Diagnosis and Management of NAFLD

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Financial Disclosures

(over past 24 months)

	Speaker	Advisory	Research	Consultant
Gilead Sciences			√	√
Intercept		√	√	
Novo-Nordisk		√		

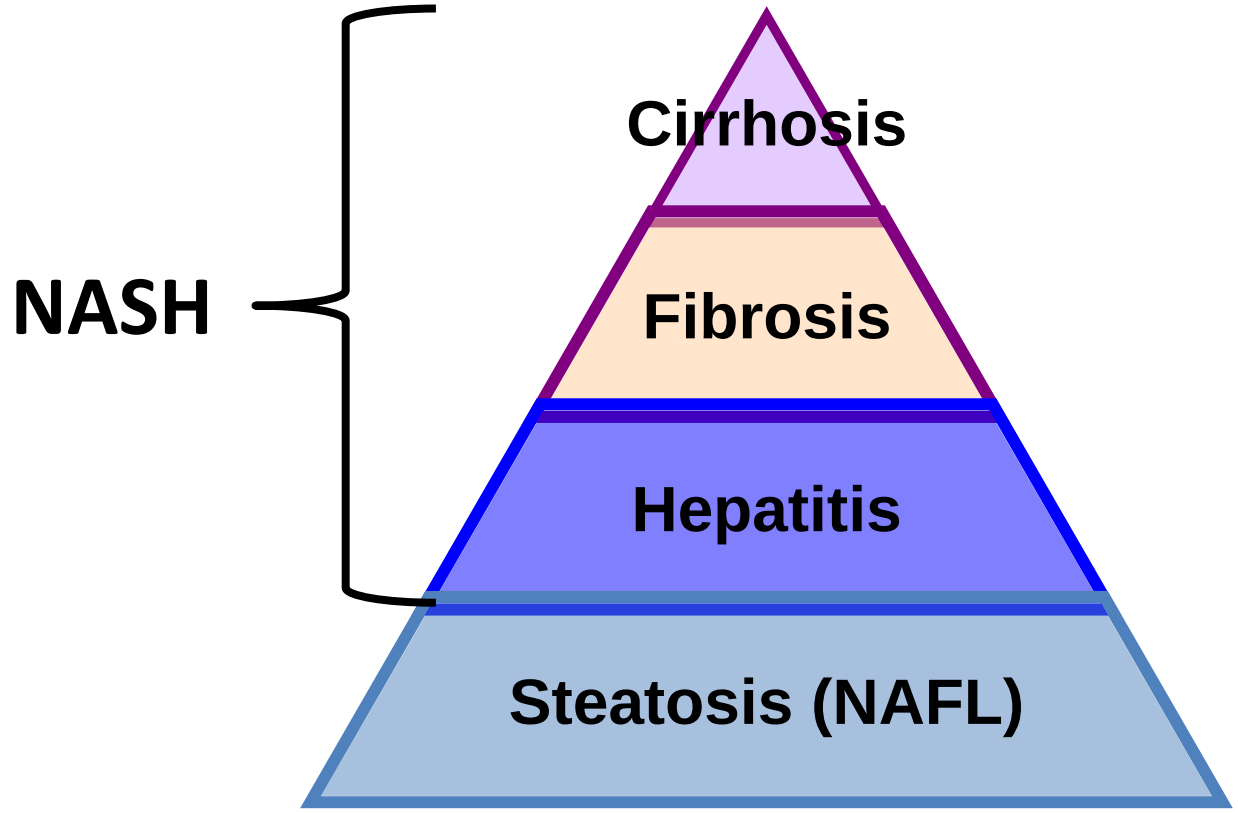
CanMEDS Roles Covered: Patel, K- “Canadian Obesity Weekend 2022”

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.)
	Collaborator (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
X	**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.)
	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.)

Objectives

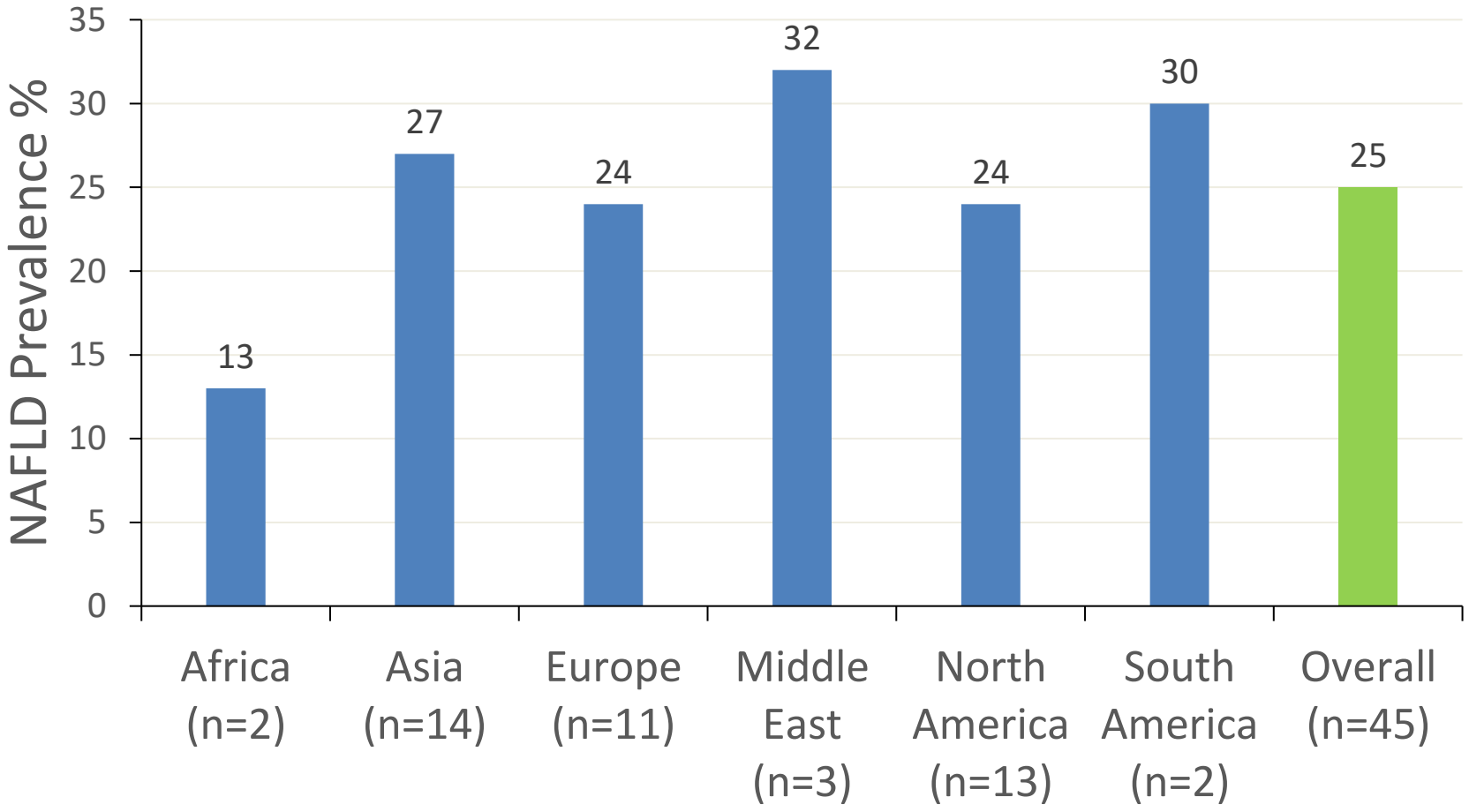
- NAFLD Epidemiology
- Diagnosis of NASH and Advanced Fibrosis
- Current management
  - Lifestyle
  - Medical
  - Bariatric Surgery and NAFLD outcomes
- Emerging Pharmacotherapy in Clinical Trials

Nonalcoholic Fatty Liver Disease (NAFLD)



Global Prevalence of NAFLD

Meta-analysis 57 studies (>8 million persons)
Mostly based on Imaging diagnosis



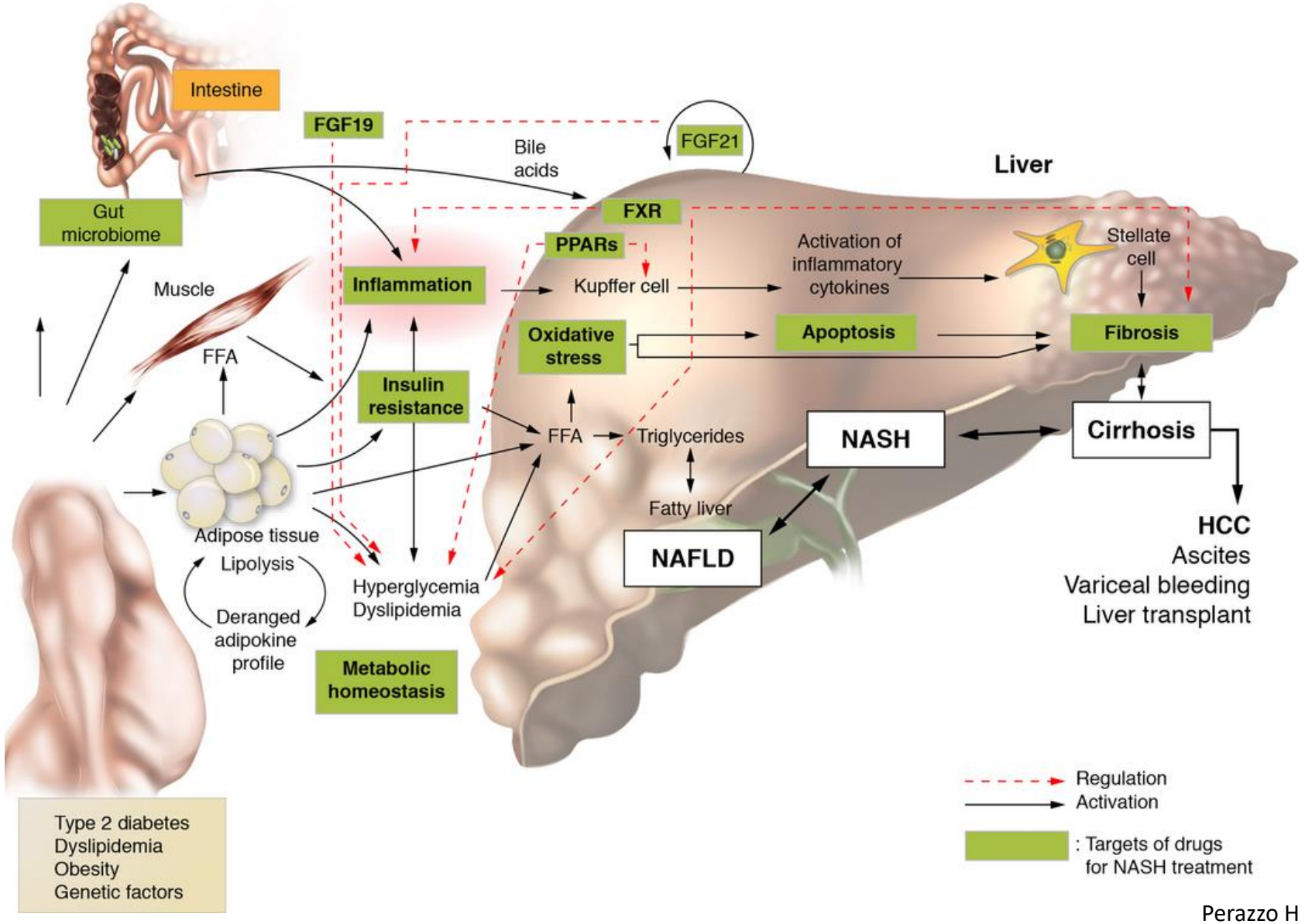
Younossi Z et al Hepatology 2016

Global Prevalence of NAFLD

- Global prevalence NAFLD estimated ~25%
  - NASH prevalence 2-7%
  - T2DM (40-60%)
  - Patients with Obesity (60-80%)
  - Dyslipidemia (~50%)
  - Bariatric cohorts with morbid obesity (95%)

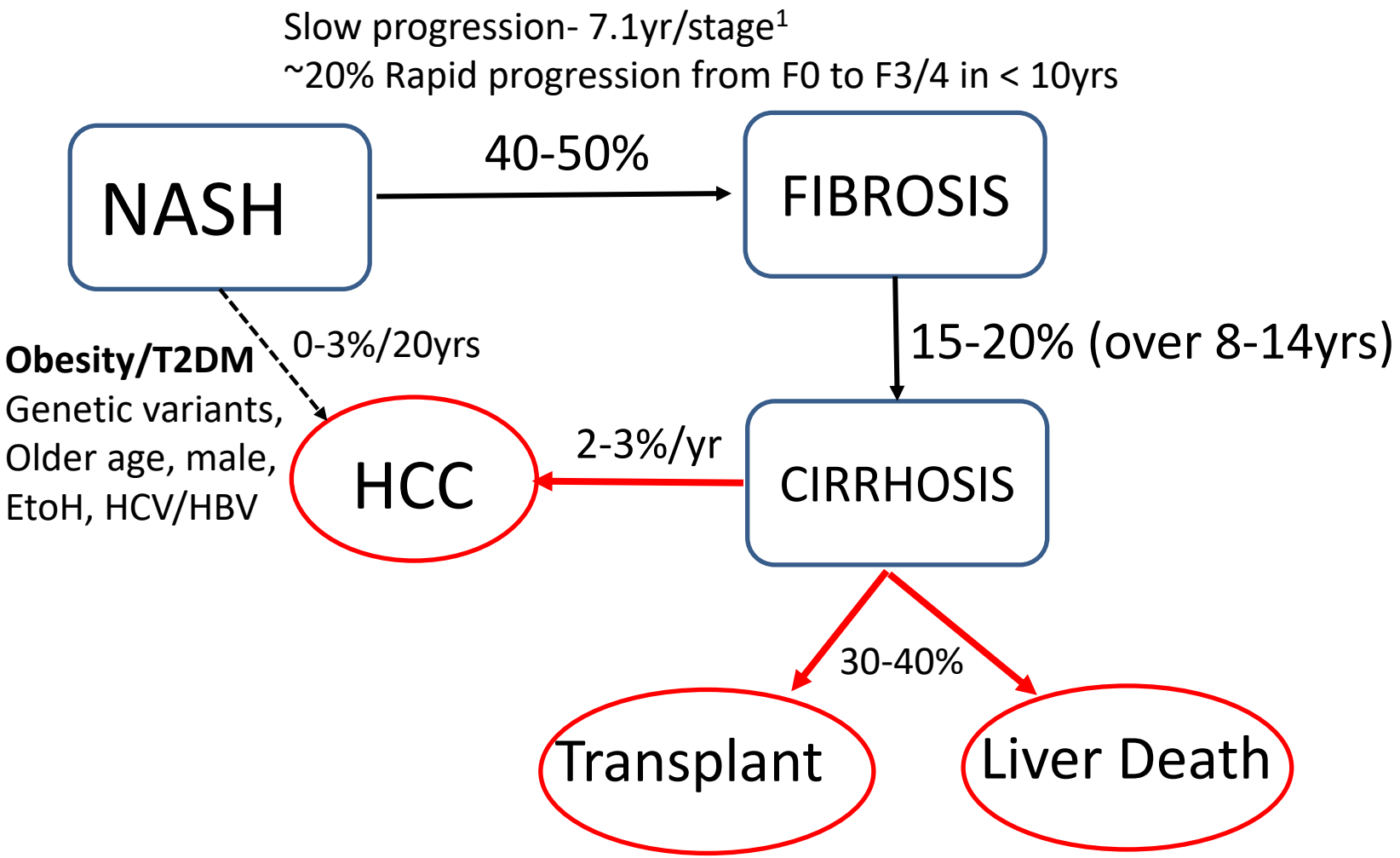
Younossi Z et al Hepatology 2016

Pathogenesis of NAFLD



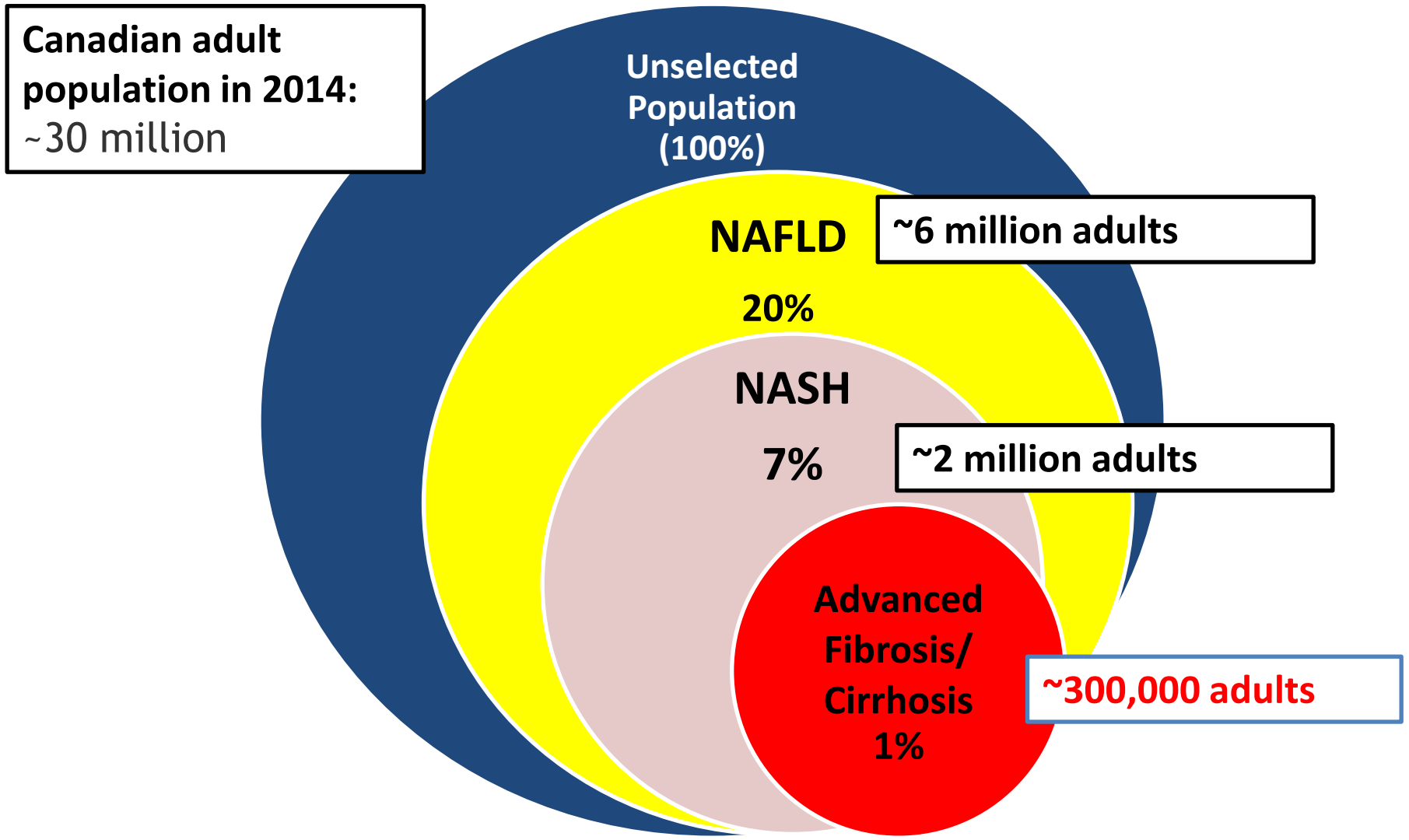
Perazzo H Liver Int 2016

Natural History of NAFLD

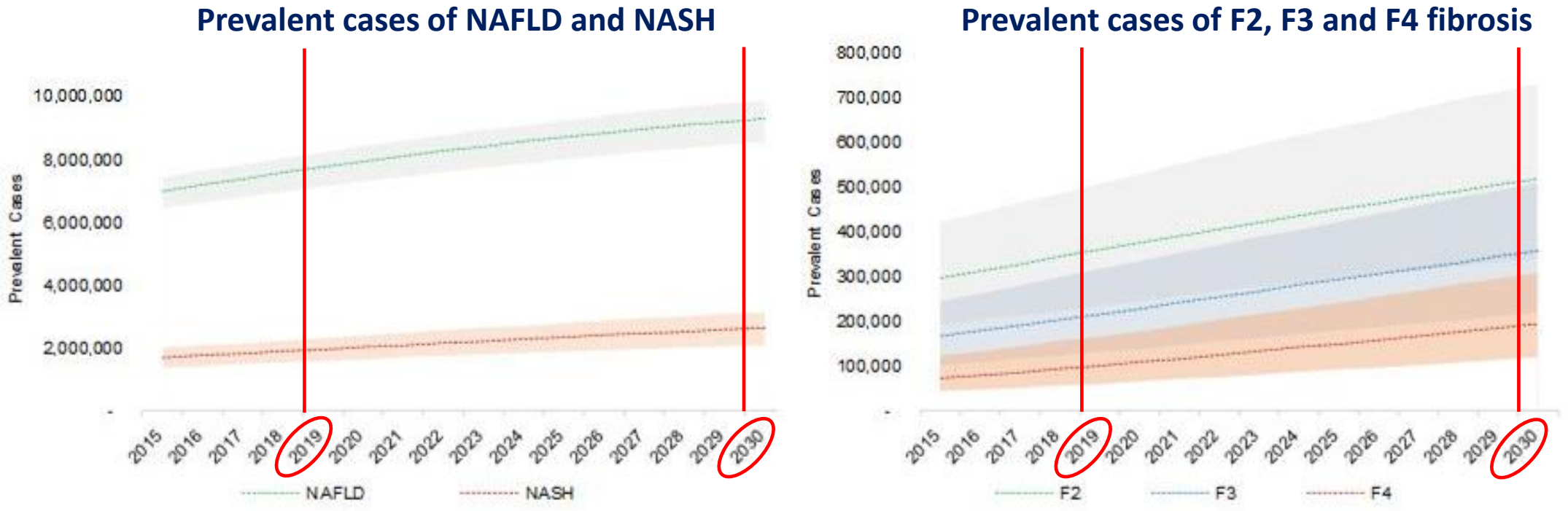


1. Singh S et al CGH 2015

Relative Prevalence of NAFLD and NASH



Modeling Prevalence of NAFLD in Canada, 2019–2030



Between the years 2019 and 2030:

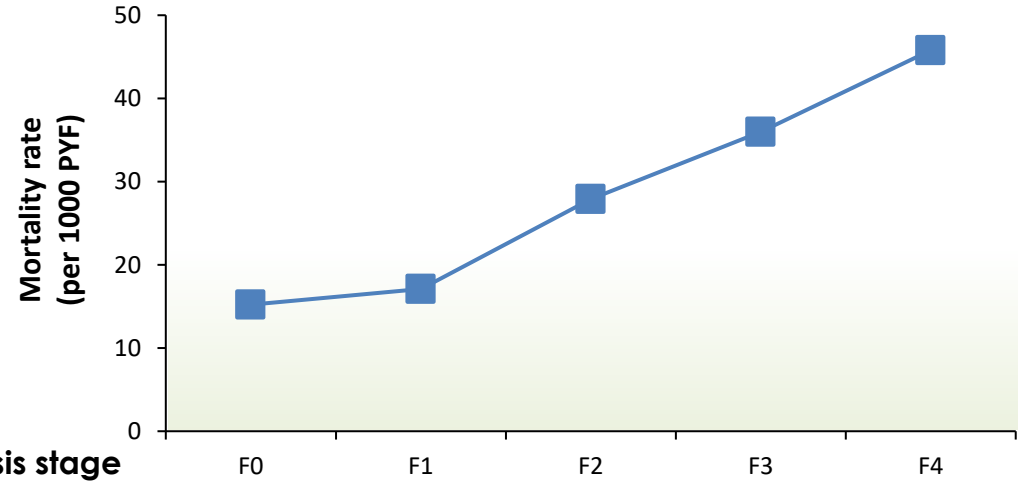
- **NAFLD** cases projected to increase **20%** (from 7,757,000 to 9,305,000)
- F3 cases will increase **65%** (from 216,000 to 357,000)
- Compensated cirrhosis (F4) cases will increase **95%** (from 101,000 to 195,000)
- Prevalent cases of HCC, decompensated cirrhosis, and LT will increase from 14,000 to 28,200

Swain MG et al. 2020. *CMAJ* 8(2):E429-E436.

Advanced Fibrosis is Associated with Increased Risk of All-cause and Liver-related Mortality

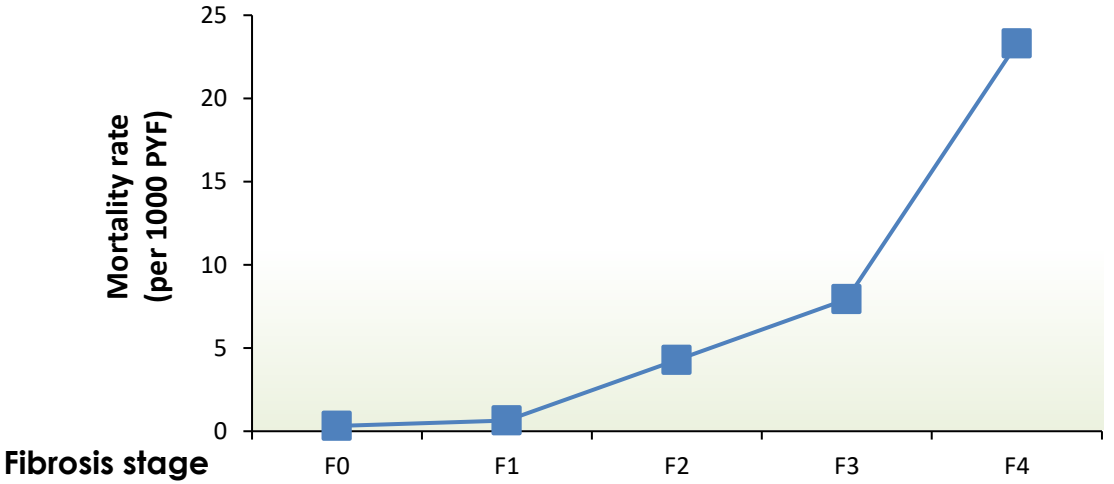
Meta-analysis of five multinational cohorts (17,452 patient-years of follow-up)

All-cause mortality by fibrosis stage[1,a]



Mortality rate ratio (95% CI)	**1.58** (1.19, 2.11)	**2.52** (1.85, 3.42)	**3.48** (2.51, 4.83)	**6.40** (4.11, 9.95)

Liver-related mortality by fibrosis stage[1,a]

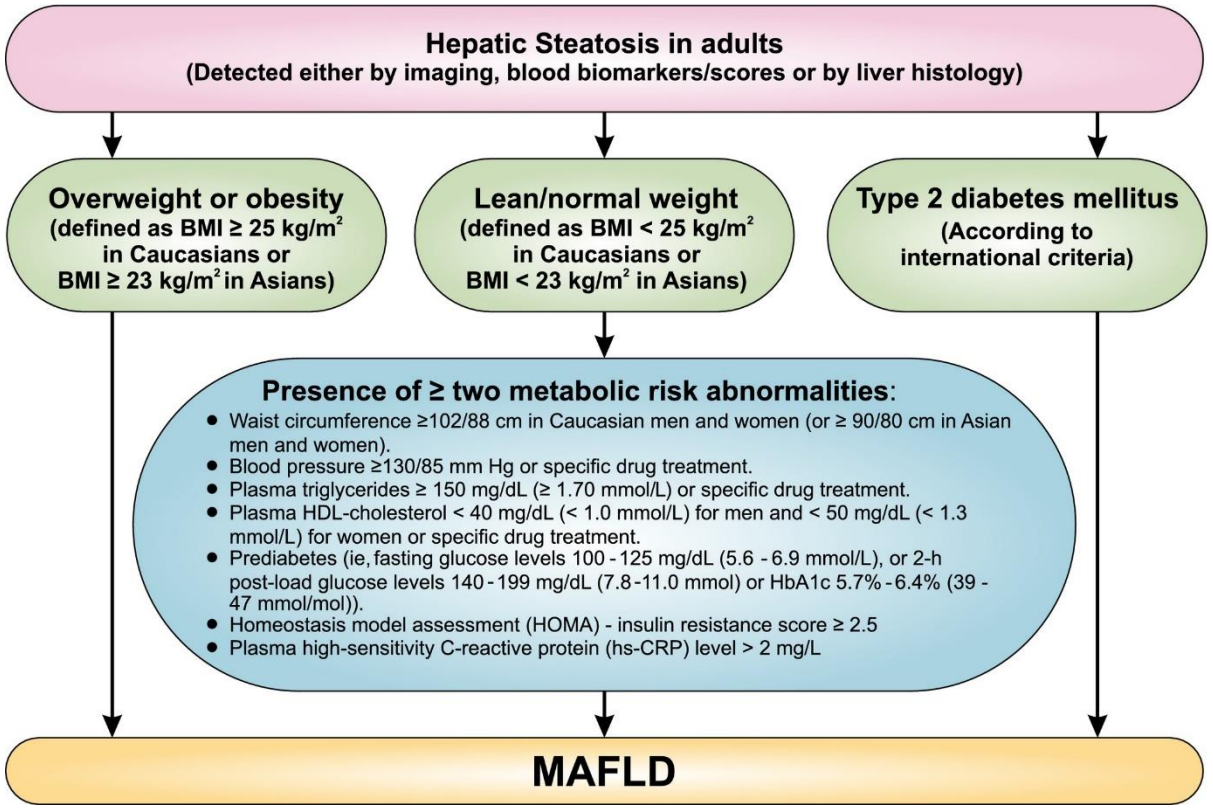


Mortality rate ratio (95% CI)	**1.41** (0.17, 11.95)	**9.57** (1.67, 54.93)	**16.69** (2.92, 95.36)	**42.30** (3.51, 510.34)

- Risk of liver-related mortality increases with fibrosis stage[1]
- Leading causes of death are **cardiovascular disease** (38.3%), non-liver malignancy (18.7%), other organ/systemic disease (18.1%); Cirrhosis complications/HCC/LT (9.3%)[2]

1. Dulai PS, et al. Hepatology 2017; 2. Angulo P, et al. Gastroenterology 2015

Metabolic Associated Fatty Liver Disease (MAFLD)

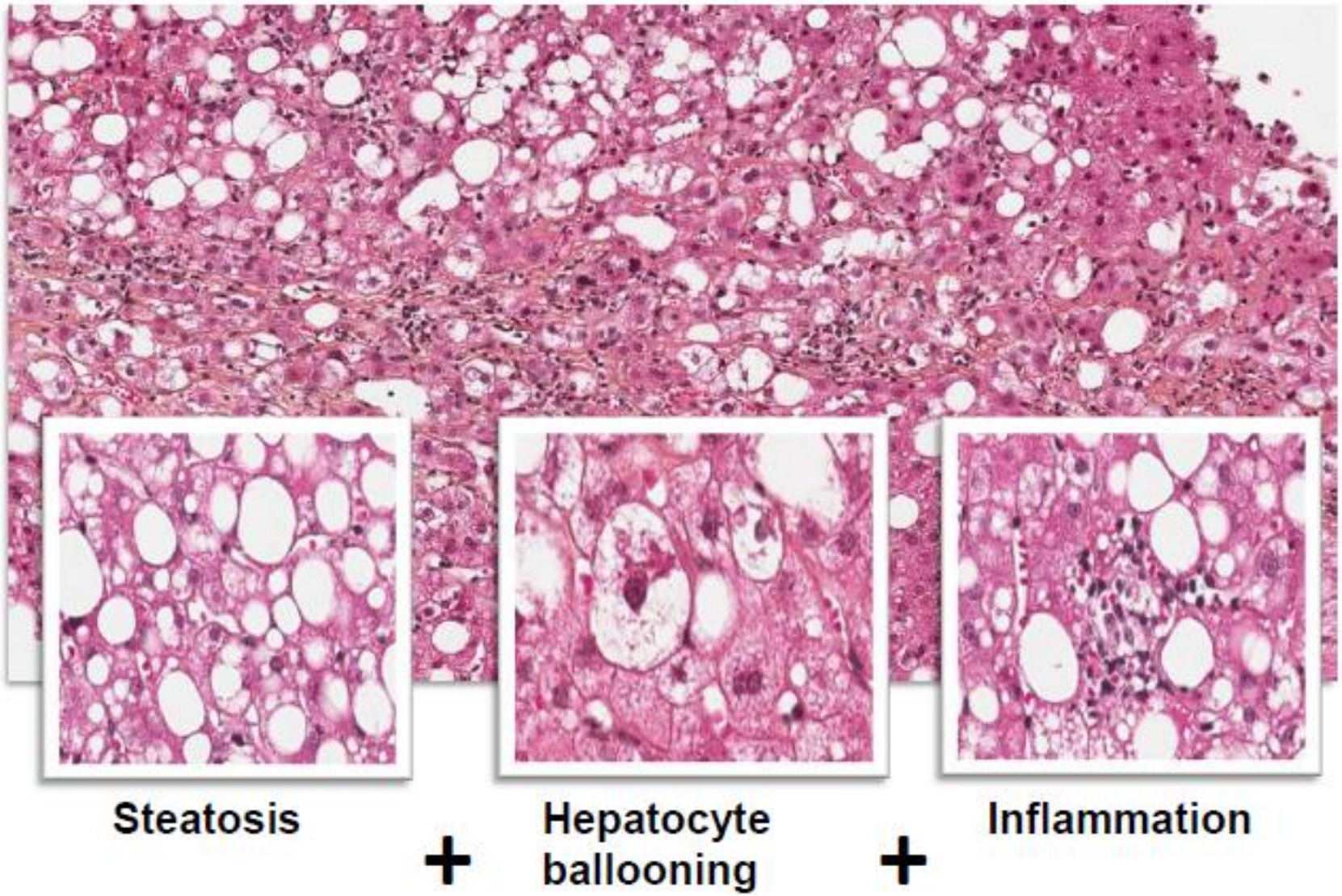


- MAFLD based on the <u>presence</u> of metabolic dysfunction not the absence of other conditions.
- Removes reference to alcohol
- Need to define diagnostic criteria for MAFLD or in the context of a second liver disease
- How do we reclassify MAFLD based on disease activity and stage rather than “Steatohepatitis”?

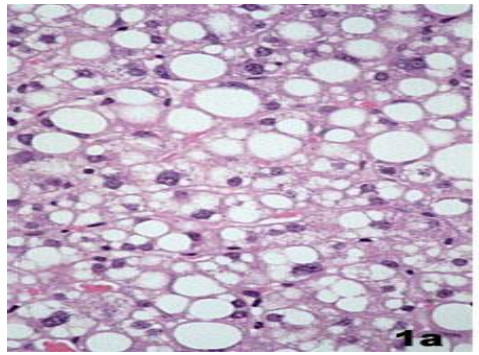
Eslam M J Hepatol 2020

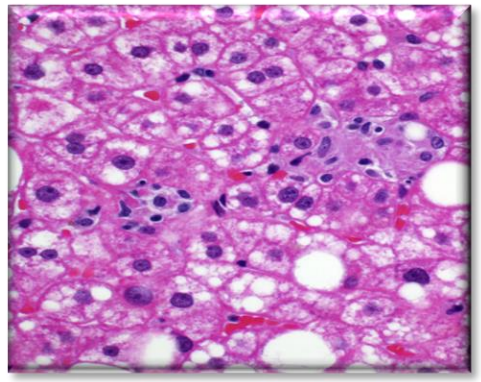
Diagnosis of NASH

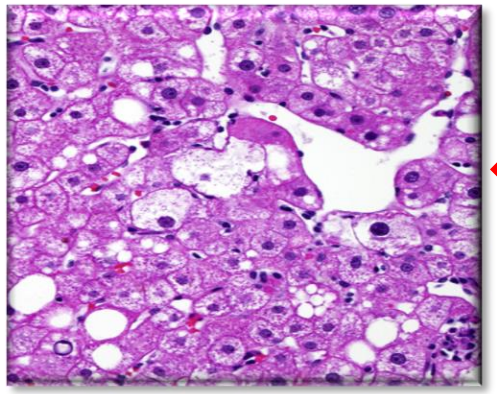
NASH is a histological diagnosis



NAFLD Activity Score







	Score
Steatosis (%)	
<5	0
5 to 33	1
>33 to 66	2
>66	3
Lobular Inflammation (foci/200x field)	
No foci	0
<2	1
2 to 4	2
>4	3
Ballooning	
None	0
Few balloon cells	1
Many cells/prominent ballooning	2

NAS ≥ 5 is NASH

Blood Markers to Differentiate Simple Steatosis from NASH

- Systematic review from n=122 studies[1]
  - Single markers (n=107) (metabolic, inflammatory, apoptosis markers)
  - Scoring systems (n=112)
  - Other diagnostic tests (n=22)
- No tests with pooled sensitivity/specificity ≥80%
- <u>No blood marker can be recommended for diagnosis of NASH</u>
- Emerging Scores for "Fibrotic NASH" (NAS ≥4 and F ≥2)
  - FAST Score™ (FibroScan LSM-CAP-AST)[2]
  - MACK 3 (AST, HOMA-IR and CK18)[3]
  - NIS4™ (miR-34a-5p, YKL-40, alpha2-macroglobulin, and HbA1c)[4]

[1]Verhaegh P et al CGH 2017
[2]Newsome P Lancet GH 2020
[3]Boursier J APT 2018
[4]Harrison S Lancet GH 2020

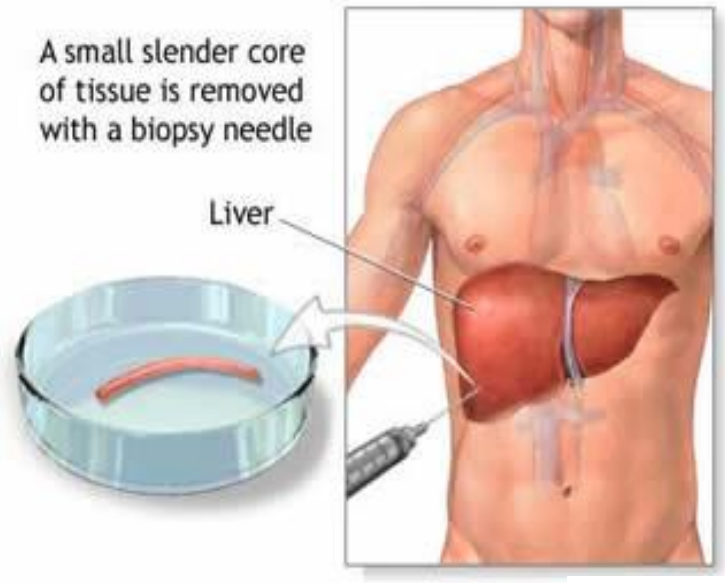
Diagnosis of Advanced Fibrosis

Diagnostic Tools for Advanced Fibrosis

- Liver Biopsy (reference standard)
- Clinical Findings
- Routine Imaging (US, CT/MRI)
- Serum Tests (FIB-4, NFS, FibroTest etc)
- Imaging Elastography (FibroScan, MRE)

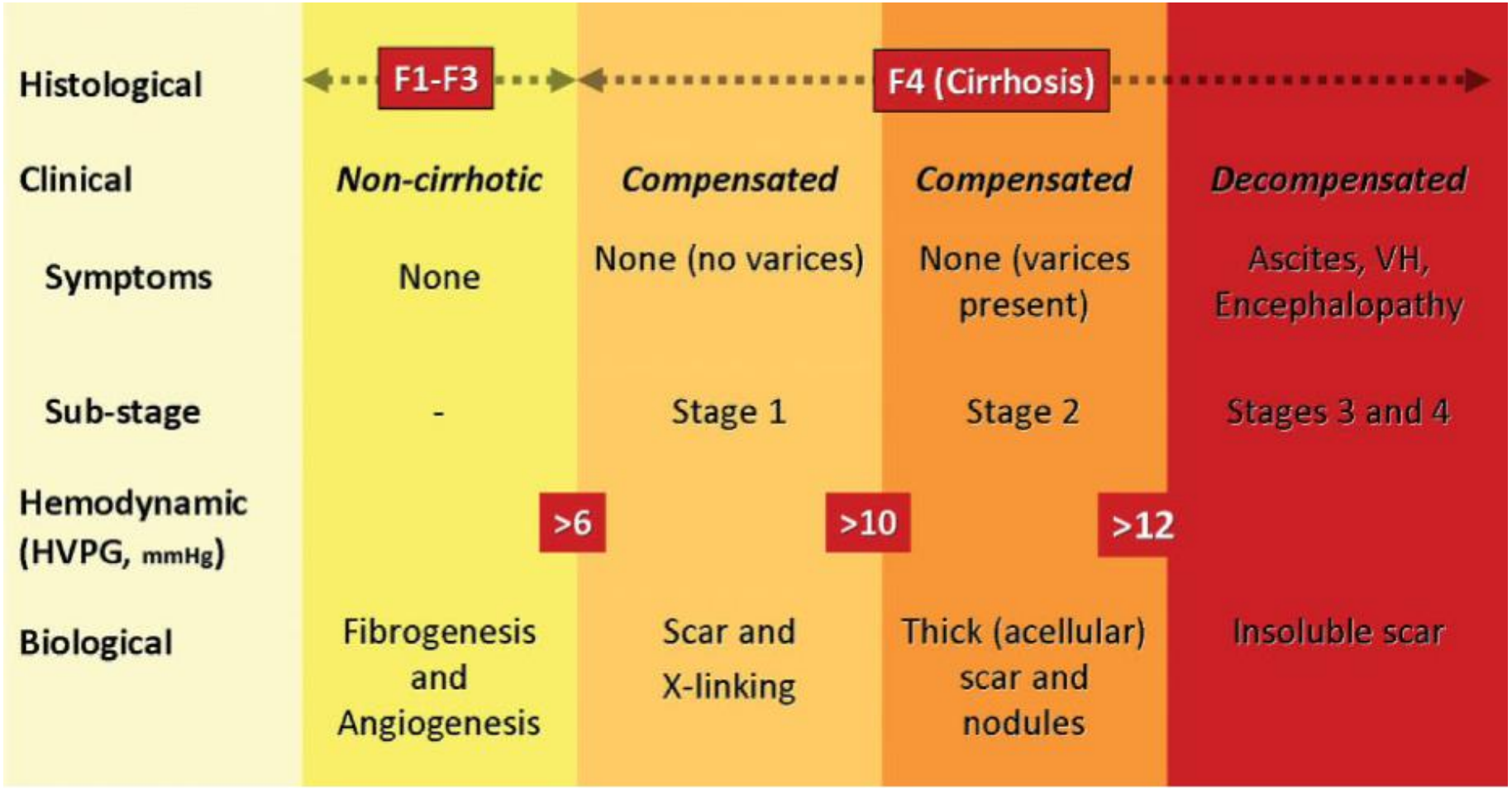
Limitations of Liver Biopsy

- Invasive
  - Morbidity (3/1,000)
  - Mortality (3/10,000)
- Observer variability
- Sampling error
  - 1/50,000th of the liver
  - 33% discordance of 1 stage[1]
- Costly
- Contraindications
- Static



1. Regev A et al AJG 2002

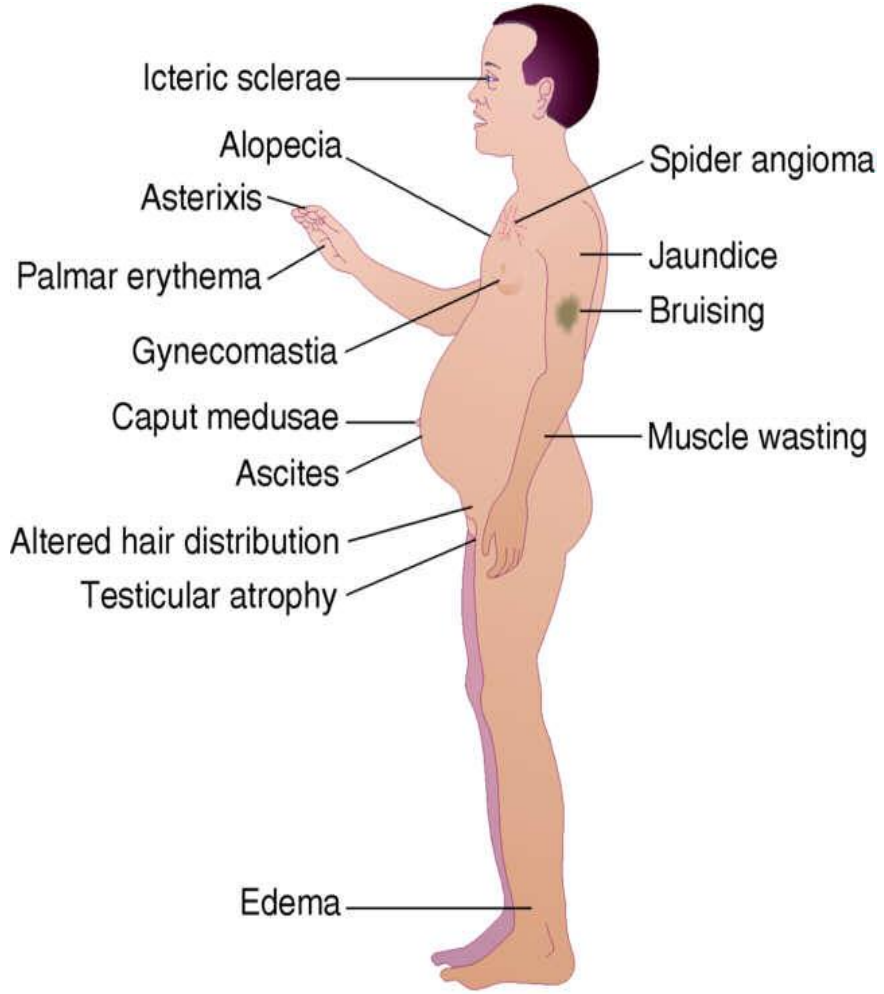
Functional Classification of Advanced Chronic Liver Disease



Garcia-Tsao G et al Hepatology 2010

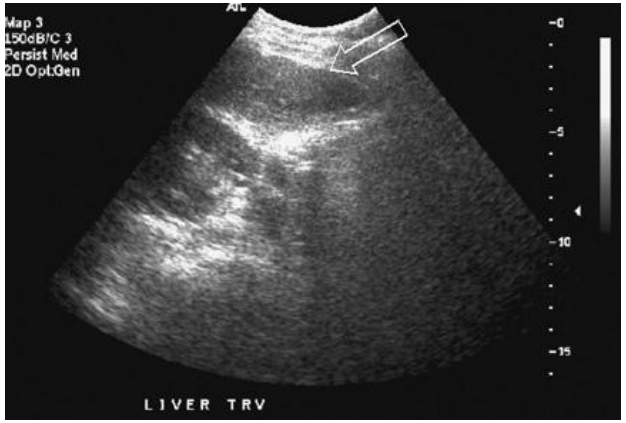
Clinical Findings in Advanced Liver Disease

- None in 40%
- Non-specific advanced stage symptoms
  - Weakness
  - Fatigue
  - Anorexia
  - Weight loss
  - Nausea etc

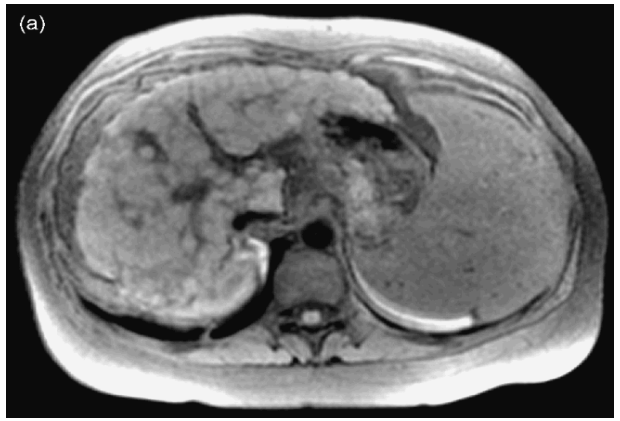


Imaging Findings in Cirrhosis

- Liver surface nodularity
- Diffuse heterogeneity of liver parenchyma
- Doppler US reversal of portal flow
- Atrophy of the right lobe and hypertrophy of the left and caudate lobes
- PHTN Vascular collaterals (varices, splenorenal shunts etc)
- Splenomegaly, Ascites etc



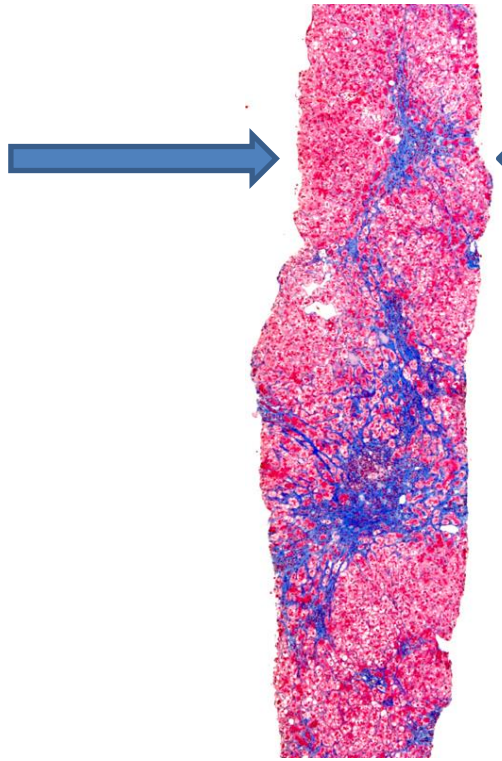
US Cirrhosis



MRI Chronic Cirrhosis

Noninvasive Diagnosis of NAFLD Advanced Fibrosis

Clinical
Age, T2DM,
BMI, MetS



Simple markers
AST, ALT, Platelets
GGT, Bilirubin,
Glucose etc
FIB-4 and NAFLD Fibrosis Score

AASLD Guidance Statement

- NFS or FIB-4 index are clinically useful tools for identifying NAFLD patients with higher likelihood of having bridging fibrosis (stage 3) or cirrhosis (stage 4)

Chalasani N et al Hepatology 2018

Simple Markers for Advanced Fibrosis

FIB-4 = $\dfrac{\text{Age (years)} \times \text{AST level (U/L)}}{\text{Platelet count } (10^9/L) \times \sqrt{\text{ALT (U/L)}}}$ =

<1.3 = F0-2
>2.67= F3-4

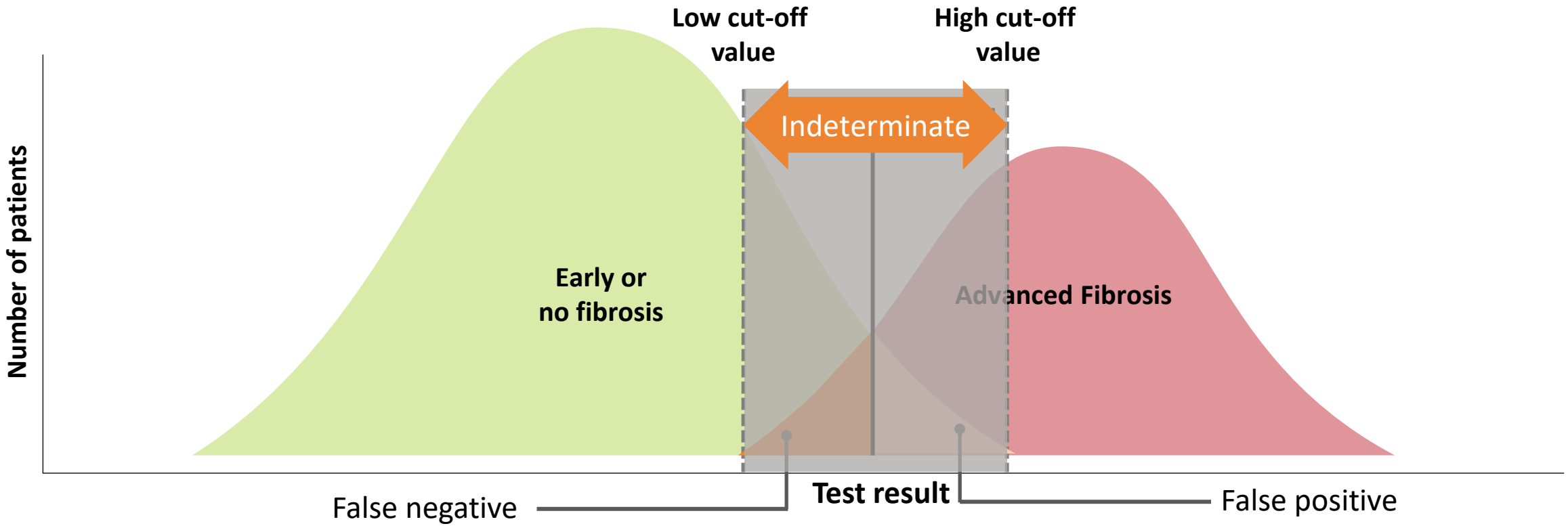
NFS =

Age		years
BMI		kg/m^2
Impaired fasting glucose / diabetes	No 0	Yes +1
AST/ALT		ratio
Platelet count		$\times 10^9/L$
Albumin		g/L

<-1.455 = F0-2
> 0.676 = F3-4

Calculator available at: https://www.mdcalc.com

Selection of Diagnostic Thresholds for Noninvasive Tests (NITs)



Simple Markers for Advanced Fibrosis

Score	NAFLD	Variables	Fibrosis stage	Cut-Offs	Sens/Spec	AUC	IND
NAFLD Fibrosis Score	N=3064	Age, glucose, BMI, platelets, AST/ALT	F3-F4	<-1.455 >0.676	0.90/0.60 0.64/0.97	0.85	20-58%
BARD	N=1506	BMI, AST/ALT, T2DM	F3-F4	2	0.72/0.64	0.78	
APRI	N=576	AST, Platelets	F3-F4	1	0.67/0.81	0.82	
FIB-4	N=541	Age, AST, ALT, Platelets	F3-F4	<1.30 >2.67	0.74/0.71 0.33/0.98	0.80	24-36%

Bedossa P and Patel K Gastro. 2016

Simple Tests for NAFLD Advanced Fibrosis

NAFLD Fibrosis Score

-0.92

Parameter	Patient
Age	55
AST	40
ALT	60
Platelet count (x 10^9)	250
BMI	30
Albumin, g/dL	4.0
Impaired fasting glucose/diabetes?	Yes

FIB-4

1.14

NAFLD Cutoff Value[1]	Stage
< -1.455	F0-F2
-1.455 to 0.676	**Indeterminate**
> 0.676	F3-F4

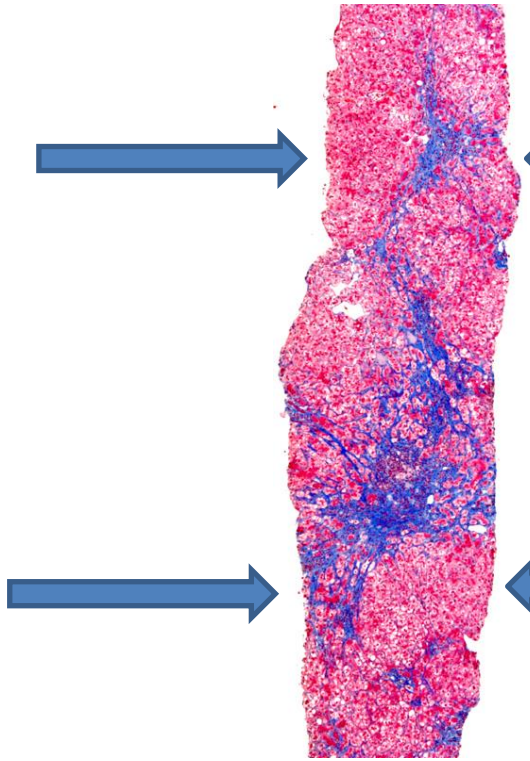
FIB-4 Cutoff Value[2]	Stage
< 1.30	**F0-F2**
1.31 to 2.67	Indeterminate
> 2.67	F3-F4

1. Angulo P, et al. Hepatology 2007
2. Shah AG, et al. CGH. 2009

Noninvasive Diagnosis of NAFLD Advanced Fibrosis

Clinical
Age, T2DM,
BMI, MetS

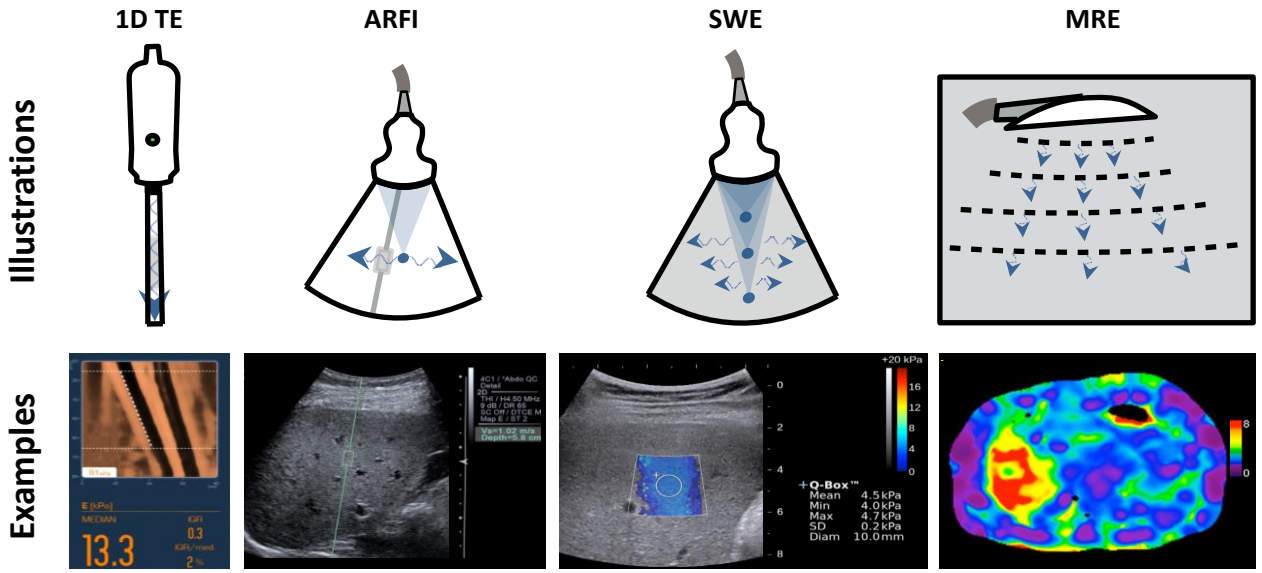
Simple markers
AST, ALT, Platelets
GGT, Bilirubin,
Glucose etc
FIB-4, NFS



Imaging
US or MR
Elastography

Complex marker panels
HA, TIMP-1, PIIINP, K18
Type IV collagen etc

Elastography Techniques for NAFLD Advanced Fibrosis

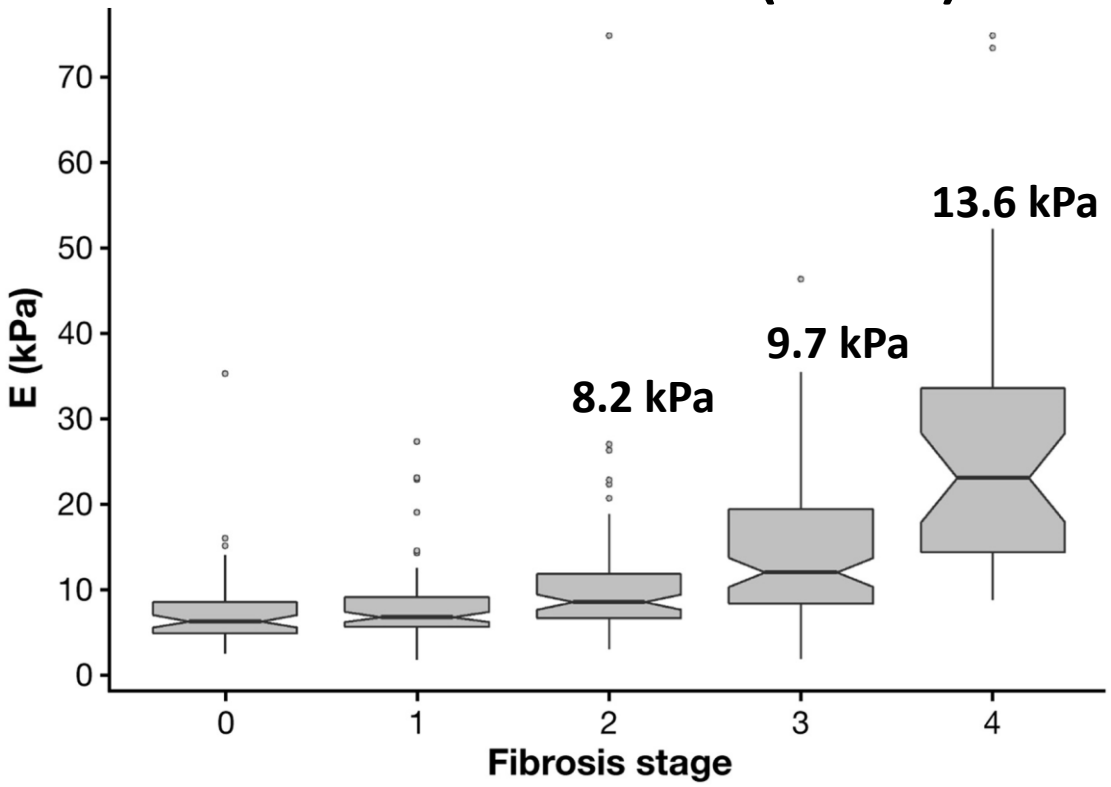


	Fibrosis stage	Cut-offs	Sens/Spec	AUC
Vibration-Controlled Transient Elastography	F3-F4	7.9-12.5 kPa	0.84/0.95	0.86-0.93
ARFI (pSWE)	F3-F4	1.55-1.61 m/s	0.92/0.85	0.89-0.94
2D-Shear wave elastography	F3-F4	8.3-9.2 kPa	0.89/0.88	0.94
MRE	F3-F4	2.99-4.80 kPa	0.83/0.89	0.92

Castera et al, Gastro 2019
Liang et al, BMC Gastro. 2020
Jiang et al, BMJ Open 2018
Lin et al, PloSOne 2020
Selvaraj E et al. J Hepatol 2021

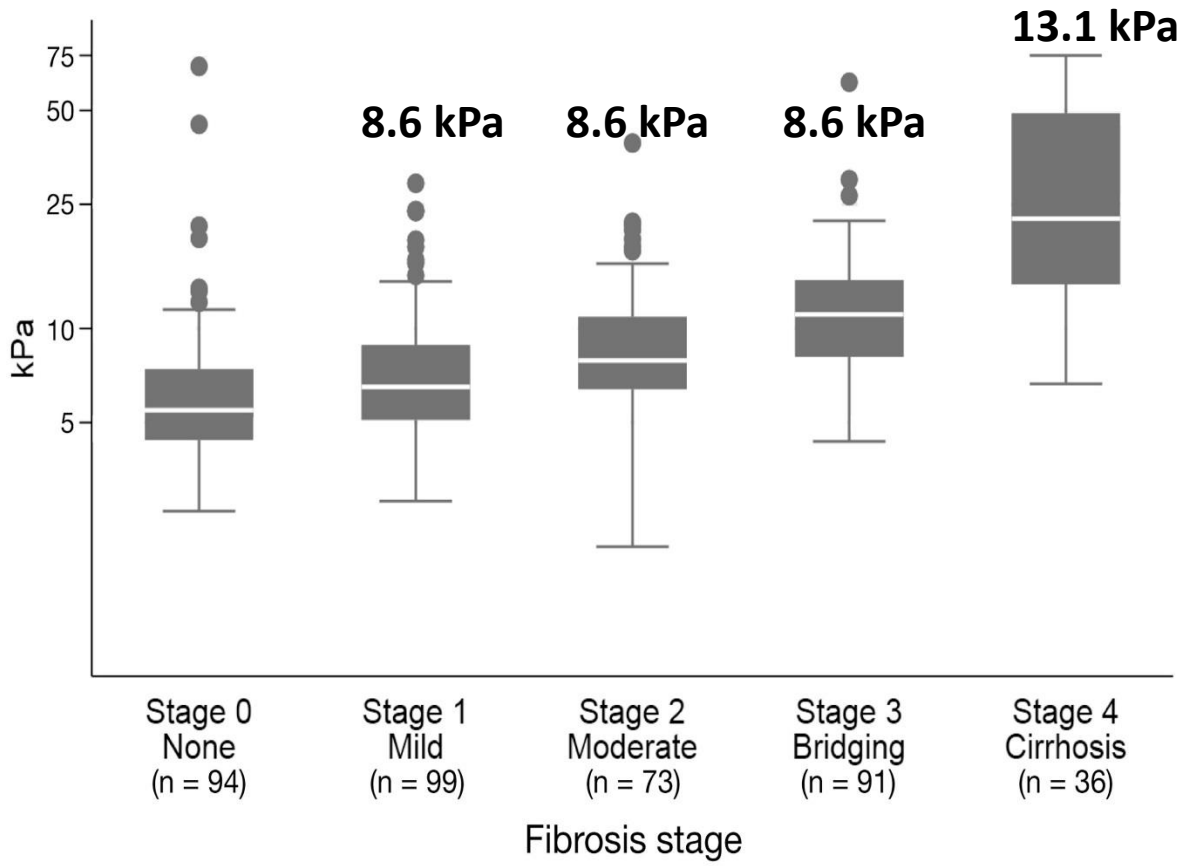
Variable FibroScan Thresholds for NAFLD Fibrosis

UK- NAFLD Cohort (n=383)



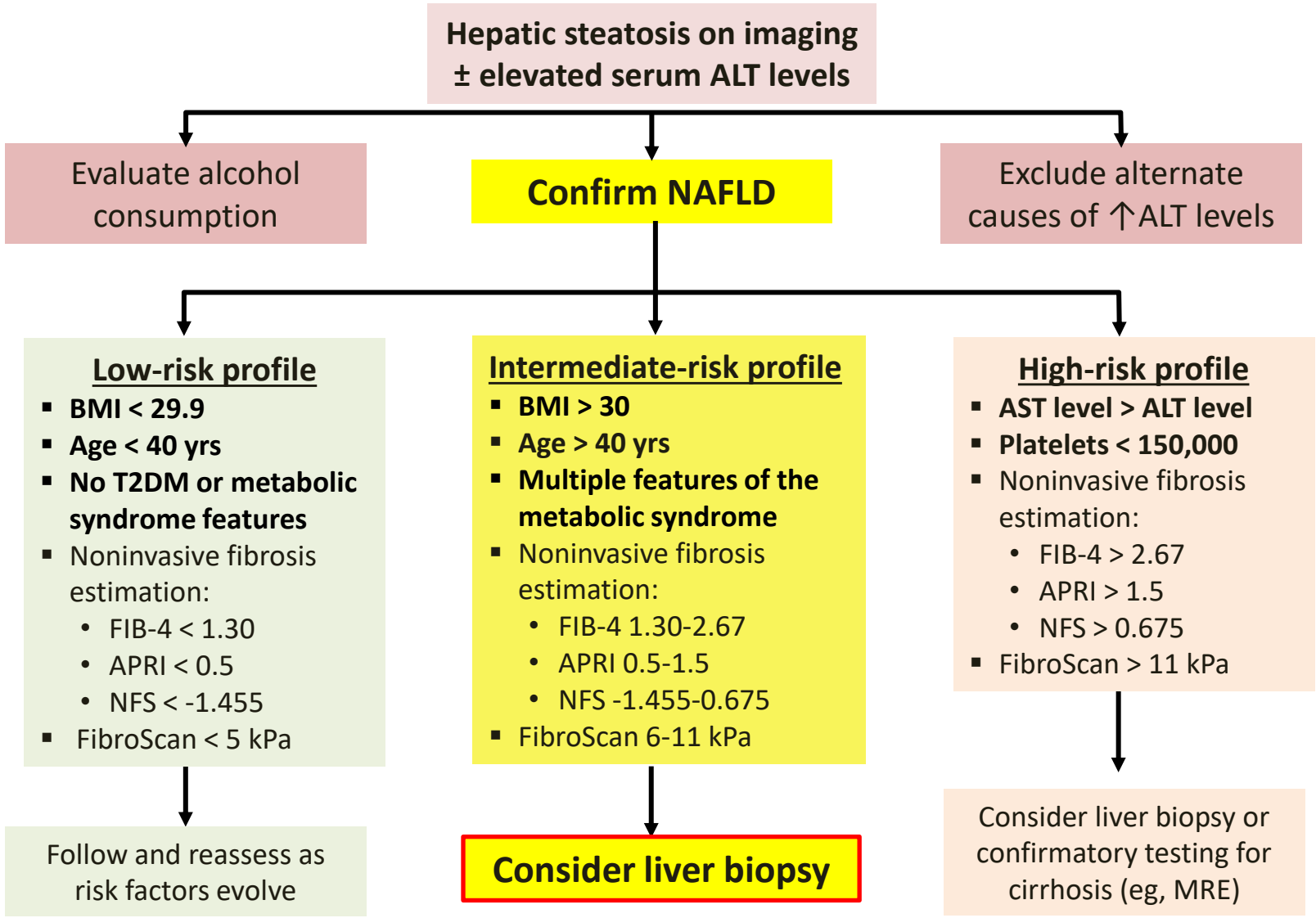
Eddowes P et al Gastro 2019

NASH CRN Cohort (n=393)



Siddiqui M et al CGH 2019

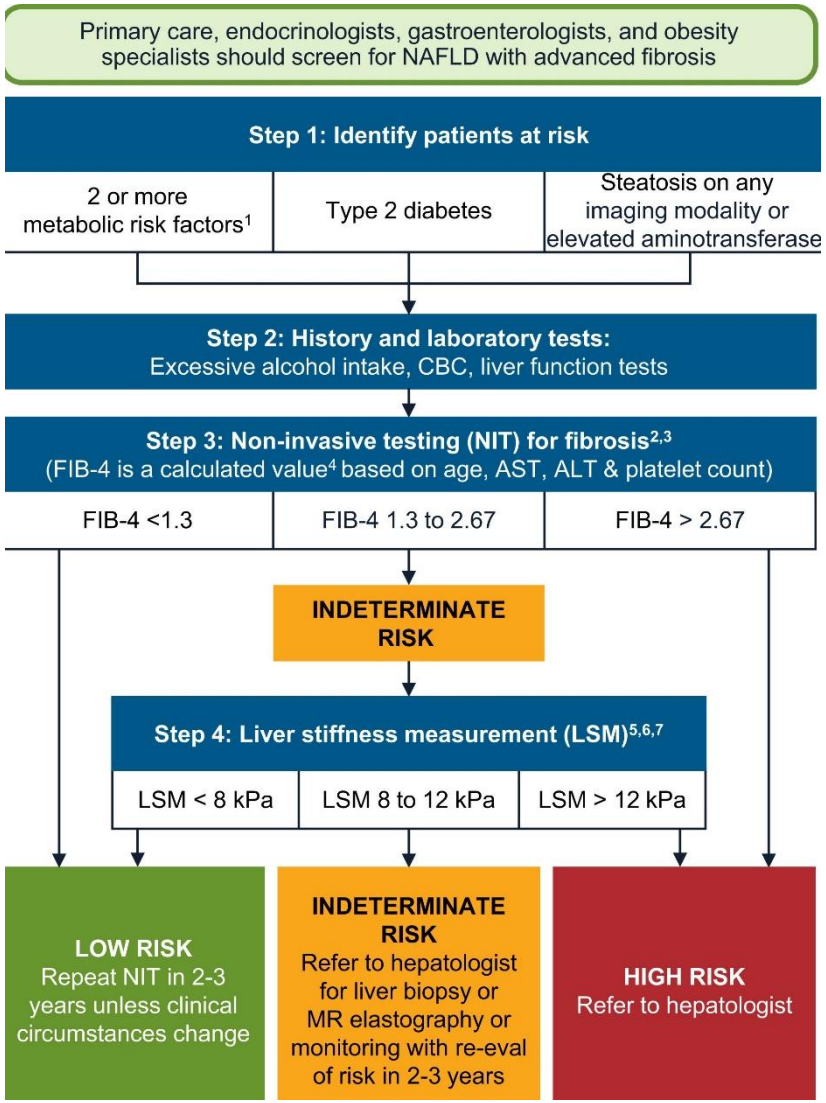
Clinical Risk Stratification in NAFLD



Rinella ME, Sanyal AJ. Nat Rev Gastroenterol Hepatol. 2016

NAFLD Screening

AGA Clinical Care Pathway



	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	HIGH RISK[1] FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4, 5, 6]	Yes[4, 5, 6, 7]
CVD risk reduction[8]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

4. Individualize and consider biopsy
5. No FDA approved therapies, but can consider Pioglitazone or GLP-1 in T2DM
6. Vit E improves steatohepatitis in non-T2DM
7. Pharmacotherapy very limited in NASH cirrhosis, best avoided until more data available.

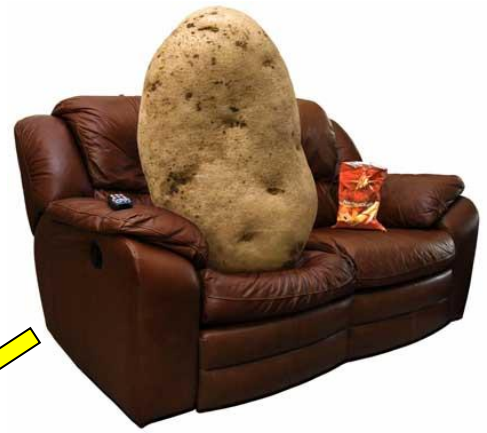
Kanwal F. Gastroenterology 2021

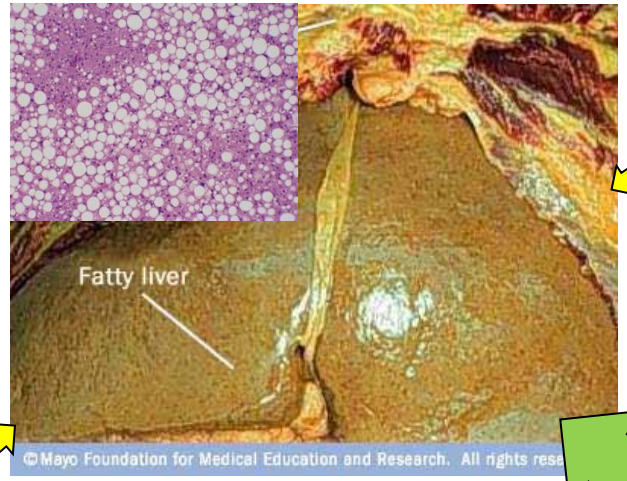
Lifestyle Management Options

Lifestyle Determinants of NAFLD

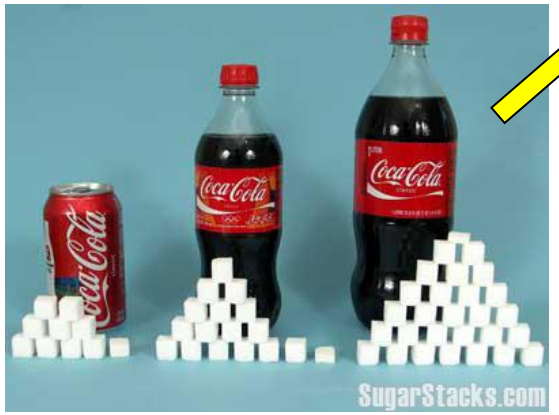
What we eat…..

What we do…..





What we drink…..



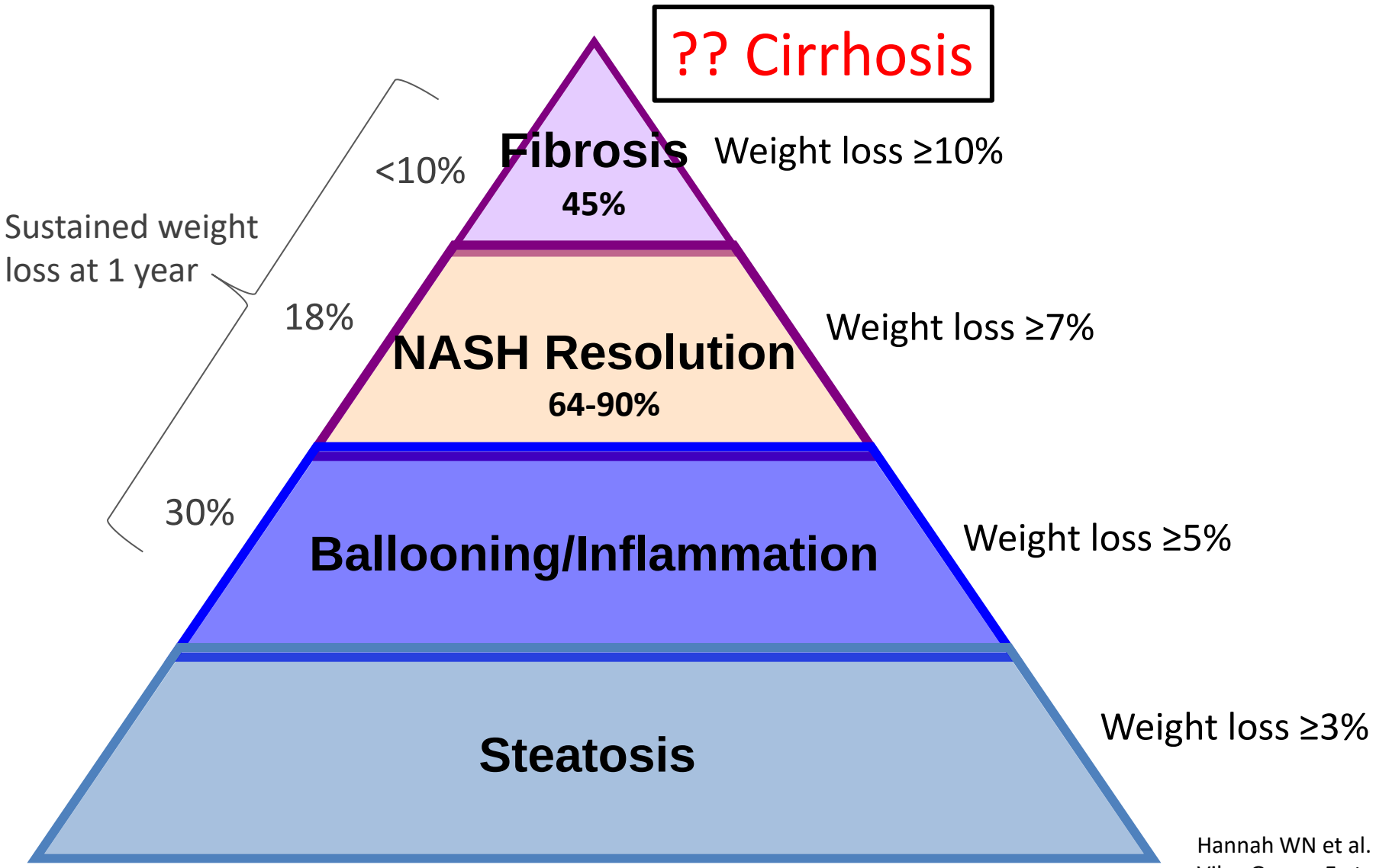
What we want…..

AGA Clinical Practice Update-Lifestyle Modification

- Lifestyle modification using diet and exercise to achieve weight loss is beneficial for all patients with NAFLD
- ≥5% weight loss can decrease steatosis, ≥7% can lead to NASH resolution, and ≥10% can result in fibrosis regression/stability

Younossi Z et al. Gastroenterology 2021

Weight Loss and NAFLD Pyramid



Hannah WN et al. Clin Liver Dis. 2016
Vilar-Gomez E et al Gastroenterology 2015

AGA Clinical Practice Update-Lifestyle Modification

Dietary advice

- Clinically significant weight loss requires hypocaloric diet
  - 1200-1500 kcal/d or 500-1000 kcal daily reduction from baseline
  - Improved insulin resistance and intrahepatic fat
- Follow Mediterranean diet (or equivalent)
  - Daily fresh vegetables, minimally processed whole grains, legumes (lentils, chickpeas, beans), fish and omega-3 FA from olive oil and nuts
  - Reduce red and processed meats
  - Avoid high-fructose corn syrup foods (soda, juices, packaged sweets)
- No data on NASH histologic end-points for specific hypocaloric diets (low CHO/high protein, intermittent fasting, meal-replacement protocols)

Younossi Z et al. Gastroenterology 2021

AGA Clinical Practice Update-Lifestyle Modification

Physical activity

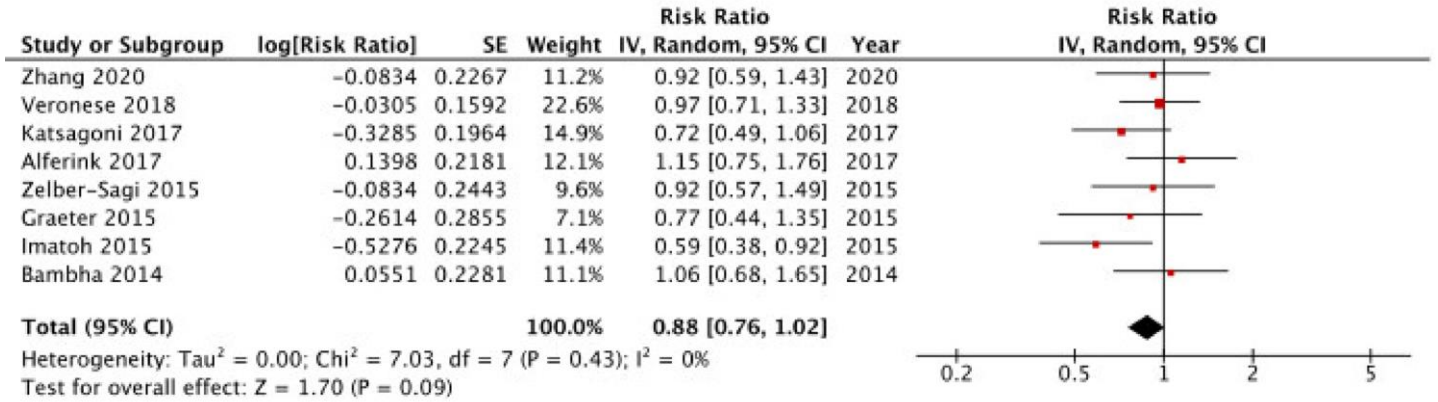
- Regular physical activity with target of 150-300 minutes moderate intensity or 75-150 mins vigorous-intensity aerobic exercise per week[1]
  - Moderate-intensity activity (3-6 metabolic equivalents)
    - Walking 3 mph, stationary bike, household activities that increase the heart rate
  - Vigorous-intensity activities (> 6 Mets)
    - Cycling >10mph or uphill, jogging, push-ups, exercise classes
  - Resistance exercise improves steatosis with less energy consumption than aerobic activity (for patients with poor cardiorespiratory fitness)[2]
  - Flexibility: Gentle stretches improve the range of motion in joints and helps with mobility
  - Exercise enhances dietary weight-reduction benefit
    - Improved IR and reduced *de novo* lipogenesis independent of weight loss

1. Younossi Z et al Gastroenterology 2021
2. Hashida R et al J Hepatology 2017

Coffee and NAFLD

Systematic Review and Meta-Analysis

NAFLD Prevalence



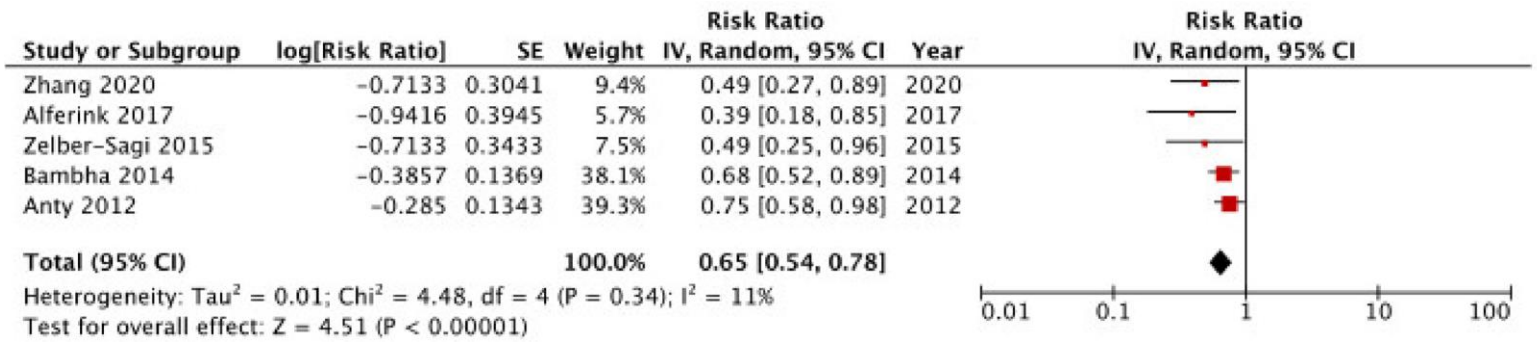
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Zhang 2020	-0.0834	0.2267	11.2%	0.92 [0.59, 1.43]	2020
Veronese 2018	-0.0305	0.1592	22.6%	0.97 [0.71, 1.33]	2018
Katsagoni 2017	-0.3285	0.1964	14.9%	0.72 [0.49, 1.06]	2017
Alferink 2017	0.1398	0.2181	12.1%	1.15 [0.75, 1.76]	2017
Zelber-Sagi 2015	-0.0834	0.2443	9.6%	0.92 [0.57, 1.49]	2015
Graeter 2015	-0.2614	0.2855	7.1%	0.77 [0.44, 1.35]	2015
Imatoh 2015	-0.5276	0.2245	11.4%	0.59 [0.38, 0.92]	2015
Bambha 2014	0.0551	0.2281	11.1%	1.06 [0.68, 1.65]	2014
Total (95% CI)			**100.0%**	**0.88 [0.76, 1.02]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.03$, df = 7 (P = 0.43); $I^2 = 0\%$

Test for overall effect: Z = 1.70 (P = 0.09)

- N=8 studies
- Mostly US diagnosis
- No significant association with prevalence

Significant Fibrosis



Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Zhang 2020	-0.7133	0.3041	9.4%	0.49 [0.27, 0.89]	2020
Alferink 2017	-0.9416	0.3945	5.7%	0.39 [0.18, 0.85]	2017
Zelber-Sagi 2015	-0.7133	0.3433	7.5%	0.49 [0.25, 0.96]	2015
Bambha 2014	-0.3857	0.1369	38.1%	0.68 [0.52, 0.89]	2014
Anty 2012	-0.285	0.1343	39.3%	0.75 [0.58, 0.98]	2012
Total (95% CI)			**100.0%**	**0.65 [0.54, 0.78]**	

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.48$, df = 4 (P = 0.34); $I^2 = 11\%$

Test for overall effect: Z = 4.51 (P < 0.00001)

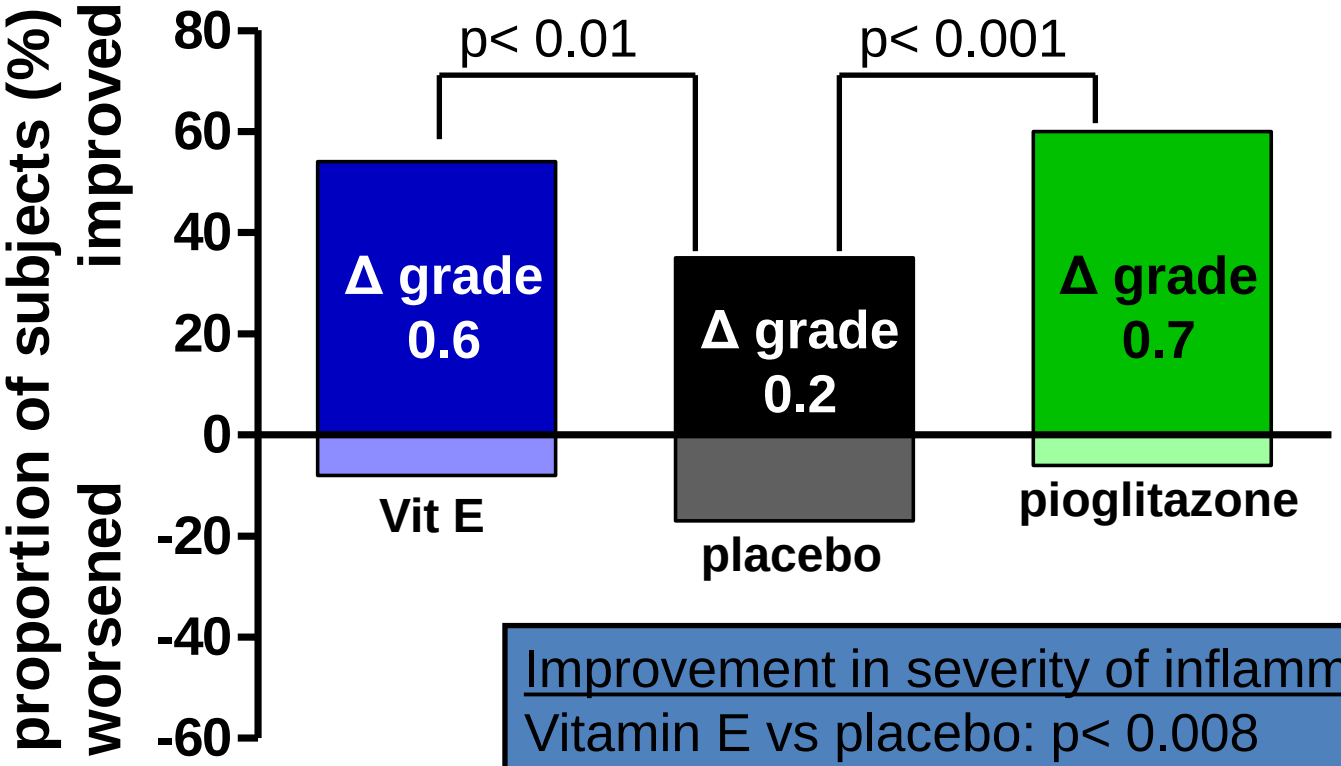
- 5 studies (Biopsy n= 3)
- Risk Ratio 0.65, I^2 11%
- 35% reduced odds of significant fibrosis
- ≥ 2-3 cups/day
- ? Brewing method/type, quantity, caffeine etc

Ebadi M et al Nutrients 2021

PIVENS: Vitamin E and Pioglitazone improve Lobular Inflammation

-Non-diabetics NASH (n=247)
-Treatment Duration: 18 months

NO improvement in Fibrosis



Improvement in severity of inflammation:
Vitamin E vs placebo: p< 0.008
Pioglitazone vs placebo: p< 0.0009

Sanyal A NEJM 2010

AASLD Guidance Statement

- Pioglitazone improves liver histology in patients with and without T2DM with biopsy-proven NASH. Therefore, it may be used to treat these patients. Risks and benefits should be discussed with each patient before starting therapy.
- Until further data support its safety and efficacy, pioglitazone should not be used to treat NAFLD without biopsy-proven NASH.

Chalasani N et al Hepatology 2018

AASLD Guidance Statement

- Vitamin E administered at a daily dose of 800 IU/day improves liver histology in nondiabetic adults with biopsy-proven NASH and therefore may be considered for this patient population.
- Until further data supporting its effectiveness become available, vitamin E is not recommended to treat NASH in diabetic patients, NAFLD without liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis.

Chalasani N Hepatology 2018

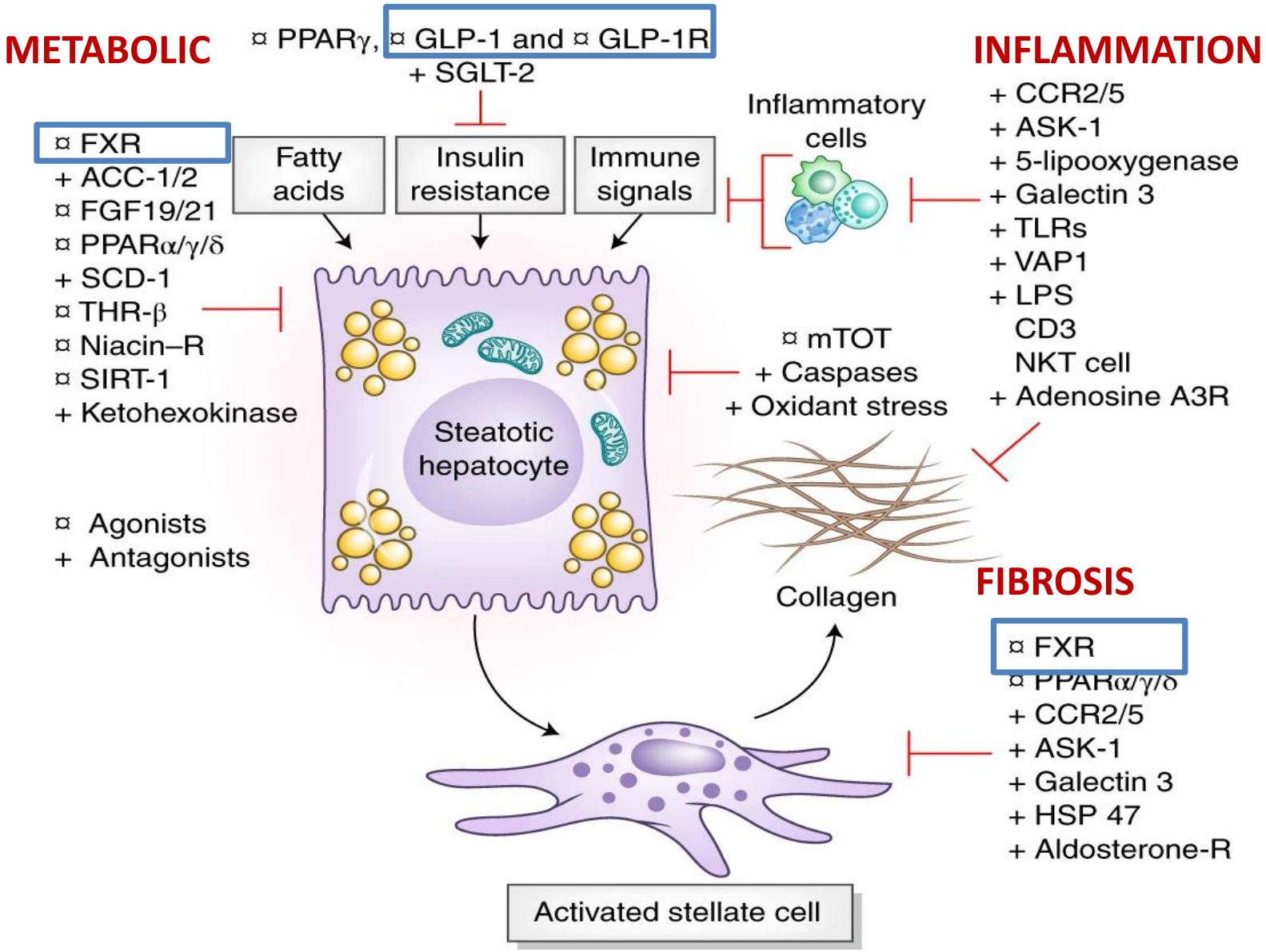
Why Not Empirically Treat Possible NASH With Vitamin E?

- ~ 50% of pts do not respond to vitamin E
  - Liver enzymes are not reliable to assess quiescence or progression
- No efficacy data for:
  - Cirrhosis regression (? role for preventing liver decompensation)
  - Diabetics
- Increased risk of hemorrhagic stroke
  - Poorly controlled Hypertension
- Prostate cancer risk?
  - Older men, FH of prostate Ca.
- ? Long-term safety
  - Remains unknown though likely safe
  - Doses > 400 IU/day may be associated with increased all-cause mortality
  - Data limited by small studies

Sanyal AJ, et al. N Engl J Med. 2010
Schürks M, et al. BMJ. 2010
Klein EA, et al. JAMA. 2011
Gaziano JM, et al. JAMA. 2009
Miller ER III, et al. Ann Intern Med. 2005
Villar-Gomez Hepatology 2020

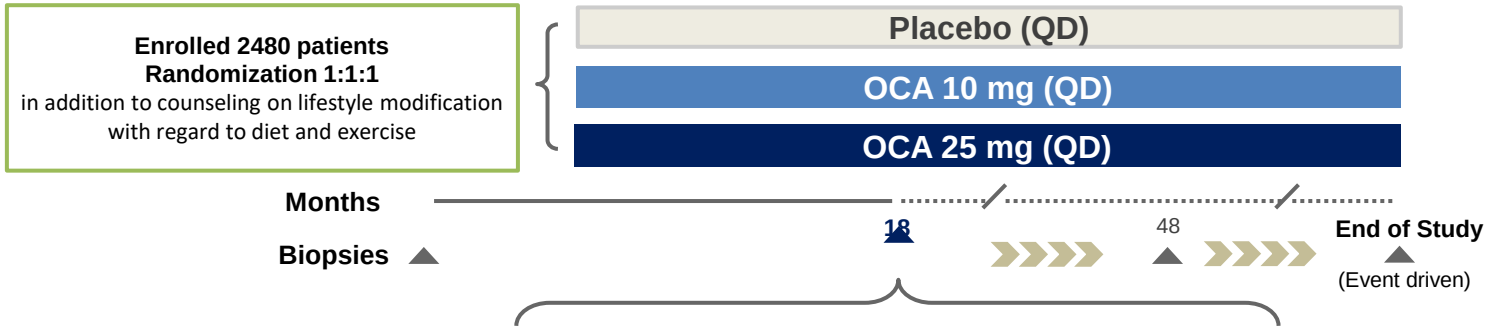
NAFLD Clinical Trials

NAFLD Therapeutic Targets



Friedman SL Nat Med 2018

REGENERATE : Obeticholic Acid (OCA) in Patients with Liver Fibrosis due to NASH (F2-F3)



Month 18 Interim Analysis
1968 patients*
One of Two Composite Primary Endpoints Required for Study Success:

Fibrosis Improvement by ≥1 Stage and No Worsening of NASH

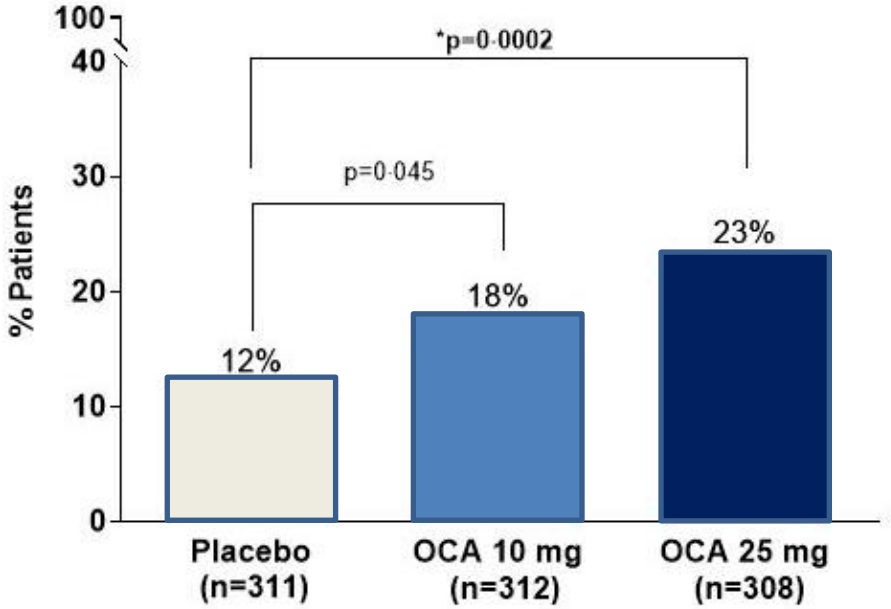
or

NASH Resolution and No Worsening of Fibrosis

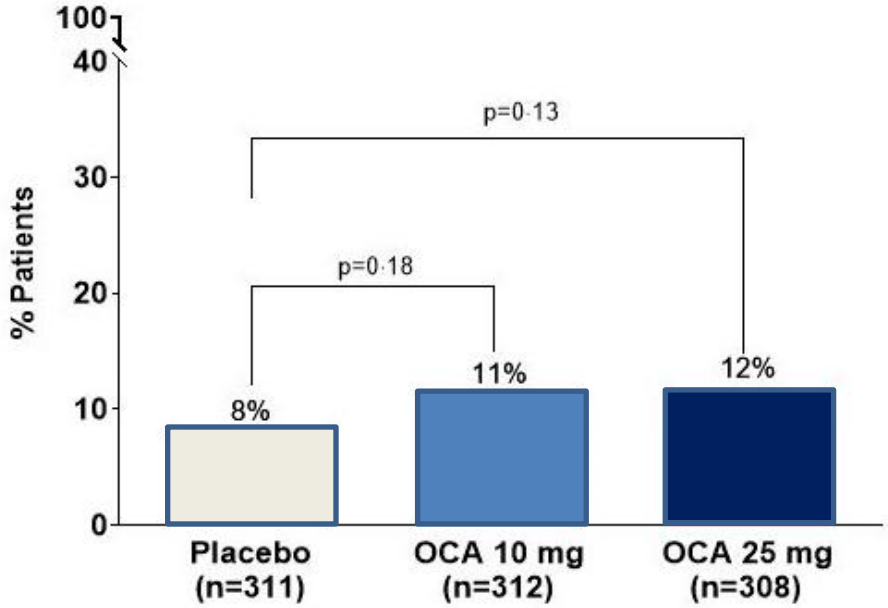
Younossi ZM et al. Lancet 2019

REGENERATE Interim Results (ITT Population)

Fibrosis Improvement by ≥1 Stage with No Worsening of NASH



NASH Resolution with No Worsening of Fibrosis



Has been submitted to FDA and EMA

- Complete Response Letter (CRL) from FDA on NDA – June 2020

  FDA recommends that Intercept submit additional post-interim analysis efficacy and safety data from the ongoing REGENERATE study in support of potential accelerated approval and that the long-term outcomes phase of the study should continued

- EMA Submission- withdrawn December 2021

Younossi ZM et al. Lancet 2019

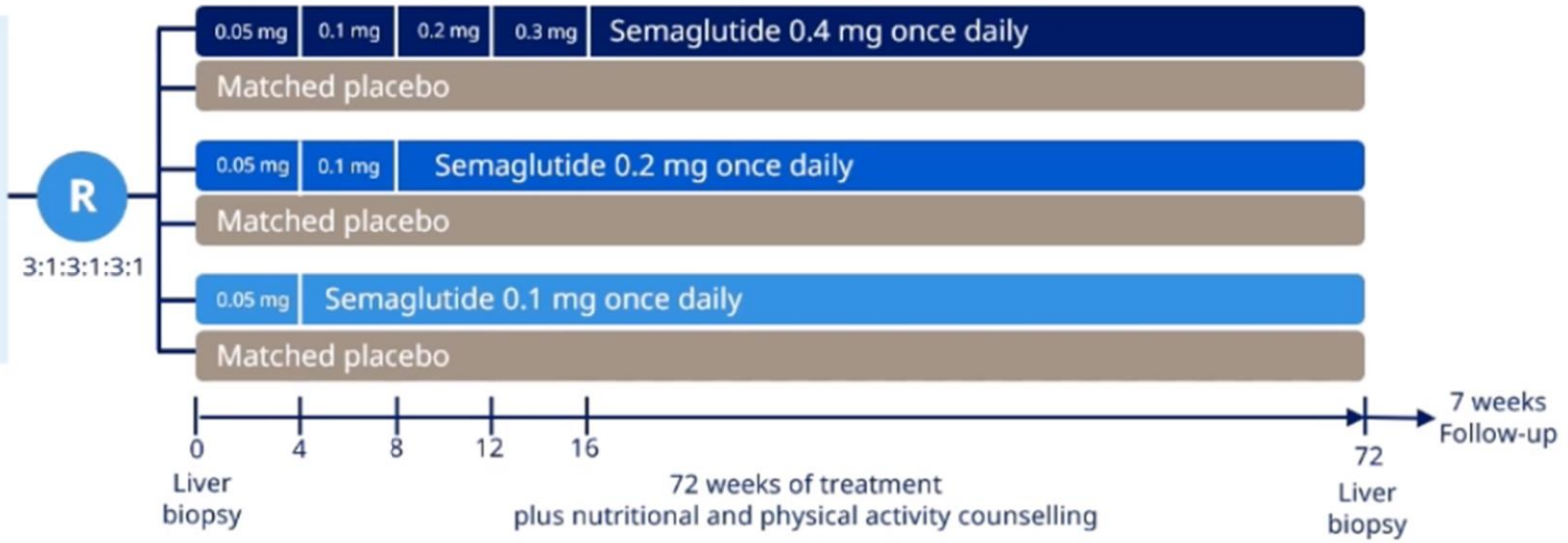
Efficacy and Safety of Subcutaneous Once-daily Semaglutide vs Placebo in NASH

Trial objective: To compare the effect of three different doses of semaglutide subcutaneous (s.c.) once daily versus placebo on histological resolution of NASH

Eligible patients

Biopsy confirmed NASH
NAS ≥ 4
Fibrosis stage 1, 2 or 3
BMI > 25 kg/m^2
HbA_{1c} ≤ 10%

N=320 Randomized



Primary endpoint:

Resolution of steatohepatitis and no worsening in liver fibrosis in patients with baseline fibrosis stage 2 or 3

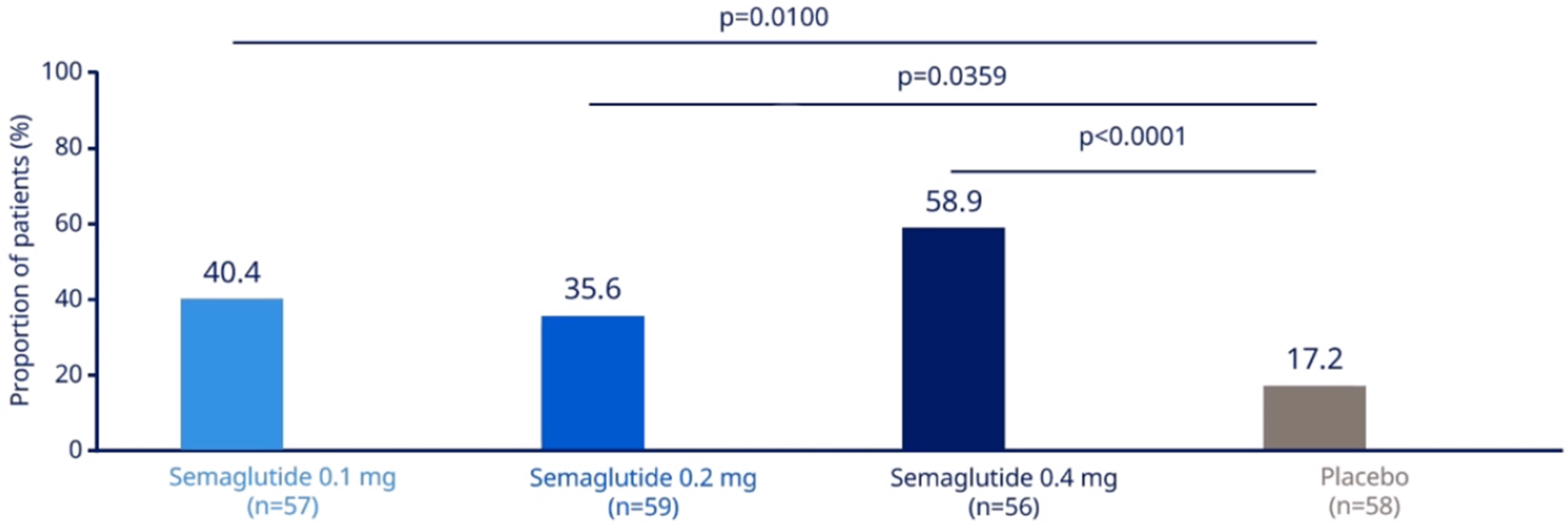
Confirmatory secondary endpoint:

Improvement in liver fibrosis and no worsening in steatohepatitis with baseline fibrosis stage 2 or 3

Newsome P NEJM 2021

Resolution of Steatohepatitis AND no worsening of Fibrosis

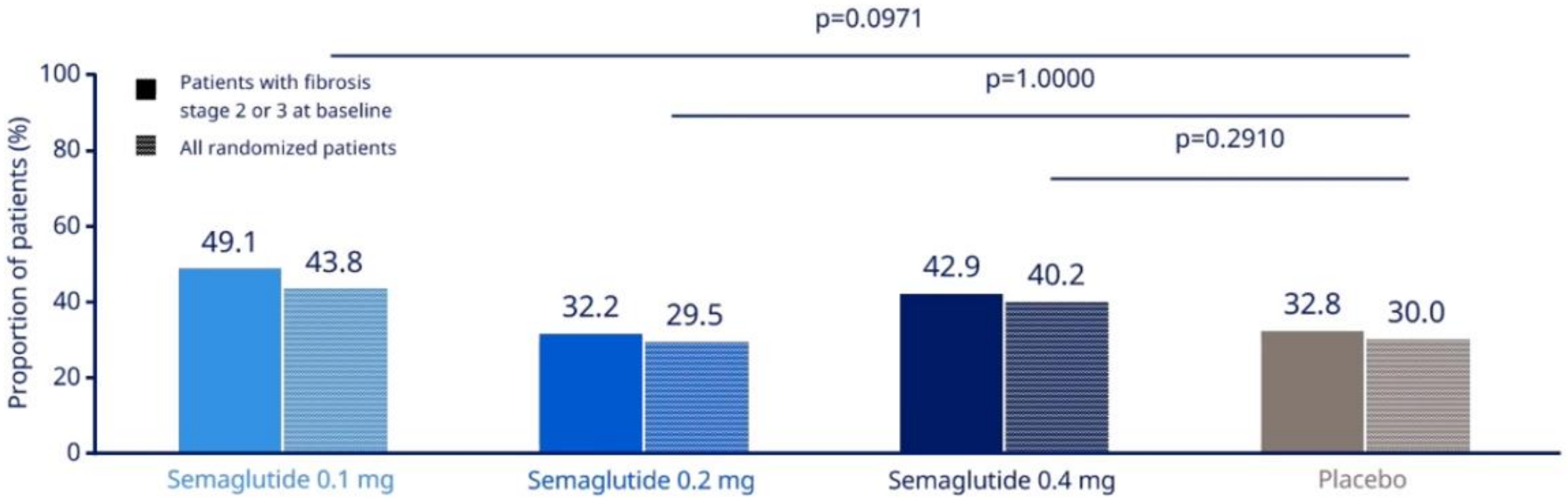
Patients with Fibrosis stage 2 or 3 at baseline



Newsome P NEJM 2021

Improvement in Liver Fibrosis AND no worsening in Steatohepatitis

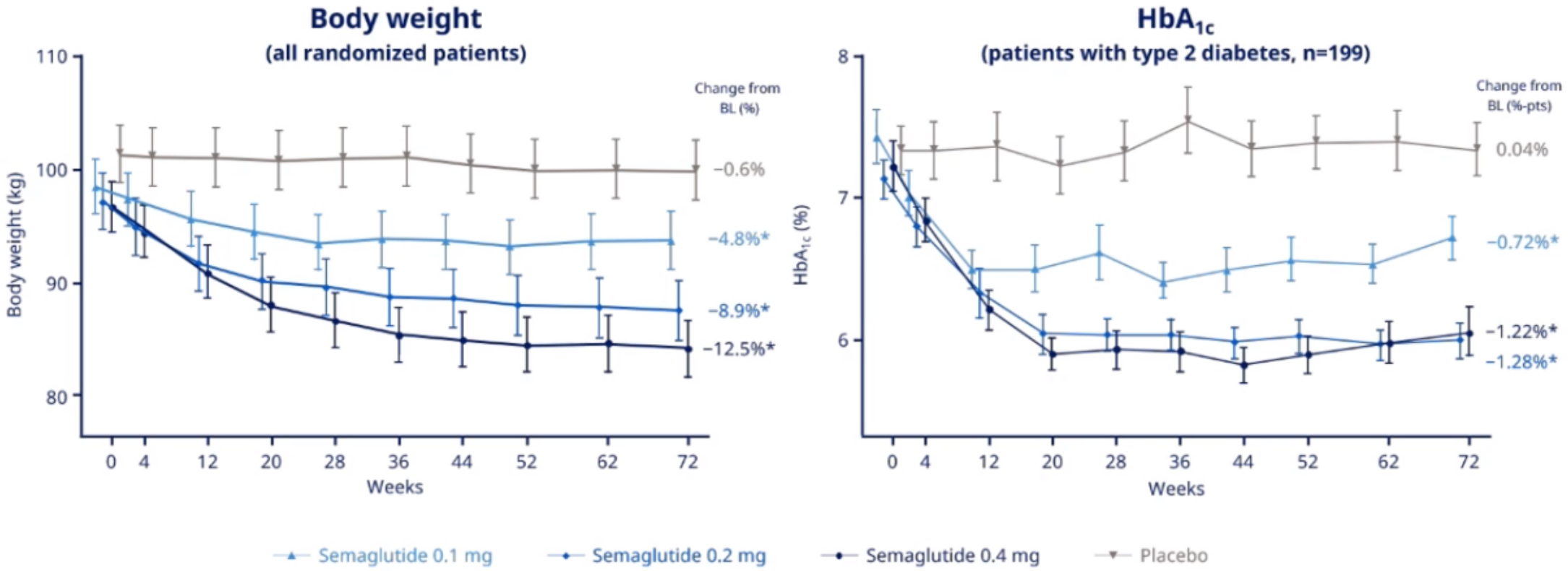
Patients with Fibrosis stage 2 or 3 and all randomized patients



High Placebo Response

Newsome P NEJM 2021

Changes in Body Weight and HbA1C

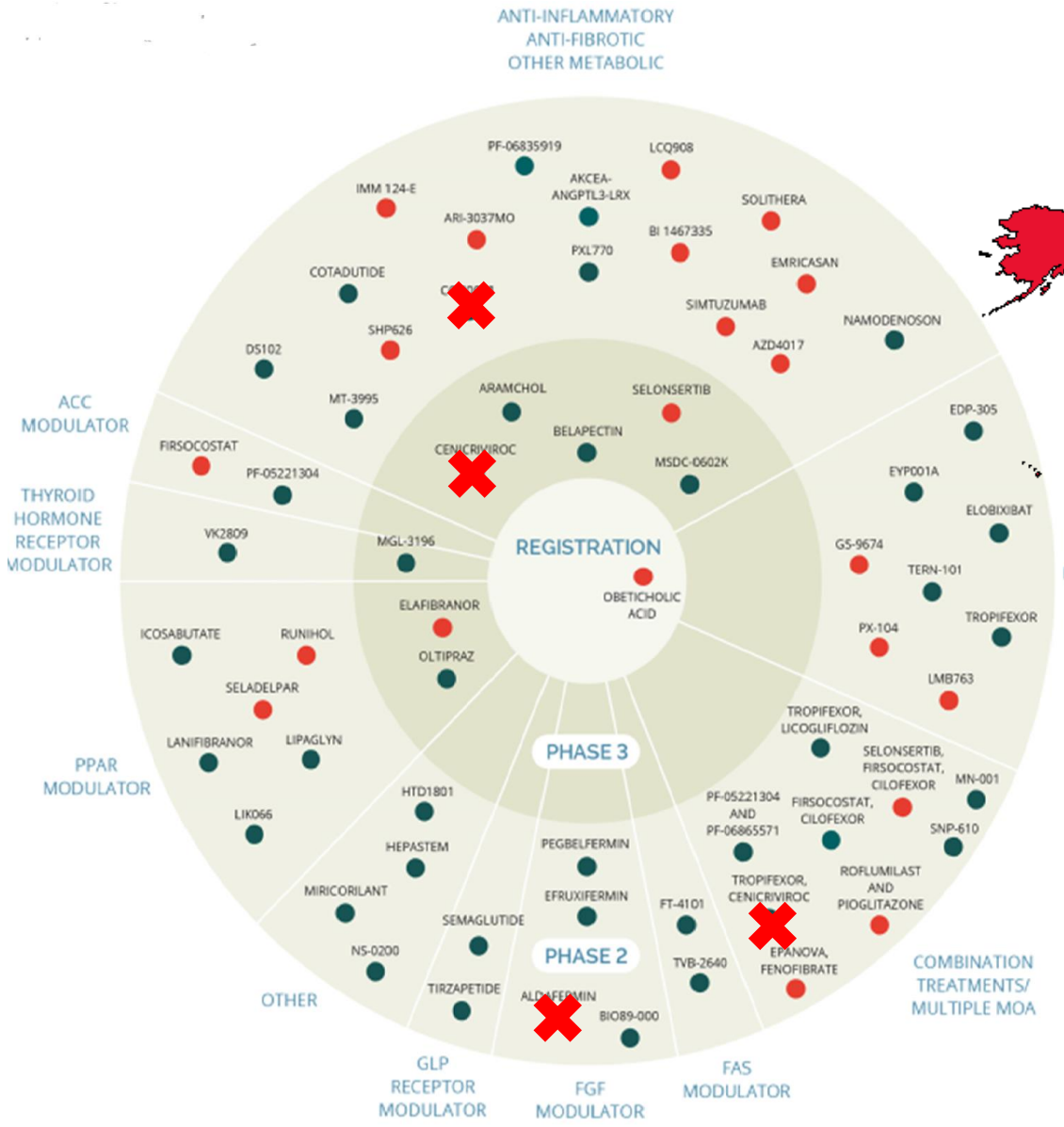


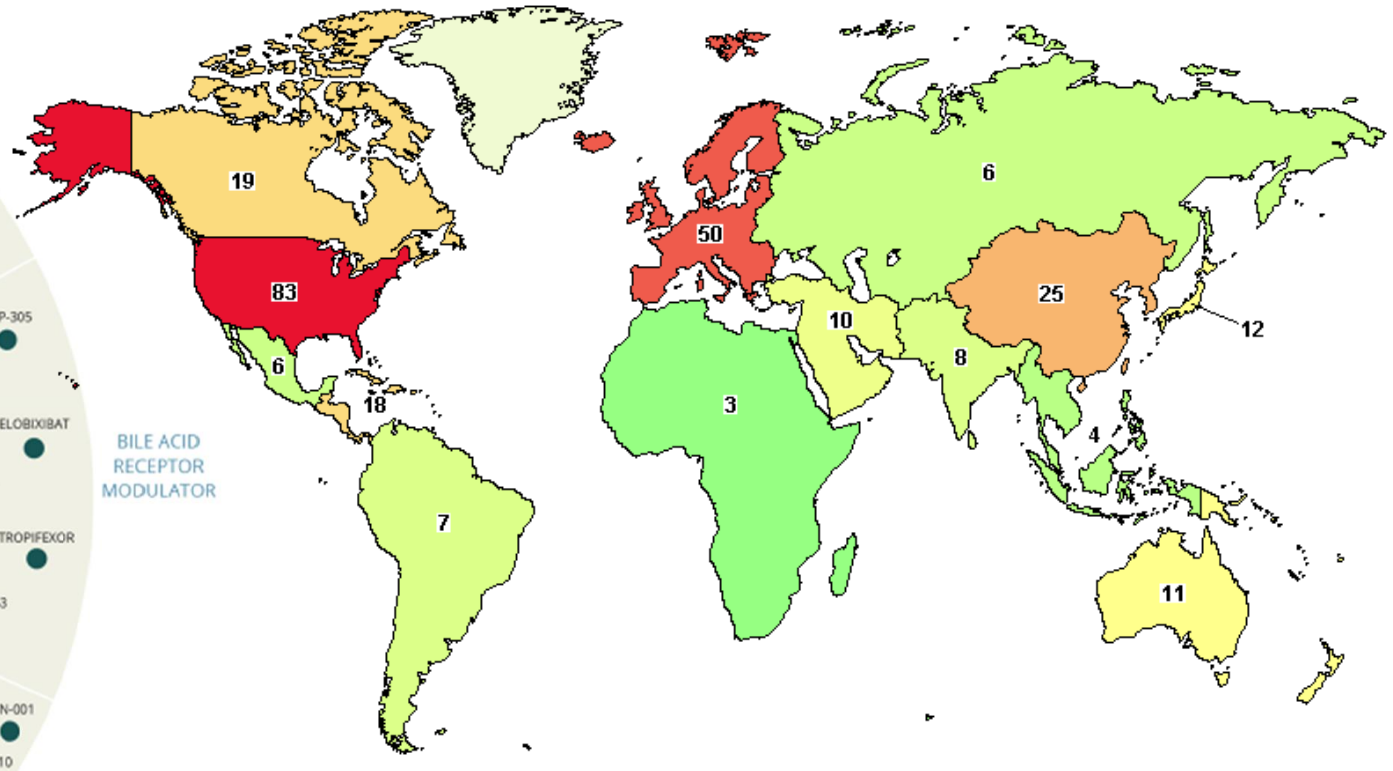
Most common AE (Semaglutide 0.4mg vs placebo)

- Nausea (42% vs 11%), Constipation (22% vs 12%), Vomiting (15% vs 2%)
- 4% Discontinued due to GI-related adverse events

Newsome P NEJM 2021

Current NASH Therapeutic Pipeline





Current NASH Studies
ClinTrials.gov (Accessed April 2022)

Available Therapy for Metabolic Disease and NAFLD

	Weight	NASH improvement	Fibrosis Regression	CVS Benefit
Vitamin E	Nil	Yes	No	No
Pioglitazone	Increase	Yes	Equivocal	Possible
GLP-1 agonists	Decrease	Yes	No	Yes
SGLT-1 inhibitors	Decrease	Possible	No	Yes
DPP-4 inhibitors	Nil	No	No	Equivocal
Metformin	Nil	No	No	Possible
Statins	Nil	No	No	Yes
UDCA	Nil	No	No	No
Bariatric Surgery	Decrease	Yes	Yes	Yes

AASLD Guidance Statement

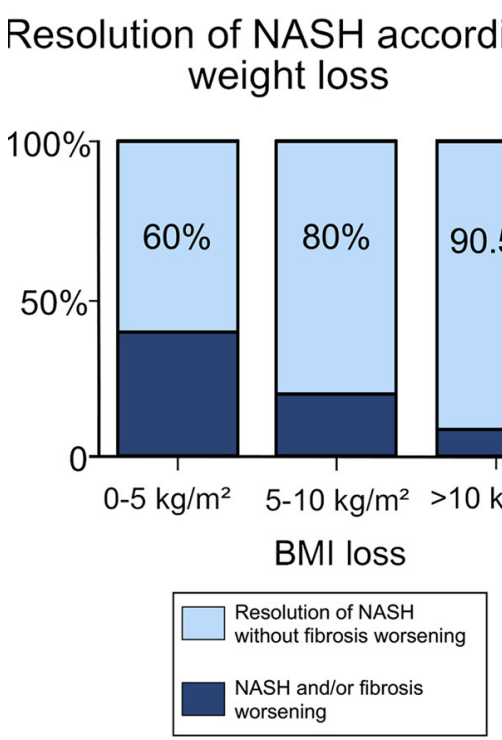
- Foregut bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH.
- It is premature to consider foregut bariatric surgery as an established option to specifically treat NASH.

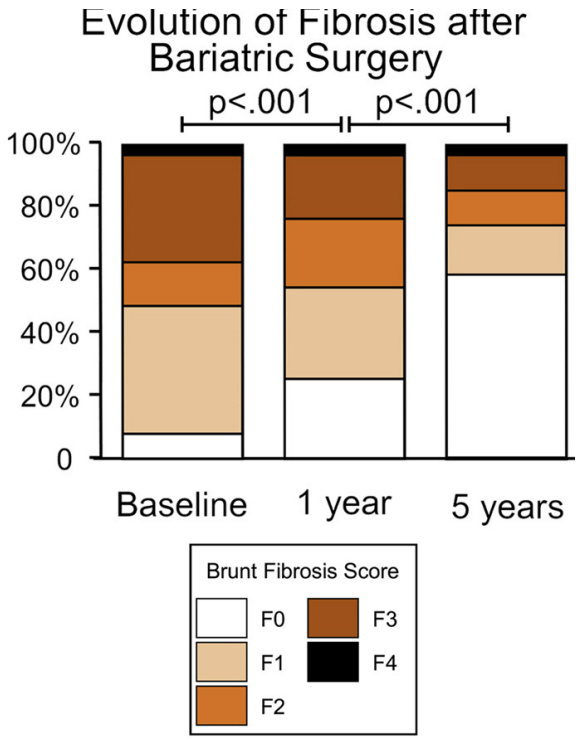
Updated 2022 AASLD Guidance awaited

Chalasani N et al Hepatology 2018

Long-term Resolution of NASH and Fibrosis Regression after Bariatric Surgery

- Lille study -180 NASH patients
  - RYGB 56%, SG in 33%, Gastric Band 11%
- Biopsy n=125 (1 yr) and n=64 (5 yrs)
- NASH resolved in 84% at 5 yrs
  - 93% in BMI loss >12 kg/m^2
  - Mostly in initial 12 months
- Fibrosis improved in 70% at 5 yrs
  - Complete resolution at 5 yrs in 63% (Baseline F1-2) and 45% (F3)
  - Resolution continued after Yr 1





Lasailly G et al Gastroenterology 2020

Resolution of NAFLD after Bariatric Surgery

Systematic Review and Meta-analysis

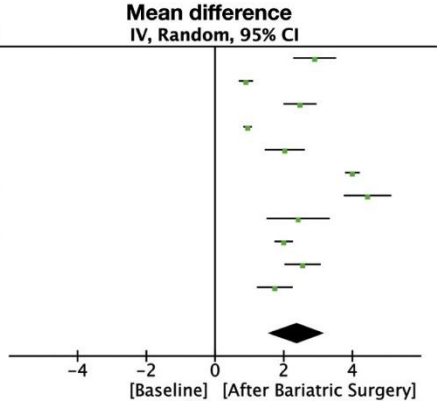
- N=32 studies
  - Low overall quality of evidence
  - Biopsy evaluation at 12 months
- Mean decrease NAS score 2.39
  - Complete resolution NASH
    - Steatosis 66%
    - Inflammation 50%
    - Ballooning 76%
  - Fibrosis resolution in 40%
- Higher NAFLD resolution for RYGB
- 12% *de novo* or worsening NAFLD

Change in NAS after Bariatric Surgery

Study or Subgroup	Before Bariatric Sx Mean	SD	Total	After Bariatric Sx Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI	Year
Liu 2007	4.87	1.89	39	1.97	0.58	39	8.9%	2.90 [2.28, 3.52]	2007
Mathurin 2009	1.97	1.33	362	1.07	1.26	267	9.4%	0.90 [0.70, 1.10]	2009
Tai 2012	3.33	1	21	0.857	0.5	21	9.1%	2.47 [1.99, 2.95]	2012
Caiazzo 2014	1.87	1.46	1201	0.92	1.13	578	9.4%	0.95 [0.83, 1.07]	2014
Raj 2015	2.6	1.3	30	0.57	0.97	30	9.0%	2.03 [1.45, 2.61]	2015
Lassailly 2015	5	0.7	81	1	0.67	81	9.4%	4.00 [3.79, 4.21]	2015
Schneck 2016	5.11	0.33	9	0.67	1	9	8.8%	4.44 [3.75, 5.13]	2016
Froylich 2016	3.6	1.8	25	1.18	1.49	25	8.4%	2.42 [1.50, 3.34]	2016
Aldoheyan 2017	4	0.5	27	2	0.5	27	9.3%	2.00 [1.73, 2.27]	2017
Manco 2017	4.15	0.67	20	1.6	0.99	20	9.1%	2.55 [2.03, 3.07]	2017
Schewenger 2018	2.07	1.53	42	0.33	0.78	42	9.1%	1.74 [1.22, 2.26]	2018
Total (95% CI)			**1857**			**1139**	**100.0%**	**2.39 [1.58, 3.20]**	

Heterogeneity: $Tau^2 = 1.81$; $Chi^2 = 759.94$, df = 10 ($P < .00001$); $I^2 = 99\%$

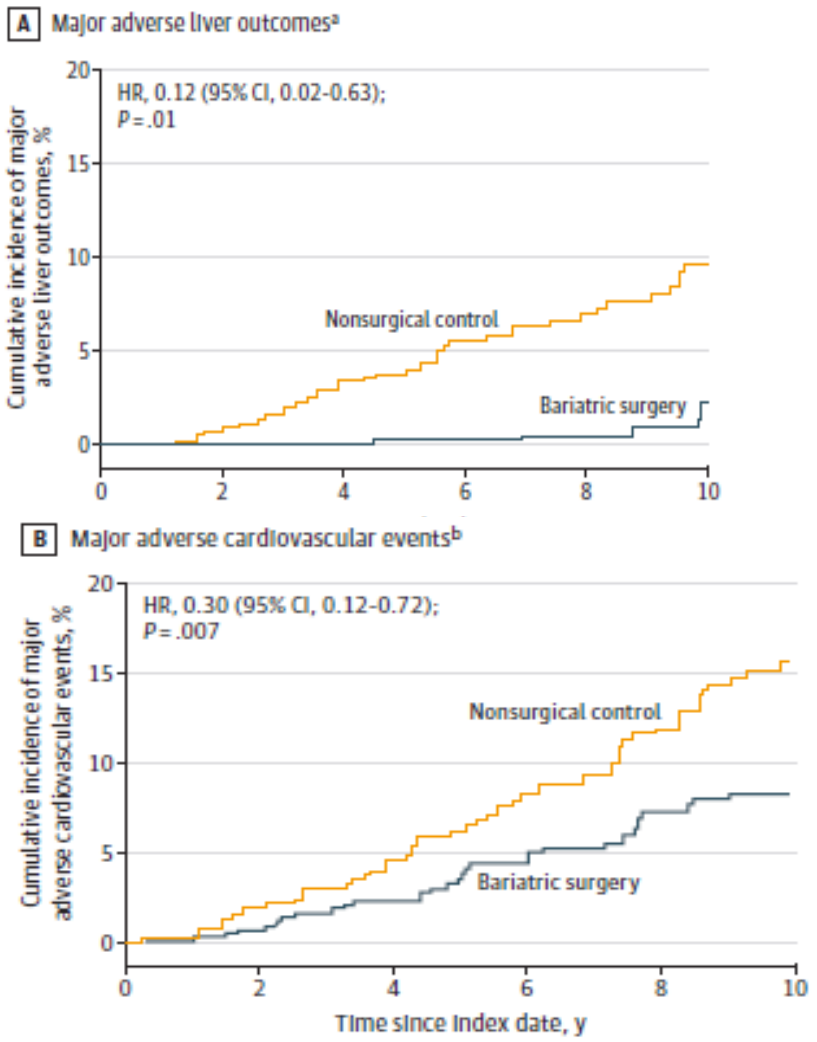
Test for overall effect: Z = 5.79 ($P < .00001$)



Lee Y et al CGH 2019

Bariatric Surgery and Liver Outcomes
SPLENDOR Study

- N=1158 retrospective cohort study
  - Bariatric Surgery n=650 (RYGB 82%)
  - Non-surgical management n=508
  - Biopsy Fibrosis stage 1-3
  - Propensity score matching for groups
- 10-year Liver outcomes (cirrhosis, decompensation, HCC, LT, death)
  - 2.3% (surgical) vs 9.6% (usual care)
- Cardiovascular outcomes
  - 8.5% (surgical) vs 15.7% (usual care)
- Bariatric surgery cohort
  - 9.5% major adverse events at 30-days
  - 12-month mortality = 0.6%
- Selection bias, non-standard usual care, progression to “cirrhosis” not clinical endpoint



Aminian A et al JAMA 2021

Bariatric Surgery reduces Cancer Risk in Patients with NAFLD and Severe Obesity

- Retrospective cohort study of US private insurance claims database (MarketScan) 2007-2017
  - ICD codes for NAFLD diagnosis
  - Mean follow-up 22 months
    - Adjusted treatment weighted analysis for confounders
  - 98,000 NAFLD patients with Severe Obesity
    - 34% had Bariatric Surgery
  - ~1900 incident cancer (non-surgical) vs 925 (surgical)
- Reduced adjusted cancer risk for BS
  - 18% (HR 0.82) for all cancers
  - 25% (HR 0.65) for obesity-related cancers

Type of obesity-related cancer	Events, No.	HR (95% CI)	
		Unadjusted	Adjusted[b]
Any obesity-related cancer	911	0.62 (0.54–0.72)	0.65 (0.56–0.75)
Colon cancer	116	0.64 (0.41–0.96)	0.66 (0.42–1.00)
Rectal cancer	15	0.41 (0.09–1.31)	0.44 (0.10–1.37)
Postmenopausal breast cancer	131	0.75 (0.51–1.08)	1.08 (0.74–1.54)
Hepatocellular carcinoma	49	0.32 (0.15–0.65)	0.48 (0.24–0.89)
Kidney cancer	120	0.81 (0.54–1.18)	0.90 (0.60–1.32)
Esophageal cancer	16	0.31 (0.07–1.01)	0.33 (0.06–1.18)
Cancer of the gastric cardia	8	0.30 (0.02–1.70)	0.46 (0.03–2.44)
Gallbladder cancer	4	1.04 (0.11–9.33)	0.99 (0.05–12.58)
Pancreatic cancer	44	0.35 (0.15–0.73)	0.46 (0.21–0.93)
Ovarian cancer	74	0.70 (0.42–1.14)	0.70 (0.41–1.15)
Endometrial cancer	135	0.45 (0.30–0.66)	0.49 (0.31–0.73)
Thyroid cancer	143	0.69 (0.47–0.98)	0.61 (0.41–0.89)
Multiple myeloma	50	0.40 (0.19–0.77)	0.33 (0.14–0.69)
Meningioma	6	0.66 (0.09–3.45)	0.52 (0.05–2.90)

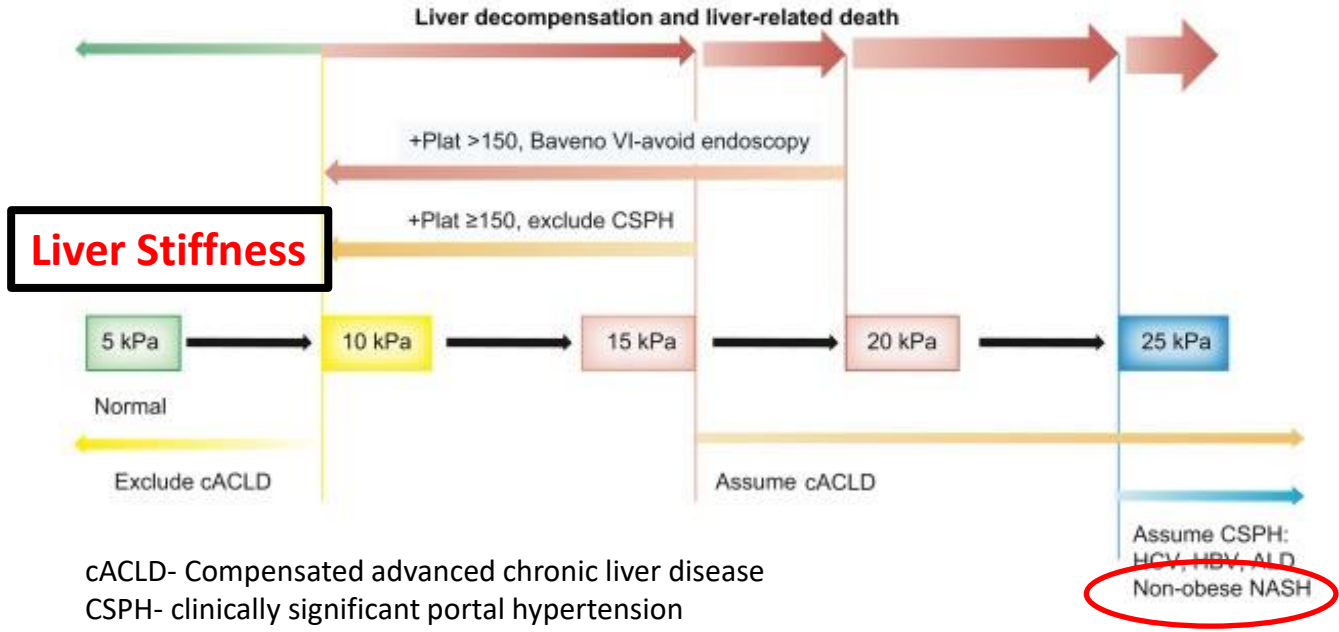
Rustgi V et al Gastroenterology 2021

Bariatric Surgery and Cirrhosis

AGA Clinical Practice Update[1]

- Bariatric surgery should be considered in selected patients with compensated cirrhosis in an effort to reduce risk for hepatocellular carcinoma and improve survival
  - Performed in compensated disease by an experienced surgeon at a high-volume bariatric center
  - Assessment for CSPH (HVPG ≥ 10mmgHg) should be included in the preoperative evaluation for bariatric surgery in patients with cirrhosis
  - Non-invasive LSM > 25 kPa **not** validated in obese NASH
  - No data in CSPH on weight-loss and improved fibrosis and portal HTN on liver-related outcomes

Baveno VII- Portal Hypertension Consensus[2]



cACLD- Compensated advanced chronic liver disease
CSPH- clinically significant portal hypertension

1. Patton H et al. CGH 2021
2. De Franchis R et al J Hepatol 2022

Bariatric Surgery and Cirrhosis

AGA Clinical Practice Update[1]

- The optimal bariatric surgical procedure for patients with cirrhosis is most likely a laparoscopic sleeve gastrectomy.
  - Allows preservation of endoscopic access to the biliary tree
  - Gradual weight loss reduces risk of malnutrition
- In decompensated liver disease, the only acceptable option is bariatric surgery concurrent with or after liver transplant
  - Single center study n=15, f/up 2-3 yrs, delayed SG > 6 months post-LT is:
    - Safe (complication rate 6.7%), no increase in allograft rejection.
    - Decreased BMI 43 to 36 kg/m^2, Insulin d/c in 60%[2]
  - Simultaneous or early post-LT procedures associated with complication rates of 25-40% (infections, staple line leaks, bleeding, reoperation, graft rejection, death)[3,4]
  - No consensus on optimal timing of Bariatric Surgery for LT recipients

1. Patton H et al. CGH 2021
2. Morris MC et al. Liver Transpl 2019
3. Zamora-Valdes et al. Hepatology 2018
4. Diwan TS et al. Liver Transpl 2018

Bariatric Surgery and Cirrhosis

In-Hospital Mortality

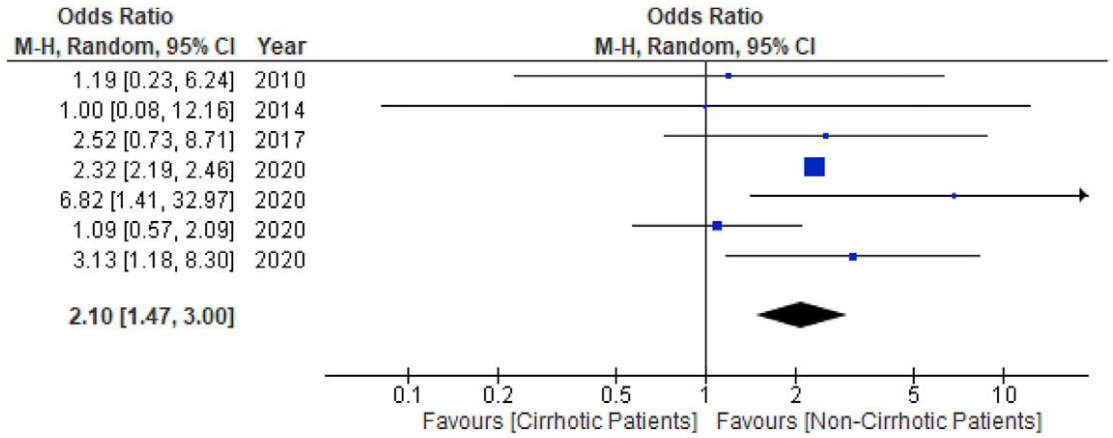
- Bariatric Surgery from Nationwide Inpatient Sample 1998-2007
  - Large US all-payer database of hospital discharges
- Overall cirrhosis in-hospital mortality rates 1.2%
  - No cirrhosis (n=670K) = 0.3%
  - Compensated (n=3888)= 0.9%
  - Decompensated (n=62) = 16.3%
- Other predictors of mortality included age, male gender, and <100 procedures/yr
- No information on type of procedure

Mosko JD CGH 2011

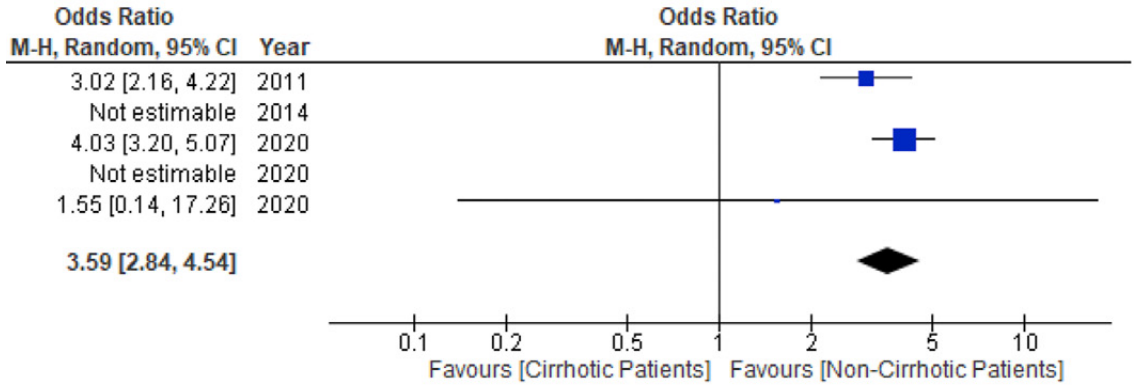
Bariatric Surgery and Outcomes in Compensated Cirrhosis

- Meta-analysis 8 studies, higher OR for
  - Overall complications (13.6%)
  - In-hospital/90 day mortality
  - Post-operative bleeding
  - Length of Stay
- No differences between cirrhosis and non-cirrhosis for
  - Intraoperative complications
  - Long-term mortality (12-24 months)
  - Weight-loss at 3/6/12 months (SG in 70%)

Overall Complications



Hospital/90-day mortality



Khajeh E et al. Surg Obes Rel Dis 2022 (in press)

Summary

- NAFLD is a major health epidemic
  - 25% global prevalence
  - Significant healthcare burden over the next decade
- Combine serum/elastography tests for diagnosis of advanced fibrosis
- No approved medical therapy for NASH/Fibrosis
  - Lifestyle measures through diet and physical activity for weight-loss are the mainstay of treatment
  - NASH therapeutic trials in progress
- Bariatric surgery resolves NAFLD/NASH, reduces fibrosis, and improves outcomes
  - Restrictive procedure for selected well-compensated cirrhosis
  - Contraindicated for decompensated disease unless part of LT protocol

Thank You!

Toronto Center for Liver Diseases
University Health Network Toronto

keyur.patel@uhn.ca