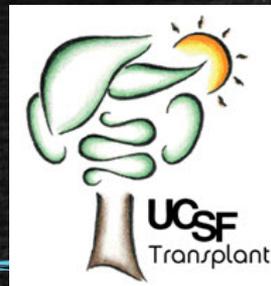


Fatty liver: The Silent Epidemic

What is it and what can we do to fight it?



Danielle Brandman, MD, MAS
Associate Professor of Medicine
Program Director, Transplant Hepatology Fellowship
Director, UCSF Fatty Liver Clinic

Outline

- NAFLD basics
- NAFLD: diagnosis and staging
- Complications of NAFLD
- Management of NAFLD

What is nonalcoholic fatty liver disease (NAFLD)?

- Nonalcoholic fatty liver disease (NAFLD) occurs when fat is deposited in the liver, without other causes of fatty liver identified



NAFLD: Non-Alcoholic Fatty Liver Disease

Spectrum of disease



NAFLD

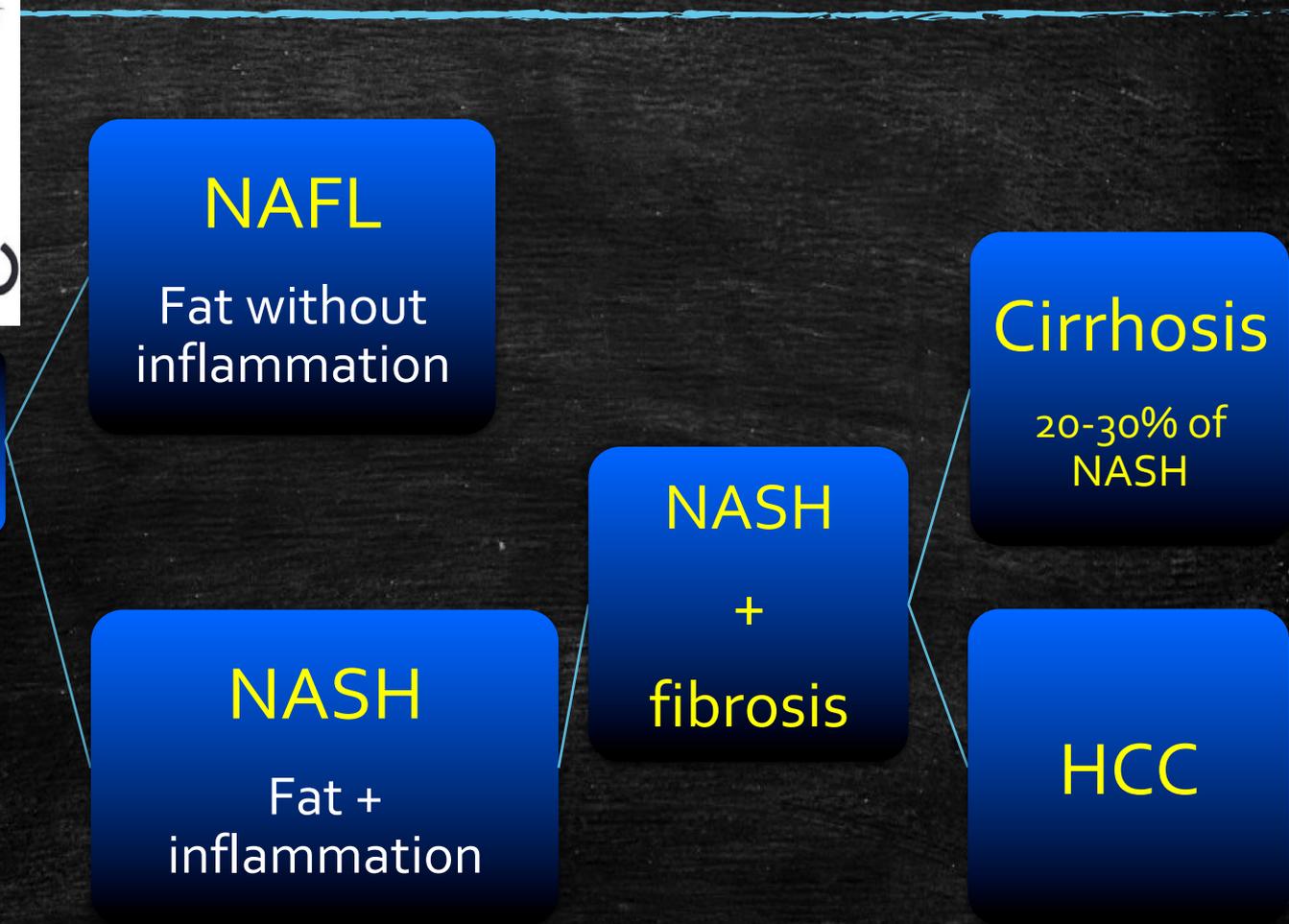
NAFL
Fat without inflammation

NASH
Fat + inflammation

NASH
+
fibrosis

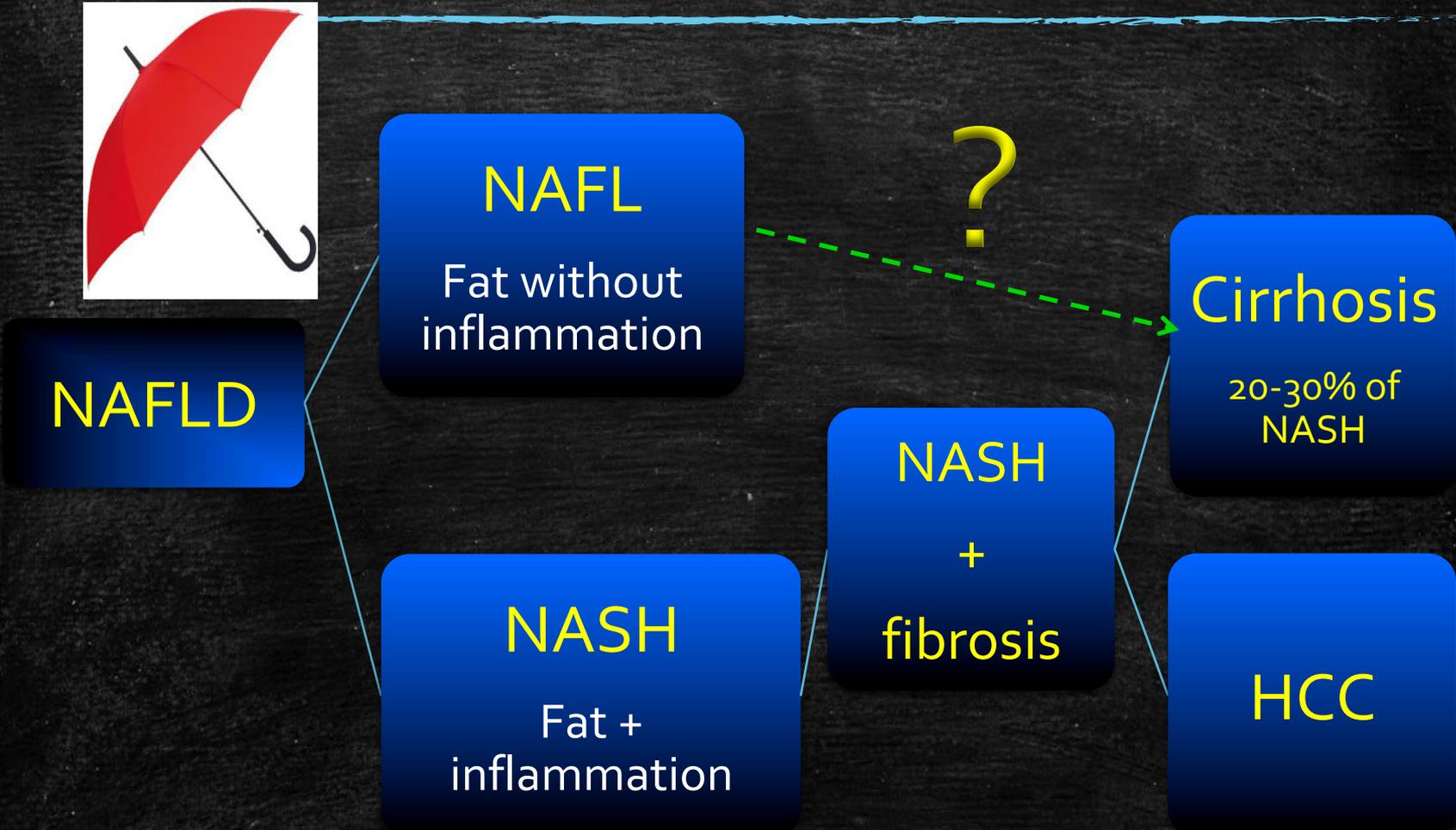
Cirrhosis
20-30% of NASH

HCC



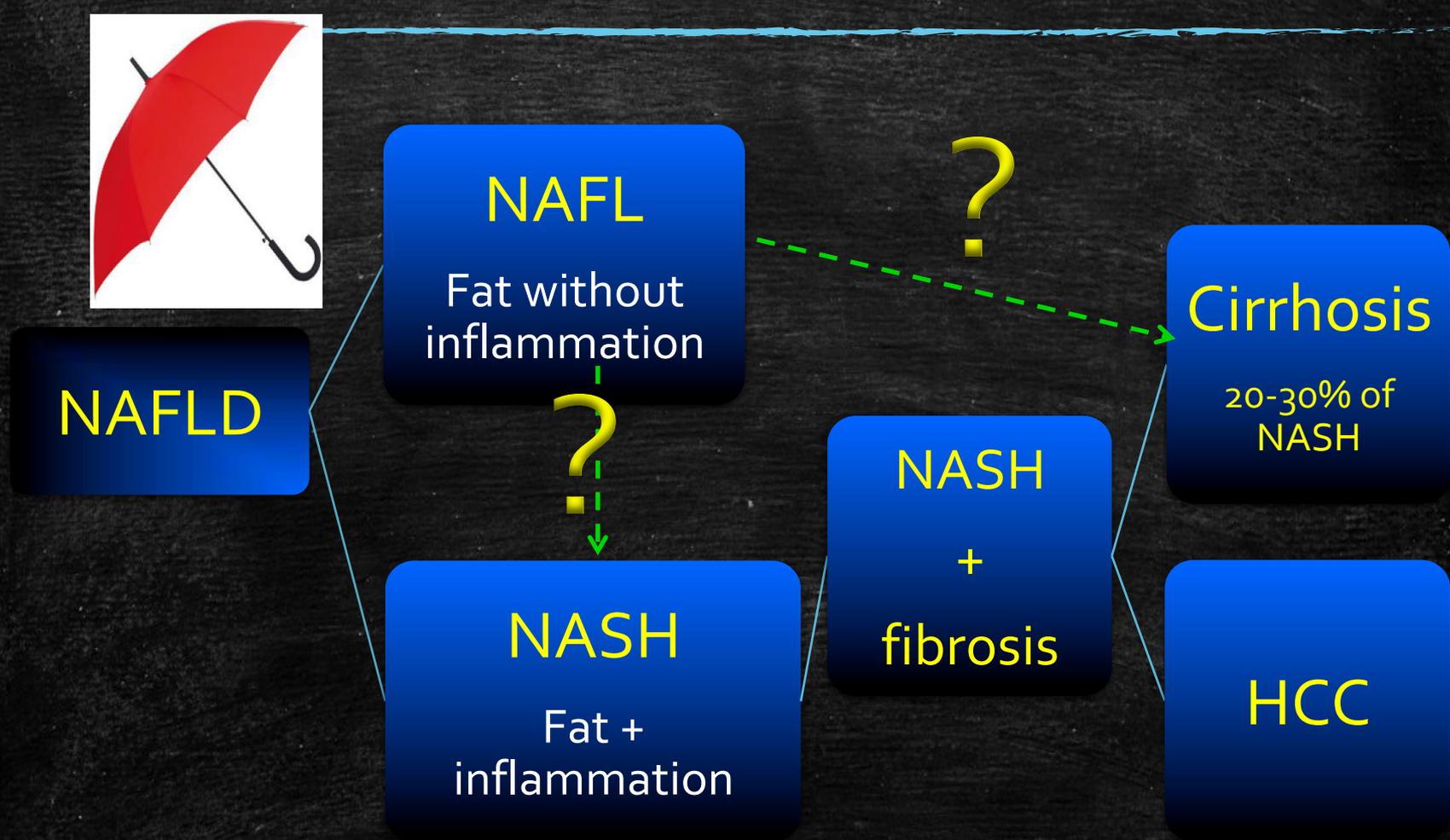
NAFLD: Non-Alcoholic Fatty Liver Disease

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NAFLD: Non-Alcoholic Fatty Liver Disease

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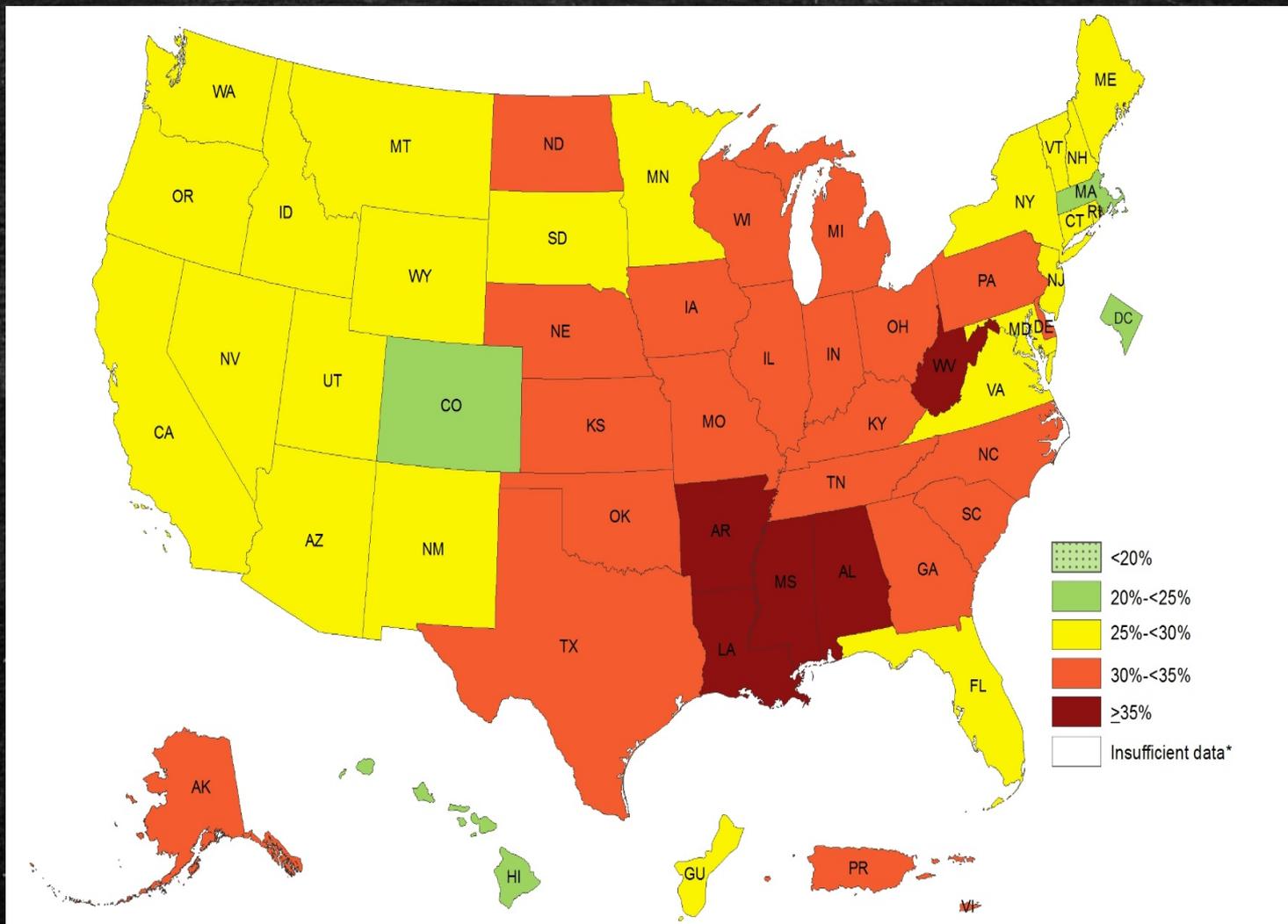
Who is at risk for NAFLD?

- Metabolic syndrome:
 - Obesity (“apples” > “pears”)
 - High blood sugar
 - High blood pressure
 - High cholesterol (and/or low “good” cholesterol)

Who is at risk for NAFLD?

- Other risk factors
 - Hispanic ethnicity
 - Hereditary/genetic
 - Polycystic ovarian syndrome (PCOS)
 - HIV
 - Sleep apnea
 - Hypothyroidism

Prevalence of Self-Reported Obesity Among Adults, 2016



Epidemiology

- Prevalence of NAFLD: ___ US population

- Prevalence of NASH: ___% population

Epidemiology

- Prevalence of NAFLD: 16-29% US population

- Prevalence of NASH: 2-7% population

Farrell, *Hepatology*, 2006.

Younoussi, *Hepatology*, 2015.

Epidemiology

- Prevalence of NAFLD: 16-29% US population
 - 2/3 of obese adults
 - 84-96% bariatric surgery population
 - Up to 76% of diabetics
- Prevalence of NASH: 2-7% population
 - 10-30% of NAFLD
 - 20% of obese adults

Farrell, *Hepatology*, 2006.

Younoussi, *Hepatology*, 2015.

How would I know if I have NAFLD?

- Symptoms
 - Many (up to 77%) of patients may have none
 - Fatigue (50-75%; may in part be related to sleep apnea)
 - Right-sided abdominal pain

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How would I know if I have NAFLD?

- Symptoms
 - Many (up to 77%) of patients may have none
 - Fatigue (50-75%; may in part be related to sleep apnea)
 - Right-sided abdominal pain
- Presence of risk factors (e.g., obesity, diabetes)
- Lab tests: elevation of ALT>AST (usual pattern)
- Radiology: fat can be seen on ultrasound, MRI, or CT scan

How would I know if I have NAFLD?

- Screening of the general population is not currently recommended
 - US guidelines (AASLD) suggest high level of suspicion in high risk patients
 - European guidelines (EASL) recommend screening all patients with obesity or metabolic syndrome with liver enzymes and ultrasound

Should I see a liver specialist if I have NAFLD?

Should I see a liver specialist if I have NAFLD?

- Accurate diagnosis
 - Make sure no other forms of liver disease
 - Determine which sub-type of NAFLD you may have (NAFL vs NASH)
 - Evaluate for liver scar (fibrosis)
 - Liver biopsy may be needed
- Monitoring
 - Look for signs of worsening of liver scar
 - Special monitoring if cirrhosis present

How is NAFLD diagnosed?

How is NAFLD diagnosed?

- Establish presence of fat in the liver: ultrasound, MRI, or biopsy
- Eliminate other causes of liver disease (blood tests)
- Alcohol intake < 2 drinks per day
- No medications known to cause fatty liver (e.g., prednisone, tamoxifen)

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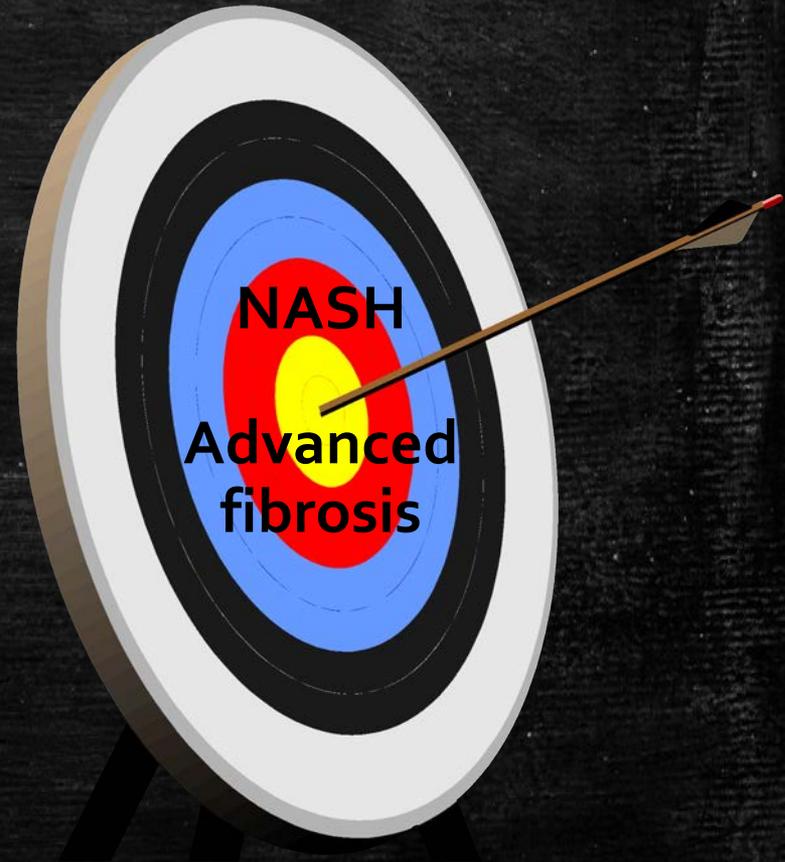
NAFLD is a diagnosis of exclusion

Role of liver biopsy in NAFLD

- Classify NAFLD accurately:
NASH vs NAFL
- Determine fibrosis stage
- Eliminate other causes of liver disease

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Liver Biopsy in NAFLD



Pros

- Most reliable means for excluding alternative etiology/co-existing liver disease
- “Gold standard” for diagnosis and staging

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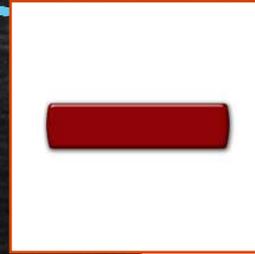


Liver Biopsy in NAFLD



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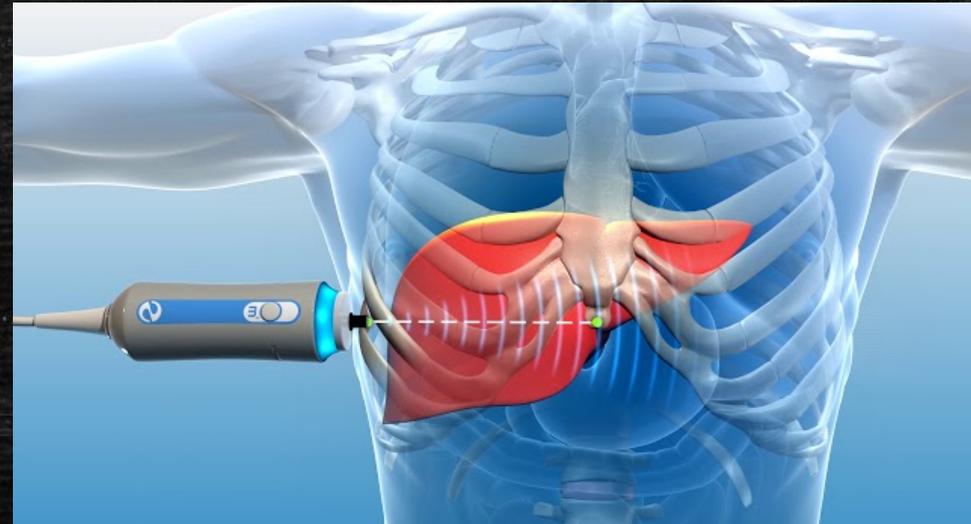


Cons

- Sampling error
- Risk of complications
- Expense
- Impossible to apply to large NAFLD population



Transient Elastography: Fibroscan



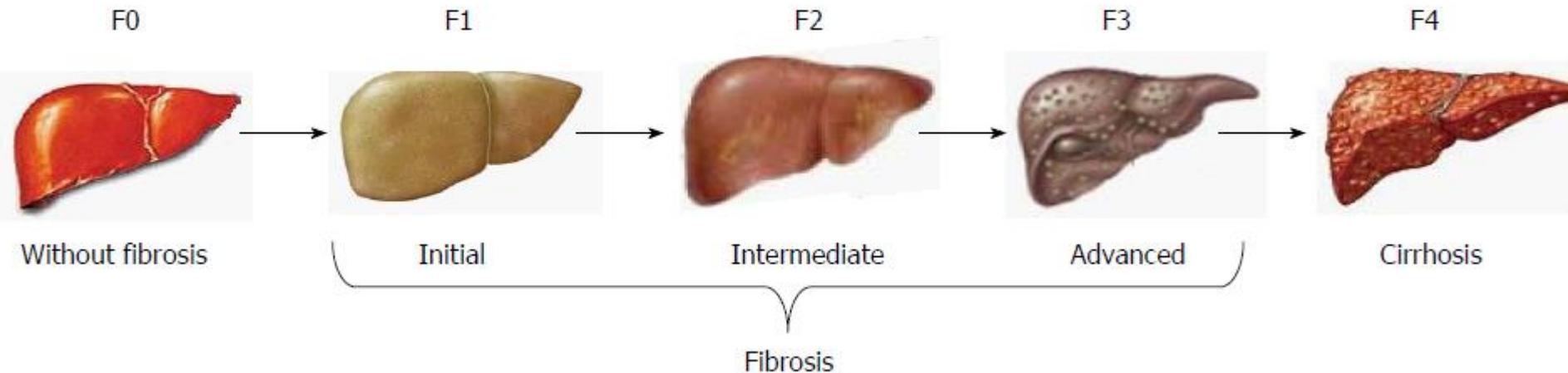
Fibroscan

- Factors that may produce inaccurate results:
 - Obesity
 - NASH
 - Alcohol use
 - Nonfasting state
 - Abnormal liver tests (ALT>100, elevated alkaline phosphatase)
 - Hispanic ethnicity
- Requires adequate experience to produce reliable results

Why is accurate diagnosis and staging important?

NAFLD: Non-Alcoholic Fatty Liver Disease

Spectrum of disease



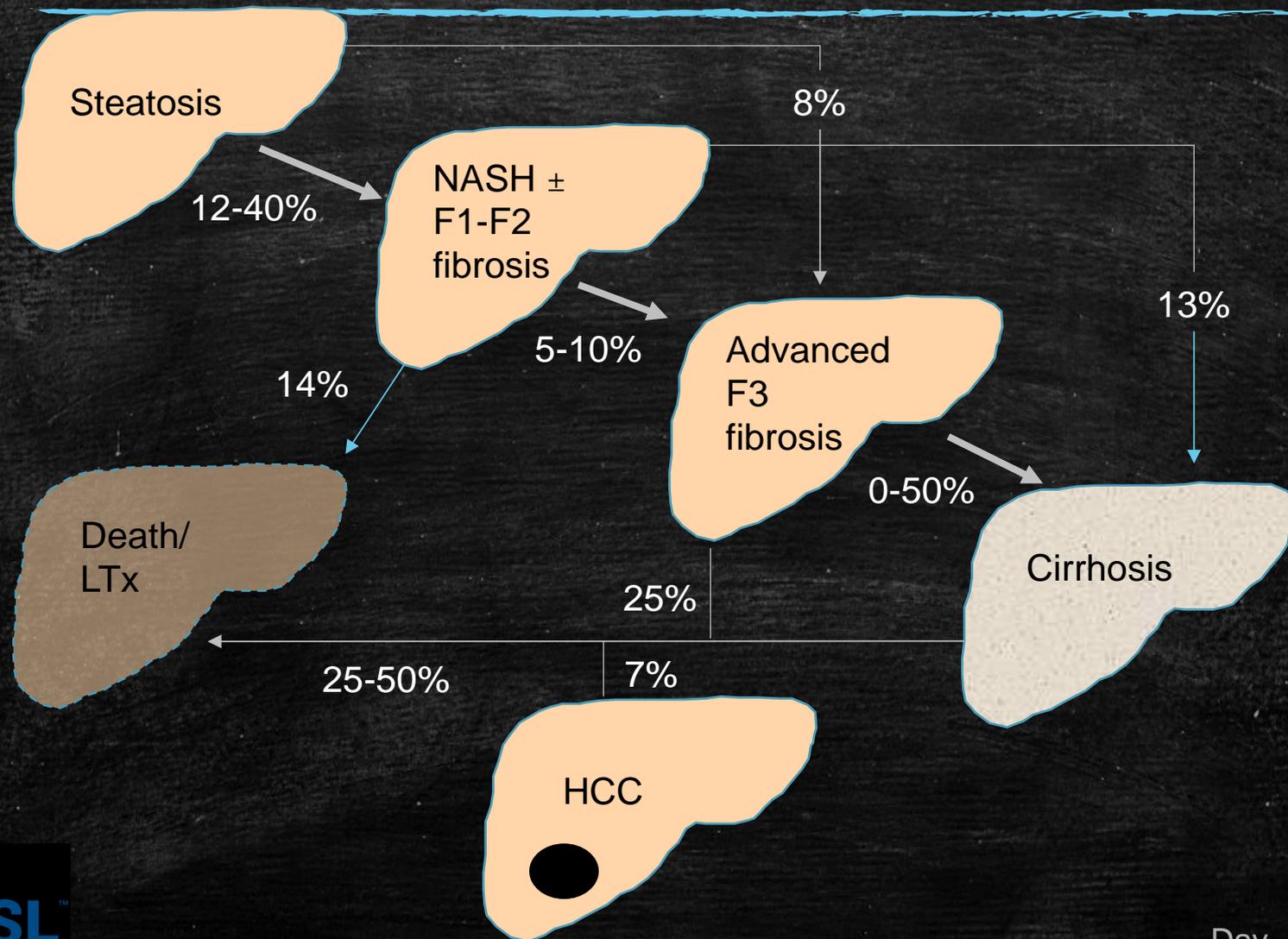
NASH

7 years per 1 stage
~28 years 0 → cirrhosis

NAFL

14 years per 1 stage
~56 years 0 → cirrhosis

Prognosis of NAFLD by fibrosis stage



What are the consequences of
NAFLD?

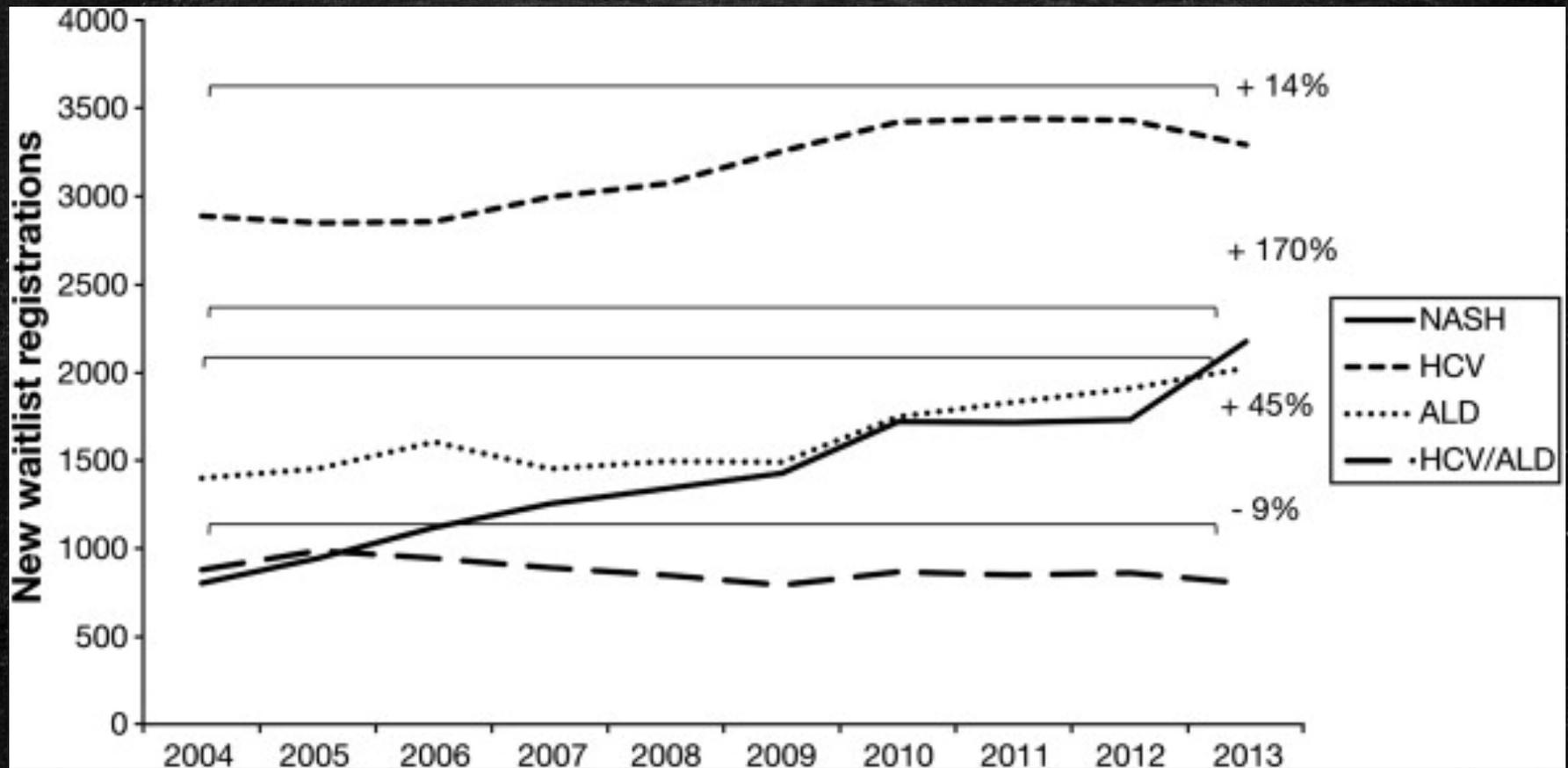
What are the consequences of NAFLD?

- Leading causes of death
 1. Heart disease
 2. Cancer
 3. End stage liver disease

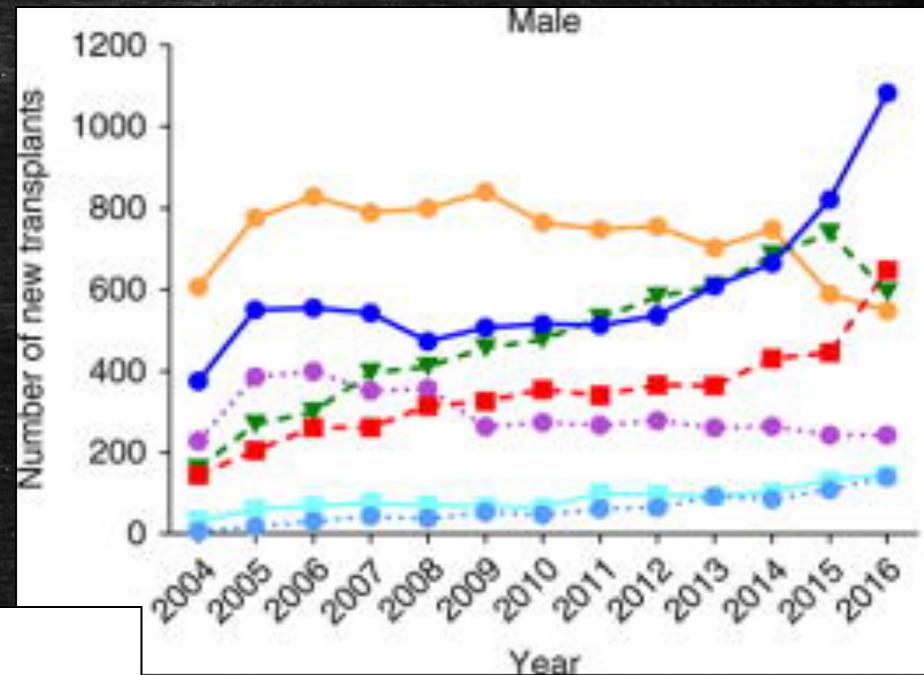
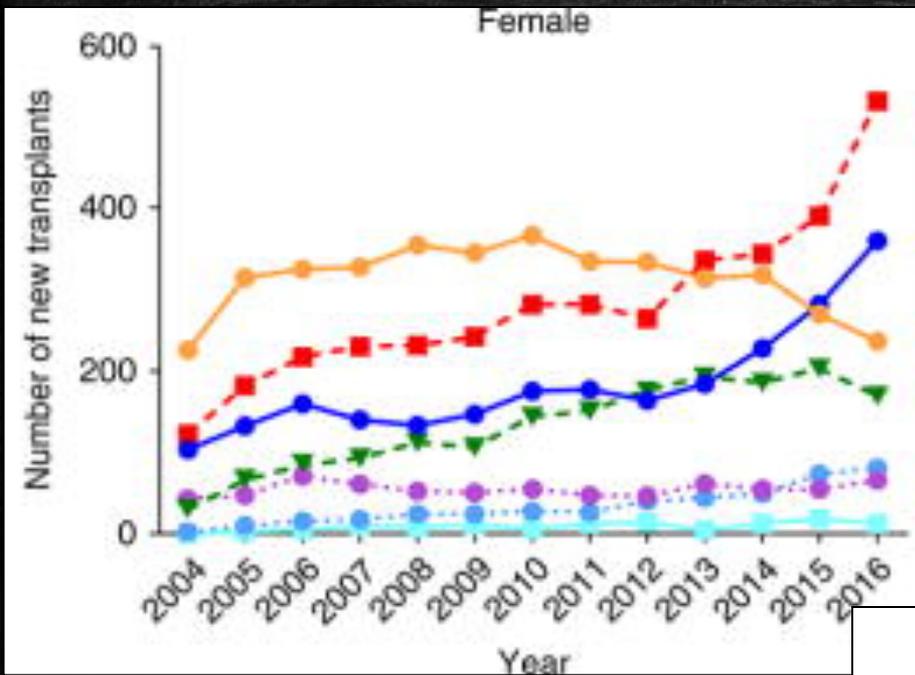
NAFLD and Liver-related events

- Severity of liver fibrosis is the most important predictor of death
- Patients with NAFLD are at risk for liver cancer (HCC)
 - 7-8-fold greater than the general population
 - Risk in NASH cirrhosis: 6.7-15% at 5-10 years
 - Unlike other diseases, cirrhosis may not need to be present

NASH is increasing as an indication for liver transplantation



NASH is the leading indication for LT in women



- HCV
- ALD
- -■- - NASH
- -▲- - HCC & HCV
- ...○... HCV & ALD
- ...○... HCC & NASH
- ...○... HCC & ALD

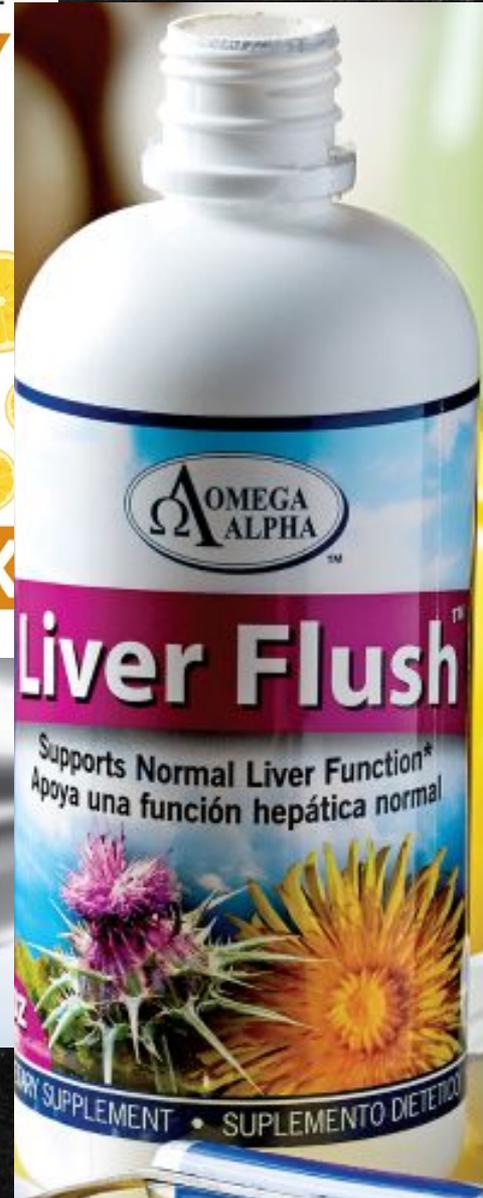
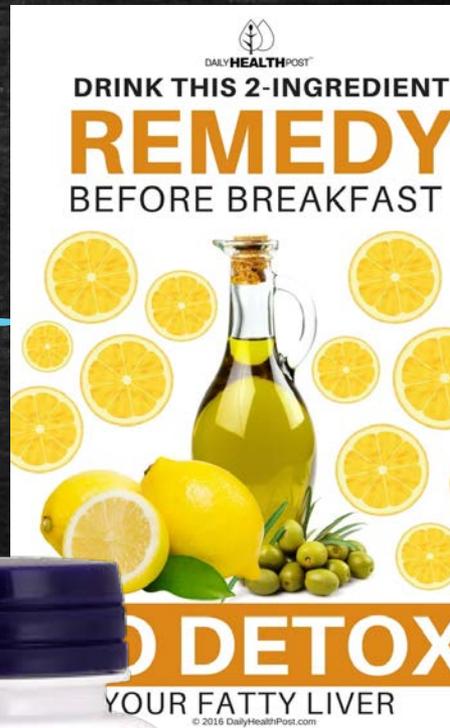
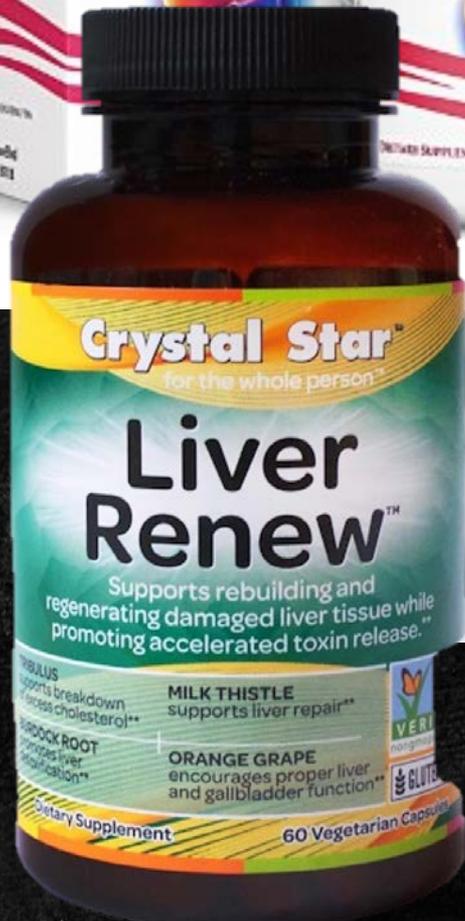
What treatments are available
that improve NASH?

What treatments are available
that improve NASH?



What treatments are available
that improve NASH?







Weight Loss

- Goal: loss of 7-10% baseline weight to improve NASH and fibrosis
- Diet
 - Portion control and simple carbohydrate avoidance
 - Avoid fructose-sweetened beverages



Harrison. *Hepatology*, 2009.
Promrat, *Hepatology*, 2010
Vilar-Gomez, *Gastro*, 2015
Chalasani, *Hepatology* 2012.

Weight Loss

- Exercise
 - Exercise alone reduces liver fat
 - Aerobic >150-250 minutes per week
 - Resistance training 45 minutes/day x 3 days/week



Harrison. *Hepatology*, 2009.
Promrat, *Hepatology*, 2010
Vilar-Gomez, *Gastro*, 2015
Chalasanani, *Hepatology* 2012.

Exercise

	Examples
Light	Walking slowly, computing, cooking, washing dishes
Moderate	Walking briskly, light biking, vacuuming, mowing lawn
Vigorous	Jogging, fast biking, Zumba, shoveling, carrying heavy loads

#10		I am dead!!!
#9		I am probably going to die!
#8		I can grunt in response to your questions and can only keep this pace for a short time period.
#7		I can still talk but I don't really want to and I am sweating like a pig!
#6		I can still talk but I am slightly breathless and definitely sweating.
#5		I'm just above comfortable, I am sweating more and can talk easily.
#4		I'm sweating a little, but I feel good and I can carry on a conversation comfortably.
#3		I am still comfortable, but I'm breathing a bit harder.
#2		I'm comfortable and I can maintain this pace all day long.
#1		I'm watching TV and eating bon bons.

Barriers to exercise

Associated comorbidities

- Obstructive sleep apnea: fatigue, headache
- Osteoarthritis: pain, decreased mobility
- Depression: decreased activity and motivation
- Balance problems
- Generalized weakness
- Cognitive deficits

Prescription for exercise: behavioral strategies

- Motivation
- Attainable
- Measurable
- Memory
- Positive thoughts
- Reinforcement
- Environmental support
- Stress management
- Social support
- Problem solve

Weight Loss

- Bariatric Surgery
 - Foregut procedures (Sleeve gastrectomy, Roux-en-Y gastric bypass, Lap band)
 - Improvement in NAFL/NASH +/- fibrosis
 - Relatively contraindicated in patients with cirrhosis
 - If needed, laparoscopic sleeve gastrectomy by an experienced surgeon is the operation of choice

Treatment of Metabolic Syndrome in NAFLD

- Statins
 - Safe for use in NAFLD
 - Potential benefits of NAFLD/liver enzyme improvement and reduced risk of liver death or HCC
 - Not proven in randomized controlled trials
- Metformin
 - Safe for use in NAFLD
 - Some studies show improvement in liver biopsy and liver enzymes
 - Not proven in randomized controlled trials
 - Possible anti-neoplastic effects

Medications to treat NAFLD

- Only patients with biopsy-proven NASH need liver-specific treatment
- Medications currently available recommended for treatment of NASH
 - Vitamin E
 - Pioglitazone (Actos)

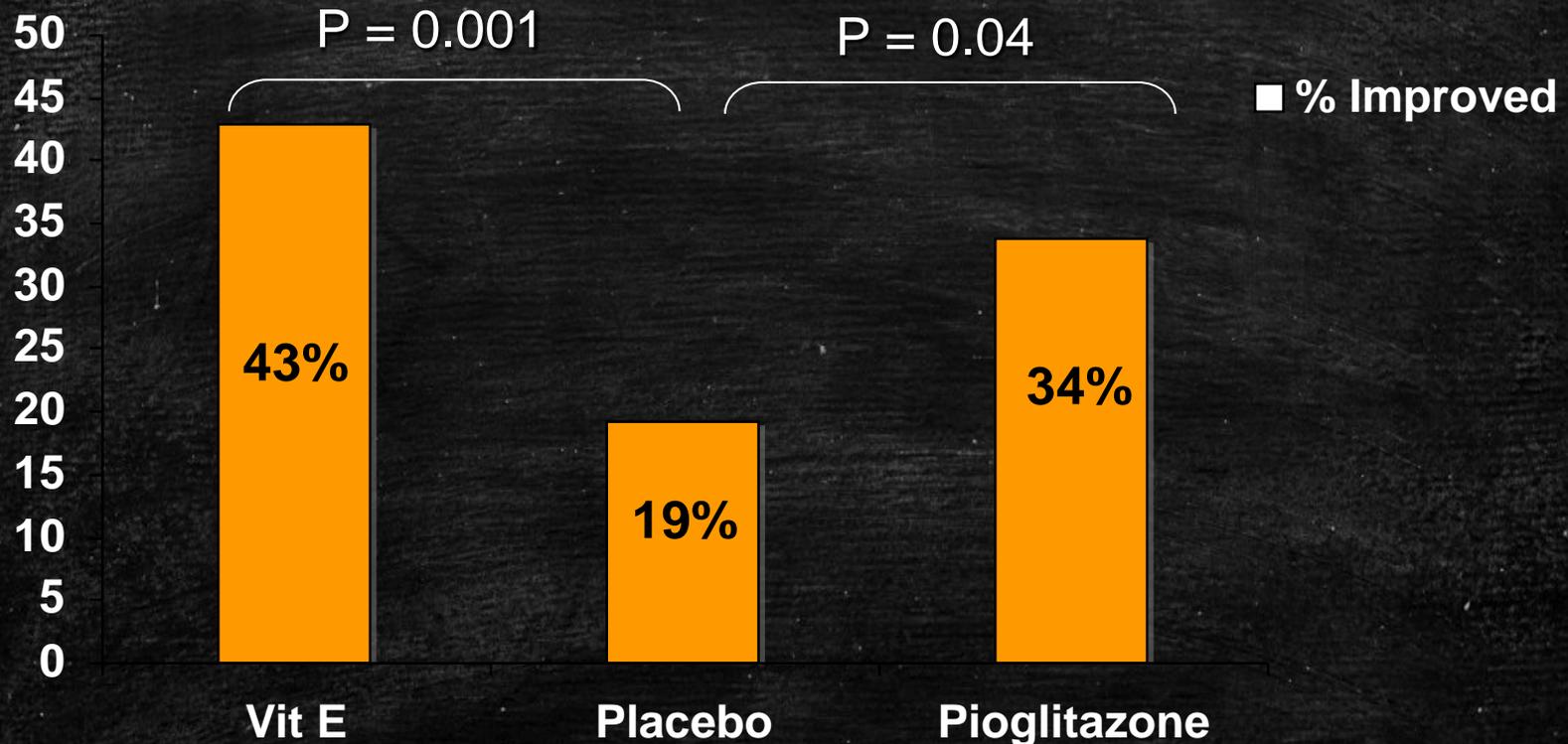




Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

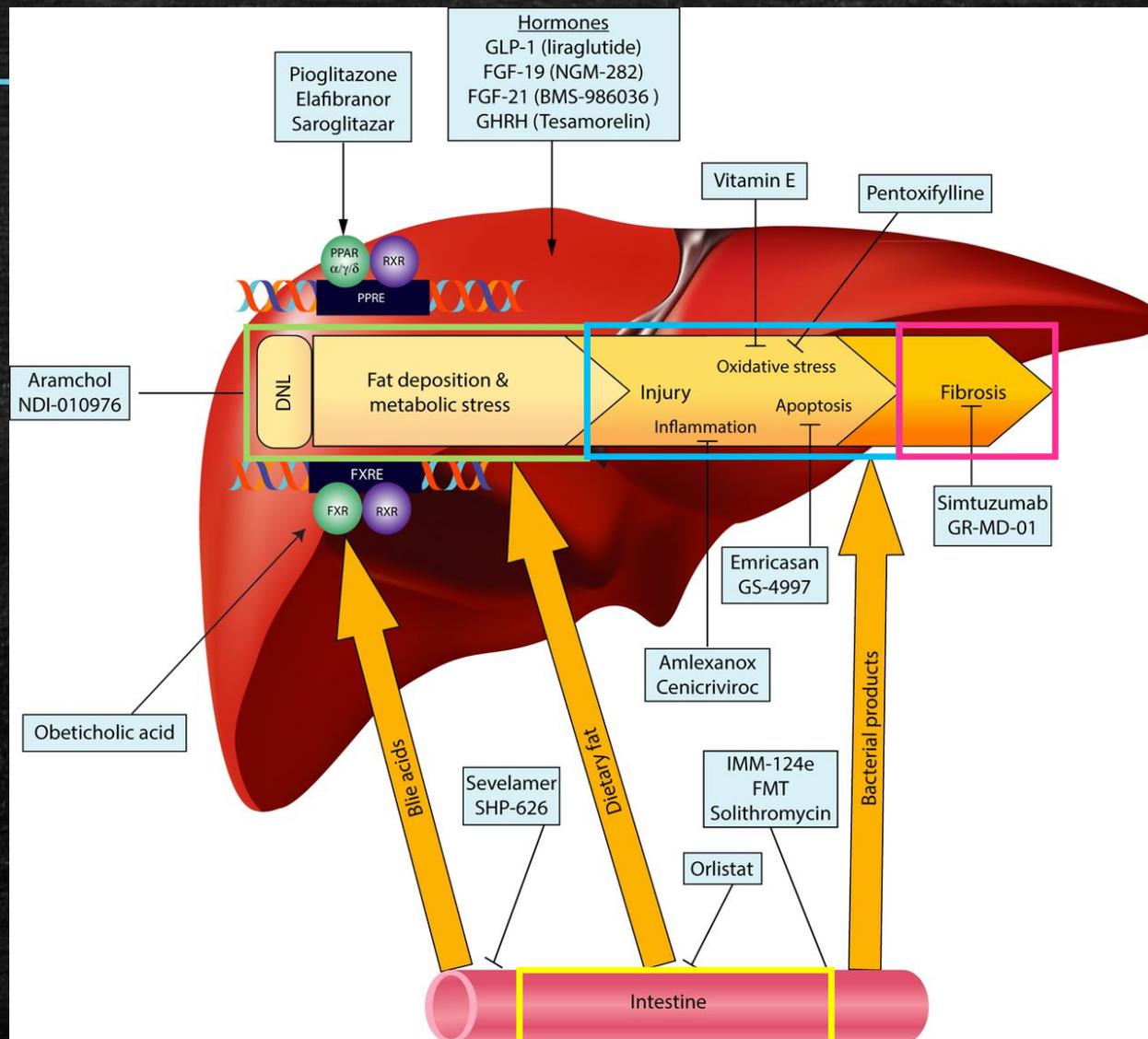
Arun J. Sanyal, M.D., Naga Chalasani, M.B., B.S., Kris V. Kowdley, M.D.,

Improvement in NASH on Liver Biopsy



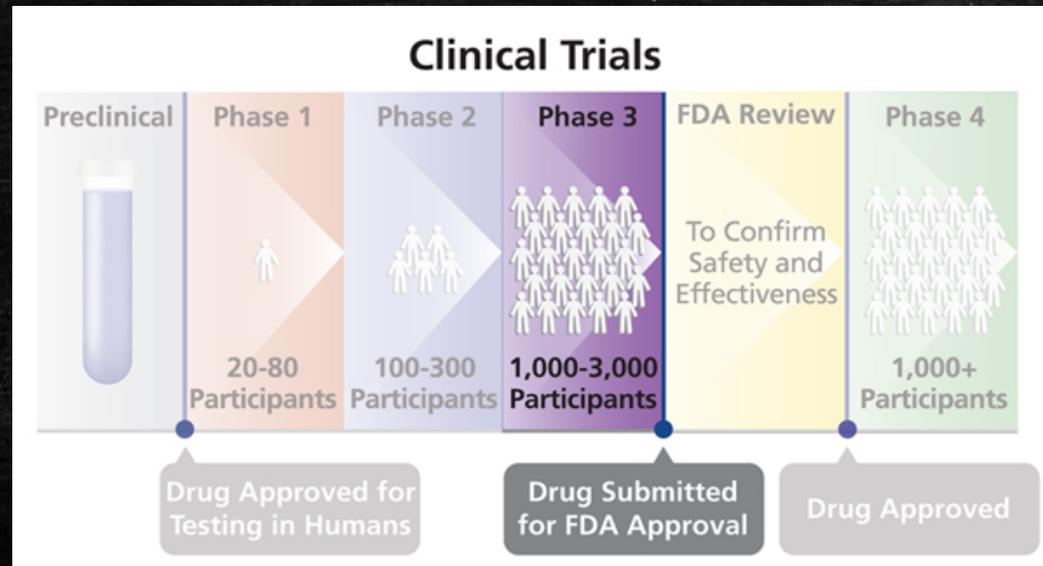
Study included only non-diabetics

NAFLD pathways/targets for treatment

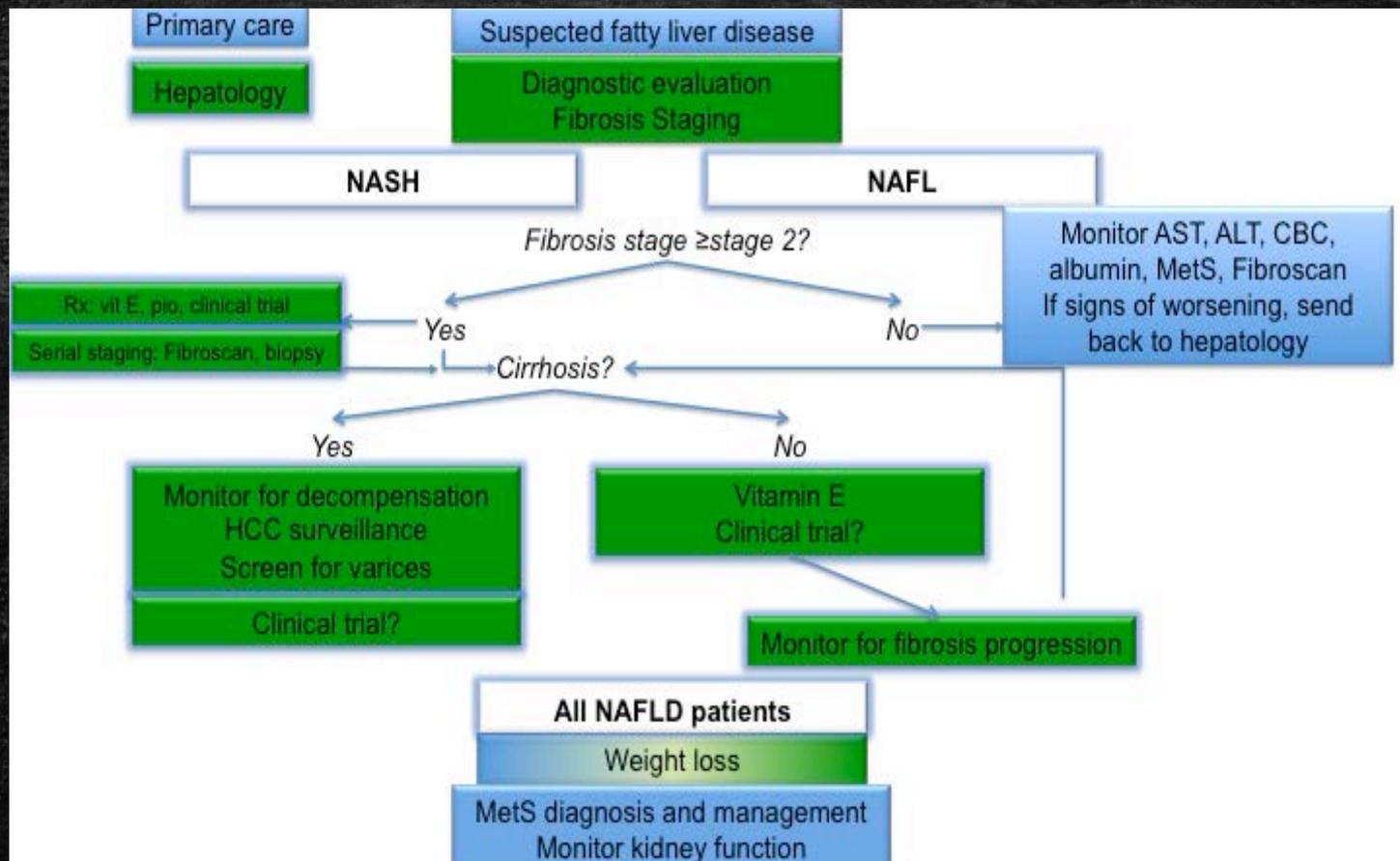


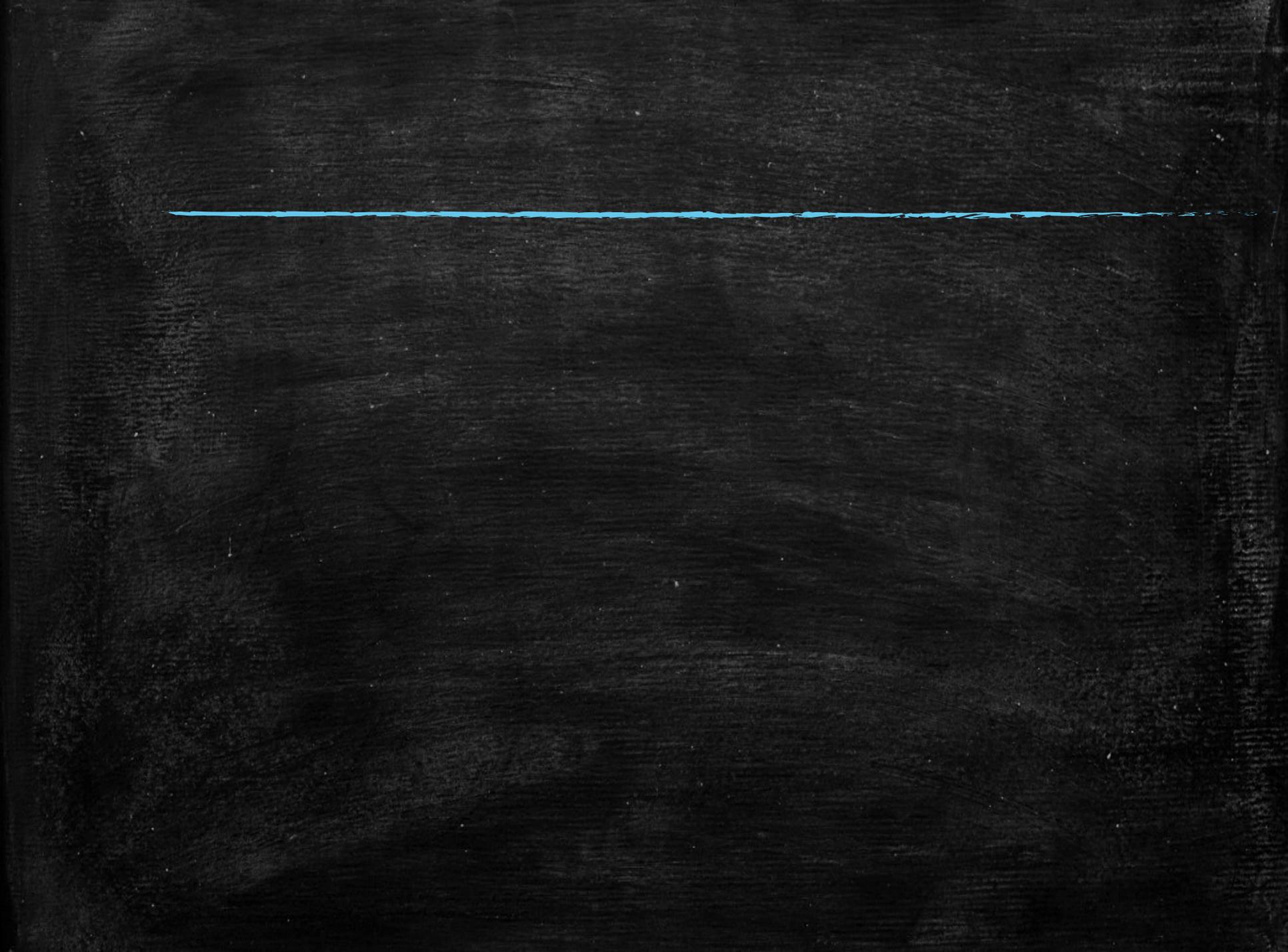
Future potential NASH treatment

- Phase 3 clinical trials:
 - Cenicriviroc
 - Elafibranor
 - Obeticholic acid
- At least 40 other medications in phase 1 and phase 2 trials



NAFLD: shared management between primary care and hepatology





Is it safe to drink
alcohol if I have NAFLD?
If so, how much?

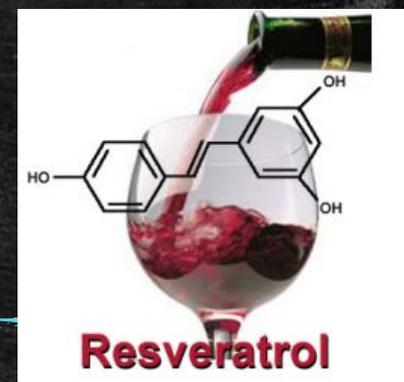
HARVARD MEDICAL SCHOOL, AND
NATIONAL INSTITUTE ON AGING
STUDY IN PROGRESS
RX = 100 BOTTLES OF RED WINE/DAY

TO SCIENCE!





Alcohol and NAFLD



- NASH prevention?
 - Possible benefits of modest alcohol intake on presence of NASH
 - Any alcohol use may prevent improvement in NAFLD over time and may increase fibrosis progression

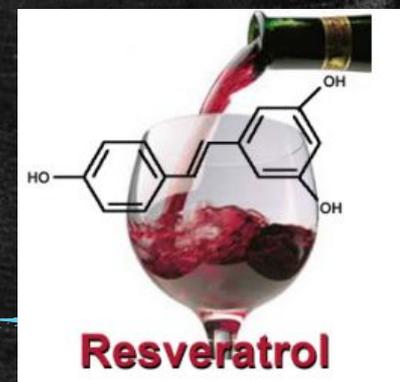
Dunn, *J Hepatol*, 2012.

Ajmera, *Clin Gastro Hep*, 2018.

Ekstedt, *World J Gastro*, 2009.



Alcohol and NAFLD



- Once NASH/NAFL diagnosed:
 - Modest or moderate alcohol intake may prevent improvement in NAFL/NASH
 - Binge drinking is associated with fibrosis progression in patients with pre-existing NAFLD

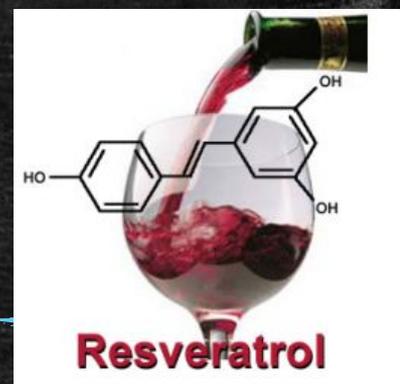
Dunn, *J Hepatol*, 2012.

Ajmera, *Clin Gastro Hep*, 2018.

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Alcohol and NAFLD



No recommendations/data regarding
"safe" alcohol intake in patients with
established NASH

Summary

- NAFLD is common, and most patients with metabolic syndrome comorbidities will have NAFLD, with at least 16 million in the US having NASH
- NAFLD is an umbrella term that includes NAFL and NASH
 - NASH>>>NAFL has risk of progression to cirrhosis
 - Biopsy is needed to characterize NAFLD
- Leading cause of death in NAFLD: Heart disease
- NAFLD is an important contributor to liver cancer and need for liver transplant

Summary

- Management hinges on weight loss, exercise, avoiding carbohydrates, metabolic syndrome control
 - Vitamin E (?pioglitazone) only for biopsy-proven NASH
 - Many drugs in the pipeline for NASH and fibrosis

Future/ongoing areas for research

- Best method for screening and diagnosis
- Which patients are at greatest risk for disease progression
 - NAFL→NASH
 - NASH or NAFL→cirrhosis
- Impact of future treatments on outcomes
 - Need for liver transplant
 - Development of HCC
 - Liver-related death
 - Cardiovascular disease

Thank you!

Danielle.Brandman@ucsf.edu

