Fatty Liver Disease: What's the Skinny?

AAPA Conference

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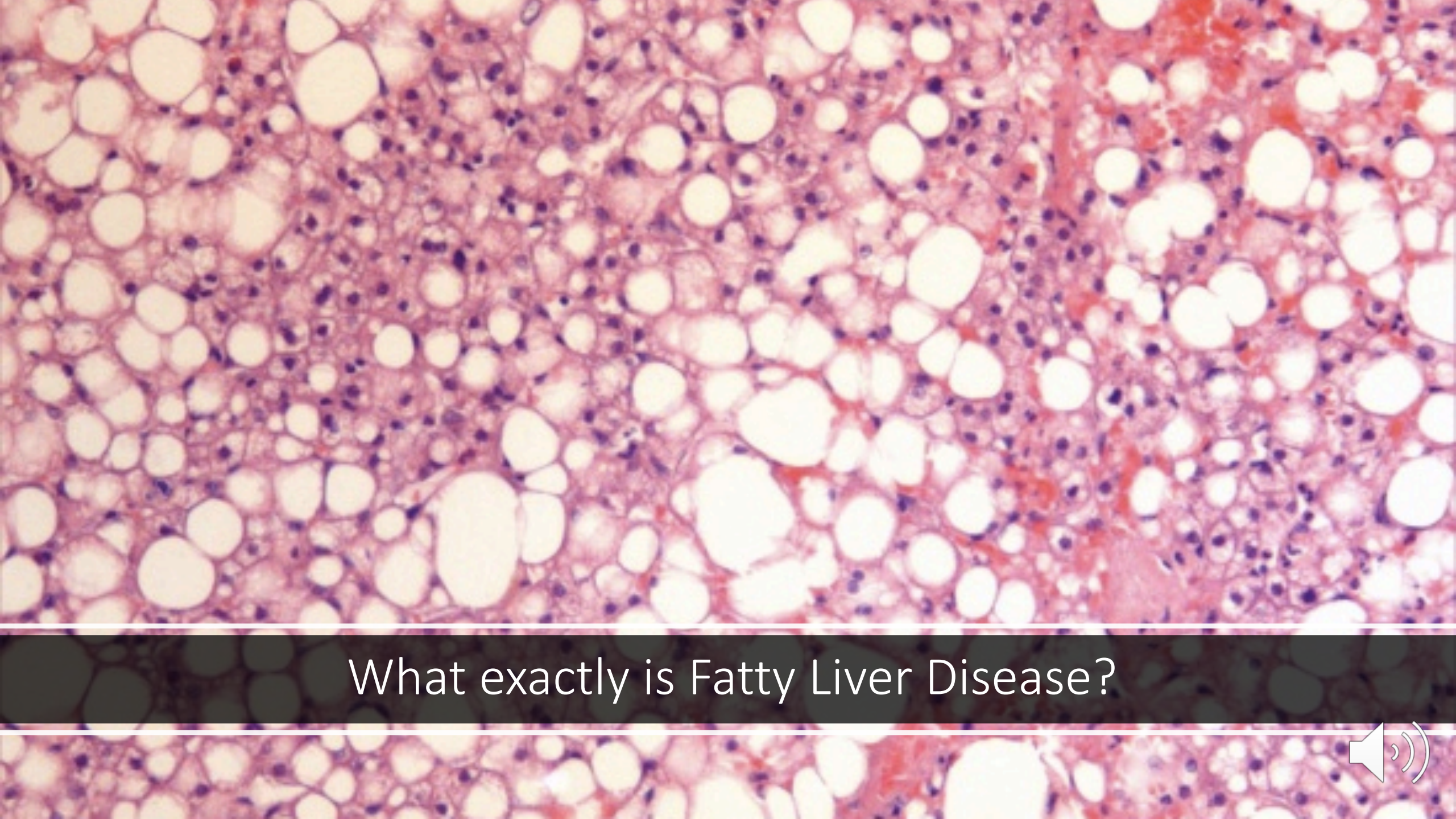
Disclosures

- I have no disclosures

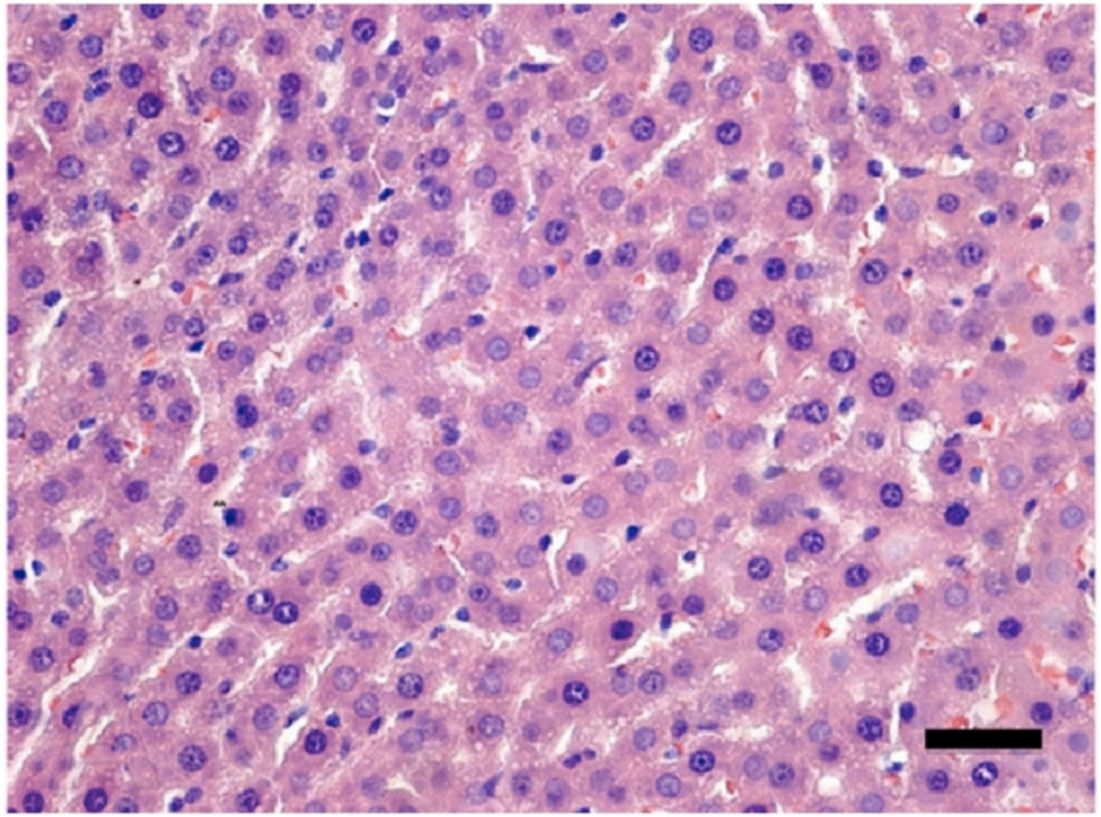
Lecture Objectives

- Define common terminology used to determine morbidity in patients with fatty liver such as simple steatosis, NAFLD and NASH.
- Recognize the importance of making a diagnosis of fatty liver disease in a patient, as it pertains to liver and general health morbidity and mortality.
- Discuss the latest treatment options for patients with fatty liver disease, including recent research trial results.

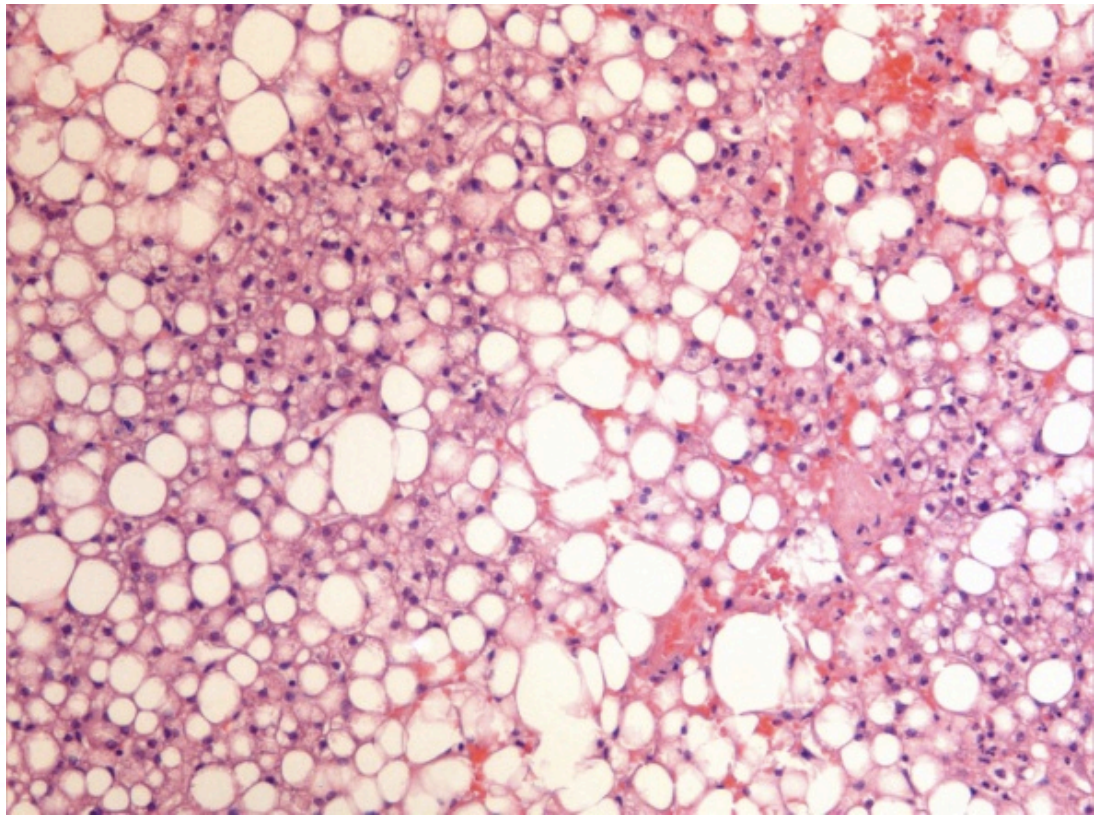


What exactly is Fatty Liver Disease?

Normal Liver Histology vs. Fatty Liver



Up to 5% steatosis



Greater than 5% steatosis

Mayo Clin Proc. 1980 Jul;55(7):434-8.

Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease.

Ludwig J, Viggiano TR, McGill DB, Oh BJ.

Abstract

Nonalcoholic steatohepatitis is a poorly understood and hitherto unnamed liver disease that histologically mimics alcoholic hepatitis and that also may progress to cirrhosis. Described here are findings in 20 patients with nonalcoholic steatohepatitis of unknown cause. The biopsy specimens were characterized by the presence of striking fatty changes with evidence of lobular hepatitis, focal necroses with mixed inflammatory infiltrates, and, in most instances, Mallory bodies; Evidence of fibrosis was found in most specimens, and cirrhosis was diagnosed in biopsy tissue from three patients. The disease was more common in women. Most patients were moderately obese, and many had obesity-associated diseases, such as diabetes mellitus and cholelithiasis. Presence of hepatomegaly and mild abnormalities of liver function were common clinical findings. Currently, we know of no effective therapy.

Comment in

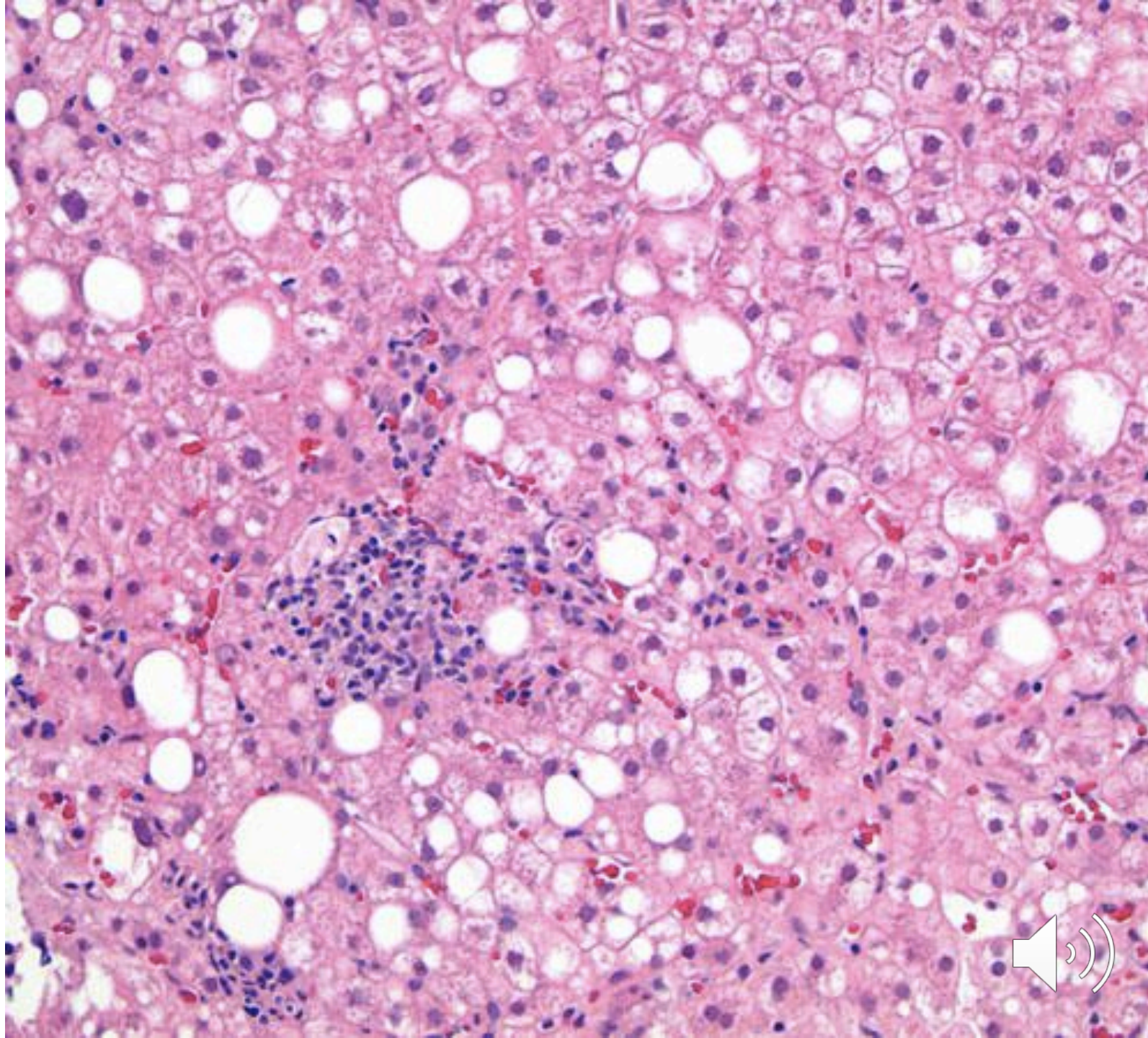
Treating NASH. [J Gastroenterol Hepatol. 2006]
Fatty liver disease: turning the tide. [Nature. 2017]

PMID: 7382552

[Indexed for MEDLINE]

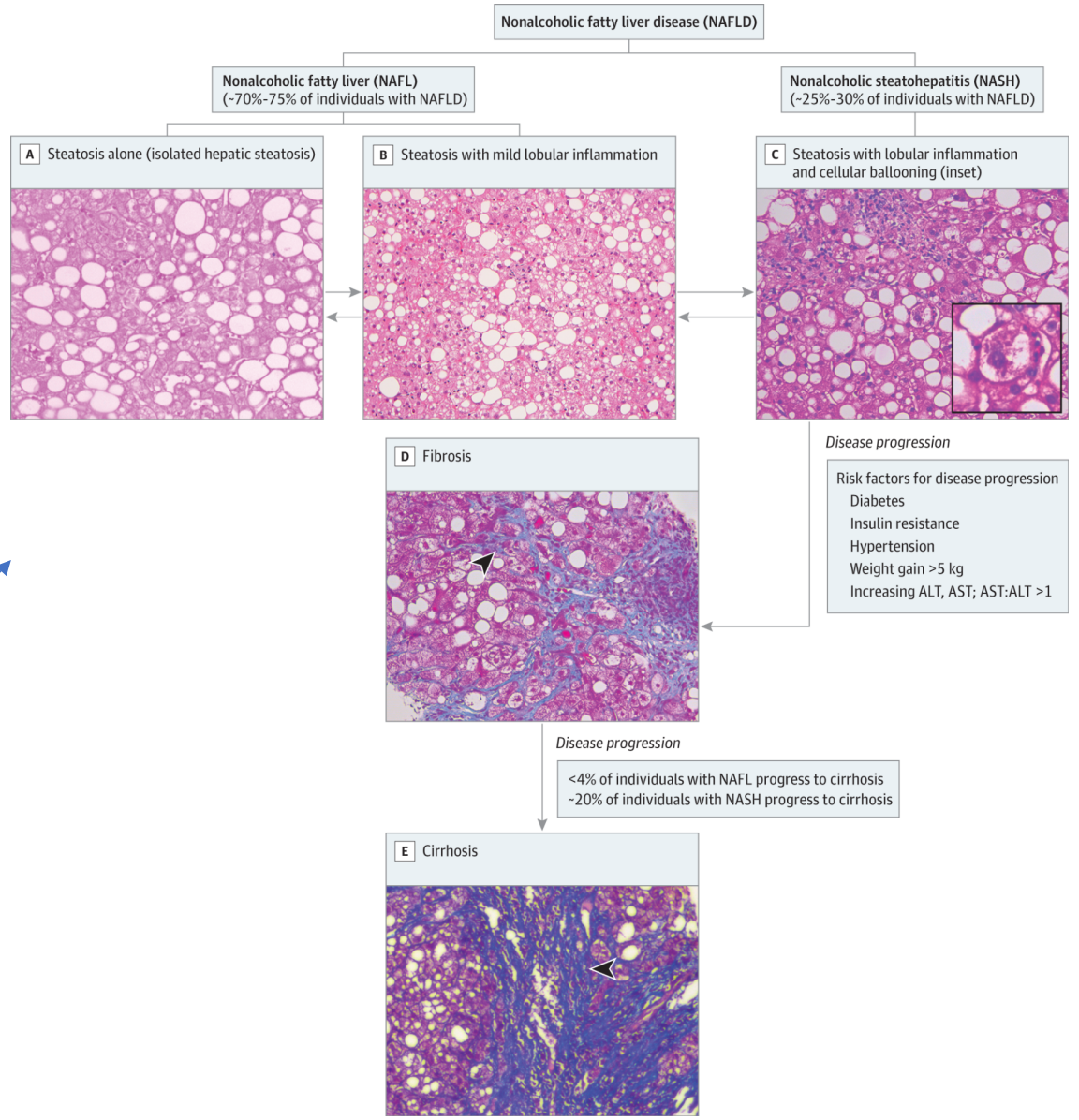
Terminology

- Hepatic Steatosis: fat accumulation in the liver
- FLD: umbrella term for fatty liver; can be non-alcoholic or alcoholic
- NAFLD: Non-alcoholic fatty liver disease, >5% steatosis without evidence of ballooning or fibrosis
  - Less severe disease course
  - 60-70% of patients with FLD
- NASH: Non-alcoholic steatohepatitis seen as steatosis, hepatocyte ballooning, lobular inflammation and perisinusoidal fibrosis
  - More severe disease course
  - 25-35% of patients with FLD



Metabolic factors

Environmental

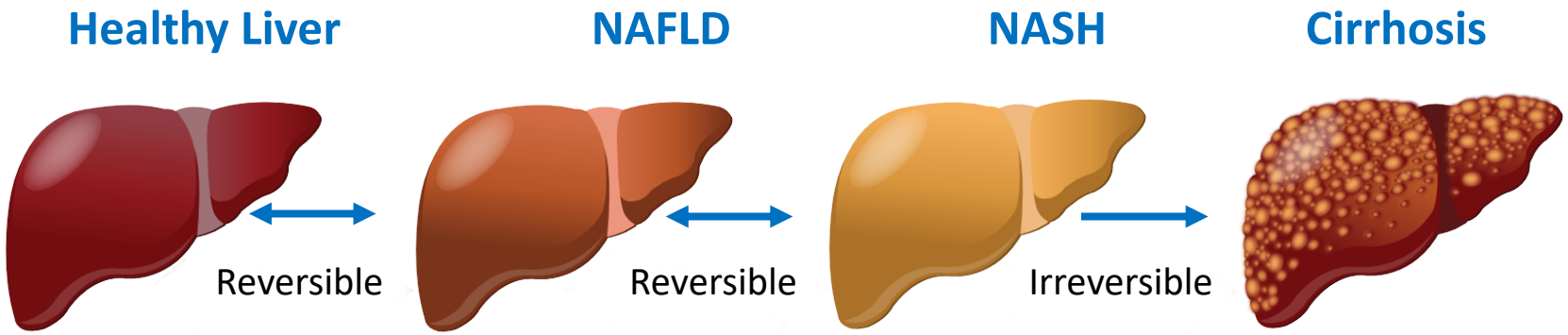


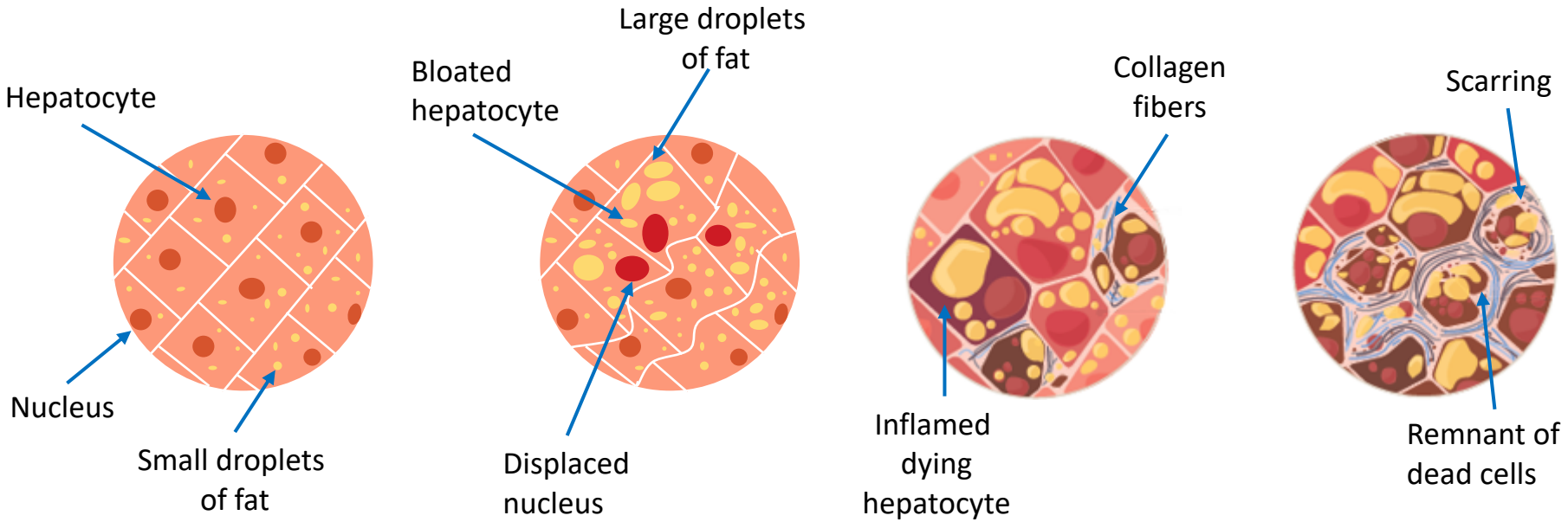
Genetics

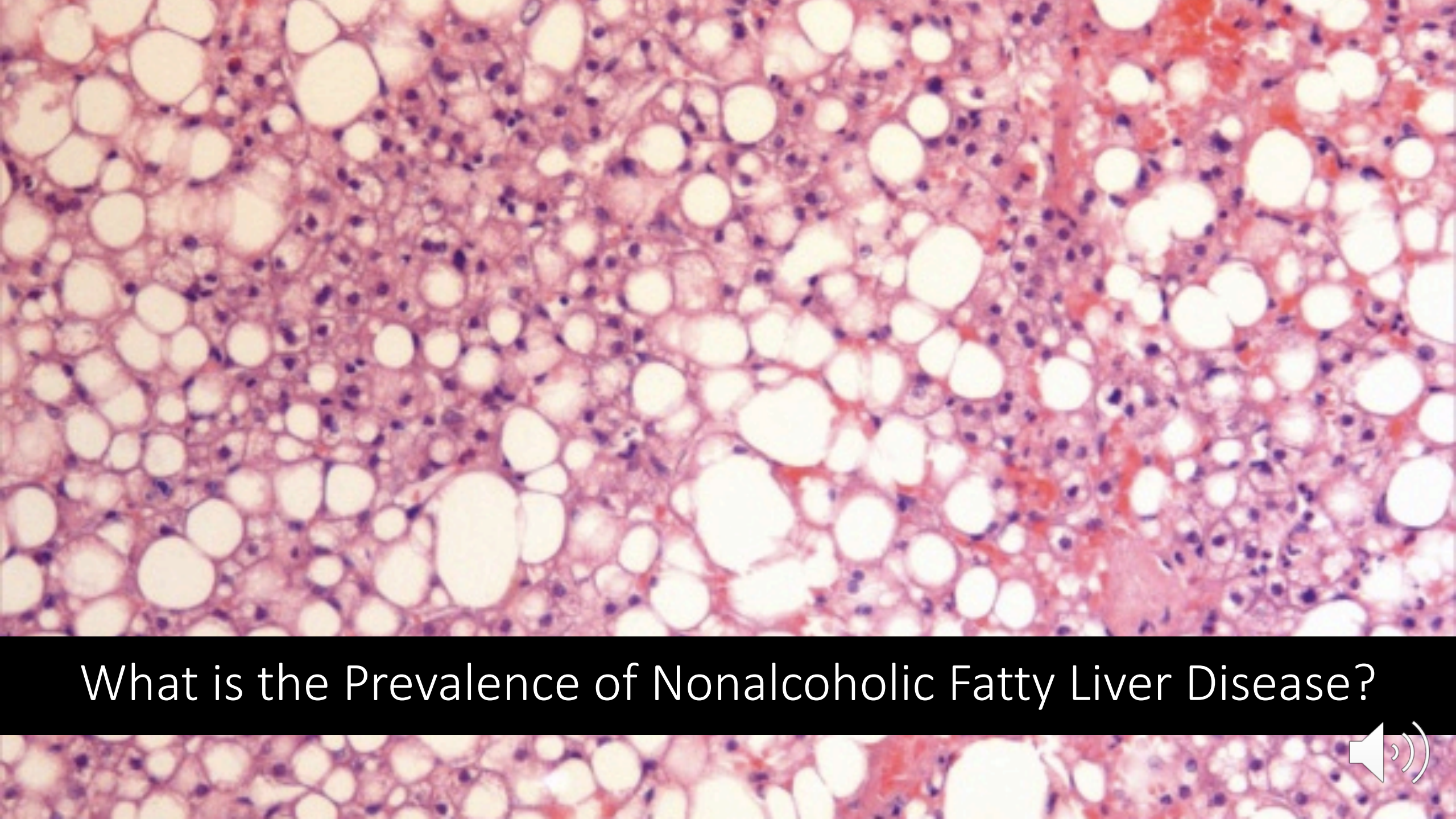
Gut Microbial factors

Rinella. JAMA 2015

NAFLD: progression of disease



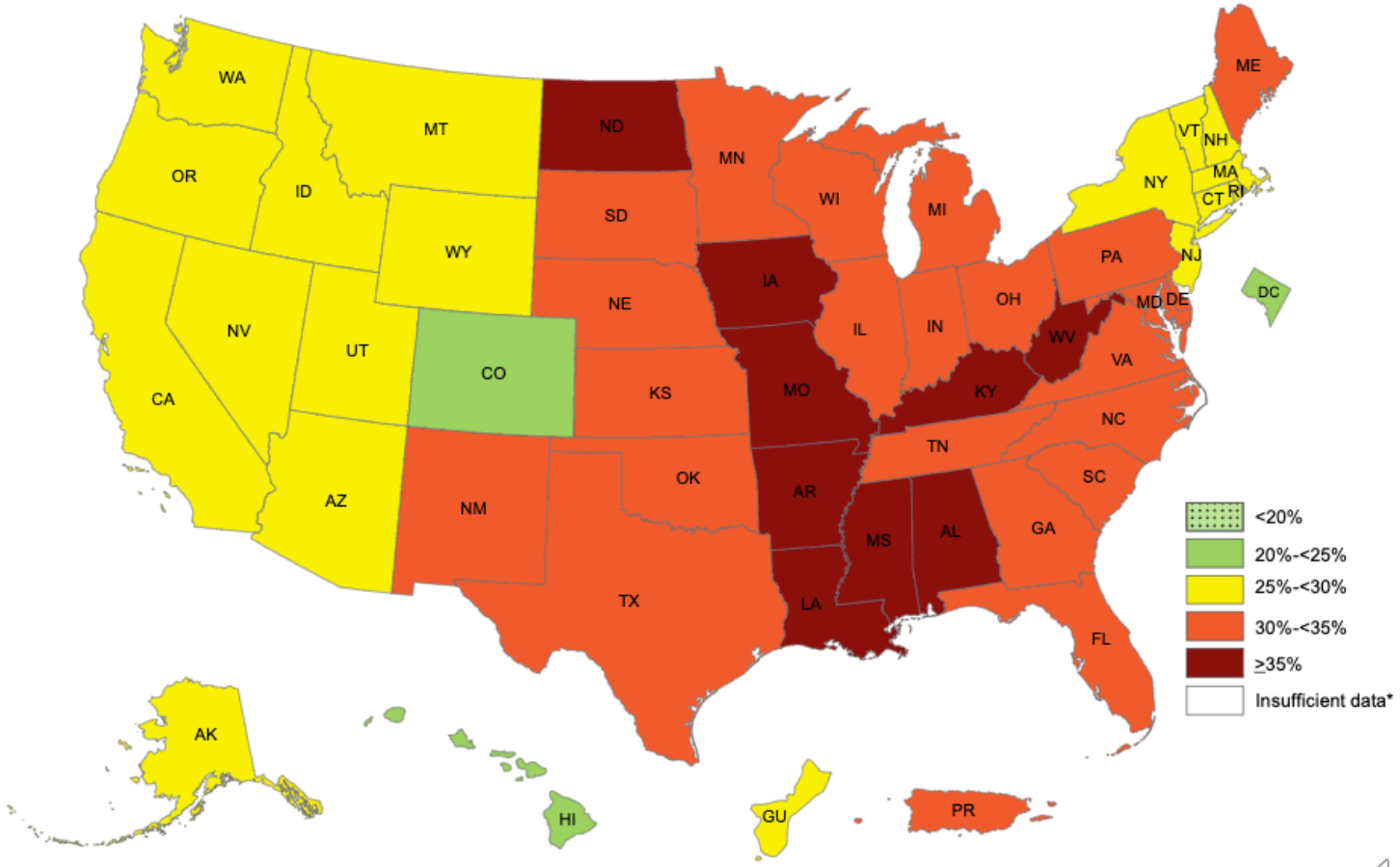




What is the Prevalence of Nonalcoholic Fatty Liver Disease?

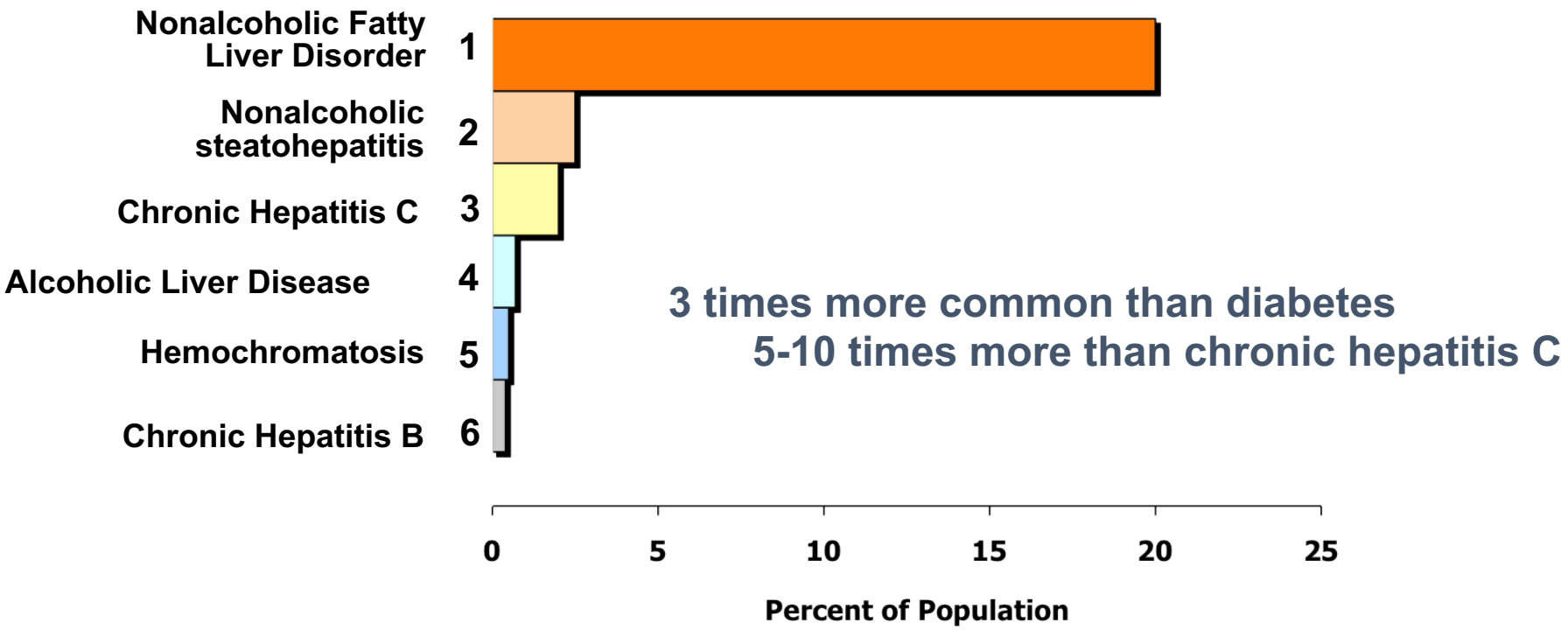
How common are these patients?

- Population: (2018)
  - 327.2 million
- Obesity:
  - 138.7 million (42.4%)
- Diabetes:
  - 34.2 million (9.6%)
- NAFLD:
  - 98 million (~30%)



Statistics courtesy of CDC

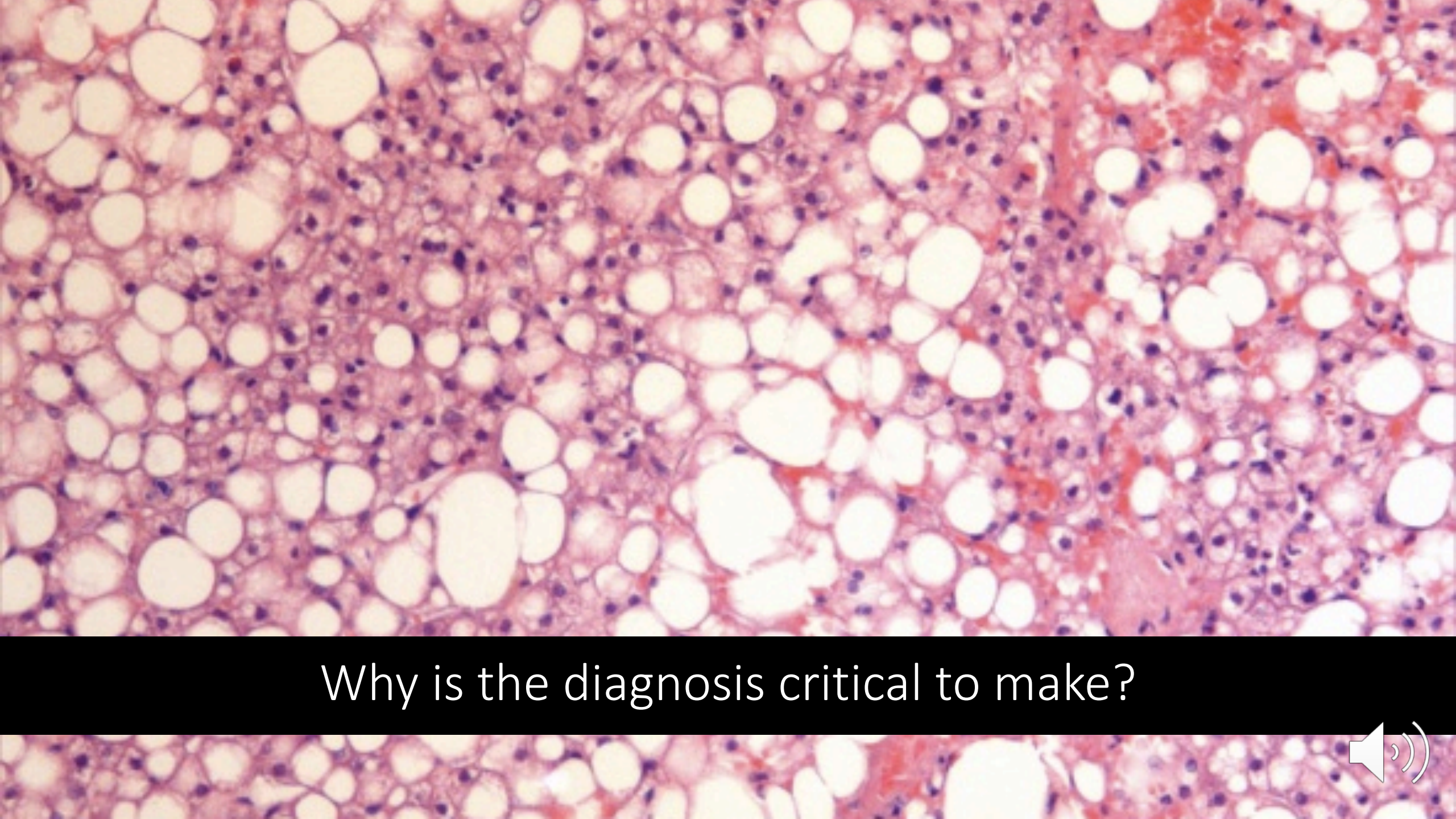
Prevalence of Chronic Liver Disease in the United States



1. Hilden M et al. *Scand J Gastroenterol*. 1977;12:593-597.
2. Ground KEU. *Aviat Spac Environ Med.* 1982;53;14-18.
3. Alter MF et al. *N Engl J Med.* 1999;341:556-562.
4. Venkataramani A et al. In: Maddrey WC, Feldman M, eds. *Atlas of the Liver.* Philadelphia: Current Medicine;1999:9.0.
5. Adapted from http://www.nhlbi.nih.gov/new/press/01/09 -25.htm. Accessed 11/01/02.
6. McQuillan GM et al. *Am J Public Health* 1999;89:14-18.

Who are the population at risk for fatty liver?

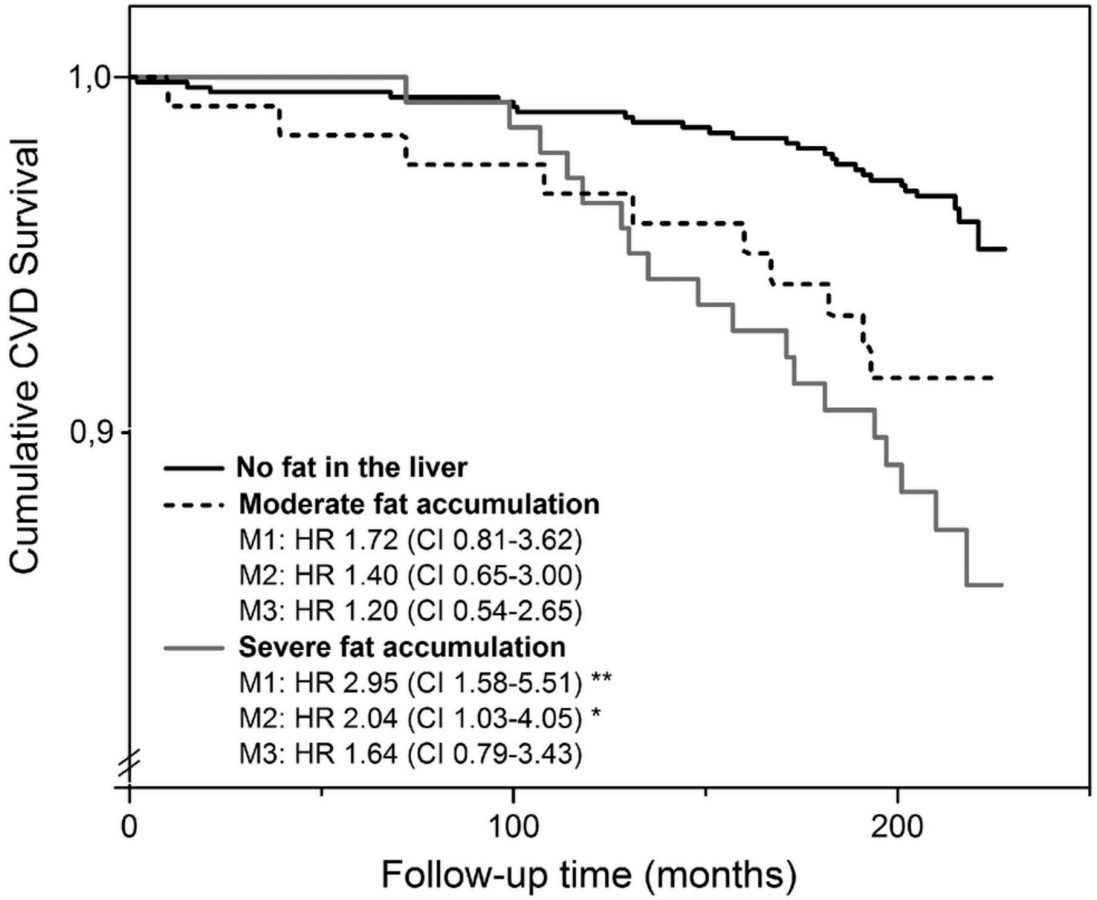
- Age
  - Both risk of NAFLD and risk of progression increase with age
- Diabetes
  - 33-66% of patients
- Obesity
  - BMI and central obesity
  - Most common risk factor
- Dyslipidemia
- Metabolic syndrome
  - Bidirectional association



Why is the diagnosis critical to make?

Why is this diagnosis important to make?

- Increased overall mortality
  - NASH: >10X
- Increased cardiovascular death risk
  - #1 cause of death in NAFLD patients
  - NASH doubles CV risk



Pisto P. *BMJ Open* 2014

Why is this diagnosis important to make?

- Increased risk of malignancy
  - #3 cause of death in NAFLD patients
  - Increased risk of HCC
  - Increased risk of GI cancers
    - Colon, stomach, pancreas, esophagus
  - Increased risk of non-GI cancers
    - Renal, breast

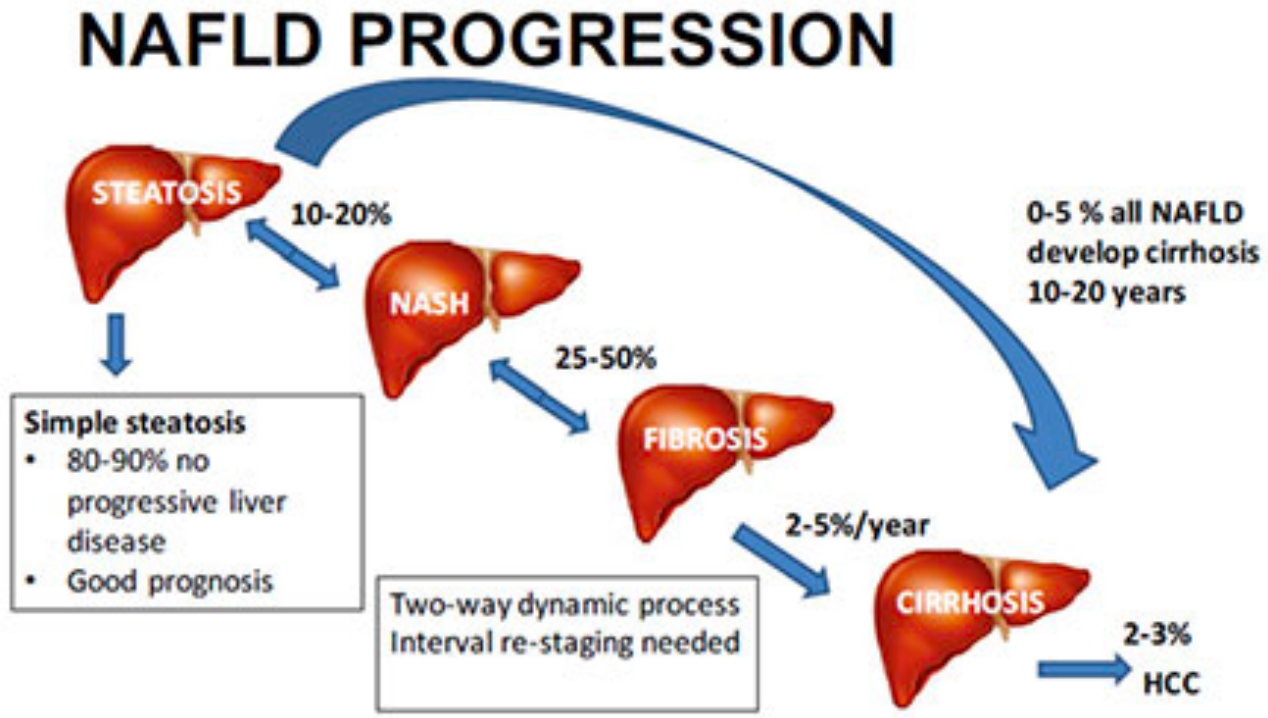
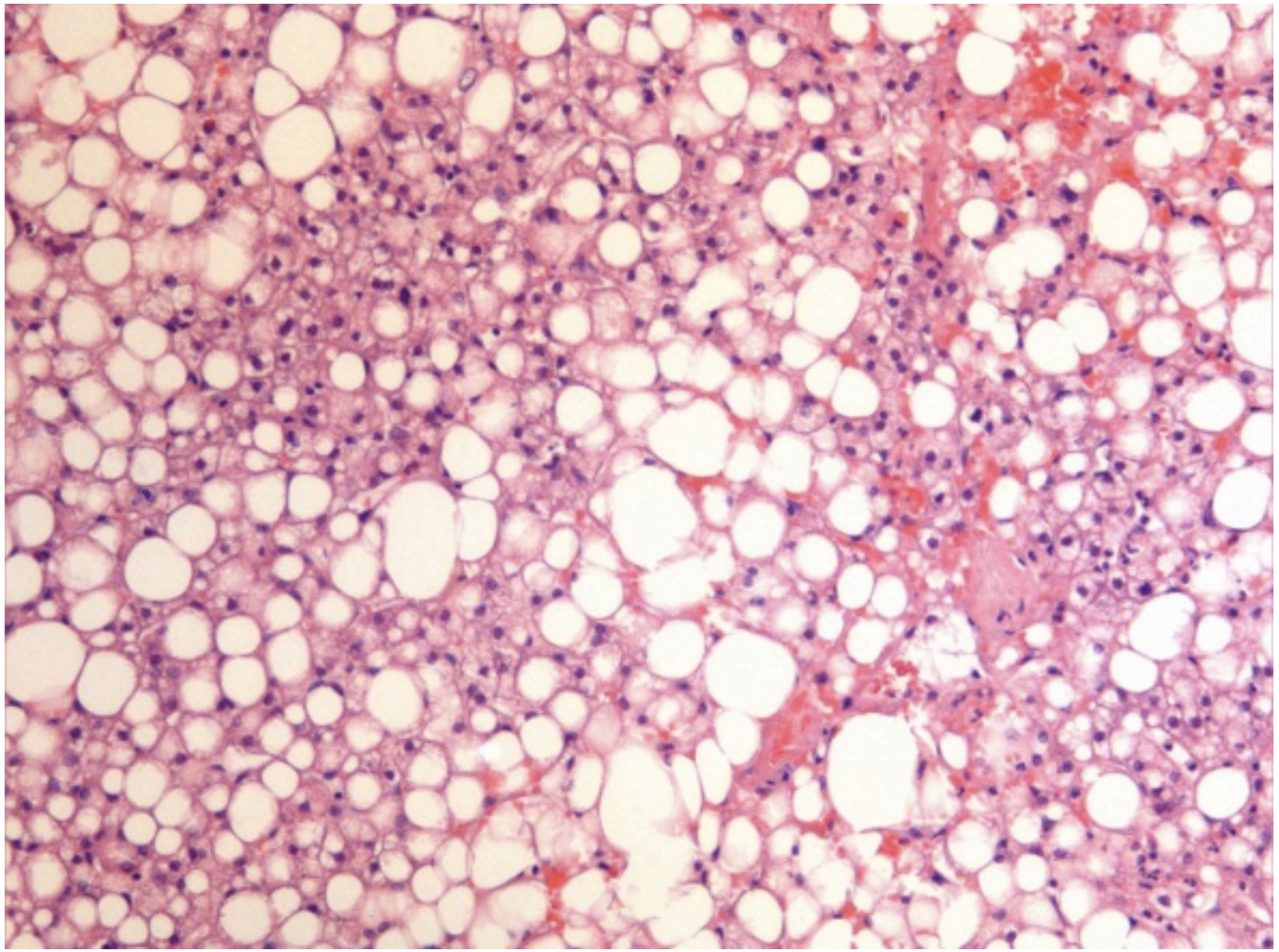


Image courtesy of Kauvery Hospital

How do you make the diagnosis of fatty liver disease?



Diagnosis of Fatty Liver Disease

- Diagnosis of exclusion (generally)
- Most patients are asymptomatic
- Evidence of hepatic steatosis on imaging or by histology
- No secondary cause for hepatic fat accumulation
  - Alcohol
  - Medications
  - Hereditary disorders
  - Medical conditions

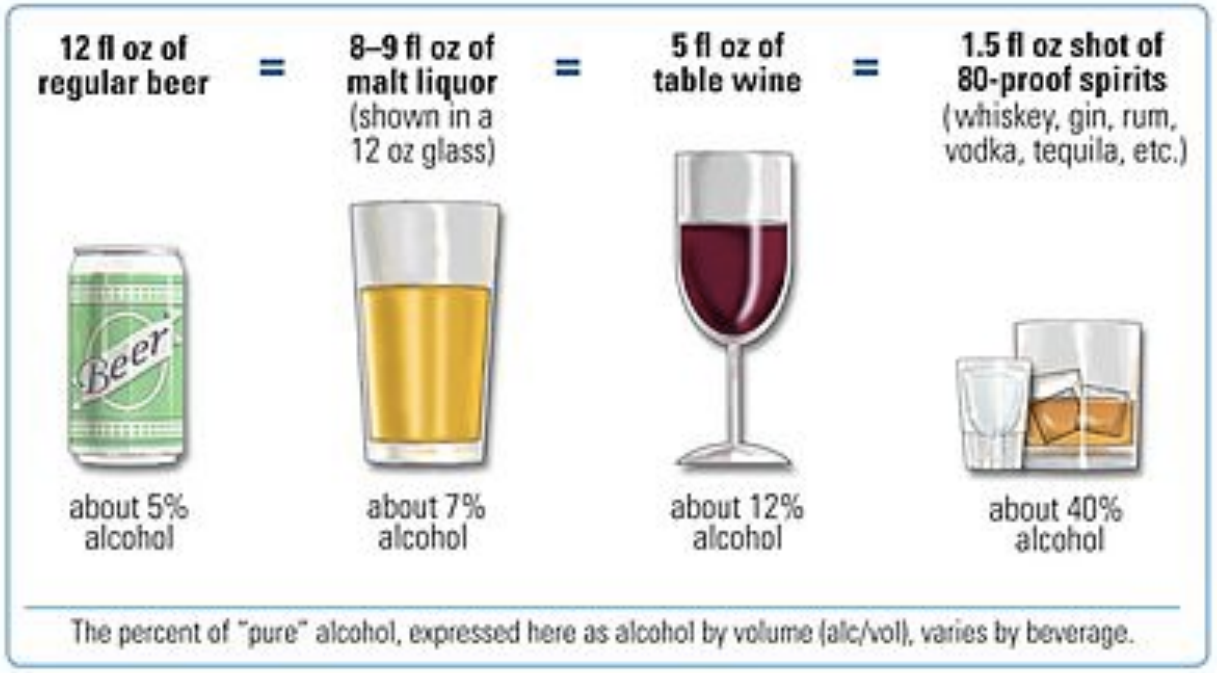
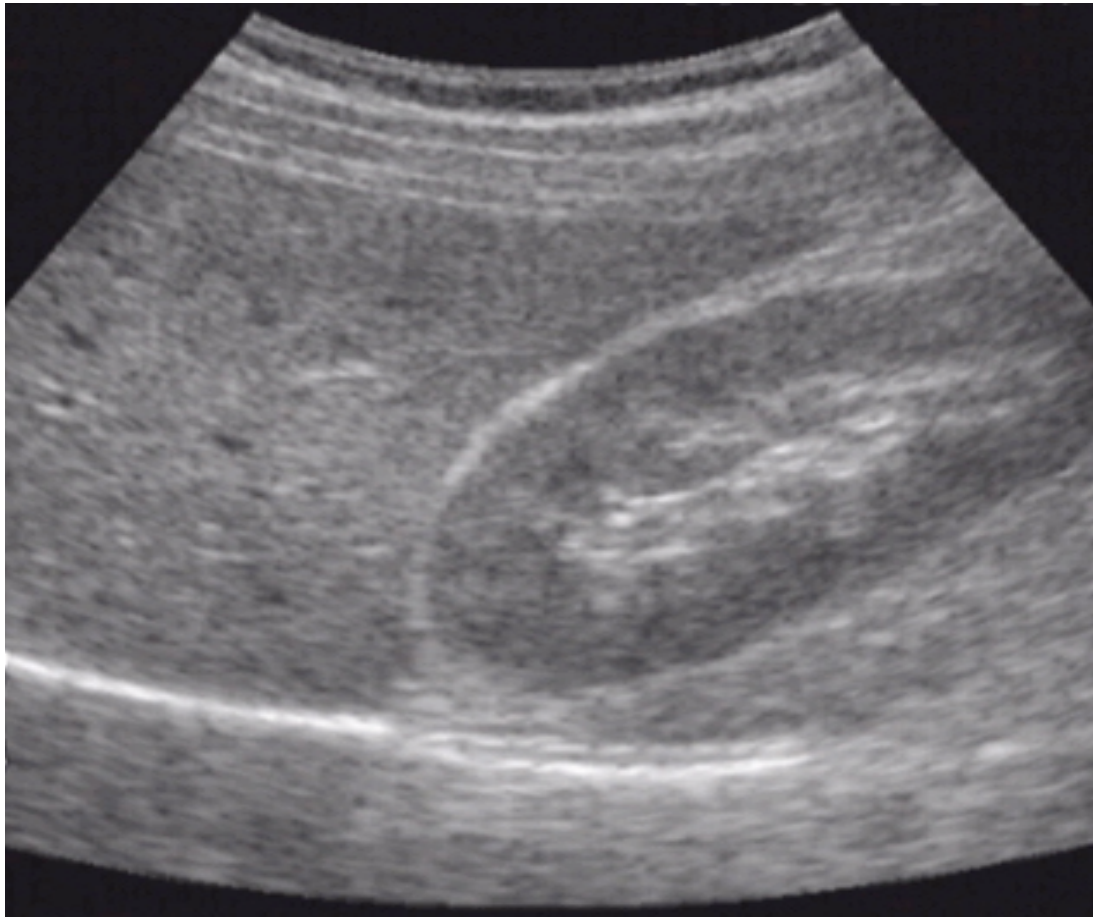
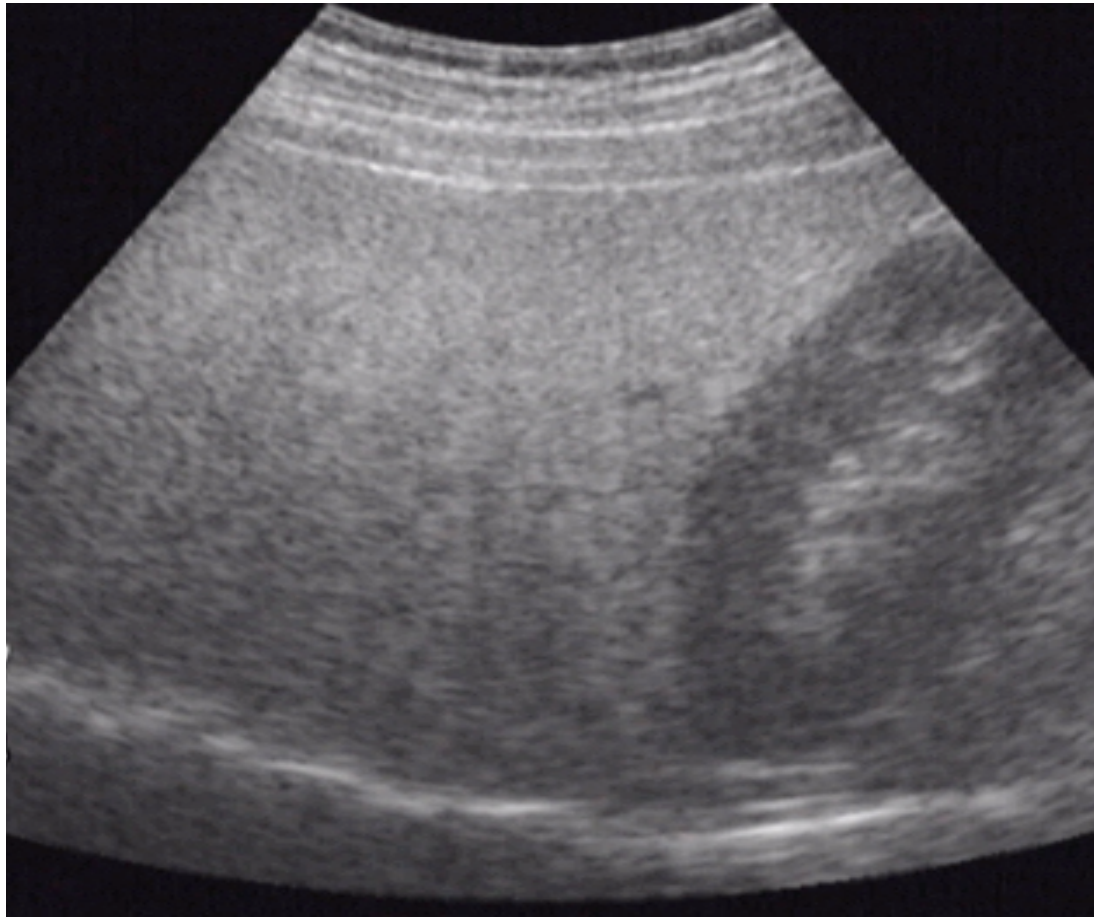


Image courtesy of Wikipedia

Imaging: Normal vs. Fatty





What about ALT level?

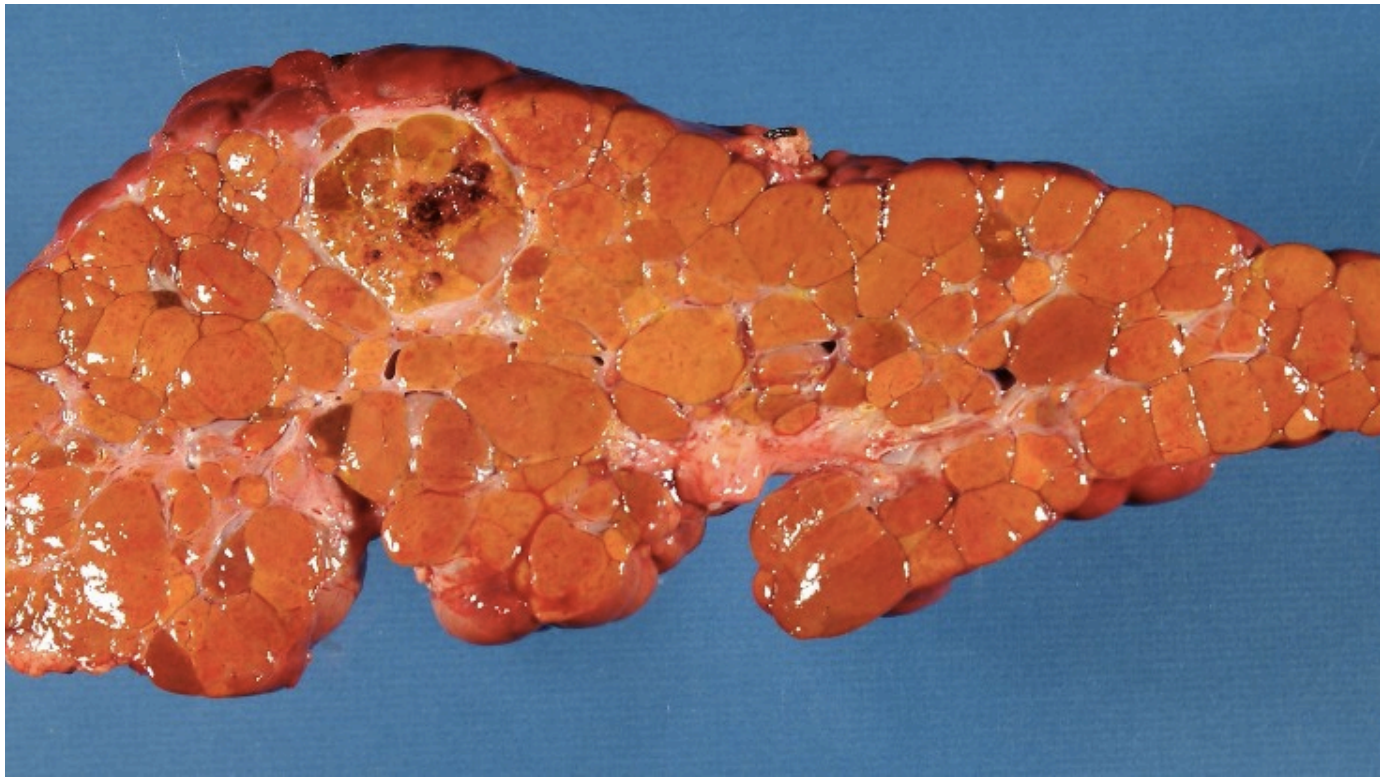
- Sensitivity and specificity of an elevated ALT for NASH is 45% and 85%
- Patients with advanced disease often have normal ALT levels
- Increased ALT levels can correlate with insulin resistance and intrahepatic fat content

- Normal ALT and DM high prevalence of NAFLD (76%) and NASH (56%)

Mofrad P. Hepatology 2003
Amarapurkar Dn. Trop gastroenterology 2004
Maximos M. Hepatology 2015
Portillo Sanchez P. J clin Endocrinology Metabolism 2014

How do you make the distinction between NAFLD and NASH?

- Risk Stratification
  - NAFLD vs. NASH
  - HCC risk



Risk Stratification

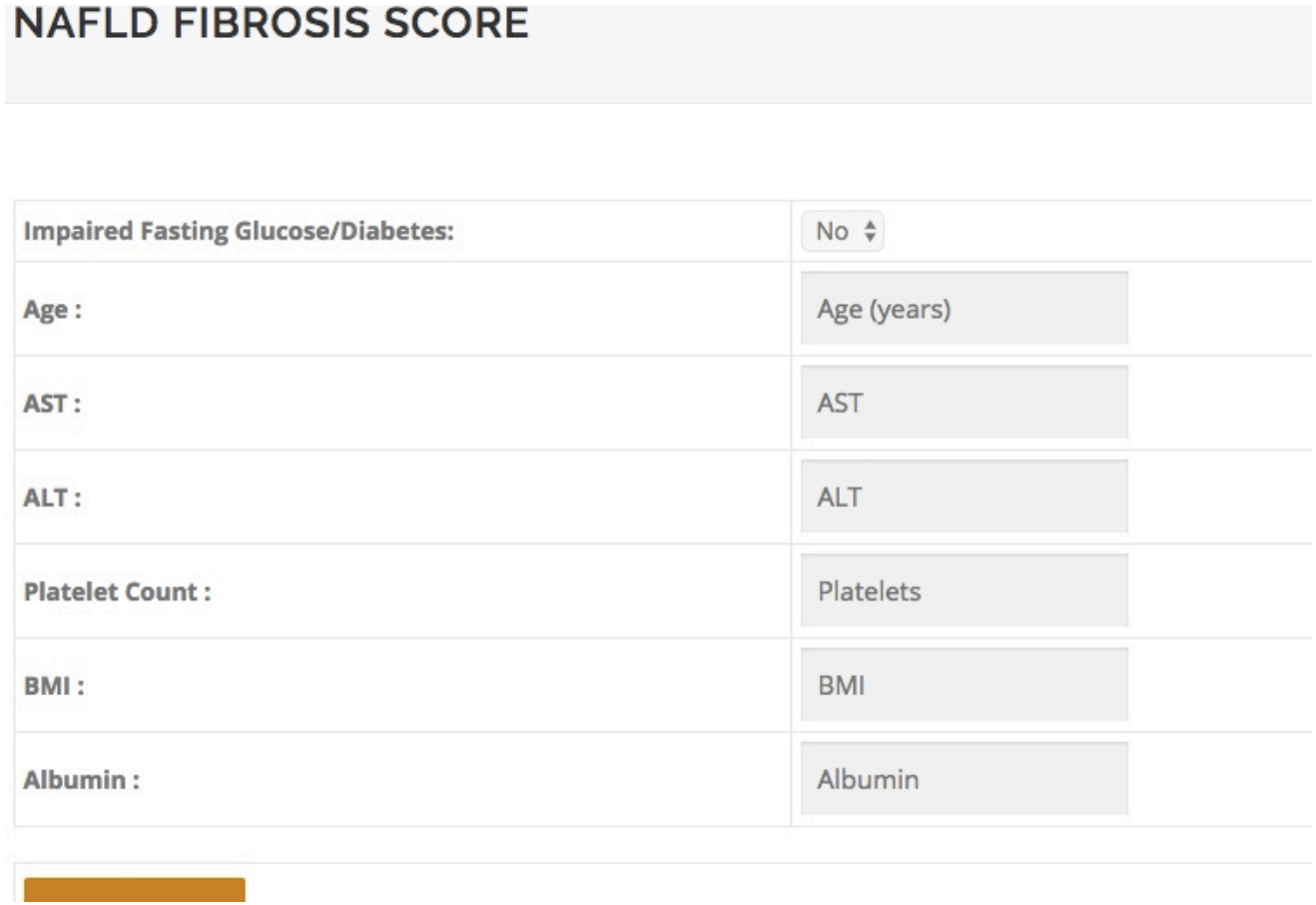
Scoring Systems

Imaging

Liver Biopsy

Risk Stratification: Scoring System

- NAFLD fibrosis score (NFS): best validated
  - Age, BMI, presence or absence of hyperglycemia, platelet count, albumin level and ratio of AST to ALT).
  - Works best at the extremes
  - Great negative predictive value
  - http://gihep.com/calculators/hepatology/nafld-fibrosis-score
  - Can be as good as imaging



NAFLD (Non-Alcoholic Fatty Liver Disease) Fibrosis Score ☆

Estimates amount of scarring in the liver based on several laboratory tests.

When to Use | Pearls/Pitfalls | Why Use

Age	46	years
BMI	38.36	kg/m^2
Impaired fasting glucose/diabetes	No 0 / Yes +1	
AST	37	U/L
ALT	61	U/L
Platelet count	275	$\times 10^3/\mu L$ ⇋
Albumin	4.7	g/dL ⇋

-2.44 points

Correlated Fibrosis Severity: F0-F2

Risk Stratification: Scoring System

- FIB-4
  - Age, AST, ALT and platelet count
  - Works best at the extremes
  - Great negative predictive value
  - https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

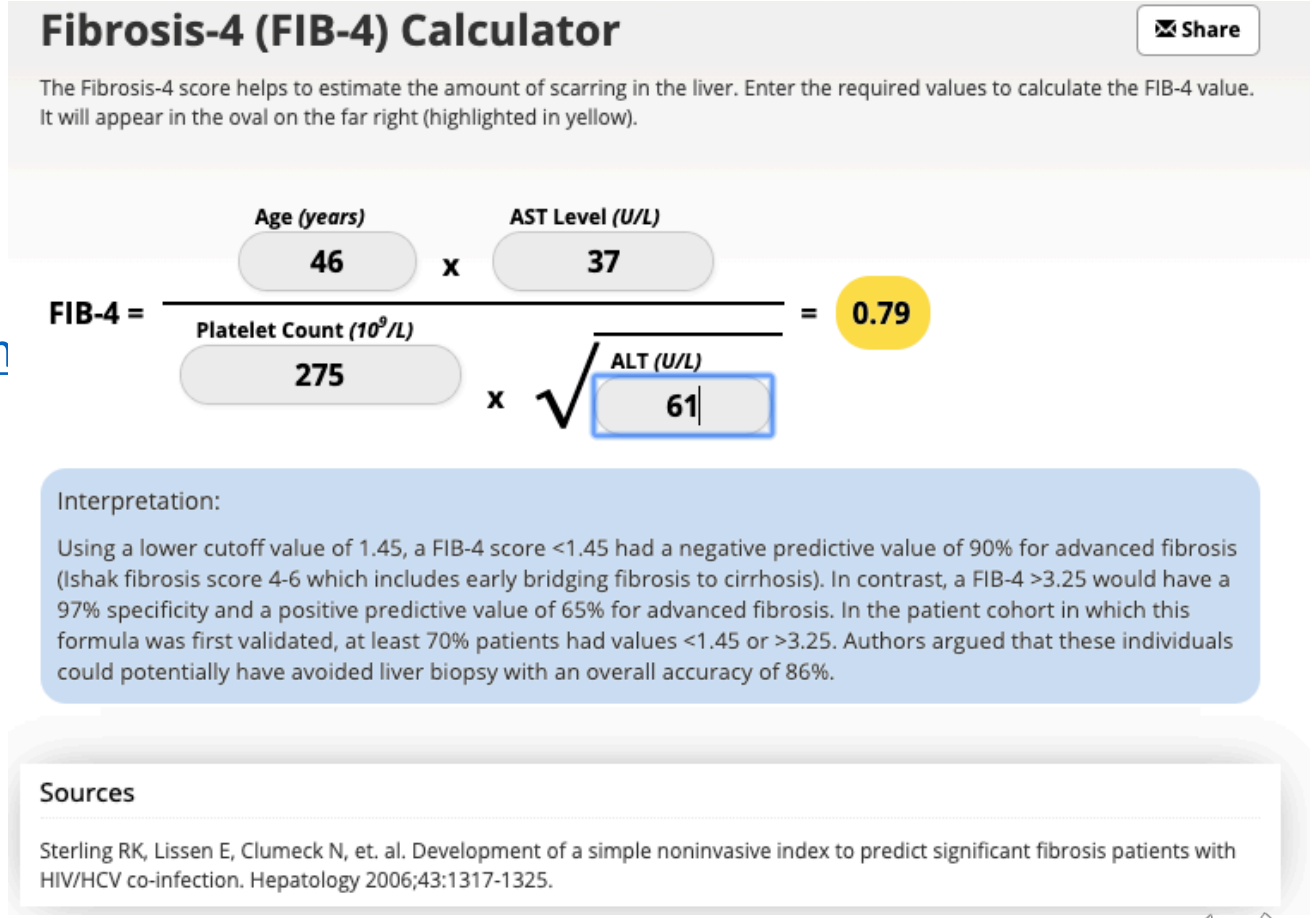


Table 1—Biomarker panels for the diagnosis of advanced fibrosis (stages 3 and 4)

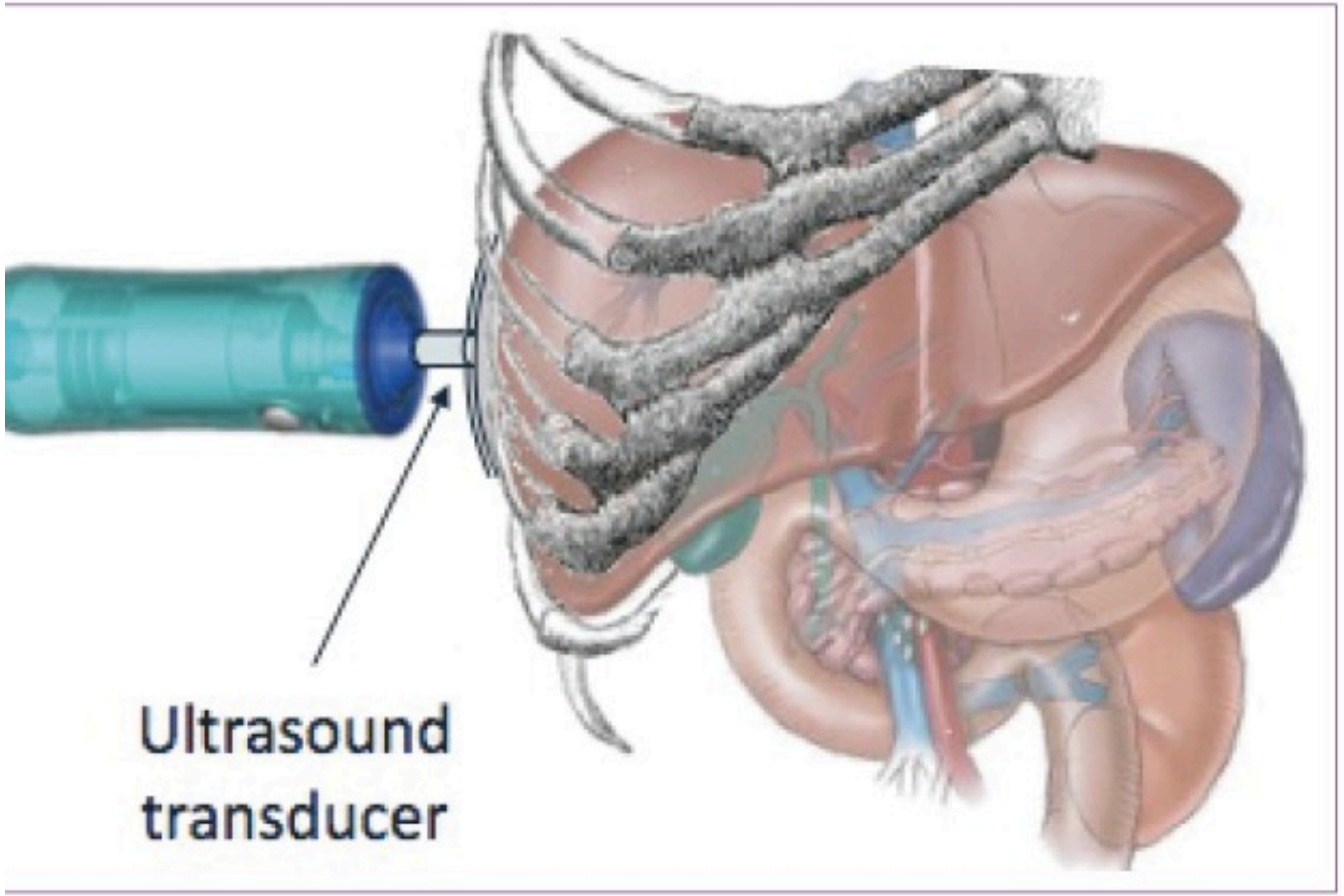
	Parameters included	*n*	PPV	NPV	Patients unable to be classified ("gray zone")
FibroTest (115)	Age, sex Total bilirubin GGT α_2-macroglobulin Apolipoprotein A1 Haptoglobin	267	60%	98%	32%
NAFLD fibrosis score (116)	Age, BMI Diabetes AST/ALT ratio Platelet, albumin	733	82%	88%	24%
†BARD score (117)	BMI Diabetes AST/ALT ratio	827	43%	96%	N/A
†FIB-4 index (118)	Age AST and ALT Platelet	541	80%	90%	30%
NAFIC score (119)	Ferritin Type IV collagen Insulin	619	36%	99%	15%
†Hepascore (120)	Age, sex Total bilirubin GGT α_2-macroglobulin Hyaluronic acid	242	57%	92%	11%

N/A, not applicable; NPV, negative predictive value; PPV, positive predictive value. †No independent validation cohort included in the study.

Bril and Cusi. Diabetes Care. 2017

Risk Stratification: Fibroscan

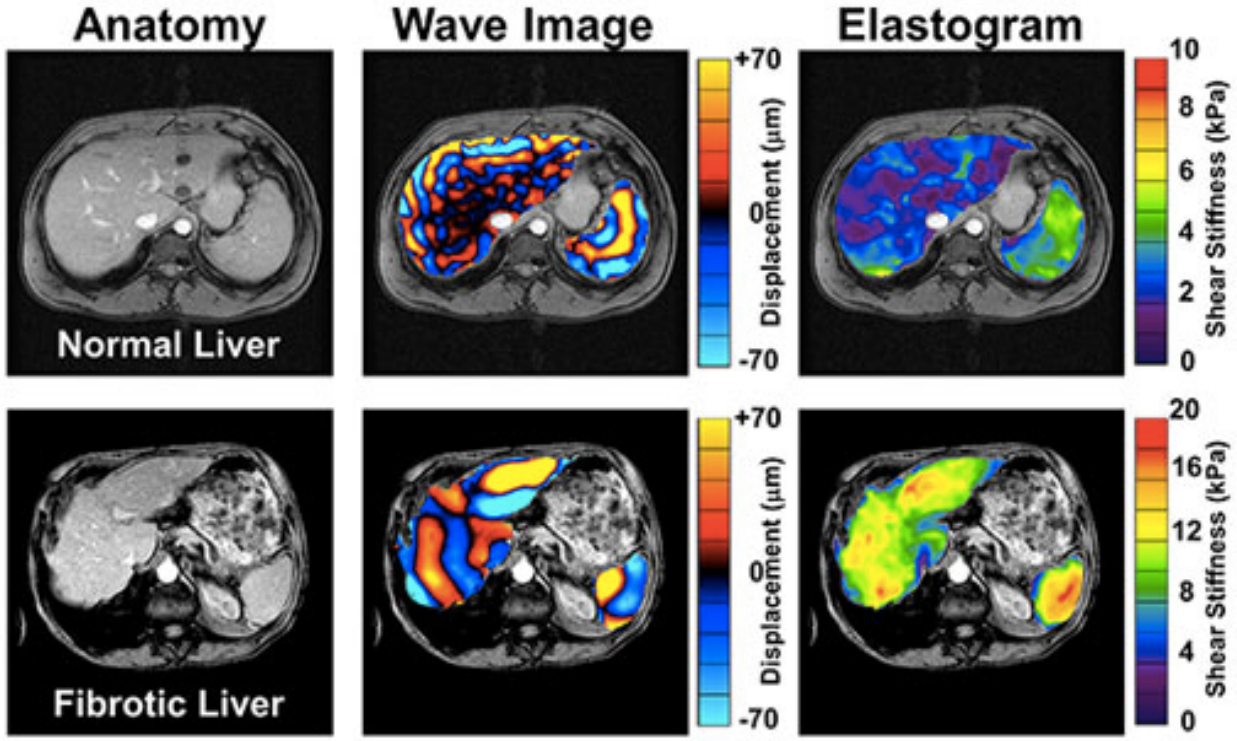
- In office use
- FDA approved
- Fairly reliable for advanced fibrosis



Afdhal NH. Gastroenterology & Hepatology. 2012.

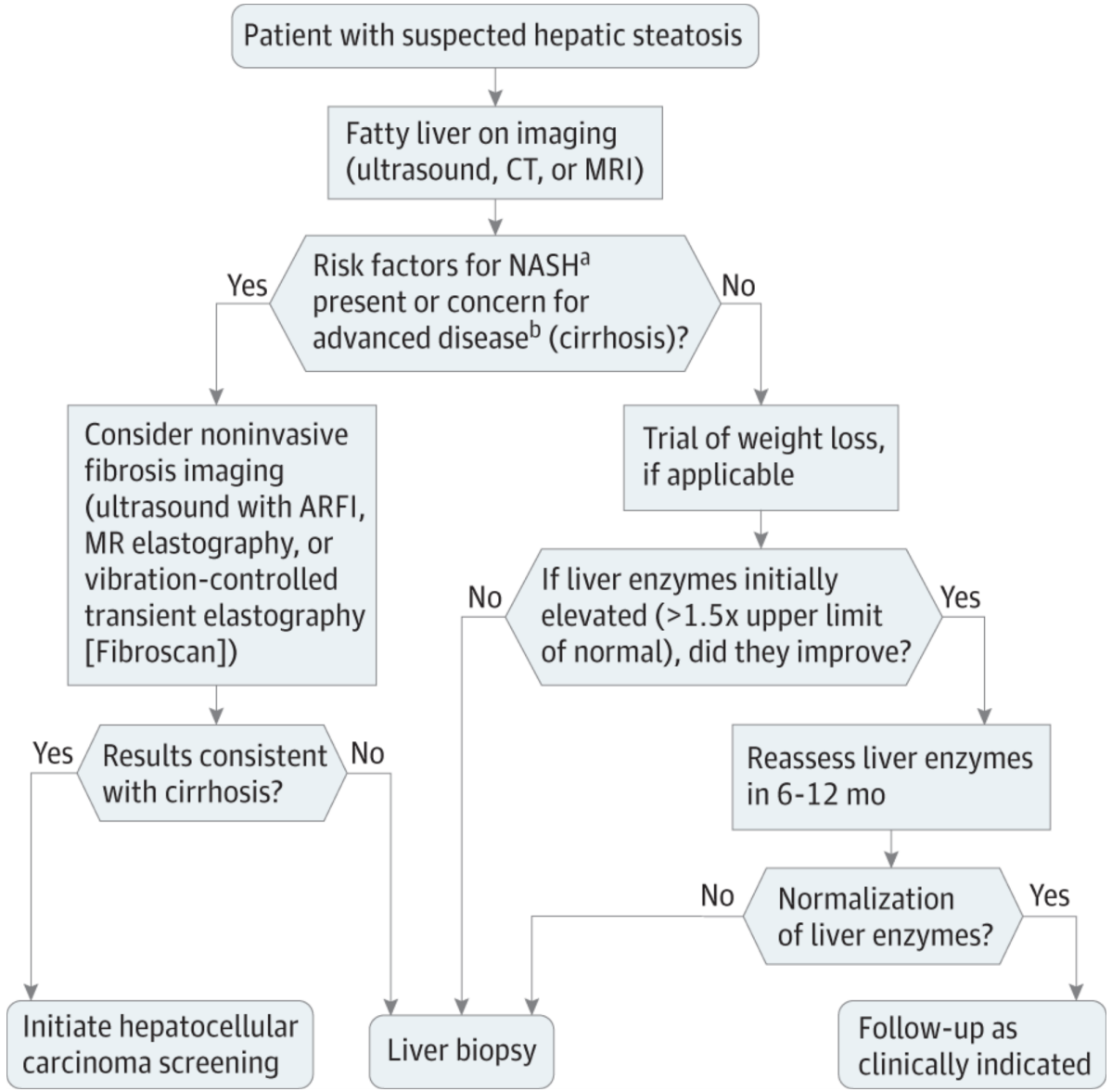
Risk Stratification: MRI

- MR Spectroscopy or Elastography
- Able to detect hepatic fat >5.5%
- Limited availability
- $$$



Risk Stratification: Liver Biopsy

- PRO
  - Only way to confirm/exclude NASH
  - Determination of disease severity
  - Insight into prognosis
- CON
  - Generally good prognosis
  - Morbidity and cost of procedure
  - No current FDA-approved treatment
  - Not reasonable way to follow progression



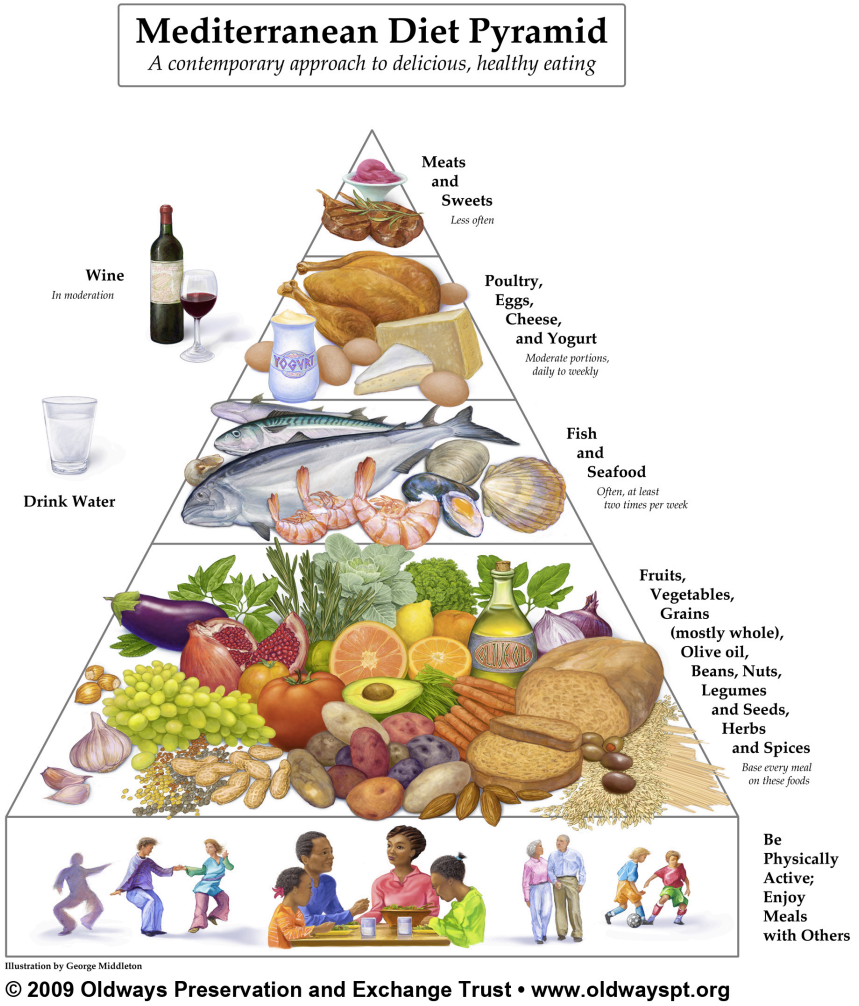
Rinella. JAMA 2015

Treatment Options

- Lifestyle changes
- Non-FDA approved treatment
- Treatment of comorbid conditions
- New therapies in trials

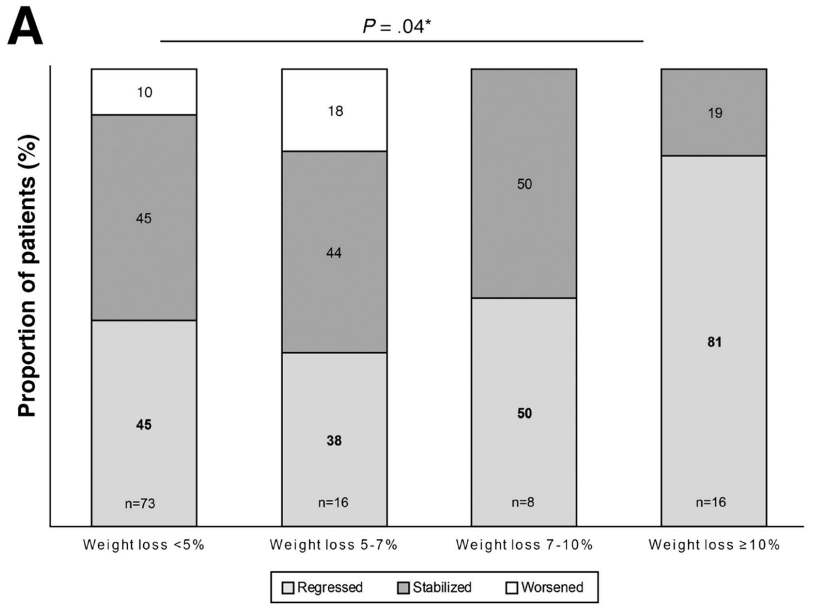
Lifestyle Changes: Diet

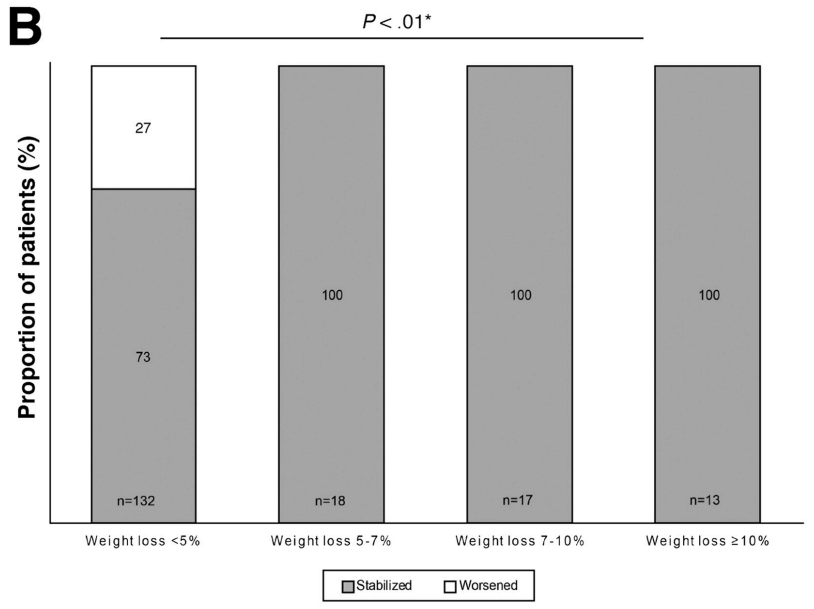
- Limit carbohydrates
- Mediterranean Diet
- Coffee
- Bariatric surgery



Lifestyle Changes: Weight Loss

- Prospective study from Cuba
- Diet changes
- Food diary
- Exercise
  - 200 minutes per week
- Behavioral sessions





Vilar-Gomez. Gastroenterology 2015

Lifestyle Changes: Recommendations

COFFEE

MEDITERRANEAN DIET

GOAL WEIGHT LOSS OF 7-10%

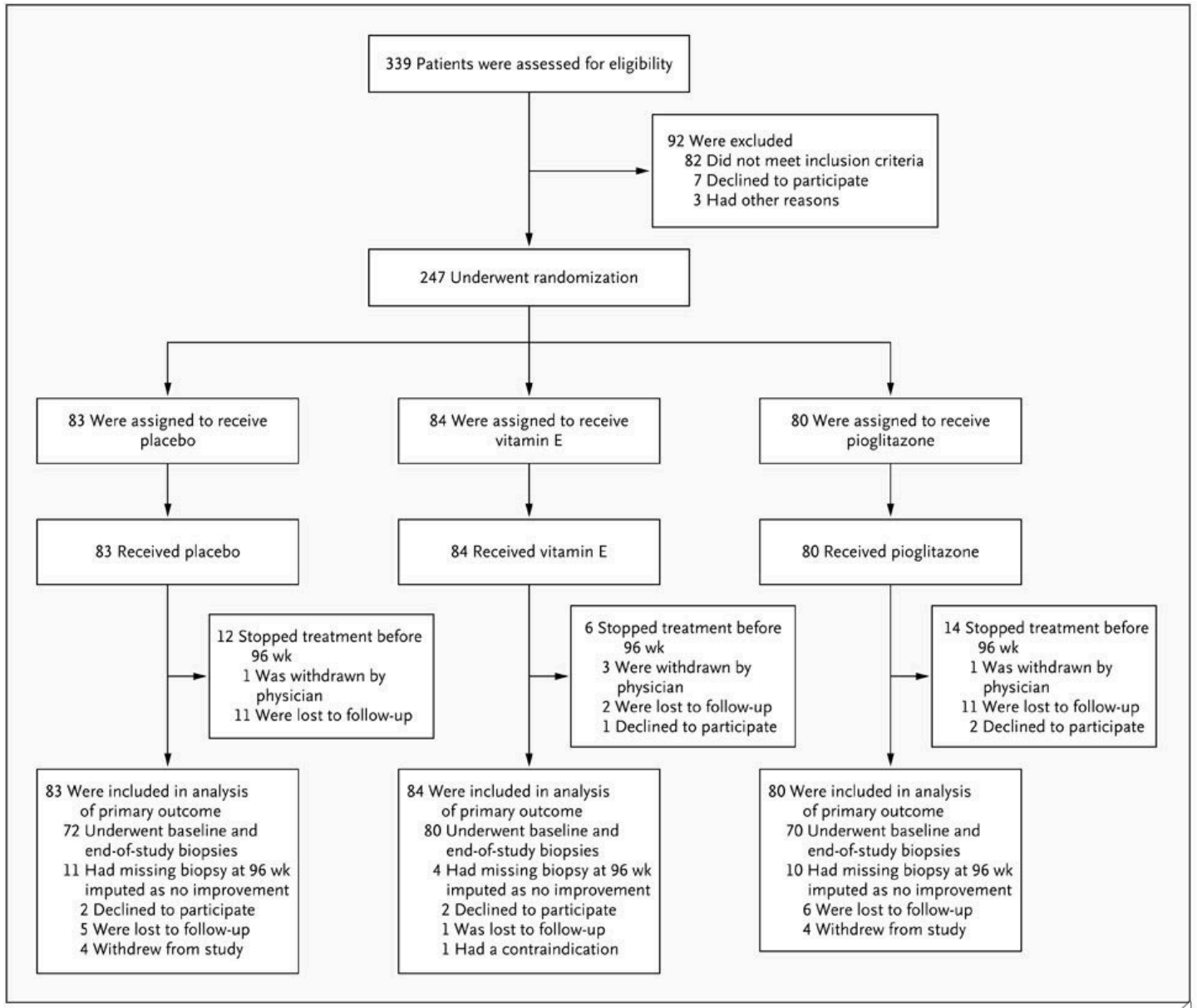
CARDIO VS. STRENGTH TRAINING

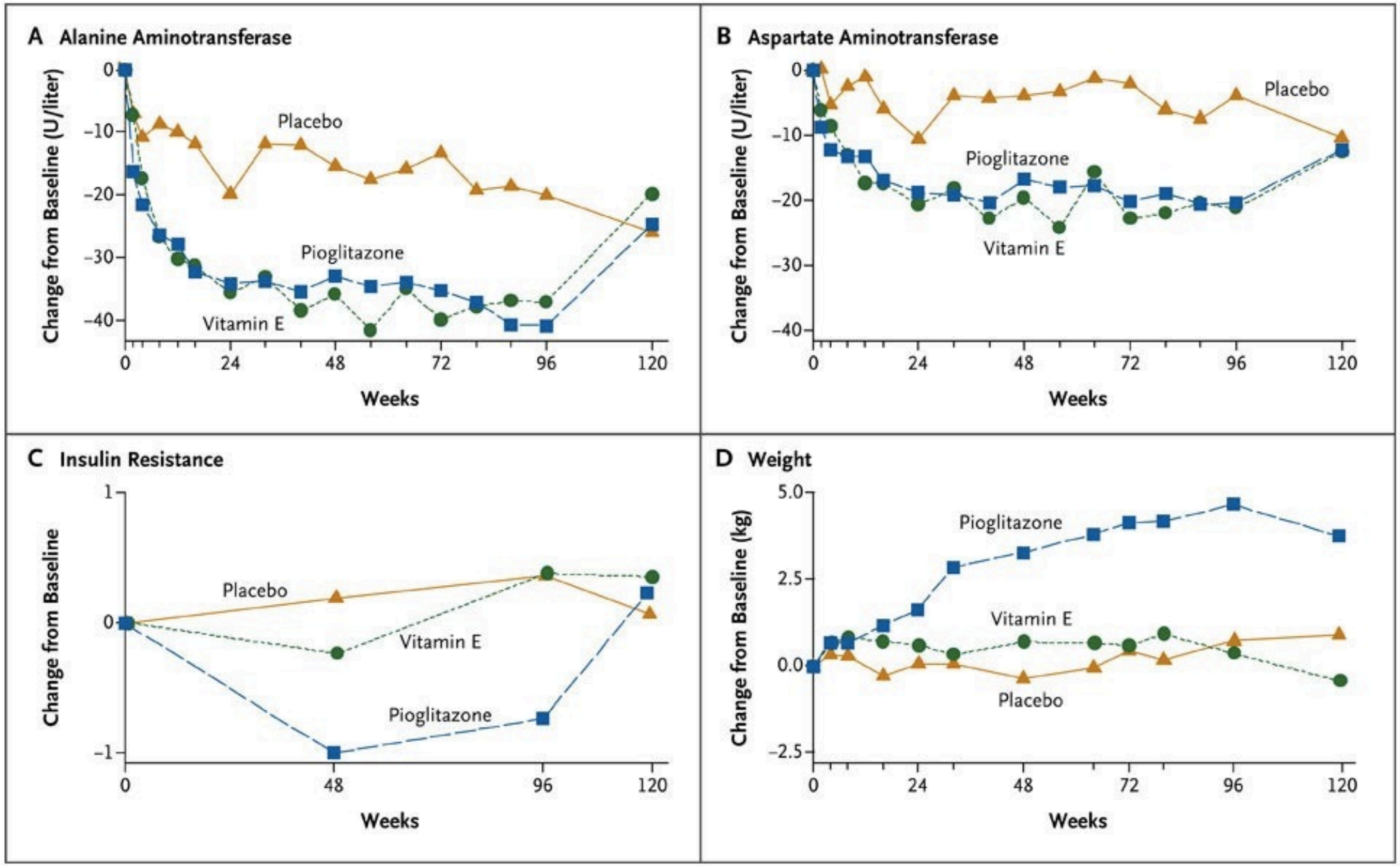
>250 MINUTES/WEEK

BARRIERS

Non-FDA Treatment Options: Vitamin E

- Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis
  - N Engl J Med, May 2010





Sanyal A. New England Journal of Medicine 2010

Non-FDA Treatment Options: Vitamin E

- Recommend 800 IU daily, plant based
- Not recommended in DM patients
- Discuss risks
- Improvement in NASH

Non-FDA Treatment Options: Pioglitazone

- May be an option for patients with DM and NASH
- Discuss risks
- Improvement in AST and ALT

Treatment of Comorbid Conditions

- Lipids
- Diabetes
- Hypertension
- Obesity

Lipids: Statins and liver disease

	Cohort 2 (n = 1437)	Cohort 1 (n = 342)	Cohort 3 (n = 2245)
Mild-moderate elevations in liver biochemistries[a]	1.9%	4.7%	6.4%
	$P = 0.002$	$P = 0.2$	
Severe elevations in liver biochemistries[a]	0.2%	0.6%	0.4%
	$P = 0.2$	$P = 0.6$	

NOTE. Cohort 1: individuals with elevated baseline liver enzymes who were placed on a statin.
Cohort 2: Individuals with normal baseline liver enzymes who were placed on a statin.
Cohort 3: Individuals with elevated liver enzymes but not placed on a statin.
[a]See Materials and Methods section for definitions.

Chalassani N. Gastroenterology 200

Recommendations for Management of patients with NAFLD or NASH

Weight loss

- Hypocaloric, goal of 7-10% weight loss

Moderate-intensity exercise

- 30 min/day, 3-5 times/week

Limit alcohol consumption

- Two or less for men, one or less for women

Coffee

- 2 cups per day

Modification of CVD risk factors

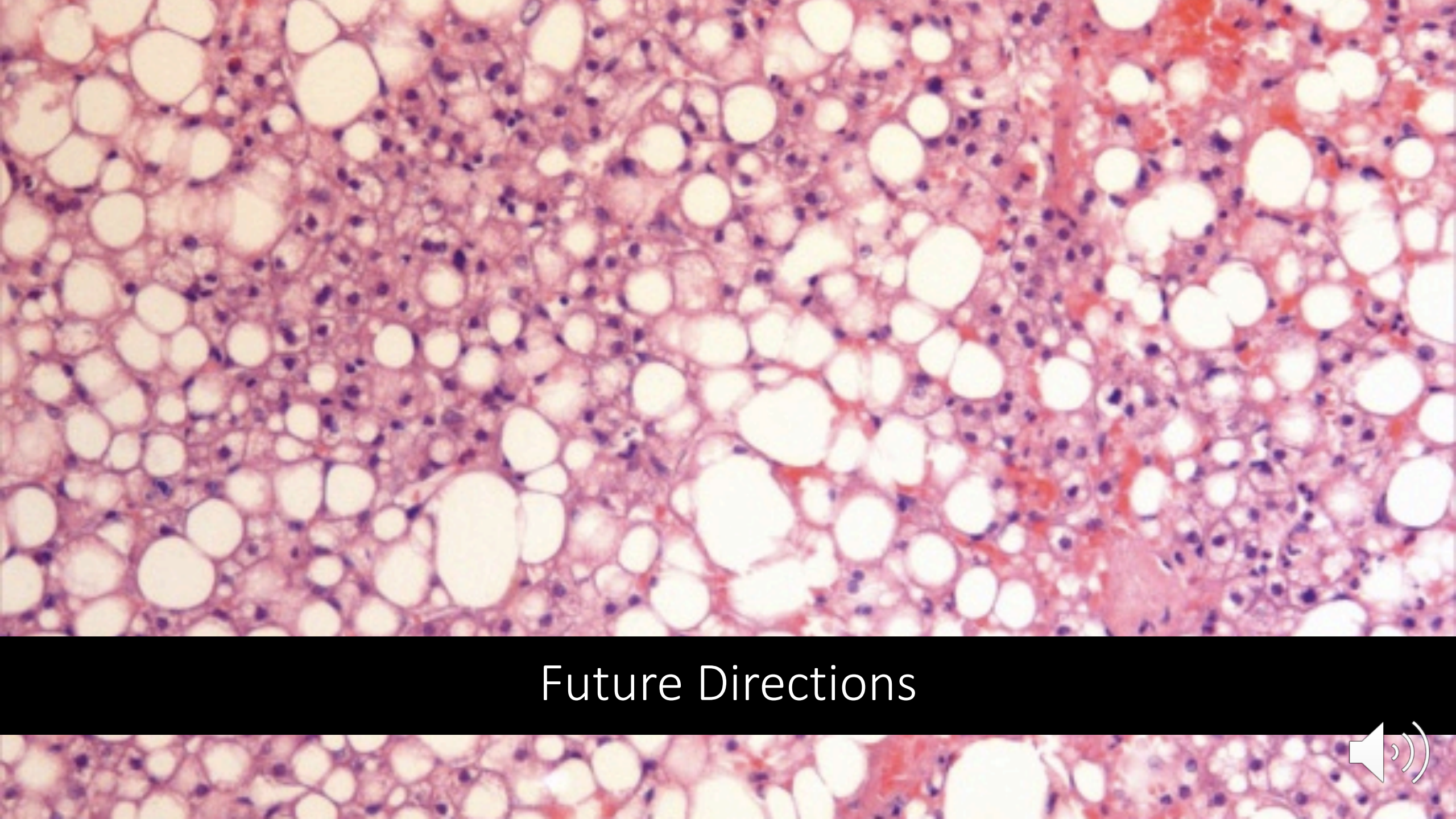
Statins

- If dyslipidemic

Interventions to *Consider* for patients with NAFLD or NASH

- Pioglitazone
  - In diabetics with NASH
- Vitamin E
  - NASH without DM
- Foregut bariatric surgery
  - If eligible
- Omega-3 fatty acids
  - If hypertriglyceridemia

Not recommended : Metformin, GLP-1 agonists (liraglutide), Systematic bariatric surgery, Ursodeoxycholid acid



Future Directions

NASH Clinical Trials

- Endpoints for clinical trials
  1. Disease Activity (steatohepatitis) = NAFLD Activity Score (NAS)
  2. Disease Progression = Fibrosis Stage
  3. Clinical outcomes: Cirrhosis (MELD, Portal hypertension), Liver-related outcome, death

NASH: Targets for Therapeutics

	Insulin Resistance	Cell Stress Apoptosis	Inflammation	Fibrogenic Remodeling
	Insulin resistance modifiers	Cell stress modifiers	Anti-inflammatory agents	Anti-fibrotic agents
Examples of Drugs in Development	PPAR FXR agonist (obeticholic acid, GS-9674) GLP-1 FABAC FGF-21 (BMS-986036) Thyroxine analog	Vitamin E ASK-1 inhibitor (selonsertib) PPAR-γ agonsit FXR agonist Dual PPAR-/δ agonist FGF-21 FGF-19-like agent	CCR2-CCR5 antagonist Vitamin E ASK-1 inhibitor PPAR-γ agonsit FXR agonist Dual PPAR-/δ agonist Galectin 3 FGF-21 FGF-19-like agent	CCR2-CCR5 antagonist ASK-1 inhibitor PPAR-γ agonsit FXR agonist Dual PPAR-/δ agonist Lysyl oxidase-like 2 inhibitor Galectin 3 FGF-21 FGF-19-like agent

Konerman. J Hepato. 2018

Diehl. NEJM 2017.

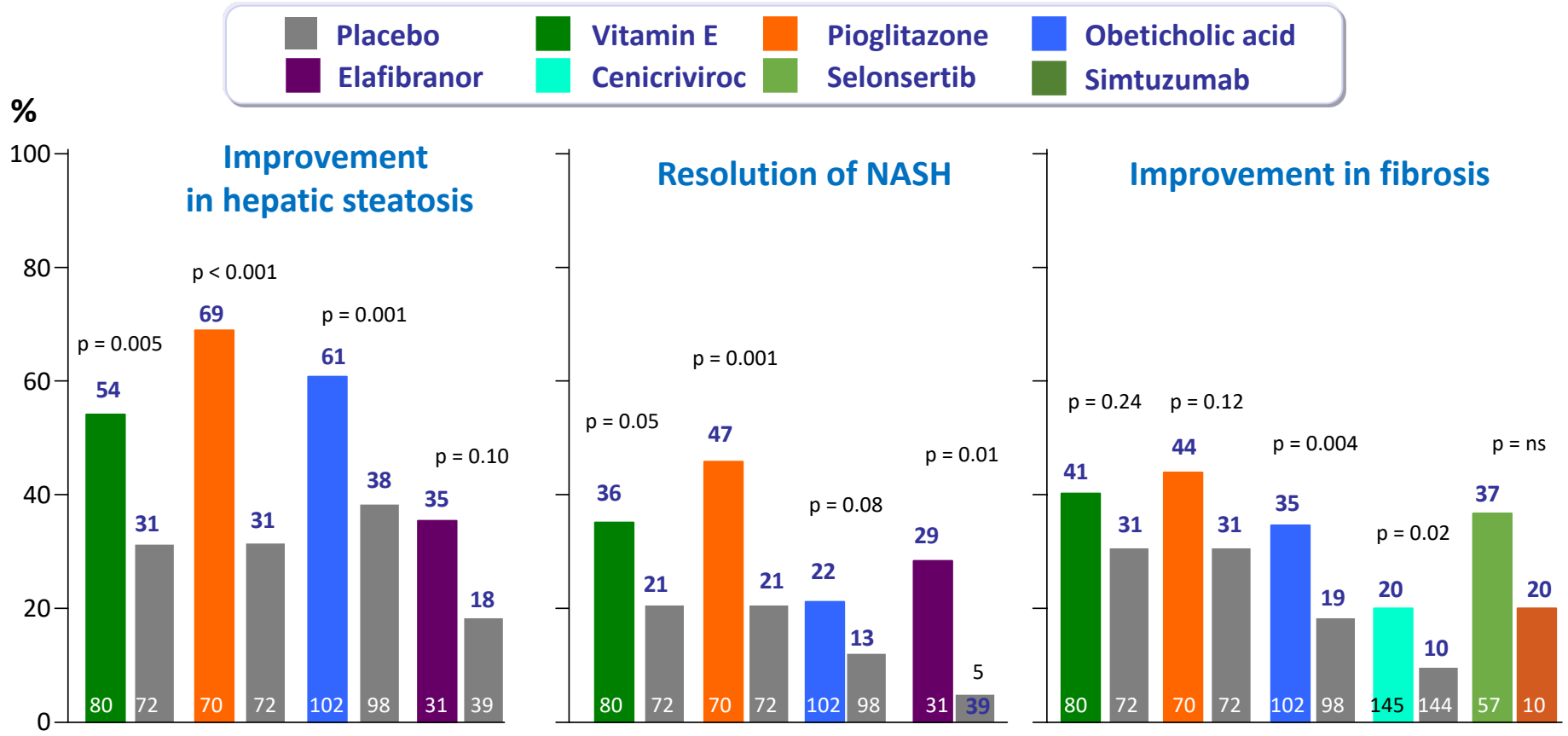
Treatment Options: Obeticholic Acid

- Bile acid
- Trial in patients with DM and NAFLD; NASH
- 25 mg per day
- Improved steatosis
- Improved insulin sensitivity
- SE: pruritus in 20% of patients (was seen in patients with histologic improvement)

Mudalier S. Gastroenterology 2013
Younossi. Lancet 2019.

Improvement of NASH with pharmacologic agents

Results of trials for individual treatment agents *



* Enrollment criteria and durations of therapy differed between studies, and the primary endpoint definitions were not identical

Adapted from Konerman MA. J Hepatol 2018.

New Treatment Options: DMR

- Duodenal Mucosal Resurfacing
- Presented at AASLD Fall 2019
- Trials in Europe and Brazil
- Showed decrease in HbA1C and liver fat content

In Summary…

- Fatty liver disease contains two main disease processes: NAFLD and NASH.
- NASH is the more severe form, with the potential for cirrhosis.
- Patients with fatty liver are VERY common.
- Having this diagnosis increases overall mortality, specifically CVD and malignancy risks
- Treatment is multifaceted, but possible!

Citations:

- Ludwig J. *Mayo Clin Proc*. 1980.
- Rinella M. *JAMA* 2015.
- Hilden M. *Scand J Gastroenterol*. 1977
- Alter MF. *N Engl J Med.* 1999.
- Venkataramani A. *Atlas of the Liver.* Philadelphia: Current Medicine;1999.
- McQuillan GM. *Am J Public Health* 1999.
- Mofrad P. *Hepatology* 2003.
- Amarapurkar Dn. *Trop Gastroenterology* 2004.
- Maximos M. *Hepatology* 2015.
- Portillo Sanchez P. *J clin Endocrinology Metabolism* 2014.
- Bril and Cusi. *Diabetes Care*. 2017.
- Afdhal NH. *Gastroenterology & Hepatology*. 2012.
- Vilar-Gomez. *Gastroenterology* 2015.
- Sanyal A. *N Engl J Med* 2010.
- Chalassani N. *Gastroenterology* 2004.
- Konerman. *J Hepatol* 2018.
- Diehl. *N Engl J Med* 2017.
- Mudalier S. *Gastroenterology* 2013.
- Younossi. *Lancet* 2019.
- Chalasani N. *Hepatology* 2018.

Thank You!

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