



# The many faces of Steatohepatitis:

Fat, Booze, and the Liver

Sept 30<sup>th</sup> 2022  
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Gastroenterology & Hepatology

# Disclosures

- I have no actual or potential conflict of interest in relation to this presentation
- I will not be discussing off-label use

# Objectives

- Appreciate the rising burden of fatty liver
- Learn how to diagnose and risk stratify pts with fatty liver
  - Focus on primary care
- Recognize mixed alcoholic-metabolic liver disease
- Acknowledge rising rates of alcohol dependence of alcoholic liver disease among women
- Understand the impact of Covid-19 on obesity and dysfunctional alcohol use

# Case 1: Elena

36 yo woman from Honduras with type II diabetes and BMI 34. No alcohol use. Strong family history of cardiovascular disease.

Presents with 'gallstone pain' and found to have fatty liver on US



## Case 2: Lee

62 yo Korean American executive with hypertension, dyslipidemia, DMII, a BMI of 41, and daily alcohol use

AST 220, ALT 134, ferritin 780

Ultrasound shows a fatty, nodular liver





## Case 3: Cheryl

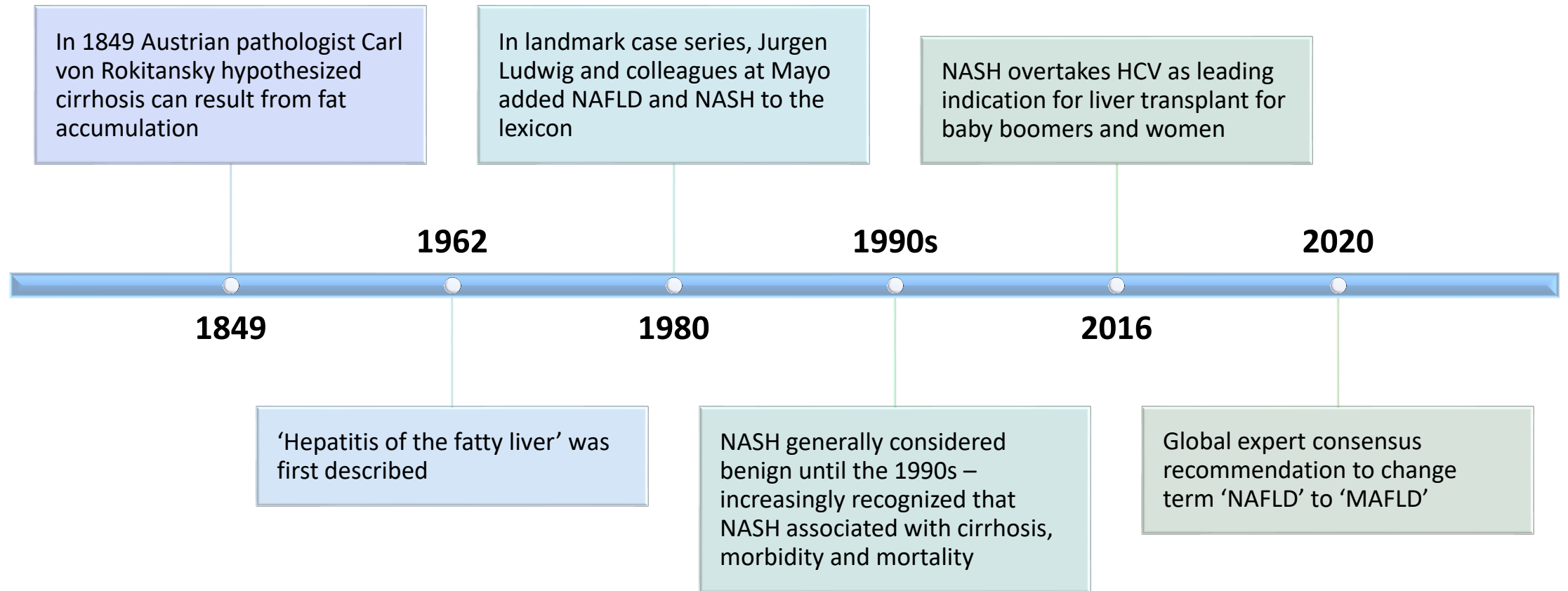
54 yo Caucasian mother of 3 presents with jaundice and upper abdominal discomfort, found to have a bilirubin of 3.3

Alcohol use rising from 2 drinks daily to 1 ½ bottles of wine during quarantine

# Non-Alcoholic Fatty Liver

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# History Lesson





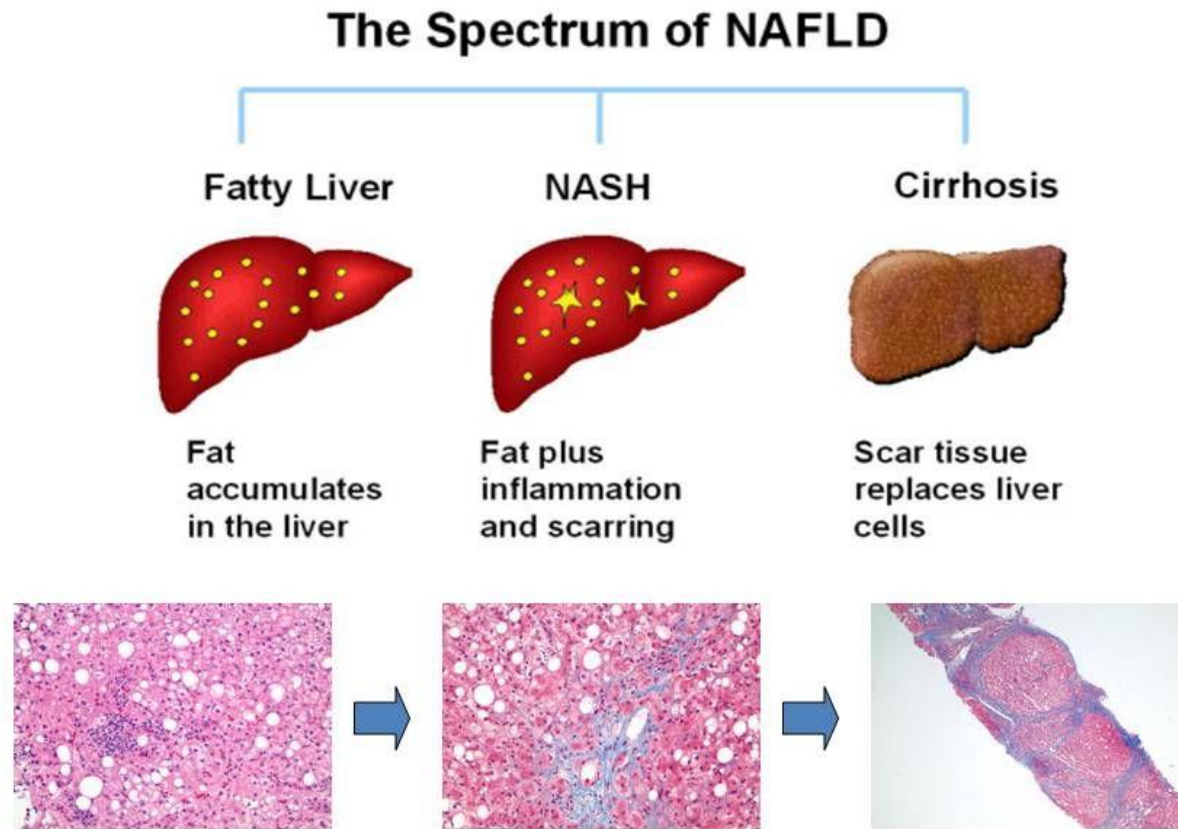
# NAFLD Epidemiology

- 40% of US adults are obese
- 30% of Americans have fatty liver; 5% have NASH
  - Dramatic 5-fold increase since 1995
- NAFLD currently affects 80 million individuals in the US
  - NASH affects 16.5 million
  - NASH cirrhosis affects 3.3 million
- NASH leading indication for transplant for women, 2<sup>nd</sup> leading for men; 7-fold increase in transplant listing
- Between 2015 → 2030, rates of decompensated cirrhosis predicted to increase by 168%, rates of liver-related deaths by 178%, and incident HCC by 137%

# NAFLD Detection

- **Screening** for NAFLD ***not*** currently recommended by US societies - even for high-risk patients
  - Not cost-effective
  - Lack of therapeutics
- NAFLD often diagnosed incidentally
  - US or CT scan
    - Requires  $\geq 20\%$  hepatic fat
  - Elevated ALT
    - May be normal in 50 and 80% of those with NASH and NAFLD
    - Degree of ALT/AST elevation does NOT correlate with severity

# Fatty liver: an umbrella term



<50% of Primary Care providers reported knowing the difference between NAFL and NASH

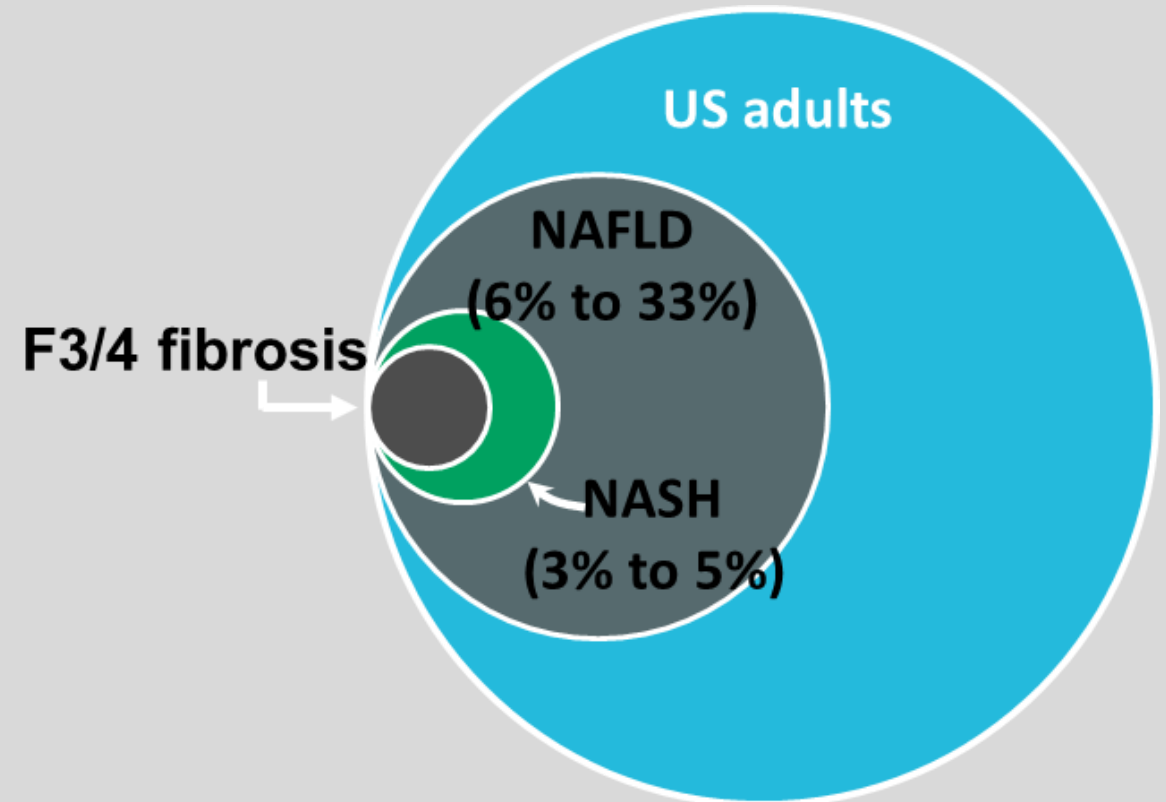
Yet 60% of those providers reported managing patients with NAFL and/or NASH

# Steatosis vs steatohepatitis: why does it matter?

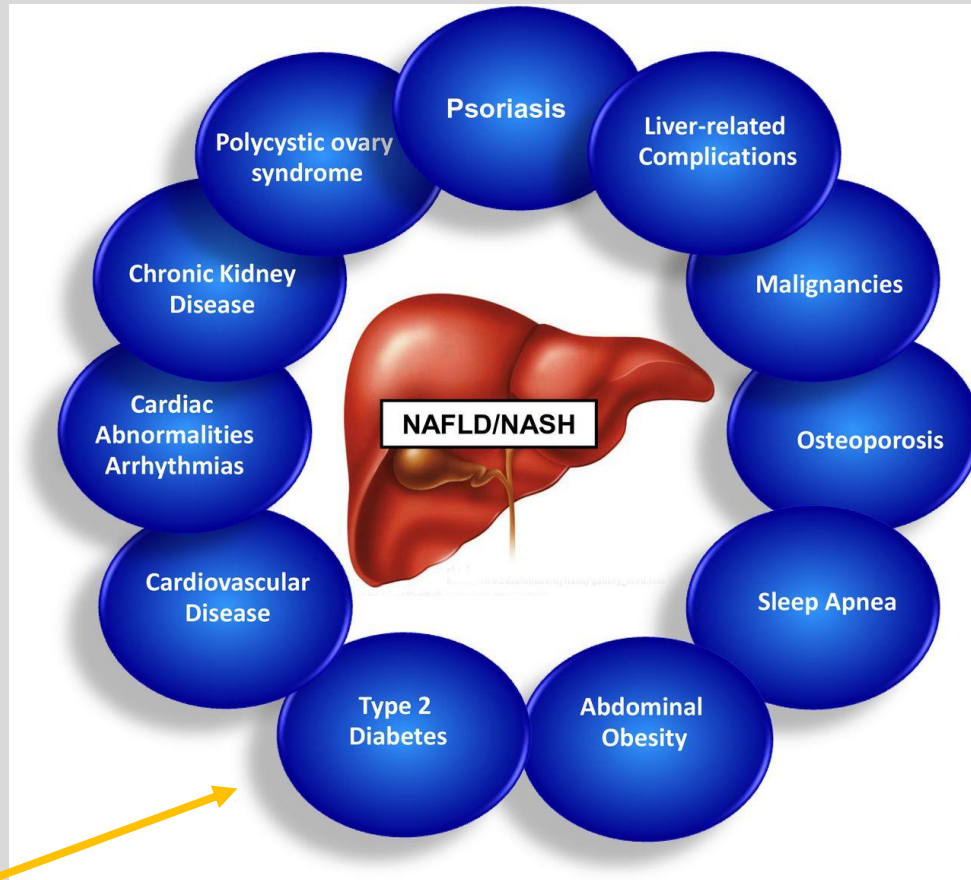
- <1% of patients with steatosis develop fibrosis = benign
- 25% of patients with NASH develop cirrhosis = progressive

## Who is most at risk for NASH?

- BMI > 30
- Age > 50
- Type II diabetes
- Metabolic syndrome
- Hispanic ethnicity, Asian, SE Asian
- Concomitant alcohol
- AST>ALT or rising AST



# Fatty liver: a component of metabolic syndrome



Cause of death in NASH:

- 1) CVD,
- 2) Cancer,
- 3) Liver disease

# Drivers of Steatohepatitis

Comorbidities	Genetic	Microbiome products	Nutrition and behavior
<ul style="list-style-type: none"> <li>• <b>Obesity</b></li> <li>• <b>Metabolic syndrome</b></li> <li>• <b>Insulin resistance</b></li> <li>• <b>Type 2 DM</b></li> <li>• Dyslipidemia</li> <li>• <b>Hypertension</b></li> <li>• OSA</li> <li>• PCOS</li> <li>• <b>Hypopituitarism</b></li> <li>• Low GH</li> <li>• Low testosterone</li> <li>• Thyroid disease</li> <li>• <b>LAL-D</b></li> <li>• Iron overload</li> <li>• Psoriasis</li> <li>• Osteoporosis</li> </ul>	<ul style="list-style-type: none"> <li>• <b>PNPLA3</b></li> <li>• <b>TM6SF2</b></li> <li>• <b>A1AT Pi*Z</b></li> <li>• HSD17B13</li> <li>• LYPLAL1</li> <li>• GCKR</li> <li>• MBOAT</li> <li>• DNA methylation</li> <li>• Chromatin remodeling</li> <li>• Non-coding RNAs</li> </ul>	<ul style="list-style-type: none"> <li>• ETOH</li> <li>• Lipopolysaccharide</li> <li>• Reactive oxygen species</li> <li>• Cholesterol oxidation products</li> <li>• Butyrate</li> <li>• Acetate</li> <li>• Phenylacetate</li> <li>• Secondary bile acids</li> <li>• Choline deficiency</li> </ul>	<ul style="list-style-type: none"> <li>• <b>Alcohol</b></li> <li>• <b>Cholesterol</b></li> <li>• <b>Fructose</b></li> <li>• <b>Exercise</b></li> <li>• <b>Coffee</b></li> </ul>
<p>Black = association with evolving evidence</p> <p>Red = established association</p> <p>Green = protective</p> <p><b>Bold = drives NASH progression</b></p>			

# My patient has fatty liver, so now what do I do?

- Check labs
- If ALT>AST elevated, rule out other etiologies
- Assess risk factors
- Assess alcohol use

Echogenic liver, most likely reflecting steatosis. Liver steatosis (fatty liver) can be an incidental benign finding, but in some individuals it can be caused by non-alcoholic steatohepatitis (NASH) or other causes of chronic liver dysfunction. If patient has not already been evaluated, consider hepatology consultation.

## *How can we improve follow up of incidental steatosis?*

- VM radiology intervention to 'tag' imaging reports with steatosis in the impression section and recommend further evaluation
- We conducted a retrospective review to identify the yield of this intervention
  1. *What proportion of patients were eventually seen in hepatology clinic?*
  2. *Of those referred, what proportion of patients had stage 2 or above fibrosis based on invasive or non-invasive staging?*
  3. *What were the predictors of NASH with advanced fibrosis?*



Total patient's charts reviewed  
(n= 812)

Not seen by hepatology  
(n= 576)

Seen by hepatology  
(n= 236)

Acknowledged and  
recommended  
lifestyle changes  
or referred to PCP  
( n= 326)

No  
acknowledgement  
of hepatic  
steatosis  
(n=250)

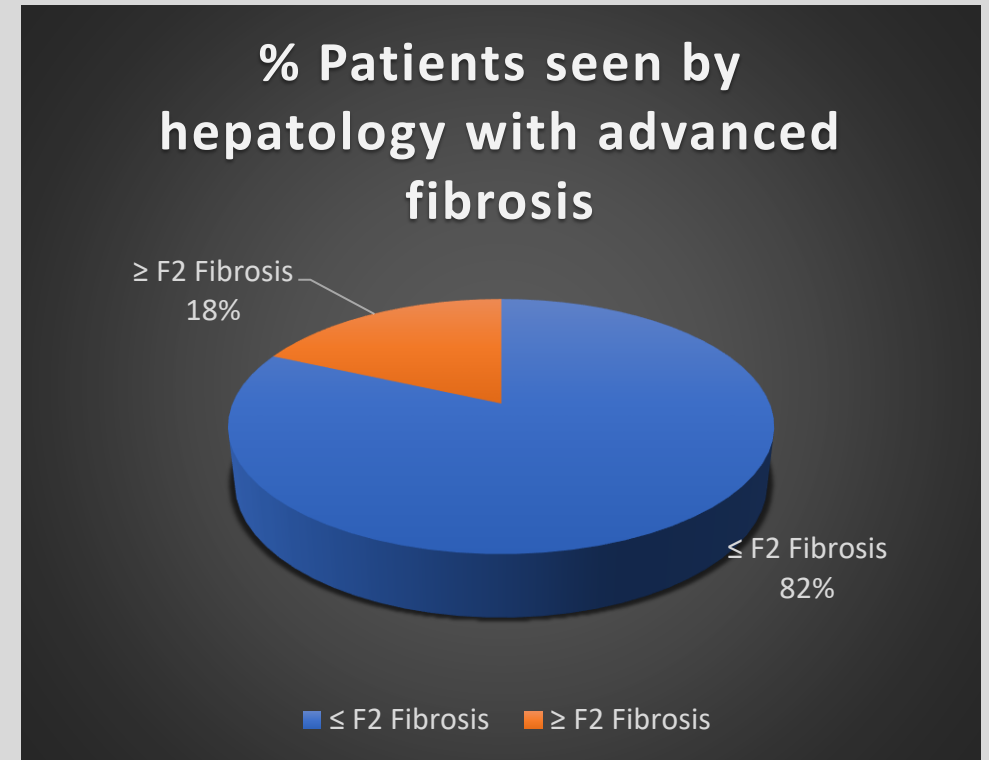
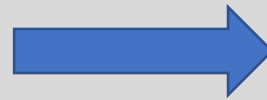
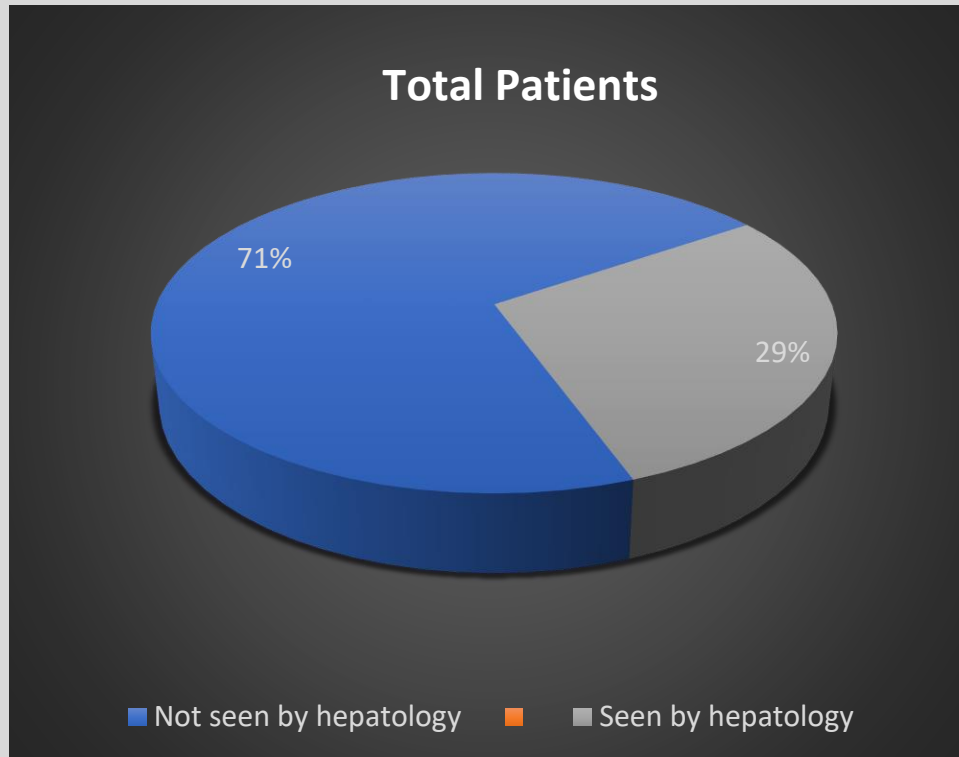
Further staging with  
either MRE, Fibroscan or  
biopsy or combination  
(n=126)

No further staging,  
recommended weight  
loss and lifestyle  
changes  
( n= 110)

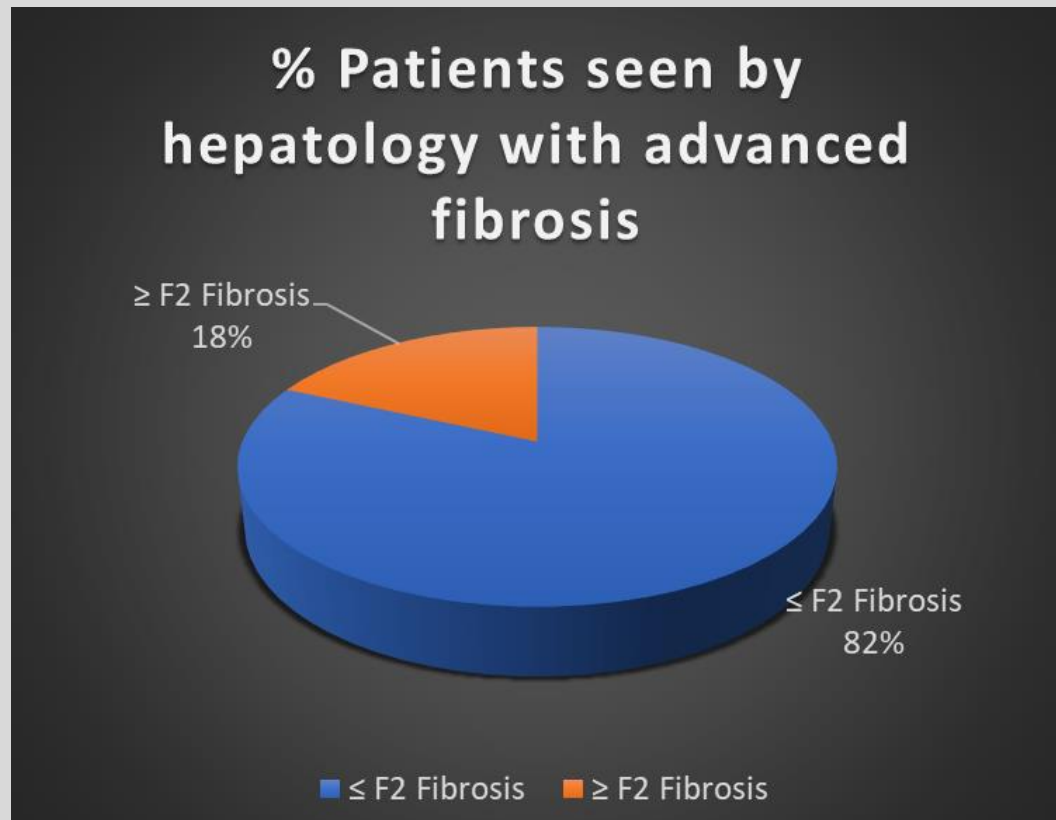
Advanced Fibrosis  $\geq$   
F2  
(n=23)

No significant  
fibrosis < F2  
(n=103)

# Incidental Steatosis: Follow Up



# Incidental Steatosis: Predictors of Referral



- Patients with elevated ALT were more likely to be referred to hepatology (though ALT not a predictor of fibrosis)
- Patients with DMII were not more likely to be referred (though diabetes is strongly associated with NASH fibrosis)
- Key opportunity for diagnosis, evaluation, and initiation of early interventions to prevent progression to advanced fibrosis and cirrhosis.

# Low Awareness

- Despite growing incidence, NAFLD is under-diagnosed and under-recognized
- Commonly discovered incidentally at an advanced stage with cirrhosis
- Under-appreciation of NAFLD by primary care clinicians, including spectrum of the disease and how it can be assessed
- Majority of patients with NAFLD have a poor understanding of the disease
- *How does lack of awareness by patients and providers impact progression?*

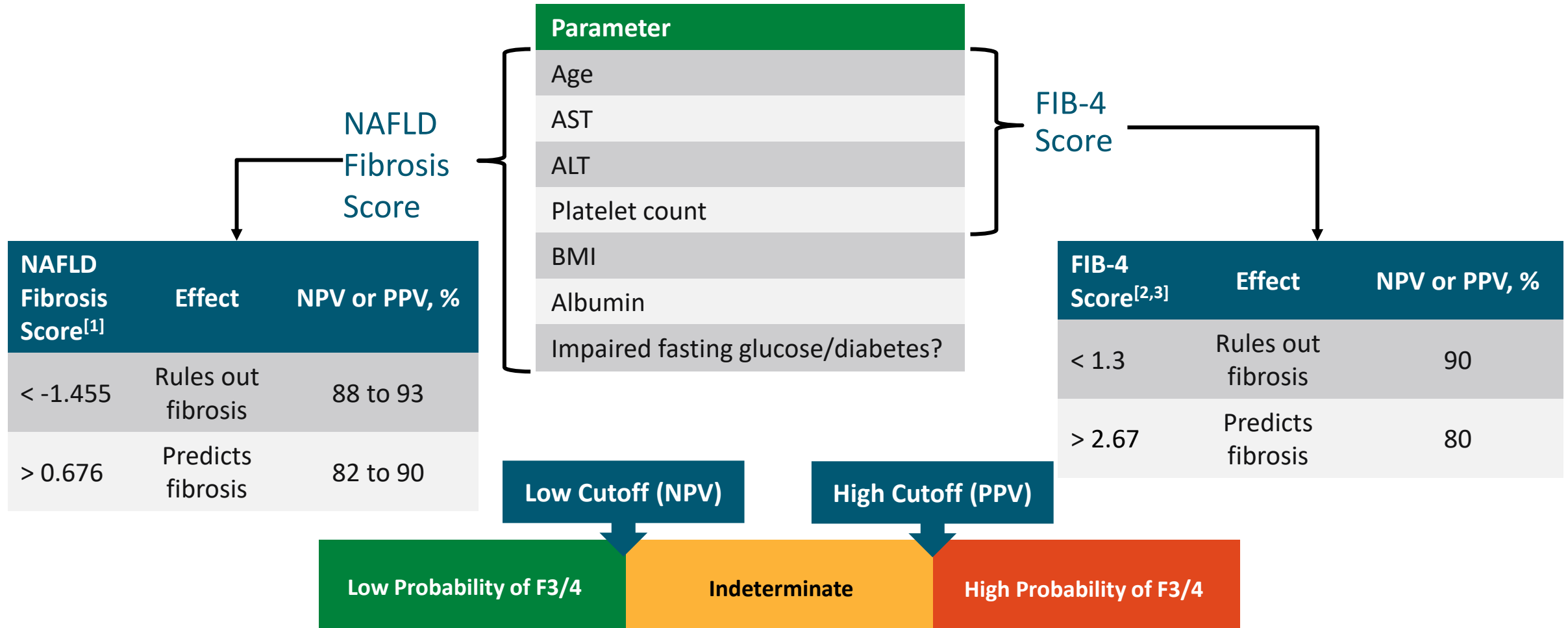
# My patient has fatty liver, so now what do I do?

What can a PCP do with basic clinical information to risk stratify these patients?

- Check labs
- If ALT>AST elevated, rule out other etiologies
- Assess risk factors
- Assess alcohol use
- Calculate a NAFLD Fibrosis Score

Echogenic liver, most likely reflecting steatosis. Liver steatosis (fatty liver) can be an incidental benign finding, but in some individuals it can be caused by non-alcoholic steatohepatitis (NASH) or other causes of chronic liver dysfunction. If patient has not already been evaluated, consider hepatology consultation.

# NASH Biomarkers: NAFLD Fibrosis Score and FIB-4



# Updated Radiology Tag

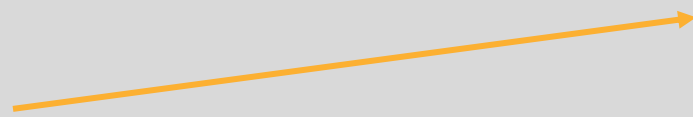
## IMPRESSION:

Echogenic liver is compatible with continued steatosis. Liver steatosis (fatty liver) can be an incidental benign finding, but in some individuals it can be caused by non-alcoholic steatohepatitis (NASH) or other causes of chronic liver dysfunction. Consider risk stratification with the NAFLD Fibrosis Score (NFS) <https://nafldscore.com/index.php> and referral to hepatology for patients at indeterminate and high risk.

NFS < -1.455 Low Risk

NFS > or = -1.455 = Indeterminate

NFS > 0.675 = High Risk



### NAFLD Fibrosis Score

Age

AST

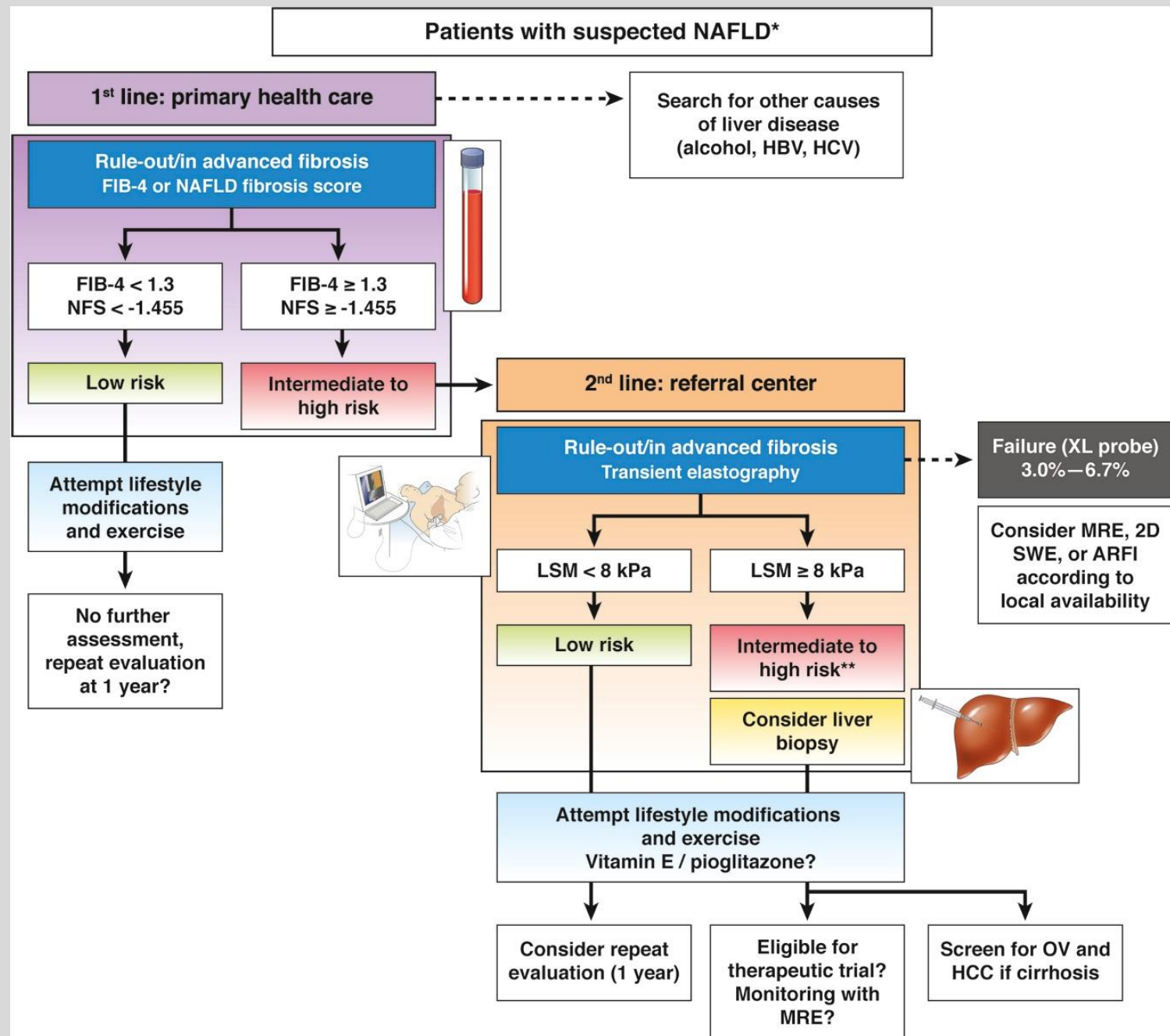
ALT

Platelet count

BMI

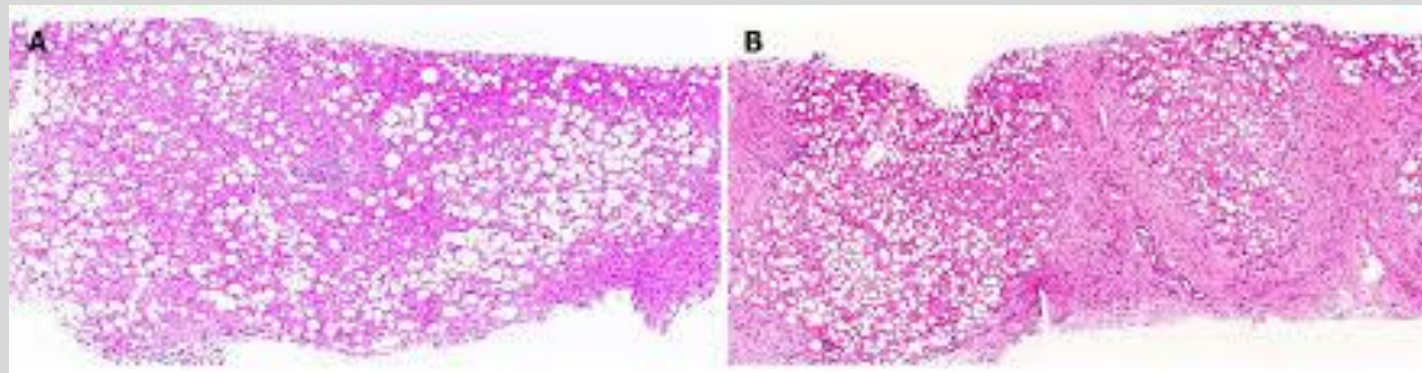
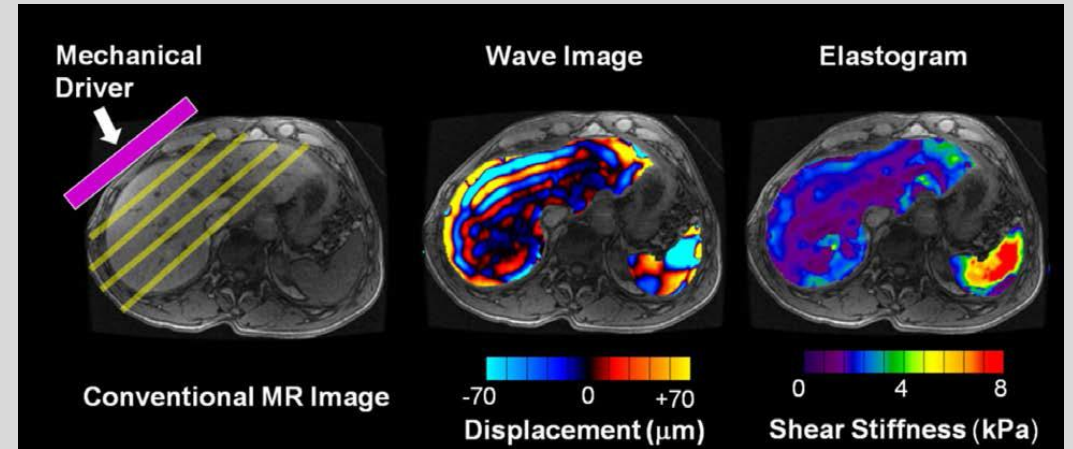
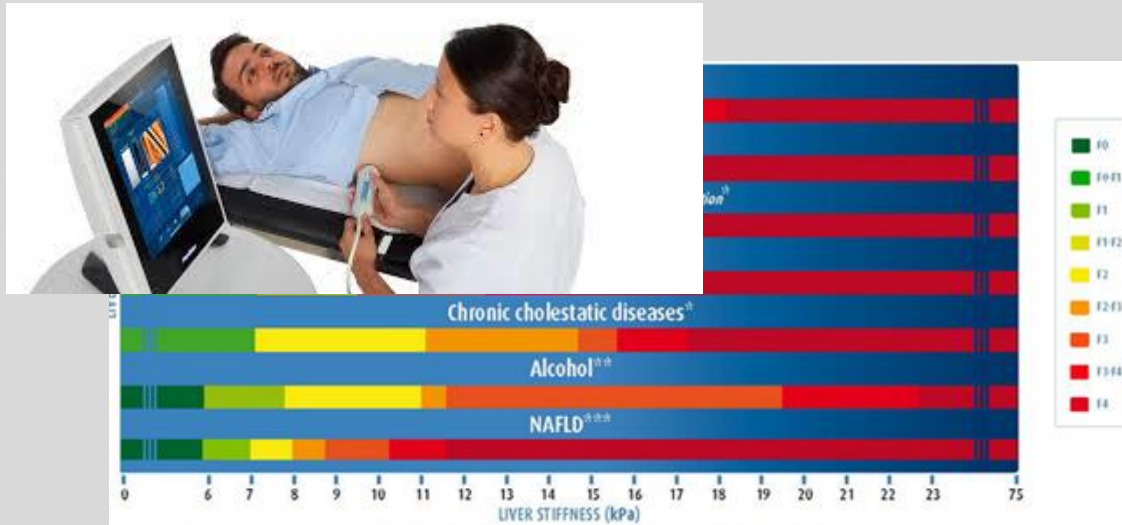
Albumin

Impaired fasting glucose/diabetes?



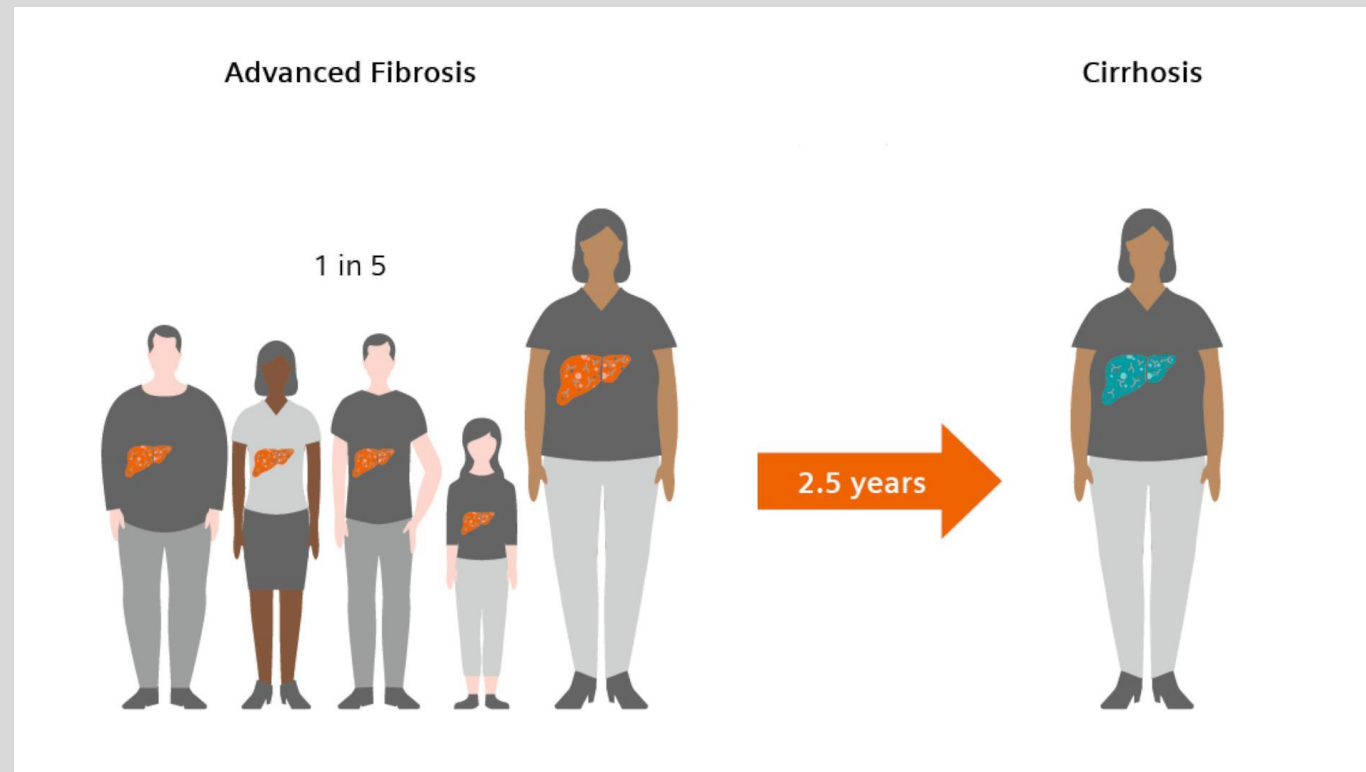


# Staging Options



If you only know one thing...

Fibrosis is the strongest independent predictor of disease progression



# Case 1: Elena

Rising burden of NASH and cirrhosis among Hispanic Americans

Elena, a 36 yo woman from Honduras with type II diabetes and BMI 34. No alcohol use. Strong family history of cardiovascular disease.

Fatty liver on US but previously normal liver enzymes



# Elena

- Steatosis on US
- Age 36, BMI 34, DMII, AST 76, ALT 104, platelet count 190,000, albumin 4.0 → -0.40 = indeterminate NAFLD fibrosis score
- Referral to hepatology
- MR elastography

## QUANTITATIVE LIVER EVALUATION:

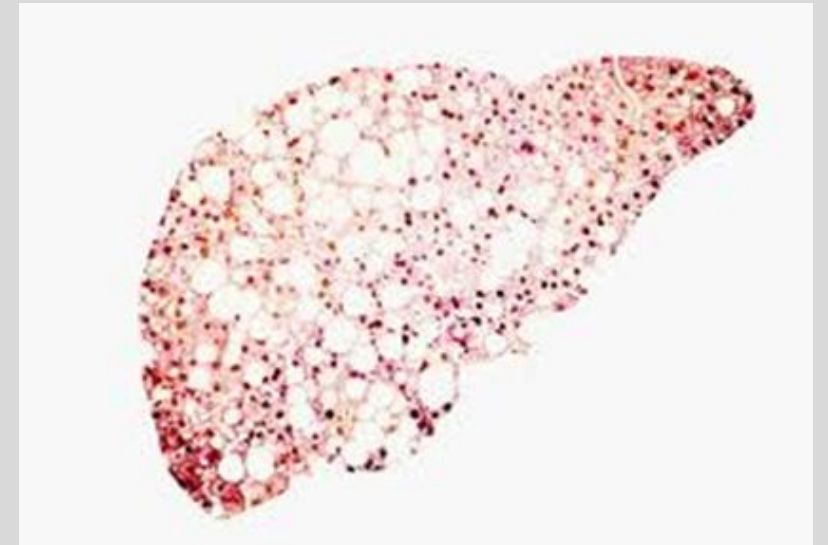
### IMPRESSION:

1. Average liver shear stiffness is abnormal at 3.6 kPa + /- 0.3 kPa, suggestive of **stage 2-3 fibrosis** according to the Mayo classification. Note that the apparent shear stiffness of the liver is heterogeneous, greater in the right lobe.
2. Average fat fraction of liver is elevated at **26.4%** + / - 2.6%.



# NAFLD and Latinos

- NAFLD has a variable prevalence and severity across ethnicities
- Interplay between genetic factors, lifestyle factors, and presence of chronic metabolic diseases
  - Differential carriage of single polymorphism PNPLA3 gene
  - Higher rates of obesity, DMII
- NAFLD affects:
  - 45% of Latinos
    - Mexico>Central>South America
  - 33% non-Latino whites
  - 24% non-Latino blacks
  - Asian Americans at lower BMI
- Latinos have earlier presentation, higher proportion NASH, more rapid progression of fibrosis





# NASH Management – Keep it Simple

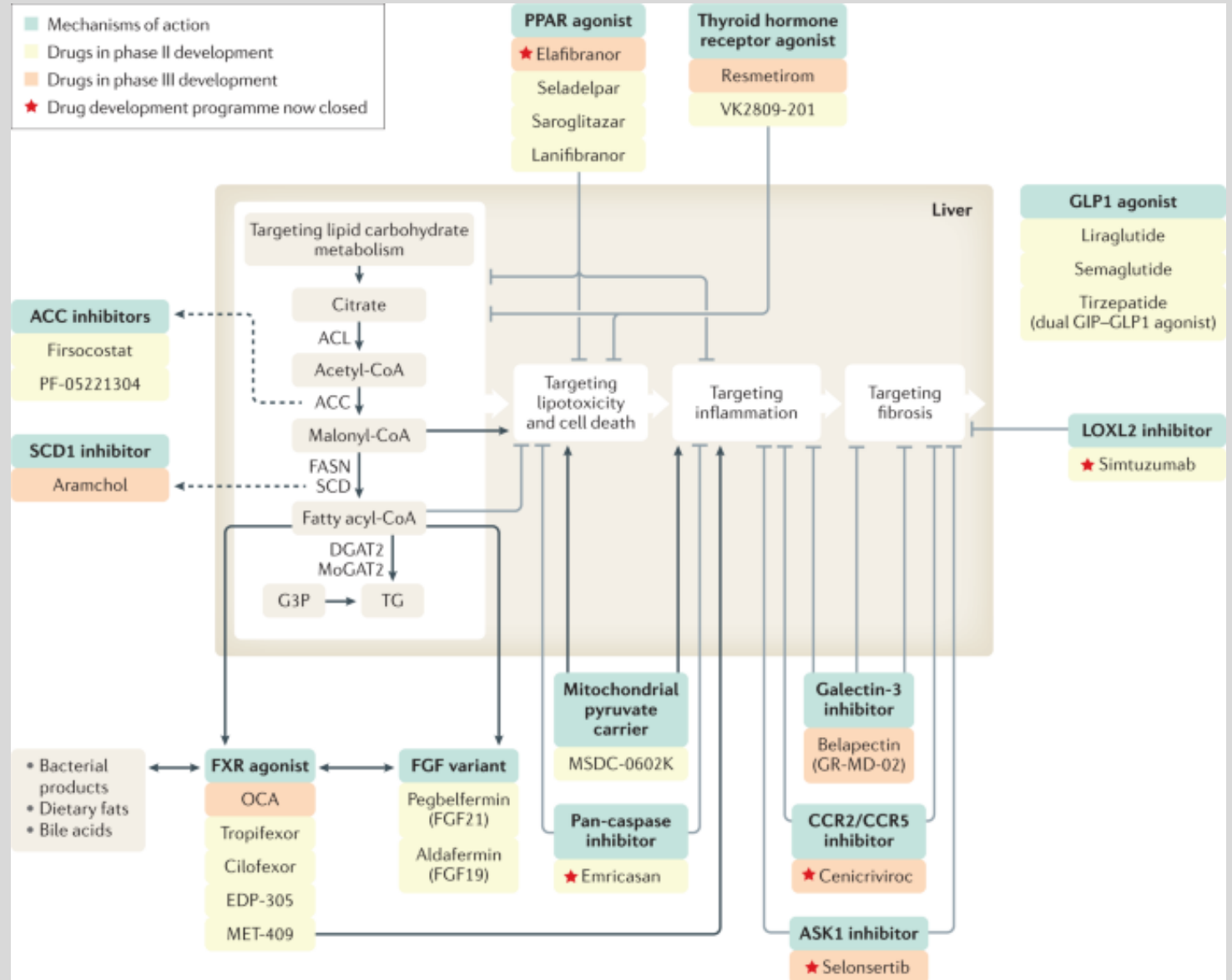
- ✓ 5-10% total body weight loss
- ✓ Increased physical activity
- ✓ Diabetic control
  - GLP-1 agonist (semaglutide)
- ✓ Vitamin E if non-cirrhotic, no contraindications
- ✓ Consider clinical trials → pharmacotherapy
- ✓ Consider bariatric surgery



# NASH Pharmacotherapeutic Pipeline

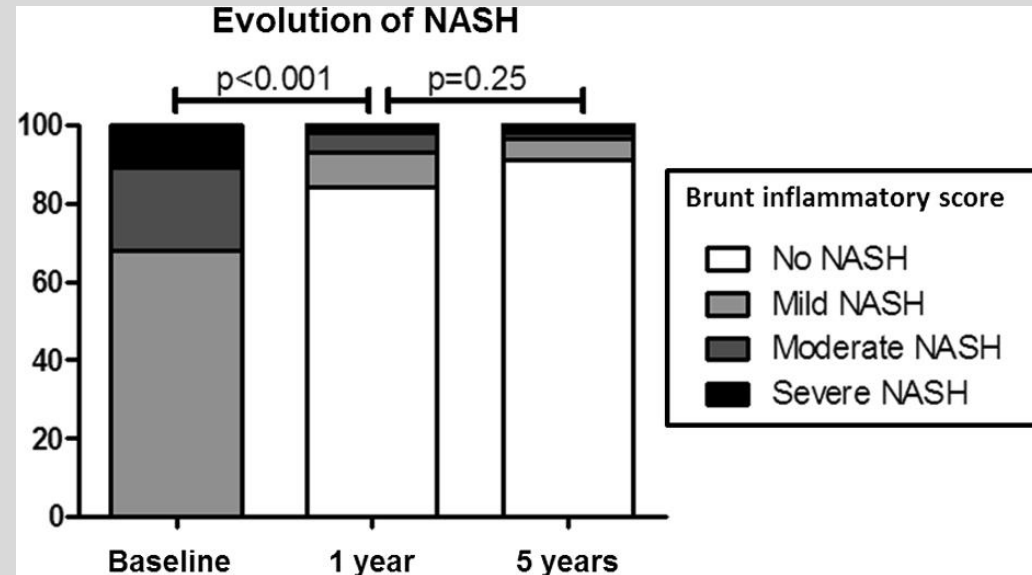
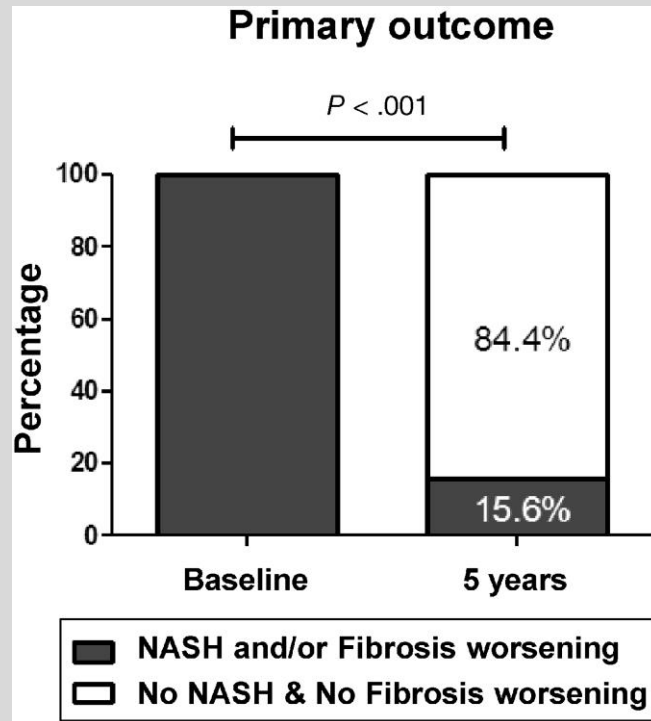
In 2023, we will see our first  
approved agent for NASH

In the future, combination  
therapy + weight loss



# Bariatric Surgery for NASH

- Assoc with disappearance of NASH in 85% of morbidly obese patients
- Highest chance for reversal of fibrosis
- Child A cirrhosis only



Lassailly et al Gastroenterology 2020;



# Bariatric Surgery for NASH

- Increased risk of alcohol use disorder (AUD) in the 5 years following bypass surgery
  - Replacing one vice with another?
- Impaired alcohol metabolism due to gastric bypass + weight loss
  - More buzz?
- We see cases of progressive liver fibrosis and cirrhosis in the years following bariatric surgery due to *minimal* amounts of alcohol
- COUNSELING IS KEY!

## Case 2: Lee

62 yo Korean American executive with hypertension, dyslipidemia, DMII, a BMI of 41, and daily alcohol use

AST 220, ALT 134, bilirubin 1.2, ferritin 780

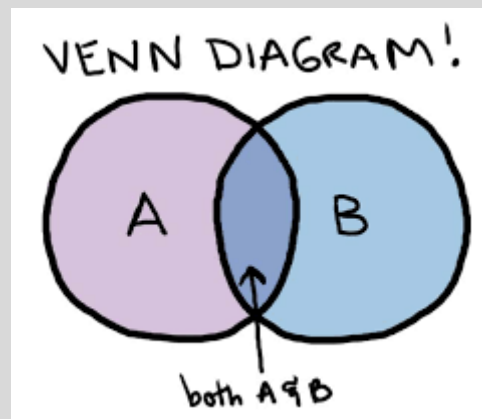
Ultrasound shows a fatty, nodular liver

Mixed alcoholic and metabolic steatohepatitis  
on the rise



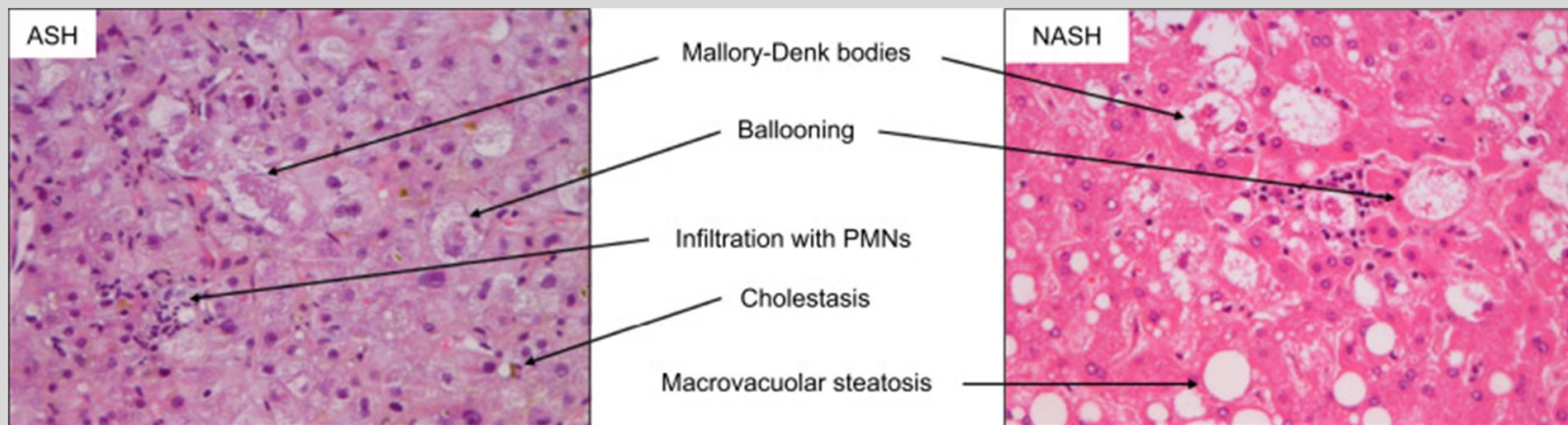
# Is it the fat or the booze?

- Definition of 'significant' alcohol remains debated
- Cutoffs for NAFLD: >30 g/day for men, 20 g/day for women
- Classification into separate groups often arbitrary and inappropriate
- Low amounts of alcohol can still cause steatosis and injury in patients with metabolic risk factors



# Is it the fat or the booze?

- Spectrum of liver injury is similar: range from steatosis to steatohepatitis to fibrosis to cirrhosis
  - Often different clinical presentations
  - Imaging similar
  - Histologically indistinguishable
  - History is key – duration of alcohol, amount, type, timing, nutritional status?

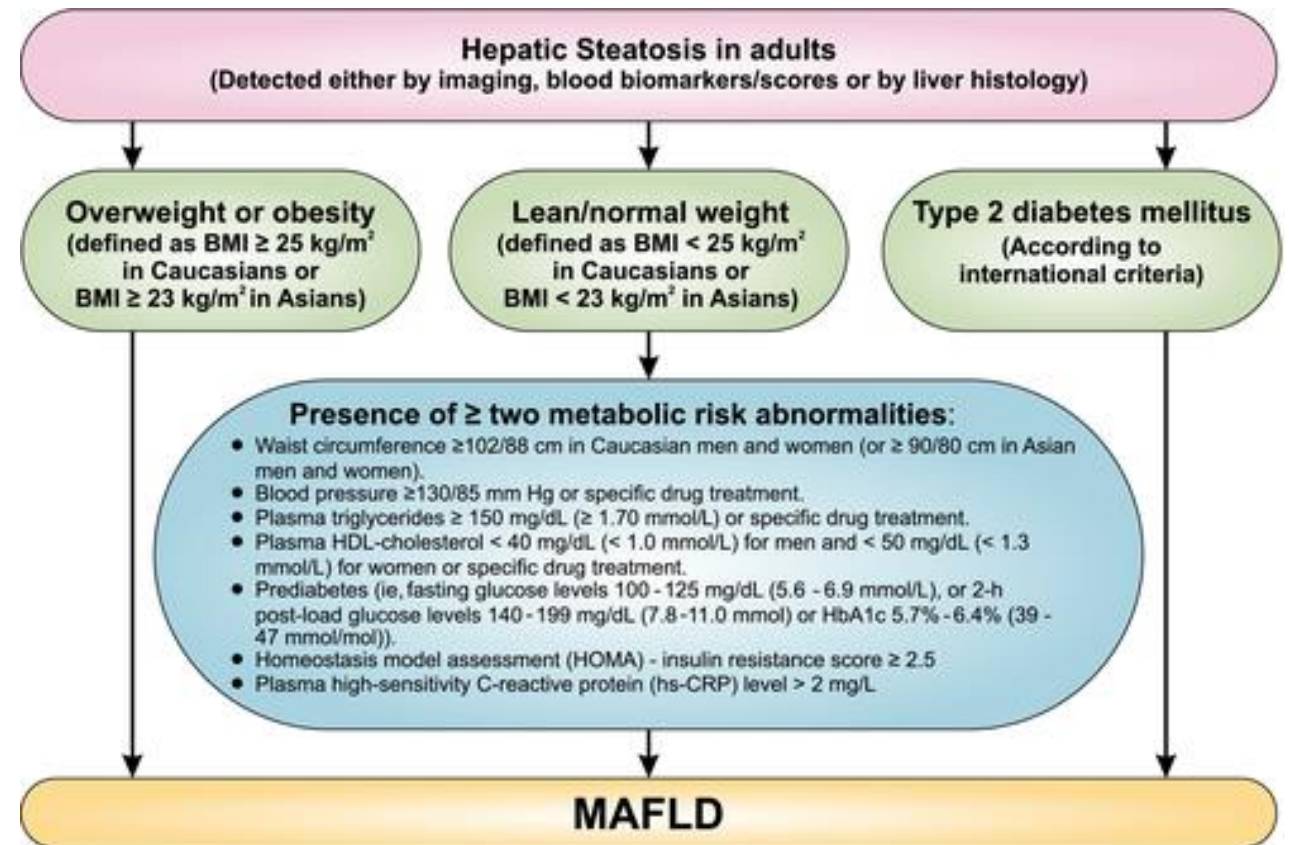


# Time to Update the Lexicon?

## Metabolic Associated Fatty Liver Disease (**MAFLD**)

No exclusion of alcohol  
? Avoids stigma

Eslam et al, A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology*. 2020

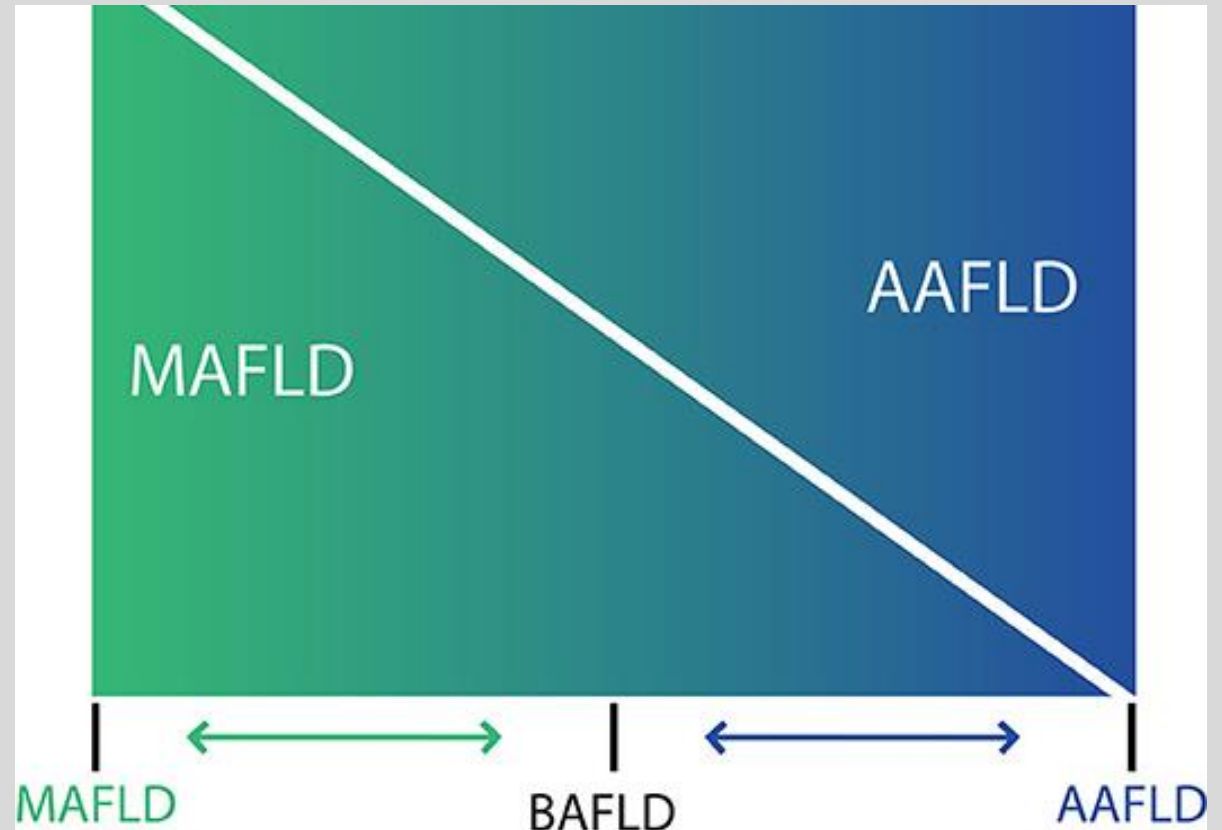


# Fat + Booze

- High prevalence of obesity and alcohol consumption worldwide →  
Frequent presence of both conditions in same individual
- One condition is **predominant** while the other is a **cofactor**
- Common pathways lead to steatosis
  - Imbalance in fatty acid synthesis and beta-oxidation
  - Inflammatory immune response
  - Intestinal permeability, dysbiosis
  - Genetic predisposition
- Synergistic increase in fibrosis progression; higher risk for liver-related death and HCC
- Combination of metabolic and alcoholic factors also increases risk of CV disease and cancer

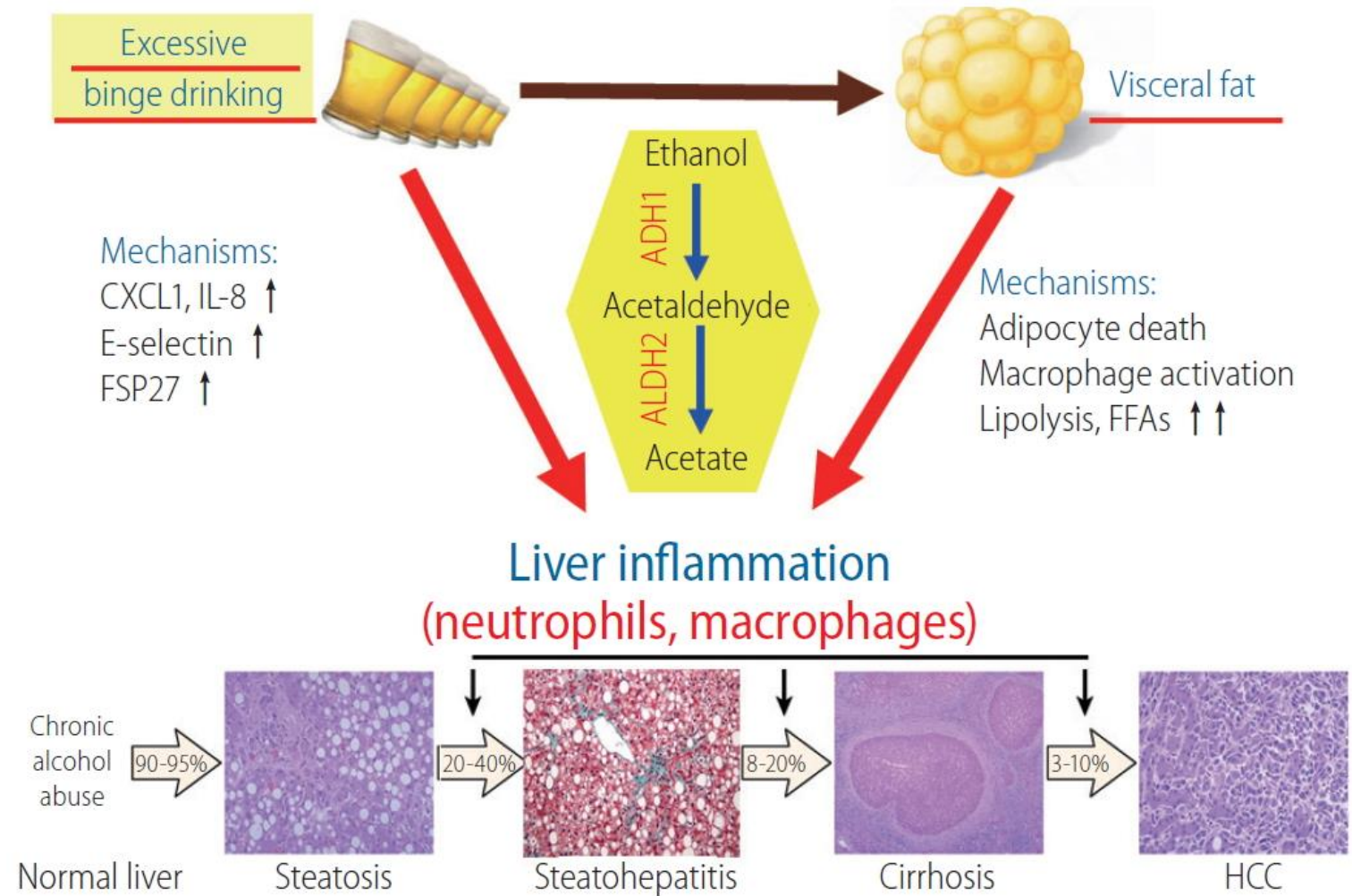
# Alcoholic / Metabolic Liver Disease

- BMI is an independent predictor of liver fibrosis among daily drinkers
- 5.8-fold relative risk of steatosis in daily drinkers who were also obese
- Obese women who drink > 150g/week have 5-fold RR of cirrhosis
- Among heavy drinking Japanese men, presence of DMII increased liver-related mortality 8-fold
- In alcohol-related cirrhosis, risk of HCC increased 6.7-fold with obesity & DMII





# Binge drinking and visceral fat synergistically promote liver injury





# Moderate alcohol in NAFLD?



- Significant controversy exists – does the ‘protective effect’ of low-risk drinking apply to those with NAFLD?
- Initially some studies suggested a CV benefit
- Recent evidence concludes there is **no** safe threshold
  - Large study of Korean adults with NAFLD (N=58,927) followed for 5 years showed that light or moderate alcohol was assoc with progression of fibrosis
  - Association stronger for more obese individuals
- In contrast to general population\*\* alcohol use does not reduce risk of CVD in patients with NAFLD

Wandji et al J Hep 2020; Chang et al, Hepatology 2019;  
VanWagner et al, Gastro 2017

## Case 2: Lee

62 yo Korean American CFO with hypertension, dyslipidemia, DMII, a BMI of 41, and daily alcohol use

AST 220, ALT 134, bilirubin 1.2, ferritin 780

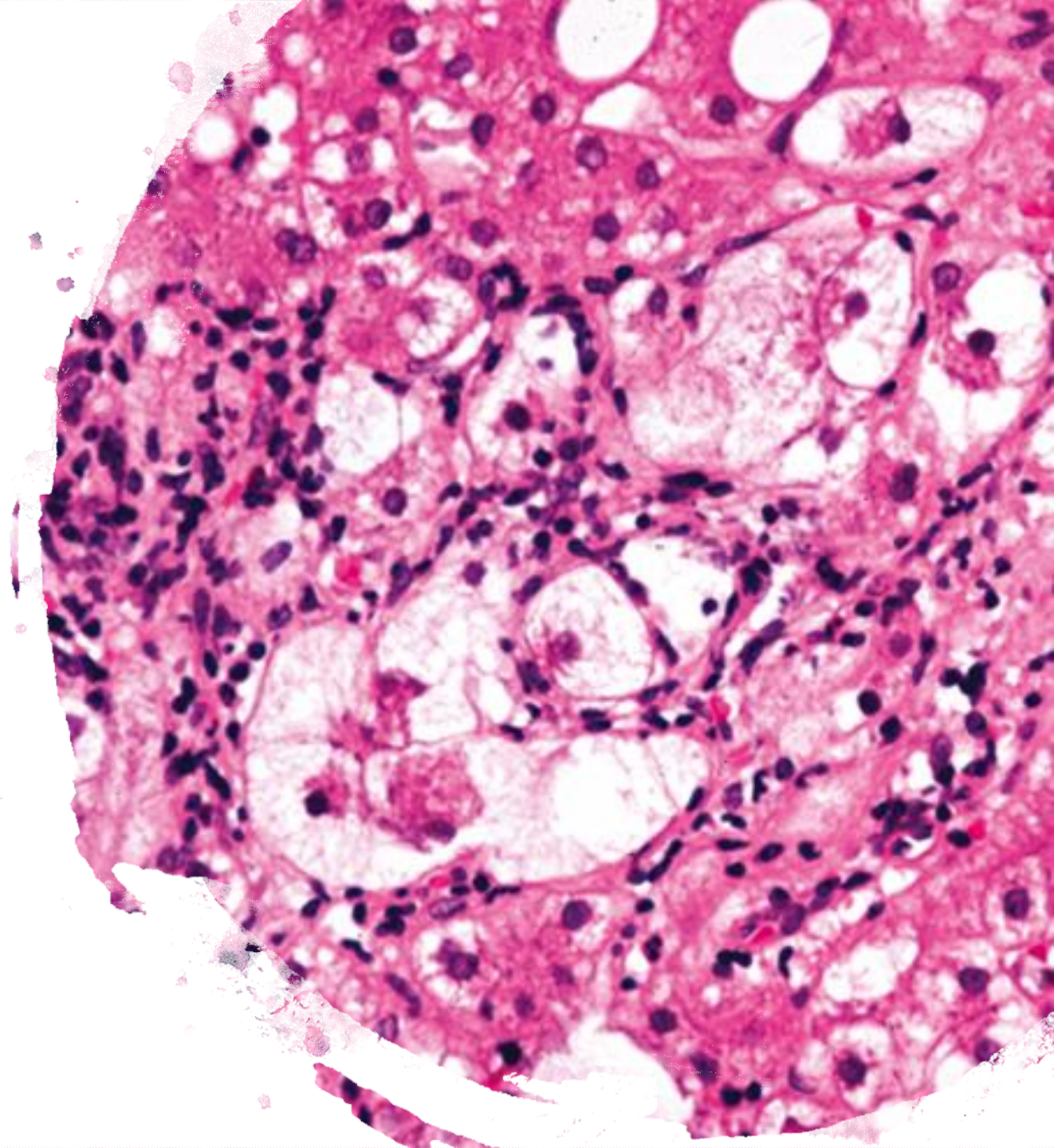
Ultrasound shows a fatty, nodular liver

What will have the biggest impact on the natural history of his liver disease? Alcohol cessation or weight loss?



# Follow up

- Given AST 220, ALT 134, ferritin 780, performed liver biopsy
- Steatohepatitis and stage 4 fibrosis
- 6 months later his ultrasound shows a 3.2cm mass consistent HCC
- Is he a transplant candidate?





## Case 3: Cheryl

54 yo Caucasian mother of 3 presents with jaundice and upper abdominal discomfort, found to have a bilirubin of 3.3

No known hx of liver disease

Alcohol use rising from 2 drinks daily to 1 ½ bottles of wine during quarantine

Increasing rates of alcohol dependence and alcoholic liver disease among women



# What is risky drinking?

- Standard drink contains 10-14g of alcohol
- **Moderate** alcohol use: 1 drink/day for women, 2/day for men
- **Binge** drinking: 4+ drinks for women or 5+ drinks for men in < 2 hours
- **Heavy** alcohol use: binge drinking 5+ times per month
- **Alcohol use disorder (AUD)**: use of large and escalating amounts of alcohol with unsuccessful efforts to cut down; much time spent recovering, obtaining, or using alcohol; recurrent alcohol use when physically hazardous; and craving and withdrawal. The accumulation of more symptoms results in a more severe AUD.



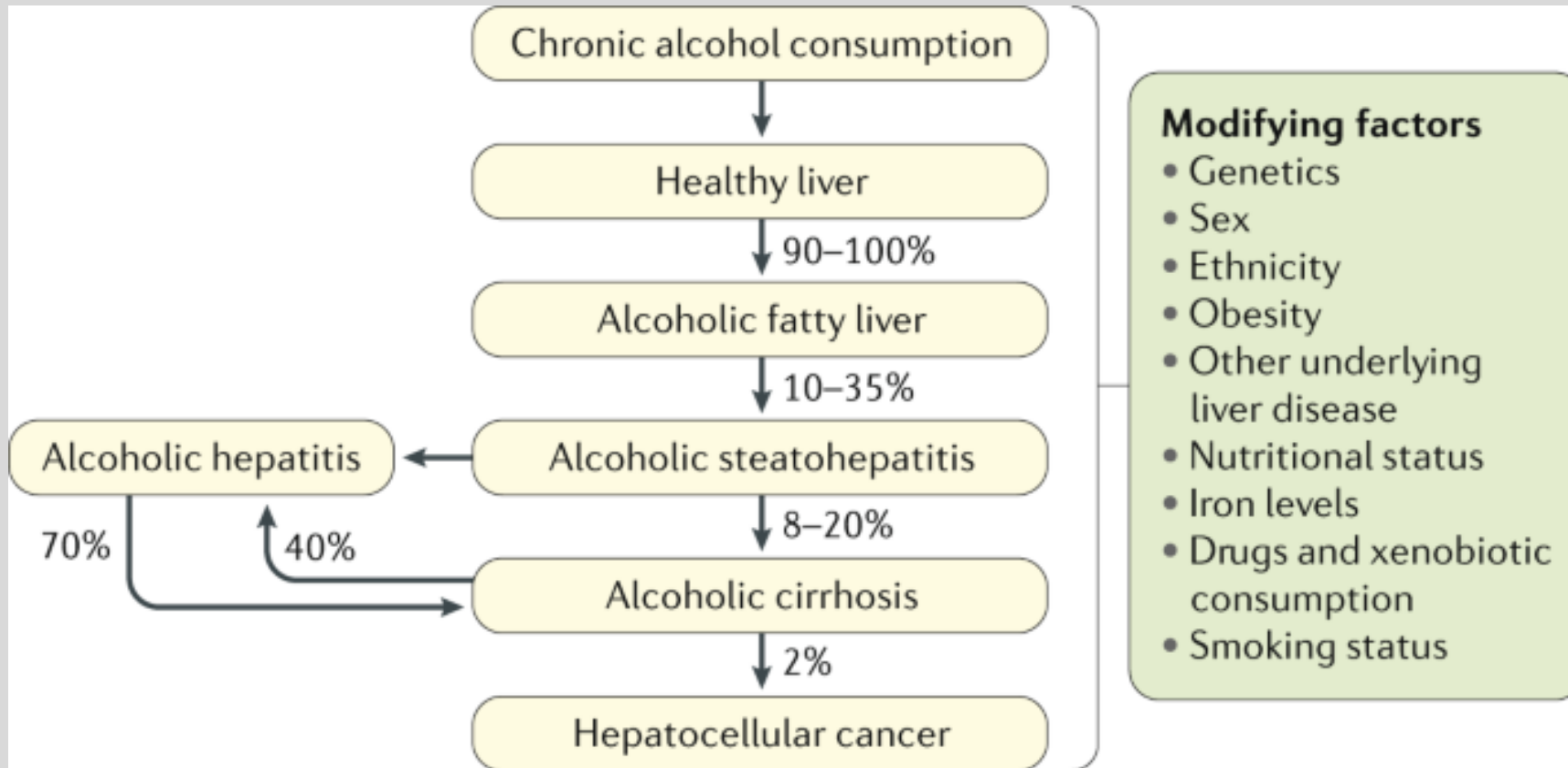
# Rising Rates of Risky Drinking

- Increased prevalence of high risk drinking over past 2 decades
- 12-month prevalence **high-risk** drinking increased almost 30% from 9.7% to **12.6%**
- 49.4% increase in **AUD** during this time from 8.5% to **12.7%**
  - representing now 30 million Americans
- Alarming increases in high-risk drinking and AUD among **women** (57.9% and 83.7%, respectively) relative to men (15.5 and 34.7%)
- Increases in alcohol use, high-risk drinking, and AUD generally much greater among minorities than white individuals

# Rising Rates of Alcohol-related Liver Disease

- Rising rates of alcohol-associated **cirrhosis** (AC) diagnoses
- Corresponding increases in liver **transplant** for ALD
  - 2004-2013 number of new wait-listed patients w/ ALD increased by 45%
- Rising rates of ALD-associated **mortality**, particularly among younger adults (aged 25-34)
  - Severe alcohol-associated hepatitis (AH)
- Significant increase in ALD-related **hospitalizations**
- Inpatient **costs** now total more than every other liver disease combined

# ALD: Familiar Pathways





# Alcohol and Liver Disease in Women

- At the same level of alcohol, women have an increased risk for cirrhosis

At 48 g/day (4 drinks in US), RR of cirrhosis for women was **double** that for men (RR 10.1 [95% CI: 7.5-13.5] vs RR 5.6 [CI: 4.5-7.0])

- Women develop ALD on average 3-5 years earlier
- Women more likely to present with *severe* alcoholic hepatitis without prior dx of ALD
- In US over past decade, largest increase of alcohol-related deaths among non-Hispanic white women
- Need a high index of suspicion to diagnose ALD early enough to be reversible – women underreport, don't ask for help

# Why are Women Drinking More?

- Norms around drinking and what is socially acceptable for women have changed dramatically
- Its everywhere! TV, movies, social media
- Direct-to-women consumer advertising
- Women drink more in response to negative emotions and anxiety than men do (NIAAA)
- Covid has been hard on women and moms...



Currently approving my kids friends based on who's parents will drink wine with me on playdates.

- WILD SUNSHINE THREADS

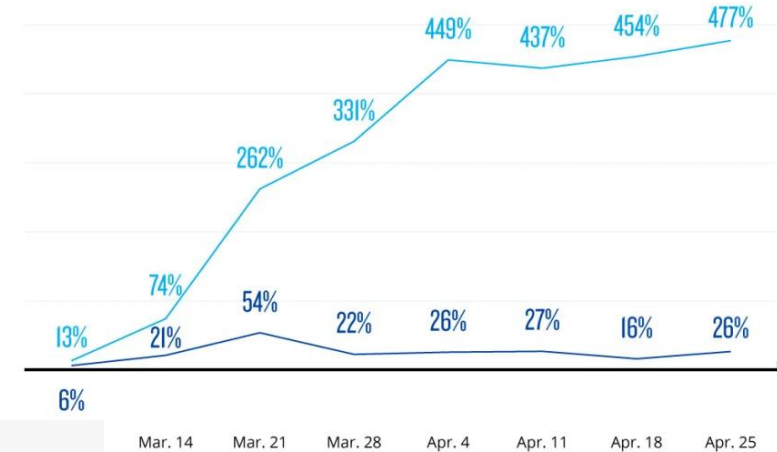
# Mommy Juice Culture

# Impact of Covid-19 on Alcohol Use

- Prior to Covid, incidence of AUD and ALD had already been rising
- First month of pandemic, 55% increase in store alcohol sales, 300% rise in online alcohol sales
- Increased purchasing more pronounced among younger adults, households with children < 18, and minorities
- Impact of economic and interpersonal stress, lockdowns, social isolation, childcare → shift to at-home drinking, and more of it

## ALCOHOLIC BEVERAGES BOOM ONLINE DURING COVID-19

Alcohol Weekly Sales Growth vs. Year Ago



Measurement Services, Total US All Outlets Combined (xAOC) including Convenience and Liquor Stores, Measurement powered by Rakuten Intelligence, Total US, 1-week periods, latest period to Apr. 25, 2020  
© 2020 Drizly Company (US), LLC. All Rights Reserved.

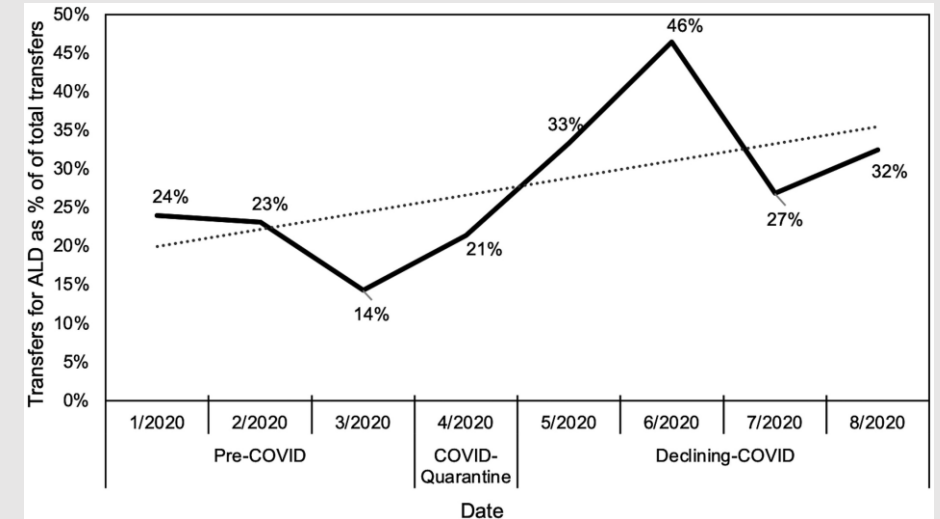


# Impact of Covid on Alcohol Use and ALD

- In US, frequency of alcohol consumption increased 15-20%
- Disproportionately high increases among women in terms of frequency (17 vs 11%), days of heavy drinking (41 vs 7%), and alcohol related consequences
- Women demonstrated a 39% increase in AUD diagnoses
- Risk of developing ALD is higher in women across all levels of consumption
  - At less alcohol, earlier onset, and more severe presentation

# Downstream Effects

- Spring of 2020 – signs that pts with cirrhosis were delaying care
  - Patients admitted had higher MELD, higher rate of ICU admissions
  - Only sickest were coming in for care
- Reopening phase - significant increase in alcohol-associated hospitalizations
  - 60% increase in proportion of inpatient consults alcohol-related GI and liver dz
  - 53% increase in severe alcoholic hepatitis
  - Higher in-hospital mortality
  - Age of those hospitalized dropped alarmingly
  - High rates of relapse among previously stable
  - High rates of 'de-listing' from transplant



Chung et al, Abstract 436 DDW 2021



## Case 3: Cheryl

54 yo Caucasian mother of 3 presents with jaundice and upper abdominal discomfort, found to have a bilirubin of 3.3

Alcohol use rising from 2 drinks daily to 1 ½ bottles of wine during quarantine

Clinical diagnosis of alcoholic hepatitis

How do we support her sobriety?



# Where do we go from here?

Cheryl has alcohol-related hepatitis, no prior diagnosis of liver disease

Women bear the burden of dealing with both work and added domestic stresses, home schooling, childcare, keeping the household from falling apart.

**74% of moms say they are mentally worse off now since before the onset of the pandemic.**

Daily alcohol use is a socially acceptable coping strategy.

We need to improve options for self care.





Same pathways of  
inflammation and injury

Same spectrum of disease

Rising rates of obesity and  
alcohol dependence,  
exacerbated by Covid

Societal level changes  
are needed

Thank You!

Questions?

Feel free to contact me personally  
blaire.burman@commonspirit.org  
(646) 306-7143