

Nonalcoholic Fatty Liver Disease (NAFLD): Screening, Current Management and Treatments on the Horizon

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Overview

- Describe the burden, disease spectrum and natural history of NAFLD.
- Discuss management strategies for patients with NAFLD:
 - Noninvasive diagnosis of disease severity
 - Novel therapeutic agents expected to be available in the near future

Case Presentation

Tony



Weakness

- 60 y.o. M with DM2, BMI of 39 kg/m² and MetS.
- Presents with persistently elevated LFTs.
- ALT 66 U/L (10-40 U/L)
- AST 76 U/L (10-40 U/L)
- Albumin 3.5 g/dL (3.5-4.5 g/dL)
- Platelet count 170 k/uL (150-400 k/uL)



Epidemiology and Natural History of NAFLD

NAFLD is the Hepatic Manifestation of Obesity/IR



Metabolic Syndrome

- Insulin Resistance
- Dyslipidemia
- Hypertension



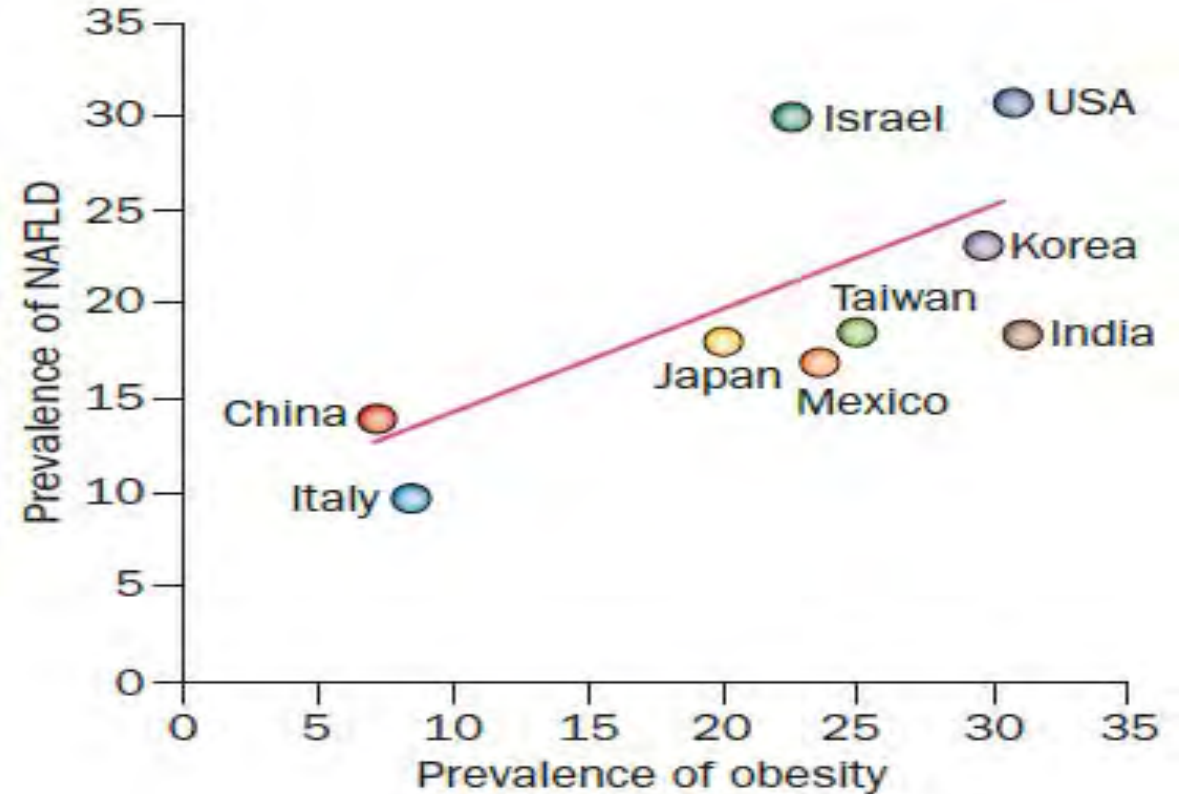
NAFLD



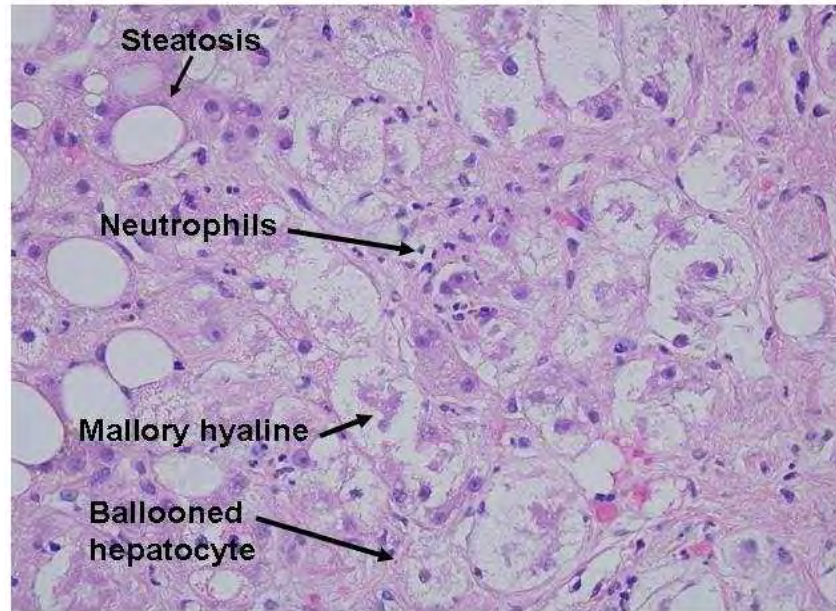
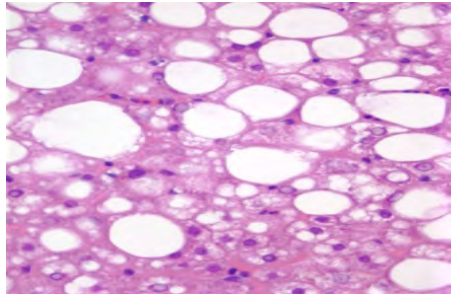
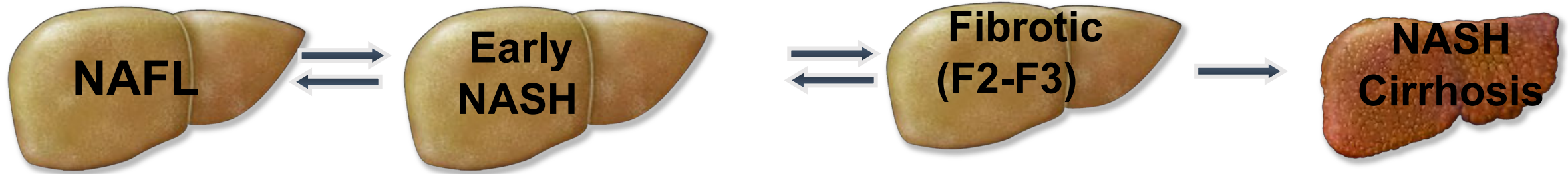
NAFLD Prevalence

Adults

- Overall: ~ 25%
- Obese: ~ 50%
- Severely Obese: ~ 85%
- **DM2:** ~ **65-75%**

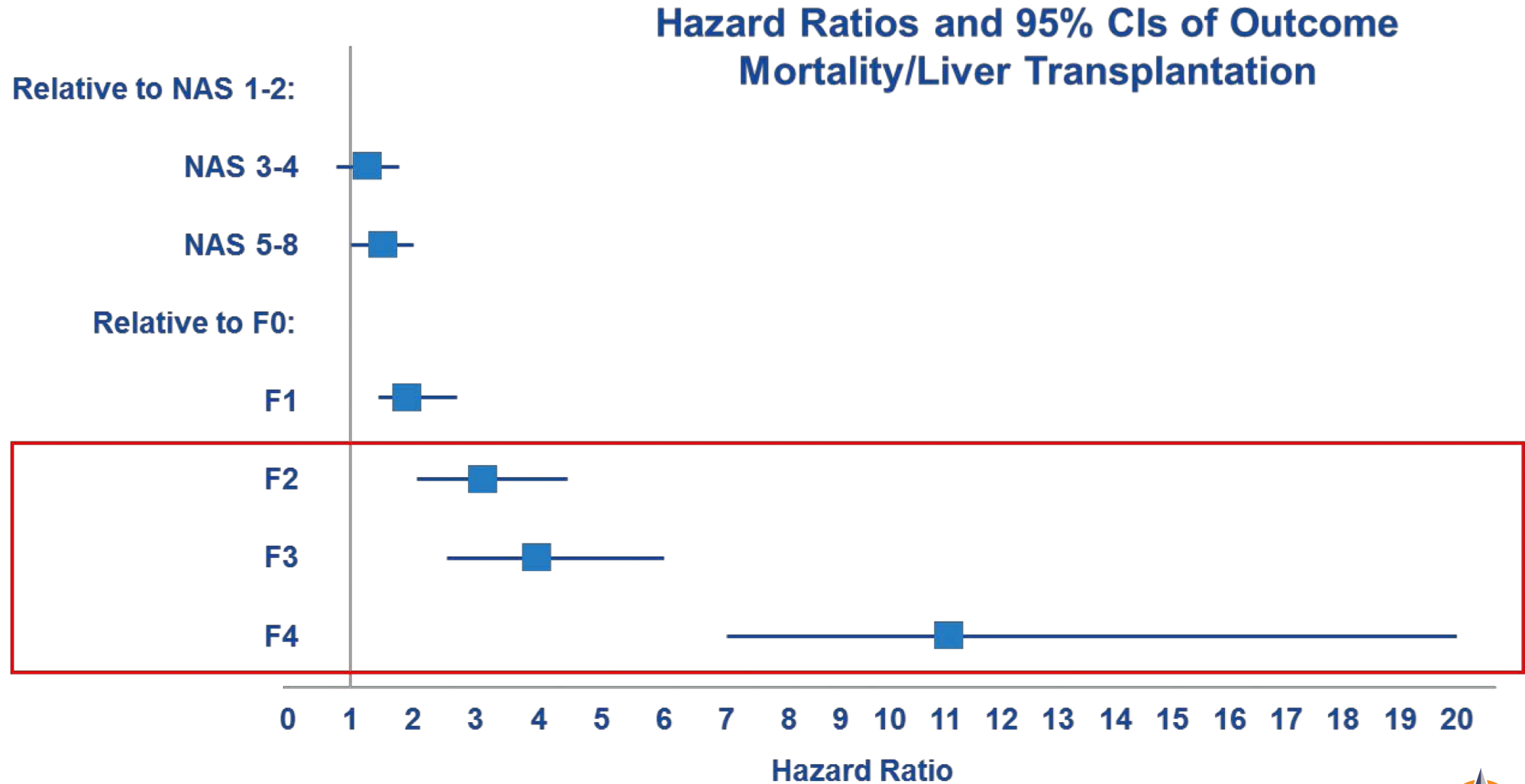


The NAFLD Spectrum

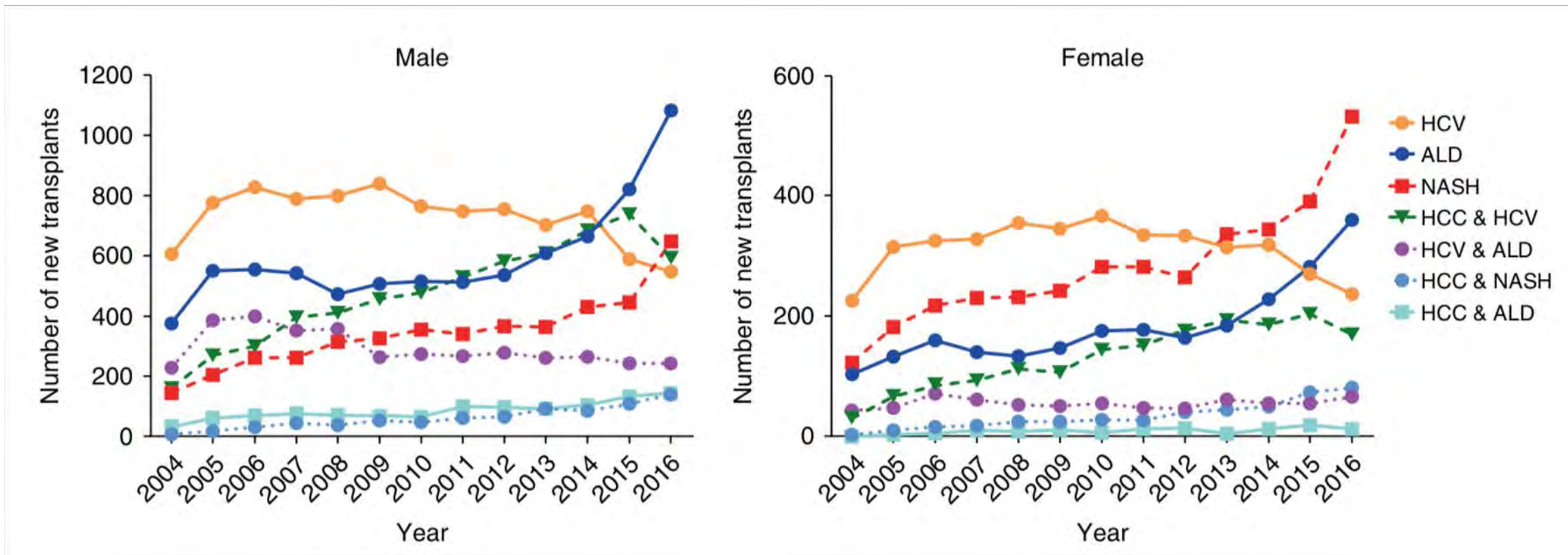


NAFLD Activity Score	
Steatosis (0-3)	
5-33%	1
34-65%	2
≥66%	3
Inflammation (0-3)	
<2 under 20x	1
2-4 under 20x	2
>4 under 20x	3
Ballooning (0-2)	
Few	1
Many	2

Fibrosis Stage is the Most Important Prognostic Factor in Predicting Liver-related Outcomes

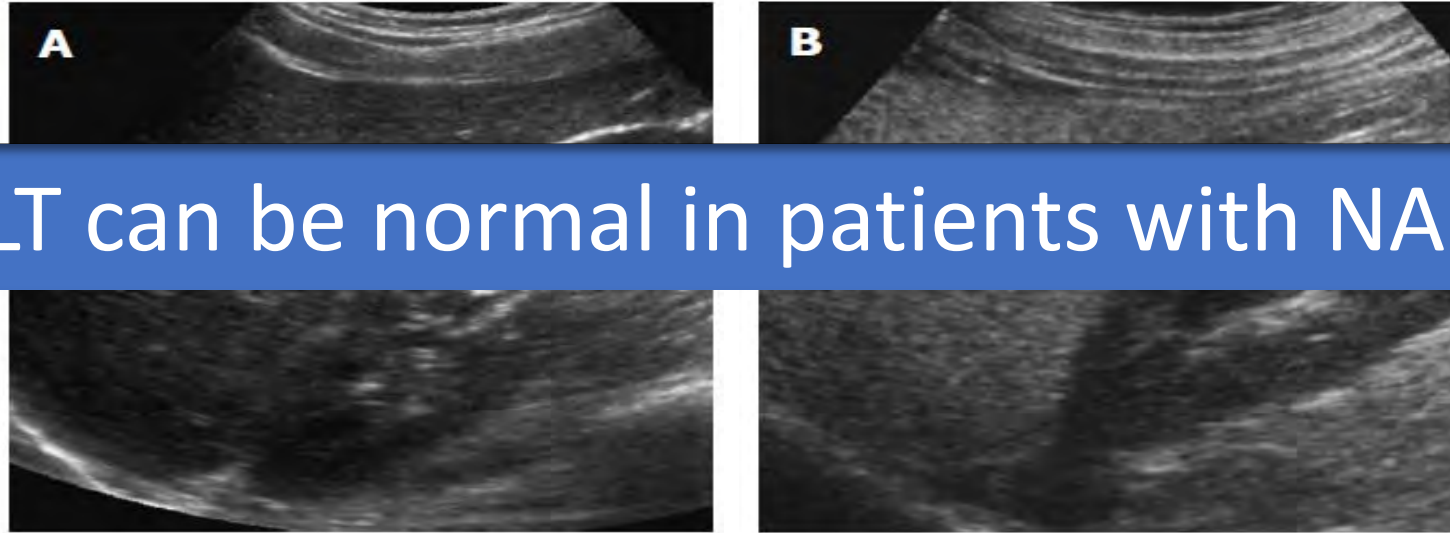


NASH is the Most Common Indication for Listing and OLT in Women in the U.S.

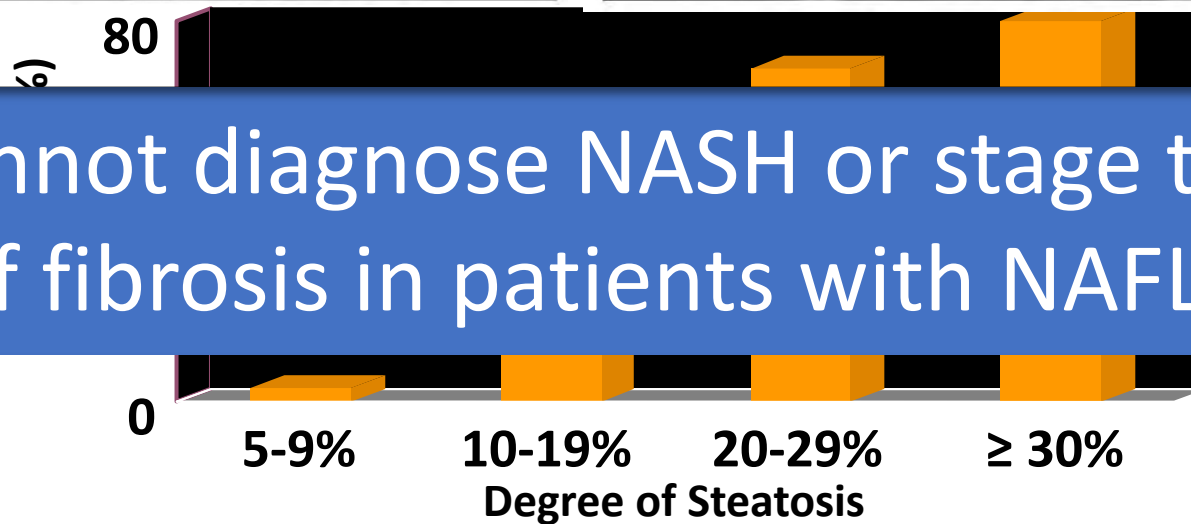


Determining the Presence and Severity of NAFLD

Current Diagnosis of NAFLD: ALT and Ultrasonography



ALT can be normal in patients with NAFLD



ALT/ US cannot diagnose NASH or stage the severity of fibrosis in patients with NAFLD

Noninvasive Diagnosis of Fibrosis

Serologic Markers

• Simple

- AST/ ALT ratio
- APRI
- FIB-4
- NFS

• Complex

- FibroSURE
- ELF
- HA

Imaging

• Elastography

- VCTE
- MRE
- ARFI

NAFLD fibrosis score Online calculator

Angulo P, Hui JM, Marchesini G et al. **The NAFLD fibrosis score**
A noninvasive system that identifies liver fibrosis in patients with NAFLD
Hepatology 2007;45(4):846-854 [doi:10.1002/hep.21496](https://doi.org/10.1002/hep.21496)

Age (years)

BMI (kg/m²)

IGF/diabetes

AST

ALT

Platelets (x10⁹/l)

Albumin (g/l)

Score **2.00**

Original score **4.040**

- < -1.455: predictor of **absence** of significant fibrosis (F0-F2 fibrosis)
- ≤ -1.455 to ≤ 0.675: indeterminate score
- > 0.675: predictor of **presence** of significant fibrosis (F3-F4 fibrosis)

Fibrosis-4 (FIB-4) Calculator

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}} = \text{Score } 3.30$$

- < 1.4: absence of significant fibrosis
- 1.4-2.66: Indeterminate
- > 2.67: presence of advanced fibrosis

FIBROSURE™

Metavir scale

- 6 Serum Markers
 - A2-macroglobulin
 - Haptoglobin
 - Apolipoprotein A1
 - Total bilirubin
 - GGT
 - ALT

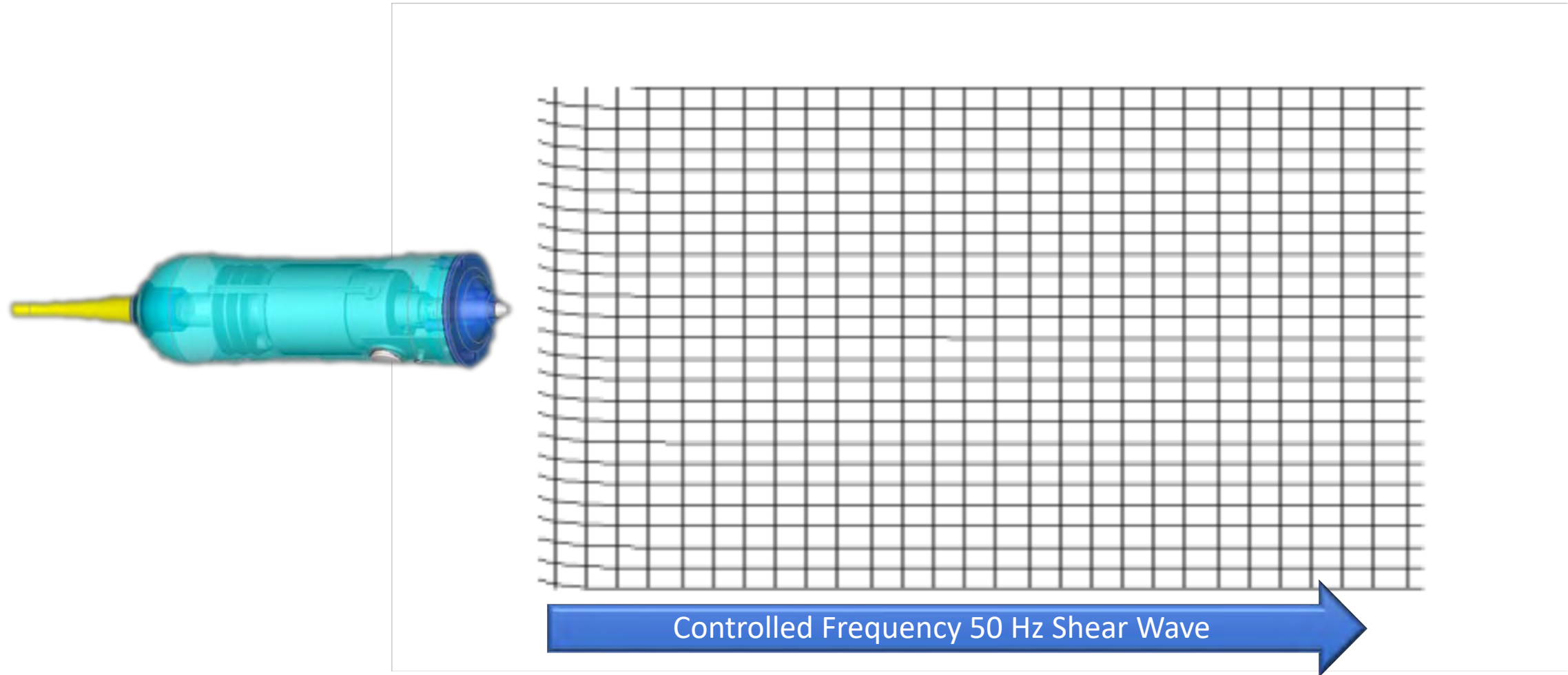
Fibrosis Stage (FibroTest)

F0 - No fibrosis	0.00 - 0.21
F0 - F1	0.21 - 0.27
F1 - Portal fibrosis	0.27 - 0.31
F1 - F2	0.31 - 0.48
F2 - Bridging fibrosis with few septa	0.48 - 0.58
F3 - Bridging fibrosis with many septa	0.58 - 0.72
F3 - F4	0.72 - 0.74
F4 - Cirrhosis	0.74 - 1.00

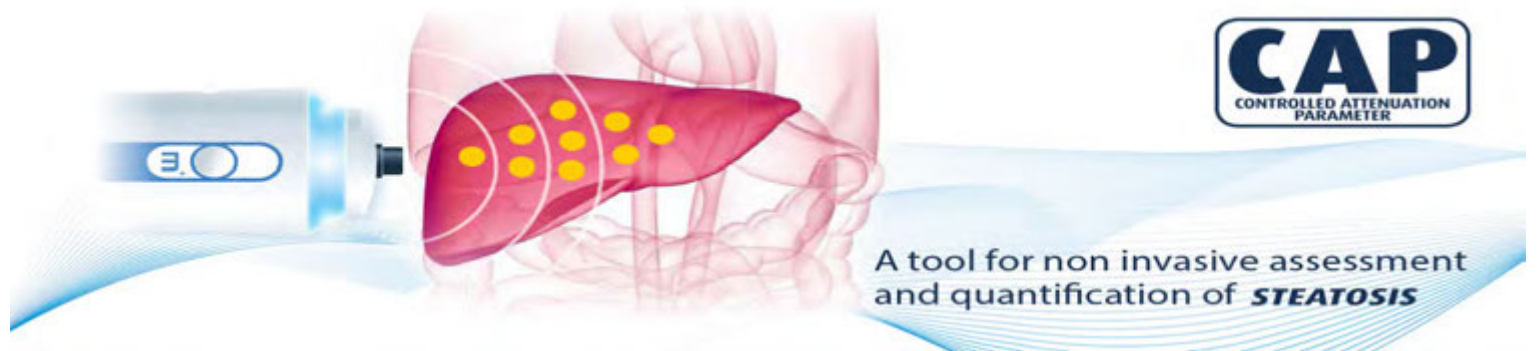
Activity Grade (ActiTest)

A0 - No activity	0.00 - 0.17
A0 - A1	0.17 - 0.29
A1 - Minimal activity	0.29 - 0.36
A1 - A2	0.36 - 0.52
A2 - Moderate activity	0.52 - 0.60
A2 - A3	0.60 - 0.63
A3 - Severe activity	0.63 - 1.00

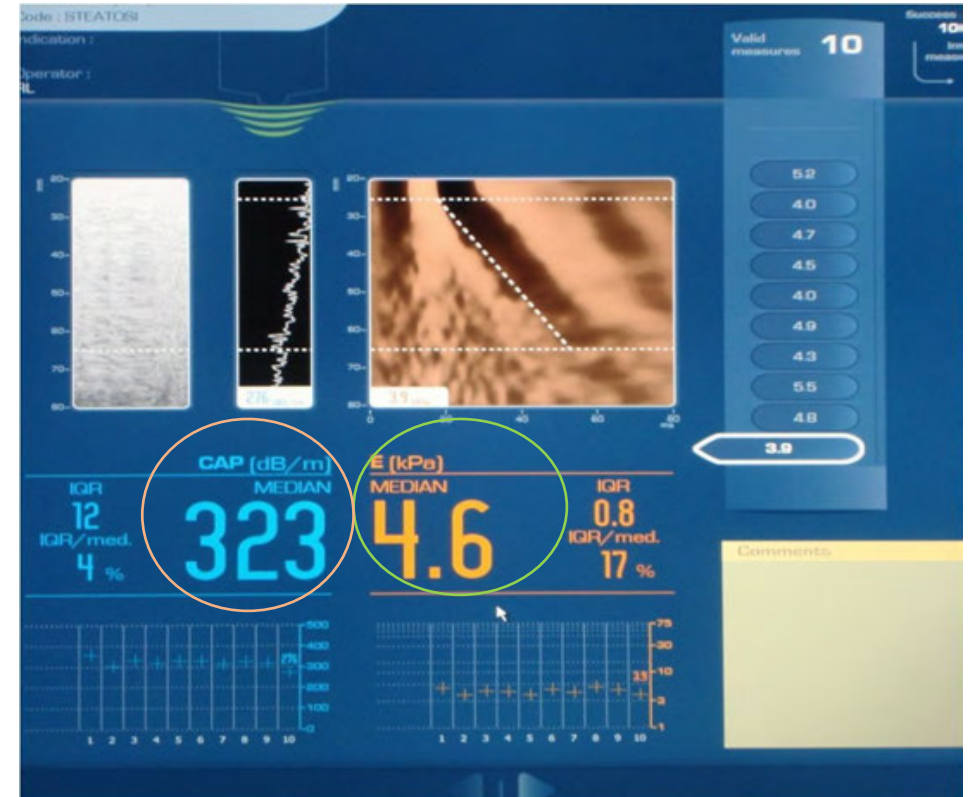
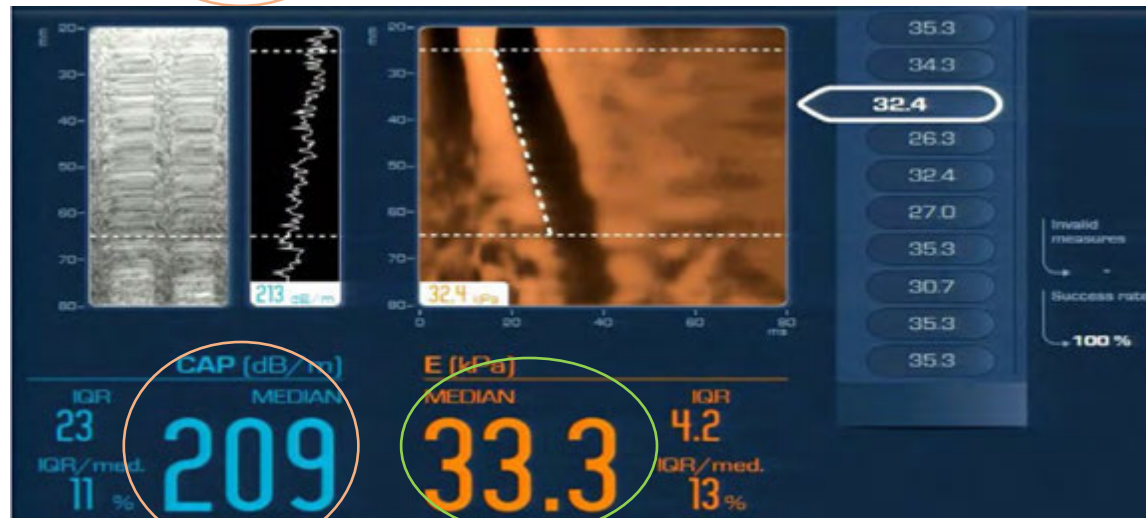
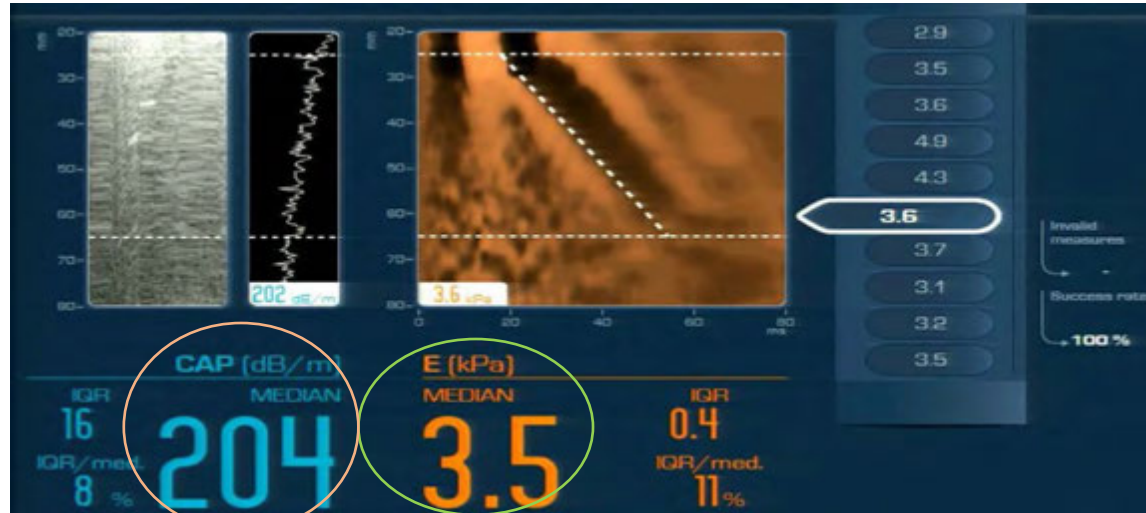
Shear Wave Movement

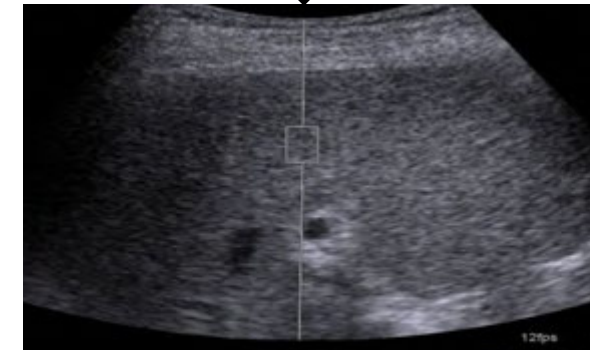
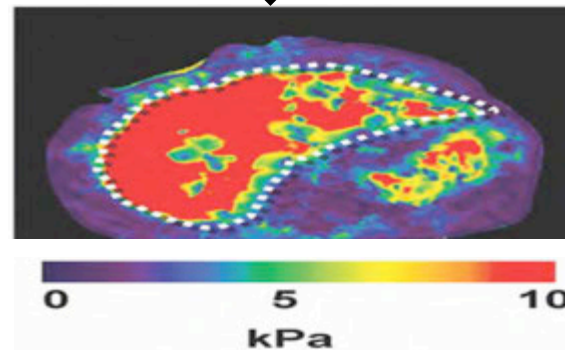
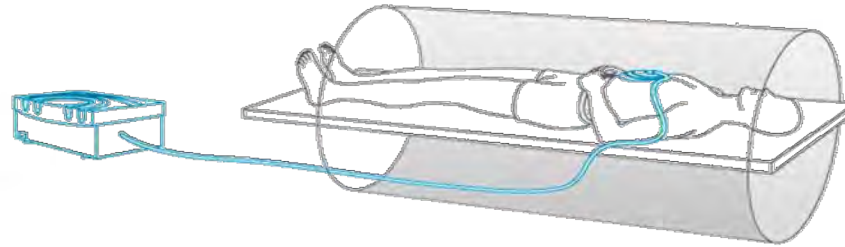


Staging the Severity of Steatosis and Fibrosis in NAFLD: VCTE + CAP



VCTE + CAP: A Powerful Tool





	Transient Elastography (kPa)	MR Elastography (kPa)	ARFI (m/s)
Advantages	<ul style="list-style-type: none"> - Can be performed in clinic with real-time results 	<ul style="list-style-type: none"> - Accurate in obese patients and examines the entire liver 	<ul style="list-style-type: none"> - Can be integrated into a conventional ultrasound
Disadvantages	<ul style="list-style-type: none"> - Increased failure rate with obesity - Expensive device - Cutoff values with XL probe need further validation 	<ul style="list-style-type: none"> - Expensive and time consuming - Limited availability - Only a few published studies 	<ul style="list-style-type: none"> - Increased failure rate with obesity - Cutoff values for advanced fibrosis vary significantly

NAFLD Management: Current and Future

How Do I Manage My Patient with NAFLD Today

- Rule out other etiologies of elevated ALT or fatty infiltration of the liver
- Assess for co-morbidities (DM2, HTN, Dyslipidemia, OSA)
- Assess severity (NASH, advanced fibrosis)
- Treatment:
 - Lifestyle
 - Pharmacologic

Laboratory Assessment for NAFLD

Chronic Liver Disease Panel

- CBC + AUTO DIFF
Lab, Routine, BLOOD
- HEPATIC FUNCTION PNL
Lab, Routine, BLOOD
- GGT BLD
Lab, Routine, BLOOD
- BASIC METABOLIC PNL
Lab, Routine, BLOOD
- LIPID PANEL BASIC
Lab, Routine
- PROTHROMBIN TIME/PT
Lab, Routine, BLOOD
- HEP REMOTE PANEL BL
Lab, Routine, BLOOD
- HEP A AB TOTAL
Lab, Routine, BLOOD
- ANA BLOOD
Lab, Routine, BLOOD
- SMOOTH MUSCLE AB PNL SCRIN
Lab, Routine, BLOOD
- LKM AB
Lab, Routine, BLOOD
- ALPHA-1-ANTITRYPS BL
Lab, Routine, BLOOD
- IRON + TIBC
Lab, Routine, BLOOD
- FERRITIN BLD
Lab, Routine, BLOOD
- CERULOPLASMIN BLD
Lab, Routine, BLOOD
- CELIAC SCREEN WITH REFLEX
Lab, Routine, BLOOD
- CK CREATINE KINASE
Lab, Routine, BLOOD

NASH Panel

- CBC + AUTO DIFF
Lab, Routine, BLOOD
- HEPATIC FUNCTION PNL
Lab, Routine, BLOOD
- GGT BLD
Lab, Routine, BLOOD
- BASIC METABOLIC PNL
Lab, Routine, BLOOD
- LIPID PANEL BASIC
Lab, Routine
- TSH BLD
Lab, Routine, BLOOD
- HGB A1C
Lab, Routine, BLOOD
- INSULIN ASSAY BLOOD
Lab, Routine, BLOOD
- GLUCOSE FASTING BLD
Lab, Routine, BLOOD
- C-REACTIVE ULTRA SEN
Lab, Routine, BLOOD
- LIPOPROTEIN (A)
Lab, Routine, BLOOD
- ALBUMIN RANDOM URINE
Lab, Routine, URINE
- VITAMIN D 25 HYDROXY
Lab, Routine, BLOOD

Assessment of the Severity of NAFLD

NAFLD fibrosis score Online calculator

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A noninvasive system that identifies liver fibrosis in patients with NAFLD
Hepatology 2007;45(4):846-854 [doi:10.1002/hep.21496](https://doi.org/10.1002/hep.21496)

Age (years)

BMI (kg/m²)

IGF/diabetes

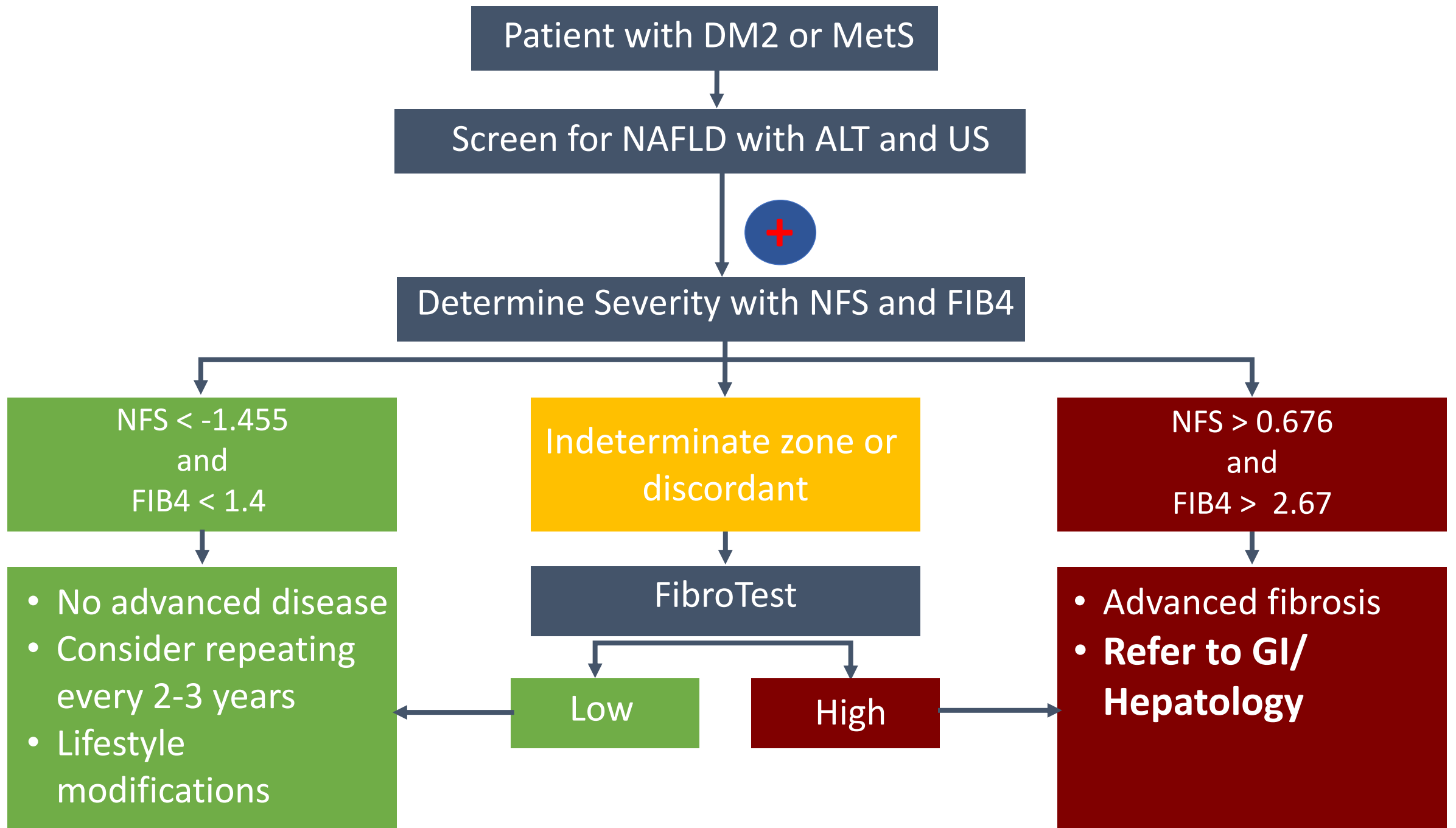
AST

ALT

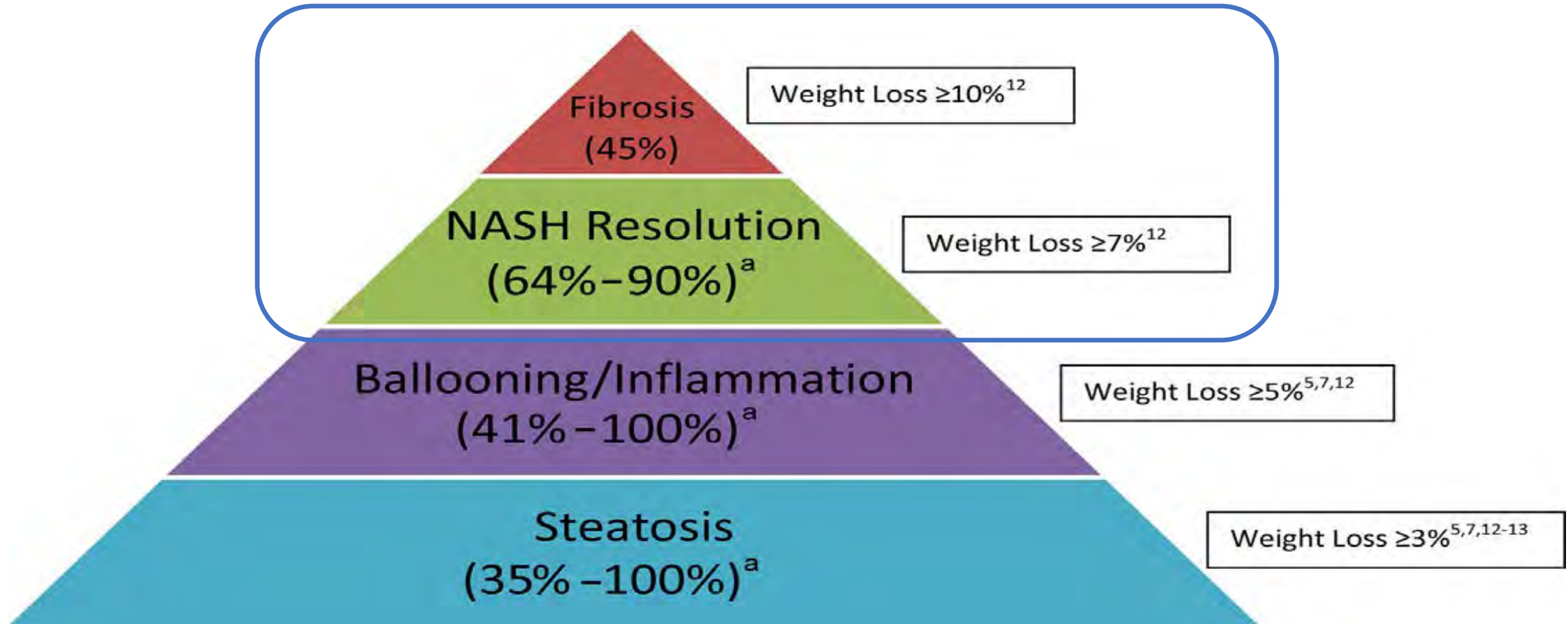
Platelets (×10⁹/l)

Albumin (g/l)





Treatment: % Weight Loss Associated With Histological Improvement



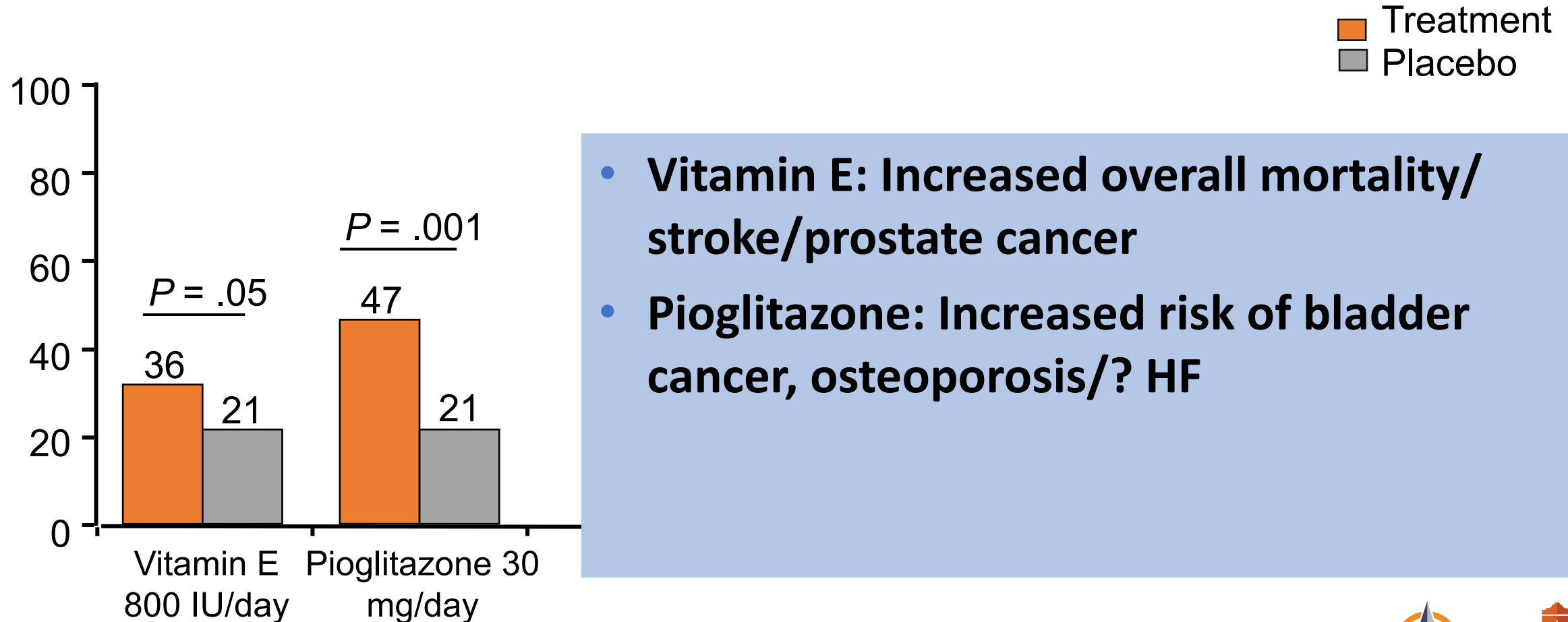
Changing the Attitude Toward Healthy Lifestyle in Texas



Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

- 247 patients with NASH and w/o DM
 - Pioglitazone: 30 mg/d
 - Vitamin E: 800 IU/d
 - Placebo
- Primary outcome: Improvement in histologic features of NASH

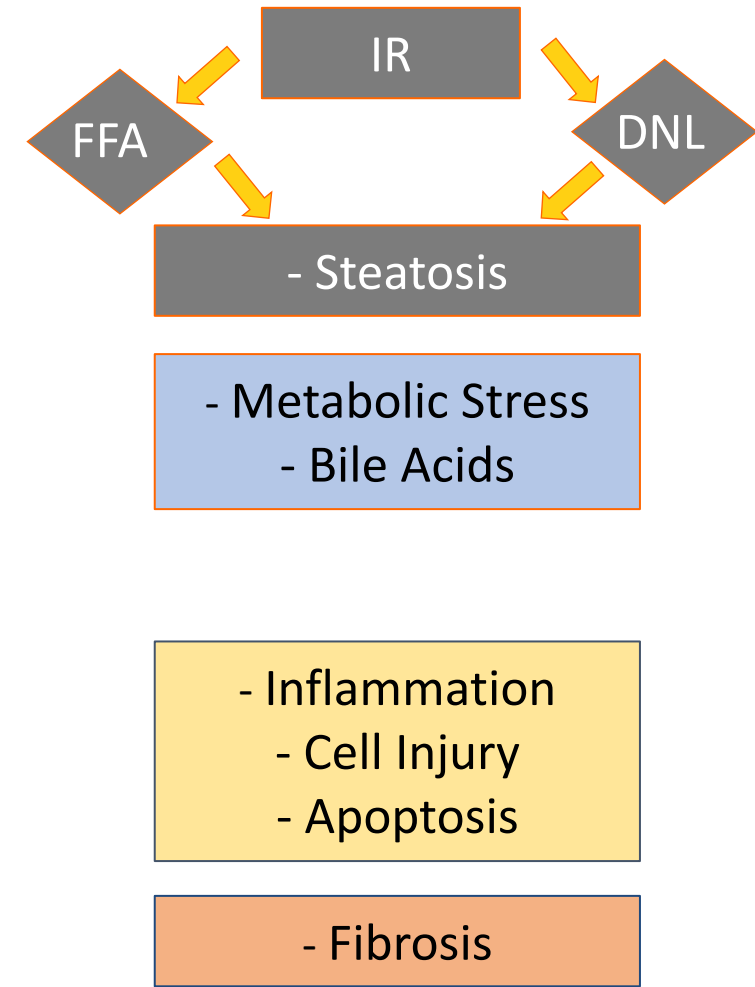
Resolution of NASH with Vitamin E and Pioglitazone Compared to Experimental Drugs



- **Vitamin E: Increased overall mortality/stroke/prostate cancer**
- **Pioglitazone: Increased risk of bladder cancer, osteoporosis/? HF**

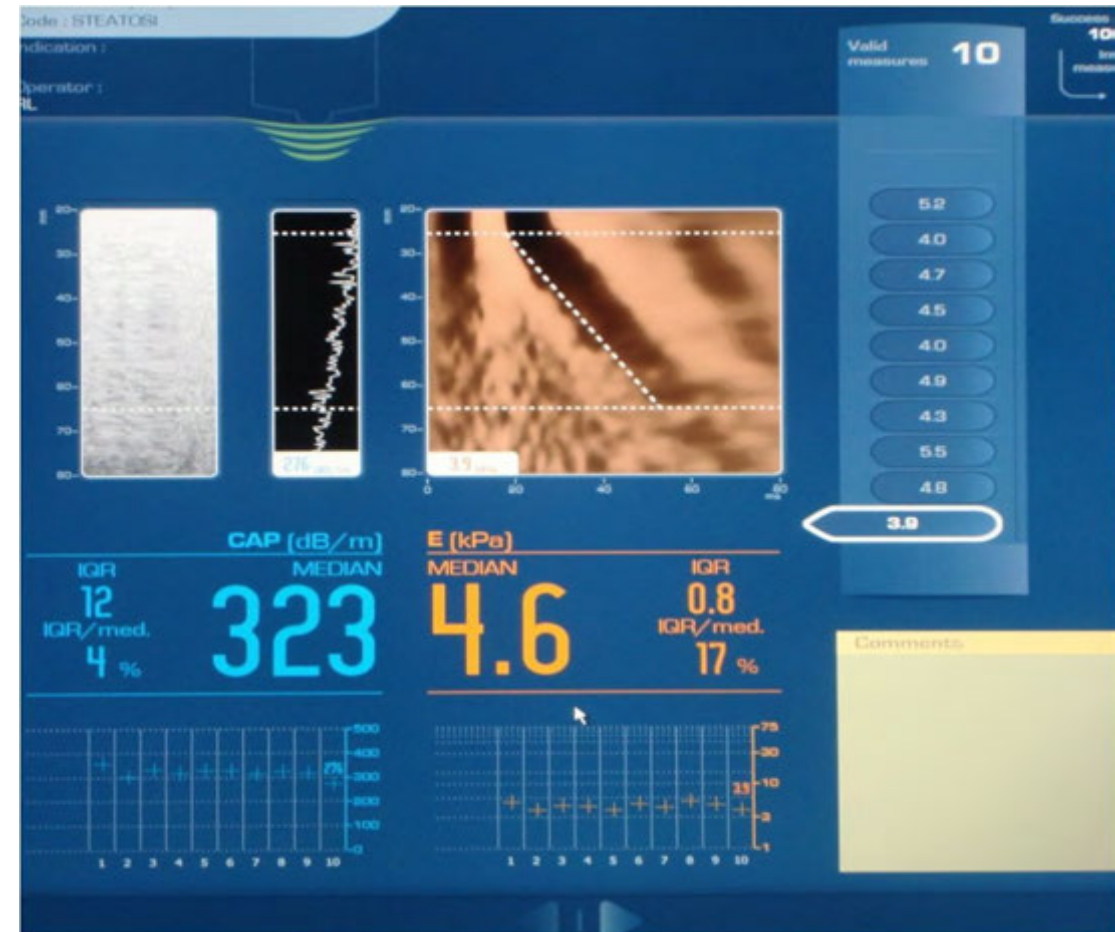
The Race to Cure NASH: Six Medications in Phase III Controlled Trials

- **Elafibranor**
 - **Aramchol**
 - **MGL-3196**
- Steatosis
- **Obeticholic acid (OCA):** FXR agonist (REGENERATE)
 - **Cenicriviroc (CVC):** CCR2/CCR5 inhibitor (AURORA)
 - **Selonsertib:** Apoptosis signal-regulating kinase (ASK1) inhibitor (STELLAR-3)

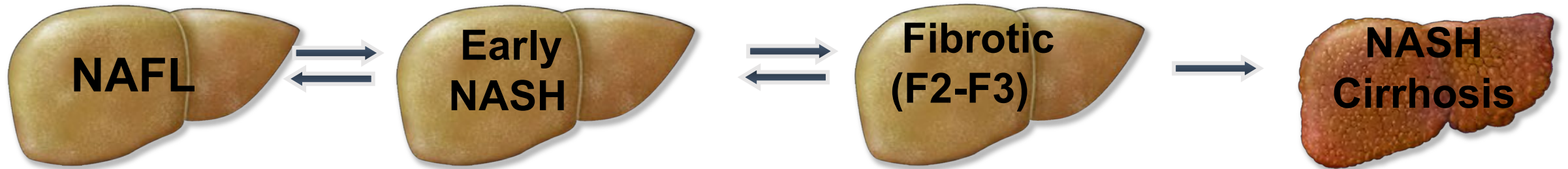


NAFLD is the New Type 2 Diabetes!

TE with CAP is the New HbA1C



The NAFLD Spectrum



HbA1C 5.7-6.4
Pre-Diabetes

HbA1C 6.5-8.5
Controlled
DM2

HbA1C > 8.5
Uncontrolled DM2

Diabetes
Complications
CKD,
Retinopathy,
CAD

TE < 6 kPa
CAP > 250 db/m

TE 7-8 kPa
CAP > 250 db/m

TE 9-14 kPa
CAP > 250 db/m

TE >15 kPa
TE > 25 kPa

Lifestyle
Modifications

Elafibranor
ACC inhibitor

OCA, CVC, ASK1

Combination
HCC/EV Screening

How Do We Manage NAFLD at The Texas Liver Institute?

Tina



- 50 y.o. F with BMI of 42 kg/m² and MetS presents with elevated LFTs. ALT 66, AST 56, albumin 4.5, platelet count of 270.
- CAP = 356, TE = 4.8 → Consistent with NAFL (= pre-diabetes)
- **Lifestyle modifications: weight loss of 7-10% + exercise**
- Follow up Fibroscan every 1-2 years.

Weakness



How Do We Manage NAFLD at The Texas Liver Institute?

Tony



Weakness



- 60 y.o. M with DM2, BMI of 39 kg/m² and MetS presents with elevated LFTs. ALT 66, AST 76, albumin 3.5, platelet count of 170.
 - TE = 12.8 → Consistent with advanced fibrosis (F3-F4)
 - **Refer to stage 3 fibrosis clinical trials: STELLAR3 (ASK1 inhibitor), REGENERATE (OCA), or AURORA (CVC)**
 - Consider HCC screening with US every 6 months

Take Home Messages

- NAFLD is very common and a serious liver disease even among young adults.
- Screening for NAFLD should be considered in patients with DM2 and MetS.
- The severity of NAFLD-associated fibrosis can be determined with non-invasive methods.
- NASH-specific therapies are coming soon and should change the attitude toward screening and treatment.

Q&A/Panel Discussion

Drs. Lawitz, Rodas & Alkhoury



15 Minute Break

