What to do after diagnosing a patient with MASLD?

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January 20, 2023

Conflict of Interest Disclosures

Over the last 24 months

- Honoraria - Abbvie

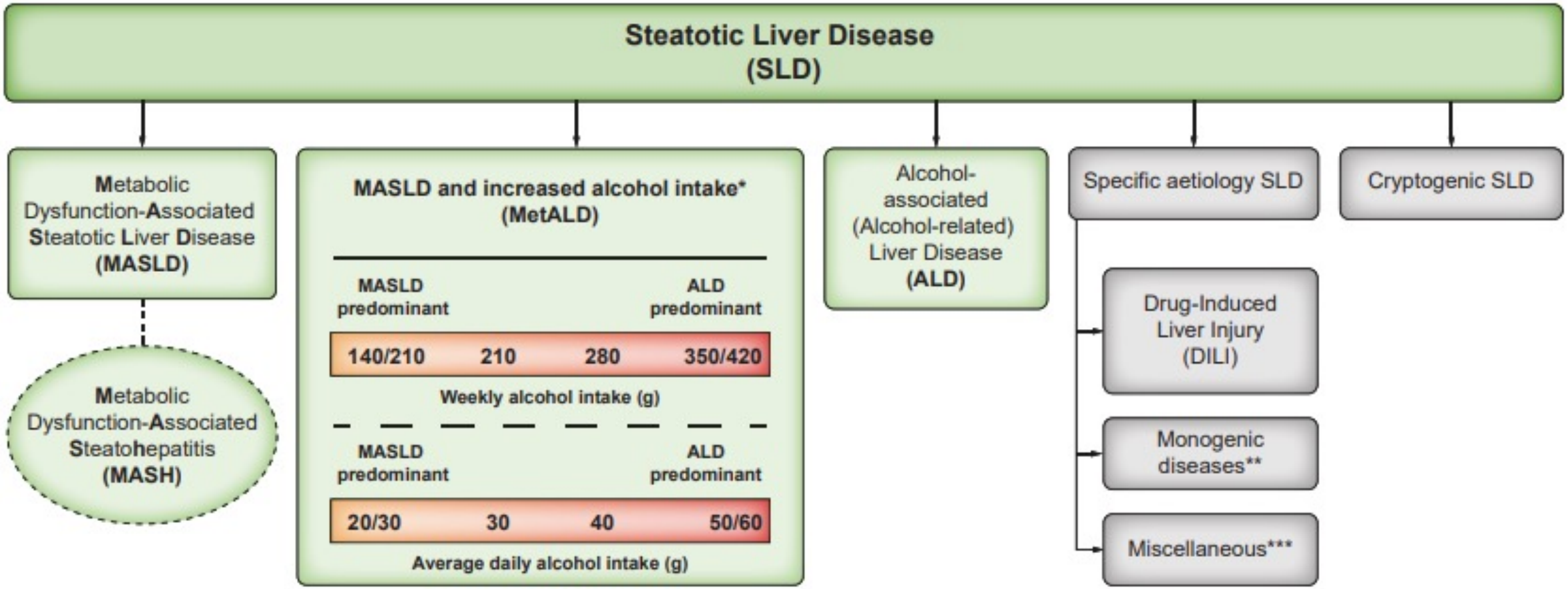
CanMEDS Roles Covered

X	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
	Communicator (as *Communicators*, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
X	**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
	Leader (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
X	**Health Advocate** (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
X	**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
	Professional (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

Learning objectives

- To review the new nomenclature for steatotic liver disease
- To discuss approaches to risk stratification in primary and secondary care
- To review current and emerging management options for MASLD

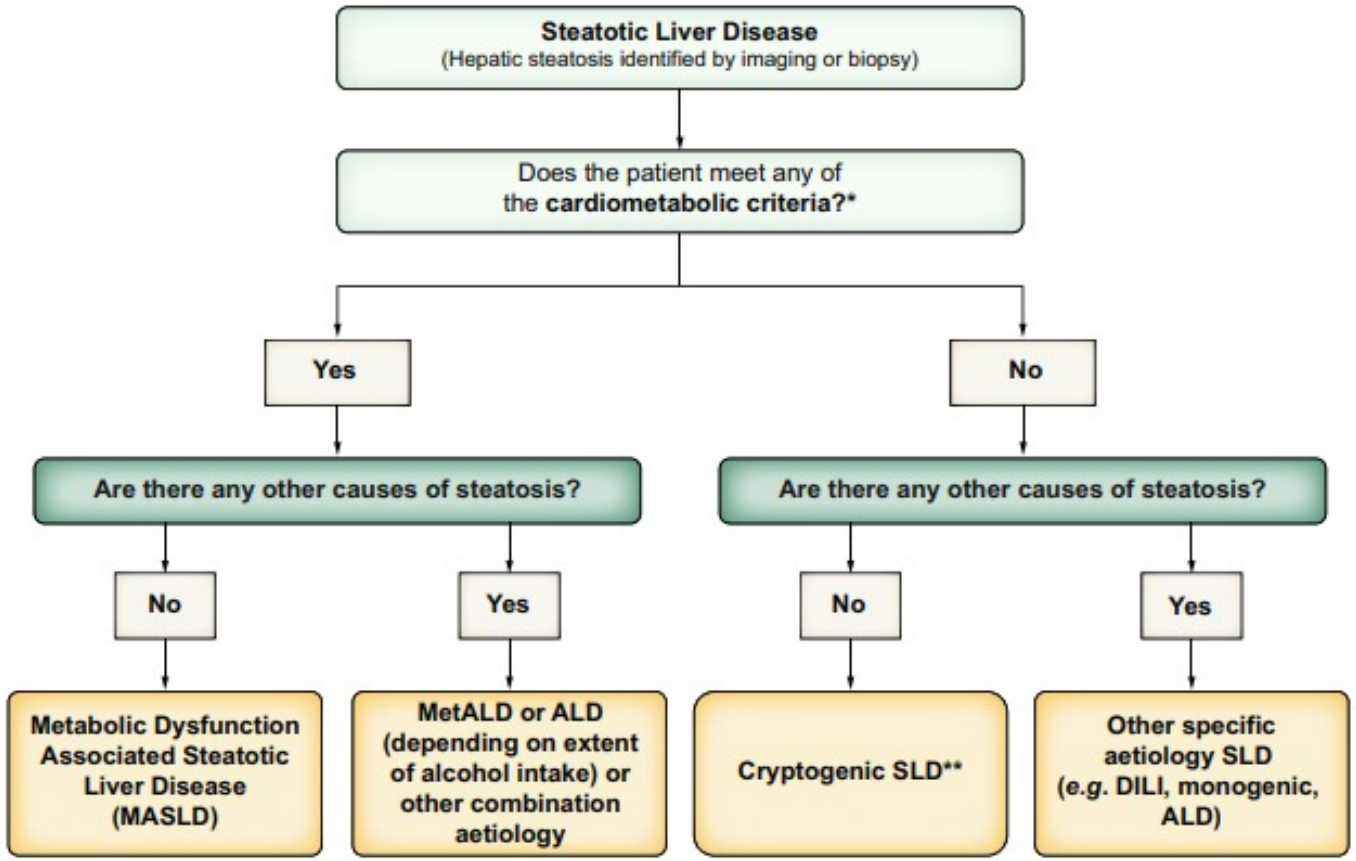
What's in a name?



- Encompass various aetiologies of steatosis, focus on pathophysiology
- Reduce stigmatising language
- Includes new category of MetALD

Rinella et al J Hep 2023

Inclusive diagnostic criteria



*At least 1 out of 5:

- BMI ≥25 (23 Asia) OR WC >94cm (M) 80cm (F) OR ethnicity adjusted equivalent
- Fasting serum glucose ≥5.6mmol/L OR 2-hour post-load glucose ≥7.8 mmol/L OR HbA1c ≥5.7% OR T2DM OR treatment for T2DM
- Blood pressure ≥130/85 mmHg OR specific antihypertensive drug treatment
- Plasma triglycerides ≥1.70 mmol/L OR lipid lowering treatment
- Plasma HDL-cholesterol ≤1.0 mmol/L (M) and ≤1.3 mmol/L (F) OR lipid lowering treatment

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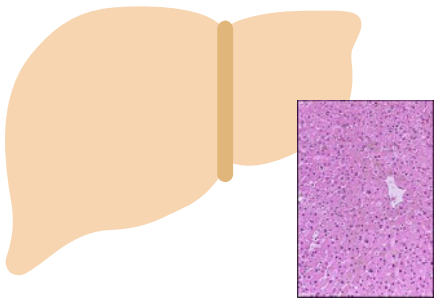
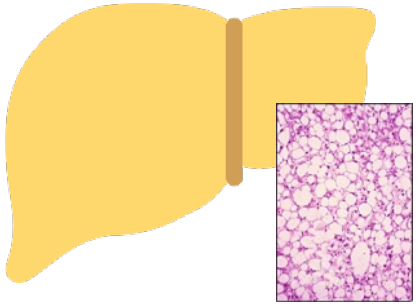
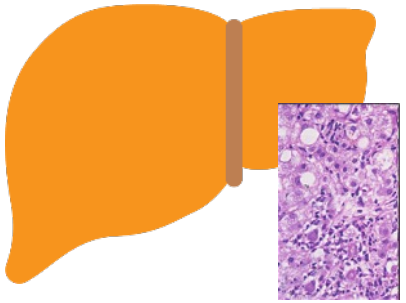
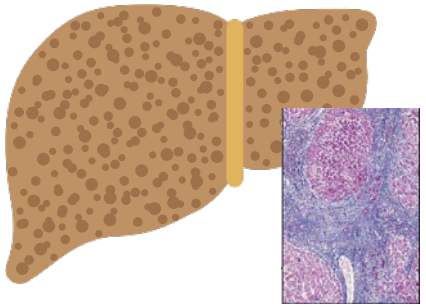
Prevalence of MASLD and MASH

MASLD

Normal Liver	Steatosis "MASLD"	Steatohepatitis "MASH"	Cirrhosis
			
	Fatty liver with trivial or no inflammation and no hepatocyte ballooning	Fatty liver with significant inflammation and hepatocyte ballooning	Increasing fibrosis leading to cirrhosis, hepatocellular carcinoma

Worldwide prevalence:	25%[1]	3%-5%[1]	1%-2% at risk*

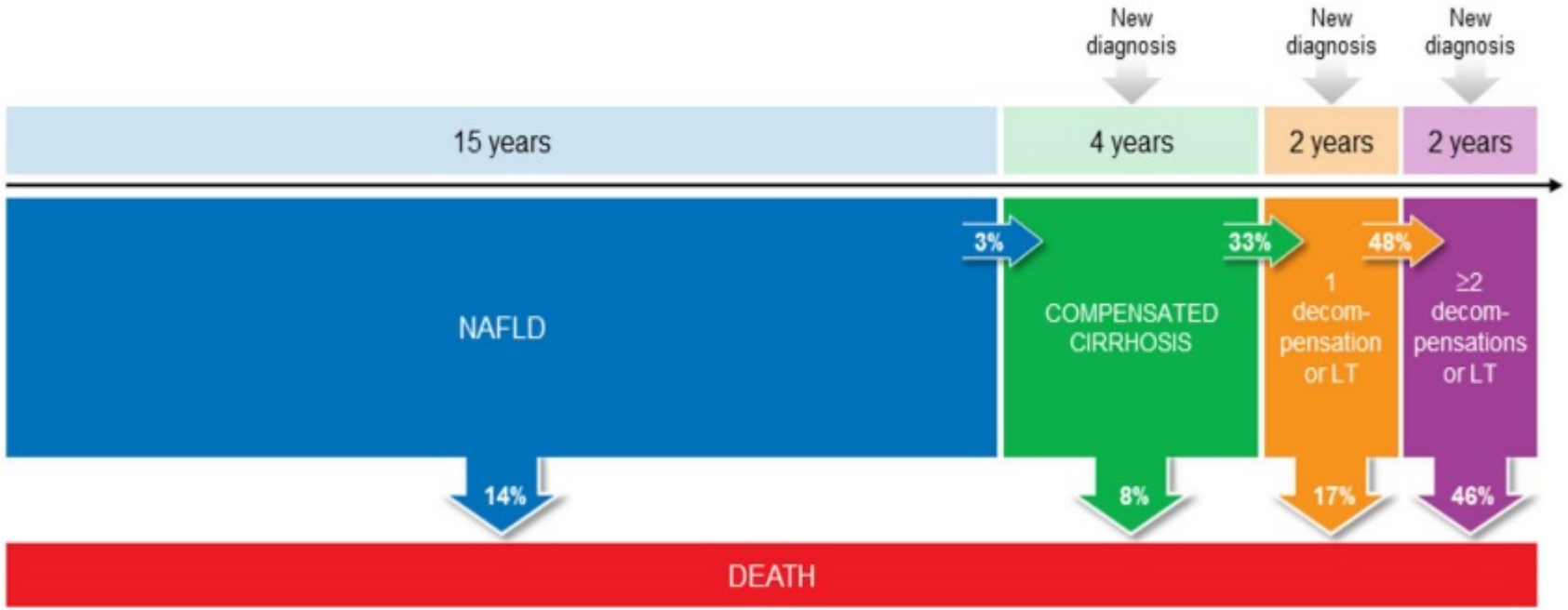
*Based on analysis of NHANES data estimating 1.74% prevalence of MASH with advanced fibrosis.[2]

Slide credit: clinicaleducationalliance.com:

cea clinical education alliance

1. Younossi. J Hepatol. 2019;70:351. 2. Kabbany. Am J Gastroenterol. 2017;112:581.

Most patients with MASLD do not progress to cirrhosis



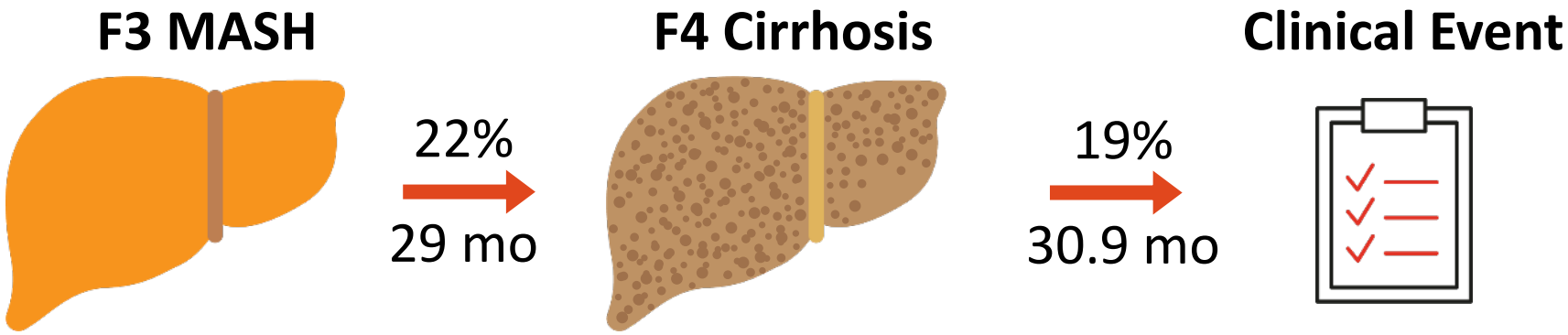
90–95% of patients will not progress to liver cirrhosis

- MASLD: fibrosis progression rate of 1 stage every 14 years
- MASH: fibrosis progression rate of 1 stage every 7 years

Individuals with MASLD increased mortality vs. general population
Patients with MASH have a significantly higher liver related mortality than patients with simple steatosis
Major cause of death in MASLD is cardiovascular disease

Allen J Hepatol 2022; Singh Clin Gastroenterol Hepatol 2015; Bril. Endocrinol Metab Clin N Am. 2016

MASH Advanced Hepatic Fibrosis May Quickly Progress to Cirrhosis



- In n = 217 MASH patients with F3, after median 29 mo, **22% had bridging cirrhosis**
- In n = 258 MASH patients with F4, after median 30.9 mo, **19% had clinical event**
  - Death, ascites, hepatic encephalopathy, esophageal variceal bleed, new varices, ≥2-point increase in Child-Pugh score and or MELD ≥15

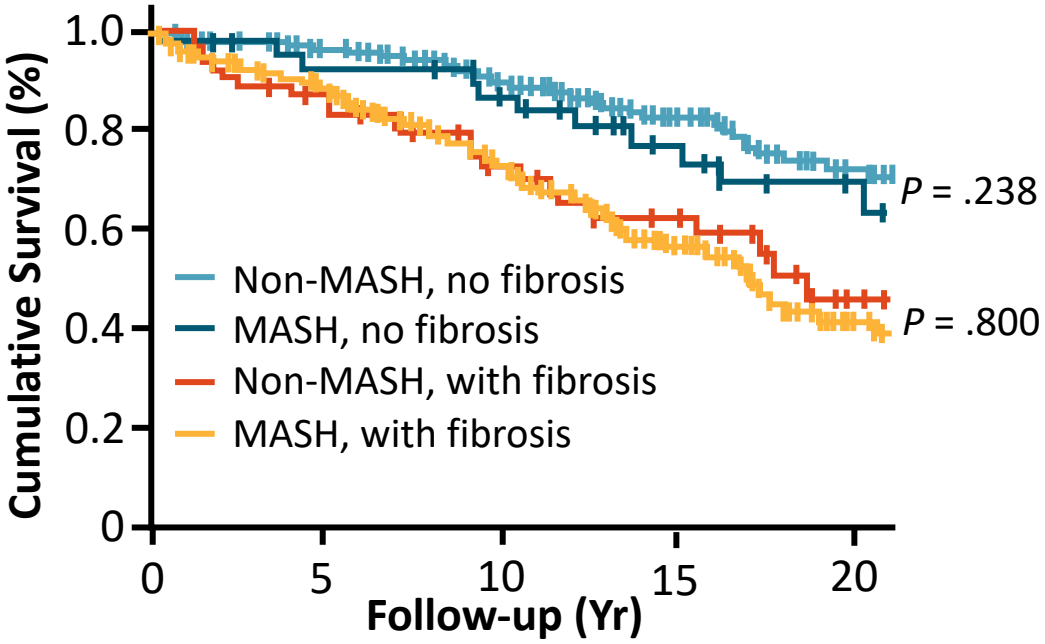
Sanyal. Hepatology. 2019;70:1913.

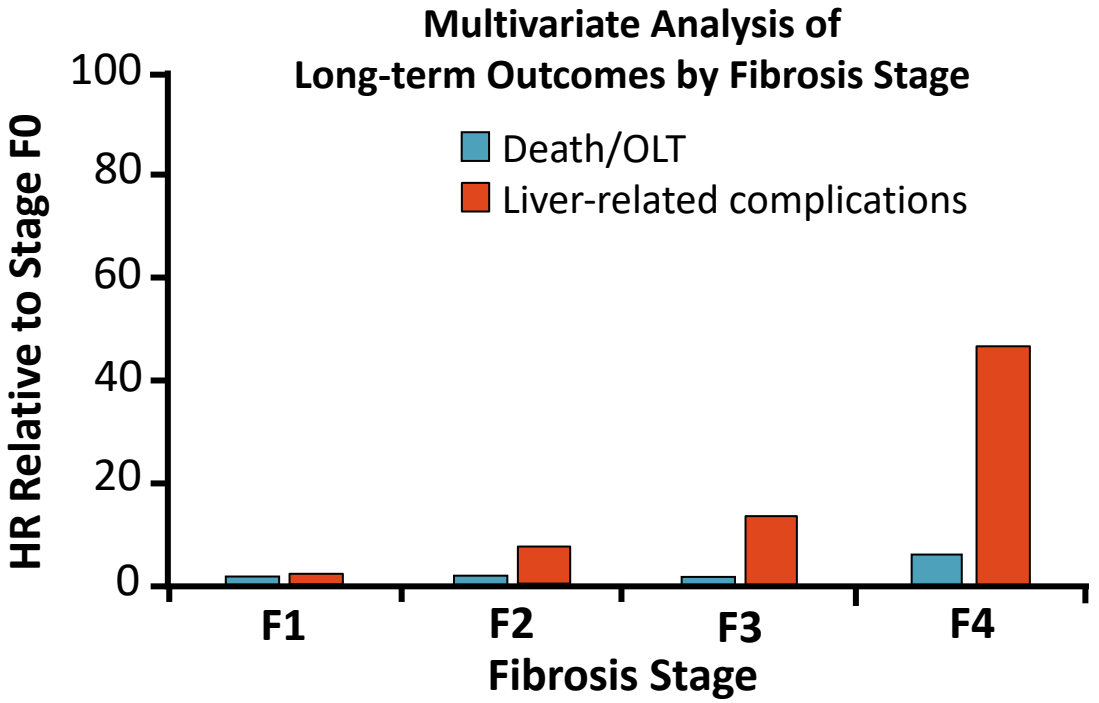
Slide credit: clinicaleducationalliance.com:

cea clinical education alliance

PRELHIN Study: Liver Fibrosis Associated With Long-term Outcomes in Patients With MASLD

- Retrospective analysis in patients with MASLD (N = 619); median follow-up: 12.6 yr (range: 0.3-35.1)

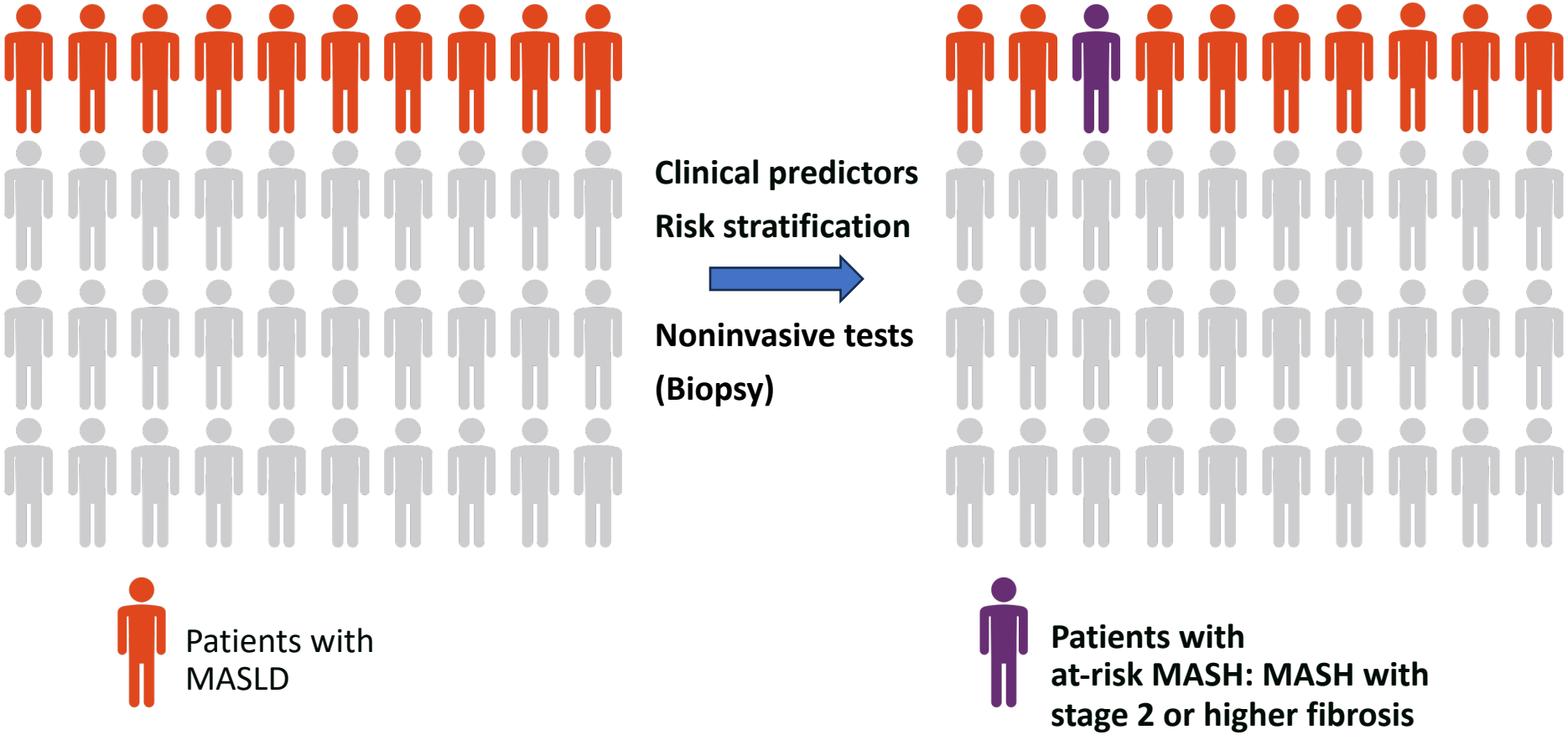




Only fibrosis stage was associated with overall mortality, OLT, and liver-related events. Presence of MASH, NAS (or any of its components) had no independent prognostic effect.

Angulo. Gastroenterology. 2015;149:389.

Aim to identify patients with “at risk” MASH



Case Finding and High-Risk Populations

Strong Clinical Predictors of MASH and Fibrosis

- Age >50 yr
- T2D
- First-degree relative with MASLD cirrhosis

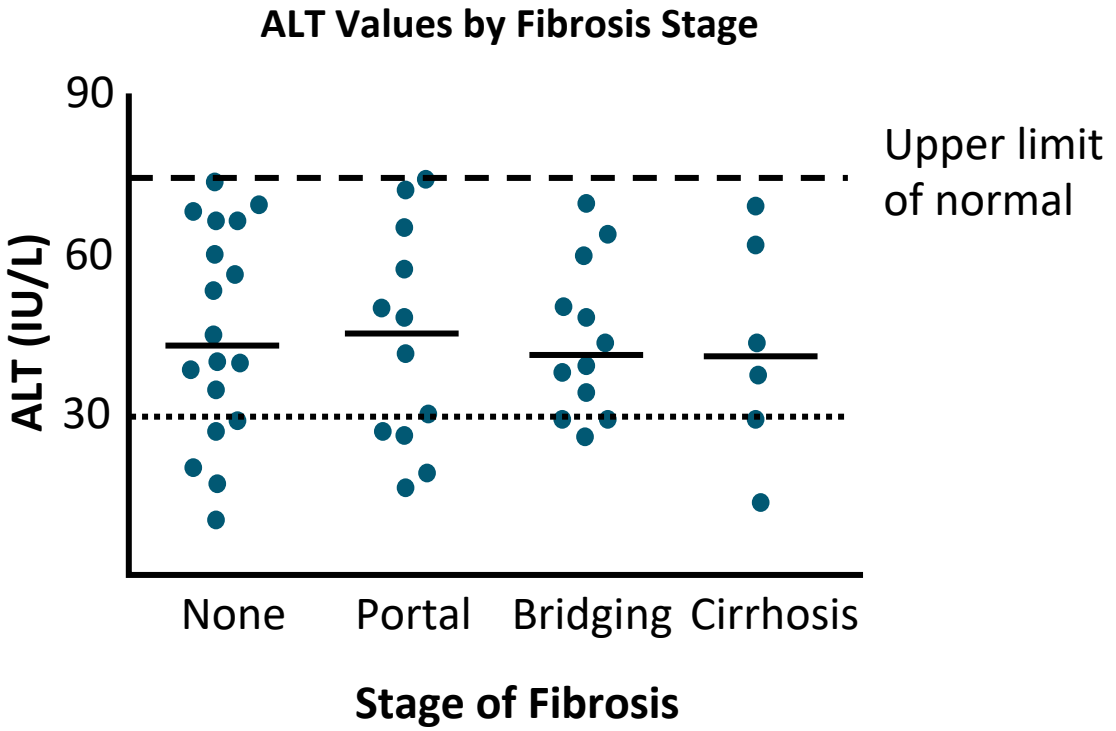
Other Risk Factors

- Sedentary lifestyle/Western diet (high fructose consumption)
- Overweight/obese
- Metabolic syndrome (≥3 features)
- Ethnicity (Hispanic/Asian)
- Dyslipidemia
- Polycystic ovary syndrome
- Endocrinopathies (panhypopituitarism)
- Obstructive sleep apnea

Angulo. NEJM. 2002;346:1221. Caussy. J Clin Invest. 2017;127:2697. Chalasani. Hepatology. 2018;67:328.

Liver Enzymes: Inadequate in Assessing MASLD/MASH

- ALT can be normal in > 50% of individuals with MASH, 80% of individuals with MASLD
- ALT can be elevated in > 50% of individuals with MASLD but without MASH
- In MASLD, ALT is neither indicative nor predictive of MASH or fibrosis stage:
  - Normal ALT does not preclude NASH/progressive disease
  - Elevated ALT cannot predict MASH or fibrosis
  - **ALT and AST not sensitive for MASLD/MASH**



Browning et al, Hepatology 2004; Dyson et al, Frontline Gastroenterol 2014; Mofrad et al, Hepatology 2003

NITs for detection of “at risk” MASH

- FAST
- MAST
- MEFIB (FIB4 + MRE)
- cT1

Have not yet reached the level of clinical evidence needed for use in routine clinical practice

Rinella et al Hepatol 2023

NITs for detection of advanced fibrosis

Clinical or Laboratory Scores

Simple

- FIB4
- NFS
- APRI
- FibroTest

Proprietary

- ELF
- FIBROSpect II

Imaging

Elastography

- VCTE (vibration-controlled transient elastography)
- ARFI (acoustic radiation force impulse)
- SWE (2D shear wave elastography)
- MRE (magnetic resonance elastography)

Validation studies show high NPV for advanced fibrosis (>90%) but lower PPV (<80%)
So these scores are most useful for ruling **out** advanced fibrosis/cirrhosis

VCTE >12kPa is associated with high likelihood for cirrhosis, although PPV is low
MRE probably the most accurate imaging NIT for fibrosis in MASLD

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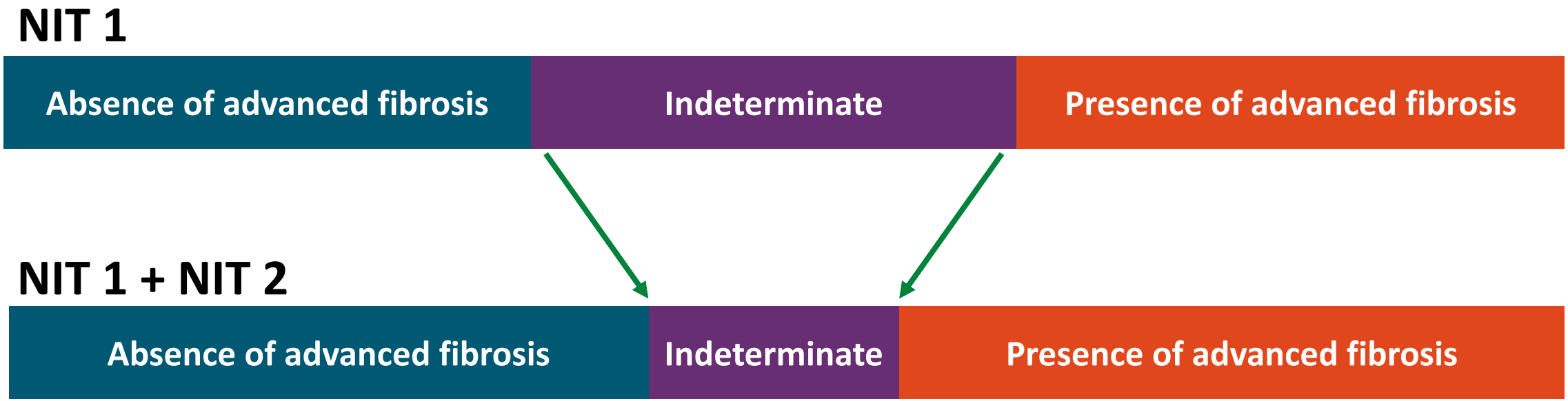
Use of Sequential Noninvasive Tests Could Reduce Number of Patients in Indeterminate Zone



Sequential use of NITs maintains sensitivity and specificity while enabling classification of larger proportion of patients

Younossi. AASLD 2018. Abstr LB-10.

Sequential Algorithms to Detect Advanced Hepatic Fibrosis due to MASH

- Study of baseline data from STELLAR trials (N = 3202) to determine performance of sequential combinations of noninvasive tests in diagnosing F3/F4 hepatic fibrosis
  - **Single tests** (either NFS, FIB-4, ELF, or VCTE) led to up to 51% indeterminate results
  - **Sequential tests** (FIB-4, then ELF or VCTE) led to up to 24% indeterminate results

Outcome With Sequential Tests, % (95% CI)*	FIB-4, Then ELF (N = 3180)	FIB-4, Then VCTE (N = 3141)
Prevalence of F3/F4	71	71
Sensitivity	69 (67-71)	77 (75-78)
Specificity	92 (90-94)	89 (87-91)
PPV	96 (94-97)	95 (93-96)
NPV	55 (53-58)	60 (58-63)
Indeterminate	24 (23-26)	20 (18-21)
Misclassified	24 (23-26)	20 (18-21)

*Using published cutoffs: FIB-4 (1.30-2.67), ELF (9.8-11.3), VCTE (9.9-11.4 kPa).

Anstee. Hepatology. 2019;70:1521.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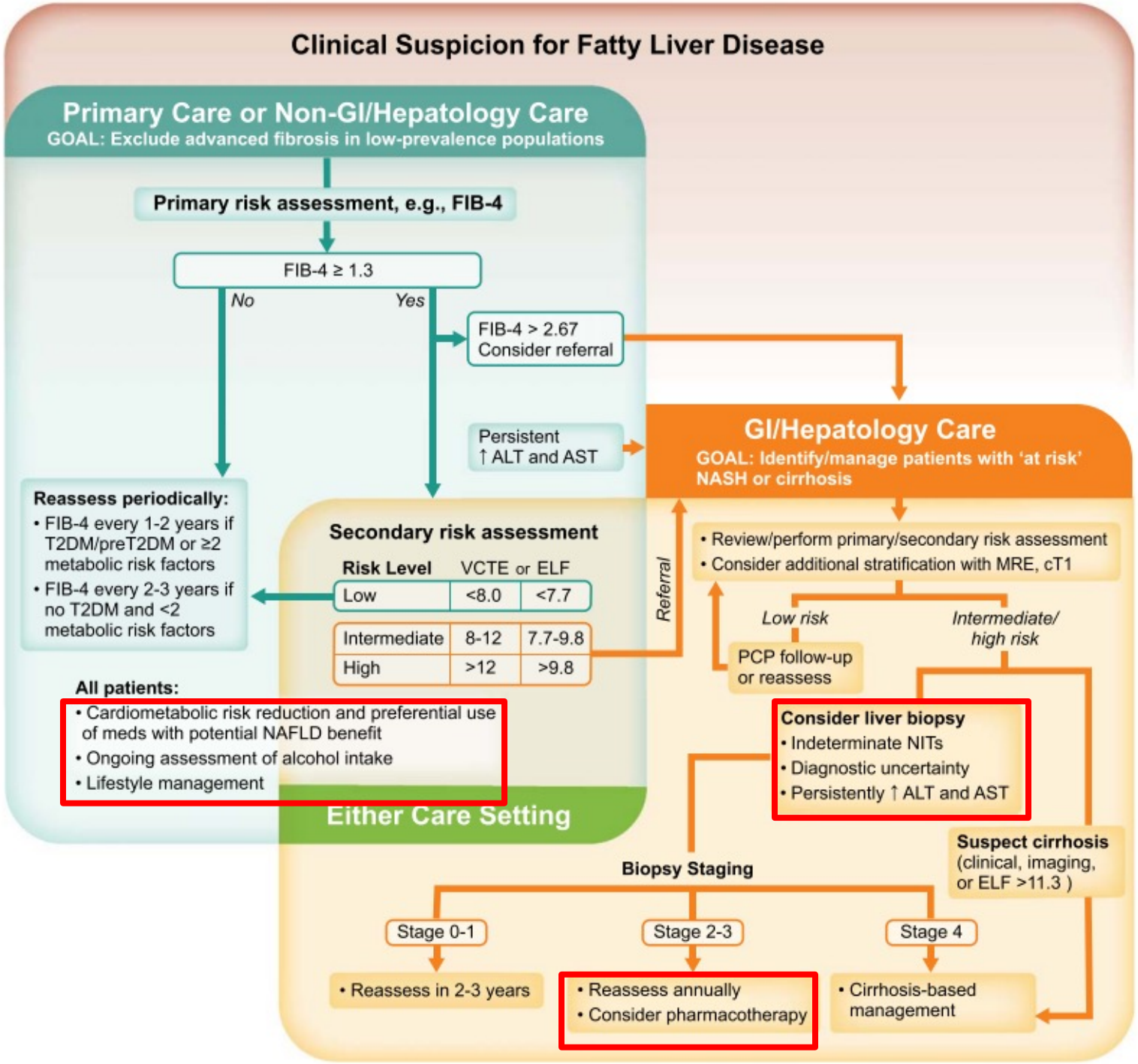
Cunningham - Game Code:
CORDUROY



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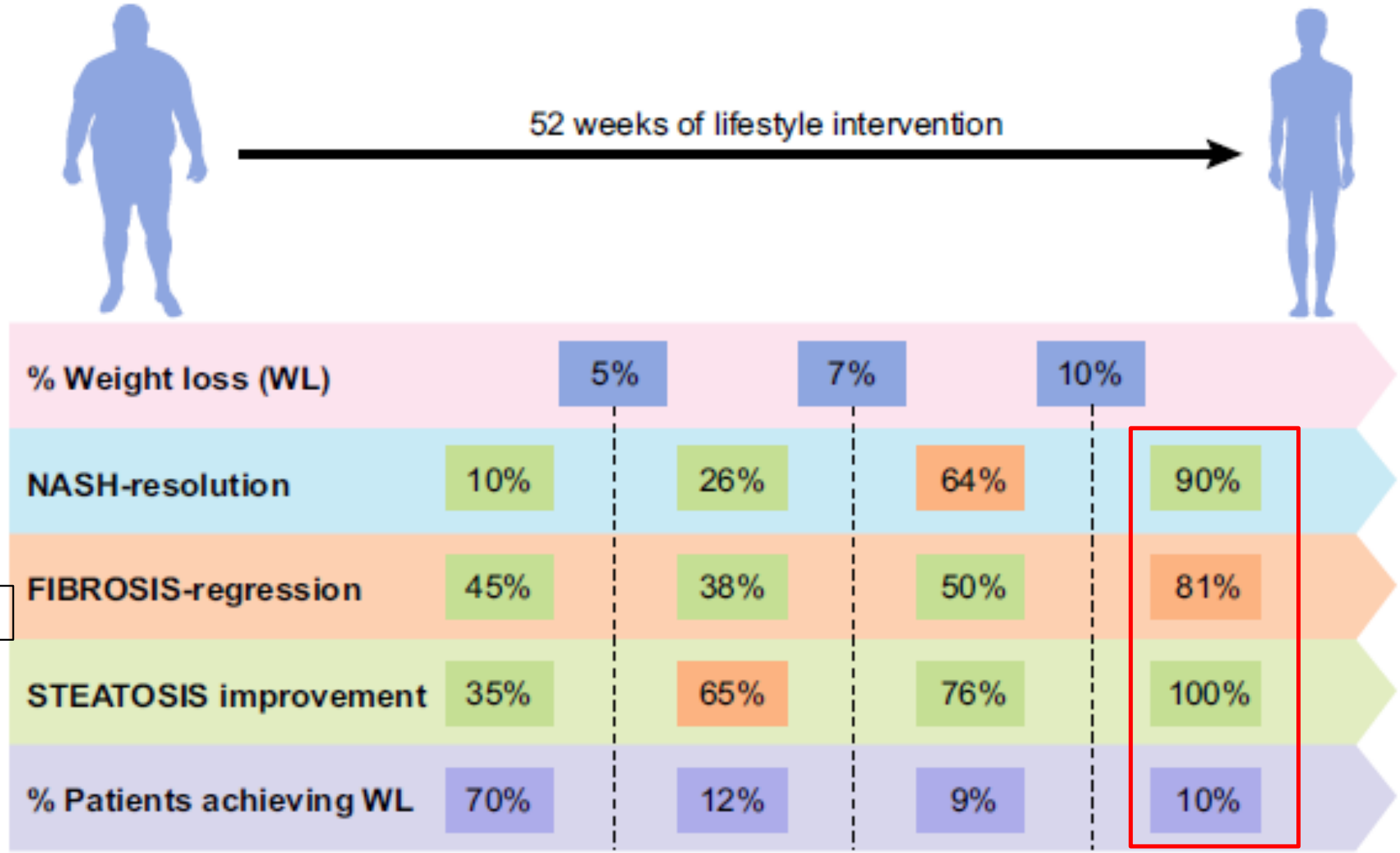


One stage

Romero-Gomez et al. J Hepatol 2017.

Energy restriction

- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

Fructose intake

- Avoid fructose-containing food and drink

Coffee consumption

Comprehensive lifestyle approach

Daily alcohol intake

- Strictly below 30 g men and 20 g women

Macronutrient composition

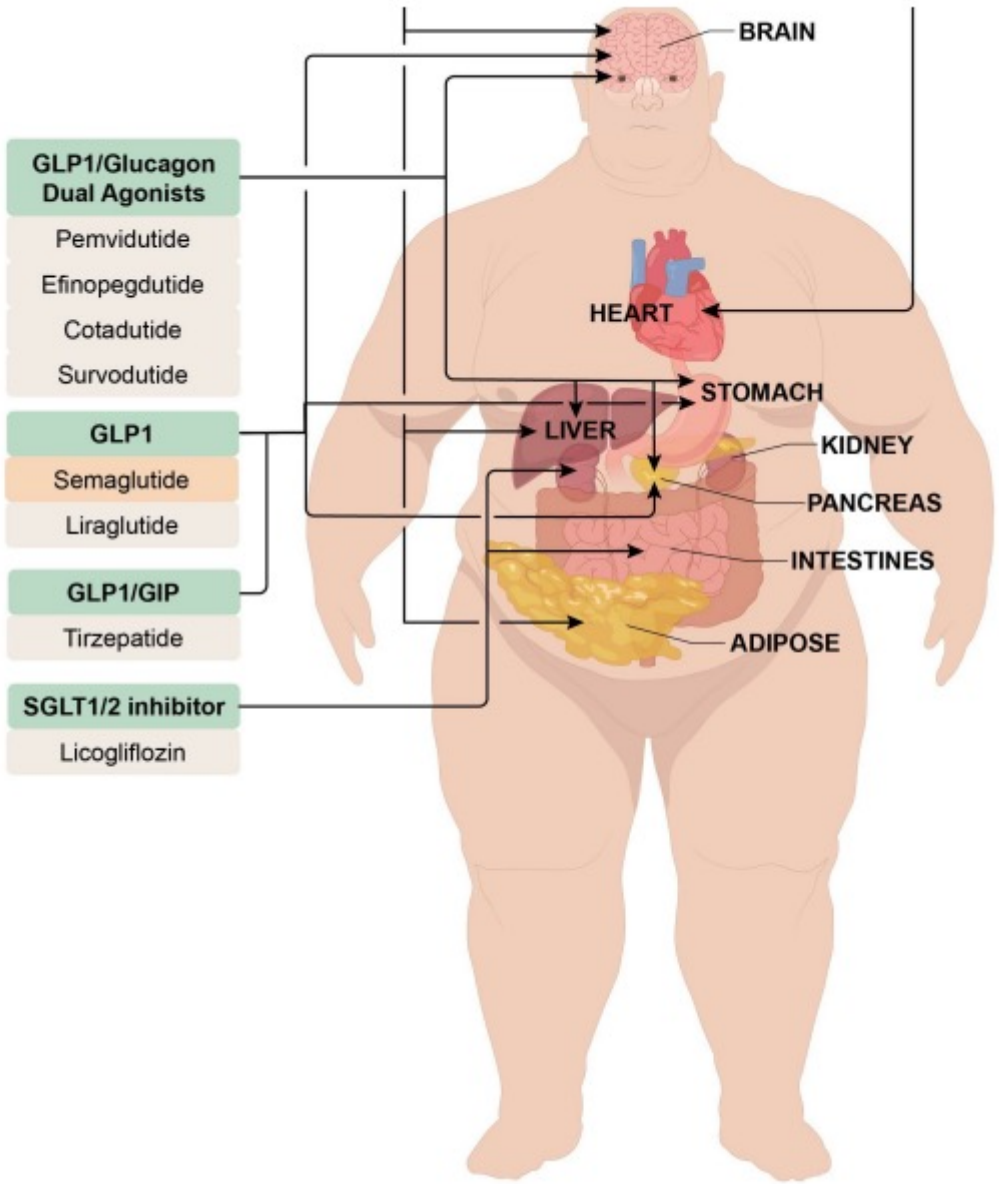
- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

Physical activity

- moderate intensity 3–5 sessions x 20’
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

EASL Guidelines

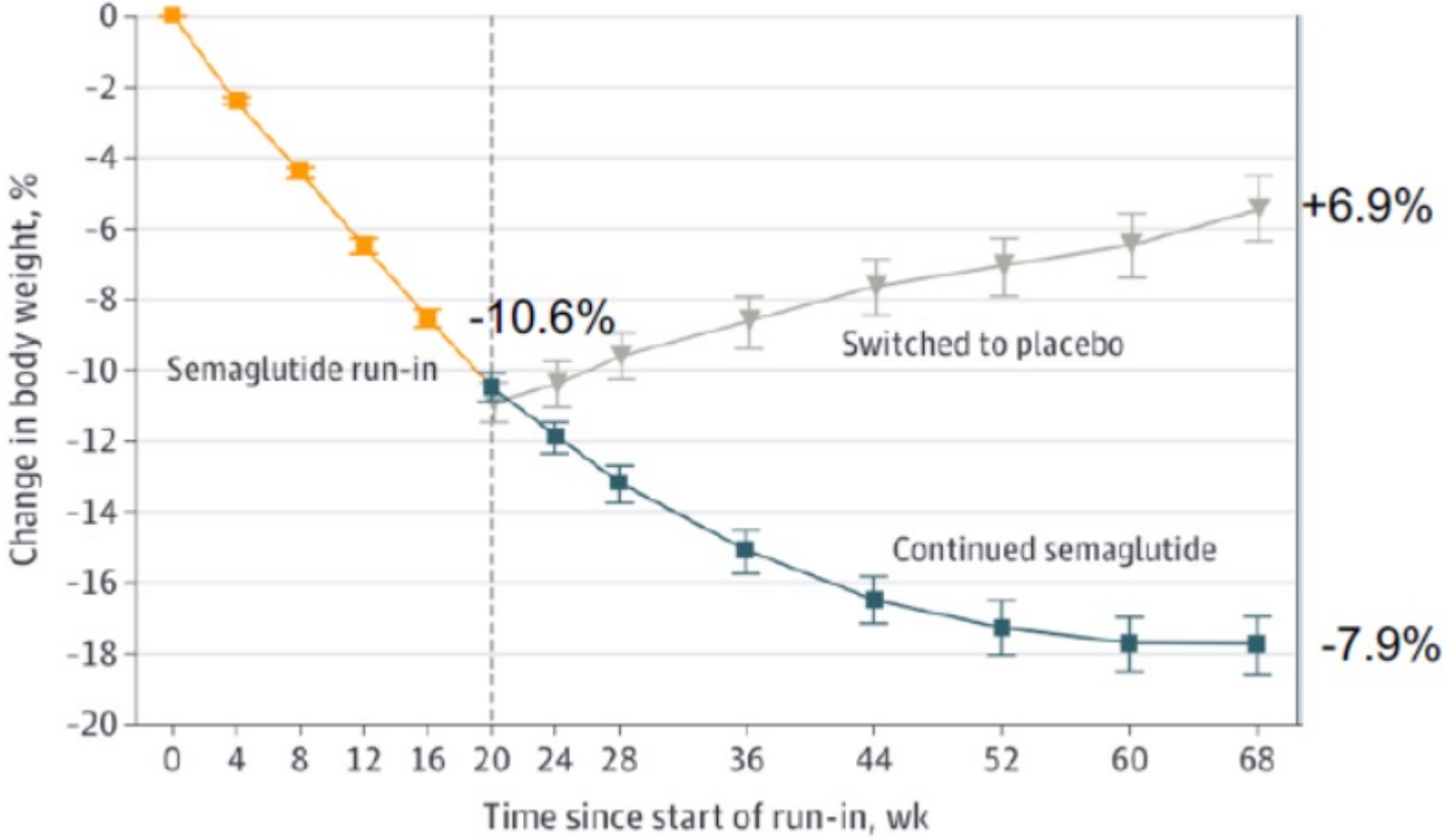
Weight loss pharmacotherapy



	Mean Weight loss %
Phentermine/Topiramate (Qsymia)	10-11%
Naltrexone/Bupropion (Contrave)	5-8%
Licogliflozin (SGLT1/2 inh)	5%
Liraglutide (GLP), sc	5-8%
Semaglutide (GLP), sc With behavior therapy Oral	11-15% 16% 15%
Tirzapetide (GLP/GIP)	22%

Noureddin Hepatology in review

Maintenance is required



Sustained weight loss will likely require either continued therapy

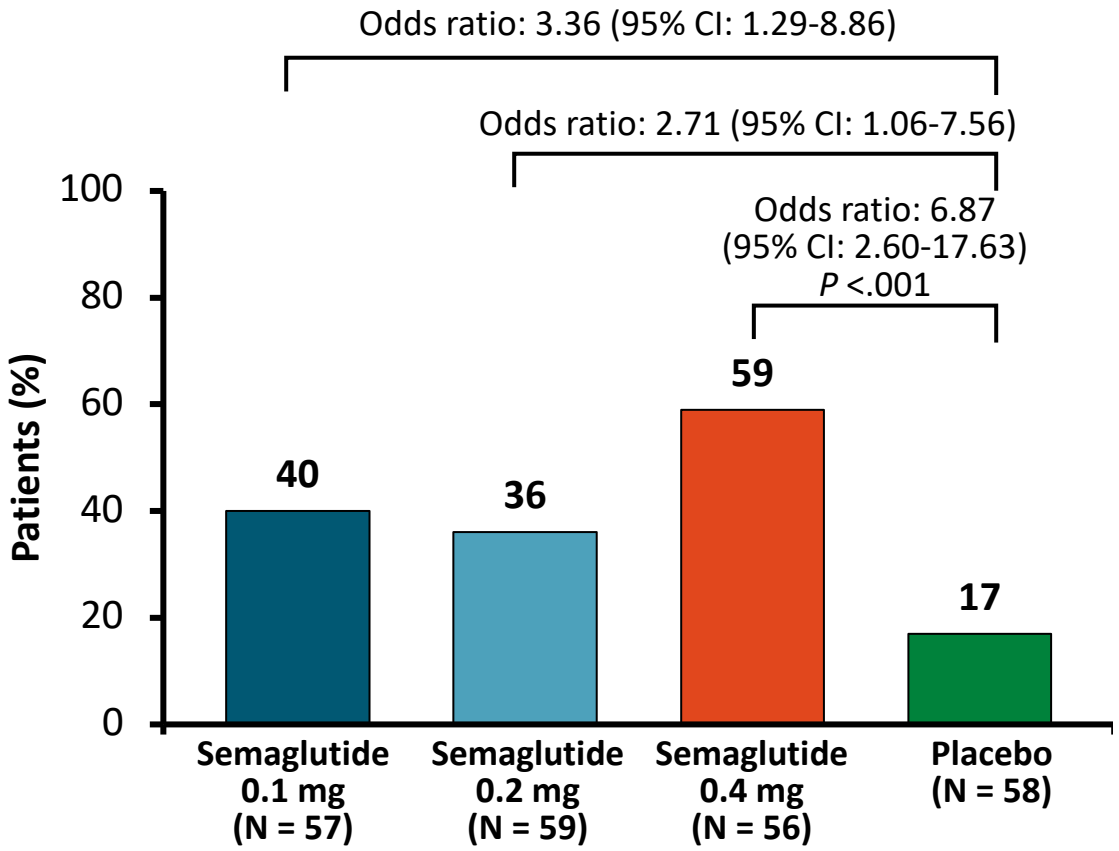
OR

Defined period of therapy plus sustained lifestyle change

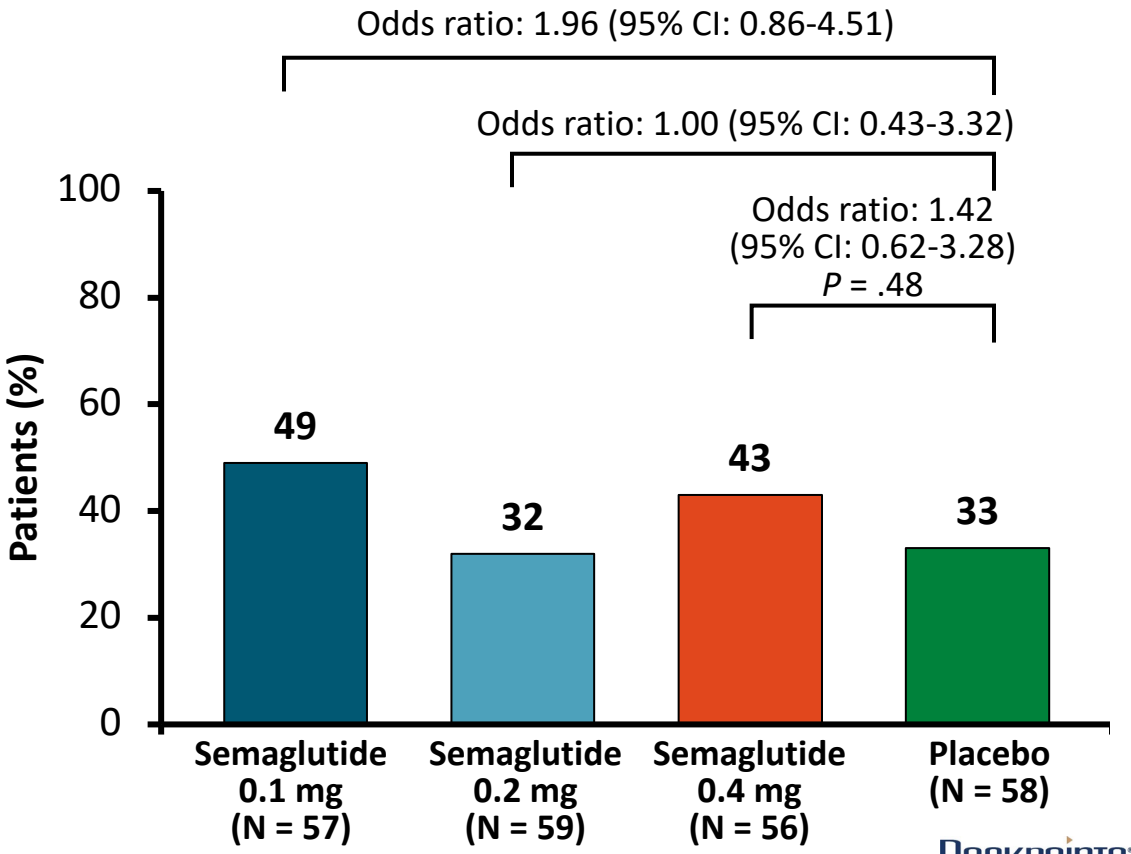
Rubino et al JAMA 2021

GLP-1 RAs: Semaglutide

Resolution of NASH With No Worsening of Liver Fibrosis (Primary Endpoint)



Improvement in Liver Fibrosis Stage With No Worsening of NASH (Confirmatory Secondary Endpoint)



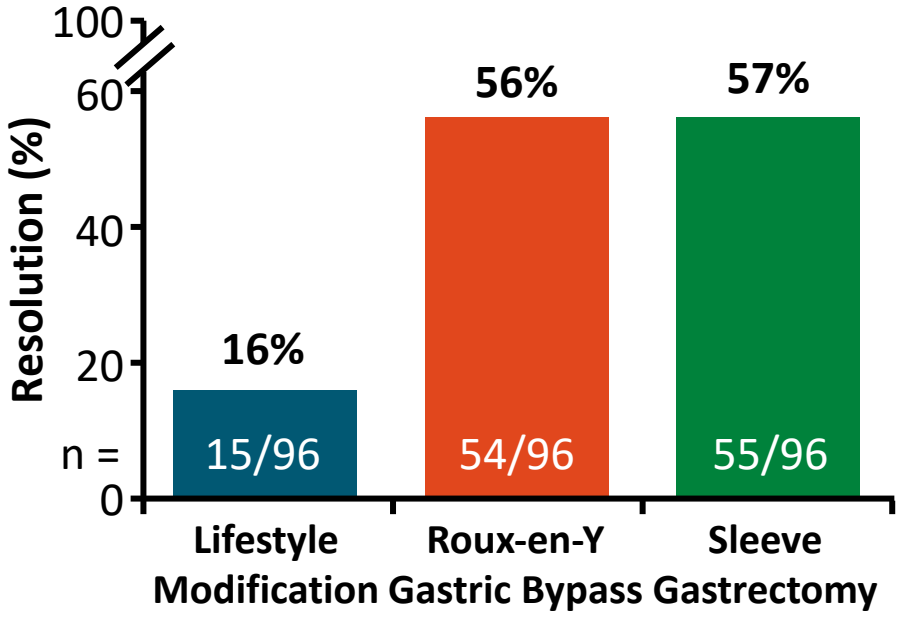
Newsome. NEJM. 2021:384:1113.

Slide credit: clinicaleducationalliance.com

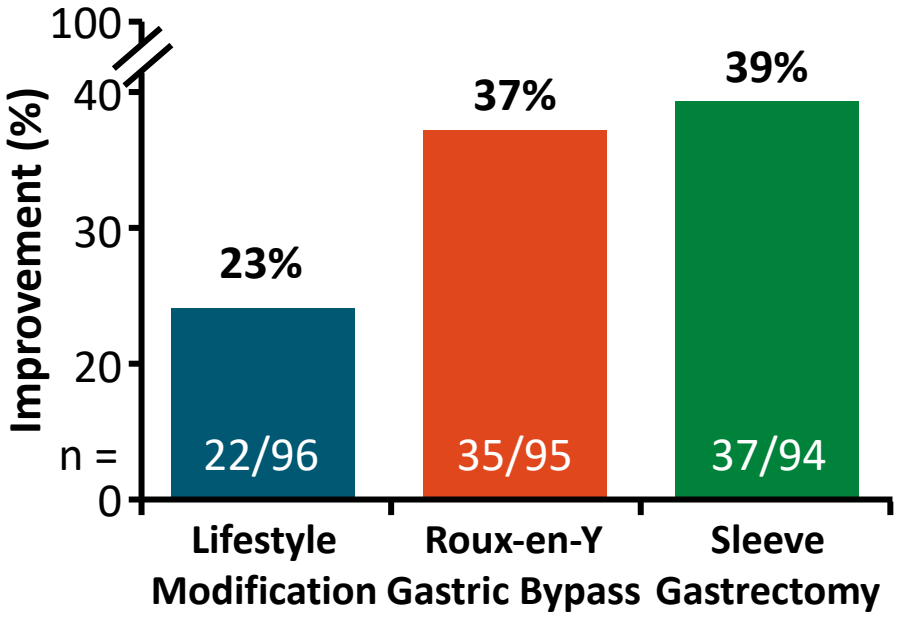
Bariatric Surgery and MASLD

- Improvement in liver histology reported in several studies

MASH Resolution Without Worsening Fibrosis (ITT)



Improvement of ≥1 Stage of Liver Fibrosis Without Worsening of MASH (ITT)



- Lap sleeve gastrectomy can be performed in select patients with compensated cirrhosis at experienced centers (>100 cases/yr)

Harrison. Hepatology. 2009;49:80. Promrat. Hepatology. 2010;51:121. Chalasani. Hepatology. 2012;142:1592.
Lassailly. Gastroenterology. 2020;159:1290. Verrastro. Lancet. 2023;401:1786. Boon-Bee Goh. World J Gastroenterol. 2018;24:3112.

Medications with possible MASLD benefit

Drug	Patient population	Benefits	Potential harms
Vitamin E	MASH without T2DM or cirrhosis	Improved steatosis, MASH No proven benefit on fibrosis	Haemorrhagic stroke Prostate cancer
Pioglitazone	MASH with and without T2DM	Improves steatosis, MASH Possible benefit on fibrosis	Weight gain; CHF exacerbation; bone loss
Statins	MASLD with increased CVD risk score Underprescribed!	May reduce fibrosis progression, portal hypertension and risk for HCC	Muscle toxicity; elevated ALT (<3%); hepatotoxicity (rare); association with AIH (rare)
SGLT-2i	T2DM	Reduction in steatosis on imaging	Genitourinary yeast infection; volume depletion; bone loss
Liraglutide	T2DM; obesity	Improved steatosis No proven benefit on fibrosis	GI side effects, gallstones, pancreatitis
Semaglutide	T2DM; obesity	Improves steatosis, MASH Possible slowing of fibrosis Phase 3 trial in progress	GI side effects, gallstones, pancreatitis
Tirzepatide	T2DM	Reduction in steatosis on imaging	GI side effects, gallstones, pancreatitis

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New drugs in Phase 3 development

PPAR agonists

- Lanifibranor, pan-PPAR agonist

Thyroid-mimetics

- Resmetirom, THR-β agonist

FGF-21 agonists

- Efruxifermin

Others

- FGF-19; lipid metabolism/lipogenesis; anti-fibrotic; oligonucleotide-based therapies

Summary

It’s not NAFLD/NASH, it’s MASLD/MASH

- And we’re going to see more of it

Utilise non-invasive assessment tools to identify those at risk

- Low risk can be managed in primary care
- There is still a role for biopsy to risk-stratify some patients

Actively promote lifestyle management and use of medications which may benefit MASLD

Approved medications for MASH/fibrosis are coming

- Consider referring high-risk patients for clinical trials