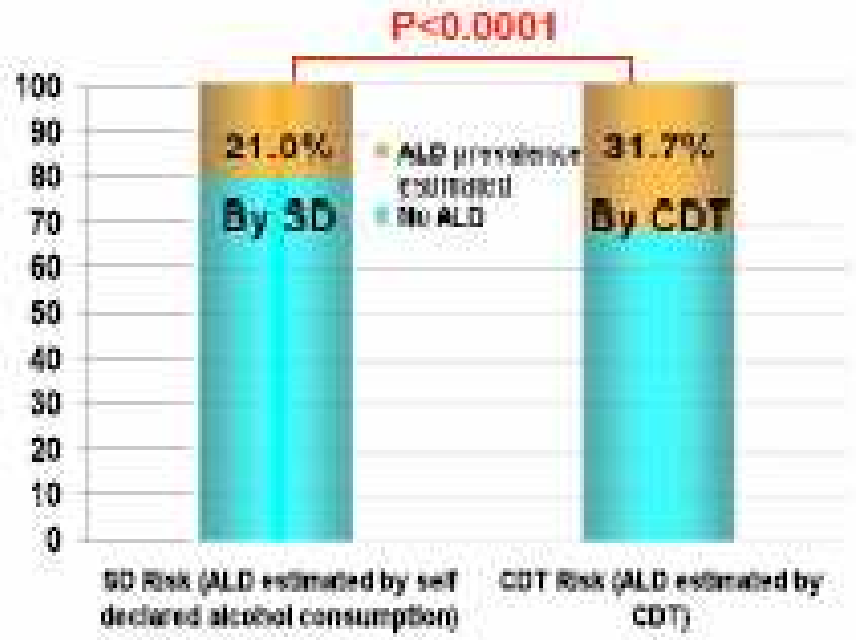
OVERESTIMATION OF « PURE » NAFLD AS A CAUSE OF LIVER FIBROSIS USING ALCOHOM CONSUMPTION ESTIMATED BY SD

Poynard et al

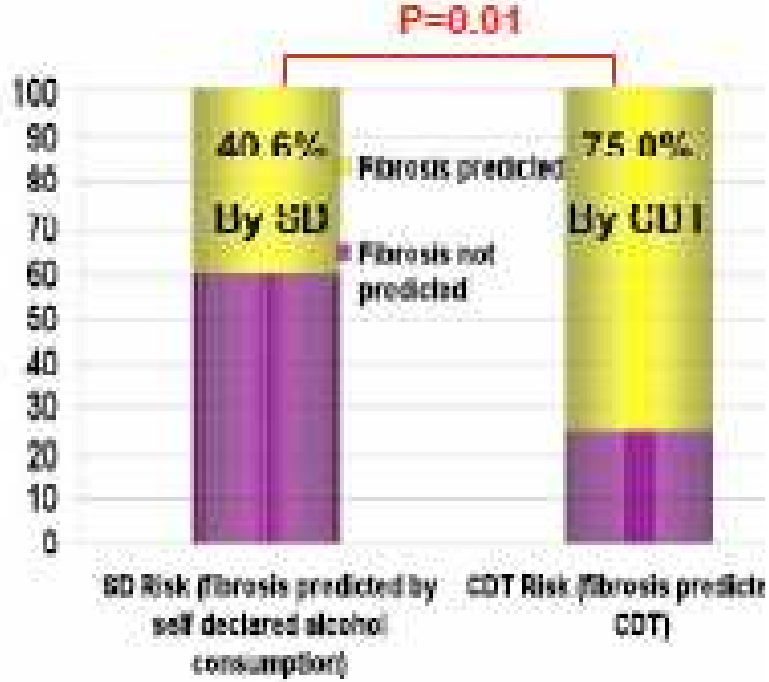




Higher ALD prevalence estimated using CDT versus self-declared alcohol consumption (SD)



Better prediction of *confirmed* advar fibrosis by using CDT versus SD R



Multivariate analyses: CDT predicted advanced fibrosis stronger than self declared (SD) risk

Factors	Odds ratio (OR)	P value
CDT	2.3	0.001
Self Declared consumption (SD)	0.99	NS

*Multivariate analyses included age, gender, metabolic factors

Triglycerides (a common marker of both metabolic and alcoholic risks) were no longer associated with advanced fibrosis after adjustment using CDT.

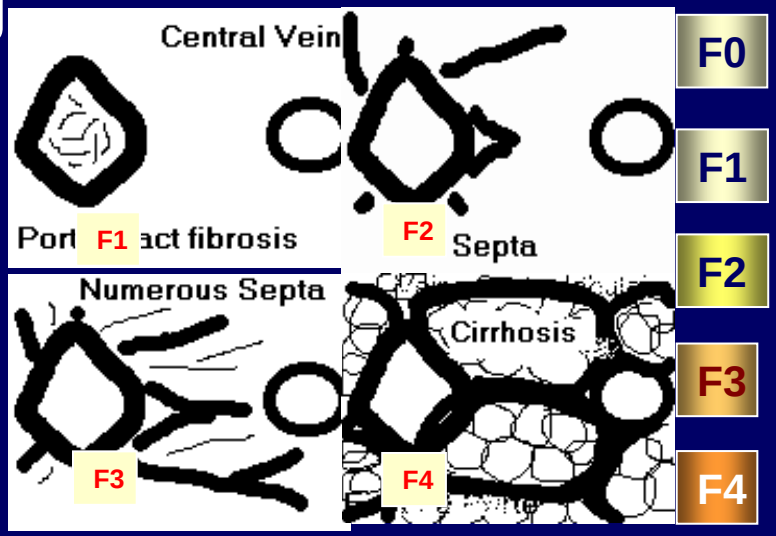
Poynard et al

Fibrosis progression
From contamination to complications

VHC infection

20% healing

80% carriers



10-50% en 20 ans

- Age (Bx & infection) > 40
- Alcool > 4-5 drinks /j
- Duration of infection
- gender
- Insulin resistance

  metb & viral
- Coinf VHB, VIH, Isupp.
- Cannabis

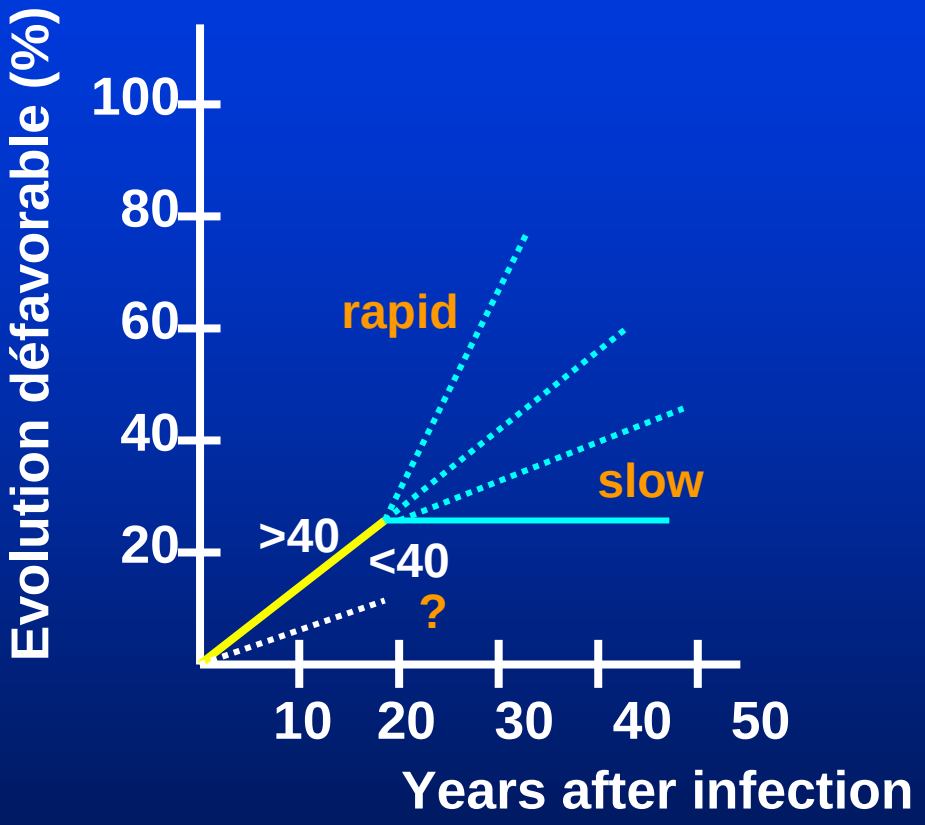
cirrhosis

Décompensation 3%, HCC 3-5% , 4 % † / y

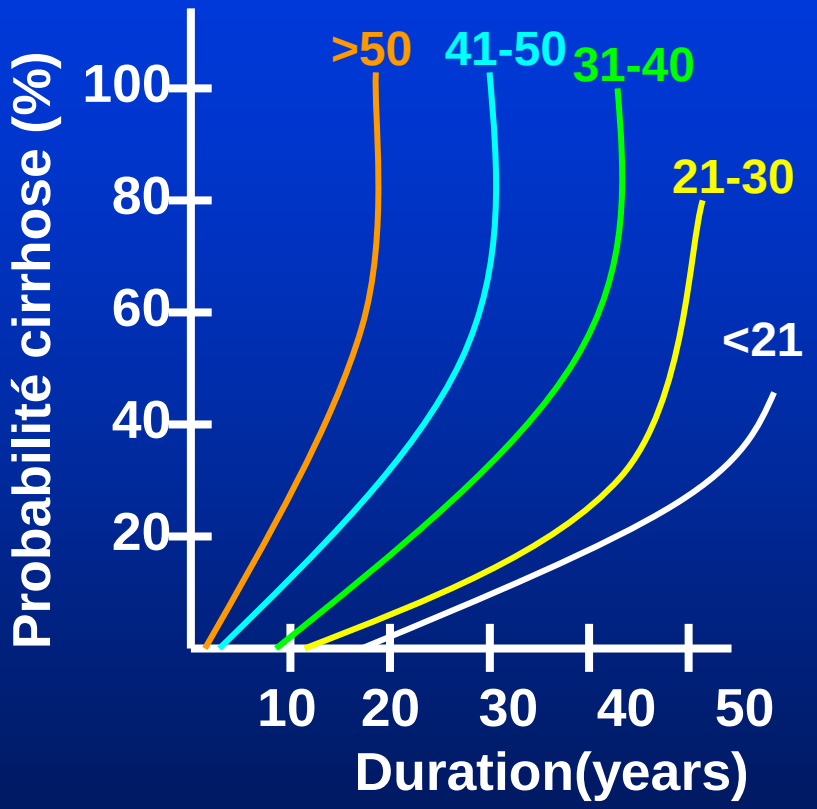
Massard 2006,Ratziu 2003

Sangiovanni 2006

HCV : fibrosis progression



Seef et al, Hepatology 2002
Zarski, J Hepatol 2003



Poynard et al, 2001

Factors not surely associated with fibrosis progression

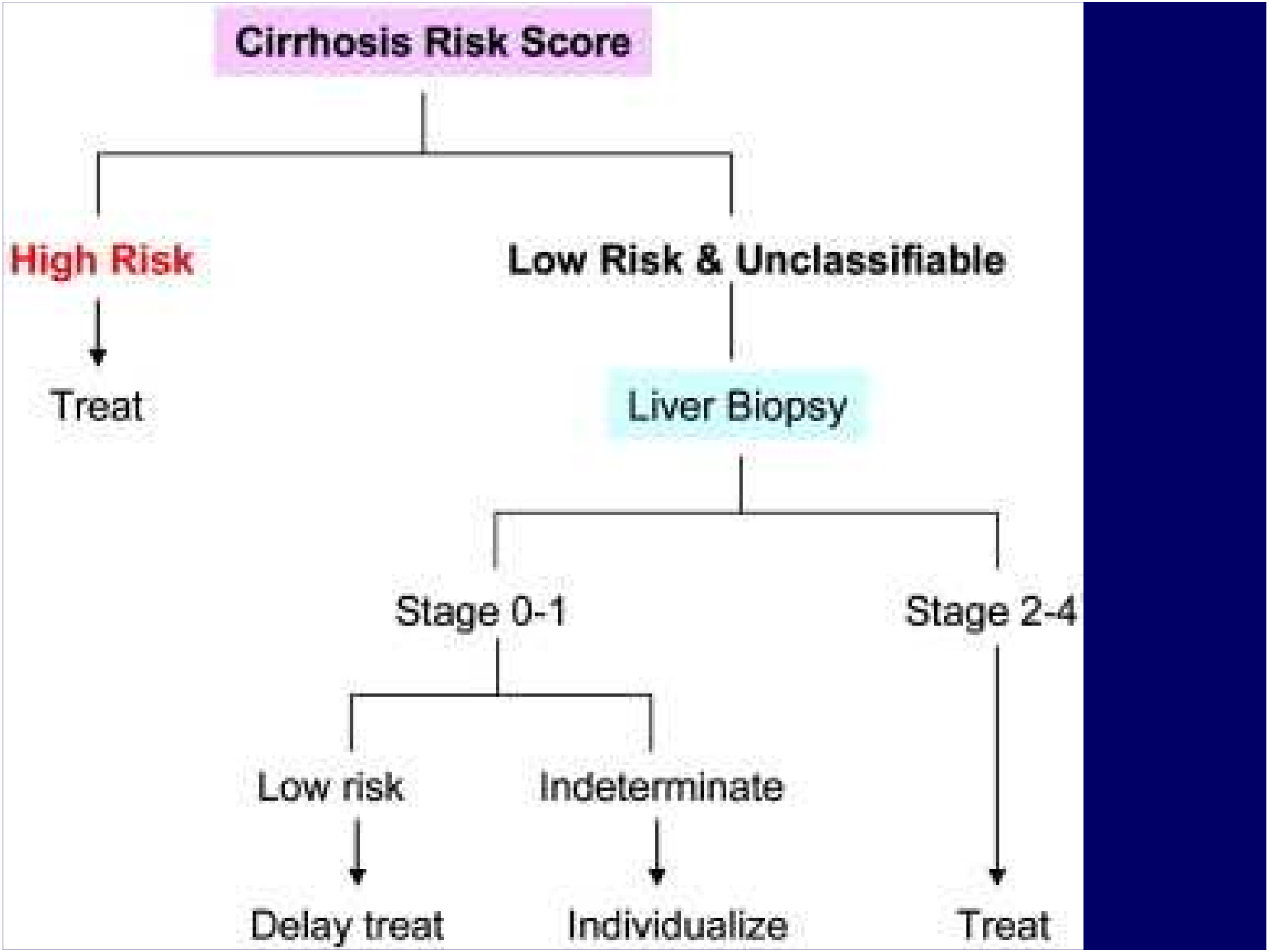
- Activity
- Iron overload
- Cigarette consumption
- Moderate alcohol
- Genotype 3

NOT SURE

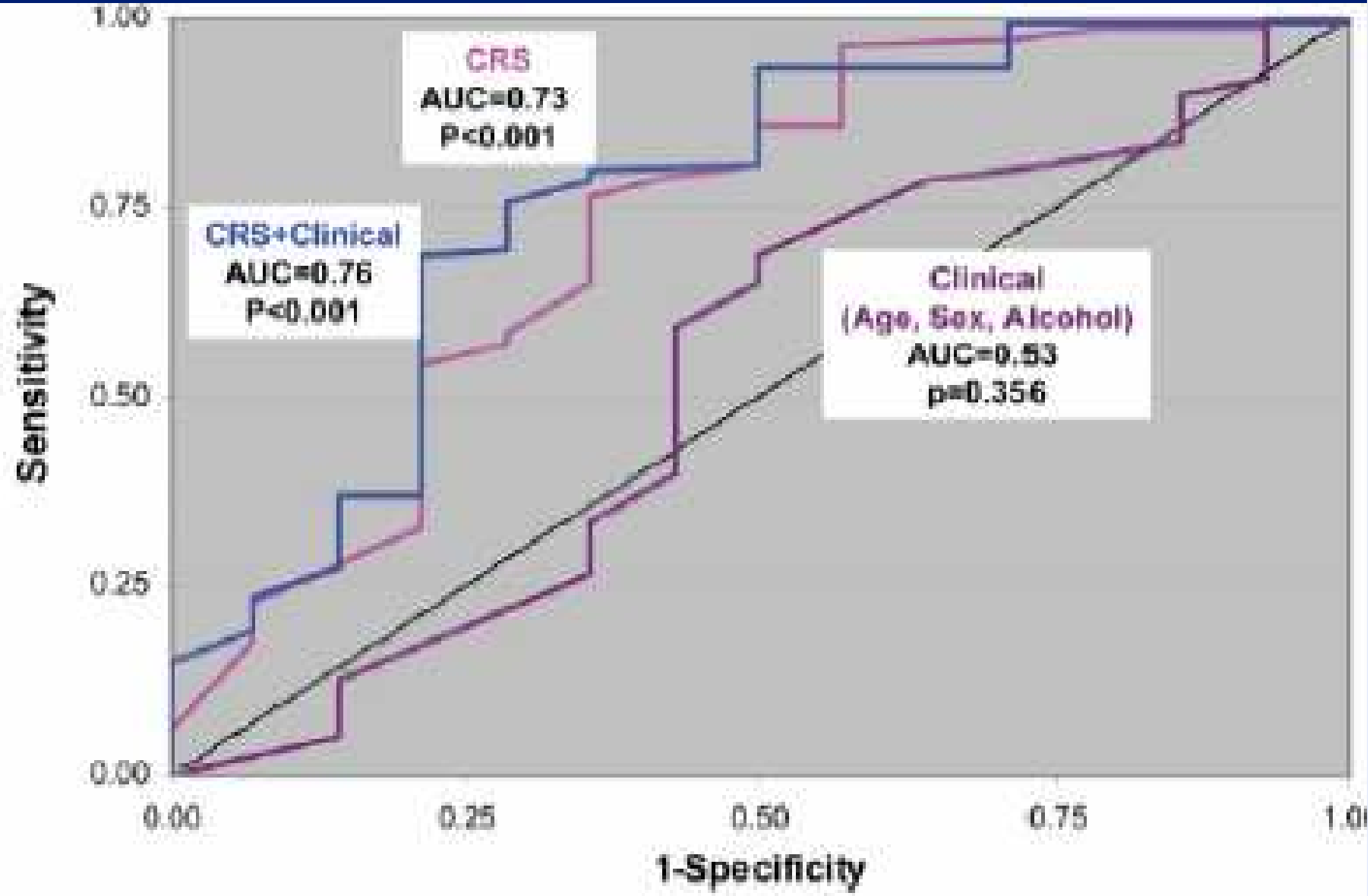
- Viral load
- Genotype
- Mode of infection
- Ethnicity

NOT ASSOCIATED

Massard 2006

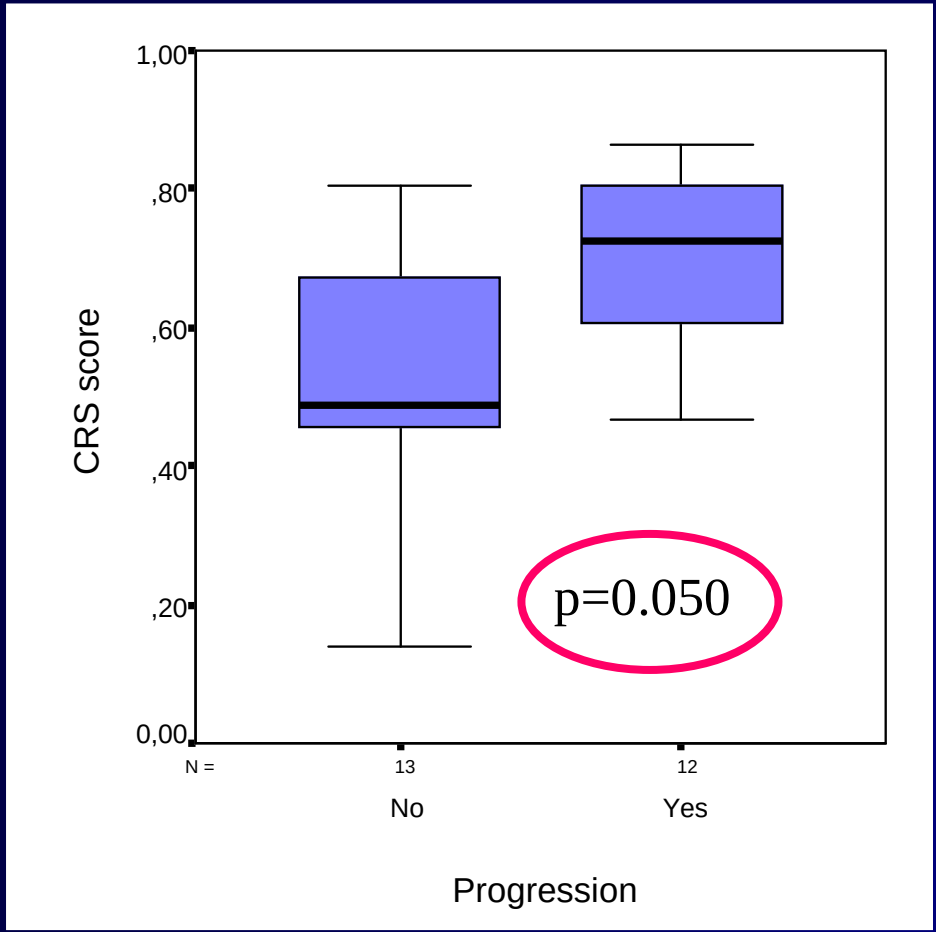

Cirrhosis Risk Score
High Risk
Low Risk & Unclassifiable
Treat
Liver Biopsy
Stage 0-1
Stage 2-4
Low risk
Indeterminate
Delay treat
Individualize
Treat

CIRRHOSIS RISK SCORE GENETIQUE



Huang 2006

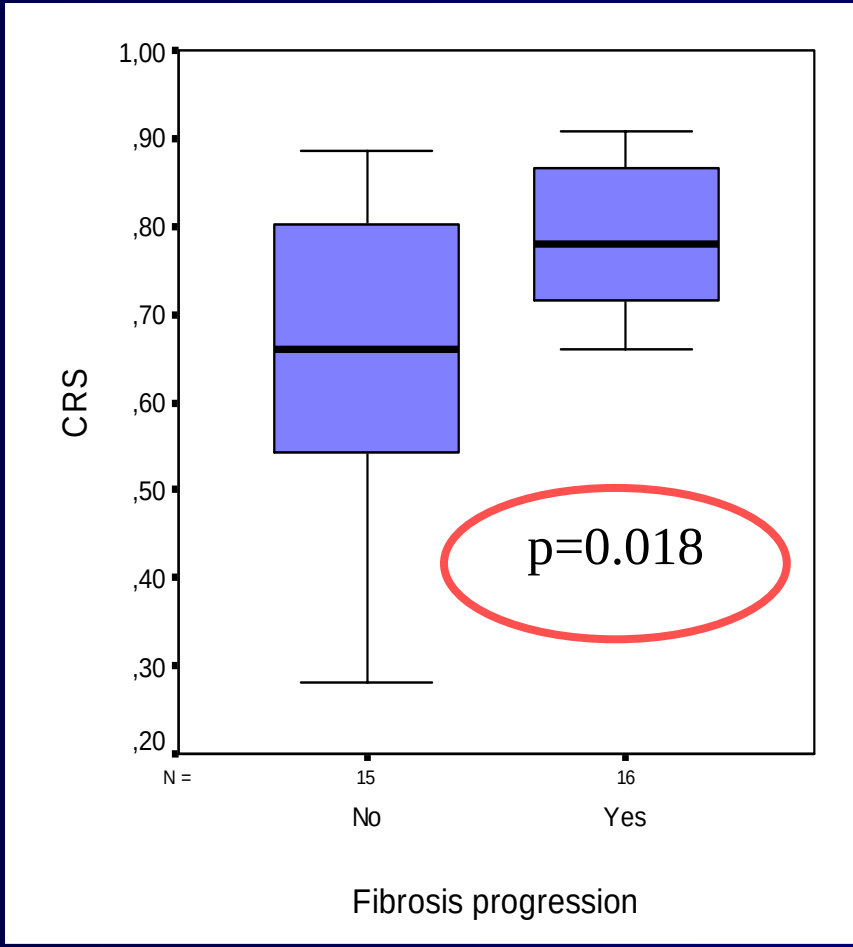
Brussels cohort - CRS in patients with or without fibrosis progression (n=25)



	N	Median CRS	Mean CRS
Progression No	13	,49	,53
Yes	12	,72	,68

CRS is predictive of fibrosis progression in F0-F1 patients

Hannover cohort - CRS in patients with or without fibrosis progression (n=31)



		N	Median CRS	Mean CRS
Fibrosis progression	No	15	,66	,63
	Yes	16	,78	,78

Combined cohorts (n=56)
ROC curve

CRS threshold defined by the ROC curve: 0.678

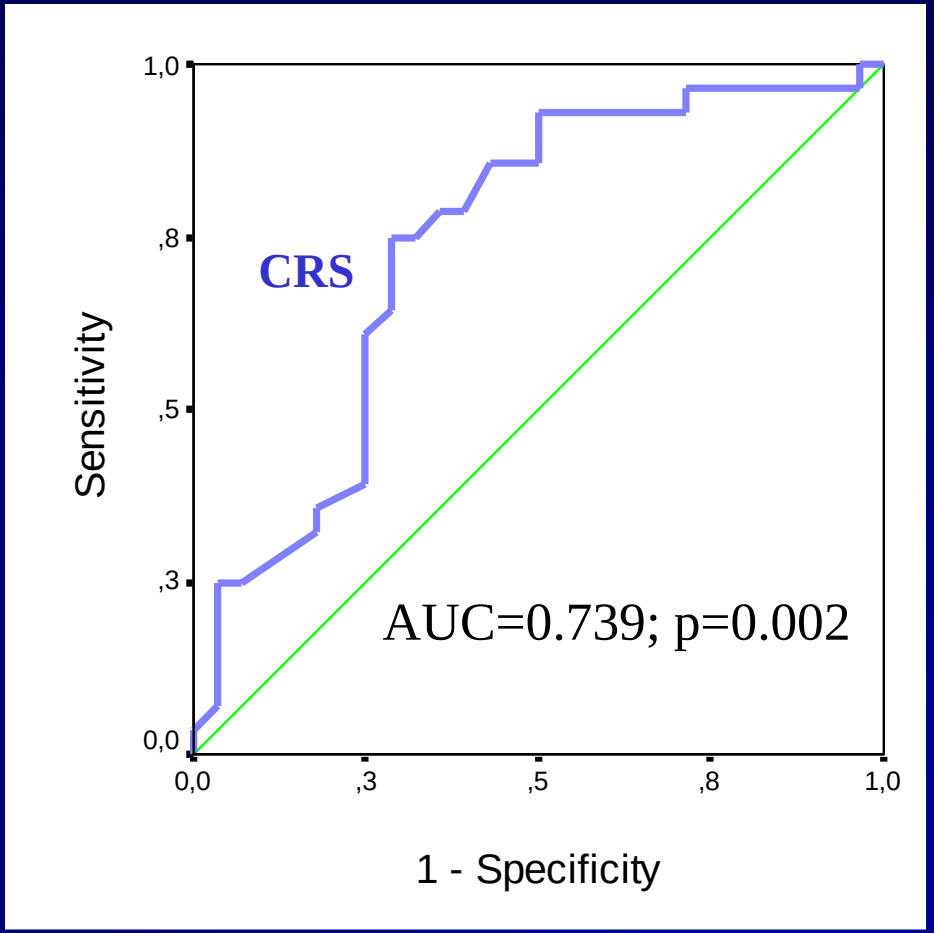
Se = 75%

Sp = 71%

PPV = 72%

NPV = 74%

Diagnostic accuracy = 73%

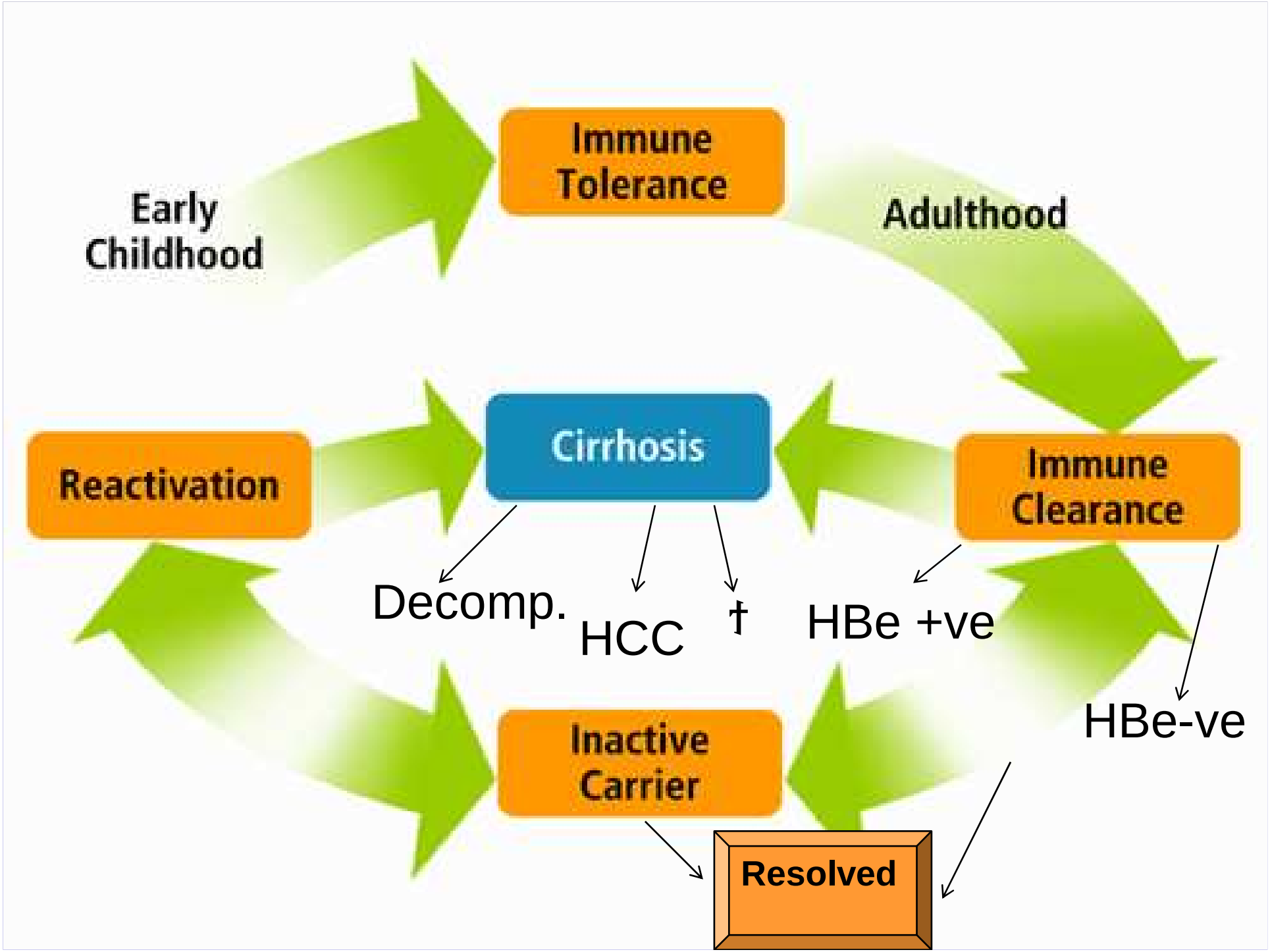


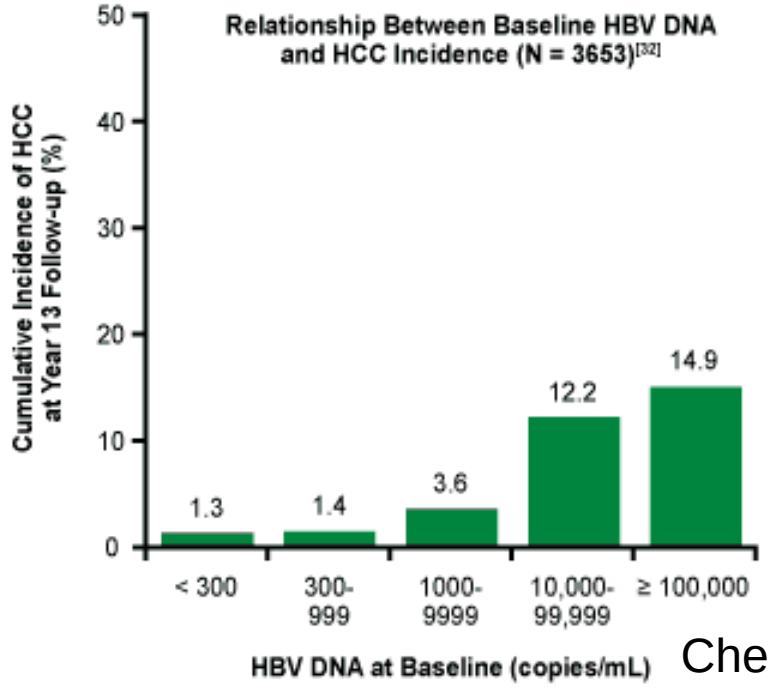
Study cut-off similar to previous cut-off by Huang et al (0.7)

Using the 0.678 threshold defined by the ROC curve:

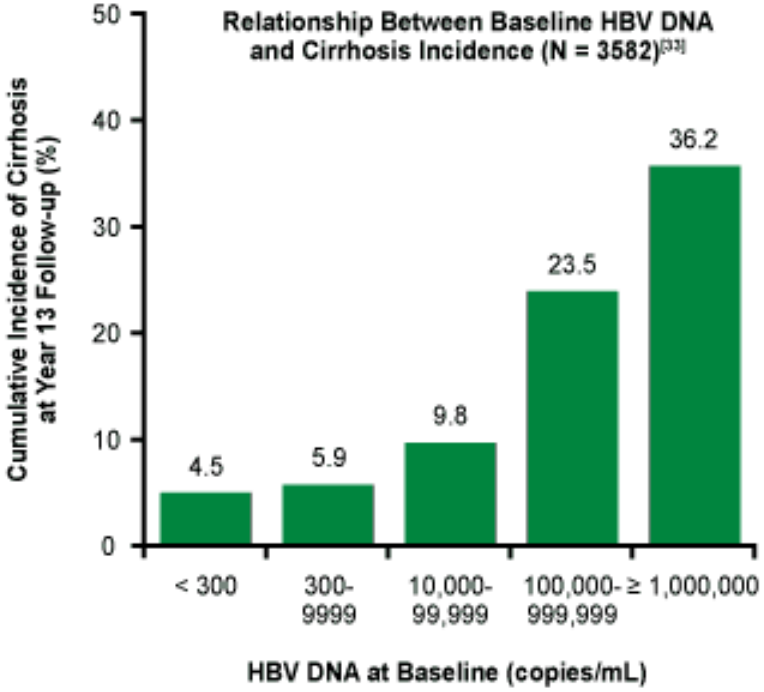
	% progressors
<=0.678	26%
>0.678	72%

p=0.001


Immune Tolerance
Early Childhood
Adulthood
Reactivation
Cirrhosis
Immune Clearance
Decomp.
HCC
†
HBe +ve
HBe-ve
Inactive Carrier
Resolved

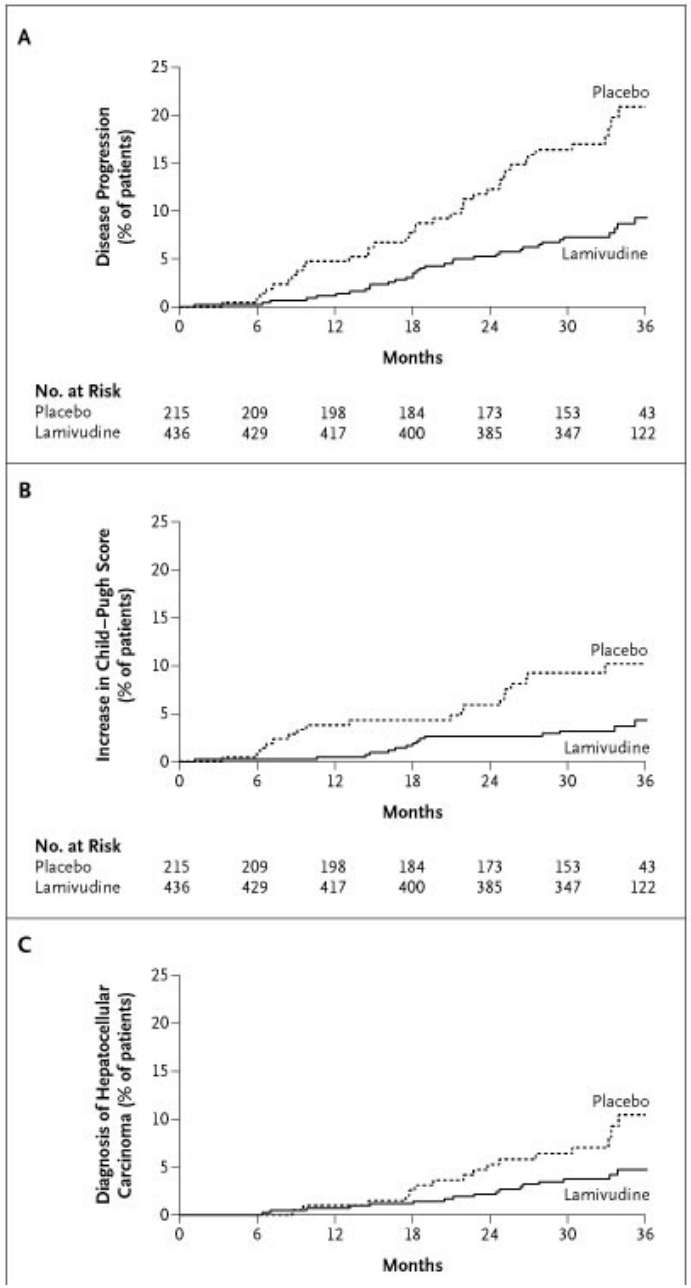


Chen et al JAMA 2006



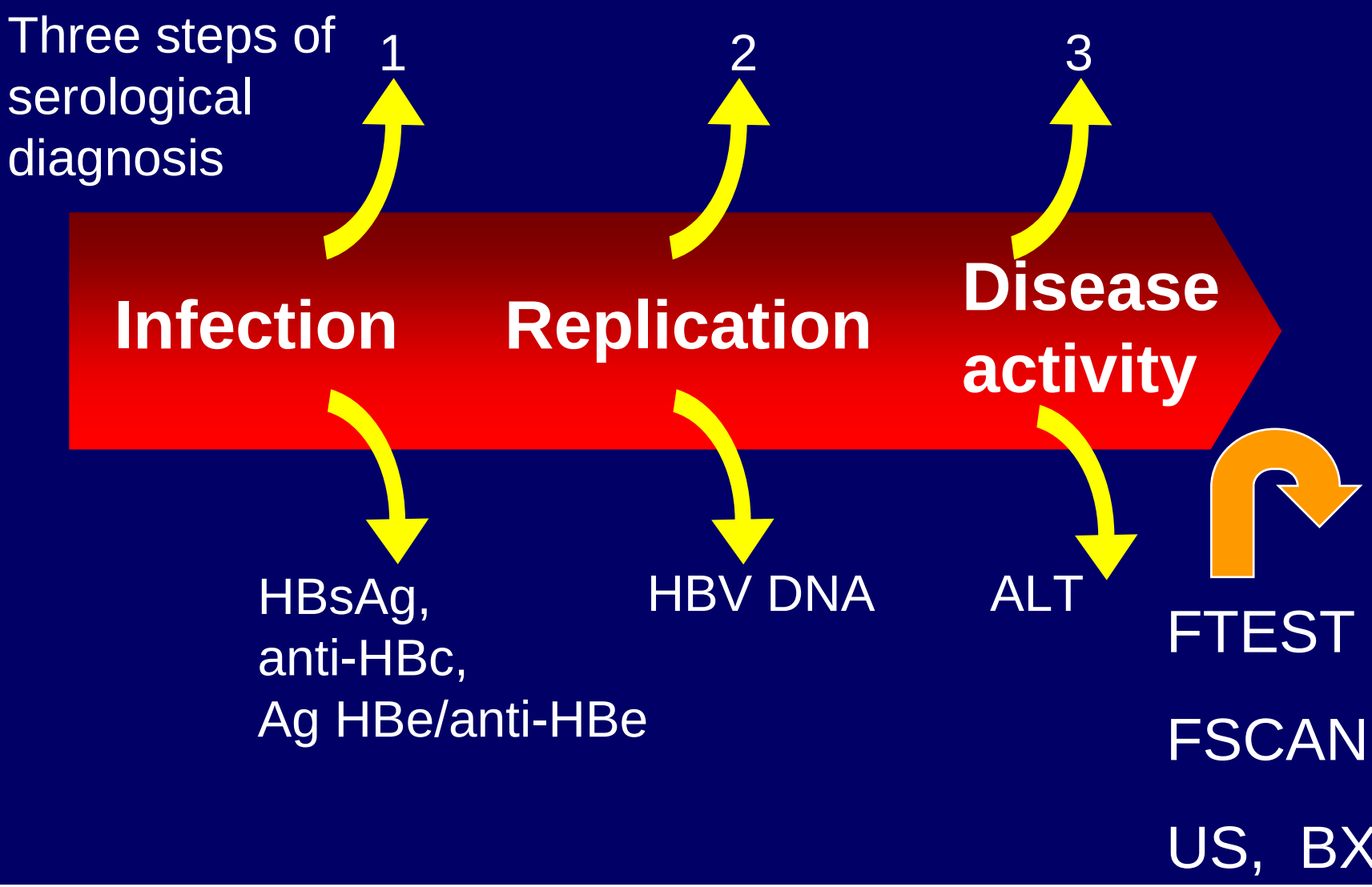
Iloeje et al

GE 2006

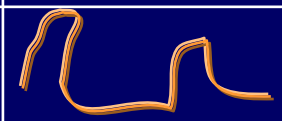
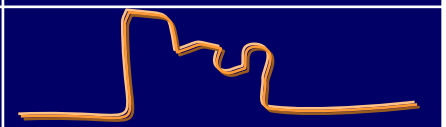


Liaw, Y. et al. N Engl J Med 2004;351:1521-1531

INITIAL WORK UP

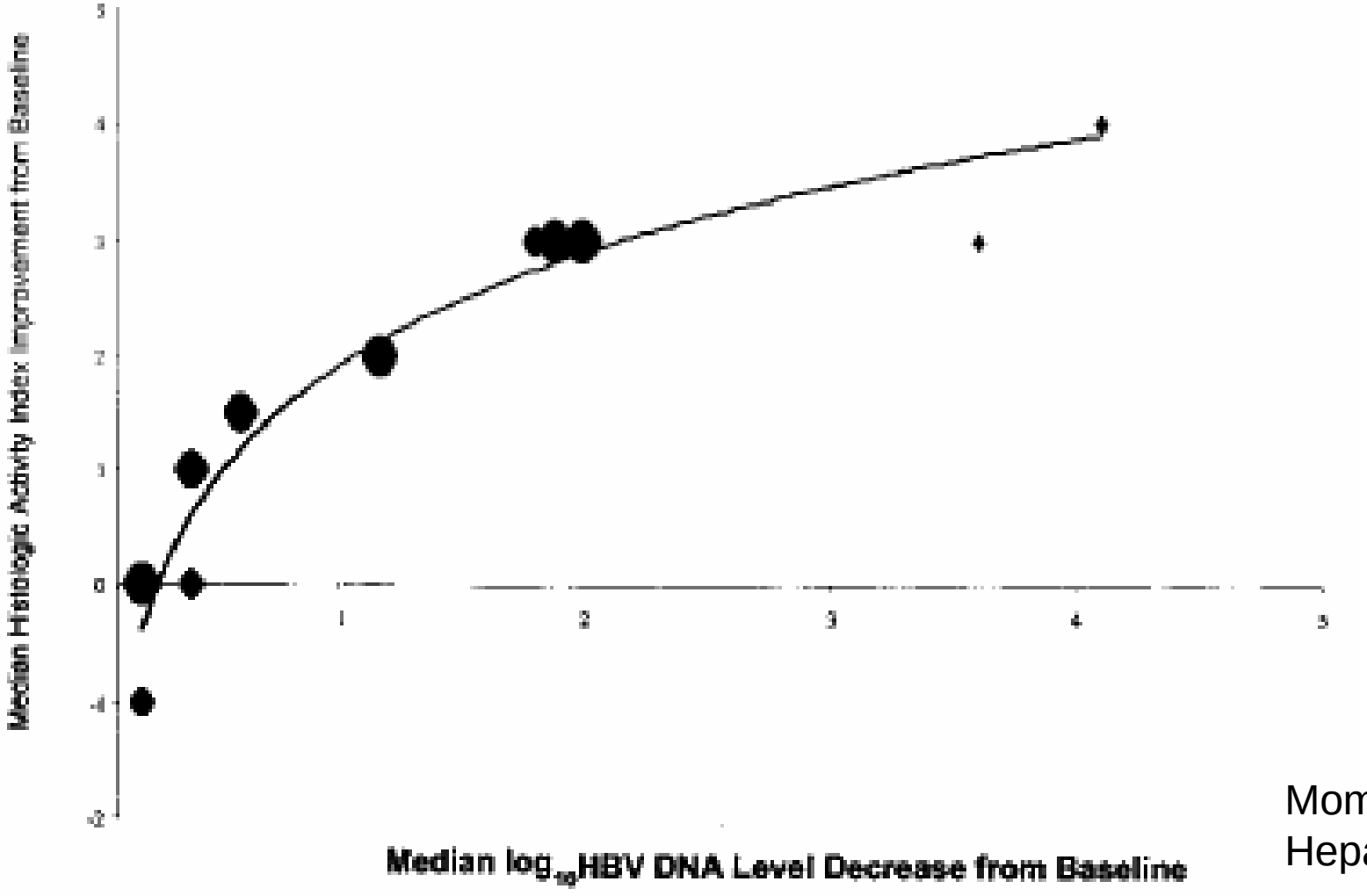


PROFILES OF CHRONIC HBV CARRIERS

	Inactive carrier	Immuno tolerant	Chron Hep Wild Virus	Chron Hep Precore mutant
AgHBe	-	+	+	-
antiHBe	+	-	-	+
ALT	p N	p N		
DNA IU	≤2.000	>2.10^6	>20.000	>2.000
TRMT considered	NO	> 30yo /Fib.	YES	YES

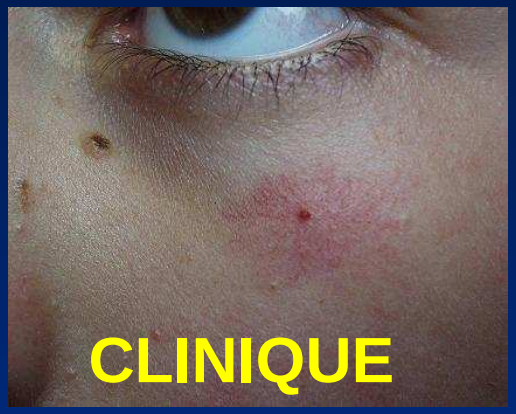
FOLLOW UP !!!!!

DIRECT CORRELATION BETWEEN A DECREASE IN VIRAL LOAD AND IMPROVED HISTOLOGY FOLLOWING ANTIVIRAL THERAPY



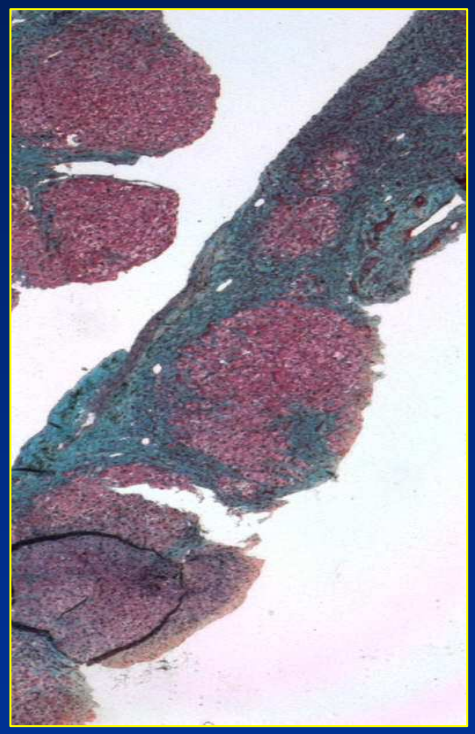
Mommeja-Marin
Hepatology 2003

DIAGNOSTIC D'UNE CIRRHOSE COMPENSEE A Σ



CLINIQUE

Angiomes ,foie dur
splénomégalie



BIOPSIE

SCORES DE FIBROSE/FIBROSCAN

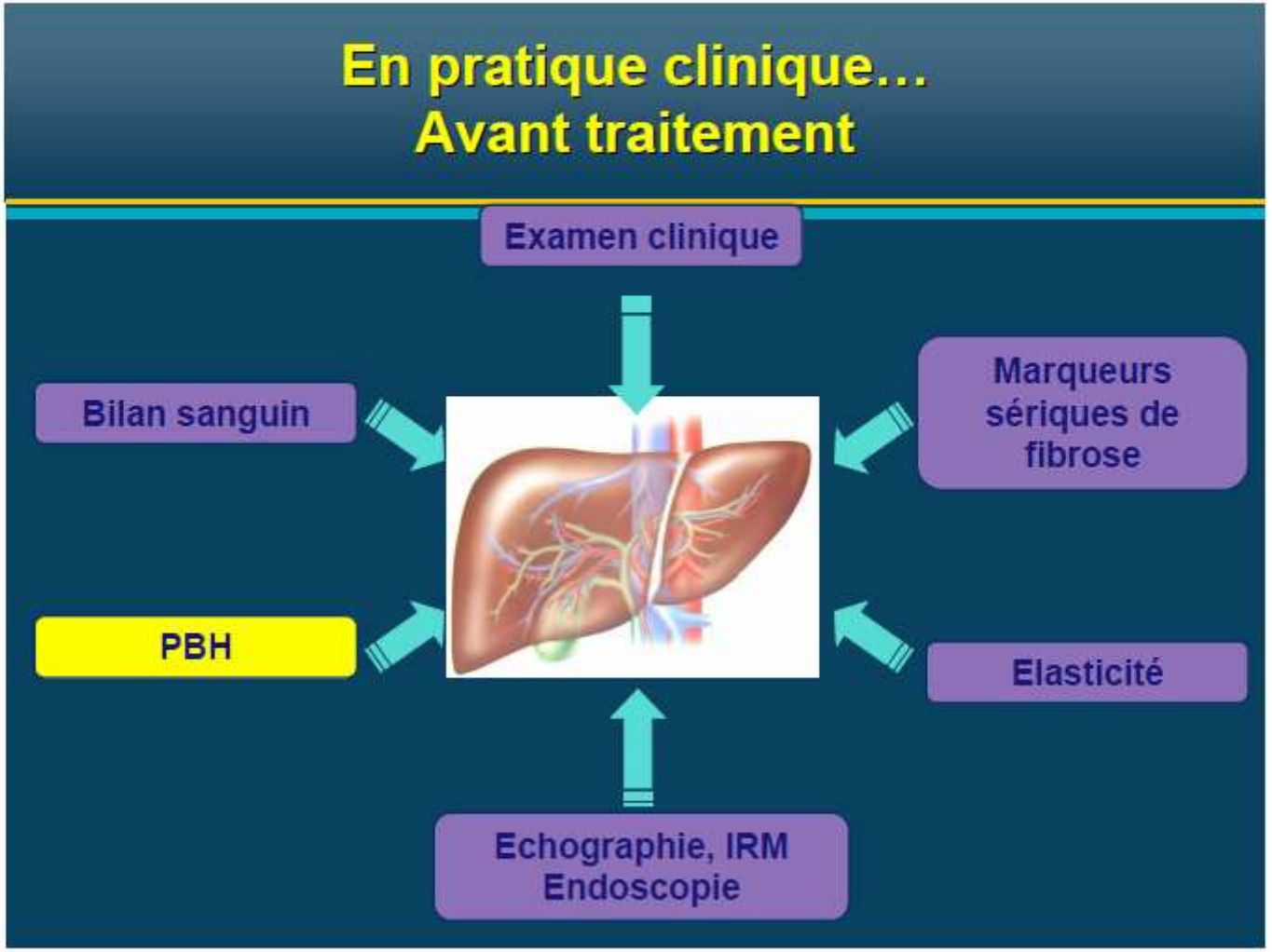
IMAGERIE

OGD, US
Doppler

BIOLOGIE

↘ PT, PLT

En pratique clinique… Avant traitement



POURQUOI EVALUER NON INVASIVEMENT LA FIBROSE HEPATIQUE

- **Intérêt diagnostique : F0-1 vs ≥ F2 vs ≥3-4**
- **Intérêt pronostique**
- **Suivi des patients traités et non traités**

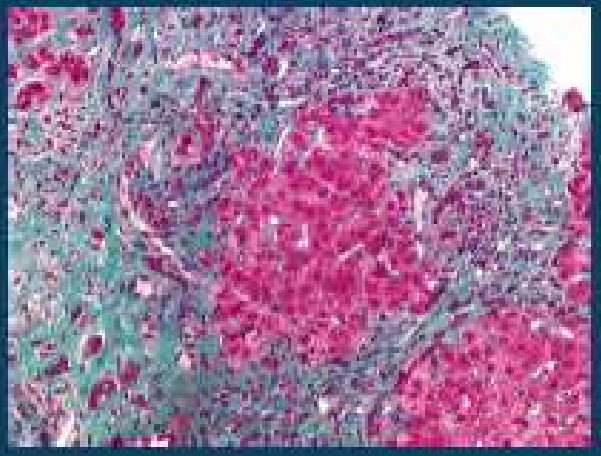
Pourquoi évaluer la fibrose?

- Y a-t-il une fibrose significative ?

⇨ Traiter si ≥ F2

- Y a-t-il une cirrhose ?

⇨ Traiter
Dépister le cancer



Liver Biopsy

PROS

. Direct assessment of A and F

. associated lesions

➢15-25 mm, > 6 PT

CONS

. Bad press in patients and GP

. 20 – 30% F-(cirrhosis) sampling error

. 20-30% intra and inter pathologists discordance

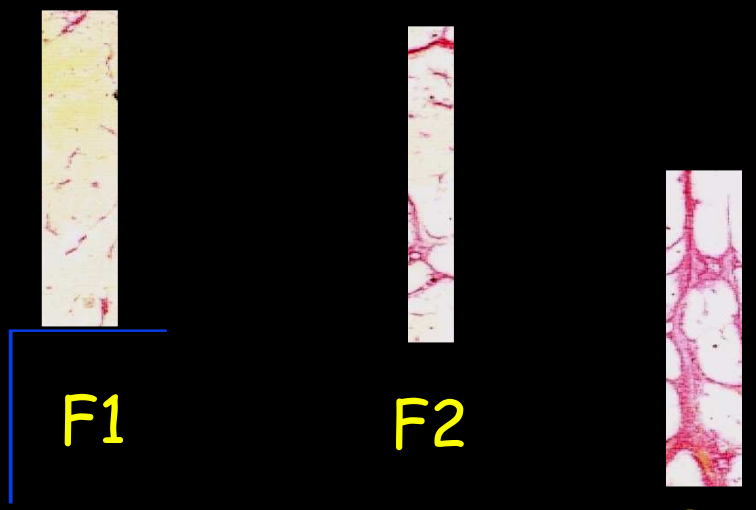
. Complications 30% pain

0.3% morbidity

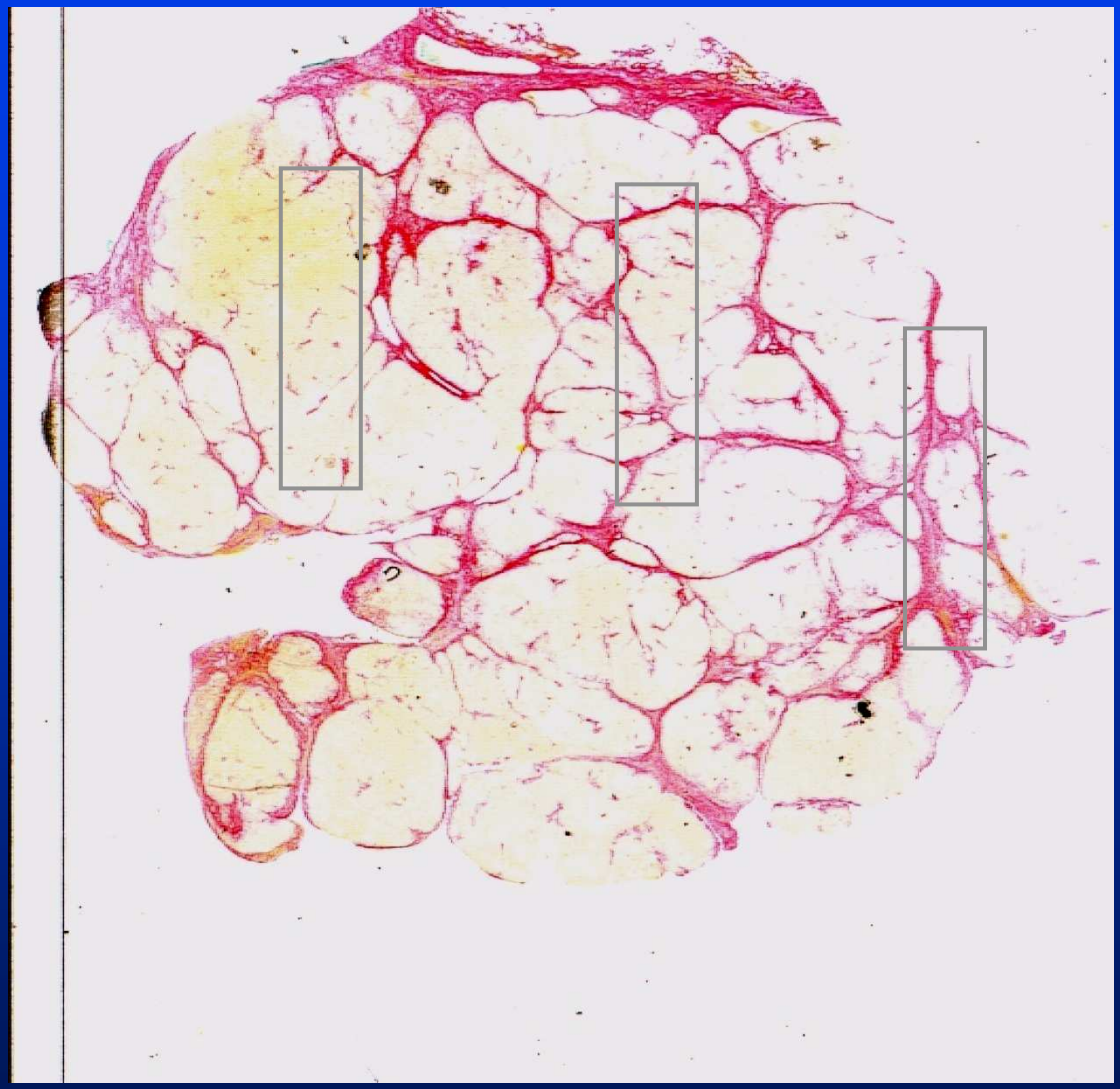
0.03% mortality

• 1/50.000 ème foie

. Cost : 220 – 700 euros



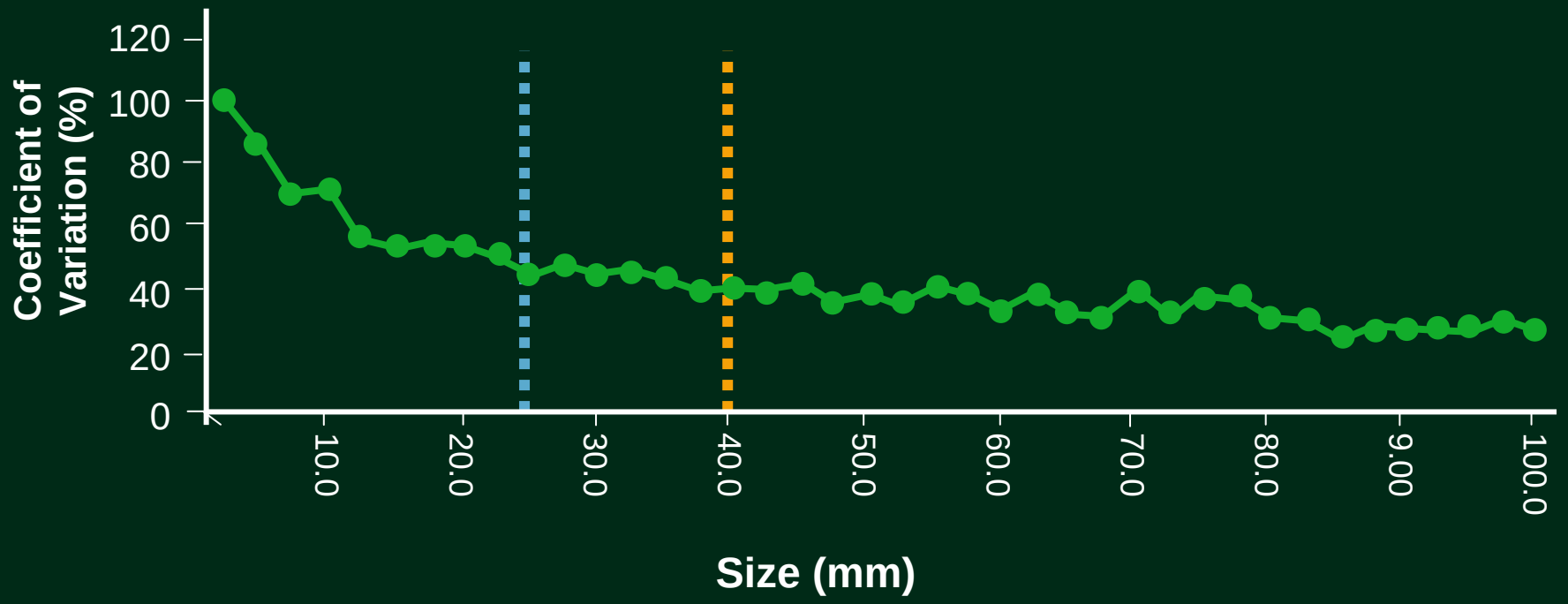
Fibrotest **F4** **F4** **F4**



Bedossa et al, Hepatology 2003

CLINICAL CARE OPTIONS
HEPATITIS

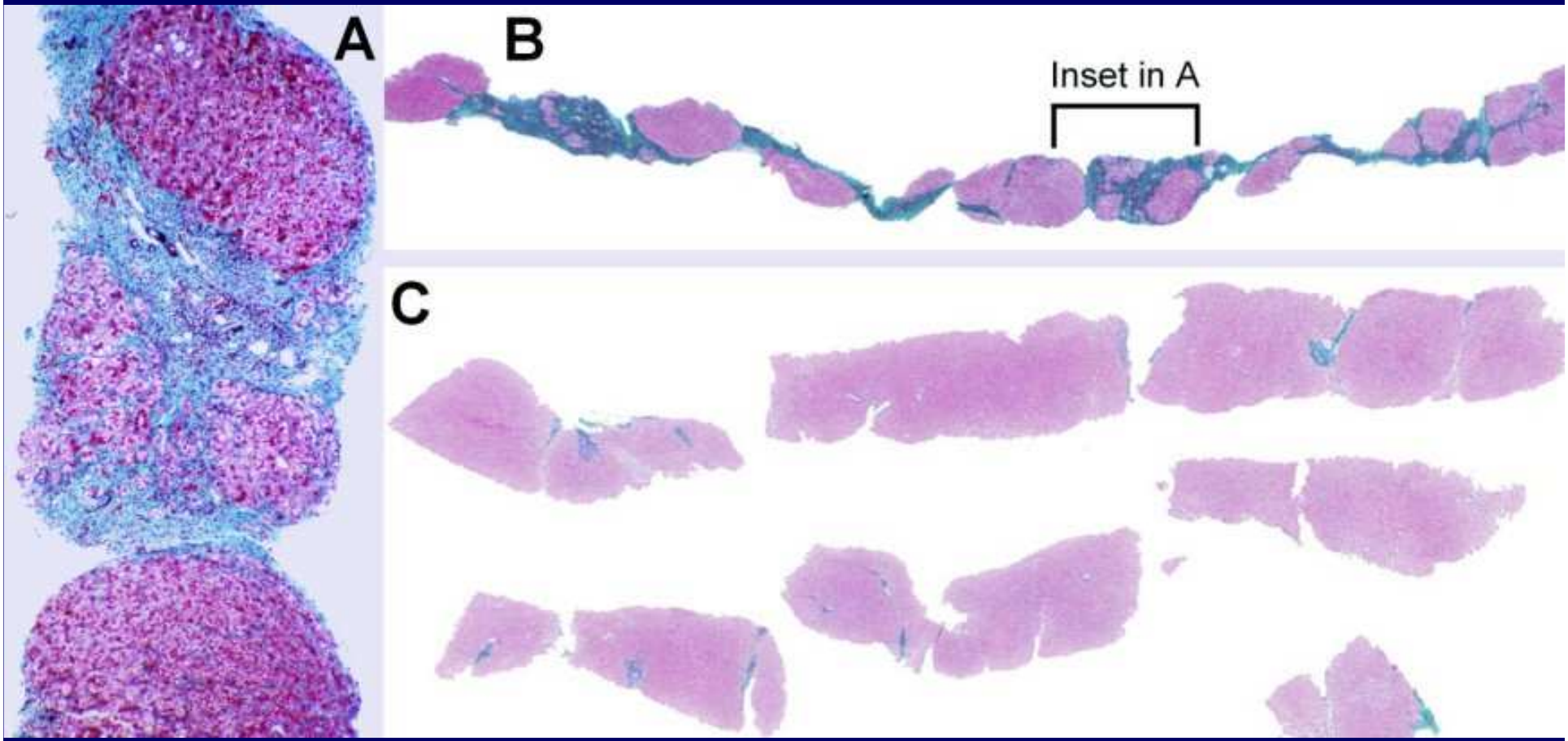
Model of Error Rate Associated With Biopsy Size



Bedossa P, et al. Hepatology. 2003;38:1449-1457.

REVERSIBILITE DE LA CIRRHOSE

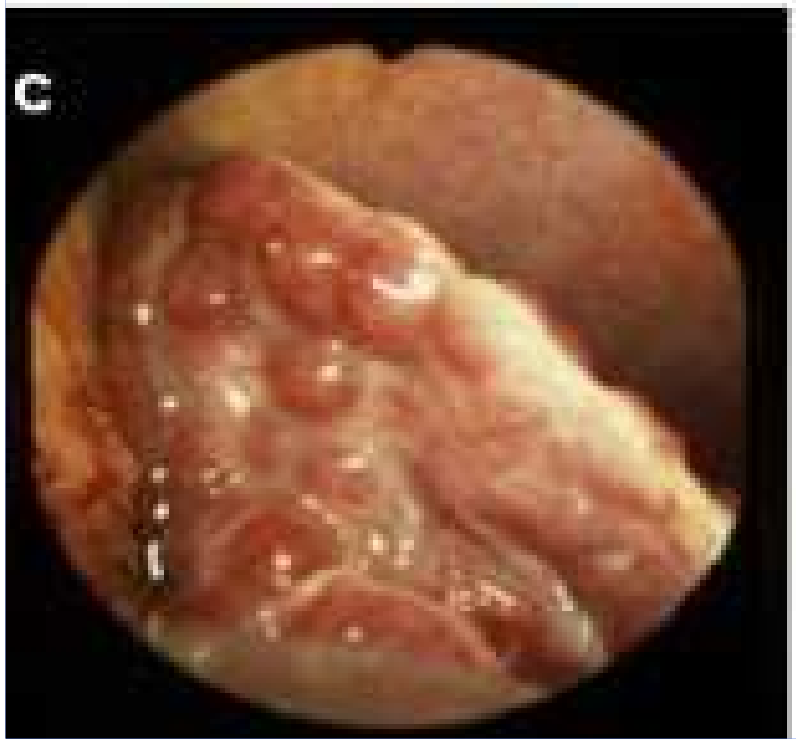
QUELLE QUE SOIT SON ORIGINE !!!!!!!

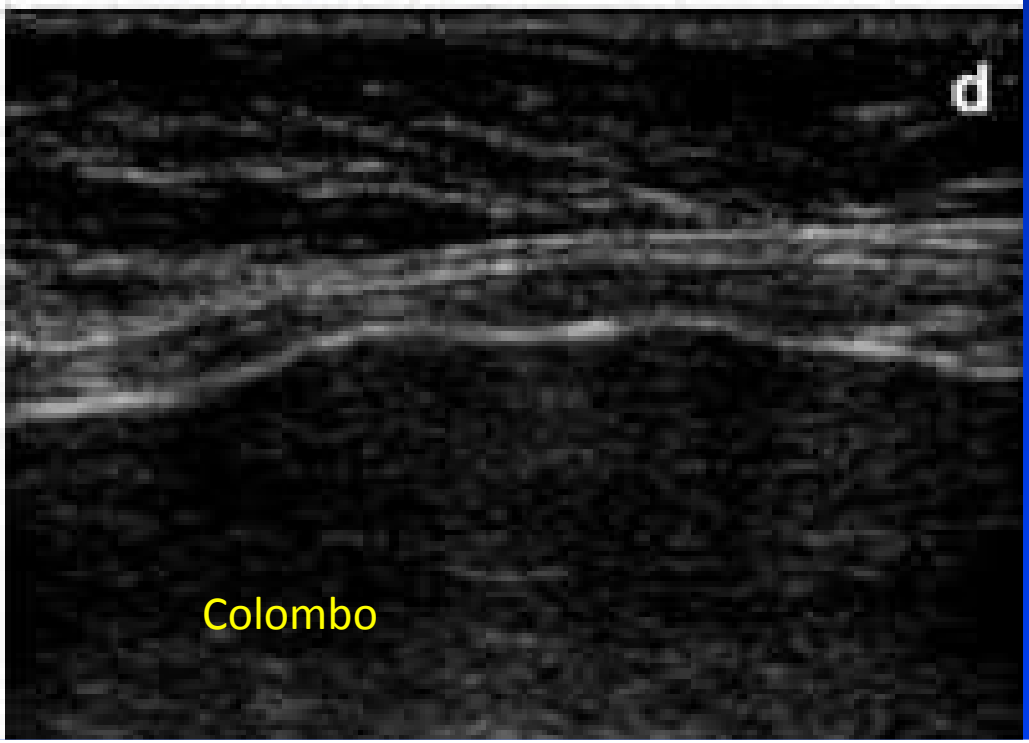


Wanless 2000

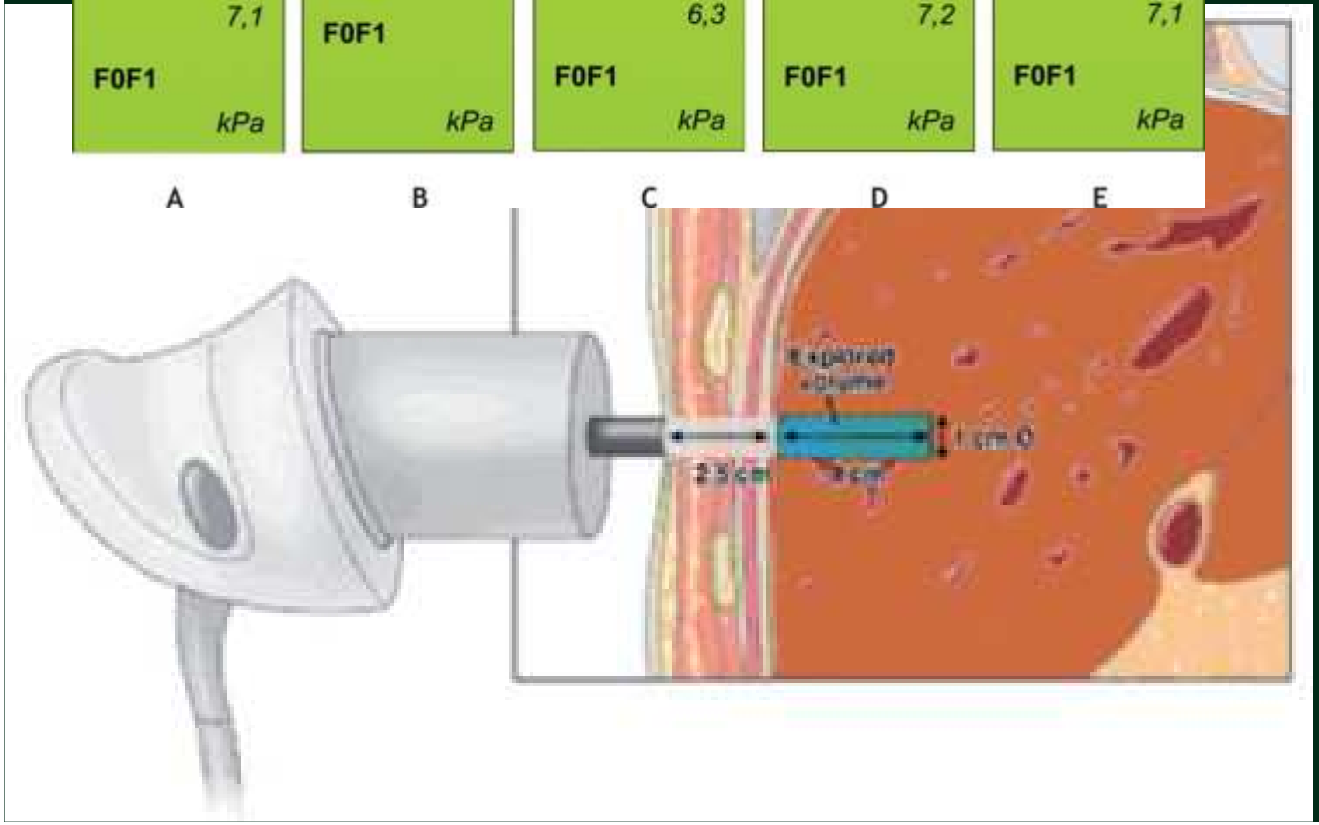

a


b


c


d
Colombo

A	B	C	D	E
F4	F4	F4	F4	F4
14,5	14,6	14,5	18,2	17,3
F3F4	F3F4	F3F4	F3F4	F3F4
12,5	11,9	11,9	11	15,6
F3		F3	F3	F3
9,5		8,5	10,5	14,7
F2	F2F3	F2	F2F3	F2F3
8,7	7,2	7,9	8,1	11,1
F1F2		F1F2	F2	F2
7,1		6,3	7,2	7,1
F0F1	F0F1	F0F1	F0F1	F0F1
kPa	kPa	kPa	kPa	kPa



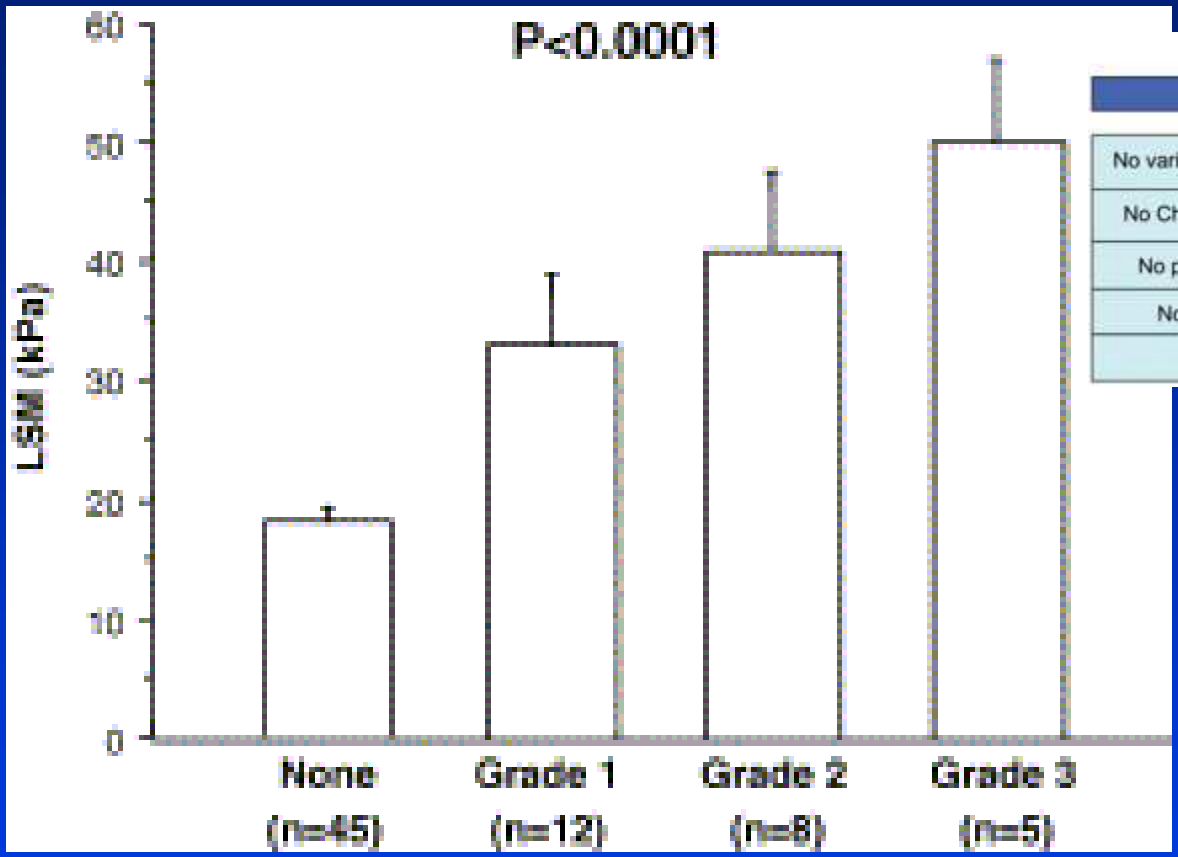
Predictive Value of Elastography Comparable to Serum-Based Tests

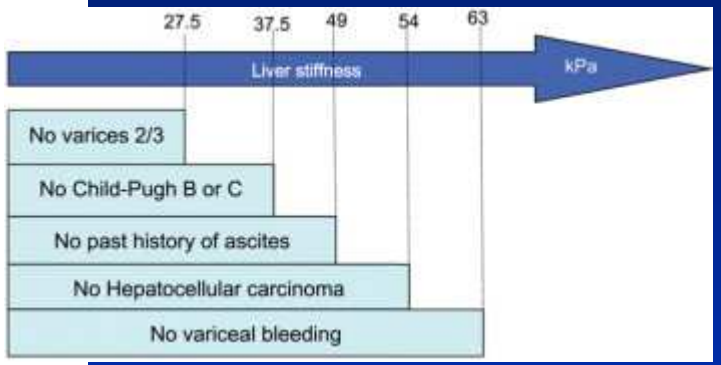
Area Under the ROC Curve (Sensitivity vs 1 – Specificity) for METAVIR Stage F0-1 vs F2-4 According to Different Fibrosis Assessment Methods[1]		
Assessment Method	**AUROC**	**95% CI**
APRI	0.78	0.70-0.85
Elastography	0.83	0.76-0.88
FibroTest	0.85	0.78-0.90
FibroTest + Elastography	0.88	0.82-0.92

- However, largest multicenter study to date found hepatic elastography ineffective at diagnosing significant fibrosis but effective at excluding cirrhosis[2]

1. Castera L, et al. Gastroenterology. 2005;128:343-350.
2. Degos F, et al. EASL 2009. Abstract 96.

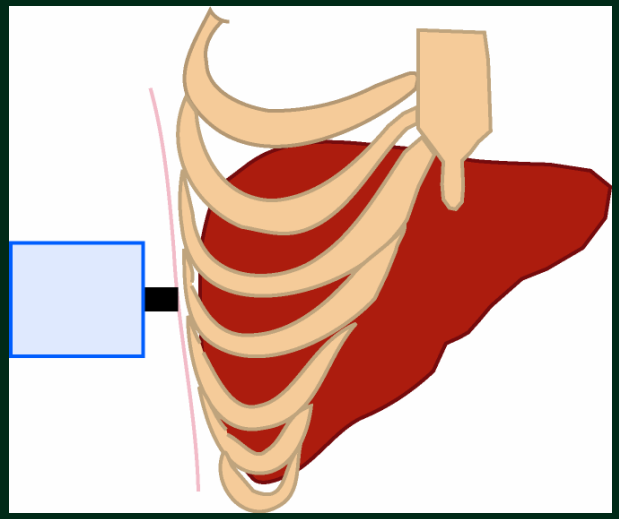
castera


P<0.0001
LSM (kPa)
60
50
40
30
20
10
0
None
(n=45)
Grade 1
(n=12)
Grade 2
(n=8)
Grade 3
(n=5)


27.5
37.5
49
54
63
Liver stiffness
kPa
No varices 2/3
No Child-Pugh B or C
No past history of ascites
No Hepatocellular carcinoma
No variceal bleeding

FibroScan

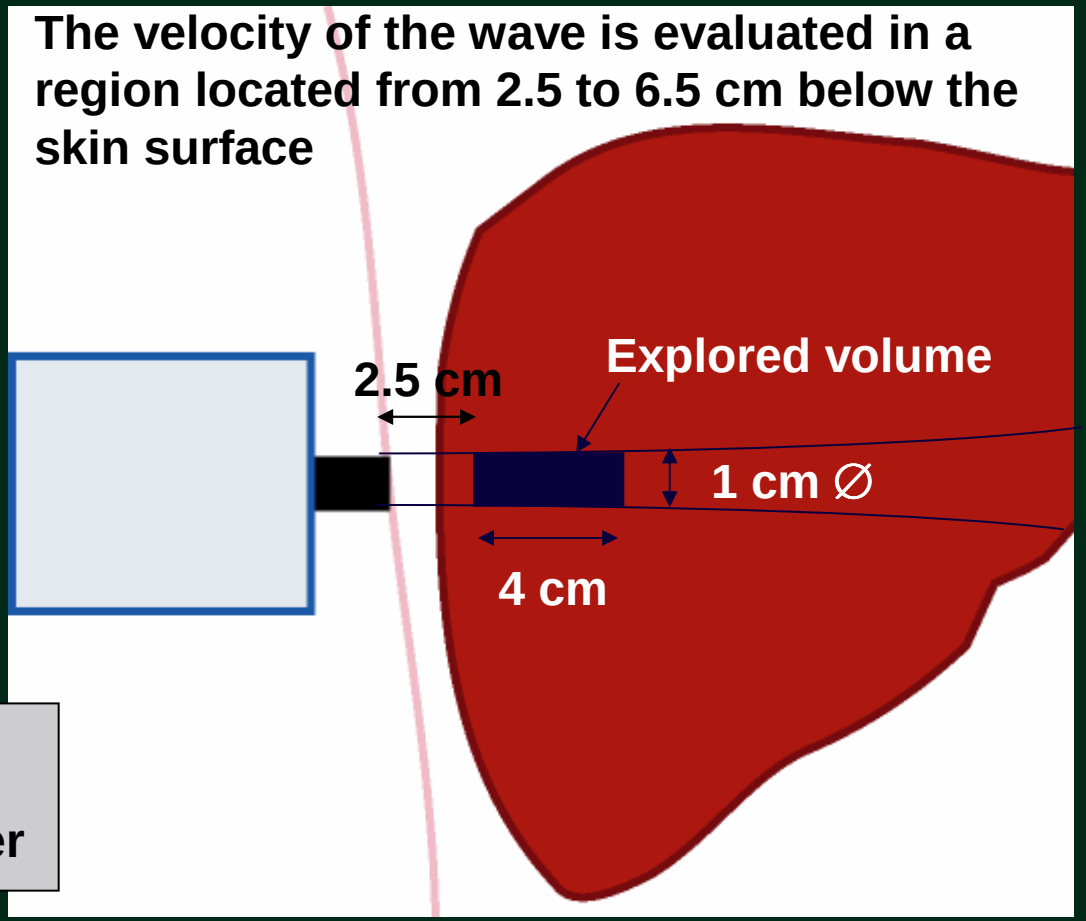
The probe induces an elastic wave through the liver



LB: 1/50,000 of the liver

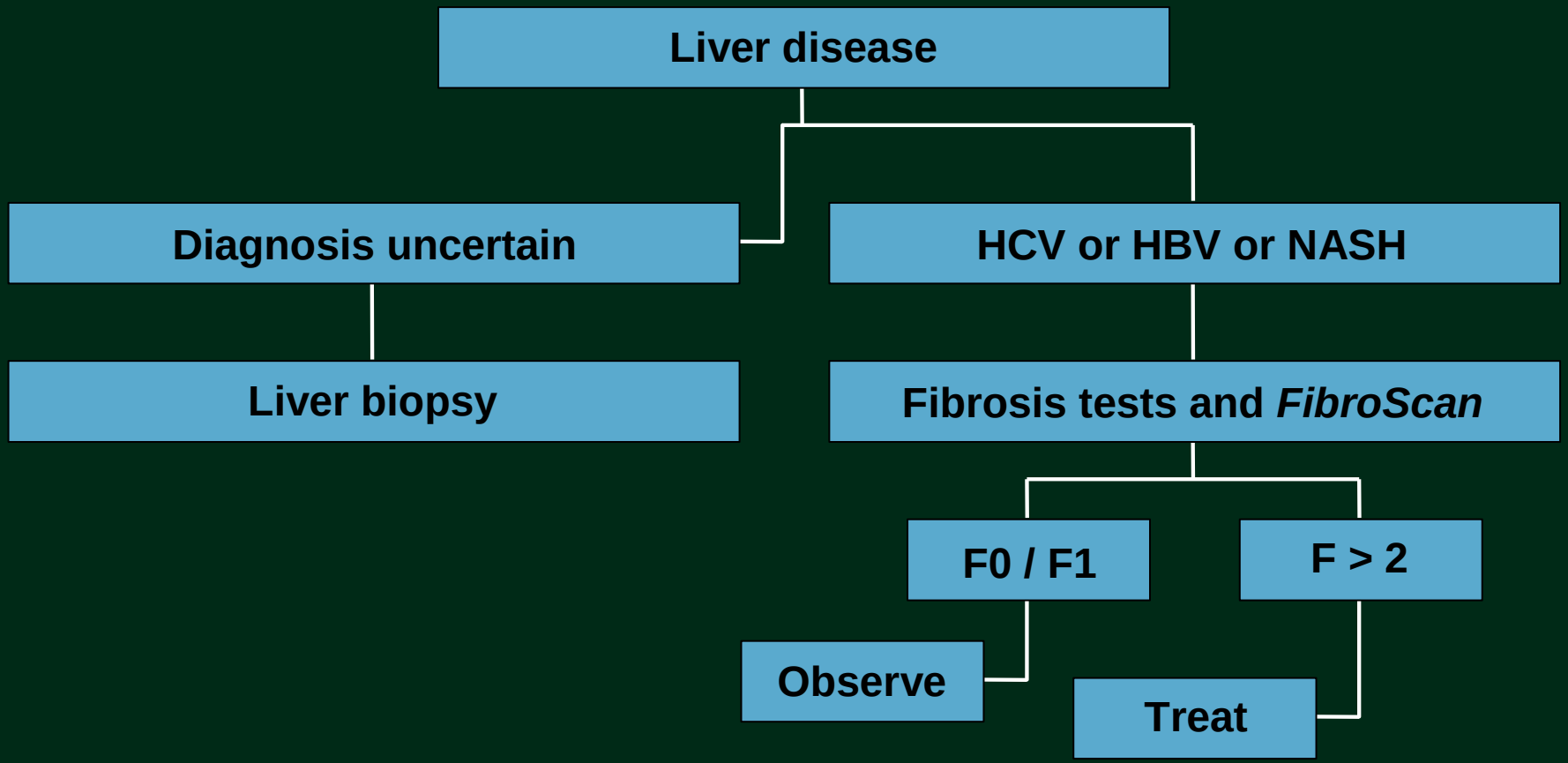
***FibroScan*: 1/500 of the liver**

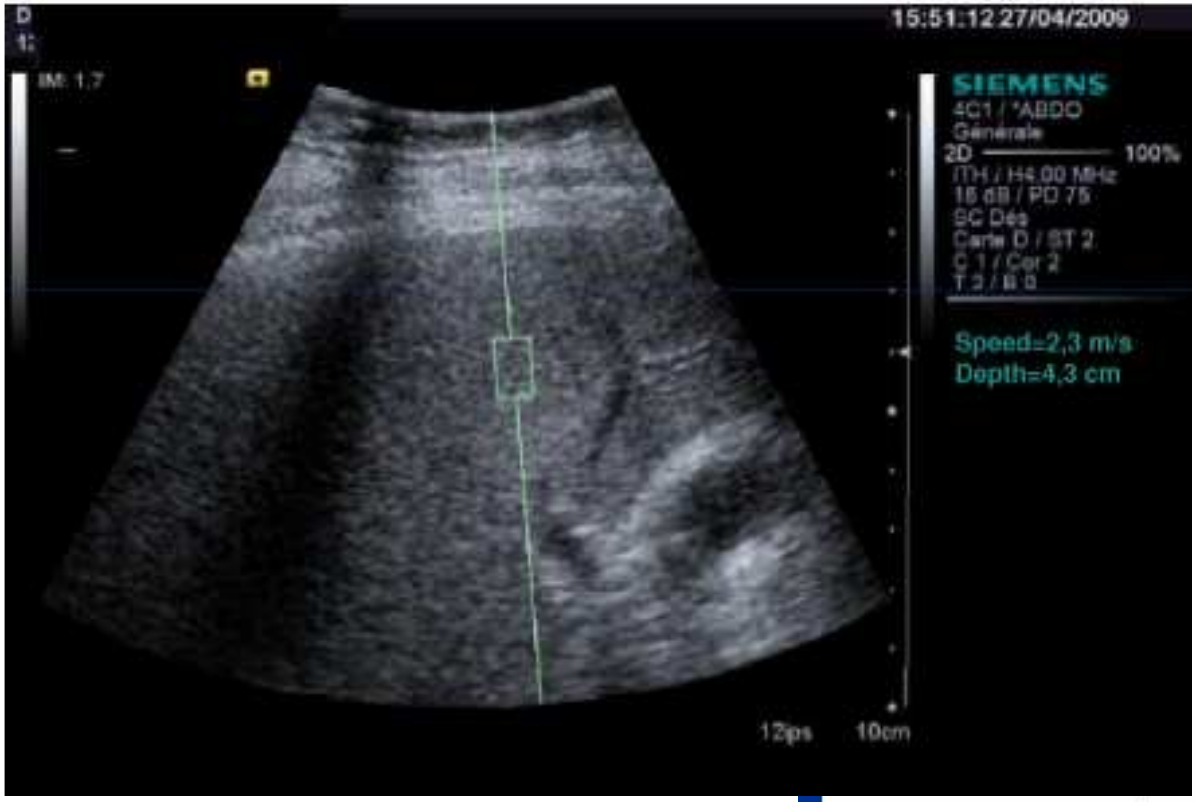
The velocity of the wave is evaluated in a region located from 2.5 to 6.5 cm below the skin surface



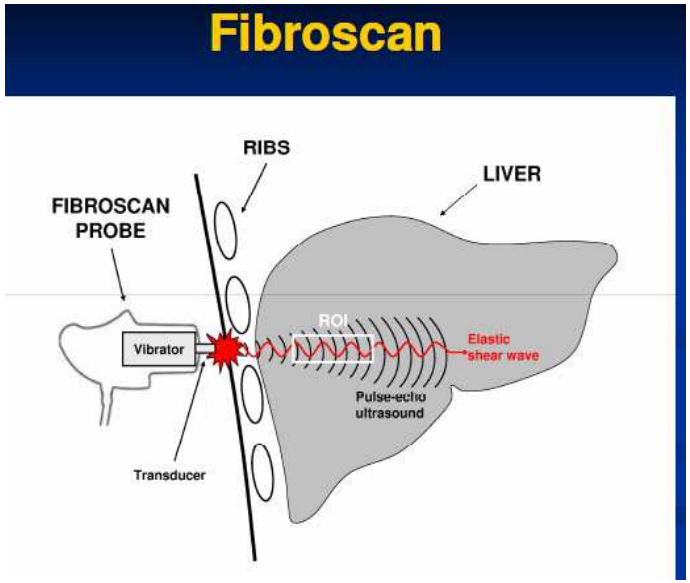
CLINICAL CARE OPTIONS
HEPATITIS

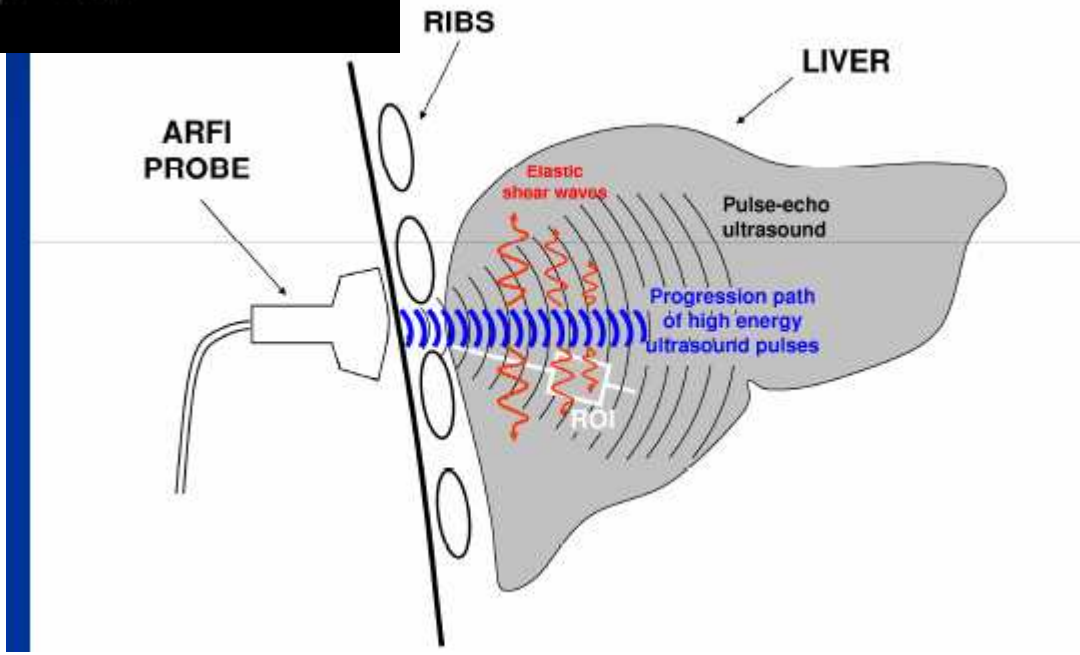
Approach to Staging Liver Disease





ACOUSTIC
RADIATION
FORCE **I**MPULSE





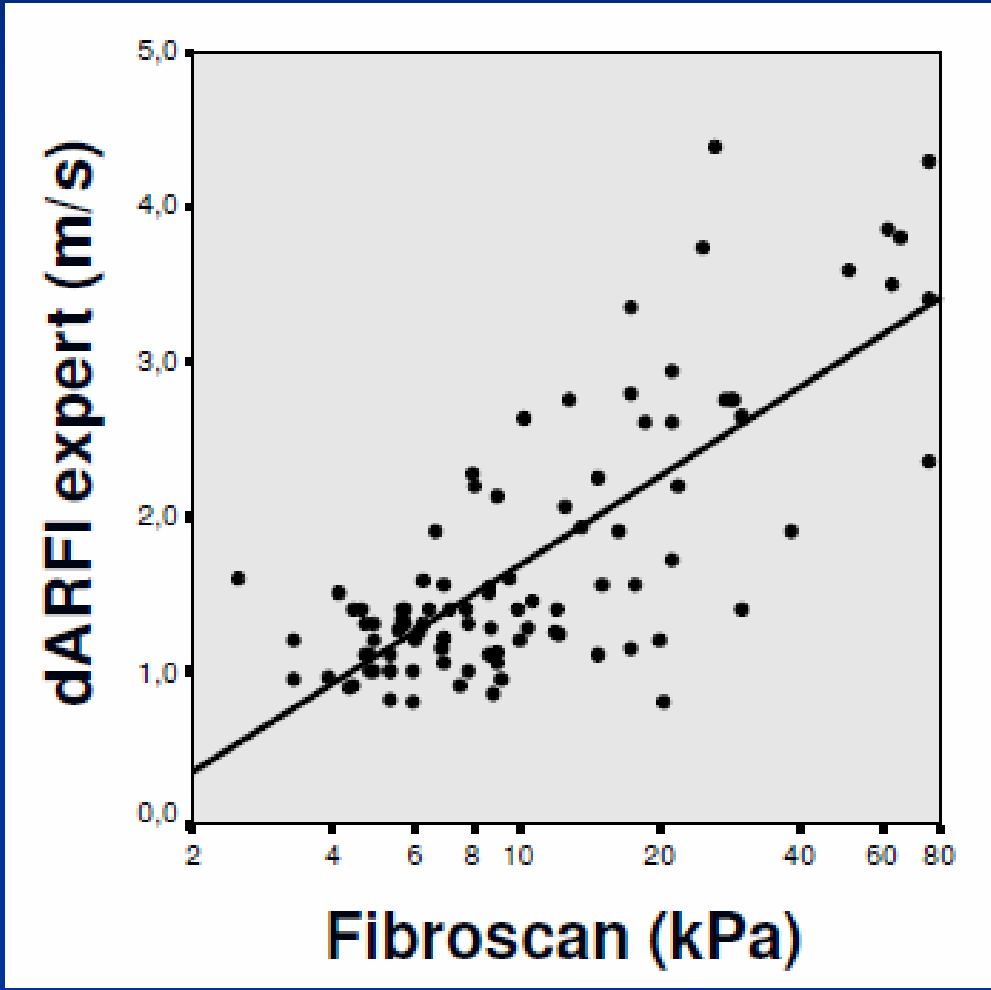
ARFI

Fibrosis Assessment Method	Stage ≥ F2 (F2, F3, F4)	Stage ≥ F2 (Adjusted)*	Stage ≥ F3 (F3, F4)	Stage F4
All patients				
ARFI imaging	0.82 (0.73, 0.91)	0.84 (0.75, 0.93)	0.91 (0.85, 0.97)	0.91 (0.84, 0.98)
TE	0.84 (0.76, 0.93)	0.86 (0.77, 0.95)	0.90 (0.83, 0.97)	0.91 (0.84, 0.97)
FibroTest	0.82 (0.75, 0.93)	0.84 (0.77, 0.95)	0.91 (0.84, 0.97)	0.82 (0.73, 0.92)
APRI	0.75 (0.64, 0.86)	0.79 (0.66, 0.88)	0.76 (0.64, 0.87)	0.76 (0.64, 0.87)
Only patients with HCV				
ARFI imaging	0.84 (0.74, 0.94)	0.86 (0.76, 0.96)	0.93 (0.87, 0.99)	0.95 (0.89, 0.996)
TE	0.85 (0.75, 0.95)	0.87 (0.77, 0.97)	0.90 (0.81, 0.08)	0.91 (0.84, 0.979)
FibroTest	0.84 (0.74, 0.95)	0.86 (0.76, 0.97)	0.93 (0.87, 0.99)	0.84 (0.74, 0.934)
APRI	0.79 (0.68, 0.90)	0.81 (0.70, 0.92)	0.80 (0.69, 0.92)	0.73 (0.59, 0.868)

- 81 malades
- 17 hépatites B

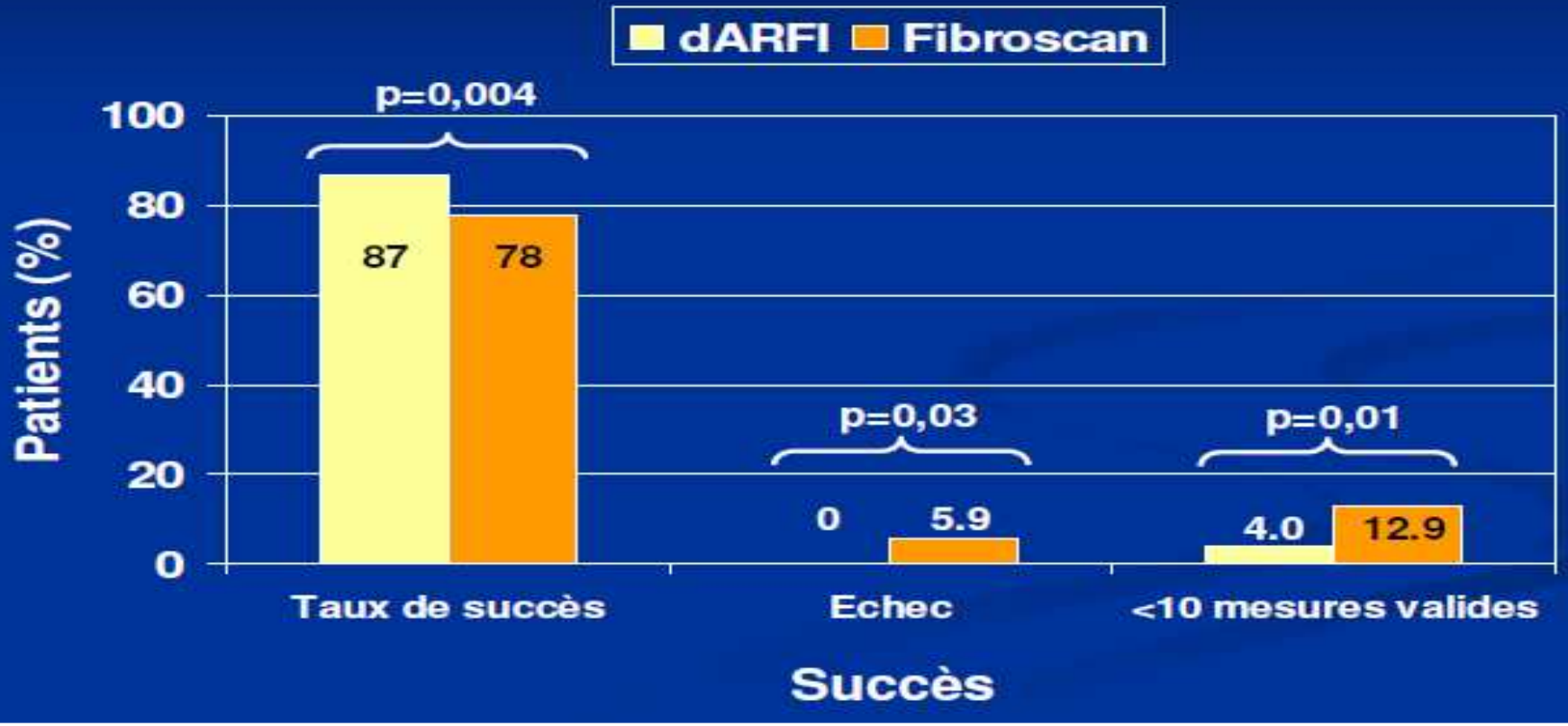
Friedrich-Rust et al. Radiology 2009; 252: 595-604

Corrélation ARFI - Fibroscan

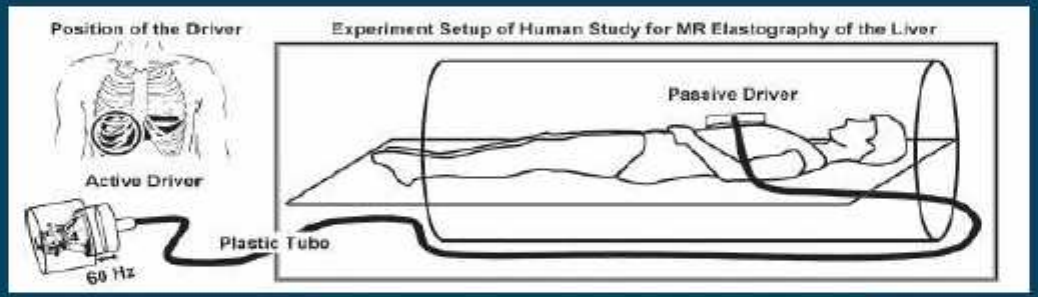


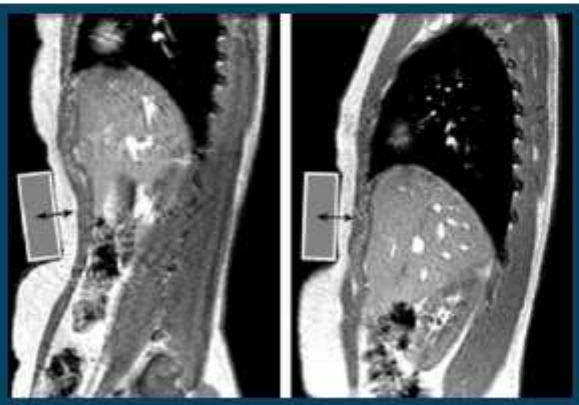
Rs = 0,76

Faisabilité de l'ARFI et du Fibroscan



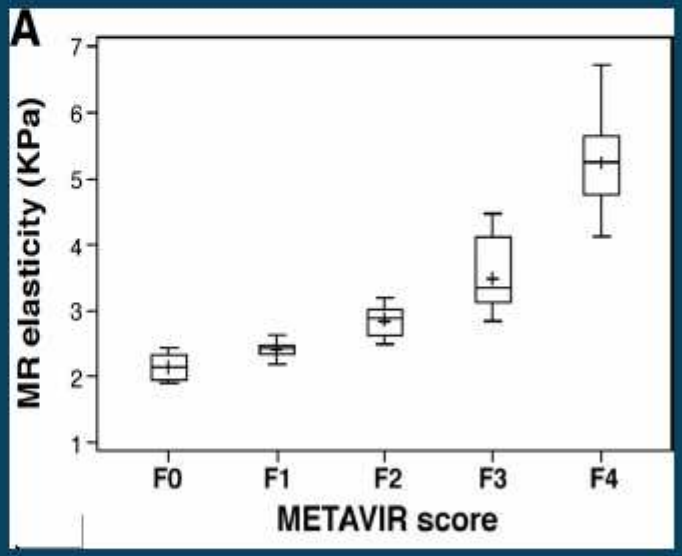
Elastométrie IRM





Yin M et al. Clin Gastroenterol Hepatol 2007;5:1207-13

Elasto IRM



AUROC	
F2F3F4	0.99
F3F4	0.98
F4	0.99

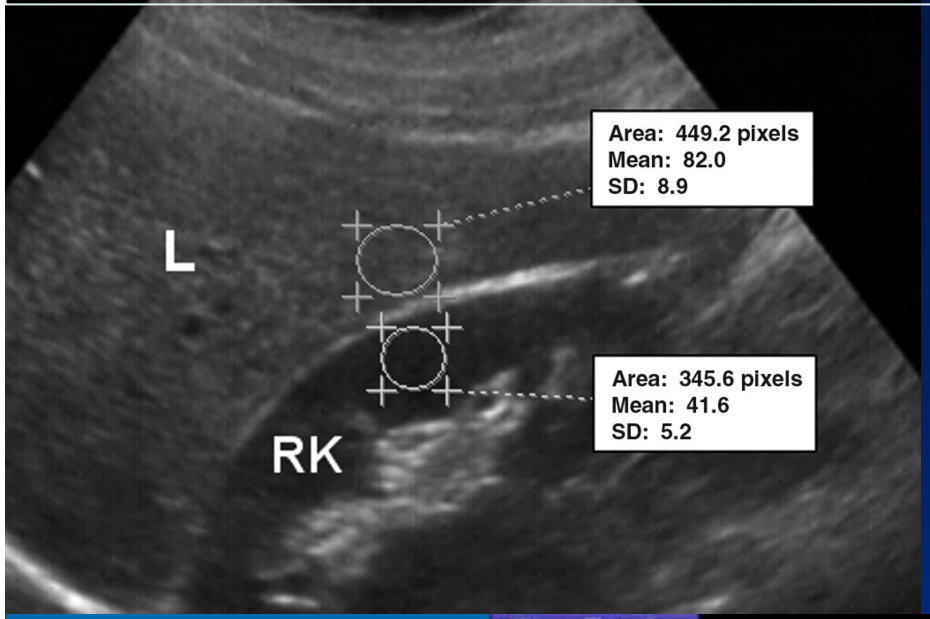
Huwart L et al. Gastroenterology 2008;32-40

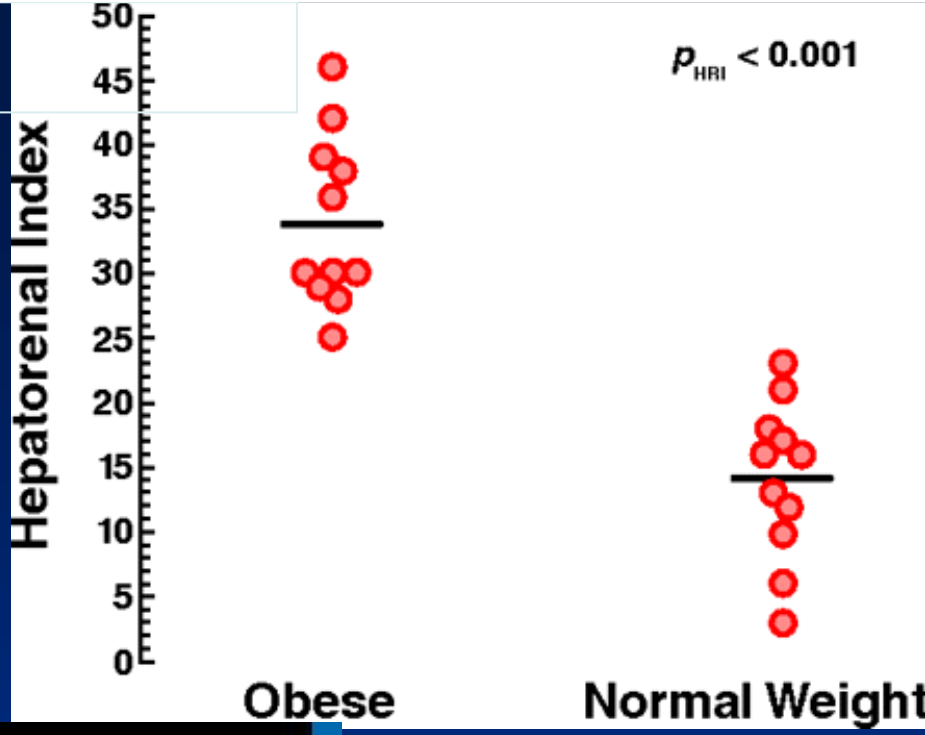
Table 1 Routine laboratory and clinical predictors of advanced fibrosis (stage 3–4) in patients who have non-alcoholic fatty liver disease.

Author	*n*	Patient population	Risk factors	Odds ratio (95% CI
Angulo et al., 1999 [16]	144	NASH	Age ≥ 45 years	5.6 (1.5, 21.7)
			Obesity (body mass index > 30 kg/m^2)	4.3 (1.4, 13.8)
			Diabetes	3.5 (1.2–9.8)
			AST:ALT > 1	4.3 (1.5, 12)
Ratziu et al., 2000 [14]	93	Overweight, raised liver tests	Age ≥ 50 years	14.1 (3.7, 54.0)
			Body mass index ≥ 28 kg/m^2	5.7 (1.6, 20.0)
			Triglyceride ≥ 1.7 mmol/L	5.0 (1.4, 17.0)
			ALT ≥ 2 × ULN	4.6 (1.3, 16.0)
Dixon et al., 2001 [26]	105	Bariatric surgery patients	Hypertension	NA
			ALT > 40 IU/L	NA
			Insulin resistance > 5.0	NA
Angulo et al., 2007 [29]	733	Nonalcoholic fatty liver disease	Age (years)	1.04 (1.01, 1.07)
			Body mass index (kg/m^2)	1.10 (1.04, 1.16)
			IFG/diabetes	3.12 (1.77, 5.51)
			AST/ALT ratio	2.70 (1.33, 5.62)
			Platelet count (× 10^9/l)	0.987 (0.98, 0.99)
			Albumin (g/dl)	0.51 (0.25, 1.05)
Harrison et al, 2008 [30]	827	Nonalcoholic fatty liver disease	Body mass index ≥ 28 kg/m^2	2.4 (1.2, 4.8)
			AST/ALT ratio ≥ 0.8	9.3 (6.3, 13.6)
			Diabetes	4.0 (2.8, 5.7)

NA: not available; ULN: upper limit of normal; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

EVALUATION STEATOSE

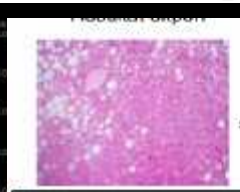




Examen FS classique

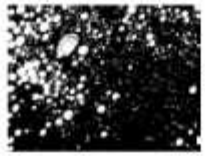
SI

examen réussi



= 50 % d'hépatocytes stéatosiques

Résultat automatique



= 20.26% de

Méthode FSE

21,36

52,19

38

55,39

$$\frac{|R_{fs} - R|}{R_{fs} + R} \times 100 = \frac{\left|\frac{21,36}{52,19} - \frac{38}{55,39}\right|}{\frac{21,36}{52,19} + \frac{38}{55,39}} \times$$

% fat = 25,27 %

*évaluation du **Controlled Attenuation Parameter (CAP)** entre 2*

(même zone du foie et même signaux que pour l'élasticité)

Table 2 Serum markers of fibrogenesis and clinical predictors of advanced (stage 3–4) fibrosis in patients who have non-alcoholic fatty liver disease.

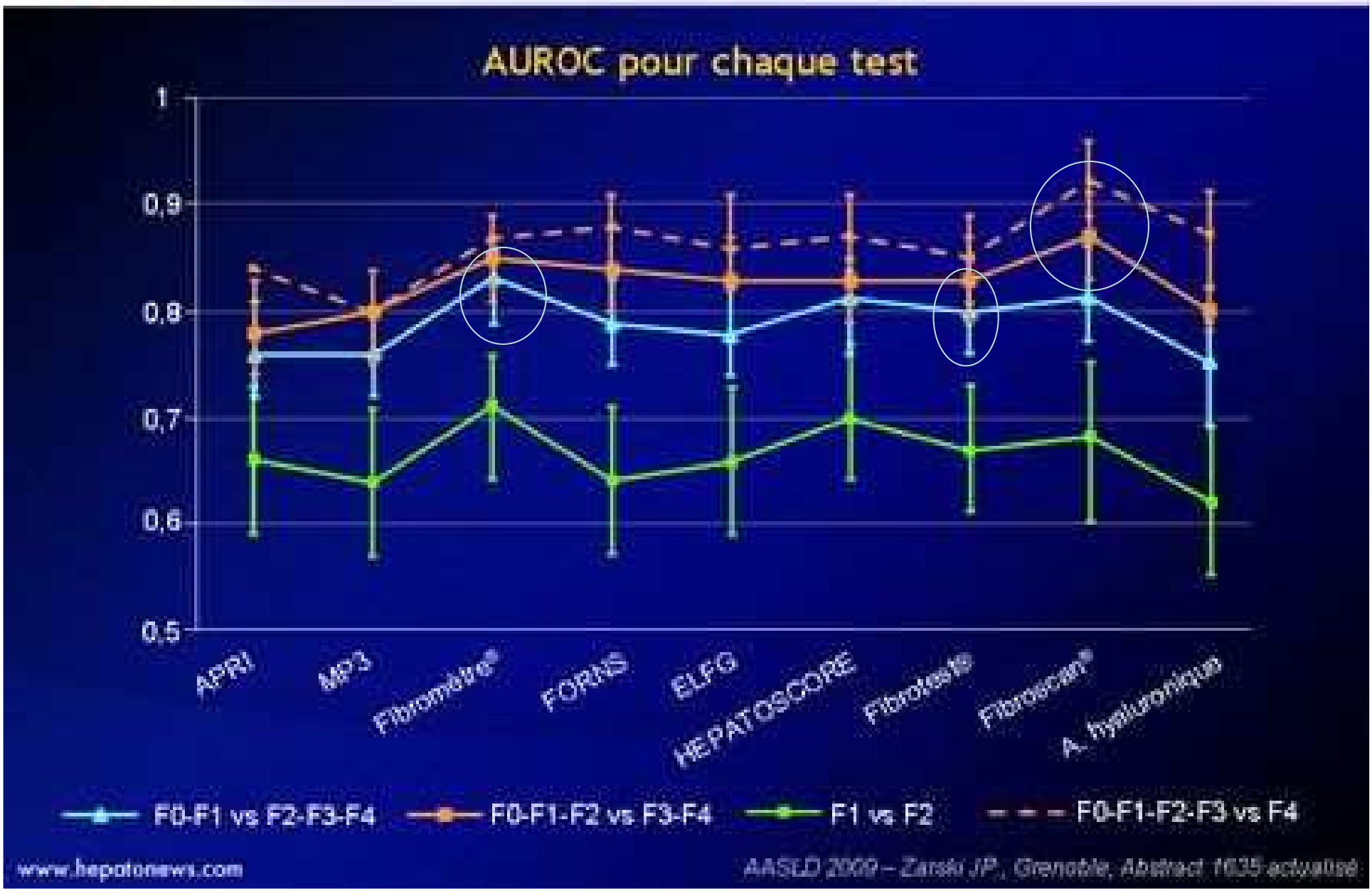
Author	*n*	Serum marker	Area under the ROC	Sensitivity (%)	Specificity (%)
Wong et al. [33]	79	Hyaluronic acid > 46.1 ng/mL	0.89	85.0	79.7
Sakugawa et al. [34]	112	Hyaluronic acid ≥50 ng/mL	0.80	68.8	82.8
		Type IV collagen 7S ≥ 5 ng/mL	0.82	81.3	71.4
Palekar et al. [7]	80	Hyaluronic acid > 45.3 ng/mL	0.88	85.7	80.3
dos Santos et al. [35][a]	30	Hyaluronic acid > 24.6 ng/mL	0.73	82.0	68.0
		Type IV collagen > 145 ng/mL	0.80	64.0	89.0
		Laminin > 282 ng/mL	0.87	82.0	89.0
Ratziu et al. [36]	267	Fibrotest 0.30	0.88	92.0	71.0
		Fibrotest 0.70	0.88	25.0	97.0
Guha et al. [37]	192	ELF score = −7.412 + (ln(HA)*0.681) + (ln(P3NP)*0.775) + (ln(TIMP1)*0.494)	0.93	80	90
		ELF = 0.3576[b]			
Nobili et al. [38]		ELF (different cutoff values)	0.90–0.99	88–100	76–98

Advanced fibrosis defined as stage 3 or 4 [9]; ELF: enhanced liver fibrosis panel.

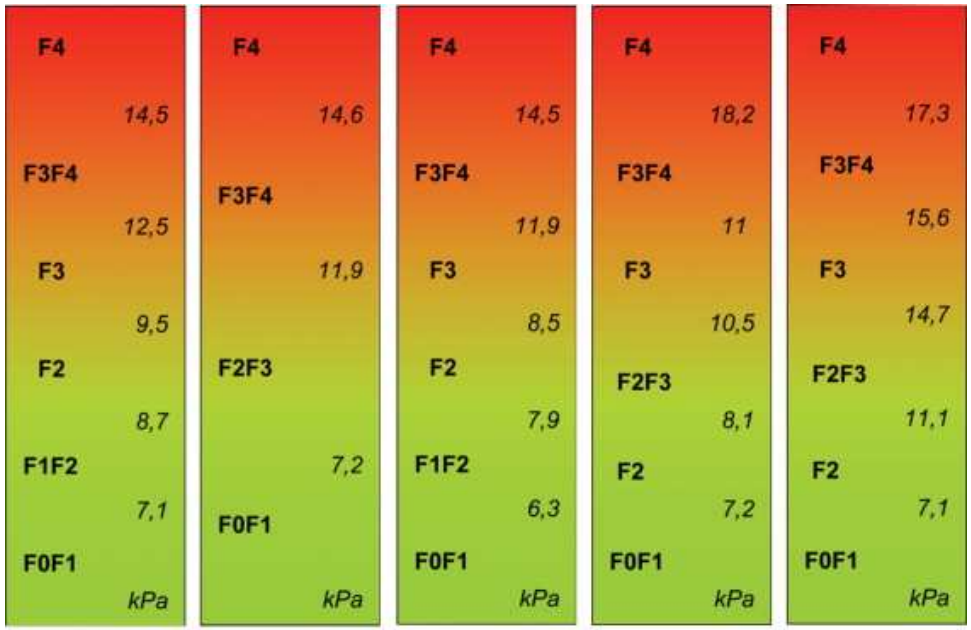
[a] Predicting presence of fibrosis versus absence of fibrosis.

[b] The area under the ROC is to distinguish between patients with and without advanced (stage 3/4) fibrosis. An ELF score of 0.3576 had a sensitivity of 80% in detecting advanced fibrosis and a specificity of 90% in ruling out advanced fibrosis.

Hépatite C et tests non invasifs de fibrose : la comparaison ultime ? *(3)*



AASLD 2009 – Zarski JP., Grenoble, *Abstract 1635 actualisé*


F4
14,5
F3F4
12,5
F3
9,5
F2
8,7
F1F2
7,1
F0F1
kPa
F4
14,6
F3F4
11,9
F2F3
7,2
F0F1
kPa
F4
14,5
F3F4
11,9
F3
8,5
F2
7,9
F1F2
6,3
F0F1
kPa
F4
18,2
F3F4
11
F3
10,5
F2F3
8,1
F2
7,2
F0F1
kPa
F4
17,3
F3F4
15,6
F3
14,7
F2F3
11,1
F2
7,1
F0F1
kPa
A
B
C
D
E

Indications au Traitement (Section 4.6)

- Un traitement doit être envisagé pour les patients ayant des taux d'ADN VHB au-dessus de 2000 UI/ml (i.e. environ 10 000 copies/ml)

Et/ou

- Des taux sériques d'ALAT au-delà de la limite supérieure de la normale (LSN),

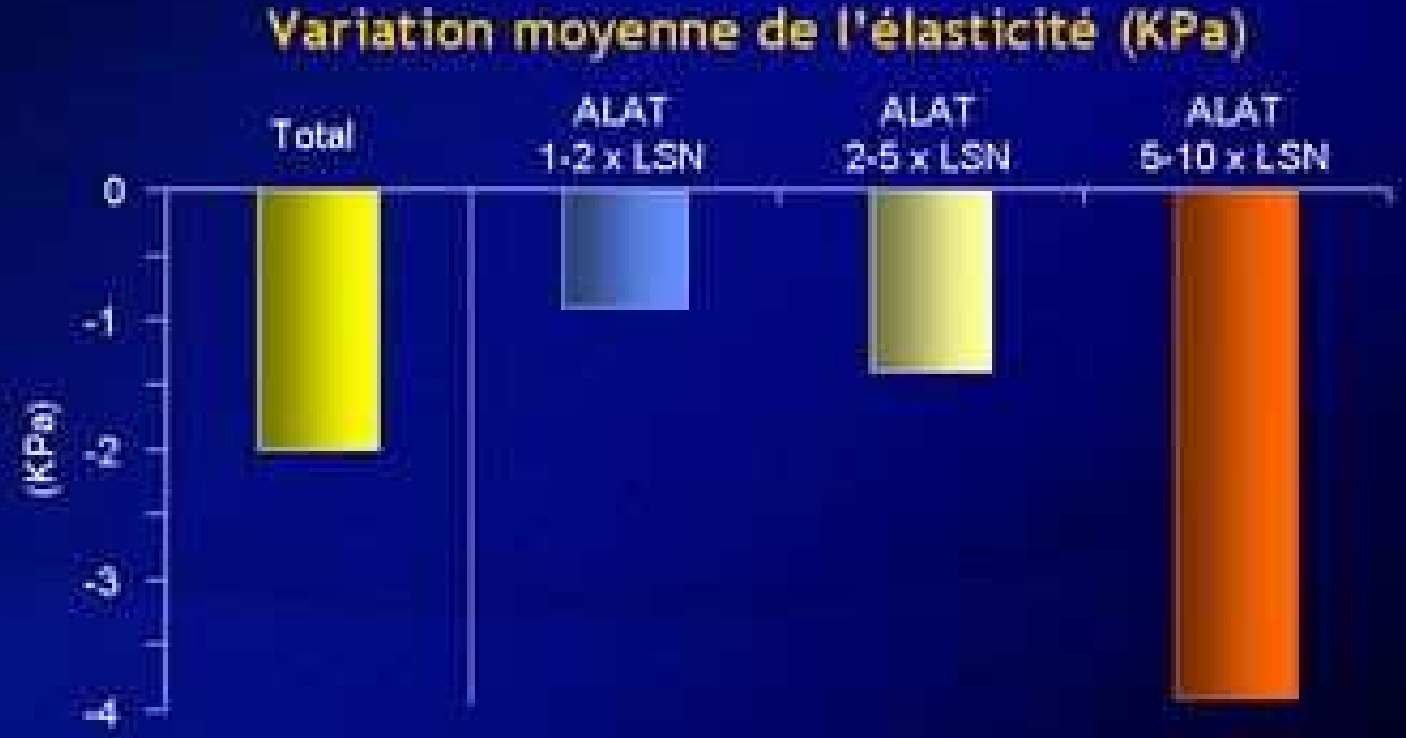
et

- Une biopsie hépatique montrant une nécro-inflammation et/ou une fibrose modérée à sévère utilisant un score standardisé (par ex. Au moins un grade A2 ou un stade F2 avec le score METAVIR). (A1)

European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of chronic hepatitis B. *Journal of Hepatology* 50 (2009) 227–242

Le taux de transaminases influence la valeur du FibroScan®

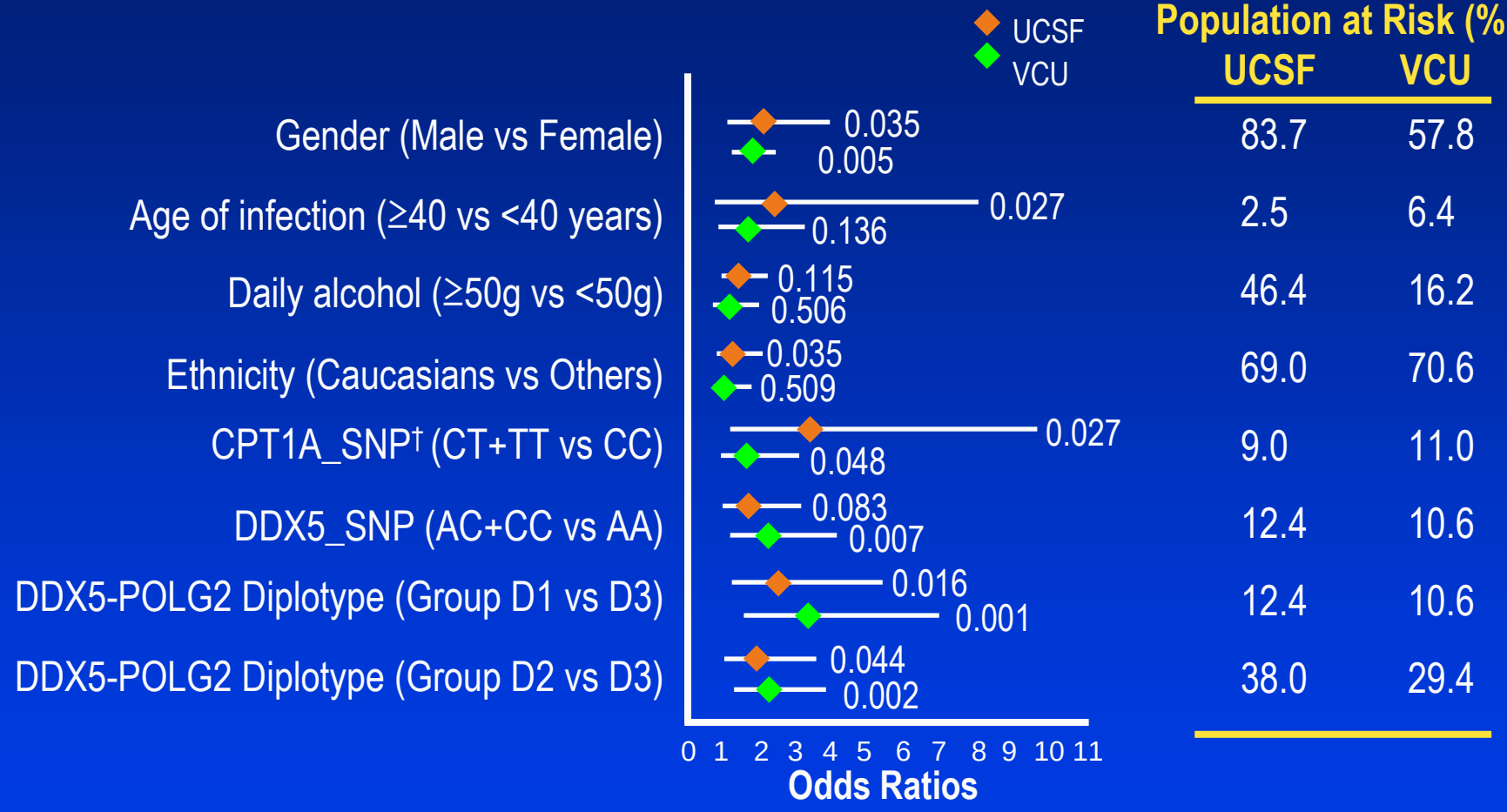
- 38 patients porteurs chroniques du VHB et ↑ ALAT (< 10 x LSN)
- Le même jour : biopsie hépatique et 1re mesure par FibroScan®
- Tous les patients avaient une fibrose ≥ F2 (metavir)
- Traitement (adéfovir ou clévudine) et 2e mesure par FibroScan® après normalisation des transaminases à 3 mois en médiane [1-7]



AASLD 2009 – Fung J, Chine, Abstract 1449 actualisé

Fibrosis Progression in Chronic Hepatitis C

Importance of 2 Gene Variants



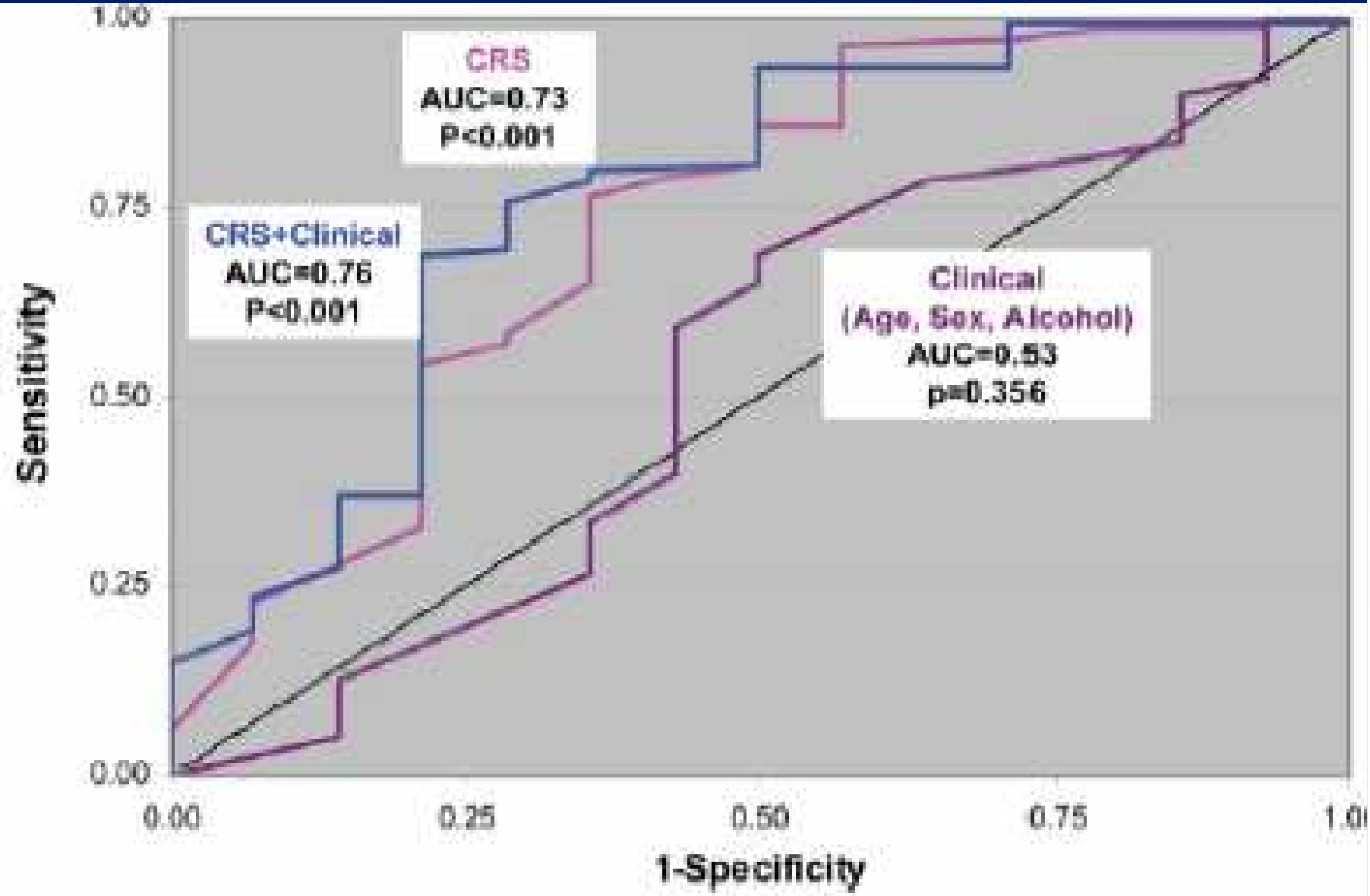
	Population at Risk (%)*	
	UCSF	VCU
Gender (Male vs Female)	83.7	57.8
Age of infection (≥40 vs <40 years)	2.5	6.4
Daily alcohol (≥50g vs <50g)	46.4	16.2
Ethnicity (Caucasians vs Others)	69.0	70.6
CPT1A_SNP† (CT+TT vs CC)	9.0	11.0
DDX5_SNP (AC+CC vs AA)	12.4	10.6
DDX5-POLG2 Diplotype (Group D1 vs D3)	12.4	10.6
DDX5-POLG2 Diplotype (Group D2 vs D3)	38.0	29.4

*Population at risk indicates the % of subjects from 2 cohorts carrying the risk factors.

†The odds ratio of CPT1A SNP was reversed to be consistent with other factors; therefore, the odds ratio for this SNP should be explained as a protective effect.

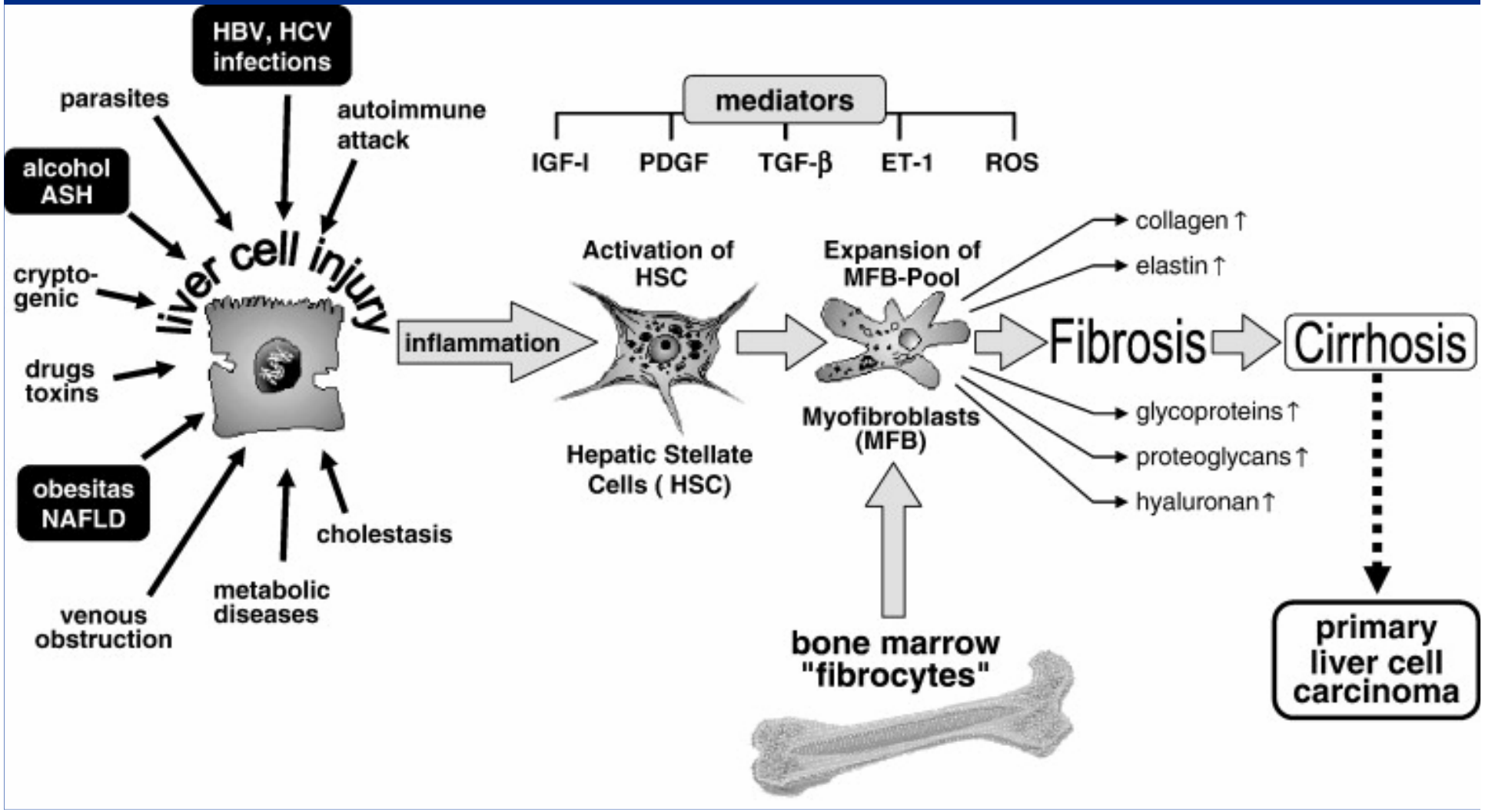
UCSF = University of California San Francisco; VCU = Virginia Commonwealth University; SNP = single nucleotide polymorphism.

CIRRHOSIS RISK SCORE GENETIQUE

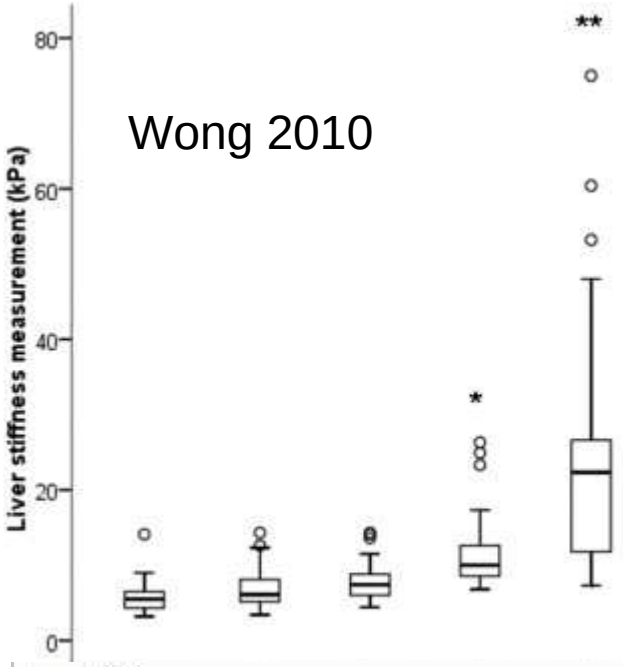


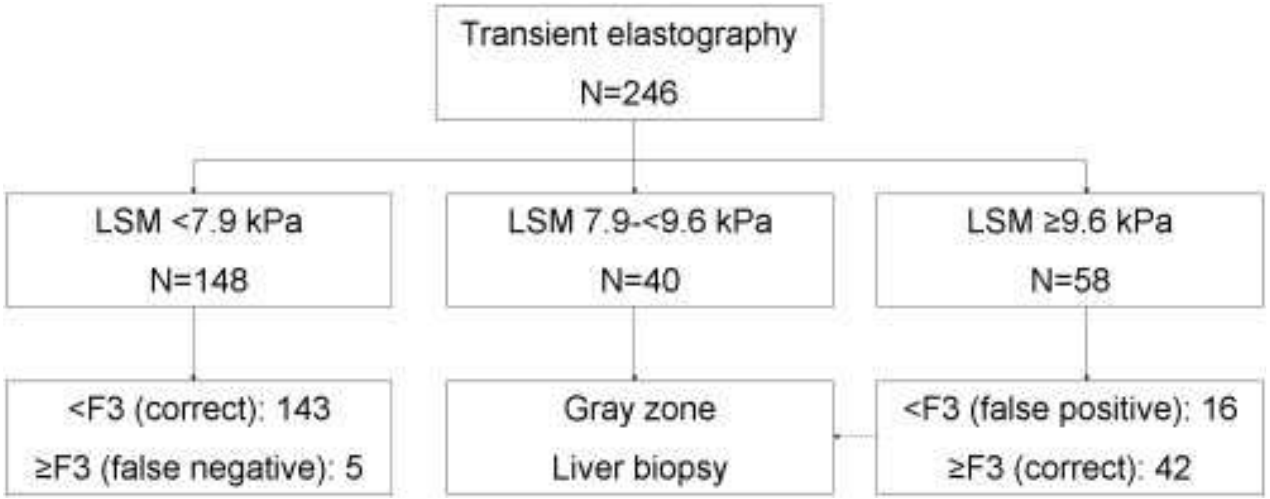
Huang 2006

ALL CLD CAN LEAD TO FIBROSIS/CIRRHOSIS

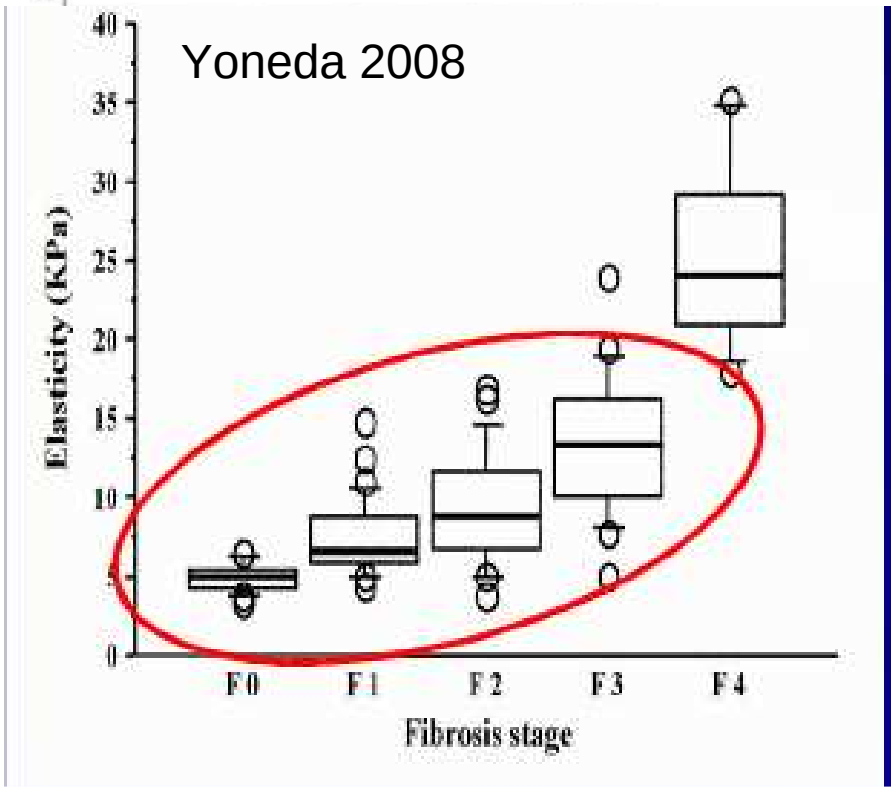


Wong 2010

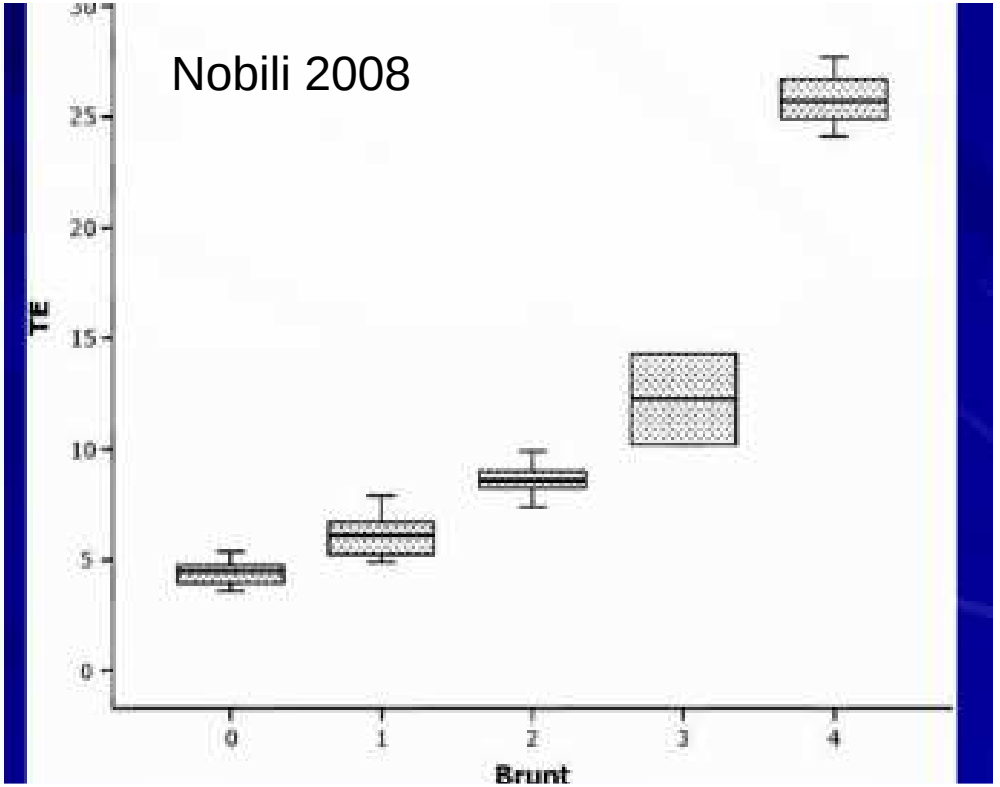




Yoneda 2008



Nobili 2008



Therapeutic Algorithm for the Long-term Management of ALD