



MASLD, Fibrosis, and Cardiometabolic Risk: A Multidisciplinary Perspective from the Hepatologist's View

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SLD: Inclusive Rather Than Exclusive Criteria

Steatotic Liver Disease (SLD)

Metabolic dysfunction–
Associated Steatotic
Liver Disease
(MASLD)

MetALD
(MASLD and increased alcohol intake*)

Alcohol-
associated
(alcohol-related)
Liver Disease
(ALD)

Specific etiology SLD

Cryptogenic
SLD

Drug-Induced
Liver Injury
(DILI)

Monogenic
diseases[†]

Miscellaneous[‡]

Metabolic
dysfunction–
Associated
Steatohepatitis
(MASH)

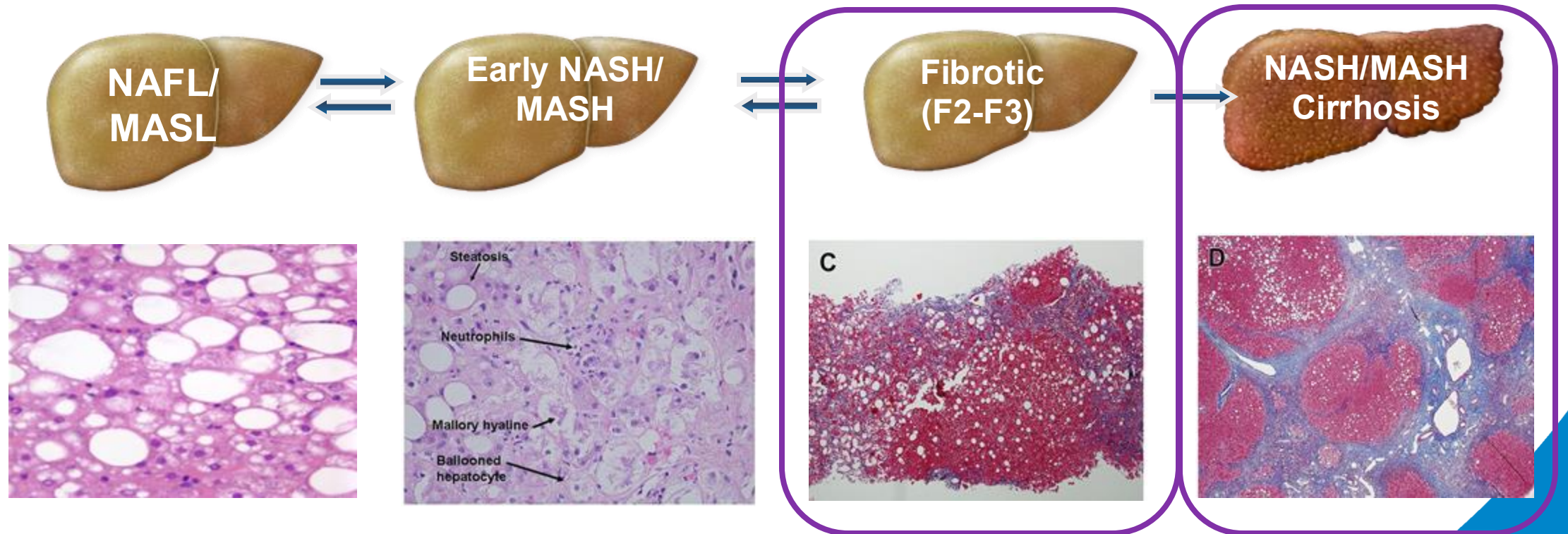
Weekly alcohol intake (g)			
MASLD predominant	210		ALD predominant
140/210	210	280	350/420
Average daily alcohol intake (g)			
MASLD predominant	30		ALD predominant
20/30	30	40	50/60

*Weekly intake 140-350 g female, 210-420 g male (average daily: 20-50 g female, 30-60 g male).

[†]eg, lysosomal acid lipase deficiency, Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism.

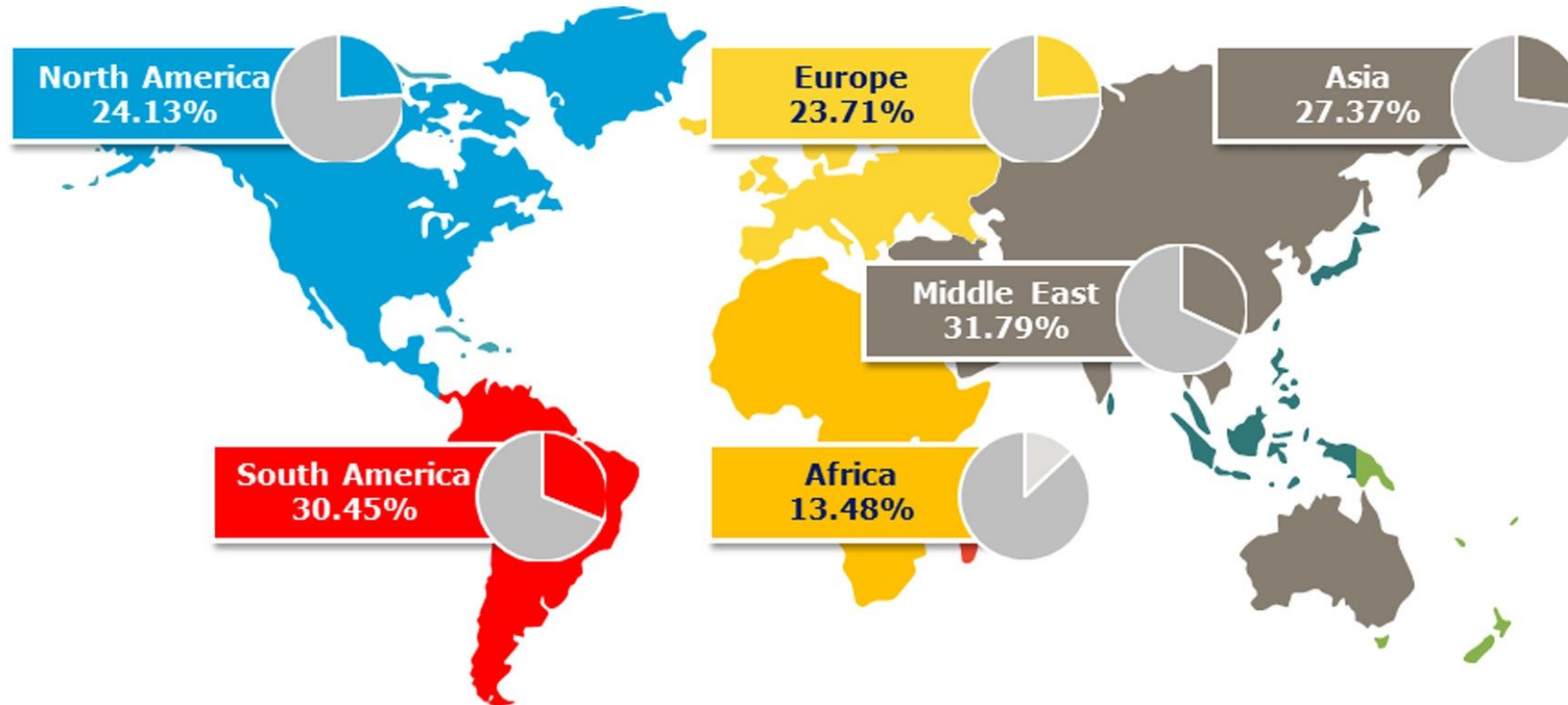
[‡]eg, hepatitis C virus, malnutrition, celiac disease.

MASLD Rules: Natural History

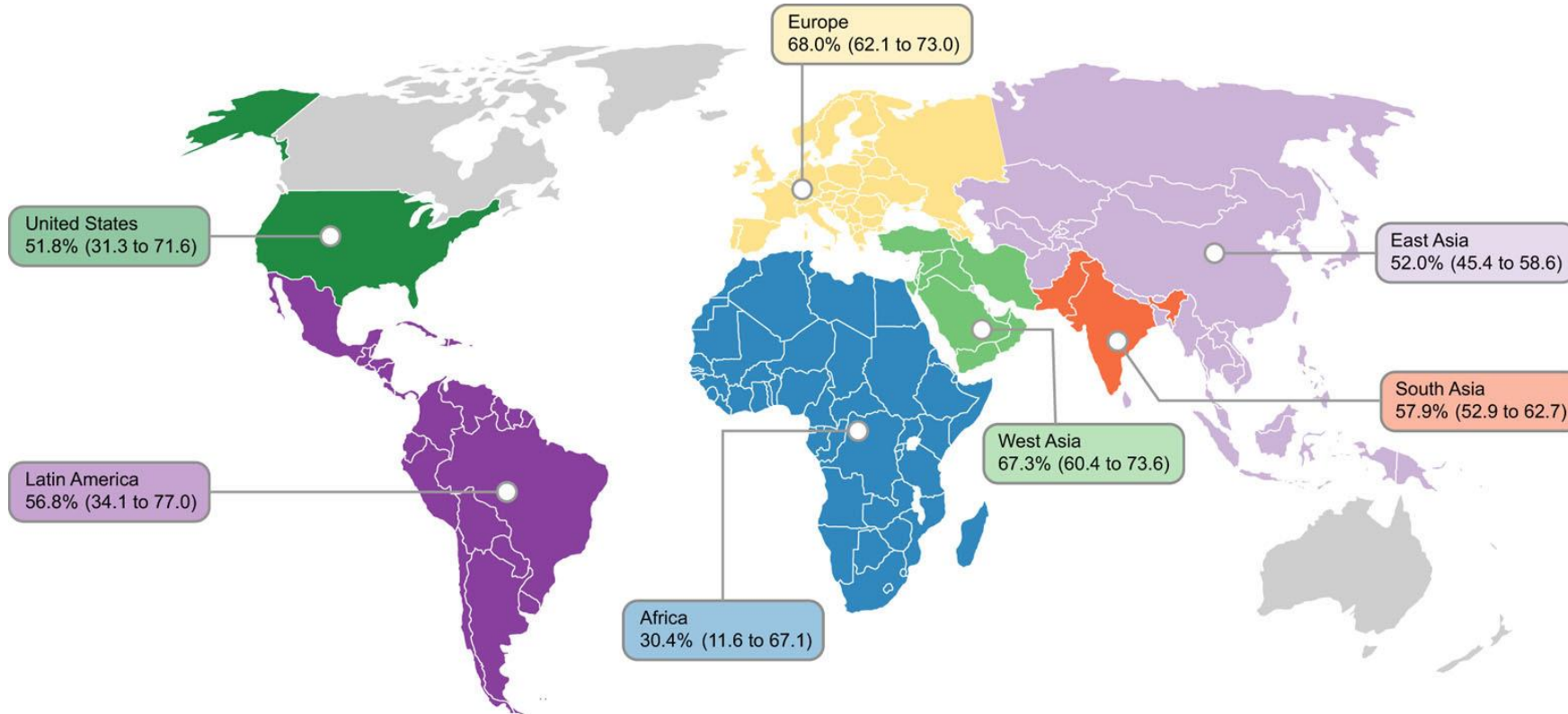


Prevalence of MASLD and MASH

- Global prevalence of NAFLD is 25.24% (95% CI: 22.10-28.65)
- Prevalence of NASH in general population is estimated between 1.5% and 6.45%



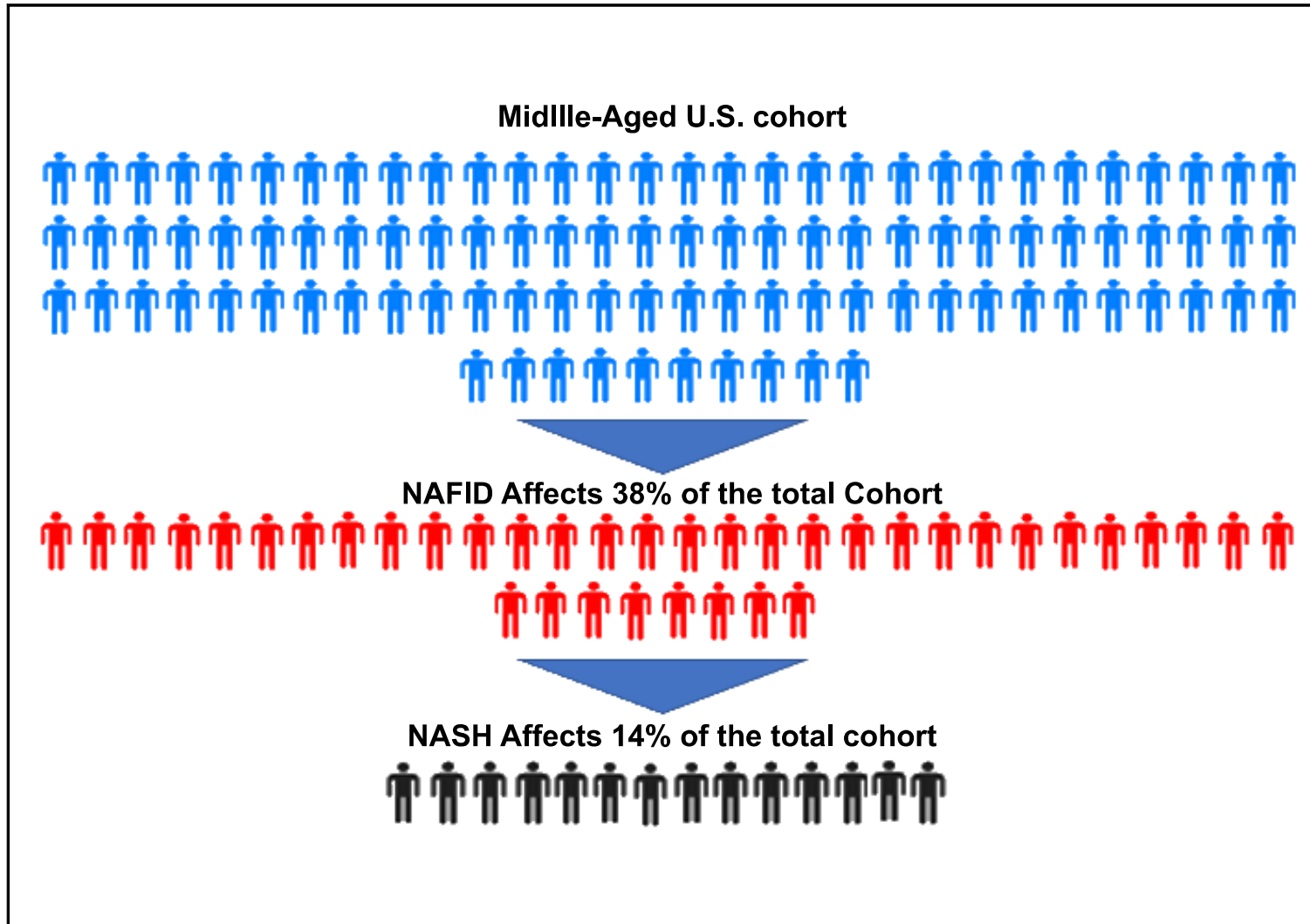
Prevalence of MASLD in Patients with Diabetes



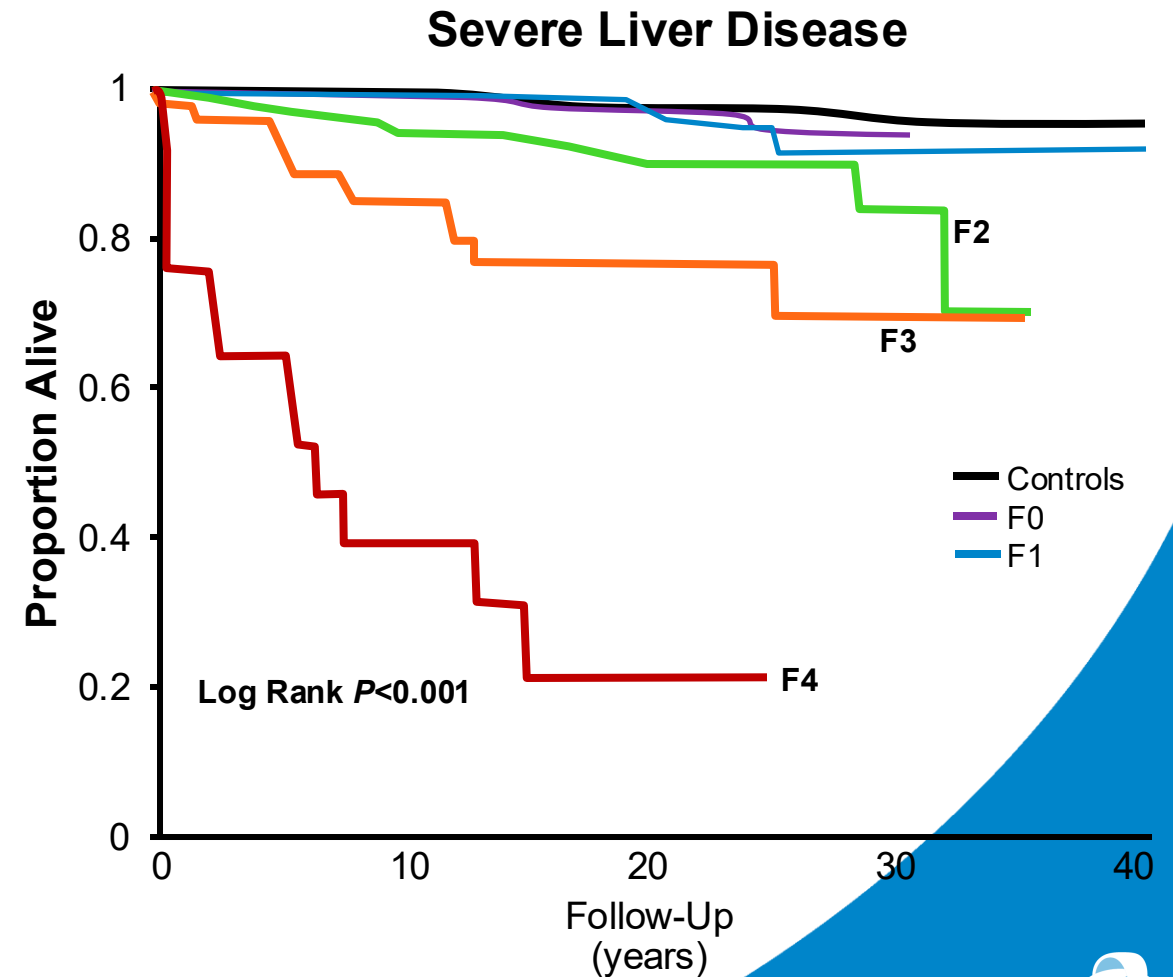
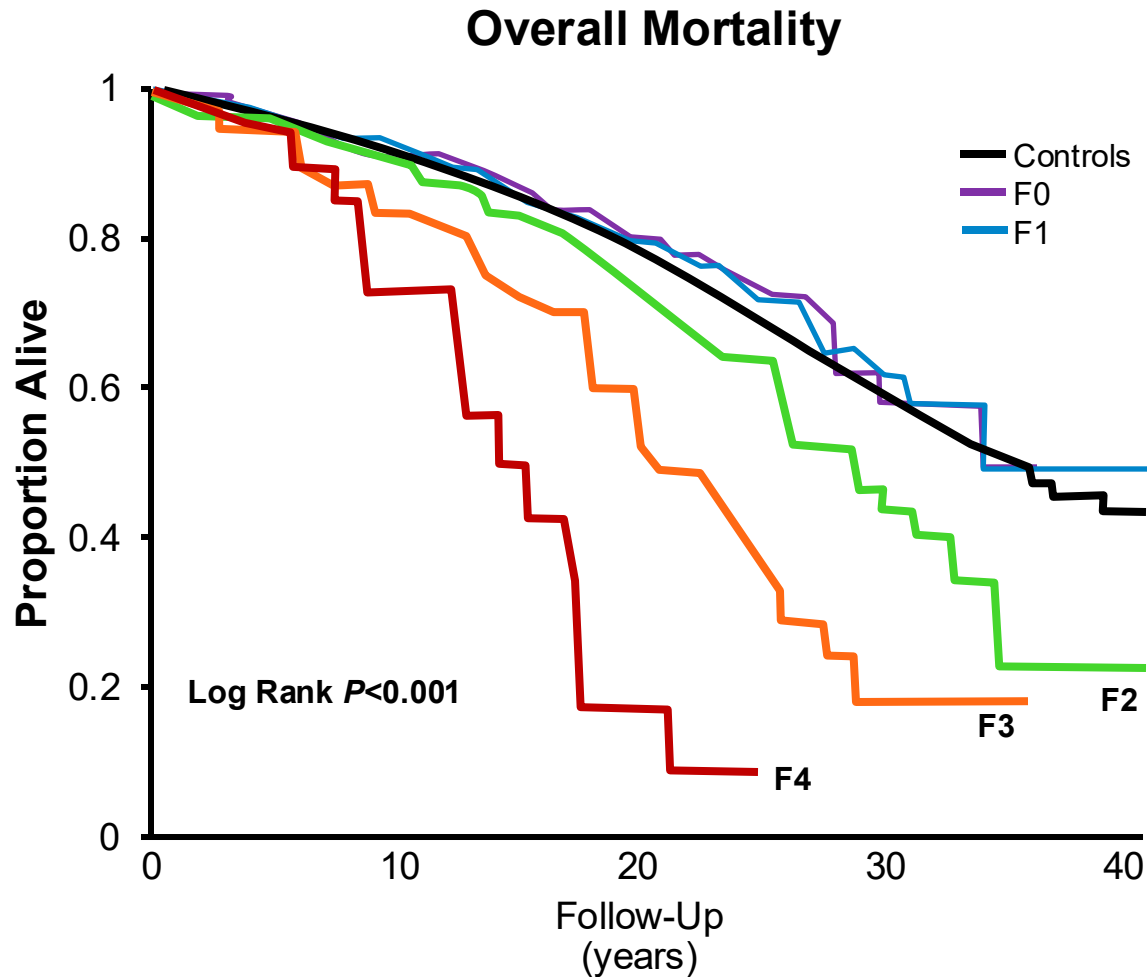
- Overall global prevalence of NASH among T2DM patients is 37.3%
- 17% of biopsied diabetics have advanced fibrosis (fibrosis \geq F3)

**Global prevalence of NAFLD among T2DM patients 55.5%
(95% confidence interval: 47.3-63.7)**

High Epidemic Areas



MASH Rules: Baseline Fibrosis Stage Predicted Mortality and Time To Development of Severe Liver Disease



The NASH CRN Prospective Data

The NEW ENGLAND JOURNAL of MEDICINE

Clinical Outcomes in Adults with Nonalcoholic Fatty Liver Disease

MULTICENTER, PROSPECTIVE STUDY

1773

Adults with nonalcoholic fatty liver disease (median follow-up, 4 yr)



Fibrosis Stage

F0 to F2
No, mild, or moderate fibrosis
N=1237

F3
Bridging fibrosis
N=369

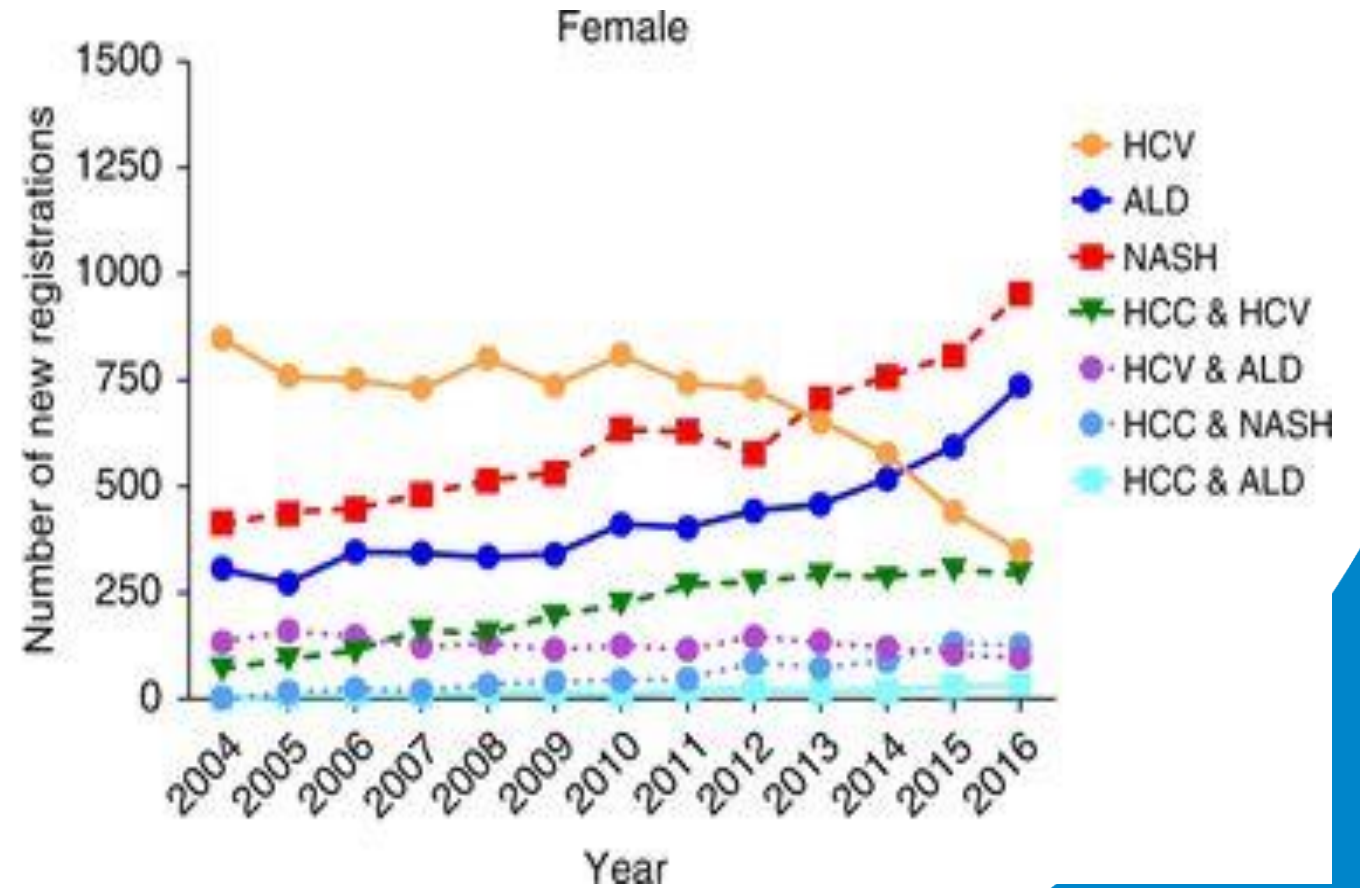
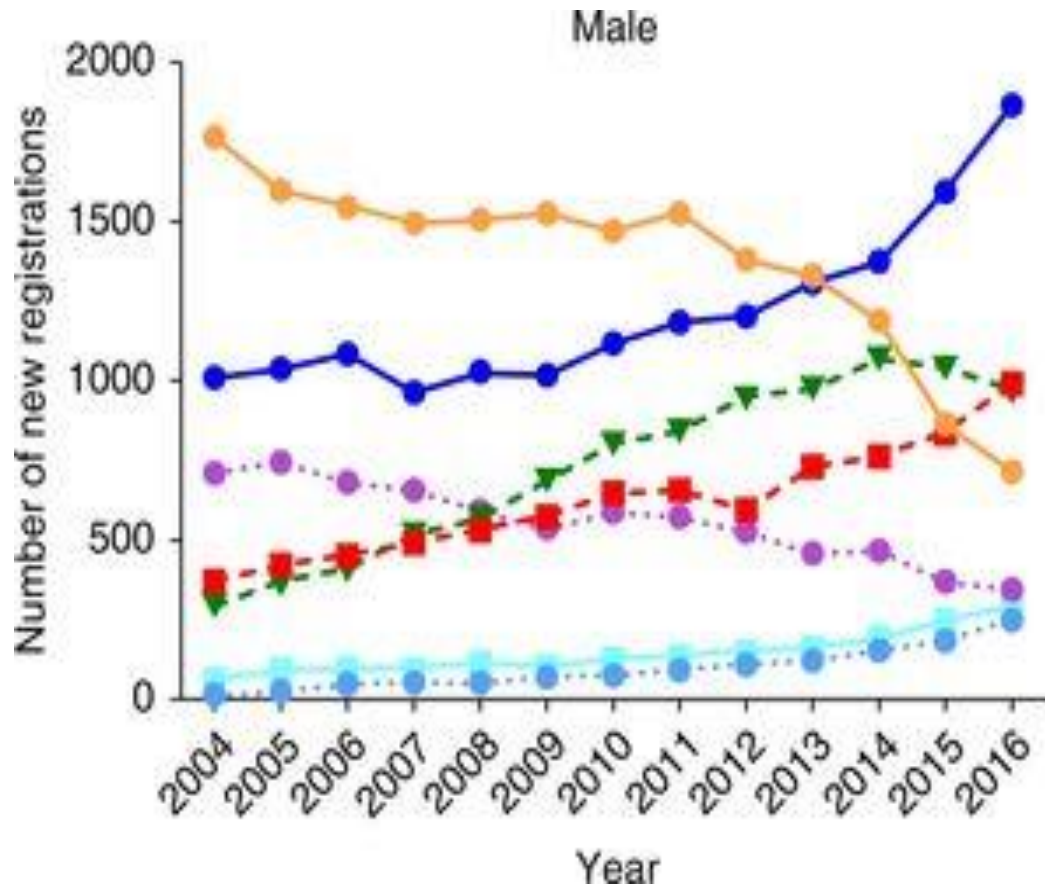
F4
Cirrhosis
N=167

Liver-related events

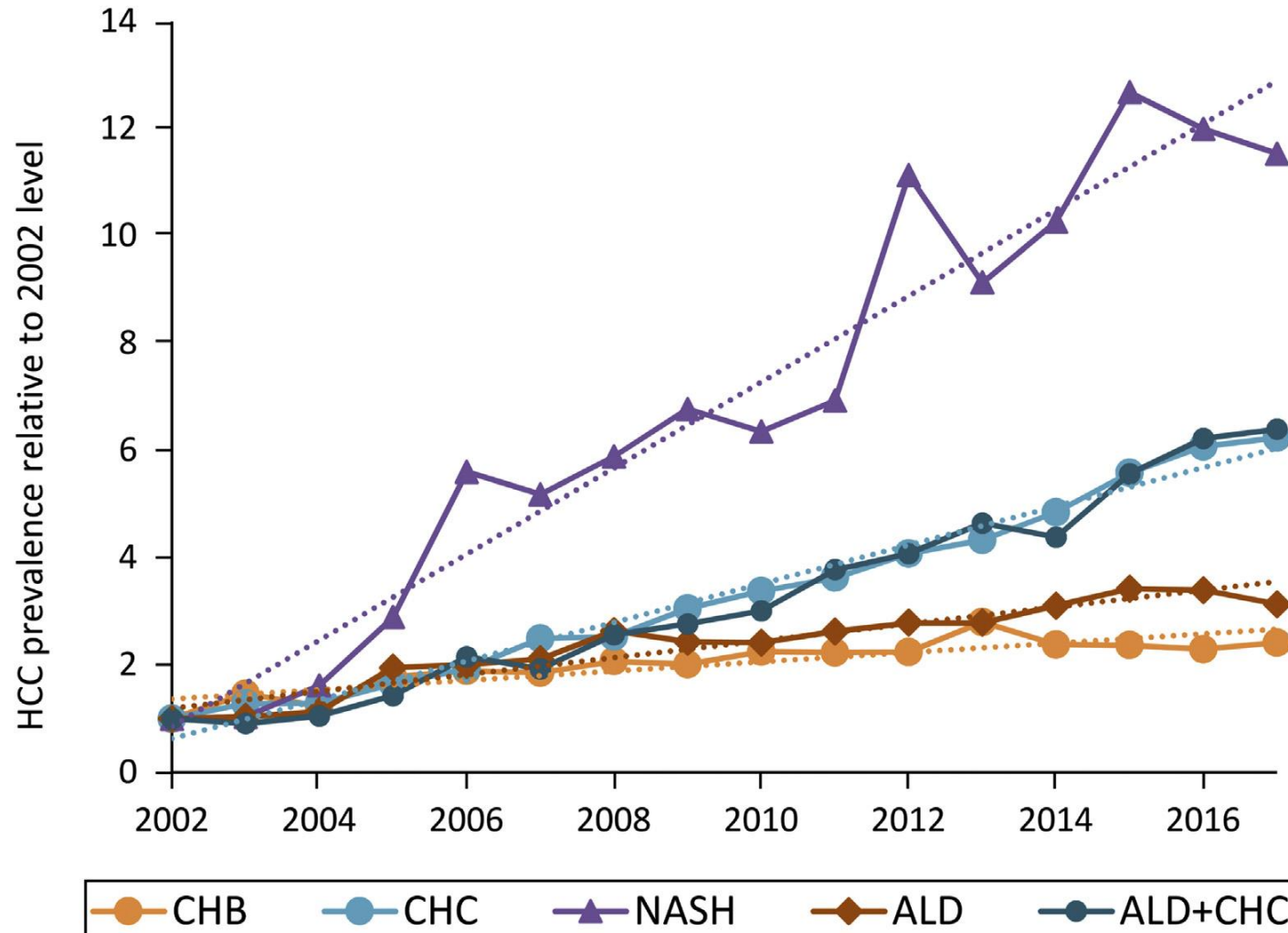
	F0 to F2	F3	F4
		rate per 100 person-yr	
Variceal bleeding	0.00	0.06	0.70
Ascites	0.04	0.52	1.20
Encephalopathy	0.02	0.75	2.39
Hepatocellular carcinoma	0.04	0.34	0.14
Death from any cause	0.32	0.89	1.76

Increasing fibrosis stage is associated with increased risks of liver-related complications and death.

MASH Leading Cause of Transplant in Women



MASH is Fastest Cause of HCC

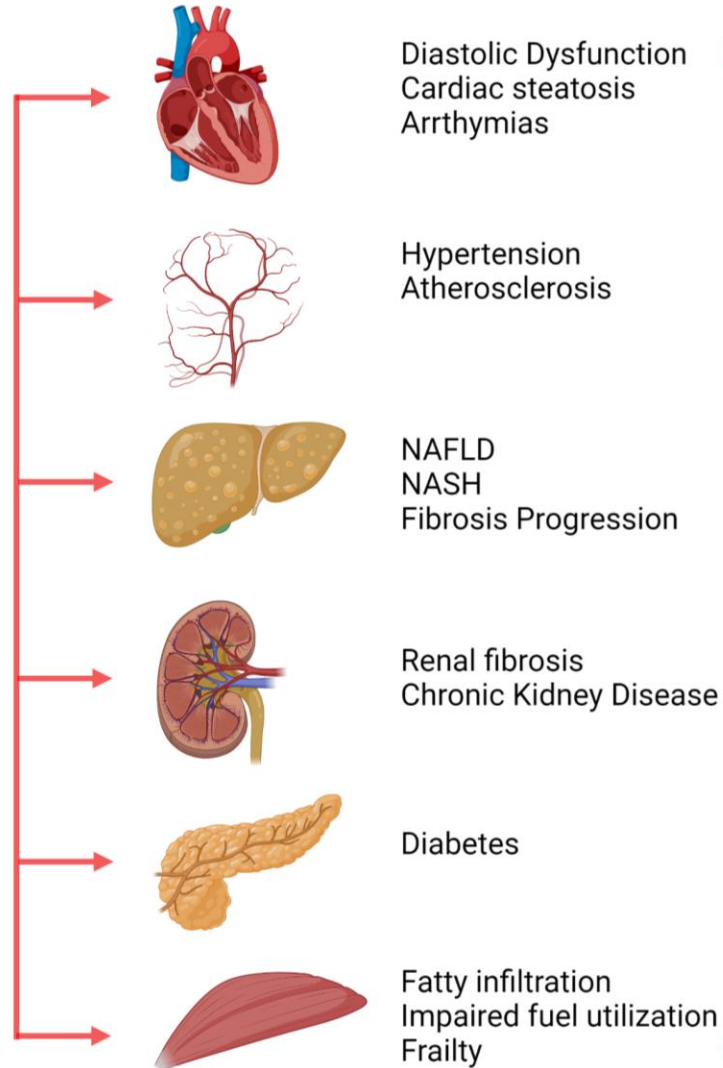


Multisystem Disease with Competing Risk

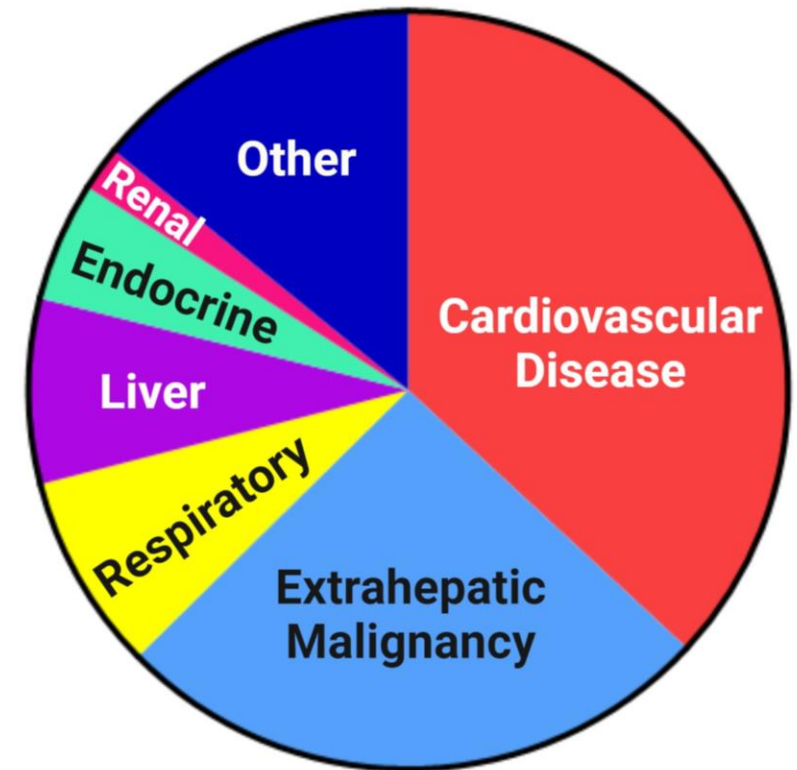
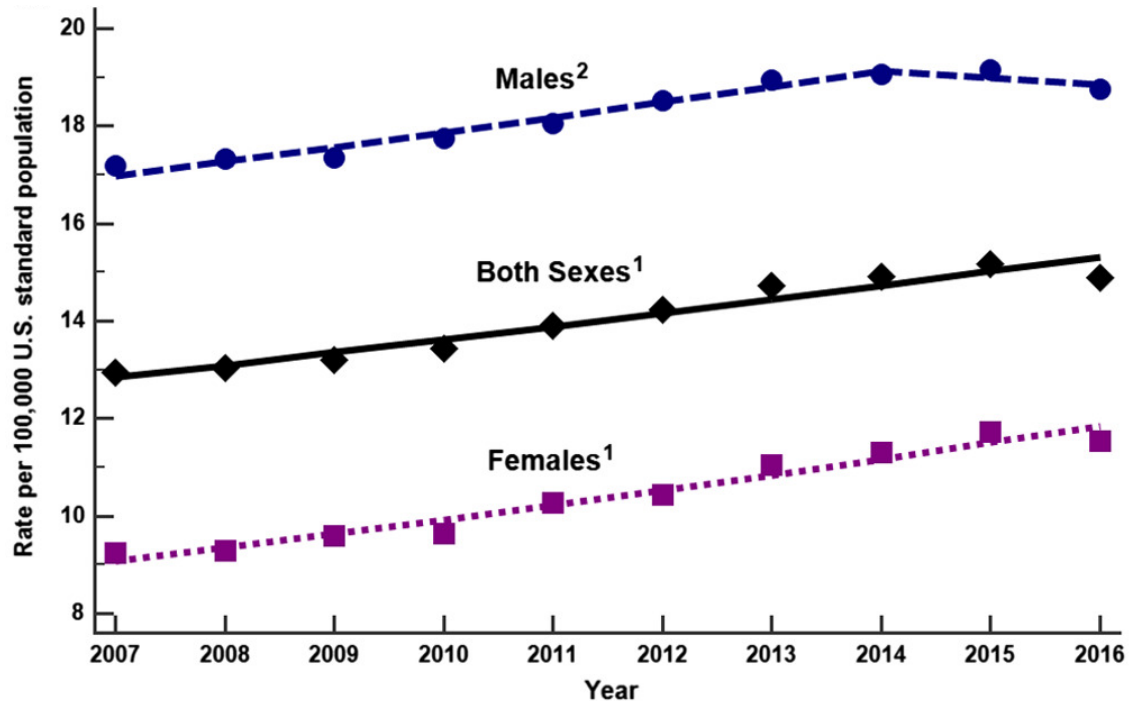
Metabolic overload
(diet, sedentary lifestyle)



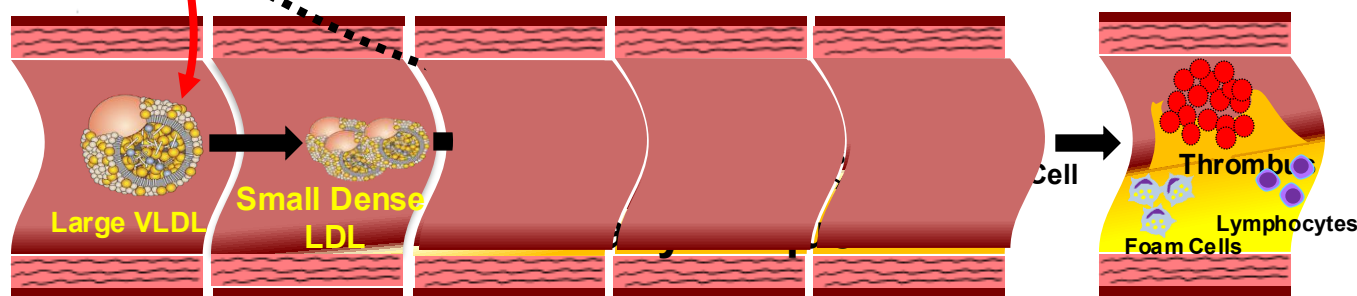
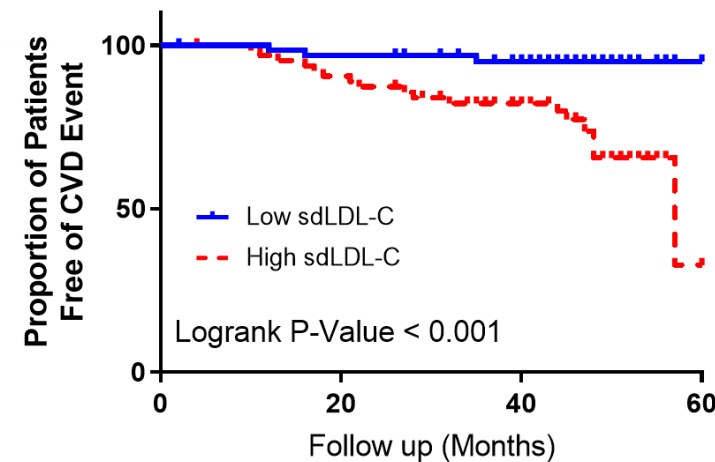
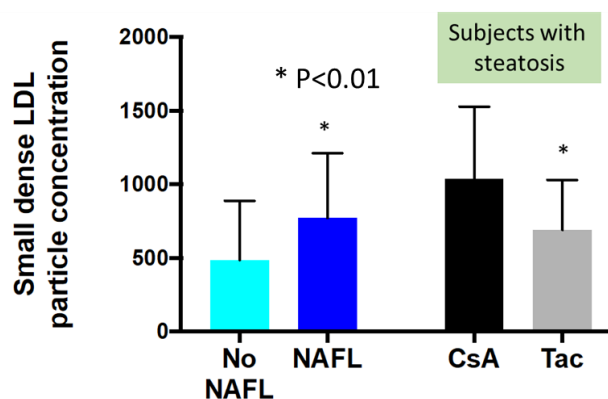
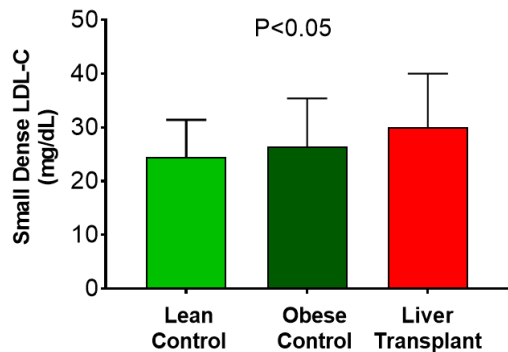
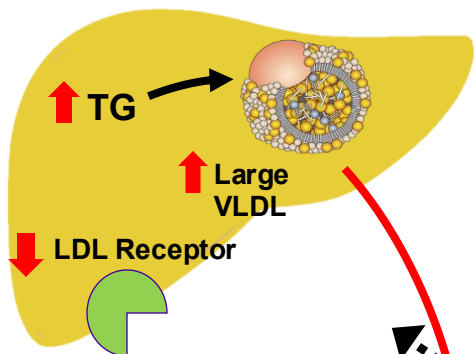
Inflammation
Injury
Fibrosis



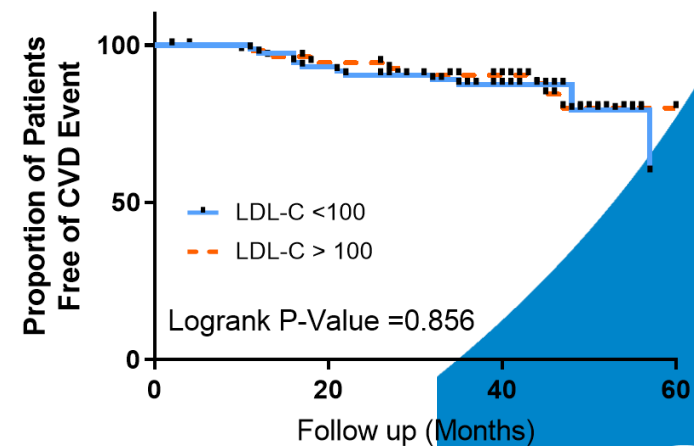
Mortality Rates in MASLD Are Increasing



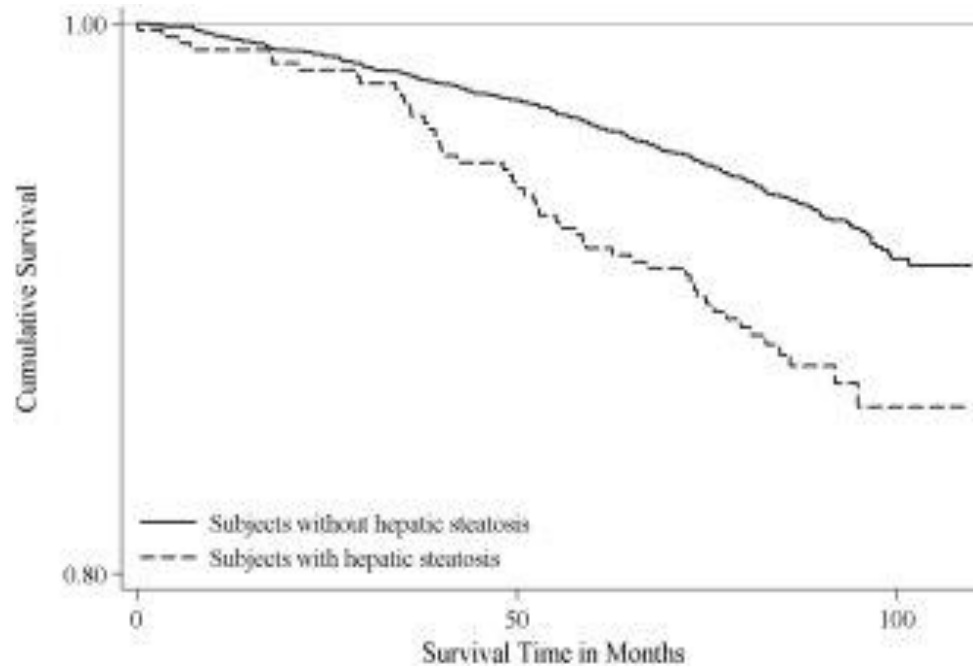
Liver Is Central To Lipoprotein Metabolism And Atherogenic Dyslipidemia



Circulation



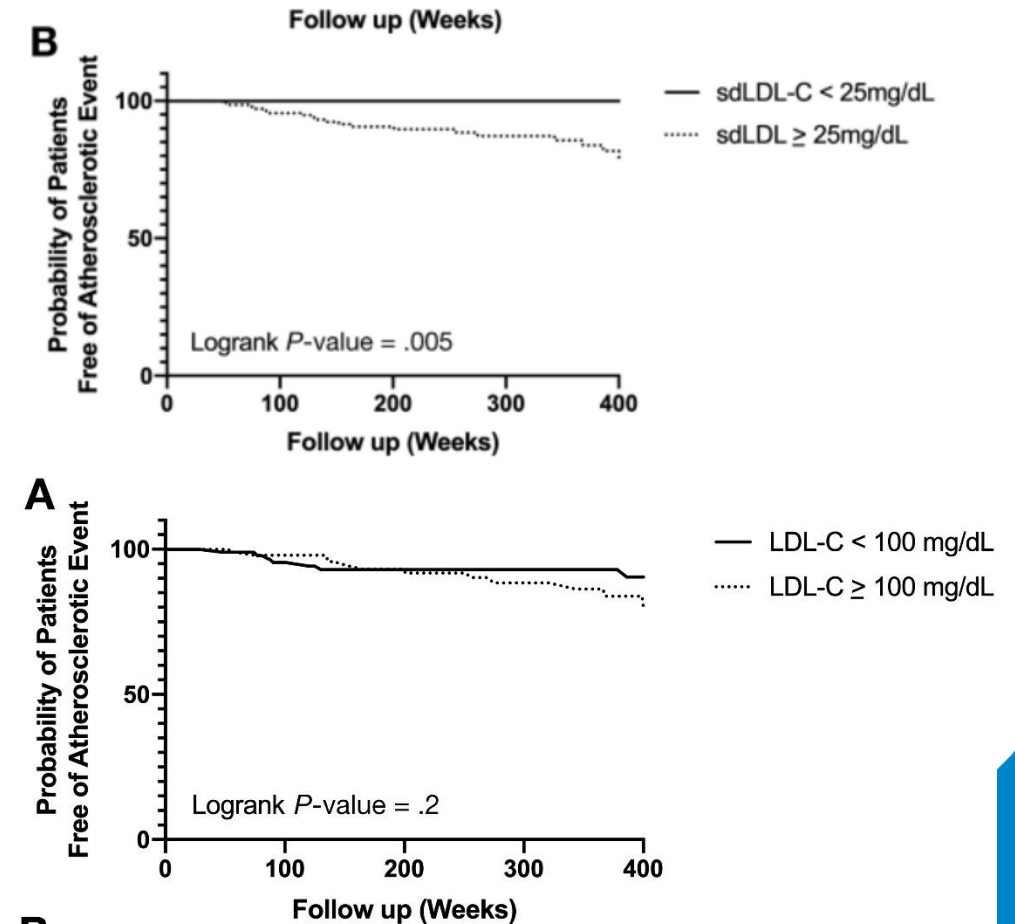
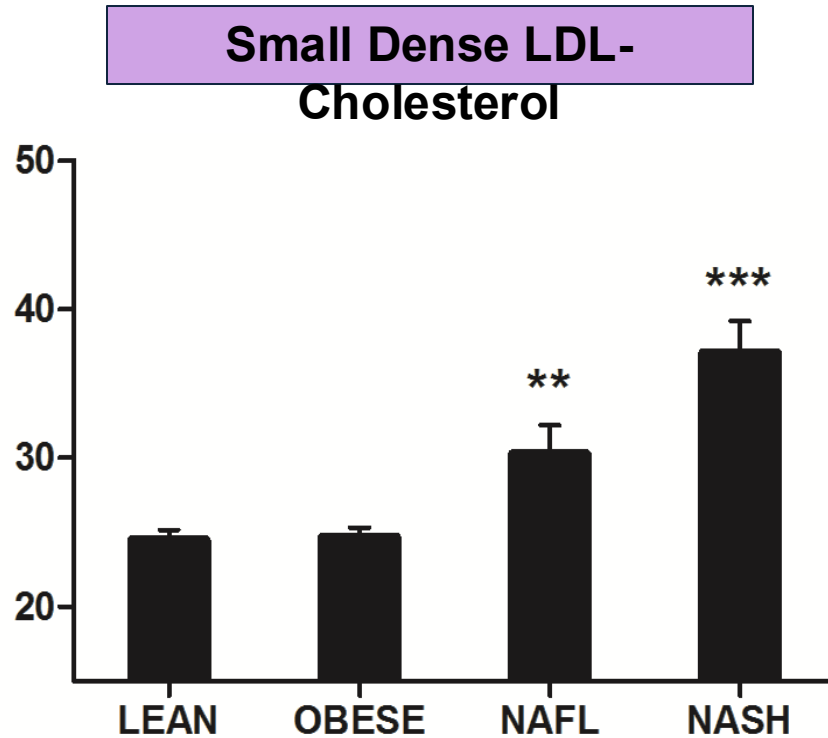
Risk Of All-Cause And CVD-Related Mortality Associated with Severity of MASLD



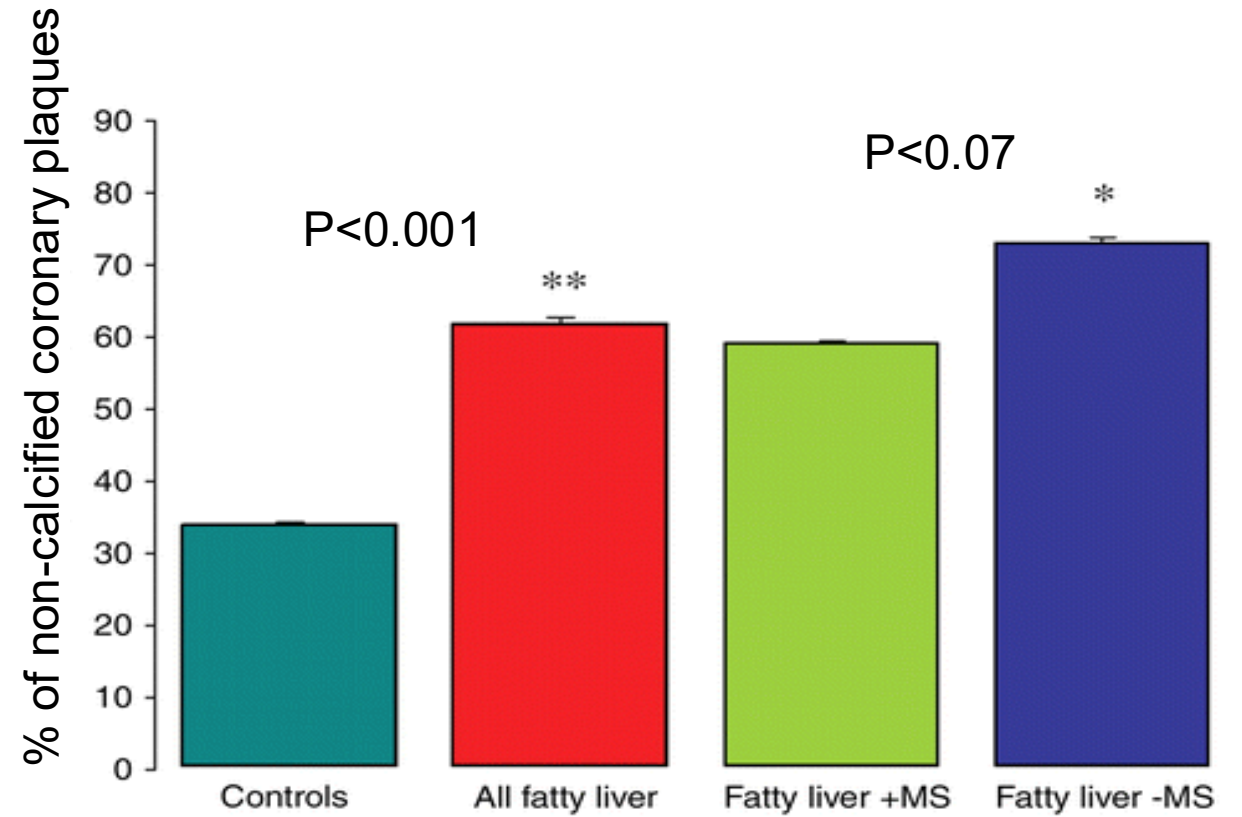
CVD-related mortality by Fibrosis

	Multivariate Adjusted Models for CVD mortality
High NFS	1.69 (1.09-2.63)
High APRI	2.53 (1.33-3.37)
High FIB-4	2.68 (1.44-4.99)

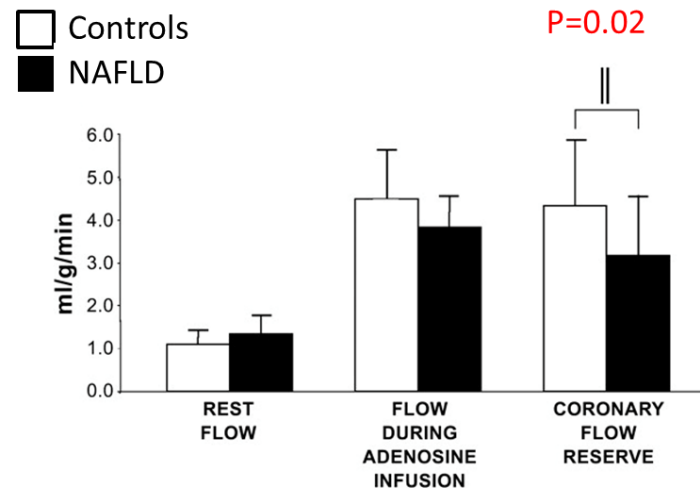
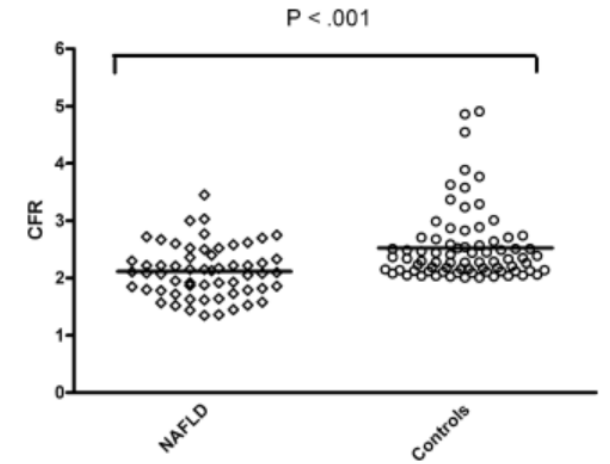
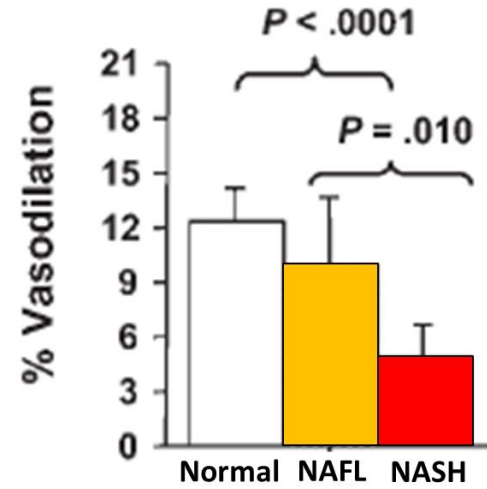
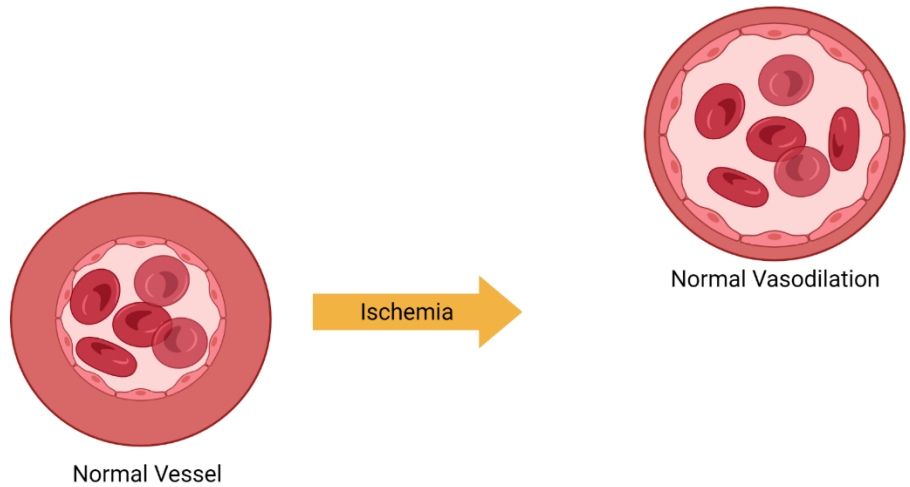
Small Dense LDL In MASLD



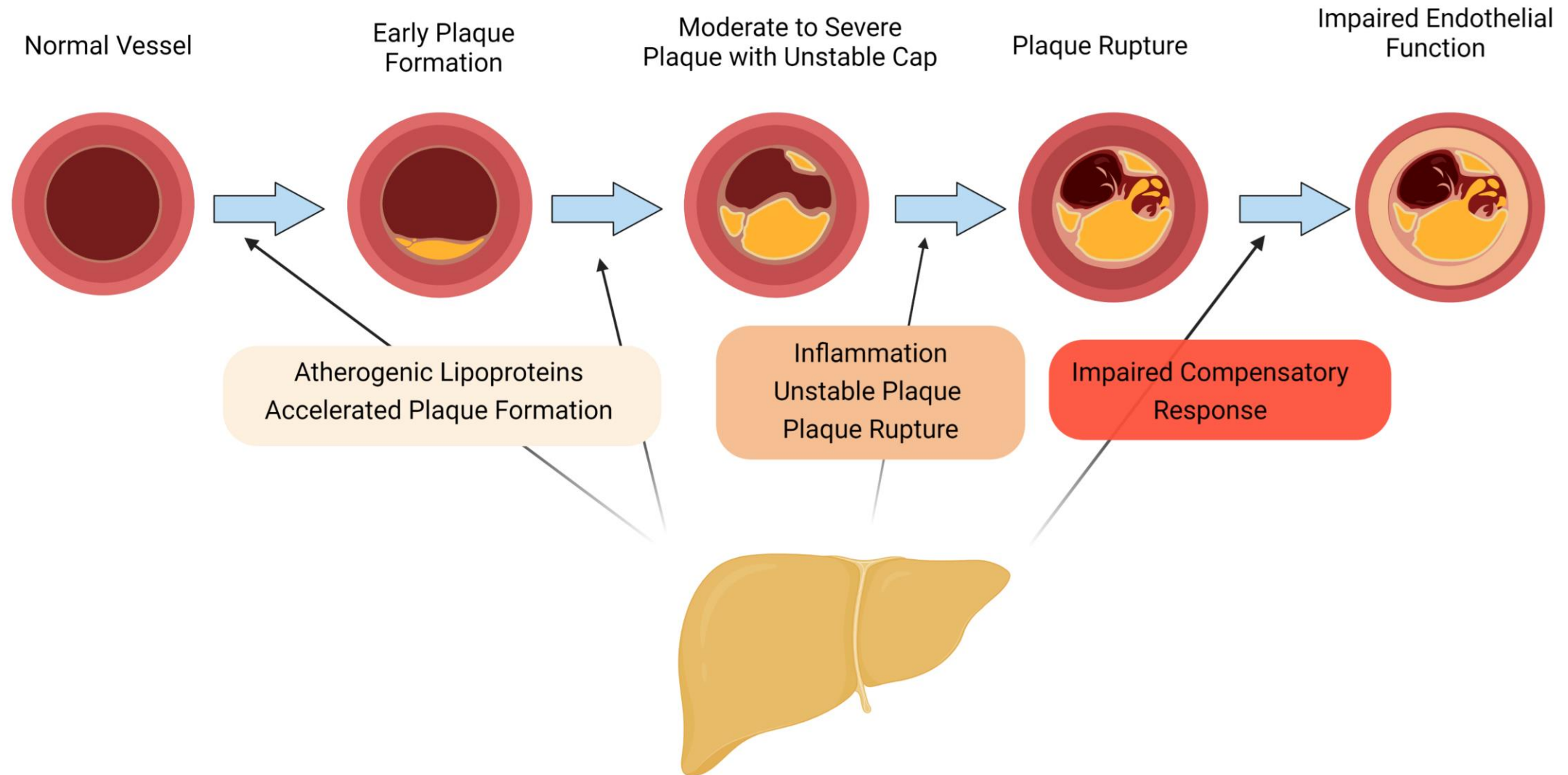
Vulnerable Coronary Plaques In MASLD



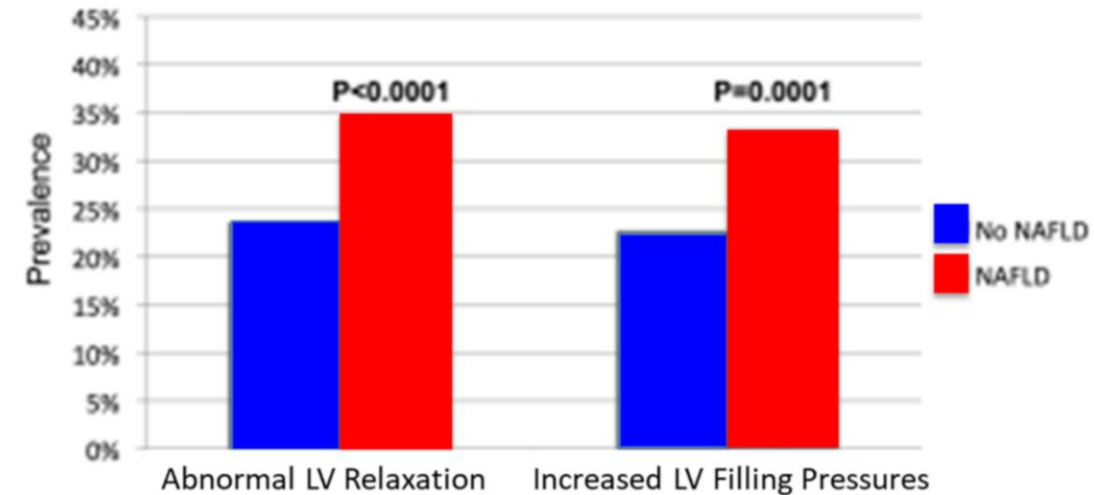
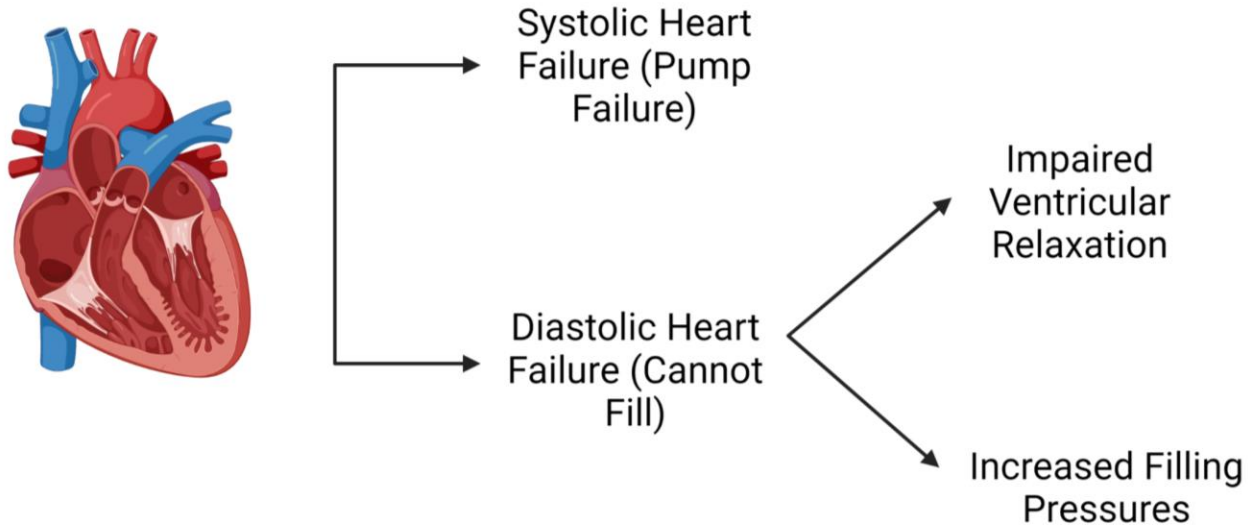
Impaired Endothelial Function In MASLD



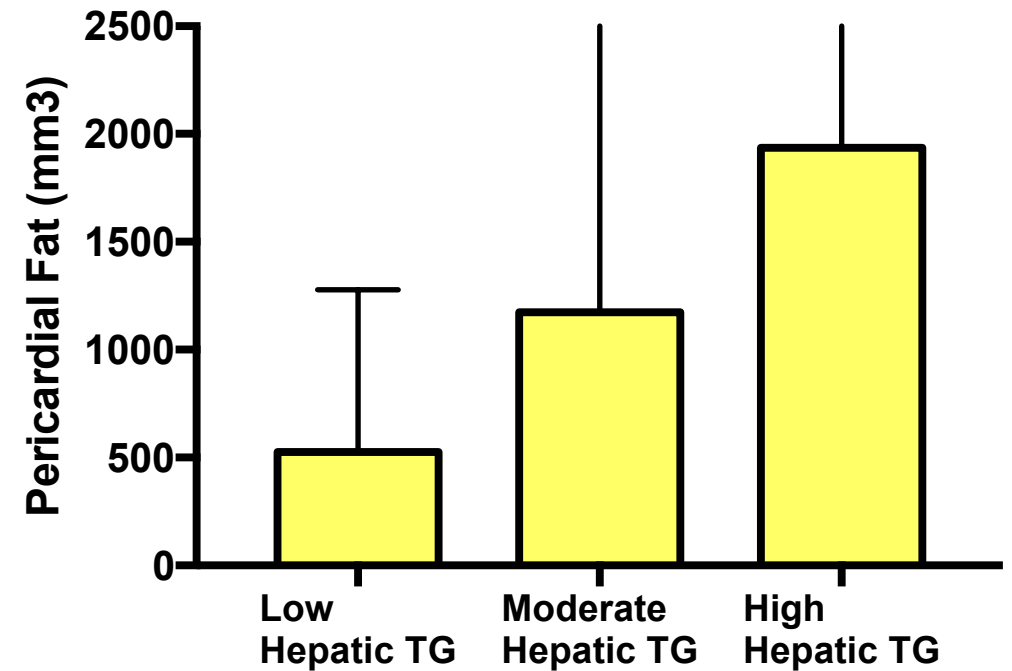
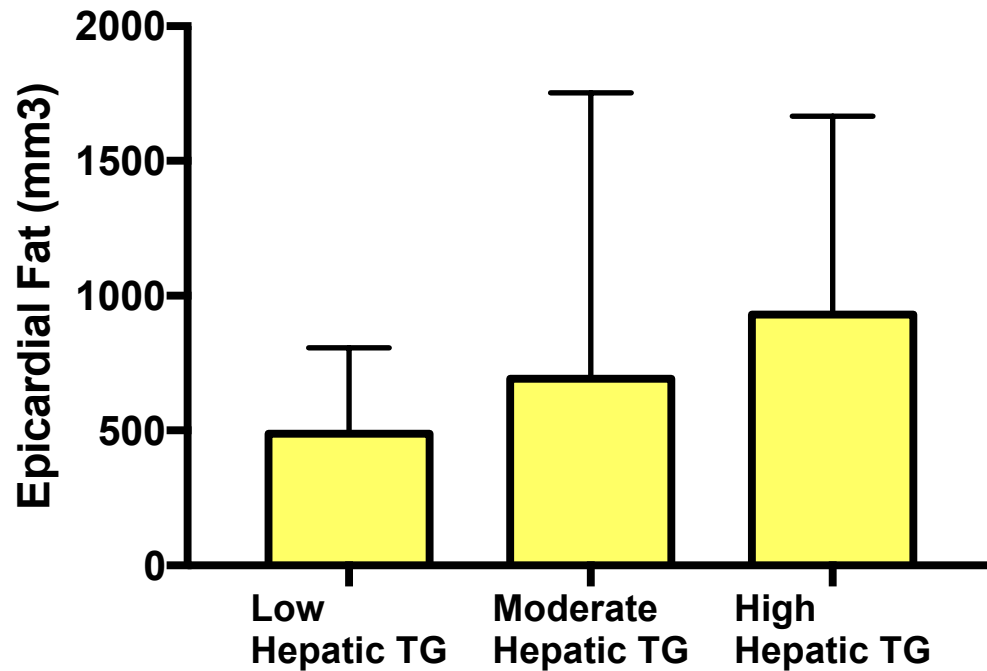
Relationship Between Dyslipidemia And MASLD



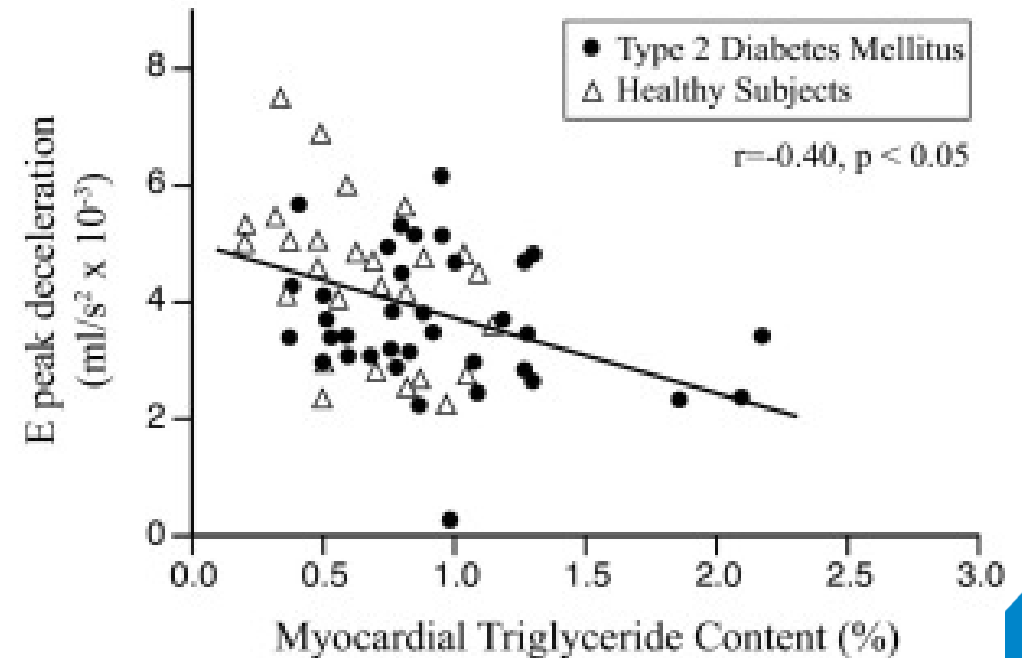
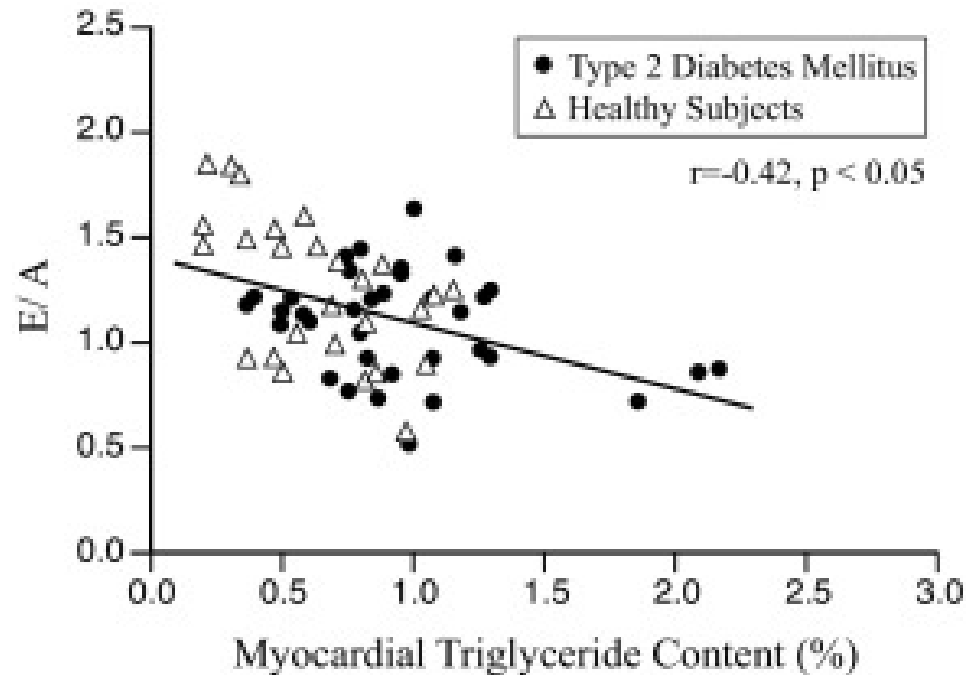
MASLD is Associated with Diastolic Dysfunction



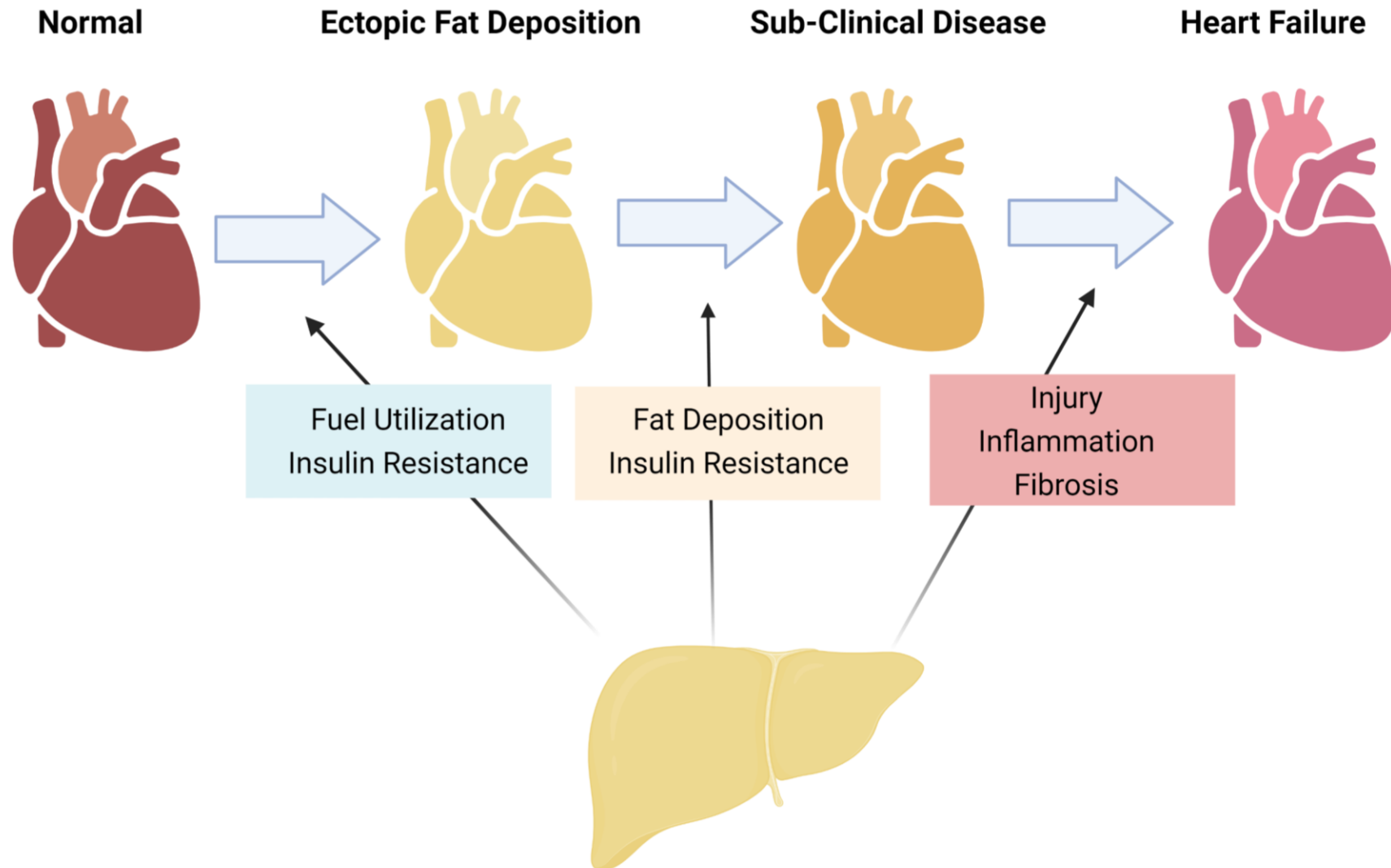
Cardiac Fat is Related to Severity of Liver Fat



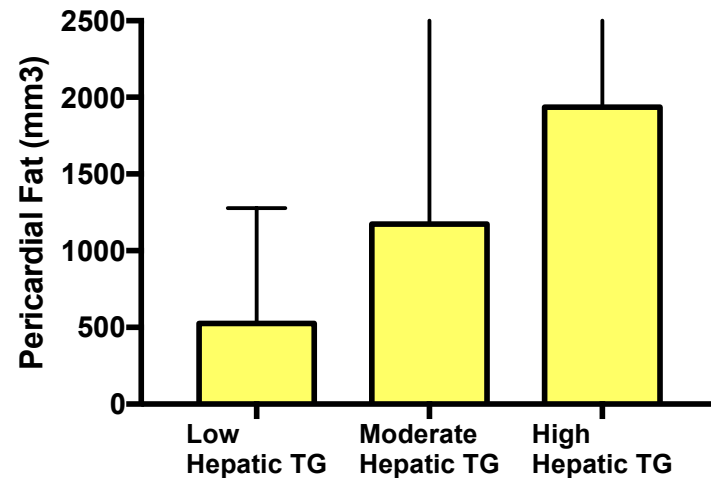
Cardiac Fat is Directly Associated with Diastolic Function



The Link Between Liver and Diastolic Dysfunction

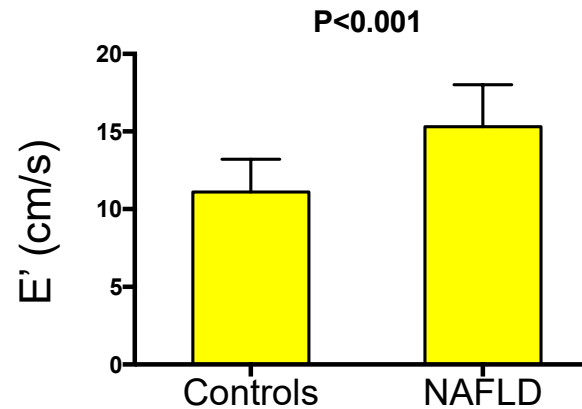


Liver Disease Severity Linked to Diastolic Dysfunction



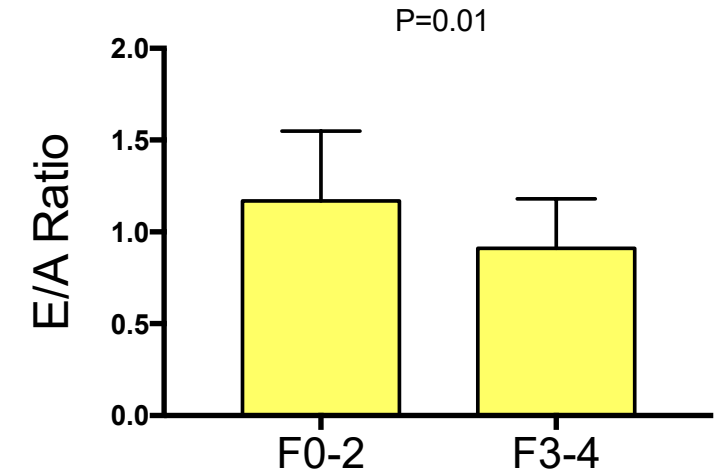
Cardiac fat is directly linked to severity of liver fat

Graner et al. Circ Cardiovasc Imaging 2014



NAFLD has elevated LV filling pressures

Hakan et al. Cardiol J. 2010

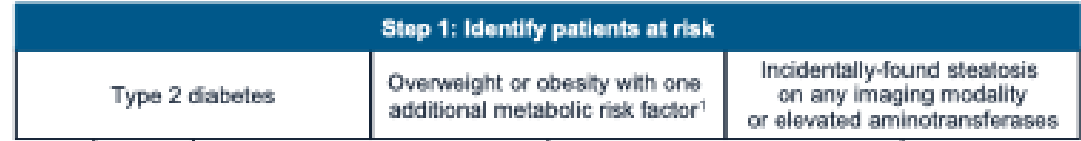


Fibrosis associated with impaired LV filling

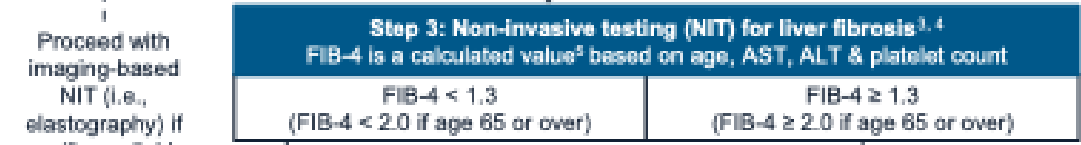
Petta et al. J Hepatol 2015

AGA 2026

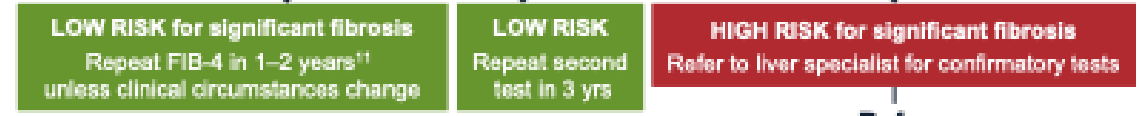
Primary care providers, endocrinologists, general gastroenterologists, diabetologists, cardiologists, and obesity specialists should screen for MASLD with clinically significant fibrosis.



*Rule out other liver diseases in patients with elevated aminotransferases (see Figure 2)

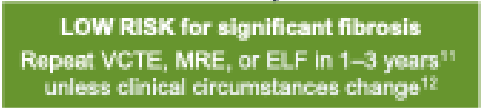
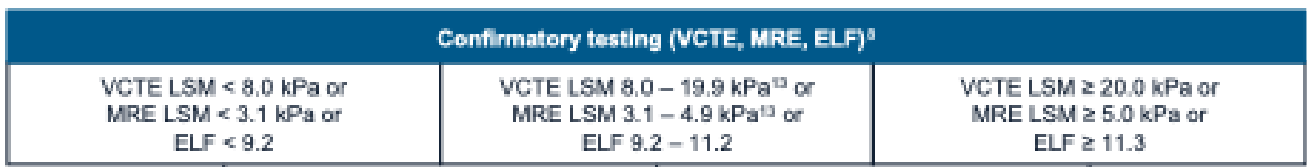


Proceed with imaging-based NIT (i.e., elastography) if readily available

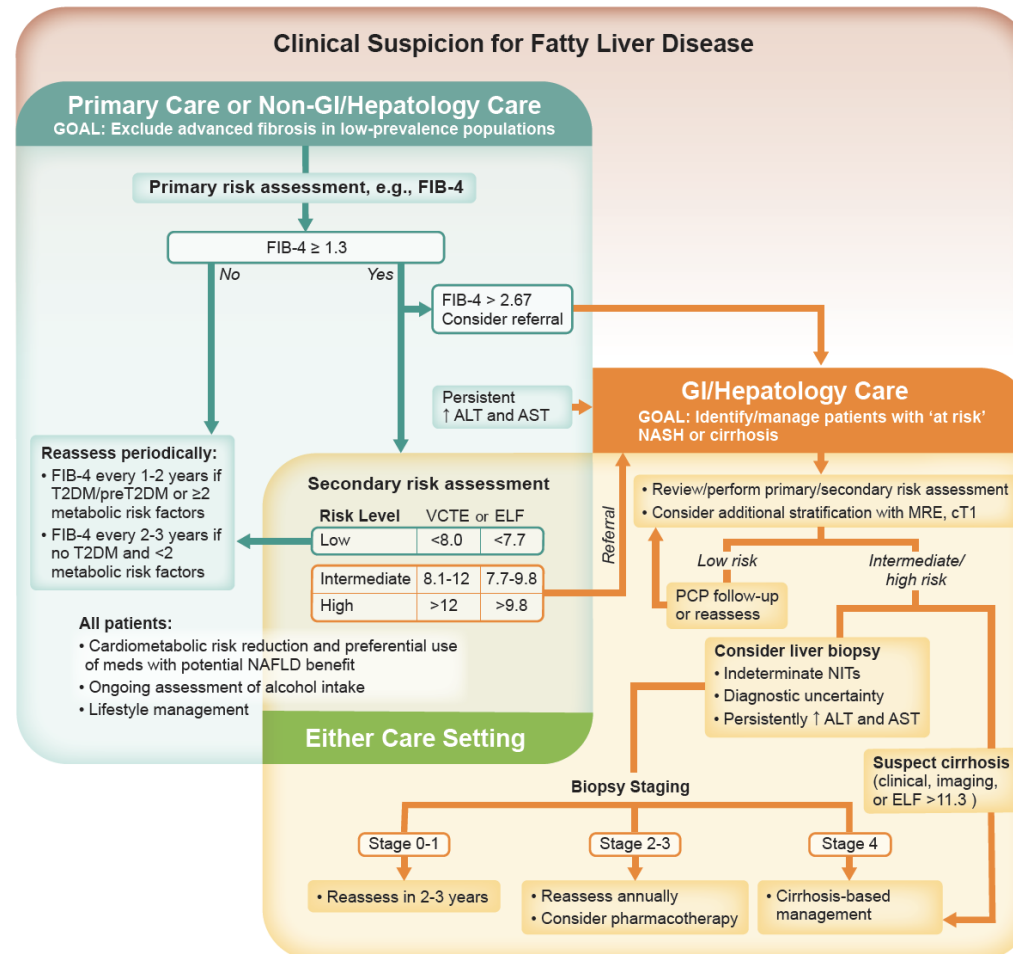


Refer

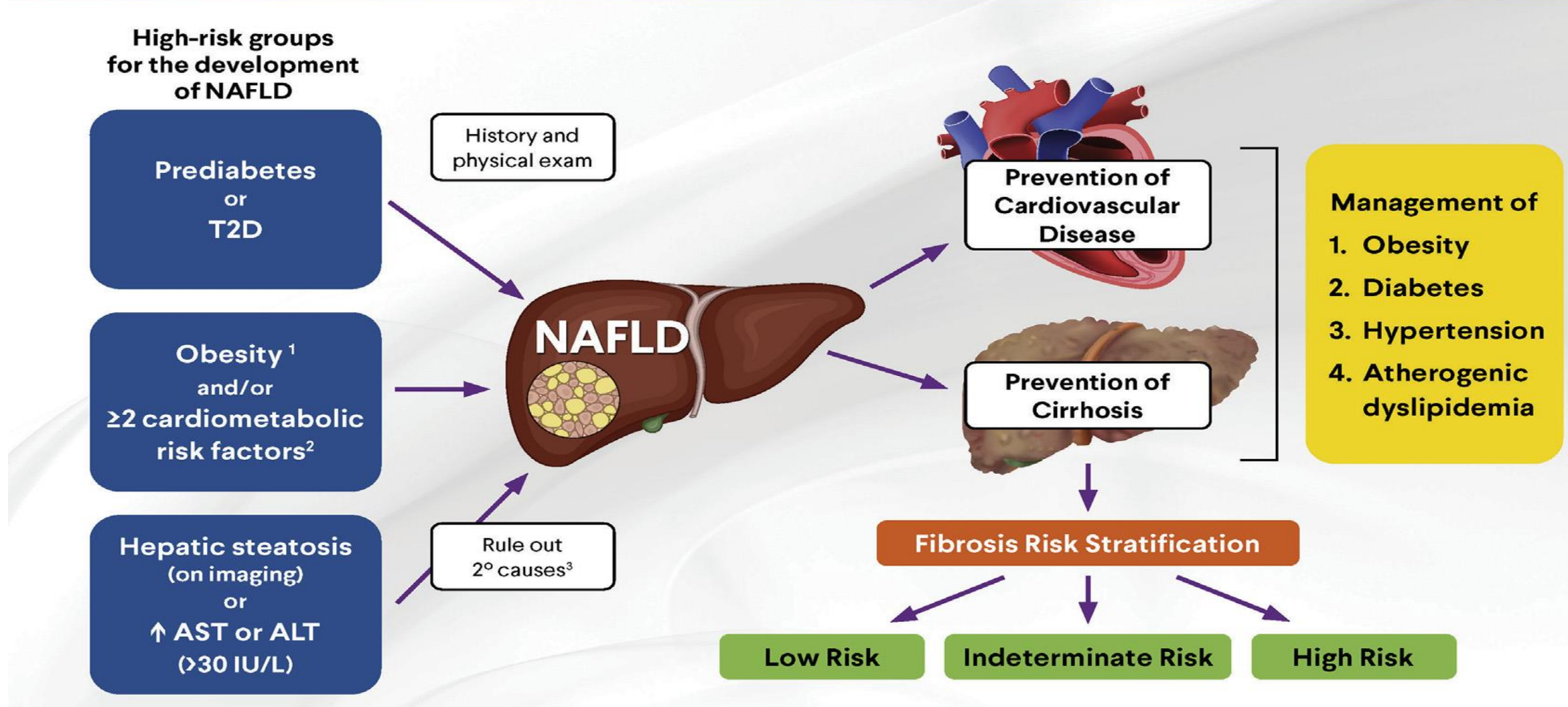
Gastroenterologists and hepatologists should diagnose clinically significant fibrosis and cirrhosis in patients with MASLD.



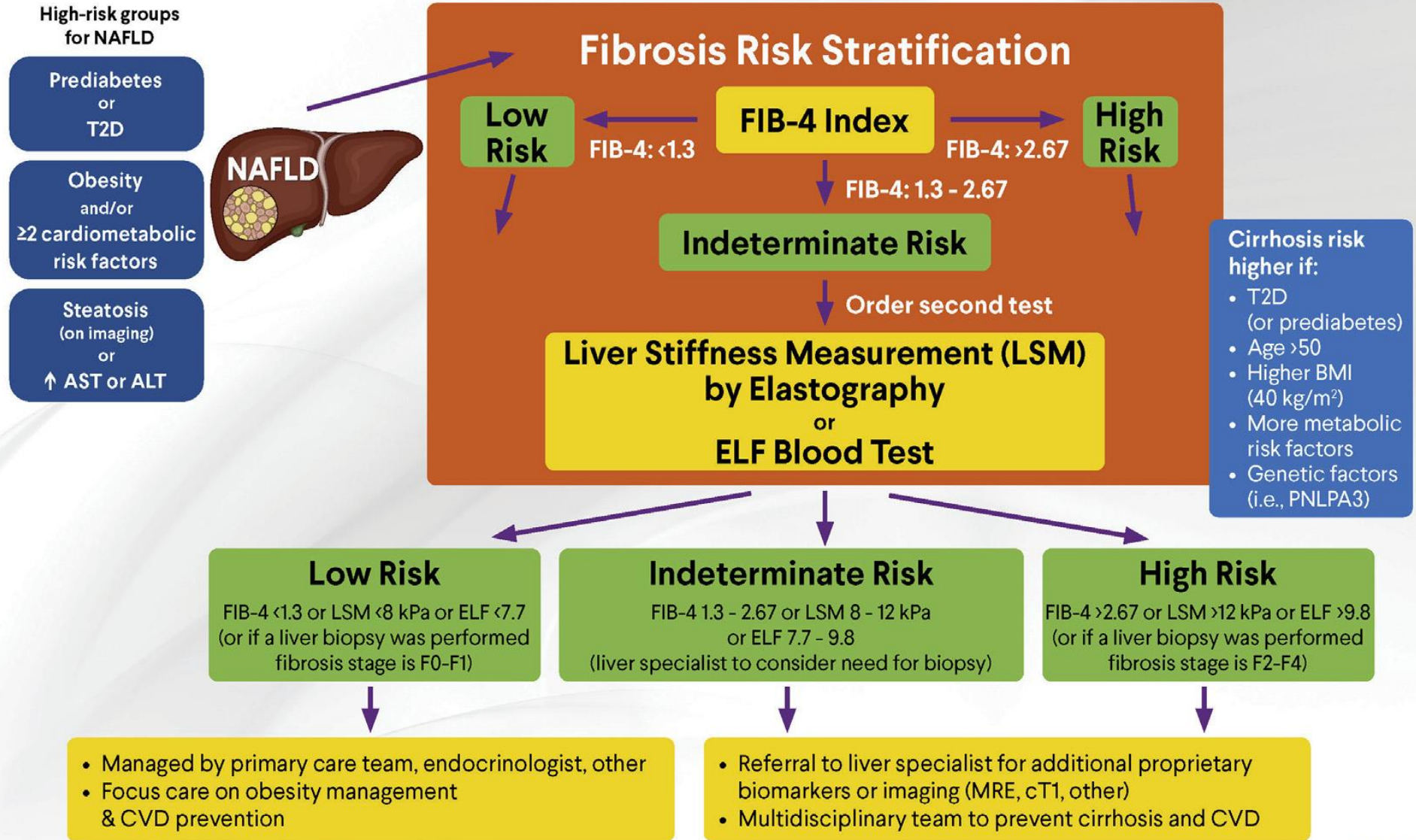
AASLD 2023 Guidance: Management of MAFLD/MASH



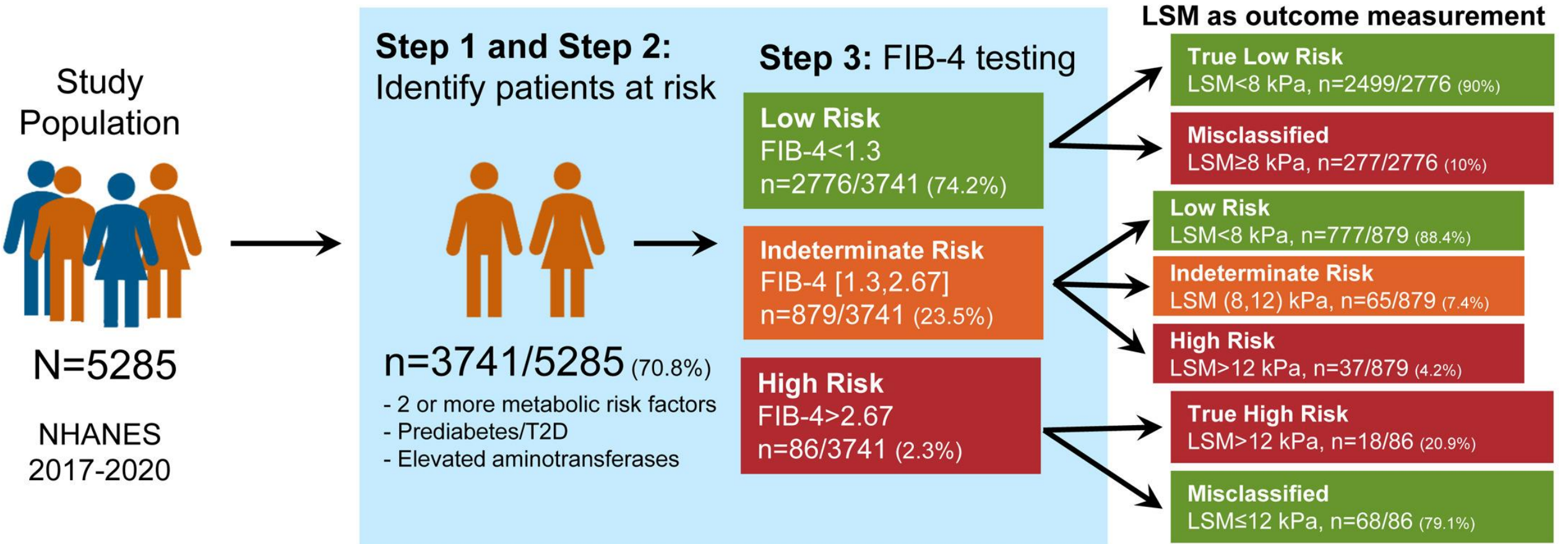
Management Algorithm for NAFLD – Overview



Cirrhosis Prevention in NAFLD



Degree of Discordance Between FIB-4 and Transient Elastography: An Application of Current Guidelines on General Population Cohort



AGA NAFLD/NASH Clinical Care Pathway

Clinical Gastroenterology
and Hepatology

AACE

AASLD: Noninvasive Parameters for “At-Risk” MASH

Identification of “At-Risk” NASH

Combined	FAST	≥ 0.67	< 0.35	<ul style="list-style-type: none"> ▪ ≤ 0.35 (sensitivity 90%) ▪ ≥ 0.67 (specificity 90%) ▪ In validation cohorts, the PPV of FAST ranged between 0.33 and 0.81^{1,2}
Combined	MEFIB	FIB-4 ≥ 1.6 plus MRE ≥ 3.3 kPa	FIB-4 < 1.6 plus MRE < 3.3 kPa	<ul style="list-style-type: none"> ▪ Sequential approach identifies patients with stage ≥ 2 fibrosis with $> 90\%$ PPV³
	MAST	≥ 0.242	≤ 0.165	<ul style="list-style-type: none"> ▪ 0.242 (specificity 90%), 0.165 (sensitivity 90%)⁴
	cT1	≥ 875 ms	< 825 ms	<ul style="list-style-type: none"> ▪ Requires further validation as data are derived from 1 study⁵

Imaging Techniques: VCTE

Vibration-Controlled Transient Elastography (VCTE)

Fibrosis

Steatosis

Liver stiffness

- Obtained through a VCTE measurement
- Correlated to extent of fibrosis

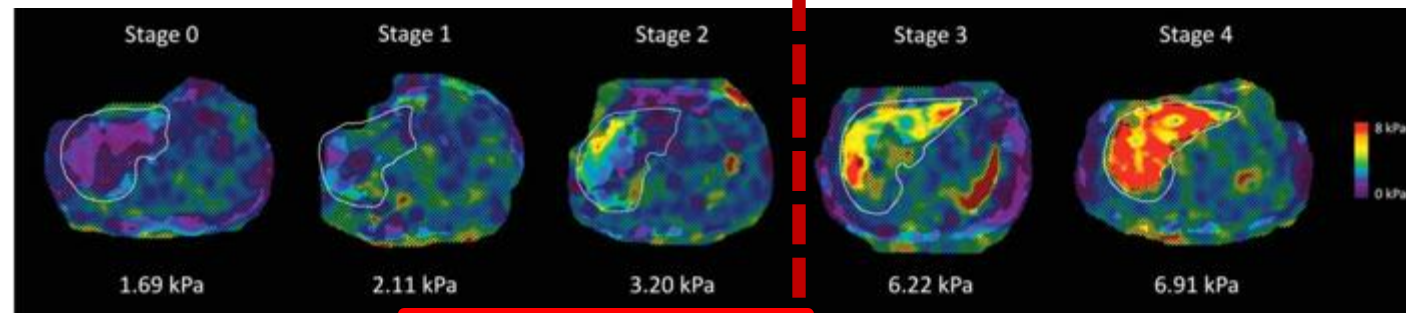
CAP

- Quantification of ultrasound attenuation obtained in VCTE measurement
- Correlated to liver steatosis

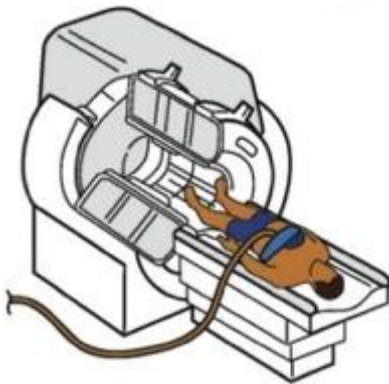


Imaging Techniques: MRE

Modified phase-contrast pulse sequence to visualize rapidly propagating mechanical shear waves (~60 Hz)



Laura: 3.3 kPa

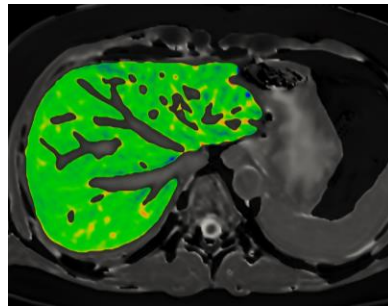


Cutoff for Detecting Advanced Fibrosis	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
MRE stiffness ≥ 3.64 kPa	0.86 (0.65-0.97)	0.91 (0.83-0.96)	0.68 (0.48-0.84)	0.97 (0.91-0.99)

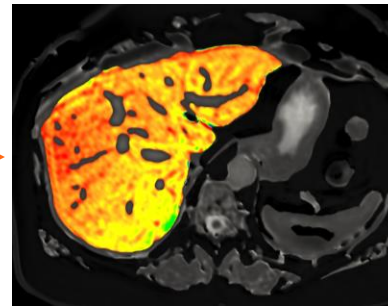
LiverMultiScan cT1 accurately identifies At-Risk MASH patients

n=543 NAFLD
n=100 Healthy
cT1 and PDFFF
Biopsy - NAS

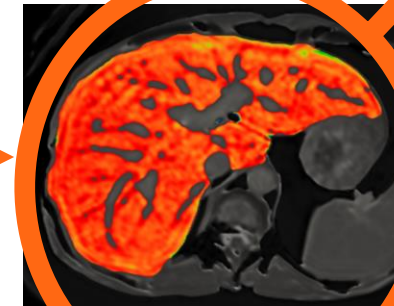
Low likelihood of
having NASH
cT1 <800ms



Evidence of
NASH
cT1 800-875ms



High likelihood of having
"High-risk" NASH
cT1 >875ms



AUROC=0.78

Proposed Algorithm for Patient Selection Using NITs

MASLD
Assess Steatosis
Rule out other causes of liver disease

*If biopsy is performed and liver histology demonstrates Stage 2 or 3 disease, can treat as long as there is no clinical or imaging evidence of portal hypertension (eg, ascites apparent on imaging, gastroesophageal varices, history of hepatic encephalopathy).
PHTN: portal hypertension.

Assess for fibrosis

Treat

VCTE $\geq 10-15$ kPa OR
MRE $\geq 3.3-4.2$ kPa OR
ELF score 9.2-10.4 OR
FAST, MAST, MEFIB
AND
platelets ≥ 140 OR
no evidence PHTN

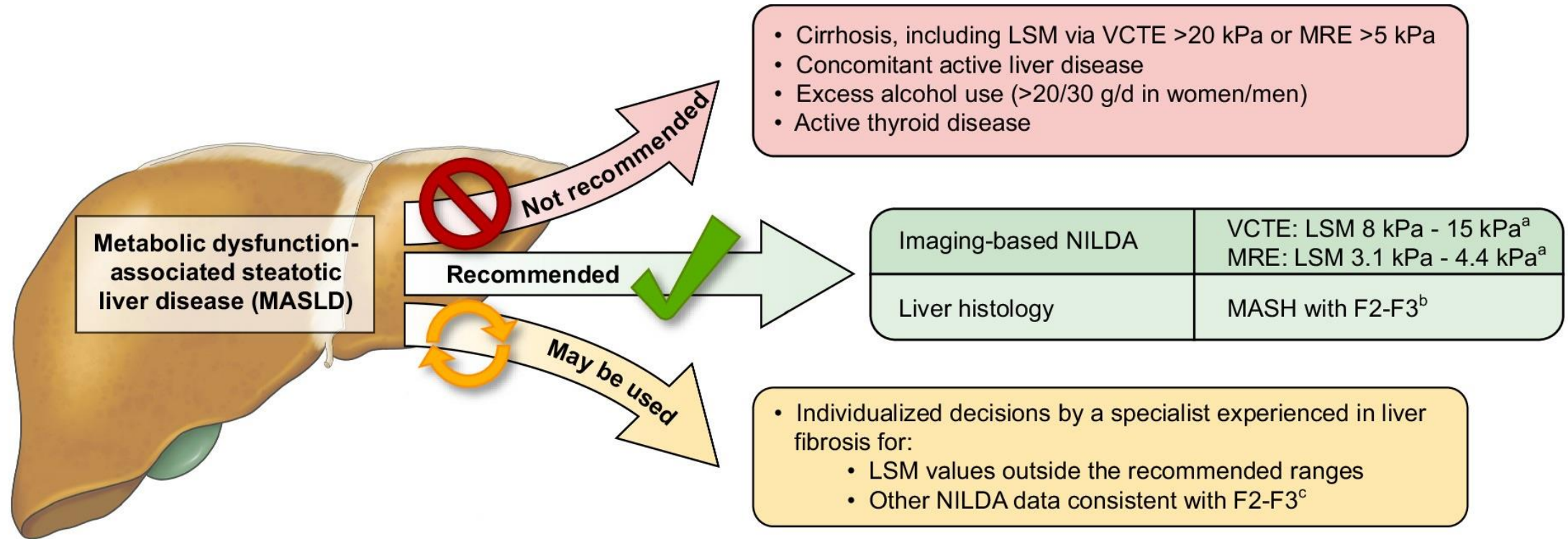
Consider treatment

VCTE 15-20 kPa OR
MRE 4.3-4.9 kPa OR
ELF score 10.5-11.3
FAST, MAST, MEFIB
AND
platelets ≥ 140 OR
no evidence PHTN^a

Do not treat

VCTE ≥ 20 kPa*
OR
MRE ≥ 5 kPa*
OR
ELF > 11.3 *

AASLD 2024 Guidelines

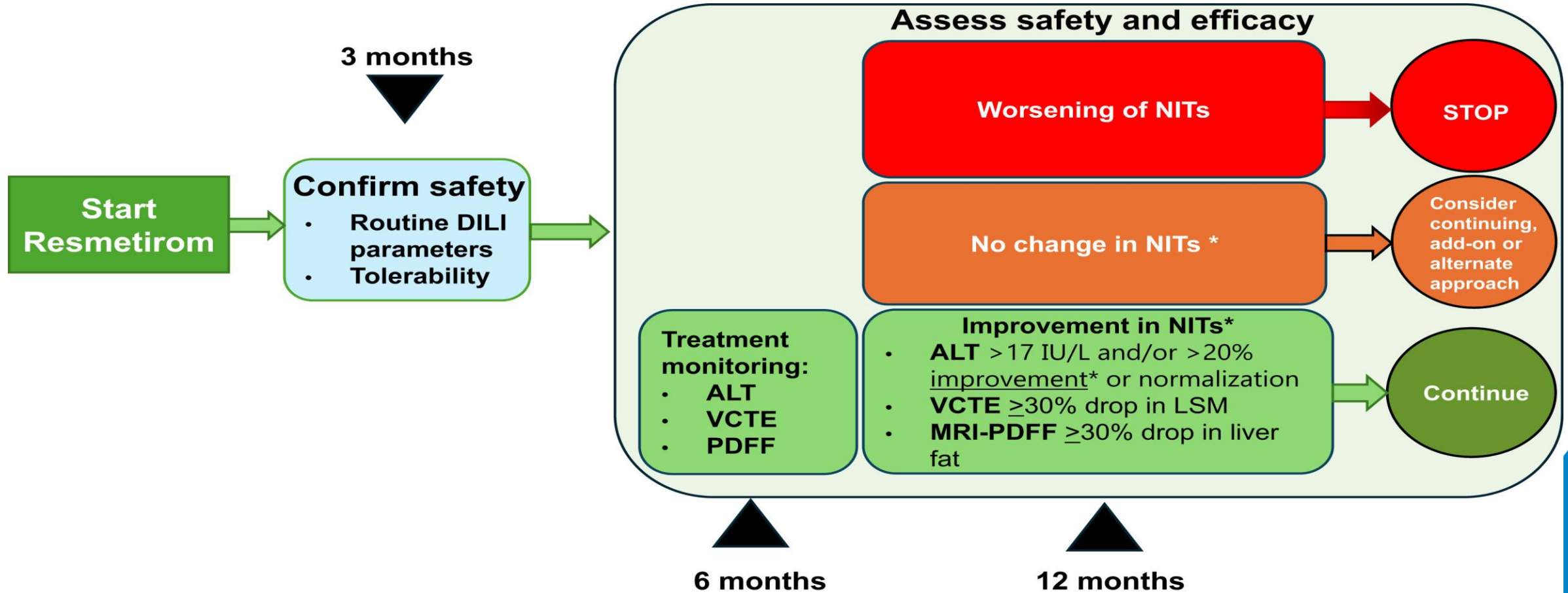


^a Modified from the AASLD NILDA guidelines.⁵

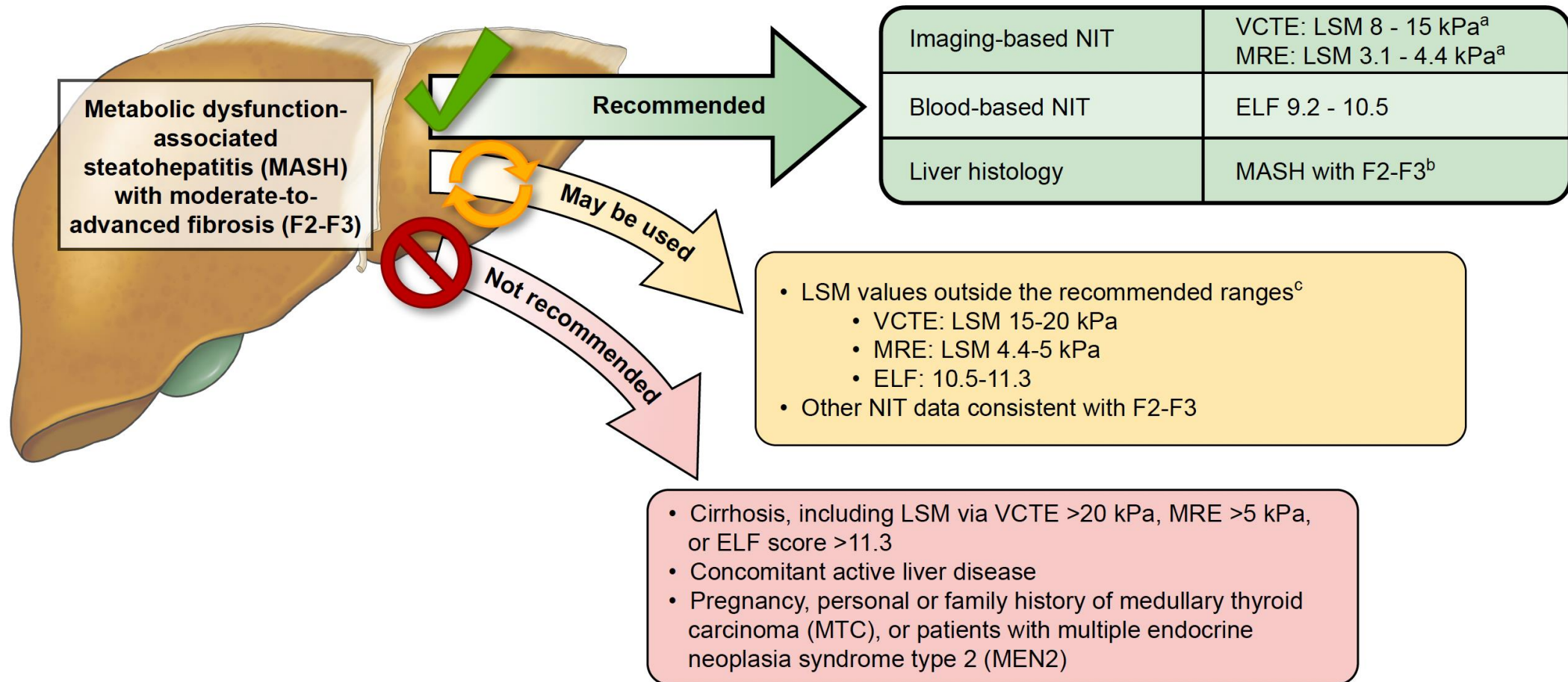
^b Liver biopsy is not routinely recommended for staging of MASH.

^c Imaging-based NILDA is preferred, eg, shear wave elastography (applying local standards for F2-F3) versus enhanced liver fibrosis score (9.2-10.4). The latter range is based on the interquartile range from the MAESTRO trial data; no recommendations are available from the AASLD NILDA guidelines.⁶

Assessing Safety and Treatment Response of Resmetirom



Use of NITs for determining eligibility for semaglutide (Wegovy®) for the treatment of MASH with moderate-to-advanced fibrosis (F2-F3)



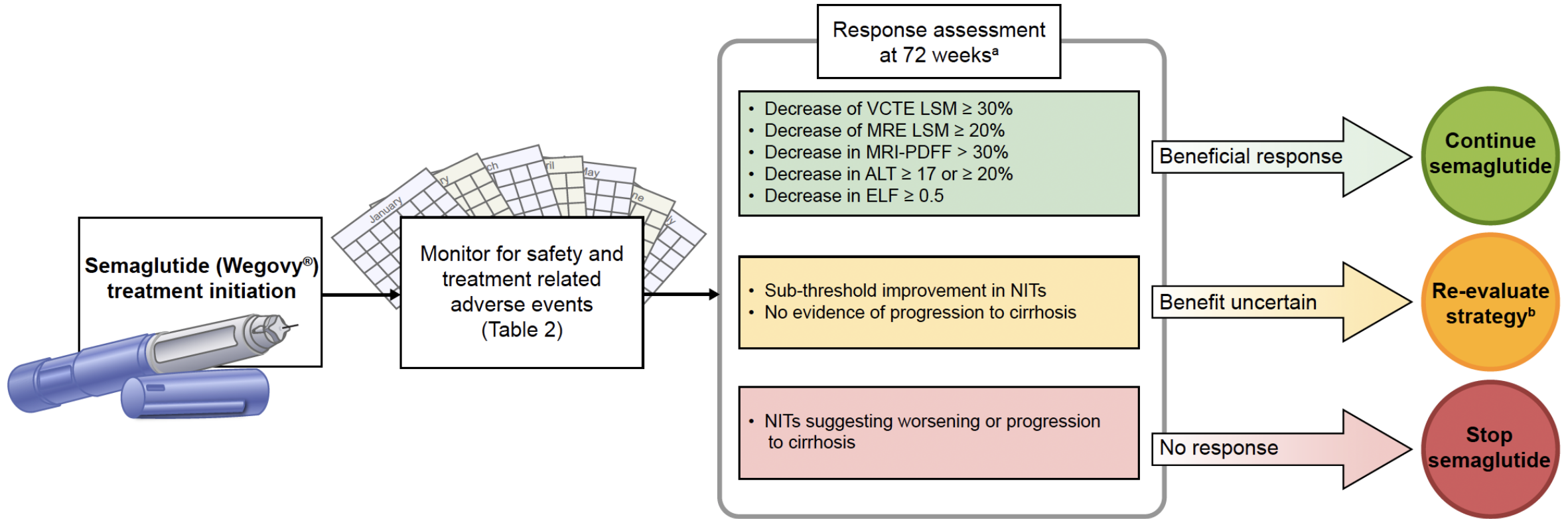
^a Modified from the AASLD NILDA guidelines.⁵

^b Liver biopsy is not routinely recommended for the diagnosis and staging of MASH with F2-3

^c Refer to “Whom to treat” for details

VCTE – Vibration-controlled transient elastography; MRE – Magnetic resonance elastography; ELF – Enhanced liver fibrosis; LSM – Liver stiffness measurement; NIT – Non-invasive test.

Assessment of safety and response to semaglutide (Wegovy®) for the treatment of MASH with moderate-to-advanced fibrosis (F2-F3)



^a Assess based on the same imaging-based or blood-based markers used to determine treatment eligibility.

^b Options may include re-optimizing lifestyle interventions and considering other therapy, with or without stopping semaglutide.

VCTE – Vibration-controlled transient elastography; MRE – Magnetic resonance elastography; ELF – Enhanced liver fibrosis; LSM – Liver stiffness measurement; NIT – Non-invasive test.