

NAFLD

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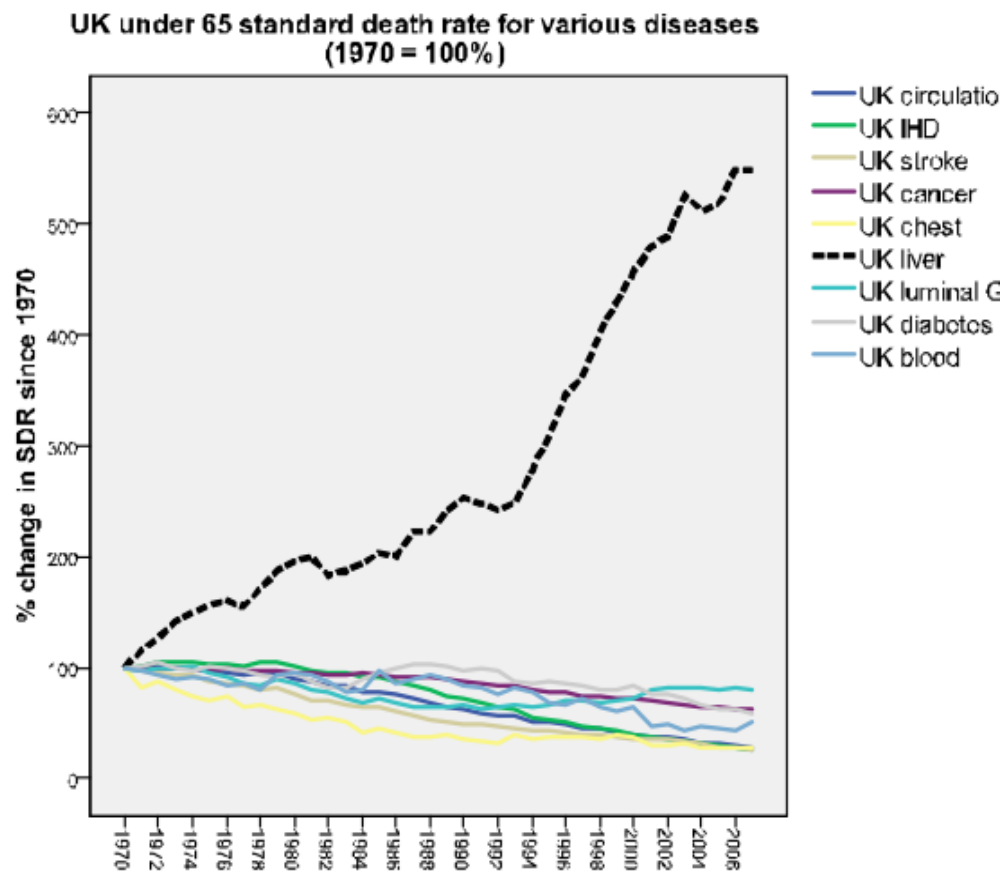
Liver disease

Scale of the problem

- Liver disease is the 5th commonest cause of death in the UK
- Liver disease is the only major cause of mortality and morbidity which is increasing in England
- Liver disease is decreasing in the rest of Europe

Liver disease

Scale of the Problem

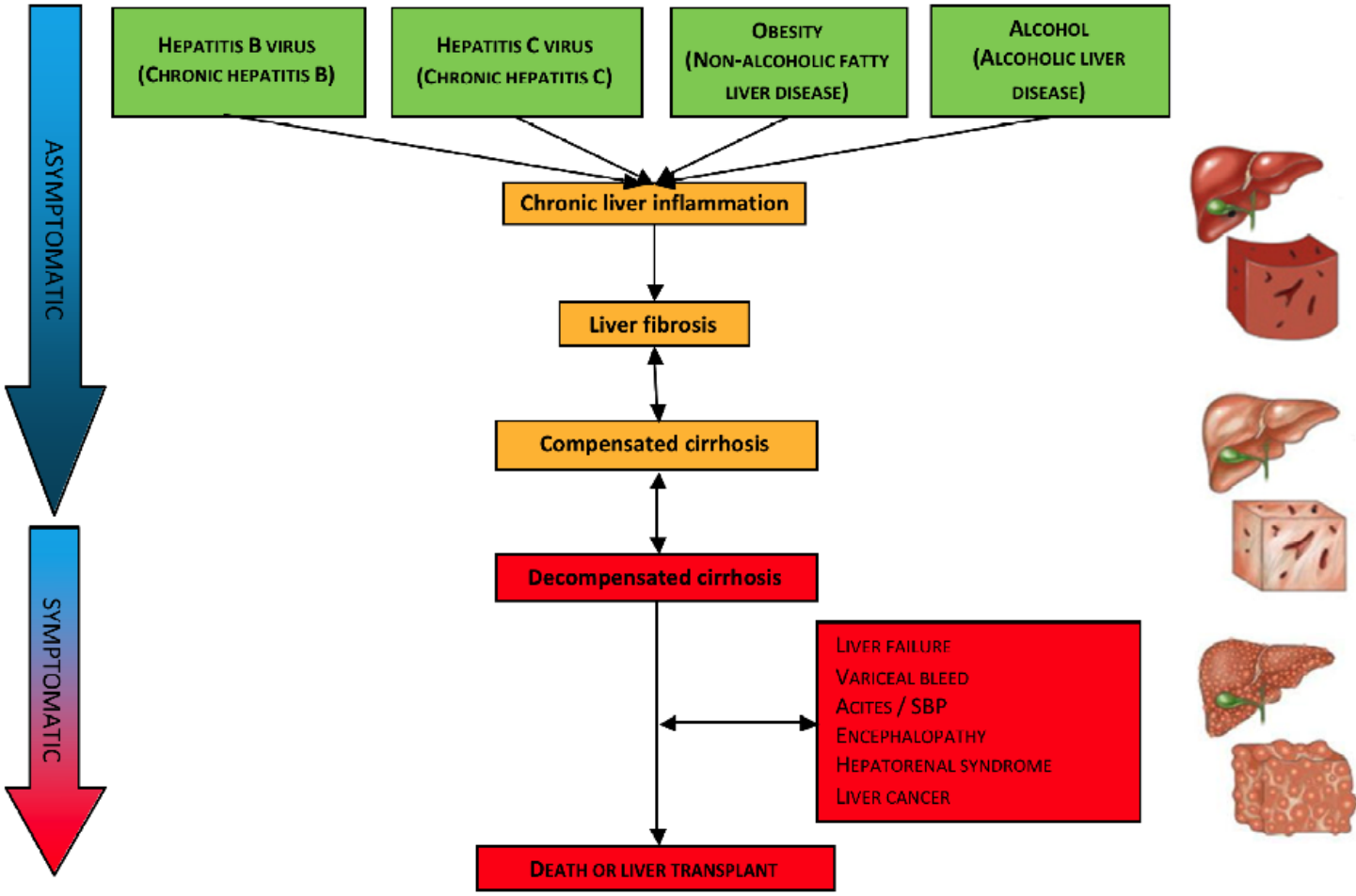


Chronic liver disease

Scale of the Problem

- Main drivers of increasing CLD
- Alcohol
- Obesity
 - Prevalence 11% (16-24), 32% (55-64), 25% (≥ 75)
- Hepatitis B virus
- Hepatitis C virus
 - Peak notifications in 2009 (8633)
 - 93% have IVDU as main risk factor

Natural history of liver disease

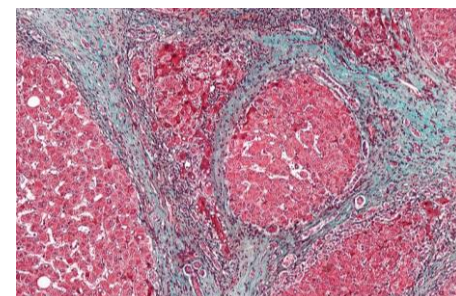
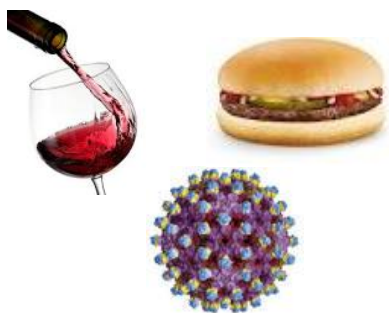
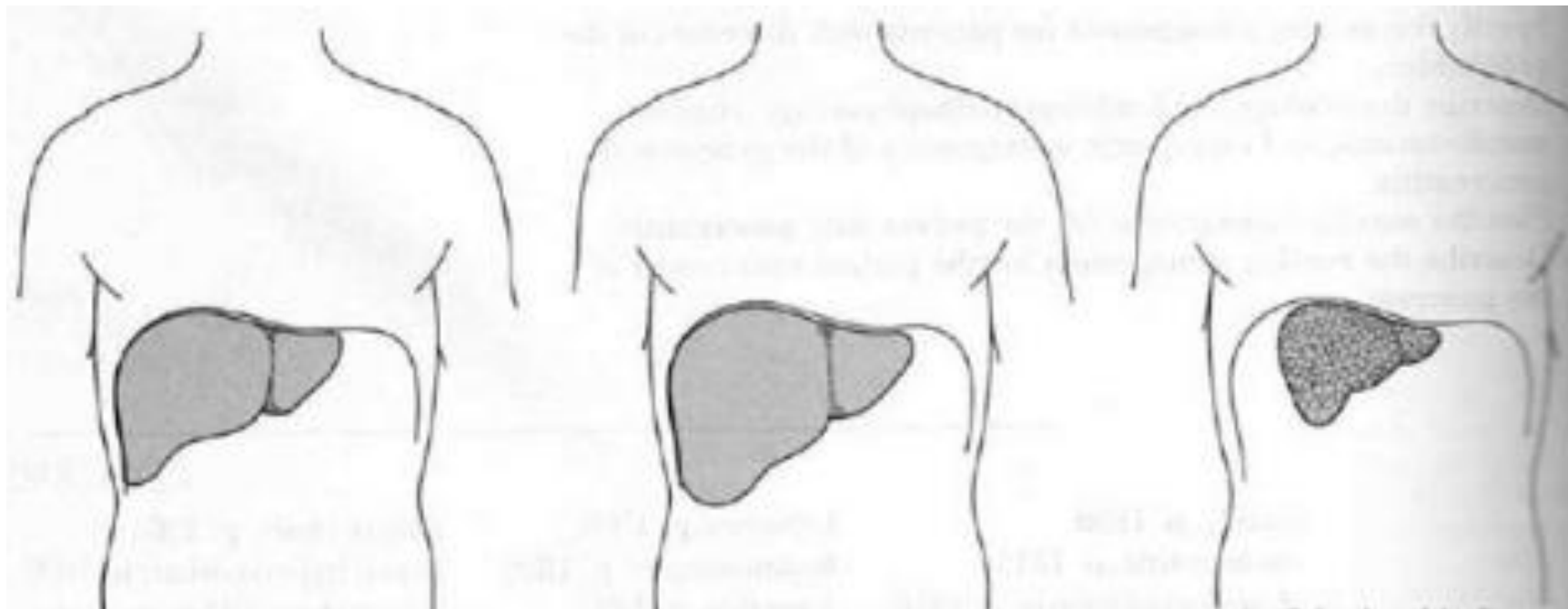


Liver Damage

NORMAL

INFLAMMATION

CIRRHOSIS



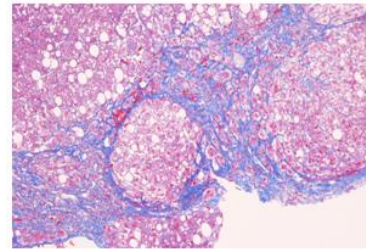
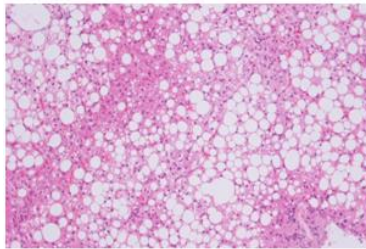
NAFLD

- Spectrum of pathology starting with hepatic steatosis through inflammation (steatohepatitis) to fibrosis
- ‘Hepatic manifestation’ of the metabolic syndrome
- Accumulation of fat in the liver
- Prevalence 20-30%

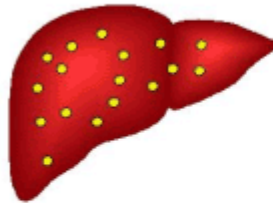
Risk factors for NAFLD

- Obesity
- Hypertension
- Dyslipidemia
- Insulin resistance / type 2 diabetes

Spectrum of disease in NAFLD

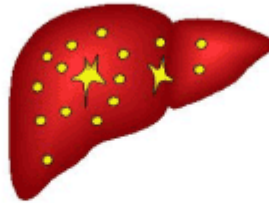


Fatty Liver



Fat
accumulates
in the liver

NASH



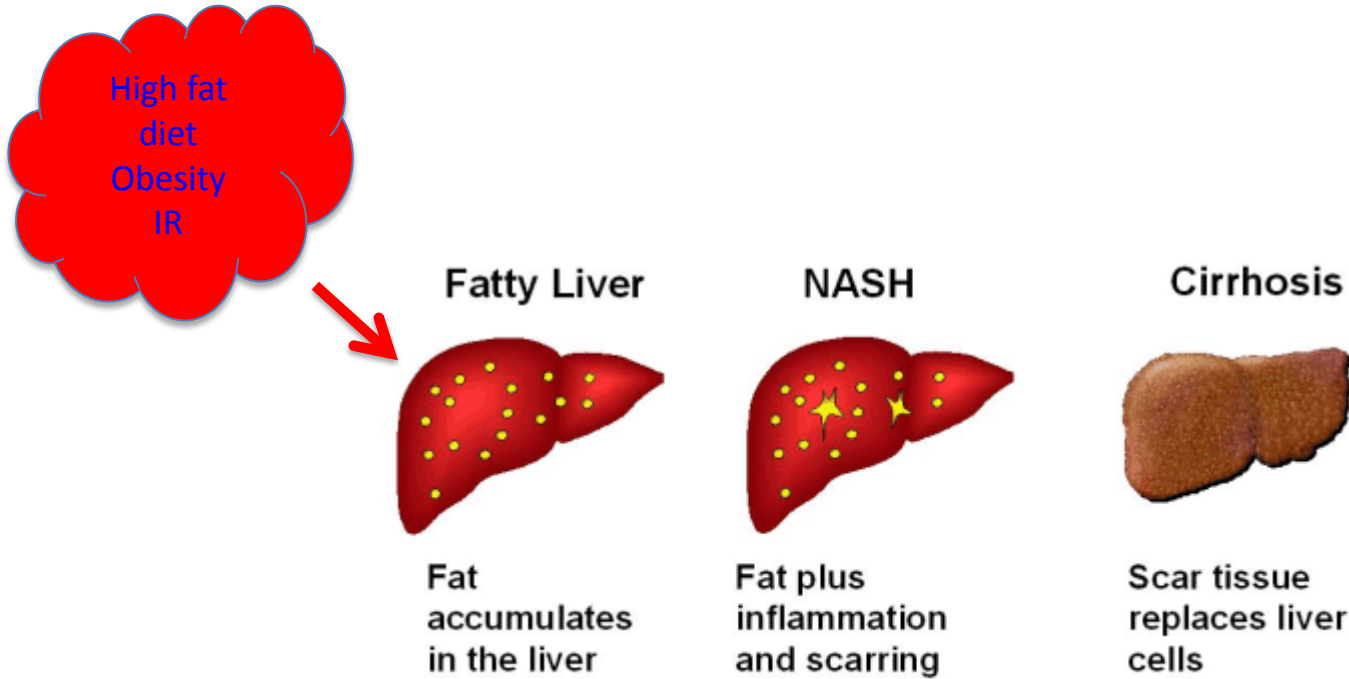
Fat plus
inflammation
and scarring

Cirrhosis

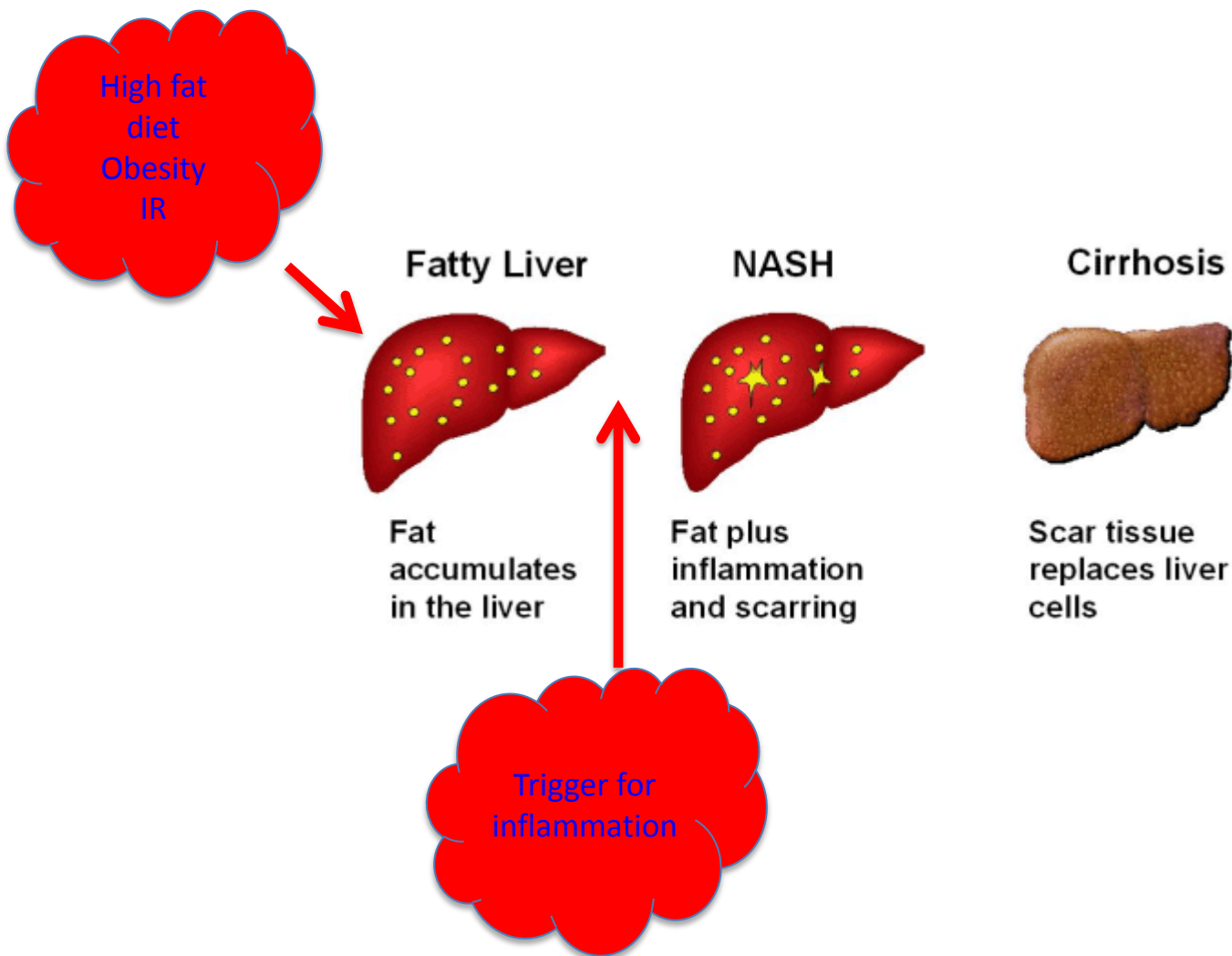


Scar tissue
replaces liver
cells

Spectrum of disease in NAFLD



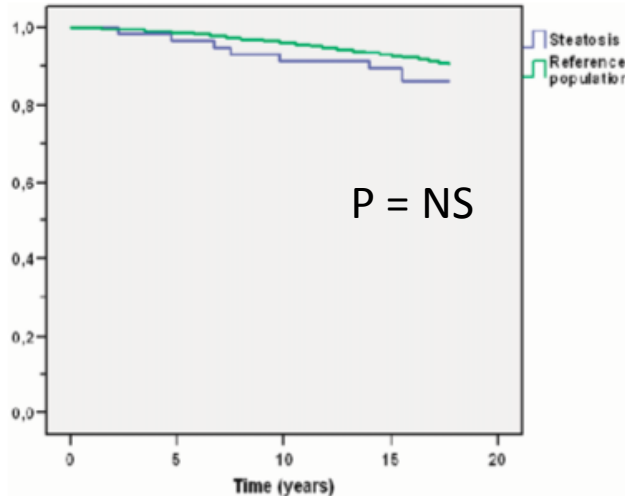
Spectrum of disease in NAFLD



Spectrum of disease in NAFLD



Simple steatosis is safe, NASH is not

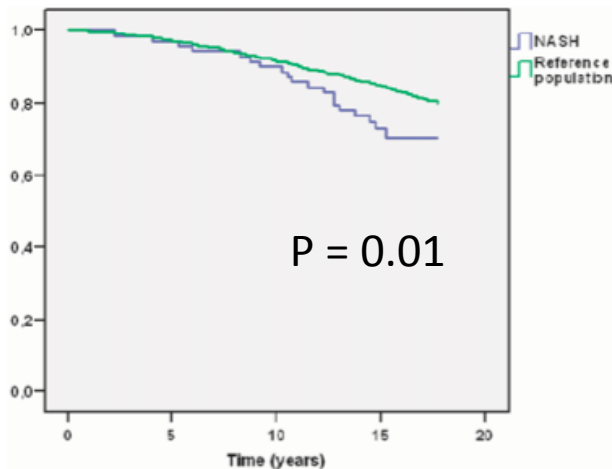


129 patients with biopsy-proven NAFLD

Survival & cause of death matched to reference population

14 year follow up

No increase in mortality with simple steatosis



Significantly lower survival in NASH
CVS and liver deaths

Diagnosis of NAFLD

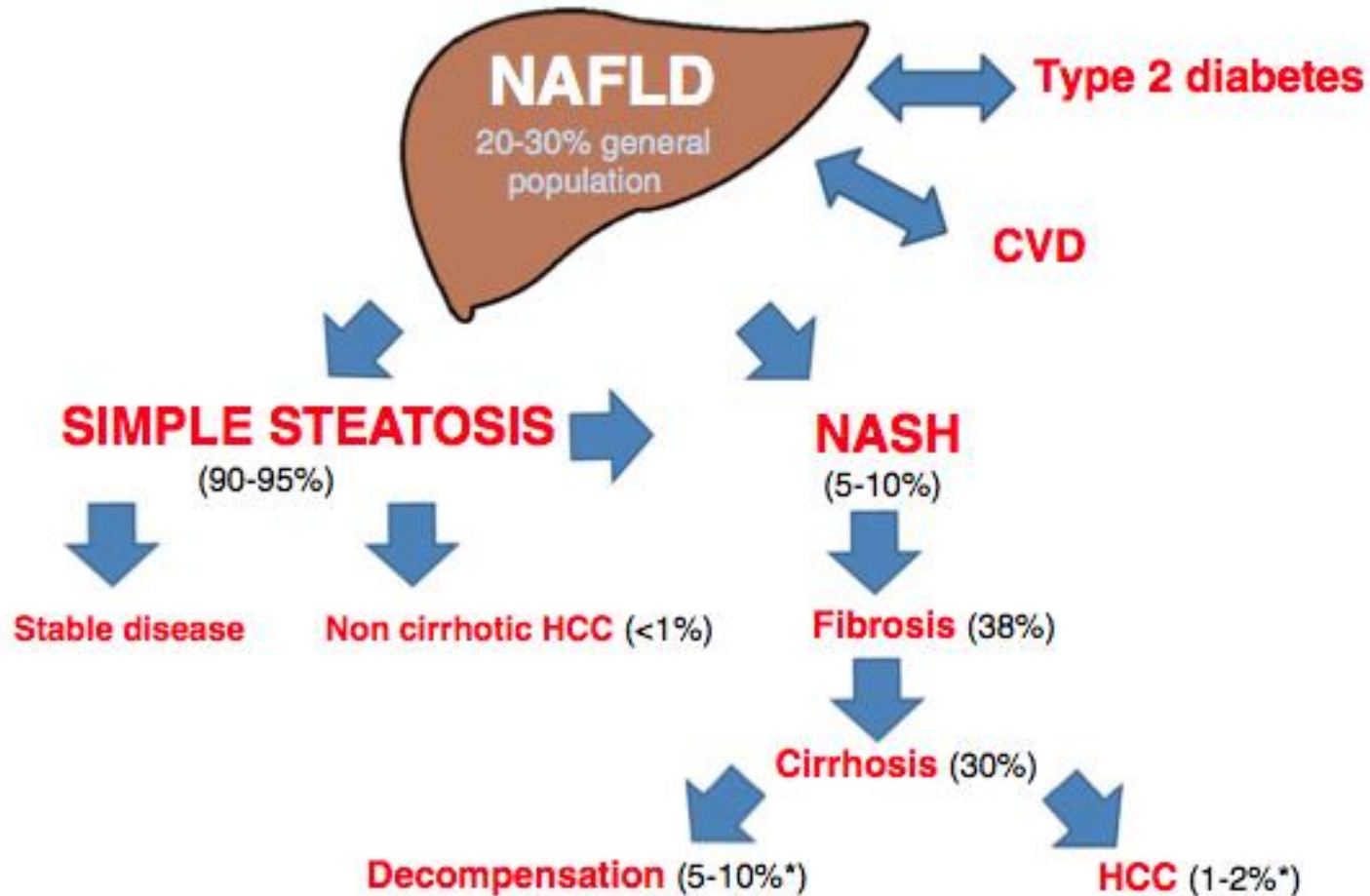
- Screen in high risk groups
 - Obese
 - Type 2 diabetes / metabolic syndrome
- Liver USS to identify steatosis
 - USS detects >30% steatotic hepatocytes
 - Normal USS ≠ no NAFLD
- If abnormal LFTs, exclude other causes of liver disease
 - HBsAg, HCV Ab, immunoglobulins, autoantibodies, A1AT level, ferritin
- Consider secondary causes of steatosis
 - Medications (steroid, valproate, amiodarone, tamoxifen)
 - Inborn errors of metabolism (LAL deficiency)

Diagnosis of NAFLD

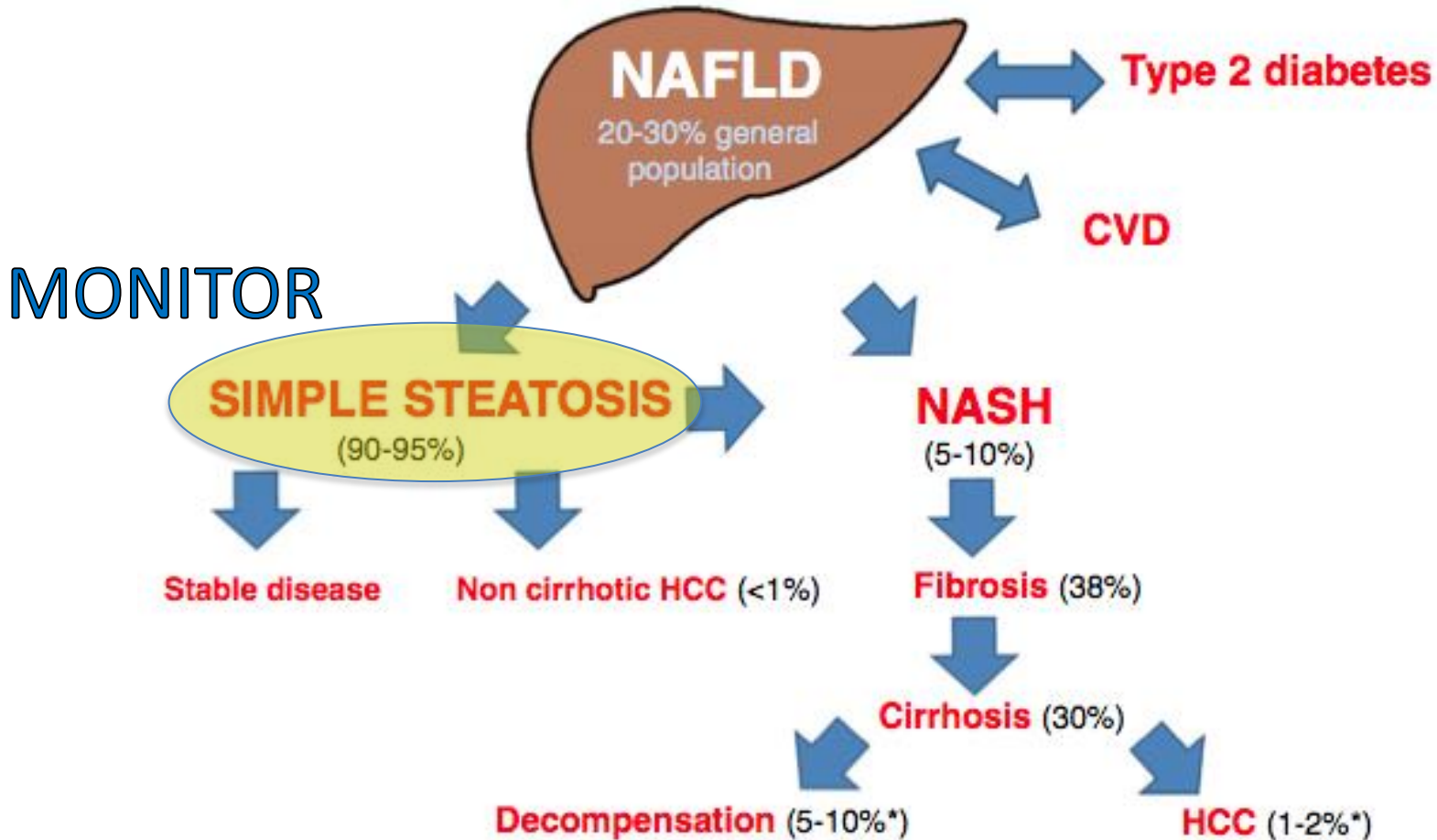
- Liver biopsy not required unless diagnostic uncertainty
 - Benefits
 - Steatosis
 - Inflammation
 - Fibrosis
 - Limitations
 - Painful
 - Risk
 - Sample variation
 - Inter-observer variation



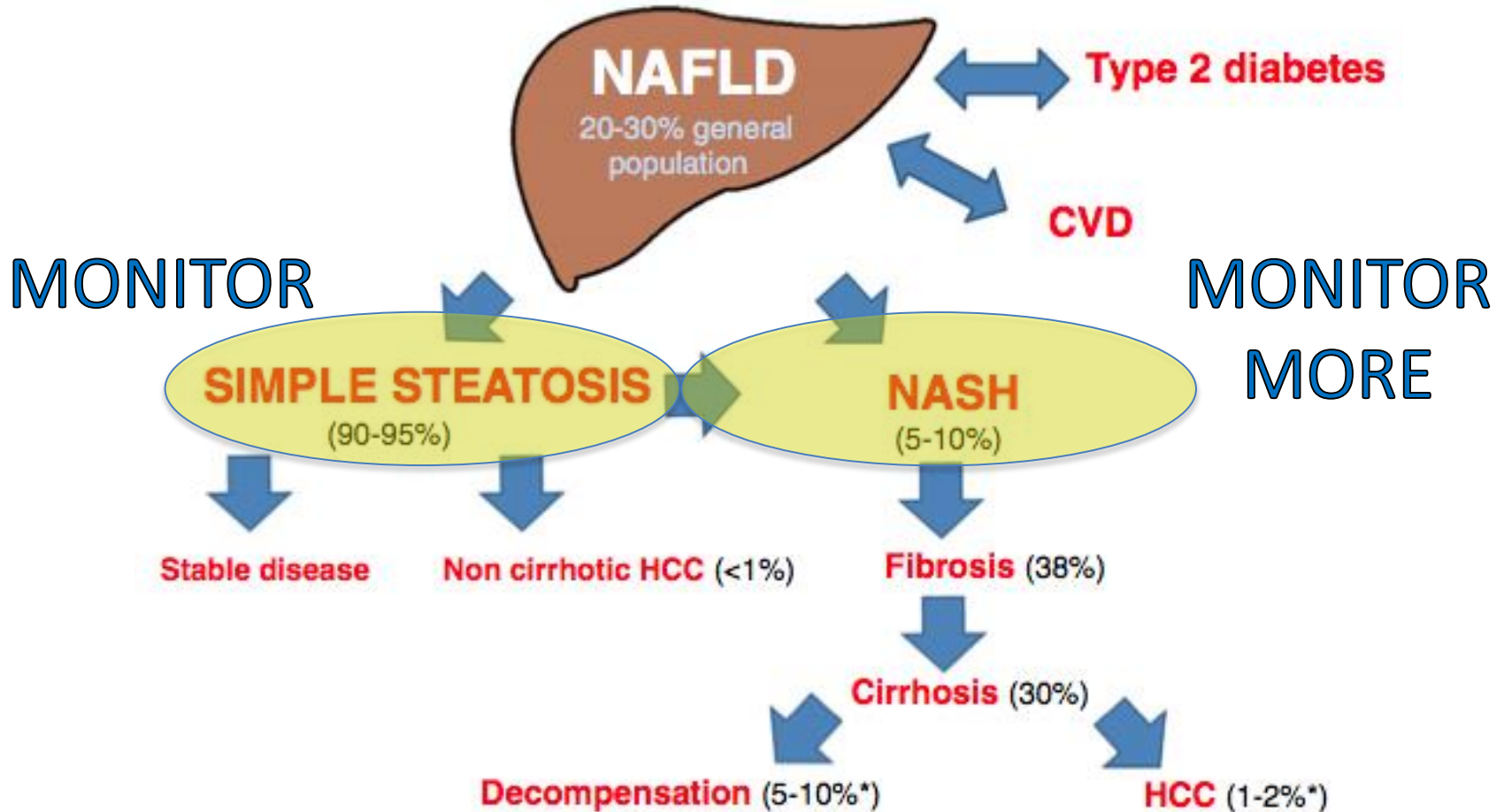
Ultrasound and LFTs useful to diagnose NAFLD but not to stratify risk



Ultrasound and LFTs useful to diagnose NAFLD but not to stratify risk



Ultrasound and LFTs useful to diagnose NAFLD but not to stratify risk



Risk Stratification

- Inflammation
 - Distinguishing simple steatosis from NASH
 - Preferably identifying (and treating) NASH before fibrosis develops
- Fibrosis
 - Distinguishing non-advanced fibrosis from advanced fibrosis
 - Fibrosis rather than inflammation predicts outcome

Diagnosing NASH

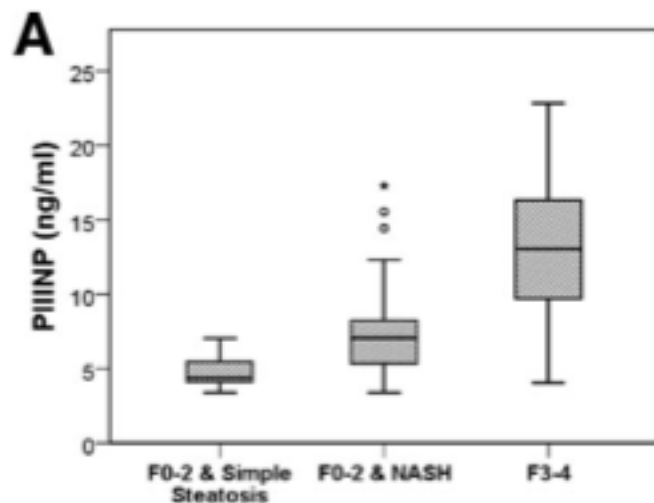
Distinguishing NASH from steatosis

- LFTs
 - Normal in 50% of patients with NAFLD and in 20% of patients with NASH
 - ALT does not correlate with steatosis or disease severity
- Liver biopsy
 - Invasive, hazardous, expensive, inter-observer variation
- Non-invasive markers
 - TNF-alpha, leptin, IL6, IL8
- Commercial biomarker panels
 - SteatoTest, NASHTest

Biomarkers for NASH

No NASH biomarkers in clinical practice

TIMP-1 (a fibrosis marker) showing promise

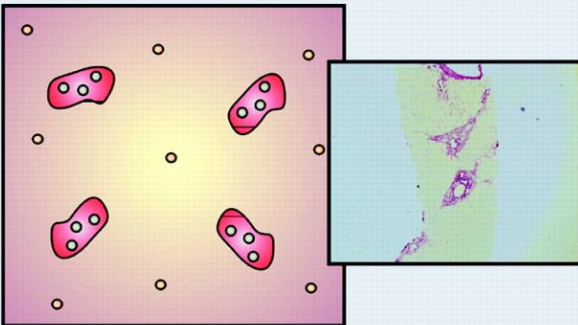
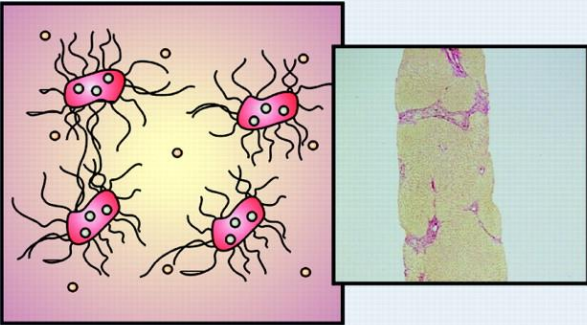
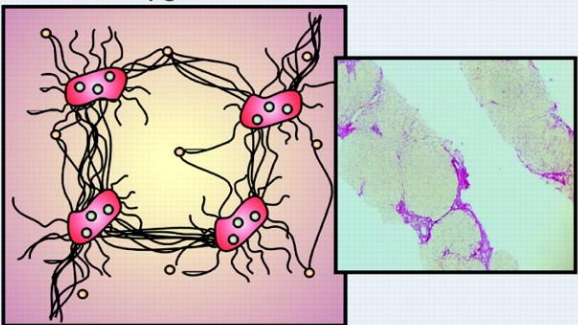
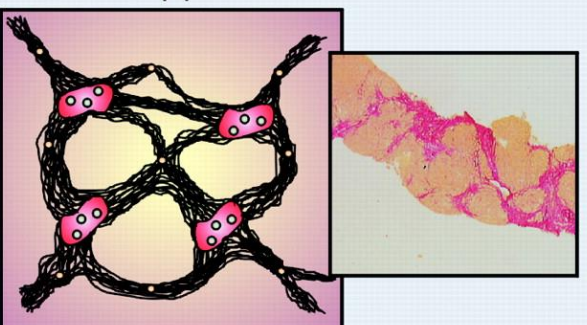


Validation of Terminal Peptide of Procollagen III for the Detection and Assessment of Nonalcoholic Steatohepatitis in Patients With Nonalcoholic Fatty Liver Disease

Sudeep Tanwar,¹ Paul M. Trembling,¹ Indra N. Guha,² Julie Parkes,³ Philip Kaye,² Alastair D. Burt,⁴ Stephen D. Ryder,² Guruprasad P. Aithal,² Christopher P. Day,⁴ and William M. Rosenberg¹

Fibrosis Assessment

Staging according to Metavir Score

<p>F1</p>  <p>Portal fibrosis</p>	<p>F2</p>  <p>Portal fibrosis with few septa</p>
<p>F3</p>  <p>Septal fibrosis</p>	<p>F4</p>  <p>Cirrhosis</p>

Fibrosis Assessment

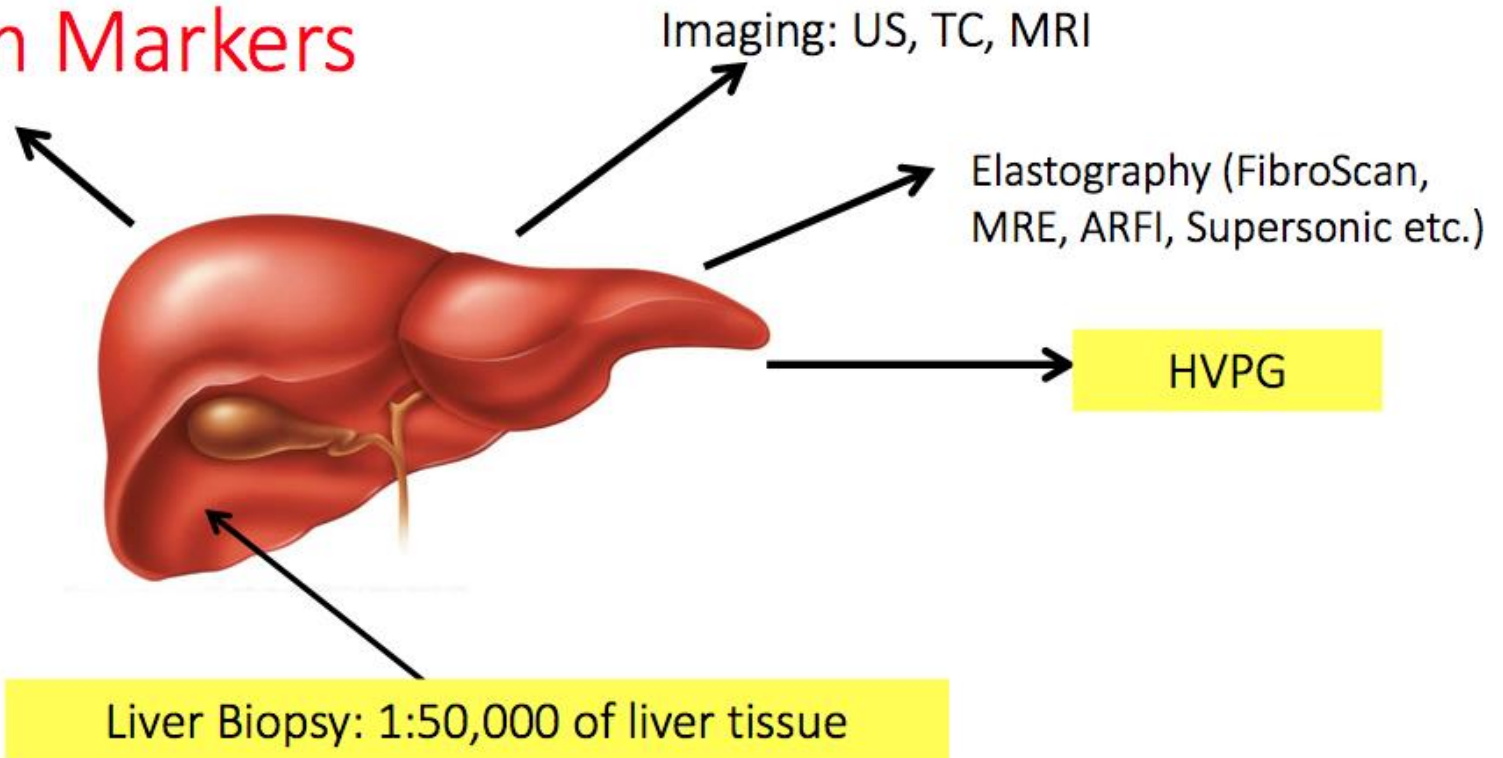
Serum Markers

Imaging: US, TC, MRI

Elastography (FibroScan,
MRE, ARFI, Supersonic etc.)

HVPG

Liver Biopsy: 1:50,000 of liver tissue



Liver Biopsy

- Traditional 'gold' standard
- Allows diagnosis and assessment of inflammation as well as fibrosis
- High level of sampling error and inter-observer variability, particularly in mid-range (F2-F3)
- Potentially hazardous
- Painful
- Patients often reluctant to undergo serial assessment

Serum Markers

- Non-invasive
- Repeatable
- Algorithms comprising simple blood markers and clinical parameters
- Usually more accurate in diagnosing significant fibrosis

Indirect

Not related to fibrogenesis

Markers

- AST
- ALT
- GGT
- HOMA-IR
- PLT
- INR
- Bilirubin

Algorithms

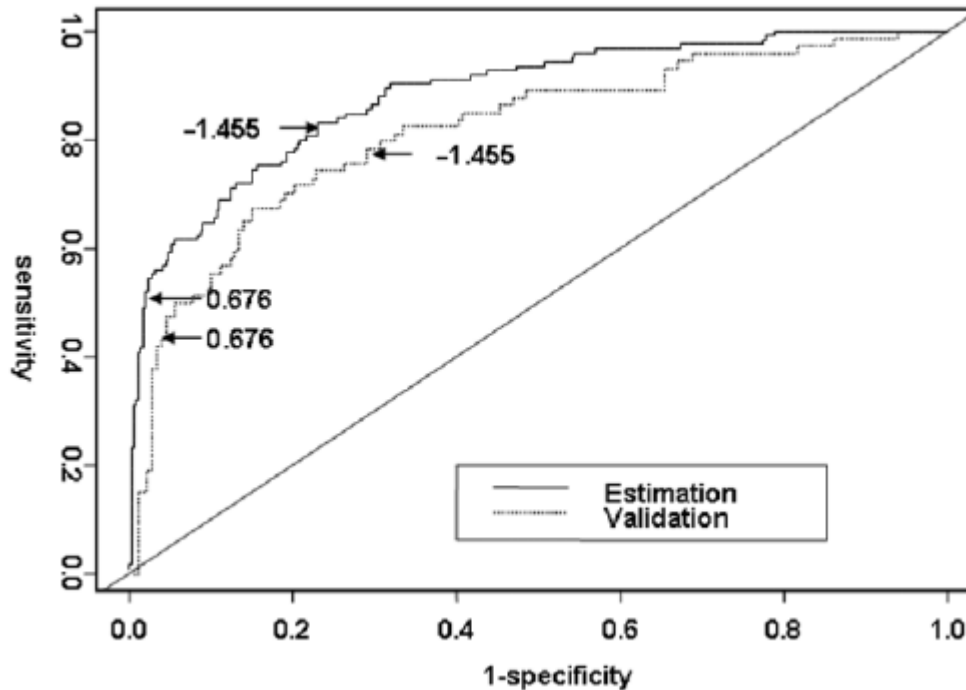
- APRI (AST/PLT ratio)
- AST/ALT
- Fib-4
- NAFLD fibrosis score

NAFLD fibrosis score

- Algorithm comprising
 - Age
 - Diabetes
 - BMI
 - PLT
 - Albumin
 - AST/ALT
- Devised and validated in cohort of 733 patients with biopsy-confirmed NAFLD

NAFLD fibrosis score

- Excellent diagnostic accuracy in predicting advanced fibrosis (F3-4)



AUROC >0.8

NAFLD fibrosis score

- Cut off scores derived:
 - Below -1.455 predicts absence of advanced fibrosis (NPV 93%)
 - Above 0.676 predicts presence of advanced fibrosis (PPV 90%)
 - Between -1.455 and 0.676 is indeterminate
 - Would require a liver biopsy to determine fibrosis stage
 - 30% of patients in the study
- On-line calculator available

Enhanced Liver Fibrosis (ELF) Test

- Panel of 3 markers of matrix turnover
 - Hyaluronic acid (HA)
 - Tissue inhibitor of metalloproteinase 1 (TIMP1)
 - Amino-terminal peptide of pro-collage III (P3NP)
- Validated in NAFLD, PBC, hepatitis C, hepatitis B
- Requires routine blood sample (100µl serum)

< 7.7	None to mild
≥ 7.7 to < 9.8	Moderate
≥ 9.8	Severe

Fibroscan



Probe sends an elastic wave through the liver

Velocity of the wave is related to liver stiffness

Limited by

Obesity

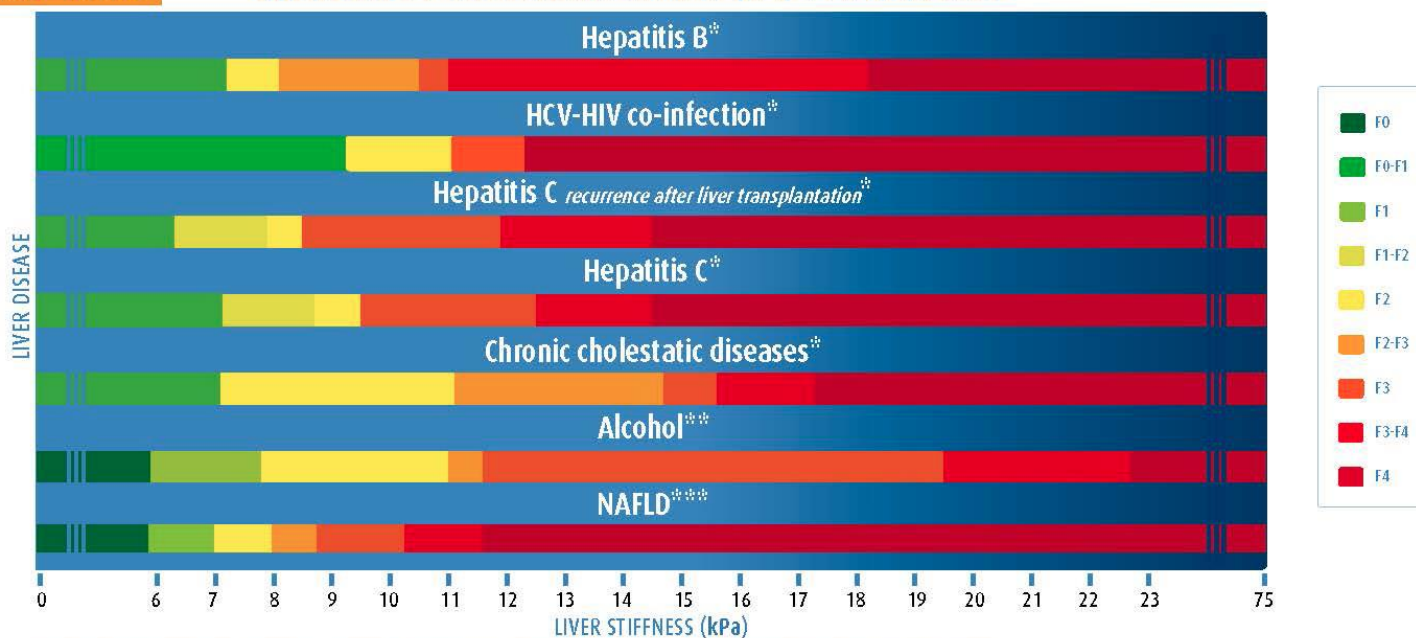
Ascites

Inflammation & steatosis

Interpreting results

SCORING CARD

CORRELATION BETWEEN LIVER STIFFNESS (kPa) & FIBROSIS STAGE



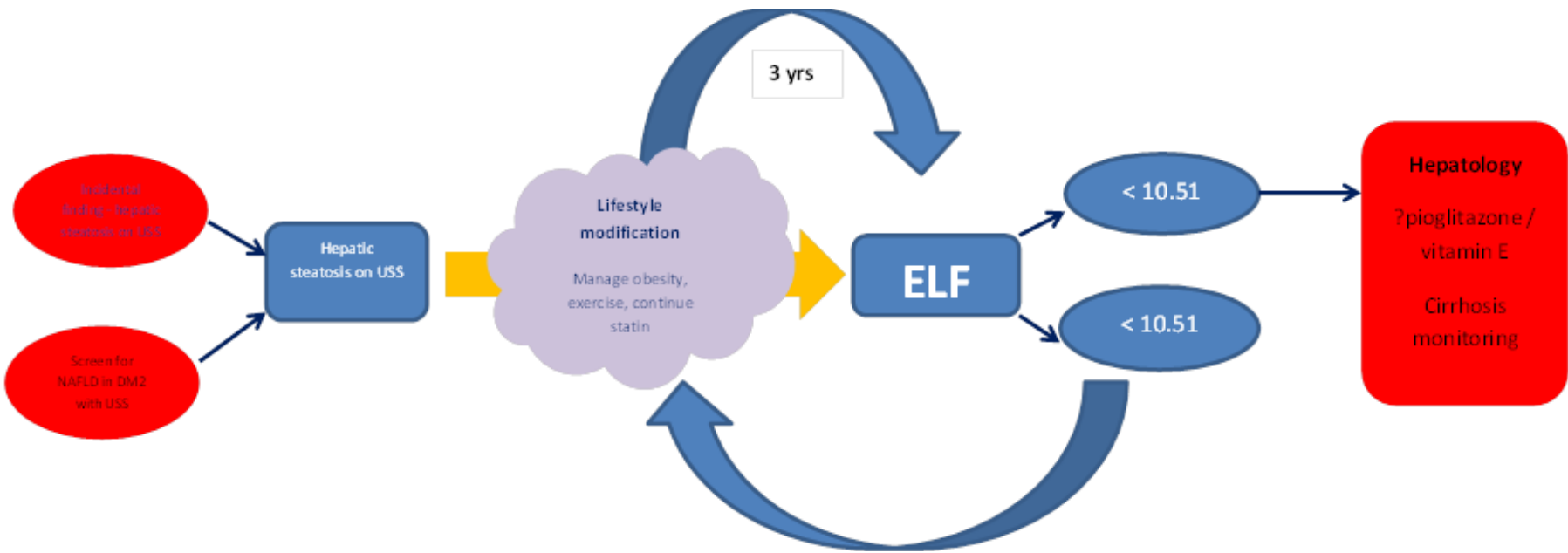
*According to Metavir score: Transient elastography (FibroScan): V. de Lédinghen, J. Vergniol, Gastroentérologie Clin Bio (2008) 32, 58-67

**According to Brunt score: Nahon et al. J Hepatol (2009) 49, 1062-68, Nguyen-Khac et al., Aliment Pharmacol Ther (2008), 28, 1188-98

***According to Brunt score: Wong et al. Hepatology (2010) 51, 454-62 Transient elastography (FibroScan®): V. de Lédinghen, J. Vergniol, Gastroentérologie Clin Bio (2008) 32, 58-67

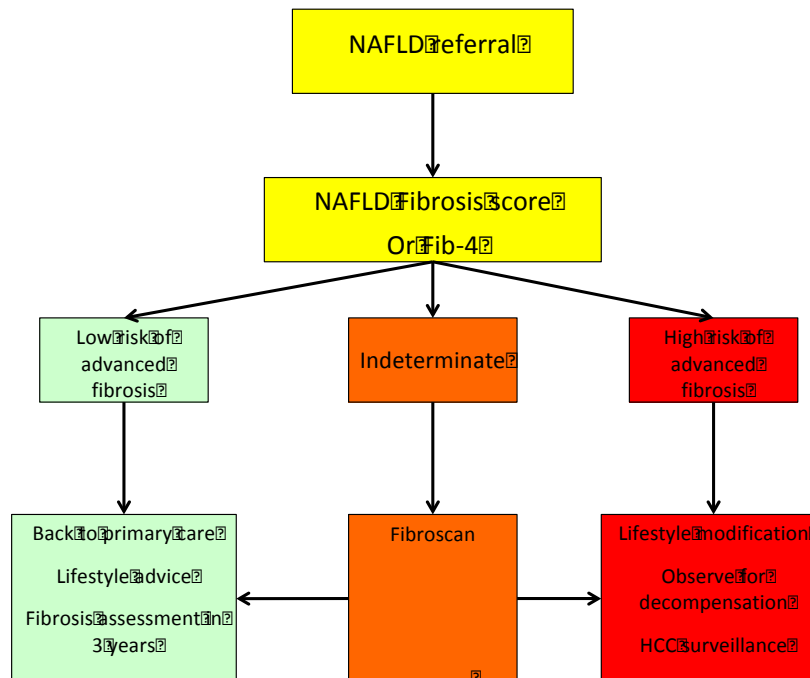
Risk stratification

NICE Non-alcoholic fatty liver disease 2016



A practical approach

- Encourage GPs to follow NICE guidance
- Fibrosis assessment for all NAFLD referrals
- Modified stratification pathway



Management of NAFLD

- Lifestyle modification
- Managing the metabolic syndrome
- Liver specific treatment
- Managing cirrhosis

Management of NAFLD

General management

- Identification and optimisation of metabolic risk factors
 - Lipid profile
 - Fasting glucose
 - BMI and waist circumference
- Weight loss
 - 5% weight loss to improve steatosis, 10% to improve inflammation

Metabolic syndrome

- Type 2 diabetes
 - Associated with increased fibrosis in NASH
 - First line – metformin
 - Second line – pioglitazone (rather than gliclazide)
 - Third line - GLP-1 (rather than insulin) particularly if obese

Metabolic syndrome

- Dyslipidaemia
- Statins
 - Mild ALT rise common and insignificant
 - ALT >3 ULN – rare (and unpredictable)
 - Safe in compensated cirrhosis
 - Probably reduces portal hypertension and risk of HCC

Metabolic syndrome

- Hypertension
 - ACE-I / ARB may reduce steatohepatitis and fibrosis

Management of NAFLD

There is no liver-specific treatment

- Vitamin E
 - PIVENS trial
 - Multicentre RCT
 - Pioglitazone v vitamin E v placebo in non-diabetic patients with NASH
 - Vitamin E 800 IU/day for 96 weeks
 - Improved NASH on biopsy
 - To be considered according to NICE guidelines (but not licensed)
 - Meta-analysis – increase in all-cause mortality
 - ?optimal dose / duration
- Pioglitazine
 - Insulin sensitiser
 - PIVENS
 - Non-significant improvement in NASH on biopsy
 - Risk of CCF in meta-analysis
 - ?optimal dose / duration
- Antifibrotics
 - Clinical trials

Management of NAFLD

Secondary care management of advanced liver disease

- Assessment for features of decompensation
 - Hepatic synthetic dysfunction
 - Ascites
 - Hepatic encephalopathy
- Screening for and treatment of portal hypertension
 - Endoscopy
 - HVPG
- Hepatocellular carcinoma screening
 - HCC risk 2-3% / year
 - USS and AFP 6 monthly

Summary

- NAFLD is common
- NAFLD-related CLD is not common
- Management centres on modification of metabolic risk factors
- Non-invasive markers of liver fibrosis can be used to stratify risk of progressing to established liver disease

Thank you

