East and North Hertfordshire NHS
NHS Trust

NAFLD

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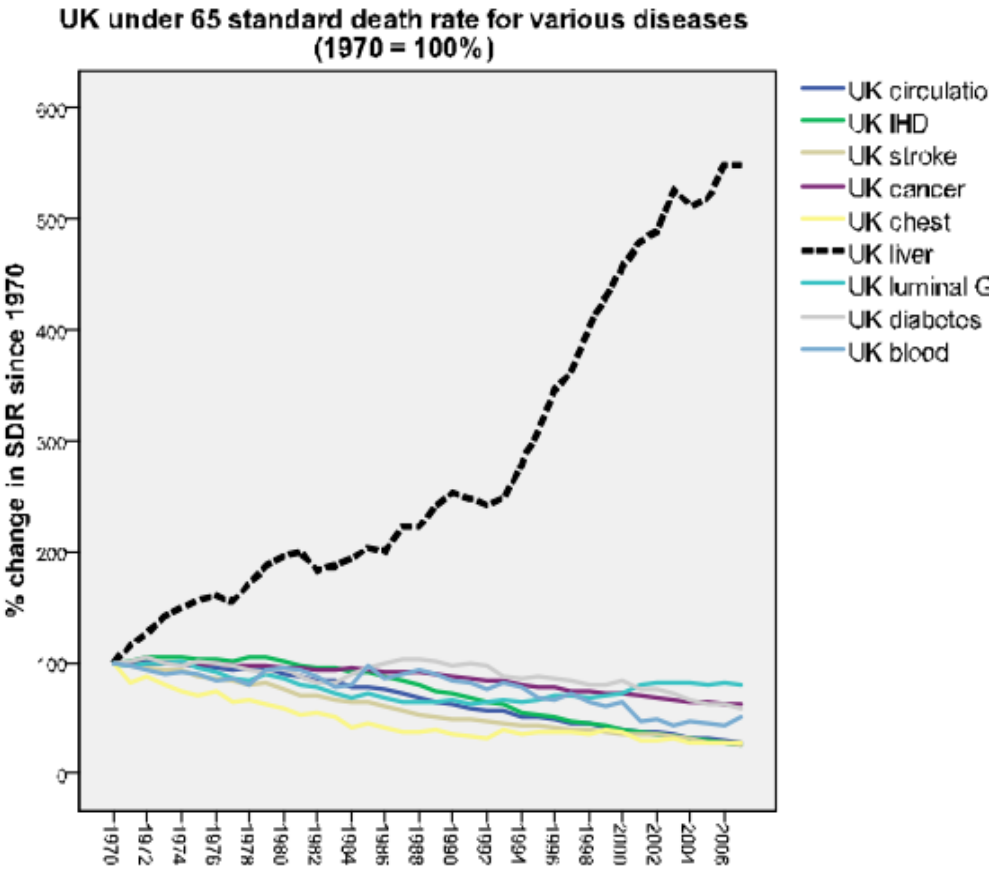
Liver disease
Scale of the problem

- 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

CMO Annual Report, Nov 2011. Department of Health

Liver disease
Scale of the Problem



WHO European Health for All Database 2009

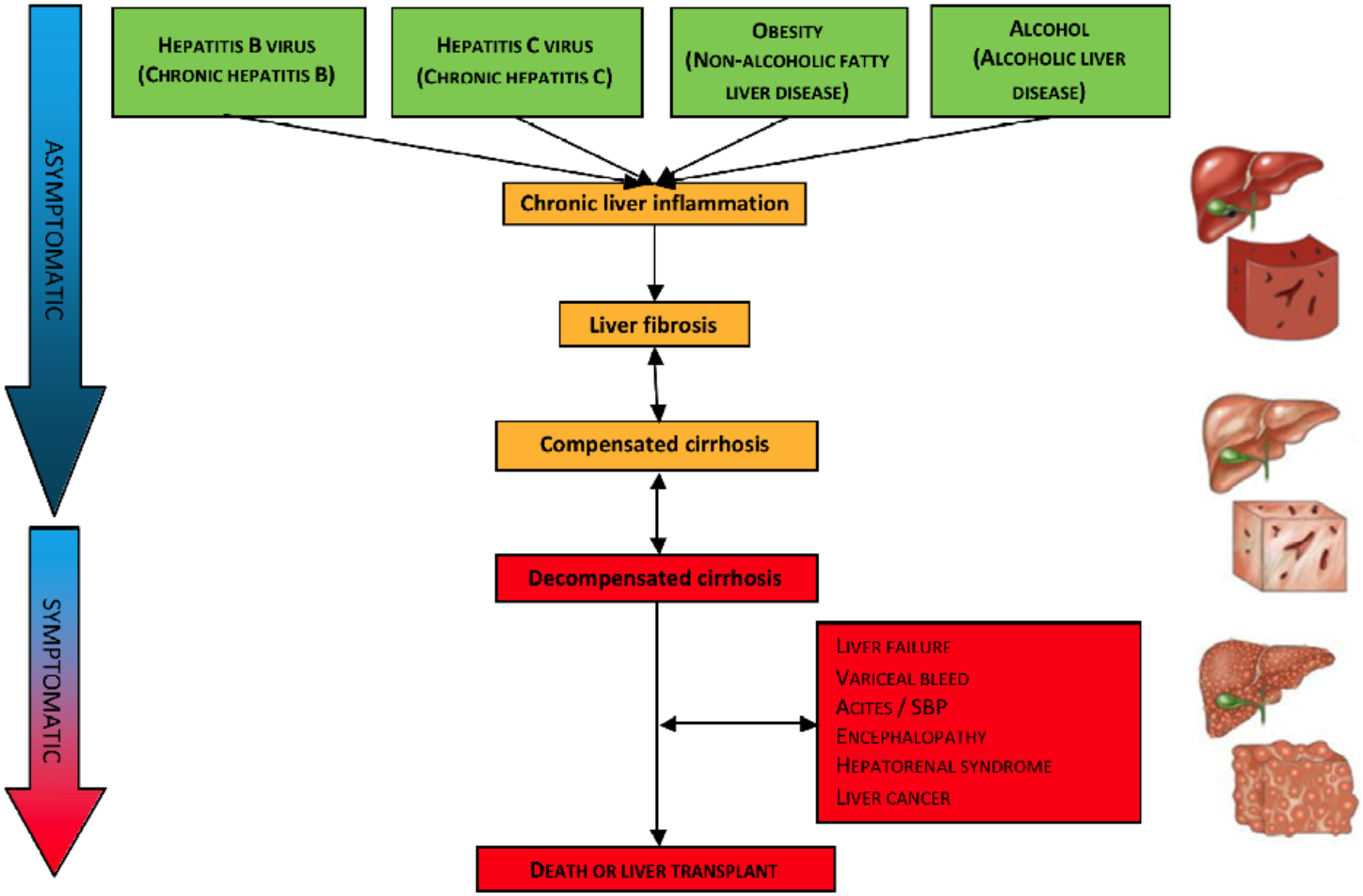
BASL / BSG. A Time to Act: Improving Liver Health and Outcomes in Liver Disease. The National Plan for Liver Services UK. 2009

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

CMO Annual Report, Nov 2011. Department of Health

Natural history of liver disease



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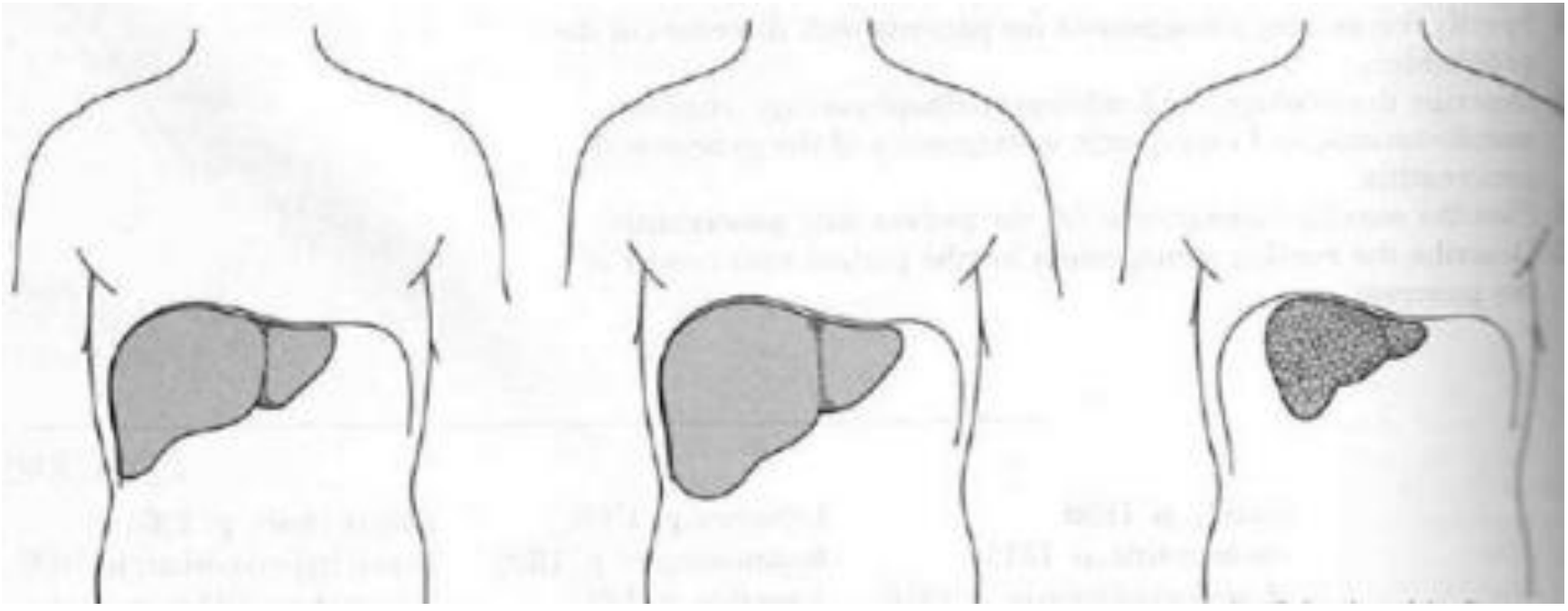
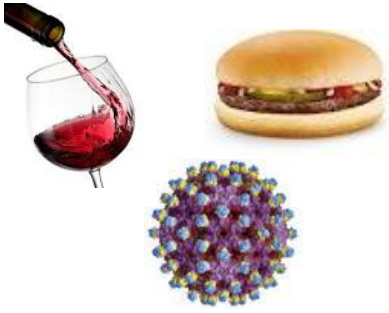
Liver Damage

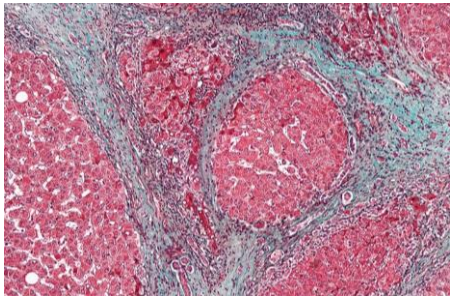
NORMAL

INFLAMMATION

CIRRHOSIS







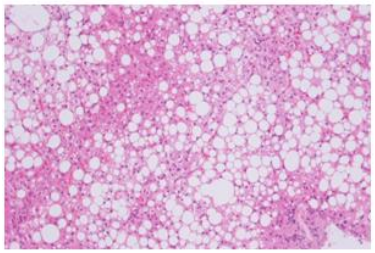
NAFLD

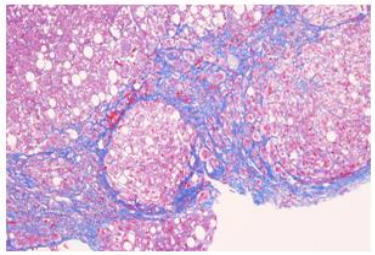
- Spectrum of pathology starting with hepatic steatosis through inflammation (steatohepatitis) to fibrosis
- ‘Hepatic manifestation’ of the metabolic syndrome
- Accumulation of fat in the liver
- Prevalence 20-30%

Risk factors for NAFLD

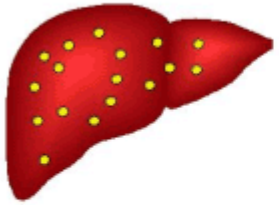
- Obesity
- Hypertension
- Dyslipidemia
- Insulin resistance / type 2 diabetes

Spectrum of disease in NAFLD



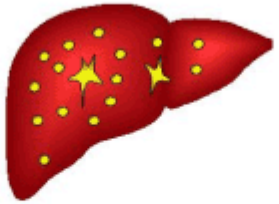


Fatty Liver



Fat accumulates in the liver

NASH



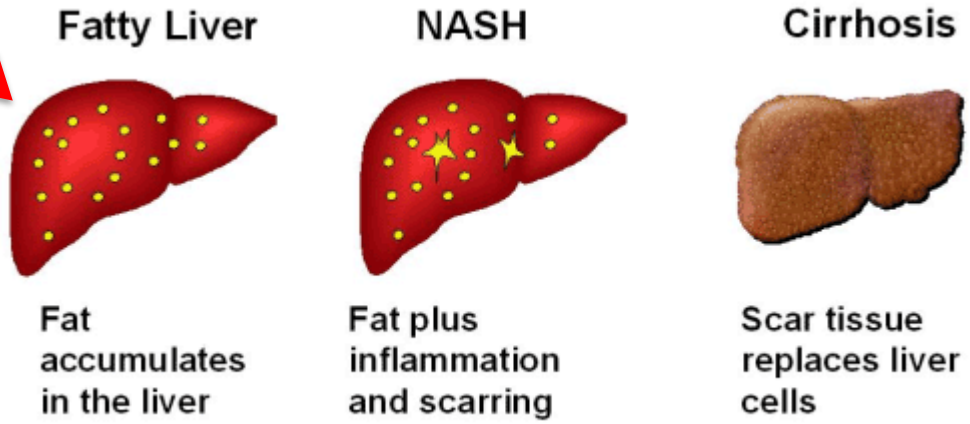
Fat plus inflammation and scarring

Cirrhosis

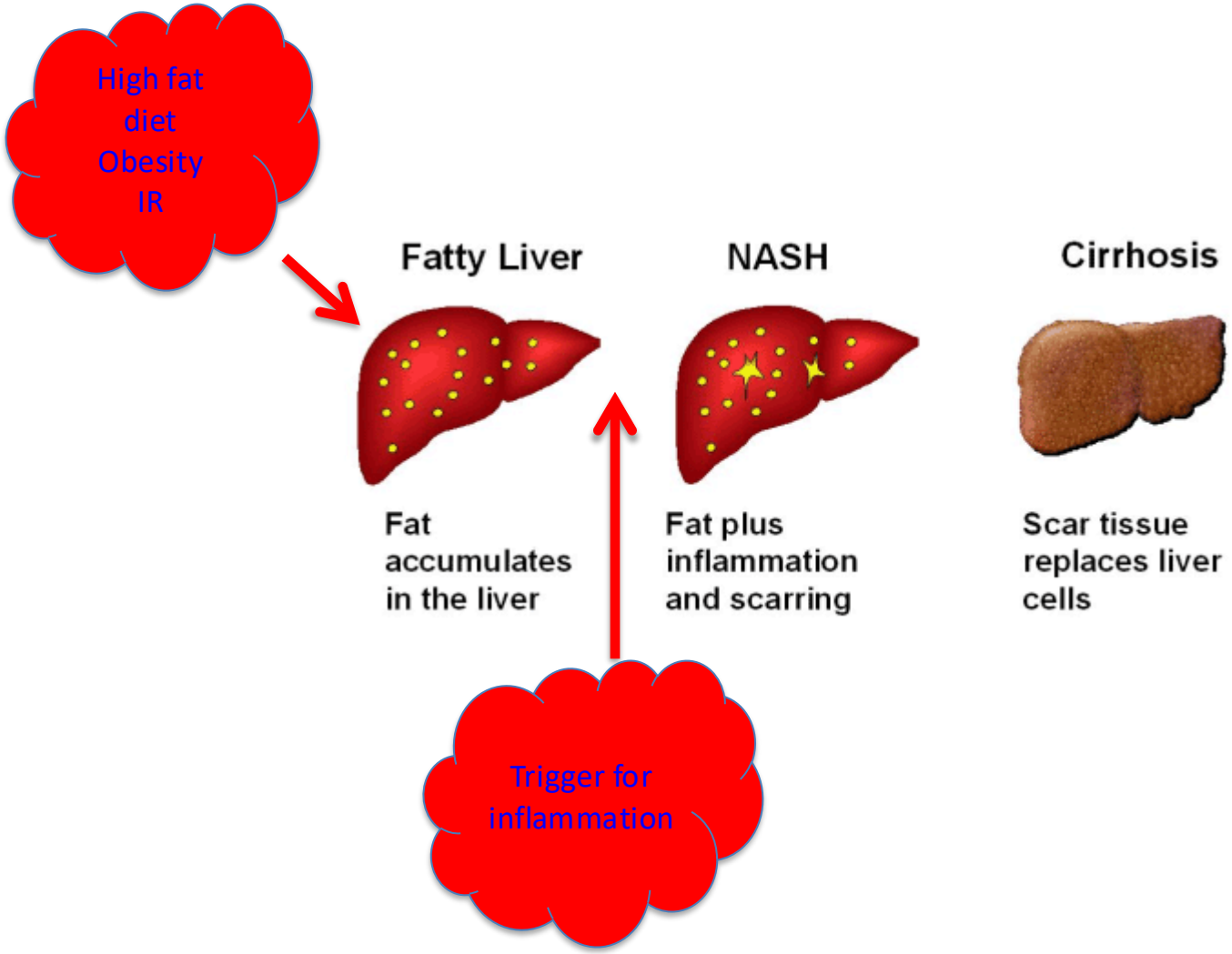
Scar tissue replaces liver cells

Spectrum of disease in NAFLD

High fat diet
Obesity
IR

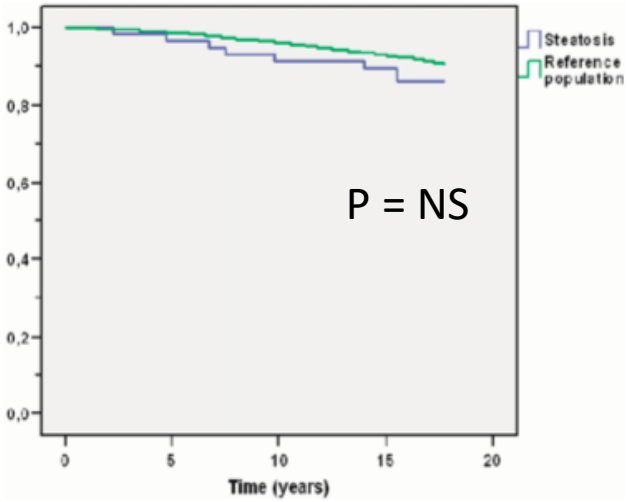


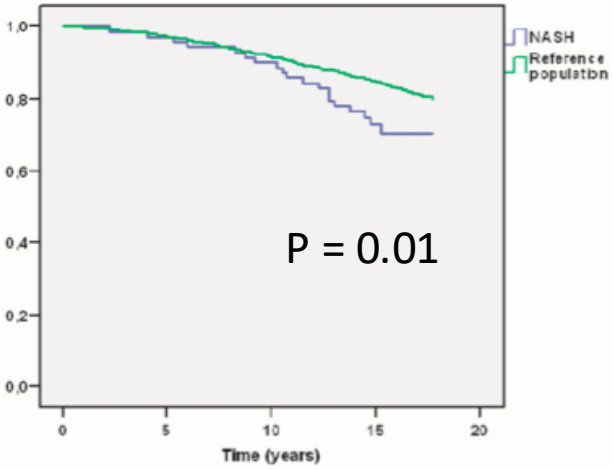
Spectrum of disease in NAFLD



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

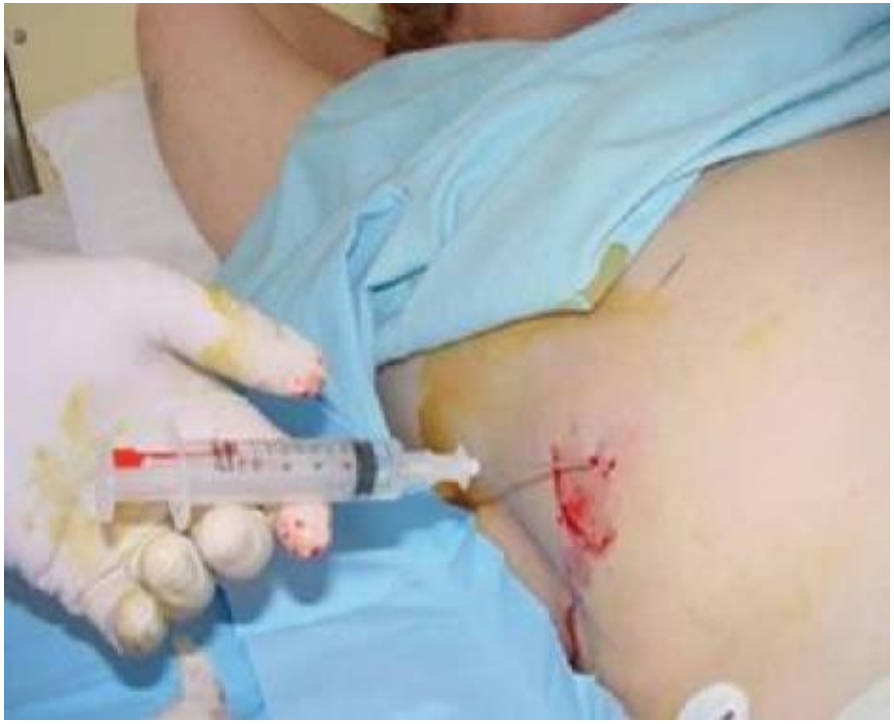
Ekstedt et al. Hepatology 2006

Diagnosis of NAFLD

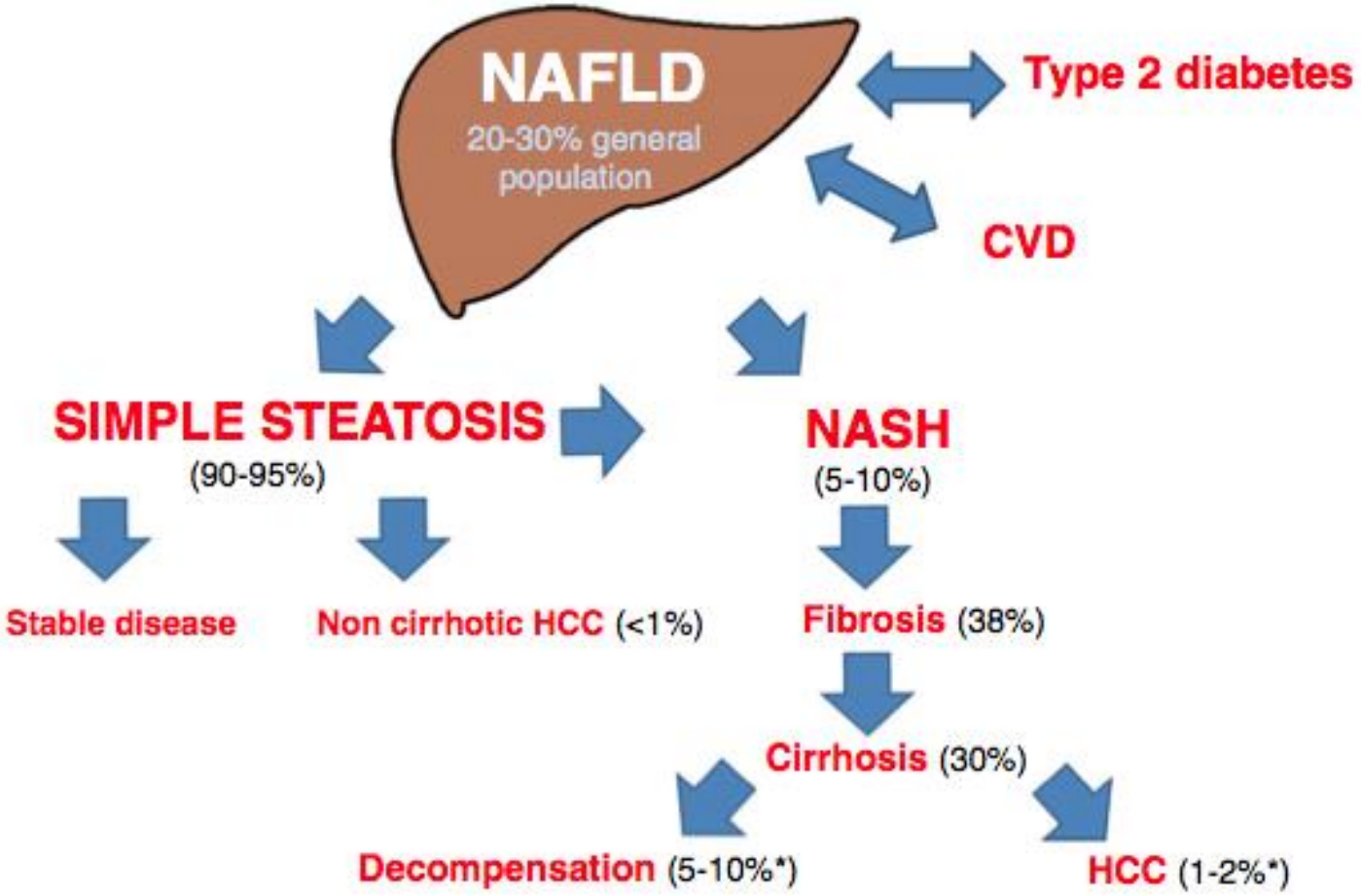
- Screen in high risk groups
  - Obese
  - Type 2 diabetes / metabolic syndrome
- Liver USS to identify steatosis
  - USS detects >30% steatotic hepatocytes
  - Normal USS ≠ no NAFLD
- If abnormal LFTs, exclude other causes of liver disease
  - HBsAg, HCV Ab, immunoglobulins, autoantibodies, A1AT level, 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



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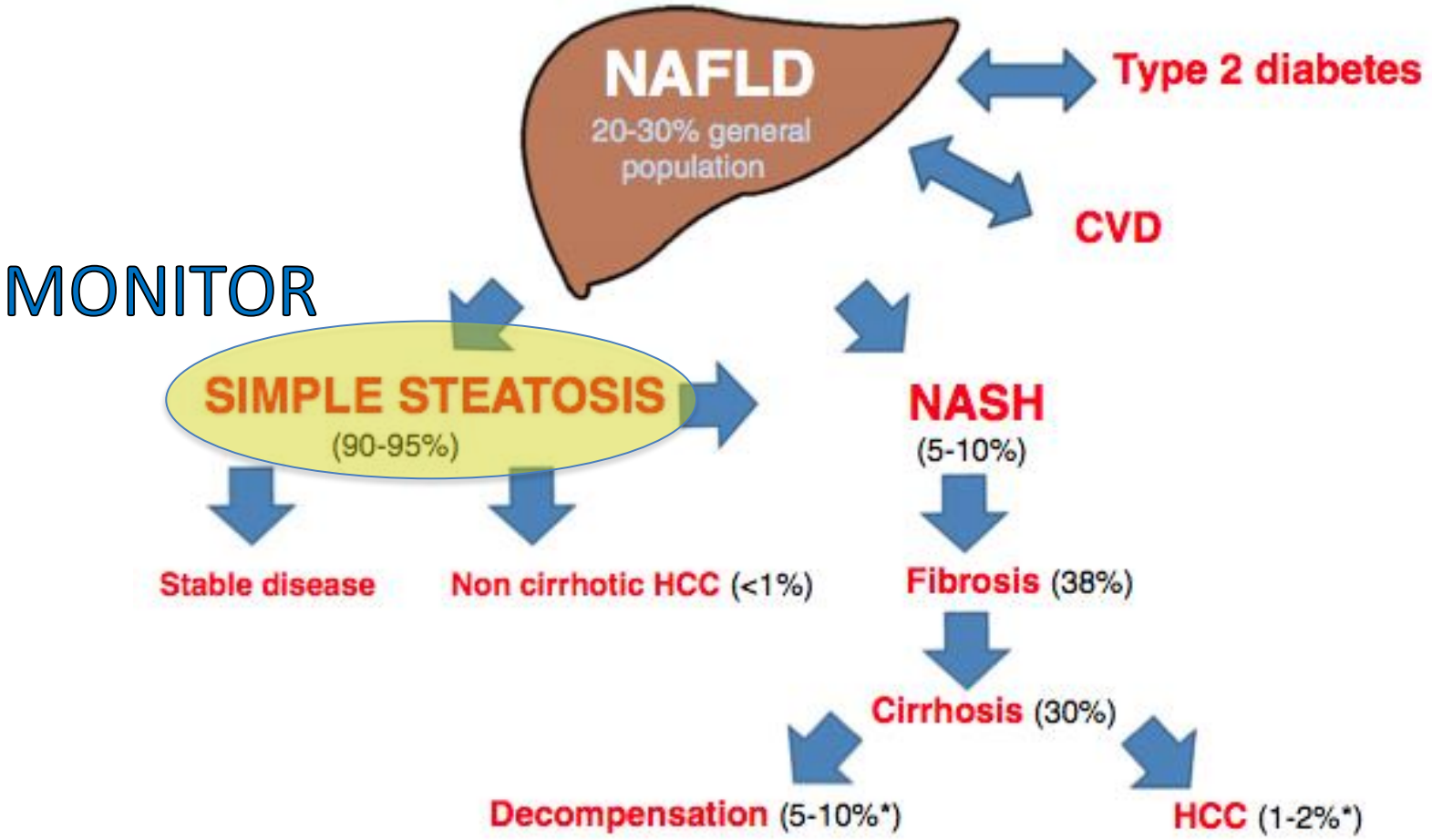

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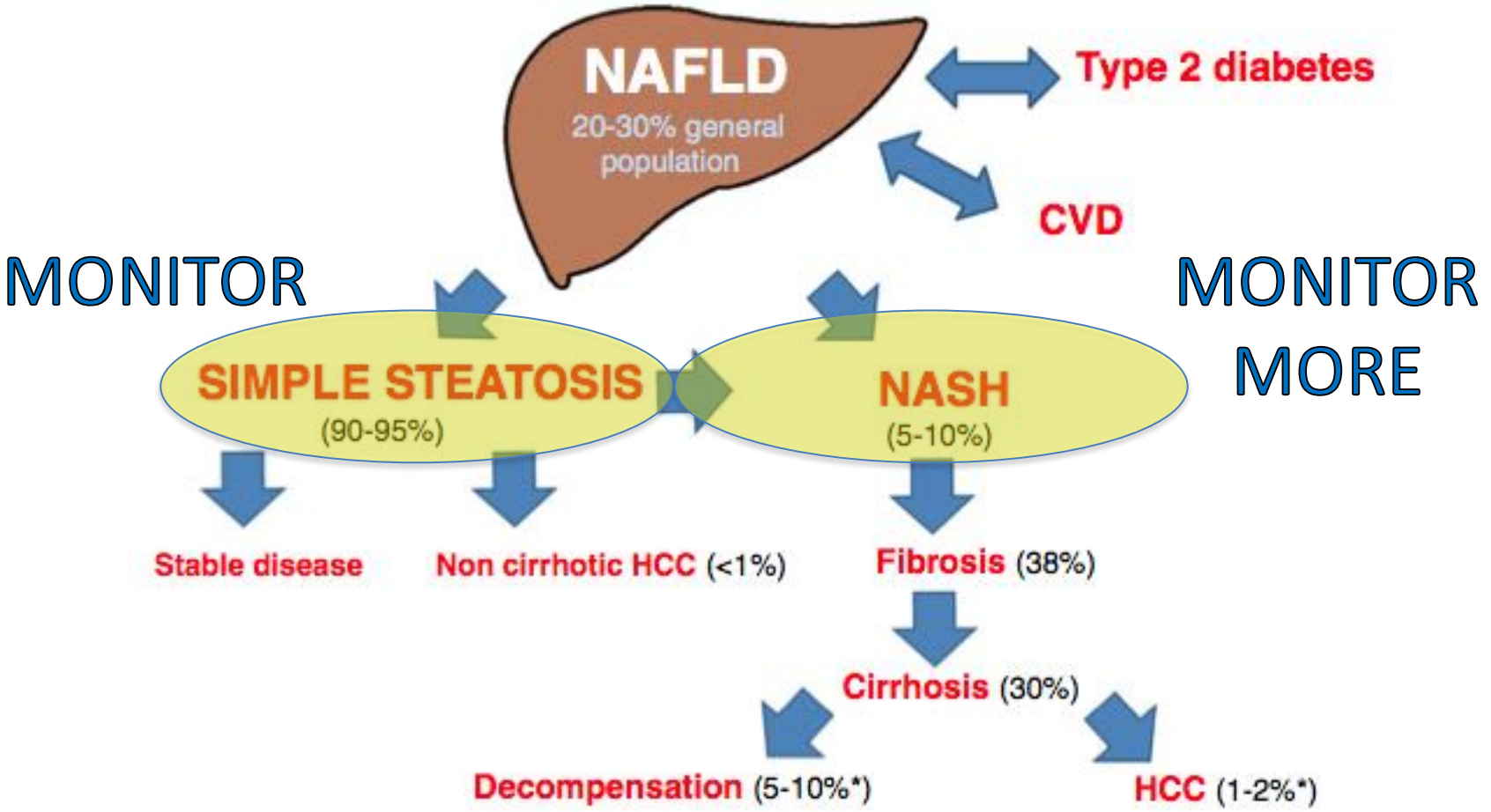


Risk Stratification

- 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

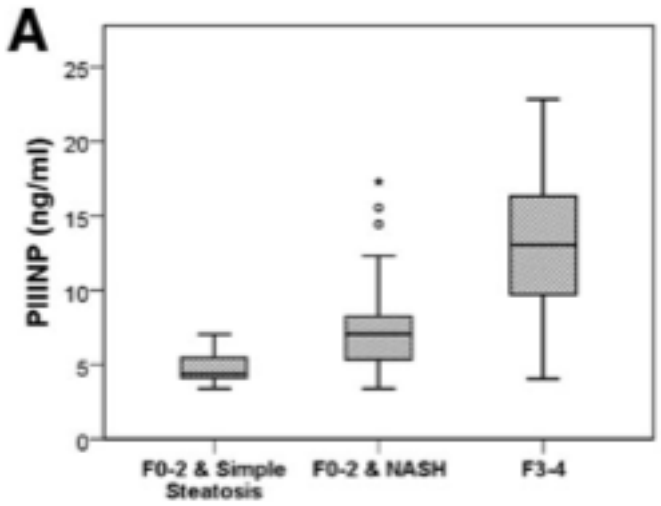
Diagnosing NASH
Distinguishing NASH from steatosis

- 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

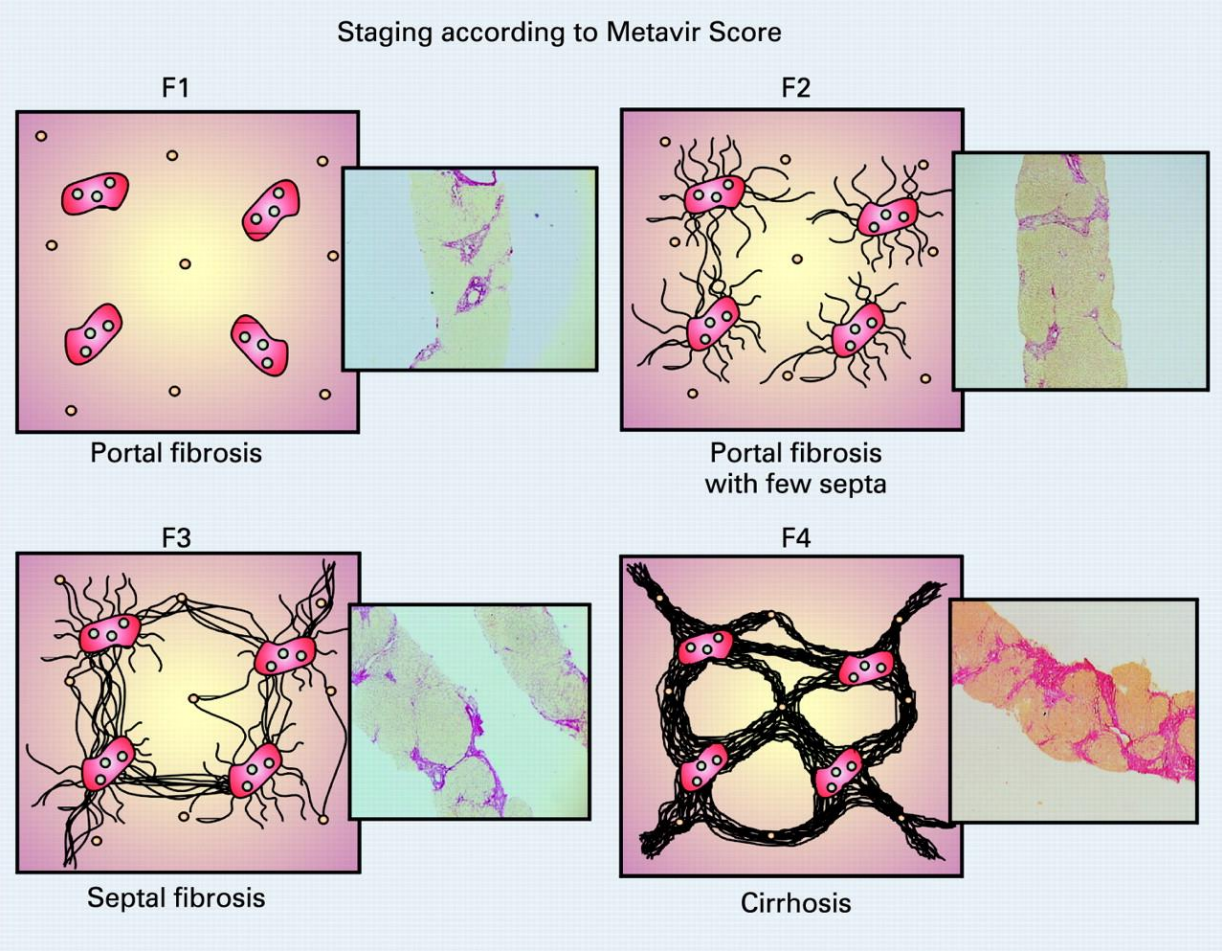


Validation of Terminal Peptide of Procollagen III for the Detection and Assessment of Nonalcoholic Steatohepatitis in Patients With Nonalcoholic Fatty Liver Disease

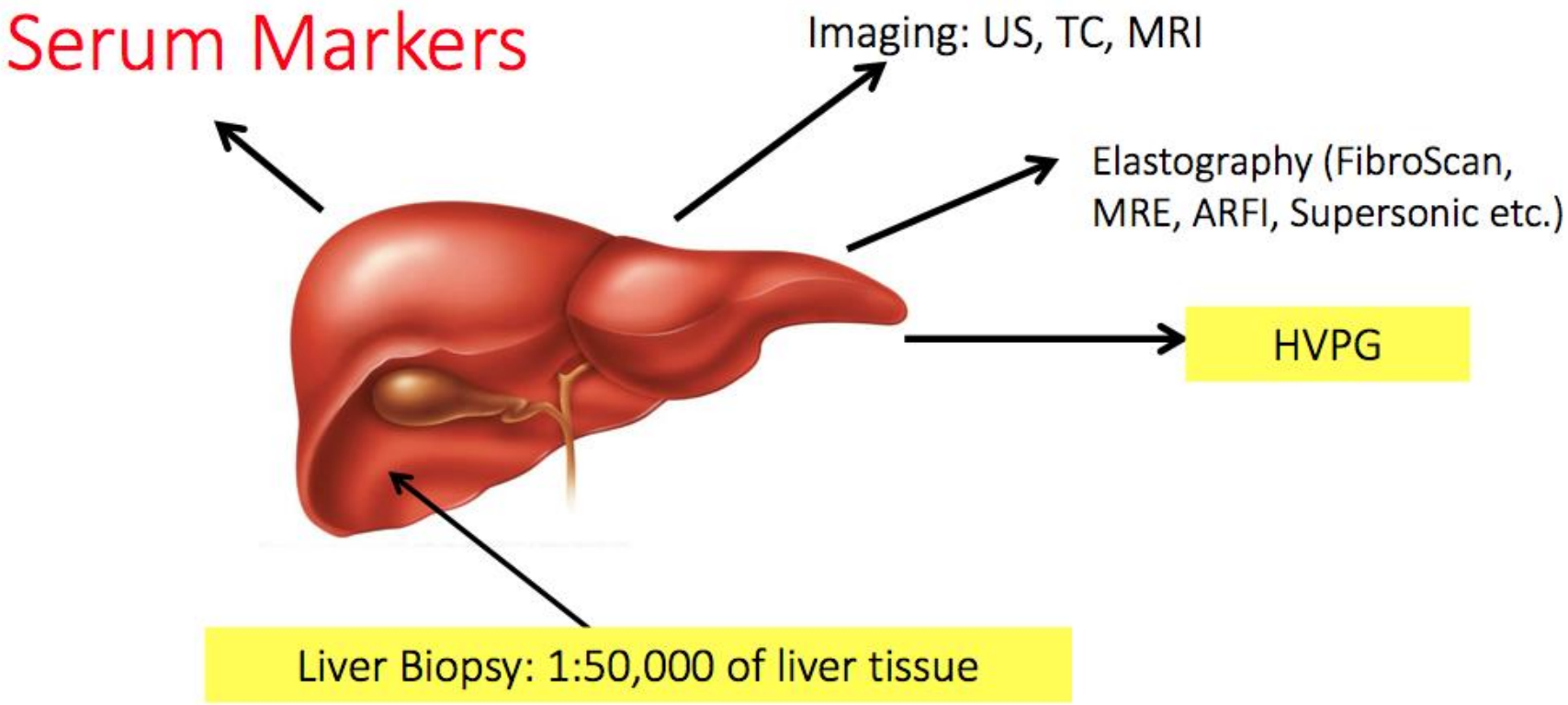
Sudeep Tanwar,[1] Paul M. Trembling,[1] Indra N. Guha,[2] Julie Parkes,[3] Philip Kaye,[2] Alastair D. Burt,[4] Stephen D. Ryder,[2] Guruprasad P. Aithal,[2] Christopher P. Day,[4] and William M. Rosenberg[1]

HEPATOLOGY, Vol. 57, No. 1, 2013

Fibrosis Assessment



Fibrosis Assessment



Pinzani, M. 2017

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

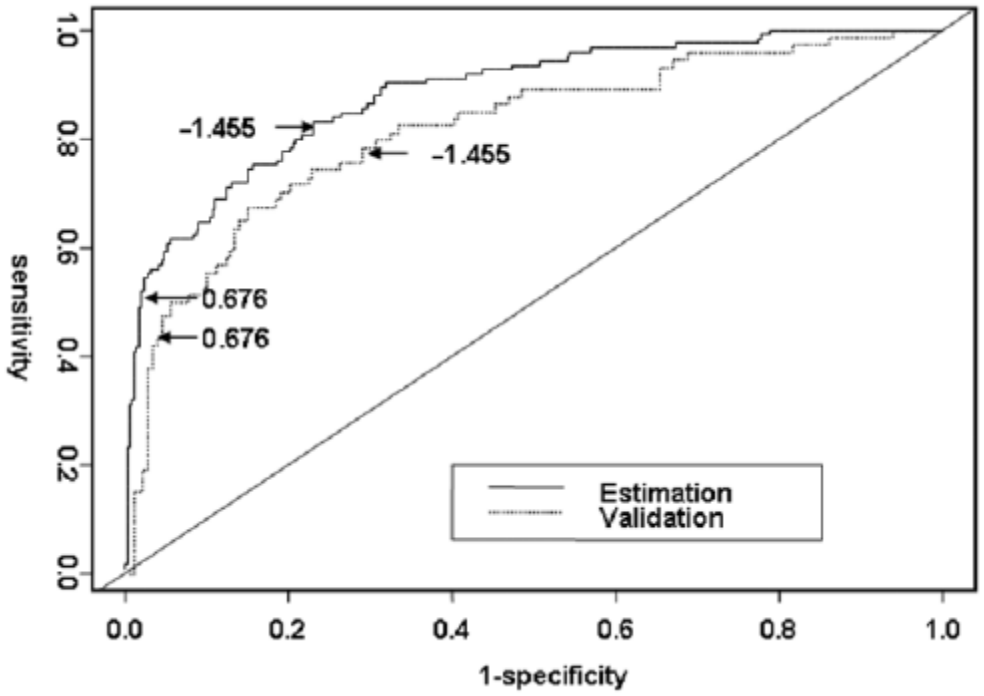
- APRI (AST/PLT ratio)
- AST/ALT
- Fib-4
- NAFLD fibrosis score

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

Angulo P, et al. Hepatology 2007

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

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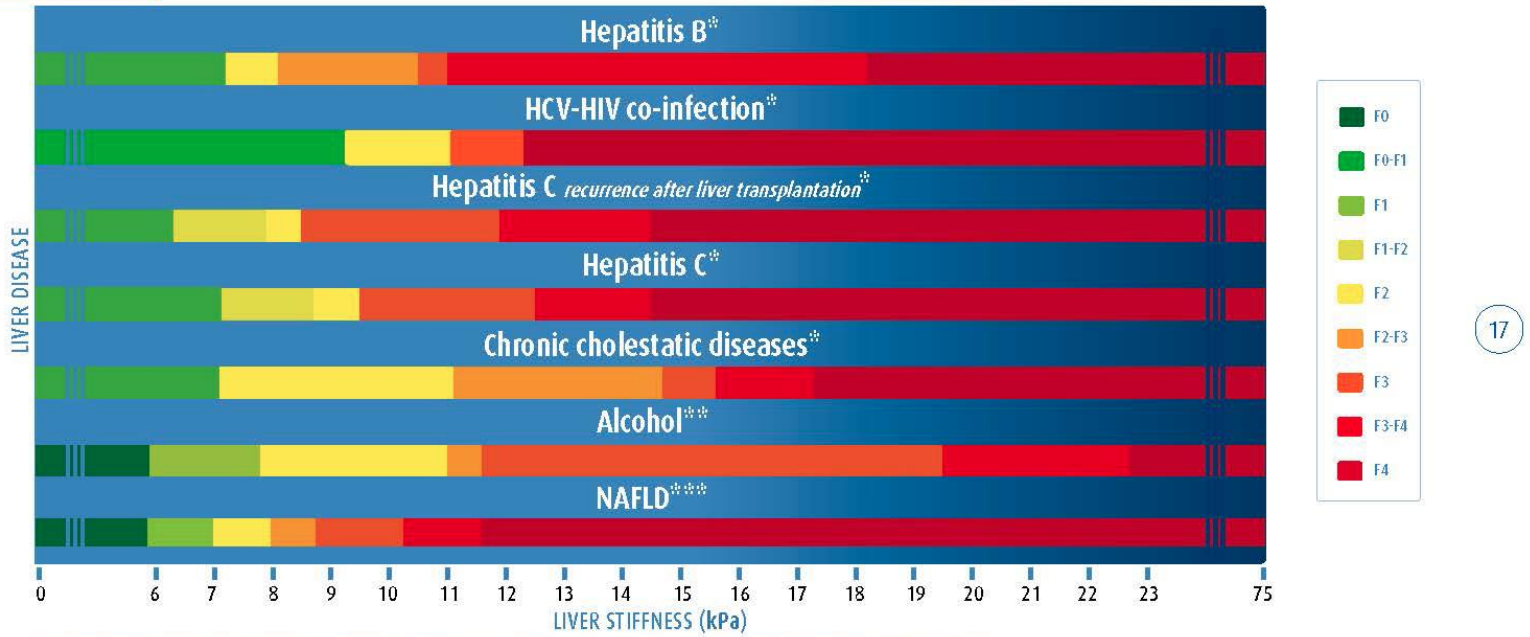
Interpreting results

SCORING CARD

CORRELATION BETWEEN LIVER STIFFNESS (kPa) & FIBROSIS STAGE



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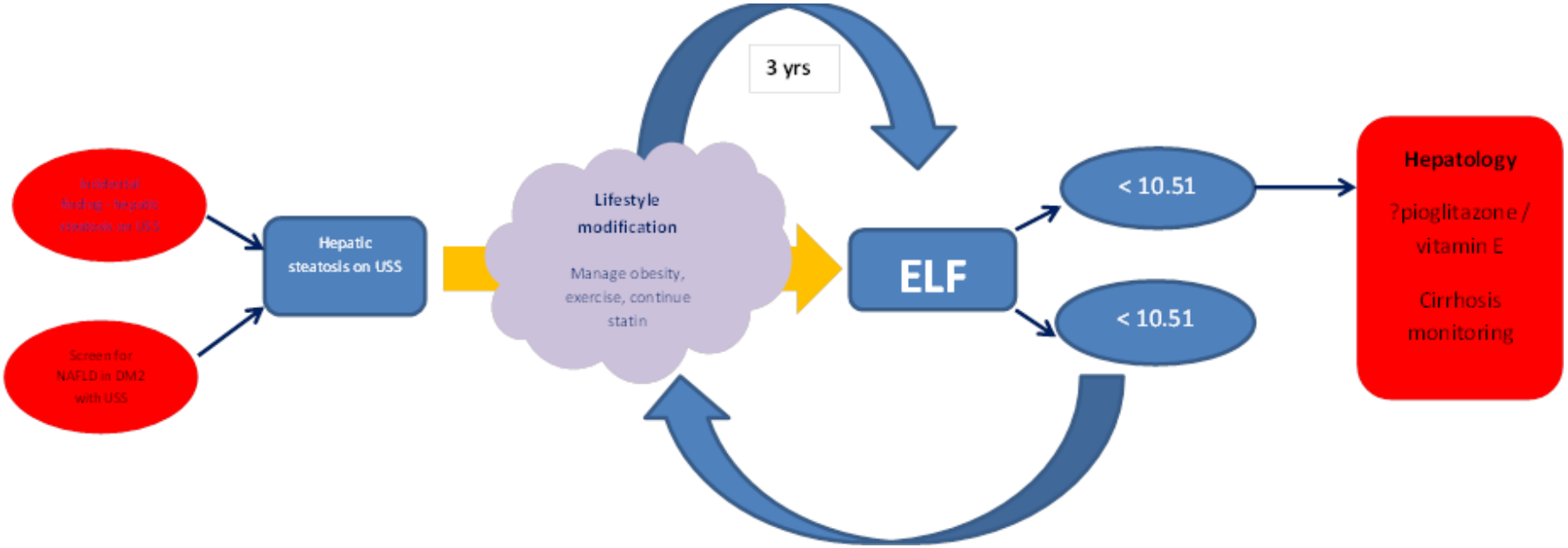
*According to Metavir score: Transient elastography (FibroScan): V. de Lédinghen, J. Vergniol, Gastroentérologie Clin Bio (2008) 32, 58-67
**According to Brunt score: Nahon et al. J Hepatol (2009) 49, 1062-68, Nguyen-Khac et al. , Aliment Pharmacol Ther (2008), 28, 1188-98
***According to Brunt score: Wong et al. Hepatology (2010) 51, 454-62Transient elastography (FibroScan®): V. de Lédinghen, J. Vergniol, Gastroentérologie Clin Bio (2008) 32, 58-67

FibroScan®, a reliable tool in hepatology

SCORING CARD

Risk stratification
NICE Non-alcoholic fatty liver disease 2016



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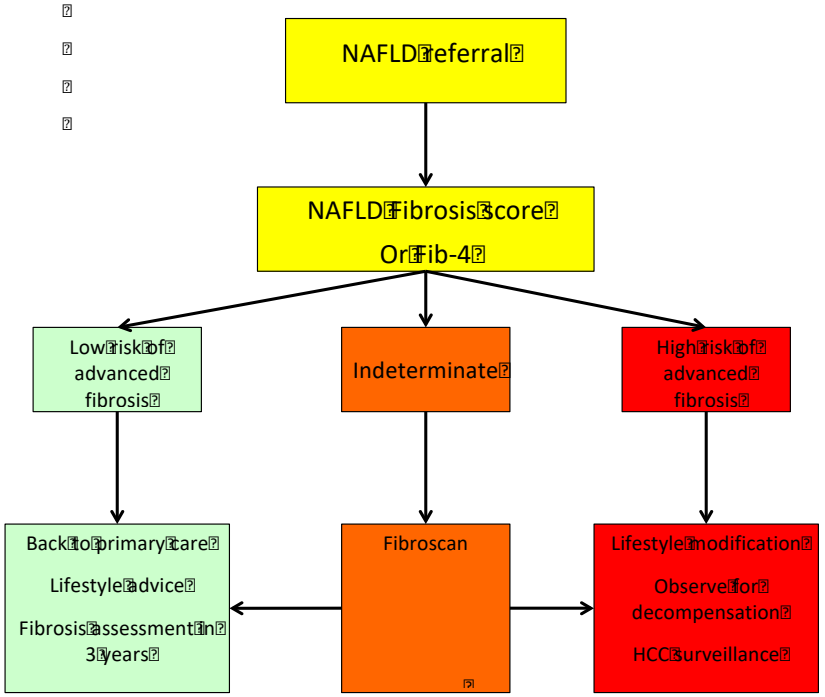
A practical approach

- 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

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Thank you