NON-ALCOHOLIC FATTY LIVER DISEASE

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DISCLOSURES

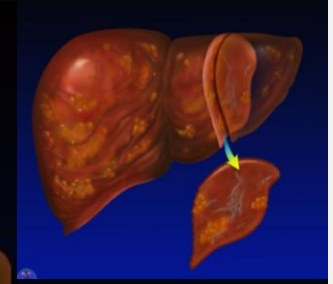
Scientific Advisory Board Member: Bristol Myer Squibb, Novo Nordisk, Theratechnologies

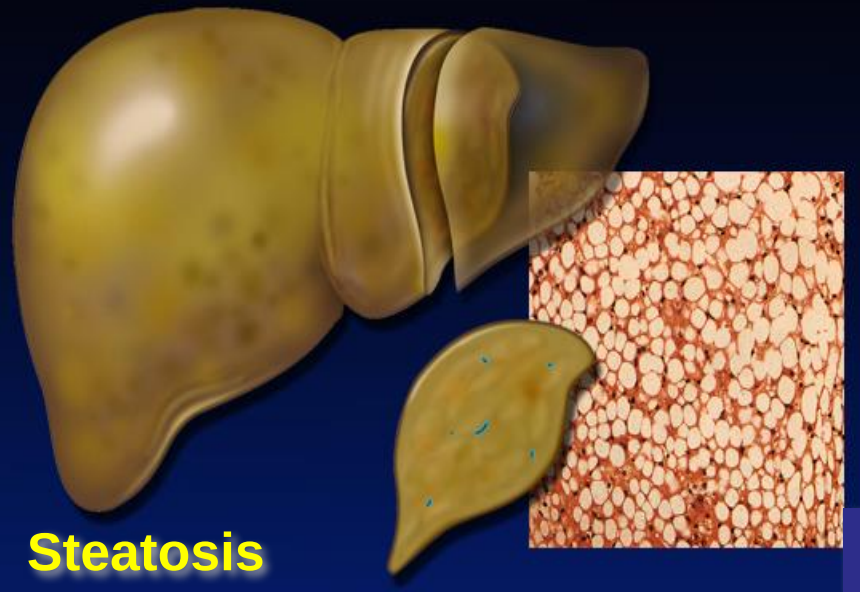
Grant funding: Bristol Myer Squibb, Novartis, Boehringer-Ingelheim

LEARNING OBJECTIVES

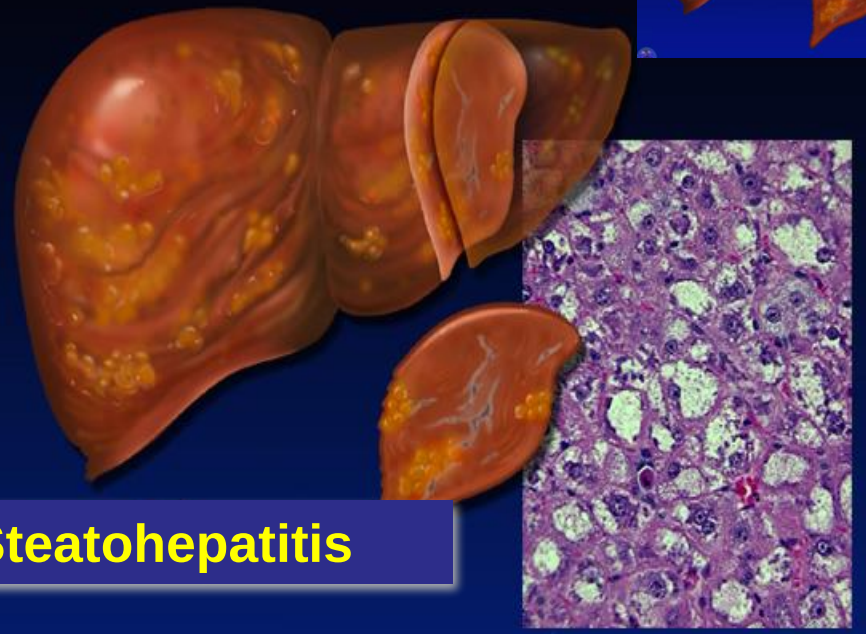
- Understand how to stage fibrosis in NAFLD
- Identify the fundamentals of NAFLD treatment for all stages of disease
- Identify when to refer patients for specialty care
- Understand the current environment of NAFLD pharmacotherapy

Nonalcoholic Fatty Liver Disease

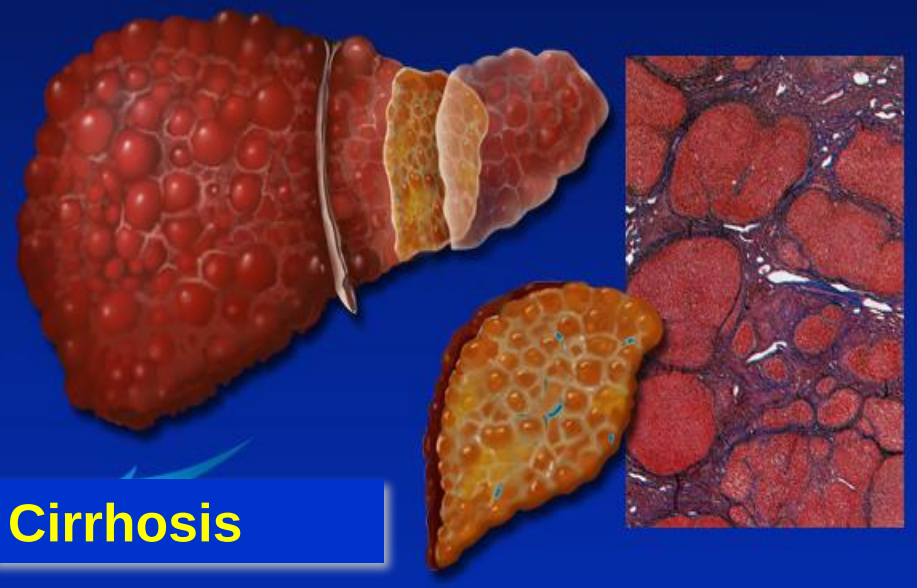




Steatosis



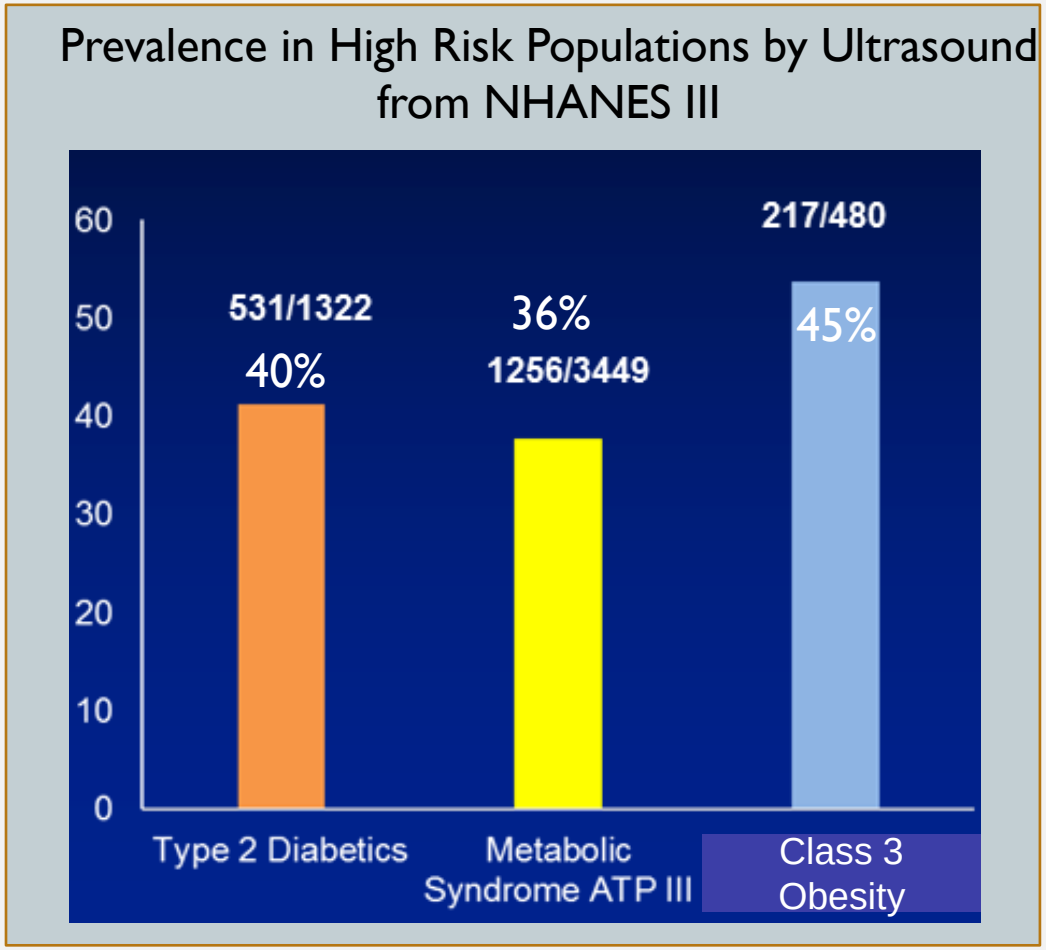
Steatohepatitis



Cirrhosis

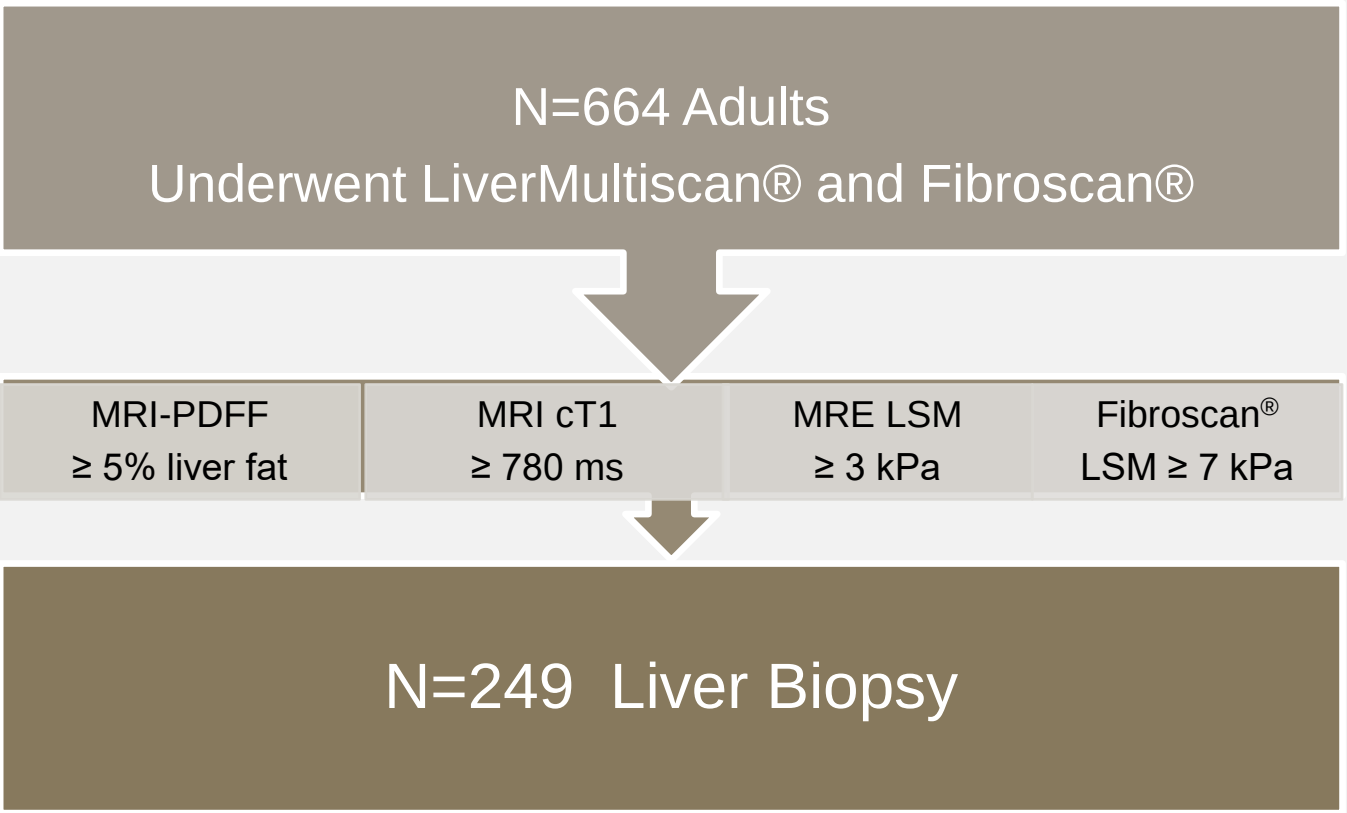
NAFLD GLOBAL PREVALENCE: 25%

NASH Prevalence: 2-7%



Z. Younossi et, Hep 2016, Z. Younossi et al. Medicine 2012

NEW PREVALENCE DATA ON NAFLD, NASH & FIBROSIS IN UNITED STATES



- Adults referred for colonoscopy classes at an AMC offered enrollment
- **NAFLD prevalence** by MRI-PDFF: 37.5%
- **NAFLD prevalence in subgroups**
  - Men (45%) vs. Women (30%)
  - Black (25%) vs. White (41%)
  - Hispanic/Latinx: 55% prevalence
  - Obesity (57%)
  - Diabetes (70%)

SA Harrison et al., Prospective evaluation of the prevalence of NAFLD and steatohepatitis in a large middle-aged cohort. J Hepatol 2021

Adapted slide courtesy of Dr. George Agyapong from Boston Area NAFLD Journal Club: Health Equity Session

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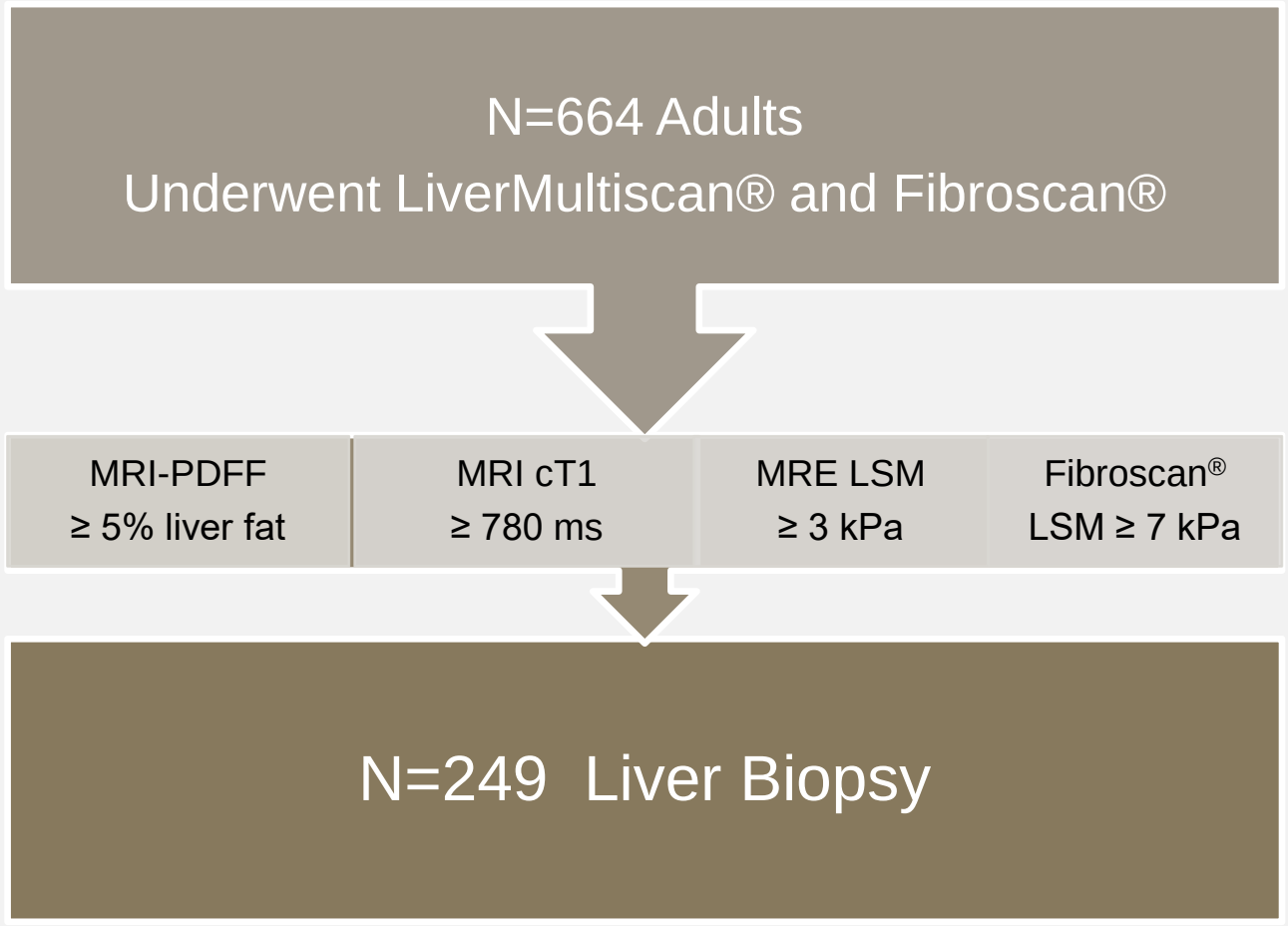

- Overall **NASH prevalence**: 14%
- NASH in all who underwent biopsy: 37%

- **Significant fibrosis (≥2)**
  - Entire cohort: 5.9%
  - Biopsy-confirmed NAFLD: 20%; 5.6% had bridging fibrosis
  - Biopsy-confirmed NASH: 35%

SA Harrison et al., Prospective evaluation of the prevalence of NAFLD and steatohepatitis in a large middle-aged cohort. J Hepatol 2021

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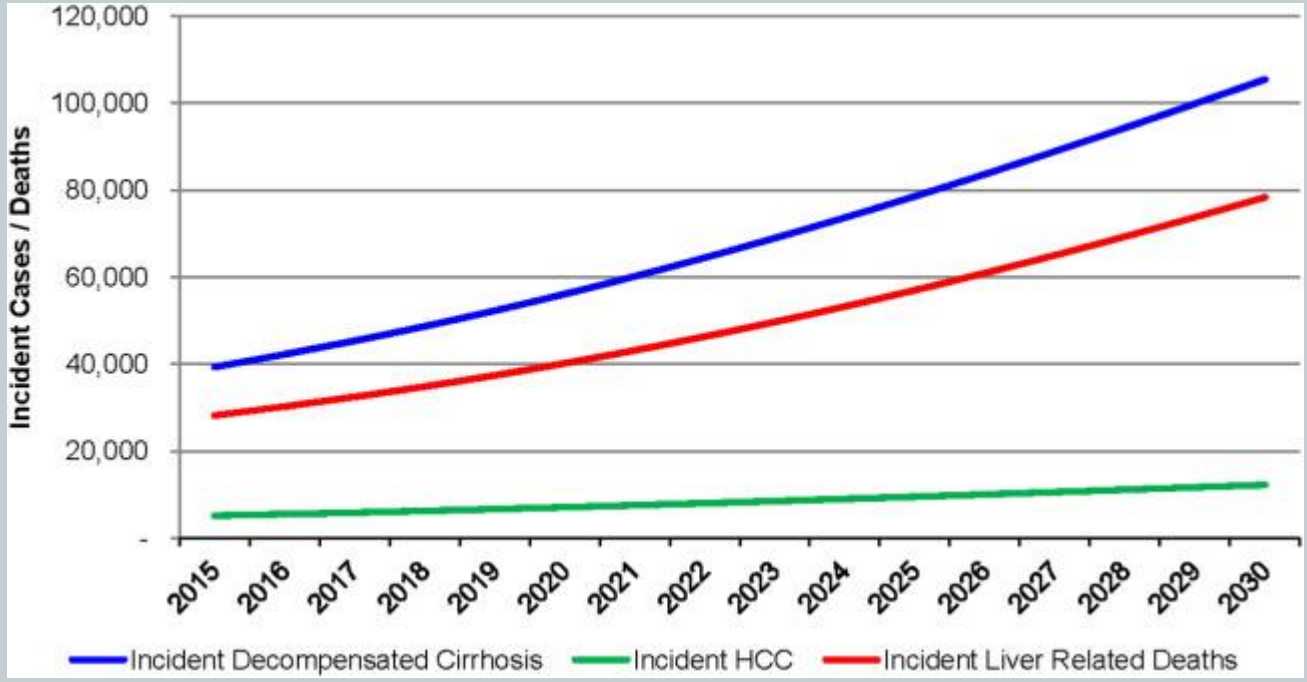
LIVER-RELATED COMPLICATIONS IN NAFLD



↑180%, CI 1.1 million cases

↑146% CI 135,00 cases

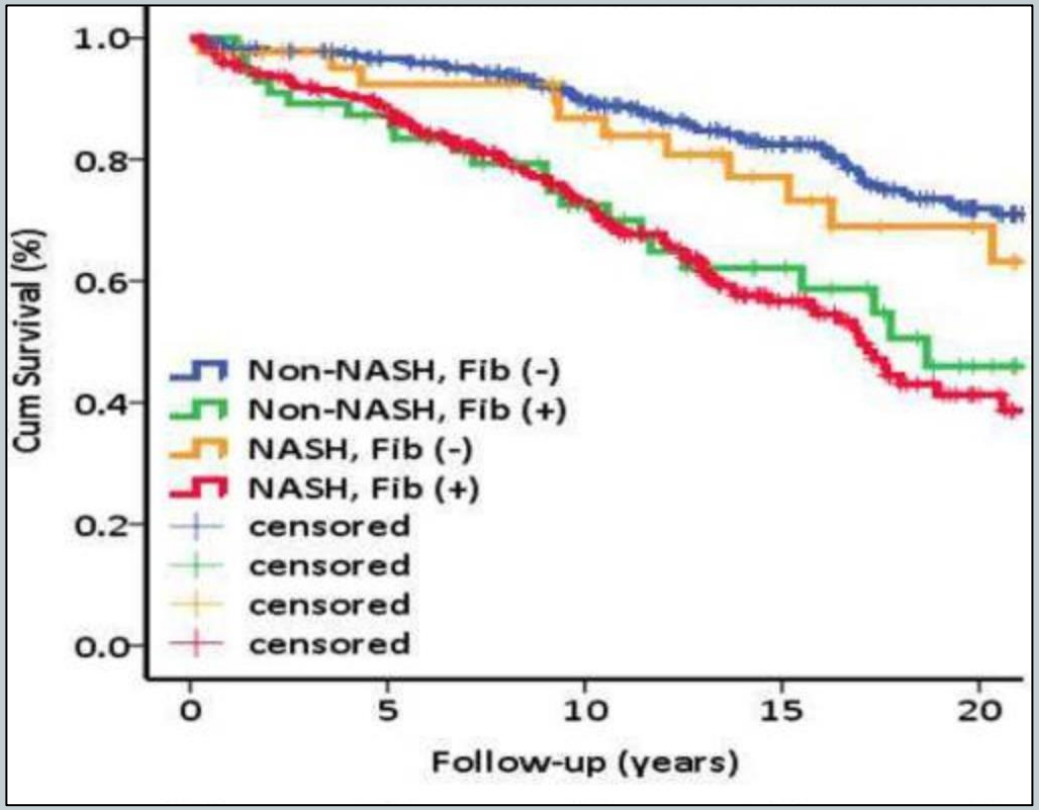
↑178% CI 799,000 deaths

Liver transplants for NAFLD: Increase 59% to 7,610 cases/year

C. Estes Hepatology 2017

ALL FIBROSIS STAGES PREDICT DEATH/LIVER TRANSPLANT

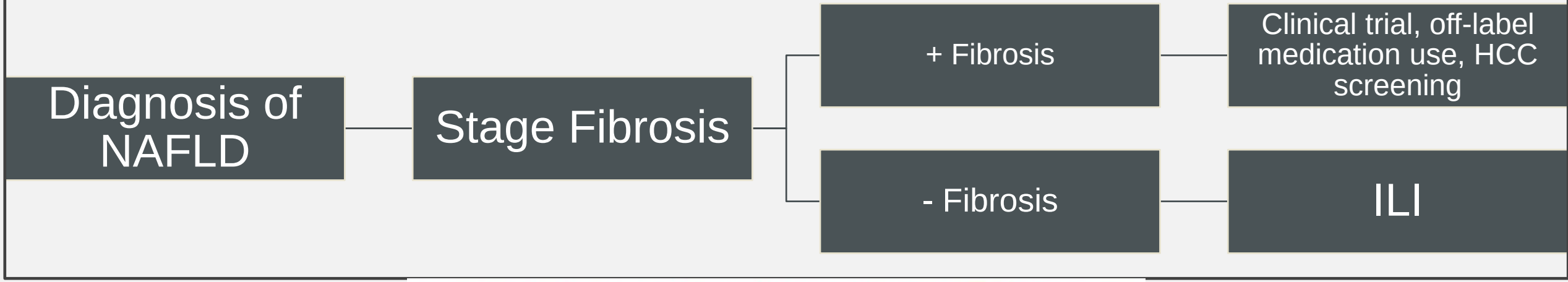
Transplant-Free Survival Lower in NASH/non-NASH Adults with Fibrosis Compared to NASH/non-NASH without Fibrosis

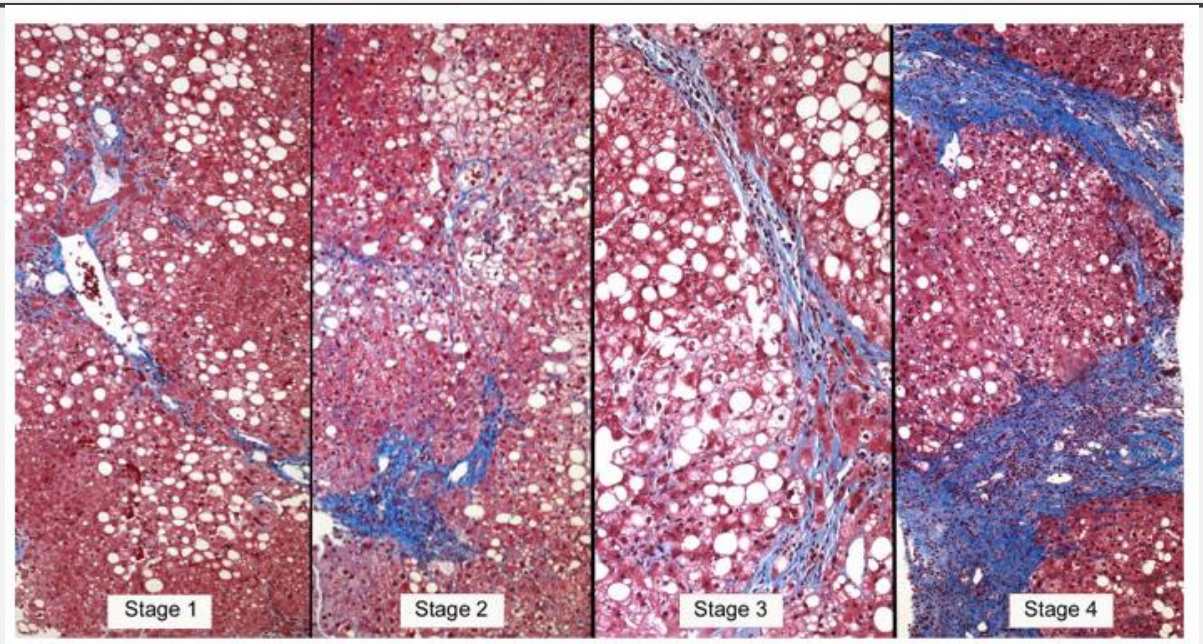


	Hazard ratio	95% CI of HR	*P* value
Model 1			
Fibrosis, stage 0	1 (reference)		
Fibrosis, stage 1	2.07	1.40–3.08	<.001
Fibrosis, stage 2	3.02	2.0–4.56	<.001
Fibrosis, stage 3	3.97	2.50–6.30	<.001
Fibrosis, stage 4	11.97	6.47–22.12	<.001
Model 2			
Fibrosis, stage 0	1 (reference)		
Fibrosis, stage 1	1.82	1.18–2.81	.007
Fibrosis, stage 2	1.91	1.20–3.03	.007
Fibrosis, stage 3	1.90	1.16–3.12	.01
Fibrosis, stage 4	6.35	3.35–12.04	<.001
Age, *y*	1.07	1.05–1.08	<.001
Diabetes, yes	1.60	1.11–2.30	.01
Smoking			
Never	1 (reference)		
Former	1.11	0.71–1.73	.640
Current	2.62	1.67–4.10	<.001
Statin use, yes	0.32	0.15–0.71	.005

P Angulo et al. Gastro 2015; Taylor RS, Taylor RJ, Bayliss S, et al. Association between fibrosis stage and outcomes of patients with non-alcoholic fatty liver disease: a systematic review and meta-analysis. Gastroenterology 2020; 158: 1611–25

PROGNOSIS AND TREATMENT OF NAFLD REVOLVES AROUND FIBROSIS STAGE





N. Chalasani et al, AASLD NAFLD Guidelines, Hepatology 2018; ; Z Younossi et al., Diagnostic Modalities for NonalcoholicFatty Liver Disease, NonalcoholicSteatohepatitis, and Associated Fibrosis. Hepatology 2018

Non-Invasive Tests (NITs) to Estimate Advanced Fibrosis

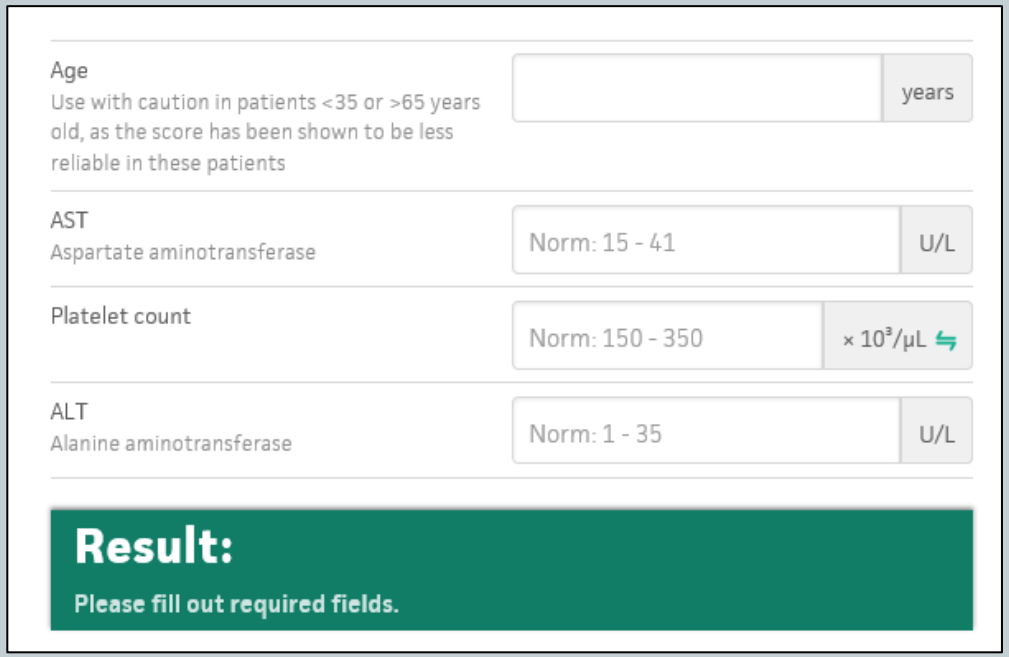
Modality	Performance	Advantages	Disadvantages	Best For
Fibrosis Scores				
FIB-4 (>2.67)	AUROC 0.73-0.78 PPV 66% NPV 85%	Calculate w/ age & labs Inexpensive Readily available	Indeterminant group; performance varies by age & demographics	Ruling out advanced fibrosis
Enhanced Liver Fibrosis (ELF) Score 1 (TIMP, PIIINP & HA)	AUROC 0.83 PPV< 80% unless> 30% F3-4 prevalence	Blood based	Impacted by age, gender and prevalence; **not yet available at MGH**	Ruling in advanced disease in high prevalence settings
Pro-C3 (marker of type III collagen formation)	AUROC 0.73-0.78	Blood based	Research Only, Not available at MGH	
ADAPT Score (Pro-C3, age, diabetes and platelet count)	AUROC 0.86-0.87 PPV 48.4% NPV 96.6%	Blood based	Research Only, Not available at MGH	
NIS-4 (miR-34a-5p, alpha-2-macroglobulin, YKL-40, A1C) – **Two Cut-Offs**	AUROC 0.76-0.83 PPV 79.2% NPV 77.9%	Blood based **For at-risk NASH	Research Only, Not available at MGH **Has indeterminant group**	

SJ Daniels e al., ADAPT: An Algorithm Incorporating PRO-C3 Accurately Identifies Patients With NAFLD and Advanced Fibrosis. Hepatology 2019

FIBROSIS-4 SCORE

- Developed initially to predict fibrosis in HIV/HCV co-infection
- Used in various liver disease etiologies

FIB4= age (years) x AST [U/L]/(platelets [109/L] x (ALT [U/L])1/2)



RK Sterling et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006

FIBROSIS-4 SCORE

Advantages

- Well-validated
- Simple
- Inexpensive
- Readily available and non-proprietary
- Can monitor for disease progression

Test	AUROC (95% CI)	Cut-off	Sens (%)	Spec (%)	PPV (%)	NPV (%)
AST/ALT ratio	0.83 (0.74 to 0.91)	0.8	74	78	44	93
		1	52	90	55	89
APRI	0.67 (0.54 to 0.8)	1	27	89	37	84
BARD score	0.77 (0.68 to 0.87)	2	89	44	27	95
FIB-4 score	0.86 (0.78 to 0.94)	1.30	85	65	36	95
		3.25	26	98	75	85
NAFLD fibrosis score	0.81 (0.71 to 0.91)	−1.455	78	58	30	92
		0.676	33	98	79	86

Disadvantages

- Significant “indeterminate” range scores
- Unreliable diagnostic performance age < 35, use different cut-offs >65 years (FIB-4 = 2.0 for F2-4)

RK Sterling et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006; S McPherson et al., Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Hepatology 2010. S McPherson et al. Age as a Confounding Factor for the Accurate Non-Invasive Diagnosis of Advanced NAFLD Fibrosis. AJG 2017

Non-Invasive Tests (NITs) to Estimate Fibrosis and Identify Patients in Need of Liver Biopsy (advanced fibrosis)

Modality	Advanced Fibrosis Performance	Advantages	Disadvantages	Best For
Elastography				
VCTE (FibroScan)	AUROC 0.83 PPV 58.7% NPV 88.7%	Point of care testing	No abdominal imaging; Detect advanced fibrosis Failure rate 2.6-10%	Ruling out advanced fibrosis
Sheer Wave (2D) Elastography	AUROC 0.80 PPV 88.2% NPV 93.4%	Provides imaging	Requires specialized training	Ruling out advanced fibrosis
MR Elastography	AUC 0.93 PPV 71.0% NPV 93.4%		Cost Availability	Research Confirming advanced fibrosis

https://pubmed.ncbi.nlm.nih.gov/29908362/

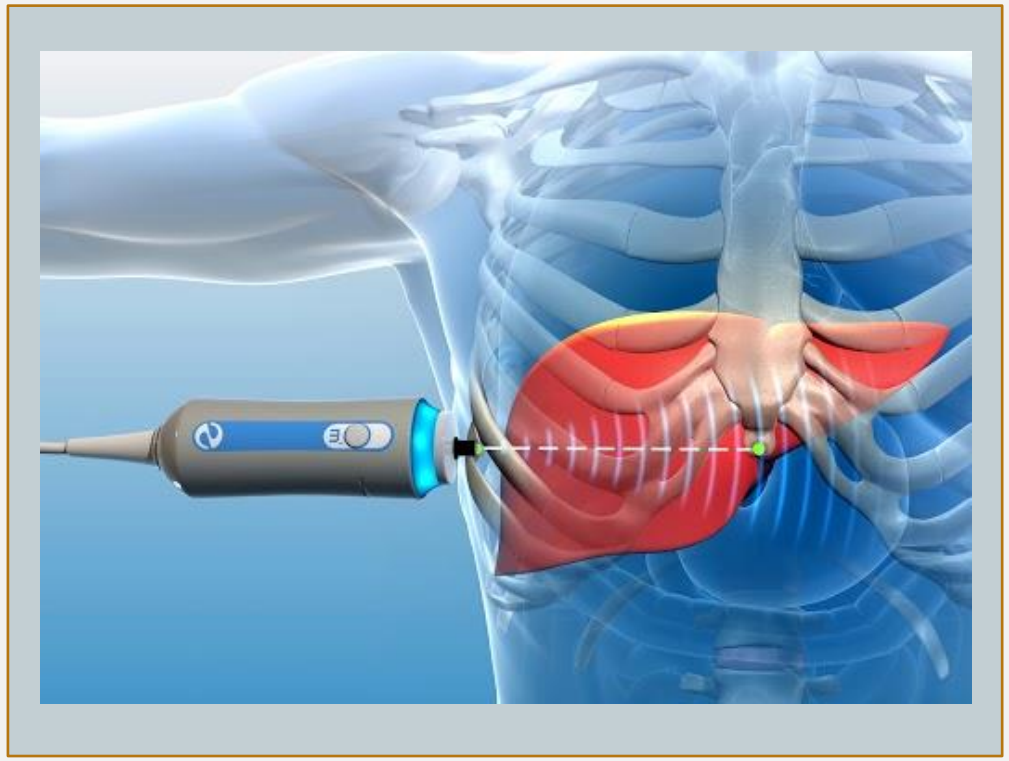
CONCEPT OF ELASTOGRAPHY

- “Imaging-based counterpart to palpation”

- Disease impacts mechanical properties of tissues (Ex. fibrosis)

- Elastography allows quantitative assessment of tissue mechanical properties

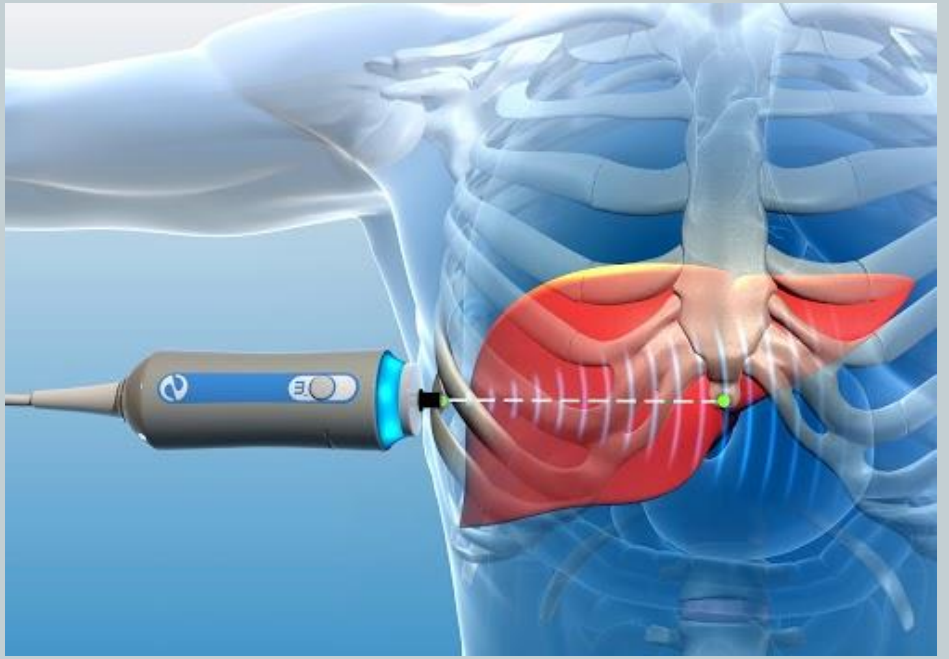
- Inducing harmonic vibrations of acoustic-range frequencies in tissue and imaging the propagation of these vibrations in the tissue to calculate quantitative values for tissue mechanical parameter



YK Mariappan et al., Magnetic Resonance Elastography: A Review. Clinical Anatomy 2011

VIBRATION CONTROLLED TRANSIENT ELASTOGRAPHY (VCTE, FIBROSCAN)

- **How it works**
  - Liver shear wave speed expressed as liver stiffness measurement (LSM)
  - Faster shear wave propagates through liver, higher the LSM, indirectly indicating a greater degree of fibrosis
- **Advantages**
  - Point of care test
  - Total area of tissue evaluated ~3 cm^3 = liver volume 100x larger than biopsy
- **Disadvantages**
  - Need adequate acoustic window for elastic wave; limited depth of penetration
  - Area of interest limited to right intercostal area
  - Access limited, high upfront cost for VCTE
  - Confounded severe inflammation, cholestasis, congestion, recent ingestion, obesity



YK Mariappan et al., Magnetic Resonance Elastography: A Review. Clinical Anatomy 2011

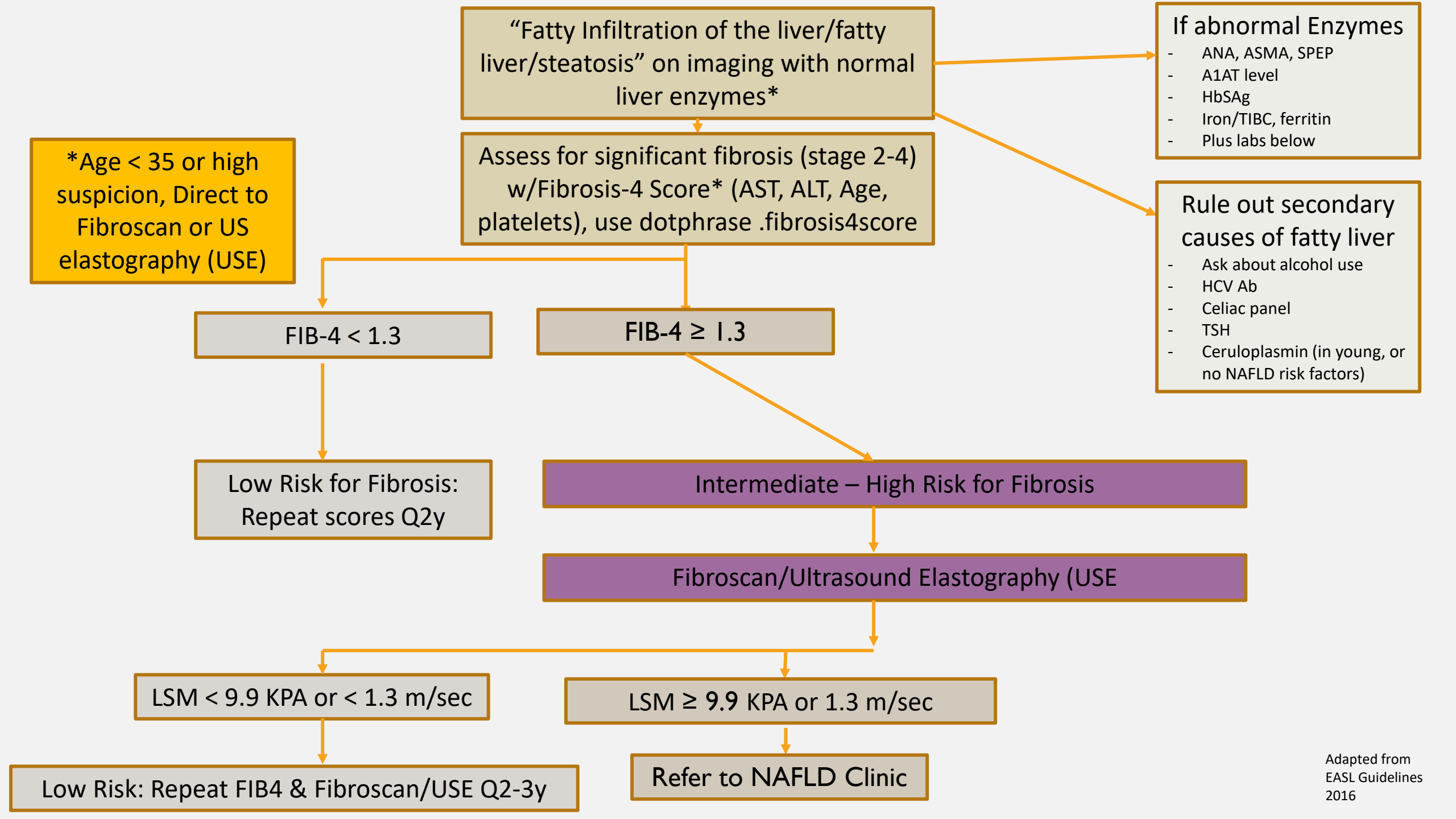
VIBRATION CONTROLLED TRANSIENT ELASTOGRAPHY (VCTE, FIBROSCAN)

- **Methods**
  - Patients from STELLAR Trials (selonsertib) w/ histology, included in analysis; 1765 patients underwent VCTE
  - Assessed predictive ability of non-invasive tests (NITs) for fibrosis using biopsy as gold standard
- **Findings**
  - No single threshold for any individual NIT sufficiently balanced sensitivity and specificity
  - Dual cut-offs to rule out (LSM < 9.9 kPA) and rule in (LSM ≥ 11.4 kPA) advanced fibrosis
  - VCTE ↑ Accuracy, ↑ reliability improves as ↑ fibrosis stage, best for cirrhosis

TABLE 4. Performance of Individual NITs at Low and High Thresholds Derived From the Literature to Discriminate Advanced Fibrosis (F3-F4 vs. F0-F2)

Variable	NFS (n = 2,417)	FIB-4 (n = 3,123)	ELF (n = 3,173)	LS by VCTE (n = 1,765)
Prevalence of F3-F4	80%	71%	71%	84%
AUROC (95% CI)	0.74 (0.74, 0.74)	0.78 (0.78, 0.78)	0.80 (0.80, 0.80)	0.80 (0.79, 0.8)
Thresholds	<–1.455, ≥0.676	<1.3, ≥2.67	<9.8, ≥11.3	<9.9, ≥11.4 kPa
Sensitivity*	89 (88, 91)	82 (81, 84)	74 (72, 75)	83 (81, 85)
Specificity*	89 (86, 92)	93 (91, 94)	98 (96, 99)	71 (66, 76)
PPV*	97 (96, 98)	97 (96, 97)	99 (98, 99)	94 (92, 95)
NPV*	67 (63, 71)	68 (65, 70)	60 (58, 63)	45 (40, 50)
Indeterminate*	51 (49, 53)	43 (41, 45)	45 (43, 47)	8 (7, 9)
Misclassified*	11 (10, 12)	15 (13, 16)	19 (18, 21)	19 (17, 21)

Q Anstee et al., Noninvasive tests accurately identify advanced fibrosis due to NASH: Baseline Data from the STELLAR Trials. Hepatology 2019


"Fatty Infiltration of the liver/fatty liver/steatosis" on imaging with normal liver enzymes*
If abnormal Enzymes
- ANA, ASMA, SPEP
- A1AT level
- HbSAg
- Iron/TIBC, ferritin
- Plus labs below
Rule out secondary causes of fatty liver
- Ask about alcohol use
- HCV Ab
- Celiac panel
- TSH
- Ceruloplasmin (in young, or no NAFLD risk factors)
Assess for significant fibrosis (stage 2-4) w/Fibrosis-4 Score* (AST, ALT, Age, platelets), use dotphrase .fibrosis4score
*Age < 35 or high suspicion, Direct to Fibroscan or US elastography (USE)
FIB-4 < 1.3
FIB-4 ≥ 1.3
Low Risk for Fibrosis: Repeat scores Q2y
Intermediate – High Risk for Fibrosis
Fibroscan/Ultrasound Elastography (USE
LSM < 9.9 KPA or < 1.3 m/sec
LSM ≥ 9.9 KPA or 1.3 m/sec
Low Risk: Repeat FIB4 & Fibroscan/USE Q2-3y
Refer to NAFLD Clinic
Adapted from EASL Guidelines 2016

WEIGHT LOSS IS FOUNDATION OF NASH AND FIBROSIS TREATMENT

- **What magnitude of weight loss is needed to impact liver histology?**

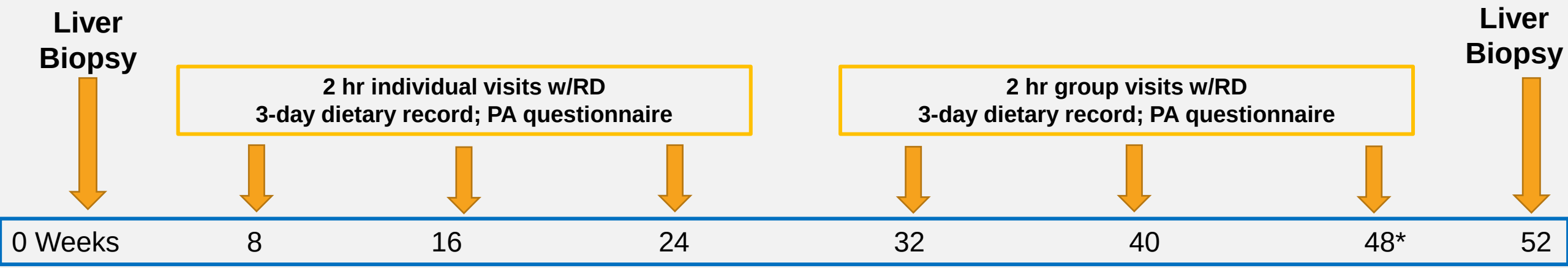
- Prospective cohort study lifestyle changes defined by
  - Hypocaloric diet
  - Aerobic exercise

- Enrolled 293 adults with biopsy-proven NASH

- Paired biopsies available for 261 adults

E. Vilar-Gomez et al. Gastroenterology 2016

WEIGHT LOSS IS FOUNDATION OF NASH AND FIBROSIS TREATMENT



Dietary Intervention

- Low-fat hypocaloric diet, 750 kcal/day > daily energy need
- 64% carbs, 22% fat, 14% protein,dietary fiber > 20g/d, <10% saturated fat
- Food diary

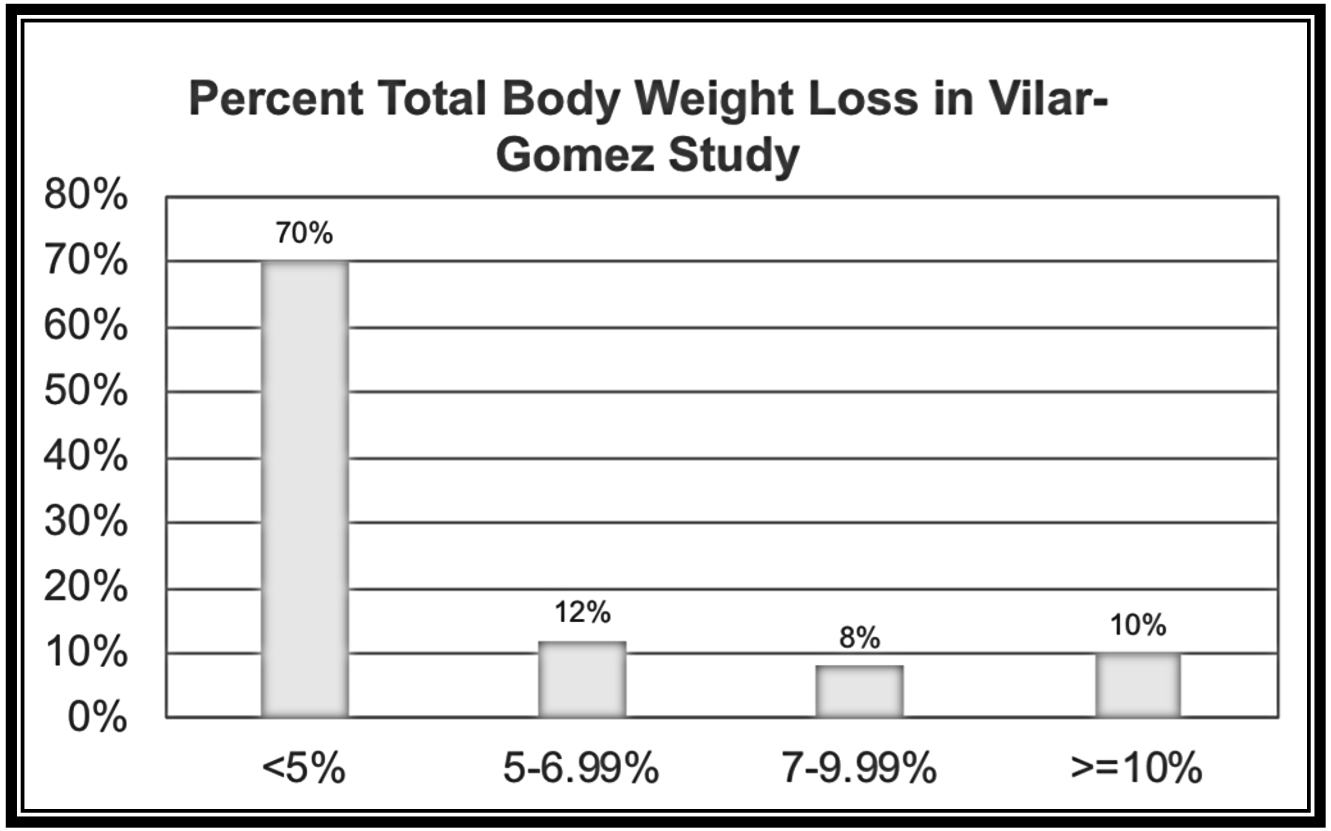
Physical Activity

Walk (moderate intensity), starting 90 minutes/week, increasing to 200 minutes/week

E. Vilar-Gomez et al. Gastroenterology 2016

* Dietary record and PA questionnaire not collected

WEIGHT LOSS VARIED AMONG SUBJECTS



E. Vilar-Gomez et al. Gastroenterology 2016

WEIGHT LOSS CAN MEANINGFULLY IMPACT NASH

Variables	Overall (n = 293)	WL <5 (n = 205)	WL = 5–6.99 (n = 34)	WL = 7–9.99 (n = 25)	WL ≥10 (n = 29)	*P* value
Weight loss, %	3.8 ± 2.7	1.78 ± 0.16	5.86 ± 0.09	8.16 ± 0.22	13.04 ± 6.6	—
Resolution of steatohepatitis[a]	72 (25)	21 (10)	9 (26)	16 (64)	26 (90)	<.01
NAS improvement[b]	138 (47)	66 (32)	21 (62)	22 (88)	29 (100)	<.001
Change in NAS from baseline	−1.58 ± 0.27	−0.89 ± 0.13	−1.94 ± 0.36	−3.84 ± 0.29	−4.10 ± 0.23	<.001
Steatosis improvement[c]	142 (48)	72 (35)	22 (65)	19 (76)	29 (100)	<.001
Change from baseline	−0.63 ± 0.10	−0.36 ± 0.07	−1 ± 0.13	−1.40 ± 0.19	−1.69 ± 0.12	<.001
Lobular inflammation improvement[c]	147 (50)	72 (35)	24 (71)	22 (88)	29 (100)	<.001
Change from baseline	−0.49 ± 0.15	−0.29 ± 0.05	−0.53 ± 0.22	−1.32 ± 0.09	−1.21 ± 0.11	<.001
Ballooning improvement[c]	115 (39)	54 (26)	14 (41)	21 (84)	26 (90)	<.001
Change from baseline	−0.45 ± 0.17	−0.24 ± 0.04	−0.41 ± 0.13	−1.12 ± 0.13	−1.34 ± 0.08	<.001
Fibrosis status[d]						<.01
Regression	56 (19)	33 (16)	6 (18)	4 (16)	13 (45)	
Stabilized	191 (65)	129 (63)	25 (74)	21 (84)	16 (55)	
Worsened	46 (16)	43 (21)	3 (8)	0 (0)	0 (0)	
Change from baseline	−0.01 ± 0.02	0.09 ± 0.07	−0.02 ± 0.03	−0.17 ± 0.12	−0.86 ± 0.20	<.001**
Portal inflammation improvement[c]	44 (15)	27 (13)	3 (9)	5 (20)	9 (31)	.049
Change from baseline	0.02 ± 0.02	0.06 ± 0.01	0.09 ± 0.03	−0.07 ± 0.01	−0.31 ± 0.08	<.01**
NAS status						<.001
NAS ≤2	119 (41)	48 (23)	20 (59)	22 (88)	29 (100)	
NAS 3–4	79 (27)	74 (36)	2 (6)	3 (12)	0 (0)	
NAS ≥5	95 (32)	83 (41)	12 (35)	0 (0)	0 (0)	

E. Vilar-Gomez et al. Gastroenterology 2016

LIMITATIONS

- Only assessed impact of weight loss on histology after 12 months; no longer term follow-up of weight or histology
- Only 30% achieved >5% TBW
- **Recommendations**
  - Goal ≥ 7-10% total body weight loss
  - If patients have 1) failed lifestyle interventions & 2) have indications for weight loss surgery, consider referral

AGA Clinical Practice Update on Lifestyle Modification Using Diet and Exercise to Achieve Weight Loss in the Management of Nonalcoholic Fatty Liver Disease: Expert Review

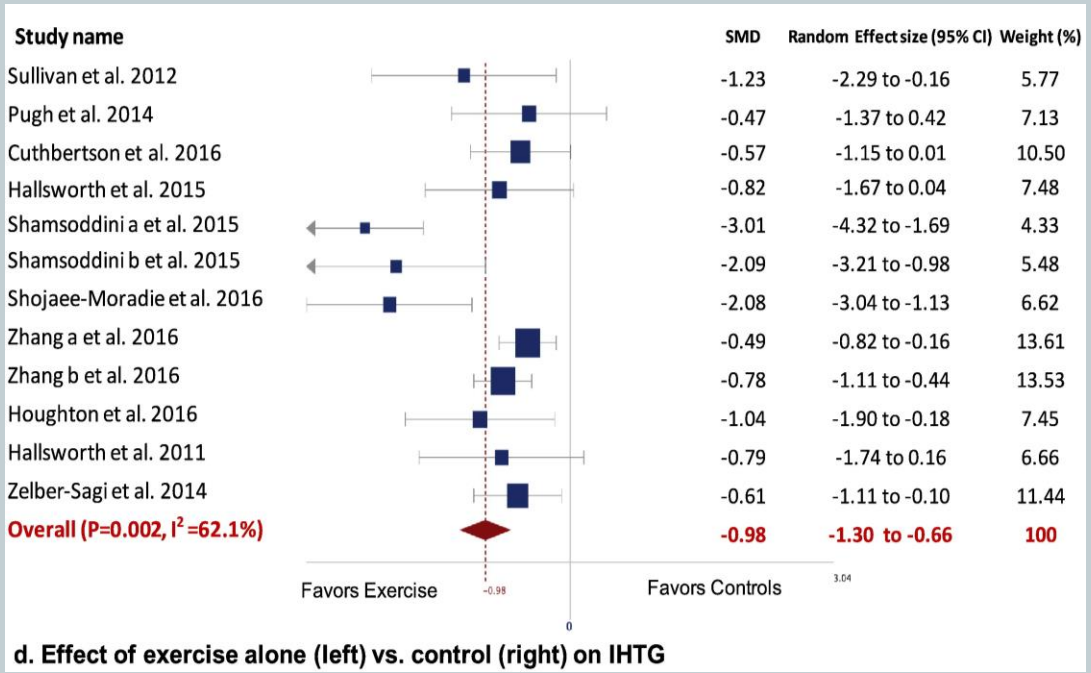
Zobair M. Younossi,[1,2,*] **Kathleen E. Corey**,[3,*] and Joseph K. Lim[4]

- **Dietary Advice**
  - **Hypocaloric diet**: reduce 500-1000 kcal/day from baseline
  - **Mediterranean diet**
    - Fresh vegetables, fruit, legumes, minimally processed whole grains, and fish
    - Omega-3-fatty acids (fish, olive oil, nuts, and seeds) primary fat sources
    - Minimize saturated fatty acid intake: diary, red and processed meat
    - **Can reduce liver fat even without weight loss**

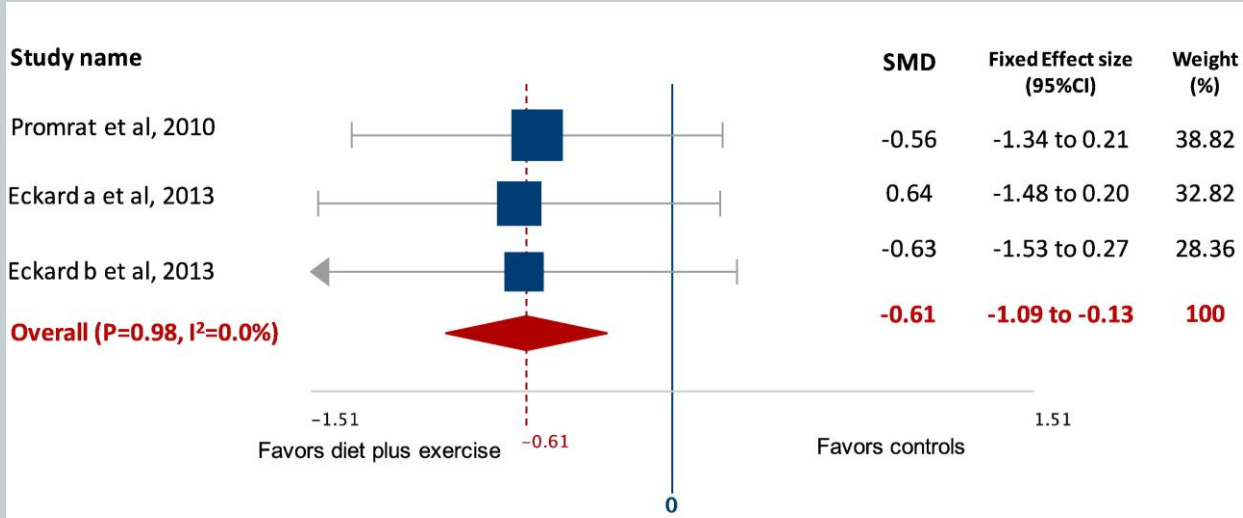
ZM Younossi, **KE Corey**, JK Lim. Gastroenterology 2021

LIFESTYLE MODIFICATIONS FOR NAFLD: EXERCISE

- Meta-analysis of 20 studies with 1073 NAFLD patients
- Exercised improved ALT, AST, IHTG regardless of weight loss
- Exercise with diet improved NAFLD Activity Score
- No difference between aerobic exercise and resistance training



d. Effect of exercise alone (left) vs. control (right) on IHTG

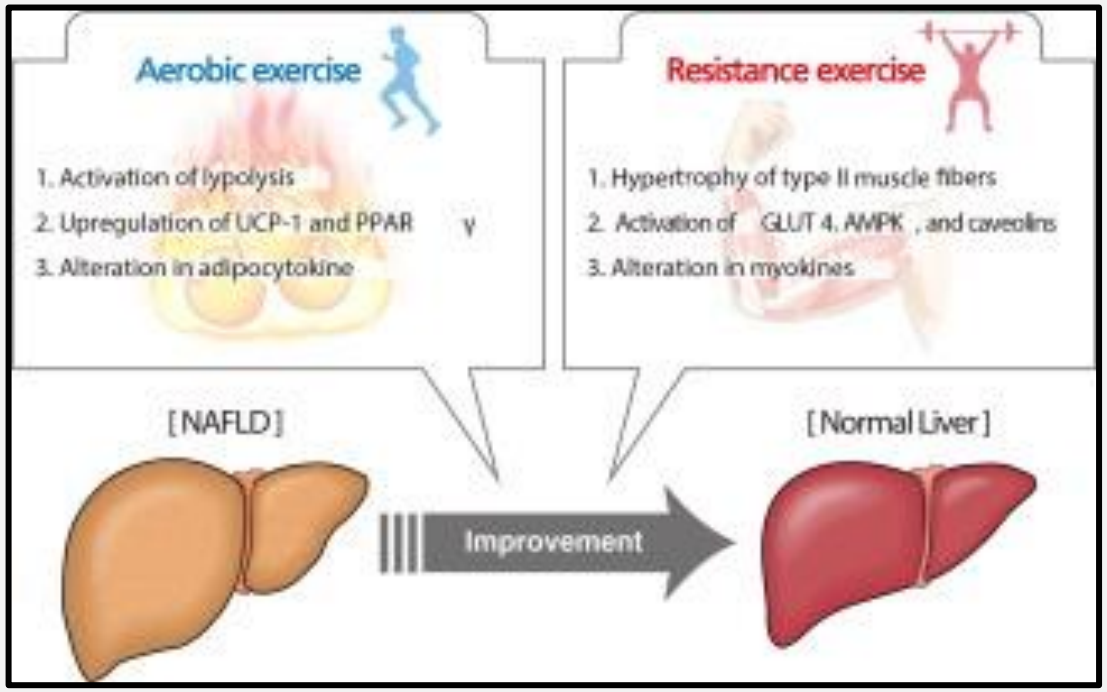


d. Effect of diet plus exercise (left) vs. control (right) on NAS score

CN Katsagoni et al., Metabolism - Clinical and Experimental 2017

LIFESTYLE MODIFICATIONS FOR NAFLD: CLINICAL PRACTICE UPDATE

- **Aerobic Exercise**
  - Moderate-intensity activity 150-300 minutes per week
  - Vigorous-intensity activity 75-150 minutes per week
- **Resistance training**
  - May also be beneficial, 120-140 min/week
  - Can compliment aerobic exercise
  - Less intense, less energy consumption
  - May be feasible for those with limited cardiorespiratory fitness



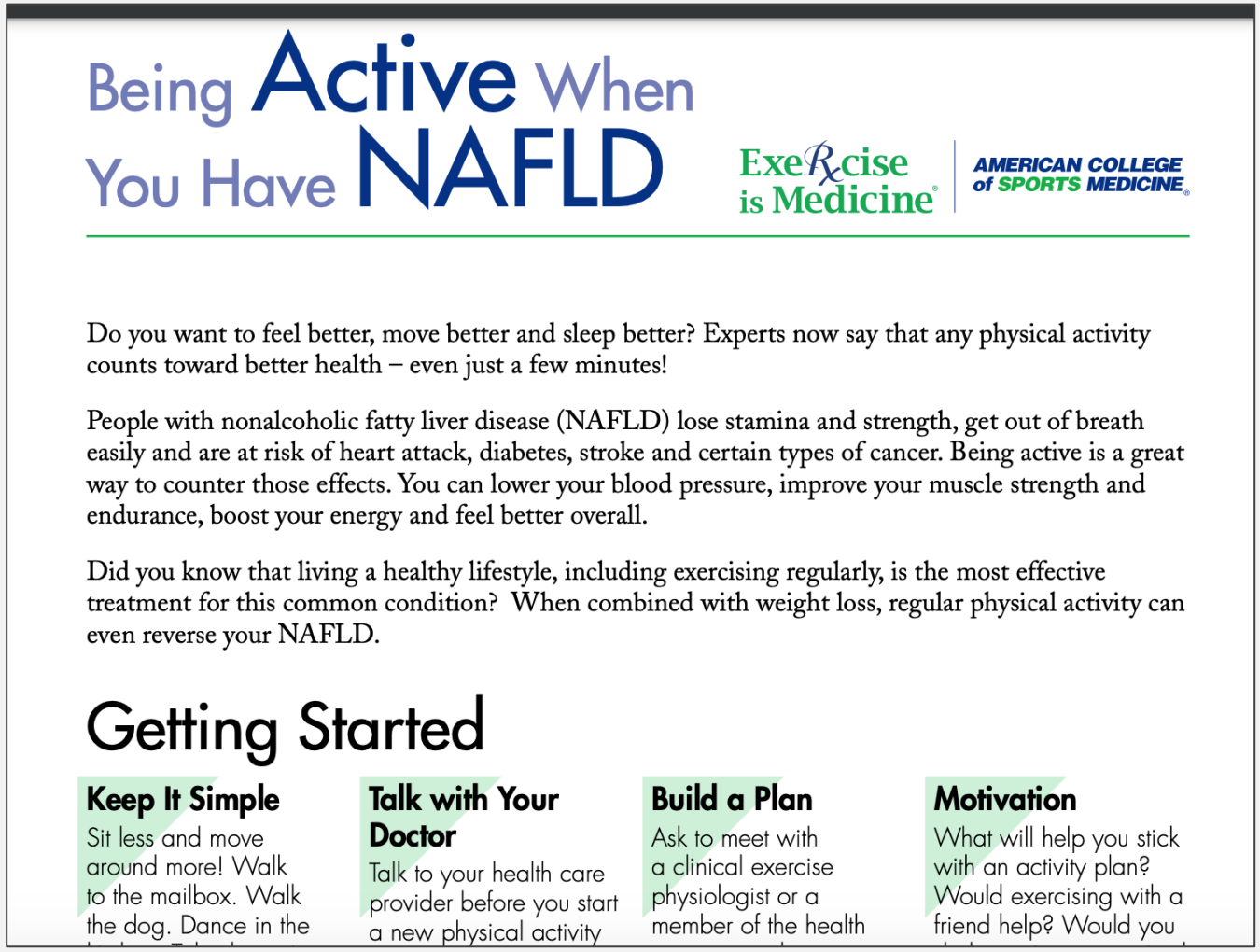
ZM Younossi, **KE Corey**, JK Lim. Gastroenterology 2021
R Hashda et al., Journal of Hepatology 2017

LIFESTYLE MODIFICATIONS FOR NAFLD:

"Any engagement in physical activity or increase over previous levels is however better than continuing inactivity"

-EASL Clinical Practice Guidelines 2016

EXERCISE AS MEDICINE



Being Active When You Have NAFLD

Exercise is Medicine® | AMERICAN COLLEGE of SPORTS MEDICINE®

Do you want to feel better, move better and sleep better? Experts now say that any physical activity counts toward better health – even just a few minutes!

People with nonalcoholic fatty liver disease (NAFLD) lose stamina and strength, get out of breath easily and are at risk of heart attack, diabetes, stroke and certain types of cancer. Being active is a great way to counter those effects. You can lower your blood pressure, improve your muscle strength and endurance, boost your energy and feel better overall.

Did you know that living a healthy lifestyle, including exercising regularly, is the most effective treatment for this common condition? When combined with weight loss, regular physical activity can even reverse your NAFLD.

Getting Started

Keep It Simple
Sit less and move around more! Walk to the mailbox. Walk the dog. Dance in the

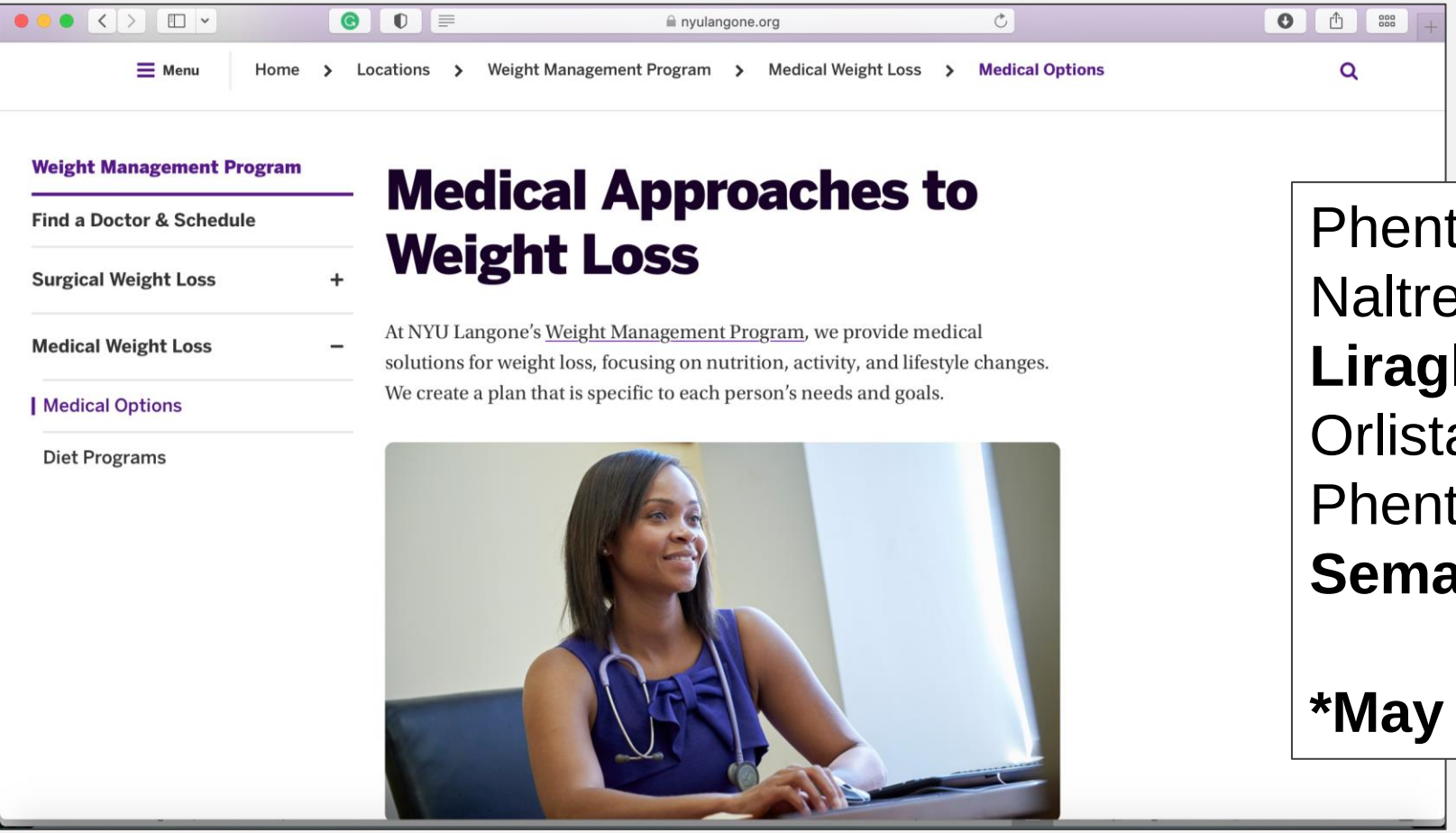
Talk with Your Doctor
Talk to your health care provider before you start a new physical activity

Build a Plan
Ask to meet with a clinical exercise physiologist or a member of the health

Motivation
What will help you stick with an activity plan? Would exercising with a friend help? Would you

https://www.exerciseismedicine.org/wp-content/uploads/2021/04/EIM_Rx-for-Health_NAFLD.pdf

PHARMACOTHERAPY FOR WEIGHT LOSS



Phentermine / Topiramate (Qsymia®)
Naltrexone / Bupropion (Contrave®)
Liraglutide (Saxenda®, Victoza®)*
Orlistat (Xenical®, Alli®)
Phentermine (Adipex®)
Semaglutide (Wegovy®)*

***May have benefit in NASH**

REFERRING PATIENTS FOR HELP WITH WEIGHT LOSS

Indications for RD referral: overweight, obesity, need for specialized dietary counselling.

Indications for pharmacotherapy: BMI ≥30 kg/m^2 or ≥ 27 kg/m^2 with weight-related complications

Indications for bariatric surgery: BMI ≥ 40 kg/m^2 or 35 kg/m^2 with weight-related complications

https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/weight-management/talking-adult-patients-tips-primary-care-clinicians#morehelp

STANDARD OF CARE NASH TREATMENT: MEDICATIONS

Treatment	Dose	Population	Outcomes
Vitamin E	800 units daily	NASH without DM	Improvement in steatosis and inflammation
Pioglitazone	30-45 mg daily	NASH with DM	Improvement in steatosis and inflammation

Ekstedt et al., J of Hep 2007

Mummadi et al., CGH 2008

Pomrat et al., Hep 2010

Taitano et al,. J Gastro Surg 2015
Musso et al. Hep 2010
LB Van Wagner Ann Hep 2011

POTENTIAL RISKS

- **Vitamin E**
  - Prostate CA: May increase risk of prostate cancer
  - Mortality**:** May increase risk of all-cause mortality
  - Use: Only in biopsy-proven NASH in non-diabetics
- **Pioglitazone**
  - CHF: May increase risk of CHF exacerbations
  - Bladder CA: May increase risk
  - Weight gain: 2.5 kg - 4.7 kg
  - Use: Only in biopsy-proven NASH in diabetics

SEMAGLUTIDE FOR NASH

72-week, double-blind phase 2 trial of 320 patients with biopsy-proven NASH & stage F1, F2, or F3 (230 w/F2 & 3)

Randomly assigned, in 3:3:3:1:1:1 ratio, to daily SQ semaglutide 0.1, 0.2, or 0.4 mg or placebo

Primary end point: resolution of NASH with no worsening of fibrosis

Secondary end point: improvement of >= 1 fibrosis stage with no worsening of NASH.

Endpoint Analyses performed only in F2 or F3 fibrosis; other analyses were performed in all the patients

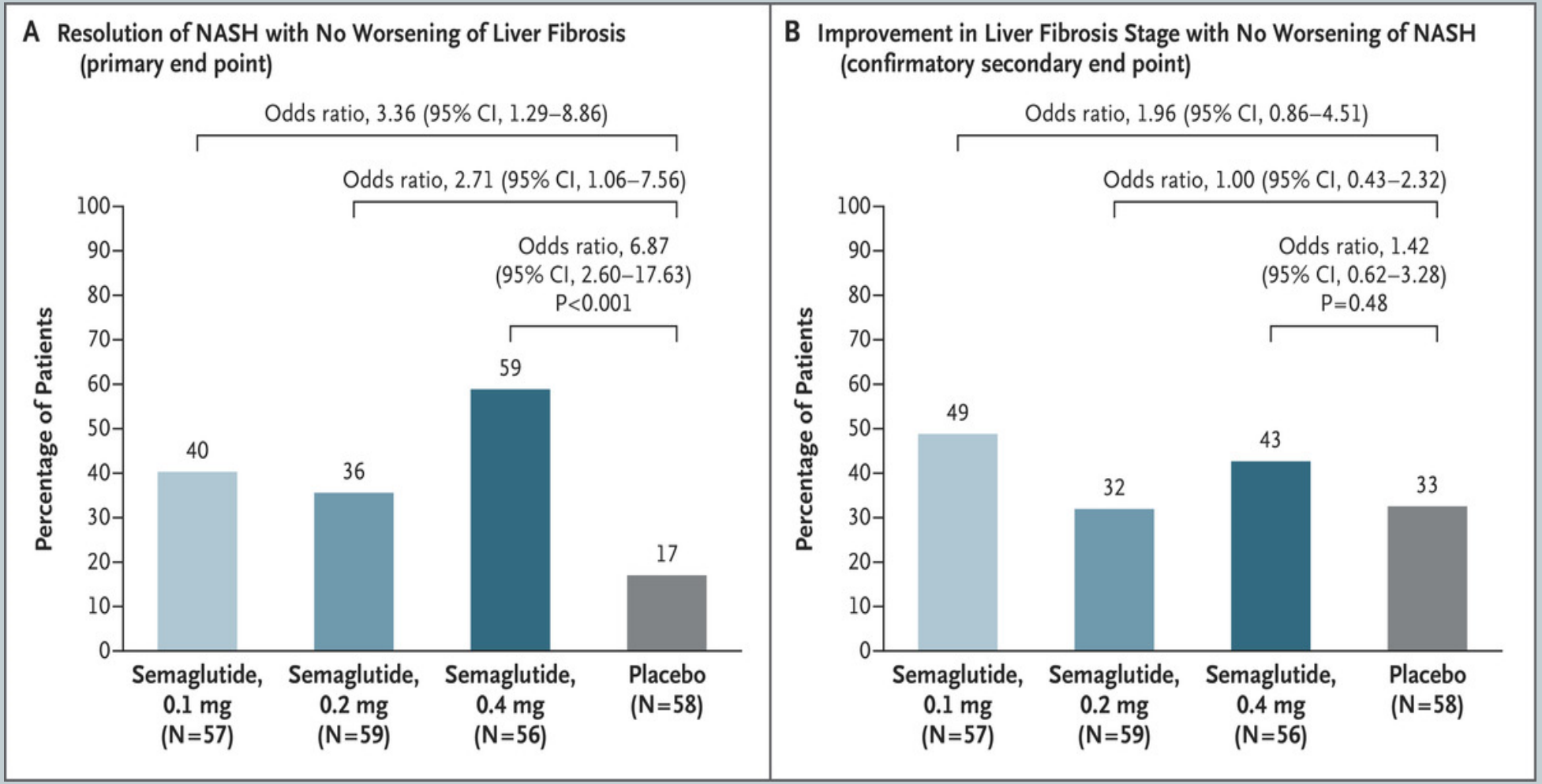
Baseline Characteristics

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=82)	Placebo Group (N=80)
Age — yr	55.2±10.9	58.1±9.9	54.3±10.2	52.4±10.8
Female sex — no. (%)	51 (64)	52 (67)	47 (57)	44 (55)
Body weight — kg	98.4±21.1	97.1±22.0	96.6±20.1	101.3±23.3
Body-mass index	36.1±6.4	35.6±6.1	35.2±6.6	36.1±6.6
Type 2 diabetes — no. (%)	49 (61)	51 (65)	49 (60)	50 (62)
Glycated hemoglobin level among patients with type 2 diabetes — %†	7.4±1.3	7.2±1.0	7.2±1.2	7.3±1.2
Liver-enzyme levels — U/liter				
Alanine aminotransferase	55±90	53±78	54±84	55±92
Aspartate aminotransferase	44±82	43±73	44±78	42±83
Liver fibrosis stage — no. (%)‡				
F1	23 (29)	19 (24)	26 (32)	22 (28)
F2	18 (22)	18 (23)	14 (17)	22 (28)
F3	39 (49)	41 (53)	42 (51)	36 (45)
Total activity score for nonalcoholic fatty liver disease§	4.9±0.8	4.9±0.9	4.8±0.9	4.9±0.9
Noninvasive measures of liver steatosis and fibrosis				
Liver steatosis, as assessed by FibroScan — dB/m¶	332.0±46.2	347.4±55.0	335.7±55.8	348.6±35.2
Liver stiffness, as assessed by FibroScan — kPa¶	10.4±78.5	12.3±74.0	11.5±87.1	8.7±90.0
Enhanced liver fibrosis test score‖	9.8±1.0	9.8±0.9	9.9±1.0	9.6±0.9

PN Newsome et al. N Engl J Med 2020.

SEMAGLUTIDE FOR NASH: PRIMARY & SECONDARY ENDPOINTS



Mean weight loss was 13% in 0.4-mg group vs. 1% in placebo

PN Newsome et al. N Engl J Med 2020.

SEMAGLUTIDE FOR NASH: ADVERSE EVENTS

Higher in semaglutide 0.4 mg group vs. placebo

- Nausea: 42% vs. 11%
- Constipation: 22% vs. 12%;
- Vomiting: 15% vs. 2%

Malignant neoplasms in 3 (1%) semaglutide vs. 0 placebo

Total neoplasms in semaglutide 15% vs. placebo 8%

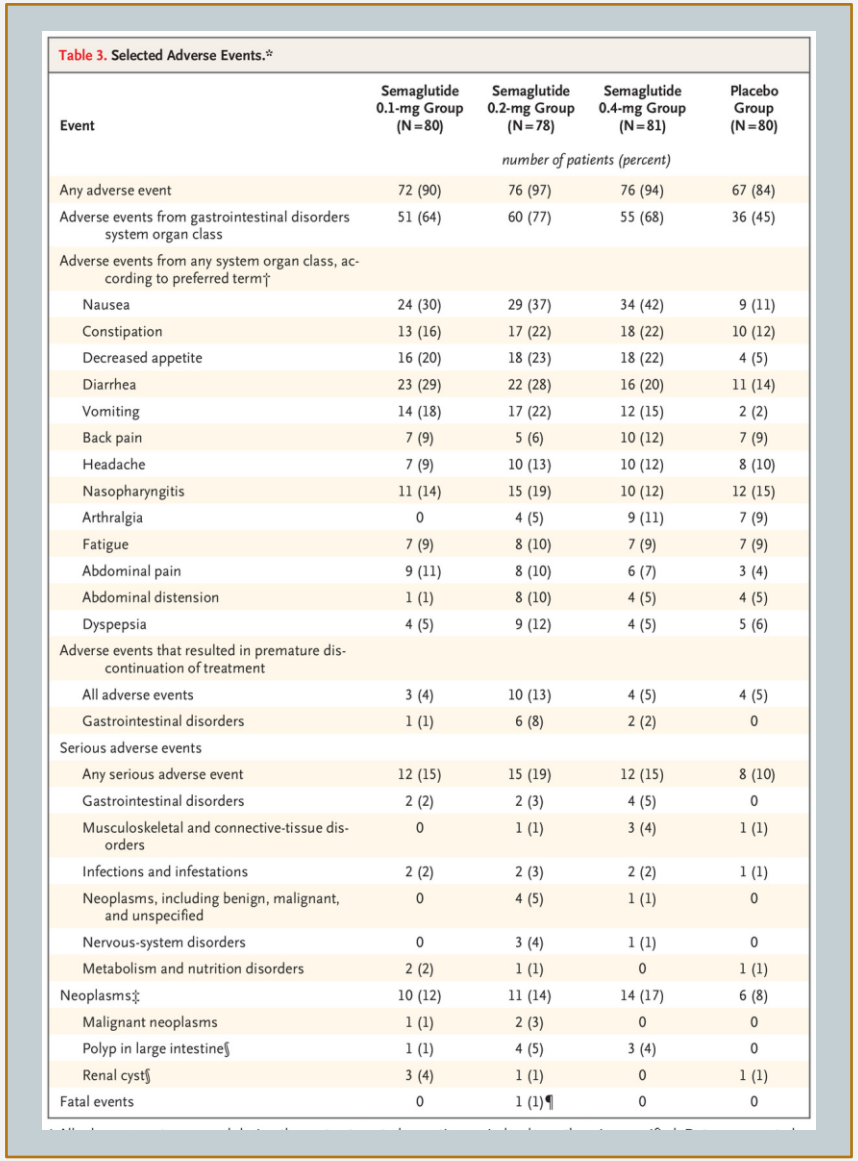


Table 3. Selected Adverse Events.*

Event	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=81)	Placebo Group (N=80)
	number of patients (percent)			
Any adverse event	72 (90)	76 (97)	76 (94)	67 (84)
Adverse events from gastrointestinal disorders system organ class	51 (64)	60 (77)	55 (68)	36 (45)
Adverse events from any system organ class, according to preferred term†				
Nausea	24 (30)	29 (37)	34 (42)	9 (11)
Constipation	13 (16)	17 (22)	18 (22)	10 (12)
Decreased appetite	16 (20)	18 (23)	18 (22)	4 (5)
Diarrhea	23 (29)	22 (28)	16 (20)	11 (14)
Vomiting	14 (18)	17 (22)	12 (15)	2 (2)
Back pain	7 (9)	5 (6)	10 (12)	7 (9)
Headache	7 (9)	10 (13)	10 (12)	8 (10)
Nasopharyngitis	11 (14)	15 (19)	10 (12)	12 (15)
Arthralgia	0	4 (5)	9 (11)	7 (9)
Fatigue	7 (9)	8 (10)	7 (9)	7 (9)
Abdominal pain	9 (11)	8 (10)	6 (7)	3 (4)
Abdominal distension	1 (1)	8 (10)	4 (5)	4 (5)
Dyspepsia	4 (5)	9 (12)	4 (5)	5 (6)
Adverse events that resulted in premature discontinuation of treatment				
All adverse events	3 (4)	10 (13)	4 (5)	4 (5)
Gastrointestinal disorders	1 (1)	6 (8)	2 (2)	0
Serious adverse events				
Any serious adverse event	12 (15)	15 (19)	12 (15)	8 (10)
Gastrointestinal disorders	2 (2)	2 (3)	4 (5)	0
Musculoskeletal and connective-tissue disorders	0	1 (1)	3 (4)	1 (1)
Infections and infestations	2 (2)	2 (3)	2 (2)	1 (1)
Neoplasms, including benign, malignant, and unspecified	0	4 (5)	1 (1)	0
Nervous-system disorders	0	3 (4)	1 (1)	0
Metabolism and nutrition disorders	2 (2)	1 (1)	0	1 (1)
Neoplasms‡	10 (12)	11 (14)	14 (17)	6 (8)
Malignant neoplasms	1 (1)	2 (3)	0	0
Polyp in large intestine§	1 (1)	4 (5)	3 (4)	0
Renal cyst§	3 (4)	1 (1)	0	1 (1)
Fatal events	0	1 (1)¶	0	0

PN Newsome et al. N Engl J Med 2020.

LANIFIBRANOR: NATIV TRIAL

- Pan-peroxisome proliferator-activated receptor (PPAR) agonist
- 24 week phase 2b trial in 247 adults with non-cirrhotic, highly active NASH (228 completed trial)
- Used Steatosis Activity Fibrosis (SAF) score as inclusion criteria & outcomes
  - Steatosis score: 0-3
  - Activity (ballooning and lobular inflammation) grade: 0-4; A3=moderate, A4 severe activity
  - Fibrosis stage: 0-4
- Inclusion: ≥ 1 in steatosis, lobular inflammation and ballooning; SAF-A 3-4, F<4

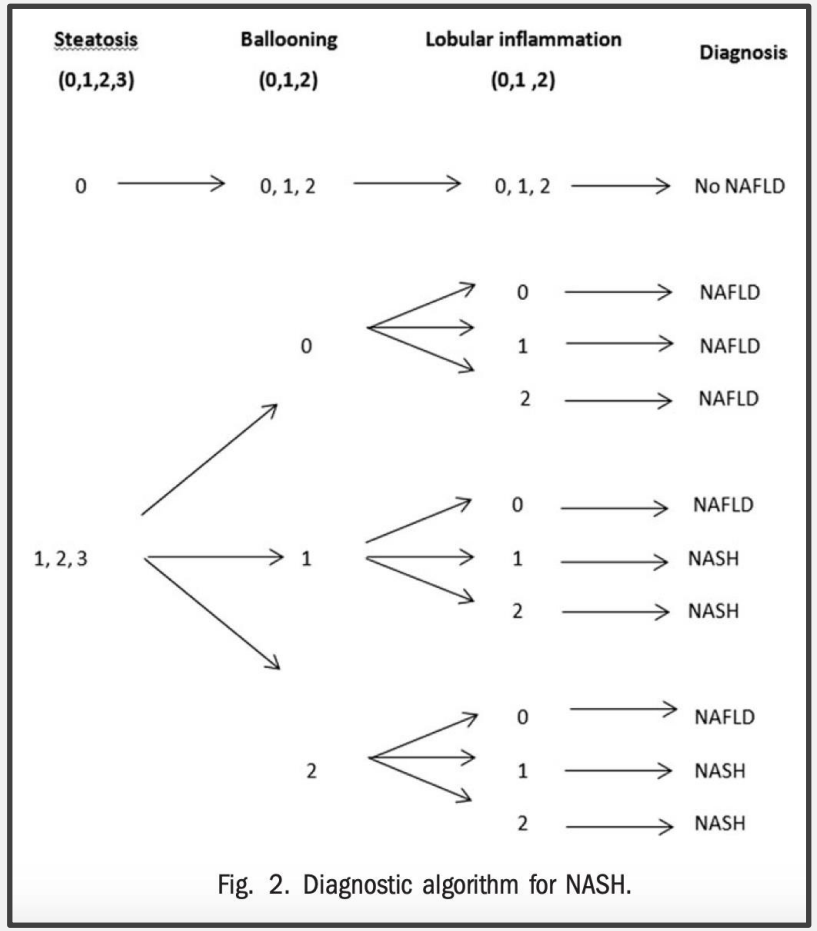


Fig. 2. Diagnostic algorithm for NASH.

SM Franque et al., NEJM 2021, P Bedosa et al., Hepatology 2012

LANIFIBRANOR: NATIV TRIAL

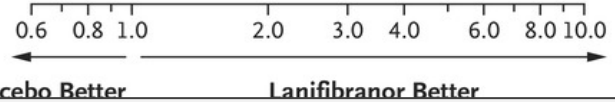
- Randomized 1:1:1 to lanifibranor 800mg QD, 1200 mg QD or placebo
- Primary Outcome: ≥ 2 decrease in SAF Activity w/o worsening of fibrosis
- Secondary Outcomes: NASH resolution (ballooning =0, lobular inflammation ≤ 1) & no worsening of fibrosis; improvement in fibrosis stage ≥ 1 w/no worsening of NASH; improvement in NAFLD activity score; composite of resolution of NASH and improvement in fibrosis stage ≥ 1.

SM Franque et al., NEJM 2021, P Bedosa et al., Hepatology 2012

LANIFIBRANOR: NATIV TRIAL

- Primary outcome: 55% in 1200mg (p=0.007) vs. 48% in 800mg (NS) vs. 33% PBO

End Point	Placebo	Lanifibranor	Risk Ratio (95% CI)	P Value
	percent of patients with response			
Primary end point: reduction of ≥2 points in SAF-A score and no worsening of fibrosis				
Lanifibranor, 800 mg	33	48	1.45 (1.00–2.10)	0.07
Lanifibranor, 1200 mg	33	55	1.69 (1.22–2.34)	0.007
Secondary end point: resolution of NASH without worsening of fibrosis				
Lanifibranor, 800 mg	22	39	1.70 (1.07–2.71)	
Lanifibranor, 1200 mg	22	49	2.20 (1.49–3.26)	
Secondary end point: improvement in fibrosis stage of ≥1 without worsening of NASH				
Lanifibranor, 800 mg	29	34	1.15 (0.72–1.85)	
Lanifibranor, 1200 mg	29	48	1.68 (1.15–2.46)	
Composite secondary end point: resolution of NASH and improvement in fibrosis stage of ≥1				
Lanifibranor, 800 mg	9	25	2.57 (1.20–5.51)	
Lanifibranor, 1200 mg	9	35	3.95 (2.03–7.66)	



- AE: Diarrhea, nausea, peripheral edema, anemia, weight gain

SM Franque et al., NEJM 2021, P Bedosa et al., Hepatology 2012

LANIFIBRANOR: PHASE 3 CLINICAL PROGRAM

- NATiV3 Trial
  - Ongoing randomized controlled phase 3 study
  - Currently enrolling adults with NASH and stage 2-3 liver fibrosis (estimated N = 2000)
  - Primary objectives:
    - Part 1: assess the effect of lanifibranor vs. placebo on NASH resolution and improvement of fibrosis assessed by liver histology
    - Part 2: assess the effect of lanifibranor vs. placebo on delaying NASH disease progression measured by the composite endpoint of progression to cirrhosis, liver-related clinical events, and all-cause death

ClinicalTrials.gov. NCT04849728. Accessed 10/16/2021 at: https://clinicaltrials.gov/ct2/show/NCT04849728

18 MONTH INTERIM ANALYSIS OF REGENERATE STUDY: DESIGN

- Phase 3 study of obeticholic acid (OCA)
- 931 with biopsy-confirmed NASH, F2 or F3
  - OCA 10 mg/day (n=312), OCA 25 mg/day (n=308), or placebo (n=311)
- Primary endpoints: 1) fibrosis improvement with no worsening of NASH or 2) NASH resolution with no worsening of fibrosis

Z. Younossi et al., ILC 2019, Vienna, Austria

REGENERATE STUDY: RESULT

- OCA 25 mg met primary endpoint of fibrosis improvement with no worsening of NASH in 23.1% (p=0.0002 vs placebo 12%)
- NASH resolution endpoint not met
- 35.1% OCA 25 mg had improvement in ballooning (p=0.0011 vs placebo), and 44.2% of in lobular inflammation (p=0.0322 vs placebo)

Z. Younossi et al., ILC 2019, Vienna, Austria

18 MONTH INTERIM ANALYSIS OF REGENERATE STUDY: ADVERSE EVENTS

- Pruritus
  - 51% of the OCA 25 mg/day
  - 28% of the OCA 10 mg/day
  - 19% of the placebo group

- More participants withdrew due to pruritus in OCA 25 mg/day group (9%) than OCA 10 mg/day (<1%) or placebo (<1%) groups.

Z. Younossi et al., ILC 2019, Vienna, Austria

CONCLUSIONS

- NAFLD staging with FIB4 score and Fibroscan
- Fundamentals of treatment include weight loss, physical activity and nutrition
- RD, obesity medicine physicians and bariatric surgeons can play key roles in treatment of obesity and weight-related conditions
- Current NASH specific pharmacotherapy remains limited but many promising, emerging therapies