Update on Liver Disease
Conference 2022

UT Southwestern
Medical Center

Emerging Topics in NAFLD

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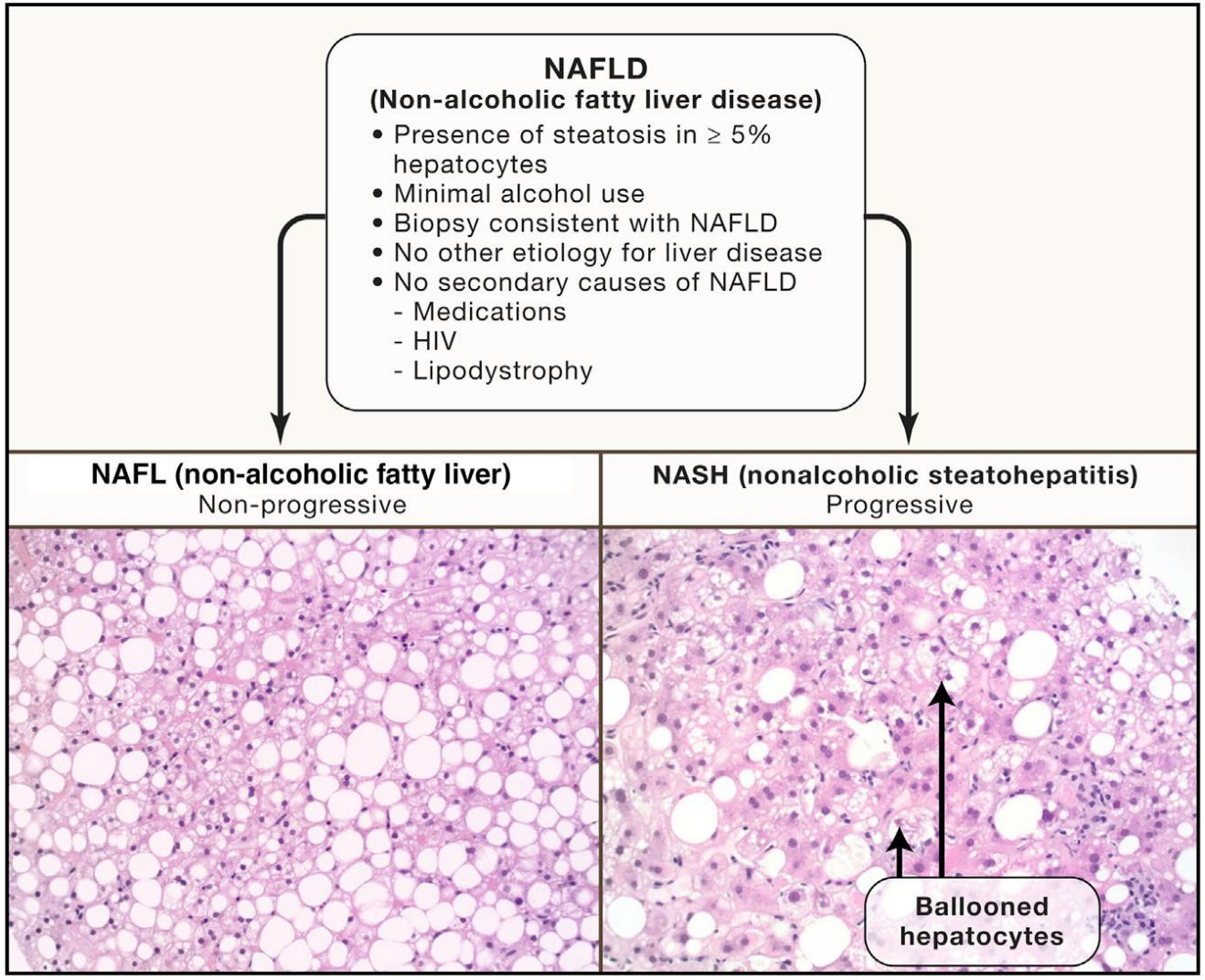
Talk outline

- Case presentation
- Definitions
- Natural history of NAFLD
- Disease initiation and modifiers of disease progression
- How/who to evaluate for NAFLD
- Risk stratification in NAFLD
- NAFLD management
  - Lifestyle Interventions
  - Role of Bariatrics
  - *Nutrition & Pharmacotherapy*

Patient Presentation – J.P.

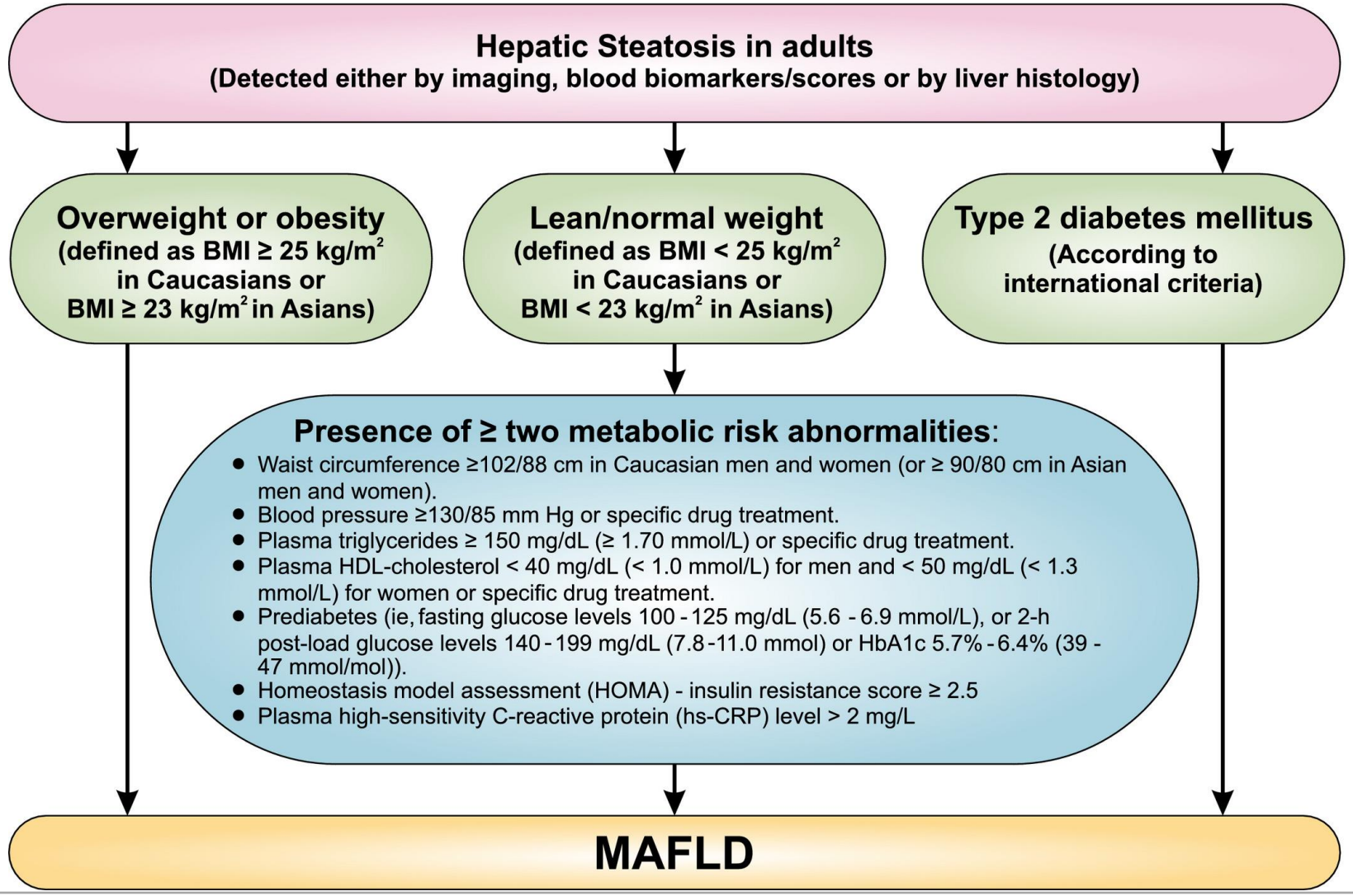
- 65-year-old man, referred for elevated aminotransferases
  - Endorses RUQ discomfort; 20 lb weight gain over two years
  - Mostly “normal” liver chemistries over previous 5 years, mild intermittent elevations; ALT 60, AST 55, normal ALP and TB
- PMHx: obesity (210 lbs, BMI 31), diabetes (HbA1c 7.2), hypertension
- FHx: mother with cryptogenic cirrhosis
- SHx: from Mexico, rare alcohol consumption
- Medications: Metformin, Lisinopril
- Exam: central adiposity (waist circumference 104 cm)

What is Non-Alcoholic Fatty Liver Disease?

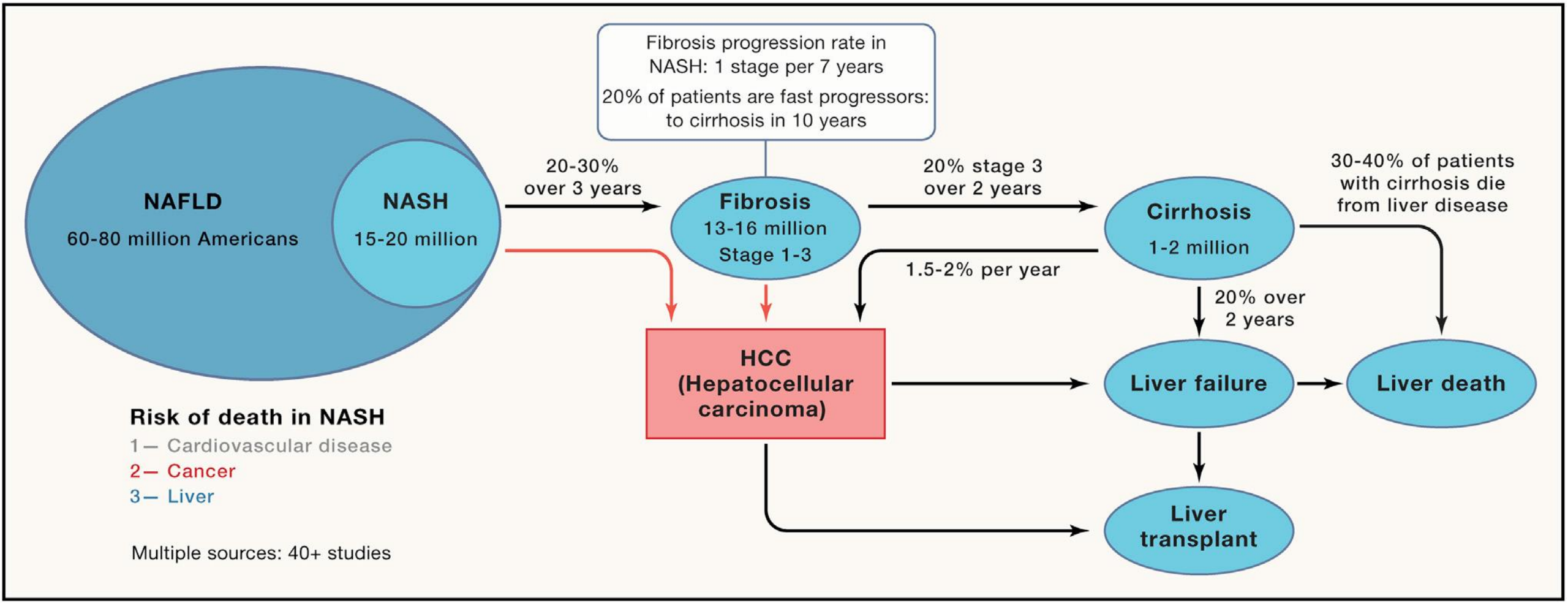


Loomba et al, Cell, 2021.

Shift in Paradigm: NAFLD to MAFLD

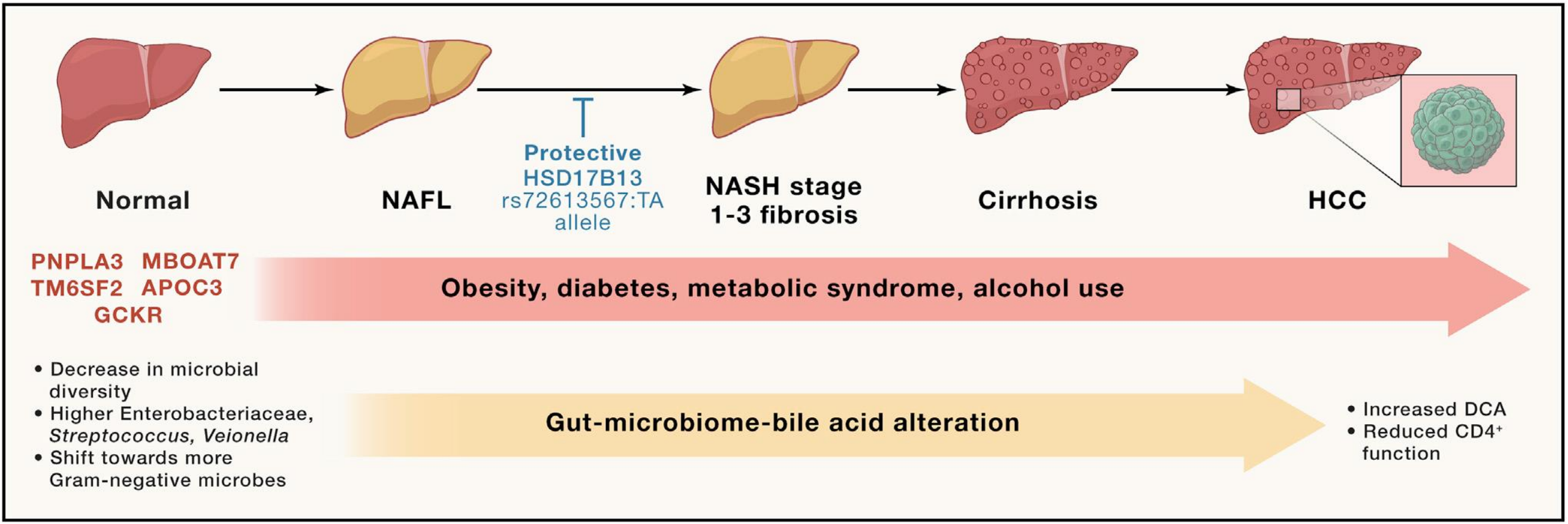


Natural History of NAFLD



Loomba et al, Cell, 2021.

NAFLD Initiation and Progression



Loomba R et al, Cell, 2021.

How to Evaluate for NAFLD

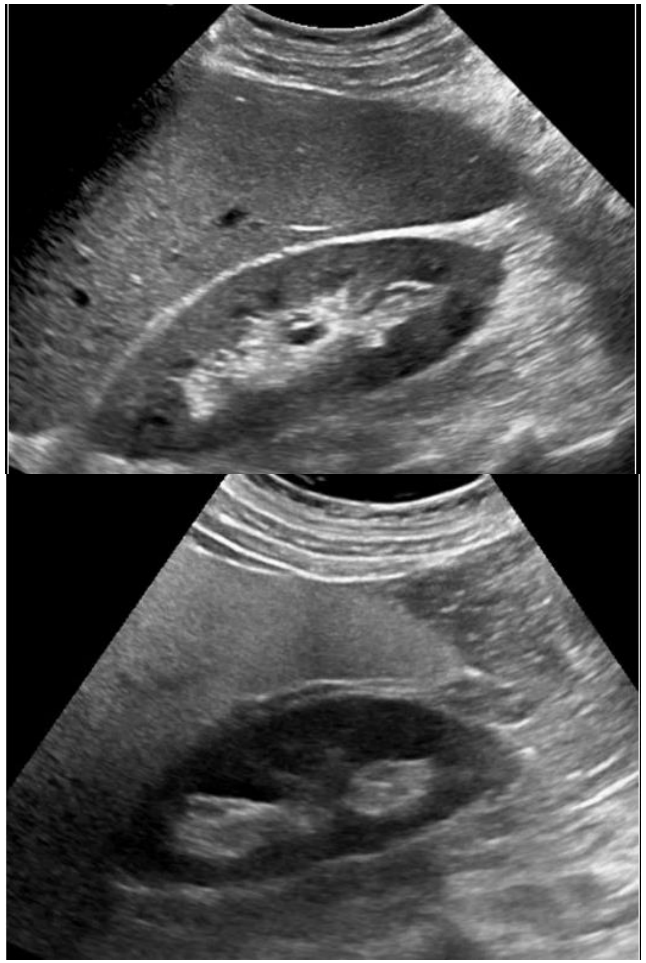
- Detailed medical history: alcohol, medications, secondary causes of steatosis

Medications
– Amiodarone
– Methotrexate
– Tamoxifen
– Corticosteroids
– Valproate
– Antiretrovirals

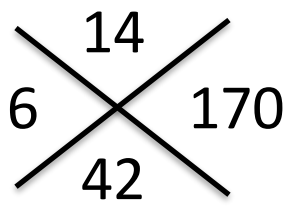
Additional etiologies
- HCV and Wilson's Disease
- Lipodystrophy/HIV
- Starvation/Malnutrition
- Post Whipple
- Parenteral nutrition
- Inborn errors of metabolism

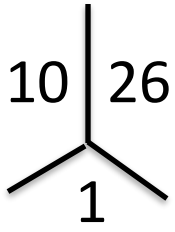
How to Evaluate for NAFLD

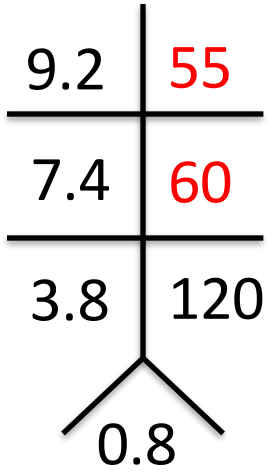
- Laboratory evaluation:
  - Viral hepatitis serologies
  - Ferritin*
  - ANA*, ASMA*, IgG
  - A1AT
  - Ceruloplasmin
  - CBC, CMP, INR
  - HIV Ab
  - Lipid panel
  - HbA1c
  - Thyroid function
- Imaging: Abdominal ultrasound

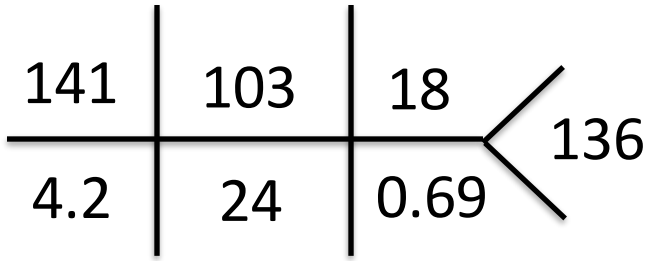


Back to our Patient, J.P.









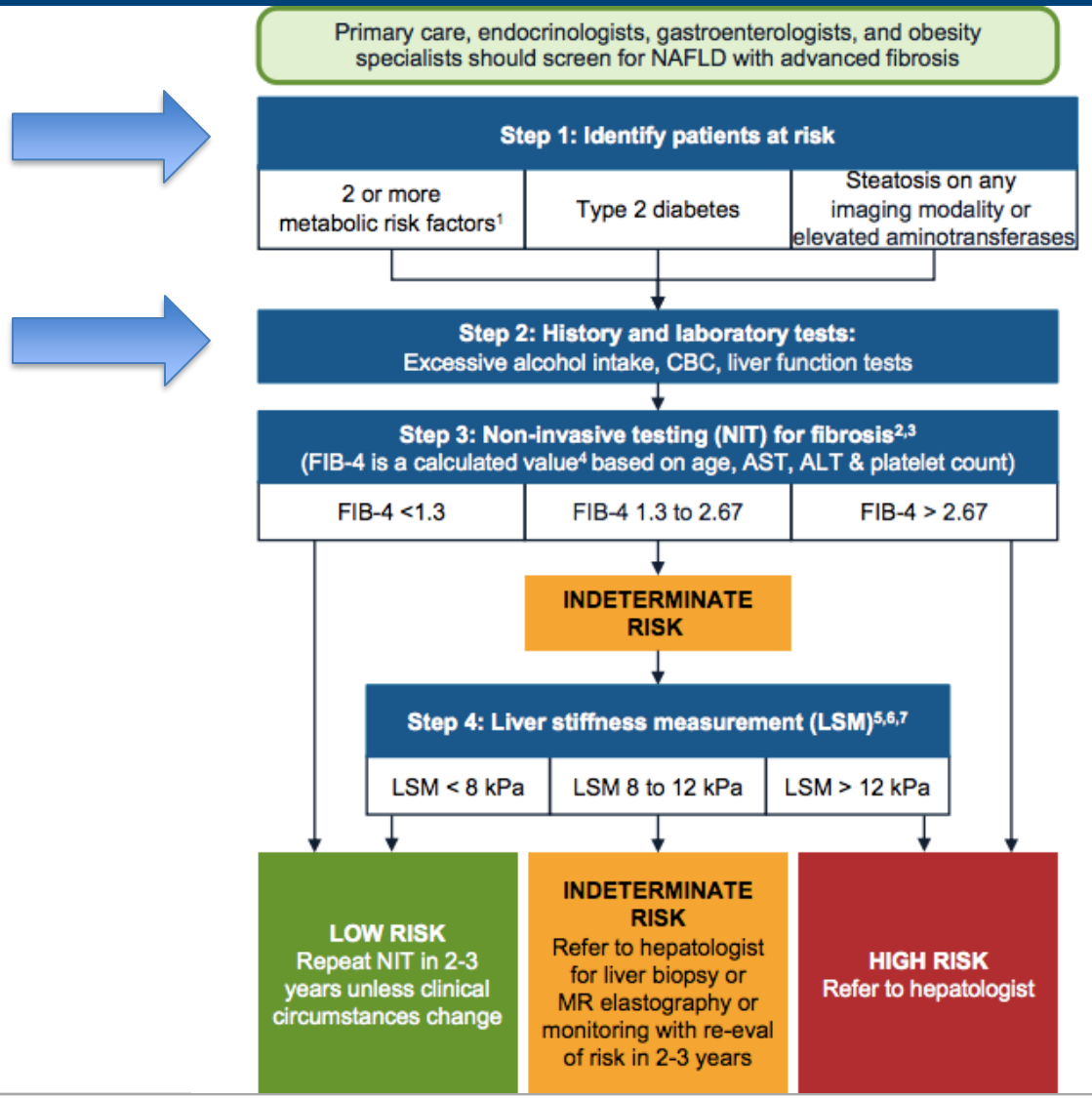
Labs otherwise notable for:

ANA + 1:80

Ultrasound Liver:

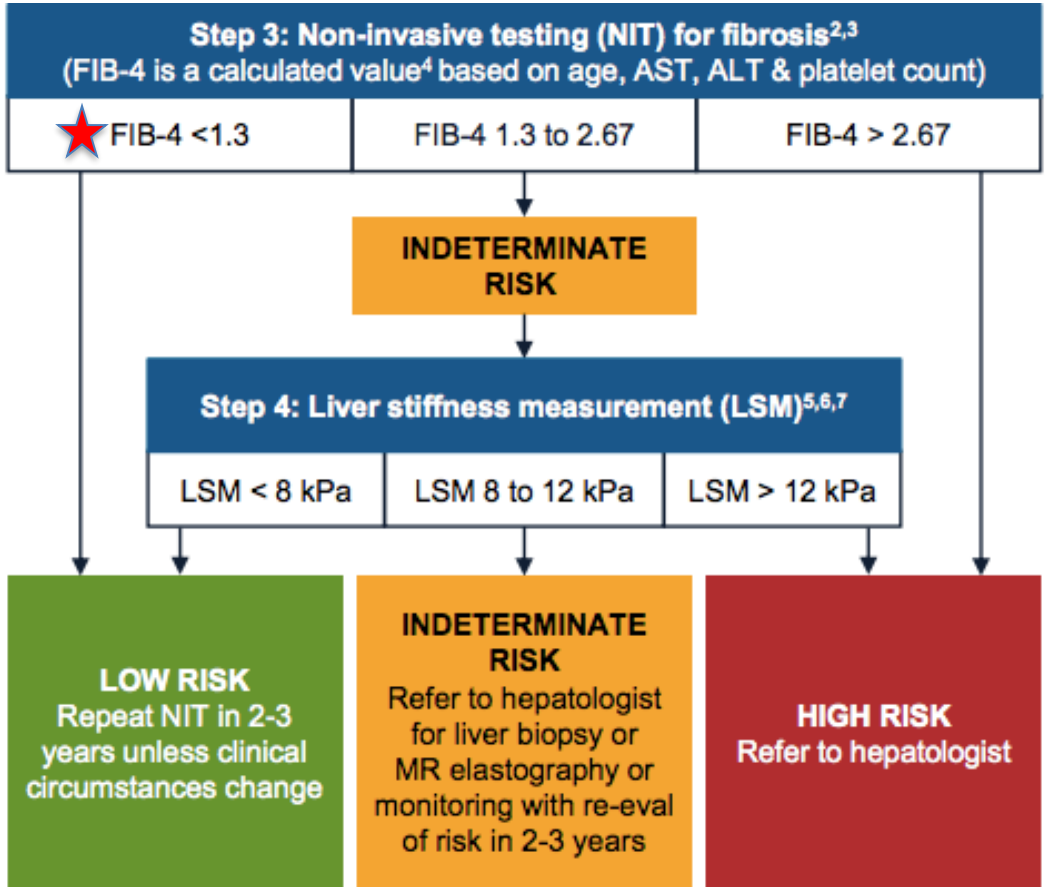
- Severe increase in hepatic echogenicity with typical regions of focal sparing
- The contour appears smooth
- Spleen size 9.5 x 9.4 x 3.5 cm
- **Impression: Hepatic steatosis. No evidence of portal hypertension.**

Risk Stratification



Kanwal et al, Gastroenterology, 2021.

Risk Stratification

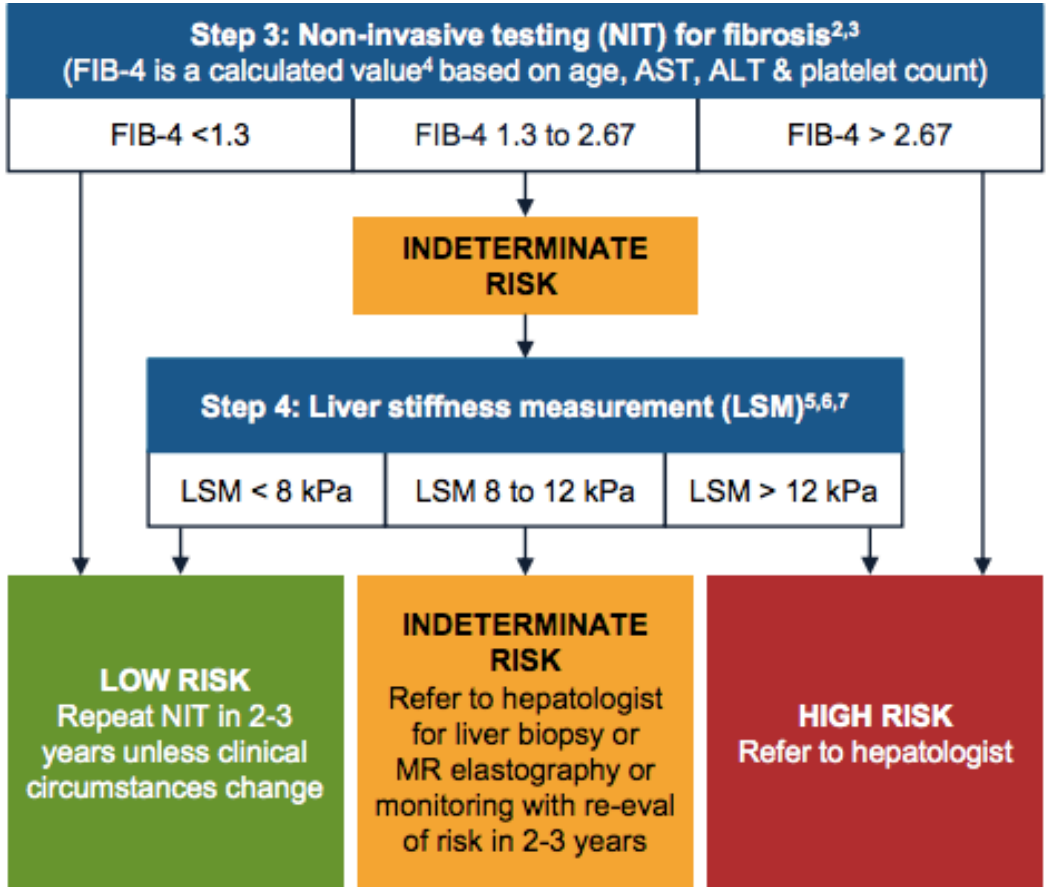


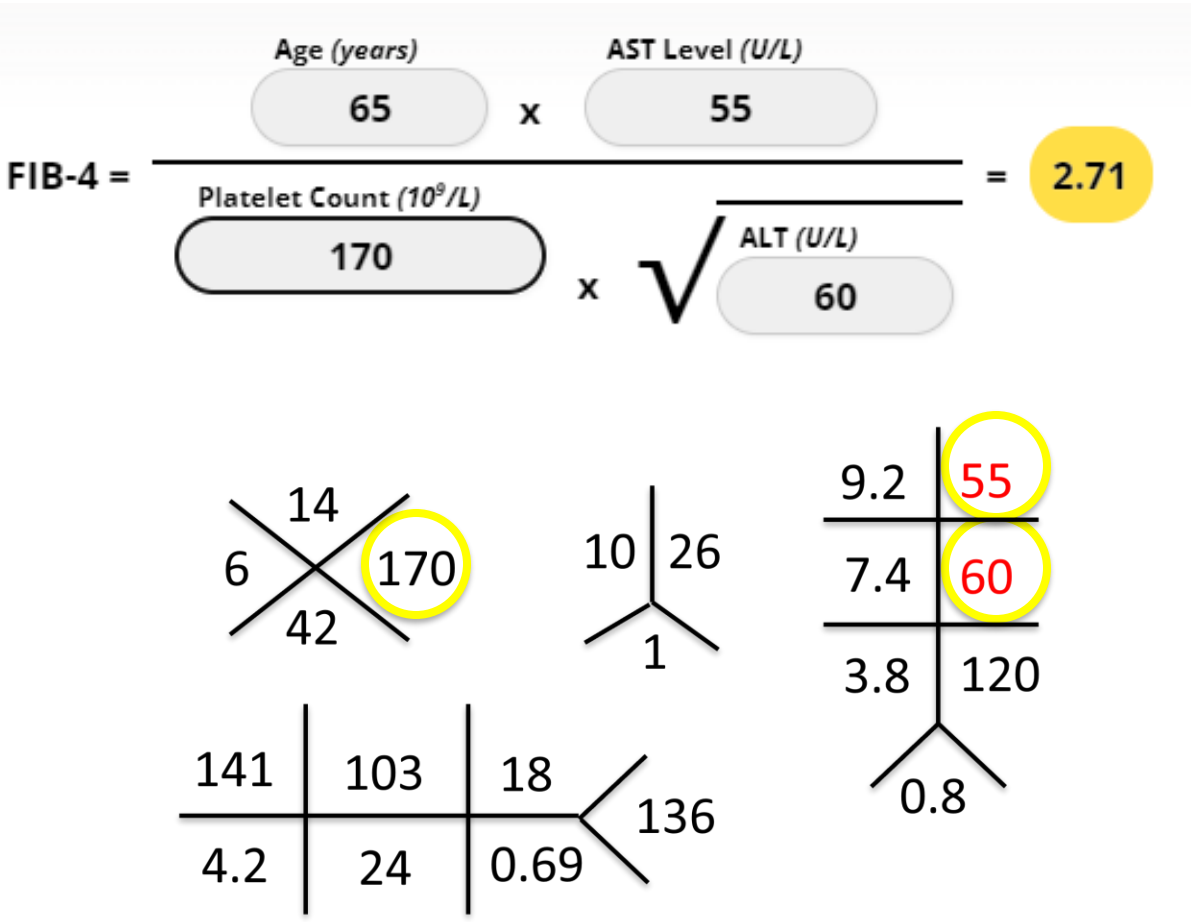
$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count } (10^9/L) \times \sqrt{\text{ALT (U/L)}}}$$

★ For patients 65+, use FIB-4 <2.0 as lower cutoff

Kanwal et al, Gastroenterology, 2021. Sterling et al, Hepatology, 2006.

Risk Stratification

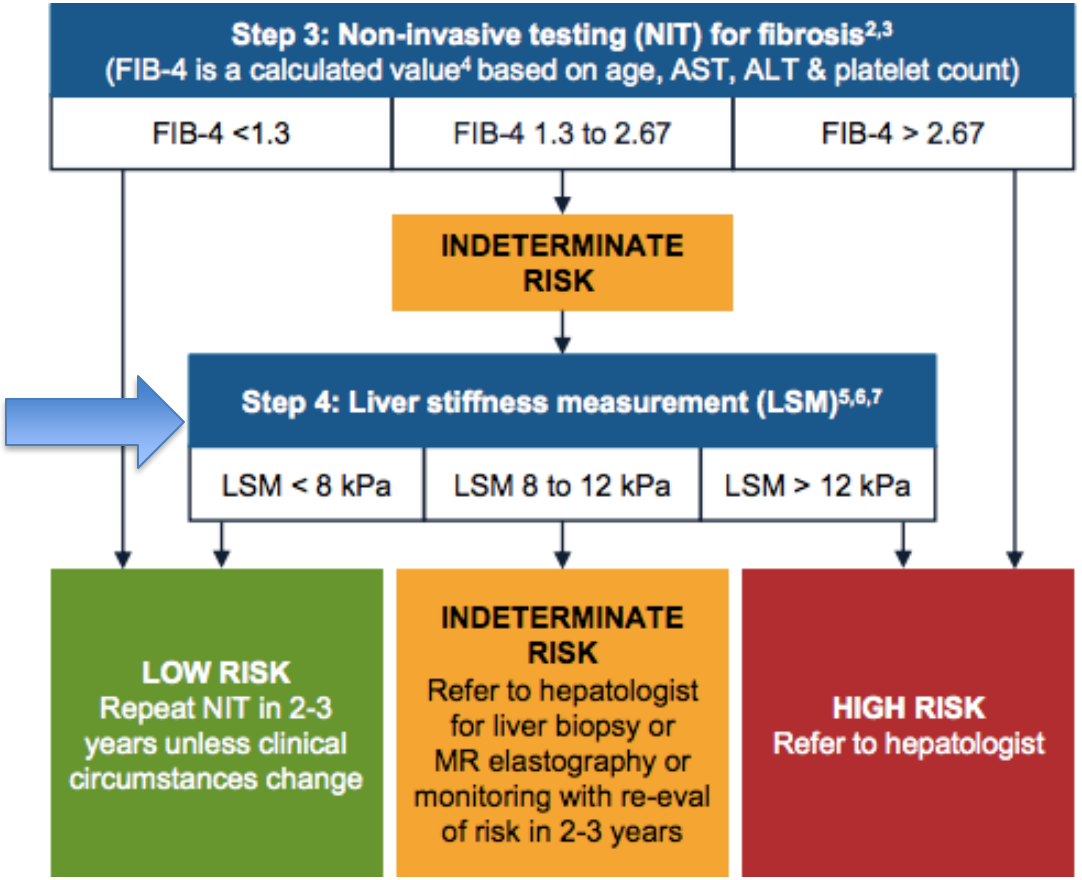


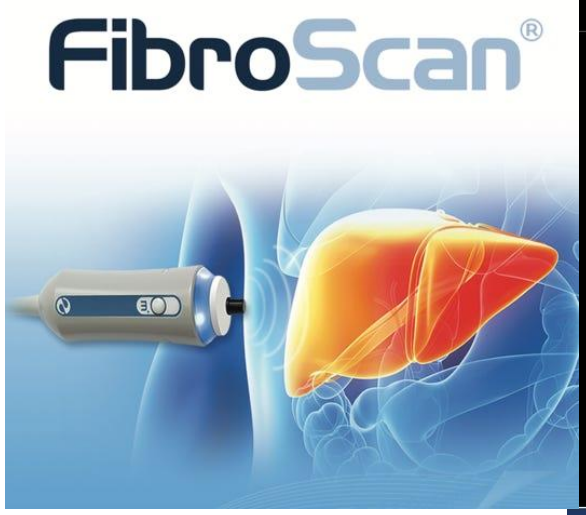


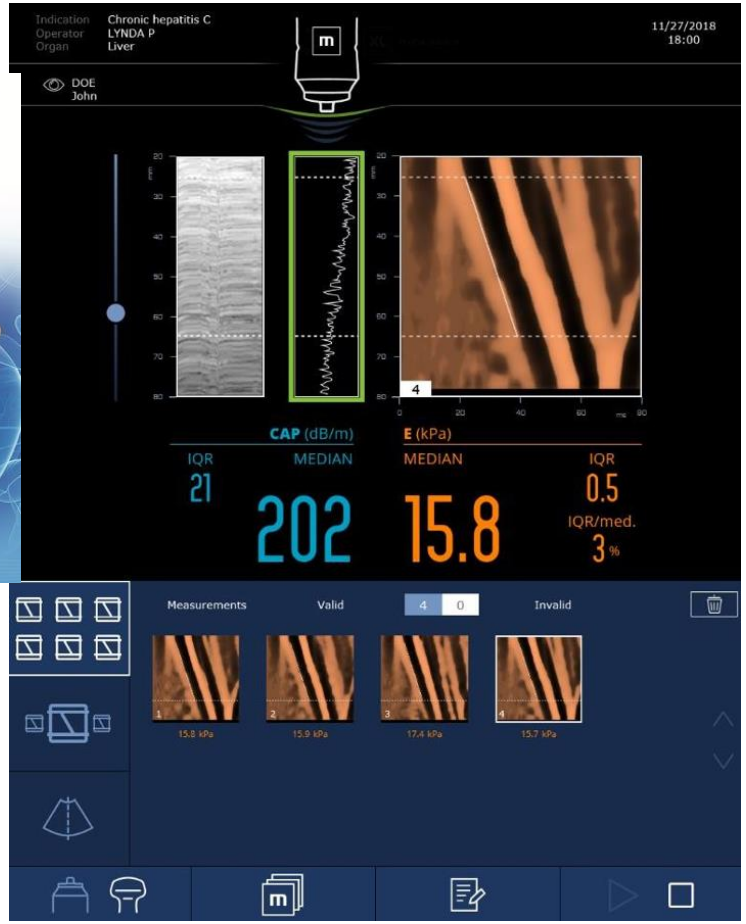
Kanwal et al, Gastroenterology, 2021.

Risk Stratification

Vibration Controlled Transient Elastography (VCTE)

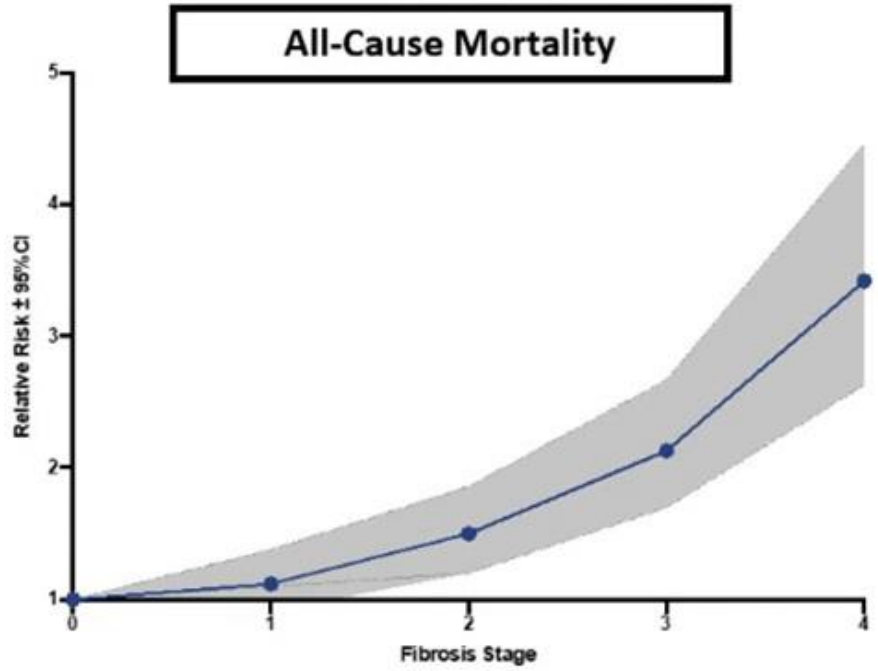


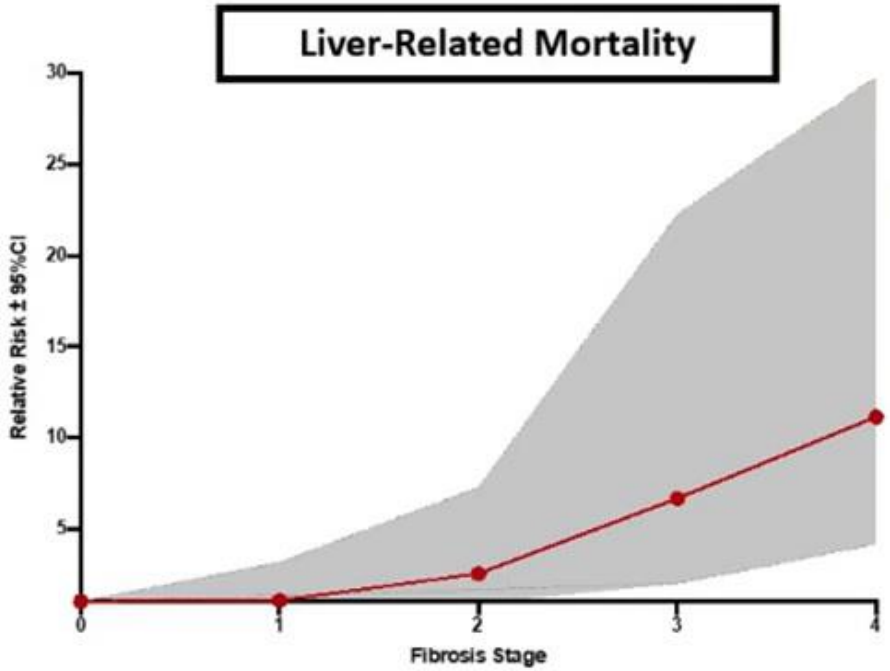




Kanwal et al, Gastroenterology, 2021.

Why Fibrosis Stage Matters

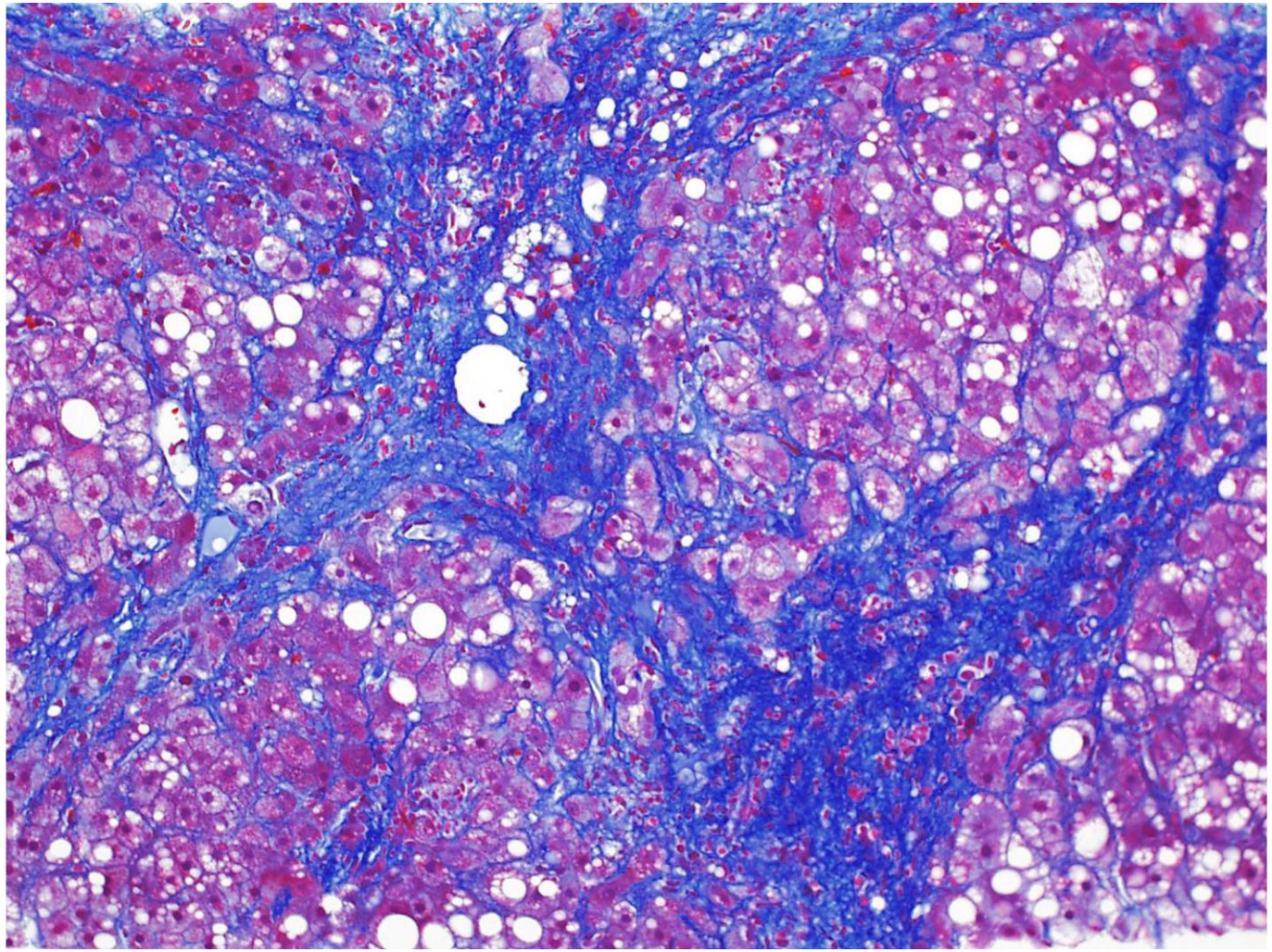




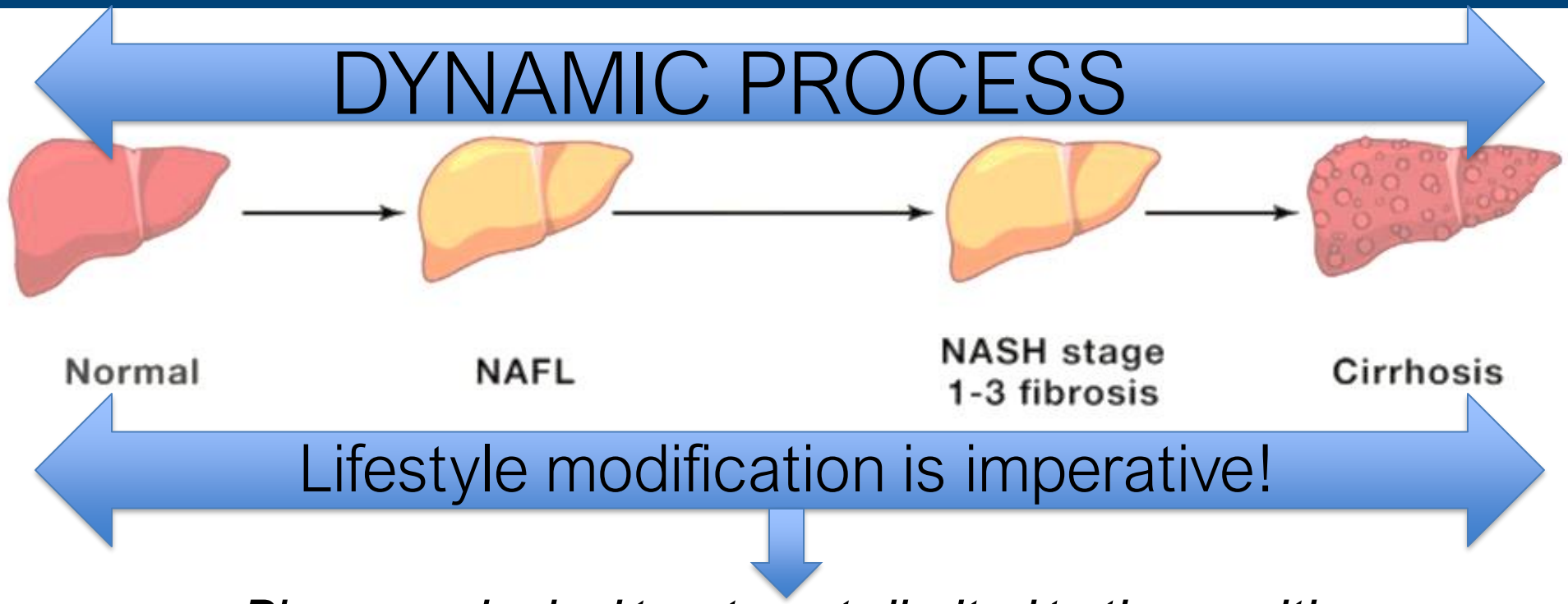
2018 AASLD Practice Guidance: *Patients with suspected or known NAFLD and a high risk of NASH (MetS) or advanced fibrosis should be referred for consideration of liver biopsy*.

Taylor et al, Gastroenterology, 2020. Chalasani et al, Hepatology, 2018.

J.P. - Liver Biopsy



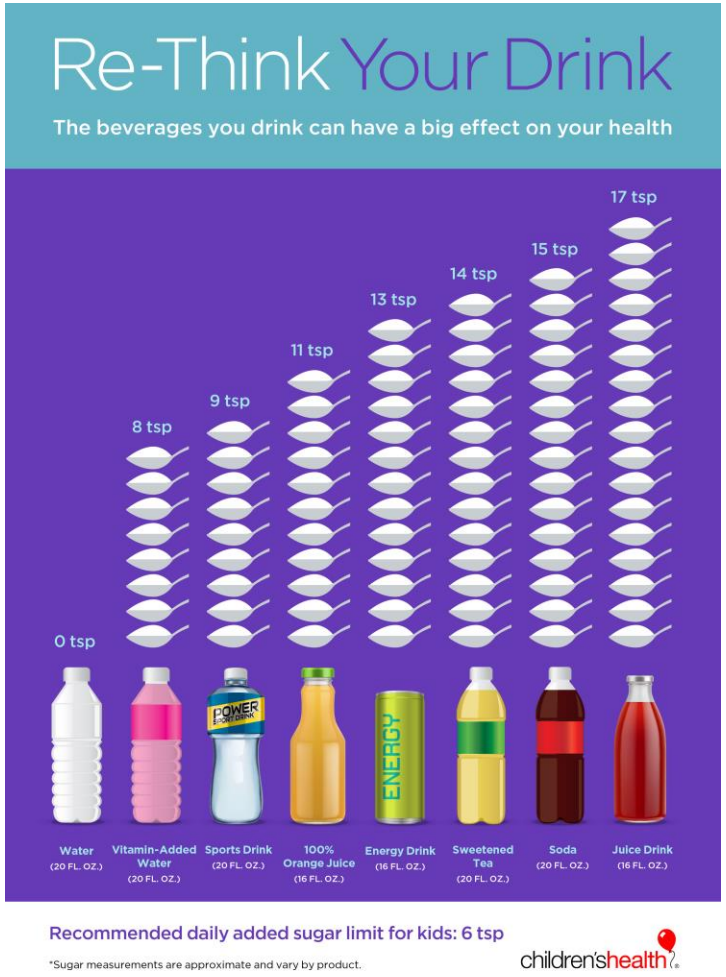
Management Principles of NAFLD



Pharmacological treatments limited to those with biopsy-proven NASH and fibrosis

Medical treatment unsuccessful: consider bariatric surgery/endoscopy, or clinical trial referral

Treatment of Obesity is Foundation of NAFLD Care



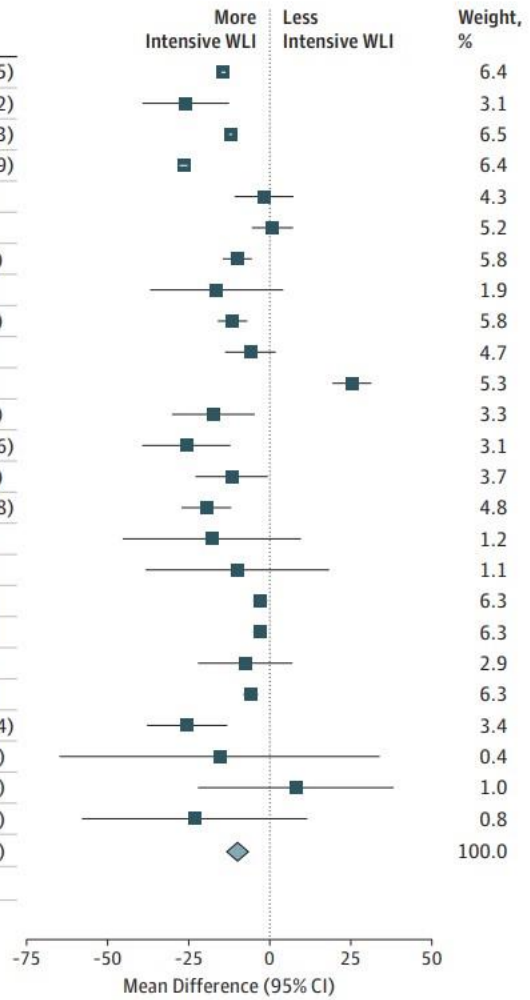
Weight Loss Improves Aminotransferases

Figure 2. Association Between Weight Loss Intervention (WLI) and Alanine Aminotransferase (ALT)

Source	More Intensive WLI Mean (SD)	More Intensive WLI Total	Less Intensive WLI Mean (SD)	Less Intensive WLI Total	Mean Difference in ALT, U/L (95% CI)	Weight, %
Al-Jiffri et al,[37] 2013	-13.6 (1.6)	50	0.7 (1.7)	50	-14.30 (-14.95 to -13.65)	6.4
Promrat et al,[45] 2010	-42.4 (23.0)	20	-16.5 (14.2)	10	-25.90 (-39.28 to -12.52)	3.1
Abd El-Kader et al,[35] 2016	-11.7 (1.3)	50	0.4 (1.1)	50	-12.10 (-12.57 to -11.63)	6.5
Sun et al,[34] 2012	-22.9 (9.2)	674	3.7 (9.2)	332	-26.60 (-27.81 to -25.39)	6.4
Bahmanadabi et al,[30] 2011	-7.5 (10.9)	20	-5.7 (17.6)	20	-1.80 (-10.87 to 7.27)	4.3
Abenavoli et al,[36] 2017	0.5 (7.2)	20	-0.3 (8.9)	10	0.80 (-5.55 to 7.15)	5.2
Wong et al,[47] 2013	-17.0 (17.7)	77	-7.0 (9.5)	77	-10.00 (-14.49 to -5.51)	5.8
Armstrong et al,[38] 2016	-26.6 (34.4)	23	-10.2 (35.8)	22	-16.40 (-36.93 to 4.13)	1.9
Asghari et al,[29] 2018	-4.3 (7.5)	30	-7.2 (10.3)	30	-11.50 (-16.06 to -6.94)	5.8
Axley et al,[39] 2018	-12.0 (8.1)	8	-6.0 (10.4)	14	-6.00 (-13.82 to 1.82)	4.7
Selezneva et al,[33] 2014	-4.0 (22.0)	58	-21.3 (11.4)	116	25.30 (19.27 to 31.33)	5.3
Katsagoni et al,[42] 2018 (D)	-20.0 (26.1)	21	-2.6 (10.5)	11	-17.40 (-30.17 to -4.63)	3.3
Lim et al,[27] 2018	-35.3 (39.3)	43	-9.6 (23.2)	43	-25.70 (-39.34 to -12.06)	3.1
St George et al,[46] 2009 (M)	-19.1 (29.7)	73	-7.3 (18.5)	17	-11.80 (-22.92 to -0.68)	3.7
Katsagoni et al,[42] 2018 (D+E)	-22.2 (9.7)	21	-2.6 (10.5)	10	-19.60 (-27.32 to -11.88)	4.8
Zelber-Sagi et al,[48] 2006	-30.6 (59.0)	21	-12.7 (26.6)	23	-17.90 (-45.38 to 9.58)	1.2
Harrison et al,[41] 2009	-55.0 (58.8)	23	-45.0 (32.4)	18	-10.00 (-38.3 to 18.31)	1.1
Cheng et al,[31] 2017 (D+E)	-1.5 (4.0)	29	1.5 (3.3)	15	-3.00 (-5.22 to -0.78)	6.3
Dong et al,[32] 2016	-4.7 (8.1)	130	-1.6 (8.5)	130	-3.10 (-5.12 to -1.08)	6.3
St George et al,[46] 2009 (L)	-14.9 (35.6)	36	-7.3 (18.5)	17	-7.60 (-22.18 to 6.98)	2.9
Cheng et al,[31] 2017 (D)	-4.4 (4.0)	28	1.5 (3.3)	14	-5.90 (-8.18 to -3.62)	6.3
Lee et al,[44] 2012	-53.0 (13.3)	8	-27.5 (13.3)	10	-25.50 (-37.86 to -13.14)	3.4
Eckard et al,[40] 2013 (MF)	-19.8 (54.9)	9	-4.3 (38.7)	5	-15.50 (-64.87 to 33.87)	0.4
Khoo et al,[43] 2017	-34.0 (27.0)	12	-42.0 (46.0)	12	8.00 (-22.18 to 38.18)	1.0
Eckard et al,[40] 2013 (LF)	-27.5 (27.9)	12	-4.3 (38.7)	6	-23.20 (-57.96 to 11.56)	0.8
Total (95% CI)		1496		1062	-9.81 (-13.12 to -6.50)	100.0

Heterogeneity $\tau^2 = 44.17$; $\chi^2_{24} = 924.44$; $P < .001$; $I^2 = 97\%$

Test for overall effect: $z = 5.81$; $P < .001$

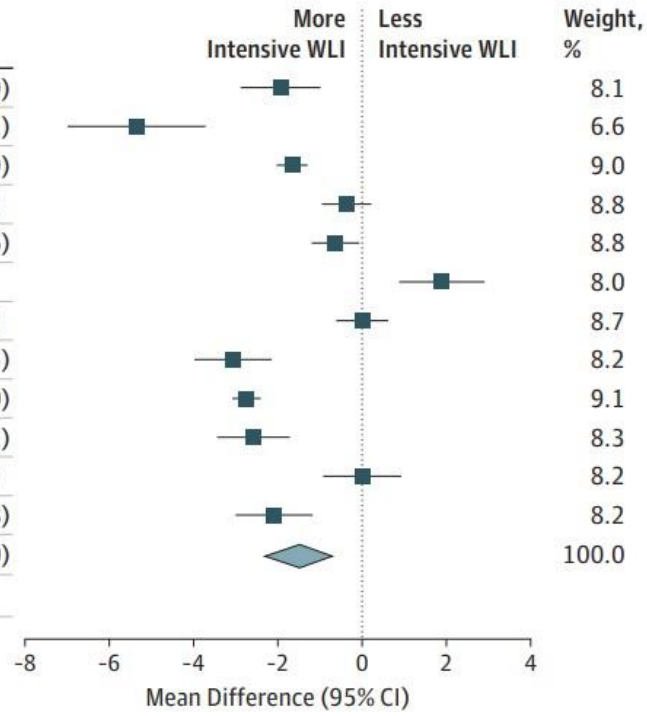


Koutoukidis et al, JAMA Internal Medicine, 2019.

Weight Loss Improves Hepatic Steatosis

Figure 3. Association Between Weight Loss Intervention (WLI) and Liver Steatosis

Source	More Intensive WLI Mean (SD)	More Intensive WLI Total	Less Intensive WLI Mean (SD)	Less Intensive WLI Total	Standardized Mean Difference in Steatosis (95% CI)	Weight, %
Promrat et al,[45] 2010	-1.1 (0.4)	18	-0.3 (0.4)	10	-1.94 (-2.89 to -0.99)	8.1
Abenavoli et al,[36] 2017	-1.0 (0.2)	20	0.1 (0.2)	10	-5.35 (-6.99 to -3.71)	6.6
Wong et al,[47] 2013	-6.8 (3.1)	77	-2.1 (2.5)	77	-1.66 (-2.03 to -1.29)	9.0
Armstrong et al,[38] 2016	-0.7 (0.8)	23	-0.4 (0.8)	22	-0.37 (-0.96 to 0.22)	8.8
Asghari et al,[29] 2018	-0.1 (0.2)	24	0 (0.1)	26	-0.63 (-1.20 to -0.06)	8.8
Zelber-Sagi et al,[48] 2006	0.1 (0.3)	11	-0.6 (0.4)	12	1.90 (0.88 to 2.91)	8.0
Harrison et al,[41] 2009	0 (0.2)	23	0 (0.2)	18	0.00 (-0.62 to 0.62)	8.7
Cheng et al,[31] 2017 (D+E)	-7.6 (3.6)	29	2.8 (2.7)	15	-3.07 (-3.99 to -2.15)	8.2
Dong et al,[32] 2016	-1.1 (0.4)	130	0 (0.4)	130	-2.74 (-3.08 to -2.40)	9.1
Cheng et al,[31] 2017 (D)	-5.4 (3.3)	28	2.8 (2.7)	14	-2.58 (-3.45 to -1.72)	8.3
Lee et al,[44] 2012	-1.0 (0.3)	8	-1.0 (0.3)	10	0.00 (-0.93 to 0.93)	8.2
Ye et al,[28] 2017	-7.8 (3.1)	14	-1.9 (2.4)	16	-2.09 (-3.00 to -1.18)	8.2
Total (95% CI)		405		360	-1.48 (-2.27 to -0.70)	100.0
Heterogeneity $\tau^2 = 1.74$; $\chi^2_{11} = 190.62$; $P < .001$; $I^2 = 94\%$						
Test for overall effect: $z = 3.70$; $P < .001$						

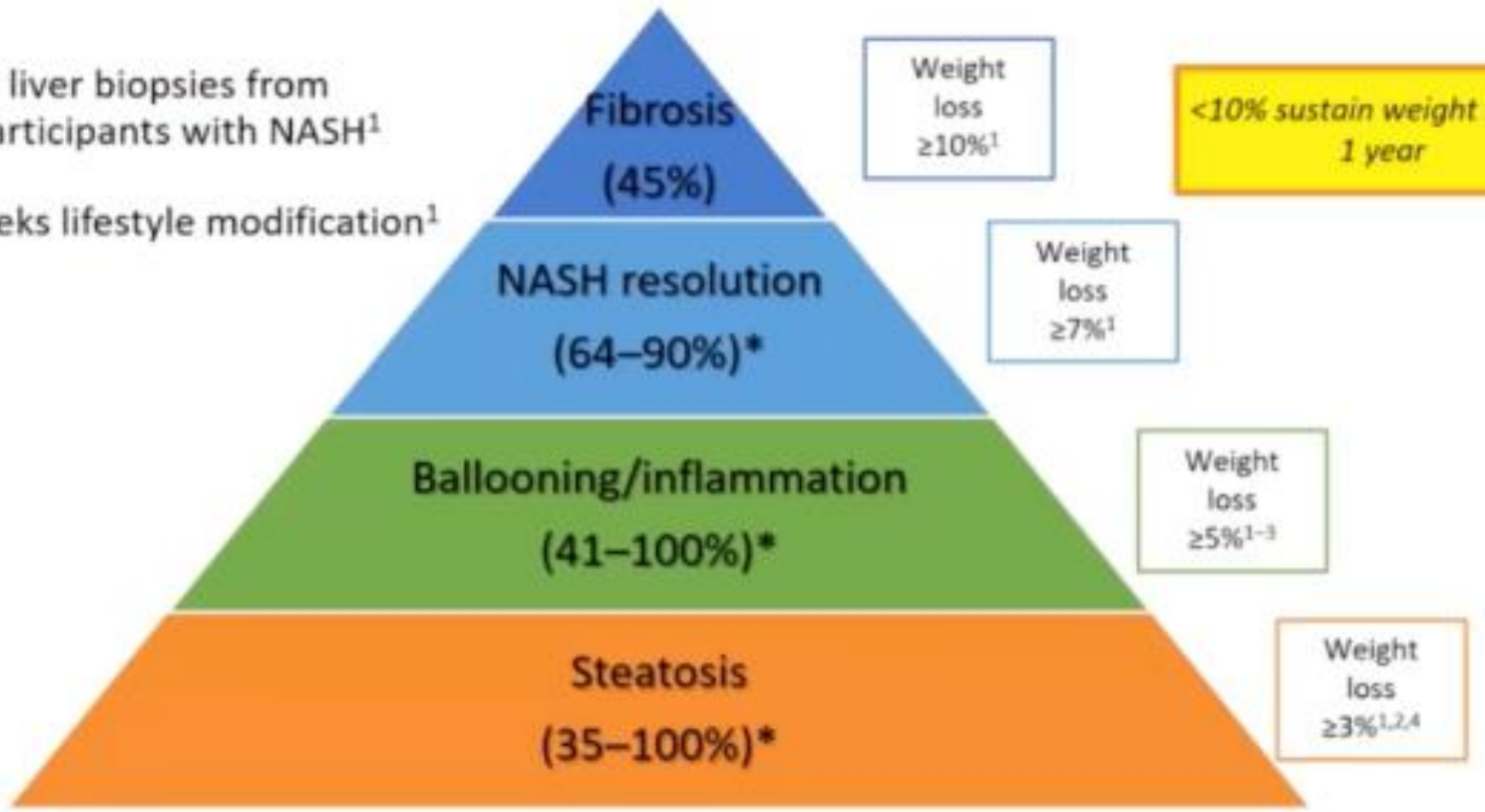


Standardized mean difference was assessed by histologic examination, magnetic resonance imaging, or ultrasonography. D indicates diet group; D+E, diet and exercise group.

Koutoukidis et al, JAMA Internal Medicine, 2019.

Weight Loss and Histologic Improvement

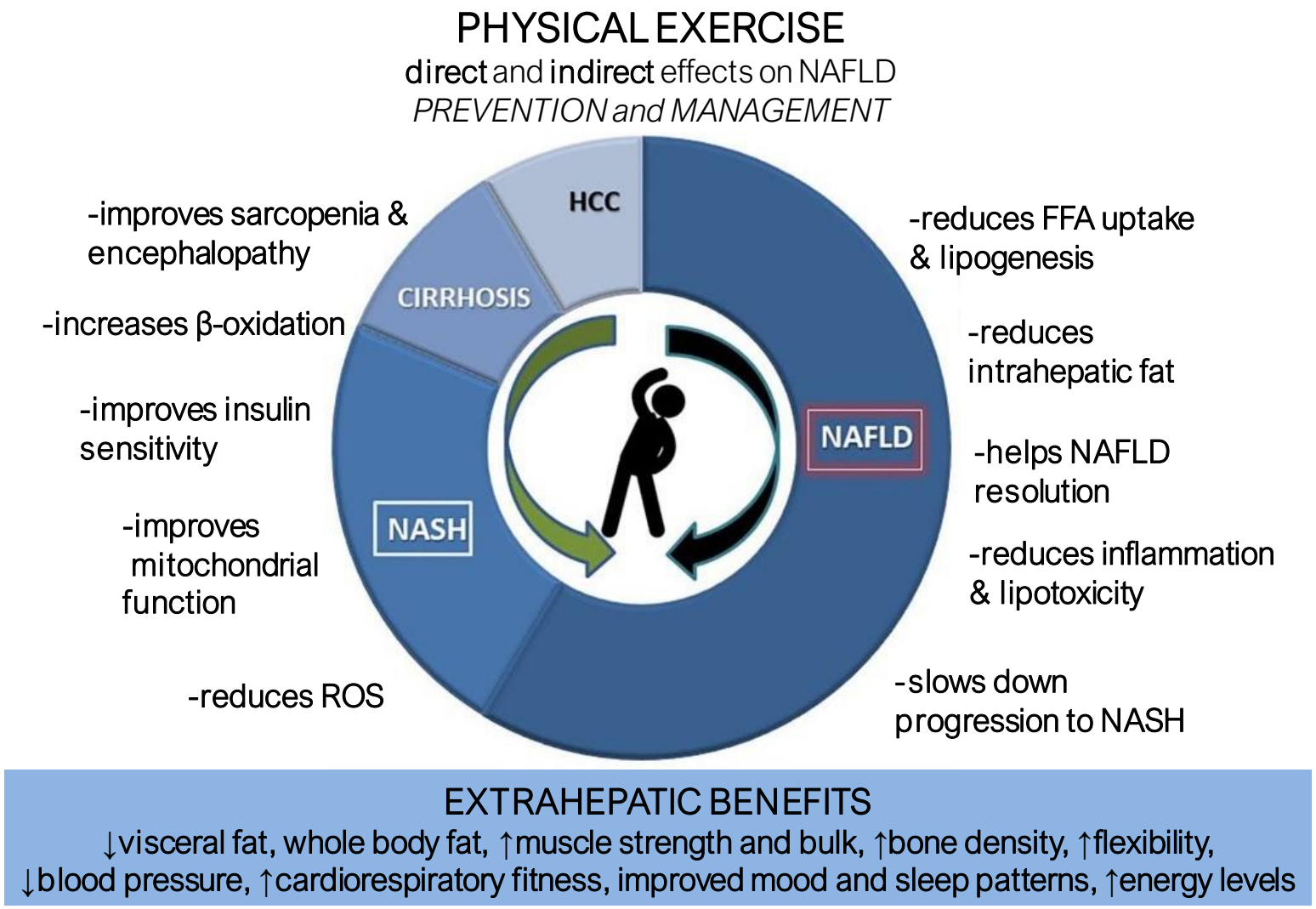
- Paired liver biopsies from 261 participants with NASH[1]
- 52 weeks lifestyle modification[1]



Greater Weight Loss (>7%) = BETTER Histologic Improvement

Vilar-Gomez, Gastroenterology, 2015.

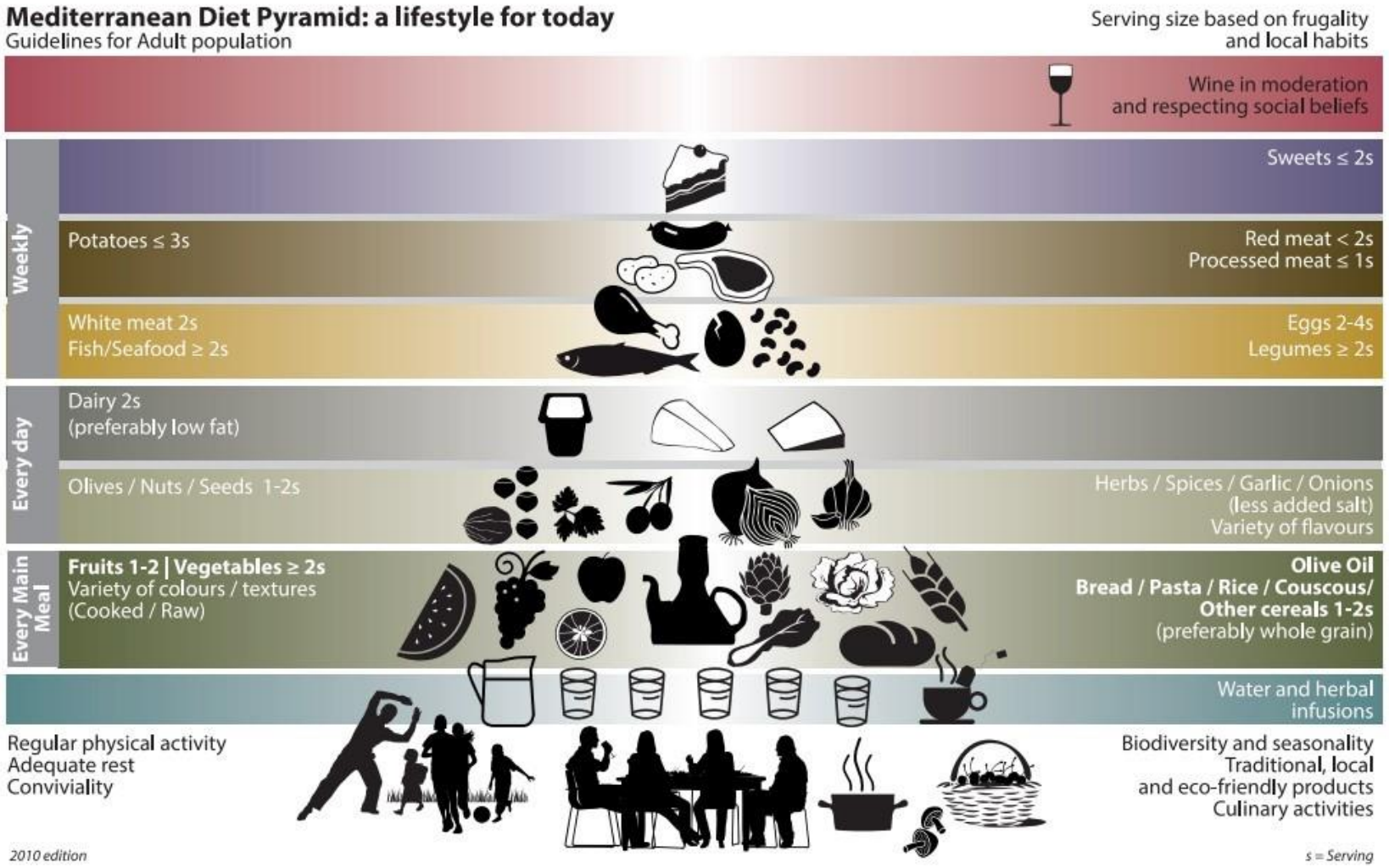
Exercise in NAFLD



- Exercise alone may prevent/reduce hepatic steatosis irrespective of weight loss
- Both aerobic exercise and resistance training reduce liver fat; tailor to patient preferences

Berkovic et al, Frontiers in nutrition, 2021.

Dietary Interventions in NAFLD



- Increased fat: monounsaturated fat >>> saturated fat
- Reduced carbohydrate: 40% of caloric intake
- Unprocessed/minimally processed foods

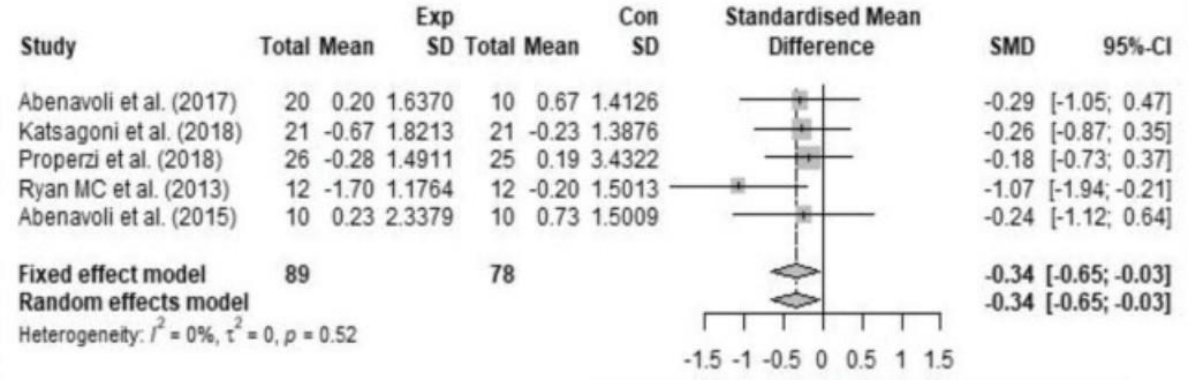
Fundacion Dieta Mediterranea, 2010.

Effects of Mediterranean Diet

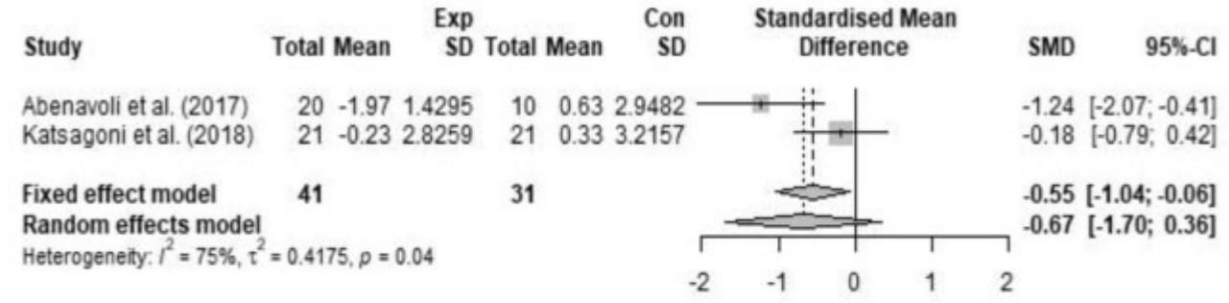
- Improvement in markers of insulin resistance

- Reduction in hepatic steatosis and liver stiffness

HOMA-IR



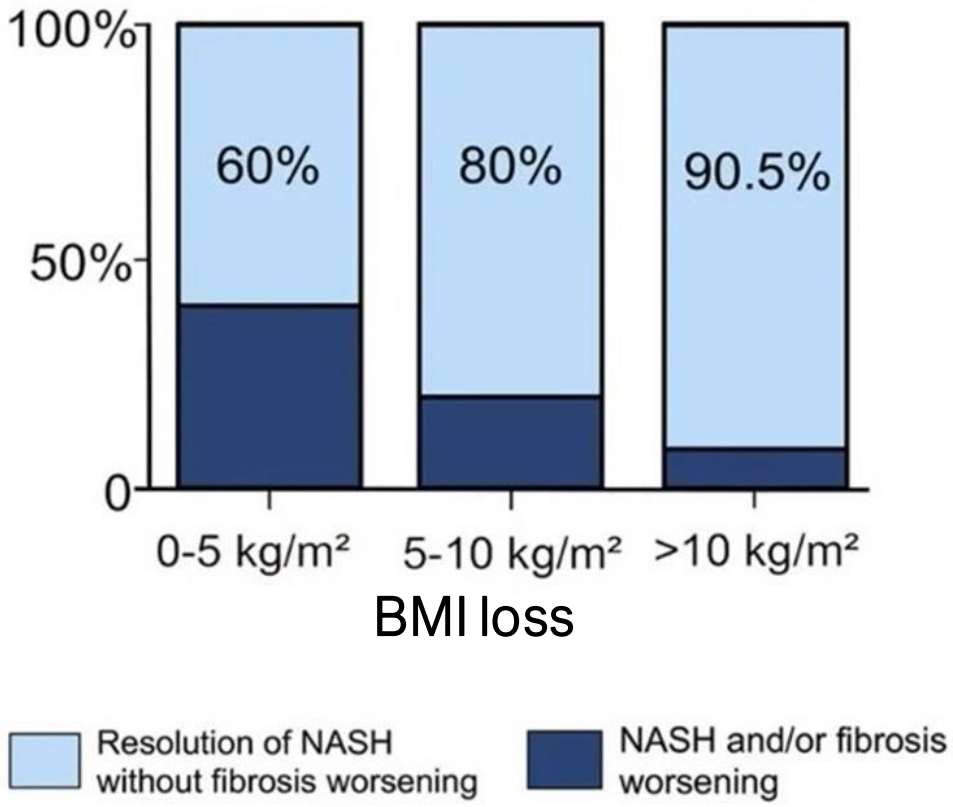
Liver stiffness



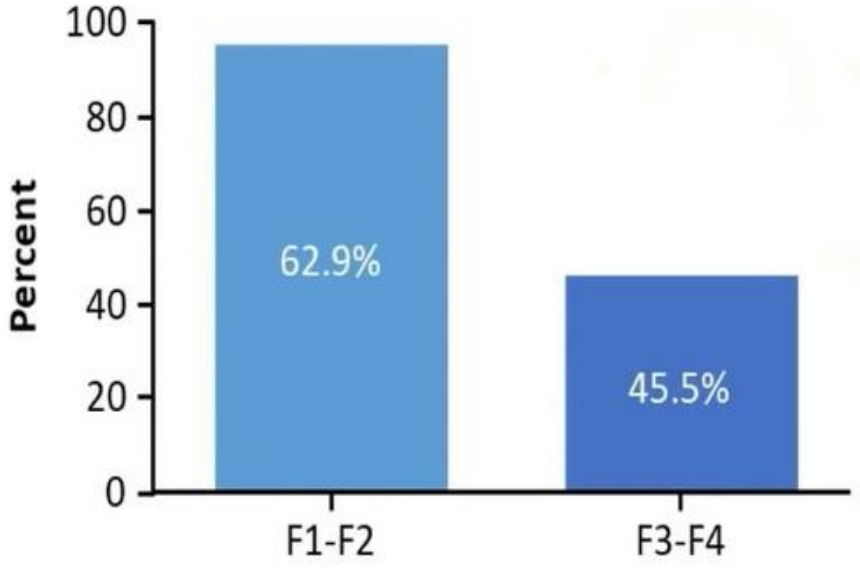
Kawaguchi et al, Seminars in liver disease, 2021.

Bariatric Surgery

Resolution of NASH according to weight loss

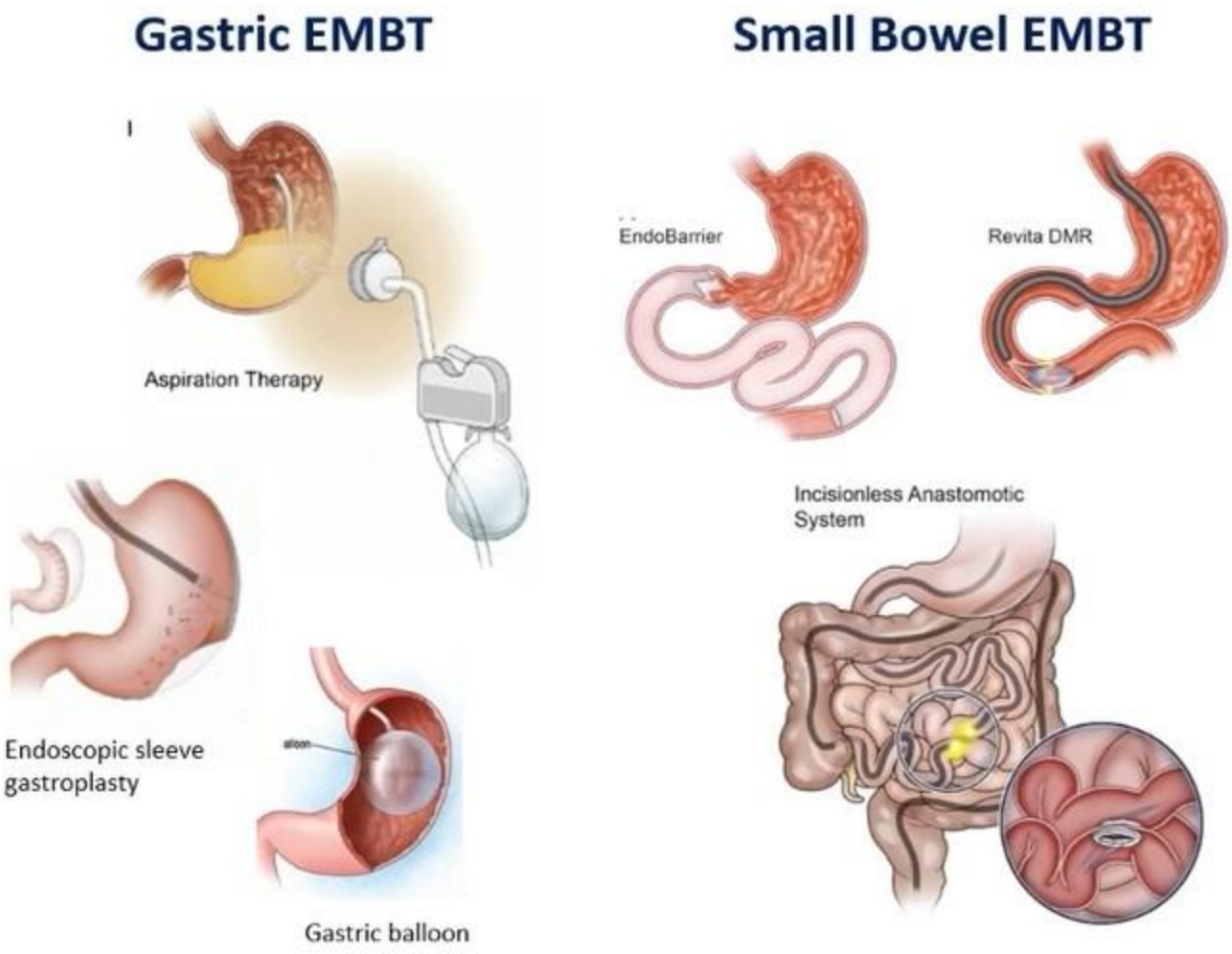


Fibrosis resolution at 5 years after surgery



Lassailly et al, Gastroenterology, 2020.

Endoscopic & Metabolic Bariatric Therapies



- Gastric EMBT: weight loss dependent improvements in biochemical and histologic NAFLD/NASH
- Small bowel EMBT: improve insulin resistance and weight loss dependent and independent pathways
- Large randomized trials are needed to define safety and efficacy

Abu-Dayyeh et al, Journal of Hepatology, 2021.

What happened to J.P.?

- Switched from Metformin to GLP1-RA with assistance from endocrinology
- In 6 months, lost close to 20 pounds (10% of body weight)
- Improved dysglycemia HbA1c 7.2 → 6.7
- Normalization of liver chemistries: AST 25, ALT 30

THANK YOU!