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Workshop: Liver BLOOD tests
11th April 2019

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Aims

1) **Causes of liver disease**

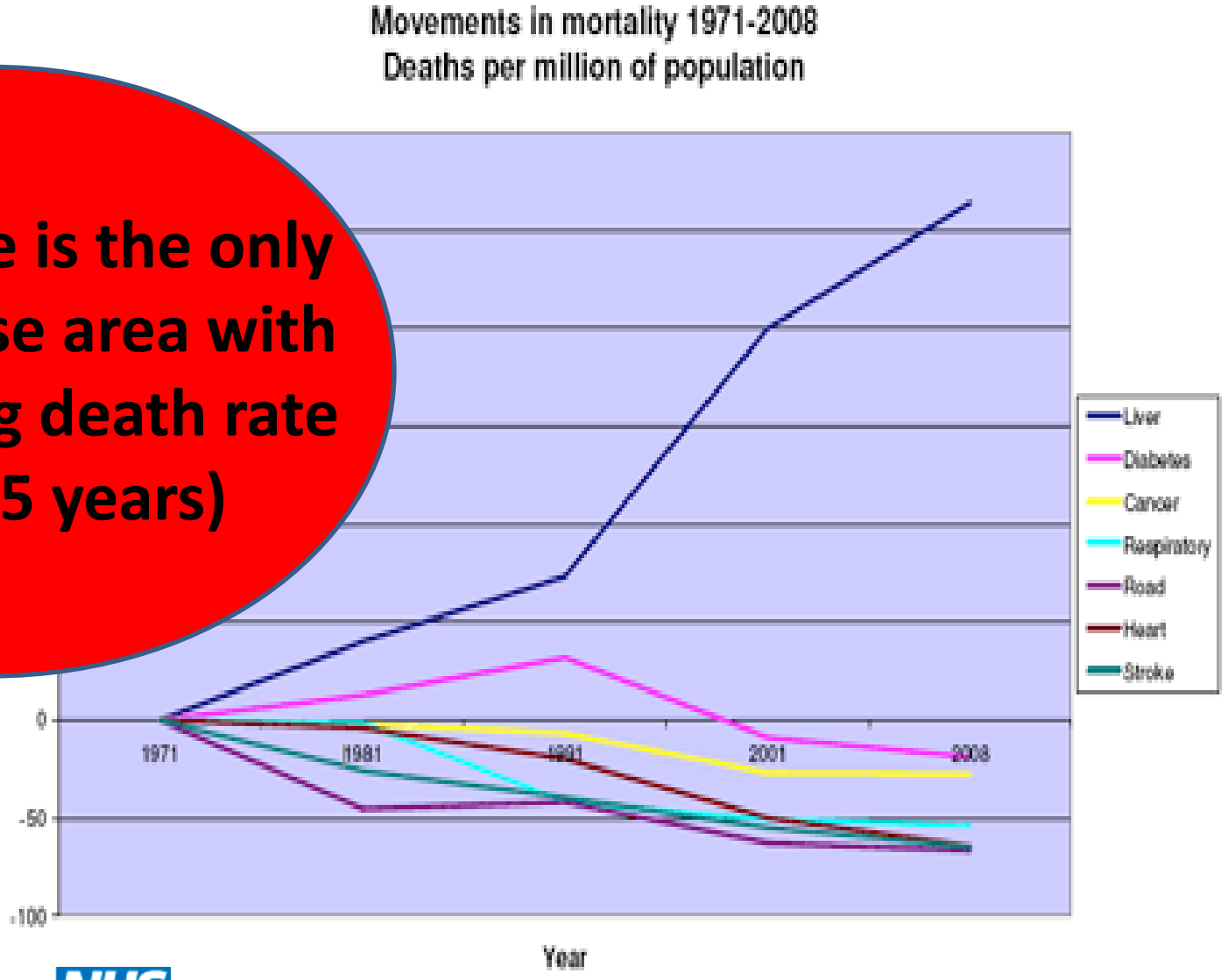
2) **LFTs - poor marker of liver disease**

3) **FibroScan – novel, non-invasive test**

4) **Case Finding**

Liver Disease in the UK

Liver disease is the only major disease area with an increasing death rate (under 65 years)



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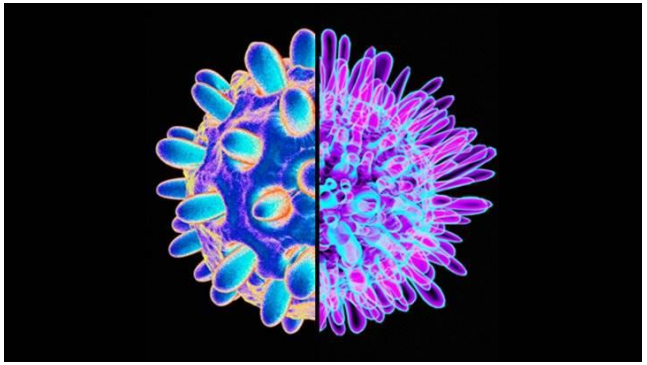
WHO European Health for All 2009

95% of liver disease in UK



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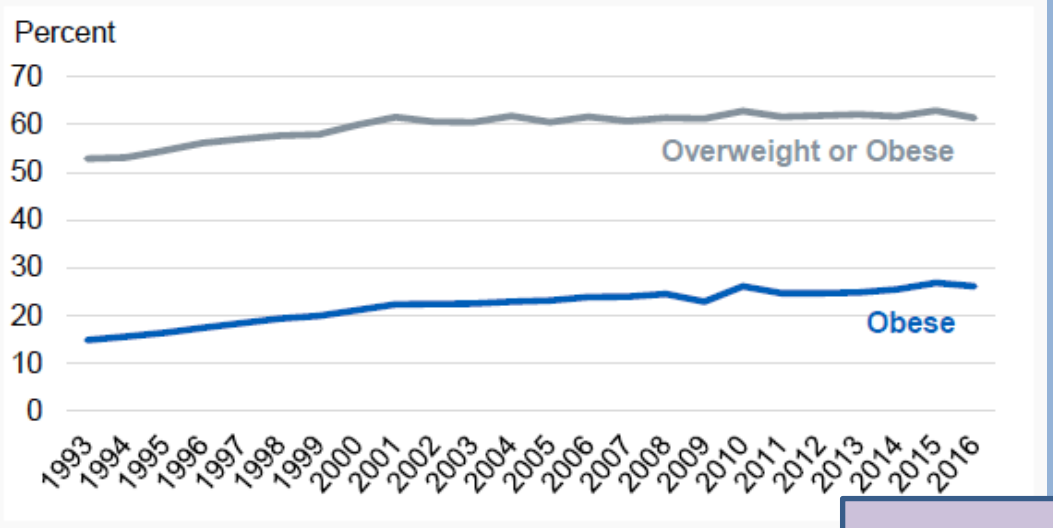
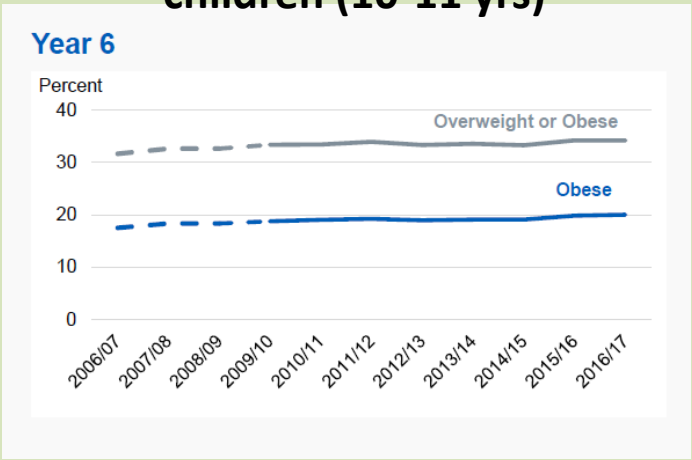
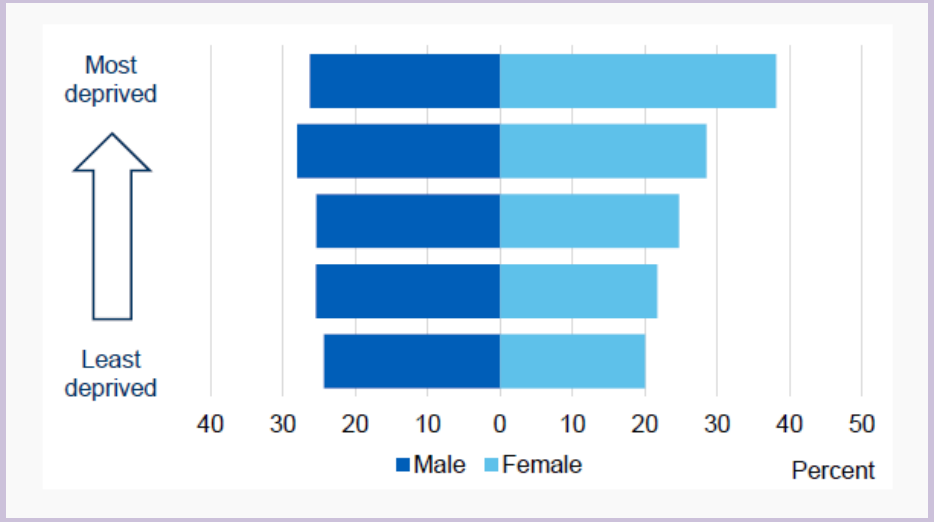
Prevalence of overweight and obese adults in England



Prevalence of overweight and obese children (10-11 yrs)



Obesity prevalence by sex and area deprivation



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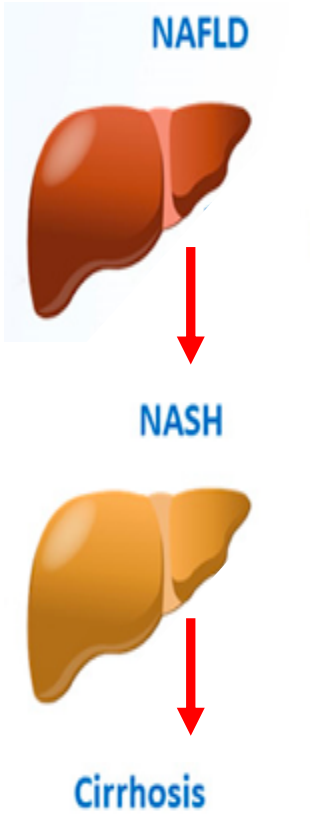
NHS Digital and National Statistics 2018

Liver disease in the 21st century



NAFLD
Global prevalence
24%

	UK cohort	
NAFLD	14,678,931	22%
NASH	905,022	1.3%
NASH fibrosis	352,273	0.5%
NASH cirrhosis	128,976	0.2%
HCC	1,684	0.003%

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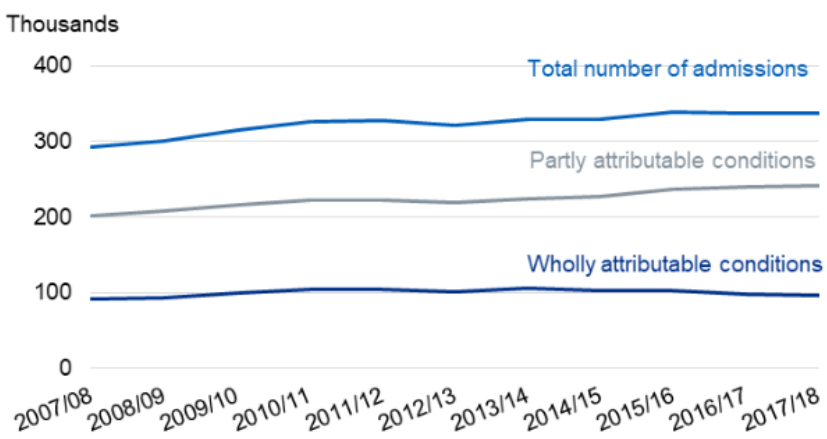
Younossi et al. Hepatology 2016 64;5pp1577-86

Alcohol

	Women	Men	
Hazardous	14 – 35 units/week	21 – 50 units/week	Increases risk of harm
Harmful	> 35 units/week	> 50 units/week	Causes medical / physical damage

Alcohol-related hospital admissions



21%

adults (16+) drank more than 14 units of alcohol per week

28% of men, 14% of women

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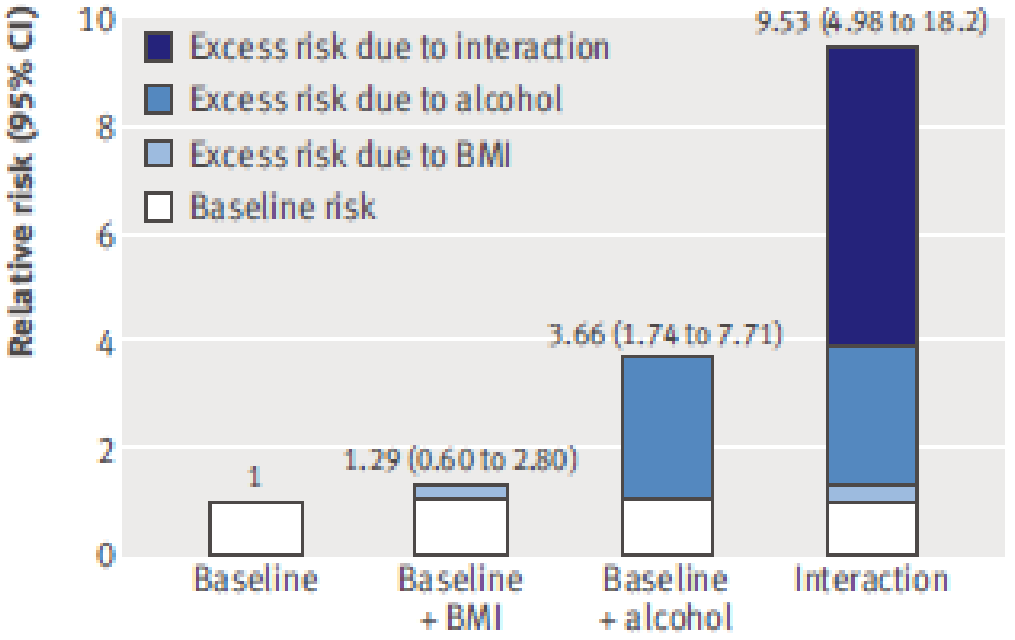
Statistics on Alcohol (NHS Digital, National Statistics, 2019)

Effect of BMI and alcohol consumption on liver disease: analysis of data of two prospective cohort studies.

Hart CL, Morrison DS *et al*

- Prospective cohort study of 9559 men
- Follow-up 29years
- 146 deaths liver disease (80 'main' cause)
- Alcohol intake: 0, 1-14 or ≥15u/week
- Weight: under/normal<25,BMI 25-29, BMI≥30



Relative risks of contributions of BMI and alcohol to liver disease mortality (adjusted for all risk factors).

BMJ 2010;340;c1240

Aims

1) **Causes of liver disease** → NAFLD, Alcohol, Hepatitis B / C

2) LFTs - poor marker of liver disease

3) FibroScan – novel, non-invasive test

4) Case Finding

Liver “function” tests (LFTs)

- Renowned for being poor markers of liver disease
- Liver blood tests are often normal in fibrosis and cirrhosis
- Equally often abnormal in the face of no fibrosis or cirrhosis
- Liver disease is not common in those with abnormal LFTs

BALLETS Study

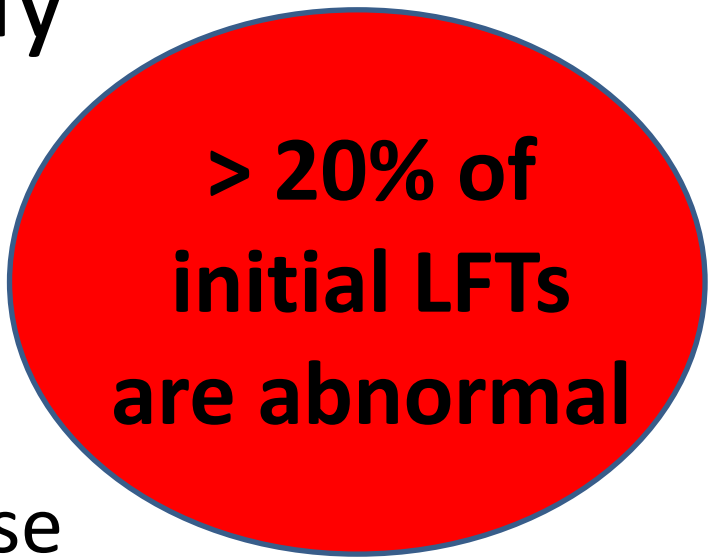
11 GP practices (Brum and Lambeth)

Prospective study

No obvious or pre-existing liver disease

Significant liver disease prevalence ~ 5%

ALFIE Study



Tayside

15 year follow-up

No obvious signs of liver disease

95,977 patients

21.7% had one abnormal liver blood test

1.14% developed liver disease

Health Technology Assessment 2009 **13**(25)

Aims

1) **Causes of liver disease** → NAFLD
   → Alcohol
   → Hepatitis B / C

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Alternatives?

Liver Biopsy

- Not without risk
- Significant morbidity and mortality

“Serious bleeding 1 in 200”

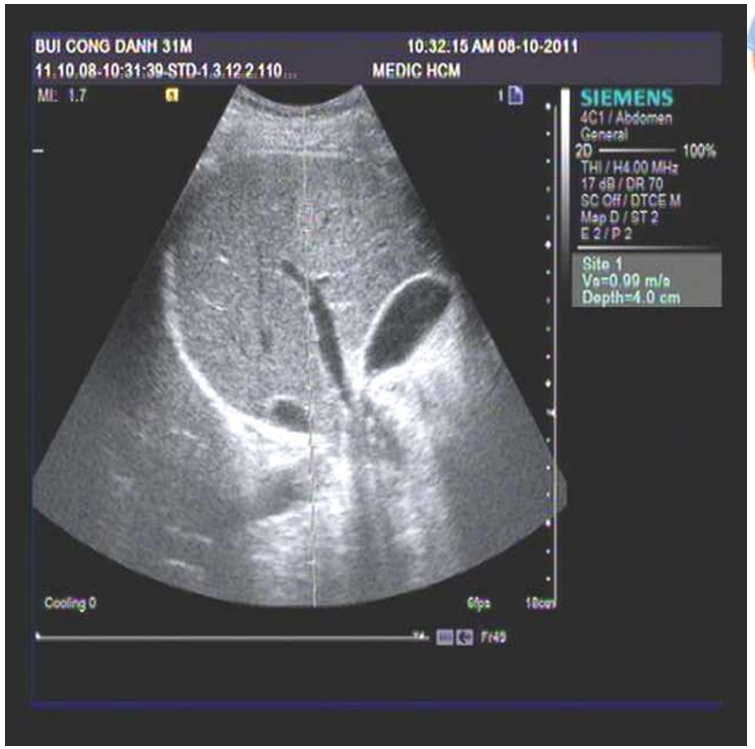
“Bleeding mortality 1 in 2000”

- Perrault *et al.* reviewed 1000 patients

5% hospitalised secondary to procedure

Perrault et al. 1978 *Gastroenterology* 74(1)pp103-6

Non invasive assessment



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Composite Scores

Score	Serological composite		Diagnostic accuracy	
			Sensitivity	Specificity
AST to platelet ratio index (APRI)[48]	AST	Platelet count	81%	55%
European Liver Fibrosis (ELF®)[54]	HA TIMP-I	PIIINP	91%	69%
Fibrometer®[46]	Platelet count Prothrombin index AST	HA Urea α-2macroglobulin	80%	84%
Fibrospect®[55]	HA α-2-macroglobulin	TIMP-II	71%	74%
Fibrotest®[56]	Age Gender ∝GT α-2-macroglobulin	Total bilirubin Haptoglobin Apolipoprotein-A	61%	80%
Forns Score[57]	Platelet count ∝GT	Age Cholesterol	30%	95%
HepaScore®[58]	∝GT Age Gender	HA Total bilirubin A2- macroglobulin	70%	79%
For NAFLD only				
BARD score[59]	BMI AST / ALT ratio	T2DM	44%	70%
NAFLD Fibrosis Score (NFS)[60]	Age BMI IFG / Diabetes	AST / ALT ratio Platelet count Albumin	77%	70%
Fibrosis-4 (Fib-4)[59]	Age AST	Platelet count ALT	54%	88%

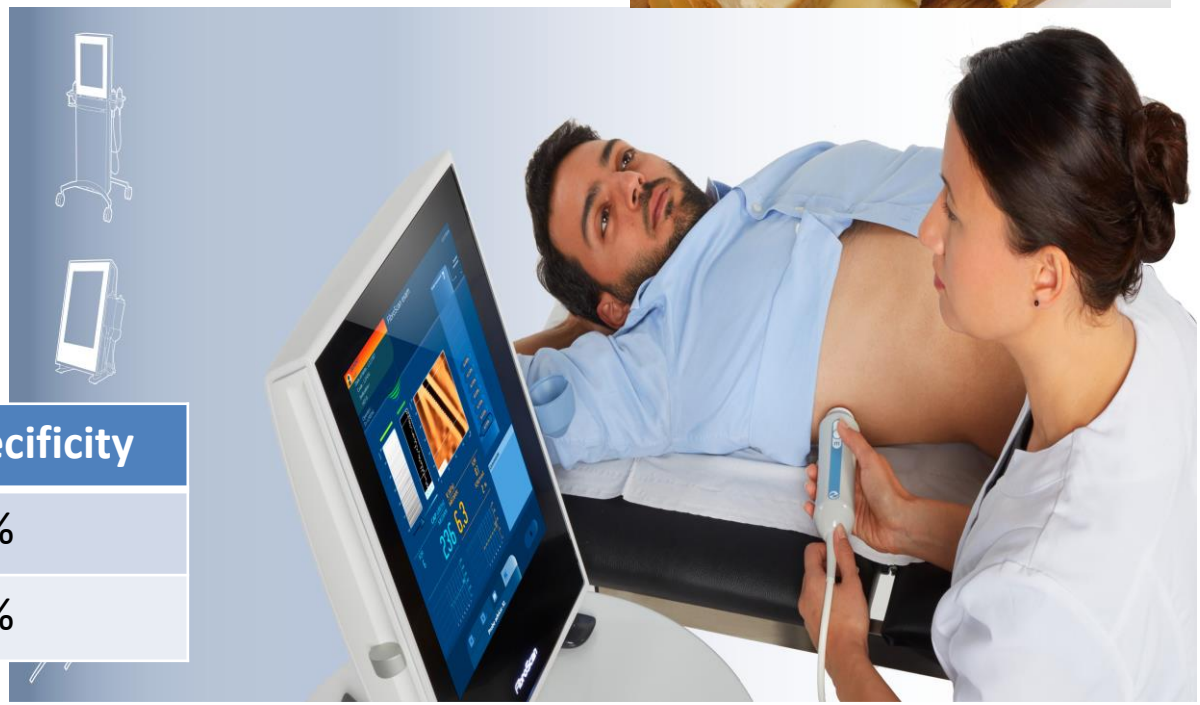
Transient Elastography

"Fibroscan"

New tool for assessment

Quick

Non-invasive



	Sensitivity	Specificity
Fibrosis	83%	83%
Cirrhosis	98%	84%

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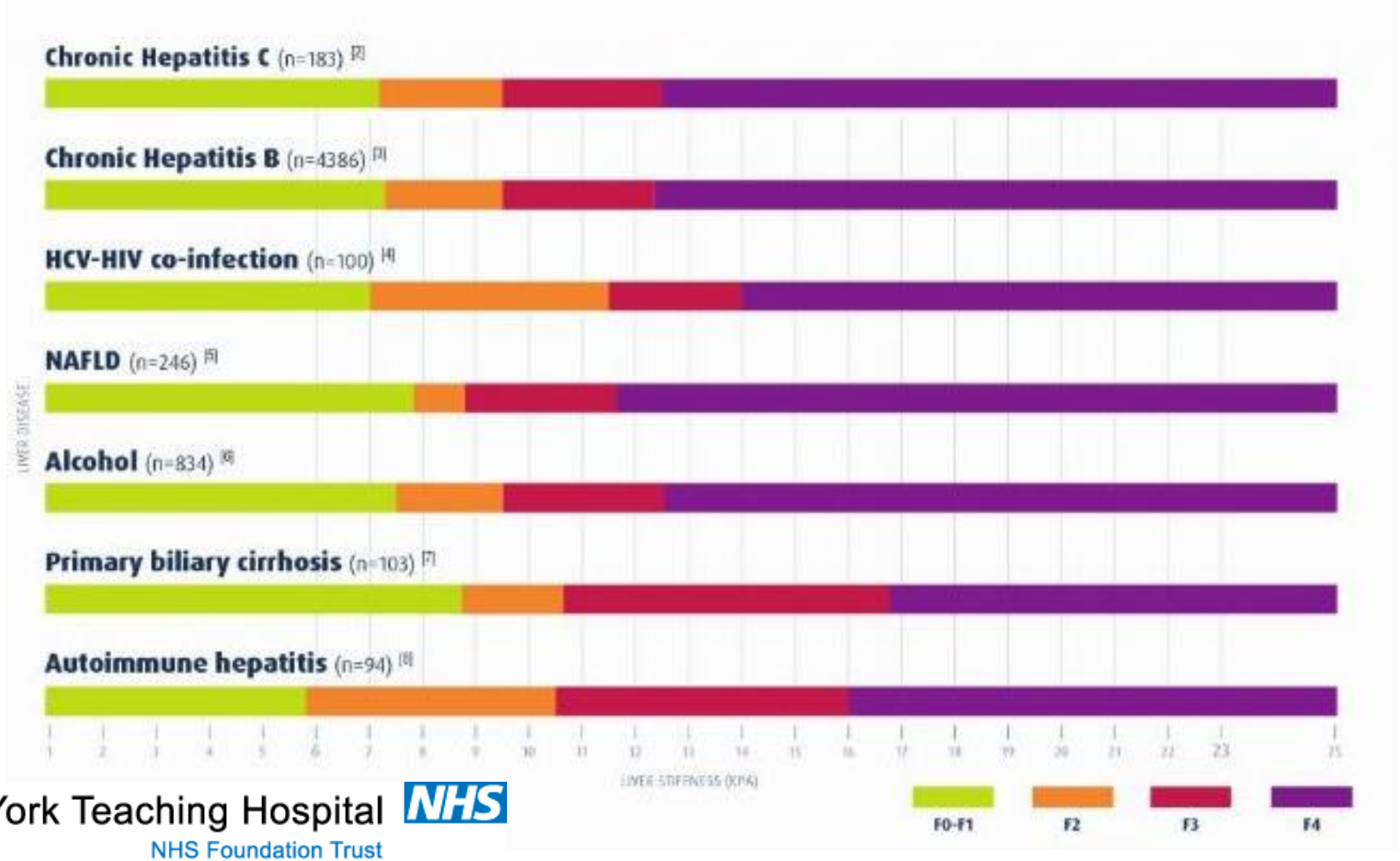
Talwalker et al. 2007 Clinical Gastro and Hep 5(10)pp1214-1220

Interpretation Guide



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Why Transient Elastography?

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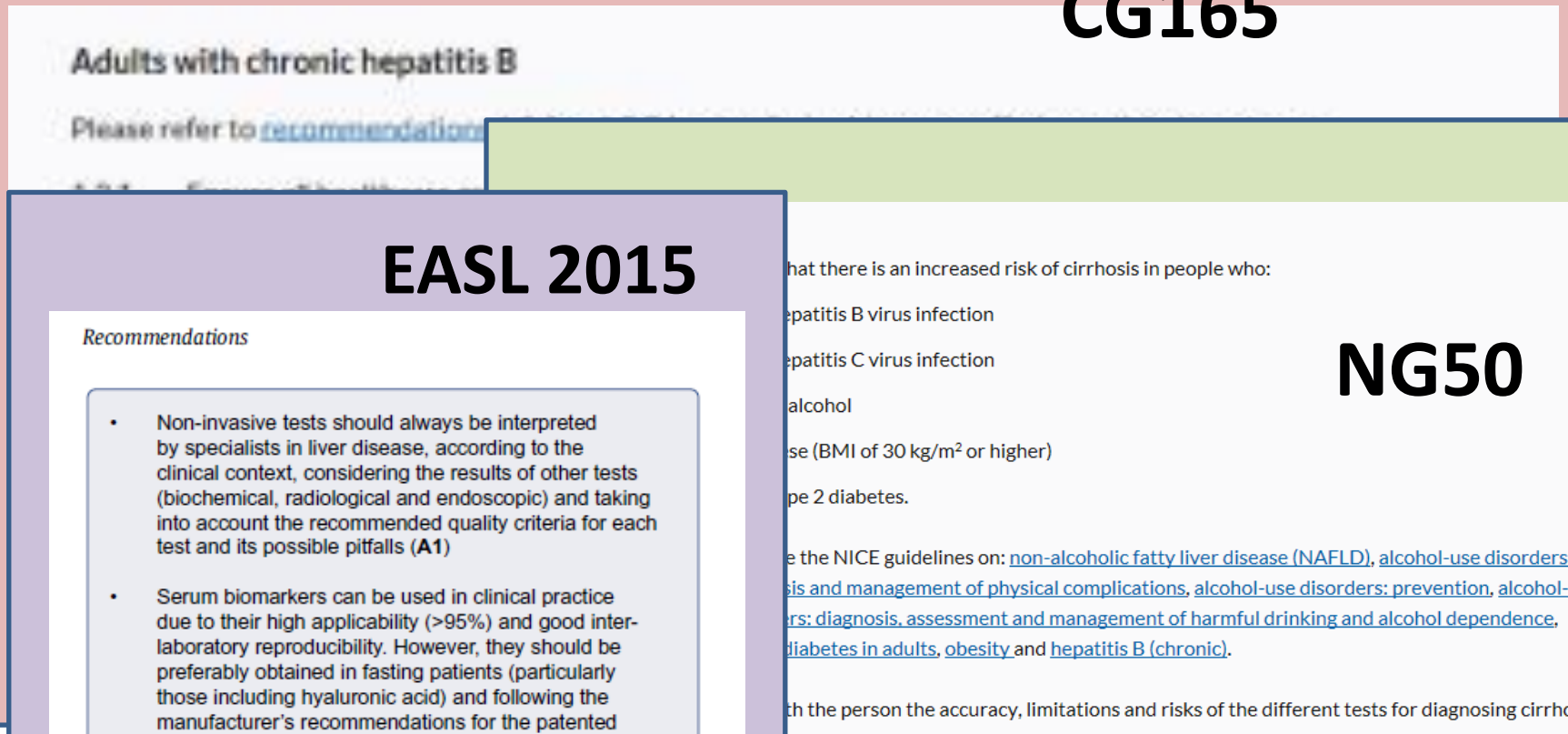

Adults with chronic hepatitis B

Please refer to recommendations

EASL 2015

Recommendations

- Non-invasive tests should always be interpreted by specialists in liver disease, according to the clinical context, considering the results of other tests (biochemical, radiological and endoscopic) and taking into account the recommended quality criteria for each test and its possible pitfalls (**A1**)
- Serum biomarkers can be used in clinical practice due to their high applicability (>95%) and good inter-laboratory reproducibility. However, they should be preferably obtained in fasting patients (particularly those including hyaluronic acid) and following the manufacturer's recommendations for the patented tests (**A1**)
- TE is a fast, simple, safe and easy to learn procedure that is widely available. Its main limitation is the impossibility of obtaining results in case of ascites or morbid obesity and its limited applicability in case of obesity and limited operator experience (**A1**)
- TE should be performed by an experienced operator (>100 examinations) following a standardized protocol with the patient, fasting for at least 2 hours, in the

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hat there is an increased risk of cirrhosis in people who:

epatitis B virus infection

epatitis C virus infection

alcohol

se (BMI of 30 kg/m² or higher)

pe 2 diabetes.

e the NICE guidelines on: non-alcoholic fatty liver disease (NAFLD), alcohol-use disorders: sis and management of physical complications, alcohol-use disorders: prevention, alcohol-use rs: diagnosis, assessment and management of harmful drinking and alcohol dependence, diabetes in adults, obesity and hepatitis B (chronic).

th the person the accuracy, limitations and risks of the different tests for diagnosing cirrhosis.

sient elastography to diagnose cirrhosis for:

with hepatitis C virus infection

o drink over 50 units of alcohol per week and women who drink over 35 units of alcohol per nd have done so for several months

diagnosed with alcohol-related liver disease.

York

Aims

1) **Causes of liver disease** → NAFLD
→ Alcohol
→ Hepatitis B / C

2) **LFTs - poor marker of liver disease**

3) FibroScan – novel, non-invasive test

FibroScan > 7 kPa = concerning?

4) Case Finding

Case finding

1) High risk of metabolic syndrome?

2) Hazardous alcohol use?

3) Have they ever injected drugs?

Case finding

1) High risk of metabolic syndrome?

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1.1 Assessment for NAFLD

Identifying NAFLD in higher-risk groups

1.1.1 Be aware that non-alcoholic fatty liver disease (NAFLD) is more common in people who have:

- type 2 diabetes or
- metabolic syndrome.

1.1.2 Take an alcohol history to rule o

1.1.3 Do not use routine liver blood te

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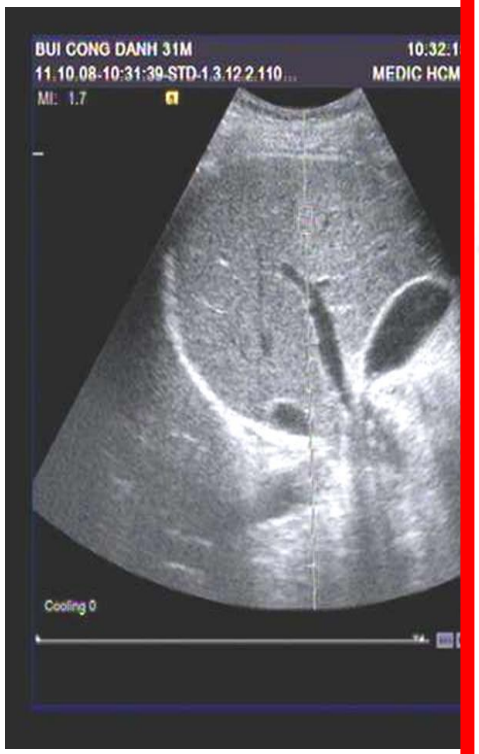
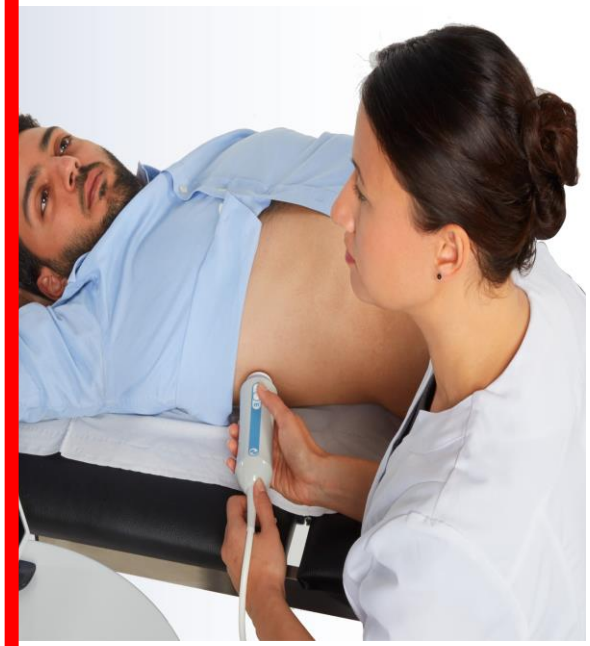
What action should they take?

- GPs and practice nurses should offer testing for hepatitis B and C to adults and children at increased risk of infection, particularly migrants from medium- or high-prevalence countries and people who inject or have injected drugs (see Whose health will benefit?).
- GPs and practice nurses should offer testing for hepatitis B and C to people who are newly registered with the practice and belong to a group at increased risk of infection (see Whose health will benefit?).
- GPs and practice nurses should ask newly registered adults if they have ever injected drugs, including image and performance enhancement substances at their first consultation.
- GPs and practice nurses should offer hepatitis B testing and vaccination to men who have sex with men who are offered a test for HIV and have not previously tested positive for hepatitis B antibodies (see NICE guidance on Increasing the uptake of HIV testing among men who have sex with men).
- GPs and practice nurses should offer hepatitis B vaccination to people who test negative for hepatitis B but remain at increased risk of infection (see the Green book).
- GPs and practice nurses should offer annual testing for hepatitis C to people who test negative for hepatitis C

Non invasive assessment





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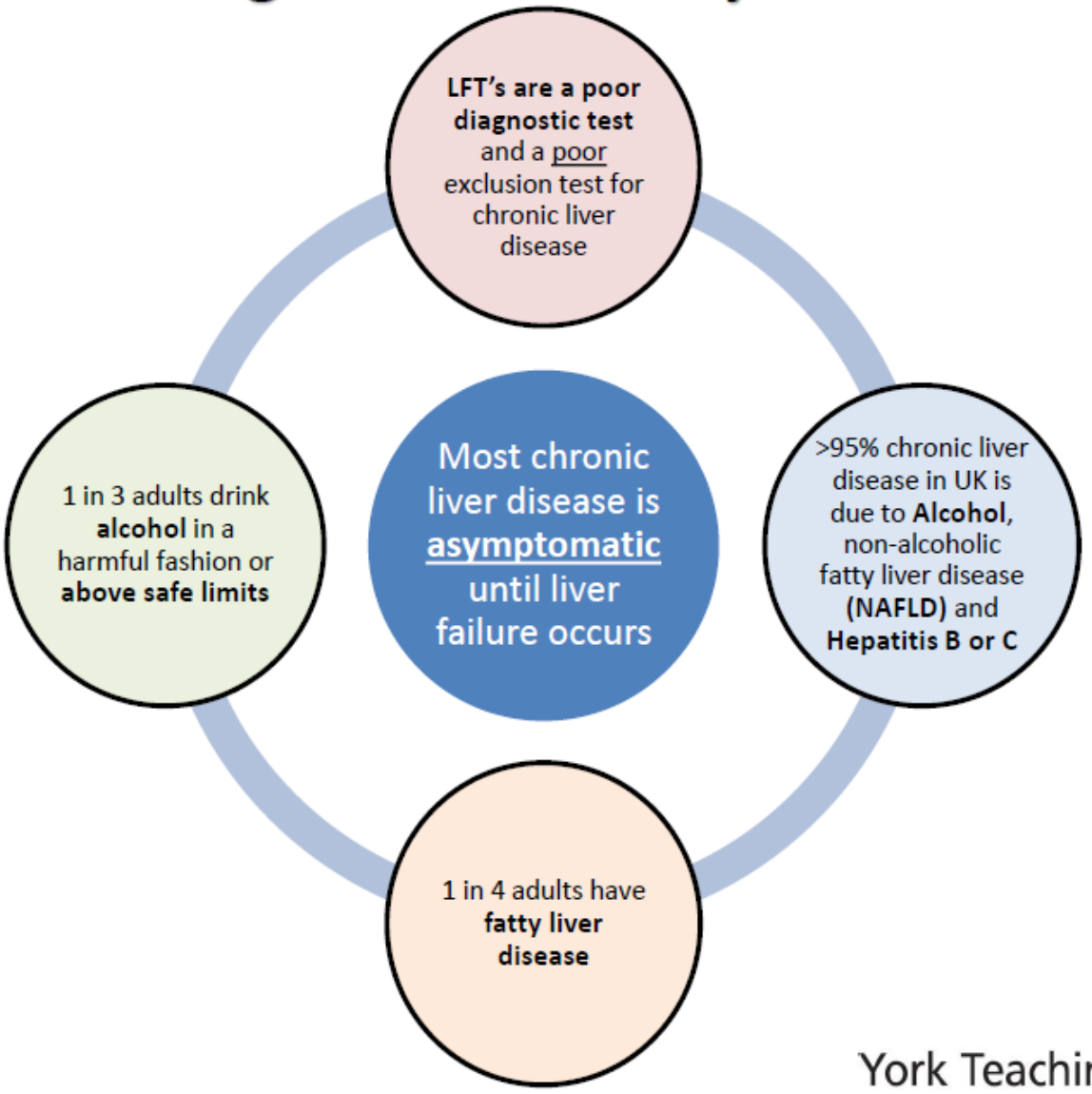
FibroScan > 7 kPa = concerning?

4) Case Finding

- **1) Metabolic syndrome?**
- **2) Hazardous alcohol?**
- **3) Ever injected drugs?**

Liver Disease and Liver Function Tests: A guide for Primary Care



Filename: CB-INF-ABNLFT
Version: 1.0
Date of Issue: January 2019

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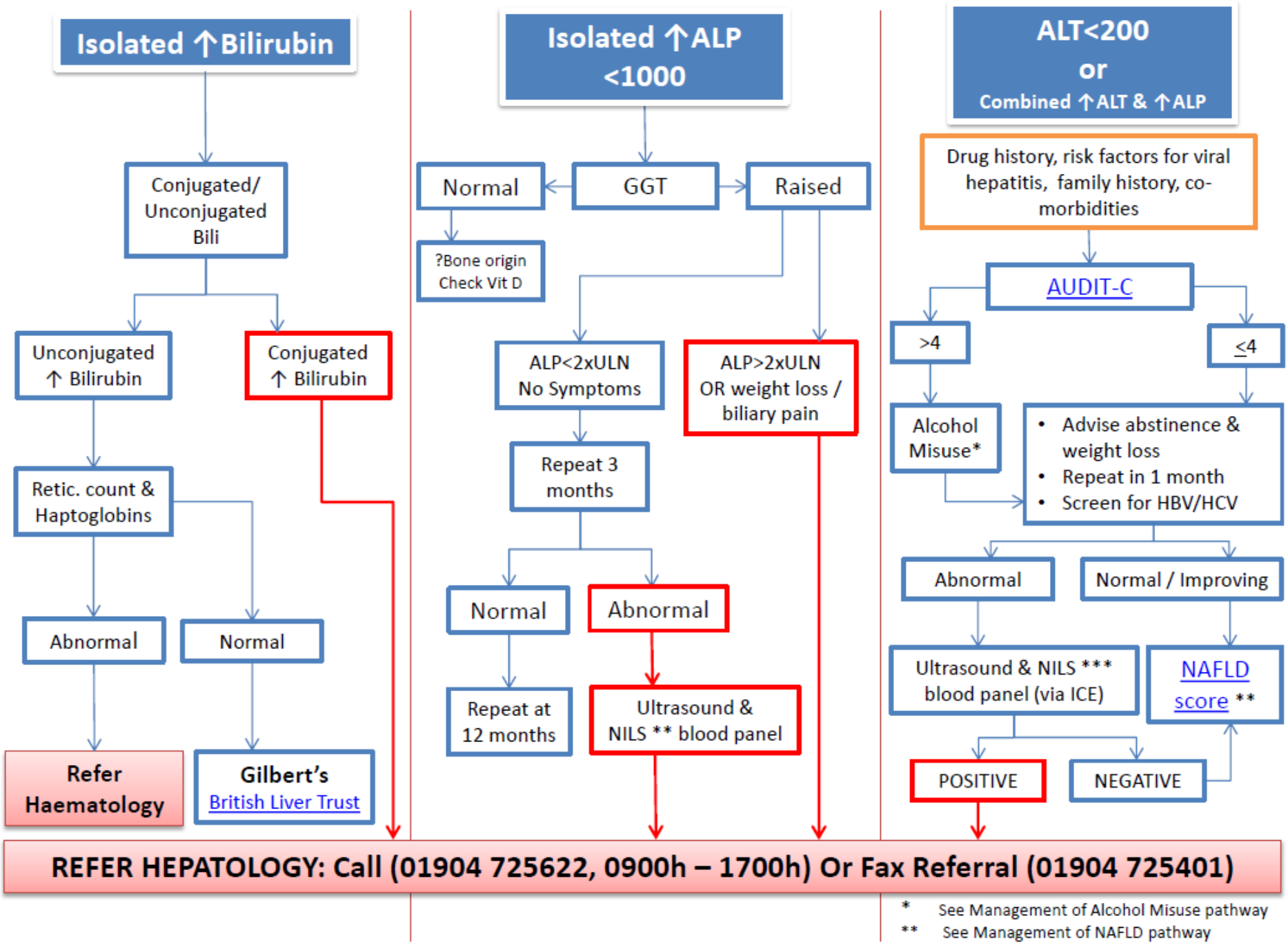
Isolated ↑Bilirubin
Conjugated/ Unconjugated Bili
Unconjugated ↑ Bilirubin
Conjugated ↑ Bilirubin
Retic. count & Haptoglobins
Abnormal
Normal
Refer Haematology
Gilbert's
British Liver Trust
Isolated ↑ALP <1000
Normal
GGT
Raised
?Bone origin Check Vit D
ALP<2xULN No Symptoms
ALP>2xULN OR weight loss / biliary pain
Repeat 3 months
Normal
Abnormal
Repeat at 12 months
Ultrasound & NILS ** blood panel
ALT<200 or Combined ↑ALT & ↑ALP
Drug history, risk factors for viral hepatitis, family history, co-morbidities
AUDIT-C
>4
≤4
Alcohol Misuse*
• Advise abstinence & weight loss
• Repeat in 1 month
• Screen for HBV/HCV
Abnormal
Normal / Improving
Ultrasound & NILS *** blood panel (via ICE)
NAFLD score **
POSITIVE
NEGATIVE
REFER HEPATOLOGY: Call (01904 725622, 0900h – 1700h) Or Fax Referral (01904 725401)
* See Management of Alcohol Misuse pathway
** See Management of NAFLD pathway
*** NILS = Non-Invasive Liver Screen

Alcohol use disorders identification test consumption (AUDIT C)

This alcohol harm assessment tool consists of the consumption questions from the full alcohol use disorders identification test (AUDIT).

Questions	Scoring system					Your score
	0	1	2	3	4	
How often do you have a drink containing alcohol?	Never	Monthly or less	2 to 4 times per month	2 to 3 times per week	4 or more times per week	
How many units of alcohol do you drink on a typical day when you are drinking?	0 to 2	3 to 4	5 to 6	7 to 9	10 or more	
How often have you had 6 or more units if female, or 8 or more if male, on a single occasion in the last year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	

AUDIT C score	

Scoring:

- A total of 5 or more is a positive screen

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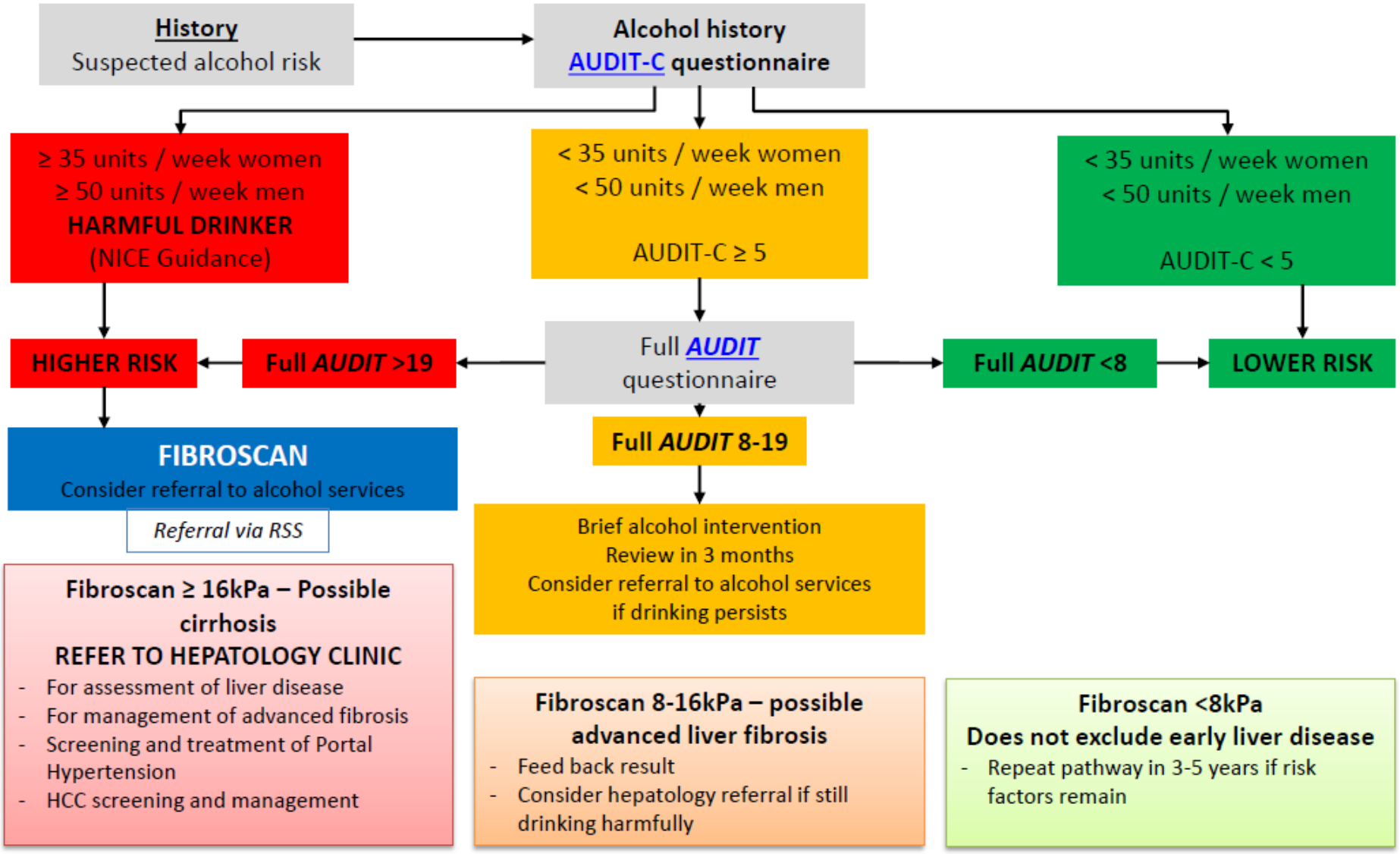
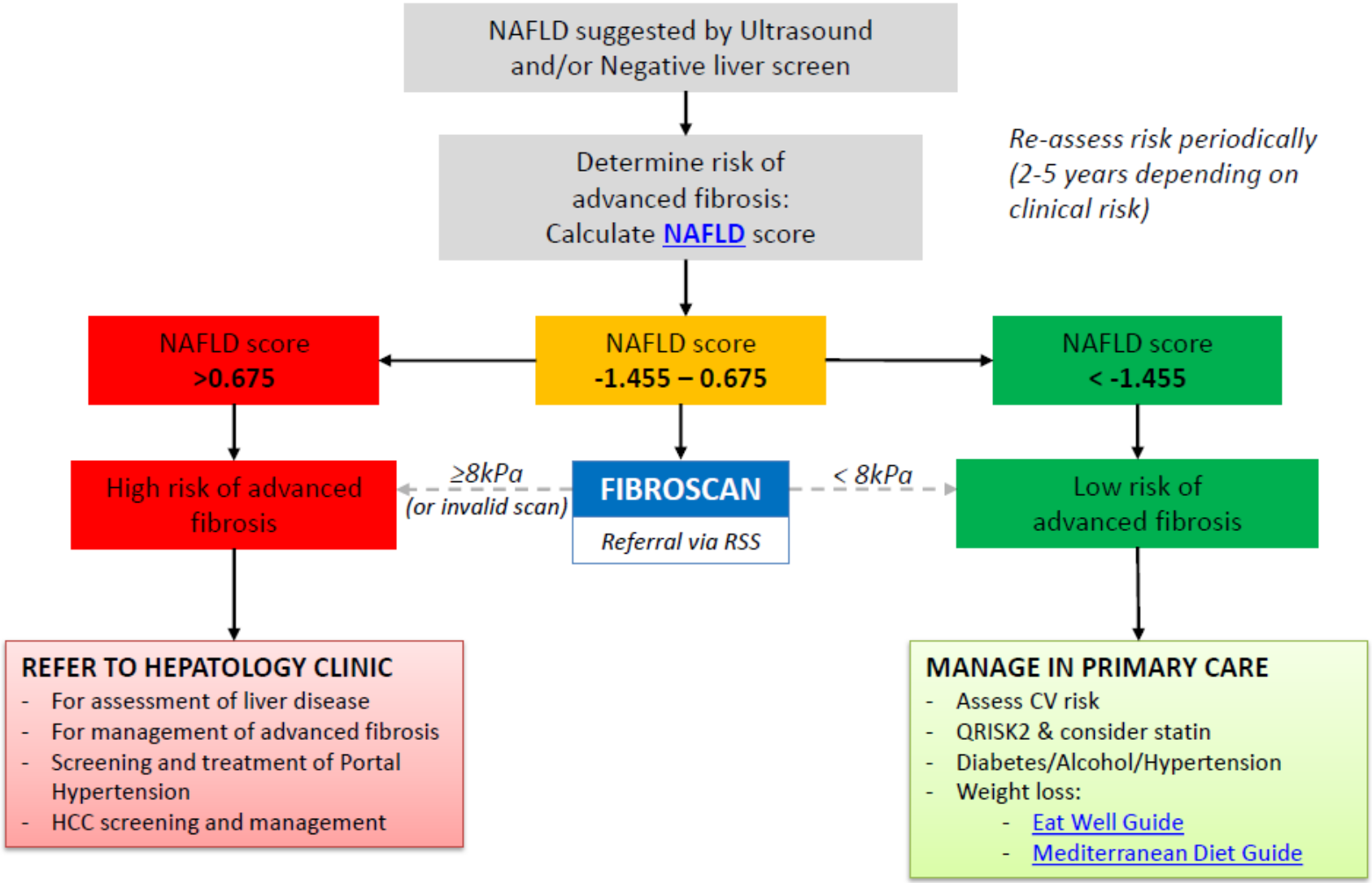
Management of Alcohol Misuse

Ref: Newsome PN, *et al. Gut* 2018; **67**:6-19



Management of NAFLD

Ref: Newsome PN, *et al. Gut* 2018; **67**:6-19



In conclusion

Liver blood tests are poor markers of liver disease

Liver disease; silent yet highly prevalent ~ 24% have NAFLD

Case finding:

- Alcohol
- Metabolic syndrome (high BMI)
- Viral hepatitis

If yes → Refer for FibroScan +/- hepatology opinion

A sign of things to come….?

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Development and validation of diagnostic triage criteria for liver disease from a minimum data set enabling the 'intelligent LFT' pathway for the automated assessment of deranged liver enzymes

FREE

Michael Hugh Miller[1], Andrew Fraser[2], Gillian Leggett[2], Alastair MacGilchrist[3], George Gibson[4], James Orr[4], Ewan H Forrest[4], Ellie Dow[5], William Bartlett[5], Chirstopher Weatherburn[5], Axel Laurell[1], Kirsty Grant[1], Kathryn Scott[6], Ronald Neville[5], John F Dillon[1]

Author affiliations

Abstract

Background Liver function tests (LFTs) are commonly abnormal; most patients with 'incidental' abnormal LFTs are not investigated appropriately and for those who are, current care pathways are geared to find an explanation for the abnormality by a lengthy process of investigation and exclusion, with costs to the patient and to the health service.

Objective To validate an intelligent automatable analysis tool (iLFT) for abnormal liver enzymes, which diagnoses common liver conditions, provides fibrosis stage and recommends management

Design A retrospective case note review from three tertiary referral liver centres, with application of the iLFT algorithm and comparison with the clinician's final opinion as gold standard.

Results The iLFT algorithm in 91.3% of cases would have correctly recommended referral or management in primary care. In the majority of the rest of the cases, iLFT failed safe and recommended referral even when the final clinical diagnosis could have been managed in primary care. Diagnostic accuracy was achieved in 82.4% of cases, consistent with the fail-safe design of the algorithm. Two cases would have remained in primary care as per the algorithm outcome, however on clinical review had features of advanced fibrosis.

Conclusion iLFT analysis of abnormal liver enzymes offers a safe and robust method of risk stratifying patients to the most

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