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Liver tests in type 2 diabetes
What and when?

Guruprasad P. Aithal

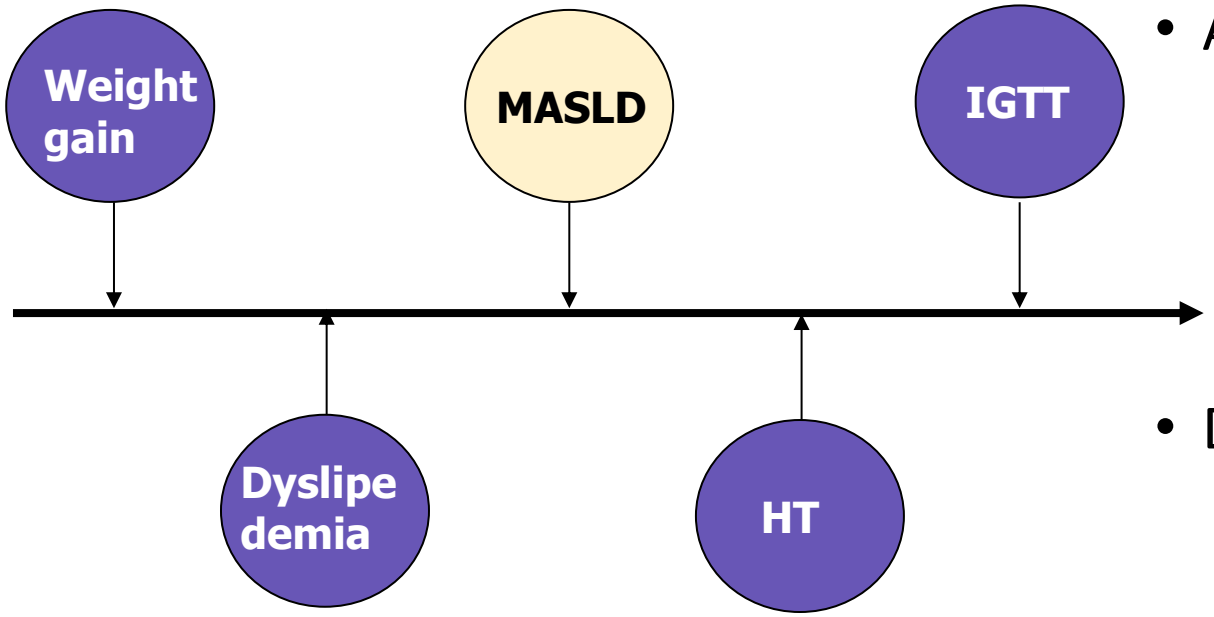
Conflict of interest

- All consultancy on behalf of the University of Nottingham or Nottingham University Hospitals NHS Trust

What and When?

- Interpreting liver function tests
- Identifying different types of fatty liver disease
- Identifying and referring for fibrosis

Chronology of the cluster of Multiple long-term conditions

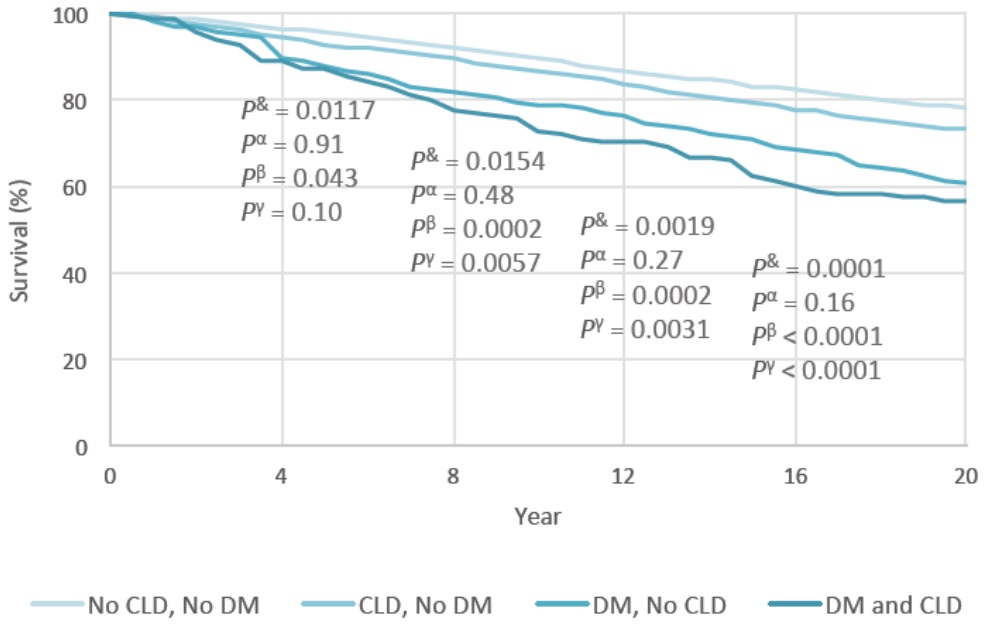


- 1,773 NAFLD (median 4 yrs FU)
- All-cause mortality:
  - 0.57 compared to 0.4 (expected) deaths/ 100 person yrs.
  - 0.32 (F0-2), 0.8 (F3) to 1.76 (F4)/100 person yrs.
- Decrease in eGFR of >40%
  - 0.97 (F0-2), 1.3 (F3) to 2.98 (F4)/100 person yrs.
- Incident diabetes
  - 4.45 (F0-2), 6.2 (F3) to 7.53 (F4)/100 person yrs.

Suzuki A *et al, Hepatology* 2005;41(1):64-71
Sanyal AJ *et al, N Engl J Med* 2021; ;385(17):1559-1569.

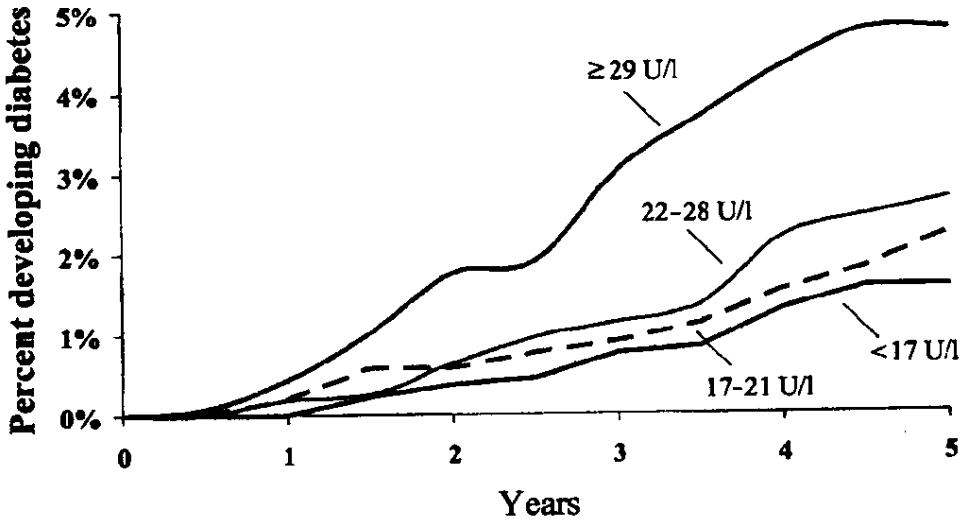
Chronic liver disease and Diabetes

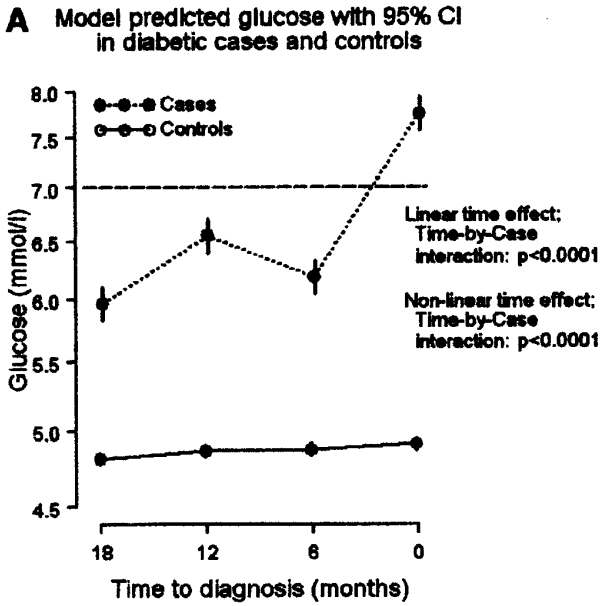
- Increased incidence of diabetes and cardiovascular events
- Insulin resistance is associated with progression of fibrosis
- Type 2 diabetes acts synergistically to increase all-cause mortality.

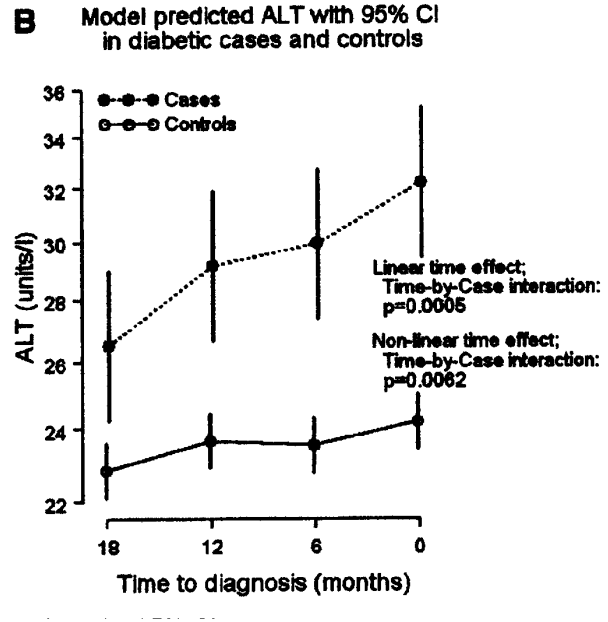


Ekstedt *et al. Hepatology* 2006
Targher *et al. J hepatol* 2016
Stepanova *et al. Clin Diabetes* 2017

Liver test before T2DM



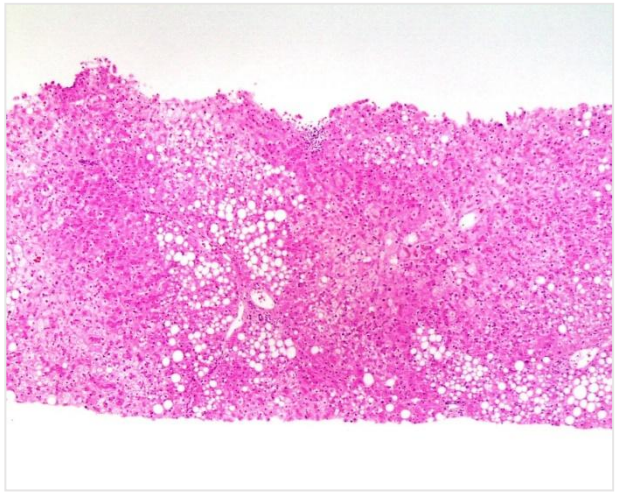




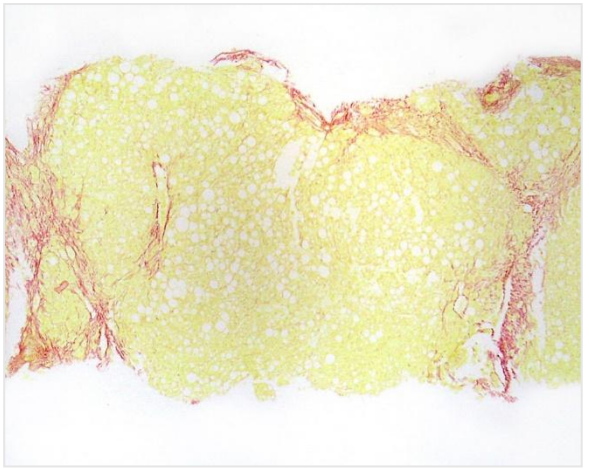
Sattar *et al.*, *Diabetes* 2005; Diabetes 2007

Spot the difference

- 38 yr man, non-cardiac chest pain
- Bil 21, ALT, 161, ALP 163
- Negative serology
- US: enlarged liver with increased echogenecity



- 67 yr lady, tired
- On bendrofluazide
- No signs of CLD
- ALT 65, GGT 85
- Negative serolgy
- US: increased echogenecity



Spot no difference

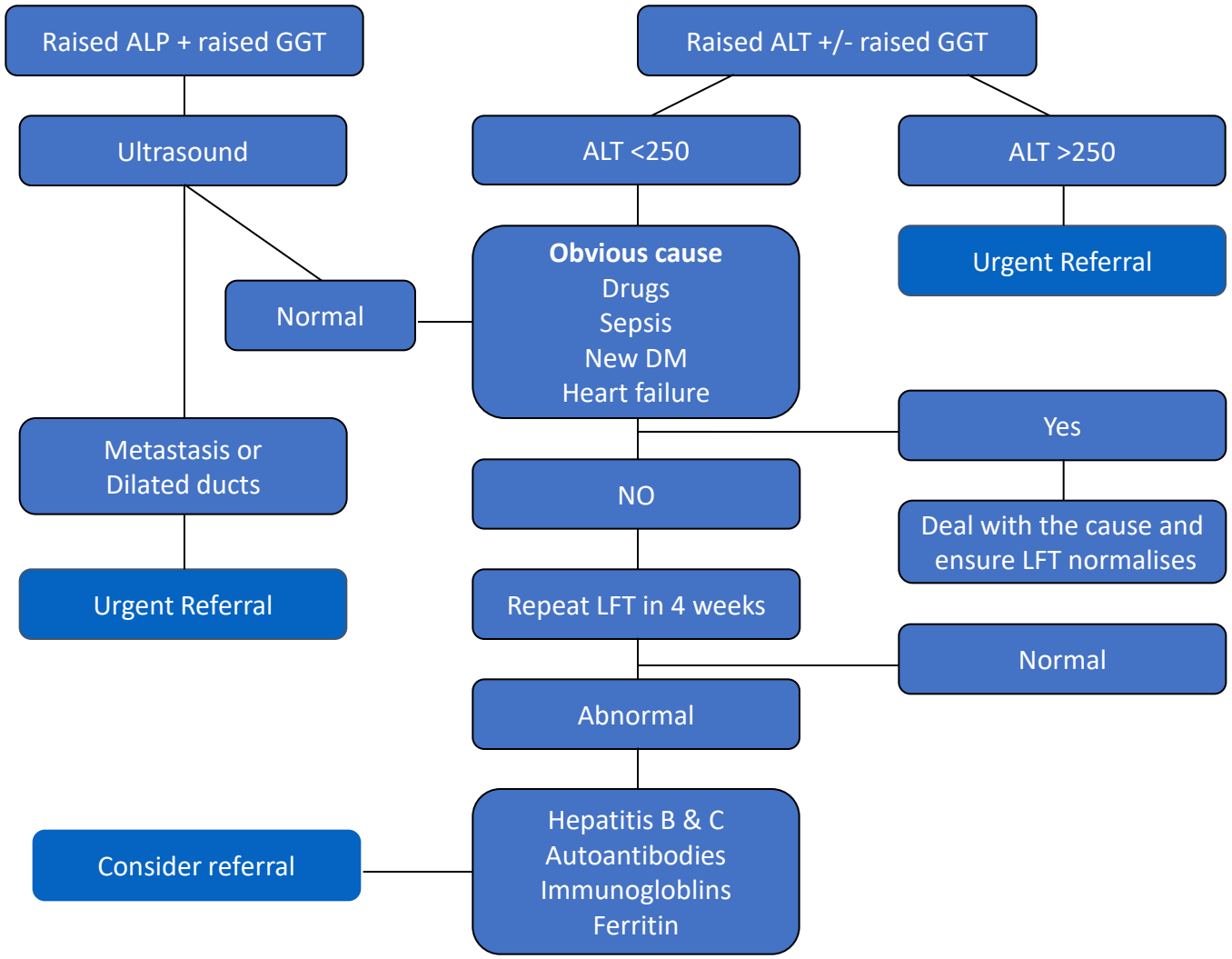
- 386 patients with non-alcoholic fatty liver disease (NAFLD)
- 50 with abnormal LFT and 50 normal LFT
- No differences in demography or clinical parameters
- 24%- advanced fibrosis in both groups
- 12%- cirrhosis in both groups
- **Apparent normality doesn’t ensure safety**

Mofrad et al., *Hepatology* 2003

Appearances are deceptive

- 115 200 men, 67 932 women aged 35-59 yrs
- Health examination 1990-92
- Those with any known disease or died before 1993 excluded
- Mortality from liver disease 1993-2000 identified
- Compared with ALT <20 IU/l, RR of mortality- 2.9 (ALT 20-29) and 9.5 (ALT 30-39 IU)
- **All are normal, but some are more normal**

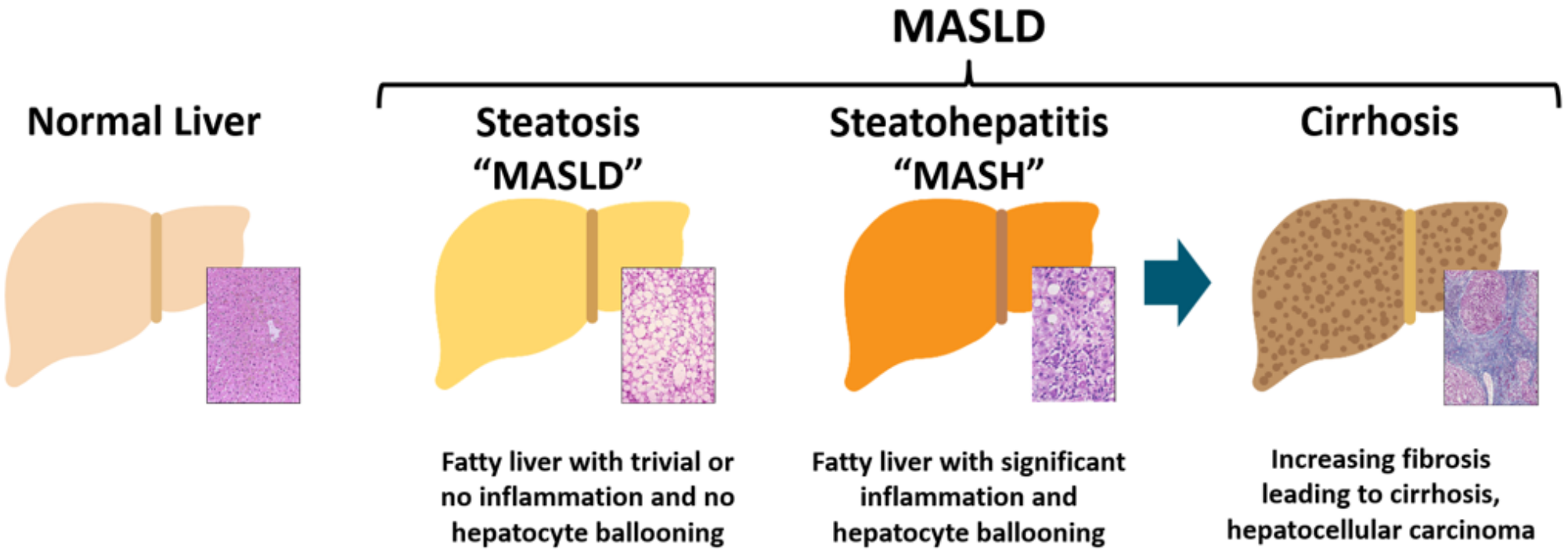
Interpreting Liver Enzymes elevation



Pattern of liver injury

- 60 male, ALT=159 , ALP=431
- ALT ratio= patient's/upper limit of normal
- ALP ratio= patient's/upper limit of normal
- ALT ratio/ALP ratio
  - ≥5 = hepatocellular
  - ≤2 = cholestatic
  - 1.9-4.9 = mixed

MASLD Natural History



*Based on analysis of NHANES data estimating 1.74% prevalence of MASH with advanced fibrosis.[2]

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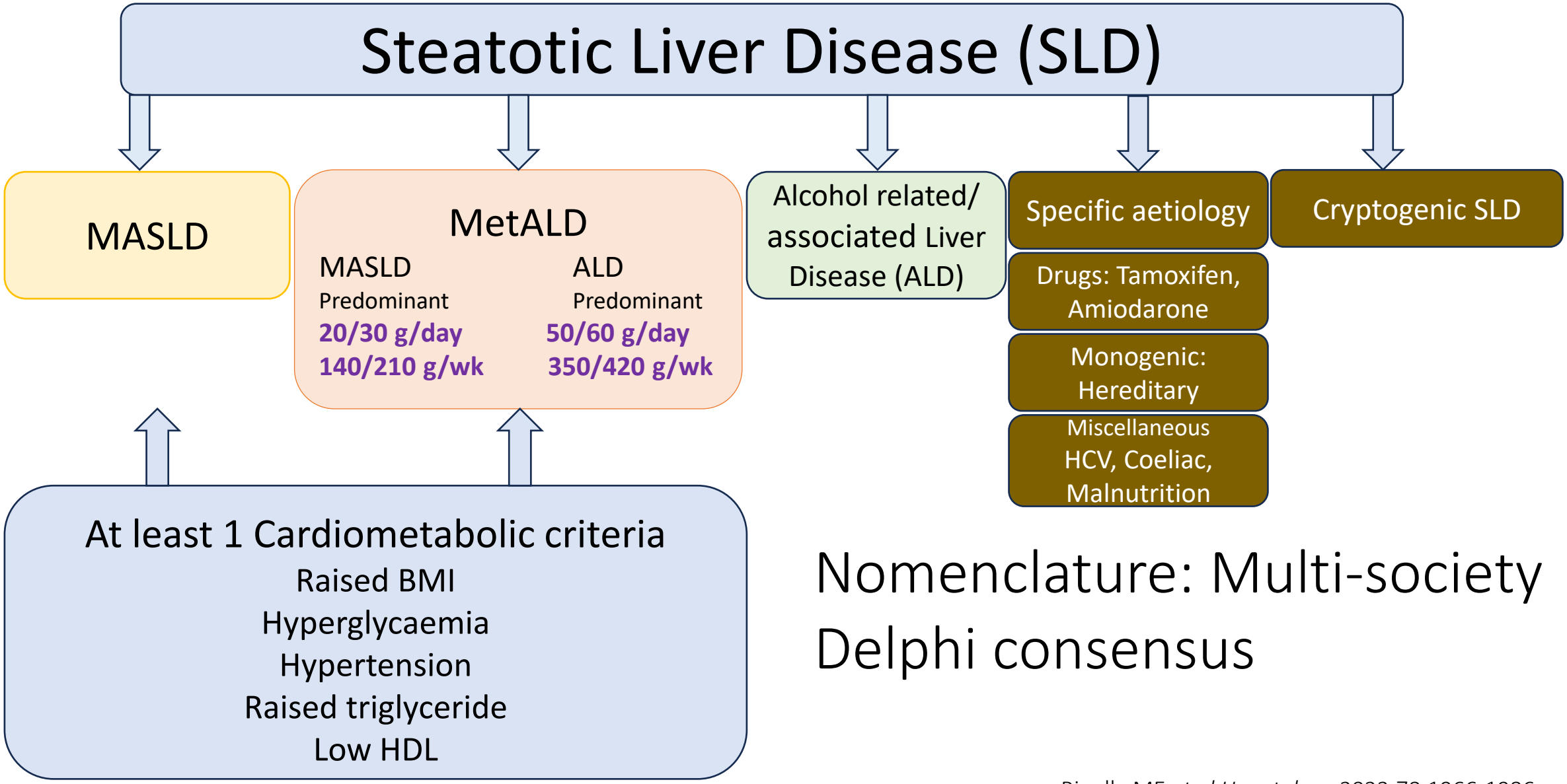
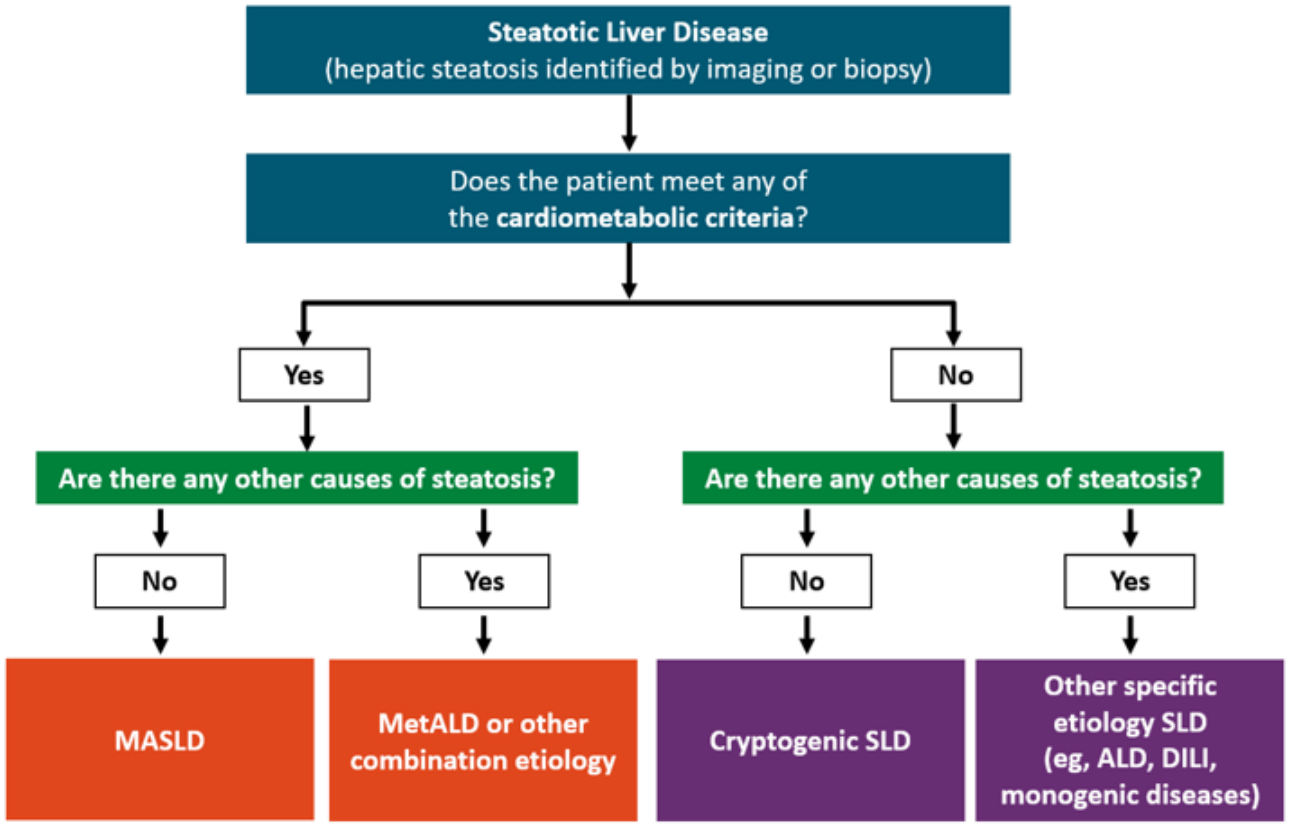
Younossi Z et al.Hepatology. 2019 Jun;69(6):2672-2682
Kabbany MN et al Am J Gastroenterol. 2017 Apr;112(4):581-587



Nomenclature: Multi-society Delphi consensus

Rinella ME *et al Hepatology* 2023;78:1966-1986
Grove JI *et al. JHEP Rep* 2023;5(8):100764
Carter A *et al. J Hepatol* 2019;70:142-150

Metabolic Dysfunction Associated Steatotic Liver Disease



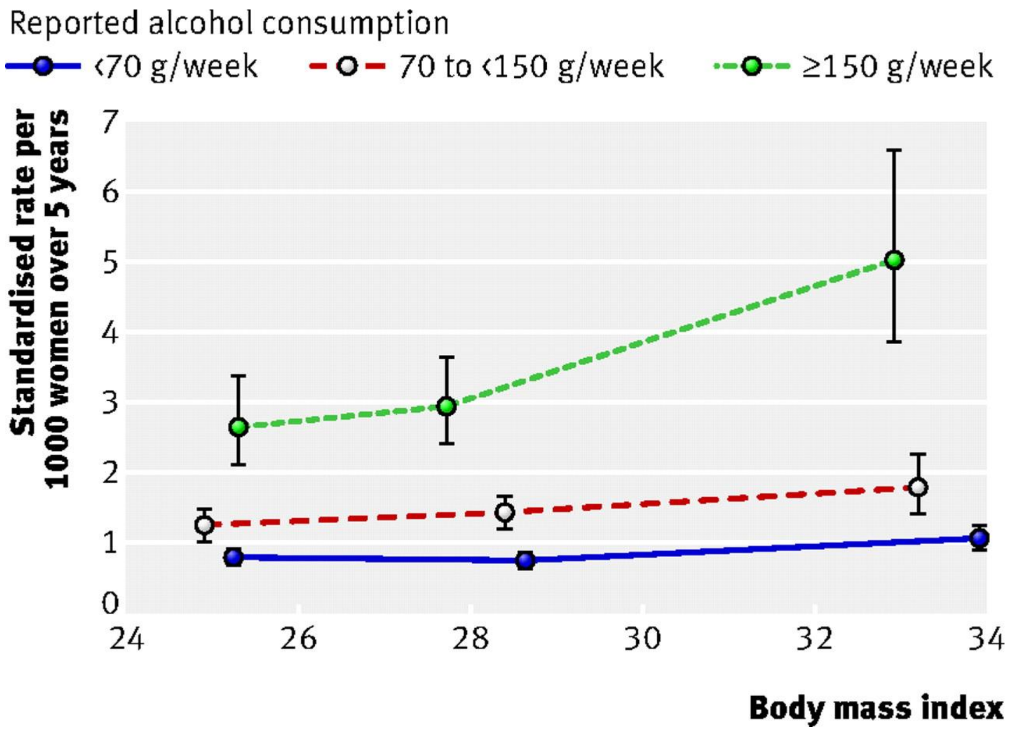
Cardiometabolic Criteria

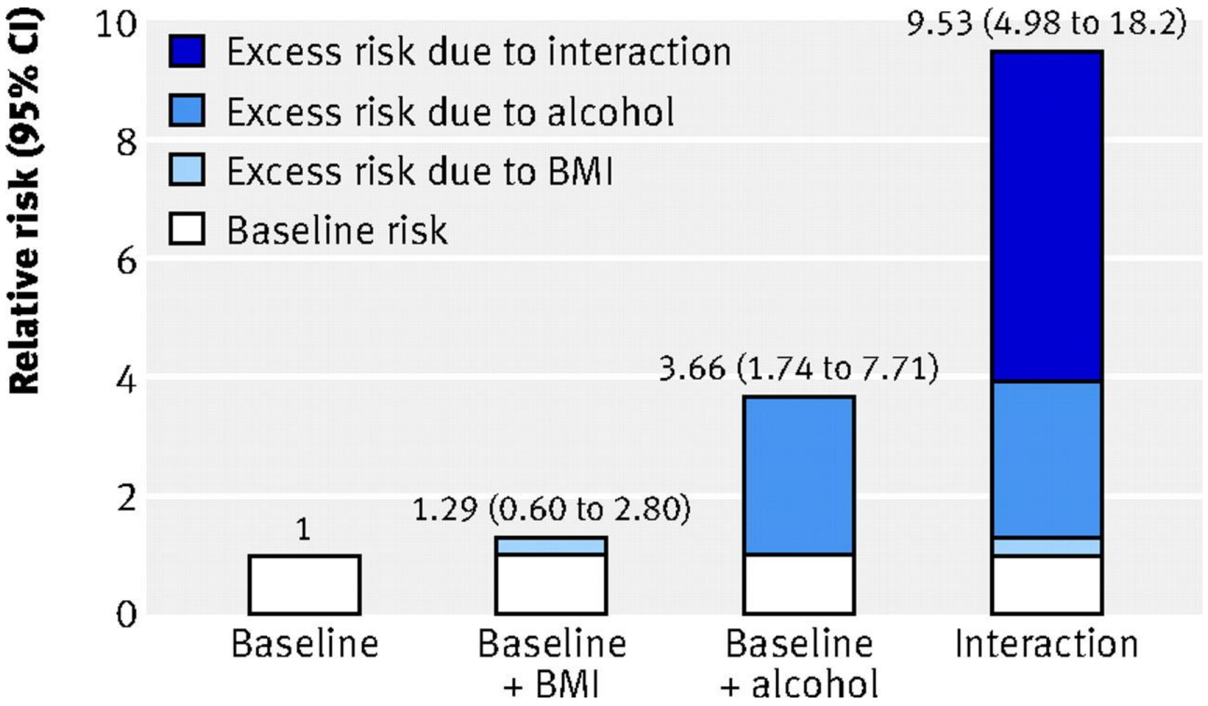
At least 1 of 5:

- BMI ≥25 kg/m^2 (23 Asia) **OR** WC >94 cm (M) and 80 cm (F) **OR** ethnicity-adjusted equivalent
- Fasting serum glucose ≥5.6 mmol/L (100 mg/dL) **OR** 2-hr postload glucose levels ≥7.8 mmol/L (≥140 mg/dL) **OR** A1C ≥5.7% (39 mmol/L) **OR** T2D **OR** treatment for T2D
- Blood pressure ≥130/85 mm Hg **OR** specific antihypertensive drug treatment
- Plasma triglycerides ≥1.70 mmol/L (150 mg/dL) **OR** lipid-lowering treatment
- Plasma HDL cholesterol ≤1.0 mmol/L (40 mg/dL) (M) and ≤1.9 mmol/L (50 mg/dL) (F) **OR** lipid-lowering treatment

Rinella ME *et al Hepatology* 2023;78:1966-1986
Grove JI *et al. JHEP Rep* 2023;5(8):100764
Carter A *et al. J Hepatol* 2019;70:142-150

Met-ALD: Interaction





Liver cirrhosis per 1000 women over 5 years by BMI and alcohol consumption. (n=1,230,662 women; mean age 56 yrs X 6.2 yrs FU; 1811 hospitalisation/ death.

Contributions of BMI and alcohol to liver disease mortality (adjusted for all risk factors). RR increased in obese with 1-15 units and >15 units in overweight (n= 9559 men; 1965-2007)

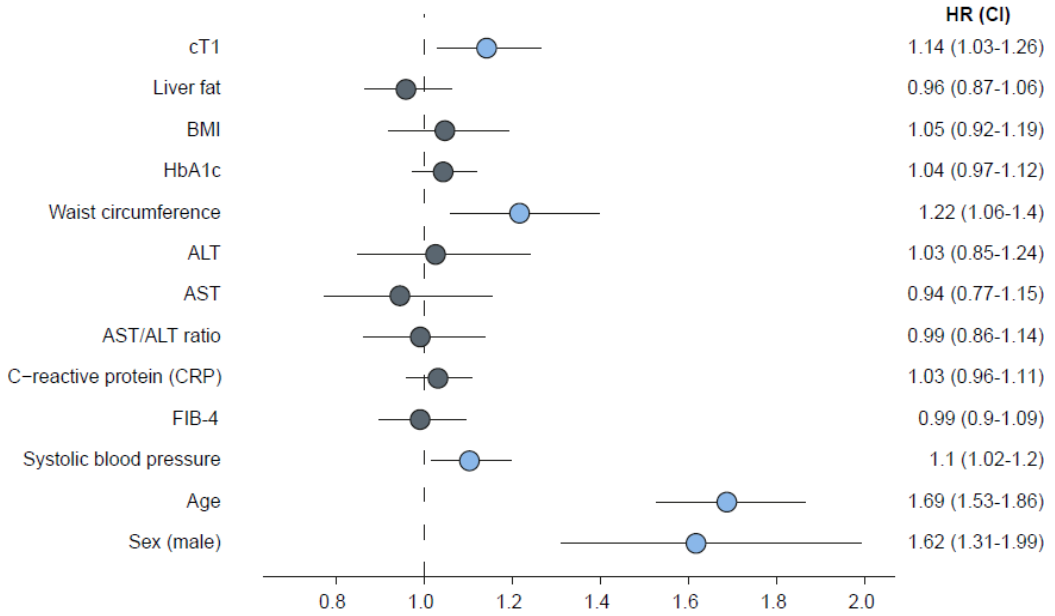
Liu B, *et al. BMJ* 2010;340:c912
Hart CL *et al. BMJ.* 2010;340:c1240.

Liver fibrosis in UK Biobank cohort (n=33,616)

Risk of any major cardiovascular event in the whole cohort

Outcome	HR	*p* value
cT1 (ms)		
CVD hospitalisation	1.27 (1.18–1.37)	<0.001
Atrial fibrillation	1.3 (1.12–1.51)	<0.001
Heart failure	1.3 (1.08–1.58)	0.004
All-cause mortality	1.19 (1.02–1.38)	0.026
Any CVD event	1.14 (1.03–1.26)	0.008

Risk of any major cardiovascular event in the whole cohort



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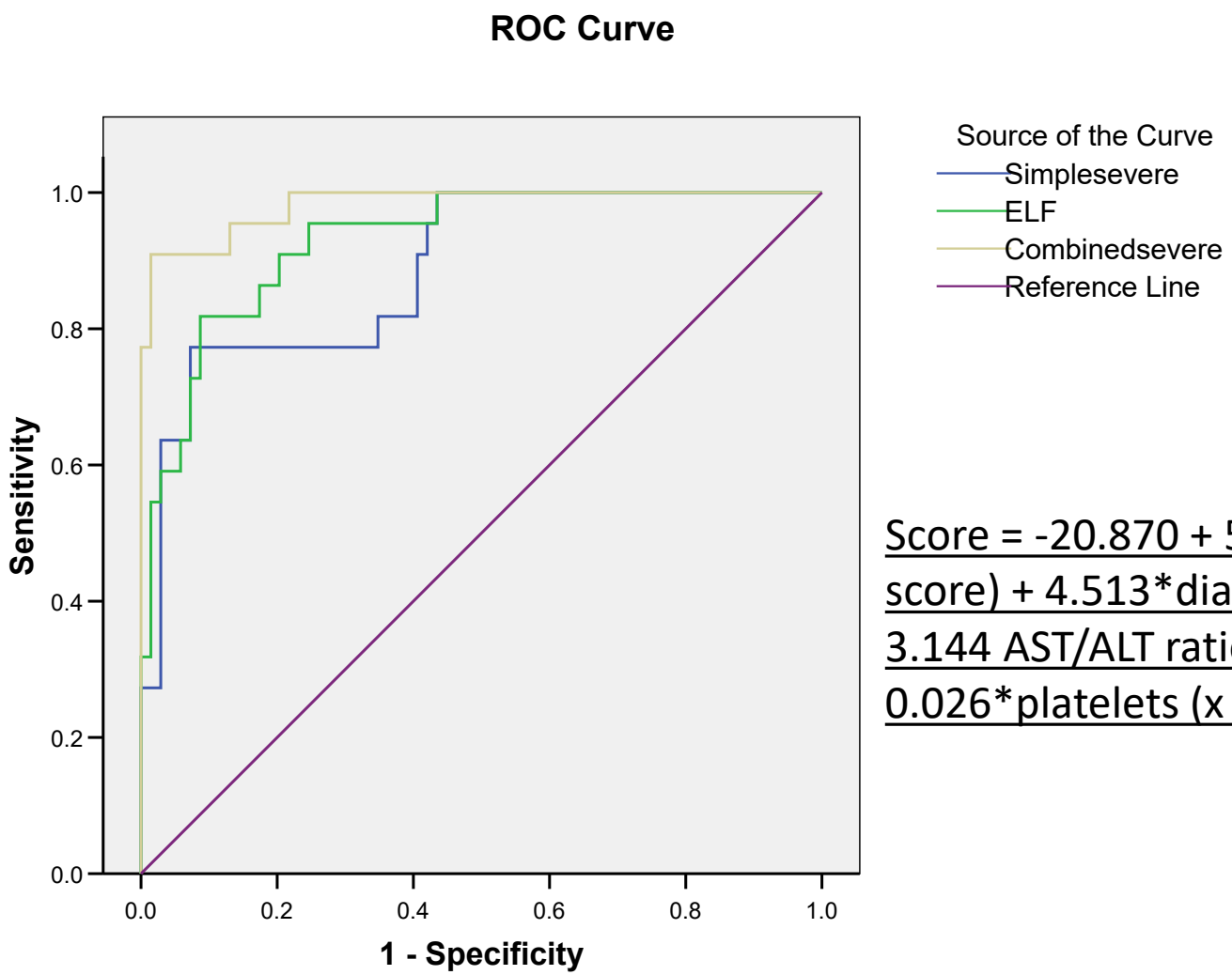
Roca-Fernandez A *et al. J Hepatol* 2023;79:1085-1095

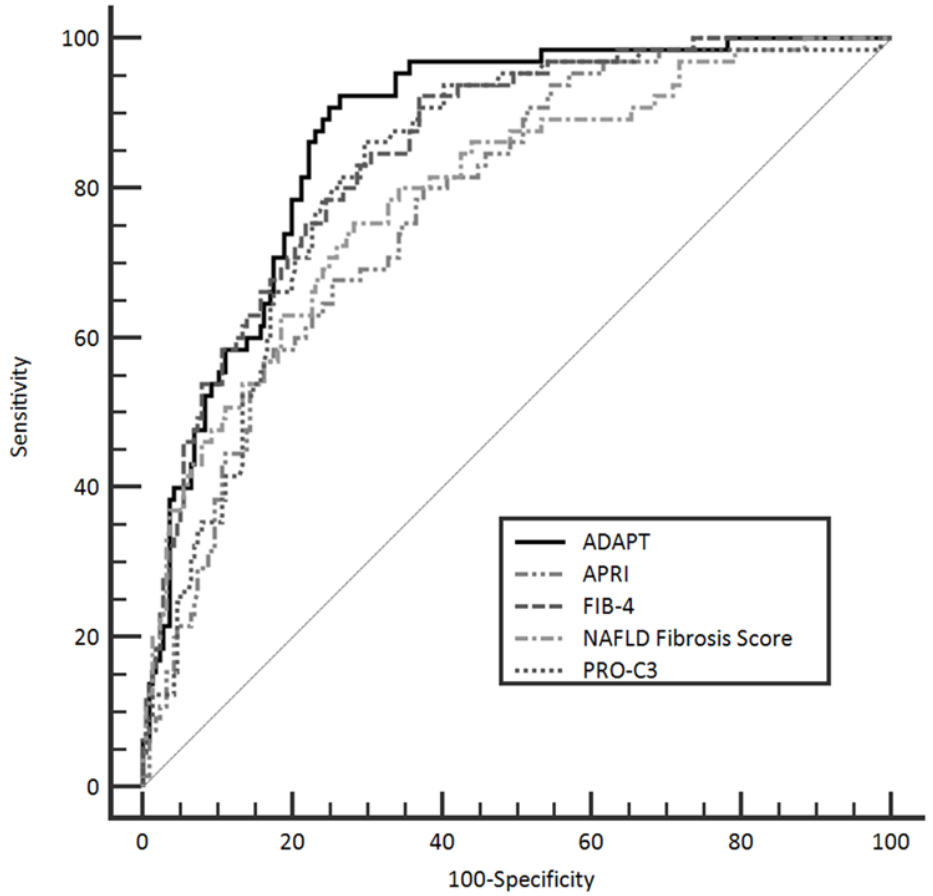
Enhanced Liver Fibrosis (ELF) Panel



Score = -20.870 + 5.506*ELF (discriminant score) + 4.513*diabetes/IFG (yes=1,no=0) – 3.144 AST/ALT ratio – 0.058*BMI (kg/m2) – 0.026*platelets (x 10^9/l) + 0.639*alb (g/l)

Guha *et al. Hepatology* 2008

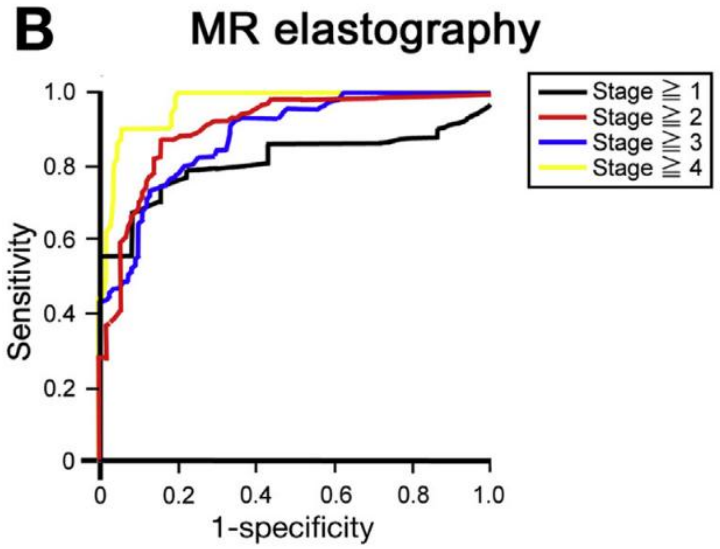
ADAPT: Age Diabetes ProC3 PlaTlet

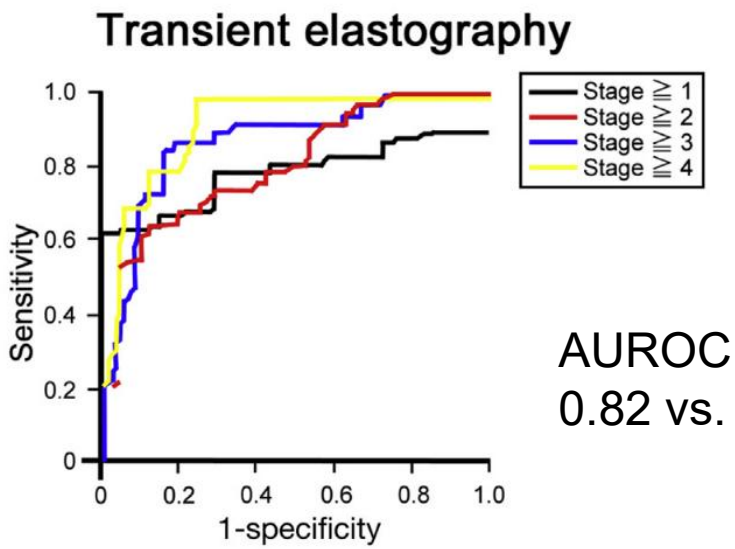


	Validation Cohort			
Non-invasive test	**AUROC**	**Adj AUROC**	**SD**	**95% CI**
APRI	0.78	0.80	0.03	0.73 to 0.83
FIB-4	0.85	0.87	0.02	0.80 to 0.89
NAFLD Fibrosis Score	0.79	0.81	0.03	0.74 to 0.84
PRO-C3	0.83	0.84	0.03	0.78 to 0.87
ADAPT	**0.87**	**0.89**	**0.02**	**0.83 to 0.91**

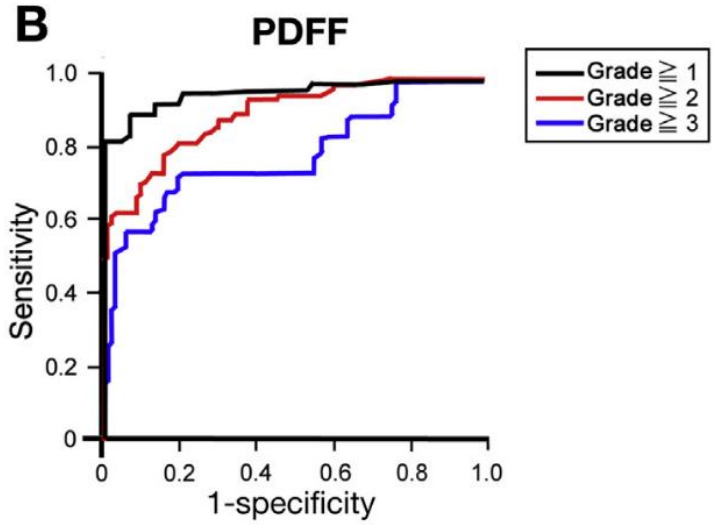
Daniels. *Hepatology* 2019

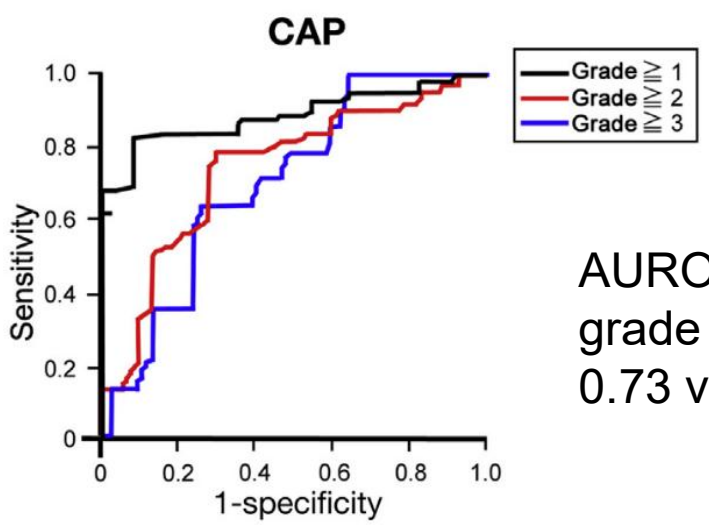
TE vs MRE





AUROC F2:
0.82 vs. 0.91

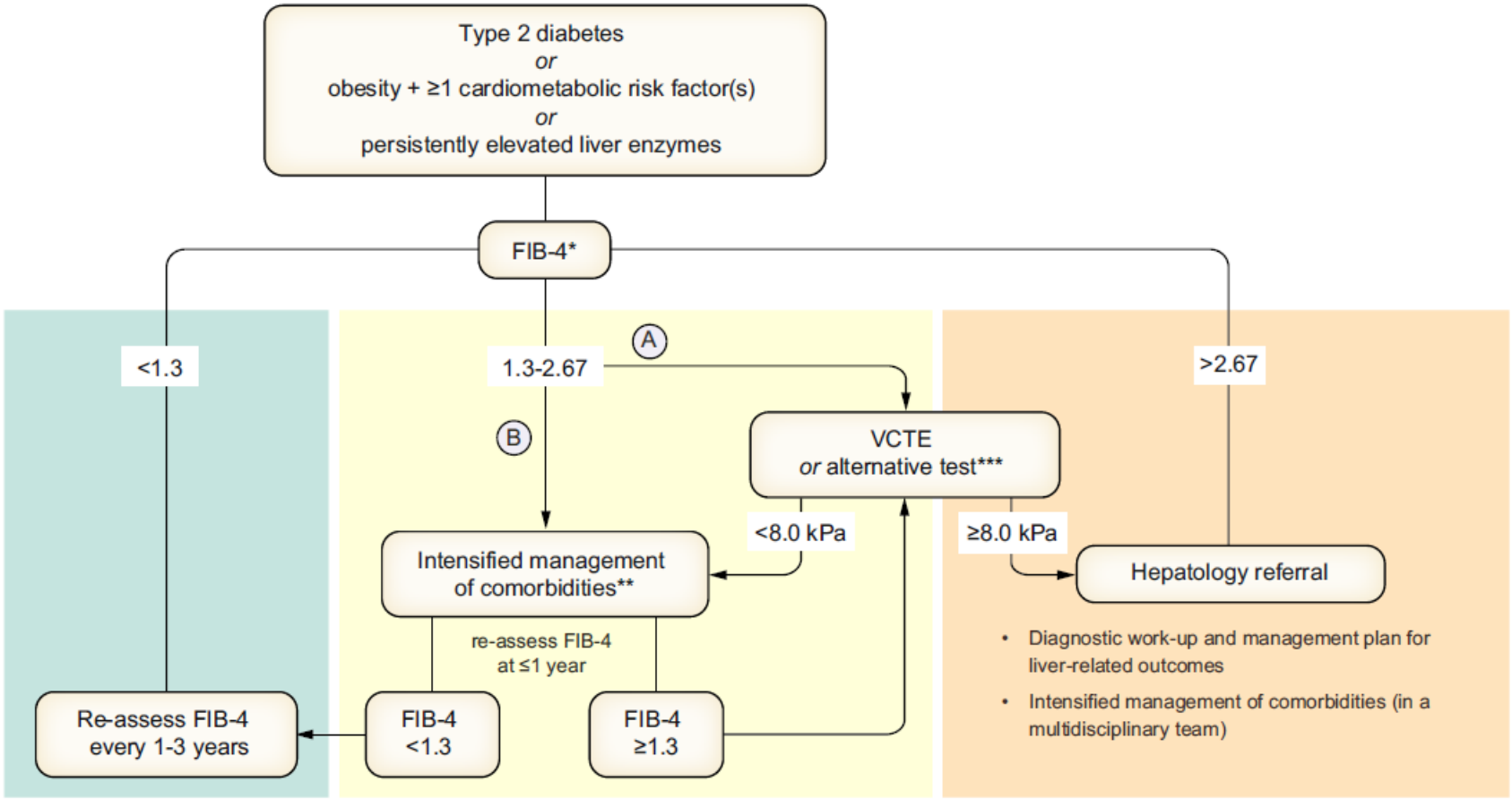




AUROC
grade 2:
0.73 vs. 0.90

Imajo. *Gastroenterology* 2016

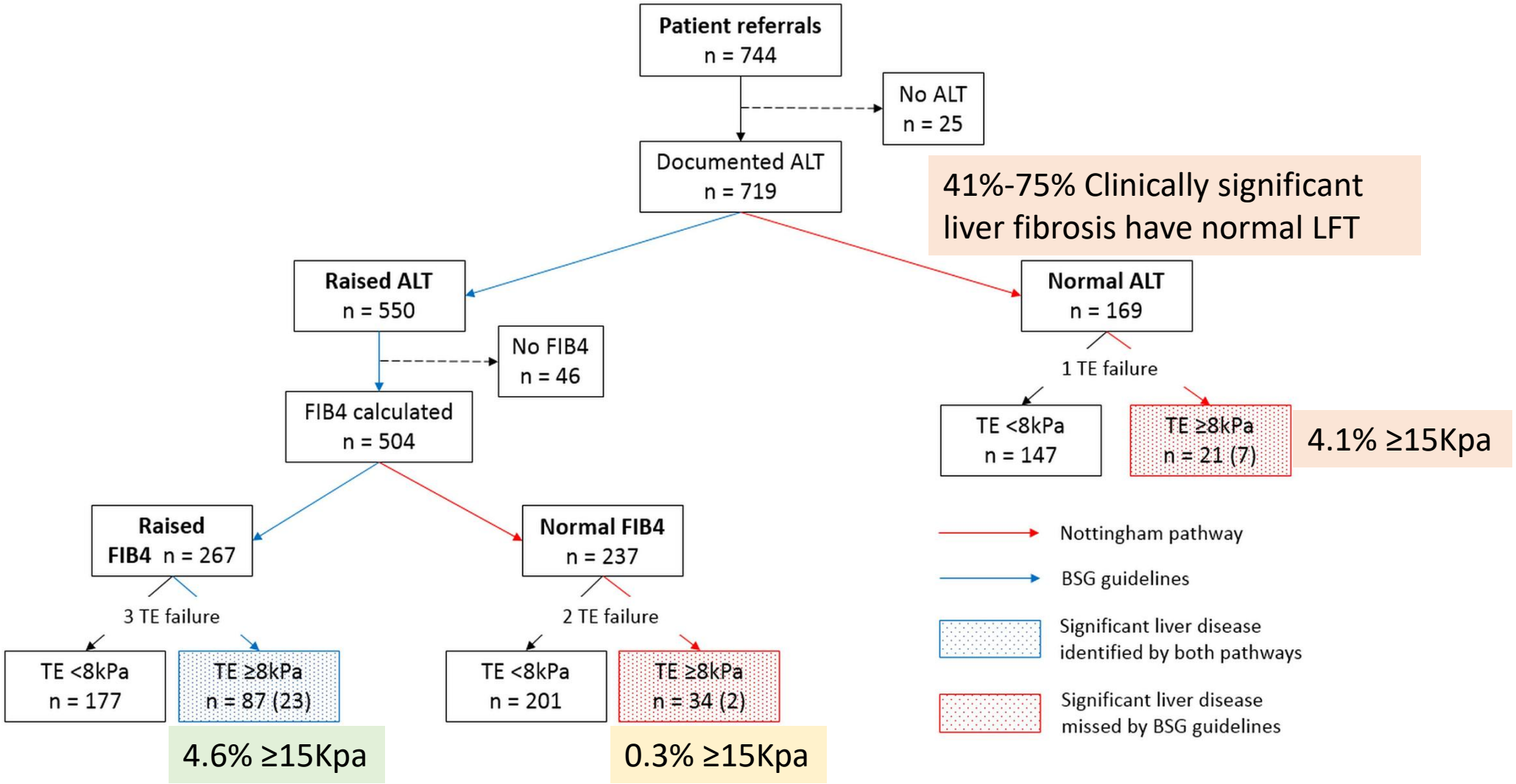
Non-invasive assessment



* FIB-4 thresholds valid for age ≤65 years (for age >65 years: lower FIB-4 cut-off is 2.0)
** *e.g.* lifestyle intervention, treatment of comorbidities (*e.g.* GLP1RA), bariatric procedures
*** *e.g.* MRE, SWE, ELF, with adapted thresholds
Ⓐ and Ⓑ are options, depending on medical history, clinical context and local resources

EASL-EASD-EASO. *J Hepatol* 2024;81:492-542

Non-invasive test fibrosis: When? Why?



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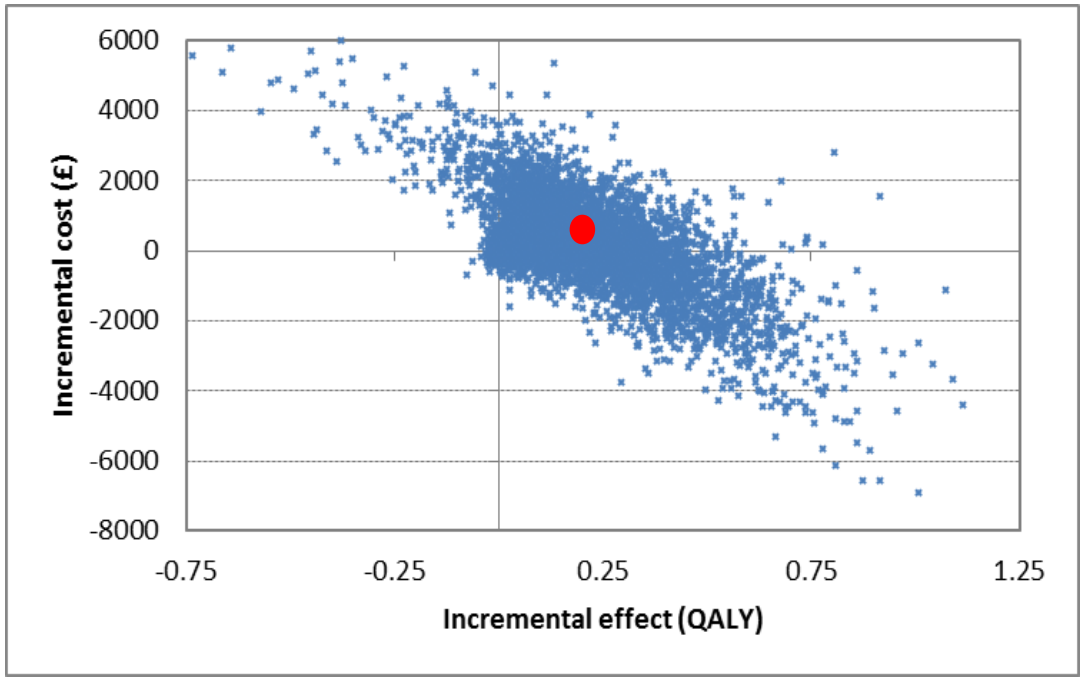
Harris R *et al. Lancet Gastroenterol Hepatol* 2017;2:288-297
Chalmers J *et al. Frontline Gastroenterol.* 2020;11(2):86-92

Incremental Cost effectiveness Ratio (ICER)

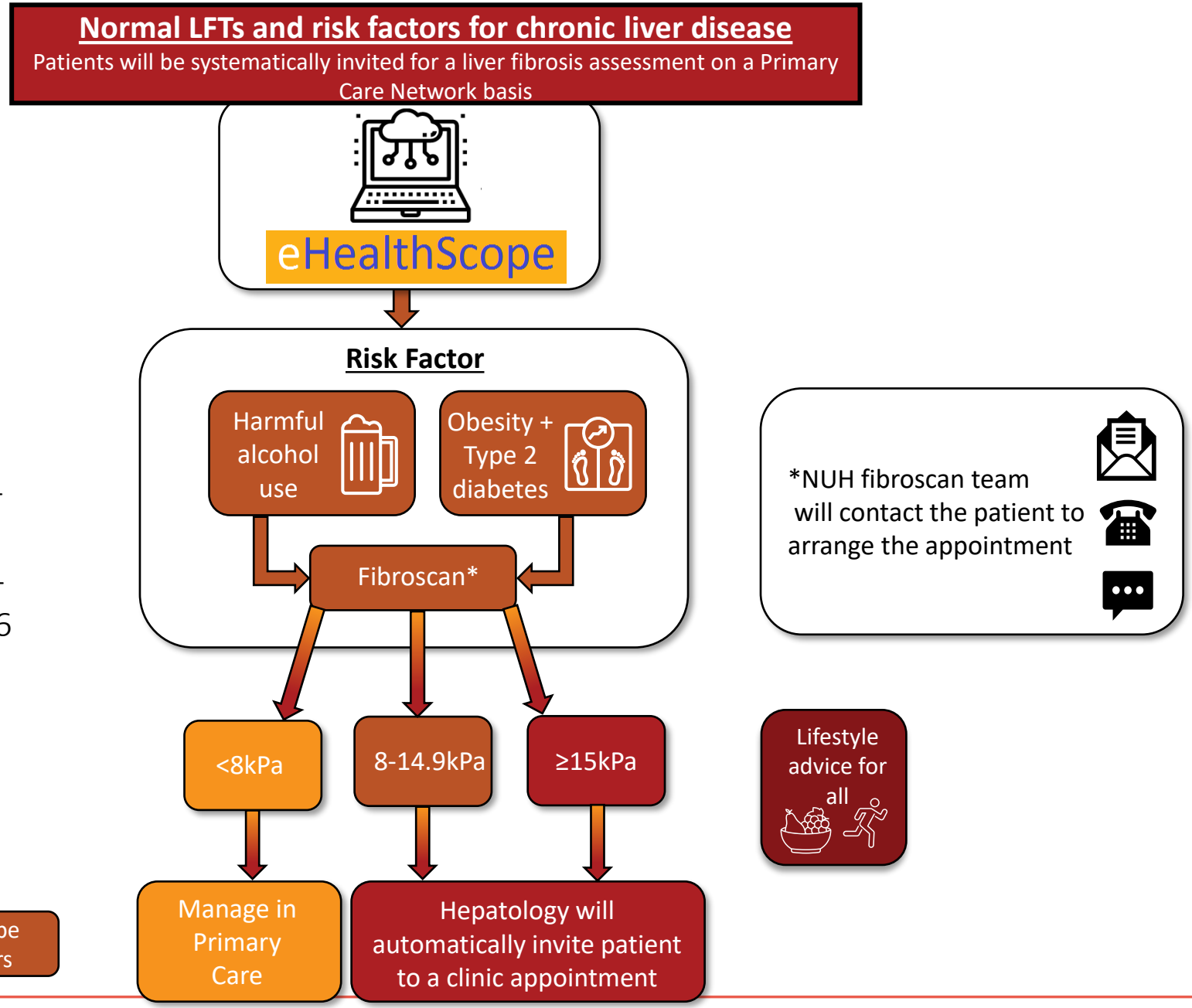
- Scarred Liver, N'ham:
  - Feasibility study of TE to identify F2 fibrosis in primary care.
  - £2,138 per extra year adjusted for quality of life.
  - 85% probability of cost-effectiveness at the UK willingness-to-pay
- Multi-national cohort :
  - 2,500-6,500 euros per extra year adjusted for quality of life.
  - 12% chance of cost saving



Tanajewski L *et al. BMJ Open* 2017;7:e015659.
Serra-Burriel M *et al. J Hepatol* 2019;71:1141-51/

Community liver health check

https://www.england.nhs.uk/long-read/commissioning-integration-delegation-of-specialised-services-to-integrated-care-boards-2025-26

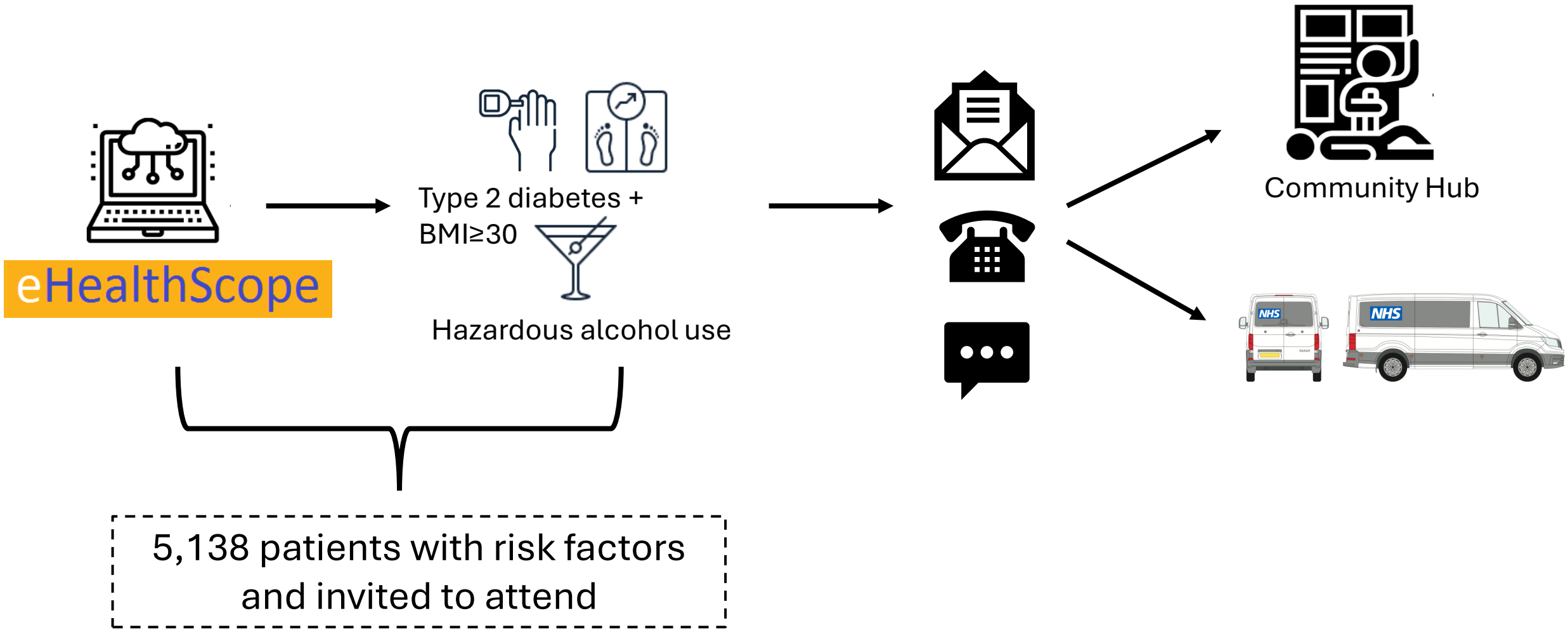


Patients who continue to have risk factors can be referred for an interval fibroscan after 3-5 years

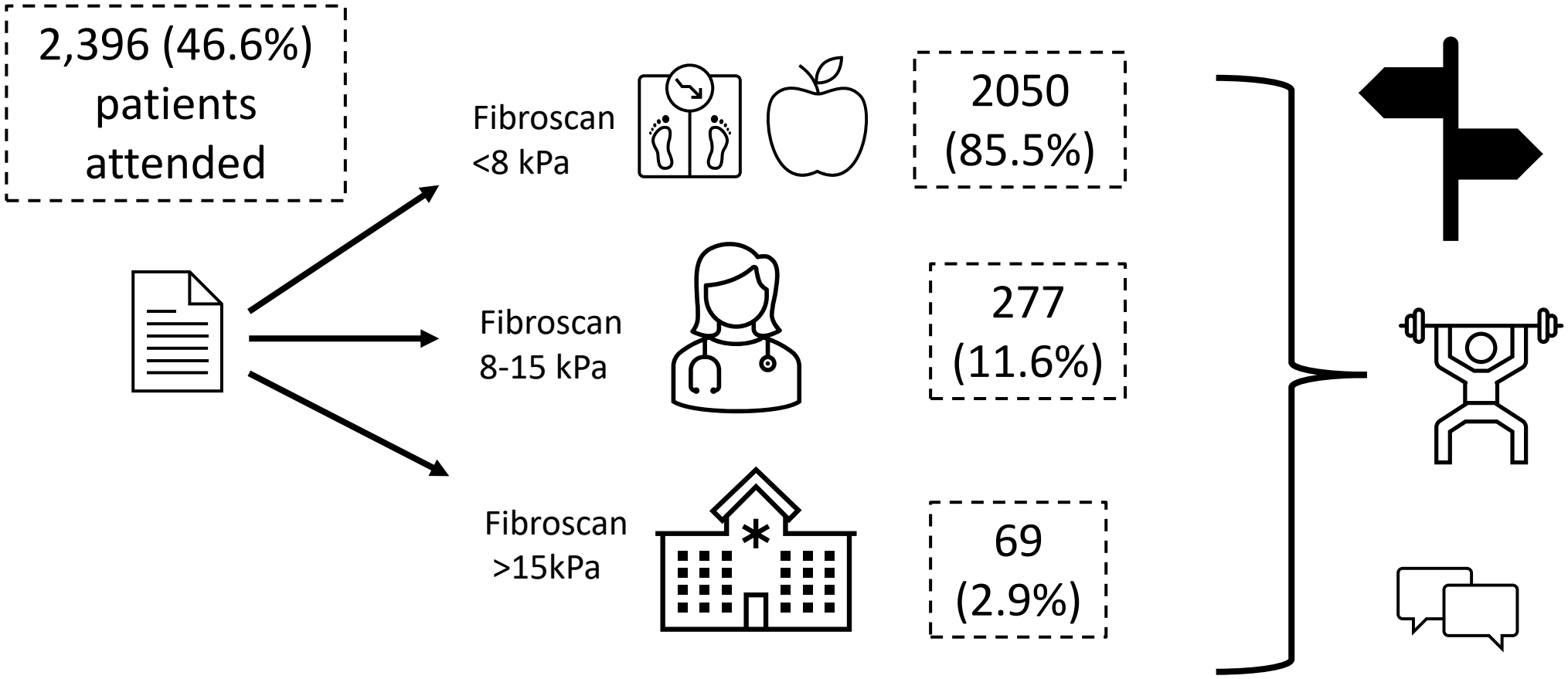
eHealthScope

- A unique and secure online integrated database of:
  - Primary care: Read Codes
  - Secondary care: Admission and discharges from all three hospitals
  - Community
  - Mental Health
  - Social care data: from city and county councils
- Includes all patients in Nottinghamshire
- Data received every night
- eHealthScope Home

Systematic case finding: PCN 6, PCN5, Notts West + Rosewood

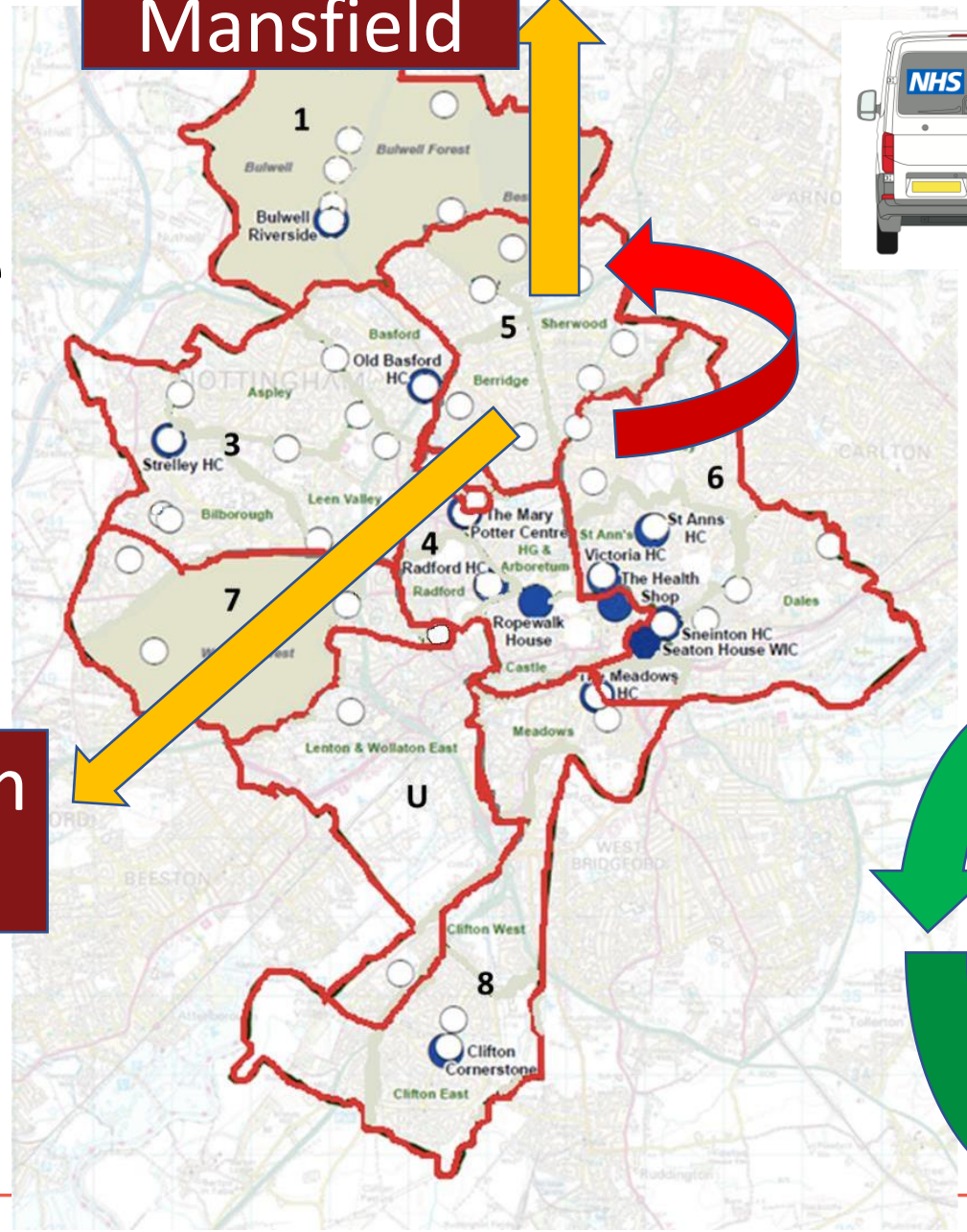


Results: PCN 6, PCN5, Notts West + Rosewood



Systematic case finding across Nottinghamshire

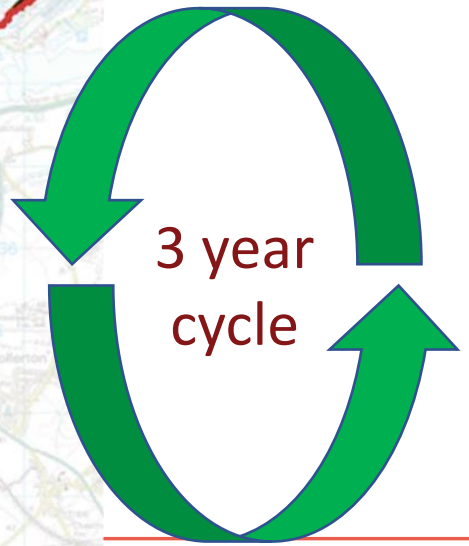
Mansfield



Nottingham West PCN

Alternative sites

- CGL Mansfield/ Hucknall
- Nottingham Recovery network
- Edwin house
- Homeless shelters



Summary

- Metabolic dysfunction associated steatotic liver disease is an archetypal MLTC.
- Laboratory thresholds for ALT are not optimally set to identify progressive MASLD.
- Non-invasive markers of liver fibrosis are important to identify at risk MASLD
- TE a point of care test, can identify and stratify MASLD

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