Nottingham
Biomedical Research Centre

NHS
National Institute for
Health Research

Why to biopsy?
Indications for liver biopsy in common medical liver diseases- how are they changing?

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UK | CHINA | MALAYSIA

NDDC
Nottingham Digestive Diseases Centre

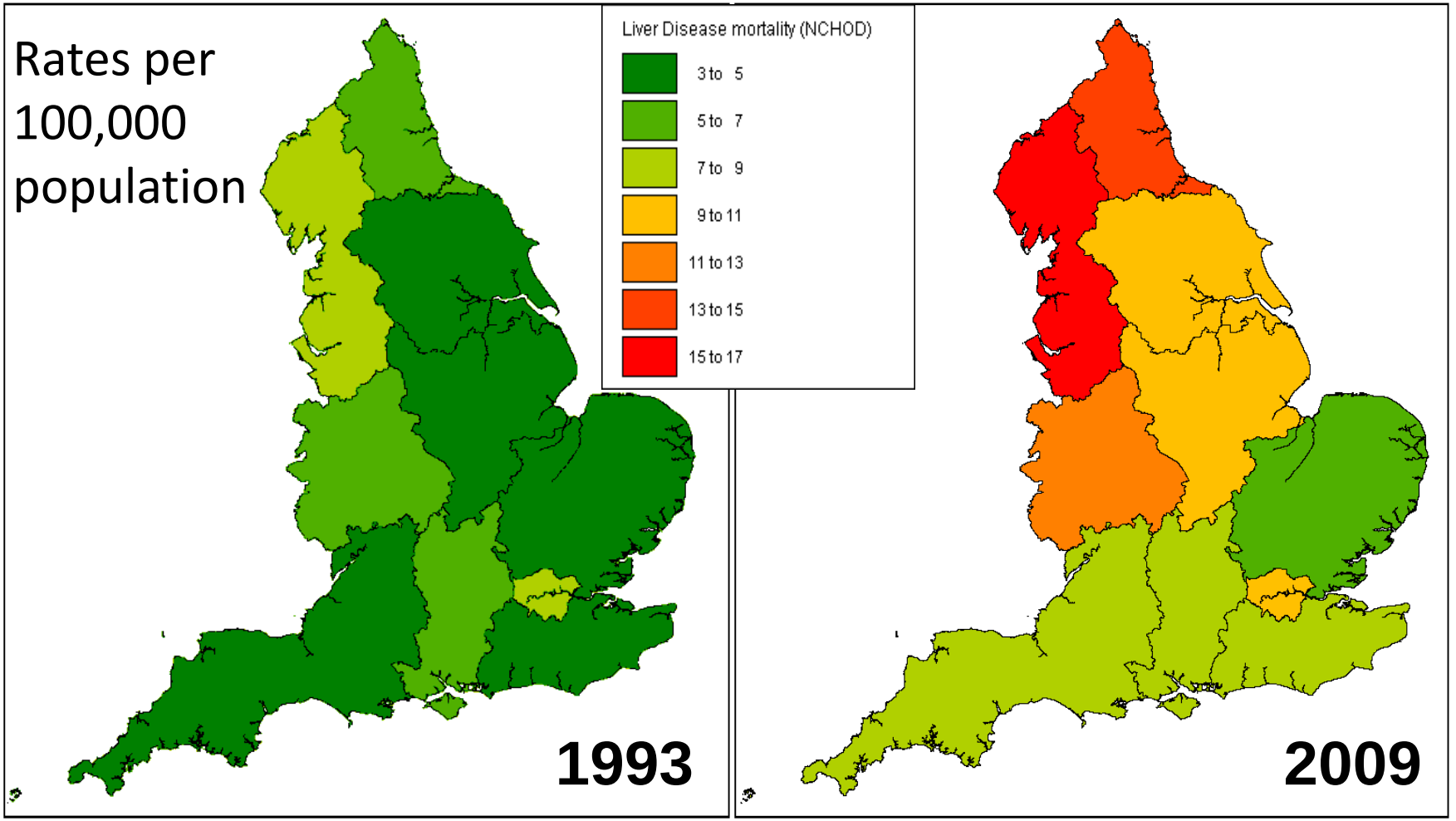
What are we currently using liver biopsy for?

Assessing severity of Clinically/serologically diagnosed disease

Adding additional diagnoses

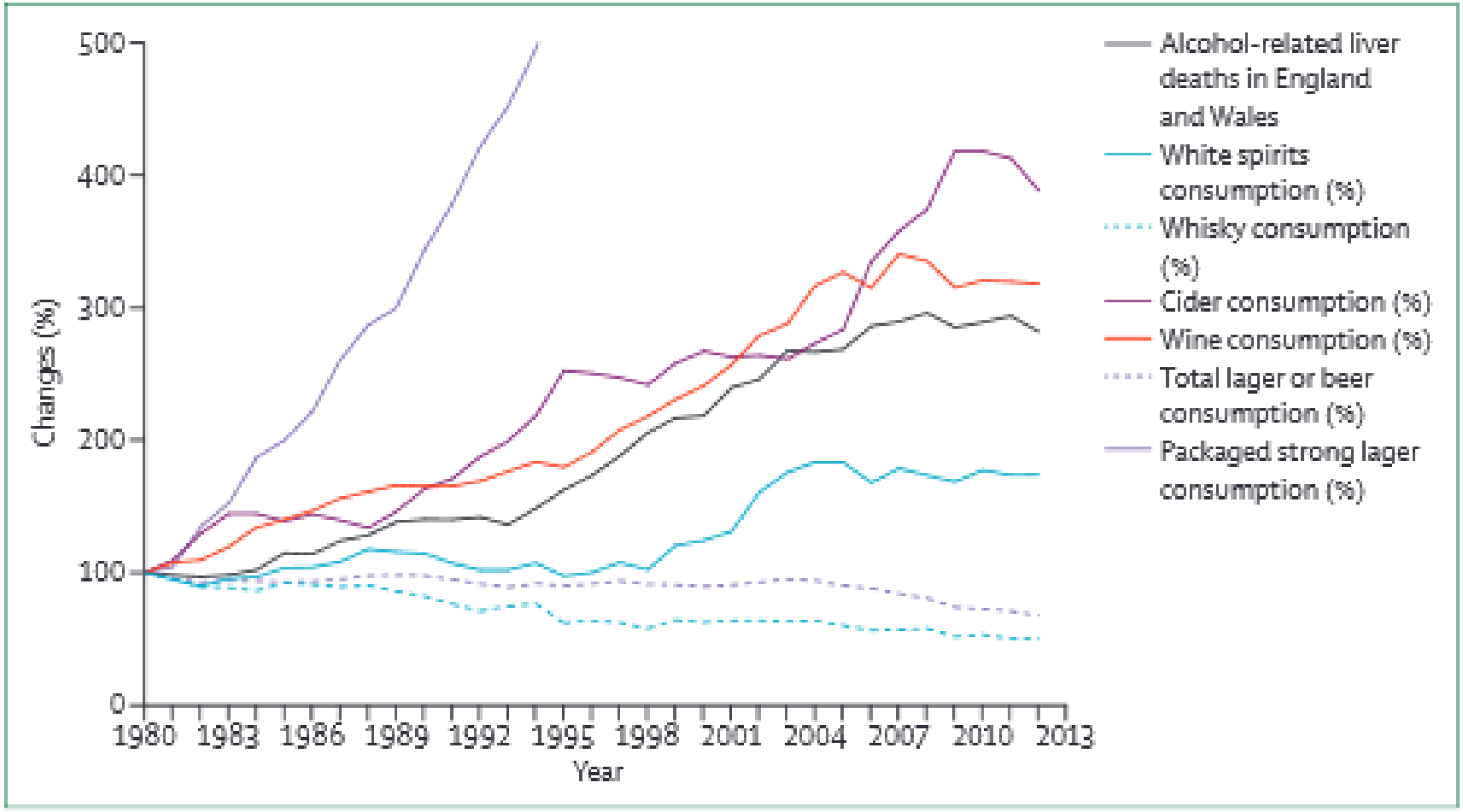
Providing a diagnosis (and prognosis) for undiagnosed liver disease

Deaths from Chronic Liver Disease in 1993 & 2009



Bhala, Aithal & Ferguson, *BMJ*, 2013

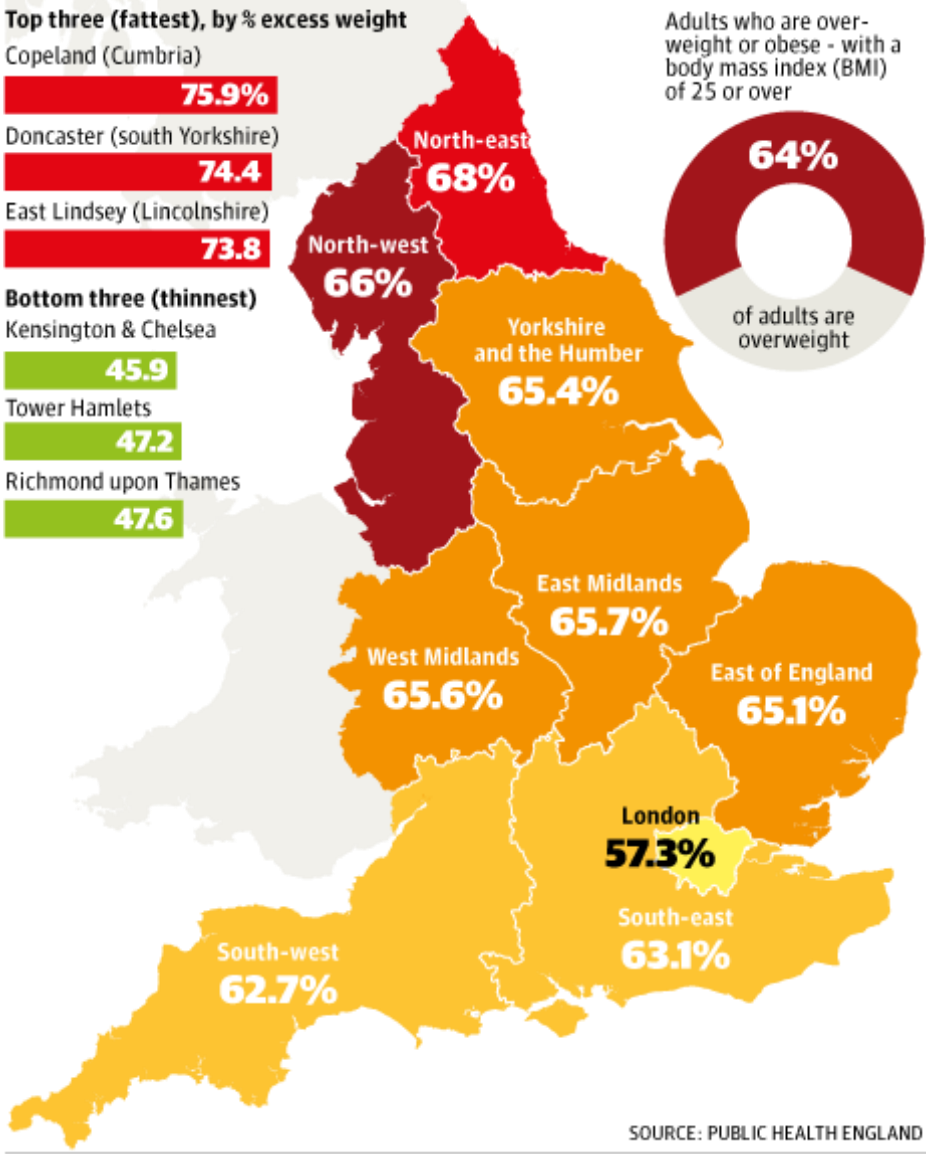
Alcohol Consumption in the UK



Williams et al, Lancet, 2014

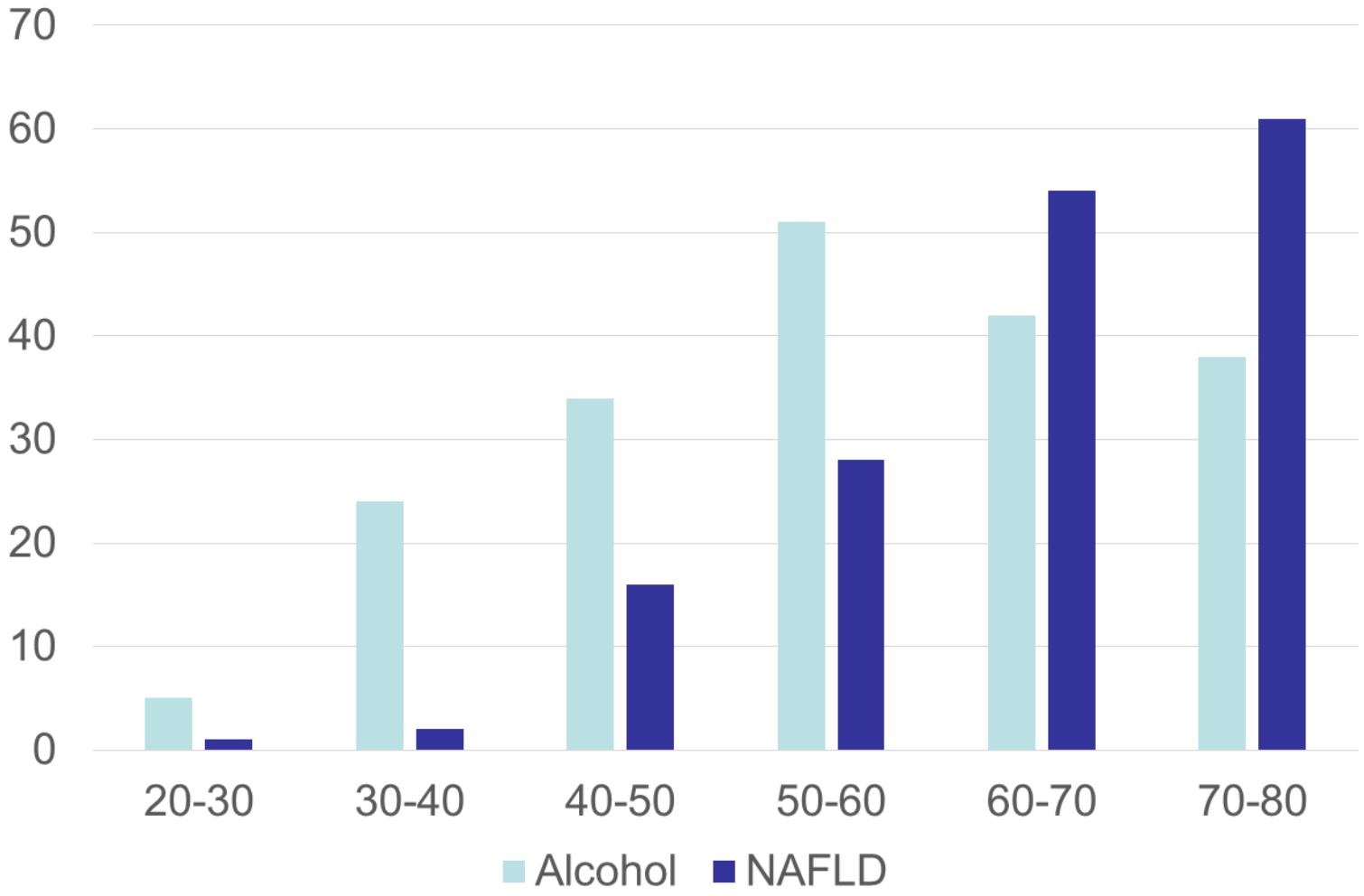
Map of excess weight

Adults aged 16 or over. England, January 2012 to January 2013



SOURCE: PUBLIC HEALTH ENGLAND

Rates of progression?



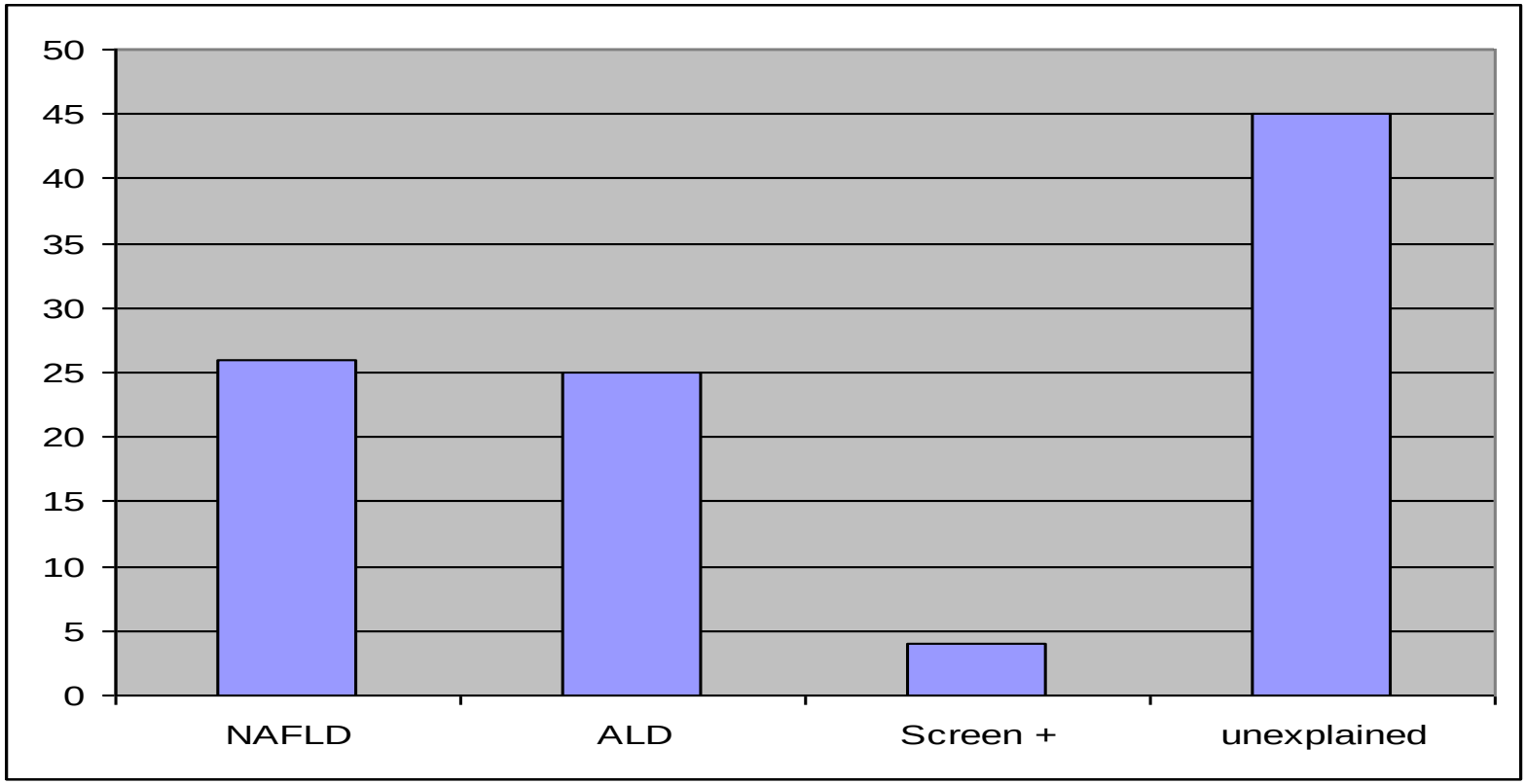
BALLETS study

- 8 practices in Birmingham
- 2006-2008
- Abnormal test in liver panel
- No symptoms of liver disease
- No history of liver disease/alcohol/ivdu

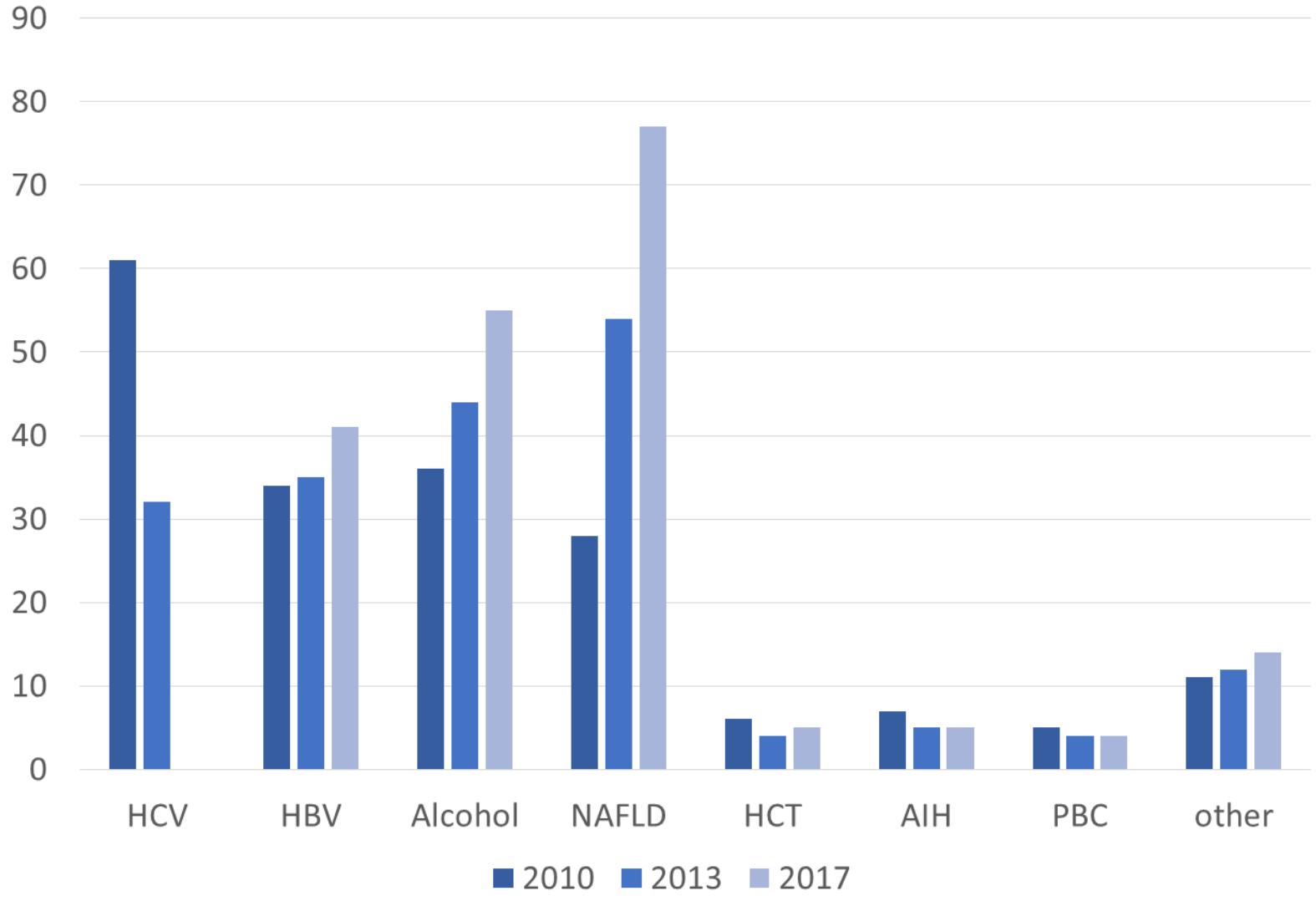
Armstrong MJ et al. J Hepatol 2012;56:234

Cause of Abnormal LFTs

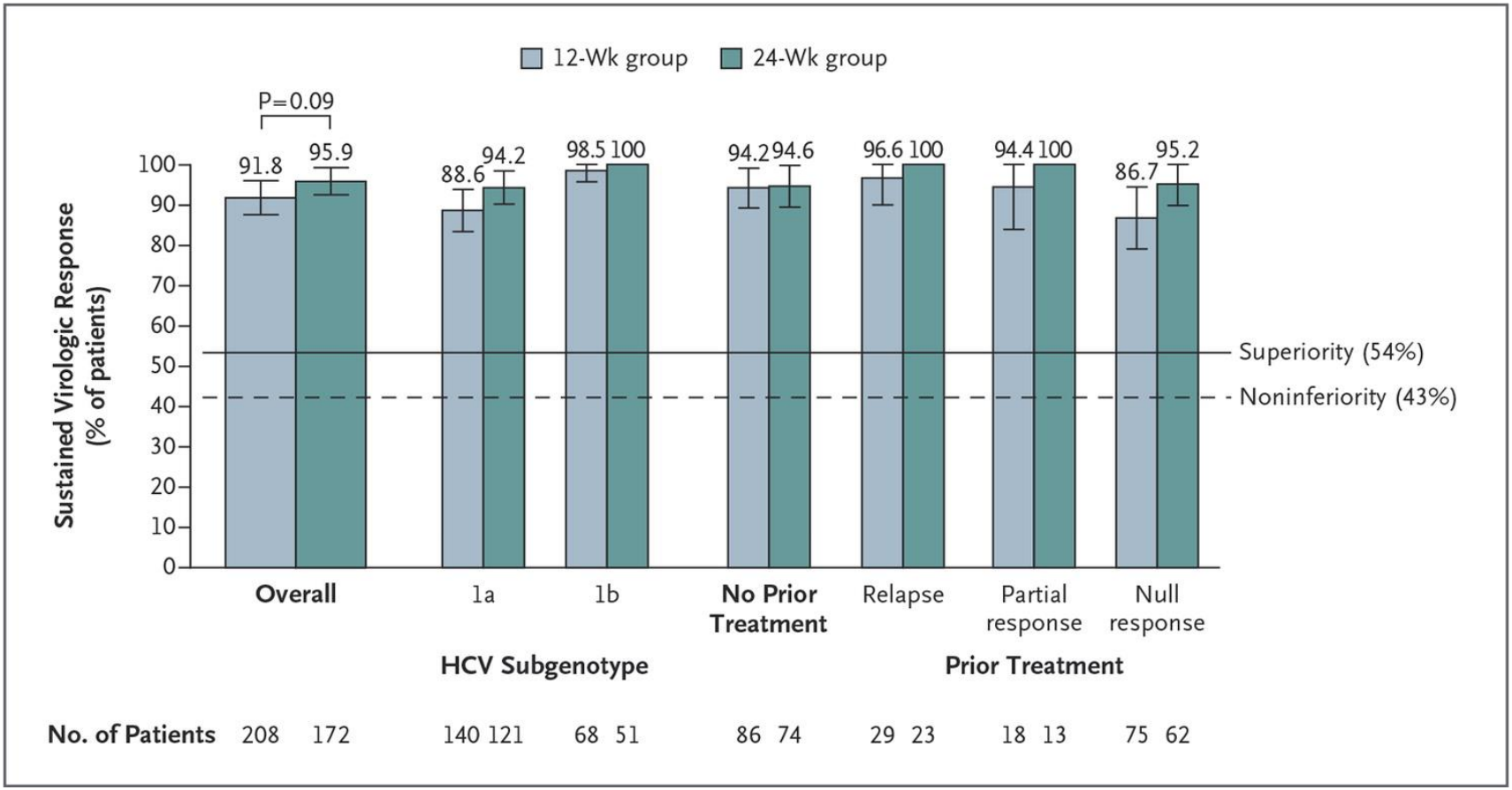
- 54.9% had a cause identified



Current diagnostic liver biopsy



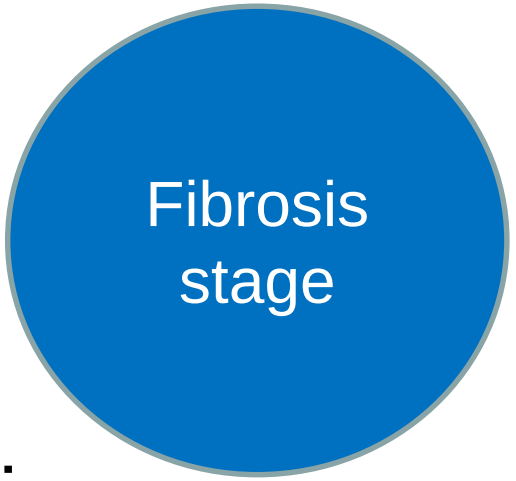
Abbvie in G1 cirrhosis

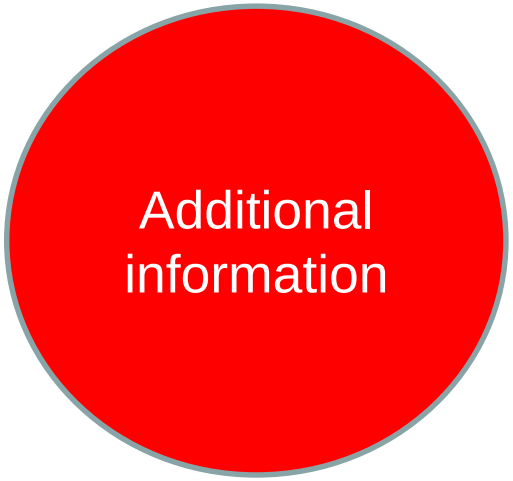


Poordad F et al. N Engl J Med 2014;370:1973-1982.

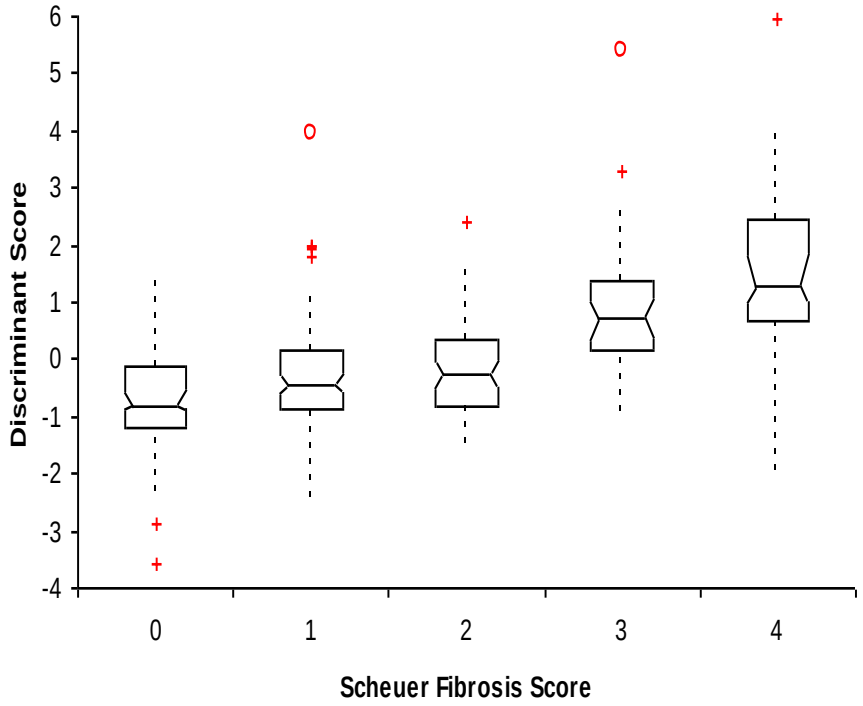
Biopsy in diagnosed disease

- AMA
- Anti-HCV
- HBsAg
- C282Y Haemochromatosis
- Alcohol
- NAFLD



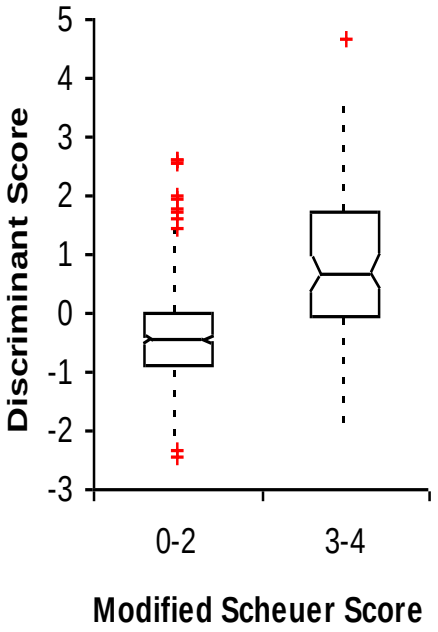


Typical Algorithm Performance: ELF



Rosenberg et al Gastroenterology 2004

ELF markers Performance F0,1,2 vs F3,4



Fibroscan

Natural History of Chronic Liver Disease

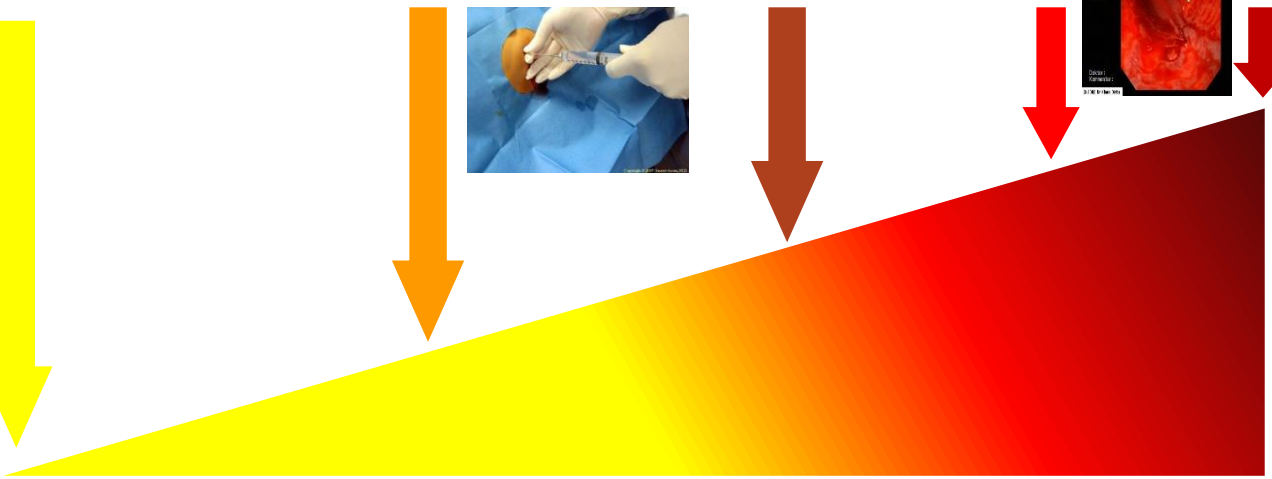
Risk Factors
Alcohol
Obesity / Diabetes
Viral hepatitis

Scarring

Severe Scarring (Cirrhosis)

Symptoms

Death

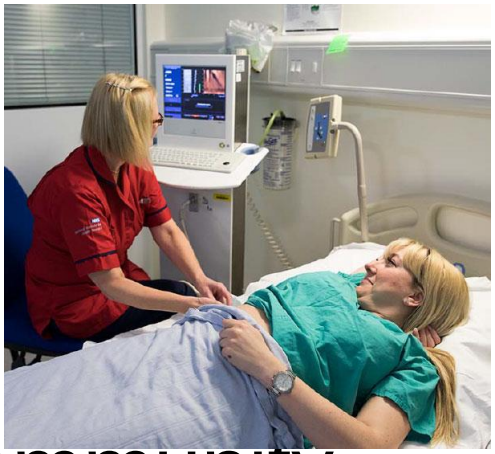


5-20 yrs

10-20 % year

Novel community pathway

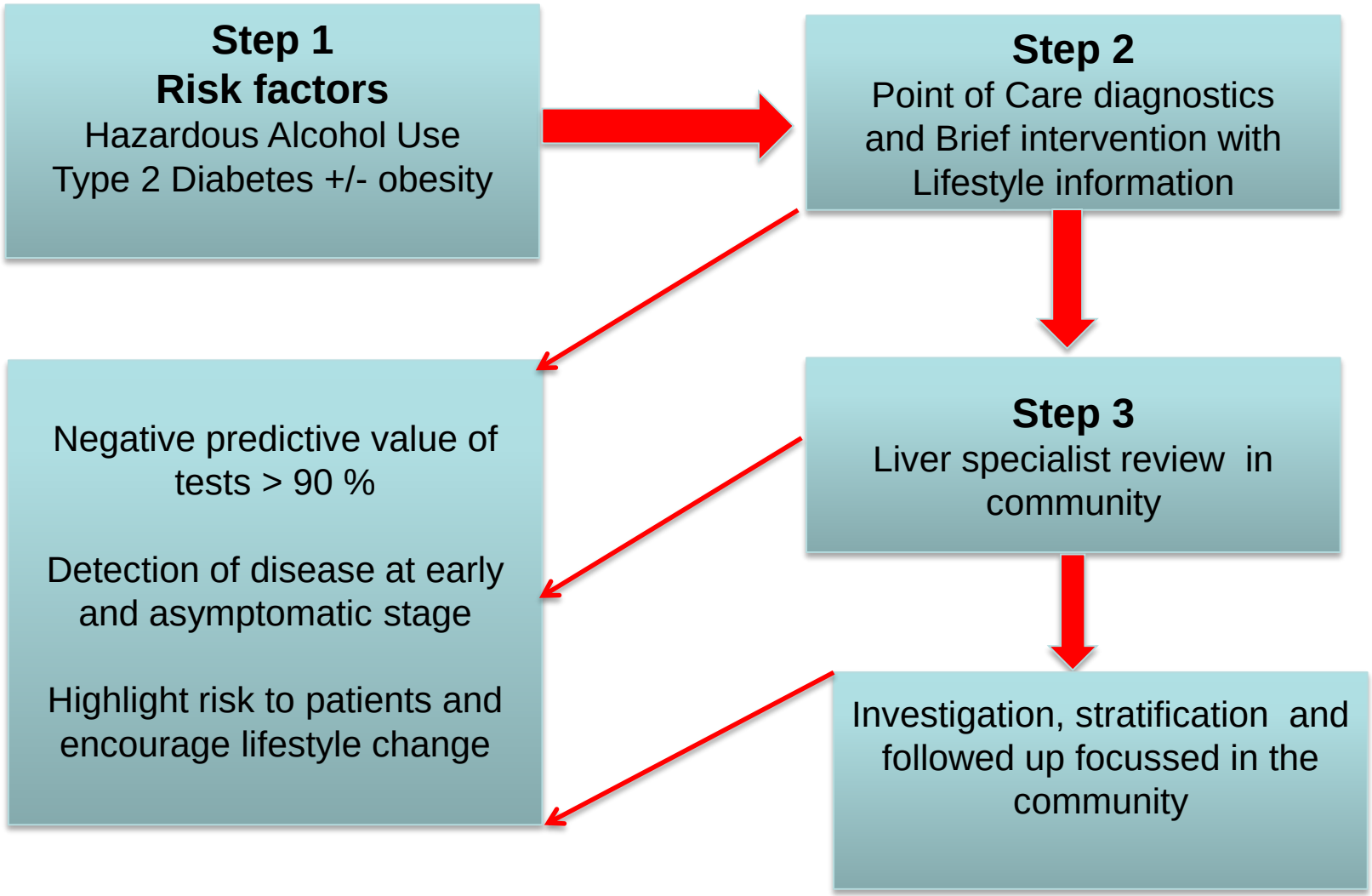
- Targeting risk factors
  - Synergistic in effect
  - Applicable to multiple aetiology



- Diagnostics performed in the community
  - Point of care diagnostics in primary care
  - Diagnostics/brief intervention delivered by nurses

McCorry et al QJM 2012
Dolman et al Liv Int 2013
Harman et al BMJ Open 2015
Gines et al Lancet Gastroenterol/Hep 2016
Harris et al Lancet Gastroenterol/Hep 2017
Tanajewski et al BMJ Open 2017
Harman et al APT 2017

3 step pathway

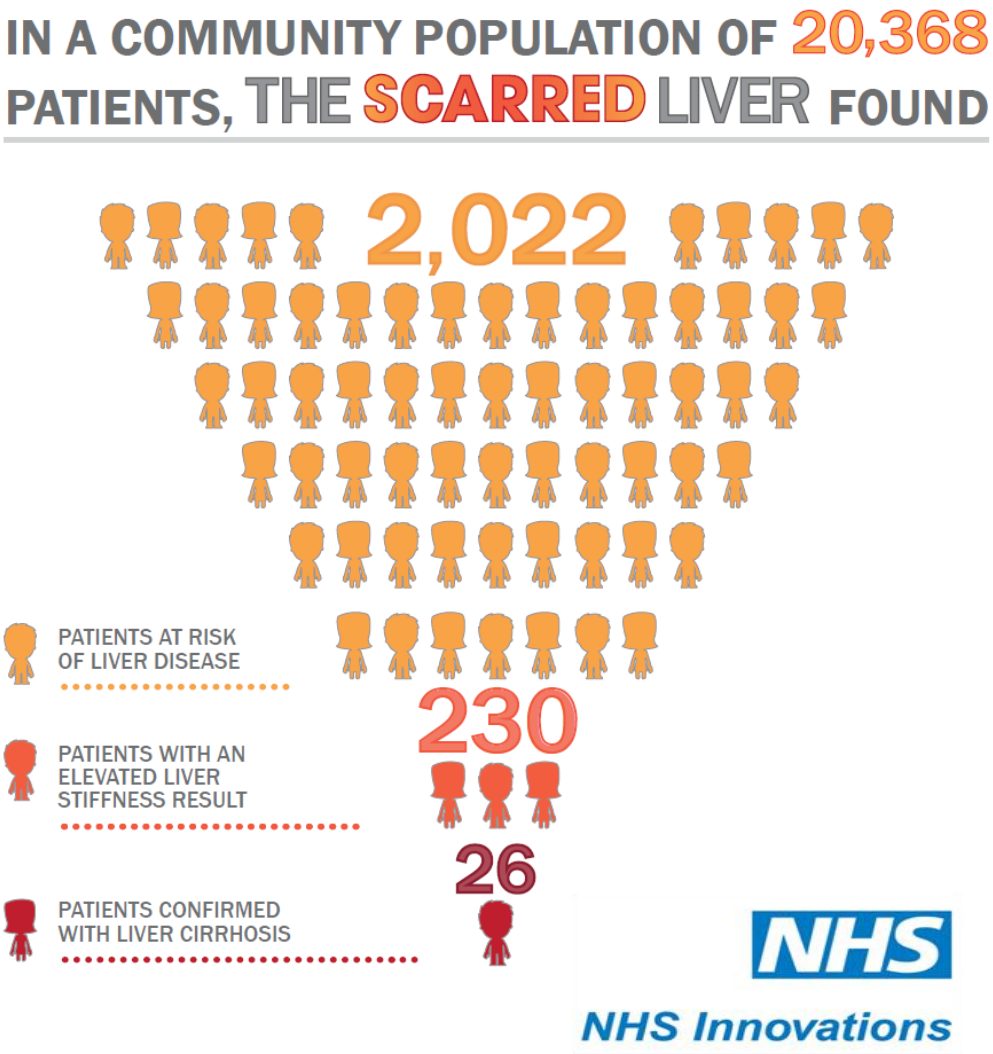


Harman et al BMJ open 2015

General Practice Population Risk Factors for Nottingham (phase 1 and 2)

Group	Population	Type 2 Diabetes	Alcohol
Practice A	7,612	304	522
Practice B	2,867	86	136
Practice C	6,412	391	482
Practice D	3,977	226	298
TOTAL	**20,868**	**1,007**	**1,438**

Changing our Approach to Liver Disease



Current approach:

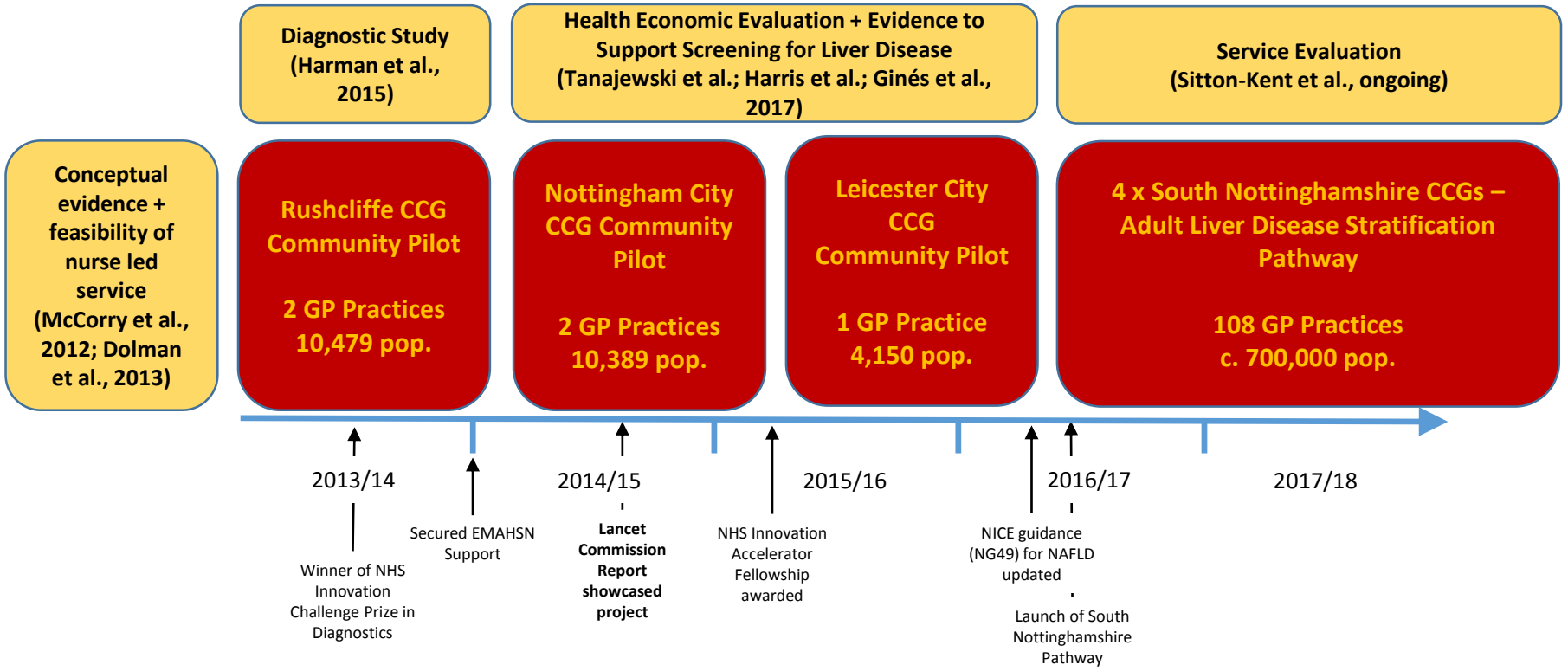
- Lacks accuracy
- Late detection
- Hospital based
- Costly and invasive

Alternative approach:

- Focus on risk factors
- Early detection
- Community testing
- Cost saving

NHS innovations award winners 2013
BMJ team of the year finalists 2015

Evolution of the clinical pathway



NICE guideline-Cirrhosis

1.1.3 Offer transient elastography to diagnose cirrhosis for:

- people with hepatitis C virus infection
- men who drink >50 u/wk and women >35 units of alcohol per week

1.1.4 Offer either transient elastography or ARFIE to diagnose cirrhosis for people with NAFLD and advanced liver fibrosis (ELF score of 10.51+).

https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0683

Non-alcoholic fatty liver disease: NICE guideline

1.1.11 Use the ELF test for advanced liver fibrosis if NAFLD has been diagnosed

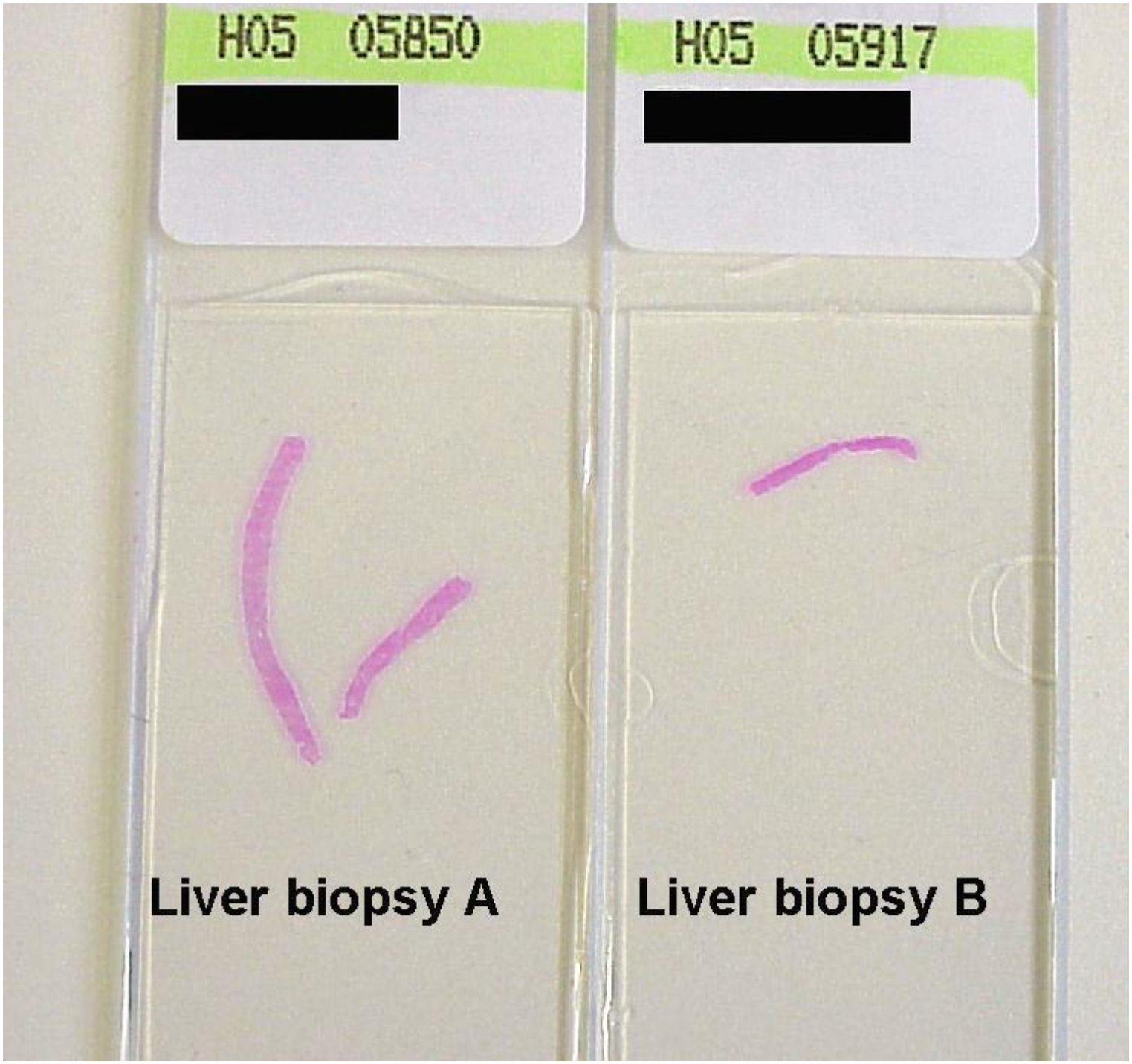
1.1.12 Diagnose people with advanced liver fibrosis and refer them to a relevant specialist in hepatology, if they have:

- an ELF score of 10.51 or above **and**
- NAFLD.

https://www.nice.org.uk/guidance/GID-CGWAVE0692/documents/short-version-of-draft-guideline

Mixed aetiology

- “pure” pathology now relatively uncommon
- 25% of population obese
- Overlap between aetiology very frequent
- Helpful if histological pattern points to dominant aetiology


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

Colloredo J Hepatol 2003;39:275

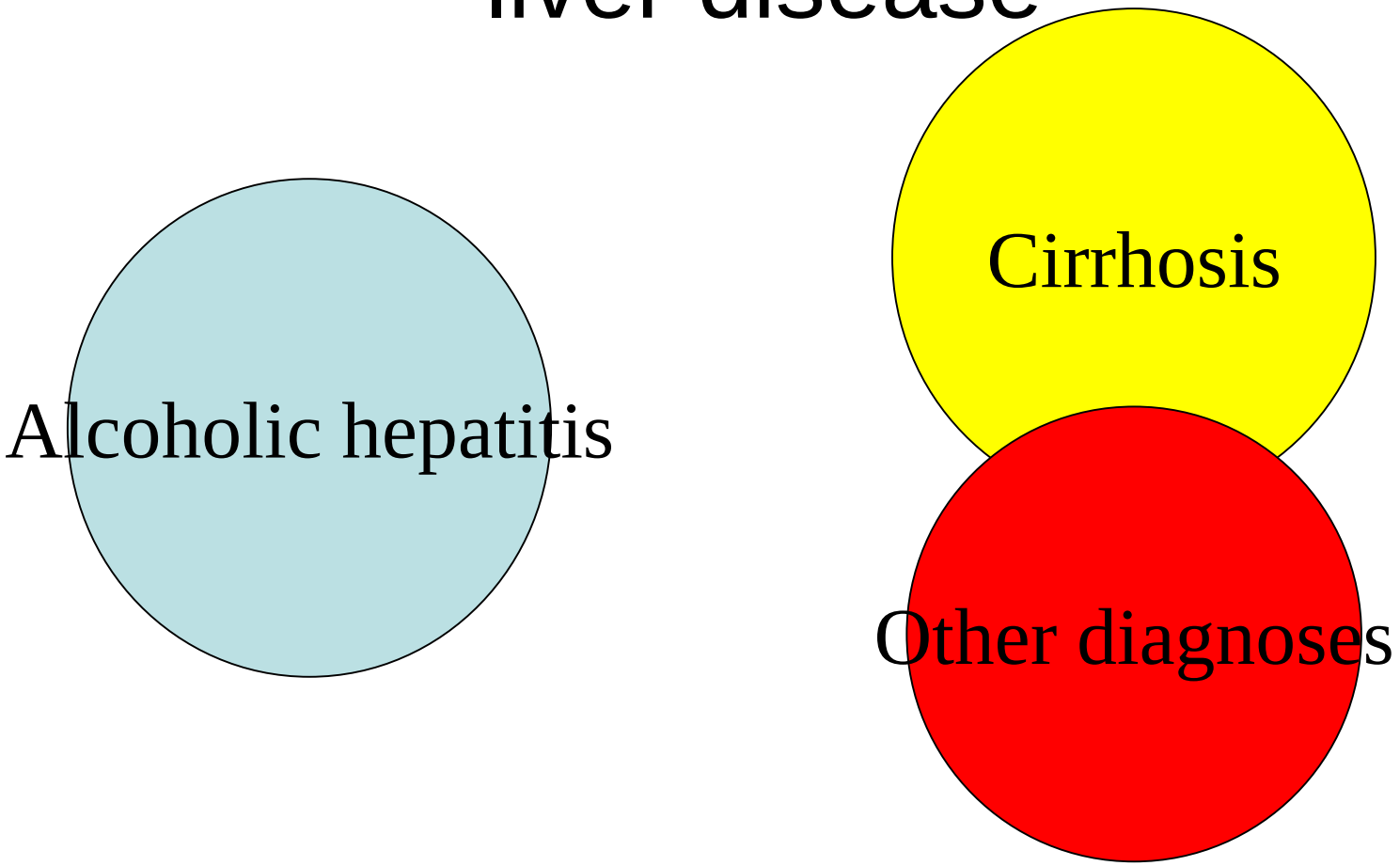
161 biopsies

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

Clinician and Pathologist interaction

- Adequacy of core
  - Size
  - Number of portal tracts
- Stage of disease
- Grade of inflammation
- Narrative comment

Liver biopsy in alcohol related liver disease



Route of biopsy

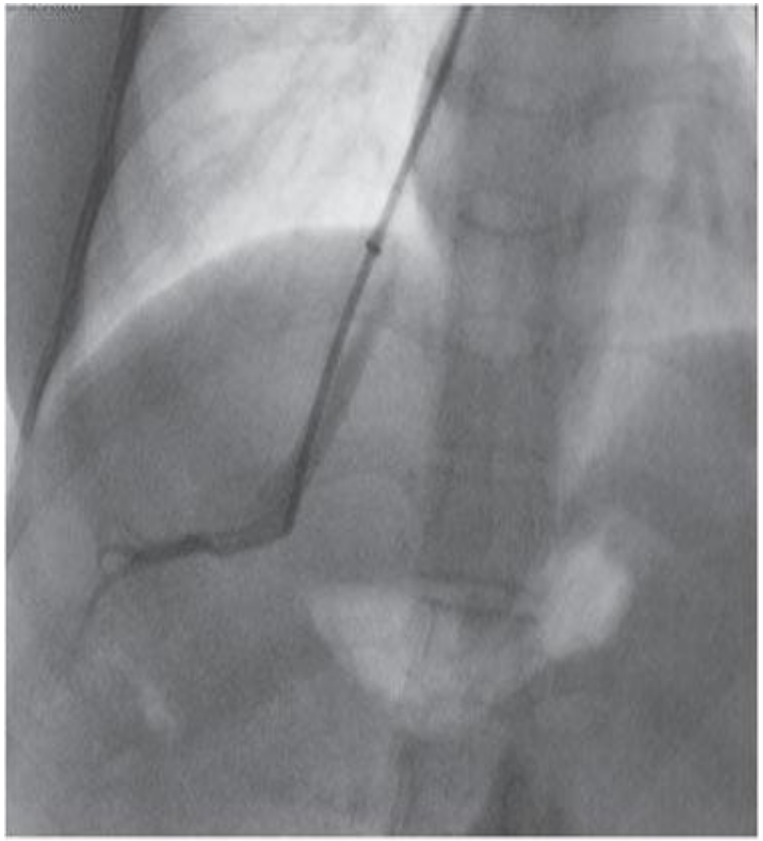
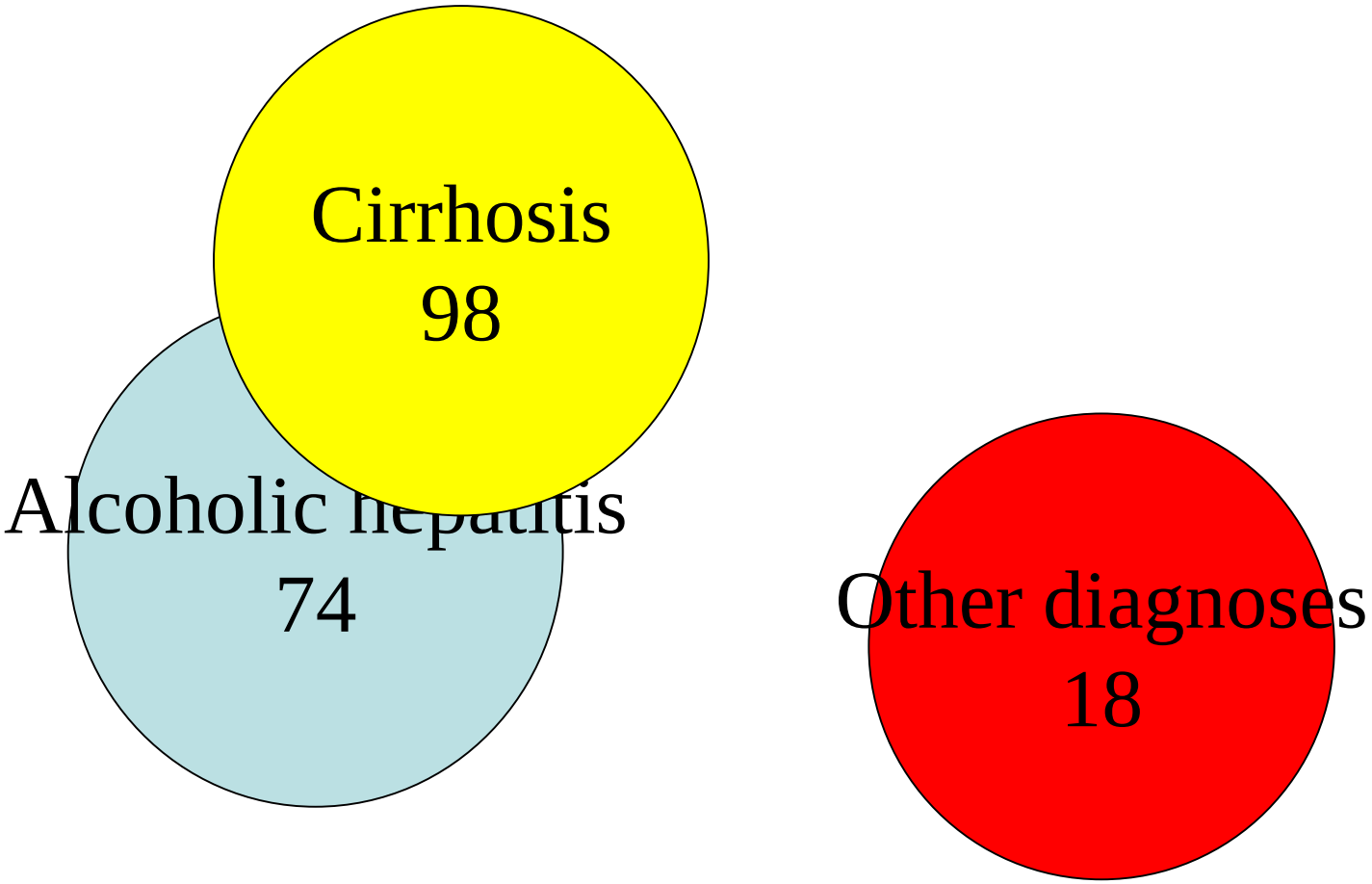


Figure 4: After confirmation of position of the catheter, the stiff TJLB cannula is positioned in the RHV and its tip wedged along the vein wall.

- Transjugular common
- 60% of ALD biopsies
- Can get good sized cores
- Portal pressure helpful extra

Liver biopsy in ALD (n=130)



El Sharkwary EJ Gastro Hepatol 2006

Cryptogenic hepatitis	9%
Drug reactions	8%
Normal liver	6%
Alcohol	3%
PBC/PSC	2.5%
Autoimmune hepatitis	1.9%
Granulomas/sarcoid	1.7%
Others	1.9%

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

Liver biopsy in NAFLD

- Fibrosis markers will screen most out
- Biopsy still important in those with high marker scores
- CRN score (ballooning) useful clinically in terms of progression risk
- End point in trials is histological

ENDPOINTS AND POPULATION IN CLINICAL TRIALS IN NASH.

Phase	Primary Endpoint	Target Population
Early phase trials/ Proof-of-concept	Endpoints should be based on mechanism of drug. Reduction in liver fat with a sustained improvement in transaminases; Improvement in biomarkers of liver inflammation, apoptosis and/or fibrosis. Consider using improvement in NAS (ballooning and inflammation) and/or fibrosis.	Ideal to enroll patients with biopsy-proven NASH but acceptable to enroll patients at high risk for NASH (i.e., evidence of fatty liver, two components of the metabolic syndrome, evidence of liver stiffness by imaging).
Dose ranging/phase 2	Resolution of NASH without worsening of fibrosis; alternatively, improvement in disease activity (NAS)/improvement in ballooning/ inflammation without worsening of fibrosis.	Biopsy-proven NASH and NAS ≥4. Include patients with NASH and liver fibrosis. Include a sufficient number of patients with NASH and fibrosis stage 2/3 to inform phase 3.
Trials to support a marketing application: phase 3	Resolution of steatohepatitis and no worsening of fibrosis. Improvement in fibrosis with no worsening of steatohepatitis. A co-primary endpoint of the above or depending on the mode of action, either one or the other can be used.	Patients with biopsy-confirmed NASH with moderate/advanced fibrosis (F2/F3).
Trials to support a marketing application: phase 4 (postmarketing part)	Clinical outcome trial underway by the time of submission: Composite endpoint: histopathologic progression to cirrhosis; MELD score change by >2 points or MELD increase to >15 in population enrolled with MELD ≤13; death; transplant;	Patients with biopsy-confirmed NASH with moderate/advanced fibrosis (F2/F3).

Conclusions

- Liver biopsy still an essential test
- Fibrosis markers now validated and in use
- Population having biopsy likely to be “enriched” for more fibrotic disease
- HCV no longer feature
- Clinical interaction with reporting pathologist will make best use of biopsy