Fatty Liver Disease: Alcohol, NAFLD or both??

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Disclosures

Research Support: Enanta, Genfit, Intercept all paid to Institution

Consulting: Intercept

Liver Disease in the US

1 in 12 persons worldwide is living with viral hepatitis

Viral hepatitis is the leading infectious cause of death in Americans

Liver disease was the 12th leading cause of death in 2007 in the US

Likely underestimated, perhaps as high as 8th overall

As high as 4th in certain populations

40-60% due to HCV, 10-15% due to HBV

Liver Disease in the US

Cost of liver disease in the US:

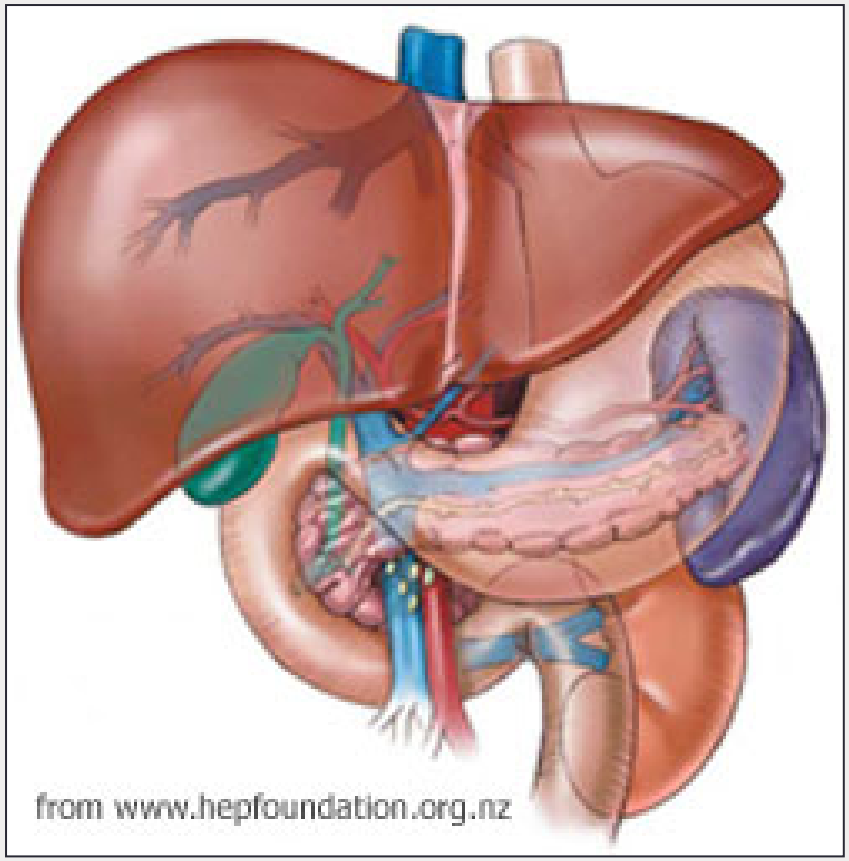
In 2004, NIH estimated the annual costs in US of chronic liver disease and cirrhosis is $1.6 billion

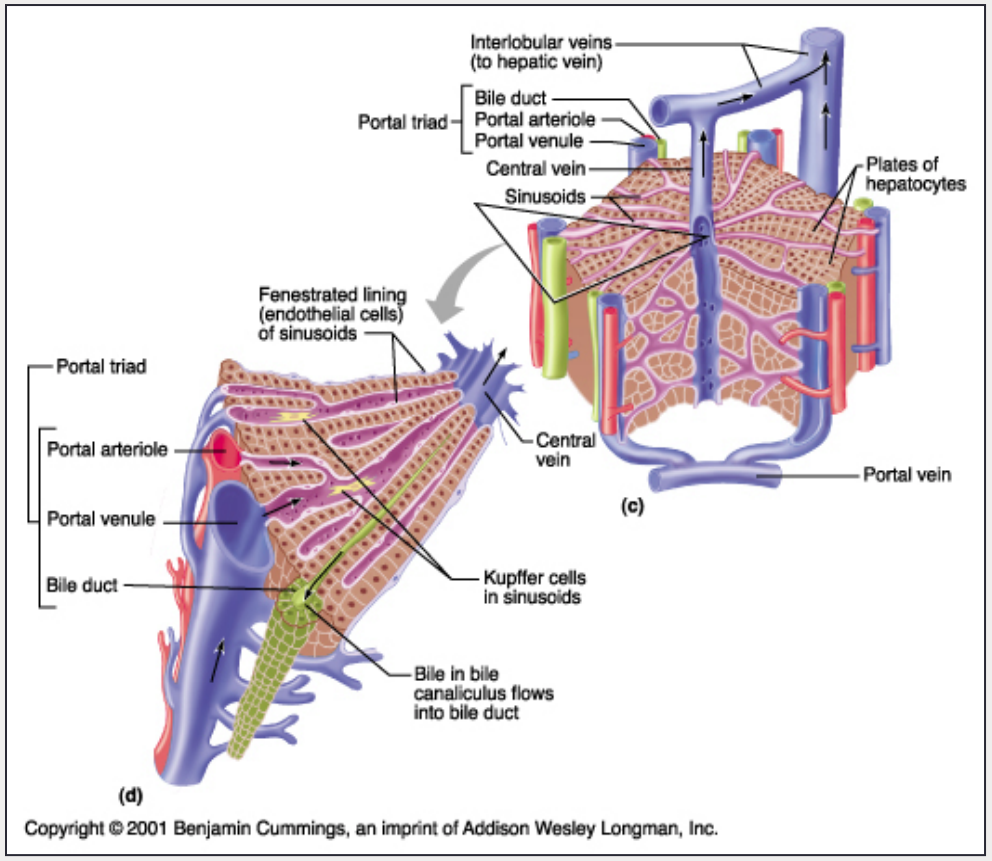
- Based upon an estimate of 5.5 million people with liver disease

More recent estimates of the population with liver disease in the US ranges from 15 to 30 million – indicating *annual cost may range from $5 to $10 billion*

Most of the *3-6 million* Americans with viral hepatitis *don't know they are infected*

Liver Anatomy





Aminotransferases

ALT

- Liver specific
- Located in the cytosol

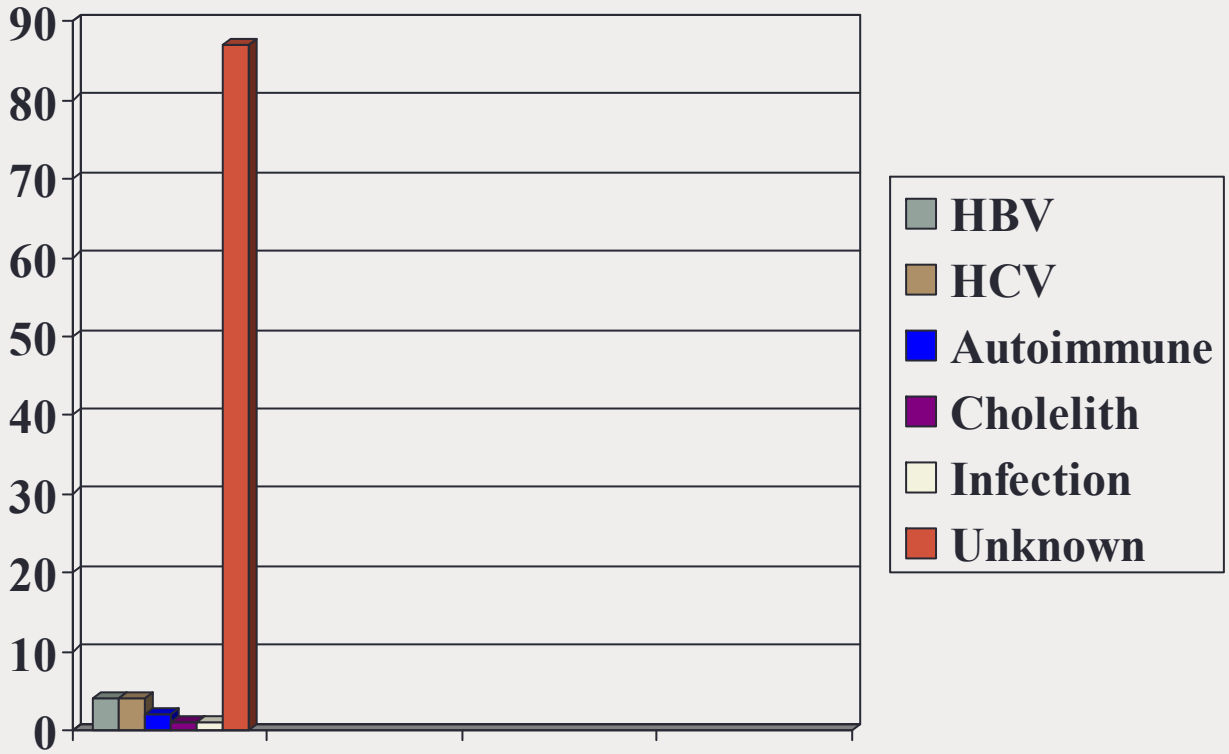
AST

- Found in liver, skeletal and cardiac muscle, kidney, brain, pancreas, and blood cells
- Present in both cytosol and mitochondria

AST/ALT Ratio

- In most liver injury (including NASH), the ratio is ≤ 1
- In alcohol-related hepatitis, ratio may be > 2
  - Vitamin B6 (pyridoxine) deficiency
  - Mitochondrial AST release

Abnormal ALT



19,877 Air Force Recruits, 99 (.5%) with elevated ALT, 12% of these with identifiable cause

Kundrotas et al. Dig Dis Sci, 1993

What is a normal ALT?

- Levels may not rise with cirrhosis or in the absence of significant ongoing liver injury
- Levels may fluctuate in normal people
- 4% of the general population have abnormal liver function tests
- **10-20% will develop cirrhosis**
- ~15% of patients with chronic liver disease (HCV, NAFLD) have normal tests despite abnormal histology
- New cutoff recommendations
- **Men-35 IU/ml**
- **Women-25 IU/ml**

Alkaline Phosphatase

Elevation results from increased synthesis and release into serum rather than from impaired biliary secretion

May not become elevated for a day or two following acute biliary obstruction

Half life is one week

May remain elevated for several days after resolution of biliary obstruction

Levels up to three times normal are nonspecific

Striking elevations can be seen with infiltrative disease or with biliary obstruction

With focal intrahepatic duct obstruction, AP may be elevated while bilirubin remains normal

Gamma Glutamyl Transpeptidase

Catalyzes the transfer of glutamyl groups of peptides such as glutathione to other amino acids

Derived from hepatocytes and biliary epithelia

Not found in bone

Can confirm hepatic origin of elevated AP

Induced by alcohol

GGT/AP ratio > 2.5 has been reported to be suggestive of significant alcohol use

Unconjugated Hyperbilirubinemia

Indirect bilirubin fraction>85%

Increased production

Hemolysis (transfusions, medications, ineffective erythropoiesis), resorption of a hematoma, or muscle injury

Disorders of conjugation from mutations in bilirubin uridine diphosphate glucuronyl transfersase (UGT)

Crigler-Najjar syndrome

Gilbert's syndrome

Acquired defects in uptake or conjugation

Conjugated Bilirubinemia

Impaired biliary excretion

Choledocholithiasis

Malignancy

Primary biliary cirrhosis, primary sclerosing cholangitis

Infiltrative Disease

End stage liver disease

Disorders of canalicular bile transport

Dubin-Johnson syndrome

Rotor syndrome

Sepsis

Liver Synthetic Function

"Liver function test" is a misnomer

Liver function is measured by synthetic ability:

Protein Synthesis:

Albumin, prothrombin time/INR

Nutrient Metabolism

Gluconeogenesis, ammonia

Biotransformation

Bilirubin (glucoronidation)

Immune Defense

Bile Acid Synthesis

Prothrombin Time

PT measures rate of conversion of prothrombin into thrombin

Requires factors II, V, VII, X

Prolonged PT may occur in patients with acute or chronic liver disease secondary to hepatocellular dysfunction or chronic cholestasis

All major coagulation factors (*except factor VIII*) are synthesized in the liver

Factors in PT have a short half-life (6 hrs)

Useful in monitoring synthetic capacity in patients with acute liver failure in real time

Prothrombin Time

Vitamin K deficiency:

Cholestasis causes fat and fat-soluble vitamin (A, D, E, K) deficiency

Required for factors II, VII, IX, X

In the setting of deficiency, vitamin K should reduce PT by 30% within 24 hours

Route of administration may be important

May give intravenously if concerned about oral absorption

Albumin

- 10g of albumin is synthesized and excreted by the liver daily
- Low albumin is not specific for liver disease
- **Dependent on extrahepatic factors: Inflammation, nutrition, volume status, vascular integrity, catabolism, loss in urine or stool, hormonal factors**
- Long half-life (20 days)
- Less useful than PT in assessing hepatic synthetic function in the acute setting
- Can take weeks to normalize after resolution of an acute illness

Hepatitis vs. Cholestasis

	Hepatitis	Cholestasis
Aminotransferases	2-100x	1-5x
Alkaline Phosphatase	1-3x	2-20x
Bilirubin	1-30x	1-30x
PT response to vitamin K	None	Decrease in prolongation
Albumin	Decreased	Normal or decreased (chronic)

Acute v. Chronic

	Acute	Chronic
Duration of elevation	< 6 months	> 6 months
Prognosis	Can be self-limiting	Spontaneous recovery rare
Regeneration	Can result in normal liver	Results in fibrosis
Presentation	Can have severe increases in liver tests	Liver tests less elevated
Transplantation	For fulminant liver failure patients	Decompensated cirrhosis

Chronic Liver Disease and Cirrhosis

Cirrhosis is end stage scarring of the liver

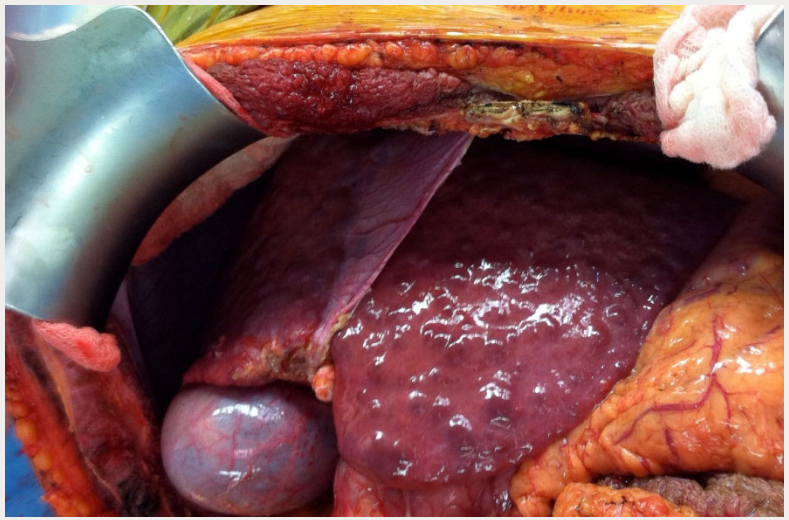
12th leading cause of death in US in 2006

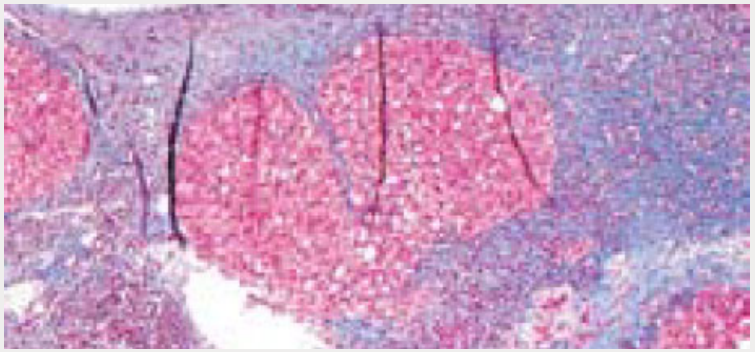
1.1% of all deaths

Age-adjusted death rate of 9.6 per 100,000 population

Probably underestimated

10 year mortality 34-66% depending on cause





Rosen H. NEJM, 2011

Chronic Liver Disease and Cirrhosis

Etiology

Hepatocellular

- Viral: HBV, HCV
- Alcohol
- NAFLD
- Hemochromatosis
- Medications
- Autoimmune
- Vascular
- Metabolic

Cholestatic

- PBC, PSC
- Secondary biliary cirrhosis
- Medications
- Neoplastic

Evaluation of Abnormal Liver Tests
Serologies

Acute Liver Disease

- Hepatitis A IgM
- HBsAg, HBc IgM
- HCV RNA
- Acetaminophen, tox screen
- Pregnancy test
- ANA, ASMA, quant IgGs
- Ceruloplasmin if appropriate age

Chronic Liver Disease

- HCV Ab
- HBsAg, HBc IgG
- Ferritin, iron studies
- A1c, FG, lipids
- ANA, ASMA, quant IgGs, AMA
- Ceruloplasmin, α 1 AT

Evaluation of Abnormal Liver Tests
Imaging

- Ultrasound
- Test of choice for gallstones, dilated ducts, ascites
- Can also image vessels with doppler
- Not optimum for CBD, pancreas, mass lesions <2 cm
- Limitations dependent on body composition
- CT scan
- Mass lesions, CBD, pancreas, extrahepatic structures
- Better for obese patients, differentiating intra and extrahepatic obstruction, small mass lesions
- Can usually diagnose Budd-Chiari
- Limited in patients with renal disease, need IV contrast

Evaluation of Abnormal Liver Tests

Imaging

- MRI
  - Little advantage over CT except regarding vessels, vascular tumors
  - Good for determining if cancer is resectable
  - No longer used for patients with significant renal failure
- HIDA
  - Can evaluate cholecystitis and CBD obstruction
  - Need functioning liver and gallbladder, not helpful in the setting of significant cholestasis
- EUS/ERCP
  - Excellent delineation of biliary anatomy and may have therapeutic applications
  - Best for pathology near papilla (stones, strictures, malignancies)

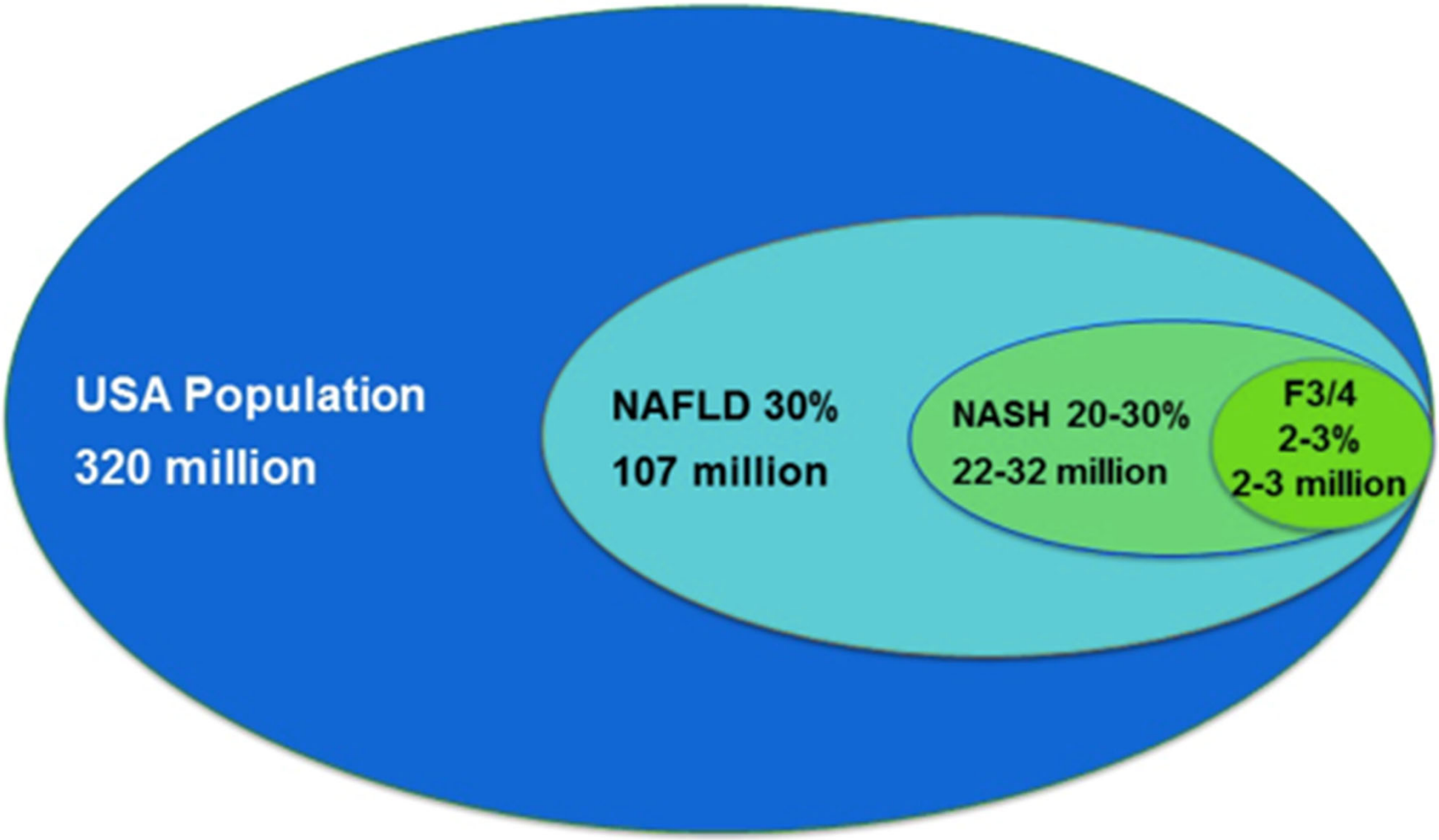
Clinical Challenges in NAFLD

- There are no screening recommendations
- There are no FDA approved treatments
- Diet and Exercise Are Difficult
- Expected leading cause for transplant in 2020

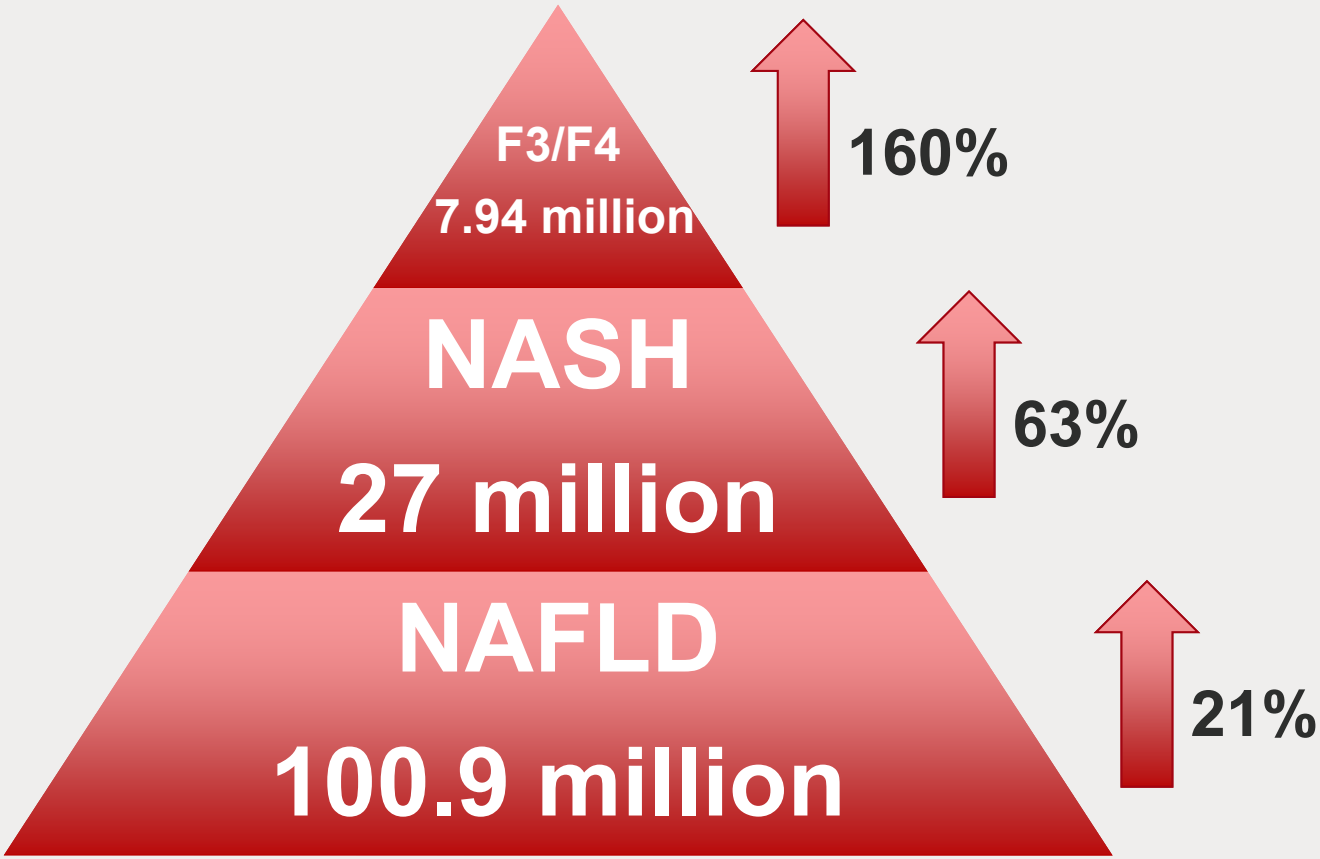
Definitions

Nonalcoholic Fatty Liver Disease	**Entire spectrum of fatty liver disease <u>without significant alcohol use</u>, ranges from fatty liver to steatohepatitis to cirrhosis**
Nonalcoholic Fatty Liver (NAFL) or Simple Steatosis	Hepatic steatosis with no evidence of hepatocellular injury (ballooning) or fibrosis
Nonalcoholic steatohepatitis (NASH)	Hepatic steatosis + inflammation with hepatocyte injury (ballooning) with or without fibrosis
NASH cirrhosis	Cirrhosis + previous histological evidence of steatosis or steatohepatitis

NAFLD Common in the United States

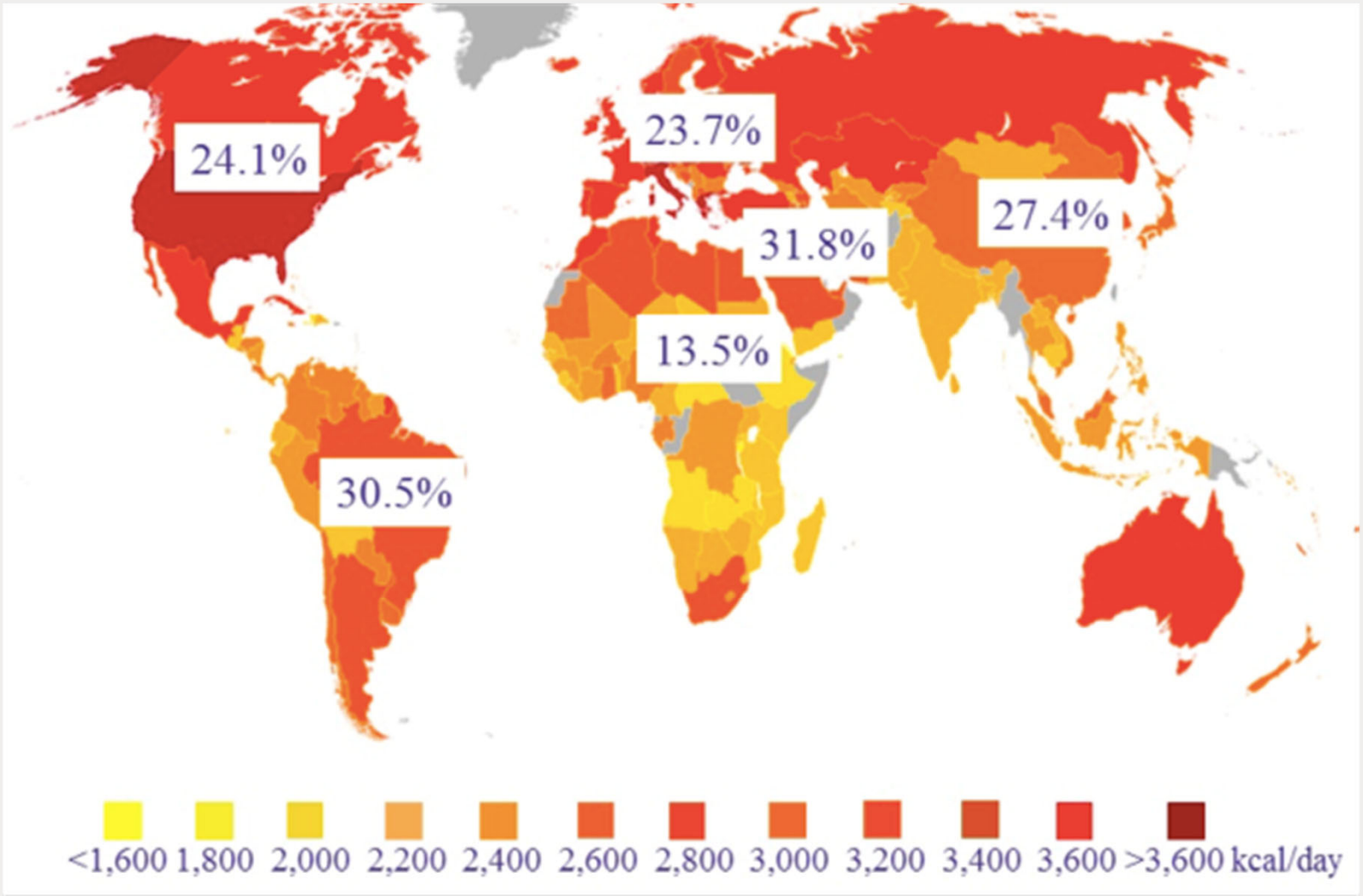


NAFLD Estimates: 2030



Estes, Hepatology 2018

NAFLD Seen Globally



Culprit in NAFLD is High Fructose Corn Syrup

De novo Lipogenesis

- No regulation of liver uptake
- No regulation of conversion to fat
- No increase in leptin

Insulin Resistance and Dietary Free Fatty Acids Are Key Mediators in Pathogenesis

Pancreas

Insulin resistance

↑ Insulin

Increase in Triglycerides and Free Fatty Acids Lead to Liver Cell Death

Increased Lipolysis

DNL

FFA

β-oxidation

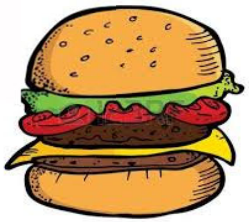
↑ Free fatty acids (FFA)

Adipose tissue

TG ↑

Very low density lipoproteins (VLDL)

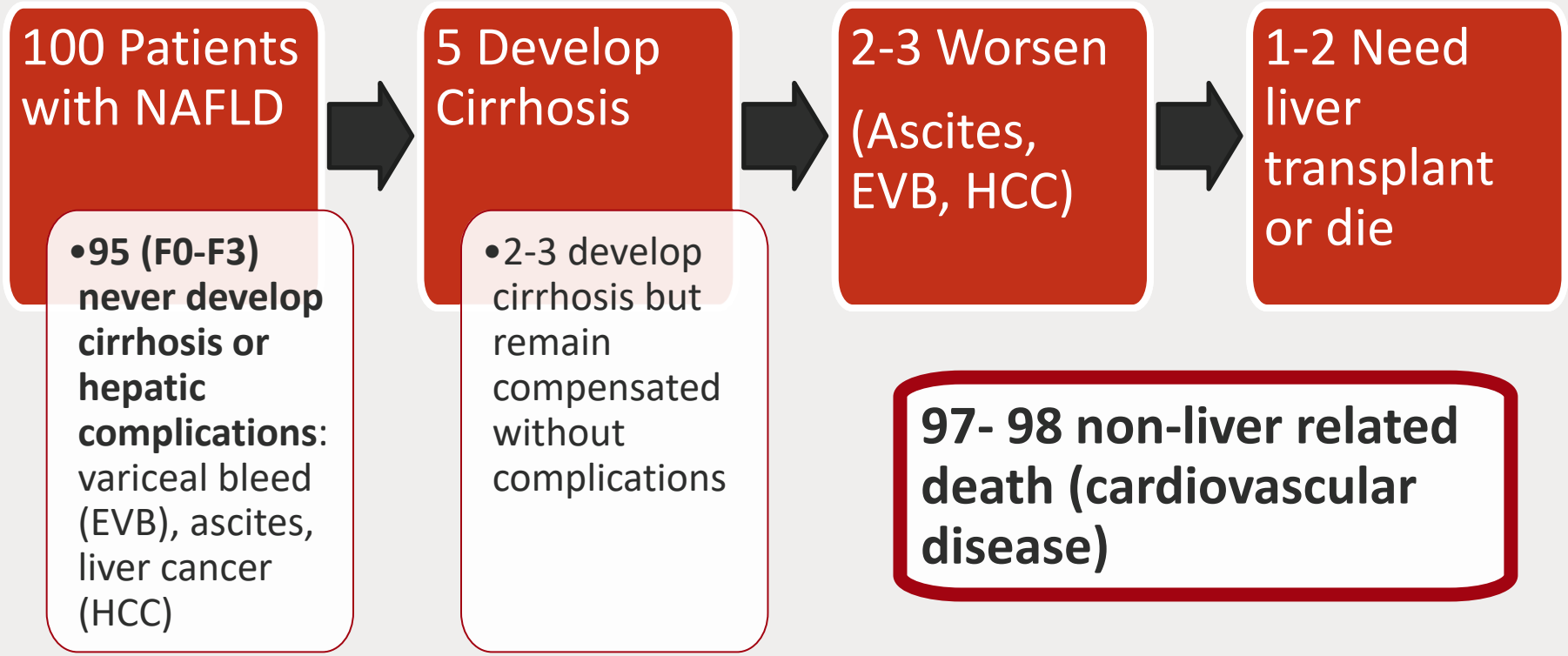
Dietary FFA



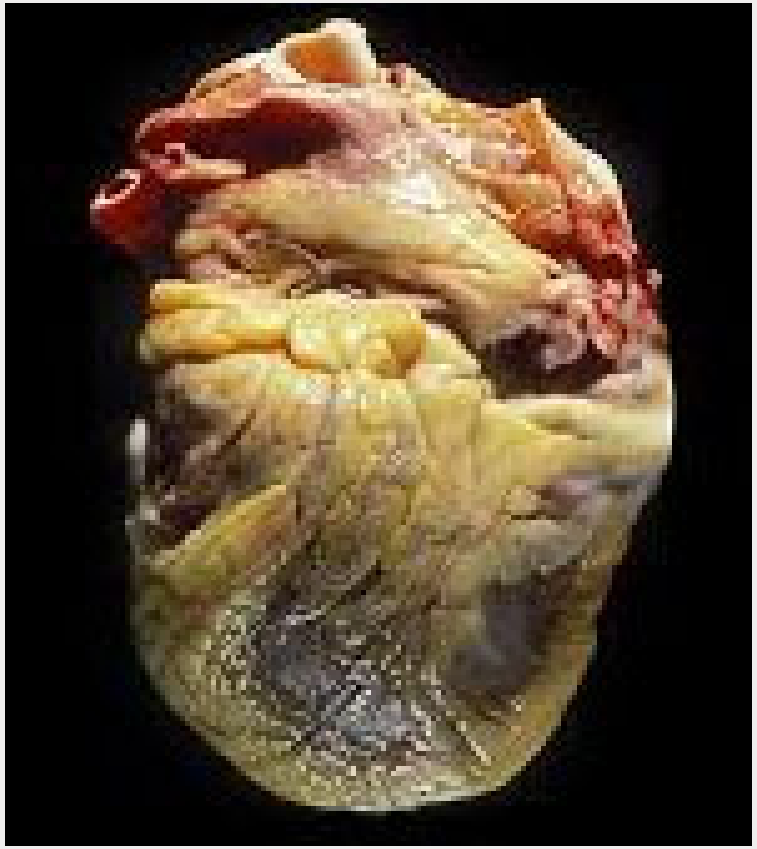
NAFLD Outcomes Depend on Disease Severity

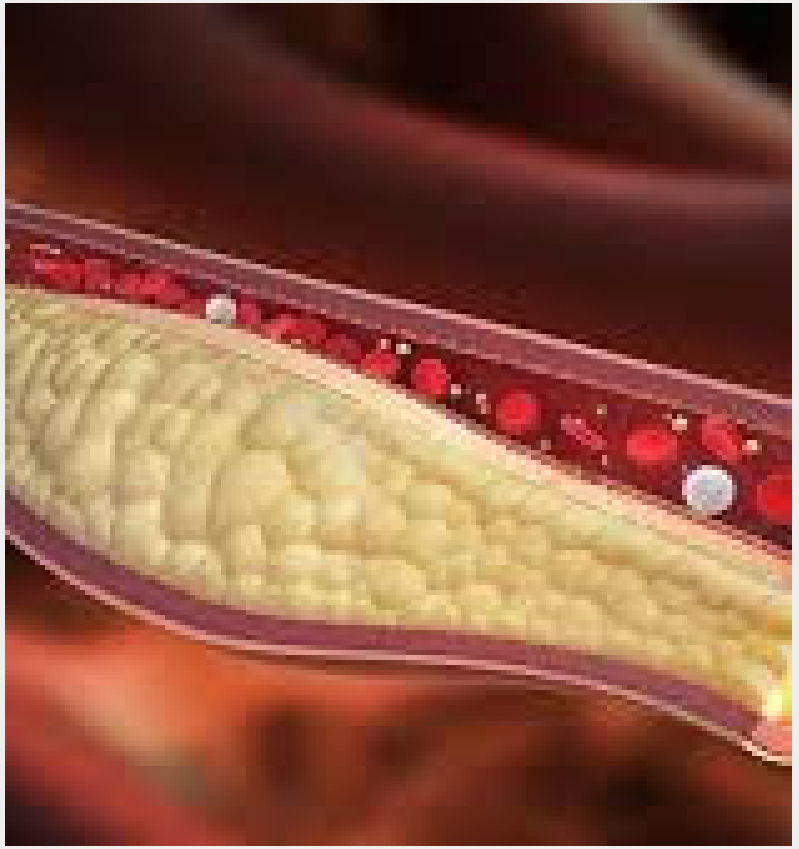
- Simple steatosis is largely benign with minimal risk of cirrhosis
- NASH is progressive with 20% risk of cirrhosis over 10 years
- **NASH cirrhosis carries liver cancer risk: 2-4% per year**

NAFLD
Natural History



Patients with NAFLD Are Twice as Likely To Die of Heart Attack and Stroke





Statins should be started when indicated

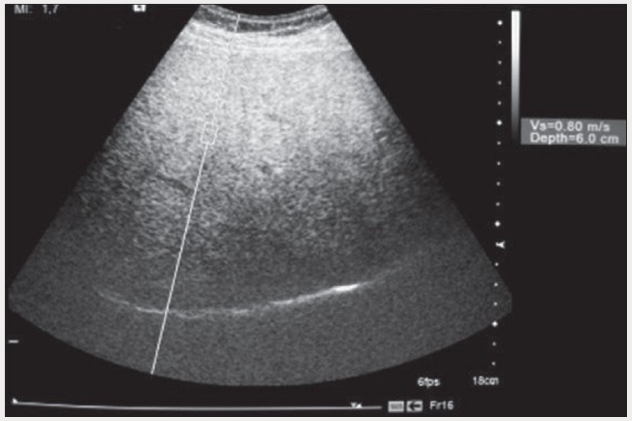
There Are No Recommended Screening Guidelines for NAFLD

- Long term outcomes unknown
- Treatment options limited
- Not proven to be cost-effective

- Higher index of suspicion for patients with diabetes

Most Patients with NAFLD Have No Symptoms

- Right upper quadrant pain and fatigue
- Hepatomegaly
- Unexplained serum aminotransferase (ALT) abnormalities
- Incidental finding of fat in liver on imaging done for another reason



Screening for NAFLD

Ultrasounds are expensive

60-94% sensitivity, increases with severity

84-95% specificity

Lack of effective pharmacologic treatment options

General population screening is NOT recommended

INSTEAD

Attempt to identify high risk patients

Use of ALT to identify NASH

Advantages:

Part of routine monitoring

Cheap

Disadvantages:

Poor correlation with histology

Patients with cirrhosis can have normal ALT

Different labs have different “normal” values

ALT fluctuates

Diagnosis Can Be Difficult

- AST and ALT elevation in 90% of patients
  - AST/ALT ratio < 1 in NAFLD
  - AST/ALT ratio > 1 in Alcoholic liver disease
- Biopsy only way to differentiate between simple steatosis and NASH

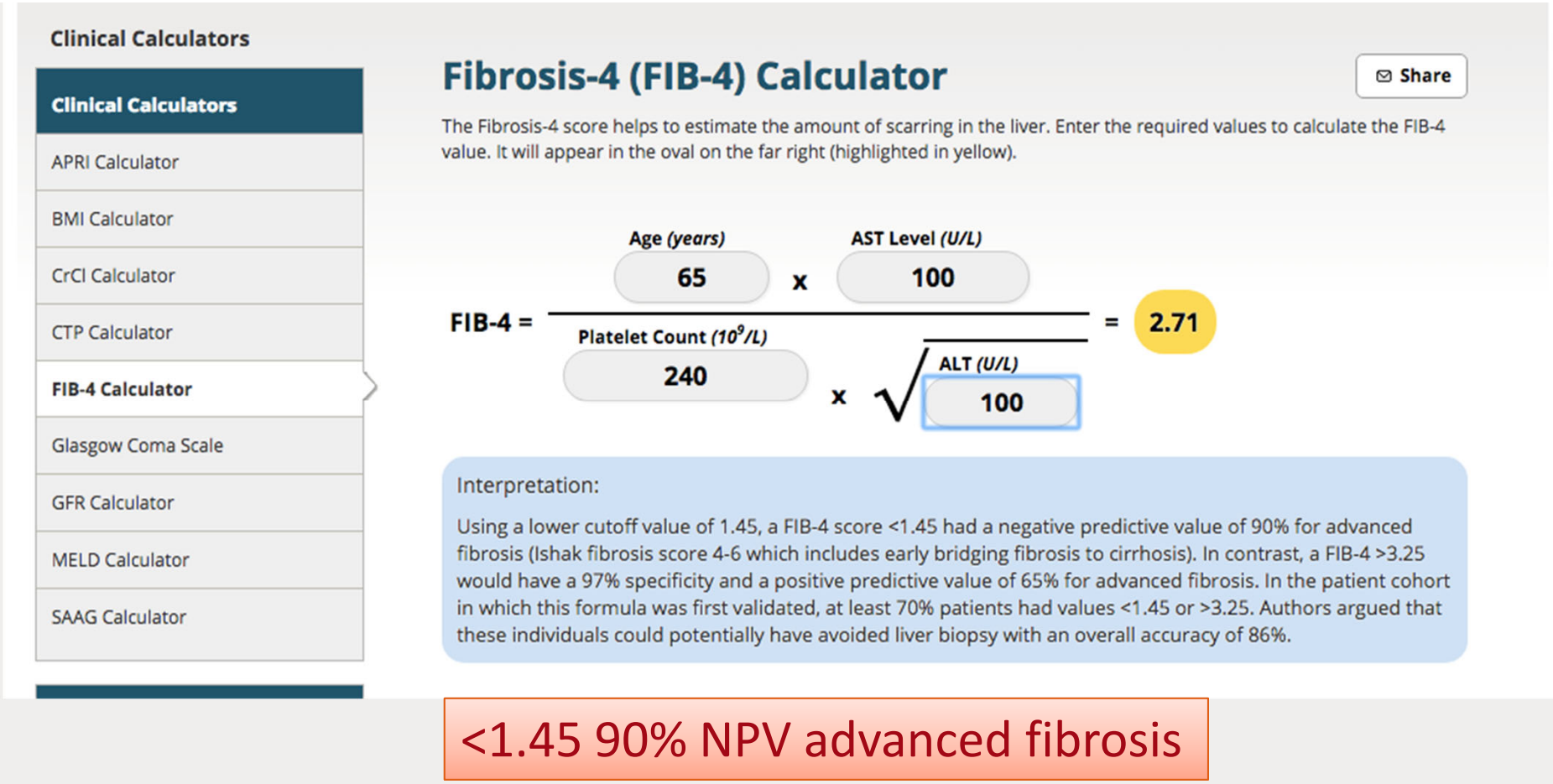
- Non-invasive testing can help guide management

Non-Invasive Testing of Fibrosis Can Help Delineate Need for Biopsy/Liver Cancer Screening

Test	Parameters
AST/ALT ratio	AST/ALT
BARD*	**B**MI ≥ 28 kg/m^2 = 1 **A**ST/ALT **R**atio ≥ 0.8 = 2 **D**iabetes = 1
APRI	AST, platelets
NAFLD Fibrosis Score (NFS)*	IFG/diabetes, AST/ALT, Age, BMI, platelets, albumin
FIB-4	ALT, AST, platelets, age

- Similar components
- BARD and NFS specific for NAFLD
- **Reliable for excluding advanced fibrosis**
- NFS and FIB-4 >80% PPV for advanced fibrosis

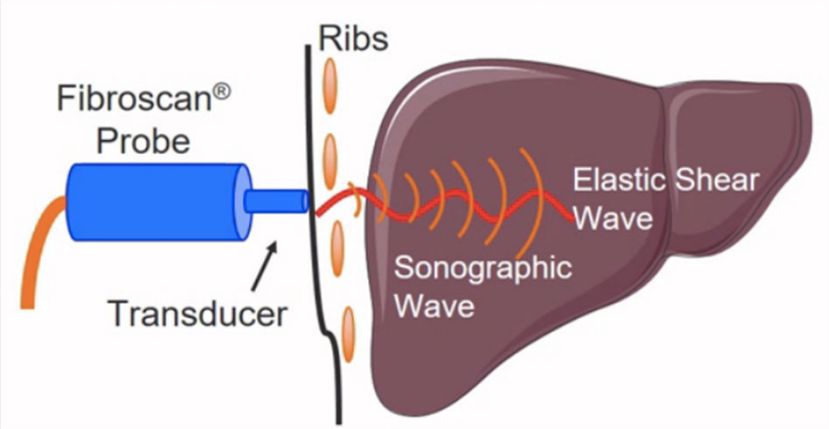
Fibrosis-4 Score Can Guide Need For Biopsy and Provide Assurance



<1.45 90% NPV advanced fibrosis

Transient Elastography Can Be Helpful in Ruling Out Fibrosis and Advanced Fibrosis

- Probe delivers mechanical impulse-induces a shear wave through the liver
- Velocity reflects hepatic elasticity and stiffness
- Excellent accuracy for advanced fibrosis (AUC 0.9)
- High Negative Predictive value >90%



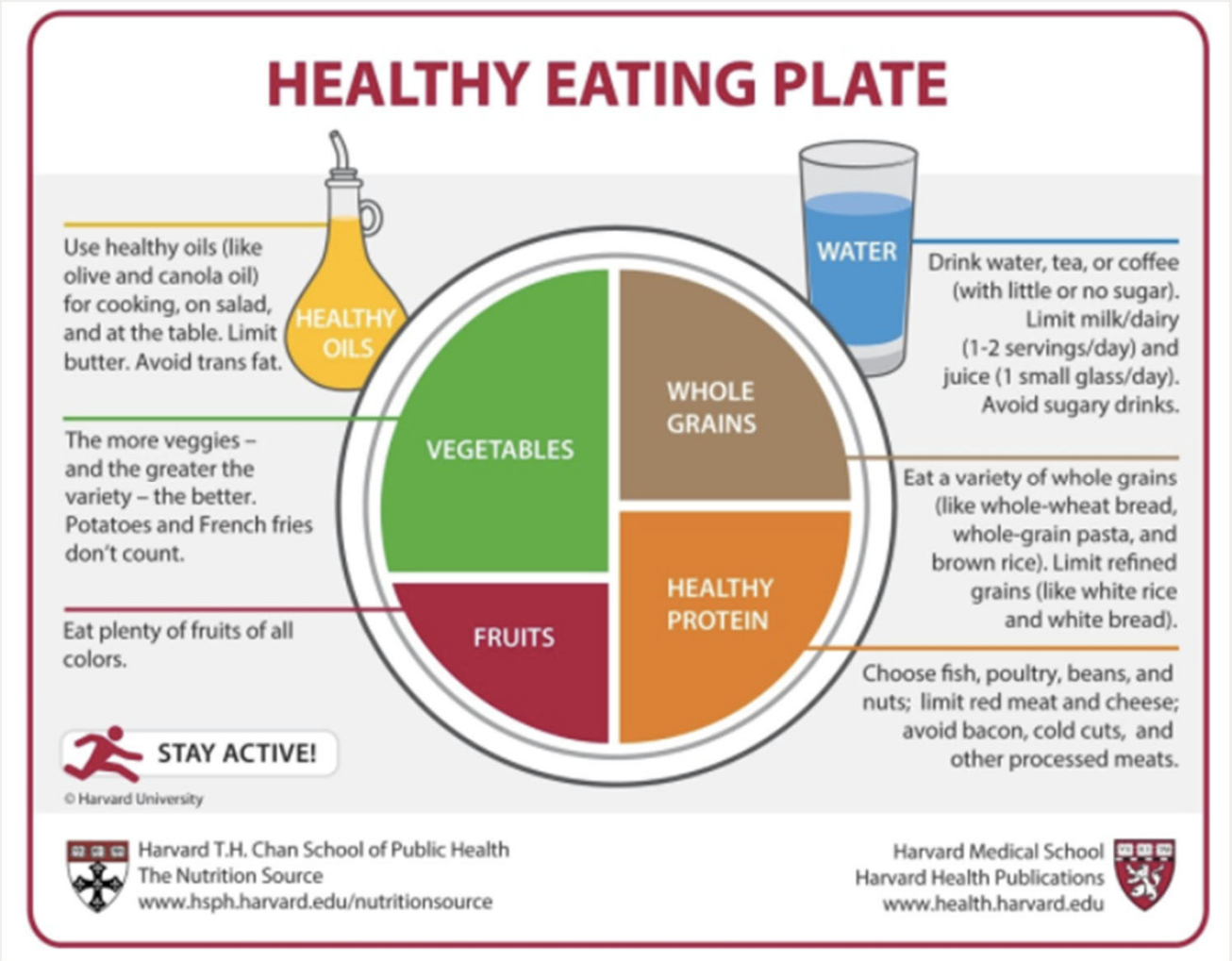
Weight Loss and Exercise Cornerstone of Treatment of NAFLD

- **Up to 3-5% weight loss improves steatosis**
- **Up to 7-10% weight loss has been associated with significant improvement in NAFLD Activity Score**

Healthy Eating Should Be Cornerstone of Treatment

- Keep the focus positive
  - Goal is lifelong consistency
  - Not “Dieting”
- Limit simple sugars
- Use healthy oils and limited amounts
- Include protein in meals
- Avoid large portions
  - Split restaurant meals

Harvard Healthy Eating Plate Can Be Used to Guide Patients



Available in 20 languages

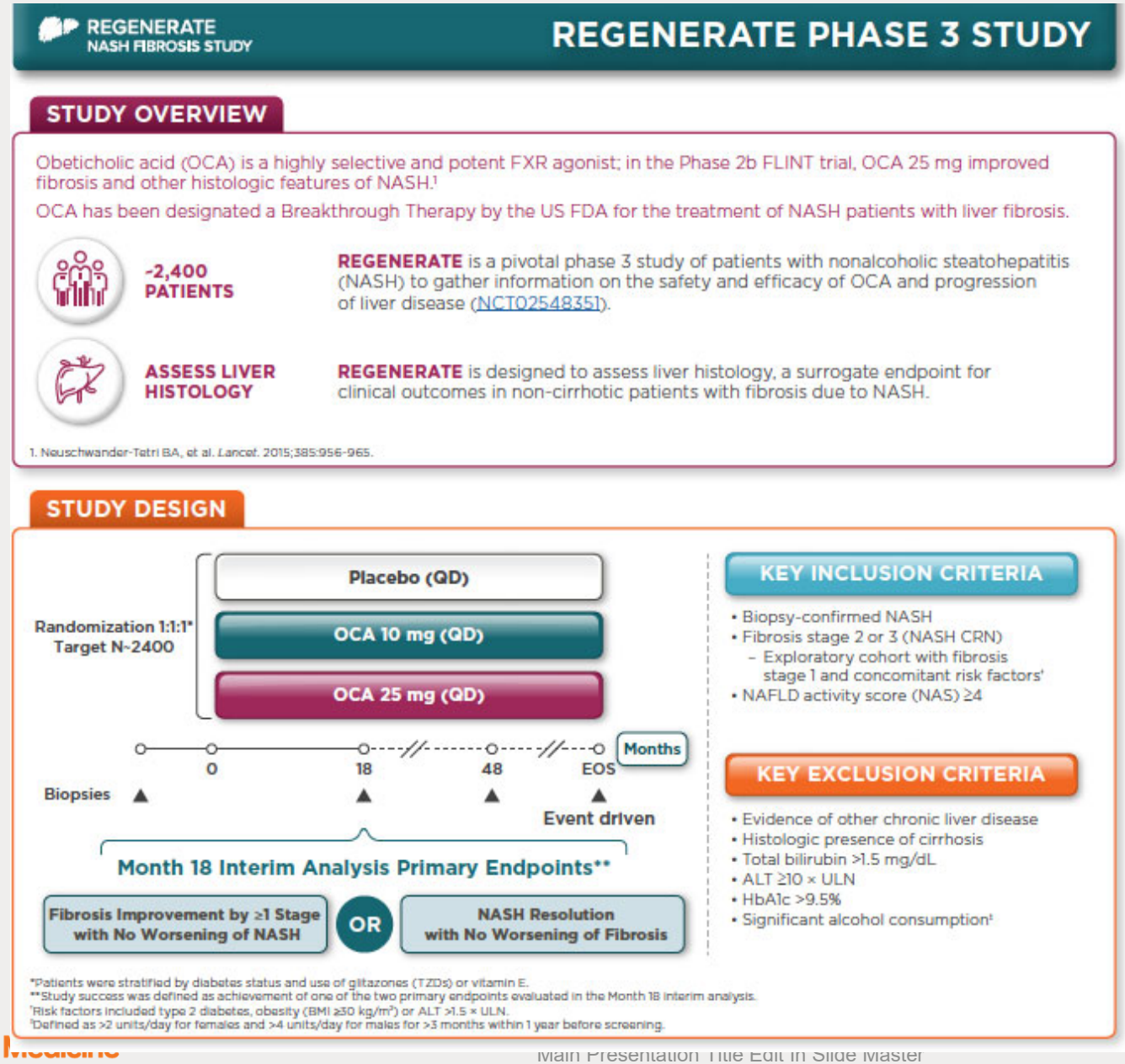
Medications

Not specifically for NAFLD	Specifically for NAFLD
Vitamin E	NONE!
Pioglitazone	
GLP-1 analogues (ie, liraglutide)	
SGLT2 inhibitors (ie, Invokana)	
Statins	
Weight loss medications/surgery	

Vitamin E Can Be Used to Treat Biopsy-Proven Non-Diabetic NASH

- Prior studies showed improvement in enzymes and inflammatory activity
- No improvement in fibrosis
- Not FDA approved
- ?Increased risk of prostate cancer
- AASLD/AGA/ACG recommend vitamin E
  - Biopsy proven NASH
  - 800 IU/ daily

Obeticholic Acid

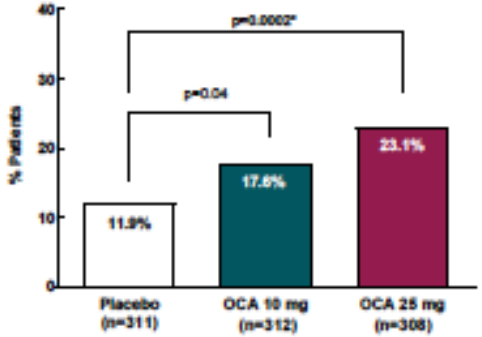


EFFICACY RESULTS

- OCA 25 mg met the primary fibrosis endpoint at the Month 18 interim analysis
- The antifibrotic effect was dose dependent and consistent across endpoints and key subgroups
- Although the primary NASH resolution endpoint was not met, OCA ameliorated steatohepatitis based on pathologist overall assessment and improvement in key disease activity parameters
- OCA rapidly and sustainably improved ALT, AST and GGT (not shown)

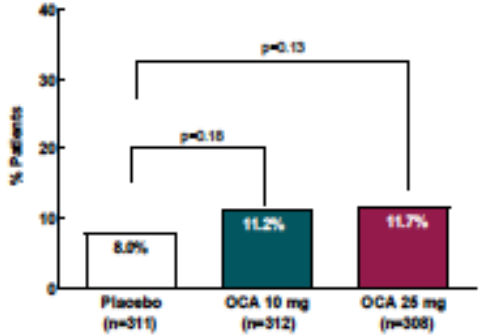
Primary Endpoint at Month 18: ITT population (NASH with stage 2 or 3 liver fibrosis, N=931)

Fibrosis Improvement by ≥1 Stage with No Worsening of NASH



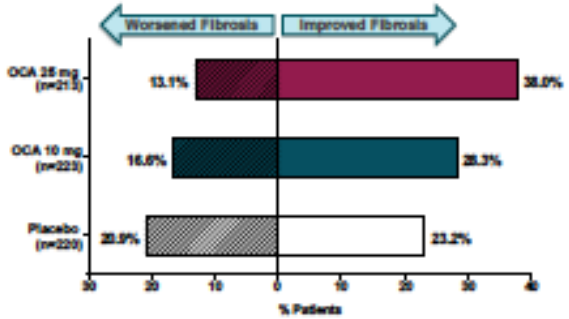
Primary endpoint definition: improvement in fibrosis by ≥1 stage (NASH CRN) with no worsening of NASH (defined as no worsening of hepatocellular ballooning, lobular inflammation, or steatosis). Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 Interim Analysis.
*Statistically significant in accordance with the statistical analysis plan as agreed with the FDA. All other p values are nominal.

NASH Resolution with No Worsening of Fibrosis



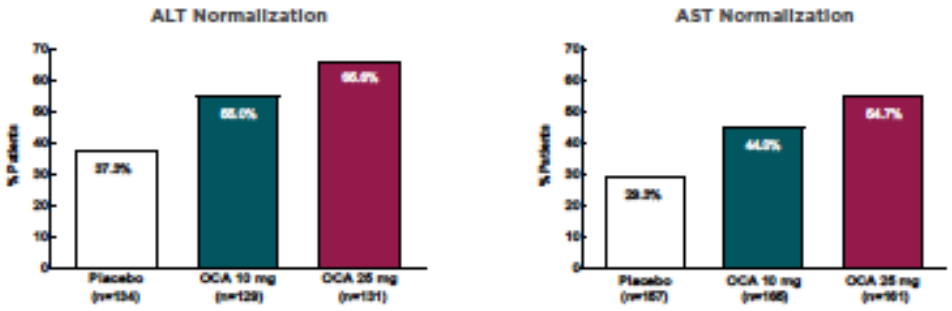
Primary endpoint definition: (i) overall pathologist assessment of "no steatohepatitis" and (ii) hepatocellular ballooning = 0 and lobular inflammation = 0 or 1; and (iii) no increase in fibrosis stage from baseline. Study success was defined as achievement of one of the two primary endpoints evaluated in the Month 18 Interim Analysis.

Regression or Progression of Fibrosis by ≥1 Stage (Per Protocol Population*)



*Per protocol population with available fibrosis stage data at Month 18 / End of Treatment (n=656)

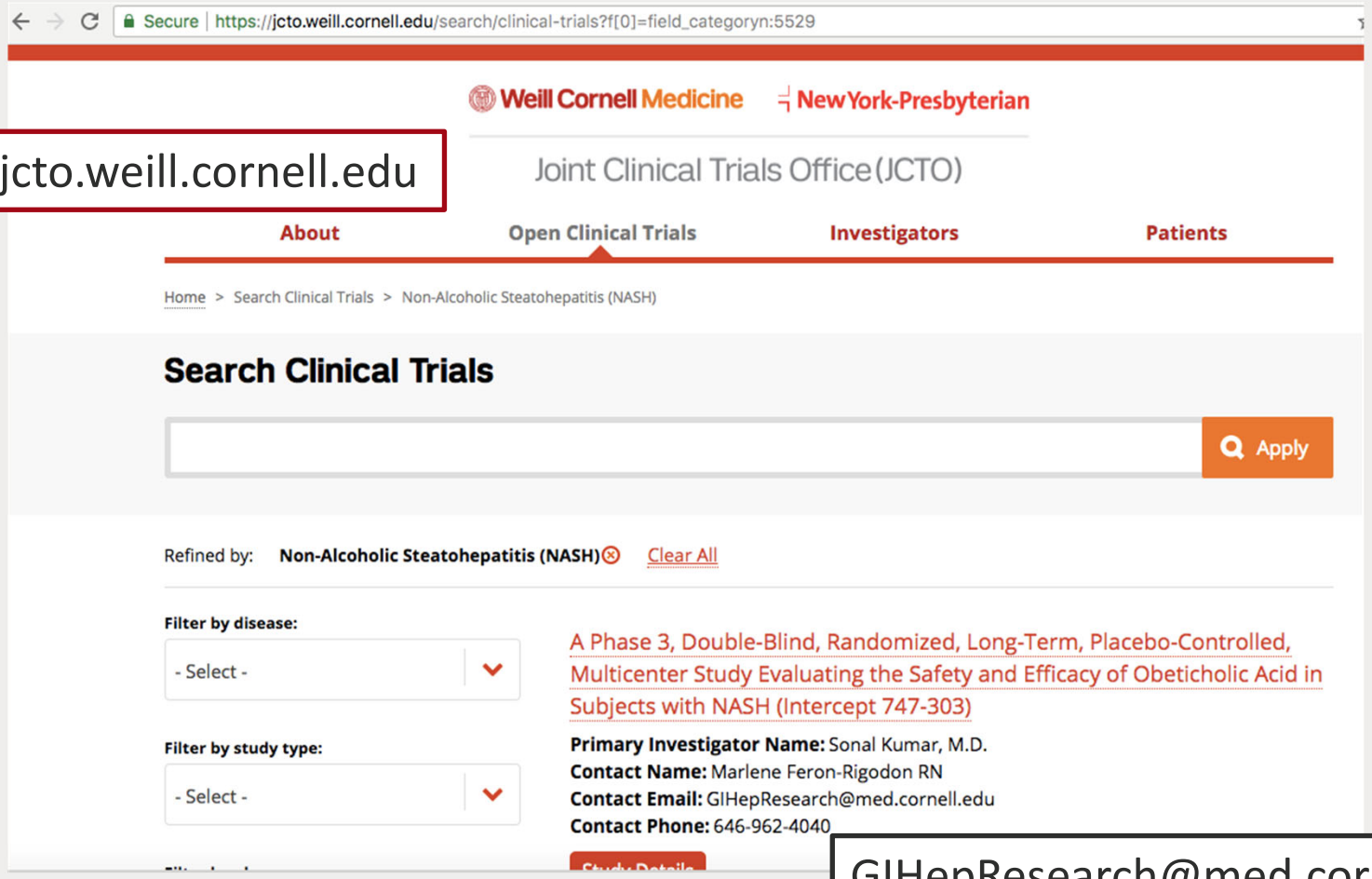
Normalization of Transaminases in Patients with Elevated Baseline Values (Per Protocol Population*)



Data for normalization by Month 18 are based on ULNs established by central laboratories: 55 U/L (ALT) and 34 U/L (AST).
*Subset of the per protocol population with elevated ALT and AST at baseline.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

Patients with Biopsy Proven NASH and Fibrosis Are Eligible for Clinical Trials

https://jcto.weill.cornell.edu



GIHepResearch@med.cornell.edu

Burden of ALD

5.9% of all global deaths attributable to alcohol in 2012

- US 2016: 88,000 alcohol v 64,000 drug overdose deaths

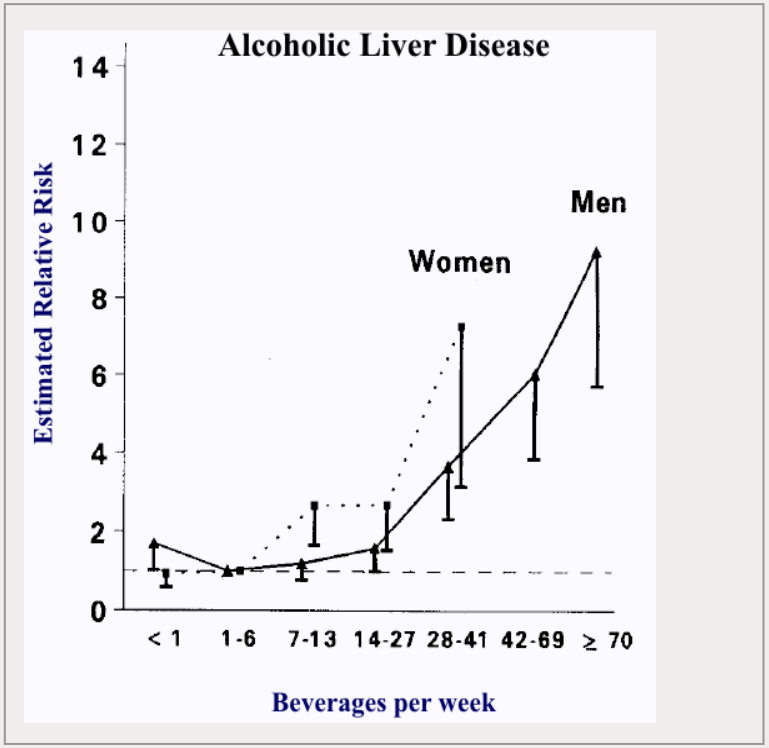
Half of the mortality in cirrhosis

- US: 48%
- UK: 84%

Defining “safe” drinking

Low Risk for AUD according to NIAAA

Pattern	Women	Men
Over 2 hours:	**≤3 drinks**	**≤4 drinks**
	or	or
Per week:	**≤7 drinks**	**≤14 drinks**



Becker *Hepatology* 1996
Dufour *Semin Liver Dis* 1998

CDC Defines Standard Drink

Recommended Amount from Centers for Disease Control and Prevention

Women: No more than **1 drink per day**, no more than 7 drinks per week

Men: No more than **2 drinks per day**, no more than 14 drinks per week

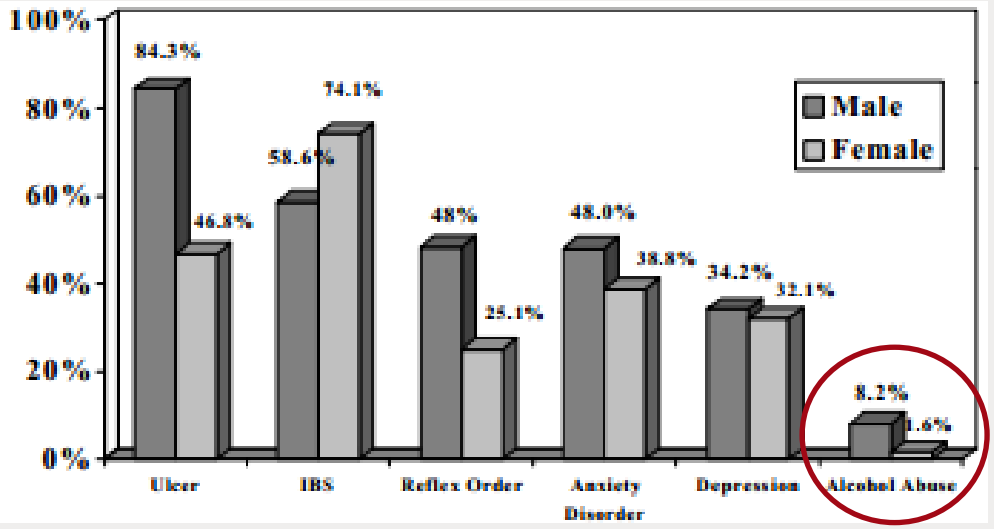
12 oz. Beer	=	8 oz. Malt	=	5 oz. Wine	=	1.5 oz. Spirits
5% Alcohol		7% Alcohol		12% Alcohol		40% Alcohol

It’s Important to Quantify How Much Is in One Glass

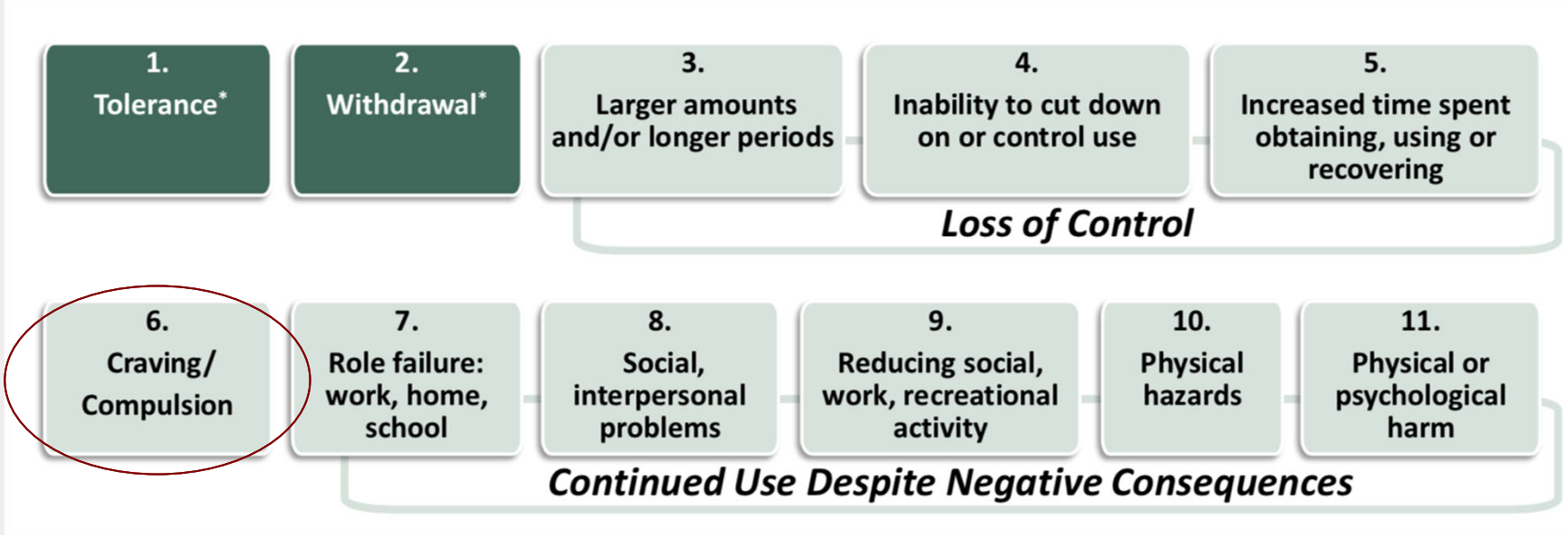
Providers are not good at diagnosing AUD

CASA National Survey

- Vignette of early alcohol abuse given to nationally representative sample of 648 PCPs
- 6% put alcohol abuse in top 5 differential
- 45% ask about alcohol during annual physical
- 32% have ever used screening instruments



What is Alcohol Use Disorder?



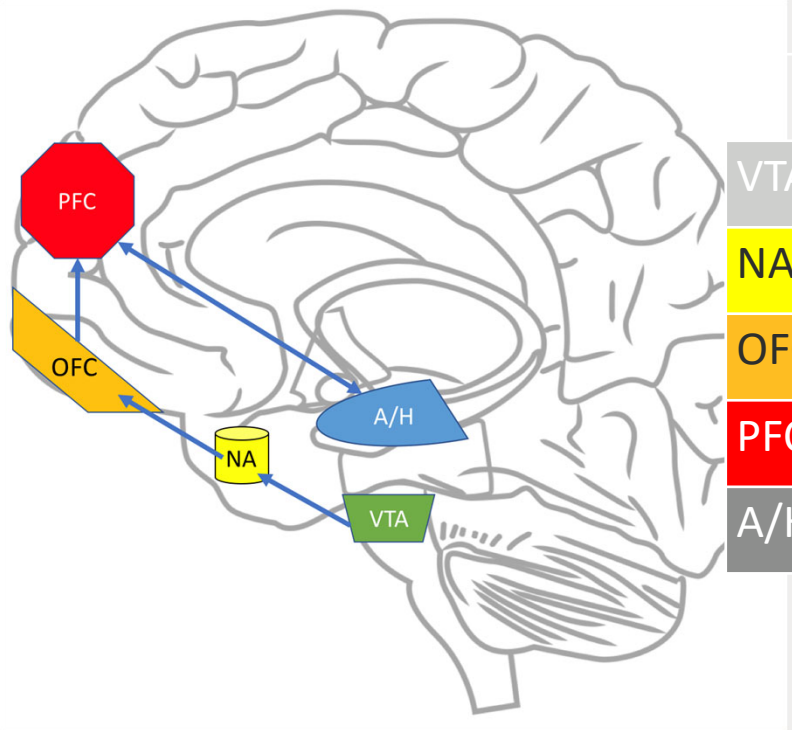
DSM – 5, 2013

What is Alcohol Use Disorder?

Primary alcohol dependence	Polydrug dependence
• 7–10% US population	• 0.5% US population
• Alcohol primary dependence	• Polysubstance dependence
• Normal childhood	• Deprivation/abuse childhood
• No conduct disorder (CD)	• CD symptoms: before age 15
• Regular use: teens, twenties	• Polydrug use: teens-middle age
• No personality diagnosis	• Adult personality disorder
• Natural remission: 30%/year	• Natural remission: 10%/year
• With treatment: 45%/year	• With treatment: 10%/year

Beresford, Lucey, Alcohol and Alcoholism 2018

What is Alcohol Use Disorder?



Addiction Neuroscience “driving a car”	
VTA: Ventral Tegmental Area	“ignition”
NA: Nucleus Accumbens	“accelerator”
OFC: Orbitofrontal Cortex	”steering wheel”
PFC: Prefrontal Cortex	“brakes”
A/H: Amygdala/Hippocampus	“updating maps”

Shenoy, Salajegheh, Shen, TGH 2019, in press

Prevalence of AUD

2013 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) III

- N=36,000 noninstitutionalized American adults
- Face-to-face interviews

	12-month	Lifetime	AOR
Total	13.9%	**29.1%**	-
18-29 years	26.7%	36.0%	~5
Male	17.6%	37.0%	2
Northeast	13.5%	28.8%	0.8

- From 2002 to 2013, there was a **49.4%** increase in AUD
- Example of greatest increase: **poor older adult minority woman**

Grant *JAMA Psychiatry* 2015
Grant *JAMA Psychiatiry* 2017

Screening for AUD

NIAAA's Single Screening Question

"How many times in the past year have you had X or more drinks in a day?"

x=5 for Men
x=4 for Women

≥1 is positive

88% sensitive/67% specific for AUD

Screening for AUD

AUDIT-C

1. How often do you have a drink containing alcohol?

- ☐ a. Never
- ☐ b. Monthly or less
- ☐ c. 2-4 times a month
- ☐ d. 2-3 times a week
- ☐ e. 4 or more times a week

2. How many standard drinks containing alcohol do you have on a typical day?

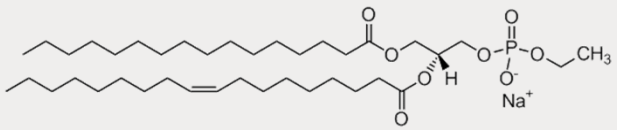
- ☐ a. 1 or 2
- ☐ b. 3 or 4
- ☐ c. 5 or 6
- ☐ d. 7 to 9
- ☐ e. 10 or more

3. How often do you have six or more drinks on one occasion?

- ☐ a. Never
- ☐ b. Less than monthly
- ☐ c. Monthly
- ☐ d. Weekly
- ☐ e. Daily or almost daily

WHO, 2019

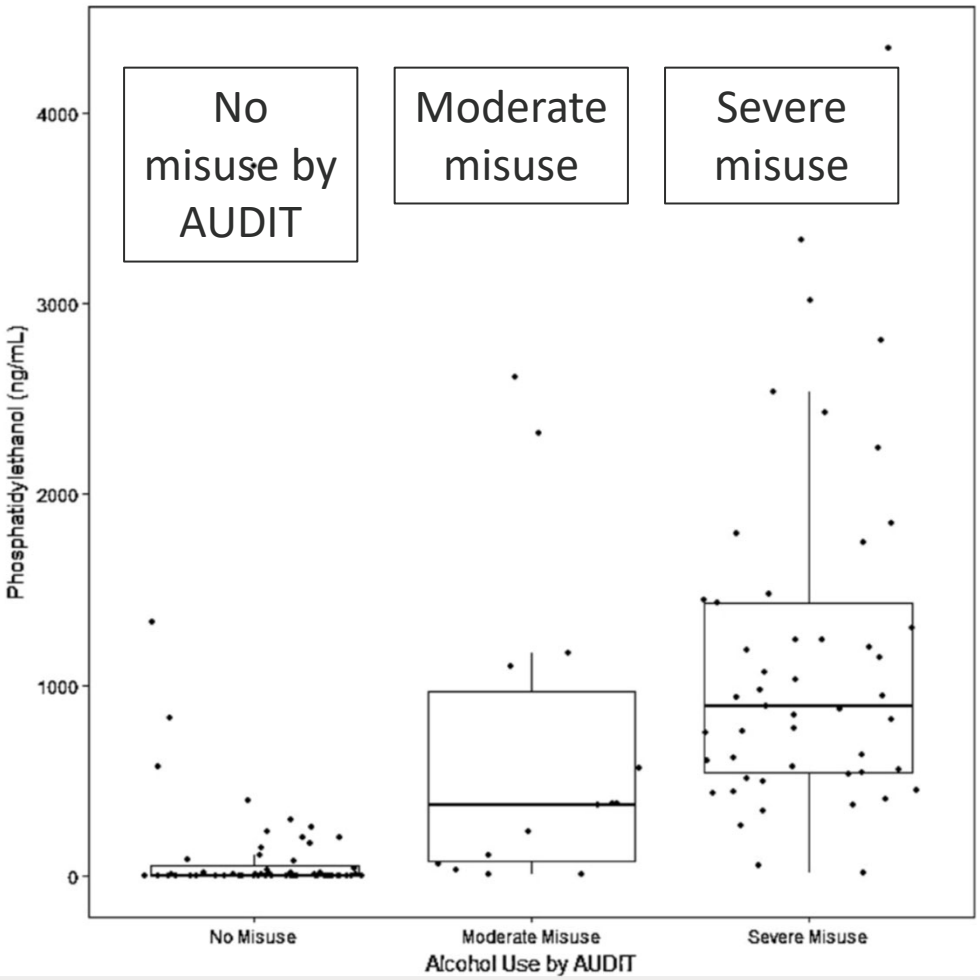
Phosphatidyl Ethanol (PEth)



Highly sensitive and specific Long detection window (up to 28 days)

- Low consumption detectable for up to 12 days
- Moderate-to-heavy consumption detectable up to 3 weeks

Schock A, et al. (2017)
Afshar M, et al. (2017)



Treatments for AUD

Psychosocial interventions increase abstinence 2-fold

- SBIRT (Screening, Brief Intervention, Referral to Treatment)
- Motivational Enhancement Therapy
- Alcoholics Anonymous
- Cognitive Behavioral Therapy
  - + medical f/u reduced alcohol relapse rates (33% vs 75%, *P*=.03)

DSM – 5, 2013

Treatments for AUD

FDA-approved medications for AUD

1. Disulfiram (Antabuse)
2. Naltrexone (ReVia and Vivitrol)
3. Acamprosate (Campral)

- Off-label: Gabapentin, topiramate

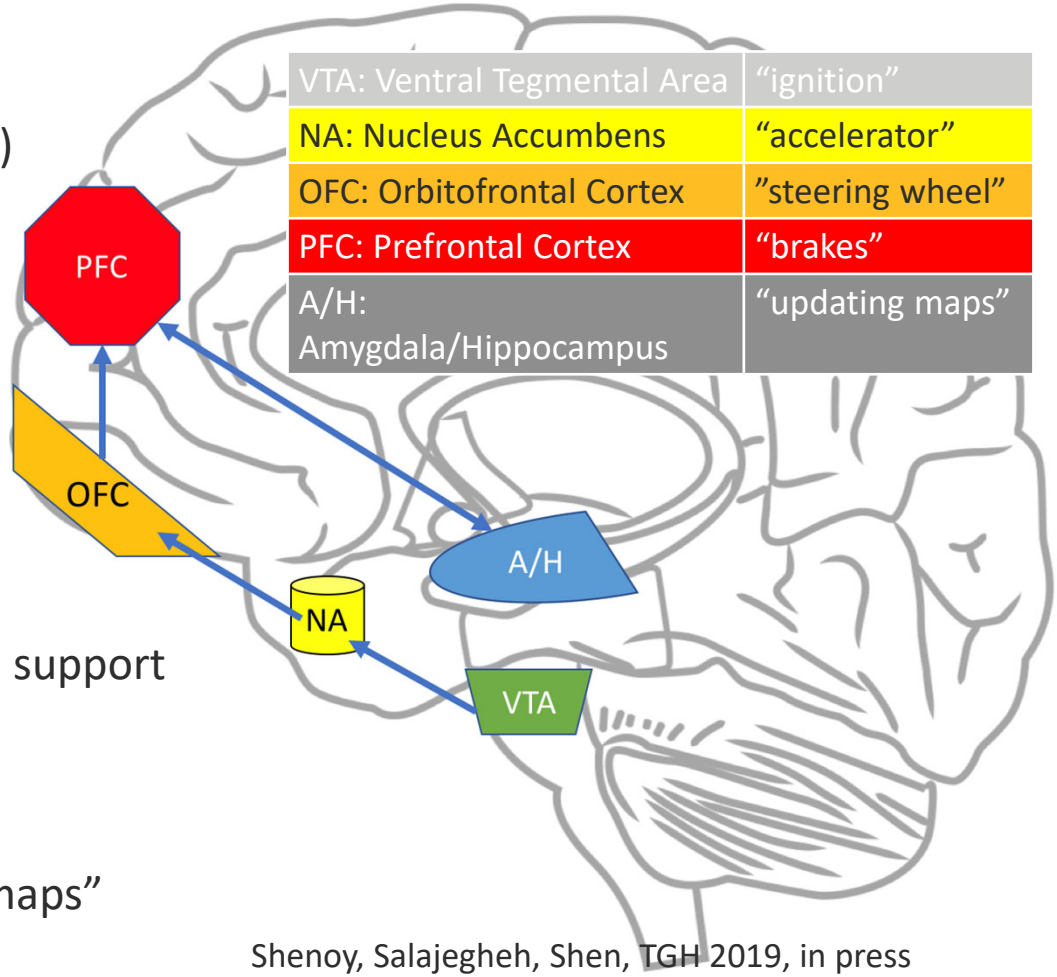
- No FDA-approved medications for AUD in advanced ALD
  - Only **baclofen** has shown efficacy and safety in 1 clinical trial

Dopamine reward circuit (VTA → NA)
"starting the ignition and accelerating"
❑Medication Assisted Treatment (MAT)

Orbitofrontal Cortex
"using the steering wheel"
❑Motivational interviewing
❑Individual therapy

Prefrontal Cortex
"using the brakes"
❑AA (12 step), SMART recovery, Group support
❑Individual therapy, CBT or DBT

Amygdala/Hippocampus
"using the guidance system, updating maps"
❑SSRIs, CBT or DBT



Shenoy, Salajegheh, Shen, TGH 2019, in press

Alcohol-related Hepatitis

Laboratory Findings

- Elevation of serum aminotransferases (hallmark of hepatitis) with AST:ALT ratio >2
- If AST> 2x ALT and no ETOH, non-liver AST source should be sought
- AST/ALT will be < 500 IU/mL
- If a combination (eg ETOH + ACM) will be higher but ratio preserved

Maddrey WC, et al. Gastroenterology 1978; 75: 193-9

Definition of Severe Alcohol-related Hepatitis

Maddrey's discriminant function was > 32 at presentation

4.6 x (PT in seconds- control PT in seconds) +Serum bilirubin in mg/dl

One month mortality 35-45%

Lille Model

3.19 – 0.101 * (age in years) + 0.147 * (albumin day 0 in g/L) + 0.0165 * (evolution in bilirubin level in πM) - (0.206 * renal insufficiency) - 0.0065 * (bilirubin day 0 in πM) - 0.0096 * (PT in seconds).

***Score > 0.45- 6 month survival is 25% compared to 85%**

Mathurin, NEJM,2011

Alcohol-related Hepatitis

Treatment

Abstinence!

Risk of progressing to cirrhosis remains

Treat nutritional deficiencies*

Steroids (1st line of therapy)

Prednisone 40 mg/day for one month followed by discontinuation or taper

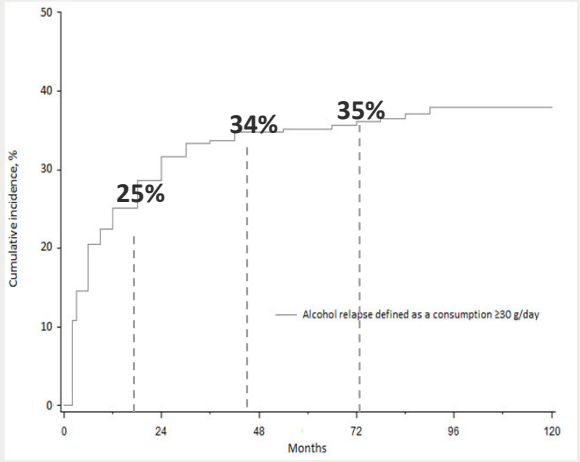
MDF ≥ 32

20-30% risk reduction in short term mortality

Abstinence is key after surviving AH

Louvet *Hepatology* 2017

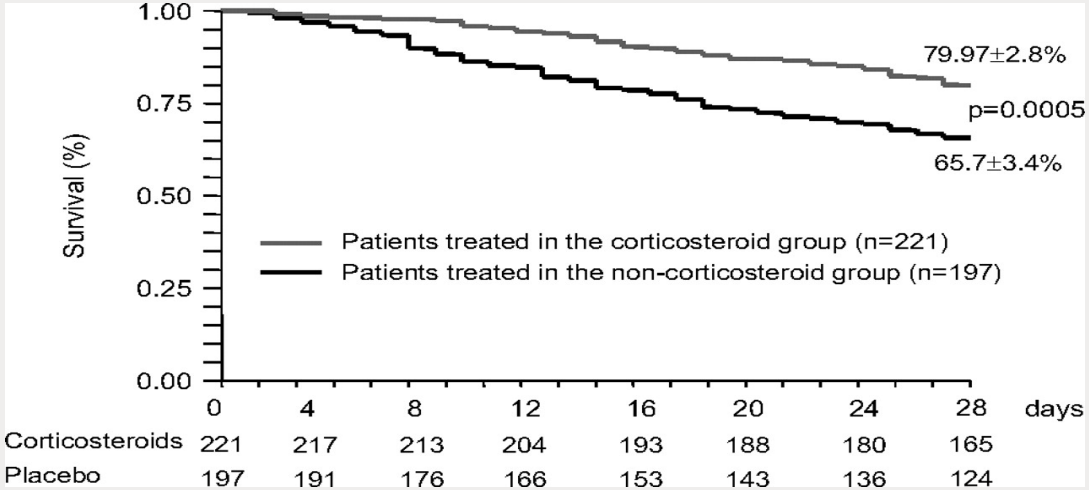
- Prospective study of 398 severe AH pts
- Short-term survival (<6mo)
  - MELD and Lille scores significant (HR 1.29, 1.35)
  - Not alcohol relapse (*P*=.24)
- Long-term survival (>6mo)
  - **Alcohol relapse** and Lille score significant (HR 4.14, 1.14)
  - Not MELD (*P*=.94)



Altamirano *Hepatology* 2017

- Retrospective study of 142 severe AH pts
- **Complete abstinence** was associated with better long-term survival
- Age >48 years and lack of prior alcohol treatments were associated with long-term abstinence

Steroids: meta-analysis

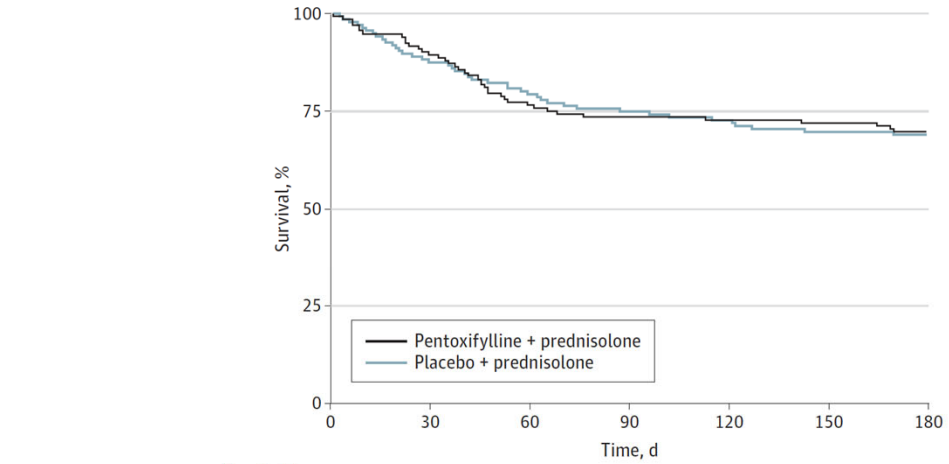


- Individual patient data from largest 5 RCTs
- 197 on placebo, 221 steroids
- All: mDF >32,
- 28 day survival 80 vs 66% (p=0.0005)

Mathurin et al. 2011

Steroids +/- Pentoxifylline

Figure 1. Probability of 6-Month Survival According to Treatment Allocation

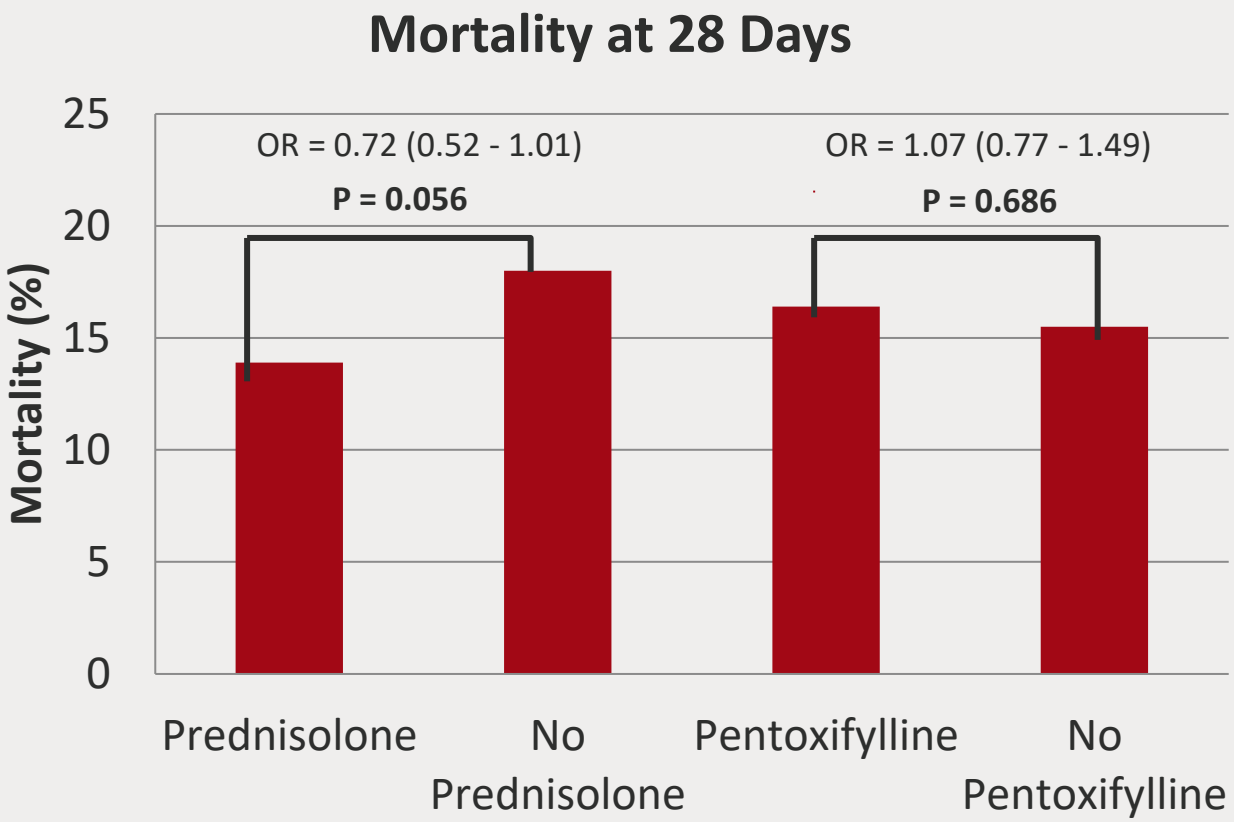


No. at risk							
Pentoxifylline + prednisolone	133	119	102	98	96	96	93
Placebo+ prednisolone	137	120	108	102	99	95	94

There was no difference in 6-month survival between the pentoxifylline+prednisolone and placebo+prednisolone groups according to intention-to-treat analysis (69.9% [95% CI, 62.1%-77.7%] vs 69.2% [95% CI, 61.4%-76.9%], *P* = .91). Comparison of hazard ratio using the Cox proportional hazards regression model was 0.98 (95% CI, 0.63-1.51; *P* = .91). The combination therapy lasted 28 days.

Mathurin et al JAMA 2013

Primary Endpoint



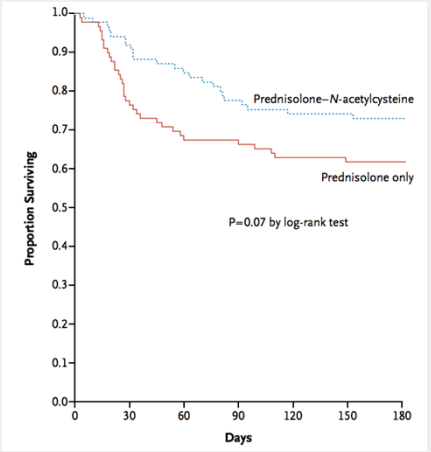
Thursz et al NEJM 2015

Emerging Therapies for Alcoholic Hepatitis

Nguyen-Khac *NEJM* 2011

Prednisolone + IV NAC vs prednisolone (N=174)

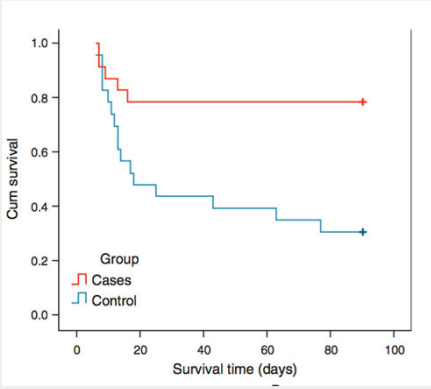
- NAC has antioxidant properties by repleting glutathione with a long history of use in acetaminophen-DILI
- NAC arm improved survival at 1 month, likely through reduction of infections and HRS
- Survival benefit not seen at 3- and 6-months



Singh *Amer J Gastro* 2014

Granulocyte-Colony Stimulating Factor + PTX vs PTX (N=46)

- G-CSF promotes mobilization of peripheral bone marrow stem cells to the liver, promoting hepatic regeneration
- G-CSF arm dramatically improved MELD and survival at 3 months
- Higher than expected mortality



DUR-928

- **Naturally occurring endogenous newly discovered regulatory Molecule**

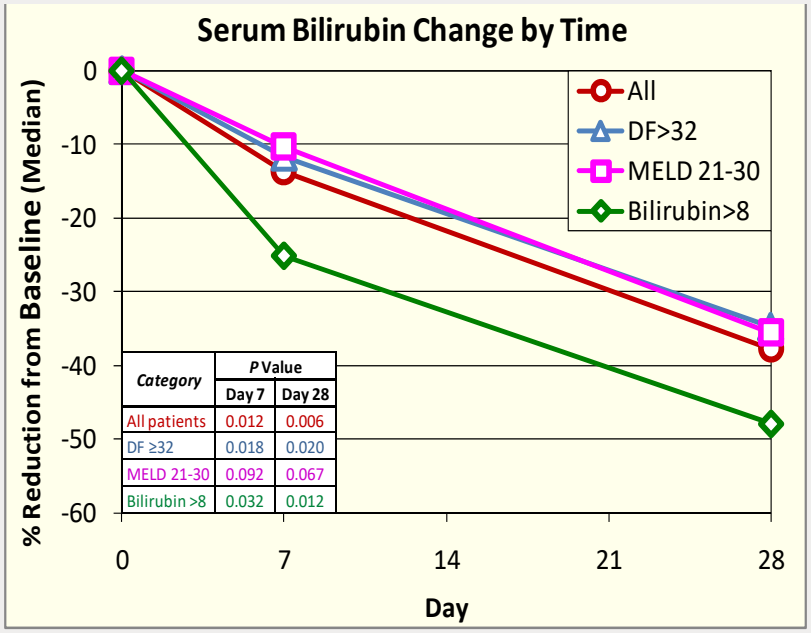
- **Sulfated oxysterol,** small molecule:
  - Produced in the cytoplasm and acts intracellulary
  - Highly conserved across 7 mammalian species studied to date, including humans (*Important in the regulation of cell function*)

- **Epigenetic regulator with broad activity**
  - Modulates gene activities
  - Regulates metabolism, inflammation, cell survival, and tissue regeneration

- **Well tolerated in multiple Phase 1 studies**

Hassanein et al AASLD 2019

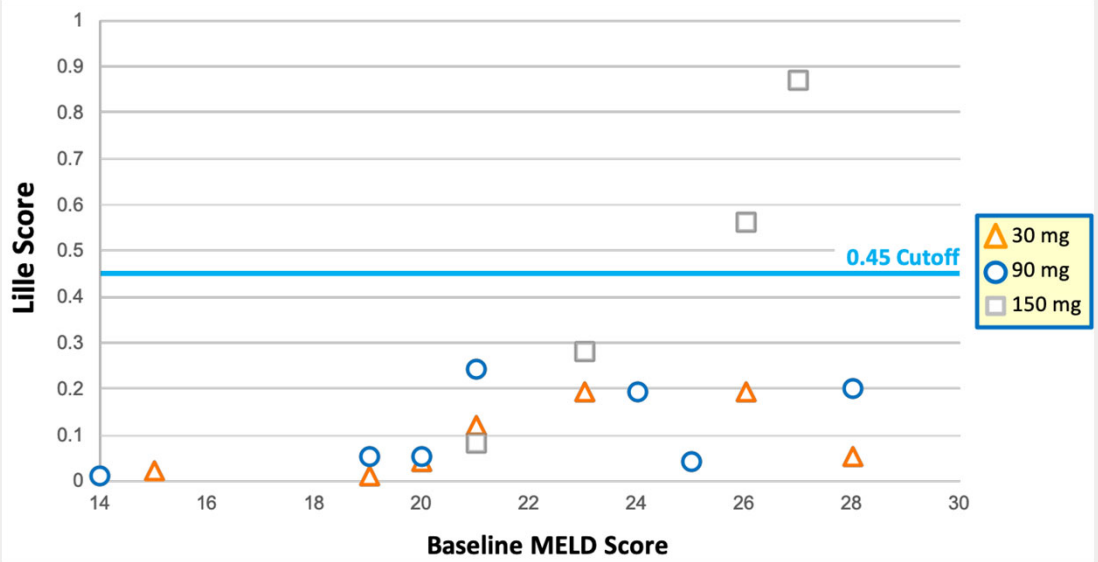
Results



One of the 19 patients did not return for the follow-up visits on Day 7 and Day 28. All data were analyzed based on those 18 who completed visits.

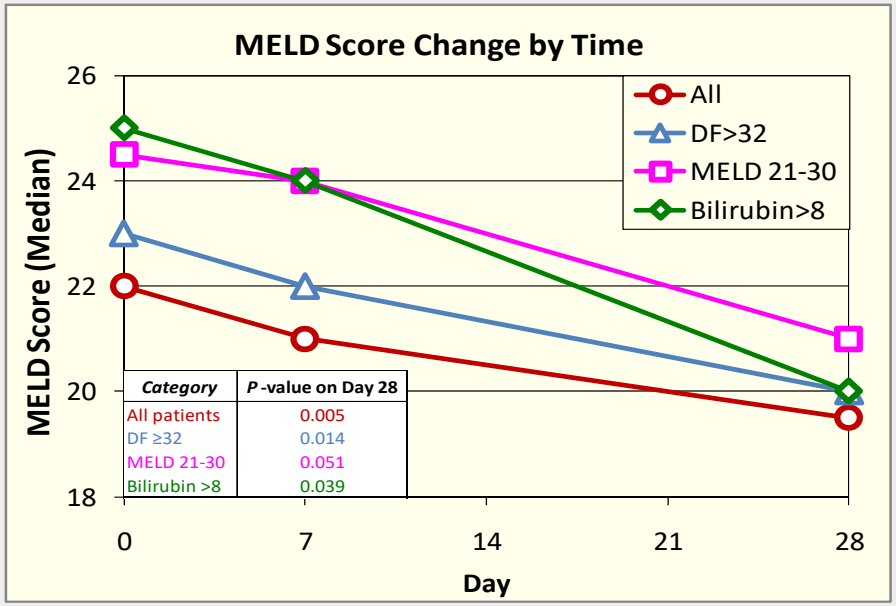
Hassanein et al AASLD 2019

Lille Score on Day 7



Hassanein et al AASLD 2019

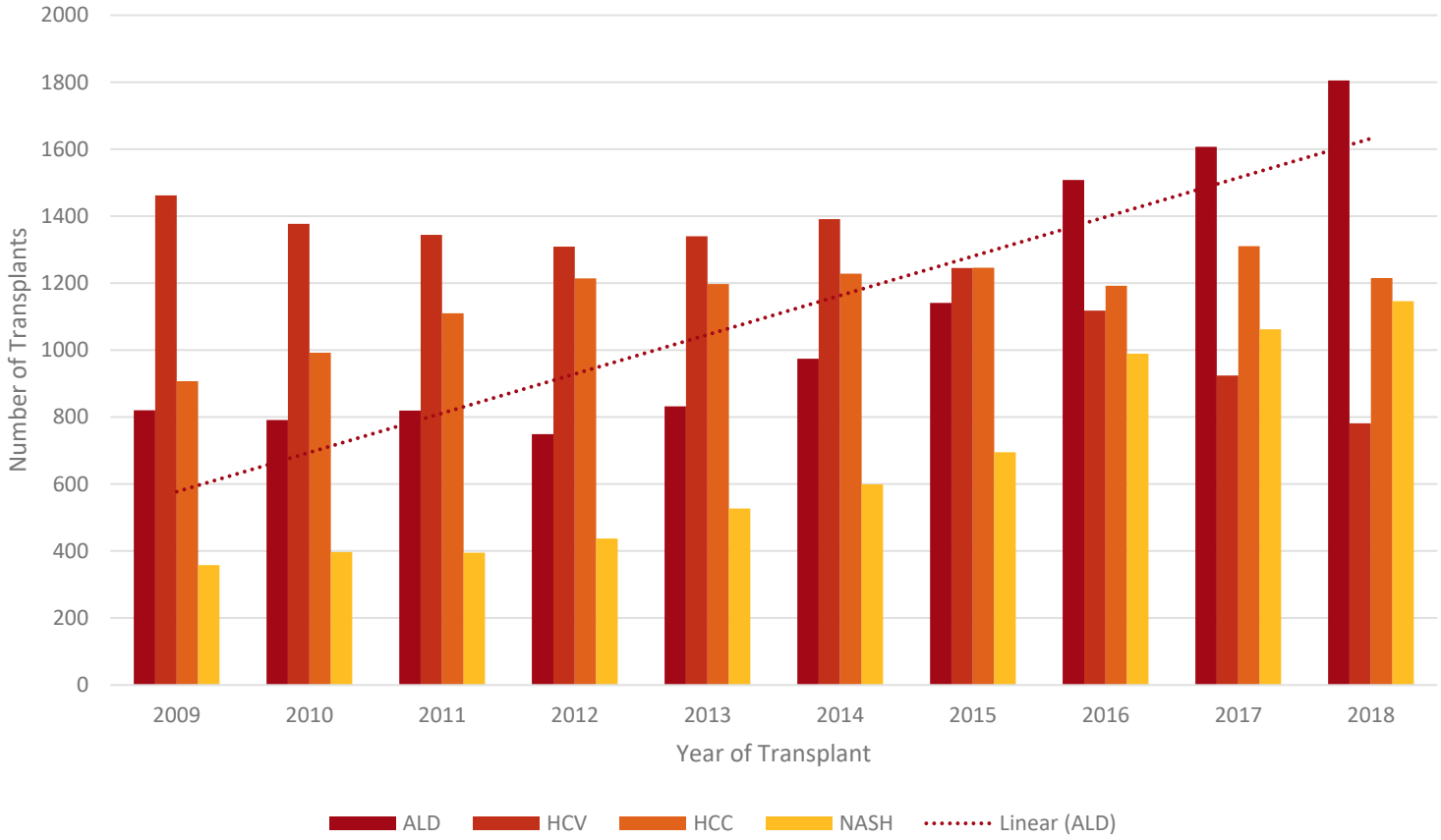
Results



Hassanein et al AASLD 2019

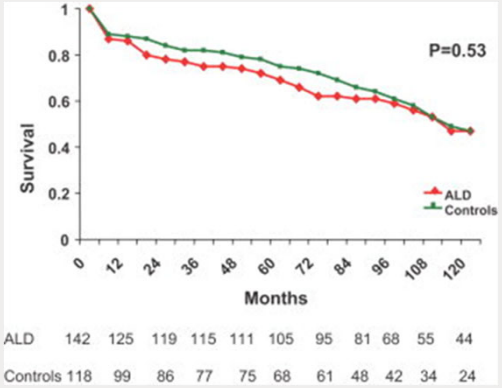
Liver Transplants in the US by Major Indications 2009 - 2018

Based on OPTN data from 7/2019



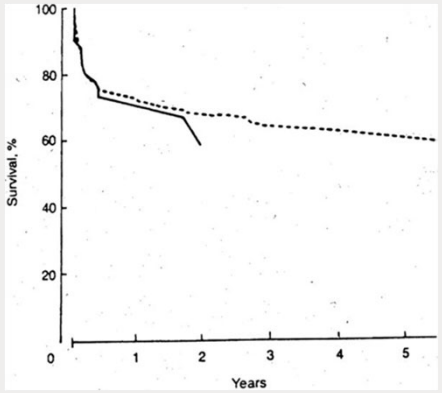
Post Transplant Survival-ALD

ALD / Controls



Wells, Liver Transplantation,2007

Cirrhosis /Other Diagnosis



P>0.77

Starzl, JAMA, 1988

The Requirements

AASLD Practice Guidelines:

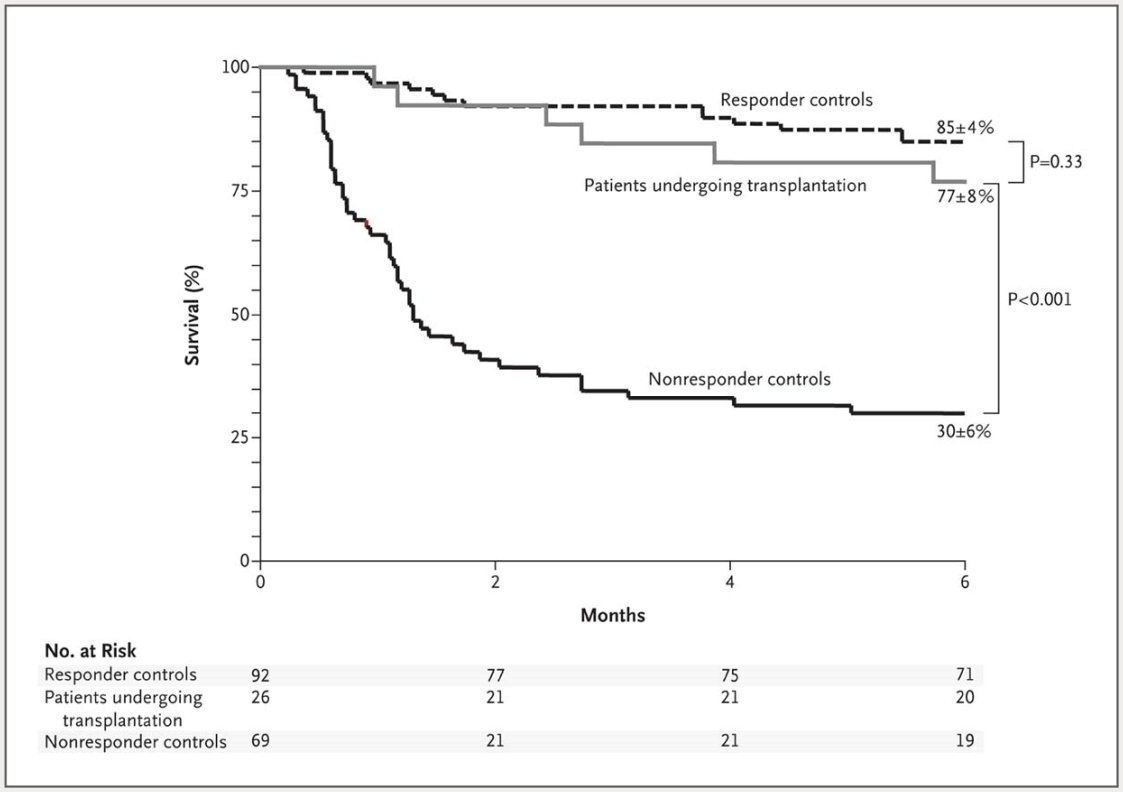
Appropriate patients with ESLD secondary to alcoholic cirrhosis should be considered for liver transplantation, just as other patients, after careful evaluation of the medical and psychosocial candidacy. In addition, this evaluation should include a formal assessment of the likelihood of long-term abstinence. *(Class I, level B)*

The Requirements

6 –month rule

- **Adopted by many centers and third-party payers**
- **Original purpose was to allow time for recovery**
- **No national or international mandate**
- **Often not a realistic goal for a severely decompensated cirrhotic or acute AH where mortality occurs in < 90 days**
- **Delays referral for transplant consideration**
- **Medical evidence to support 6 months as prognostic tool is not sufficient**
- **For alcohol dependence, sobriety becomes robust after 5 years**

Kaplan–Meier Estimates of Survival among the 26 Study Patients and Randomly Selected Matched Controls.



No. at Risk				
Responder controls	92	77	75	71
Patients undergoing transplantation	26	21	21	20
Nonresponder controls	69	21	21	19

Mathurin P et al. N Engl J Med 2011;365:1790-1800

The NEW ENGLAND JOURNAL of MEDICINE

Can we predict relapse?

Protective Factors

- Insight/Perception of negative consequences
- Social support
- Substitutive activities
- Self-esteem, hopefulness, optimism

Rice and Lucey, Liver Transplantation,2013
Gish, et al. Liver Transplantation 2001

Can we predict relapse?

Negative Factors

- Diagnosis of DSM-IV Alcohol Dependence, Type II alcoholism
- Relapse after physical and social consequences
- Hx of many failed rehabilitation attempts
- High Risk Alcohol Relapse (HRAR) scale > 3
- Shorter length of pre-transplant sobriety
- Non-compliance
- Low insight
- Psychiatric comorbidity
- Social isolation or Low social support
- Family Hx of alcoholism

Rustad et al, Psychosomatics 2015

Basic Insight

A Accepts that they had a problem with AUD, alcoholism or addiction and believes that interventions will be helpful to prevent relapse

Scored 3 = Excellent

B Accepts that they had a problem with AUD, alcoholism or addiction but believe that they do not need intervention to prevent relapse

Scored 2 = Good

C Believes that alcohol caused liver disease BUT that they do not have a problem with AUD, alcoholism, or addiction

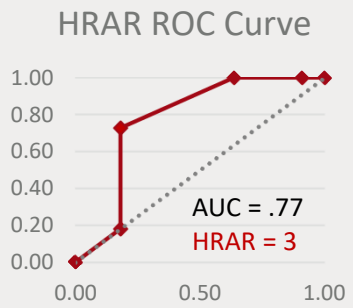
Scored 1 = Poor

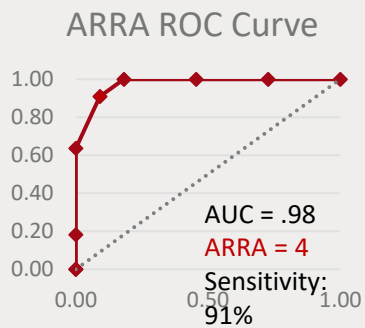
D Denies that alcohol caused liver disease despite objective evidence

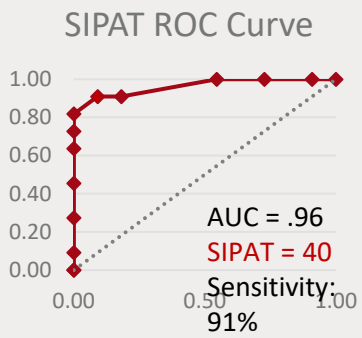
Scored 0

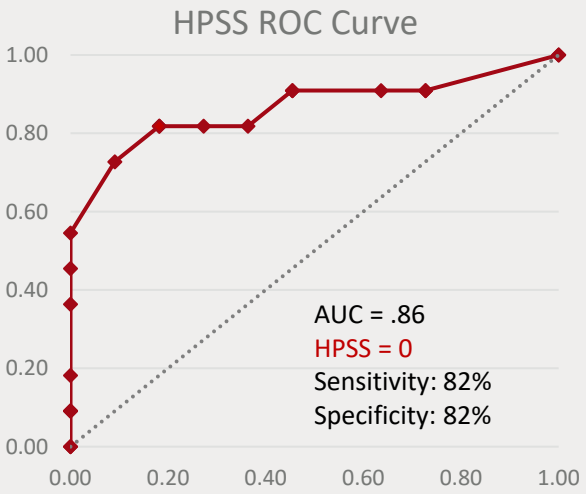
Scoring Systems	Study Cohort	Historic Factors	Modifiable Factors	Outcome of interest
HRAR	ALD LT, SC	3	0	Any incidence of 40 g alcohol/day
SIPAT	All organ, SC	7	11	Mortality/Rejection
ARRA	ALD LT, SC	2	7	Any relapse to alcohol use
HPSS	AH LT, SC	11	1	6 drinks/day or > 4 days of drinking
SALT	AH LT, multi-center	4	0	Sustained alcohol use of 100 days

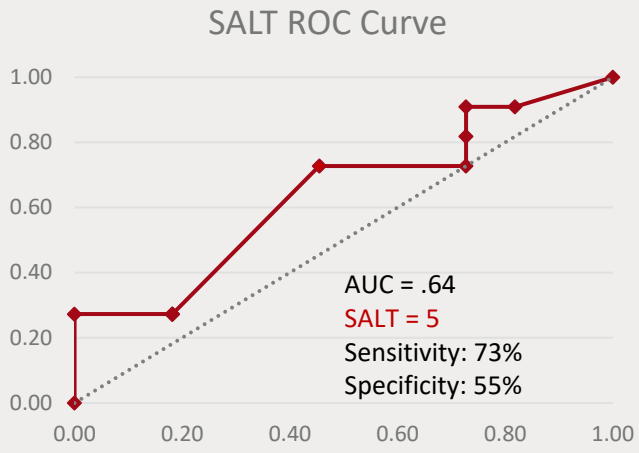
Scoring Systems compared



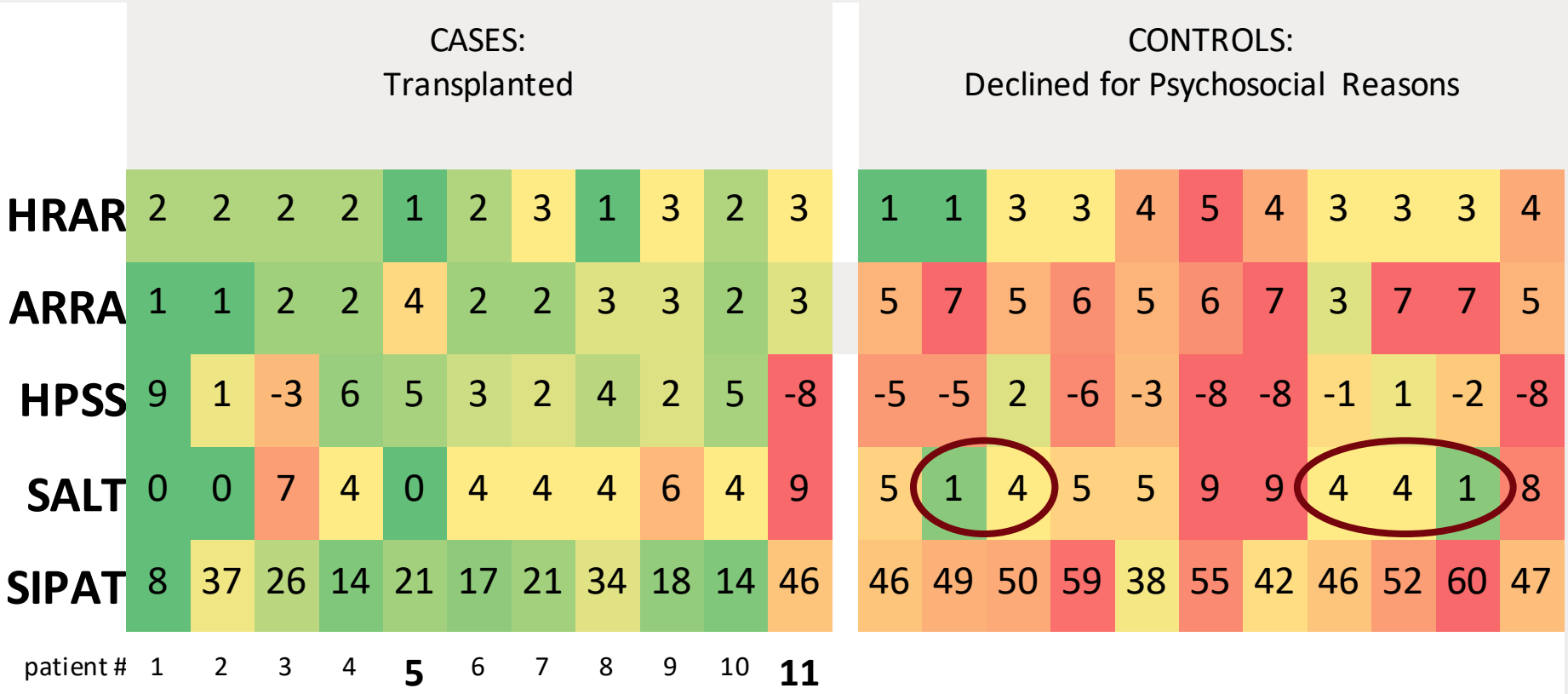








TOOLS for Risk Assessment #1, Shenoy et al, not published



TOOLS for Risk Assessment #2, Shenoy et al, not published

Evaluation of Abnormal Liver Tests

When to refer?

- When diagnosis uncertain
- **Work-up negative, multiple positive tests, biopsy needed**
- Prior to therapy for hepatitis
- Treatable biliary tract disease
- Indications for liver transplantation:
- **Hepatic synthetic dysfunction due to acute liver failure, decompensated cirrhosis**
- **Very high transaminases or concern for the development of liver failure**
- **Hepatocellular carcinoma or other malignancies**

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