Making the best use of liver biopsy: clinical perspective

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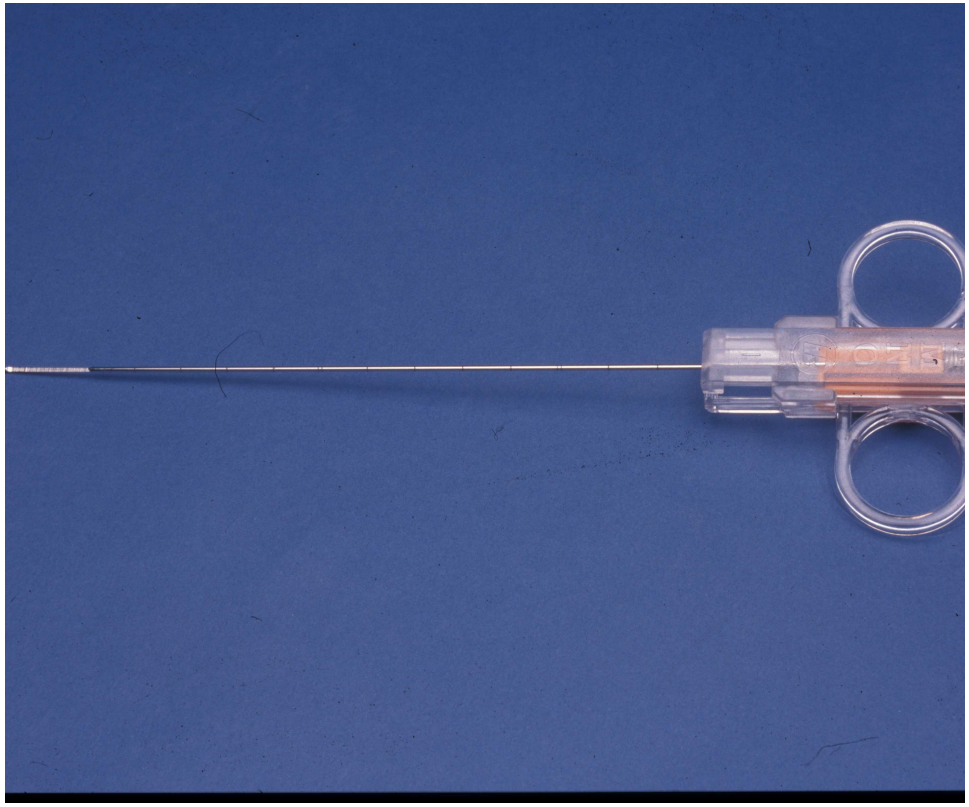
Trepanning

“ most efficacious for the relief of maladies so diverse and troublesome to the body and sprit”



Trepanning for the new milennium:
Liver biopsy circa 1883 (Erlich)

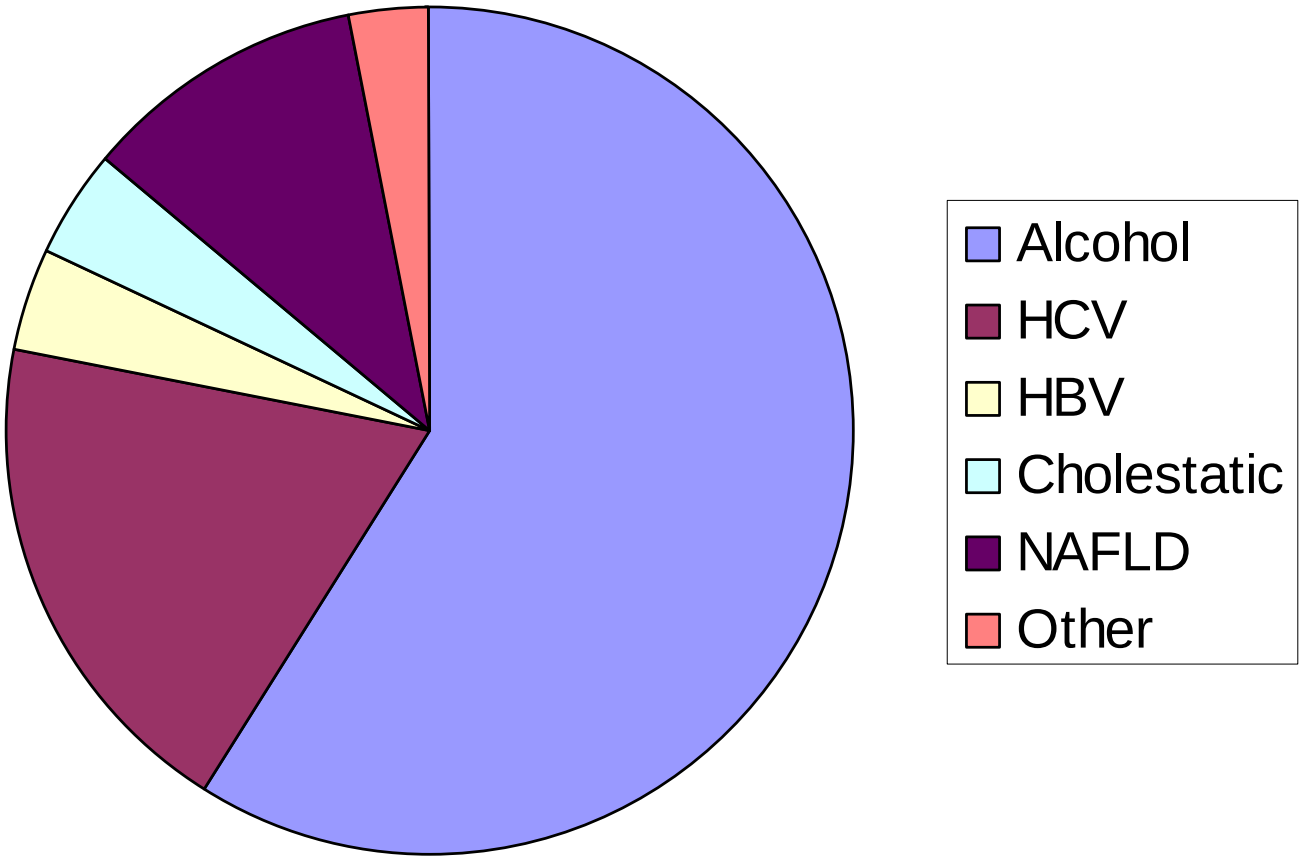
Why would you want a liver biopsy?

- to tell you the diagnosis
- to stage the degree of fibrosis
- to establish activity of disease

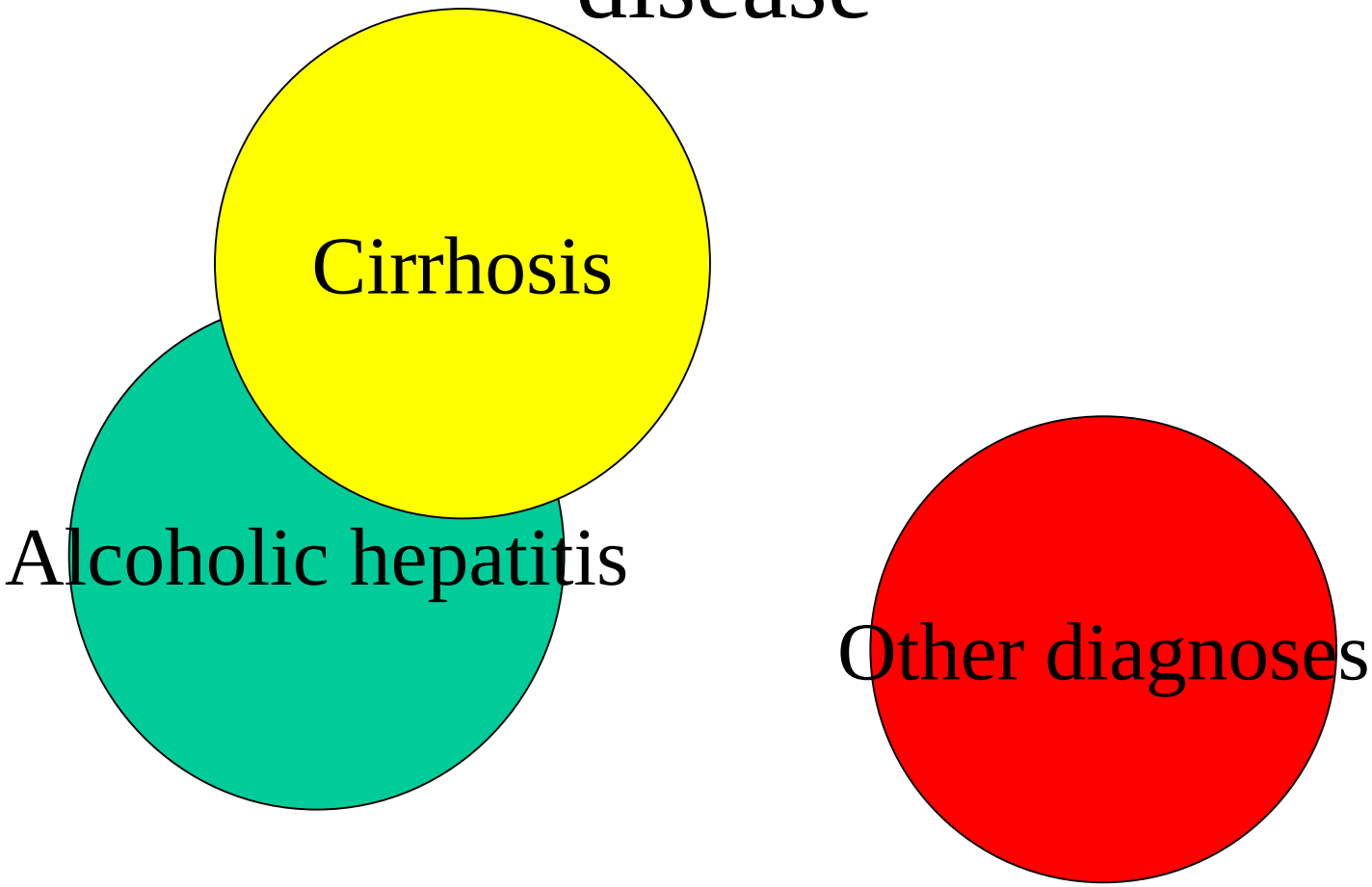
Diagnosis?

AMA
ASM/ANA
HCVAb
HBsAg
HFE mutations

Liver disease in the UK



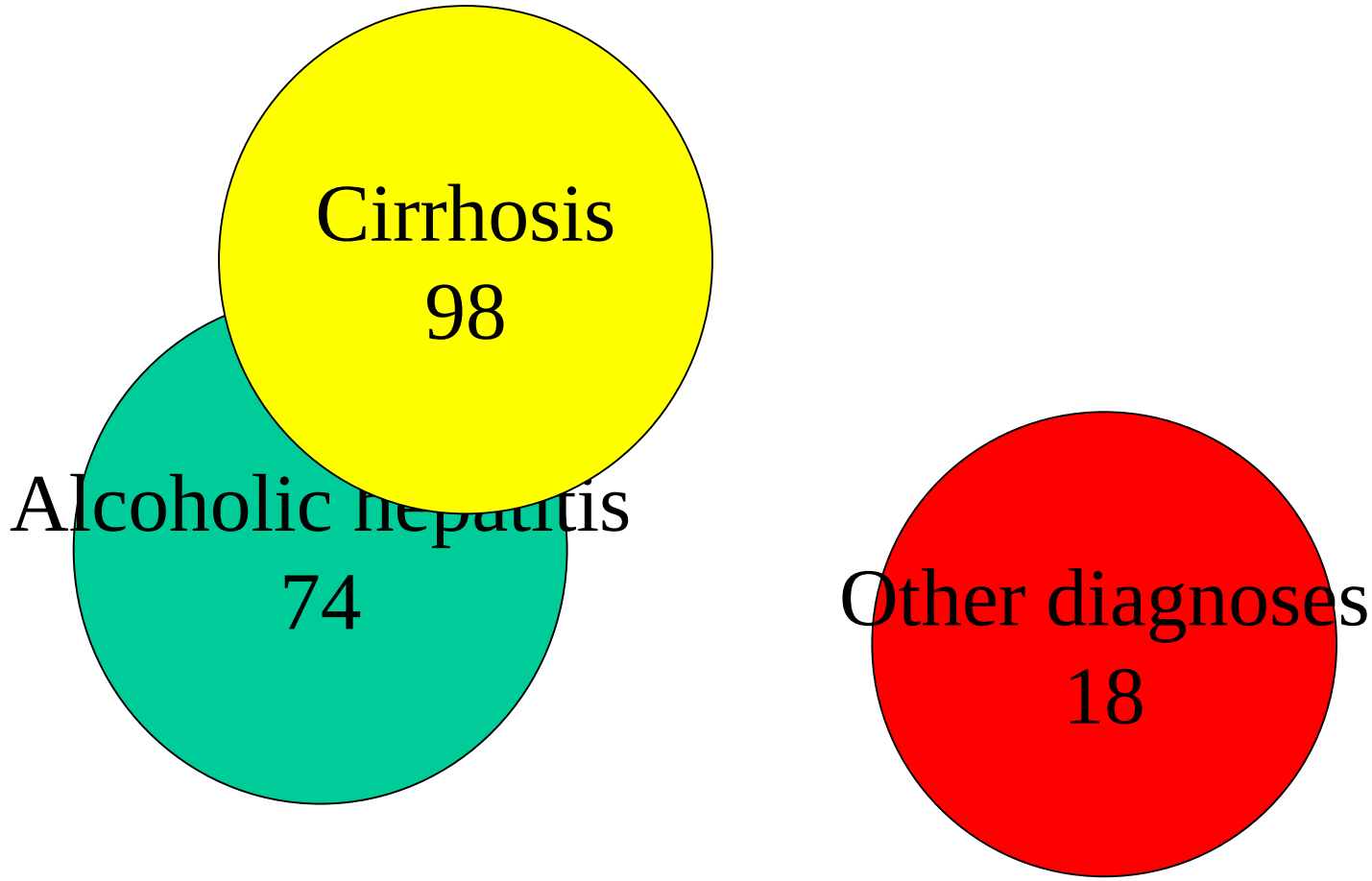
Liver biopsy in alcohol related liver disease



Liver biopsy in suspected ALD

- 130 patients with “decompensated” ALD
- Biopsy transjugular (clotting etc)
- Stage assessed and certainty rated
- Use clinically assessed post biopsy

Liver biopsy in ALD



El Sharkwary EJ Gastro Hepatol 2006

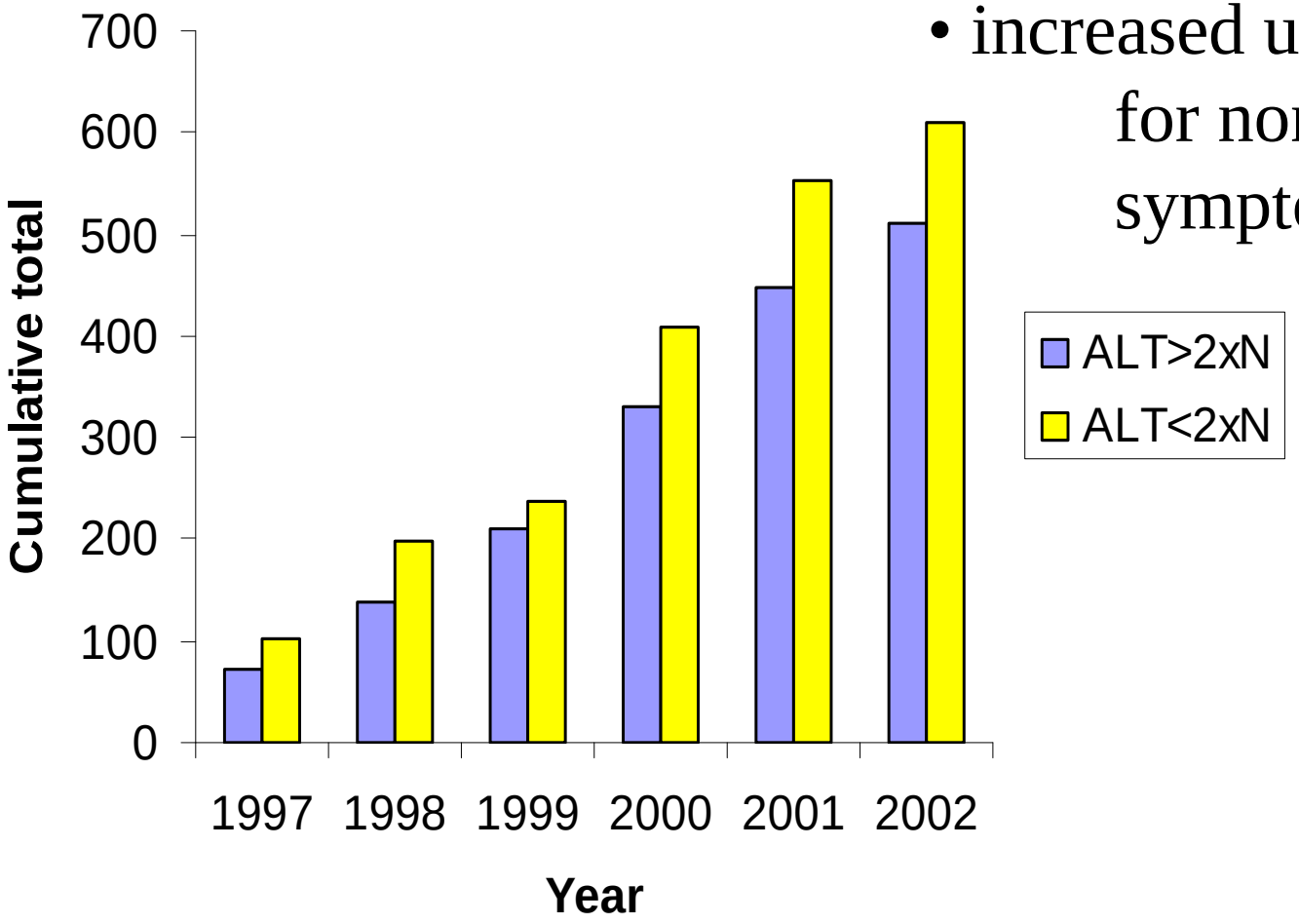
Abnormal transaminases
Normal serology

Must have a biopsy here

What diagnoses are made?

Skelly, J Hepatol 2001

- statin prescribing
- awareness of liver disease
- increased use of tests for non-specific symptoms



It’s a real mystery,
My ALT is 94

I wonder what that
could possibly
be due to!

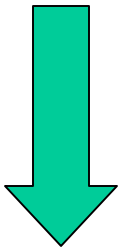
Skelly et al. J Hepatol 2001;35:195-199

Findings on Liver biopsy for abnormal LFTS

- Abnormal liver enzymes
- Negative diagnostic serology
- careful exclusion of alcohol

Again abnormal =2x ULN

397 patients



43 declined biopsy

354 underwent biopsy

Stage of liver disease	
Cirrhosis	6%
Bridging	9%
Portal	12%
None	73%

Findings in 354 patients

NASH	120 (34%)
Fatty liver	115 (32%)

cryptogenic hepatitis	32 (9%)
drug reactions	27 (8%)
normal liver	21 (6%)
Alcohol	10 (3%)
PBC/PSC	9 (2.5%)
Autoimmune hepatitis	7 (1.9%)
Granulomas/sarcoid	6 (1.7%)
Others	7 (1.9%)

Therapy for NAFLD

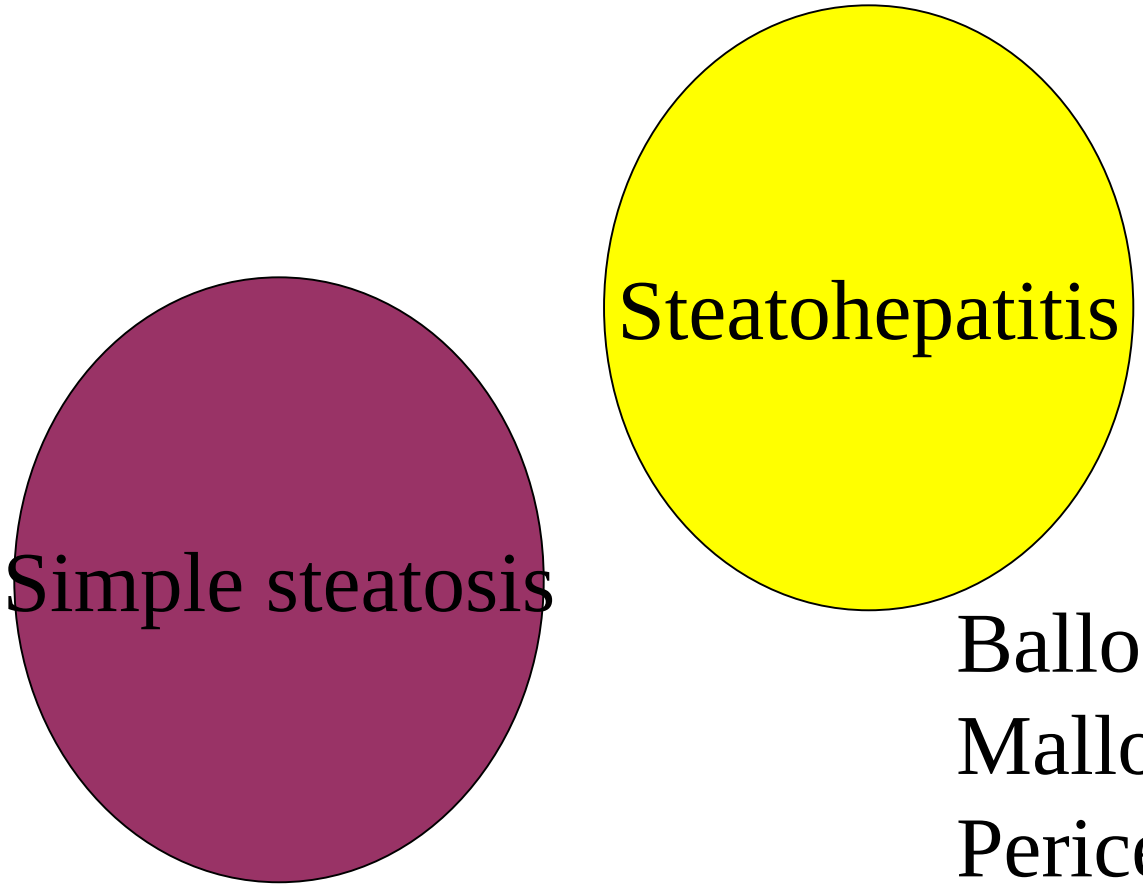
You could loose weight!

But you wont!

Liver biopsy in NAFLD

- Required for diagnosis
- Required to establish fat versus fibrosis
- Need a proven therapy before will gain wide acceptance

NAFLD and liver biopsy



Ballooning
Mallory's
Pericellular/Portal fibrosis

Liver biopsy to stage disease

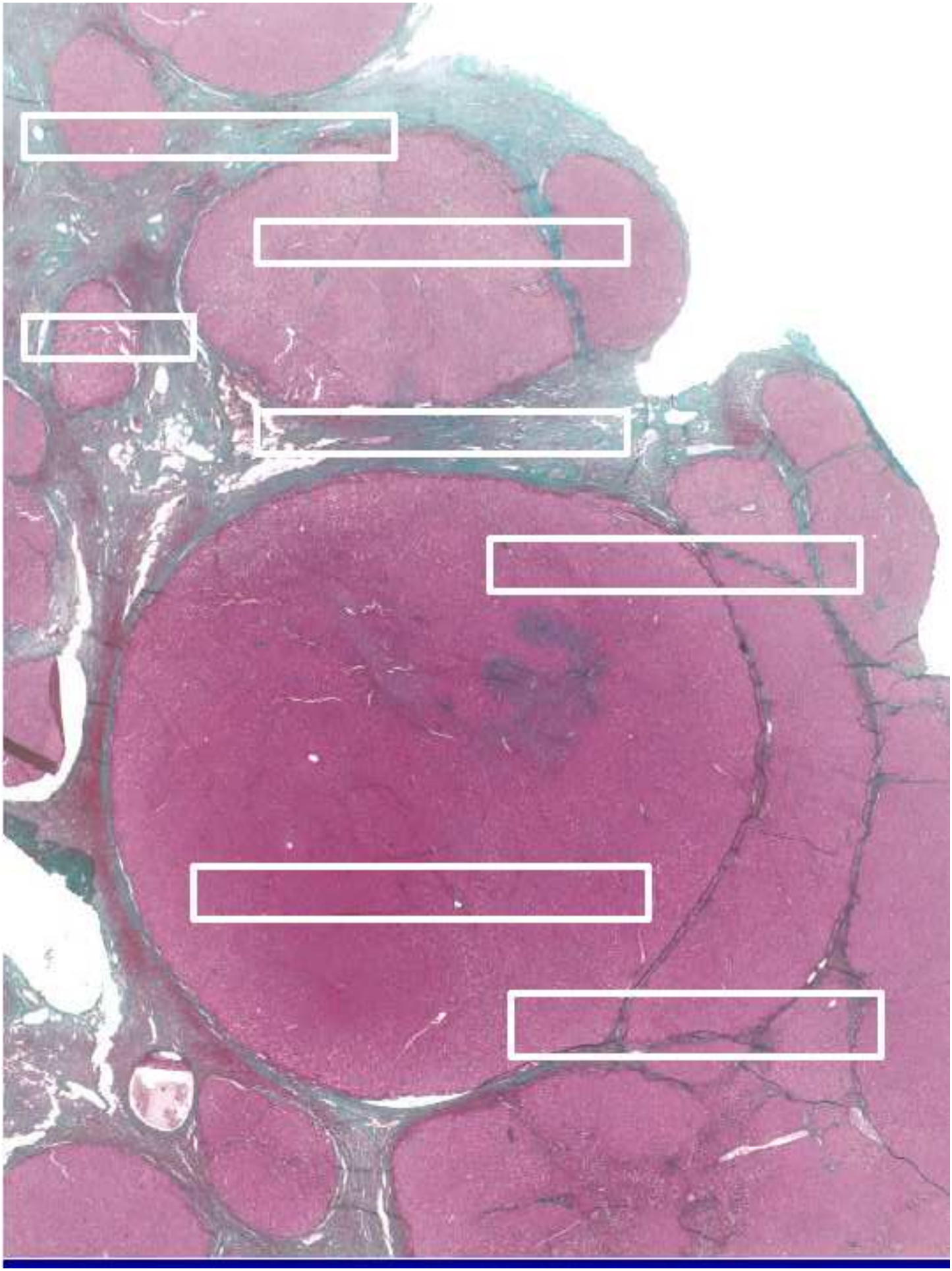
The “gold standard” to assess fibrosis

How good is liver biopsy really?

Liver biopsy in PBC

32/50 patients biopsies from Left/Right Liver differed by >1 stage

Garrido and Hubscher JClin Pathol 1996;49:556



Liver biopsy to stage disease

The “gold standard” to assess fibrosis

How good is liver biopsy really?
Hepatitis C as the paradigm

Rousselet et al. Hepatology 2005;41:257

254 liver biopsies, 15 pathologists

4 Academic pathologists, 44 biopsies

	Fibrosis	Activity	Lobular infl
Kappa	0.59	0.43	0.15

2 expert pathologists

	fibrosis	NI
Before	0.48	0.44
After	0.77	0.7

1 expert, 10 non-academic

	fibrosis	NI
Kapp	0.13	0.22

Reasons for not undertaking biopsy in US patients with HCV

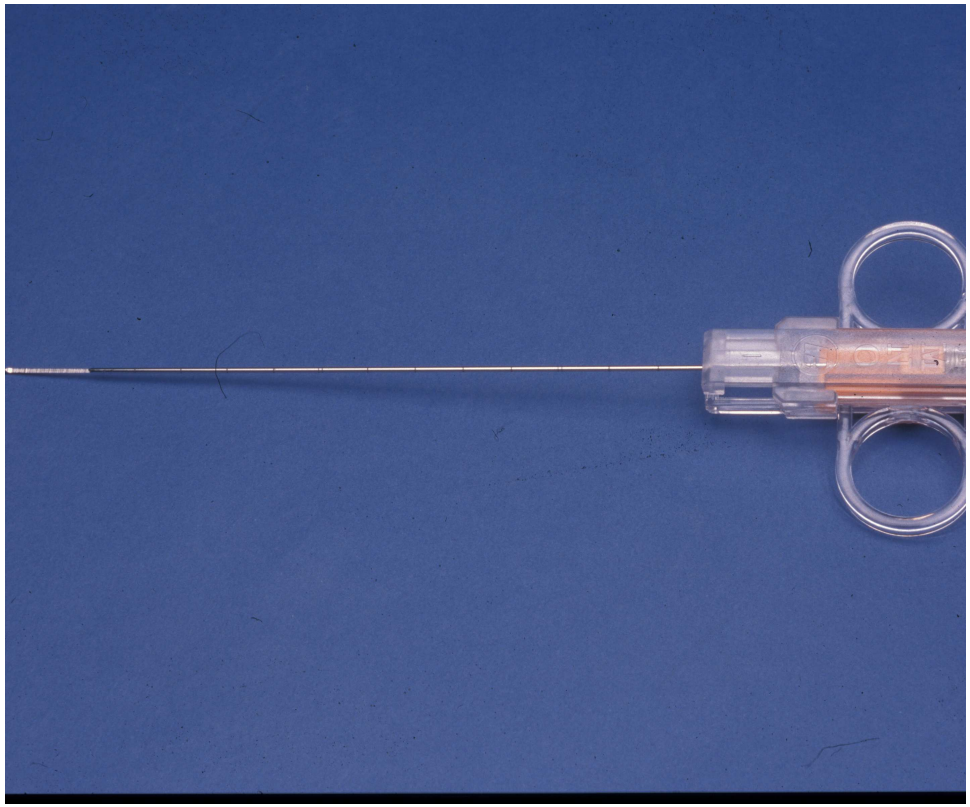
- Perceived risk
- Low reimbursement
- Logistic difficulties

Muir J Clin Gastroenterol 2002;35:86

Cadranel Hepatology 2000;32:477

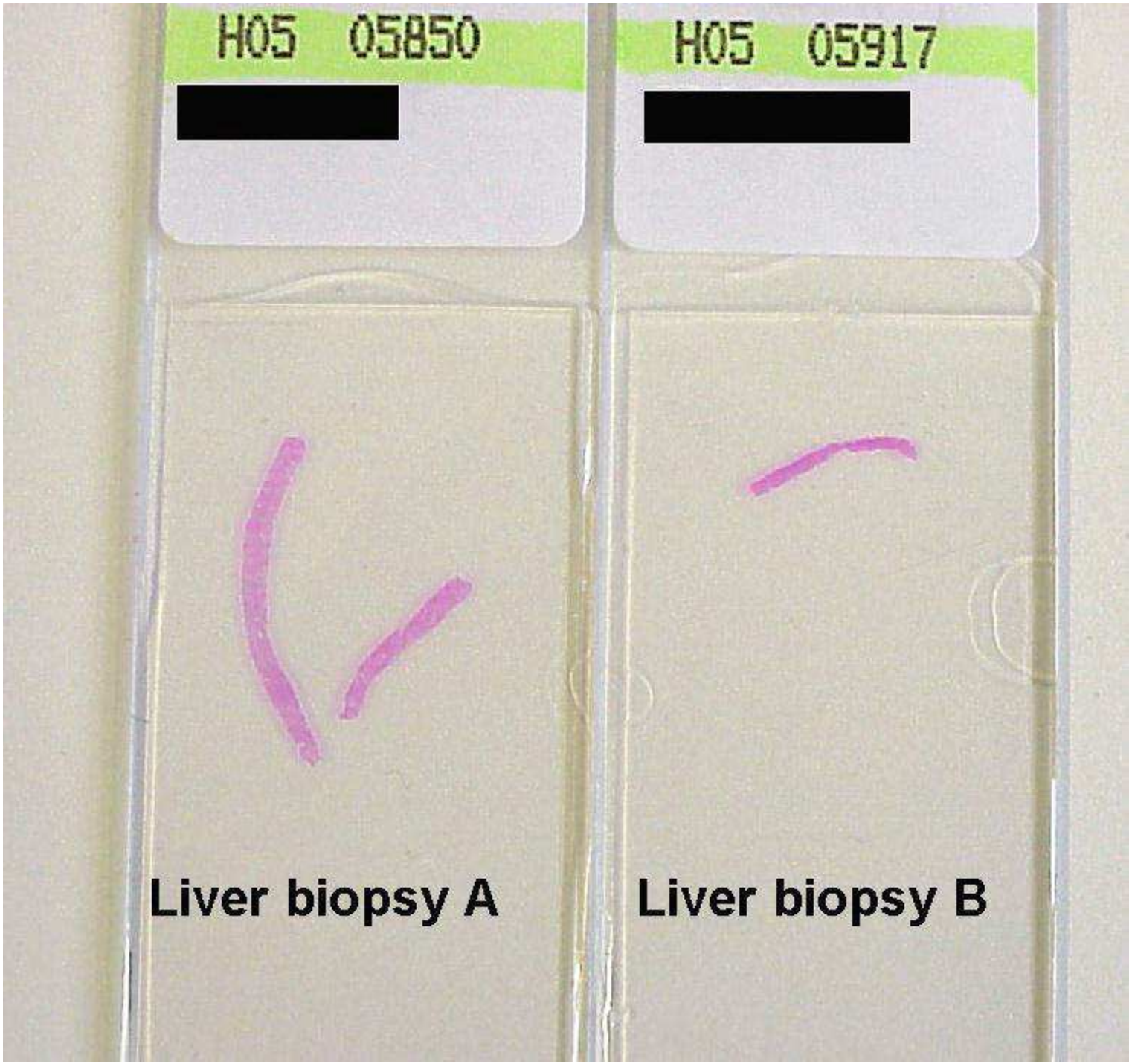
- Moderate pain 20%
- Narcotic requiring pain 3%
- Severe complication 0.6%

Clinicians don’t like doing liver biopsy



So we delegate to radiologists

Radiologists use poxy little needles


H05 05850
[redacted]
H05 05917
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Liver biopsy A
Liver biopsy B

Colloredo J Hepatol 2003;39:275

161 biopsies

	% mild disease	
Length	Grade	Stage
>3cm	50%	59%
1.5	60%	68%
1cm	87%	80%

St Elsewhere's pathology services consortium plc

Aiming for excellence in cervical cytology

Liver biopsy

Macroscopic
A core of tan tissue 0.4cm x 1.3cm

Microscopy
Liver tissue is present. There is no evidence of cancer

A Pathologist

Alternatives to liver biopsy: how good are they?

- Clinical predictors of fibrosis
- Serum fibrosis markers
- Tests of liver stiffness

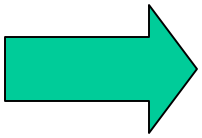
Clinical predictors of fibrosis

Trent HCV Study group data

Age
Alcohol intake
Duration of infection
Gender

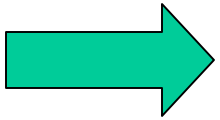
3 490 patients; 1,250 liver biopsies

Female
<40
No alcohol excess
Duration <10 years



0/193
>=I3 fibrosis

Male
>40
Duration >10 years
Alcohol excess



176/225 (78%)
I4 or greater

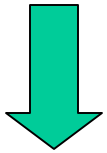
Other clinical parameters

- Hepatomegaly
- Stigmata of chronic liver disease
- Splenomegaly

Using all clinical criteria

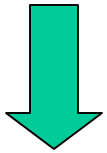
1, 250 patients

No risk of severe fibrosis



15%

High risk of severe fibrosis



18%

AST/ALT ratio

- Sensitivity for cirrhosis 31-56%
- Specificity 90-100%

Gebo et al Hepatology 2002;36:s161

Tests at Bayer AG

- ***Fibrosis***
- PIII-NP
- PIII-CP
- Hyaluronic acid
- Tenascin - lobular fibrosis
- Undulin/collagen XIV - portal fibrosis
- Laminin P1 - portal pressure
- TIMP-1
- Collagen IV

- ***Fibrolysis***
- Collagen VI
- MMP-2

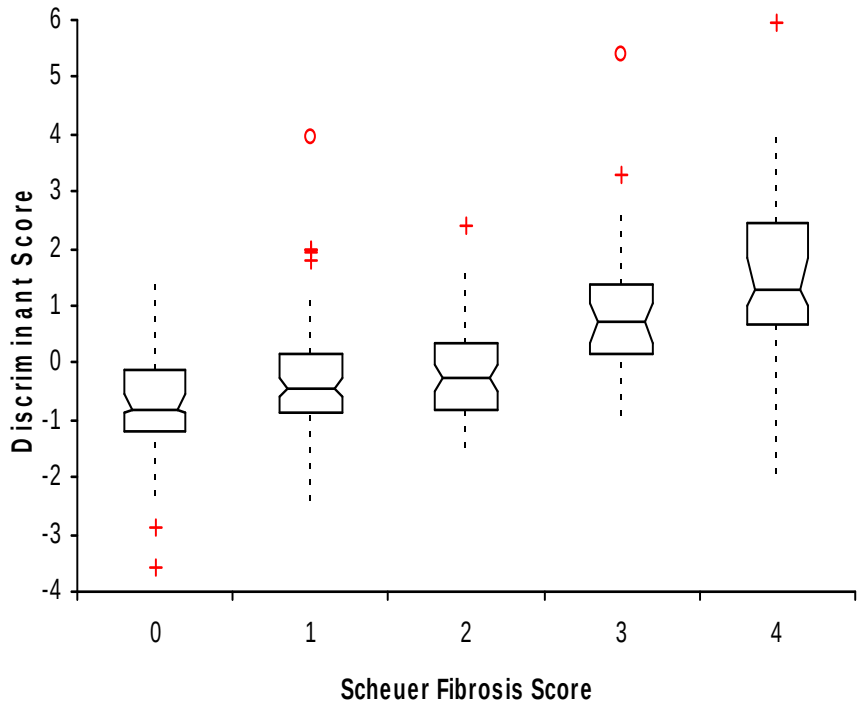
ELF Markers

Rosenberg et al. Gastro Dec 2004

Detection of Scheuer Stage 0,1,2 versus 3,4

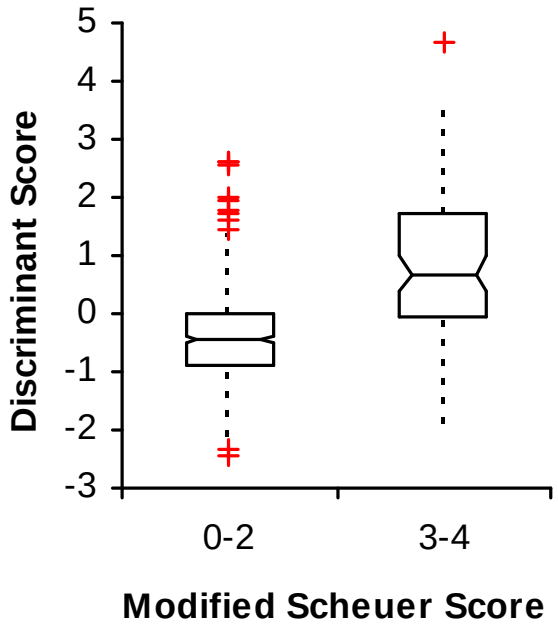
Disease	AUC	Score	Sensitivity	Specificity	PPV	NPV
NAFLD	**0.87**	**0.375**	**89%**	**96%**	**80%**	**98%**
		0.462	**78%**	**98%**	**87%**	**96%**
ALD	**0.944**	**0.087**	**100.0%**	**16.7%**	**75.0%**	**100.0%**
		0.431	**93.3%**	**100.0%**	**100.0%**	**85.7%**
HCV	**0.773**	**0.067**	**90%**	**31%**	**27.5%**	**92.3%**
		0.564	**30%**	**99%**	**89.5%**	**83.3%**

Typical Algorithm Performance



Rosenberg et al Gastroenterology 2004

Algorithm Performance
F0,1,2 vs F3,4



ELF Conclusions

- ELF Panel is useful in clinical practice
- At specified thresholds it can Rule-in or Rule-out significant fibrosis in patients with a range of CLD
- The test is sufficiently robust to provide valid information in ~ 40% of cases
- This might halve the number of patients requiring biopsy

Fibroscan

Fibroscan plus fibrosis markers

Fibroscan measure of liver stiffess

Compared with serum markers

- fibrotest
- biopredictive
- AST/platelet ratio index

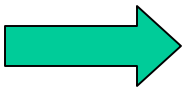
Castera Gastroenterology 2005;128:343

Fibroscan plus fibrotest

Cut off	AUC	Biopsy stage
7.1kPa	0.88	F>=2
9.5 kPa	0.95	F>=3
12.5 kPa	0.95	F=4

Where the tests agreed:

84%	F>=2
95%	F>=3
94%	F=4



Avoid 88%
Of biopsies

Alternatives for your patients are:

Blood test and scan

88% chance will be accurate

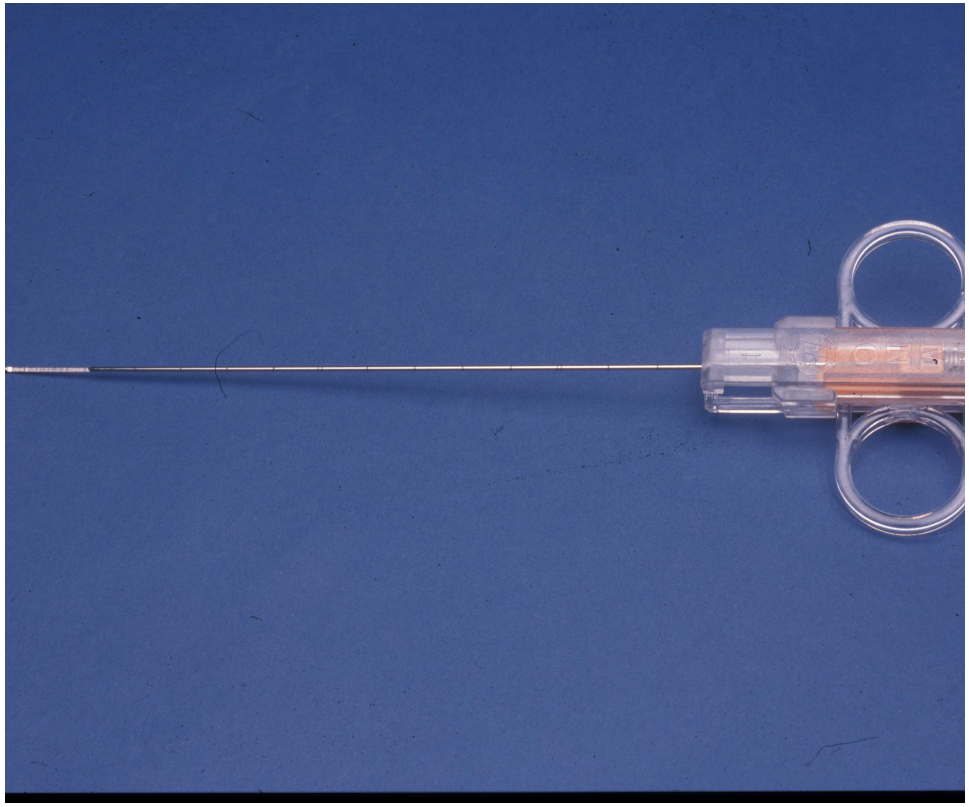
Risks: a bruise

Liver biopsy

Will provide pathologists with hours of fun arguing how bad/good your liver is

In real practice no better chance than Flip of coin in determining severity

Risks: death



Anyone who would still use this…..

Needs one of these to let the evil miasma of outdated dogma out

Reality of non-invasive markers

- May well identify non and severe fibrosis
- Likely to be left with lots in the middle where uninformative
- Studies all in single diagnostic groups: how will test perform in a range of diseases?

The future

- Liver biopsy indications will change
- Less to stage known disease (HCV)
- Use in combination with non-invasive markers for follow-up