
بسم الله الرحمن الرحيم

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- Panel Members:

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  Dr. Farahvash

  Dr. Meraat

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  Dr. Boghratian

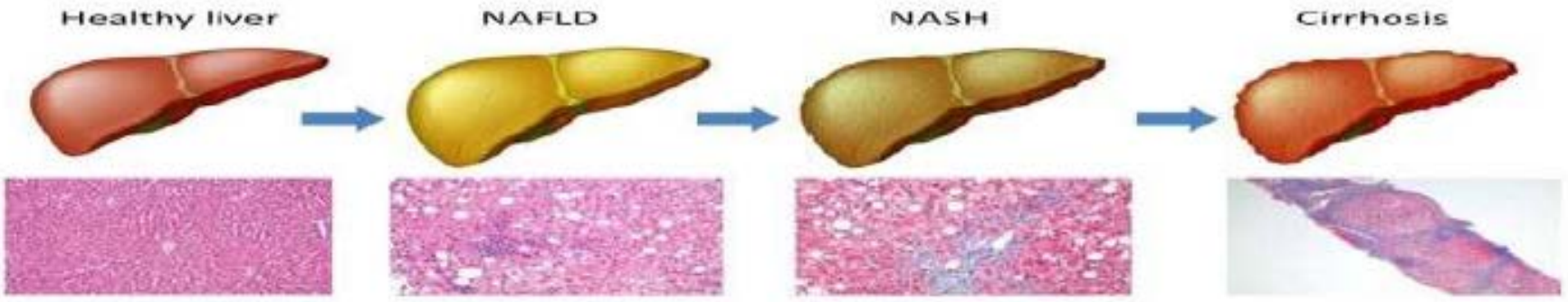
  Dr. Mahmoodi

  Dr. Taher

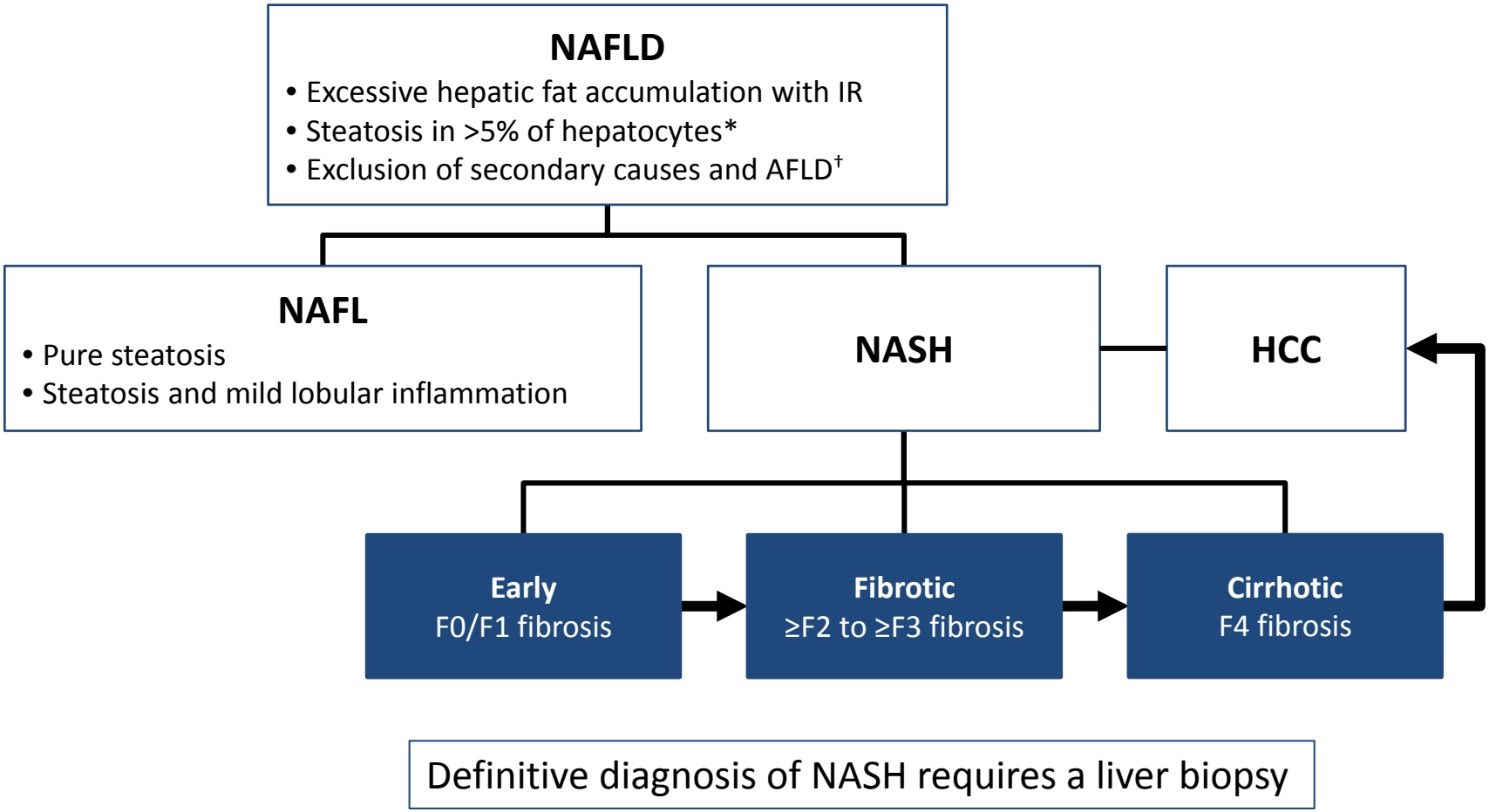
  Dr. Kalantari

  Dr. Sharifian

NAFLD-Management & Challenges involved



Definitions of NAFLD, NAFL and NASH

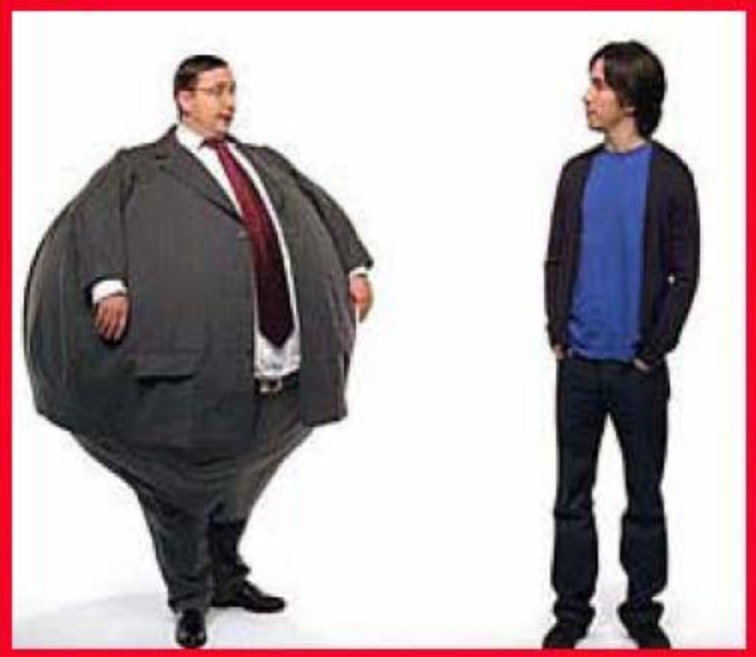


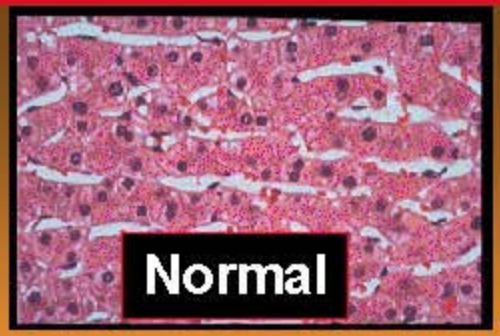
*According to histological analysis or proton density fat fraction or >5.6% by proton MRS or quantitative fat/water-selective MRI;
†Daily alcohol consumption of ≥30 g for men and ≥20 g for women
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

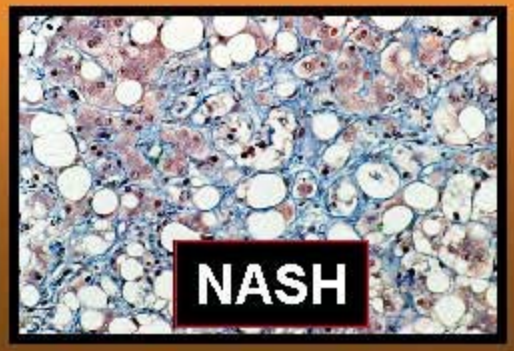
The Spectrum of NAFLD

Risk Factors

- Visceral Obesity
- Insulin Resistance/DM
- Dyslipidemia
- Metabolic Syndrome

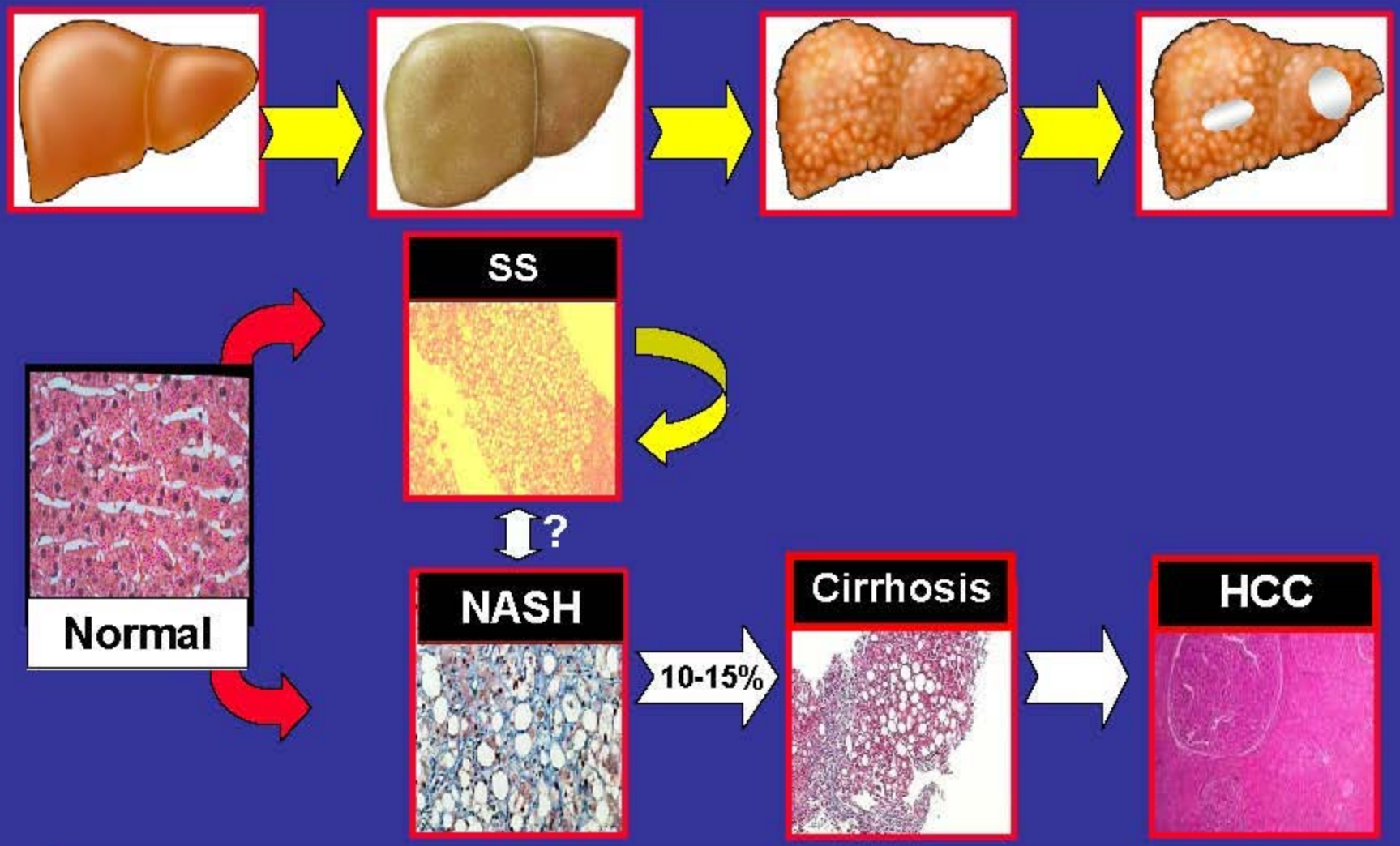






NAFLD SPECTRUM

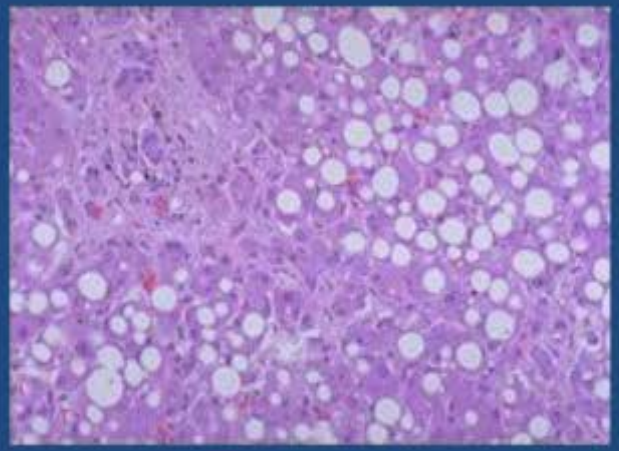
Differential Progression of NAFLD

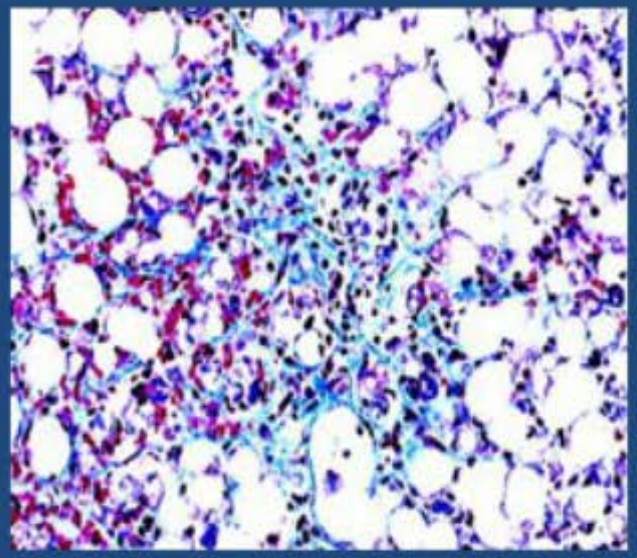


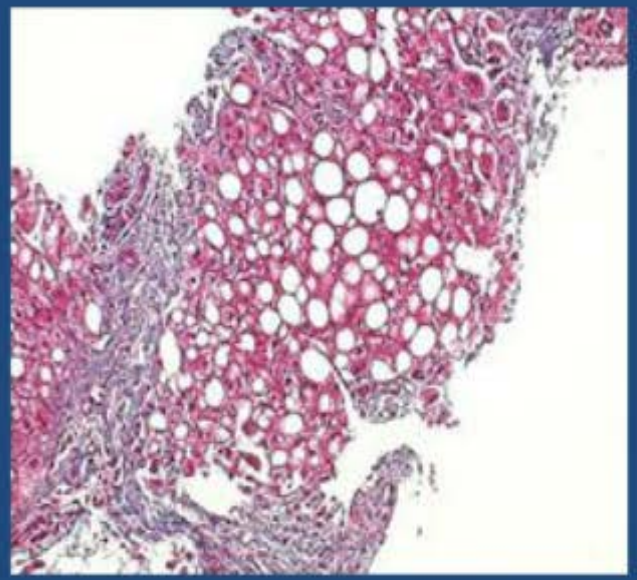
Ludwig 1980 , Diehl 1988, Lee 1989, Powell 1990, Bacon 1994, Matteoni 1999, Angulo 1999, Caldwell 1999, Ponawala 2000,, Bugianesi 2002, Marchesini 2003, Younossi 2004, Sanyal 2004, Ong 2005, Adams 2005, Ong 2006, Rafiq 2008, Soderberg 2010 , Stepanova 2010

NASH

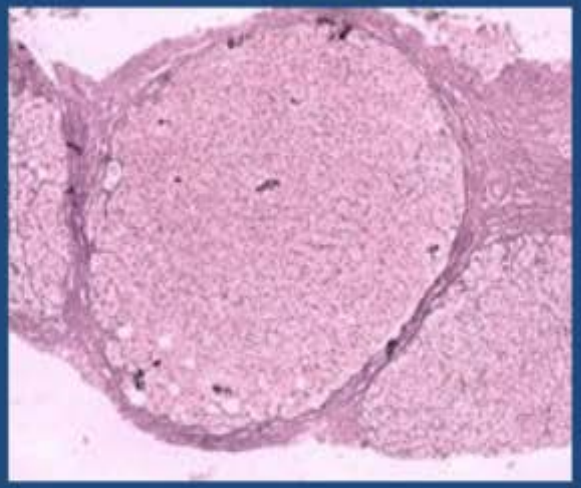
Steatosis



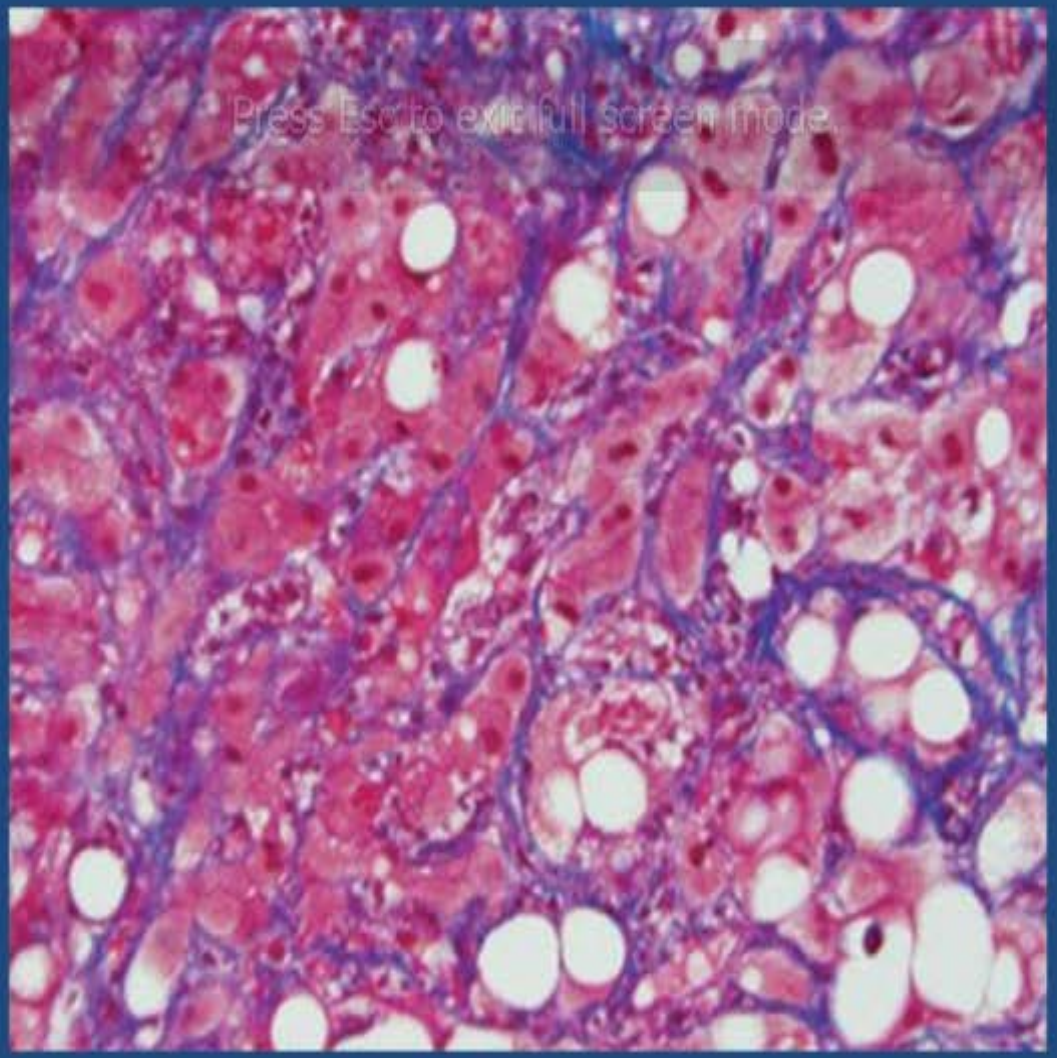




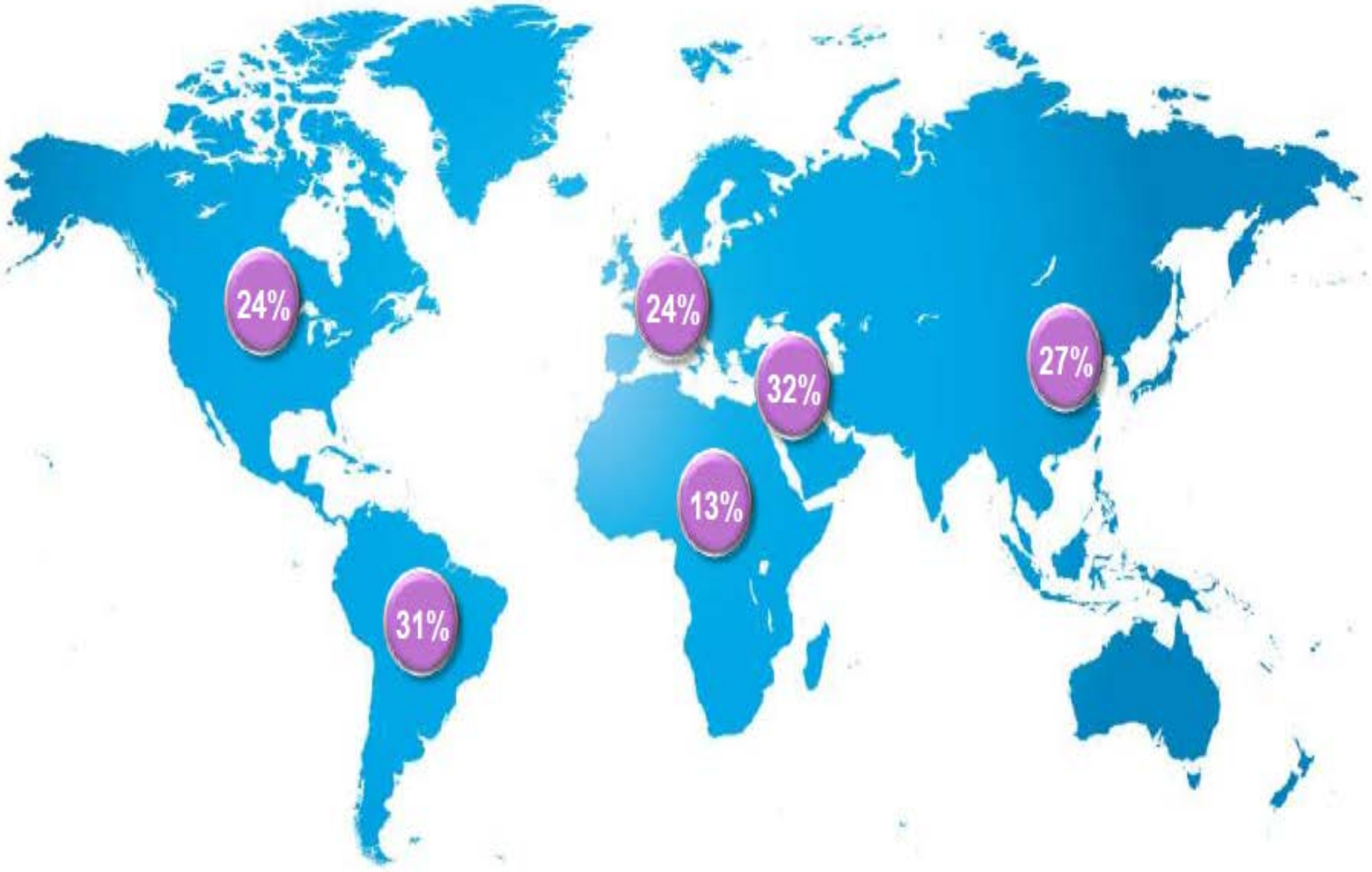
Cirrhosis



NASH- Peri-sinusiodal fibrosis



Estimated Global Prevalence of NAFLD: 25%



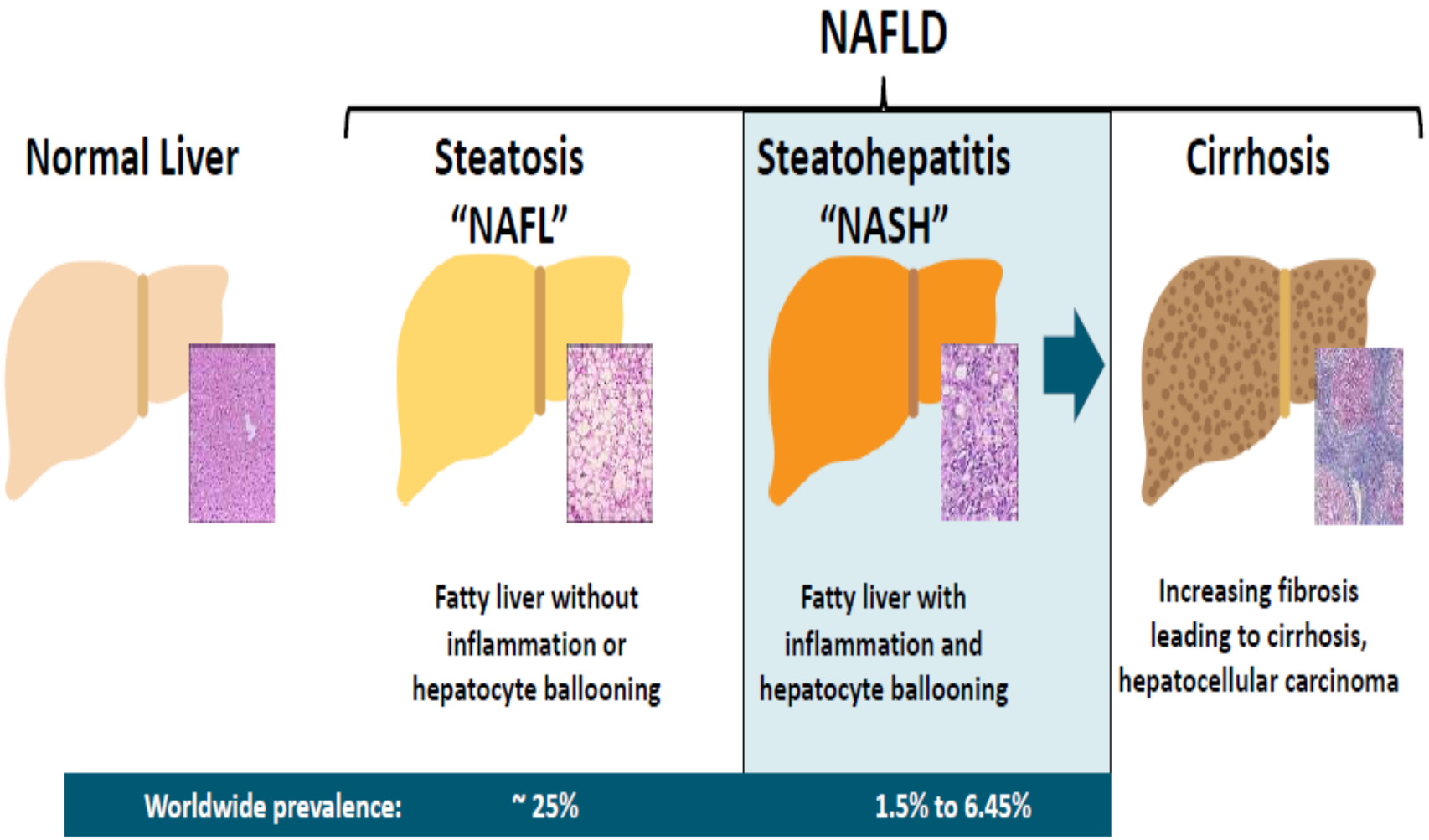
Younossi. Hepatology. 2016;64:73.

- The prevalence of NAFLD in Iran:

  - **2.9% in a population-based study (2010)[1]**
  - **21.5% in a population based study in Shiraz. (2013)[2]**
  - **15.3% in a population based study in Fars province.(2013)[3]**
  - **33.9% in a systematic review of 23 studies in Iran. (2016)[4]**

1) Sohrabpour AA and et al. MEJDD 2010;2(1):14-19
2) Bagheri Lankarani K and et al. Hepat Mon 2013; 13(5):e 9248
3) Eshraghian A and et al. Archives of Iranian Medicine 2013; 16(10): 584-9.
4) Moghadasifar I. and et al. Int J Org Transplant Med 2016; 7(3): 482-94.

The NAFLD Continuum



Chalasani. Hepatology. 2018;67:328.

Which diseases can cause fatty liver?

Spectrum of NAFLD and concurrent disease

Sub-classification of NAFLD*	Most common concurrent diseases
NAFL • Pure steatosis • Steatosis and mild lobular inflammation	**AFLD†** **Drug-induced fatty liver disease†** **HCV-associated fatty liver disease (GT 3)†** **Others†** • Haemochromatosis • Autoimmune hepatitis • Coeliac disease • Wilson disease • A/hypo-betalipoproteinaemia lipoatrophy • Hypopituitarism, hypothyroidism • Starvation, parenteral nutrition • Inborn errors of metabolism – Wolman disease (lysosomal acid lipase deficiency)
NASH • Early NASH (no or mild fibrosis) • Fibrotic NASH (significant/advanced fibrosis) • NASH cirrhosis	
HCC‡	

*Also called primary NAFLD and associated with metabolic risk factors/components of MetS: 1. Waist circumference ≥94/≥80 cm for Europid men/women; 2. Arterial pressure ≥130/85 mmHg or treated for hypertension; 3. Fasting glucose ≥100 mg/dl (5.6 mmol/L) or treated for T2DM; 4. Serum triacylglycerols >150 mg/dl (>1.7 mmol/L); 5. HDL cholesterol <40/50 mg/dl for men/women (<1.0/<1.3 mmol/L); †Also called secondary NAFLD. Note that primary and secondary NAFLD may coexist in individual patients. Also NAFLD and AFLD may coexist in subjects with metabolic risk factors and drinking habits above safe limits; ‡Can occur in the absence of cirrhosis and histological evidence of NASH, but with metabolic risk factors suggestive of ‘‘burned-out” NASH

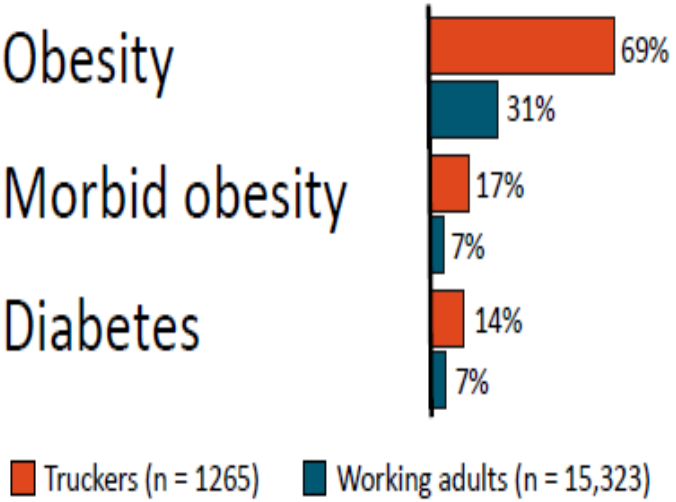
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Who is at risk for NAFLD?

Who Is at Risk for NAFLD?

Risk Factor for NAFLD[1]
Obesity
Dyslipidemia
Type 2 diabetes
Metabolic syndrome
Polycystic ovary syndrome

CDC: Self-Reported Prevalence of NAFLD Risk Factors Among Long-Haul Truckers[2]



1. Chalasani. Hepatology. 2018;67:328. 2. Sieber. Am J Ind Med. 2014;57:615.

Who is at the Risk of NASH & Advanced Fibrosis?

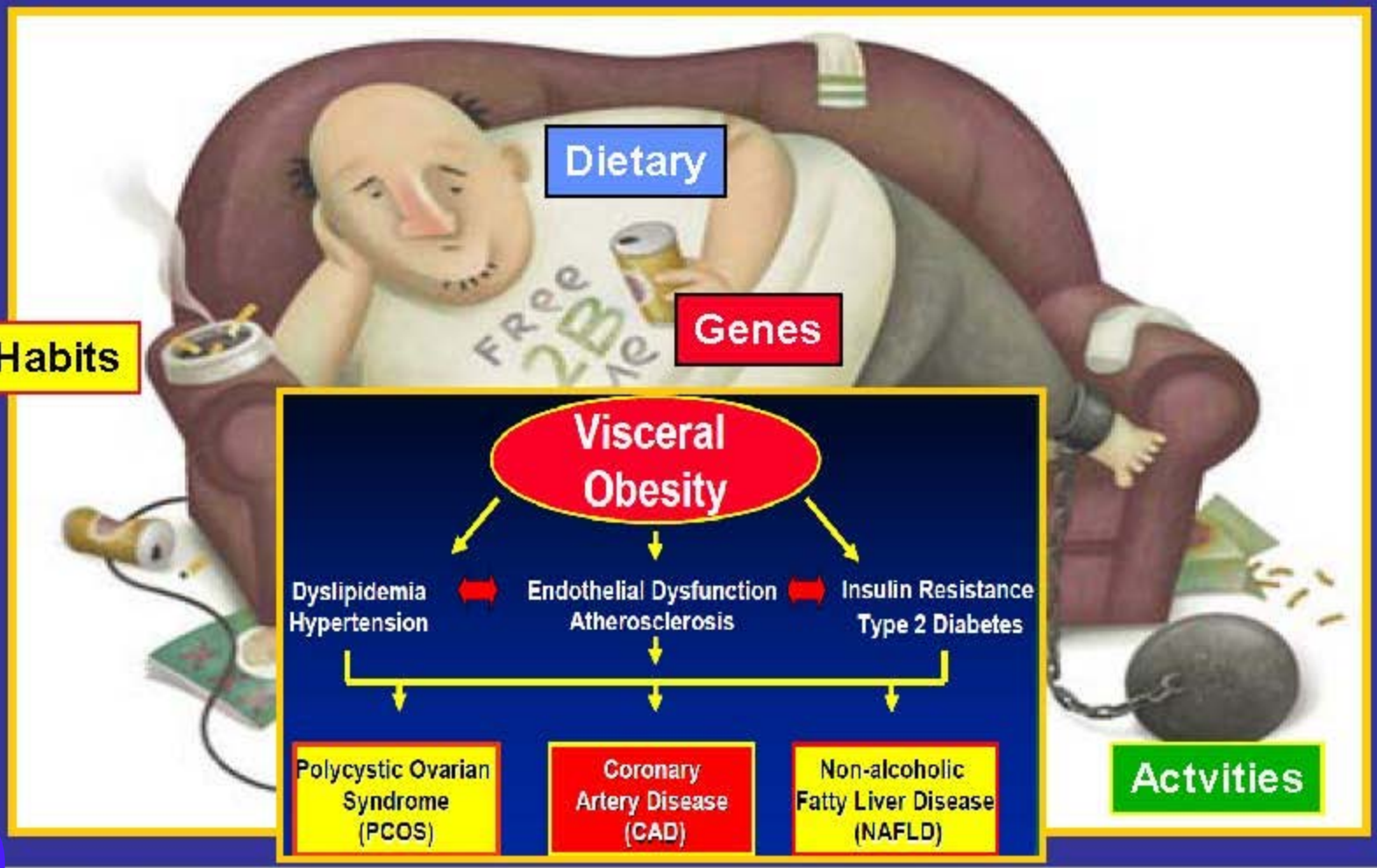
Who Is at Risk for NASH and Advanced Fibrosis?

Risk Factor for NAFLD[1]	AASLD Recommendation[1]	EASL-EASD-EASO Recommendation[2]
Type 2 diabetes	In type 2 diabetes, **suspect NAFLD and NASH** and determine patient's risk of advanced fibrosis	NAFLD **screening recommended** in persons at high CVD risk, including type 2 diabetes or metabolic syndrome
Obesity		
Dyslipidemia	Increasing number of metabolic diseases = **increasing risk of progressive liver disease**	
Metabolic syndrome		
Polycystic ovary syndrome		

1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388.

Liver Disease of the Modern Times!

NAFLD is Associated With Increasing Rate of Visceral Obesity and Metabolic Syndrome



Are Liver Enzymes adequate in Assessing NASH/NAFLD?

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Liver Enzymes: Inadequate in Assessing NAFLD/NASH

- ALT can be normal in > 50% of individuals with NASH, 80% of individuals with NAFLD[1,2]
- ALT can be elevated in > 50% of individuals with NAFLD but without NASH
- In NAFLD, ALT is neither indicative nor predictive of NASH or fibrosis stage[3]:
  - Normal ALT does not preclude NASH/progressive disease
  - Elevated ALT cannot predict NASH or fibrosis
  - ALT and AST not sensitive for NAFLD/NASH

1. Browning. Hepatology. 2004;40:1387. 2. Dyson. Frontline Gastroenterol. 2014;5:211. 3. Mofrad. Hepatology. 2003;37:1286.

What About CT/US for Distinguishing NAFLD/NASH/Fibrosis?

What About CT/US for Distinguishing NAFLD/NASH/Fibrosis?

Ultrasound or CT: Inadequate in Assessing NAFLD

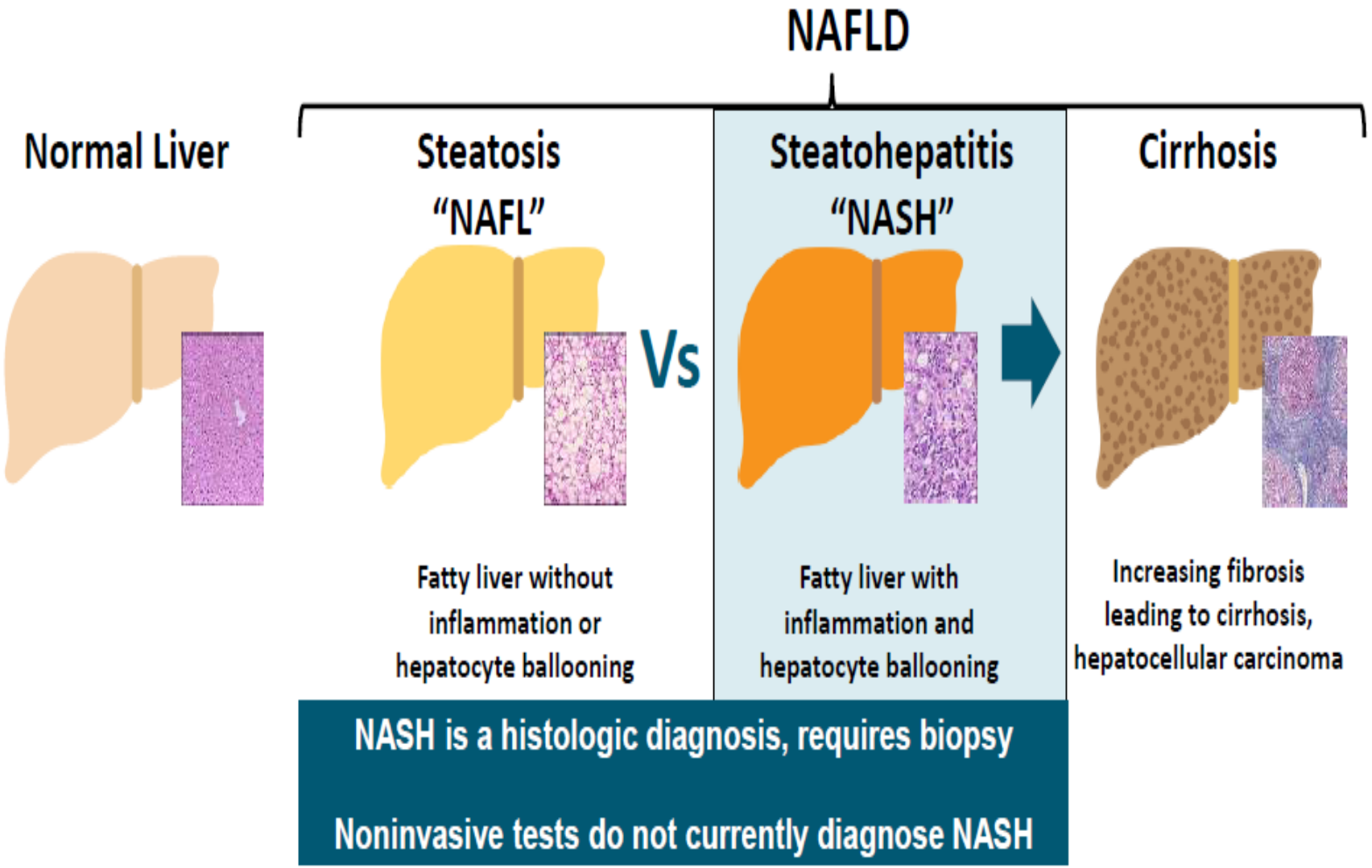
- US or CT **cannot identify most NAFLD stages/severity**
  - Cannot distinguish steatosis vs NASH or NASH fibrosis/early cirrhosis
- US or CT may identify **advanced cirrhosis**
  - Portal hypertensive changes such as varices, ascites, splenomegaly

Method for Identifying Steatosis	Sensitivity, %	Specificity, %	Comments
Ultrasound[1]			Inexpensive and accessible; cannot distinguish fibrosis/steatosis
▪ Any degree	61	100	
▪ ≥ 20%	100	90	
CT without contrast[2]			Also useful in morbidly obese; affected by iron, fibrosis; reduced accuracy with minimal steatosis
▪ > 30%	79	97	

1. Dasarathy. J Hepatol. 2009;51:1061. 3. Rogier. Liver Transpl. 2015;21:690.

What is the role liver Bx in NAFLD?

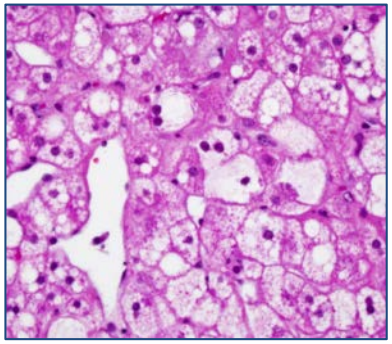
Whom to Biopsy?



Chalasani. Hepatology. 2018;67:328.

Liver biopsy

- Liver biopsy is essential for the diagnosis of NASH
  - Clinical, biochemical or imaging measures cannot distinguish NASH from steatosis
- NAFL encompasses
  - Steatosis alone plus **ONE** of lobular or portal inflammation **OR** ballooning
- NASH requires
  - Steatosis **AND**
  - Lobular or portal inflammation **AND**
  - Ballooning
- NAS scoring indicates disease severity*



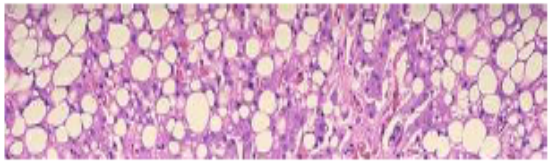
Recommendations		
	Grade of evidence	Grade of recommendation
NASH has to be diagnosed by a liver biopsy showing **steatosis, hepatocyte ballooning and lobular inflammation**	A	1

*Should not be used for initial diagnosis

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Liver Biopsy: The Imperfect Gold Standard

Isolated Steatosis

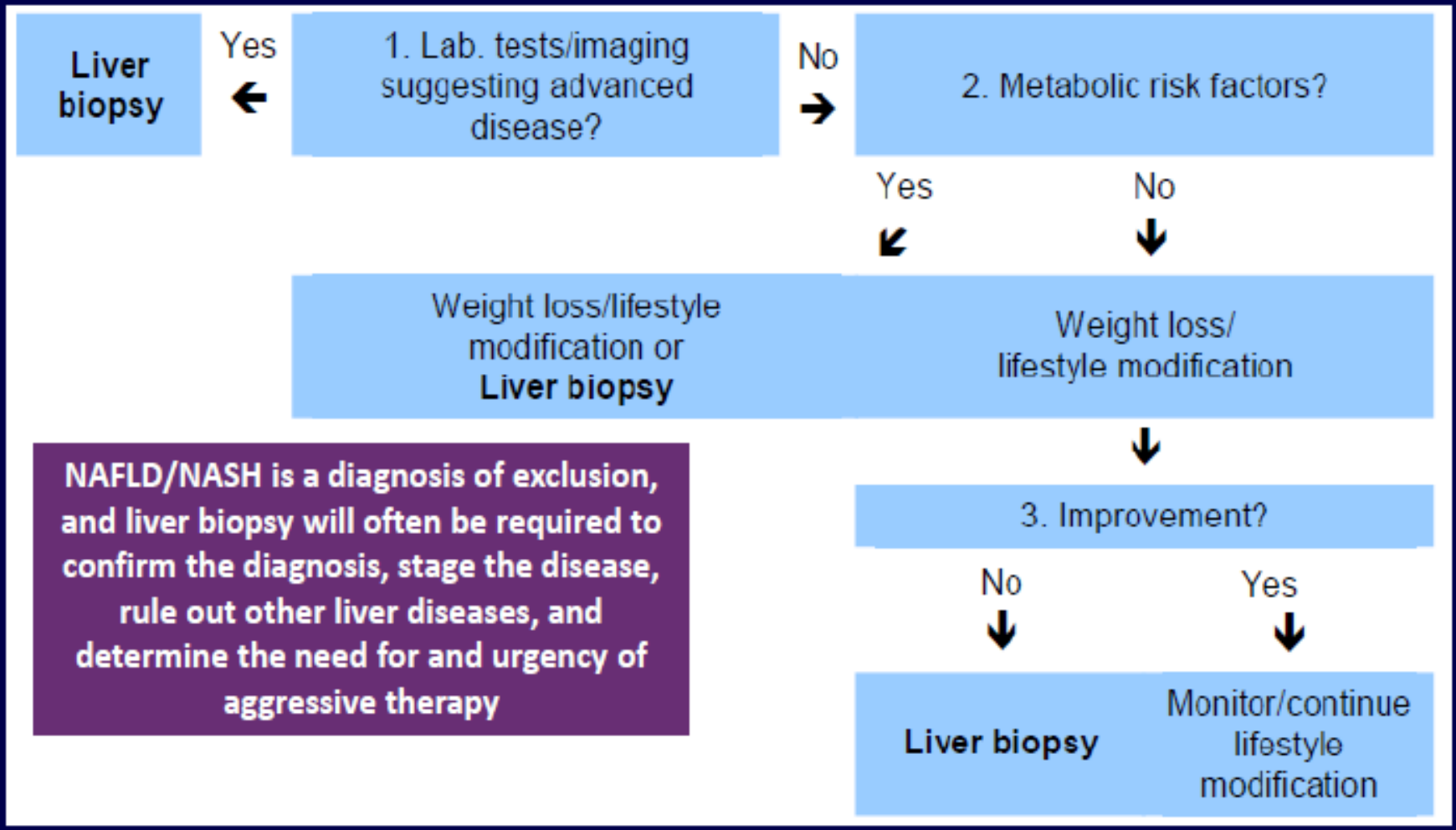


Steatohepatitis/NASH

- **Benefits**
  - Establishes diagnosis of NASH
  - Assesses early fibrosis
  - Determines prognosis
  - Rules out other processes: alpha-1 antitrypsin, iron overload, autoimmune component
- **Limitations**
  - Risk of bleeding, pain
  - Sampling variability (especially with IR biopsies if they are small)
  - Long interval between serial biopsies to monitor disease progression
  - Cost

Rockey. Hepatology. 2009;49:1017. Kleiner. Hepatology 2005;41:1313. Bedossa. Hepatology. 2012;56:1751.

Algorithm for liver biopsy in patients with suspected NAFLD after exclusion of other liver diseases



Due to Limitations of Imaging and liver Bx, What is your strategy to identify NASH/Fibrosis?

Identifying NASH and ≥ F2 Fibrosis: Newer Strategies

Because of limitations of liver enzymes, US, CT, and liver biopsy, ***better strategies and diagnostic tools*** *are needed*

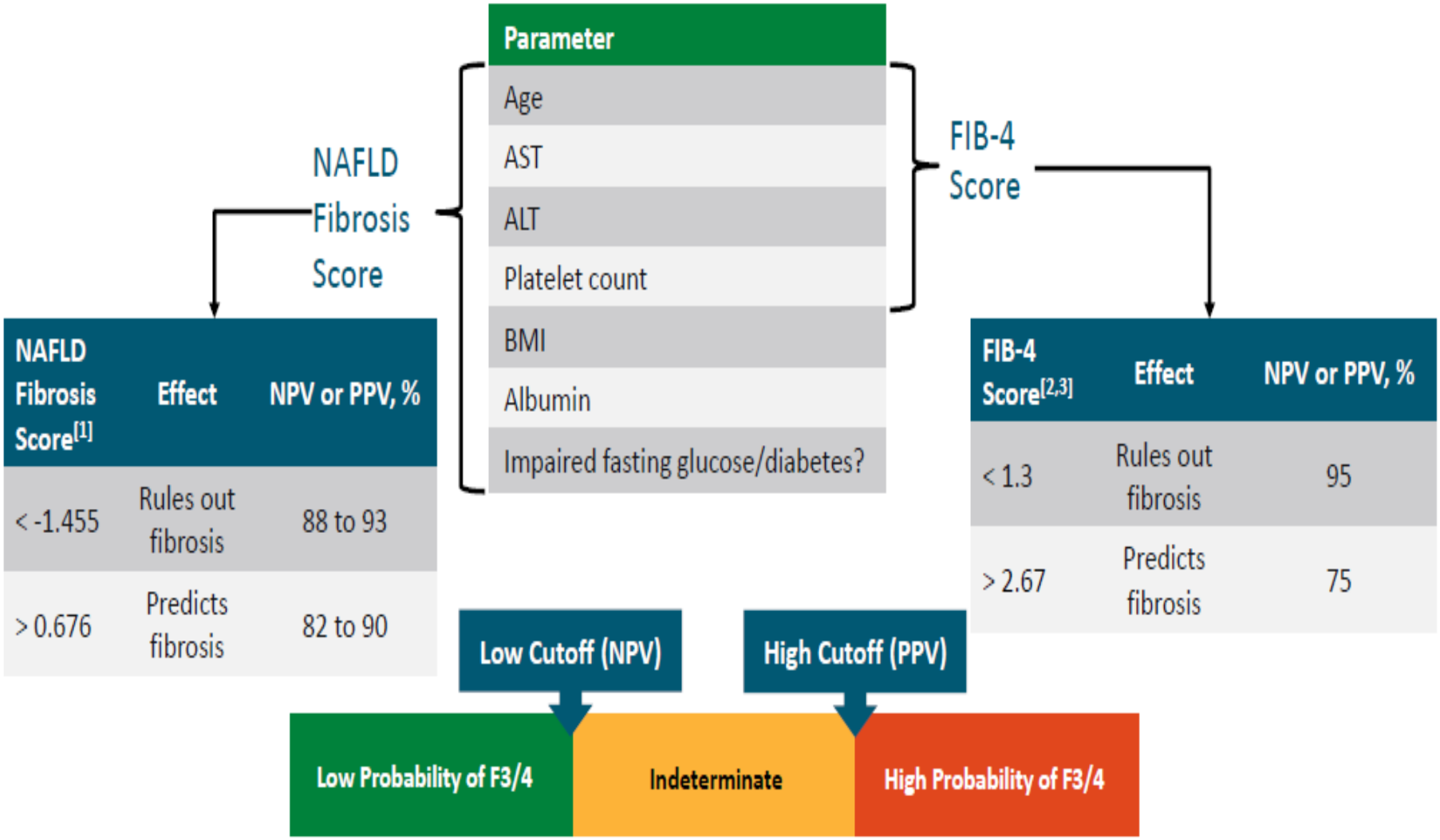
Noninvasive Staging Predictors of Advanced Fibrosis in NAFLD: Many Serum-Based Scores

Serum-Based Score	Components
APRI (AST to platelet ratio index)[1]	▪ AST, platelet count
FIB-4[1]	▪ Age, ALT, AST, platelet count
NAFLD fibrosis score[2]	▪ Age, ALT, AST, platelet count, BMI, albumin, impaired fasting glucose/diabetes
BARD[3]	▪ ALT, AST (AST/ALT ratio), BMI, diabetes

- Good negative predictive value for ruling out fibrosis
- Calculators freely available on the internet
- Various complex commercial tests also available

1. University of Washington. Clinical Calculators. 2. Dowman. Aliment Pharmacol. Ther. 2011;33:525. 3. Cichoż-Lach. 2012;18:CR735.

NAFLD Fibrosis Score and FIB-4



1. Angulo. Hepatology. 2007;45:846. 2. Sterling RK. Hepatology. 2006;43:1317. 3. McPherson. Gut. 2010;59:1265.

Noninvasive Staging of NASH: Imaging

Imaging	Comments
Vibration-controlled transient elastography (VCTE) -- *FibroScan*	▪ Can be point of care ▪ Can rule in/out advanced fibrosis
2D shear wave elastography	▪ May require radiology referral but can be point of care with minimal training
MR elastography/MR spectroscopy/ liver multiscan	▪ Requires radiology referral ▪ Most accurate of the imaging modalities

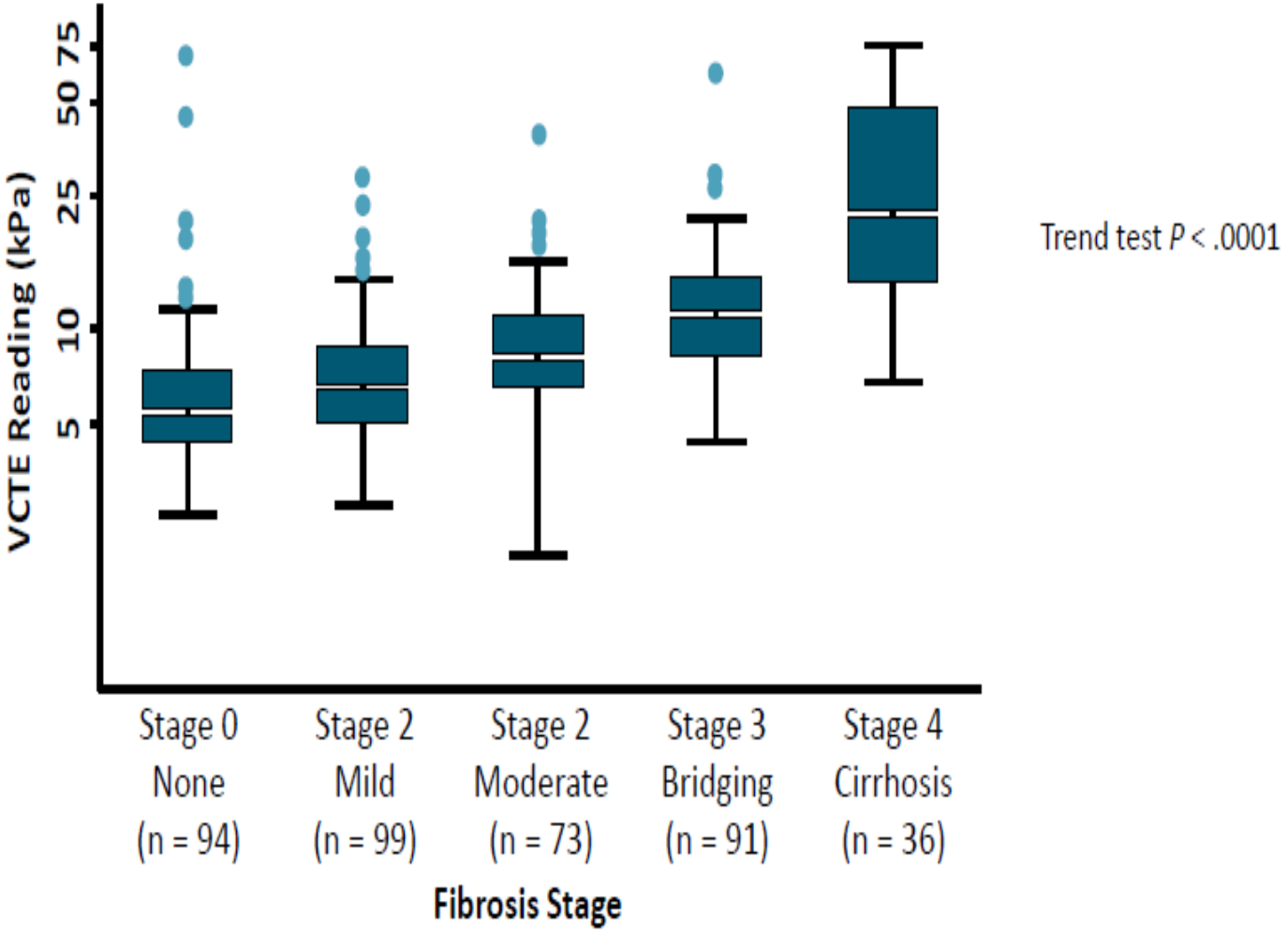
Vibration-Controlled Transient Elastography (VCTE)

- Measures 1D velocity of low-frequency shear wave
- Directly related to tissue stiffness (fibrosis)
  - The stiffer the liver, the faster the shear wave propagates
- Quick, bedside test (~ 5 mins)
- Limited by obesity, food intake, operator experience

Sigrist. Theranostics 2017;7:1303.

VCTE: Detecting Liver Fibrosis in People With NAFLD

- NASH CRN: 393 patients with biopsies within 1 yr

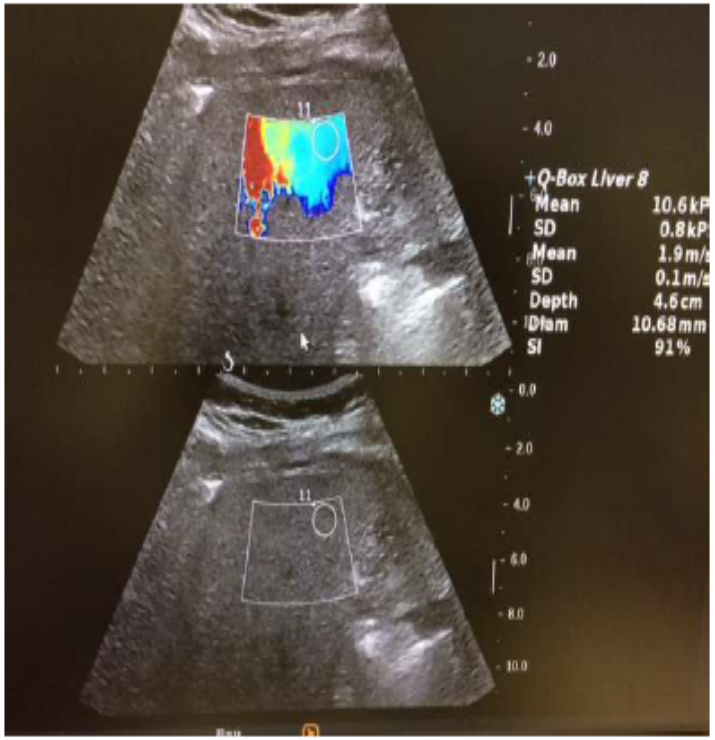


Trend test $P < .0001$

Siddiqui. Clin Gastroenterol Hepatology. 2018;18:S1542.

2D Shear Wave Elastography (SWE)

- Ultrasound system, using real-time SWE map of liver elasticity to determine liver stiffness[1]
  - 2D SWE color-coded map superimposed on B-mode image confirms readings are in liver, not in nearby vessels or kidneys[1]
- May require radiologist/sonographer [1]
- Liver elasticity measurements can be obtained in challenging cases of obesity[1]

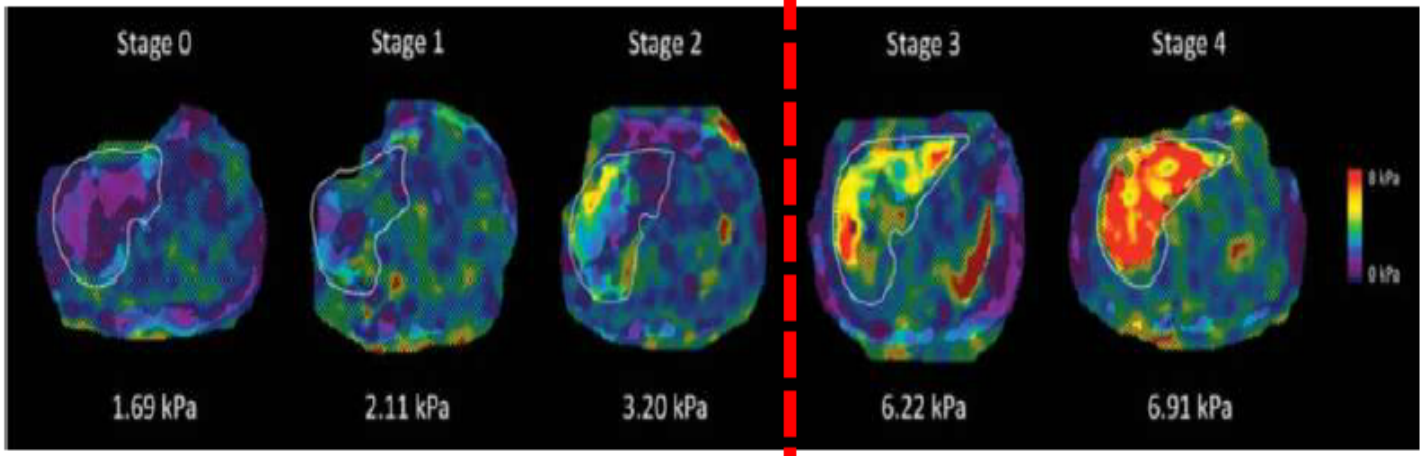


Cutoff for Detecting Advanced Fibrosis ≥ F3 in HCV[2]	Sensitivity	Specificity	AUROC
2D-SWE stiffness > 8.7 kPa	.973	.951	.98

1. Sigrist. Theranostics 2017;7:1303. 2. Ferraiolo. Hepatology 2012;56:2125.

MRE: Detecting Advanced Fibrosis in People With NAFLD

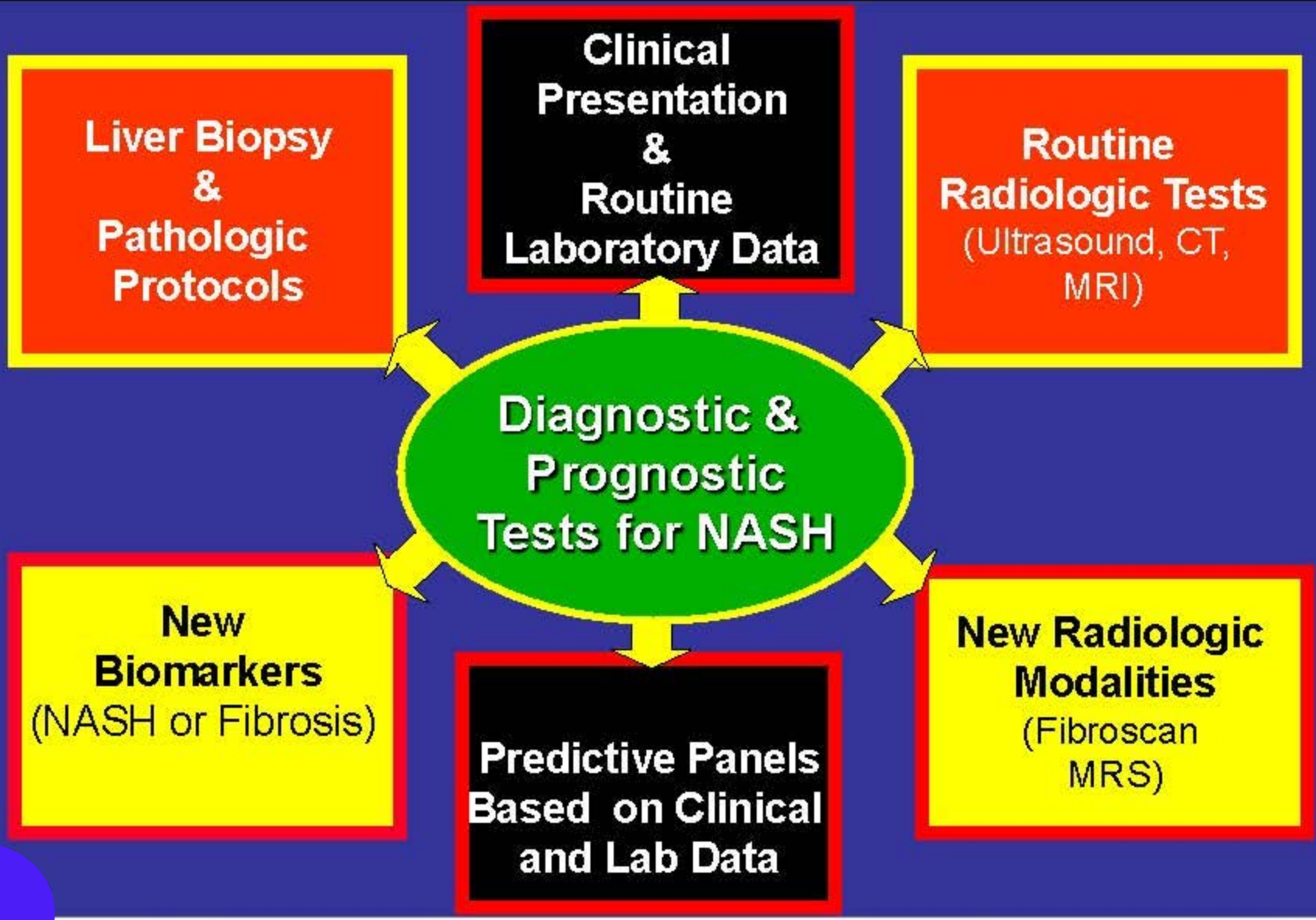
- Prospective, cross-sectional analysis of 2D MRE in N = 117 patients with biopsy-proven NAFLD



Cutoff for Detecting Advanced Fibrosis ≥ F3	Sensitivity	Specificity	AUROC
MRE stiffness > 3.63 kPa	.86	.91	.924

Loomba. Hepatology. 2014;60:1920.

Can we diagnose NASH or predict its course?



Use All Available Resources: No Single Test Accurately Assesses Hepatic Fibrosis in the Setting of NAFLD

- AST/ALT ratio
  - > 1 suggests advanced fibrosis if no alcohol (F3/F4)
  - < 0.8 rules out advanced fibrosis
- APRI (AST/ULN divided by platelet count x 100)
  - [(AST/ULN)] / platelet count] x 100
  - > 2 suggests cirrhosis
- Platelet count
  - < 150,000 suggests portal hypertension
- Serum markers of fibrosis
- CT/MRI/ultrasound
  - Splenomegaly or PV diameter > 11 mm suggests portal hypertension
- Elastography; no consensus for NAFLD, but studies suggest the following cutoffs:
  - ≥ 7.5 to < 9.5 kPa suggests moderate fibrosis (F2)
  - ≥ 9.5 to < 12 kPa suggests precirrhosis (F3)
  - ≥ 12 kPa suggests cirrhosis (F4)

Siddiqui MS. Clin Gastroenterol Hepatol. 2018;[Epub]. Chalasani. *Hepatology*. 2018;67:328.

Bringing It All Together

- Noninvasive serum tests can help stratify a patient's probability of having NASH with ≥ F2 fibrosis
  - Can reliably **exclude** advanced fibrosis
  - If intermediate or positive, move on to noninvasive imaging
- Noninvasive elastography methods can **confirm** advanced fibrosis
  - VCTE
  - 2D SWE
  - MRE

How Do You Manage NASH/NAFLD?

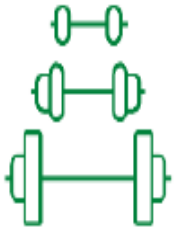
Which Nonpharmacologic Measurements Do you recommend?

AASLD Guidance: Nonpharmacologic Approaches for NASH

Weight loss

- 3% to 5% to improve steatosis, 7% to 10% to **improve** most histopathology, including **fibrosis**

Exercise



- May prevent or reduce steatosis, ability to improve other aspects of liver histology unknown

Bariatric surgery

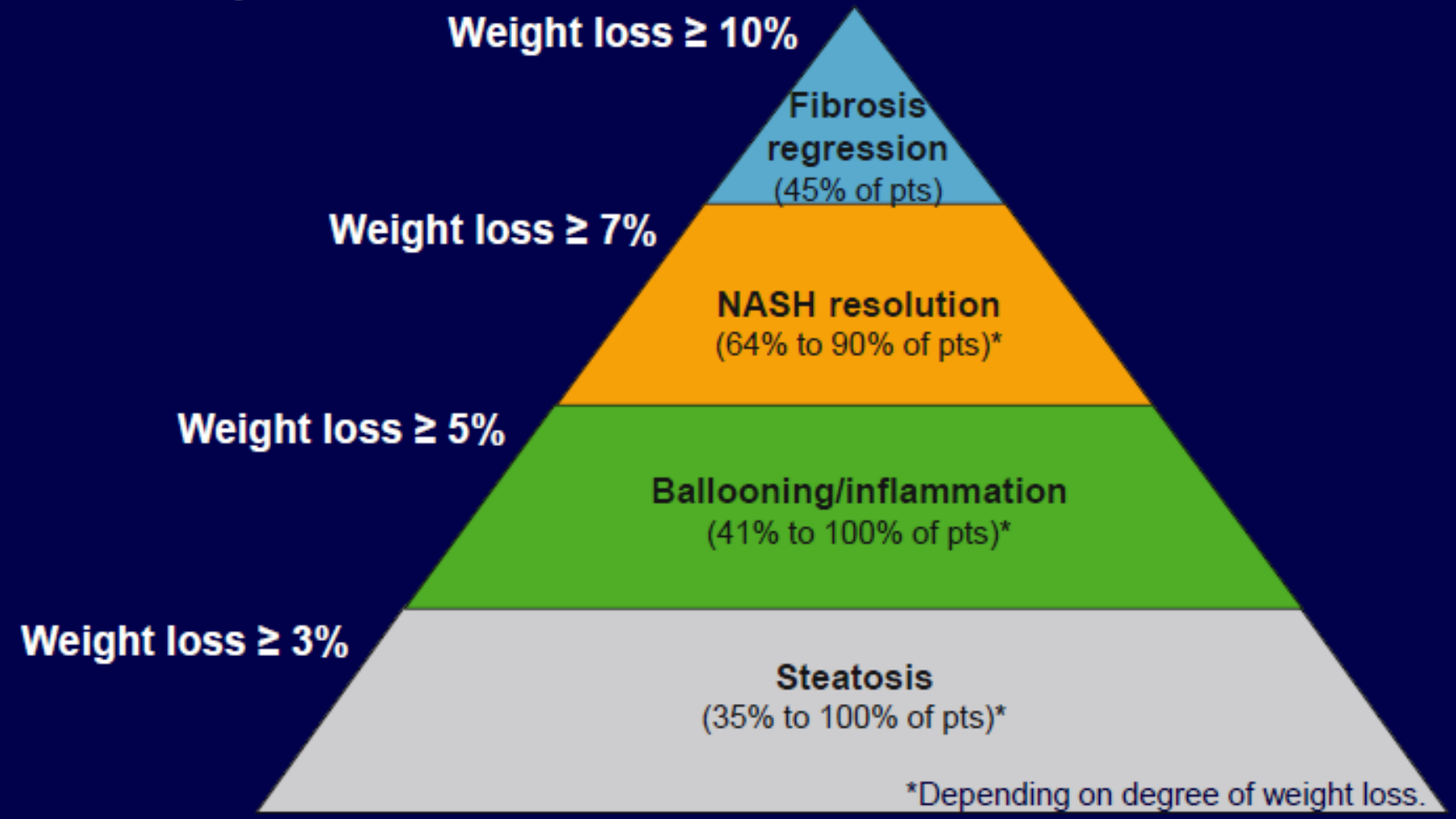
- Can be considered in obese individuals with NAFLD or NASH **WHO OTHERWISE MEET CRITERIA FOR BARIATRIC SURGERY**
- Premature to consider bariatric surgery as an established option to treat NASH

Best to combine hypocaloric diet (reduction by 500-1000 kcal/day) plus exercise, independent of macronutrient composition of diet

Chalasani. Hepatology. 2018;67:328.

Percentage of Weight Loss Associated With Histological Improvement in NAFLD

- Analysis of data from 4 randomized studies



Hannah WN, et al. Clin Liver Dis. 2016;20:339-350.

Effect of Diet in NAFLD

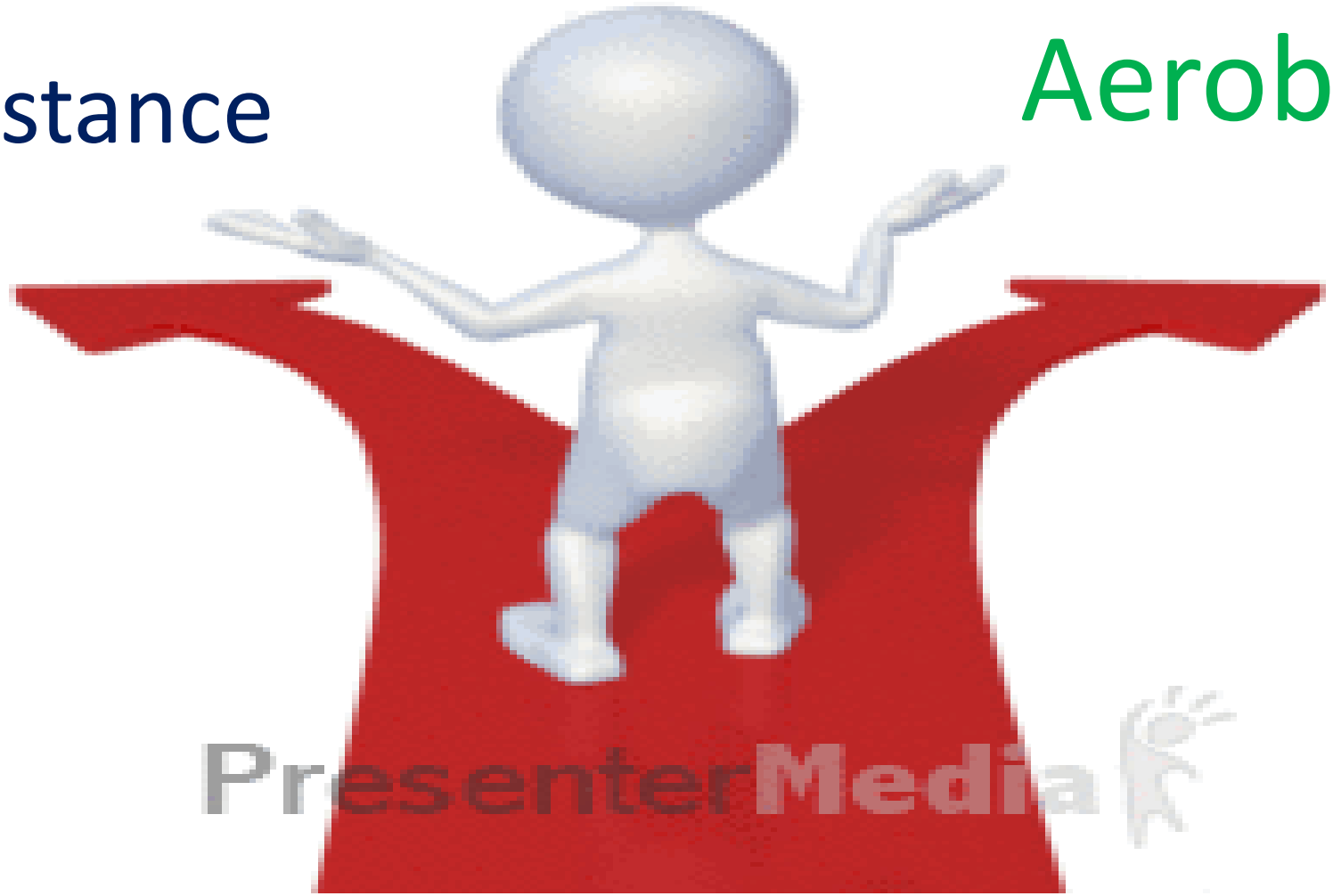
- **Limiting total caloric intake is ideal** and more important than aiming for a specific nutrient composition
- General diet recommendation: limit processed carbs!
  - White/brown bread, rice
  - White/orange potatoes
  - Flour/corn tortillas
  - Pizza/pasta
  - Chips
  - Fructose-containing sodas and juices

Hannah WN, et al. Dig Dis Sci. 2016;61:1365-1374.

Which Kind of Exercise Do You Recommend for NAFLD/NASH Pts?

Resistance

Aerobic



What Is the Right Prescription for Exercise in Pts With NAFLD?

- Data limited by small sample sizes, poor statistical power, and lack of correlation with histopathology
- Exercise associated with a reduction in hepatic fat even in the **absence** of weight loss
- Small studies suggest **resistance training** reduces hepatic fat, improves other metabolic parameters

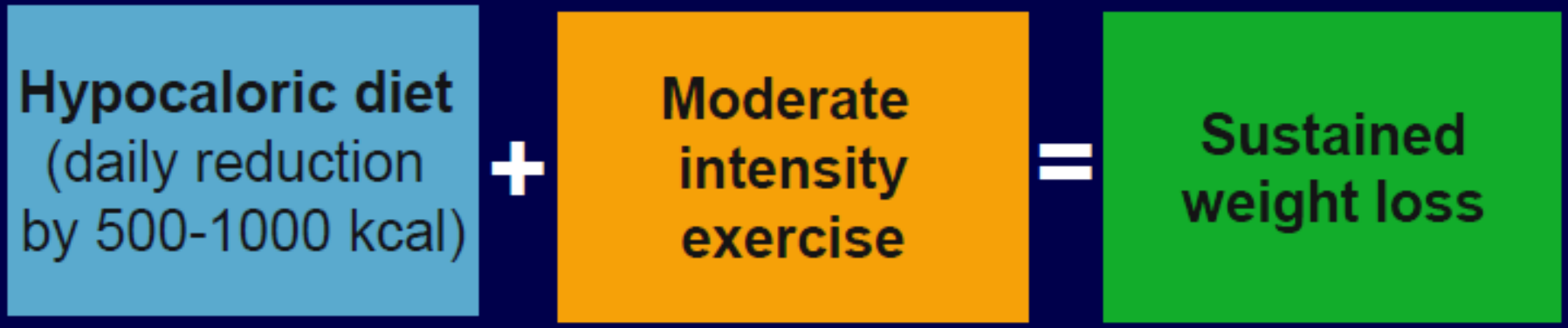
Hashida R, et al. J Hepatol. 2016;[Epub ahead of print].

Evidence for Exercise in NAFLD

- No head-to-head trials of aerobic exercise vs resistance training for efficacy in NAFLD
  - No data to suggest superiority of one exercise regimen vs another
- Current evidence reinforces utility of aerobic or resistance exercise for improving steatosis

Hannah WN, et al. Dig Dis Sci. 2016;61:1365-1374.

Recommendation



What about Diet?

Components of a lifestyle approach to NAFLD

Energy restriction

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

Fructose intake

- Avoid fructose-containing food and drink

Coffee consumption

- No liver-related limitations

Comprehensive lifestyle approach

Daily alcohol intake

- Strictly below 30 g men and 20 g women

Macronutrient composition

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

Physical activity

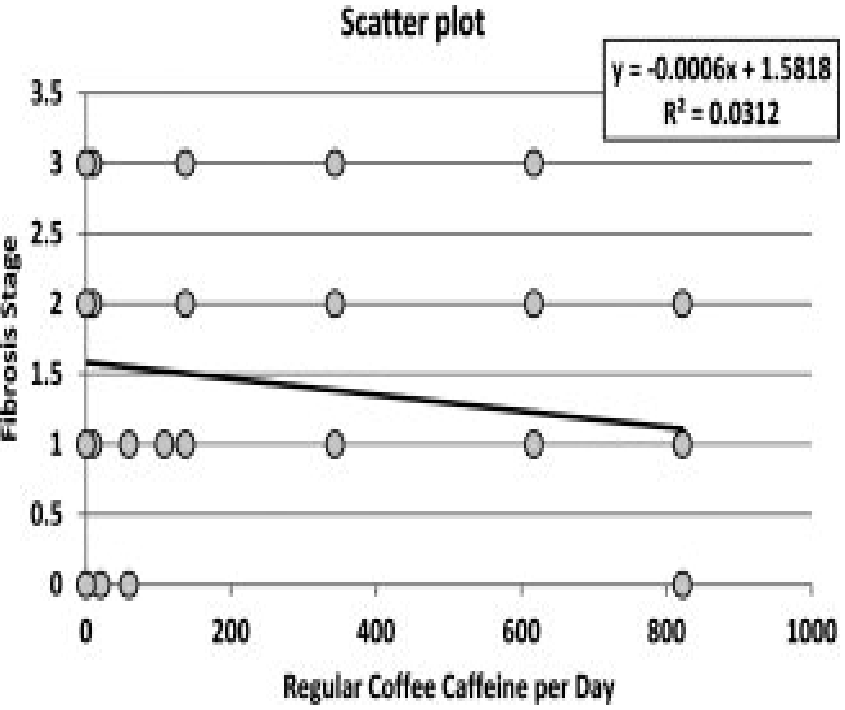
- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

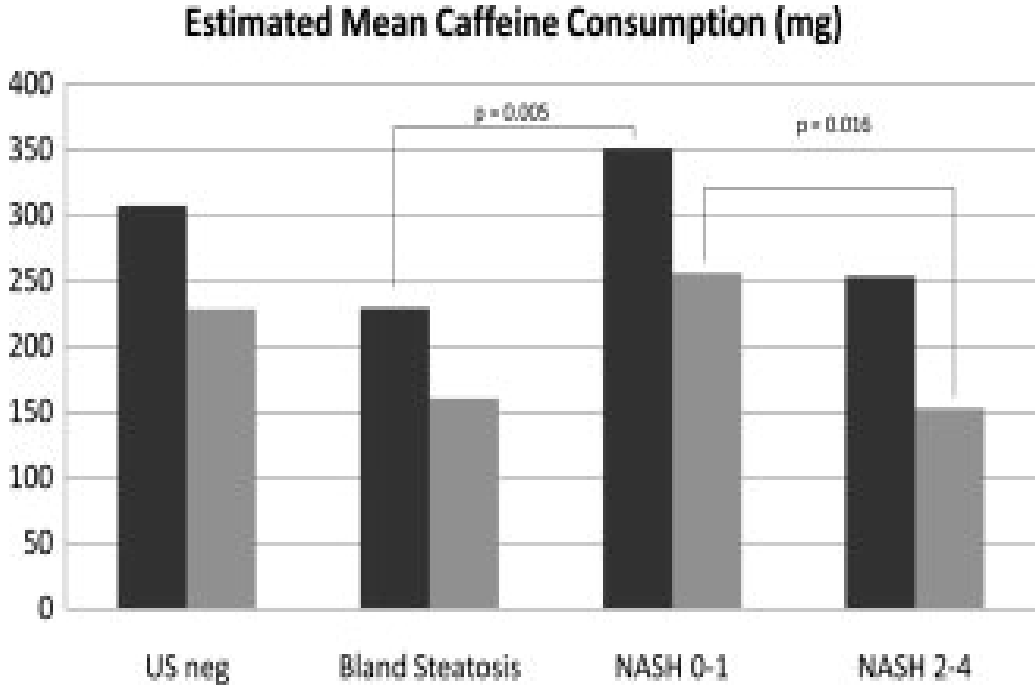
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Coffee??

Validated questionnaire in 2012 study
Showed that mild coffee consumption (2-3 cups/day)can be a benign adjunct to help prevent advanced fibrosis

Molloy JW, Calcagno CJ, Williams CD, et al. Association of coffee and caffeine consumption with fatty liver disease, nonalcoholic steatohepatitis, and degree of hepatic fibrosis. Hepatology. 2012





Which Drugs Do You Recommend?

Current Status of Pharmacologic Treatments for NASH

- No FDA-approved therapies for NASH
- Currently available therapeutics with proven efficacy
  - Vitamin E
  - Pioglitazone
- More limited data
  - Pentoxifylline
  - Liraglutide

Orlistat

- Orlistat (enteric lipase inhibitor)
- Achieve weight loss in conjunction with lifestyle modification if BMI>30 kg/m^2
- Improves ALT and steatosis
- **Target/outcome**
- Only continue if >5% loss of body weight in 3 months is achieved

Antioxidents

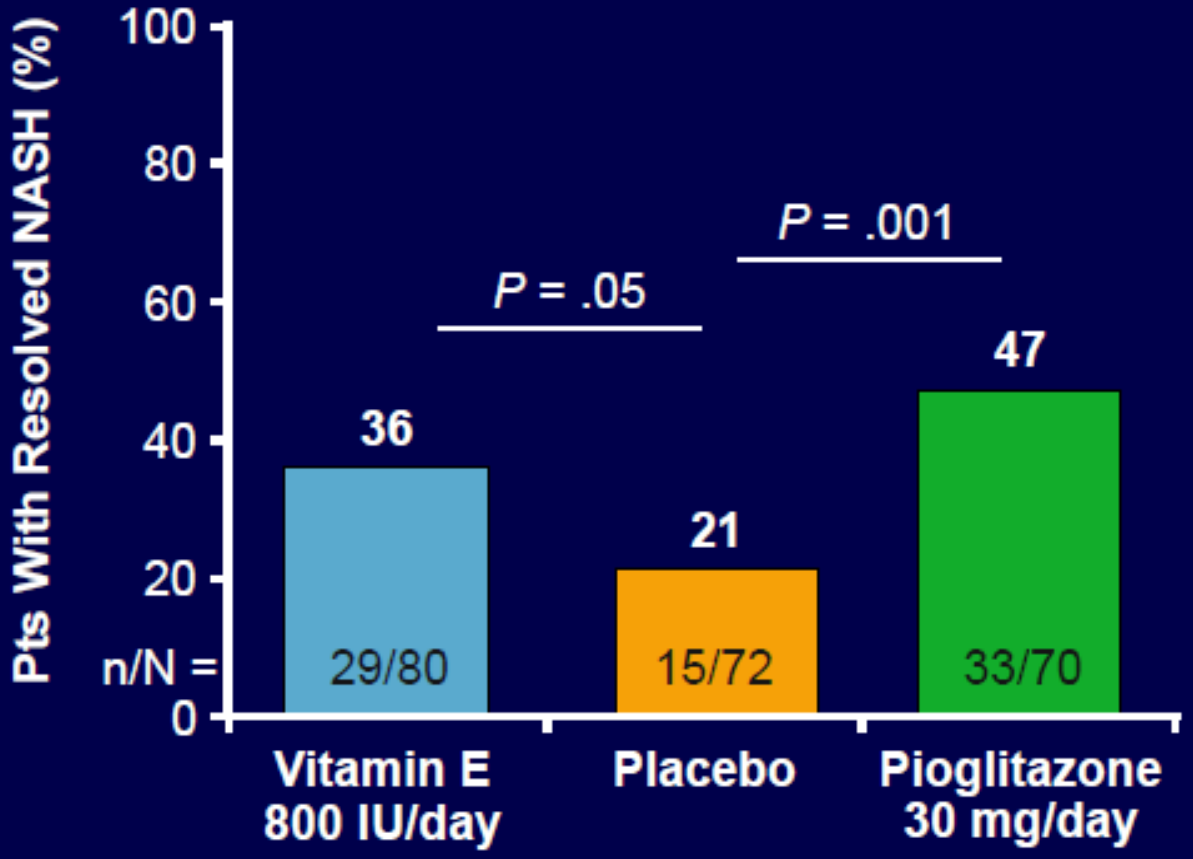
Vitamin E / Pentoxifylline

Pentoxifylline

- Phosphodiesterase inhibitor
- Inhibits TNF
- 400mg thrice daily
- RCTs showed no significant reduction in fibrosis
- Therefore cannot recommended for treatment of NASH

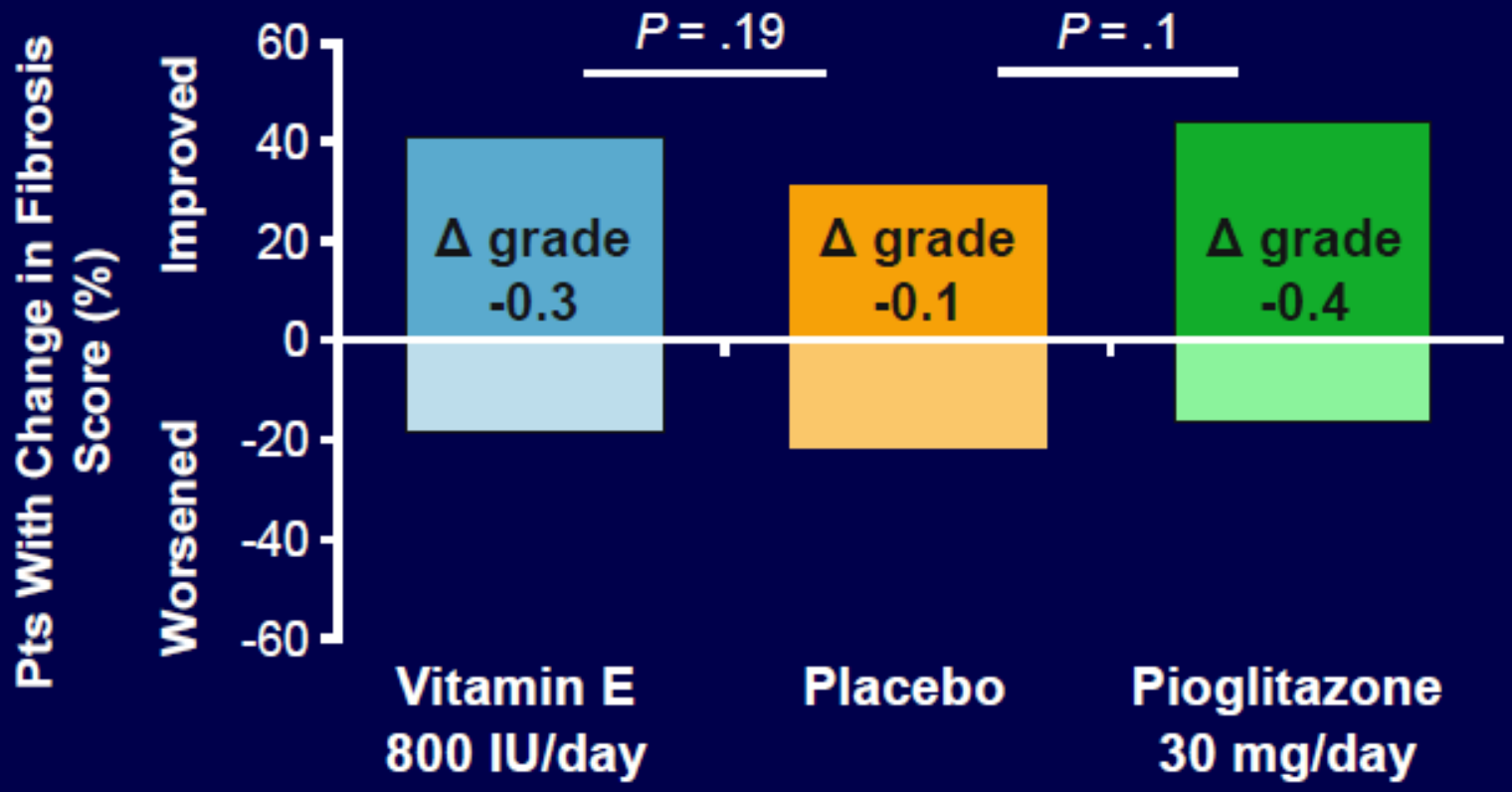
PIVENS: Histologic Resolution of NASH at Wk 96 With Vitamin E vs Pioglitazone

- Double-blind, placebo-controlled, randomized, phase III trial in adults with biopsy-proven NASH and no diabetes or cirrhosis (N = 247)



Sanyal AJ, et al. N Engl J Med. 2010;362:1675-1685.

PIVENS: No Significant Improvement in Fibrosis at Wk 96 for Vitamin E or Pioglitazone



Sanyal AJ, et al. N Engl J Med. 2010;362:1675-1685.

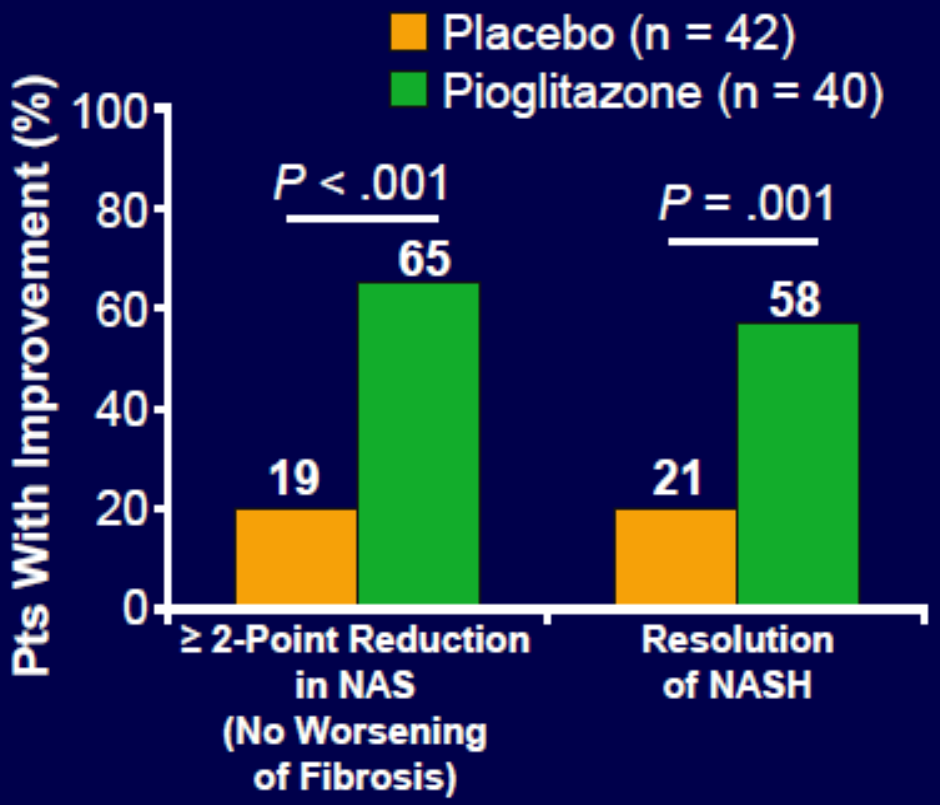
Why Not Empirically Treat Suspected NASH With Vitamin E?

Why Not Empirically Treat Suspected NASH With Vitamin E?

- ~ 50% of pts do not respond to vitamin E[1]
  - Liver enzymes are not reliable to assess quiescence or progression
- Increased risk of hemorrhagic stroke[2]
- Prostate cancer risk?
  - Absolute increase 1.6/1000 PY; synthetic form[3]
  - No effect on prostate cancer risk (n = 11,000)[4]
- Long-term safety?
  - Remains unknown though likely safe
  - Doses > 400 IU/day may be associated with increased mortality but data limited by small studies[5]

Pioglitazone in Diabetes: Improvement or Resolution of NASH at 18 Mos

- Randomized, placebo-controlled, double-blind phase IV trial of pts with NASH and prediabetes or type 2 diabetes mellitus (N = 101)[1]
  - Secondary outcome analysis of histologic scores included pts with paired biopsies from before/after tx (n = 82)



1. ClinicalTrials.gov. NCT00994682.
2. Cusi K, et al. Ann Intern Med. 2016;165:305-315.

Concerns while using Pioglitazone

- Weight gain up to 4kg
- Precipitates CHF
- Long term use a/w urological & pancreatic malignancy
- Rebound elevation of ALT and disease severity
- Response only in 40%

Pharmacologic Treatment Options Studied in NASH

Agent	Good Evidence for Use[1]	Limited or Insufficient Evidence for Use[1]	AASLD NAFLD/NASH Recommendation[2]
Vitamin E	NASH without diabetes	NASH with diabetes or cirrhosis	NASH without diabetes
Pioglitazone	NASH with or without diabetes	NASH with cirrhosis	Can be used for steatohepatitis
Metformin		No significant effect on liver histology[2]	Not recommended
Pentoxifylline		Needs further study to determine ideal subpopulation	

1. Rinella ME, et al. Gastroenterol Hepatol. 2014;10: 219-227.
2. Chalasani N, et al. Hepatology. 2012;55:2005-2023.

Can We Use Statins For Treatment Of Dyslipidemia In Pts With NASH?

AASLD Guidance on CV Risk: Statins in Patients With NASH

- "Patients with NAFLD are at high risk for cardiovascular morbidity and mortality. Thus, **aggressive modification of CVD risk factors should be considered** in all patients with NAFLD"

- "Patients with NAFLD or NASH are not at higher risk for serious liver injury from statins. Thus, **statins can be used to treat dyslipidemia in patients with NAFLD and NASH**"

Chalasani. Hepatology. 2018;67:328.

Lipid lowering agents

- Statins,Ezetimibe,Omega 3 fatty acids
- Dyslipidaemia
- Under prescribed
- Fear of statin induced hepatotoxicity (rare <1/1lakh)
- Statin associated transminitis(1-3)%,resolves on spontaneously on continued use.
- Witholding statins worsened cardiac events
- Safely used in compensated cirrhosis
- 26% reduction of HCC in statin users

NASH Treatments Currently in Phase III Investigations

Agent	MOA	Trial	N	Primary Endpoint(s)	Time Point
Cenicriviroc	CCR2/5 antagonist	AURORA[1]	2000	≥ 1 stage fibrosis improvement with no NASH worsening	12 mos
Elafibranor	PPARα/δ agonist	RESOLVE-IT[2]	2000	Resolution of NASH with no fibrosis worsening	72 wks
Obeticholic acid	FXR agonist	REGENERATE[3]	2370	≥ 1 stage fibrosis improvement with no NASH worsening; resolution of NASH with no fibrosis worsening	18 mos
		REVERSE[4]	540	≥ 1 stage fibrosis improvement with no NASH worsening	12 mos
Selonsertib	ASK1 inhibitor	STELLAR 3[5]	808	≥ 1 stage fibrosis improvement with no NASH worsening	48 wks
		STELLAR 4[6]	883		

- Phase III/IV adaptive design[7]
  - Histologic endpoints for FDA Subpart H conditional approval
  - Clinical endpoints for full approval

1. NCT03028740. 2. NCT02704403. 3. NCT02548351. 4. NCT03439254.
5. NCT03053050. 6. NCT03053063. 7. Konerman. J Hepatol. 2018;68:362.

What Is The Role Of Surgery In NASH?

Bariatric Surgery Improves Clinical Parameters

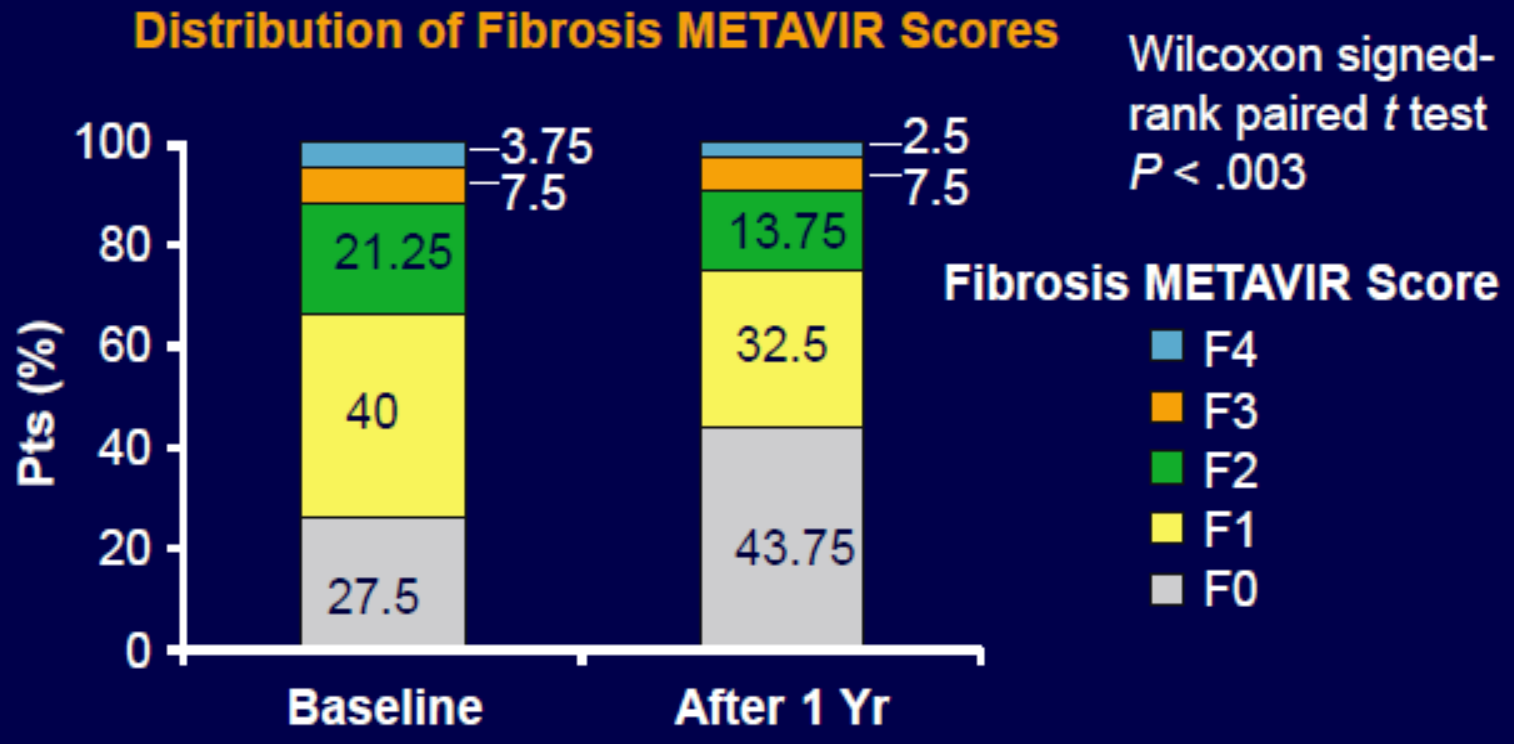
- Prospective study following bariatric surgery in pts who are severely obese (N = 381) with ≥ 1 comorbidity, no excessive drinking < 2 yrs, no chronic liver diseases
  - Liver biopsies assessed by 2 blinded reviewers for fibrosis (F0-4), NAFLD scoring to determine NASH (≥ 3, probable or definite; ≥ 5, definite)

Parameter	Before Surgery	After 5 Yrs	*P* Value
Diabetes mellitus, n (%)	94 (24.8)	24 (10.8)	.00001
Arterial hypertension, n (%)	185 (48.8)	85 (37.0)	.0005
Serum triglycerides, mean (g/L)	1.67	1.06	.00001
Fasting glucose, mean (g/L)	1.18	0.94	.00001
Insulin resistance index, mean	3.2	2.83	.00001
ALT, mean (IU/L)	30.1	22.8	.00003
GGT, mean (IU/L)	39.9	29.2	.00001

Mathurin P, et al. Gastroenterology. 2009;137:532-540.

Bariatric Surgery Improves Fibrosis in Pts With NASH

- Prospective study of bariatric surgery in pts who are morbidly obese with biopsy-validated NASH, ≥ 1 comorbidity factor for > 5 yrs, no chronic liver disease (N = 109)



Lassailly G, et al. Gastroenterology. 2015;149:379-388.


Thank you for your attention