Metabolic Dysfunction Associated Steatotic Liver Disease 'MASLD'

By Lauren Johansen

Consultant Paediatric Hepatologist

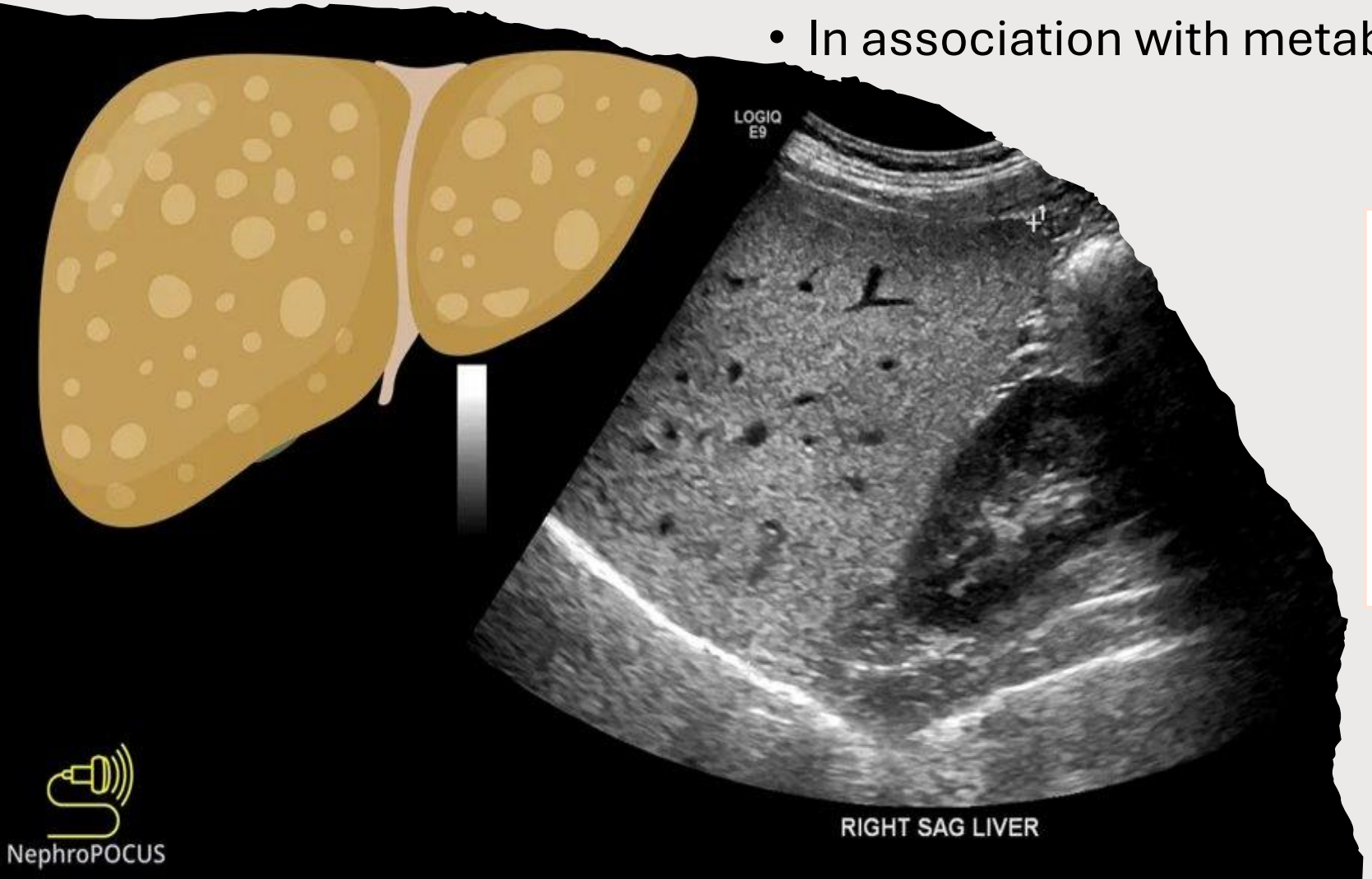
MASLD

Birmingham Women's and Children's NHS Foundation Trust

- Definition
- Prevalence
- Screening criteria
- Investigation and diagnosis
- Management
- The role of the hepatologist
- Future developments

Definition

- Metabolic dysfunction associated steatotic liver disease “MASLD”
  - Chronic condition
  - Accumulation of excess lipids in hepatocytes
  - In association with metabolic dysregulation

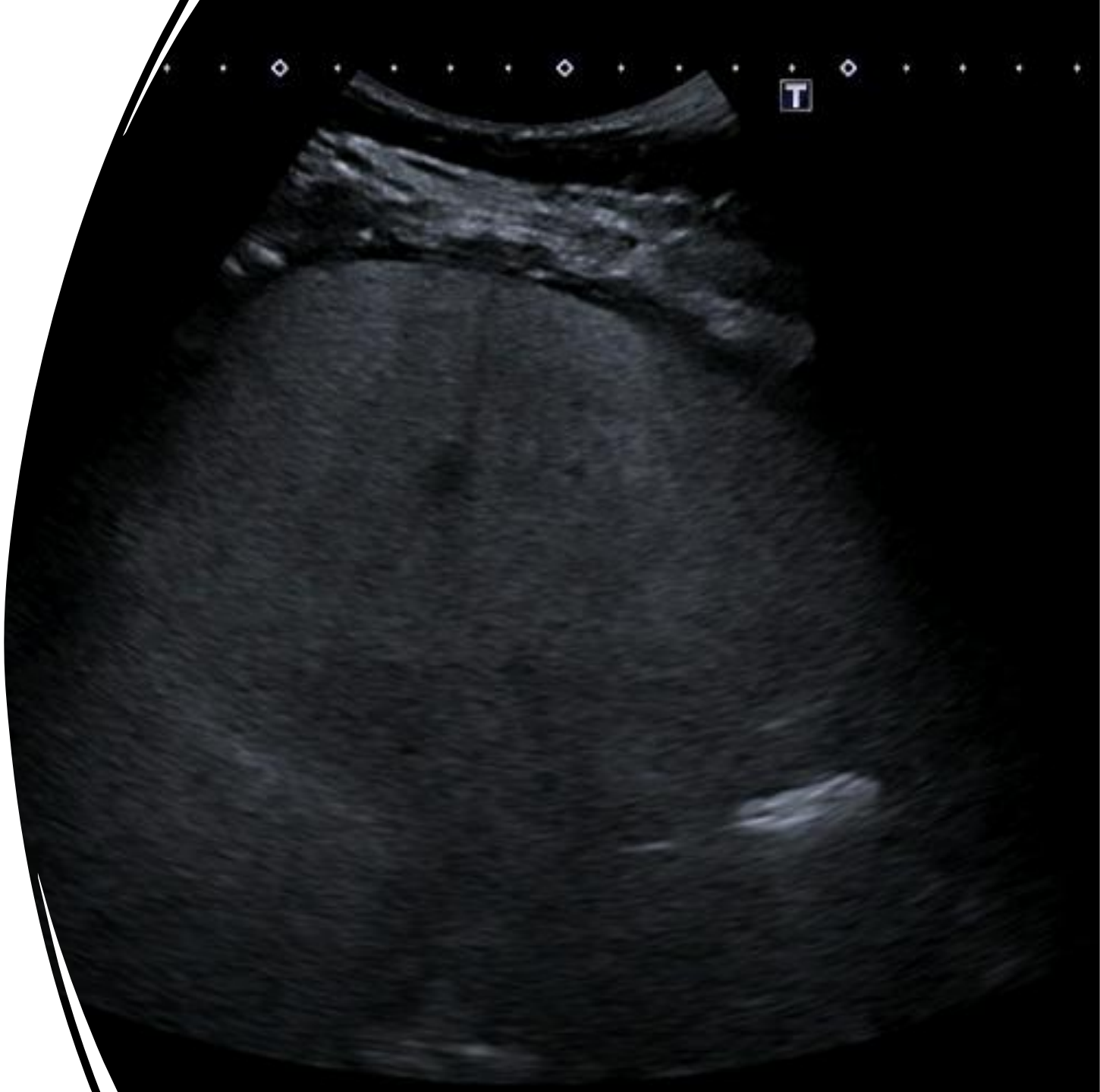


- New Nomenclature
- Positive diagnosis
- Allows for concurrent diagnoses
- “Fatty liver”
  = practical and acceptable

Case 1

- 14-year-old
- Obese BMI > 95th centile
- Non- specific abdominal pain

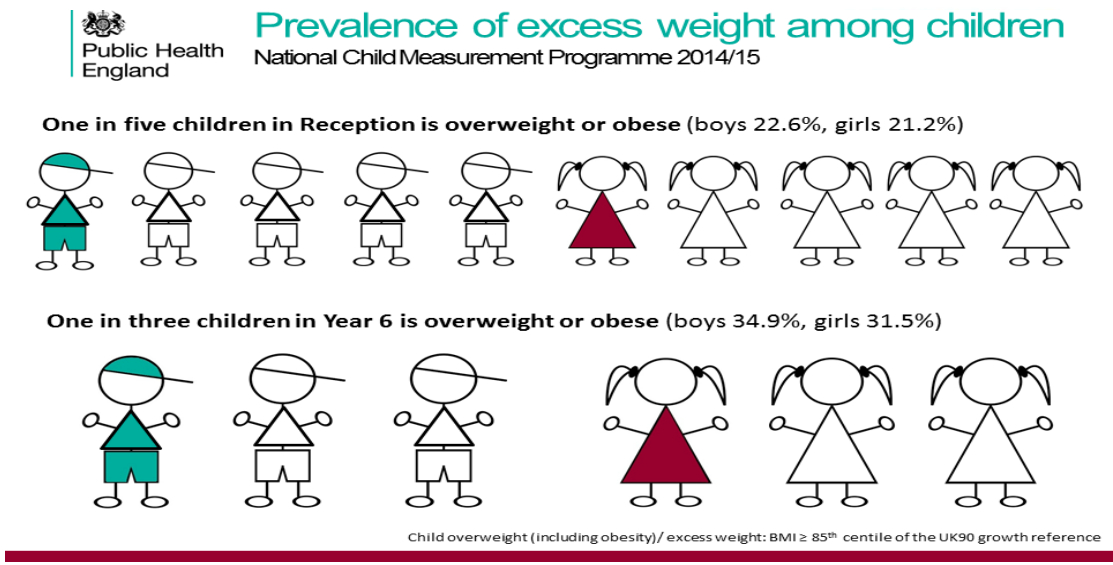
- **Q: Would you screen for MASLD?**
  - **Yes**
  - **No**



Screening for MASLD

- Significant health problem
- Natural history should be understood
- Detectable early phase
- Suitable test
- Effective management option
- Cost effective
- Ethically and practically acceptable

MASLD

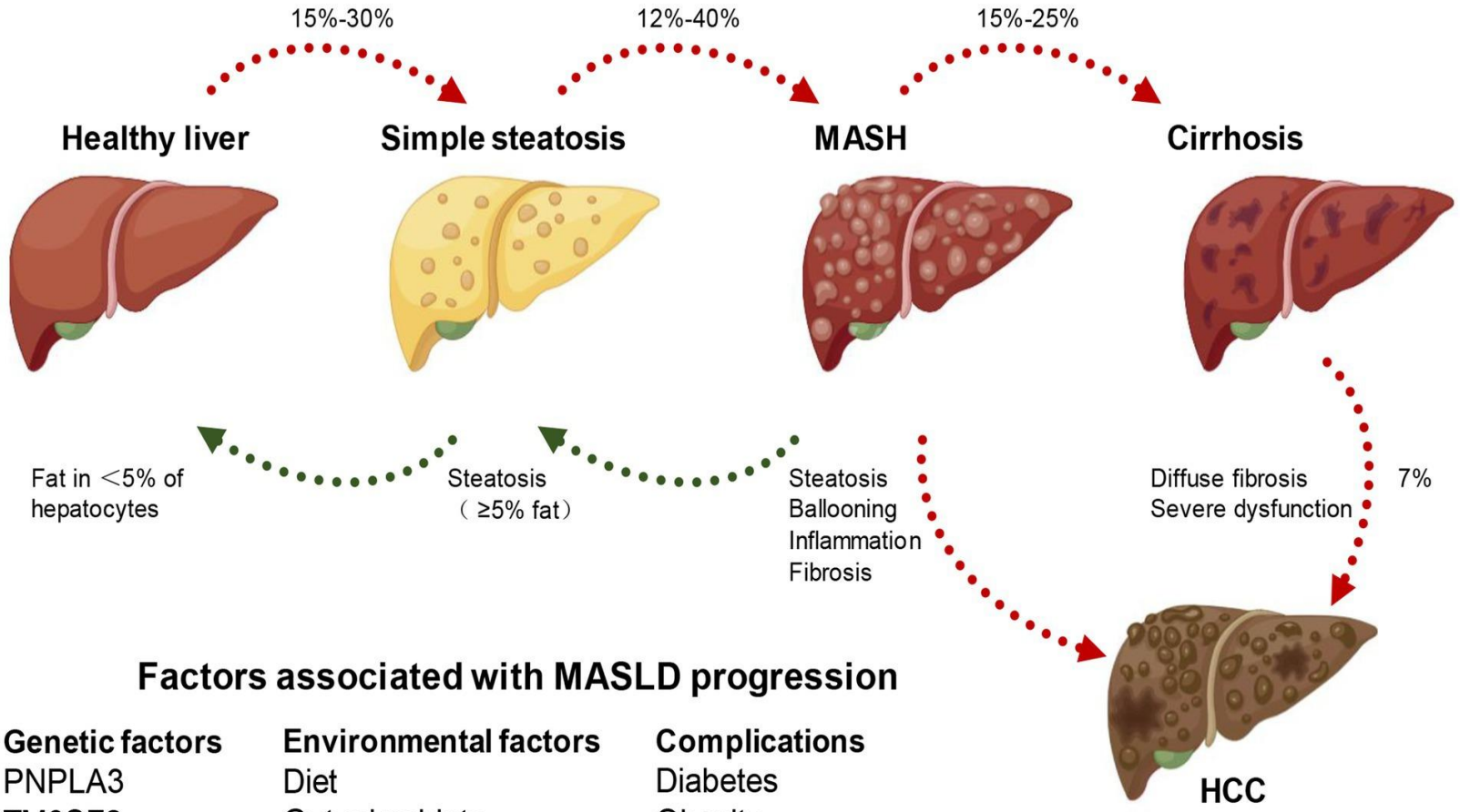


Significant health problem:

- Affects > 5% of all children in Europe
- Most common reason for abnormal liver enzymes in children
- Becoming a leading indication for transplantation in adults

Natural history

Birmingham Women's and Children's NHS Foundation Trust



- Clinical end stage disease doesn't develop in childhood
- Chronic progressive disorder

Factors associated with MASLD progression

Genetic factors	Environmental factors	Complications
PNPLA3	Diet	Diabetes
TM6SF2	Gut microbiota	Obesity
		Cardiovascular disease

Effective management option

Birmingham Women's and Children's NHS Foundation Trust

- No licenced medication for MASLD in children
- Weight loss is associated with histological improvement
- Early life-style modifications + additional monitoring

↓

reduce severity of disease

Who to screen?

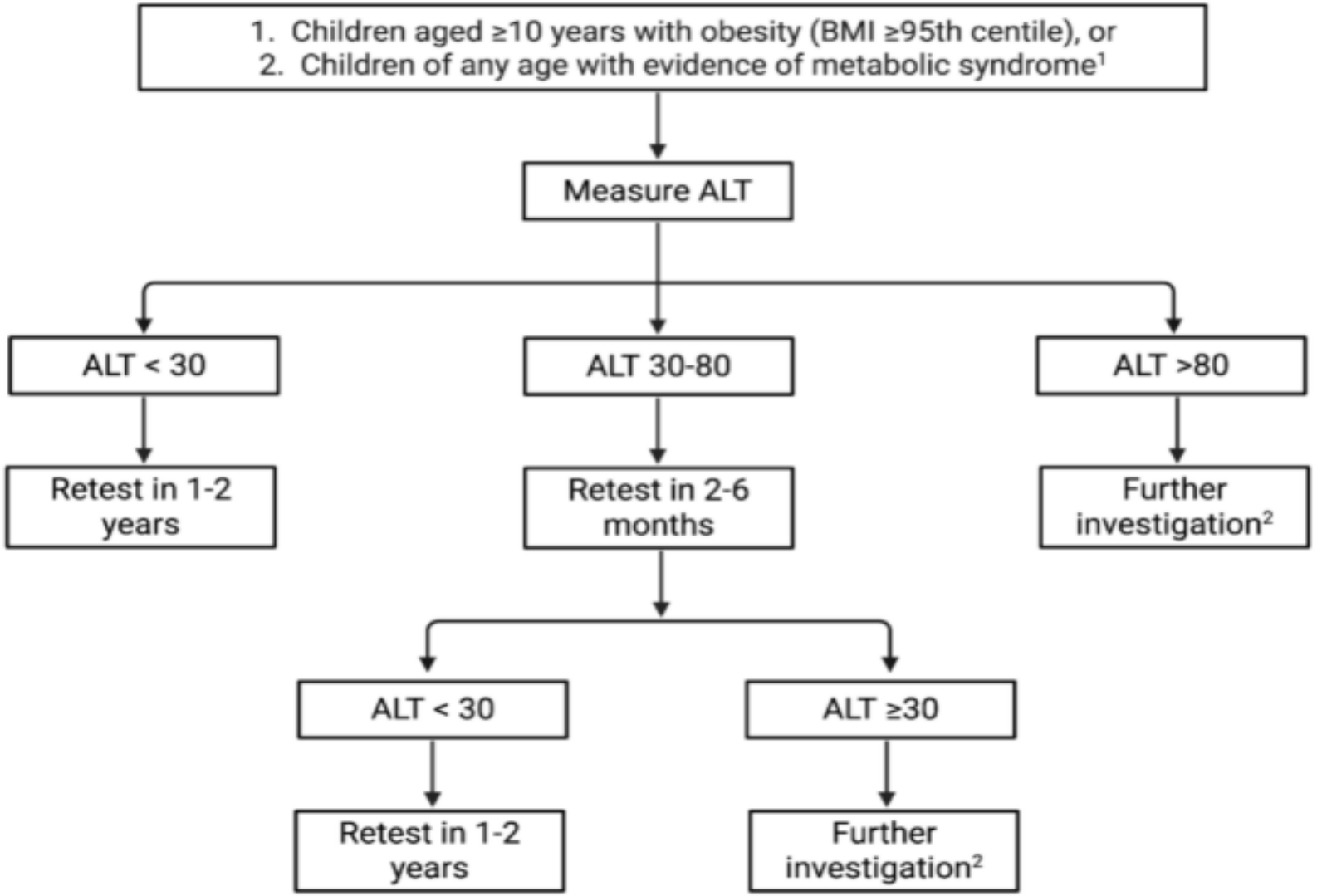
Birmingham Women's and Children's NHS Foundation Trust

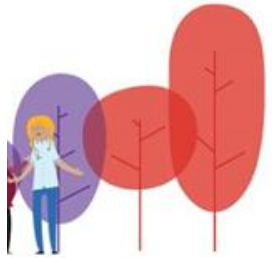
- Most the common risk factor for MASLD = Obesity

- Screen children with:
  - Obesity - BMI > 95th centile
  - Overweight – BMI 85th – 94th centile with additional risk factors
    - Insulin resistance/ acanthosis nigricans / diabetes
    - Dyslipidaemia
    - OSA
    - Central adiposity
    - FH MASLD

- Consider starting to screen from 10 years of age

Screening criteria





Case 1:

Birmingham Women's and Children's NHS Foundation Trust

- Screening performed
  - Detection of raised transaminases → ALT 82 IU/L AST 38 IU/L
  - Asymptomatic

- **Q: What would you do next?**
  - **A) Repeat LFTs in 6 months**
  - **B) Evaluate for other obesity associated co-morbidities**
  - **C) Evaluate for primary liver disease**
  - **D) Refer directly to paediatric hepatology**

Clinical assessment

- Patient identification via screening
- Nonspecific symptoms: Abdominal pain/ Malaise/ Fatigue

O/E:

- Evidence of insulin resistance - acanthosis nigricans
- Obesity- height/ weight/ BMI/ waist circumference
- Measure BP

- Organomegaly
- Peripheral stigmata of chronic liver disease

Portal hypertension/ End stage liver disease
= Alternative diagnosis

History:

Birmingham Women's and Children's NHS Foundation Trust

LIFESTYLE + CO-MORBIDITY HISTORY

- Nutritional history
- Assess for depression, anxiety and psychological stressors
- Sleep history
- Menstrual history

DRUG AND ALCOHOL HISTORY

Hepatotoxic drugs that may cause a fatty liver
Nifedipine
Diltiazem
Amiodarone
Corticosteroids
Oestrogens
Methotrexate
Valproate
L-Aspariginase
Certain antipsychotics

FAMILY HISTORY

- MASLD
- Type 2 diabetes
- Cardiovascular disease
- Dyslipidaemia
- Metabolic disease
- Liver disease

Identify Cardiometabolic criteria

1.Overweight, obesity and/or elevated waist circumference (WC)

•Body mass index (BMI) ≥ 85th percentile for age/sex
•BMI z score ≥ +1
•OR waist circumference (WC) >95th percentile (ethnicity adjusted)

2.Hypertension or treatment for hypertension
•If age <13 years, BP ≥95th percentile OR ≥ 130/80 mmHg (whichever is lower)
•if age ≥13 years, ≥130/80 mmHg
•OR receiving specific antihypertensive treatment

3.Impaired glucose control or diagnosis/treatment for type 2 diabetes mellitus
•Elevated fasting serum glucose ≥ 7mmol/l
•OR 2h glucose tolerance test glucose ≥ 11.1mmol/l
•OR haemoglobin A1c (HbA1c) ≥ 5.7%
•OR diagnosed/treated type 2 diabetes

4.Hypertriglyceridemia
•If <10 years old ≥2.8 mmol/L
•If age ≥10 years, ≥ 3.8 mmol/L
•OR lipid lowering treatment

5.Low high density lipoprotein level (or treatment with lipid lowering agents)
•Plasma/serum high-density lipoprotein (HDL)-cholesterol <1 mmol/L
•OR lipid lowering treatment.

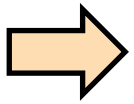
Diagnosis and assessment of MASLD

Birmingham Women's and Children's NHS Foundation Trust

Confirm presence of hepatic steatosis:

USS:
- Bright, hyper-echoic
- Portal hypertension
- Other structural abnormalities

Alternatively hepatic steatosis identifiers:
- MR- PDFF
- Cap score on fibroscan

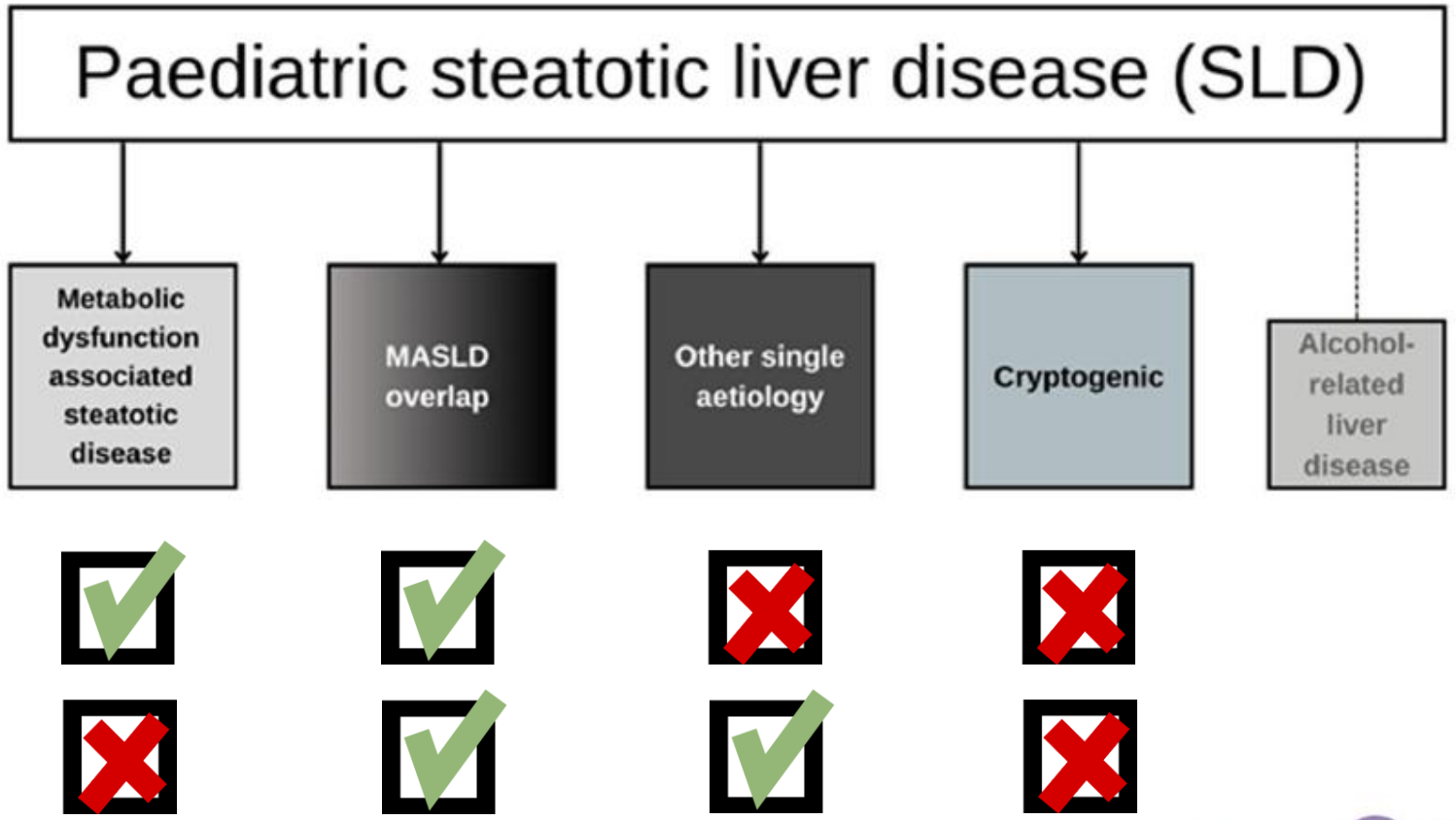


- Split bilirubin, ALT, AST, GGT, ALP
- Albumin
- Prothrombin time
- FBC
- Immunoglobulins
- Autoimmune profile to include ANA, AMA, SMA, LKM, ANCA
- Coeliac screen
- A1AT level and phenotype
- Hepatitis B and C screening
- Copper and Caeruloplasmin testing
- Thyroid function tests
- Fasting lipid profile
- HbA1C
- Fasting glucose
- CK

Paediatric Steatotic Liver Disease

Birmingham Women's and Children's NHS Foundation Trust

Pediatric cardiometabolic criteria
- **BMI** ≥ 85th percentile OR **waist circumference** > 95th percentile
+/-
- **Reduced glucose tolerance** OR DM2
- **BP** ≥ 95th percentile OR ≥ 130/85 mmHg
- **Plasma triglycerides** ≥ 100 mg/dL (< 10y) OR ≥ 150 mg/dL (≥ 10y) OR lipid lowering treatment
- **Plasma HDL-chol** ≤ 40 mg/dL or lipid lowering treatment



Modified from J Pediatr Gastroenterol Nutr 2024;78:1190–1196

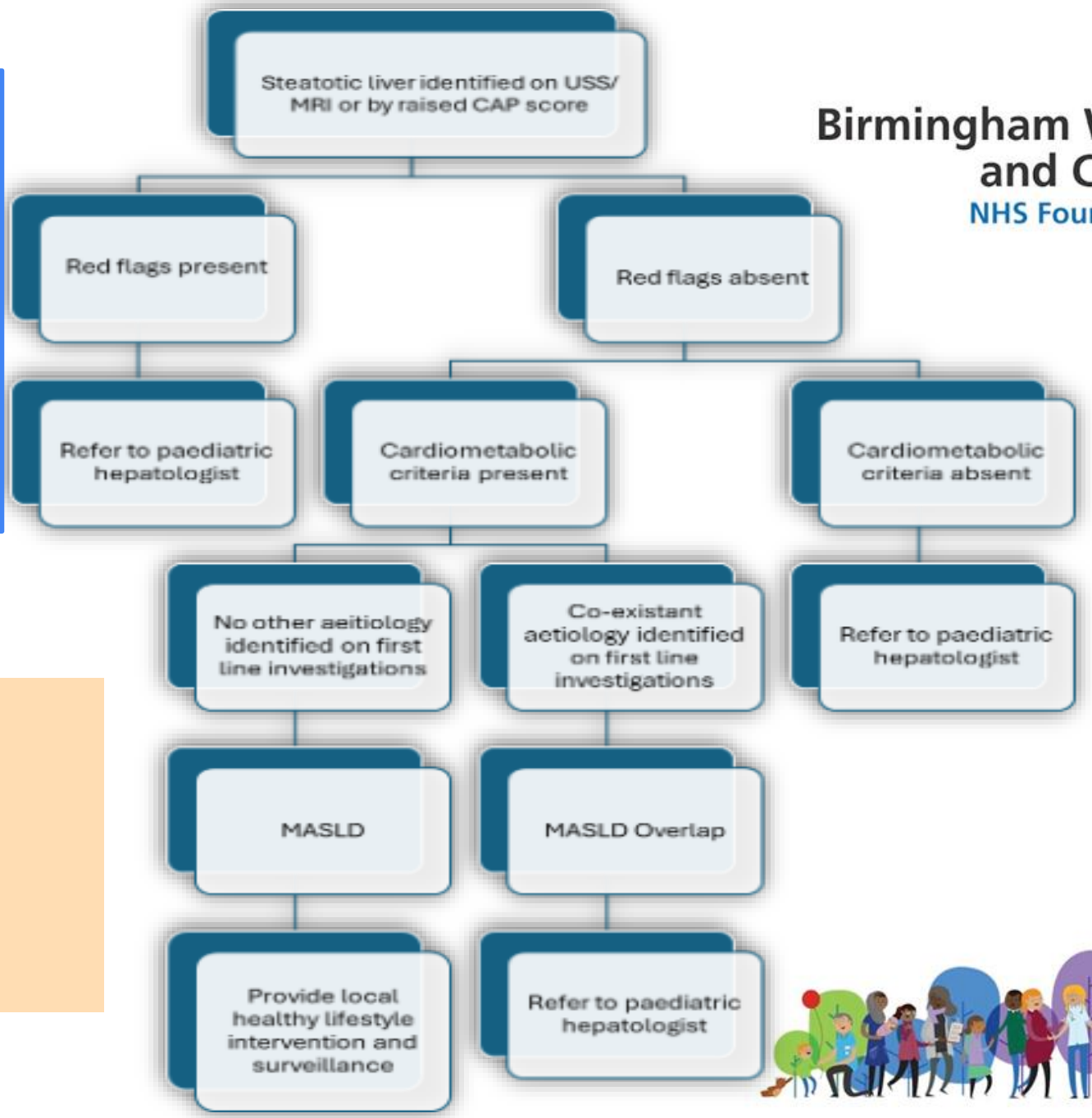
Red Flags

- 8 years and under
- Developmental delay
- Neurological signs/ symptoms
- Deteriorating school performance
- BMI z score <1
- Synthetic dysfunction (low albumin/ prolonged PT)
- Splenomegaly
- Thrombocytopenia
- Jaundice
- Sustained rise in ALT/AST ≥ 150IU/L
- Panhypopituitarism with ALT/AST ≥ 50IU/L
- Co-existent type 2 diabetes mellitus with ALT/AST ≥ 50IU/L

Case 2:
15 year old girl
BMI 87th centile
FH T2DM and HTN
ALT 86 AST 52
Screening tests:
Mildly low caeruloplasmin

Q: Can you make a positive MASLD diagnosis?

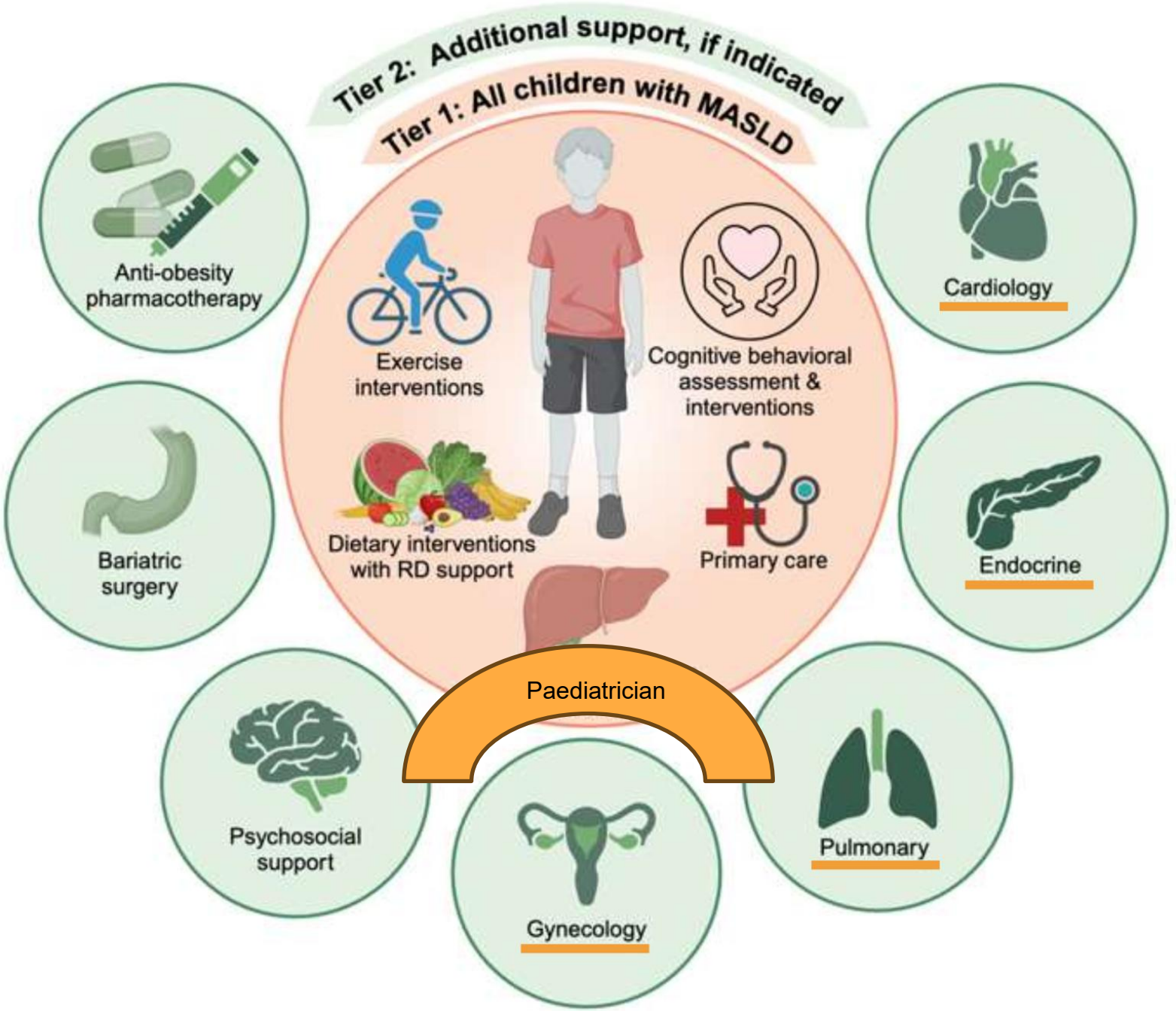
- Yes
- No



Birmingham Women's and Children's NHS Foundation Trust

Birmingham Women's and Children's NHS Foundation Trust

How should we manage these cases?



NHS
ngham Women's and Children's
NHS Foundation Trust

Weight loss targets in MASLD

Birmingham Women's and Children's NHS Foundation Trust

7% weight loss

- Histological change

10% weight loss or greater

- Steatosis reduction
- MASH resolution
- Fibrosis regression

Nobili V, Manco M, Devito R, et al. Lifestyle intervention and antioxidant therapy in children with non-alcoholic fatty liver disease: a randomised controlled trial. Hepatology 2008; 48: 119-28.
Musso G, Cassader M, Rosina F, et al. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. Diabetologia 2012; 55(4): 885-904 18.
Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of non-alcoholic steatohepatitis. Gastroenterology. 2015; 149(2):367-78 e5; quiz e14-5

Dietary Modification

- Caloric restriction
- High fibre
- High protein

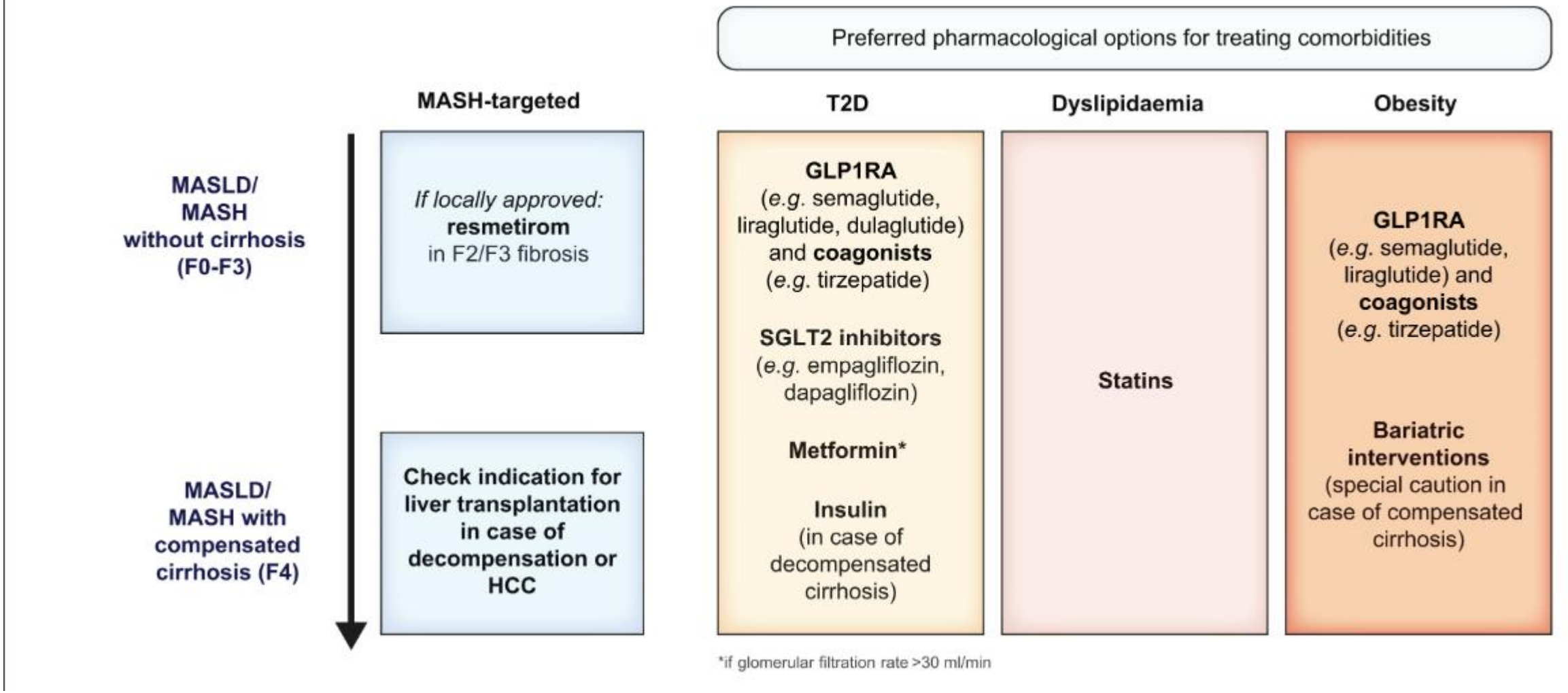
- No specific evidence to support:
  - Very low calorie diets
  - Ketogenic diet
  - Mediterranean diet
  - Paleo diet

Health promotion

- Avoidance of high-risk behaviours
  - Smoking
  - Heavy alcohol ingestion
  - Illicit drug use
- Avoidance of drug induced liver disease
  - Herbal remedies
- Vaccination
  - Hepatitis A+B

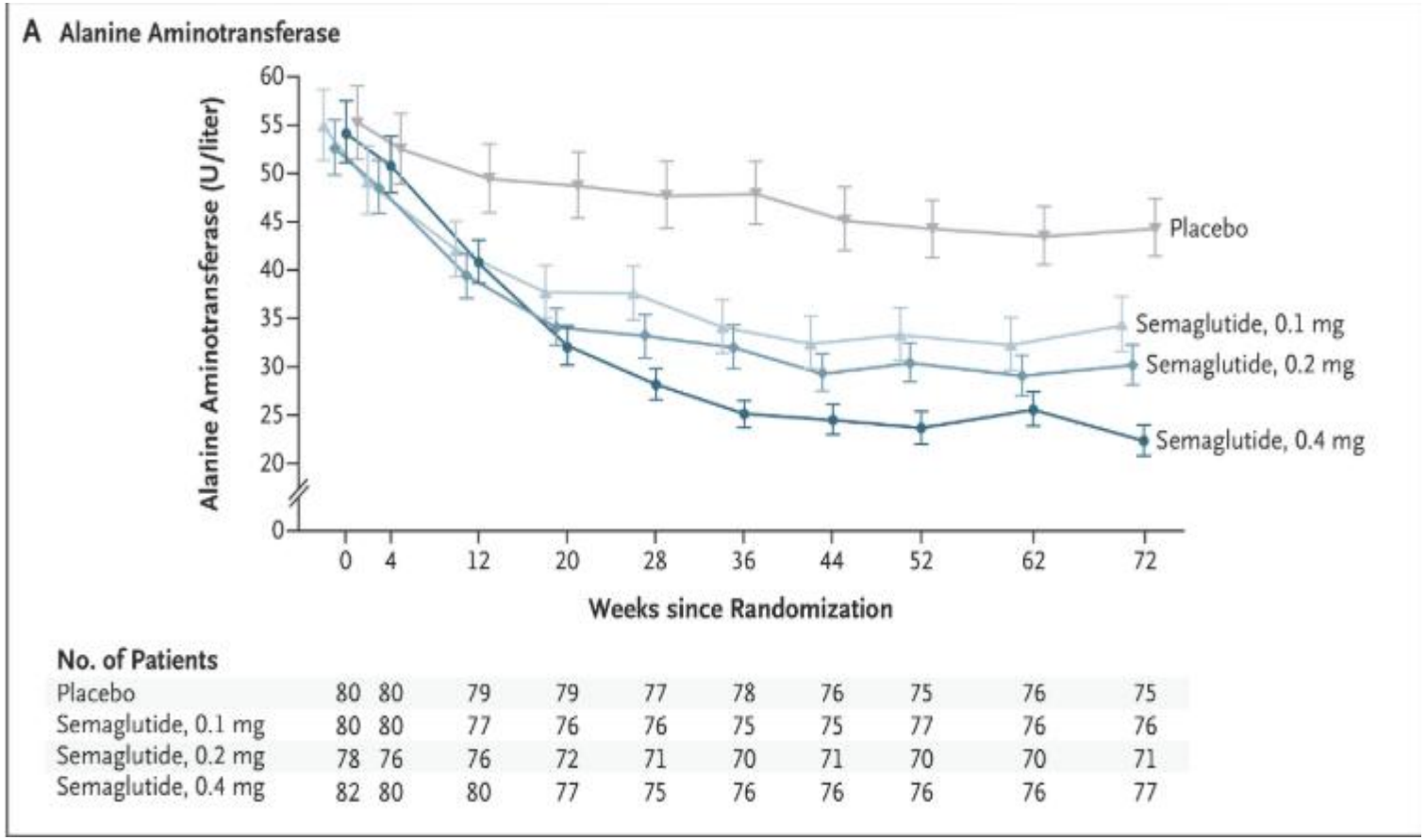
EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)

Birmingham Women's and Children's NHS Foundation Trust

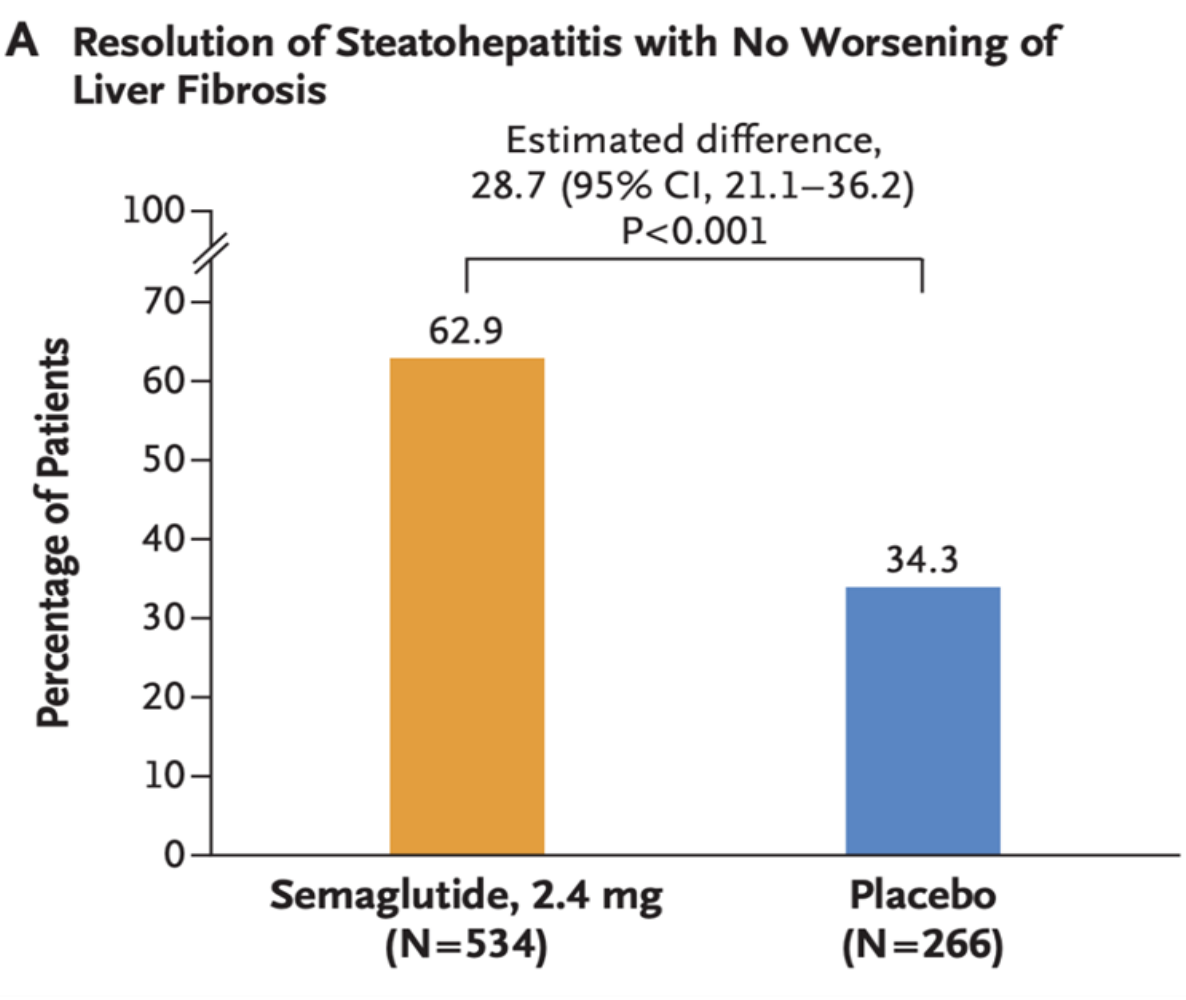


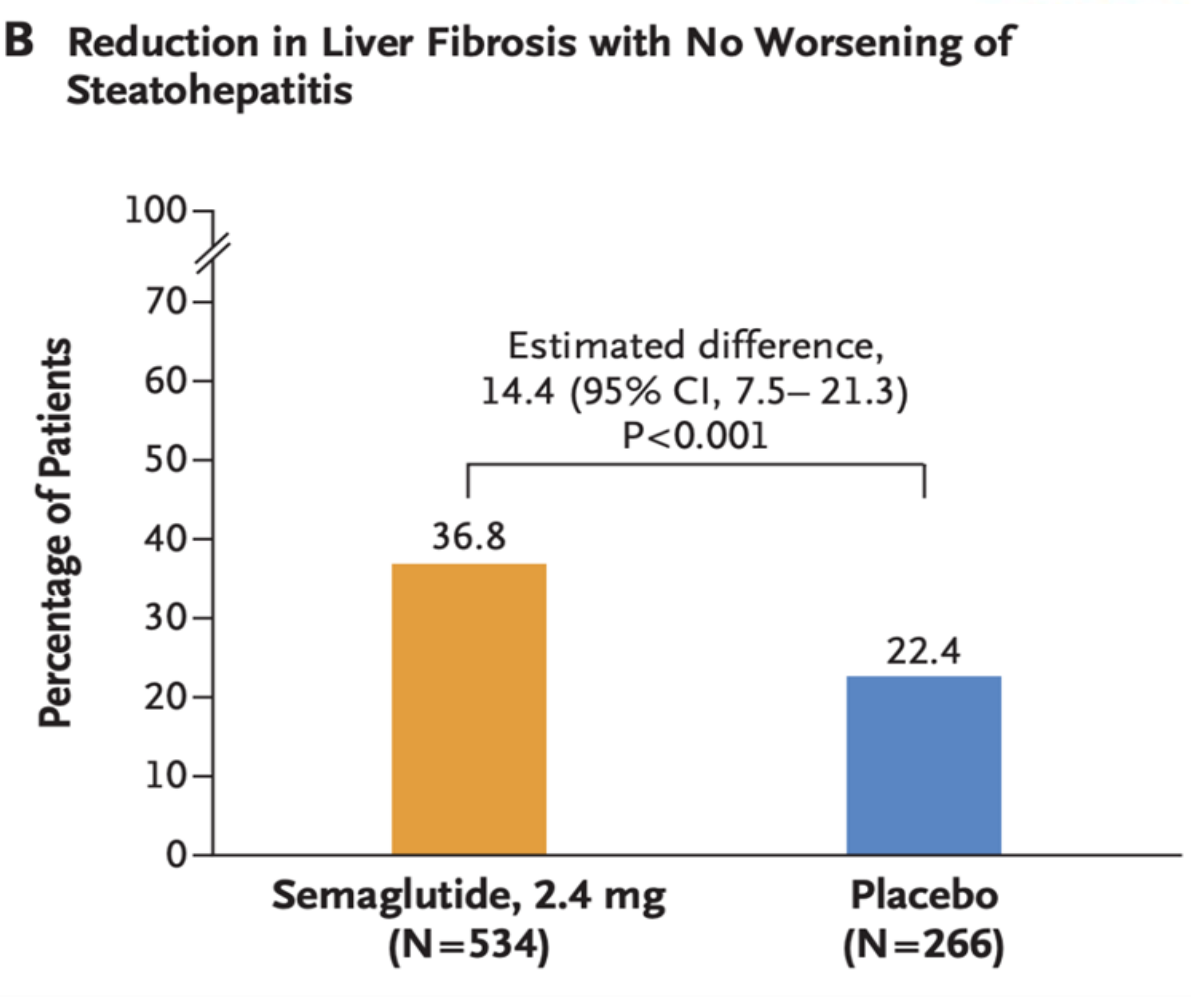
A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis
Philip N. Newsome et al. NEJM; 384 (12) March 25, 2021 Pages: 1113-1124

Birmingham Women's and Children's NHS Foundation Trust



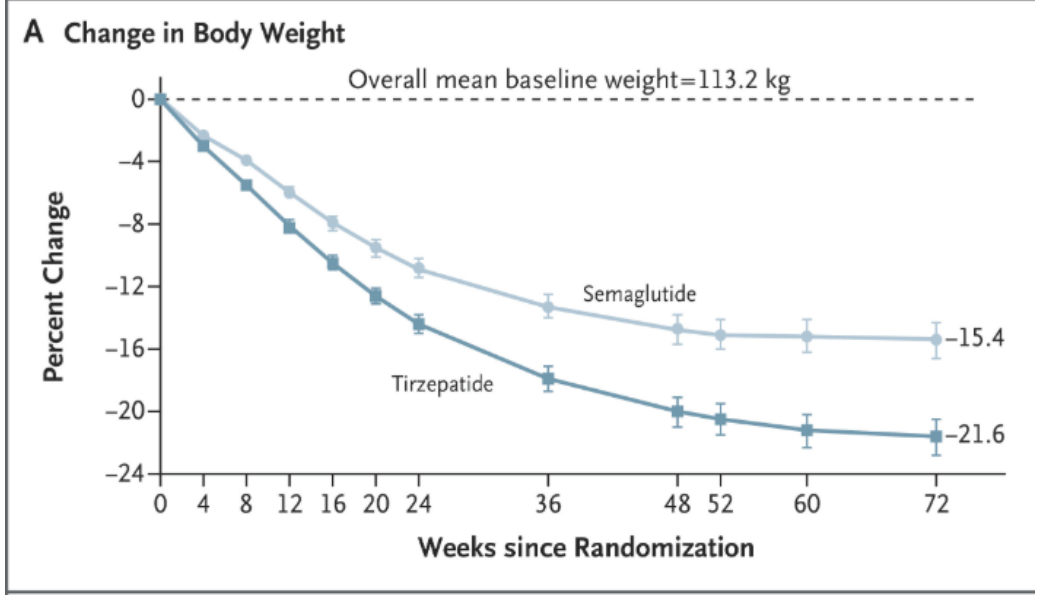
No. of Patients										
Placebo	80	80	79	79	77	78	76	75	76	75
Semaglutide, 0.1 mg	80	80	77	76	76	75	75	77	76	76
Semaglutide, 0.2 mg	78	76	76	72	71	70	71	70	70	71
Semaglutide, 0.4 mg	82	80	80	77	75	76	76	76	76	77

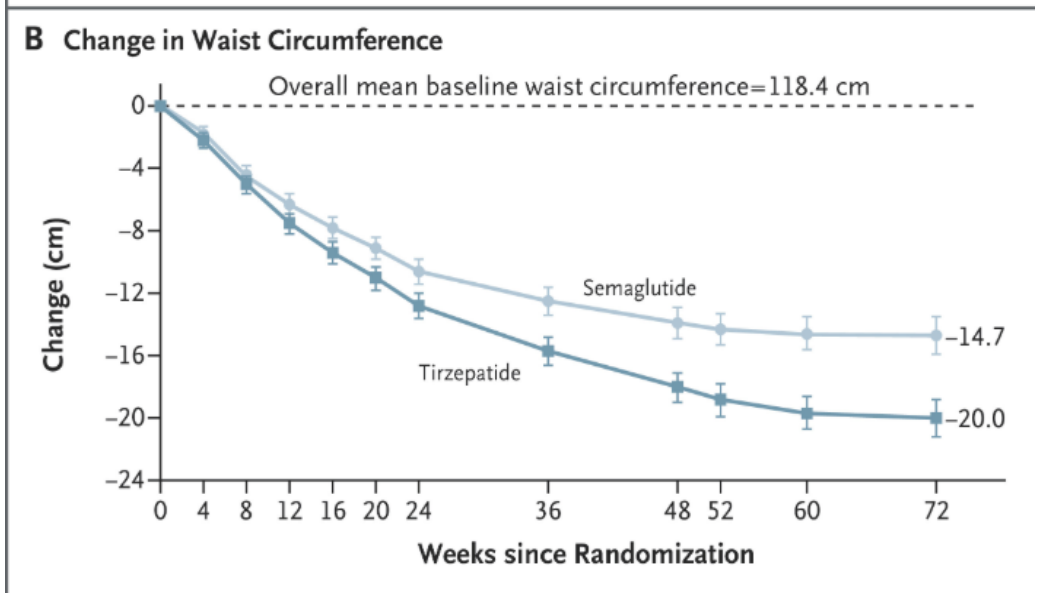


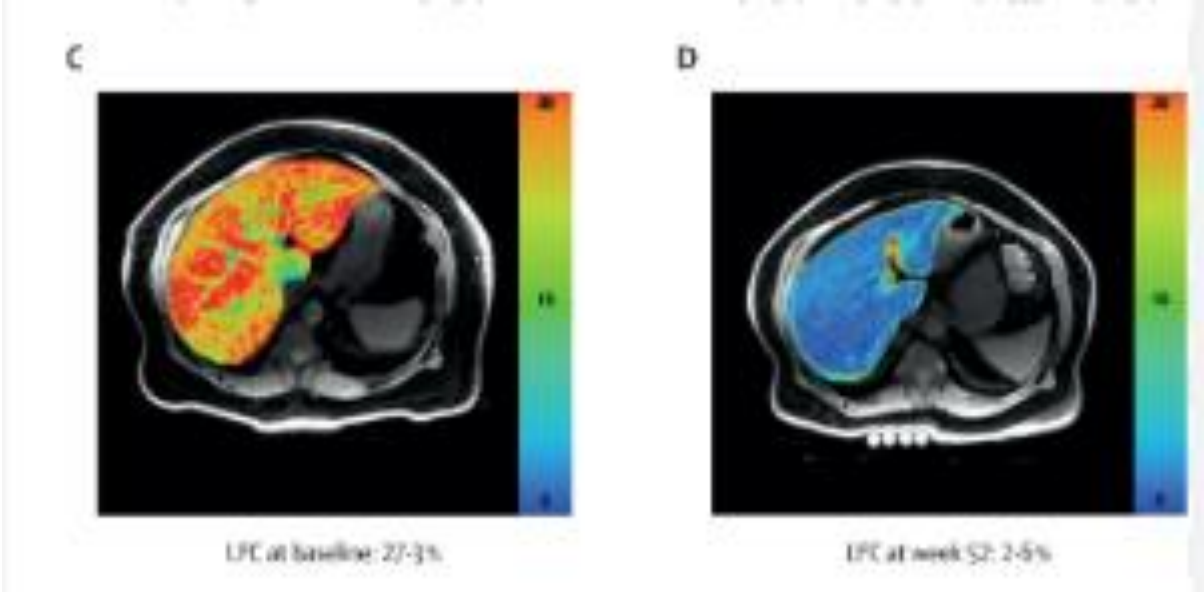


Phase 3 Trial of Semaglutide in Metabolic Dysfunction–Associated Steatohepatitis

A. J. Sanyal, et al. NEJM 392 (21) 2025;392:2089-2099
10.1056/NEJMoa2413258







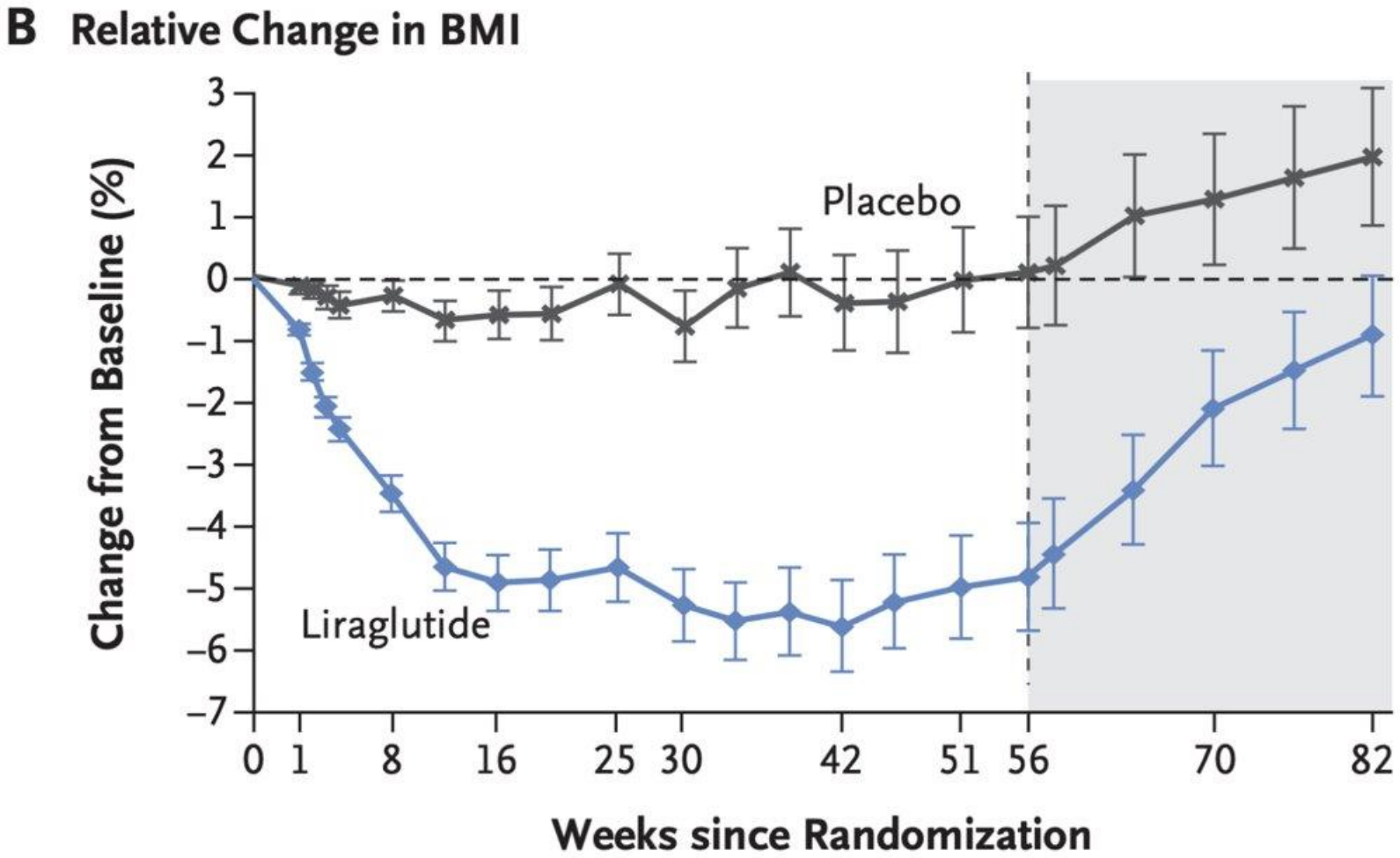
Tirzepatide:

- Drastic reduction in visceral adipose tissue
- MASH resolution
- No significant impact on fibrosis

L Aronne et al. Tirzepatide as Compared with Semaglutide for the Treatment of Obesity. NEJM. 2021 DOI: 10.1056/NEJMoa2416394

Gastaldelli et al. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial Lancet diab endocrin 2022

NHS
Birmingham Women's and Children's
NHS Foundation Trust



- Liraglutide significantly reduced liver steatosis (CAP score: 305 to 268 dB/m, $p < 0.05$)
- NLFS remained unchanged

A Kelly et al. Randomized, Controlled Trial of Liraglutide for Adolescents with Obesity. NEJM. 2020;382:2117-2128. DOI:10.1056/NEJMoa1916038

Boldys et al. Liraglutide Reduces Liver Steatosis and Improves Metabolic Indices in Obese Patients Without Diabetes: A 3-Month Prospective Study IJMS June 2025; 26(12):5883 DOI:10.3390/ijms26125883

Metformin

Birmingham Women's and Children's NHS Foundation Trust

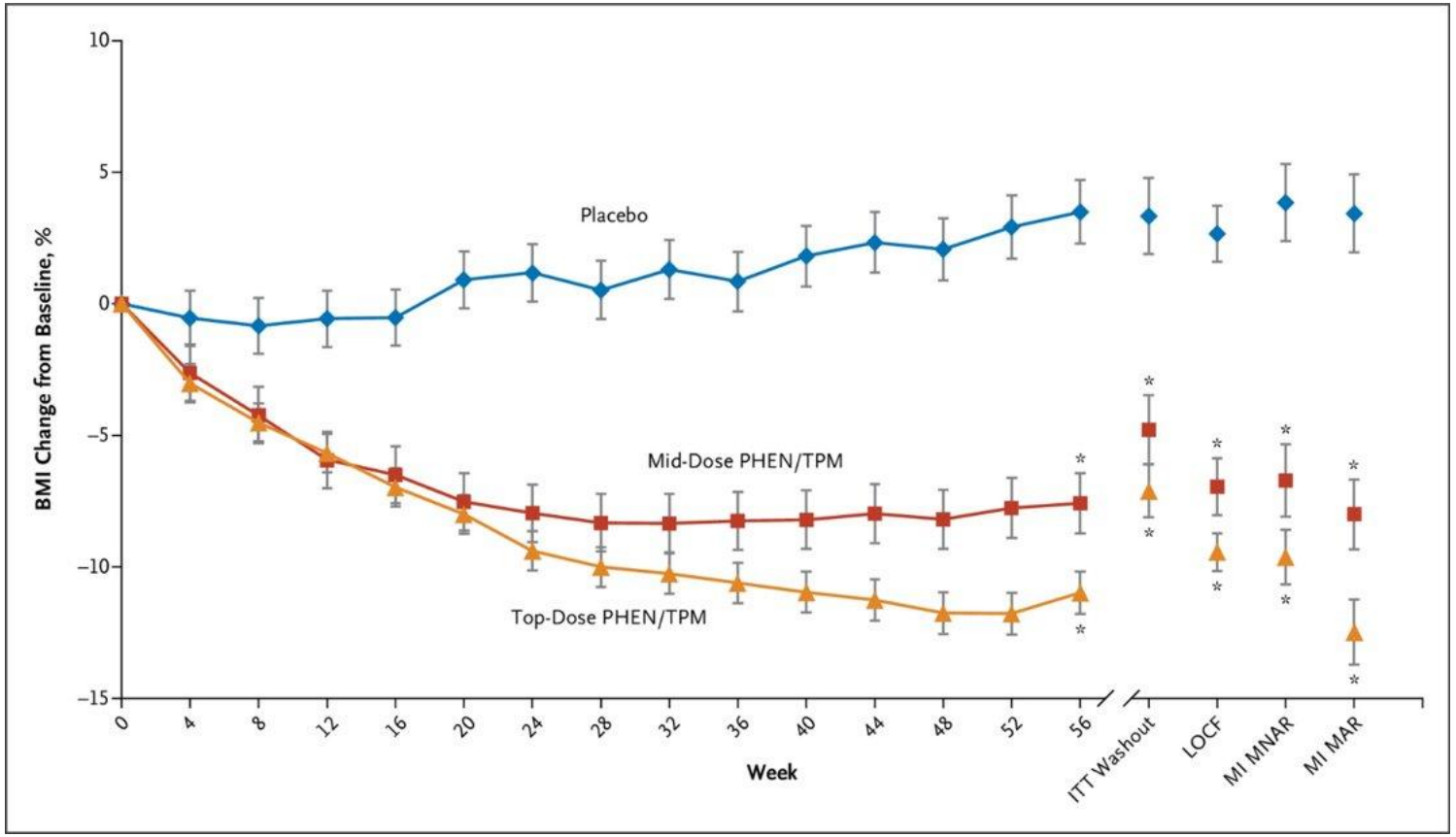
TONIC TRIAL

- Sustained reduction in ALT level similar to placebo

- Among children with NASH, the proportion who resolved at 96 weeks was 28% with placebo (95% CI, 15% to 45%; 11/39) VS 41% with metformin (95% CI, 26% to 58%; 16/39; *P*=.23).

Lavine JE, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P et al (2011) Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA 305(16):1659–68. https://doi.org/10.1001/jama.2011.520

Phentermine/topiramate



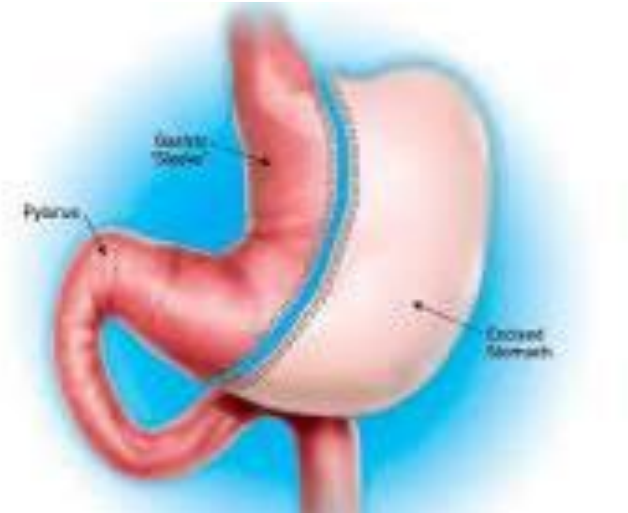
Phentermine/Topiramate for the Treatment of Adolescent Obesity. A.S. Kelly. NEJM Evid 2022; 1 (6) April 2022. DOI: 10.1056/EVIDoa2200014

Weight Loss Surgery

Birmingham Women's and Children's NHS Foundation Trust

- Roux-en-y gastric bypass and vertical sleeve gastrectomy may give clinically meaningful weight loss in severely obese adolescents
  - BMI reductions of -30% at 1 year postoperatively
- BMI reduction may improve obesity-related comorbidities
- Reduction of steatosis, steatohepatitis, and hepatic fibrosis

- Future endoscopic options:
  - Endoscopic sleeve gastroplasty



Bariatric surgery recommendation:

Birmingham Women's and Children's NHS Foundation Trust

- Select adolescents who are morbidly obese
  - BMI > 40Kg/m2
  - OR BMI 35-40Kg/m2 and other significant disease that could be improved with weight loss
- Have reached or nearly reached physiological maturity
- Have failed to achieve clinically beneficial weight loss with previously organised behavioural / medical treatments

MASLD in the absence of MASH/ fibrosis is not an indication for referral

Outcome

Birmingham Women's and Children's NHS Foundation Trust

Case 1:

- Lifestyle intervention
- Reduced weight, BMI, WC
- LFTs normalised

Case 2:

- Lifestyle intervention
- Referred to hepatologist
  - KF rings
  - High 24hr urinary copper collection
  - ATP7B compound heterozygote
- LFTs normalised on penicillamine

Annual surveillance

Monitoring of liver disease

Assessment for the development of co-morbidity

- Reduction in ALT/ GGT indicate improvement in MASLD

- Abnormal glucose tolerance is common in young people with MASLD
  - 11.1% of adolescents and 15.8% of young adults
- 2.7 hazard ratio for development of T2DM over a median of 8 years

Referral to tertiary hepatology services

- Red flags present
- Overlap condition/ alternative liver disease identified

Birmingham Women's and Children's NHS Foundation Trust

ROLE

1.Exclude alternative diagnoses and identify co-existent liver conditions (MASLD overlap)

2. Identify children at higher risk of advanced liver disease
   Monitor for disease progression and development of fibrosis using non-invasive tests
   Manage complications of advanced liver disease
   Risk stratify children for follow-up under adult hepatology services

3. Recruitment of children to trials in MASLD

4. Contribute to Paediatric MASLD registries to improve understanding of the natural history of MASLD
   EU-P-MASLD registry is currently in development

High risk patients:

Birmingham Women's and Children's NHS Foundation Trust

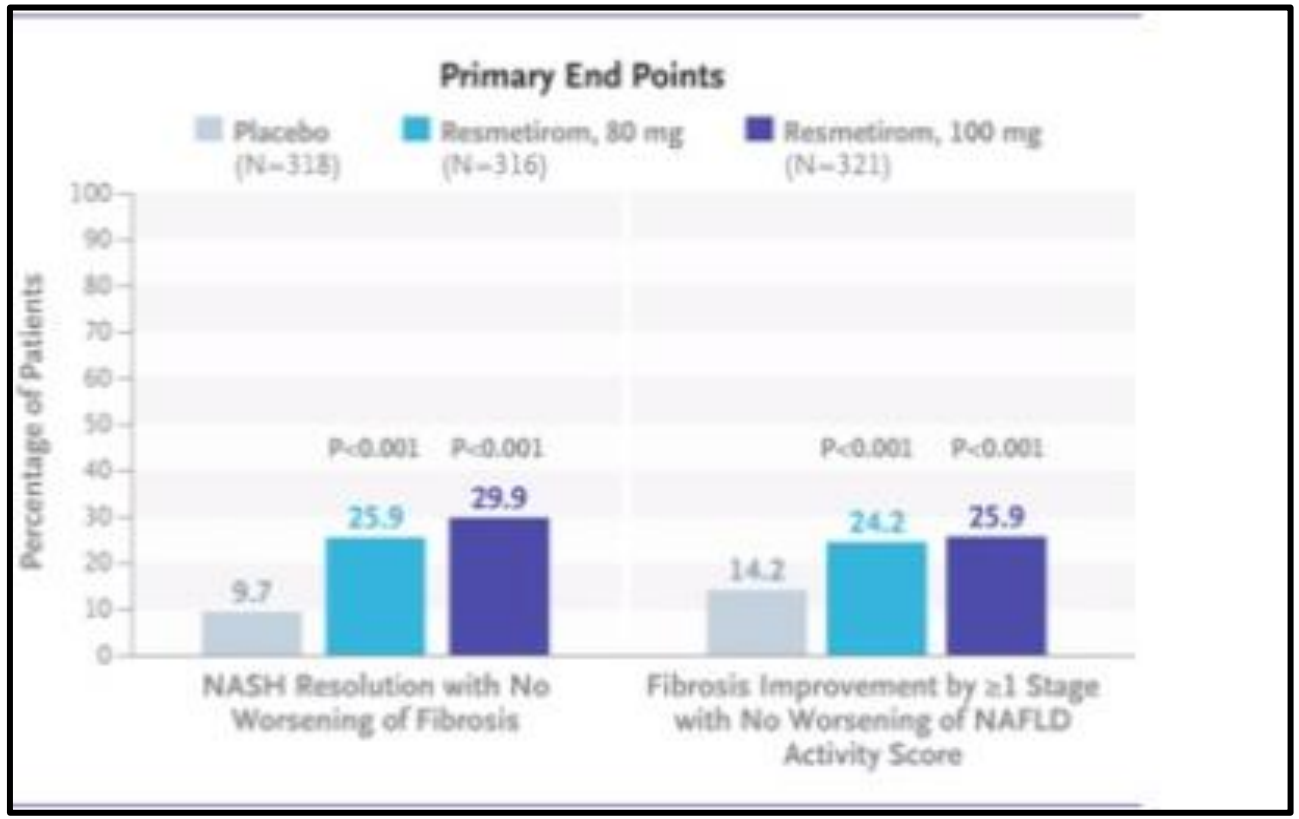
- Patients with red flags
- Patients without red flags who after > 6m follow up have:
  - ALT ≥ 80 IU/L
  - Pre-diabetes or type 2 diabetes
  - First-degree relative with advanced liver fibrosis

Newton KP, Lavine JE, Wilson L, et al. Alanine aminotransferase and gamma-glutamyl transpeptidase predict histologic improvement in pediatric nonalcoholic steatohepatitis. *Hepatology* 2021; 73:937–951.

Xanthakos SA, Lavine JE, Yates KP, et al. Progression of fatty liver disease in children receiving standard of care lifestyle advice. *Gastroenterology* 2020; 159:1731–1751.e10.

- Future Role:

  Identification of patients for MASLD Specific therapy
  Resmetirom



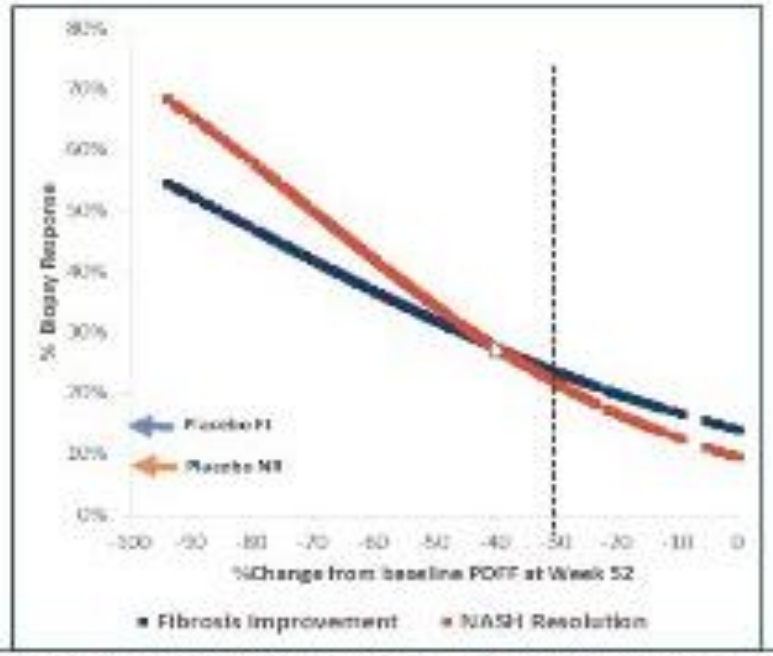
Oral liver directed THR-B selective agonist
Approved March 24 in US for treatment of adults with MASH and F2-F3

MAESTRO-NASH:
- 54m randomised double blind placebo-controlled phase 3 trial
  – efficacy and safety of 80mg + 100mg resmetirom

Non-invasive assessment methods

Birmingham Women's and Children's NHS Foundation Trust

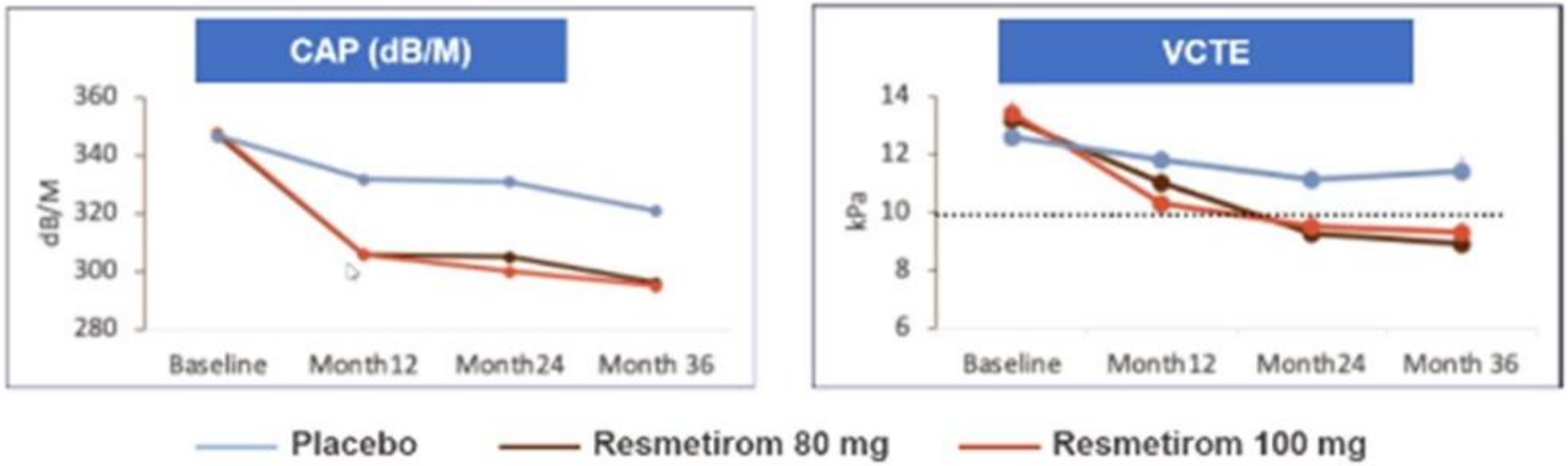
MRI-PDFF Reduction Strongly Predictive of Resmetirom Biopsy Responses on Fibrosis and Nash



All resmetirom treated patients (80 mg and 100 mg combined)
Logistic regression model, predicting response on biopsy as a function of % change from baseline in MRI-PDFF

- The graphs show that the greater the Week 52 PDFF reduction, the greater likelihood for fibrosis and NASH responses with resmetirom treatment
- PDFF reduction in resmetirom treated patients was highly associated with both NASH Resolution and Fibrosis Improvement
  - Placebo patients with more PDFF reduction had more NASH reduction but not Fibrosis Improvement
- At least a 30% PDFF response was observed in 96% and 88% of resmetirom 100 mg responders for NASH Resolution and Fibrosis Improvement, respectively
  - The % reduction in PDFF rather than resmetirom dose impacted the response on biopsy
- The response on biopsy at 80 mg and 100 mg was equally correlated with the magnitude of PDFF response. Doses were combined in this predictive model

Fibroscan Over Time (Patients with 3-Year Data)



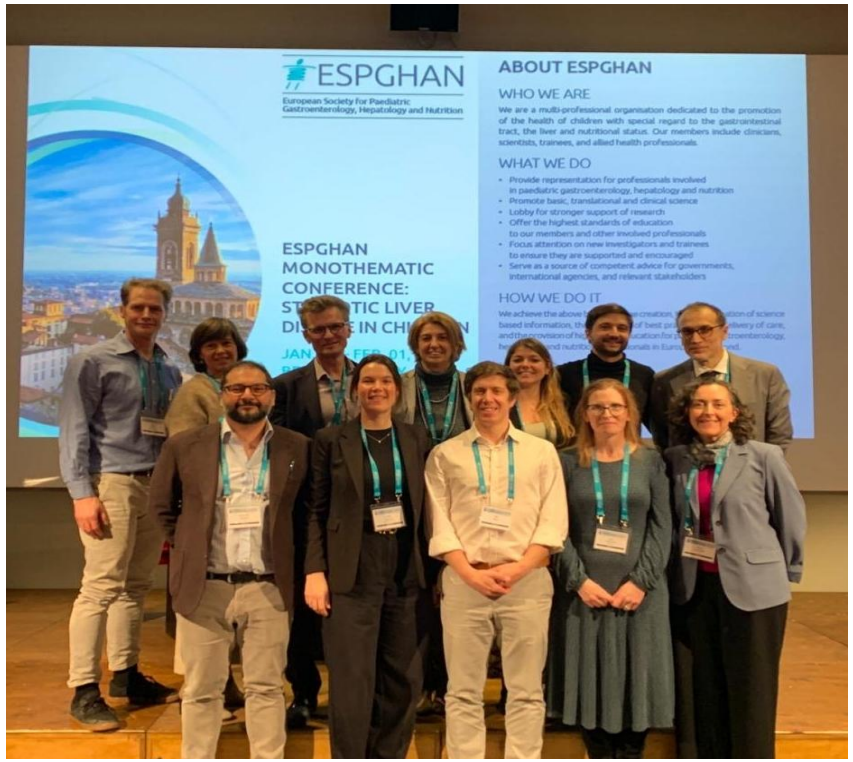
- VCTE improved over time (1-3 years) years relative to placebo in resmetirom treated patients, both doses showing a similar durable response
  - Gawreh et al (2024) new data indicated that less than 10 kpa correlated with less liver related events
- CAP was stable over time, both doses showing a similar durable response

Gawrieh S, Vilar-Gomez E, Wilson LA, et al. Increases and decreases in liver stiffness measurements are independently associated with the risk of liver-related events in NAFLD. J Hepatol. Published online May 16, 2024. doi:10.1016/j.jhep.2024.05.008

Summary

Birmingham Women's and Children's NHS Foundation Trust

- MASLD is common
- Significant long-term health implications
- First line investigations for all
- Recognise 'red flags' and investigate thoroughly
- Liver biopsy rarely used unless diagnostic uncertainty
- Weight loss by any means
- Identify and treat co-morbidity
    - Increased risk of progressive disease if co-existent type 2 DM



Questions?

NHS
Birmingham Women's and Children's
NHS Foundation Trust