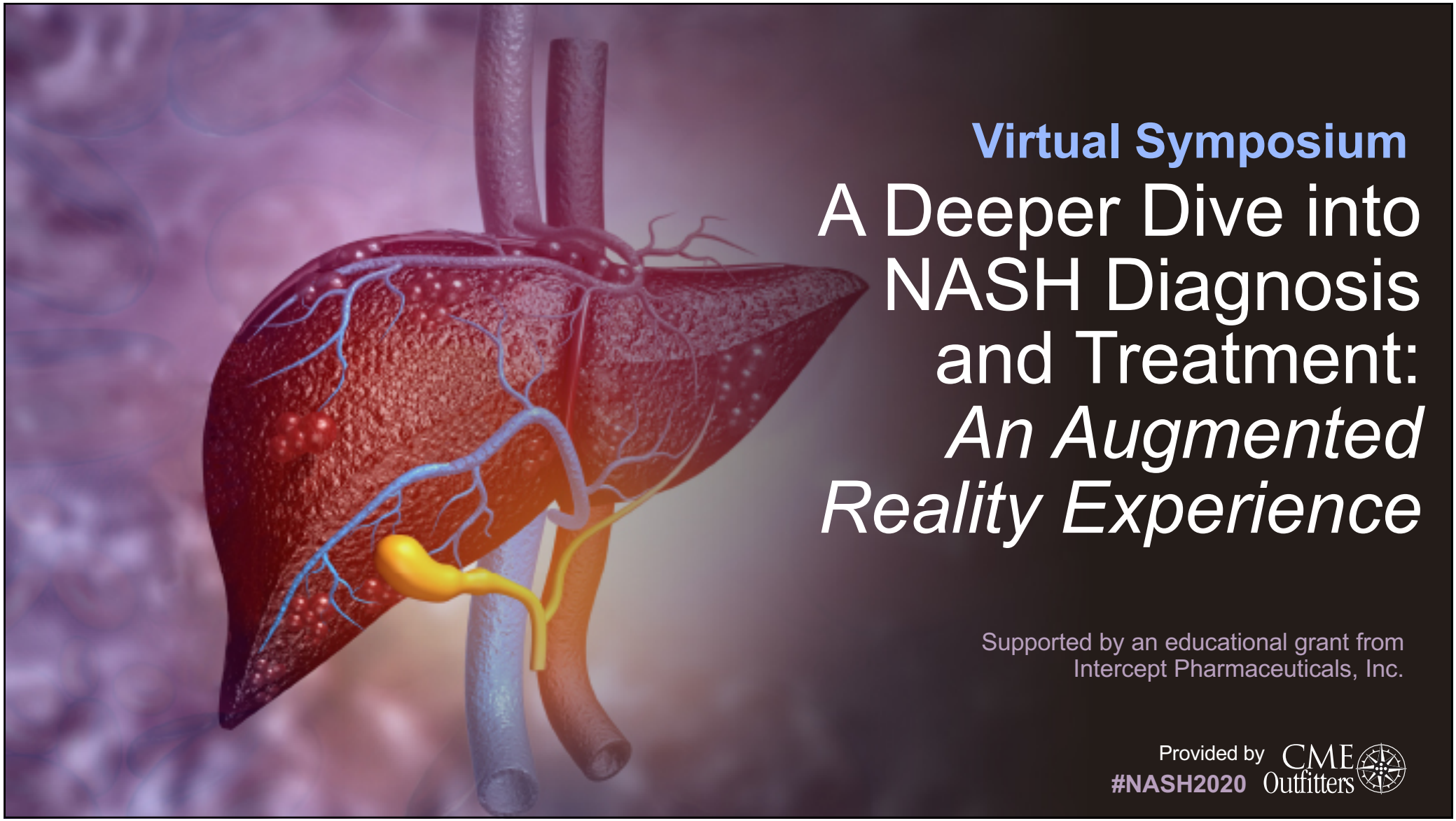

Virtual Symposium

A Deeper Dive into NASH Diagnosis and Treatment: *An Augmented Reality Experience*

Supported by an educational grant from
Intercept Pharmaceuticals, Inc.

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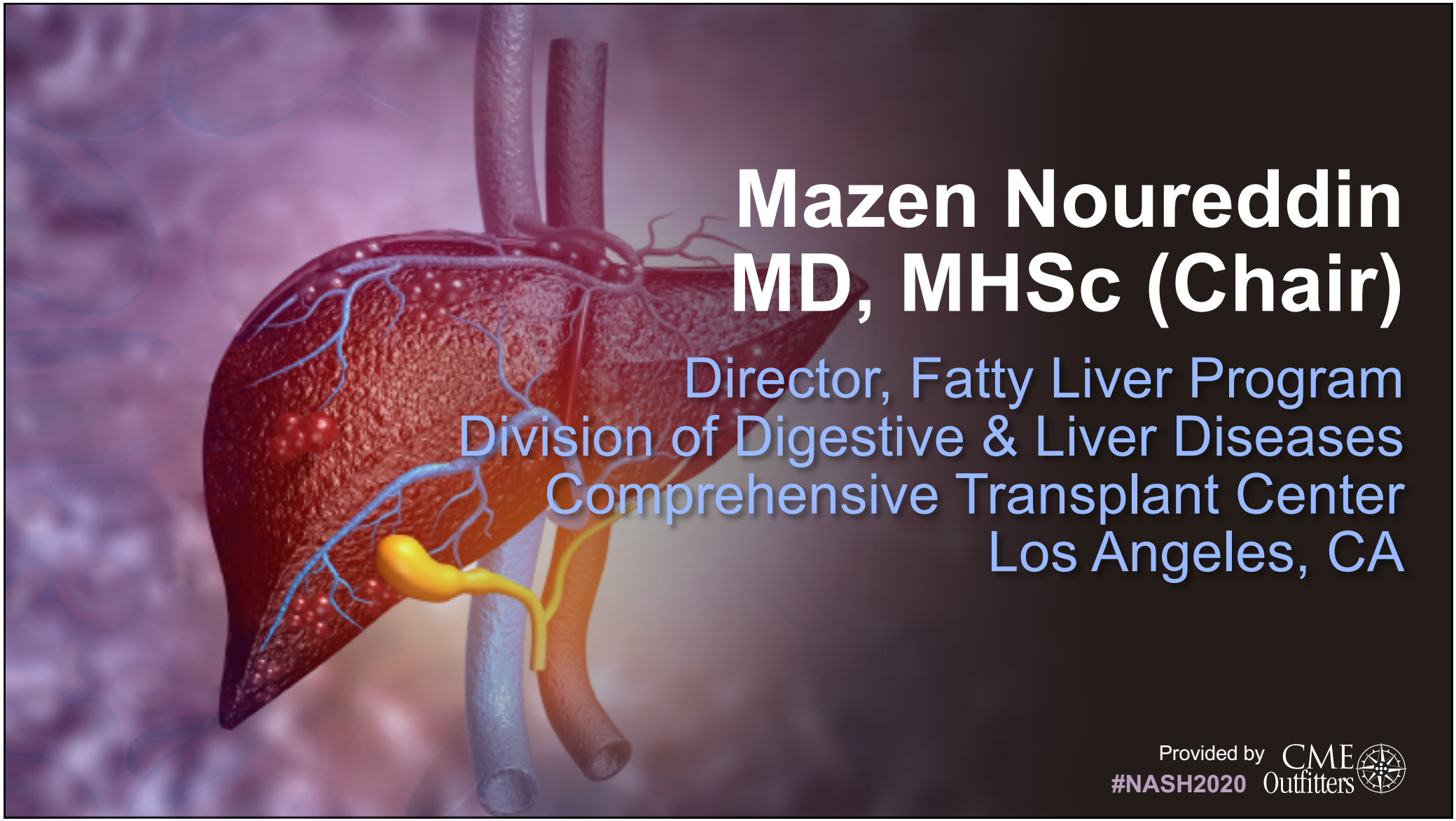

Mazen Noureddin MD, MHSc (Chair)

Director, Fatty Liver Program
Division of Digestive & Liver Diseases
Comprehensive Transplant Center
Los Angeles, CA

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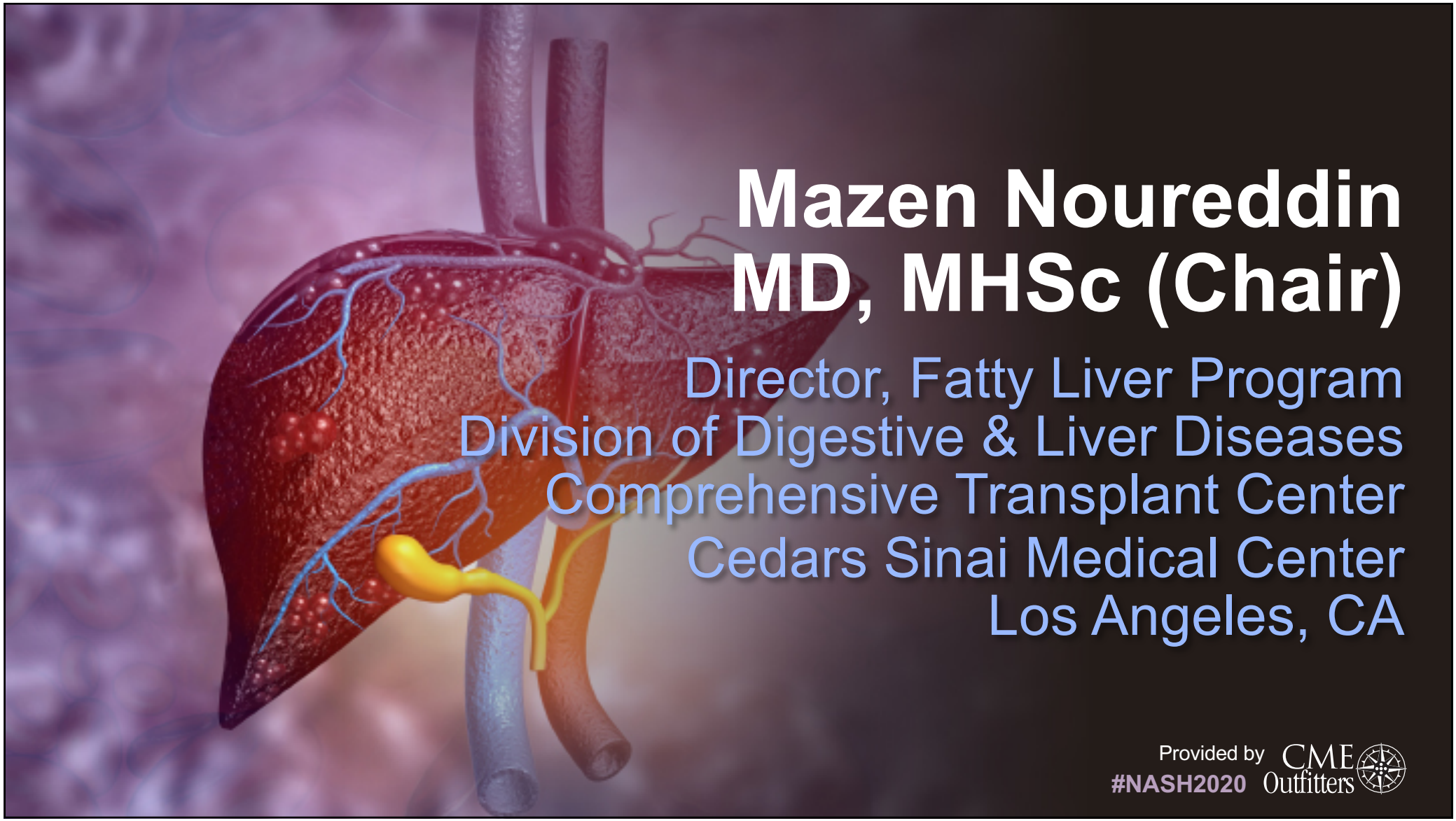

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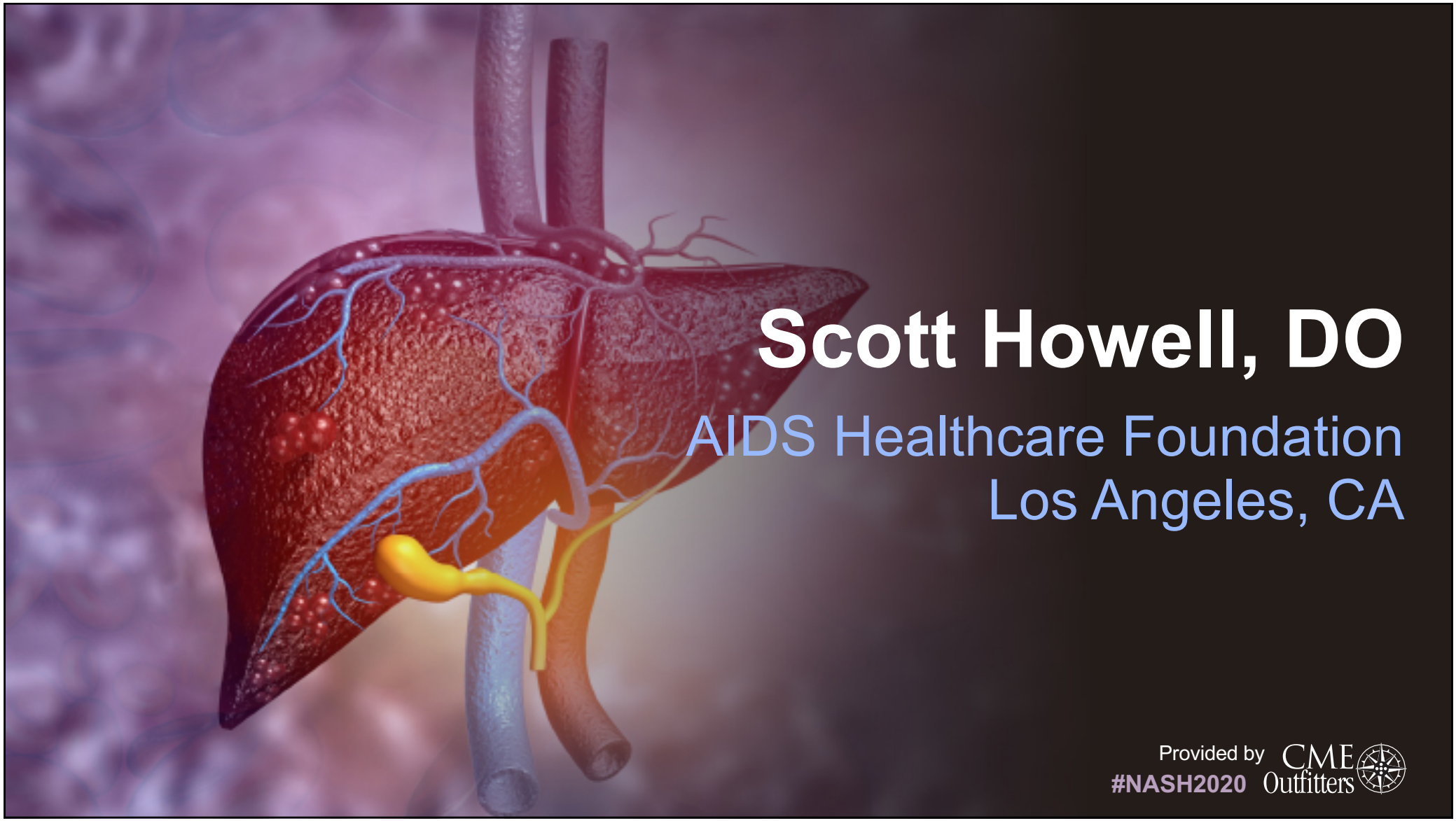

Scott Howell, DO

AIDS Healthcare Foundation
Los Angeles, CA

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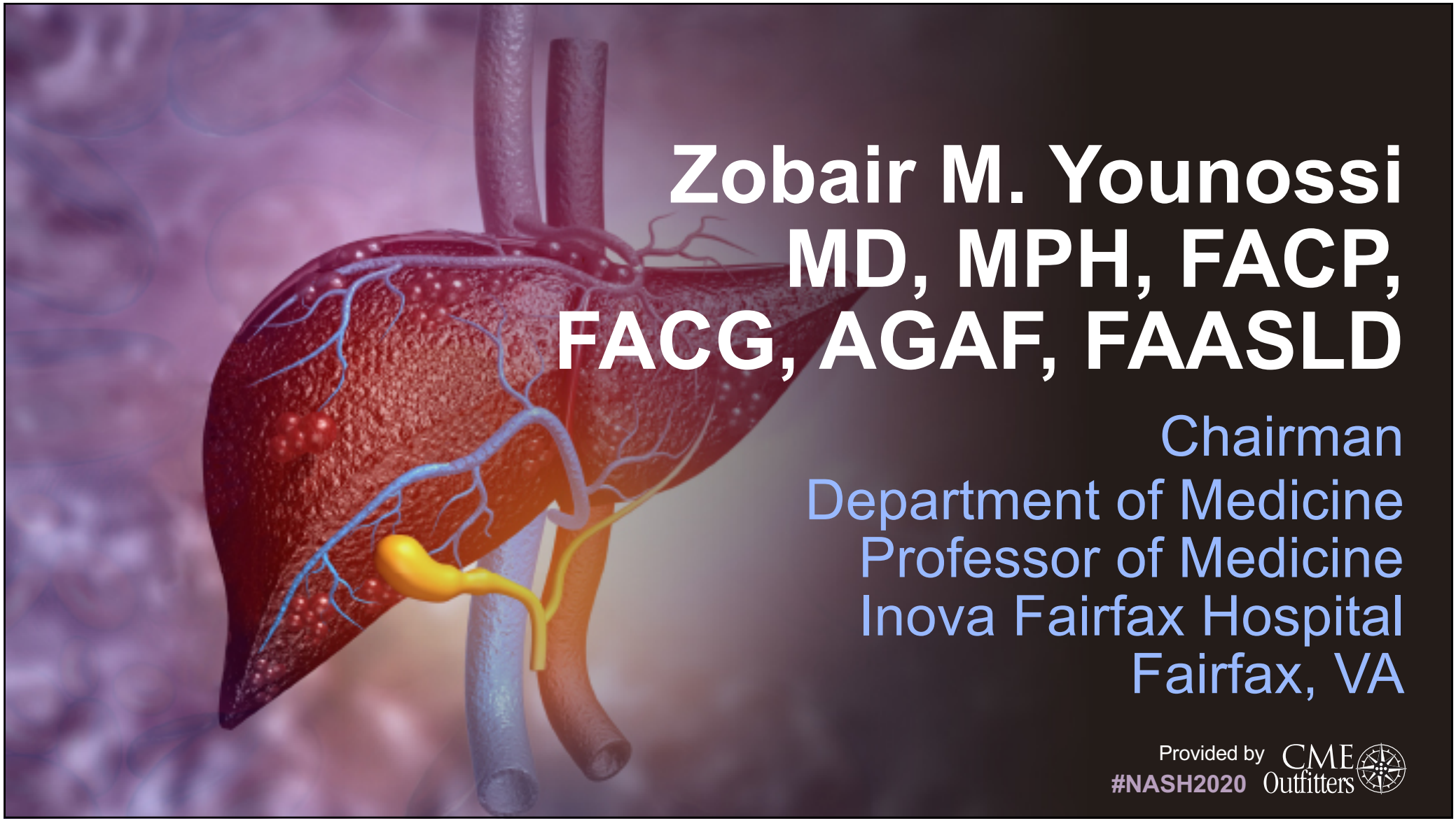

Zobair M. Younossi MD, MPH, FACP, FACG, AGAF, FAASLD

Chairman
Department of Medicine
Professor of Medicine
Inova Fairfax Hospital
Fairfax, VA

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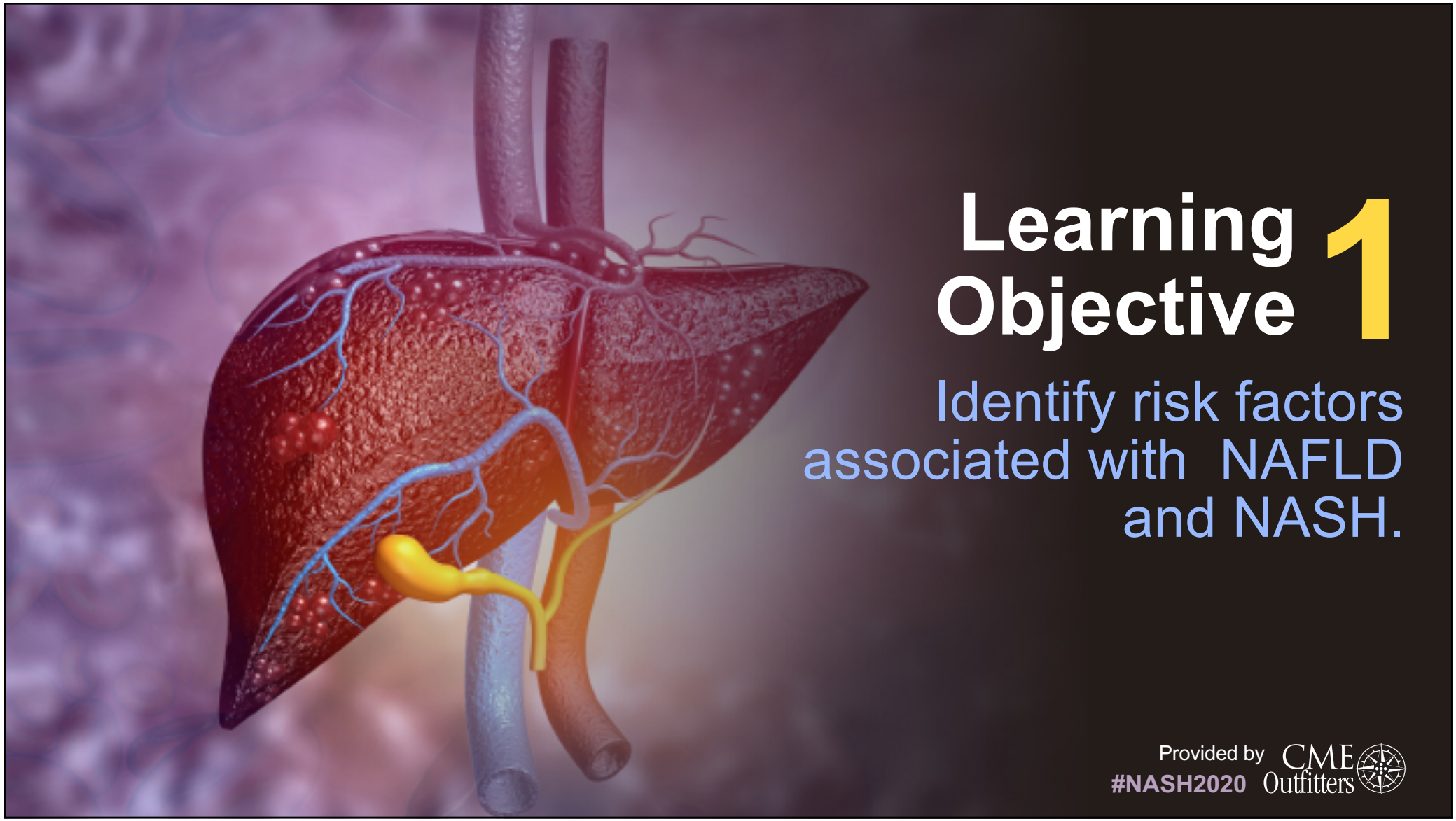
Learning Objective 1
Identify risk factors associated with NAFLD and NASH.
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Audience Response

In what proportion of at-risk patients do you screen for NAFLD?

A. 0%
B. 1-25%
C. 26-50%
D. 51-75%
E. 76-100%

George
59-year-old Mexican American male

George presents to review lab results from his recent physical

- **Medical History:** T2DM x 5 years, dyslipidemia x 2 years
- **Family History:** Mother had diabetes and father had HTN
- **Social History:** He doesn't exercise, but walks the dog daily
  - Works as attorney; drinks 3-4 beers on weekends and two glasses of wine with steak during dinners with clients
- **Prior Exam** was normal except for central obesity (BMI of 33 kg/m^2)
- **Symptoms:** Has some right upper quadrant discomfort
- **Medications:** Metformin 500 mg po twice a day and fish oil

BMI = body mass index; HTN = hypertension; T2DM = type 2 diabetes

George's Labs

Todays' Laboratory Values	
ALT	60 U/L
AST	65 U/L
Total Bilirubin	0.8 mg/dL
Albumin	4.0 g/dL
Platelets	180,000/µL
LDL	100 mg/dL
HDL	40 mg/dL
Triglyceride	240 mg/dL
Hgb A1C	6.9

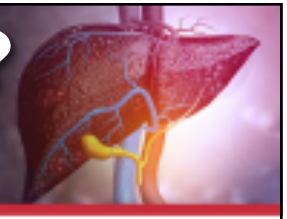
ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDL = low-density lipoprotein cholesterol; HDL = high-density lipoprotein; Hgb = hemoglobin

ARS Question #2

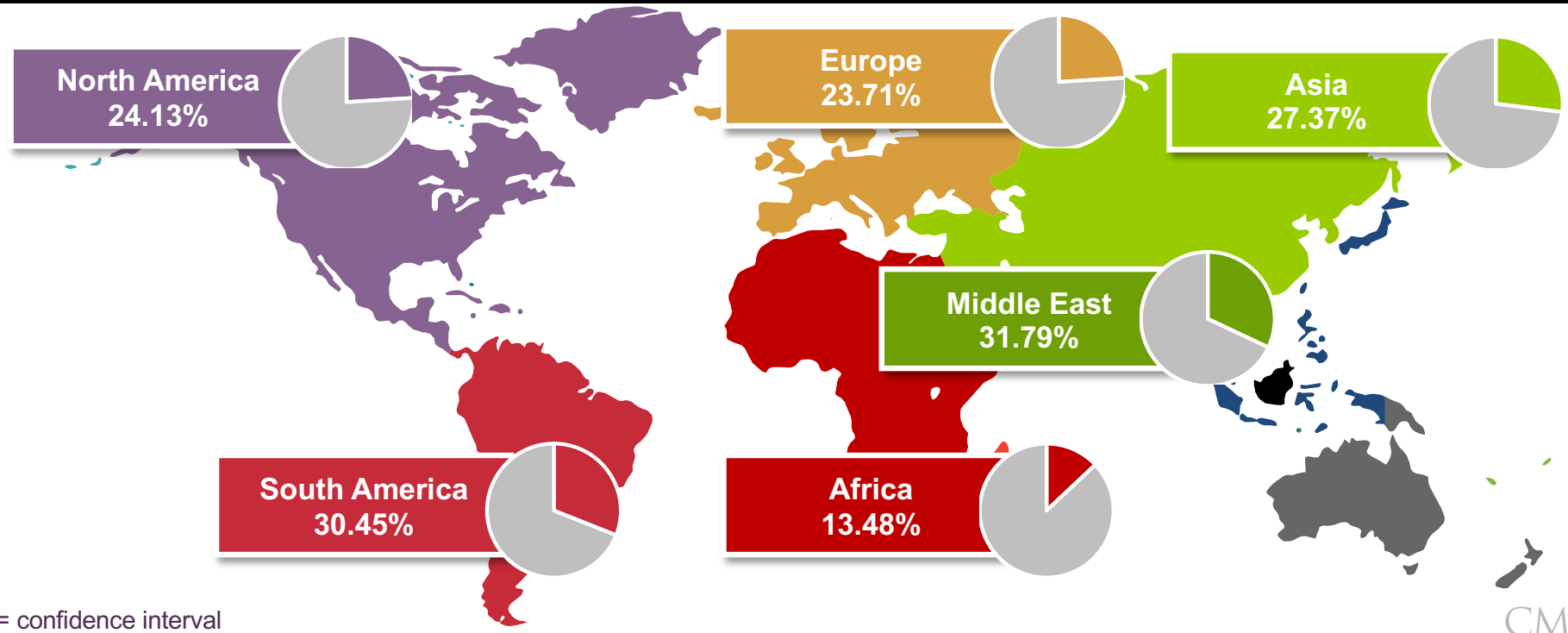
What would be your next step with George?

A. Consider changing T2DM treatment
B. Evaluate him for hepatitis
C. No change to his current meds but counsel him to reduce his drinking and increase exercise routine to address metabolic syndrome
D. Order an ultrasound of his liver to evaluate him for NAFLD
E. I don't know

Why Do We Have to Treat NAFLD and NASH? Disease Burden: Prevalence



- Global prevalence of NAFLD is 25.24% (95% CI: 22.10-28.65)
- Prevalence of NASH in general population is estimated between 1.5% and 6.45%



CI = confidence interval
Younossi ZM et al. *Hepatology*. 2016;64(1):73-84.

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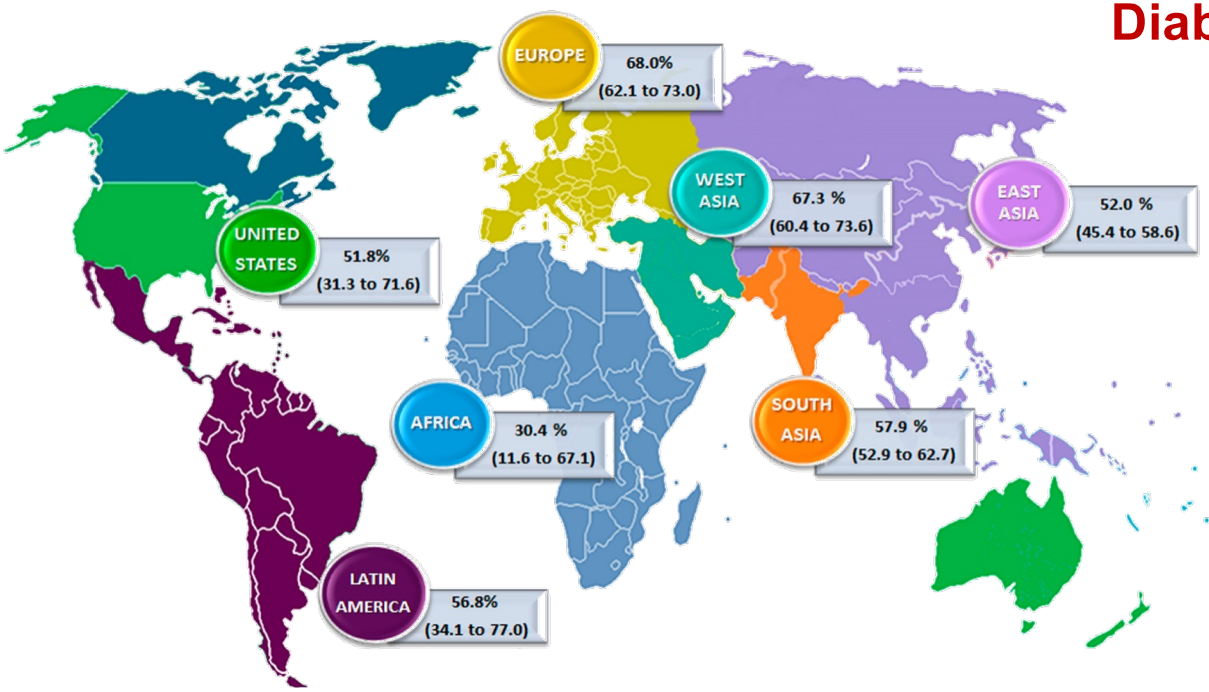
Disease Burden In Patients with Diabetes

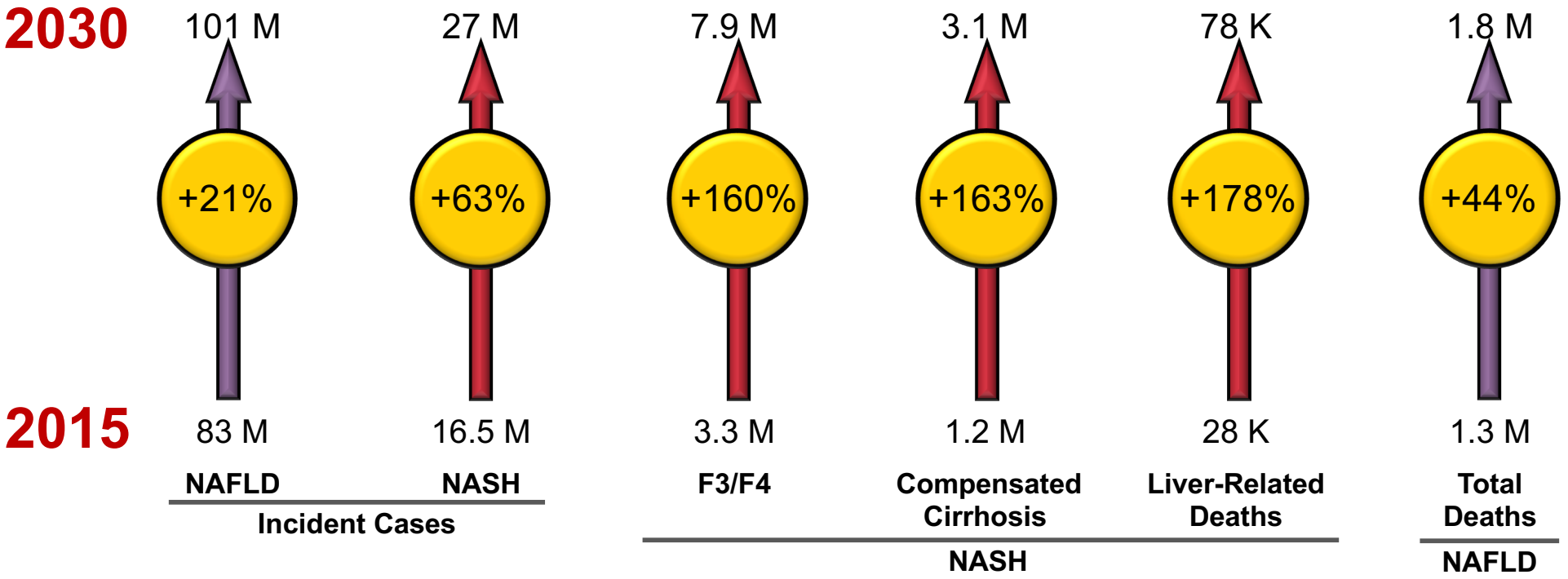


Diabetes makes everything worse

- Overall global NAFLD prevalence among diabetics is 73%
- Overall prevalence of advanced fibrosis (fibrosis ≥ F3) 17.2%
- ~2X increase in mortality in patients with cirrhosis, HCC, or liver transplant
- Total cost of NAFLD with T2DM in the U.S. over the next two decades is estimated to be $1.67 trillion

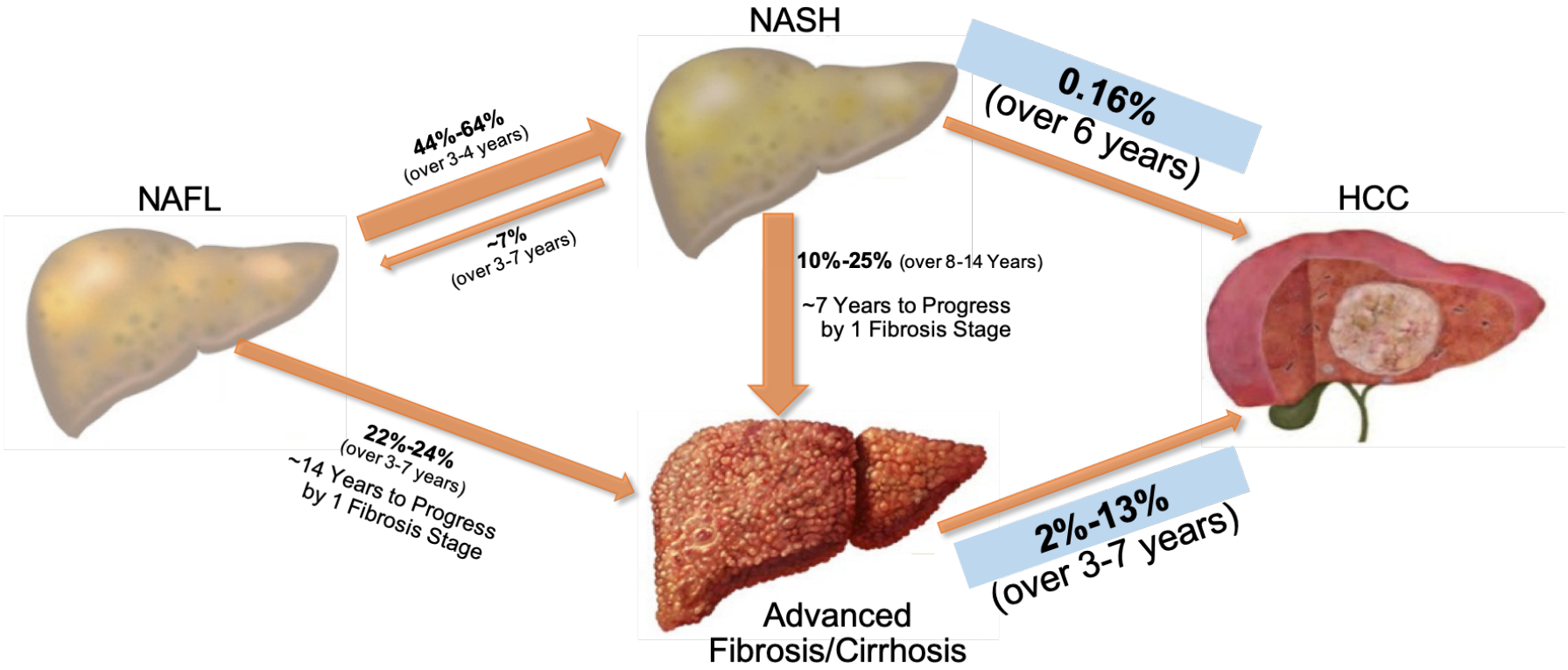
Nasrin Amiri A, et al. *Gastroenterol Hepatol Bed Bench*. 2017. 10:S1-S7. Younossi Z, et al. *Diabetes Care*. 2020.43:283-289

Changing Burden of NAFLD/NASH in The US



Estes C, et al. *Hepatology*. 2018;67:123-133.

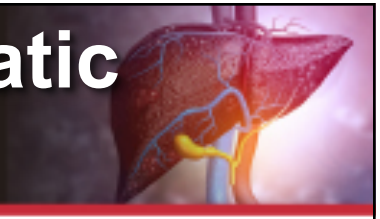
Natural History of NAFLD/NASH



HCC = hepatocellular carcinoma

Goh GB, et al. *Dig Dis Sci.* 2016;61:1226-1233; Singh S, et al. *Clin Gastroenterol Hepatol.* 2015;13:643-654; Noureddin-Vipani, et al. *Am J Gastroenterol.* 2018;113(11):1649-1659.

Most Patients With NAFLD Are Asymptomatic And In Primary Care



Abnormal liver enzymes alone are poor predictor of NAFLD or NASH

ACG considers normal health ALT ranges from 29 to 33 IU/U for males and 19 to 25 IU/l for females – lower than often reported in standard lab reports[4]

Serum ALT can be normal in up to 50% of NAFLD patients with NASH[1]

Serum ALT can be increased in up to 53% of NAFLD patients with no NASH[2,3]

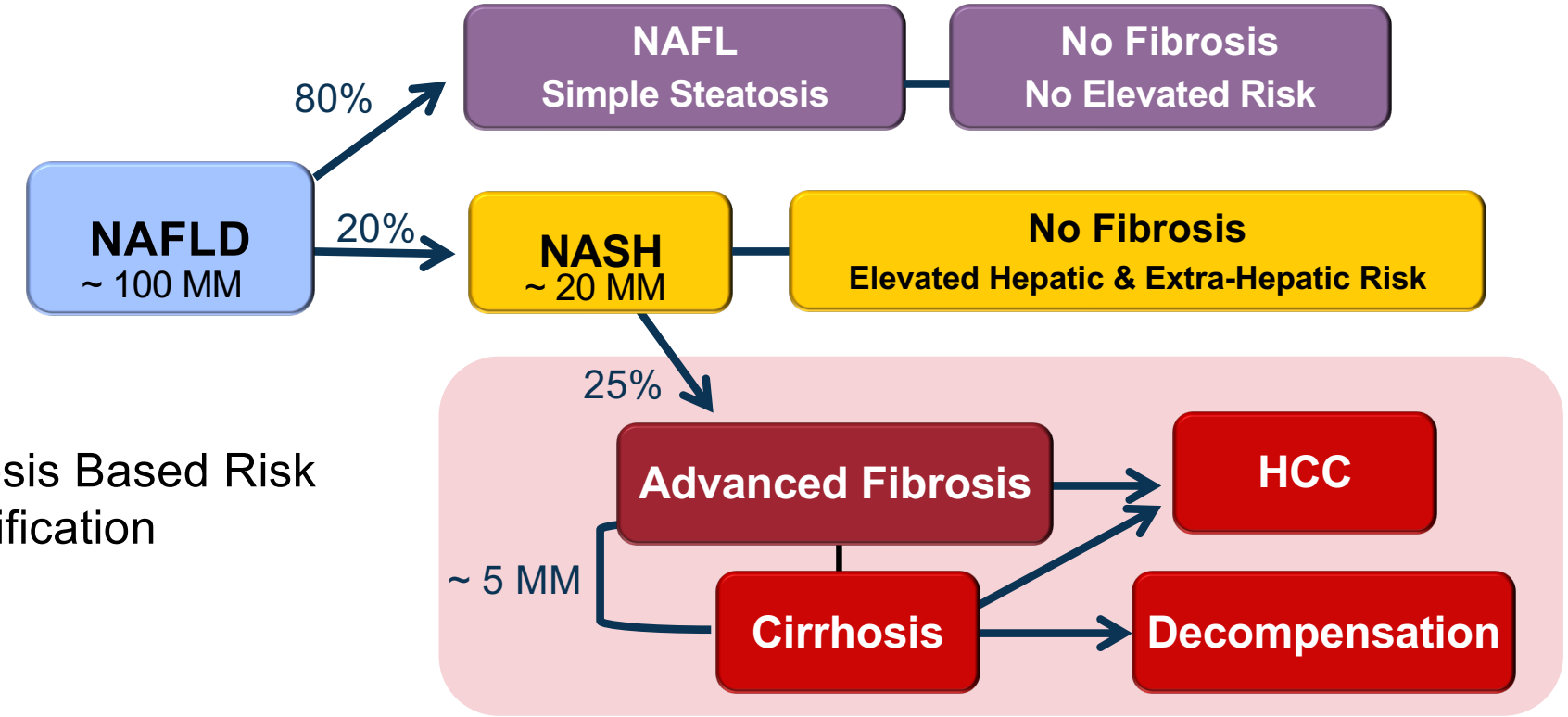
Therefore, serum ALT level alone is ***not*** predictive of NASH or fibrosis level[1-3]

- Normal ALT cannot rule out progression or NASH
- Increased ALT cannot predict NASH

ALT = alanine aminotransferase.

1. Fracanzani AL, et al. *Hepatology.* 2008;48:792-798. 2. Verma S, et al. *Liver Int.* 2013;33(9):1398-1405.
3. Torres DM, Harrison SA. *Nat Rev Gastroenterol Hepatol.* 2013;10(9):510-511; 4. Kwo, et al *AM J Gastroenterol.* 2017;112(1):18-35.

Risk Stratification Needed in Point of Care



Fibrosis Based Risk Stratification

Torres DM, et al. *Clin Gastroenterol Hepatol.* 2012;10(8):837-858.

The 20% Rule for Progression in F3/4 NASH

Bridging fibrosis → ~22% patients → 2 years → Cirrhosis → ~19% patients → 2 years → Hepatic decompensation

Key predictors of progression to cirrhosis

- Noninvasive fibrosis scores: ELF ≥ 9.8, Platelet count, FIB-4/NFS/APRI

Key predictors of decompensation/progression

- **Liver function**: MELD, Childs Pugh status, albumin
- **Portal hypertension**: Baseline HVPG ≥ 10 mm Hg, oesophageal varices
- **Non-invasive fibrosis scores**: ELF ≥ 11.3, FIB-4/NFS/APRI

ELF = enhanced liver fibrosis; FIB = fibrosis; NFS = NAFLD Fibrosis Score; APRI = AST to Platelet Ratio Index; MELD = model for end-stage liver disease; HVPG = hepatic venous pressure gradient

Loomba R, Adams LA. *Hepatology*. 2019. 70;1885-18888. Sanyal AJ, et al. *Hepatology*. 2019. 70:1913-1927

NAFLD & Metabolic Syndrome: Reciprocal Risk Factors

Primary Care

Cardiologist/Endocrinologist View of the world

Hepatologist View of the world

CVD/Cardiac Disease

T2DM & Metabolic Syndrome

NAFLD

Steatosis/ Steatohepatitis

ESLD/Hepatocellular Carcinoma (HCC)

- 610K deaths from CVD/yr*
- 735k MI/yr*

- 40k deaths from liver disease per year*

CVD/Cardiac Disease

*= CDC 2016.
CVD = cardiovascular disease; ESLD = end-stage liver disease, MI = myocardial infarction
Peters PFH, et al. *J Nutr Sci.* 2017;6:e15.

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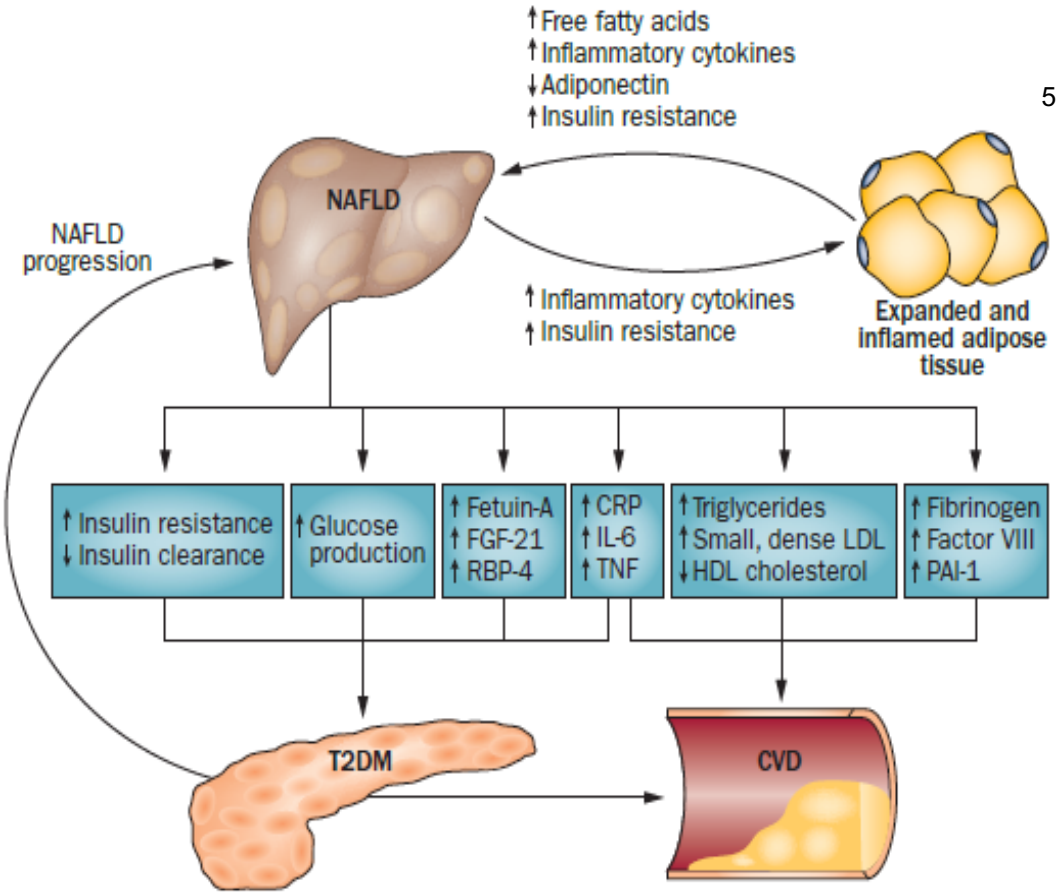
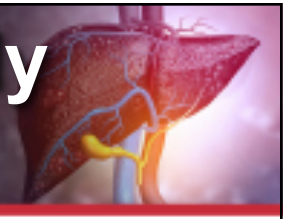
NAFLD – T2DM Disease Cycle

- T2DM and NAFLD have reciprocal risk factors
  - Diabetes more difficult to manage and NAFLD more likely to progress[1]
- NALFD is an independent predictor and associated with a > 2x increase of developing T2DM[2,3]
- T2DM has a 5.36 (4.41-6.51) age-adjusted hospital readmission rate for NAFLD compared to T2DM population[4]



1. Hazlehurst JM, et al. *Metabolism.* 2016;65:1096-1108; 2. Mantovi A, et al. *Diabetes Care.* 2018;41(2):372-383; 3. Targher G, et al. *Nat Rev Endocrinol.* 2018;14(2):99-114; 4. Wild, SH, et al. *J Hepatol.* 2016;64(6):1358-1364; 5. Antsee QM, et al. *Nat Rev Gastroenterol Hepatol.* 2013;10(6):330-344.

Diet Associations with NAFLD in an Ethnically Diverse Population the Multiethnic Cohort



(g/1,000 kcal/day)	NAFLD No Cirrhosis	NAFLD With Cirrhosis
Q 1st vs. 4th	OR (95% CI)	OR (95% CI)
Cholesterol		
≤ 75.4	1.00 (ref.)	1.00 (ref.)
> 121.4	1.09 (0.96-1.23)	1.52 (1.15-2.01)
P-value for trend	0.0889	0.0018
Fiber		
≤ 8.5	1.00 (ref.)	1.00 (ref.)
> 14.0	0.86 (0.75-0.98)	0.75 (0.55-1.02)
P-value for trend	0.0123	0.1018

- Nested case-control
- 2,974 NAFLD cases
  - 518 with cirrhosis
  - 2,456 without cirrhosis
- 29,474 matched controls
- Cases identified using Medicare claims ICD9/10
- Controls individually matched to cases on birth year, sex, ethnicity
- FFQ administered

FFQ = Food Frequency Questionnaire; kcal = kilocalorie.

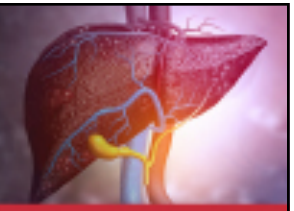
Noureddin M, et al. *Hepatology.* 2019 Sep 25. [Epub ahead of print].

Diet Associations with NAFLD in an Ethnically Diverse Population the Multiethnic Cohort (cont.)

(g/1,000 kcal/day)	NAFLD No Cirrhosis	NAFLD With Cirrhosis
Q 1ST vs. 4th	OR (95% CI)	OR (95% CI)
Total red meat ≤ 13.7 > 34.0	 1.00 (ref.) 1.10 (0.97-1.25)	 1.00 (ref.) 1.43 (1.08-1.90)
P-value for trend	0.1190	0.0121
Red unprocessed meat ≤ 9.3 > 24.1	 1.00 (ref.) 1.10 (0.97-1.25)	 1.00 (ref.) 1.52 (1.15-2.01)
P-value for trend	0.1223	0.0033
Processed red meat ≤ 3.0 > 10.0	 1.00 (ref.) 1.17 (1.03-1.32)	 1.00 (ref.) 1.31 (0.99-1.71)
P-value for trend	0.0097	0.1123
Total poultry ≤ 11.4 > 27.6	 1.00 (ref.) 1.19 (1.05-1.35)	 1.00 (ref.) 1.03 (0.79-1.35)
P-value for trend	0.0028	0.7717

Noureddin M, et al. *Hepatology.* 2019 Sep 25. [Epub ahead of print].

How Do You Make the Diagnosis?



Liver biopsy

- **Diagnosis of NASH requires the *joint presence of steatosis, ballooning and lobular inflammation***
- Diagnostic gold standard

Few symptoms

- Often asymptomatic
- Nonspecific symptoms (eg, right upper quadrant discomfort or fatigue)

Changes in liver enzymes

- Mildly elevated with ALT predominance
- Some patients may have elevated alkaline phosphatase

Aetiologies

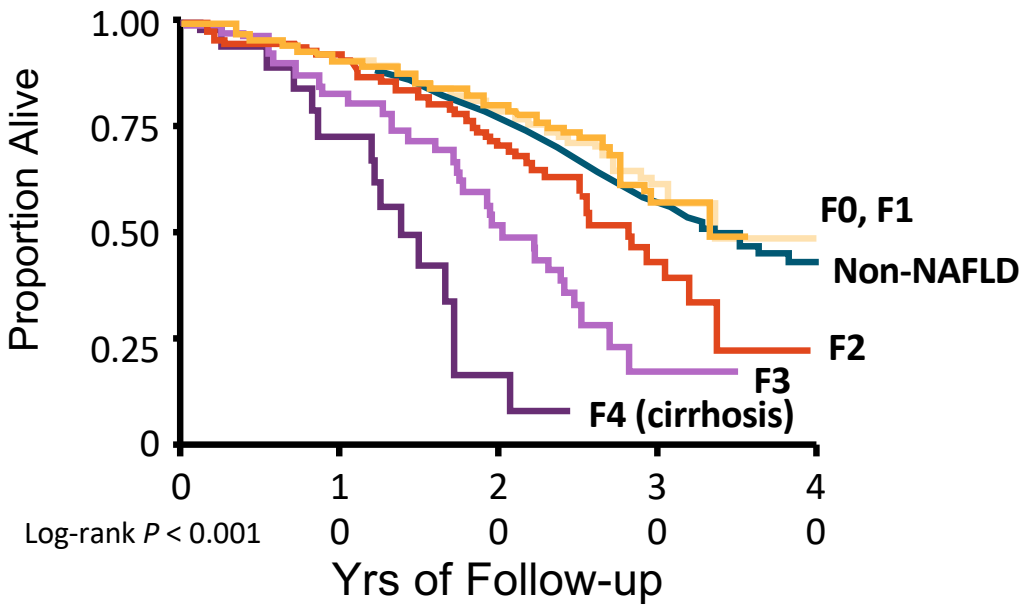
- No significant alcohol consumption
- No competing aetiologies for hepatosteatosis
- No coexisting causes of chronic liver disease

European Association for the Study of the Liver, et al. *J Hepatol* 2016;64:1388–1402; Stengel JZ, Harrison SA. *Gastroenterol Hepatol* 2006;2:440–449; Chalasani N, et al. *Hepatology* 2018;67:328-357.

Diagnosis: Goals for PCP

- Goal 1: Identify those with NASH
  - Having NASH increases the risk of progression of fibrosis
  - Identify treatment candidates[1]
- Goal 2: Identify those at risk for progressing to cirrhosis
  - Having advanced fibrosis is associated with increased mortality[1]

Retrospective Survival Analysis of 646 NAFLD Patients and Matched Controls[2]



1. Stål P. *World J Gastroenterol.* 2015;21(39):11077-11087; 2. Hagström H, et al. *J Hepatol.* 2017;67(6):1265-1273.

Let's Review George…

- **Medical history:** T2DM x 5 yrs, dyslipidemia x 2 yrs
- **Family history:** Mother had diabetes and father had HTN
- **Prior exam** was normal except for central obesity (BMI of 33 kg/m^2)
- **Symptoms:** Has some right upper quadrant discomfort
- **Medications:** Metformin 500 mg po twice a day and fish oil

Todays' Laboratory Values	
ALT	60 U/L
AST	65 U/L
Total Bilirubin	0.8 mg/dL
Albumin	4.0 g/dL
Platelets	180,000/µL
LDL	100 mg/dL
HDL	40 mg/dL
Triglyceride	240 mg/dL
Hgb A1C	6.9

ALT = alanine aminotransferase; AST = aspartate aminotransferase; HDL = high-density lipoprotein; HgB = hemoglobin; LDL = low-density lipoprotein.

ARS Question #3

What would be your next step with George *NOW*?

A. Consider changing T2DM treatment

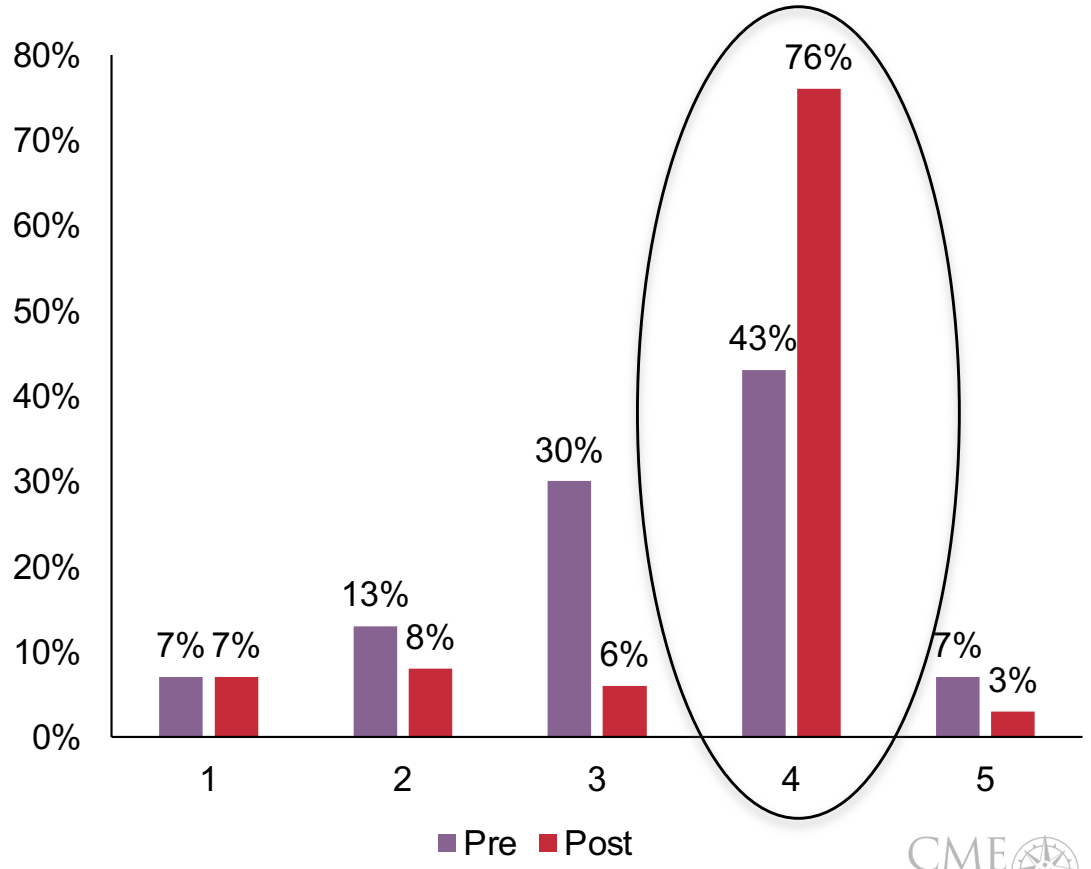
B. Evaluate him for hepatitis

C. No change to his current meds but counsel him to reduce his drinking and increase exercise routine to address metabolic syndrome

D. Order an ultrasound of his liver to evaluate him for NAFLD

What would be your next step with George *NOW*?

1. Consider changing T2DM treatment
2. Evaluate him for hepatitis
3. No change to his current meds but counsel him to reduce his drinking and increase exercise routine to address metabolic syndrome
4. Order an ultrasound of his liver to evaluate him for NAFLD (Correct)
5. I don't know



Graph reflects results recorded during the live activity on April 22, 2020.

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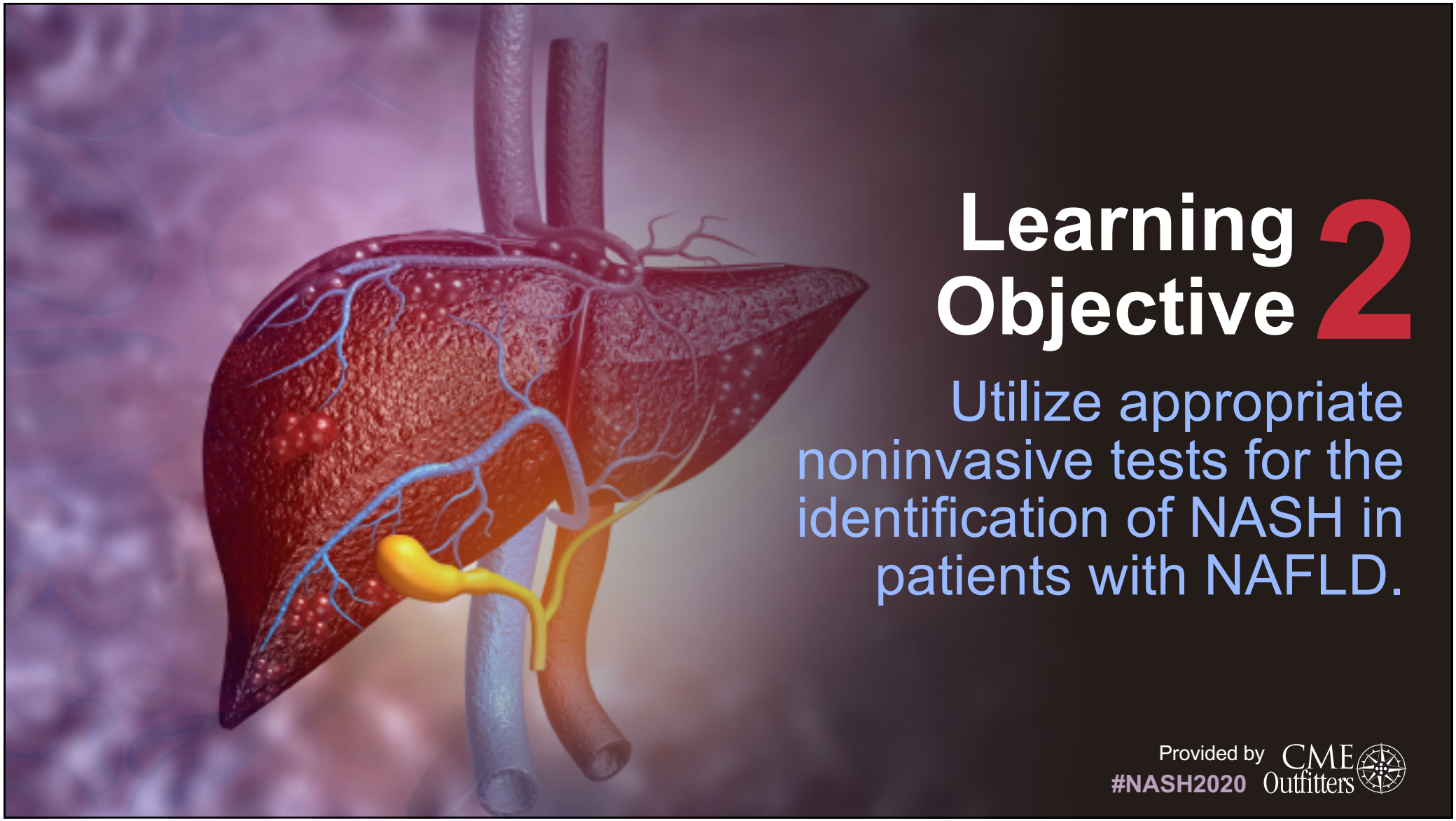
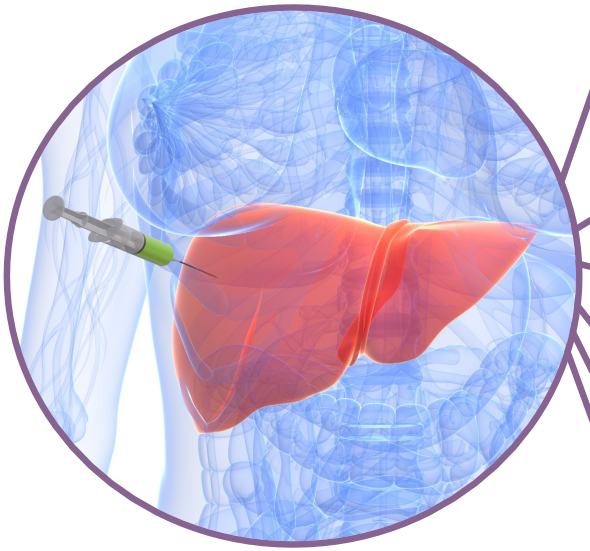

Learning Objective 2
Utilize appropriate noninvasive tests for the identification of NASH in patients with NAFLD.
Provided by CME Outfitters
#NASH2020

Indications for Liver Biopsy



- Metabolic syndrome
  - Obesity
  - ↑ TG
  - Low HDL
  - Impaired glucose tolerance
- High AST/ALT ratio
- Low platelet count or albumin level
- Cholecystectomy or bariatric surgery
- Old age
- Diabetes
  - Family history

Disadvantages of biopsies

- Sampling variability
- Pain
- Infection
- Bleeding
- Perforation
- Impractical for population management
- Death

TG = triglycerides

Non-invasive Diagnosis of NASH and NAFLD

Clinical/lab tests

- NAFLD fibrosis score
- FIB-4 index
- BARD score
- AST:ALT ratio
- AST: platelet ratio index
- Fibrotest
- Hepascore
- Fatty liver index
- Index of NASH

Imaging

- Ultrasound
- Computer tomography
- Magnetic resonance imaging
- Magnetic resonance spectroscopy
- Transient elastography
- Acoustic radiation force impulse
- Magnetic resonance elastography

Biomarkers

- Hyaluronic acid
- CK-18
- Fucosylated haptoglobin (Fuc-Hpt)
- Macroglobulin-2 binding protein (Mac-2bp)
- Fuc-Hpt + Mac-2bp
- ELF score
- FIBROSpect®

Papagianni M, et al. *World J Hepatol*. 2015;7:638–48; Golabi P, et al. *Expert Rev Gastroenterol Hepatol*. 2016;10:63–71.

ARS Question #4

George, 59 yo Mexican American male

- FIB-4: 2.1
- NFS: -1.1

Based on his FIB-4 and NFS, which risk stratification would George fall into?

A. Low risk
B. Intermediate risk
C. High risk
D. I don't know

FIB-4 = fibrosis 4; NFS = NAFLD fibrosis score

Risk Stratification

Rule-out advanced fibrosis (FIB-4 or NAFLD Fibrosis Score)

FIB-4 < 1.3
NFS < –1.455
NPV 88–95%

↓ 55–58%

Low-risk

↓

No further assessment
Repeat evaluation
at 1 year

FIB-4 : 1.3–3.25
NFS: −1.455–0.672

↓ 30%

Intermediate-risk

FIB-4 > 3.25
NFS > 0.672
PPV 75–90%

↓ 12–15%

High-risk

↓

Next step:
elastography or
ELF/FIBROspect

NPV = negative predictive value; PPV = positive predictive score
Tapper EB, Loomba R. *Nat Rev Gastroenterol Hepatol*. 2018;15:274-282.

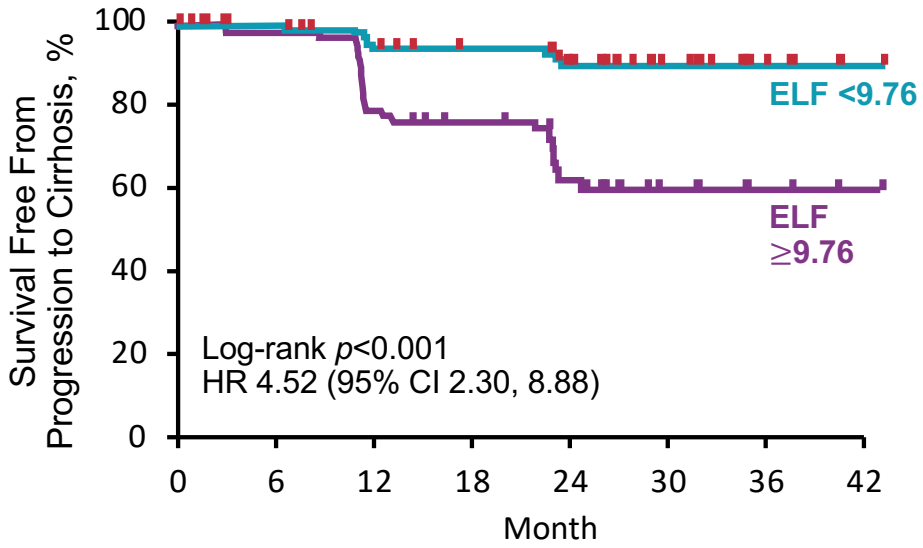
ARS Question #5

In a patient with NAFLD and bridging fibrosis, what cutpoint predicts high risk of progression to cirrhosis?

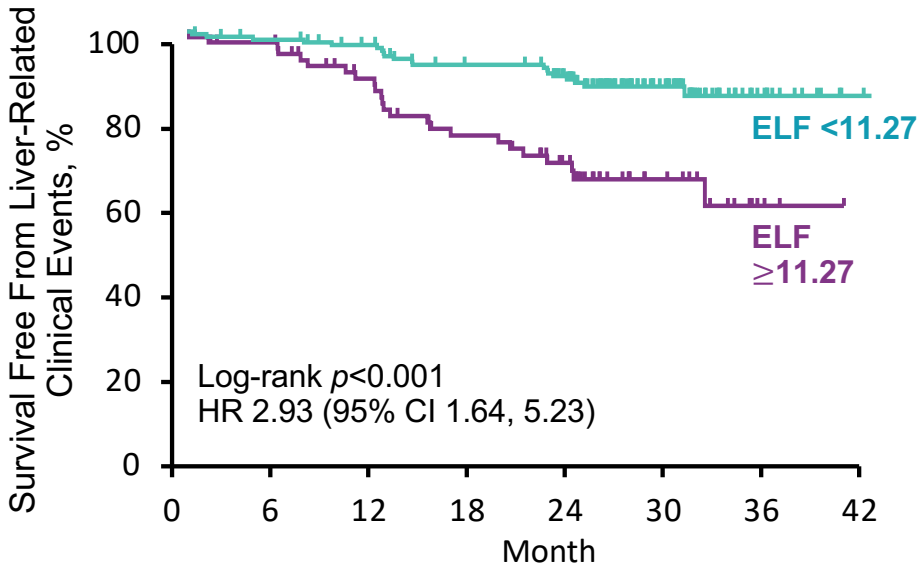
A. ELF ≥ 8.8
B. ELF ≥ 9.8
C. ELF ≥ 11.3
D. ELF ≥ 14.0

ELF Predicts Progression More Accurately than Biopsy

Progression to Cirrhosis



Liver-Related Clinical Events



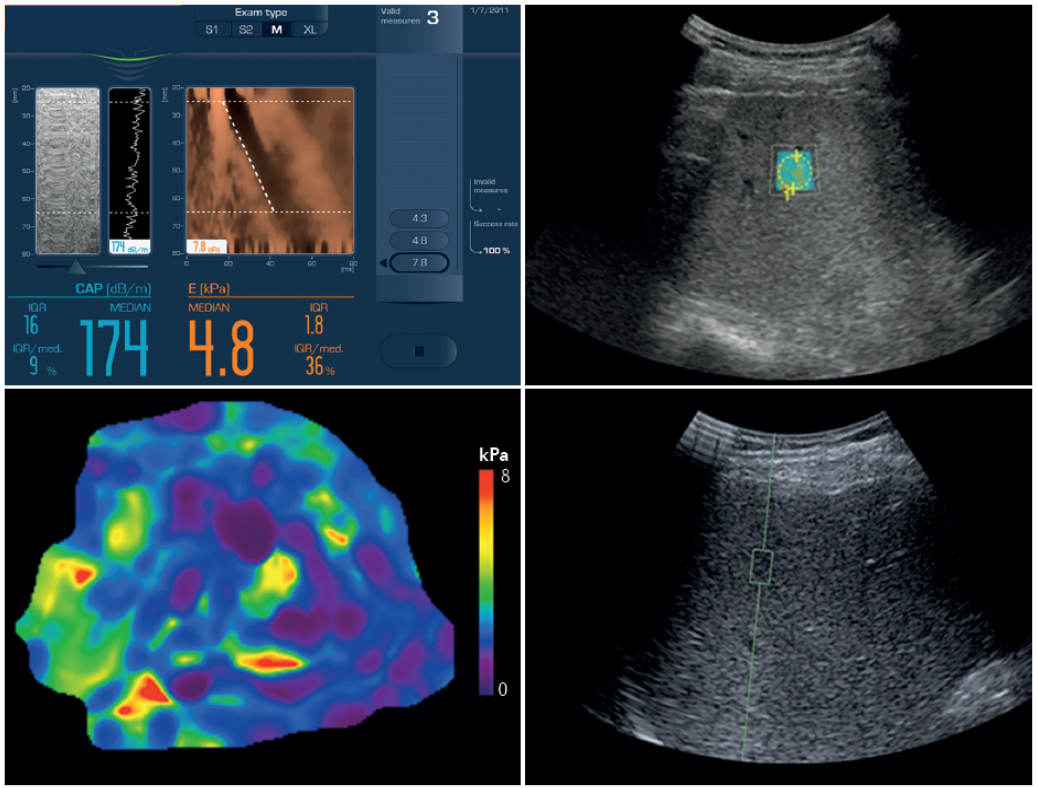
Higher baseline ELF and greater change in ELF were associated with increased risk of progression to cirrhosis and liver-related clinical events

CI = confidence interval; ELF = enhanced liver fibrosis; HR = hazard ratio

Sanyal AJ, et al. *Hepatology*. 2019;70:1913-1927

Elastography-Based Methods to Estimate Liver Stiffness

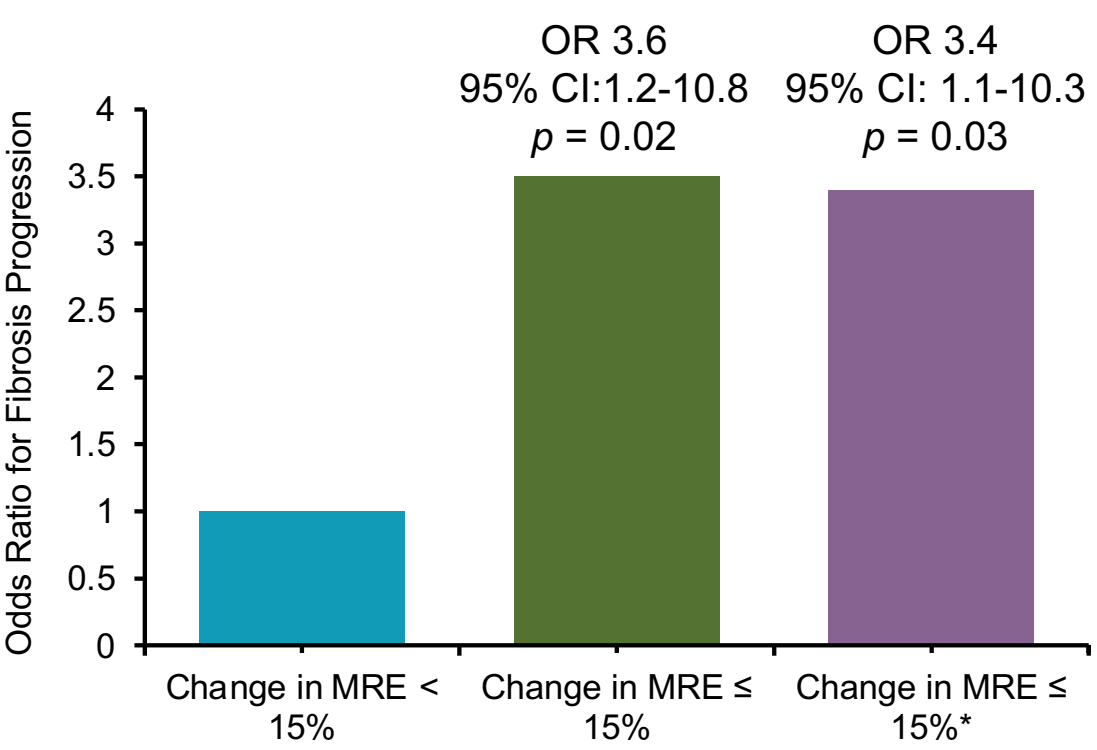
- VCTE (FibroScan) is most widely used
  - ≥10 images are required
  - Accurate for stages F3–4
  - Can estimate steatosis when used with CAP
- SWE/ARFI can be used to measure stiffness in single ROI
- MRE measures stiffness across multiple ROIs

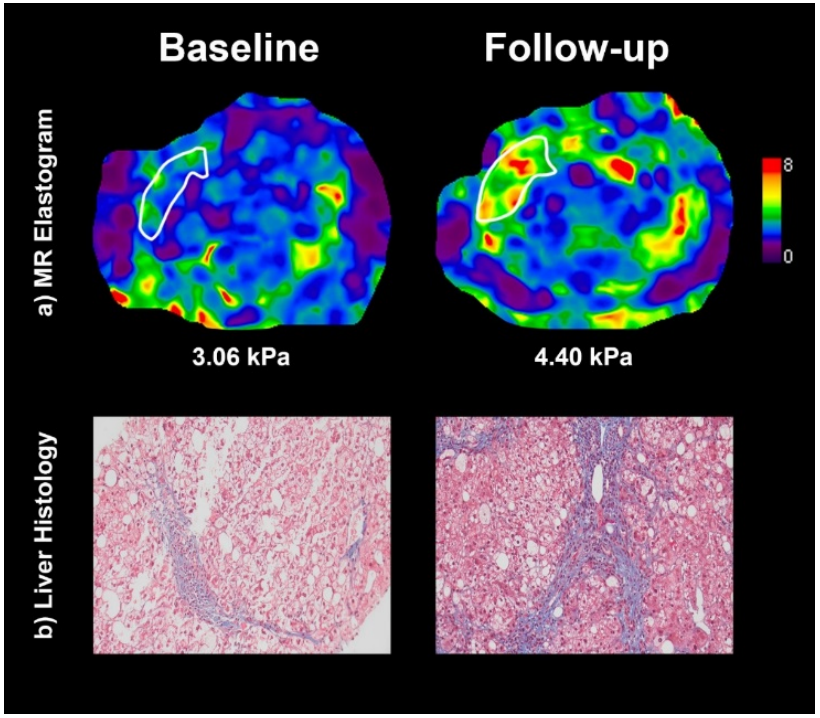


ARFI = acoustic radiation force impulse; CAP = controlled attenuation parameter; MRE = magnetic resonance elastography; ROI = region of interest; SWE = shear wave elastography

Tapper EB, Loomba R. *Nat Rev Gastroenterol Hepatol.* 2018;15:274–282.

15% Increase in MRE is Associated with Higher Odds of Fibrosis Progression





*Adjusted for age, sex, and BM
MRE = Magnetic resonance elastography
Almera VH, et al. *Hepatology.* 2020.71:849-860.

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Which Test is Better?

- FIB-4 is better than NFS
- VCTE is better than FIB-4
- MRE is better than VCTE

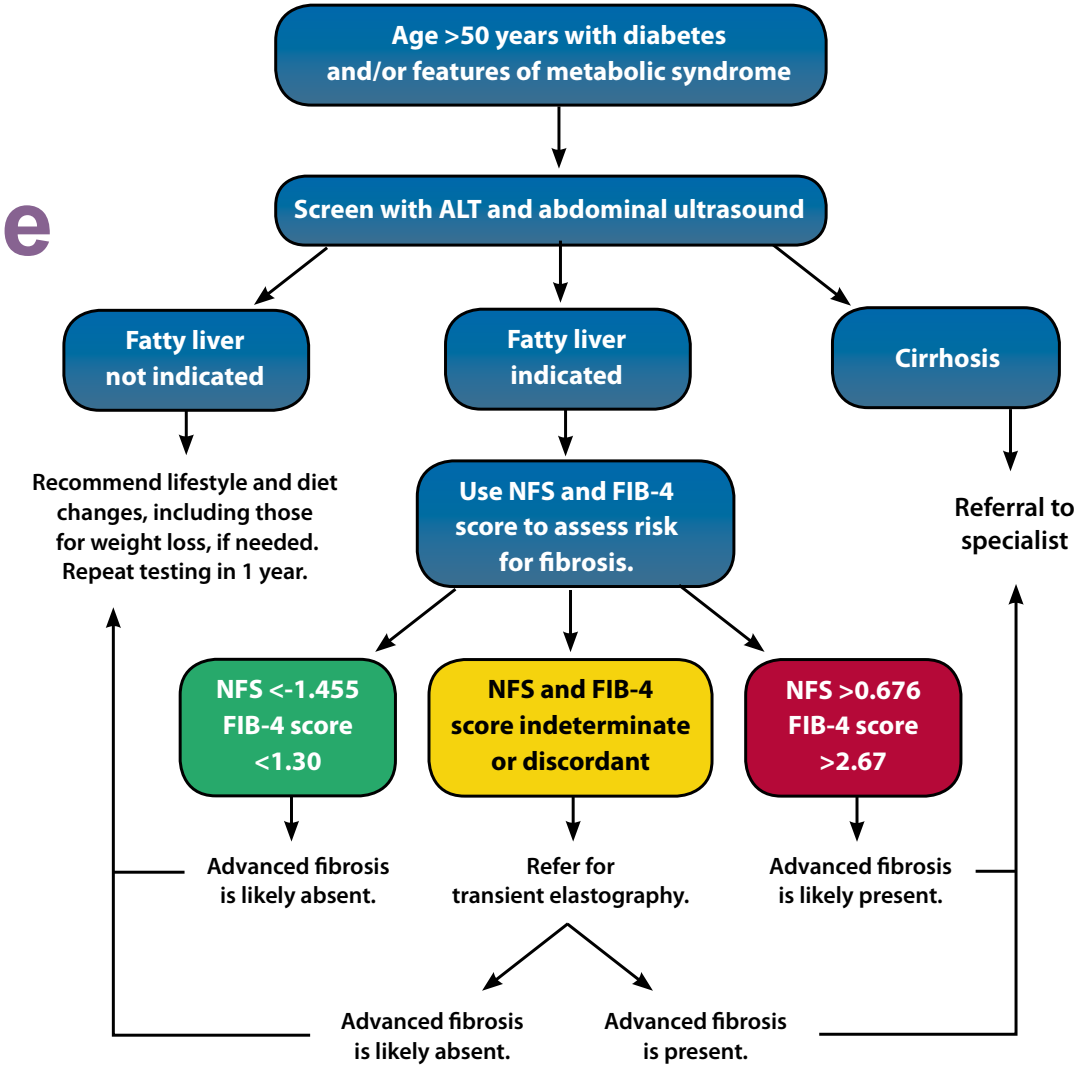
Efficiency of combining biomarkers

FIB-4 followed by ELF and/or VCTE (FibroScan) nearly eliminated the need for liver biopsy and accurately identified patients with advanced fibrosis due to NASH with misclassification rates similar to liver biopsy

VCTE = vibration-controlled transient elastography

Staufer K, et al. *United European Gastroenterol J*. 2019;7:1113–1123. Dulai P, et al. *Hepatology*. 2016. 65:1006-1016.

Screening and Testing in Clinical Practice



Pandyarajan V, et al. *Gastroenterol Hepatol*. 2019;15(7):357-365.

Results

George, 59 yo Mexican American male

- FIB-4: 2.1
- NFS: -1.1

Based on his FIB-4 and NFS, which risk stratification would George fall into?

A. Low risk
B. Intermediate risk
C. High risk

Results

George, 59 yo Mexican American male

- FIB-4: 2.1
- NFS: -1.1

Based on his FIB-4 and NFS, which risk stratification would George fall into?

A. Low risk
B. Intermediate risk
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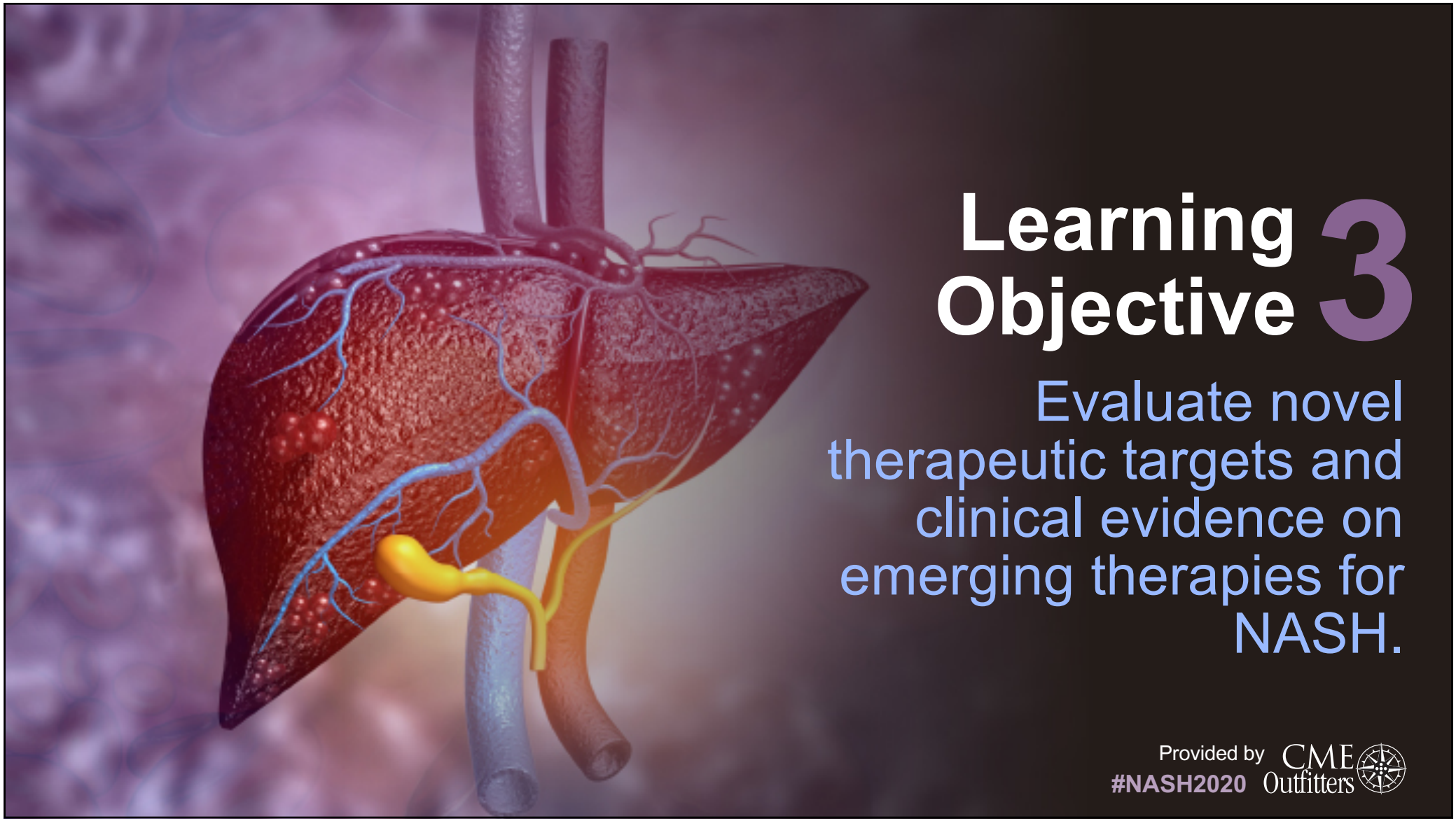
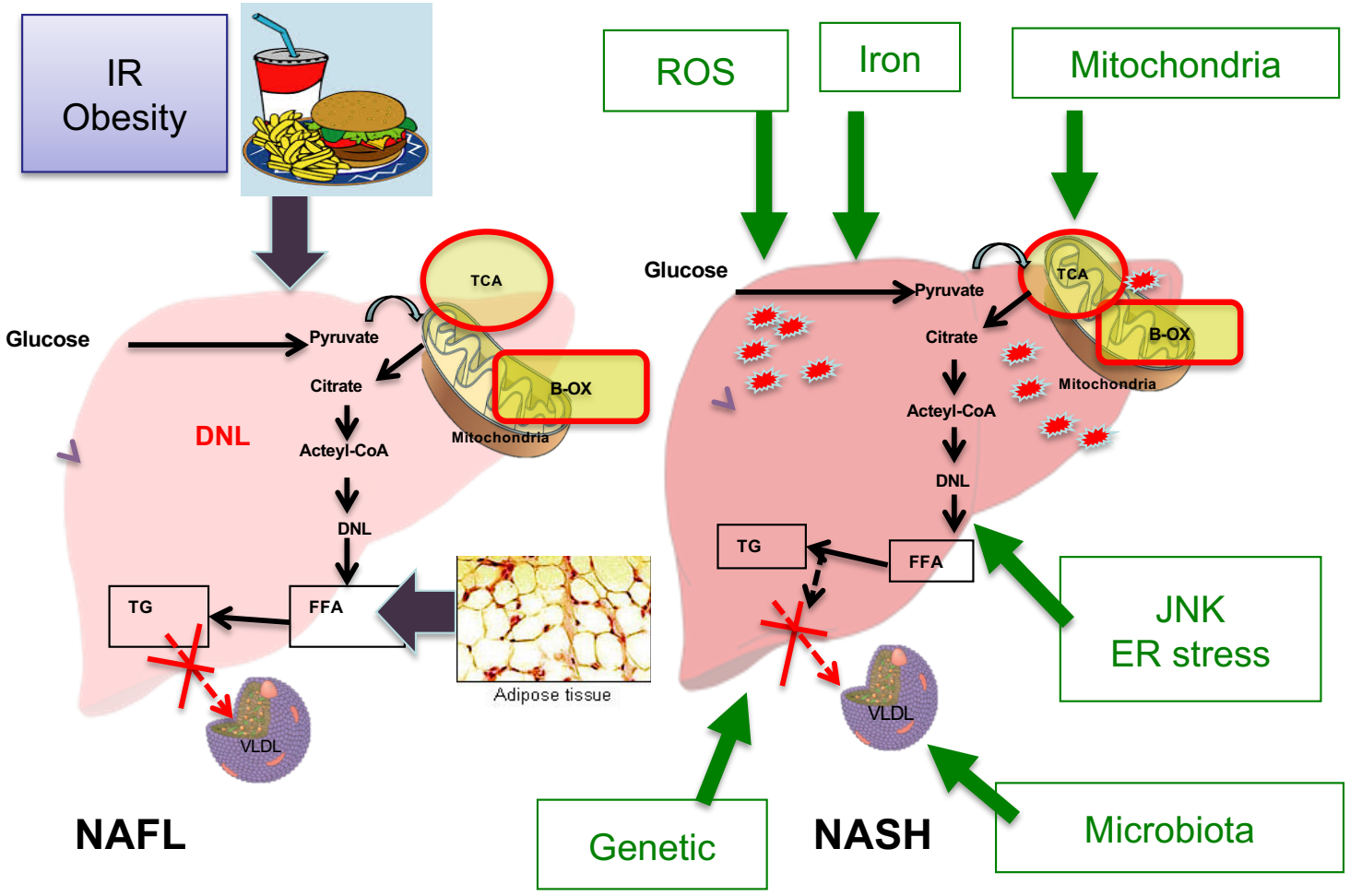
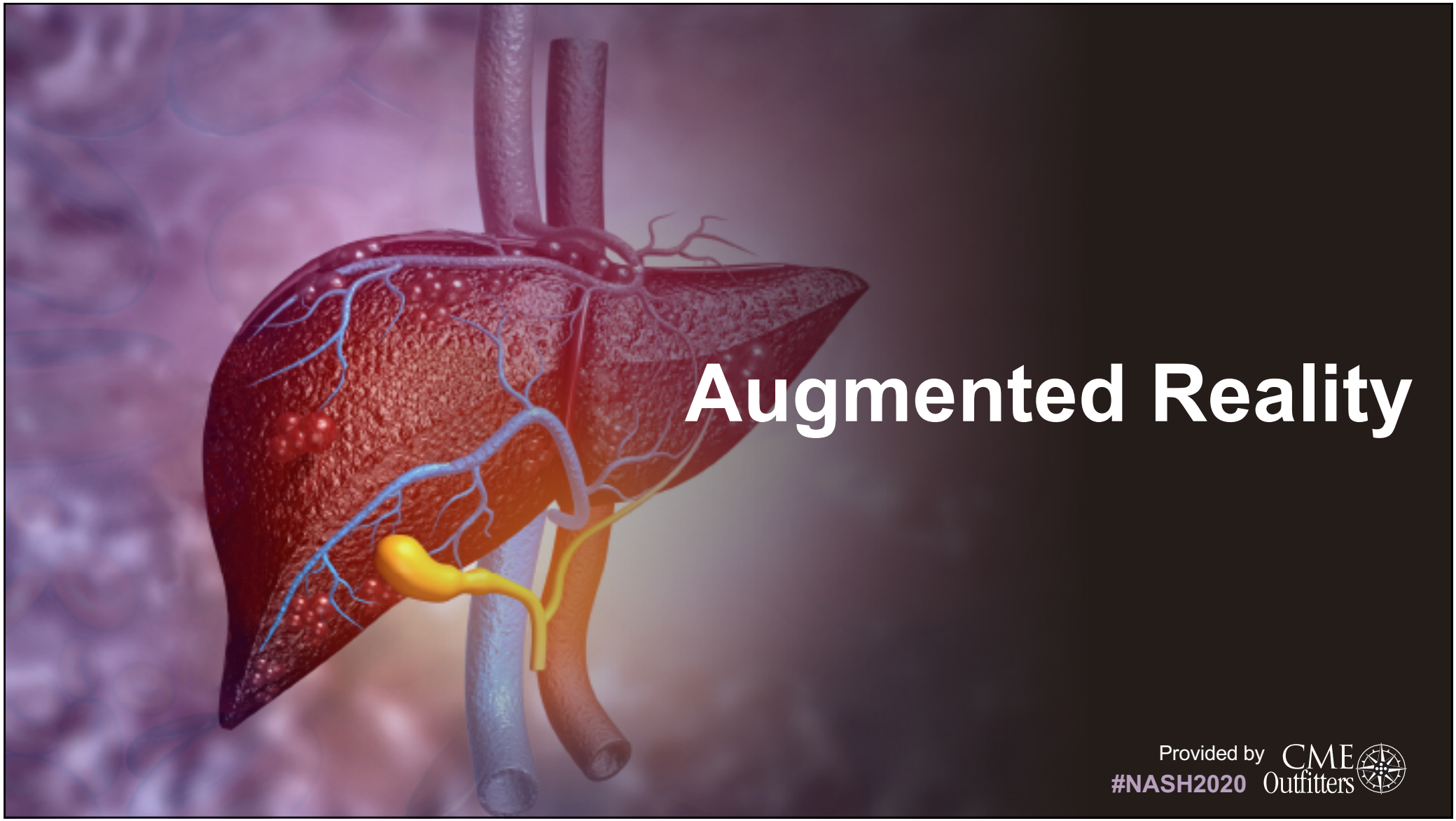

Learning Objective 3
Evaluate novel therapeutic targets and clinical evidence on emerging therapies for NASH.
Provided by CME Outfitters
#NASH2020

NAFLD:
Pathogenesis

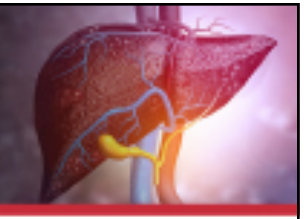


DNL = differential non-linearity; ER = endoplasmic reticulum; FFA = free fatty acid; IR = insulin resistance; JNK = c-Jun N-terminal kinases; ROS = reactive oxygen species; TCA = trichloroacetic acid; TG = thyroglobulin; VLDL = very low density lipoprotein

Noureddin M, et al. *Exp Bio Med*. 2015;240(6):809-820.


Augmented Reality
Provided by
CME Outfitters
#NASH2020

If Standard Treatment is Unsuccessful, What Future Options Exist?



Targets related to insulin resistance and/or lipid metabolism → **Targets related to lipotoxicity and oxidative stress** → **Targets related to inflammation and immune activation** → **Targets related to cell death (apoptosis and necrosis)** → **Targets related to fibrogenesis and collagen turnover**

PPARy: Pioglitazone
GLP-1: Liraglutide, Semaglutide
MPCi: PXL065
SGLT1/2: LIK066
GLP-1/GR: MEDI0382
KHKi: PF-06835919
ACCi: GS-0976, PF-05221304
DGAT2i: PF-06865571
SCD1: Aramchol
FGF21: BMS-986036

PPARα/d: Elafibranor
PPAR$\alpha/d/\gamma$: IVA337
PPARα/γ: Saroglitazar
THRβ: MGL-3196
mTOR: MSDC-0602K
FXR: Obeticholic Acid, GS-9674, LJN-45,LMB-763
TGR5: INT-767,INT-777
ASBTi: Volixibat
FGF19: NGM282
AMPKi: PXL770
VitaminE

CCR2/5: Cenicriviroc
AOC3: BI 1467335
TLR4: JKB-121
Anti-LPS: IMM-124E

ASK1: Selonsertib
Caspase: Emricasan

LOXL2: Simtuzumab
Galectin: GR-MD-02

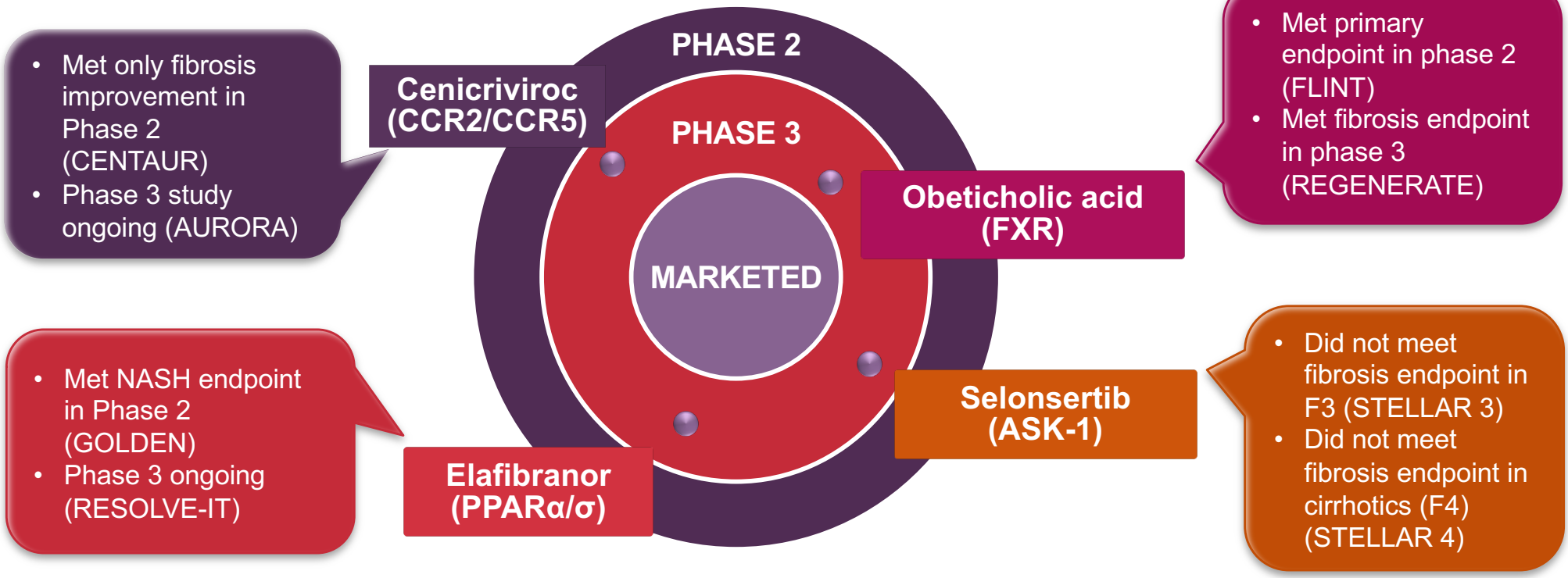
Younossi ZM, et al. *Hepatology.* 2018;68(1):361-371.

ARS Question #7

Which phase 3 trial met primary endpoint of fibrosis improvement?

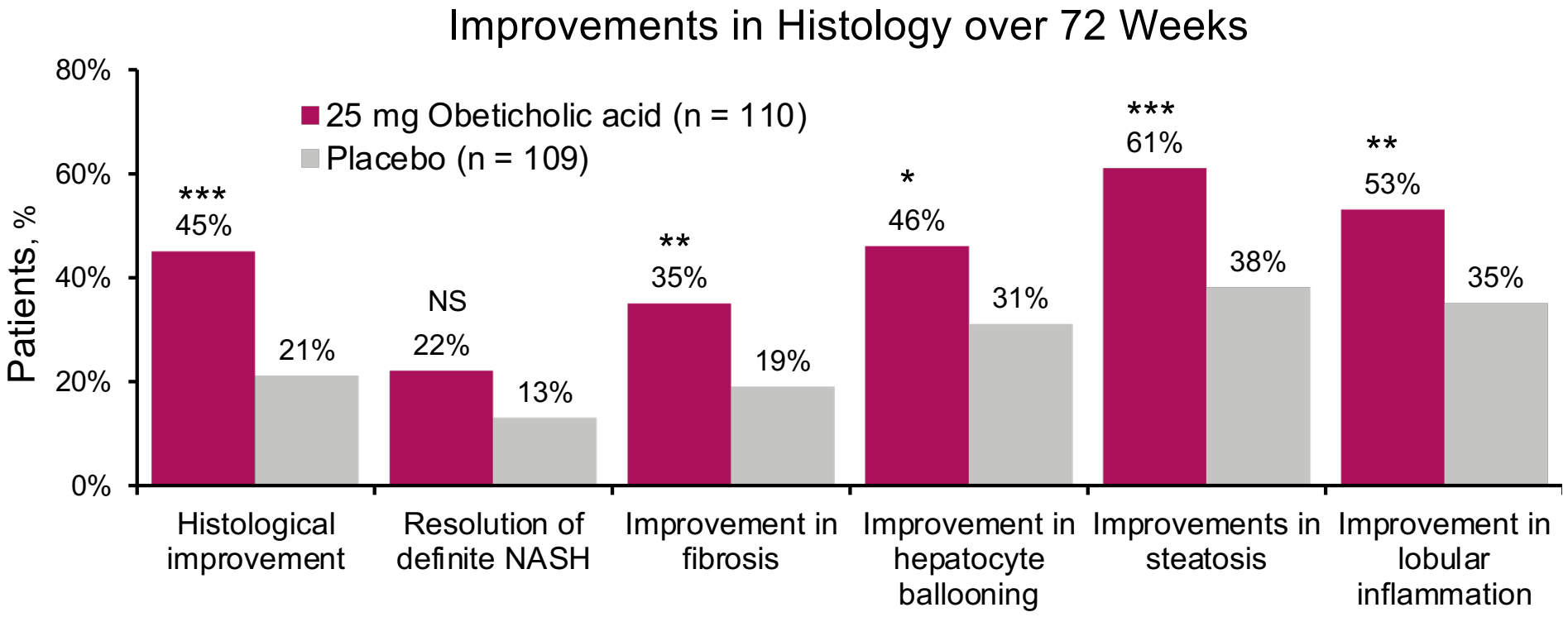
A. AURORA (cenicriviroc)
B. RESOLVE-IT (elafibranor)
C. REGENERATE (obeticholic acid)
D. STELLAR-4 (selonsertib)

Regimens in Phase 3 Clinical Trials for Treatment of NASH



Younossi ZM, et al. *Hepatology.* 2018;68(1):361-371.

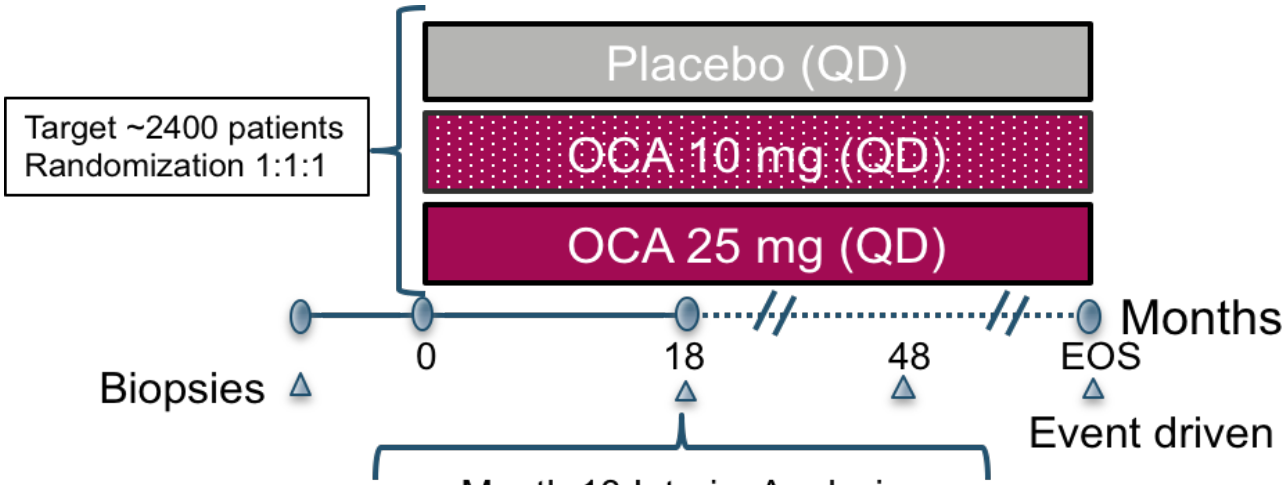
Obeticholic Acid (OCA): FLINT Study



NS = not significant; *p value ≤ 0.05; ** p value ≤ 0.01; *** p value ≤ 0.001

Neuschwander-Tetri BA, et al. *Lancet*. 2015;385:956-965;

Obeticholic Acid: REGENERATE Design

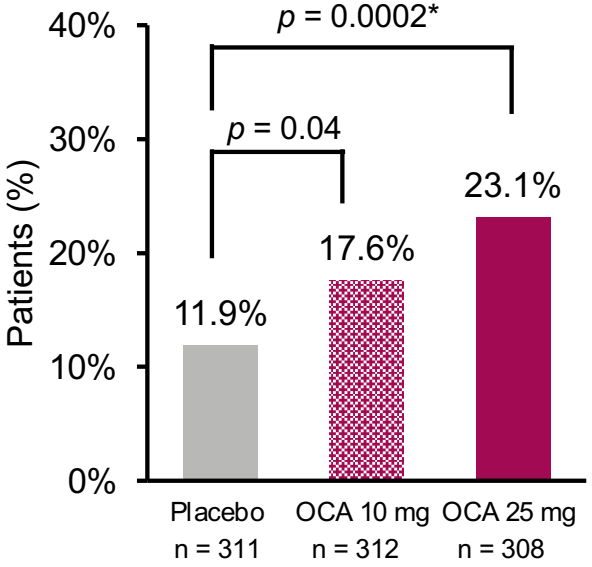


Study success was defined as achievement of one of the 2 primary endpoints

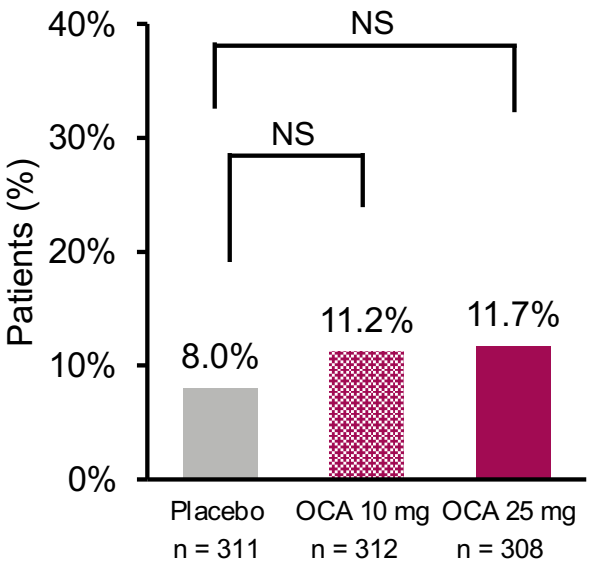
Ratziu V, et al. *Contemp Clin Trials.* 2019. 84:105803. Epub: https://doi.org/10.1016/j.cct.2019.06.017

Obeticholic Acid: REGENERATE Results

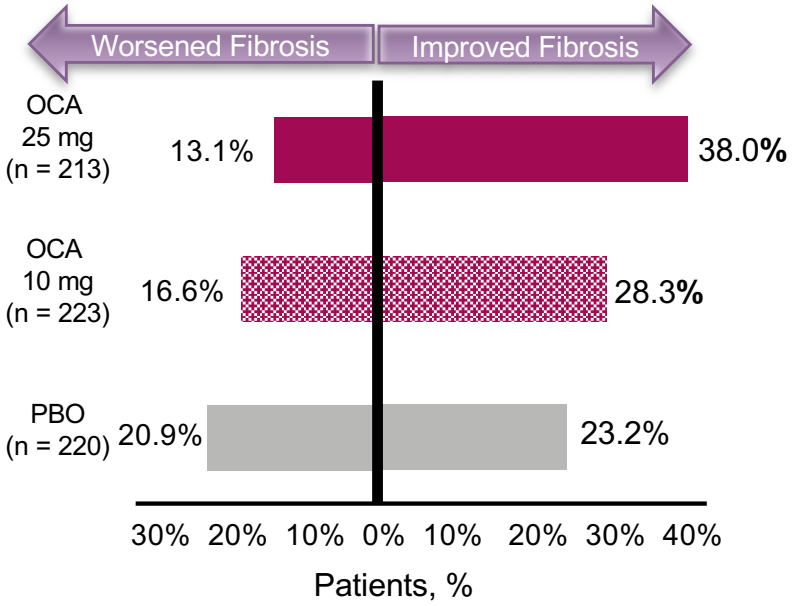
Primary Endpoint (ITT): Fibrosis Improvement by ≥1 Stage With No Worsening of NASH



NASH Resolution With No Worsening of Liver Fibrosis



Regression or Progression of Fibrosis by ≥1 Stage in the per-protocol population



*Statistically significant in accordance with the statistical analysis plan agreed with the FDA

Younossi Z, et al. *Lancet* 2019.394;2184-2196

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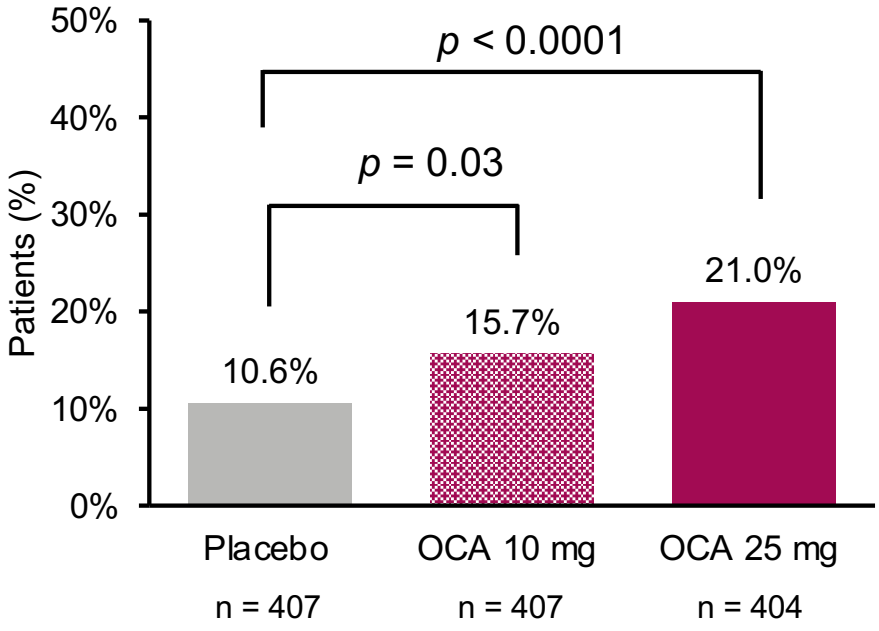
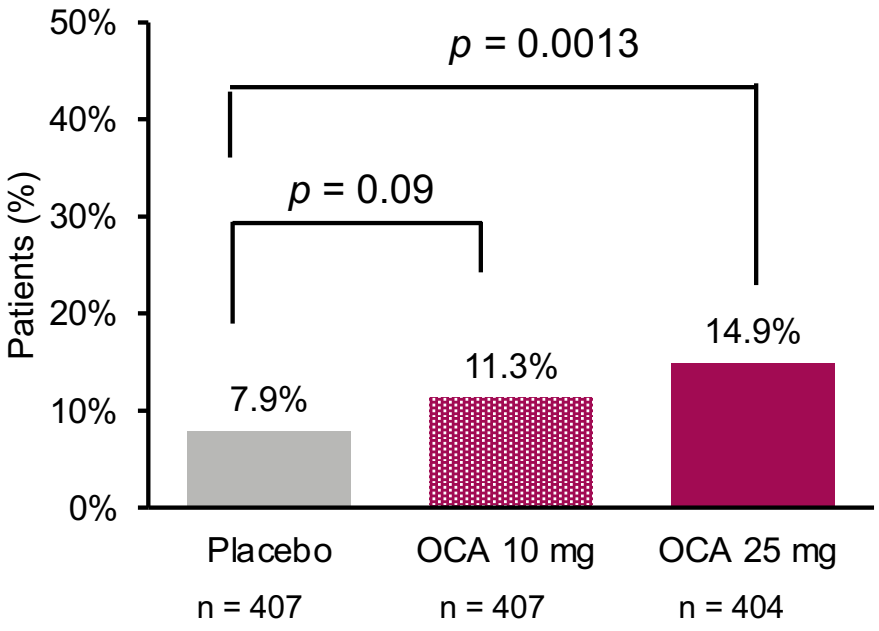
OCA: REGENERATE
Expanded Intent to Treat (ITT) Population

Fibrosis Improvement ≥1 Stage With No Worsening of NASH



NASH Resolution With No Worsening of Fibrosis



Sanyal A, et al. Abstract #34 Presented at AASLD 2019, November 8-12, 2019, Boston, MA.

Obeticholic Acid Safety

	Placebo (n = 657)	Obeticholic acid 10 mg (n = 653)	Obeticholic acid 25 mg (n = 658)
Treatment-emergent and serious adverse events			
At least one treatment-emergent adverse event	548 (83%)	579 (89%)	601 (91%)
Severity*			
Mild	160 (24%)	163 (25%)	130 (20%)
Moderate	294 (45%)	323 (49%)	338 (51%)
Severe	87 (13%)	89 (14%)	130 (20%)
Life-threatening	5 (1%)	4 (1%)	2 (<1%)
Death	2 (<1%)	0	1 (<1%)
Leading to treatment discontinuation	41 (6%)	39 (6%)	83 (13%)
Serious adverse events	75 (11%)	72 (11%)	93 (14%)

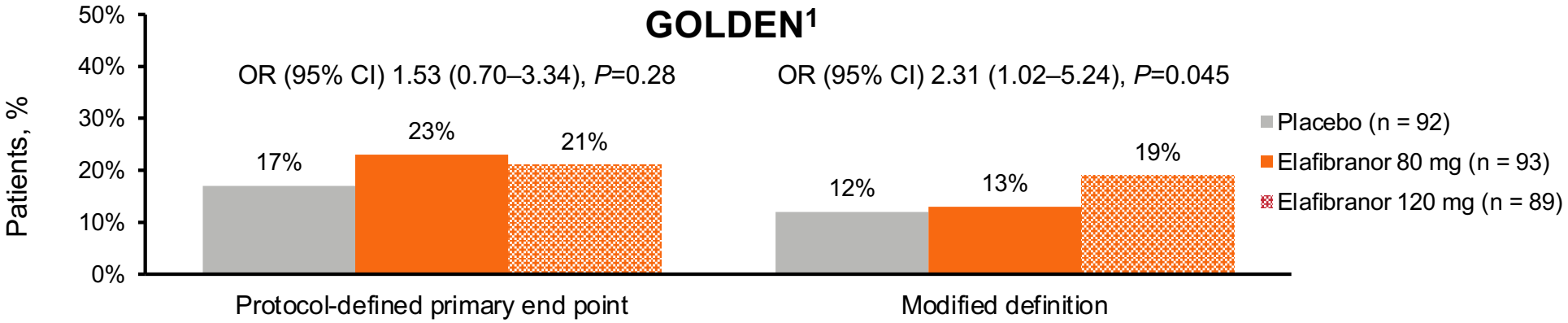
* = Patients reporting more than one adverse event are counted only once using the highest severity

Younossi ZM, et al. *Lancet*. 2019;394:2184-2196.

Elafibranor: GOLDEN and RESOLVE-IT

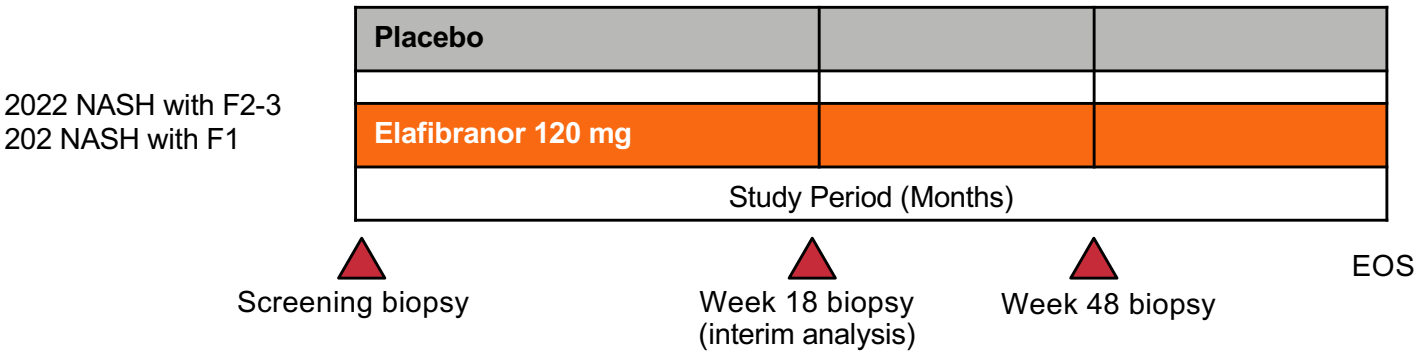
505-Peroxisome Proliferator-Activated Receptors (PPAR α/δ Pathways)

GOLDEN[1]



RESOLVE-IT[2]

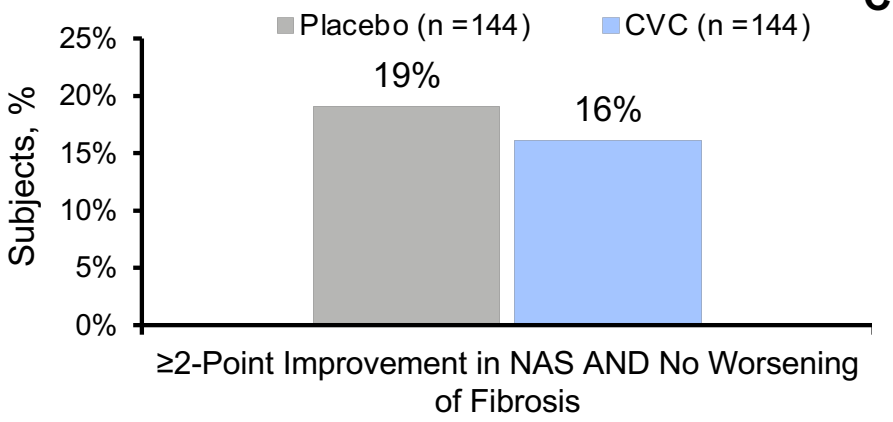
Primary Endpoint at Year 1: Resolution of NASH no worsening fibrosis

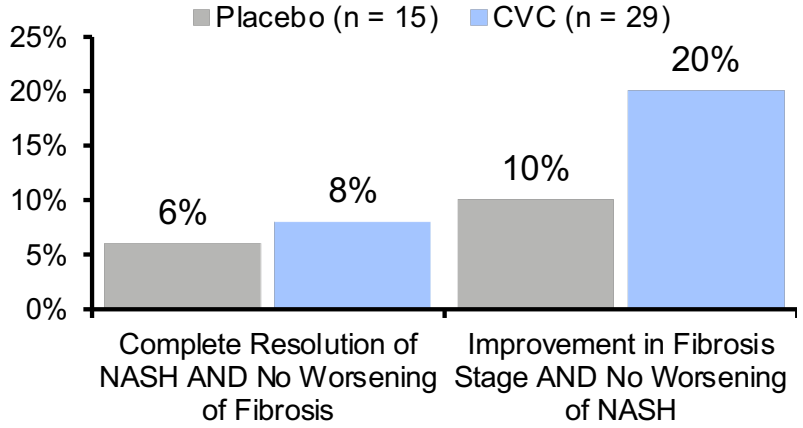


1.Ratziu V, et al. *Gastroenterology.* 2016;:1147-1159. 2. Birman P. Phase 3 Study to Evaluate the Efficacy and Safety of Elafibranor vs Placebo in Patients With Nonalcoholic Steatohepatitis (NASH) (RESOLVE-IT). ClinicalTrials.gov Identifier: NCT02704403. 2016.

Cenicriviroc: CENTAUR and AURORA

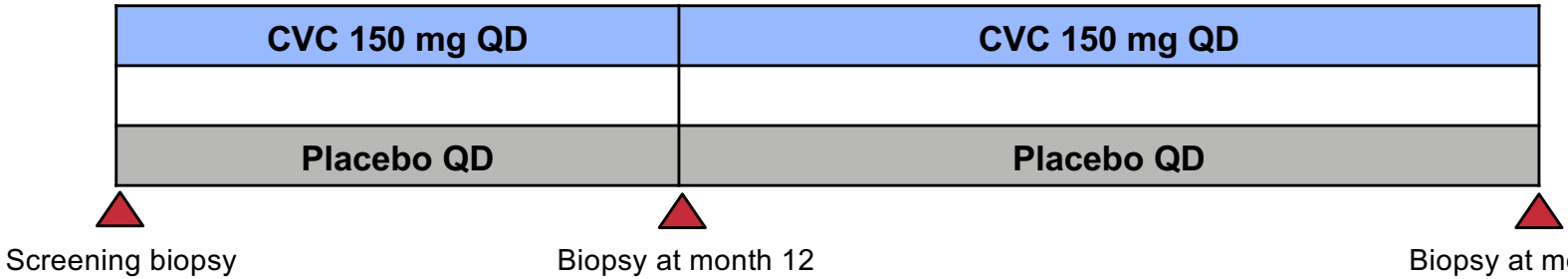
CENTAUR





NASH-AURORA

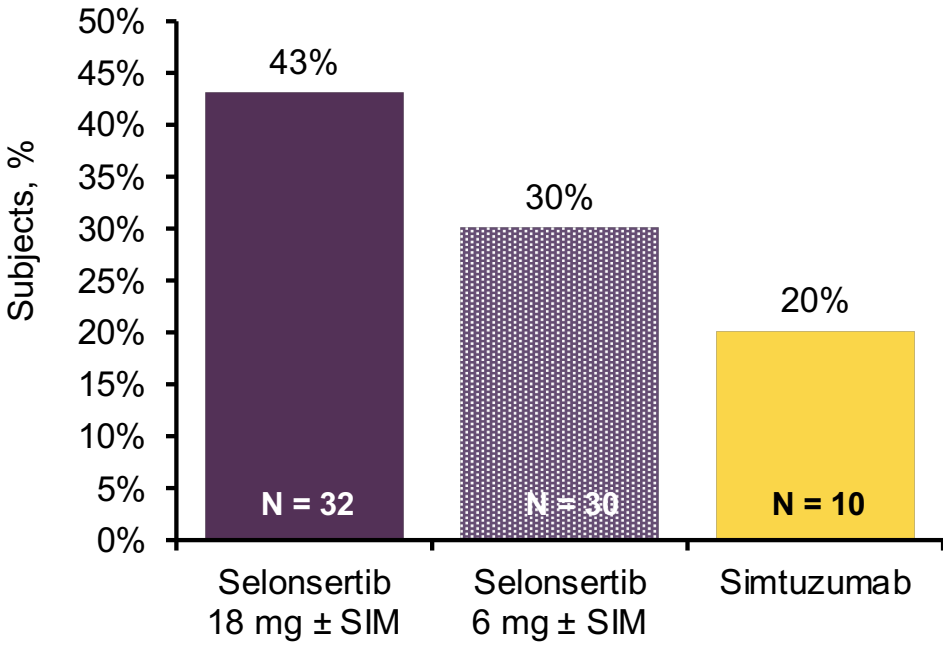
Primary Endpoint at Year 1: >1-stage improvement in fibrosis AND no worsening of NASH (N ≅ 2000)



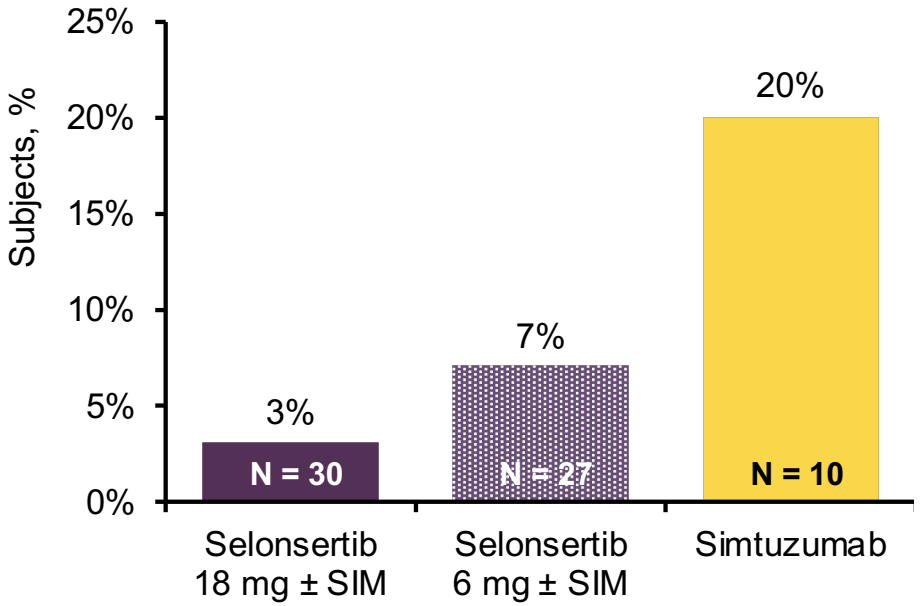
Friedman SL, et al. *Hepatology.* 2018;67(5):1754-1767; Anstee QM, et al. Contemp Clin Trials.2019;89:105922. Epub ahead of print

Selonsertib: Phase 2 Study

Fibrosis Improvement (≥1 stage from baseline)



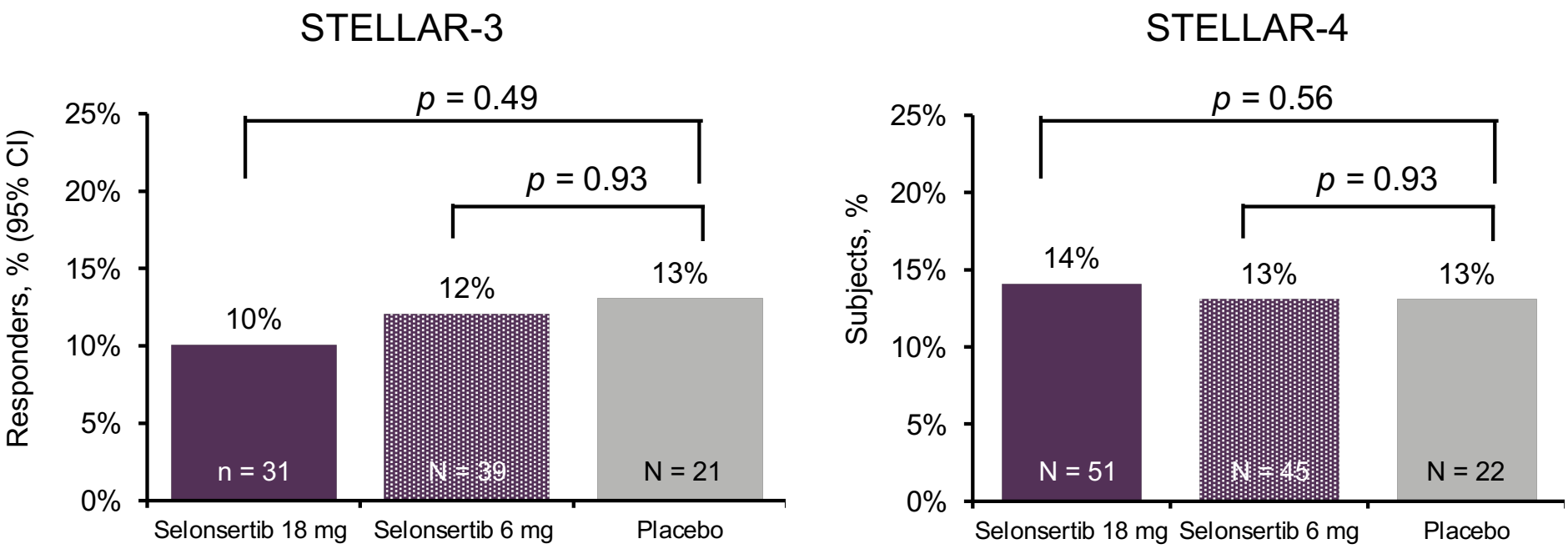
Progression to Cirrhosis at Week 24



Loomba R, et al. *Hepatology*. 2018;67(2):549-559.

Selonsertib: STELLAR-3 and STELLAR-4

Fibrosis Improvement Without Worsening of NASH



Harrison SA, *J Hepatol* 2020. Epub ahead of print: doi: 10.1016/j.jhep.2020.02.02

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Combinations with Complementary MOA

Future: Targeting Multiple Pathways

Mechanism of Action (MOA)	Disease Process/ Pathway Target(s)
ASK1 inhibitor (selonsertib) and non-steroidal FXR agonist (GS-9674) and/or ACC inhibitor (GS-0976)[1]	Inflammation, fibrosis, and lipogenesis
Combined PPAR alpha and delta agonist (elafibranor) and an FXR agonist[2]	Inflammation, fibrosis, and lipogenesis
Chemokine CCR2/CCR5 receptor blocker (cenicriviroc) in combination with a FXR agonist[3,4]	Inflammatory and fibrosis

ACC = acetyl-CoA carboxylase; ASK-1 = apoptosis signal-regulating kinase 1; CCR = chemokine (C-C motif) receptor; PPAR = peroxisome proliferator-activated receptor

1. Lawitz E, et al. ILC. April 11-15, 2018; Paris, France. Abstract PS105; 2. Ratziu V, et al. ILC. April 19-23, 2017; Amsterdam, The Netherlands. Abstract LBP-542; 3. Oseini AM, Sanyal AJ. *Liver Int*. 2017;37 Suppl 1:97-103; 4. Rotman Y, Sanyal AJ. *Gut*. 2017;66(1):180-190.

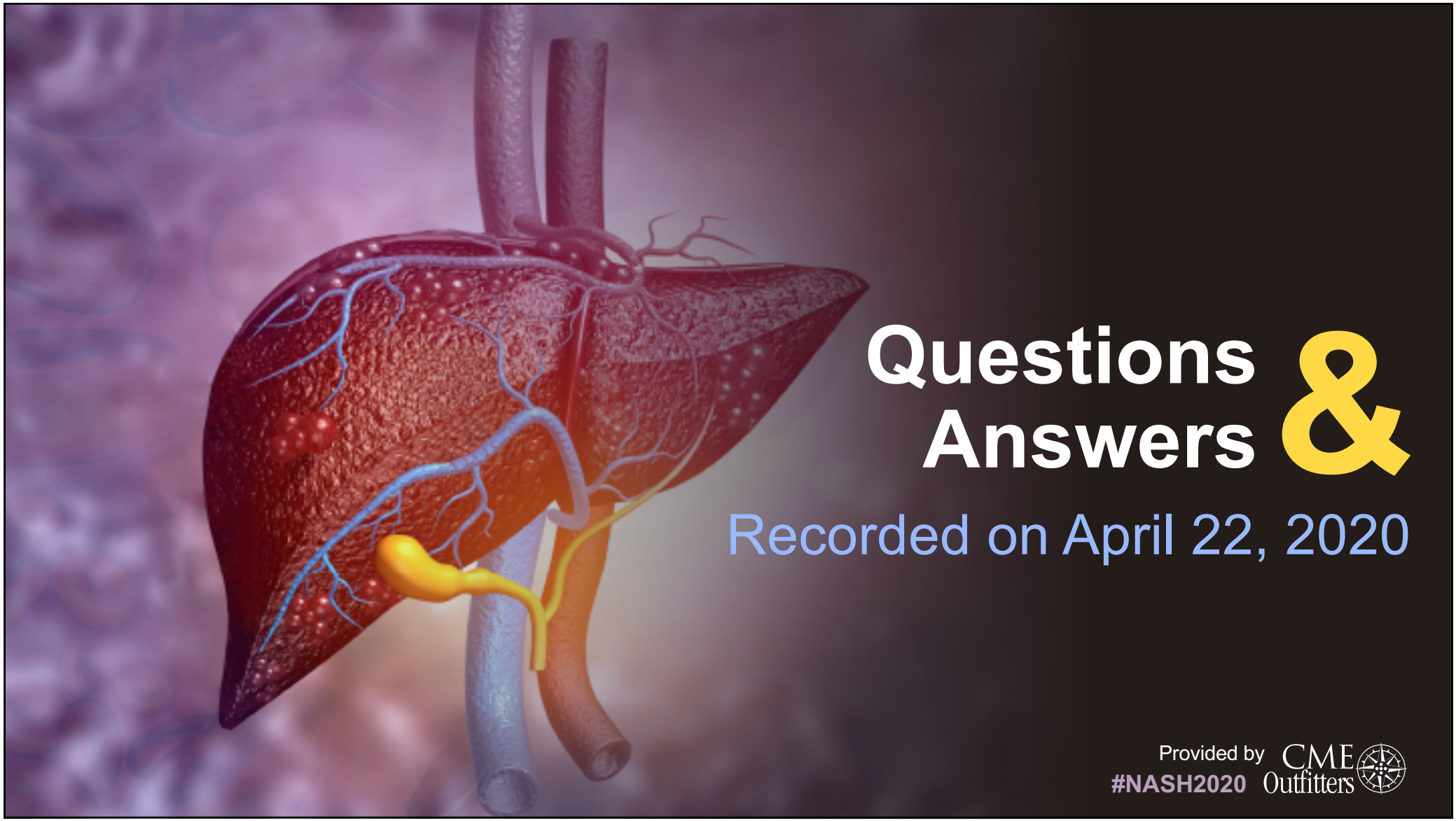
George
Intermediate Risk for NASH

How would you treat him today?

- Ultrasound
- FIB-4 or NFS
- Counsel him regarding his drinking
- Lifestyle modification
  - Diet, exercise
- Refer to GI/Hepatologist based on the results

How would you treat him in a year?

- Obeticholic acid?
- ELF assessment


Questions & Answers
Recorded on April 22, 2020
Provided by CME Outfitters
#NASH2020

SMART Goals

Specific, **M**easurable, **A**ttainable, **R**elevant, **T**imely

- Screen 100% of your patients with T2DM for NASH
- Counsel 100% of your patients with T2DM on dietary risk reduction to prevent hepatic progression
- Incorporate 2 or more non-invasive markers to risk-stratify NASH patients
- Refer 100% of confirmed NASH pts to hepatologist
- Monitor all patients with NASH for progression to cirrhosis in collaboration with hepatology