Non-Alcoholic Fatty Liver Disease: Current Medication Management Approaches and Future Therapeutics

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DISCLOSURE

I have no potential conflicts of interest to disclose.

LEARNING OBJECTIVES

- Describe the spectrum of Non-alcoholic Liver Disease (NAFLD) and its diagnosis.
- Identify the cardio-metabolic co-morbidities associated with NAFLD.
- Discuss the liver-directed and non-liver directed medication approaches to managing NAFLD.
- Give examples of future therapies in the pipeline for Non-Alcoholic Steatohepatitis (NASH).

QUESTION 1:

What is the most common cause of death in patients with NAFLD?

a) Renal failure
b) Hepatocellular carcinoma
c) Cardiovascular disease
d) Liver failure

CASE: NANCY

- Nancy is a 57 yr old Hispanic female with PMH of uncontrolled Type 2 Diabetes Mellitus (T2DM), Hashimoto's Thyroiditis s/p thyroidectomy, Hyperlipidemia (HLD), Hypertension (HTN), and obesity class II (BMI 36 kg/m^2).
- Social History: Tobacco use-never; Alcohol consumption-rarely, only special occasions.
- Liver enzymes:

	6/15/19	**9/4/19**	**2/7/20**	**4/29/20**	**7/8/2020**
AST (U/L)	35	32	35	41↑	34
ALT (U/L)	78↑	80↑	93↑	90↑	100↑

AST: aspartate aminotransferase; ALT: Alanine transaminase

CASE: NANCY

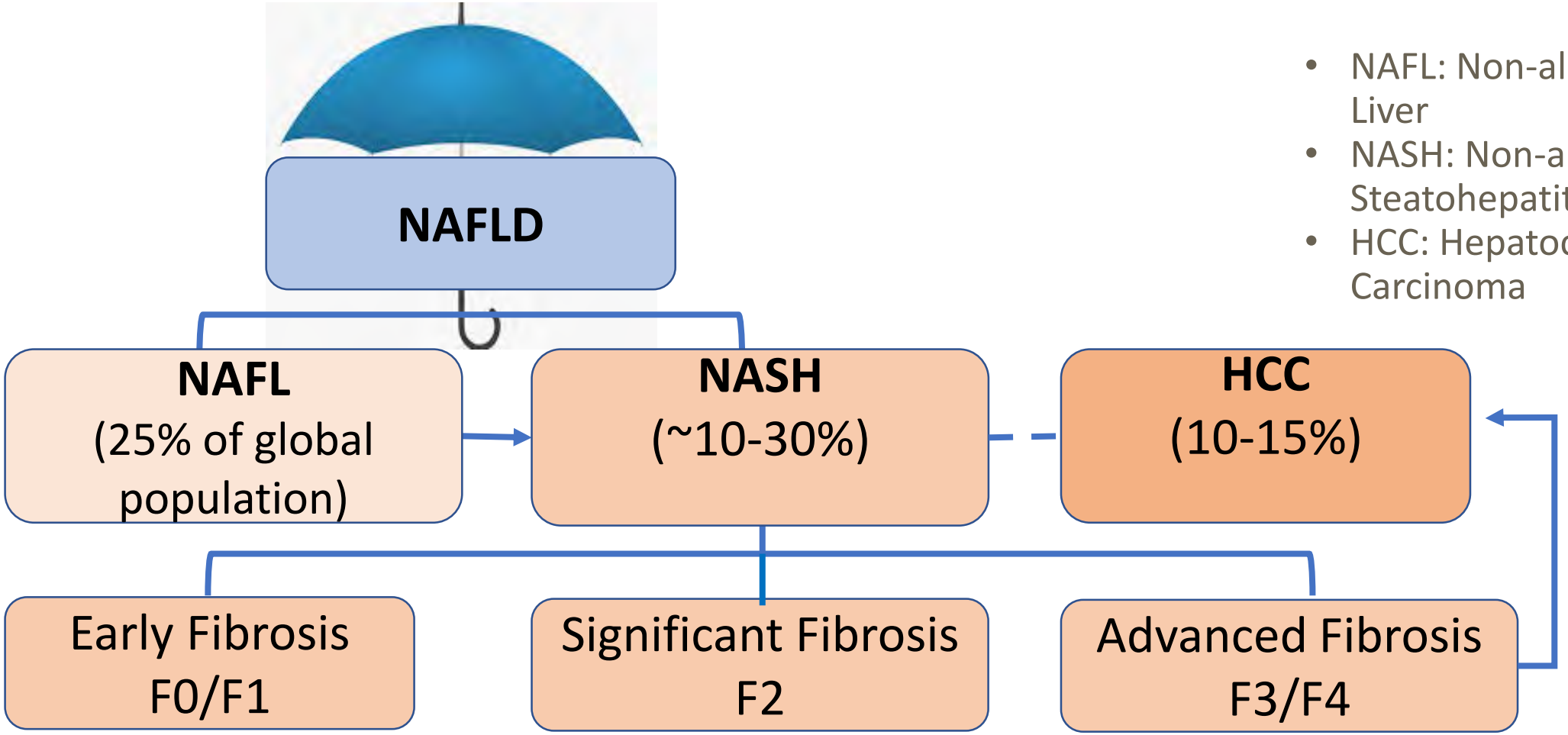
- A1c: 8%
- Platelets: 380 x10^3/uL; Serum albumin: 4.8g/dL; Total bilirubin: 0.5mg/dL
- Fasting Lipid panel:
  - TC : 230mg/dL, TGs: 320mg/dL, LDL: 190mg/dL, HDL: 32mg/dL
- Viral hepatitis screening negative
- Medications:
  - Metformin 1000mg BID
  - Glipizide 10mg BID
  - Levothyroxine 100mcg daily
  - Losartan 25mg daily
- **What could be the cause of Nancy's liver enzyme elevations?**

WHAT IS NAFLD?

- NAFLD is defined by evidence of **steatosis in ≥5% hepatocytes** in individuals who consume little or no alcohol and have no competing etiologies for steatosis.
  - Typically a diagnosis of exclusion.
- Commonly associated with **metabolic comorbidities** such as obesity, diabetes, hypertension, and dyslipidemia.
  - Hepatic manifestation of metabolic syndrome!

1. Chalasani, N. *Hepatology*. 2018.

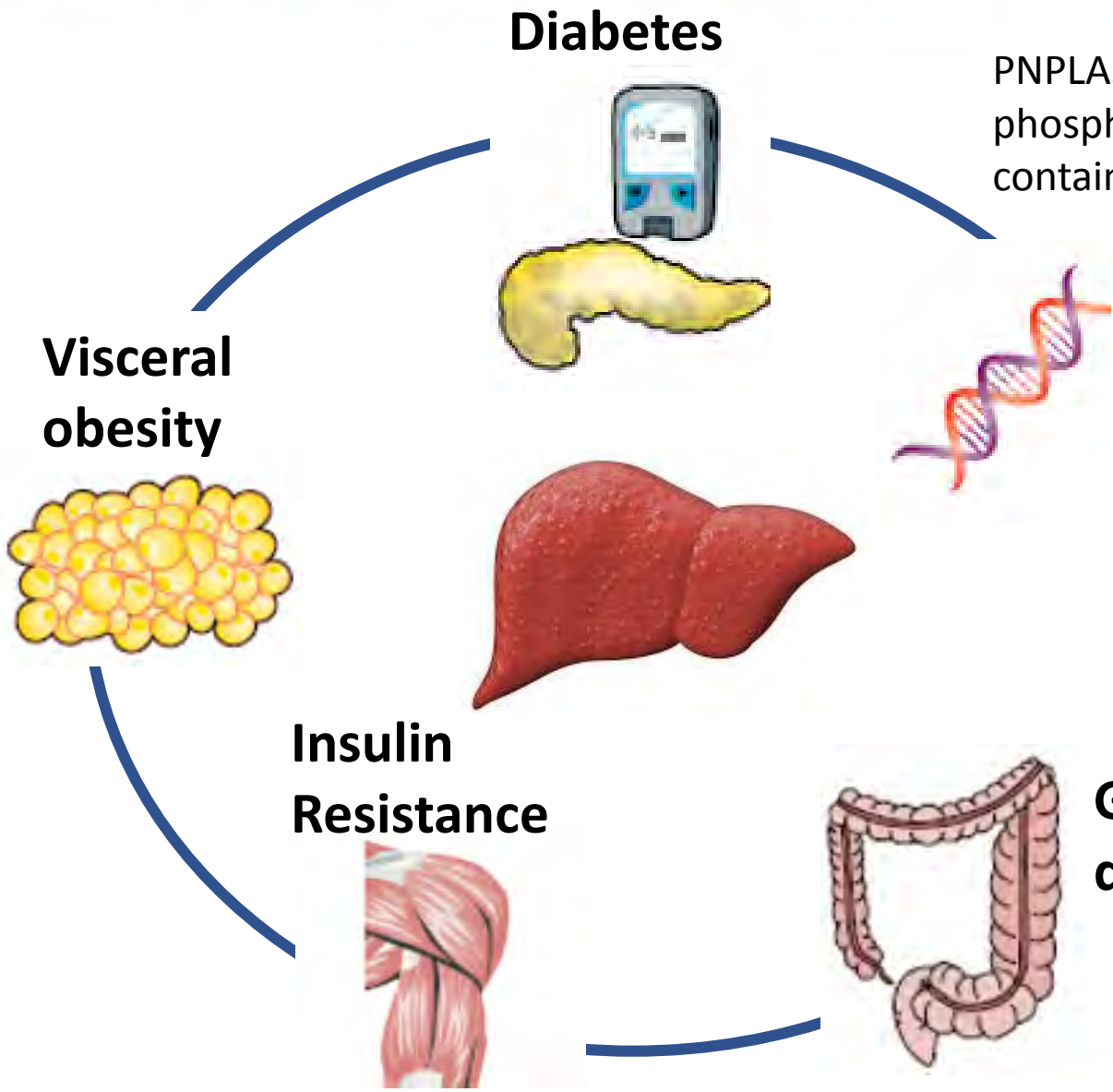
NAFLD SPECTRUM AND EPIDEMIOLOGY



- NAFL: Non-alcoholic Fatty Liver
- NASH: Non-alcoholic Steatohepatitis
- HCC: Hepatocellular Carcinoma

1. Chalasani, N. *Hepatology*. 2018.

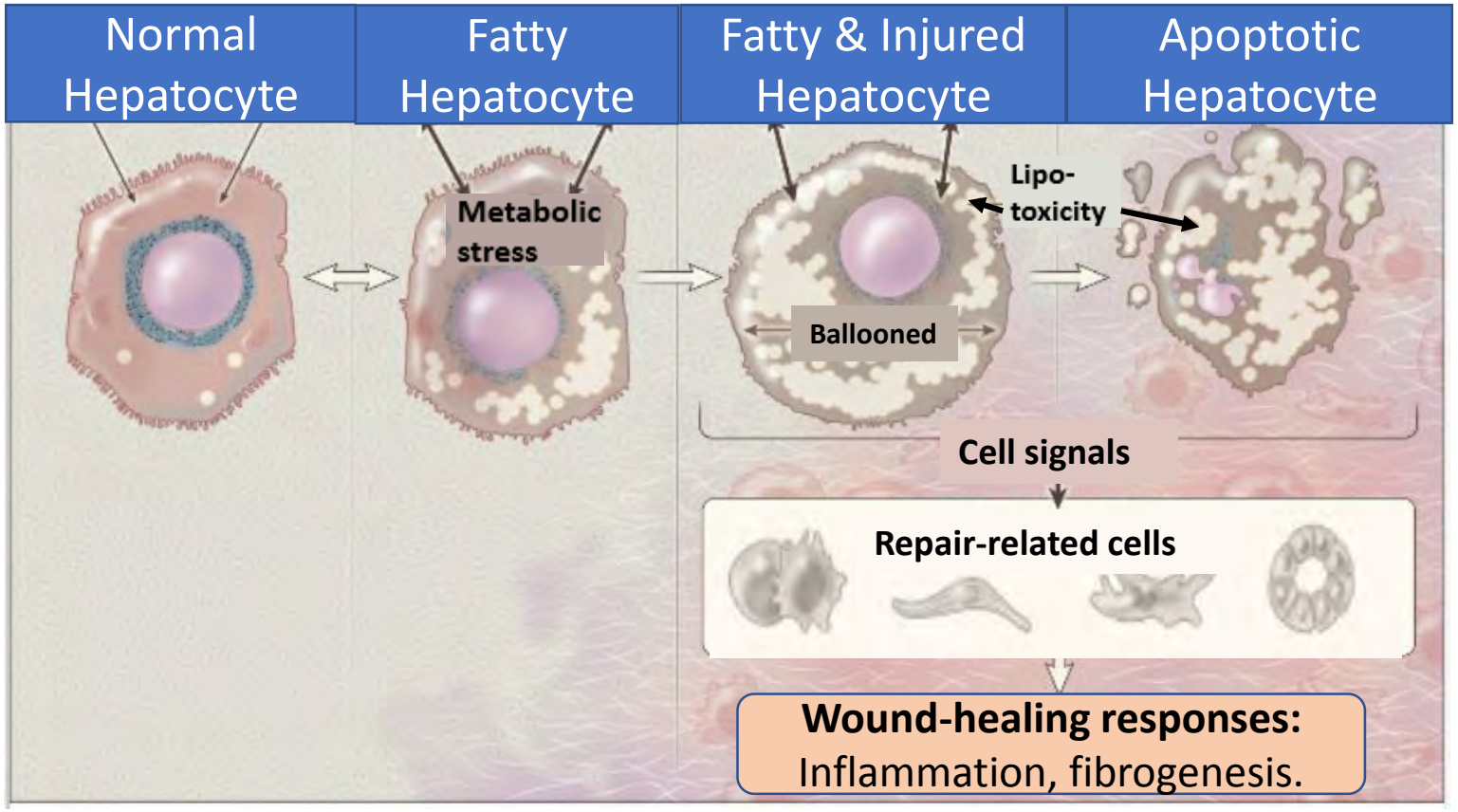
NAFLD Causes



PNPLA3: Patatin-like phospholipase domain-containing protein 3

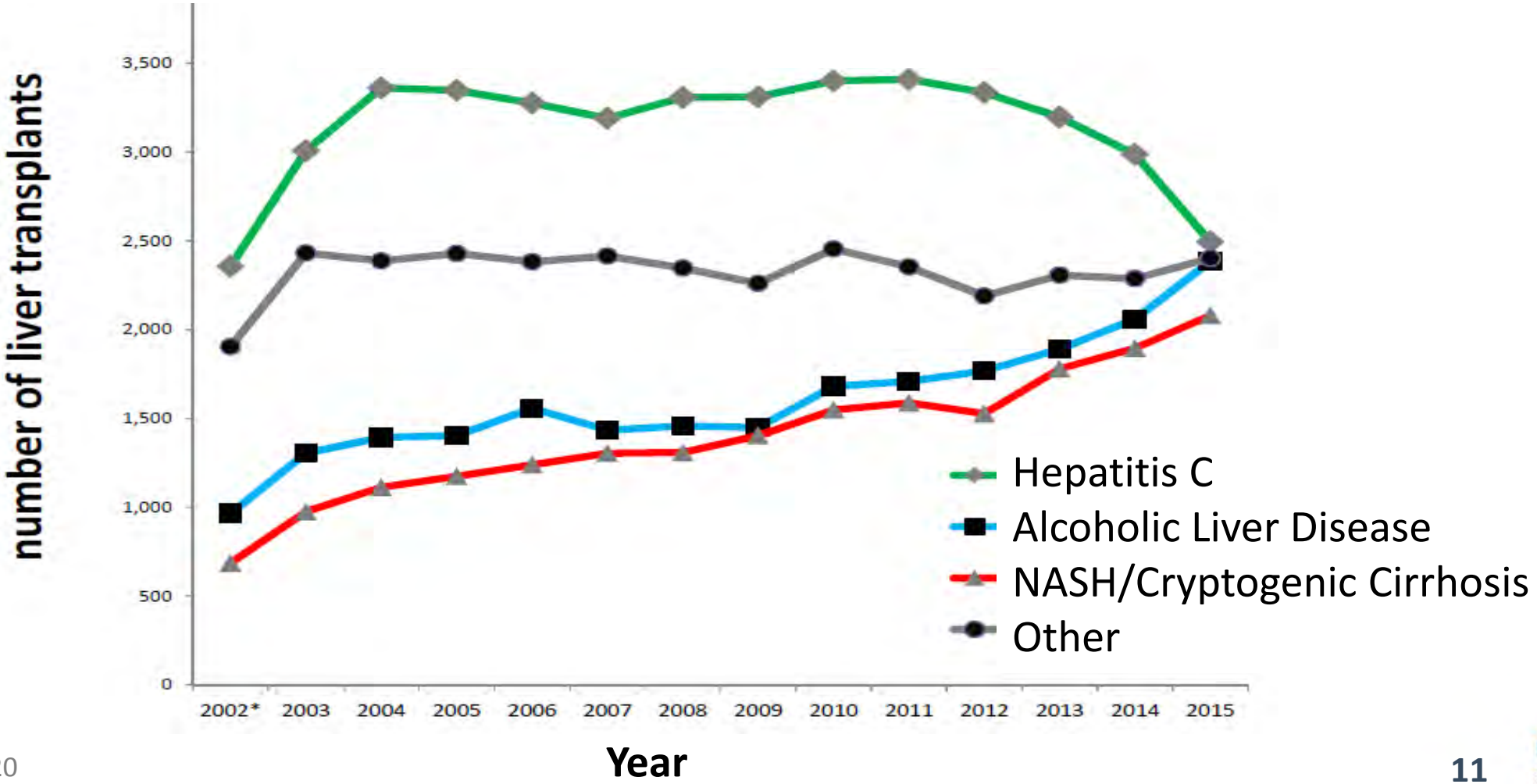
2. Stefan, N. *Lancet Diabetes Endocrinology*. 2018.

NASH PATHOGENESIS



3. Diel, A. *N Engl J Med* . 2017.

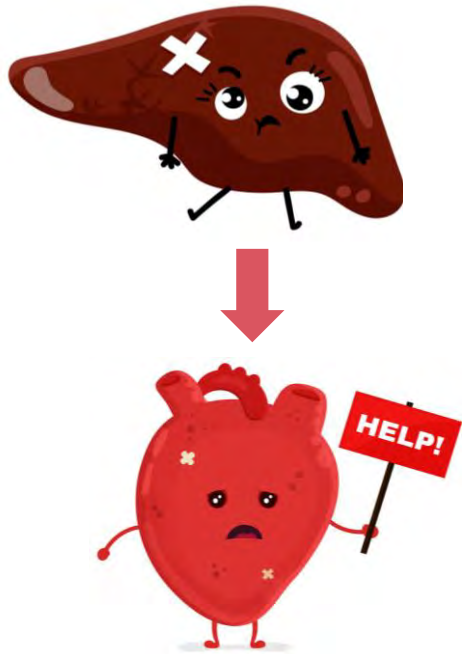
LIVER TRANSPLANTATION IN THE U.S. 2005-2013



4. Goldberg D, et al. *Gastroenterology* 2017.

Causes of Mortality in Patients with NAFLD

Top 3 causes of death or liver transplant	Total Patients who died or underwent liver transplant N= 193 (n, %)
Cardiovascular disease	**(74, 38.3%)**
Non-liver cancer	(36, 18.7%)
Cirrhosis complications	(15, 7.8%)



5. Angulo, P., et al. *Gastroenterology.* 2015.

Patient Presentation

- Typically asymptomatic
  - Some patients report right upper quadrant discomfort.

- Usually an “incidental finding” on:
  - Routine lab monitoring- elevated liver enzymes.
  - Ultrasound imaging- “increased echogenicity.”

1. Chalasani, N. *Hepatology*. 2018.

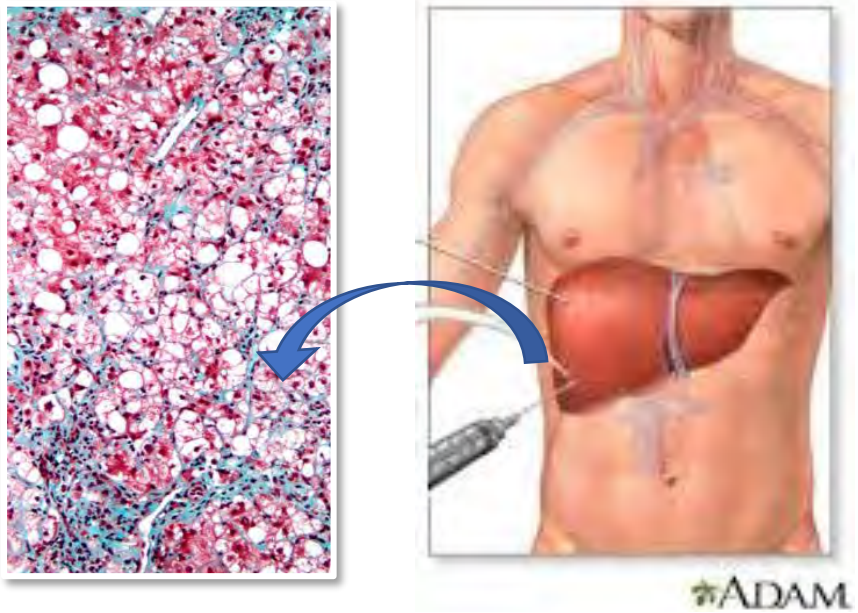
NAFLD Liver Enzyme Patterns

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are NOT sensitive for assessing NAFLD.
- If, however, liver enzymes are elevated, tend to see following patterns:
  - ALT is predominantly elevated. → Simple steatosis (NAFL)
  - As AST climbs to level of ALT or higher (AST:ALT ratio ≥ 1), this confers increased risk for fibrosis. → NASH fibrosis

6. Browning, J. *Hepatology*. 2004. 7. Dyson, J. *Frontline Gastroenterol*. 2014. 8. Mofrad, P. *Hepatology*. 2003.

DIAGNOSIS

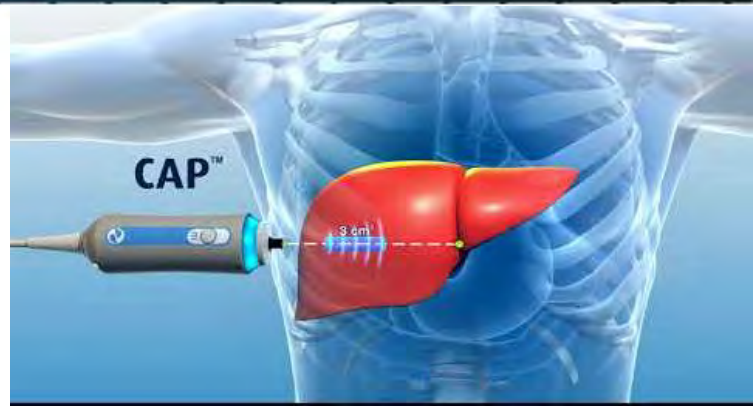
- Liver biopsy= gold standard



NAFLD Activity Score (NAS): Factors steatosis, lobular inflammation, hepatocyte ballooning	
Total Score:	**Diagnosis:**
0-2	Not steatohepatitis
3-4	Indeterminate
≥5	Steatohepatitis

1. Chalasani, N. *Hepatology*. 2018.

DIAGNOSIS



Non-invasive Tests:

- Imaging
  - MRI with elastography and Proton Density Fat Fraction (PDFF)
  - Vibration Controlled Transient Elastography (VCTE) with Controlled Attenuation Parameter
- Blood tests
- Scoring tools
  - NAFLD Fibrosis Score (NFS): Age, AST, ALT, BMI, platelet count, albumin
  - Fibrosis-4 (FIB-4): Age, platelet count, AST, ALT

1. Chalasani, N. *Hepatology*. 2018.

Risk Stratification for NASH and Fibrosis

RISK	Age, Yrs	Comorbidities	VCTE, kPA	AST, IU/L	NFS	FIB-4	Other
High	> 50	T2DM, obesity, HTN	> 8.5	> 40	>0.676	>2.67	Hispanic, AST:ALT ratio ≥ 1
Intermediate	> 40	Well-controlled T2DM, obesity, HTN	> 7.0	> 20			
Low	< 40	No T2DM, no obesity	< 7.0	< 20	< -1.455	< 1.30	

kPA: Kilopascal; NFS: NAFLD Fibrosis Score; FIB-4: Fibrosis-4

9. Konerman. *J Hepatol*. 2018.

Slide credit: clinicaloptions.com

SCREENING FOR NAFLD IN PRIMARY CARE

American Diabetes Association (ADA)- Standards of Care 2020

Recommendation

4.15 Patients with type 2 diabetes or prediabetes and elevated liver enzymes (ALT) or fatty liver on ultrasound should be evaluated for presence of nonalcoholic steatohepatitis and liver fibrosis. C

American Association for the Study of Liver Disease (AASLD)

Guidance Statements:

4. Routine Screening for NAFLD in high-risk groups attending primary care, diabetes, or obesity clinics is not advised at this time because of uncertainties surrounding diagnostic tests and treatment options, along with lack of knowledge related to long-term benefits and cost-effectiveness of screening.

5. There should be a high index of suspicion for NAFLD and NASH in patients with type 2 diabetes. Clinical decision aids such as NFS or fibrosis-4 index (FIB-4) or vibration controlled transient elastography (VCTE) can be used to identify those at low or high risk for advanced fibrosis (bridging fibrosis or cirrhosis).

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10. ADA Standards of Care. 2020.

SCREENING FOR NAFLD IN PRIMARY CARE

American Diabetes (ADA)- Standards

BOTTOM LINE:

Patients >50 yrs old with T2DM and elevated liver enzymes or incidental finding of steatosis on imaging should be further evaluated.

Recommendation

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- Liver enzymes:

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CASE: NANCY

- Nancy's primary care physician refers her to a GI/Hepatology clinic.
- Hepatology assessment:
  - (-) autoimmune hepatitis
  - (-) hemochromatosis
  - (-) alpha-1 antitrypsin deficiency
  - (-) viral hepatitis
  - NAFLD Fibrosis Score: -2.82 (F0-F2 fibrosis)
  - Fibroscan: 8 kPA, CAP=320 dB/m (moderate steatosis with F2 Fibrosis)

CASE: NANCY

What can be done next to help reduce Nancy's risk from NAFLD?

CURRENT MANAGEMENT APPROACHES

QUESTION 2:

Which of the following therapies do the American Association for the Study of Liver Diseases (AASLD) guidelines acknowledge as a potential treatment option in patients with biopsy-proven NASH?

a) Metformin
b) Liraglutide
c) Omega-3 fatty acids
d) Pioglitazone

FDA Approved Treatment

- There are currently no medications approved by the Food and Drug Administration (FDA) for NAFLD.
- So how can we use existing medications to help with fatty liver disease?

TREATMENT APPROACH

Lifestyle Changes (All NAFLD patients)	Metabolic Syndrome-Directed Therapies (All NAFLD patients)	Liver-Directed Therapies (Biopsy-proven NASH patients)
• Daily calorie reduction by 30% • Exercise (≥150min/week) • Mediterranean diet	• Obesity • T2DM • HTN • HLD	• Pioglitazone • Vitamin E

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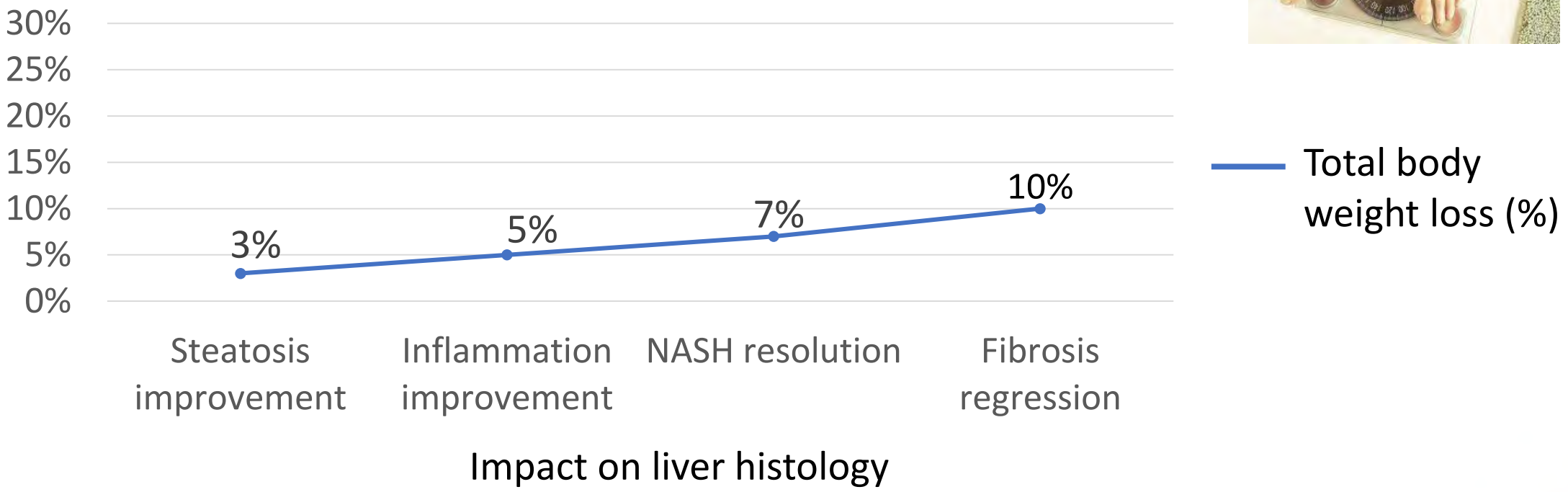
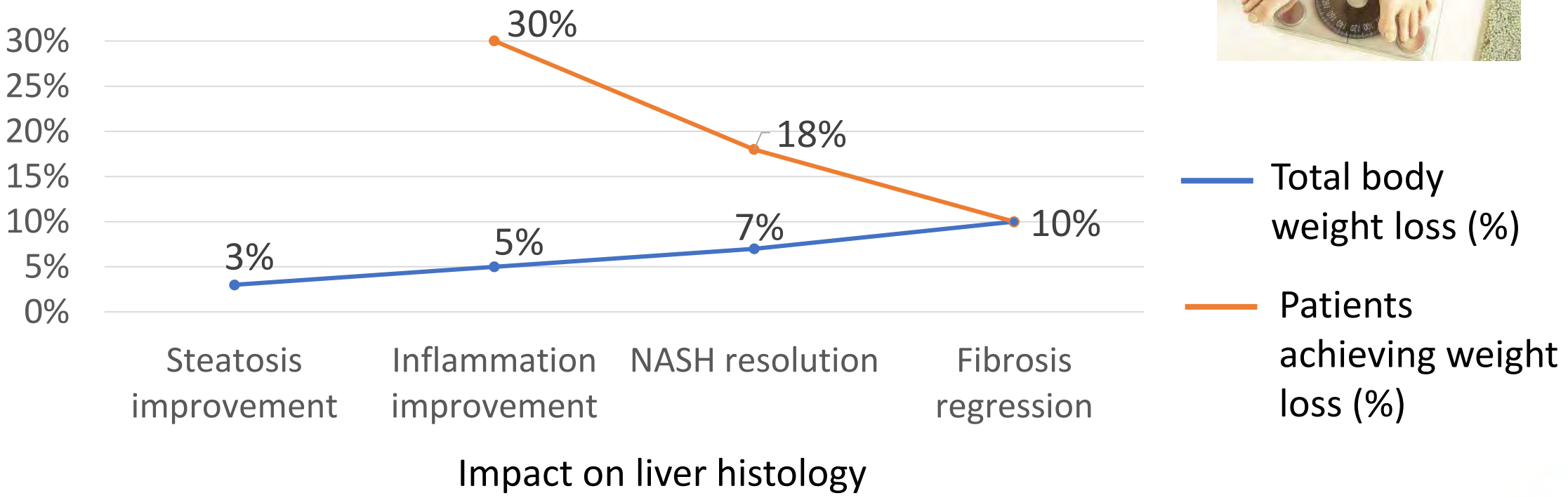
Benefit of Weight Loss



11. Vilar-Gomez, E. *Gastroenterology.* 2015.
1. Chalasani, N. *Hepatology*. 2018.

Reality of Weight Loss



11. Vilar-Gomez, E. *Gastroenterology.* 2015.
1. Chalasani, N. *Hepatology*. 2018.

When to Consider Weight Loss Therapy

Criteria:
Adults 18-64 years old.
Non-pregnant, non-breastfeeding.
BMI ≥ 30 or ≥ 27 kg/m² with one or more associated co-morbid cardio-metabolic condition AND failed to achieve 3-5% weight loss with diet and exercise for 6 months.[#]
No evidence of severe liver disease (Child Pugh Score >9) or end stage renal disease (eGFR<15ml/min).
No evidence of disordered eating.*

[#]FDA-Approved indication for all weight loss therapies.
*Assessment by specialist should occur first.

12. Garvey, T. AACE/ACE Obesity CPG, *Endocrine Practice*. 2016.

Weight Loss Medications: Mechanism of Action

Cravings

Contrave® (bupropion/ naltrexone)

Mesolimbic dopamine pathway

Norepinephrine release

Appetite

Phentermine

Norepinephrine release

Appetite

Qsymia® (phentermine/ topiramate)

Fat absorption

Xenical®, Alli® (orlistat)

Gastric and pancreatic lipase inhibitor

↓ gastric emptying

Satiety

Appetite

Saxenda® (liraglutide)

13. Lexicomp. 2020.

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13. Lexicomp. 2020.

LIRAGLUTIDE CONSIDERATIONS

PREFERRED IF…	AVOID IF…
• Patients experiencing satiety difficulty • Co-morbid pre-DM or T2DM • Co-morbid atherosclerotic cardiovascular disease (ASCVD)	• History of or at risk for pancreatitis • Gastroparesis • Personal or family hx of medullary thyroid cancer • Hx of multiple endocrine neoplasia syndrome type 2 • Triglycerides >450 mg/dL

12. Garvey, T. AACE/ACE Obesity CPG, *Endocrine Practice*. 2016
13. Lexicomp. 2020.

LIRAGLUTIDE DOSING, SIDE EFFECTS, & MONITORING

DOSAGE	SIDE EFFECTS	MONITORING
Wk 1: 0.6mg SQ daily Wk 2: 1.2mg SQ daily Wk 3: 1.8mg SQ daily Wk 4: 2.4mg SQ daily Wk 5: 3mg SQ daily	• Nausea/vomiting • Constipation • Diarrhea	• Weight (d/c if not achieved 4% total body weight loss in 16 weeks) • Baseline lipid panel (TGs) • Heart rate • Symptoms of cholelithiasis or cholecystitis

12. Garvey, T. AACE/ACE Obesity CPG, *Endocrine Practice*. 2016
13. Lexicomp. 2020.

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DIABETES AND NAFLD

- 60-70% of patients with T2DM have NAFLD.
- The presence of co-existent T2DM accelerates the progression of NAFLD and is a predictor of advanced fibrosis and mortality.
- Assess Hgb A1c regularly!
- Pre-DM:
  - Consider metformin, especially those with BMI ≥35, age <60 yrs, and women with hx of gestational DM.
- T2DM:
  - Leverage anti-diabetic therapy with weight loss effects and cardiovascular risk reduction.

14. Kim, D. *Clin Liver Dis.* 2018.

PREFERRED ANTI-DIABETICS IN CONTEXT OF NAFLD

Class	Drugs	Evidence in NAFLD	2020 ADA guidelines	2018 AASLD guidance
GLP-1 RAs	1. Victoza® (liraglutide)* 2. Ozempic® (semaglutide)* 3. Trulicity® (dulaglutide)* 4. Bydureon®/Byetta® (exenatide)	Resolution of NASH without progression to fibrosis.	First-line for those with compelling need to ↓ weight/reduce ASCVD risk and for those who need greater A1c reduction with an injectable.	Pre-mature to consider for NAFLD treatment directly.

*Demonstrated cardiovascular benefit.
GLP-1 RA: Glucagon-like Peptide Receptor Agonists

1. Chalasani, N. *Hepatology*. 2018.
10. ADA Standards of Care. 2020.
15. Armstrong, M.J. *Lancet*. 2016.

PREFERRED ANTI-DIABETICS IN CONTEXT OF NAFLD

Class	Drugs	Evidence in NAFLD	2020 ADA guidelines	2018 AASLD guidance
SGLT-2i 	1. Invokana® (canagliflozin)* 2. Jardiance® (empagliflozin)* 3. Farxiga® (dapagliflozin) 4. Steglatro® (ertugliflozin)	↓ hepatic steatosis on imaging. ↓liver enzymes. Benefit in liver histology has not been studied.	First-line treatment alongside GLP-1 for those with compelling need to↓ weight/reduce ASCVD risk.	Not mentioned.

*Demonstrated cardiovascular benefit.
SGLT-2i: Sodium-Glucose Co-Transporter-2 inhibitors.

1. Chalasani, N. *Hepatology*. 2018.
10. ADA Standards of Care. 2020.
16. Scheen, A.J. *Diabetes and Metabolism*. 2019.

PREFERRED ANTI-DIABETICS IN CONTEXT OF NAFLD

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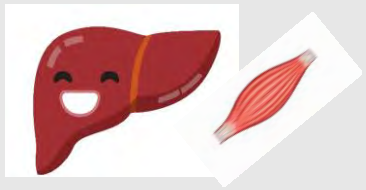
Biguanide 	Metformin *	↓liver enzymes. ↓insulin resistance. No improvement in liver histology.	First line treatment.	Not recommended for NAFLD treatment directly

*Demonstrated cardiovascular benefit.

1. Chalasani, N. *Hepatology*. 2018.
10. ADA Standards of Care. 2020.

LEAN: LIRAGLUTIDE IN NASH TRIAL

- 48-week double blind RCT where 52 patients with biopsy-proven NASH were randomized to receive placebo or liraglutide 1.8mg daily.

Inclusion Criteria:

- Biopsy confirmed NASH +/- T2DM
- NAFLD Activity Score ≥3
- 18-70 yrs old
- BMI ≥ 25 kg/m^2
- HbA1c ≤ 9 %

Exclusion Criteria:

- Child-Pugh B/C cirrhosis
- Other causes of liver dx
- Confounding concomitant drug use

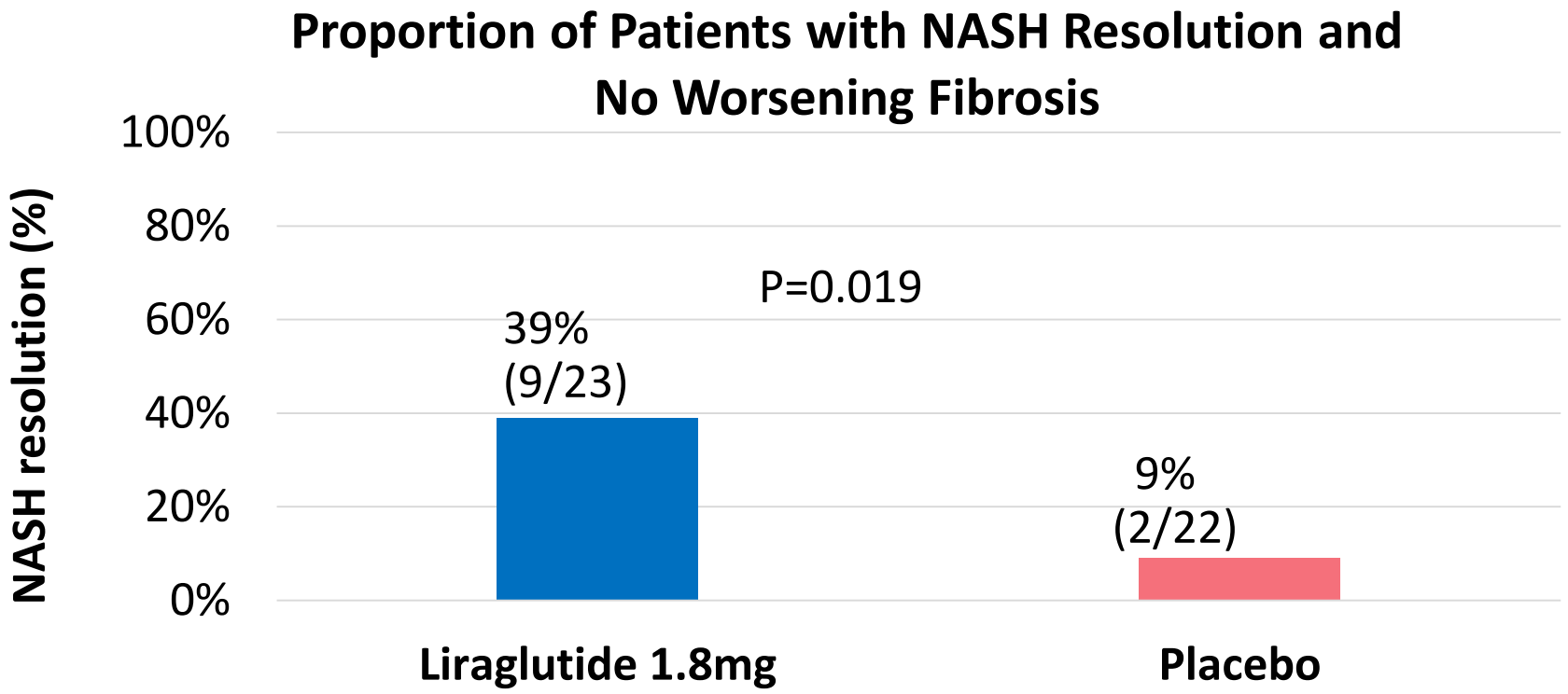
15. Armstrong, M.J. *Lancet*. 2016.

LEAN: LIRAGLUTIDE IN NASH TRIAL

- Primary outcome:
  - Proportion of patients achieving NASH resolution without worsening fibrosis
- Secondary outcomes:
  - Reduction in AST, ALT
  - Weight changes

15. Armstrong, M.J. *Lancet*. 2016.

LEAN TRIAL: RESULTS



15. Armstrong, M.J. *Lancet*. 2016.

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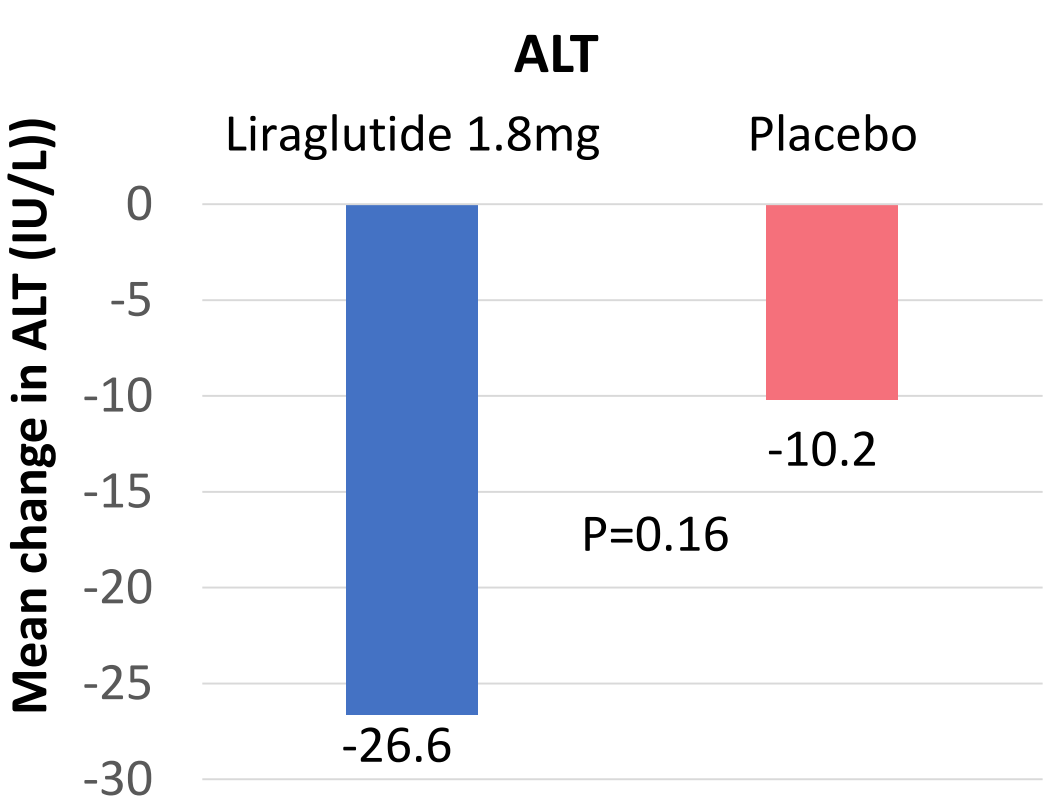
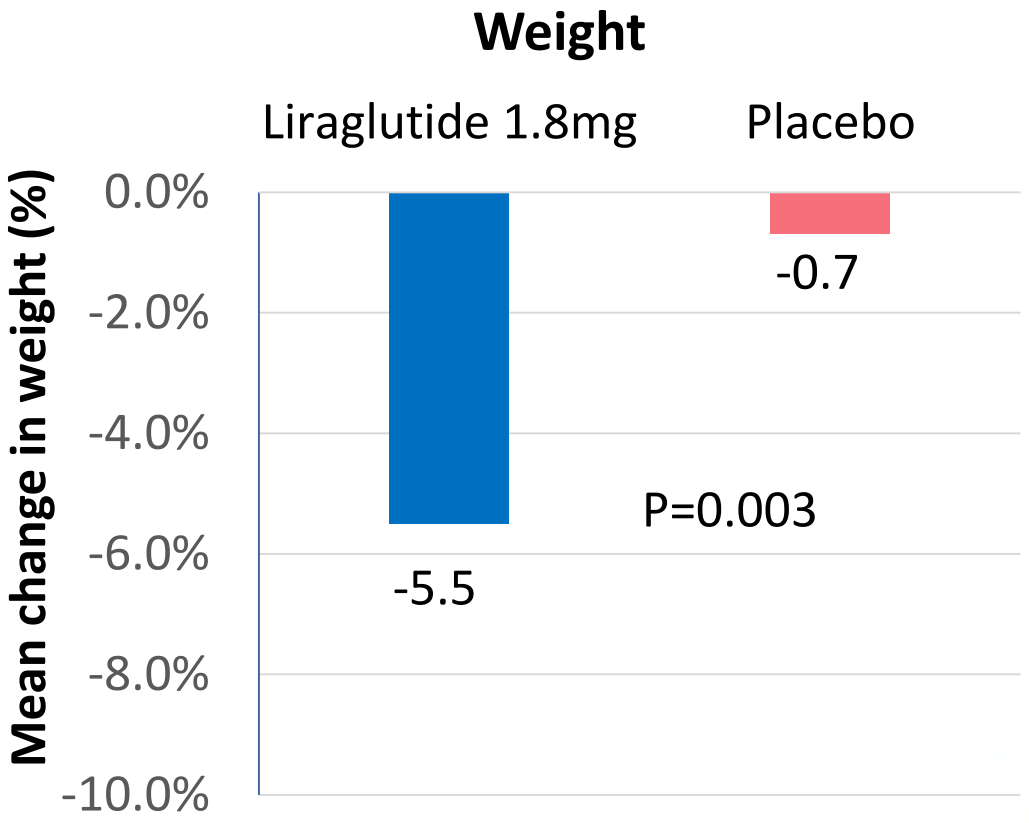




15. Armstrong, M.J. *Lancet*. 2016.

Multi-Organ Effect of GLP-1s in NAFLD

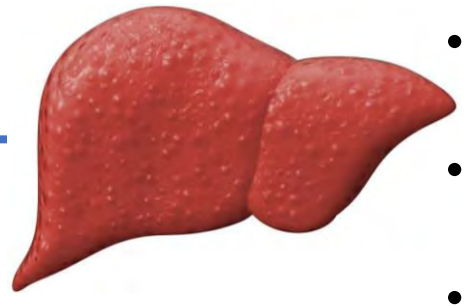
↓ Metabolic Syndrome

GLP-1

Muscle

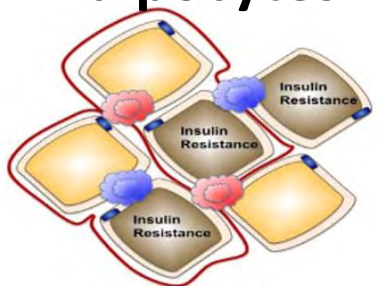
- ↓Insulin resistance
- ↑Glucose uptake

Liver



- ↓Hepatic insulin resistance
- ↓Glucose production
- ↓ Hepatic lipogenesis
- ↓Hepatic fibrosis

Adipocytes



- ↓Adipose insulin resistance
- ↓Pro-inflammatory adipokines
- ↑Anti-inflammatory adipokines

17. Armstrong, M.J. *Clinical Liver Disease*. 2017.

Safety of Anti-Diabetic Therapy in Hepatic Dysfunction

	General comments	Child-Pugh Class A	Child-Pugh Class B	Child-Pugh Class C
Pioglitazone	Avoid when liver enzymes>3x ULN. Avoid in patients with edema.	Can be used	Avoid	
SGLT-2 inhibitors	Caution due to risk of dehydration and hypotension	Can be used	Use with caution	Avoid
GLP-1 RAs		Can be used	Avoid	
Metformin	Use with caution ≤1500mg/day	Can be used	Dose should be reduced	Avoid

ULN: Upper limit of normal

18. Gangopadhyay. *Indian J Endocrinol Metab*. 2017

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Hypertension Control

- The renin-angiotensin-aldosterone system plays a regulatory role in insulin sensitivity.
- **Angiotensin II receptor blockers (ARBs)** have demonstrated significant decreases in serum liver enzyme levels, improved hepatic necroinflammation, and reduction of hepatic fibrosis in limited NAFLD studies.
- Generally, if clinically appropriate, ARBs should be used preferentially to treat HTN in patients with NAFLD.

19. Stahl, E. *Journal of the American College of Cardiology*. 2019.

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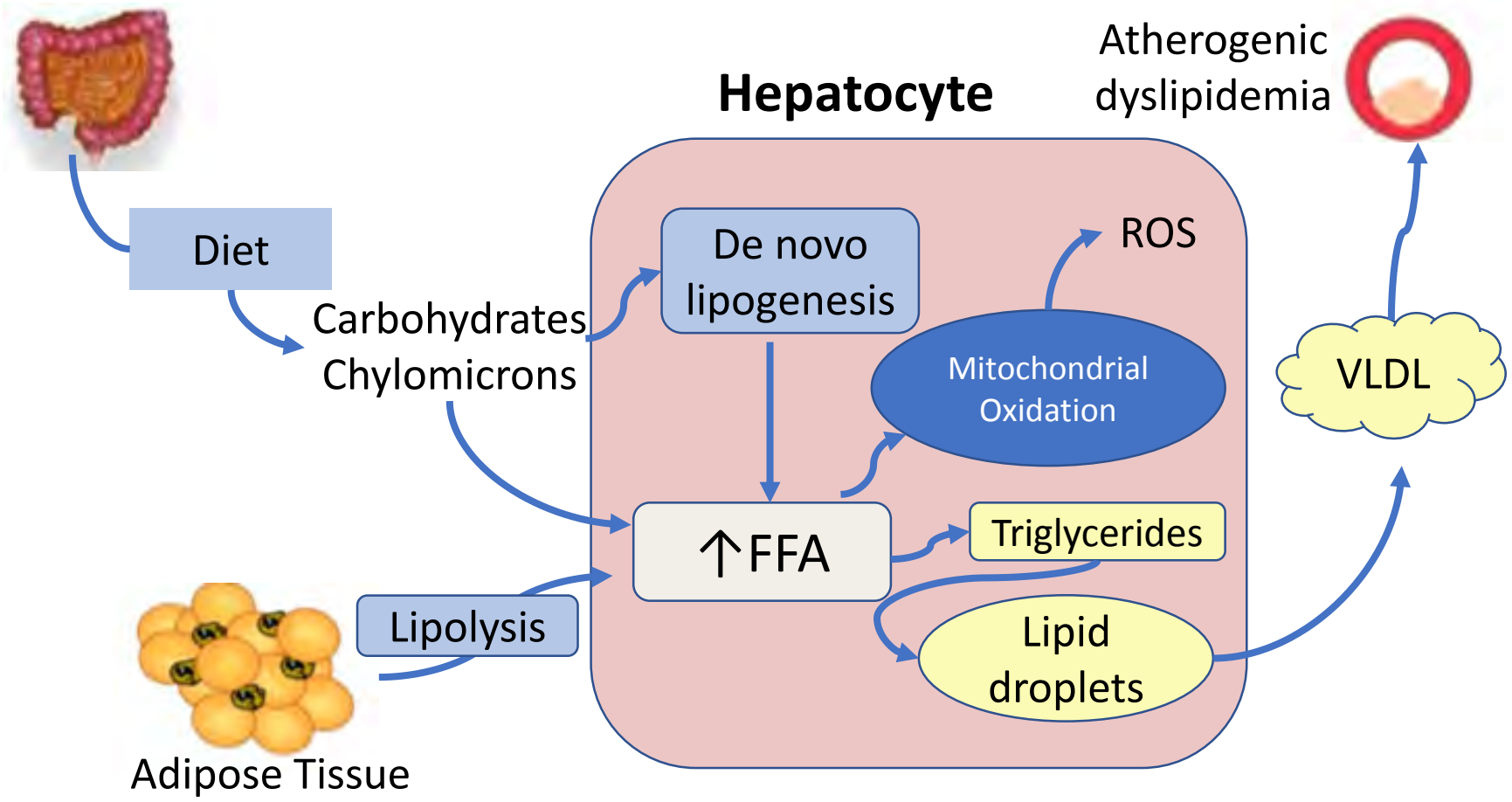
How NAFLD Contributes to Hyperlipidemia



FFA: Free Fatty Acids

ROS: Reactive Oxygen Species

VLDL: Very-low-density lipoprotein

20. Marra, F., Lotersztajn, *S. Curr Pharm Des*. 2013.

CHOLESTEROL CONTROL

- Statins are safe to use in patients with known cause for stable elevated liver enzymes.
- Statins should be avoided, however, in patients with decompensated cirrhosis.
- AASLD guidelines recommend treating dyslipidemia in patients with NAFLD using statins due to their increased CV risk.

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19. Stahl, E. *Journal of the American College of Cardiology*. 2019.

TREATMENT APPROACH

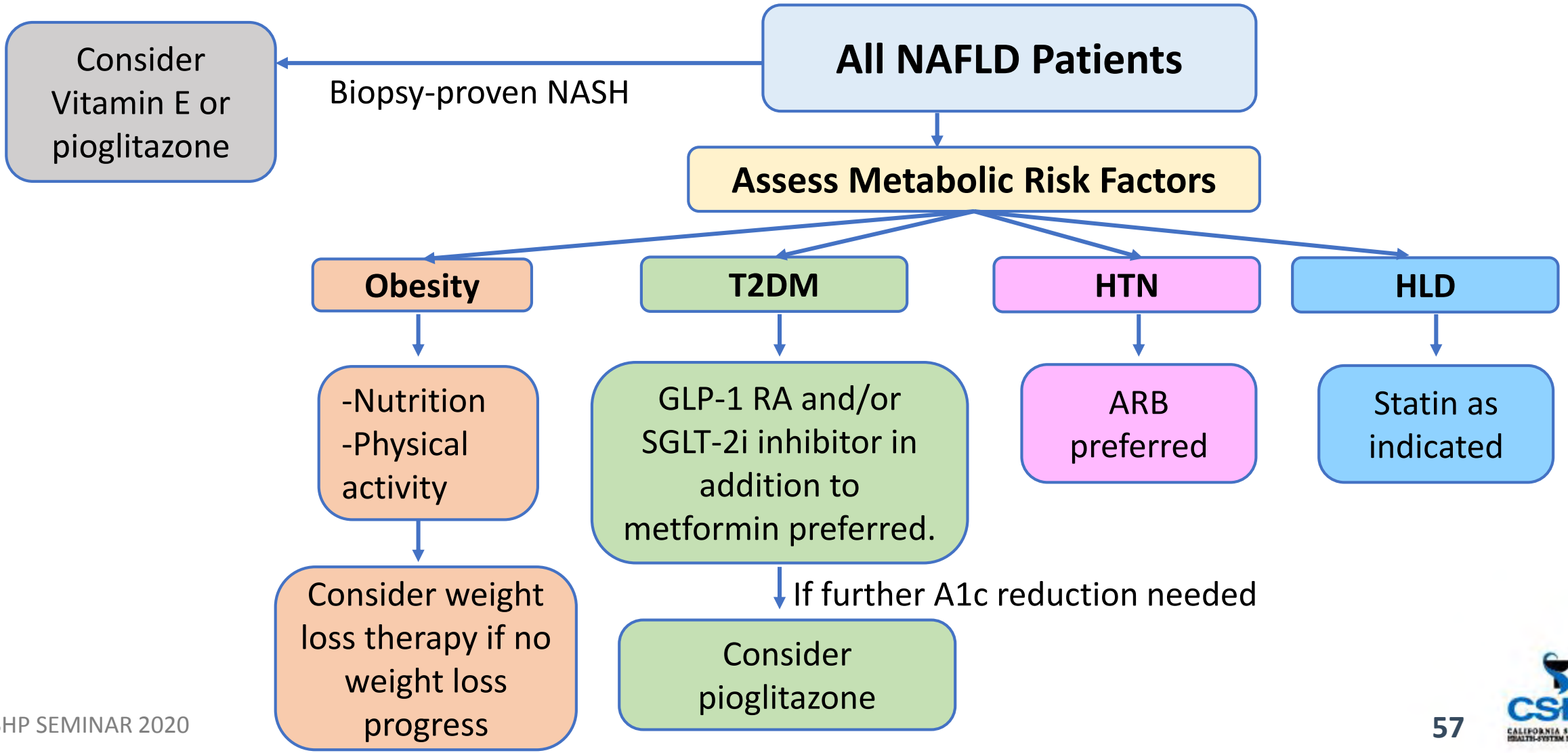
Lifestyle Changes (All NAFLD patients)	Metabolic Syndrome-Directed Therapies (All NAFLD patients)	Liver-Directed Therapies (Biopsy-proven NASH patients)
• Daily calorie reduction by 30% • Exercise (≥150min/week) • Mediterranean diet	• Obesity • T2DM • HTN • HLD	• Pioglitazone • Vitamin E

LIVER-DIRECTED TREATMENTS

Drug/Dose	MOA	Evidence in NAFLD	AASLD Recommendation	Concerns
Pioglitazone 30-45mg daily	PPARY agonist	Improves NAS ≥2 without fibrosis worsening	May be used in biopsy-proven NASH patients with or without T2DM	• Fluid retention/weight gain • Osteoporosis
Vitamin E 800IU daily	Antioxidant	Improves NAS ≥2 without fibrosis worsening in patients without T2DM	May be used in biopsy-proven NASH patients without T2DM	• Possible associated risk of prostate cancer • Hemorrhagic stroke

1. Chalasani, N. *Hepatology*. 2018.

PUTTING IT ALL TOGETHER



QUESTION 2:

Which of the following therapies does the AASLD guidelines acknowledge as a potential treatment option in patients with biopsy-proven NASH?

a) Metformin
b) Pioglitazone
c) Omega-3 fatty acids
d) Liraglutide

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CASE: NANCY

- **What can be done next to help manage Nancy's NAFLD?**
  - Hepatologist encouraged her to lose minimum 10% total body weight (~18 lbs).
  - She was referred to a nutritionist.
  - Started exercise program at her local YMCA.
  - After 8 months, she returns for follow-up. She has lost 8 lbs and feels like she has plateaued with her weight progress.

QUESTION 3:

How can we optimize Nancy's medications?

a) Add basal insulin
b) Stop glipizide
c) Stop glipizide and start semaglutide
d) Add rosuvastatin
e) C and D

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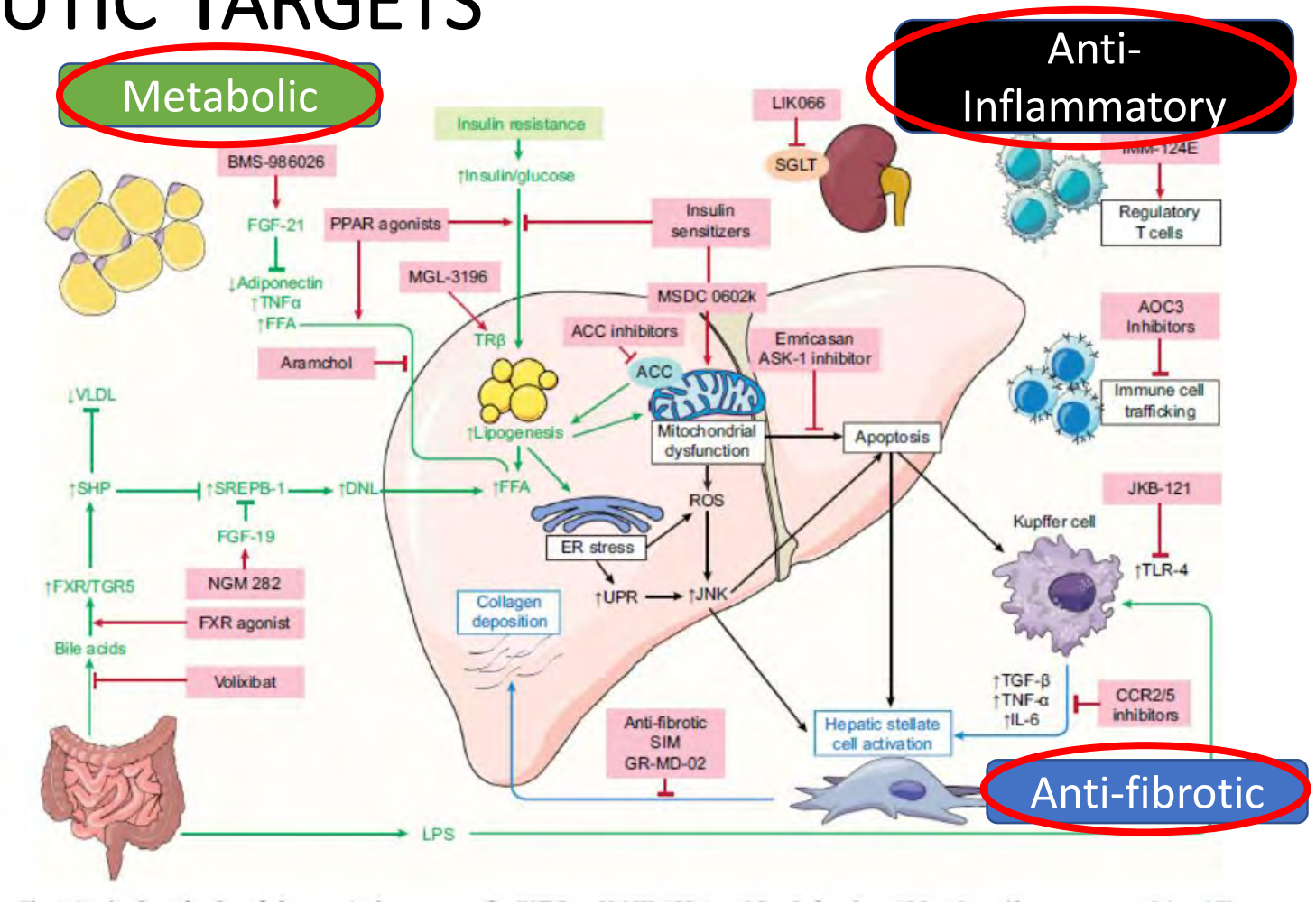
PIPELINE NASH THERAPIES

CLINICAL ENDPOINTS FOR FDA APPROVAL

NASH Resolution		Fibrosis Improvement
• Resolution of steatohepatitis on overall histopathologic reading • No worsening of liver fibrosis	**OR**	• Improvement ≥ 1 fibrosis stage • No worsening of steatohepatitis

21. FDA. Draft Guidance. Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry. December 2018.

THERAPEUTIC TARGETS



22. Konerman, M. *Journal of Hepatology*. 2018

Therapies in Phase III Clinical Trials

1. Obetacholic Acid
2. Elafibranor
3. Resmetirom
4. Cenicriviroc

Therapies in Phase III Clinical Trials

1. **Obetacholic Acid**
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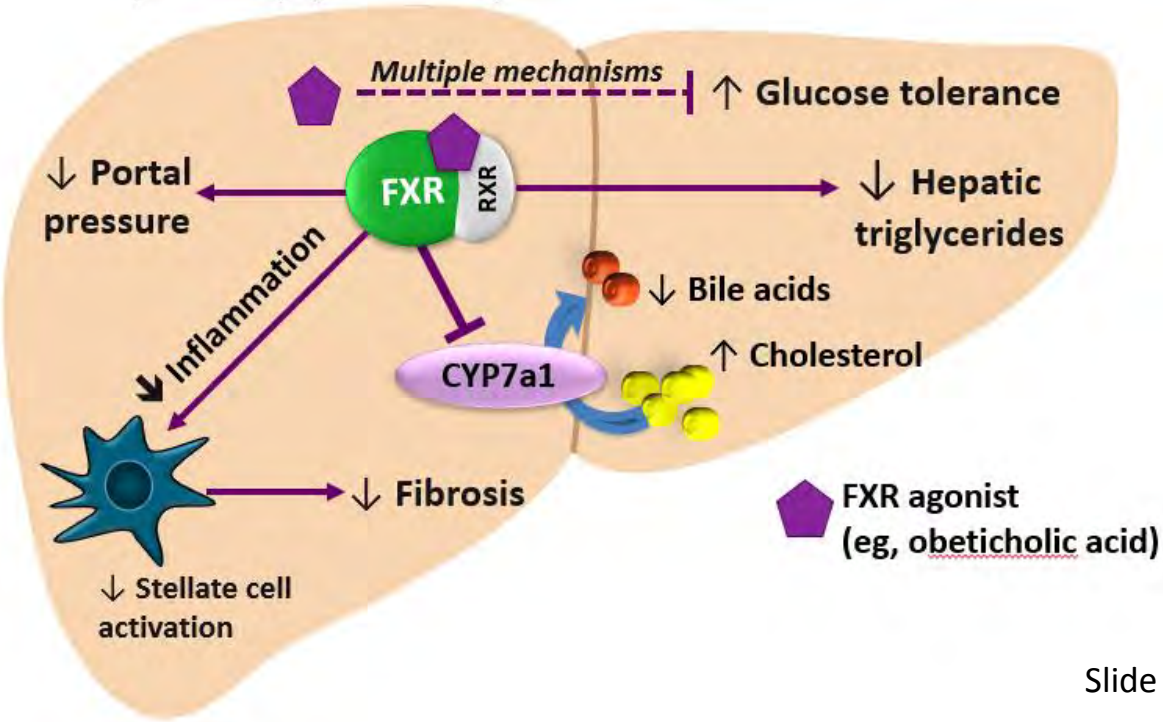
OBETICHOLIC ACID

- Targets metabolic pathway.
- MOA: Bile acid derivative that binds to **farnesoid X receptors.**



Slide credit: clinicaloptions.com

23. Verbeke, L. *Hepatology*. 2014.

OBETICHOLIC ACID

- REGENERATE phase III trial (n=2065; NASH fibrosis 1-3; OCA 25mg po daily vs 10mg vs placebo x 1 year).
  - Demonstrated significant fibrosis improvement (≥ 1 stage) with no worsening of NASH ($p<0.01$).
  - No statistical difference for NASH resolution.
  - Adverse effects: Pruritis, elevated LDL, gallstones or cholecystitis.

- REVERSE phase III trial (n=540; NASH compensated cirrhosis) investigating fibrosis improvement with no worsening of NASH.

24. Connolly, J. *Journal Clinical and Translational Hepatology*. 2018.

QUESTION 4:

What is the mechanism of action of obeticholic acid?

a) Farnesoid X receptor agonist
b) GLP-1 receptor agonist
c) SGLT-2 inhibitor
d) CCR 2/5 receptor antagonist

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FUTURE DIRECTIONS IN NAFLD MANAGEMENT

Future Directions

- Guideline development for risk stratification approach.
  - Target metabolic management in those without indication for liver biopsy.
  - NASH therapies for those with biopsy-proven disease.
- Improved non-invasive tests to determine response.
- Personalized baseline predictors of response.
- Possibility of combination therapy?

MULTI-DISCIPLINARY MANAGEMENT

Stanford Liver Clinic

- Multidisciplinary team: physicians, nutritionist, pharmacist.
- Integrated referral system to cardiology and endocrinology specialists.
- Pharmacy Referral Service
  - Pharmacist optimizes medications for cardio-metabolic conditions. GLP-1 weight loss therapy management.
- NAFLD patient group education classes.
  - Taught by hepatologist, dietitian, psychiatrist, and pharmacist.

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Session Code: