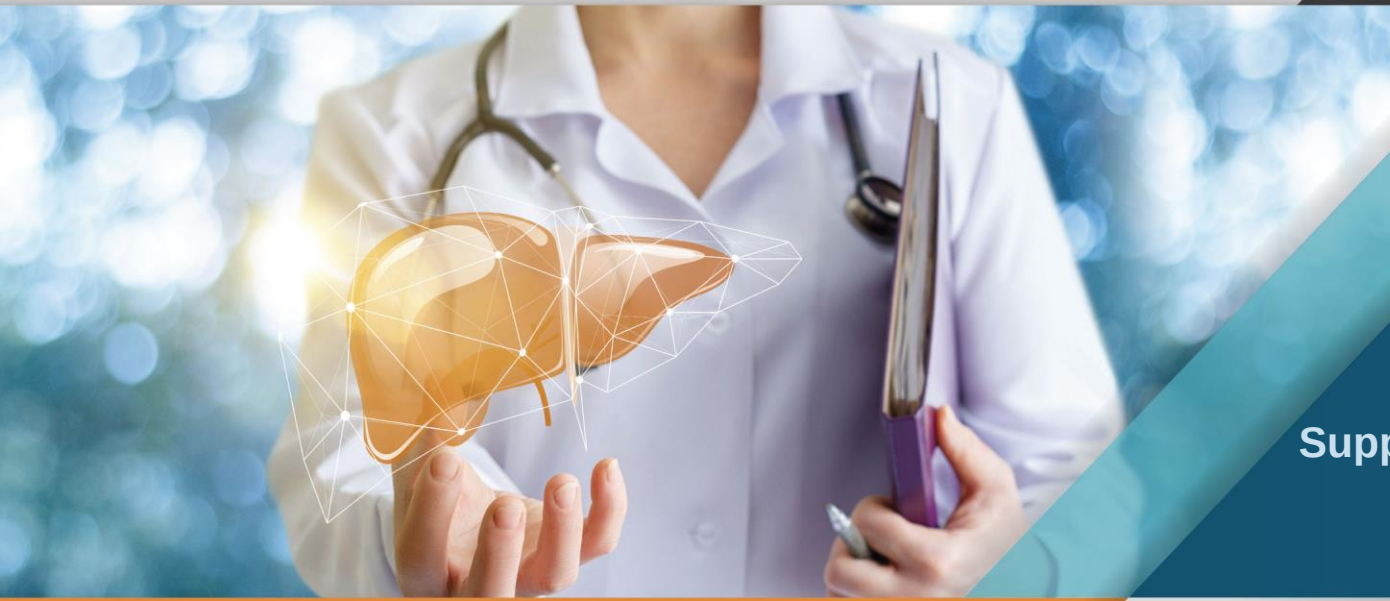
What the Future Holds for NASH:

An Augmented Reality Look into Disease Staging and Targeted Therapies



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Provided by: CME Outfitters

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Learning Objective 1

Describe the role of immune, inflammatory, and metabolic pathways in the pathogenesis of NASH.

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George

59-year-old Mexican American male

- Referred from PCP because of elevated liver enzymes
- Statins were stopped 3 months ago
- History of T2DM for 5 years
- History of dyslipidemia for 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

PCP = primary care physician; T2DM = type 2 diabetes mellitus; HTN = hypertension.

George (cont.)

- **Symptoms:** Has some right upper quadrant discomfort
- **Medications:** Metformin 500 mg po twice a day and fish oil
- **Exam** was normal except for central obesity
  - BMI of 33 kg/m2

po = by mouth; BMI = body mass index.

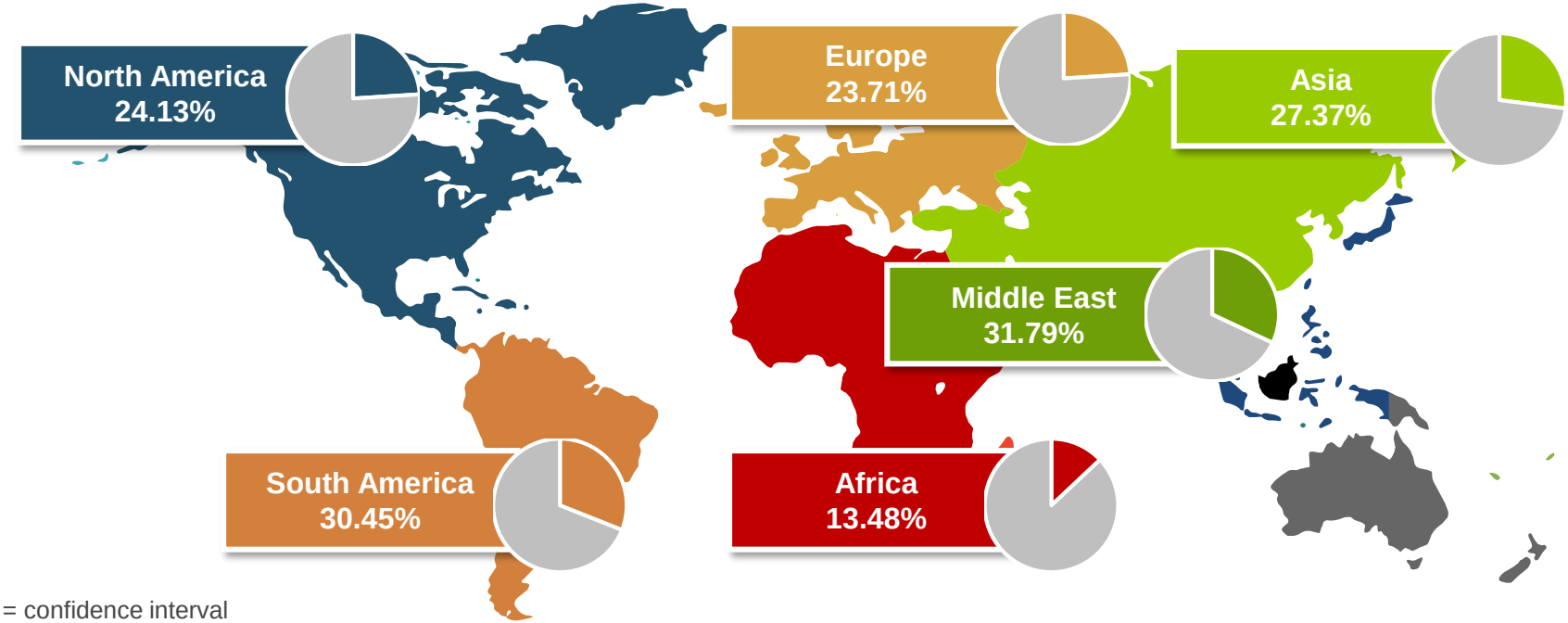
George's Labs

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 lipoproteins; Hgb = hemoglobin.

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

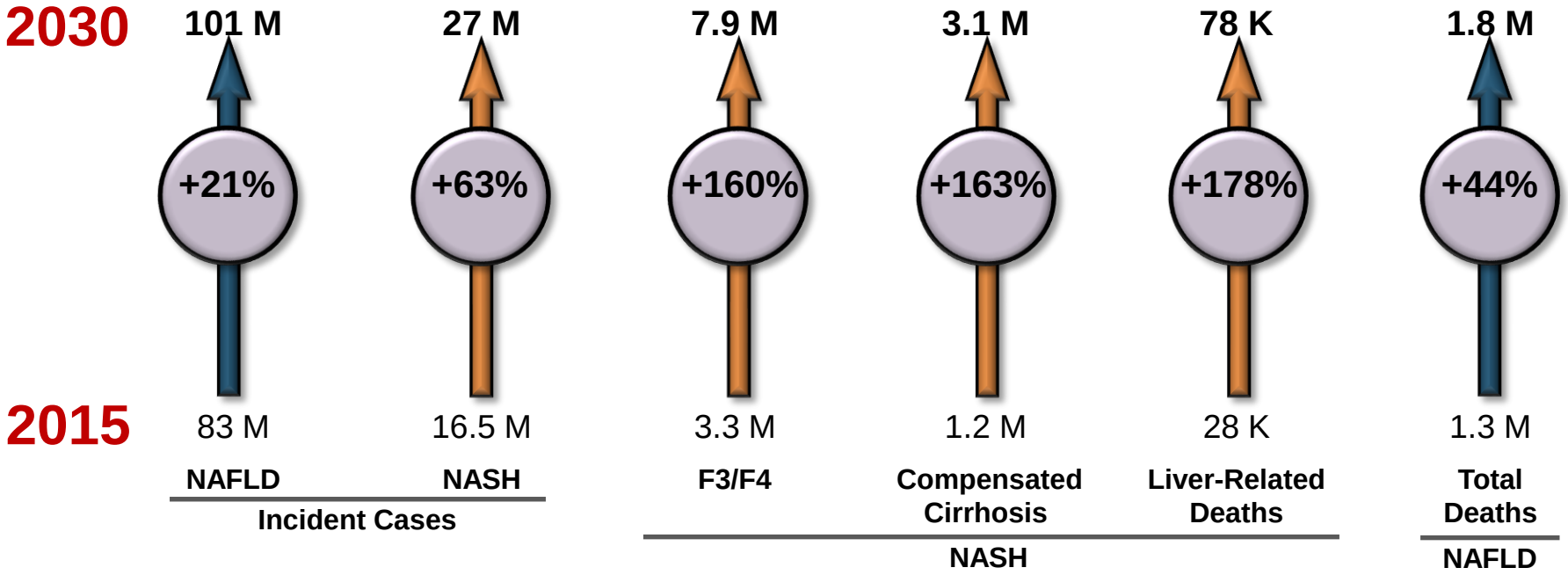
- Global prevalence of NAFLD is 25.24% (95% CI: 22.10-28.65)
- Prevalence of NASH in general population is estimated between 1.5% and 6.45%



CI = confidence interval

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

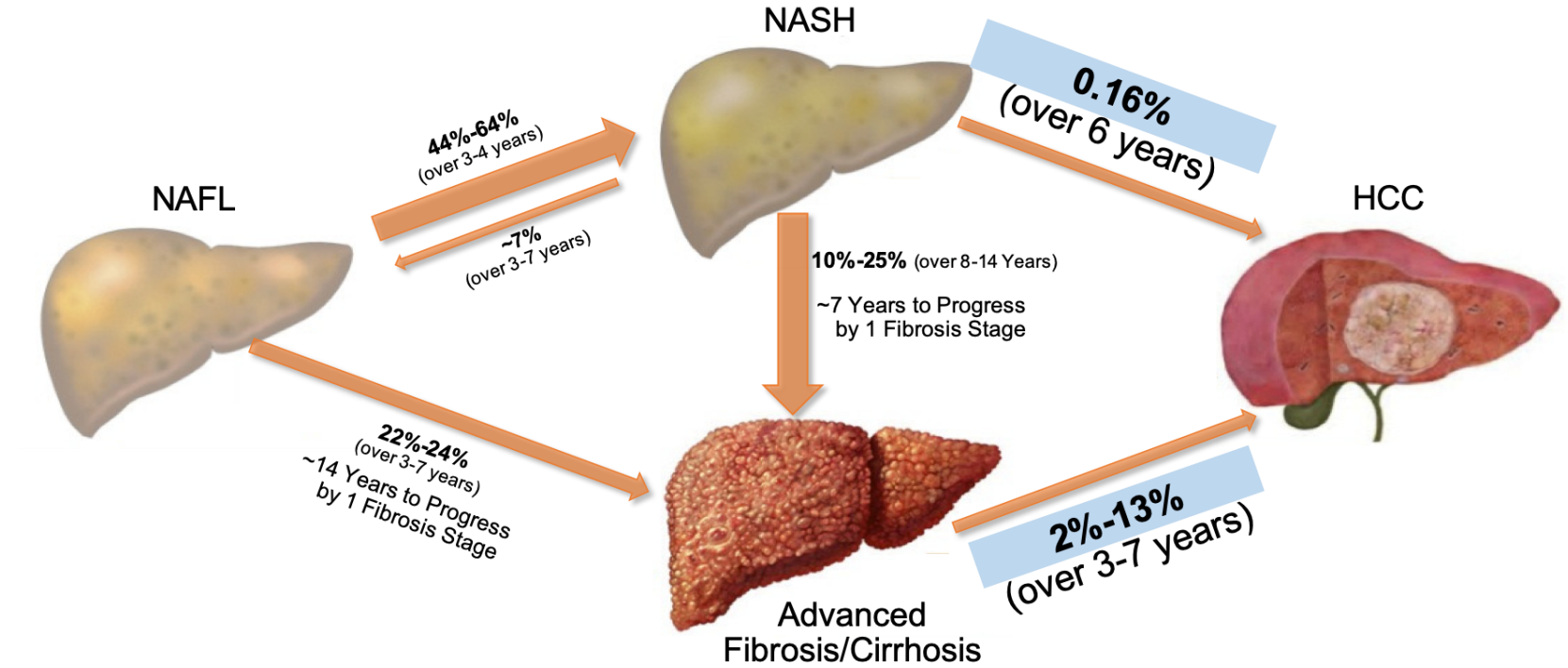
Changing Burden of NAFLD/NASH in The US



NAFLD disease progression model (Markov model key input prevalence): 2015-2030: obesity (35.1% to 42.19%) and diabetes (11.4% to 22.7%). 2015: NAFLD=30% of obesity/diabetes; NASH=20% of NAFLD; 20% of NASH with ≥F3.
Mortality adjusted for CVD; HCC progression calibrated to SEER data.

NAFLD = non-alcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis.
Estes C, et al. *Hepatology.* 2018;67:123-133.

Natural History of NAFLD/NASH



NASH was leading cause for liver transplant in women in 2016

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.

The 20% Rule for Progression in F3/4 NASH

Key predictors of progression to cirrhosis

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

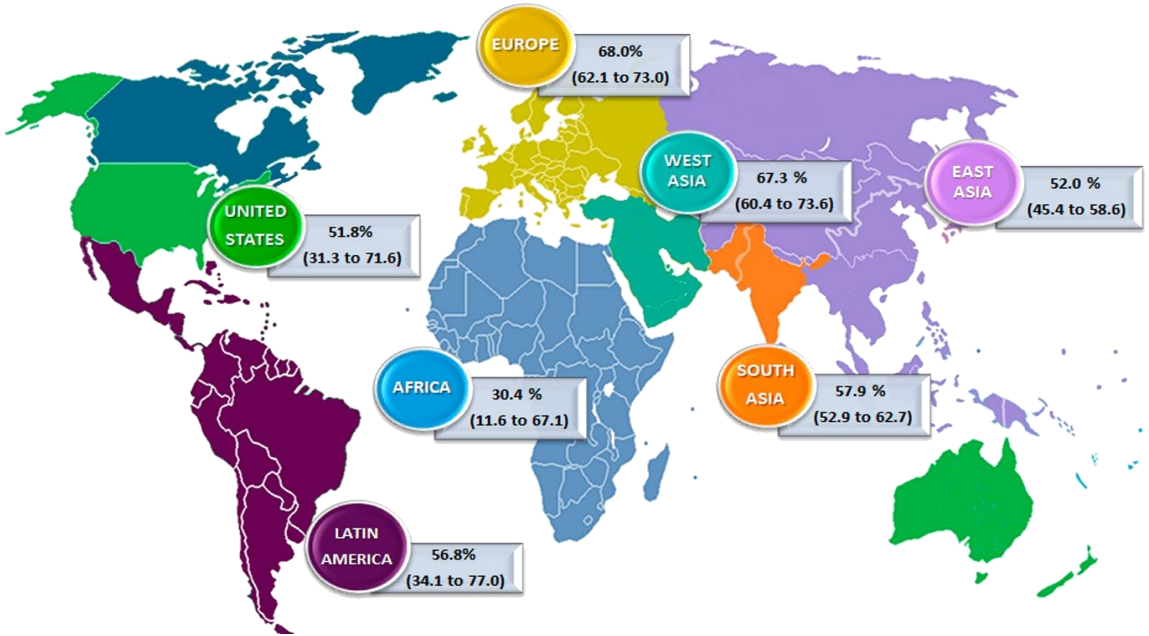
Key predictors of decompensation/progression

- Liver function: MELD, Childs Push 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 Sep 13. [Epub ahead of print]; Sanyal AJ, et al. *Hepatology*. 2019 Apr 16. [Epub ahead of print].

Disease Burden In Patients with Diabetes



Systematic review of 49,419 with diabetes in 22 countries

- Overall global NAFLD prevalence among diabetics is 55.5%
- Overall prevalence of NASH in biopsied diabetics is 67.3%
- Overall prevalence of advanced fibrosis (fibrosis ≥ F3) 17.2%

Diabetes makes everything worse

- **8X increase** in number of patients who progress from NASH to HCC
- **~2X increase** in mortality in patients with cirrhosis, HCC, or liver transplant

Golabi P, et al. M*edicine.* 2018;97(13):e0214; Younossi ZM, et al. *Nat Rev Gastroenterol Hepatol.* 2018;15(1):11-20; Younossi ZM et al. *Hepatology*. 2018;(1):349-360.

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.

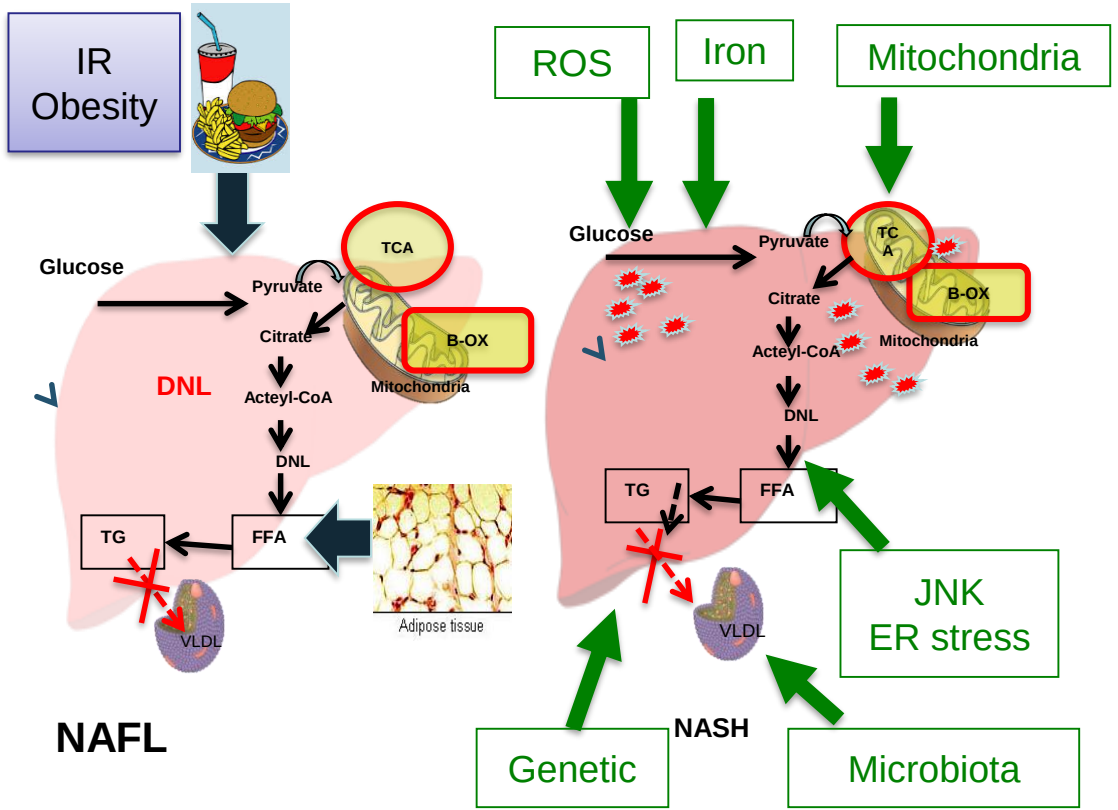
Noureddin M, et al. *Hepatology.* 2019 Sep 25. [Epub ahead of print].

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	1.00 (ref.)	1.00 (ref.)
> 34.0	1.10 (0.97-1.25)	1.43 (1.08-1.90)
P-value for trend	0.1190	0.0121
Red unprocessed meat		
≤ 9.3	1.00 (ref.)	1.00 (ref.)
> 24.1	1.10 (0.97-1.25)	1.52 (1.15-2.01)
P-value for trend	0.1223	0.0033
Processed red meat		
≤ 3.0	1.00 (ref.)	1.00 (ref.)
> 10.0	1.17 (1.03-1.32)	1.31 (0.99-1.71)
P-value for trend	0.0097	0.1123
Total poultry		
≤ 11.4	1.00 (ref.)	1.00 (ref.)
> 27.6	1.19 (1.05-1.35)	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].

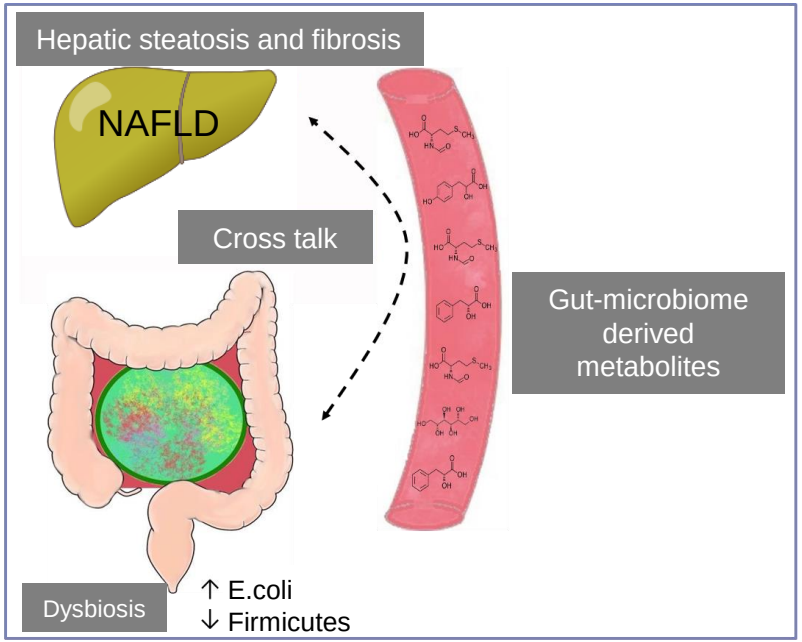
NAFLD: Pathogenesis

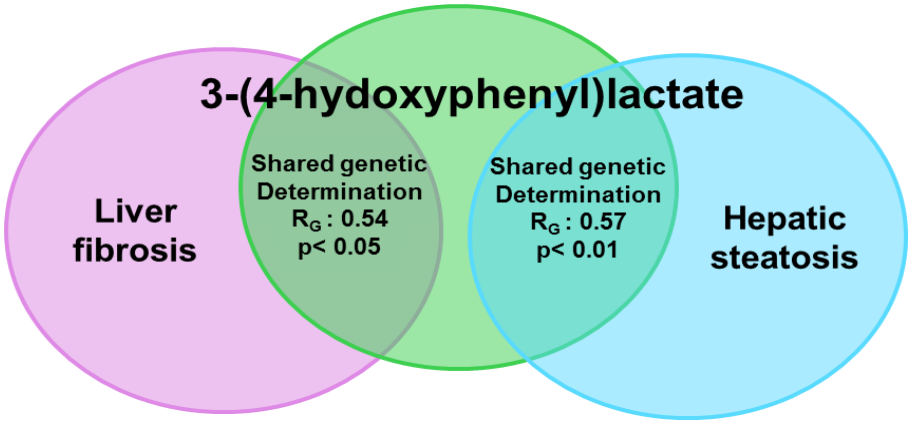


DNL = differential non-linearity; ER = endoplasmic reticulum; FFA = free fatty acid; IR = insulin resistance; JNK = c-Jun N-terminal kinases; ROS = reactive oxygen species; TCA = trichloroacetic acid; TG = thyroglobulin; VLDL = very low density lipoprotein.
Noureddin M, et al. *Exp Bio Med*. 2015;240(6):809-820.

Gut-Liver Axis and Microbial Metabolites in Advanced Fibrosis Versus Early NAFLD

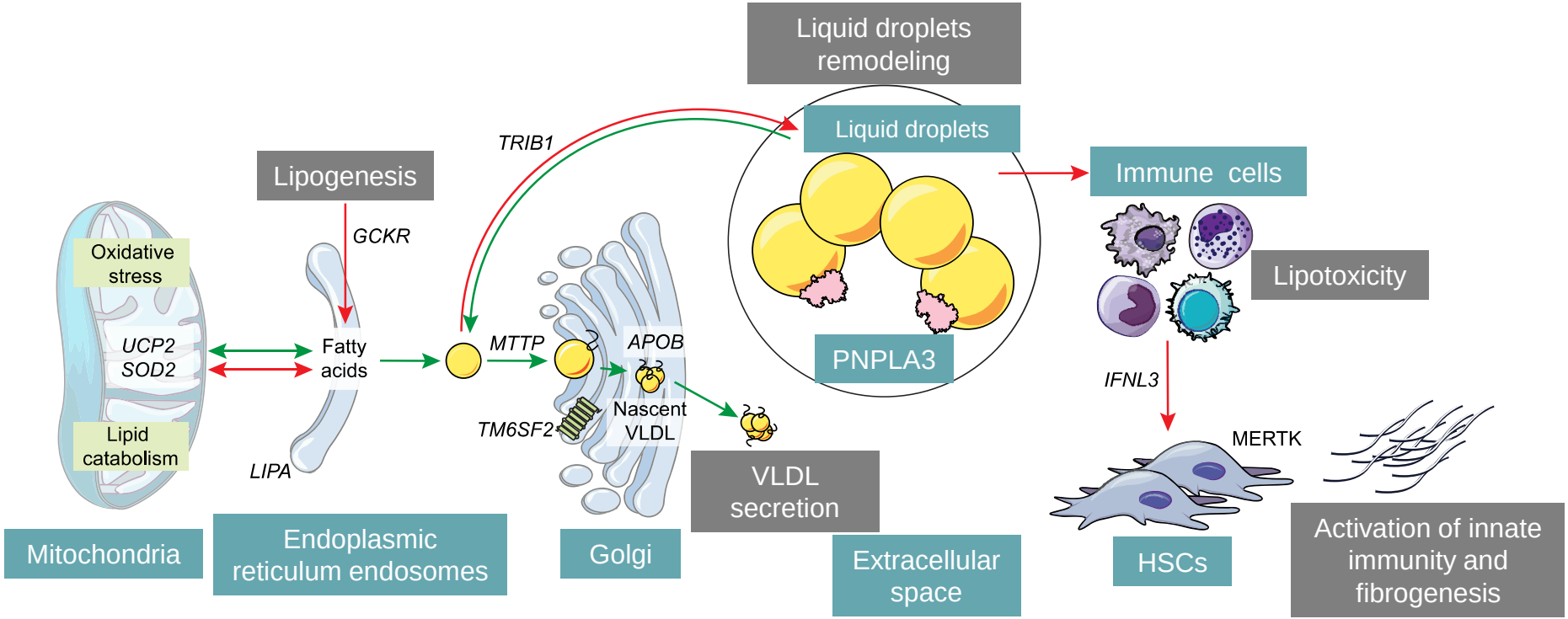
Using a twin-familial cohort and patients with biopsy-proven NAFLD, comparing advanced fibrosis (stage 3-4) versus stage 0-2 fibrosis using metagenomic sequencing





Caussy C, et al. *Hepatology.* 2018 Mar 23. [Epub ahead of print].

Genetics and Epigenetics of NAFLD and NASH



APOB = apolipoprotein B; GCKR = glucokinase regulatory protein; HSCs = hematopoietic stem cell transplantation; IFNL3 = interferon lambda 3; MERTK = MER proto-oncogene, tyrosine kinase; MTTP = microsomal triglyceride transfer protein; PNPLA3 = patanin-like phospholipase domain-containing protein 3; SOD2 = superoxide dismutase 2; TM6SF2 = transmembrane 6 superfamily member 2; TRIB1 = tribbles homolog 1; UCP2 = uncoupling protein 2.

Eslam M, et al. *J Hepatol.* 2018;68(2):268-279.

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%

Learning Objective 2

Select appropriate non-invasive and invasive modalities for the identification of advanced fibrosis in patients with NAFLD.

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Clinical Presentation of NASH

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 in most patients
- Some patients may have elevated alkaline phosphatase

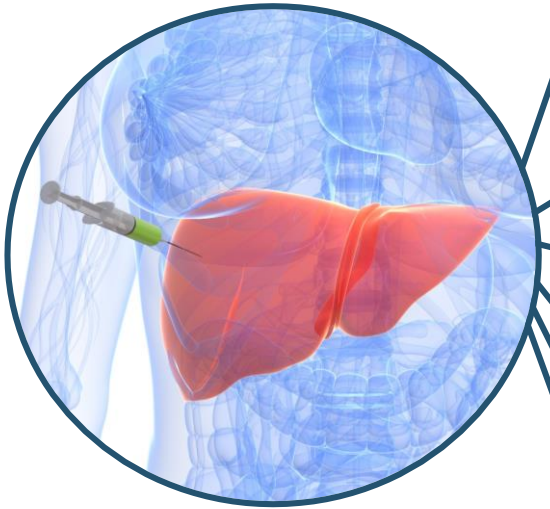
Aetiologies

- No significant alcohol consumption
- No competing etiologies 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.

Audience Q&A

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

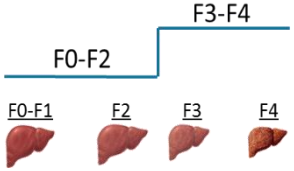
- Hyaluronic acid
- CK-18
- Fucosylated haptoglobin (Fuc-Hpt)
- Macroglobulin-2 binding protein (Mac-2bp)
- Fuc-Hpt + Mac-2bp
- ELF score
- FIBROSpect®

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

FIBROSpect® NASH is Superior to FIB-4 and NFS

Stage 0–2 vs stage 3–4

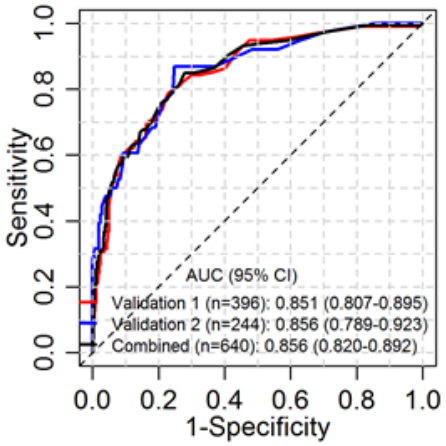
FIBROspect:

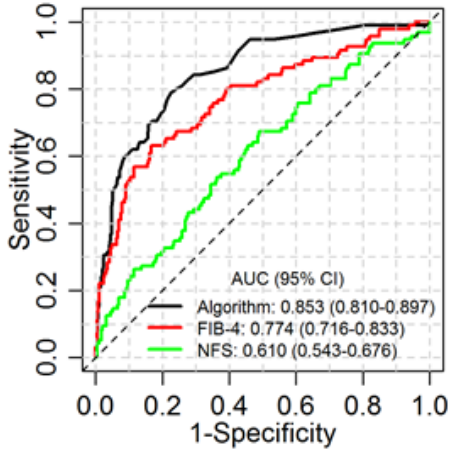


Three (3) serological markers:

- **A2M**
- **HA**
- **TIMP-1**

	Validation 1 Cohort (Duke University)	Validation 2 Cohort (UCSD)
Patients	396	244
Age (year) [mean (sd)]	49.8 (11.9)	49.2 (14.2)
Females (%)	63.6	57.0
Hispanic or Latino (%)	2.8	22.1
Not Hispanic or Latino (%)	57.6	77.9
BMI (kg/m^2) [mean (sd)]	39.5 (9.4)	31.6 (6.1)
Diabetics (%)	46.5	26.2





Fibrospect® NASH score of 17 or higher is associated with advanced fibrosis in NAFLD

A2M = alpha-2-macroglobulin.

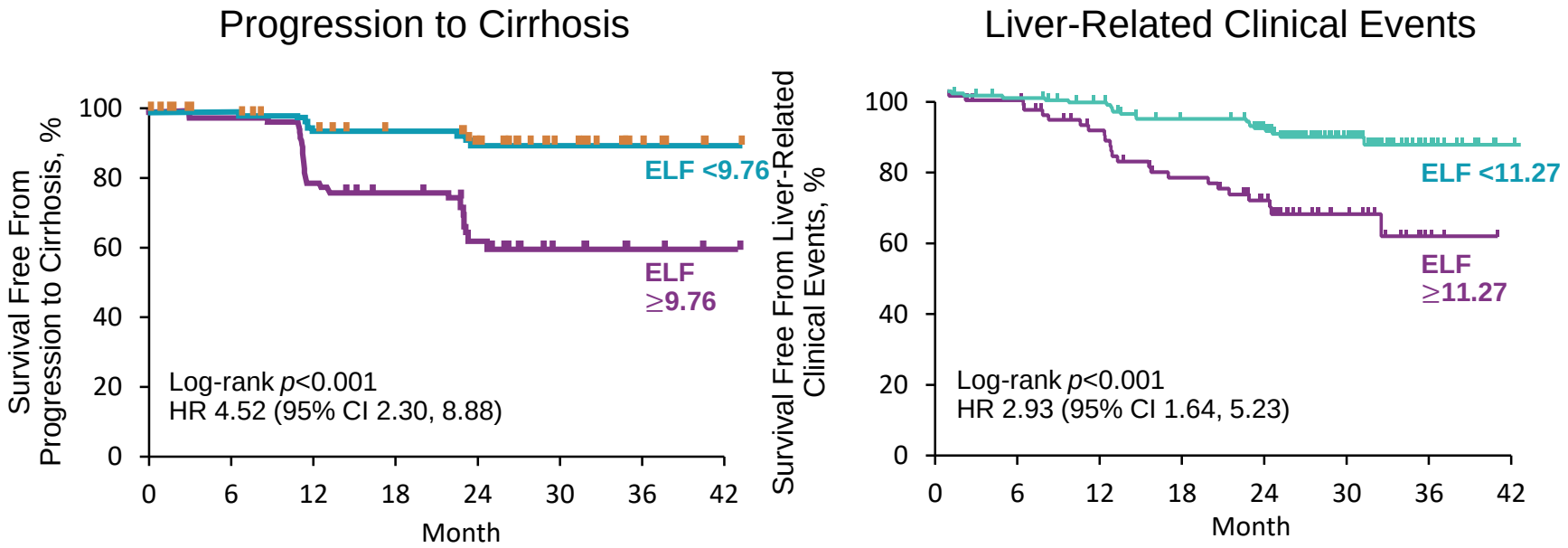
Loomba R, et al. *Clin Gastroenterol Hepatol.* 2019. (in press).

Audience Response

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: Phase 2 Simtuzumab in NASH and F3–F4

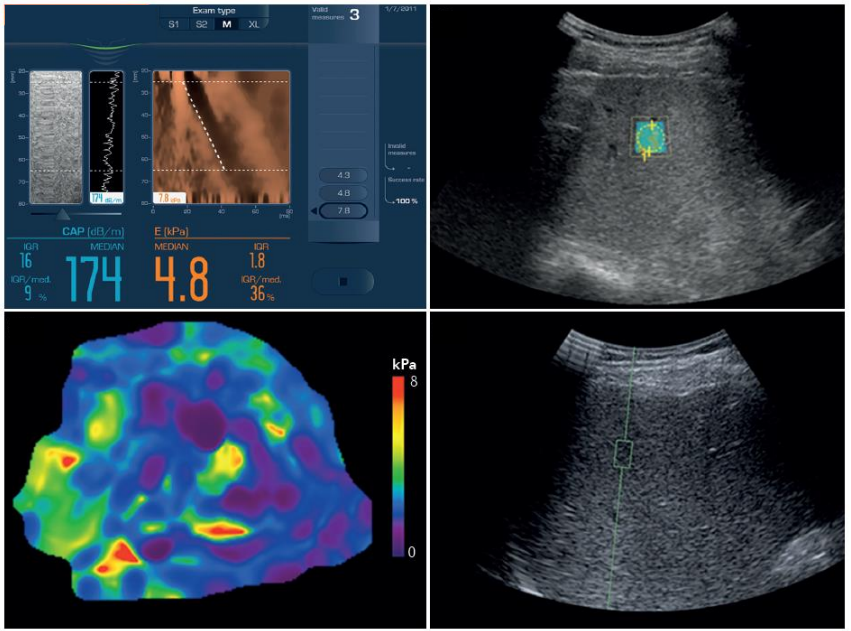


Higher baseline ELF and greater change in ELF were associated with increased risk of progression to cirrhosis and liver-related clinical events

Patients with NASH and bridging fibrosis (n=219) or compensated cirrhosis (n=258) enrolled in two Phase 2b SIM studies.
CI = confidence interval; ELF = enhanced liver fibrosis; HR = hazard ratio.
Patel J, et al. *Therap Adv Gastroenterol*. 2016;9(5):692-701.

Elastography-Based Methods to Estimate Liver Stiffness

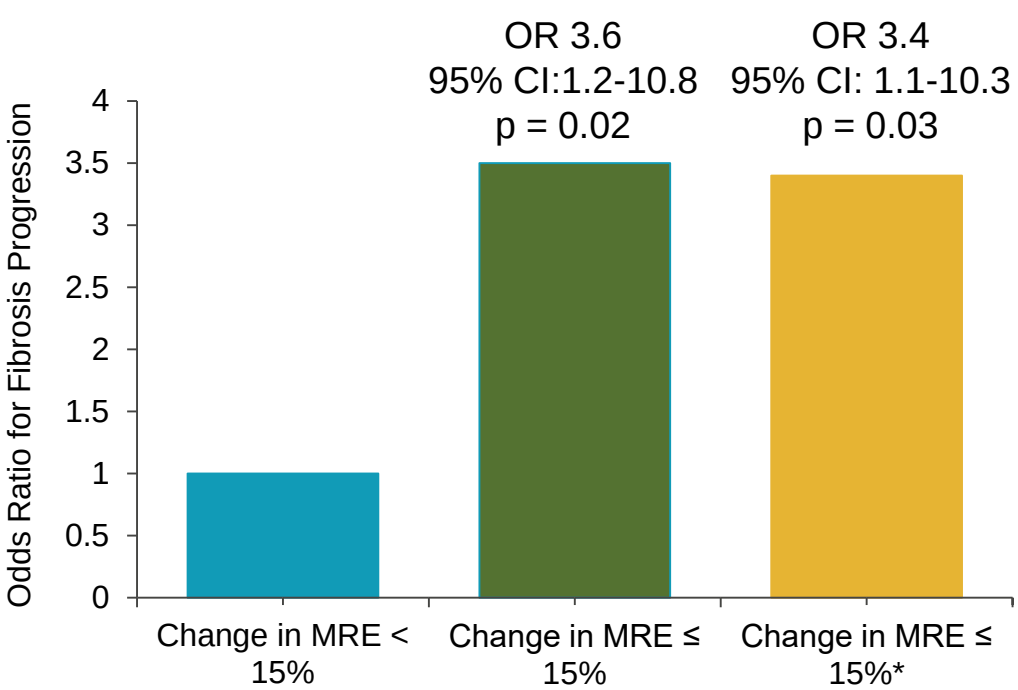
- VCTE (FibroScan) is most widely used
  - ≥10 images are required
  - Accurate for stages F3–4
  - Can estimate steatosis when used with CAP
- SWE/ARFI can be used to measure stiffness in a single ROI
- MRE measures stiffness across multiple ROIs

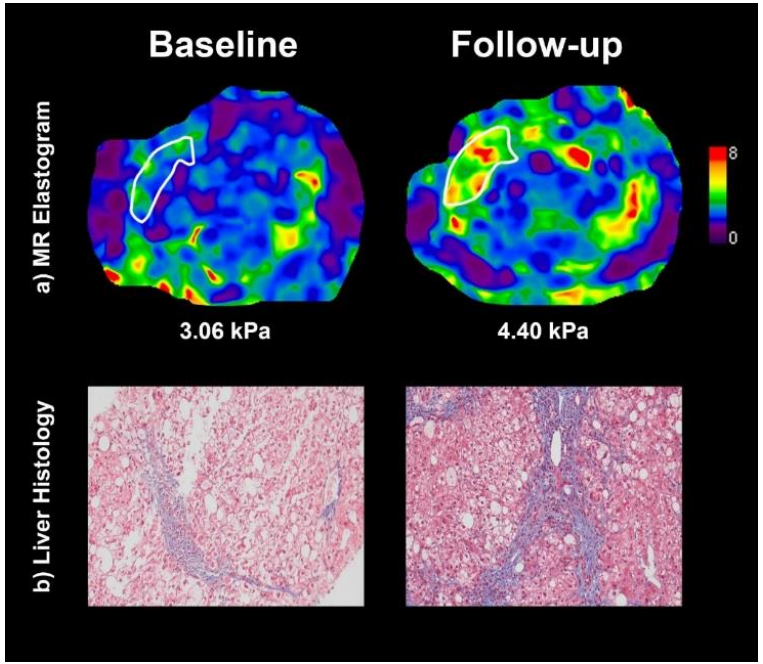


ARFI = acoustic radiation force impulse; CAP = controlled attenuation parameter; MRE = magnetic resonance elastography; ROI = region of interest; SWE = shear wave elastography.

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
Ajmera VH, et al. *Hepatology.* 2019 Sep 25. [Epub ahead of print].

Which Test is Better?

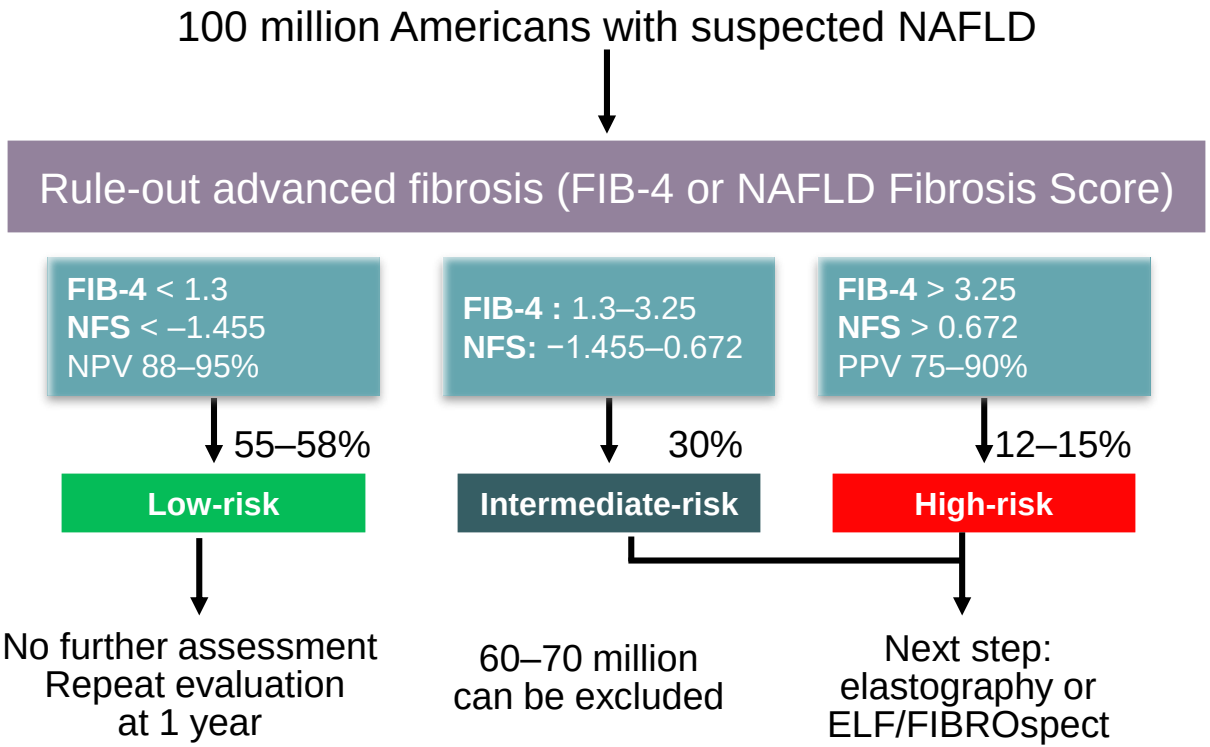
- FIB-4 is better than the rest of CPR
- VCTE is better than FIB-4
- MRE is better than VCTE

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

CPR = clinical prediction rules; FIB-4 = fibrosis 4.
Younossi Z, et al. *Hepatology.* 2018;67(1):328-357.

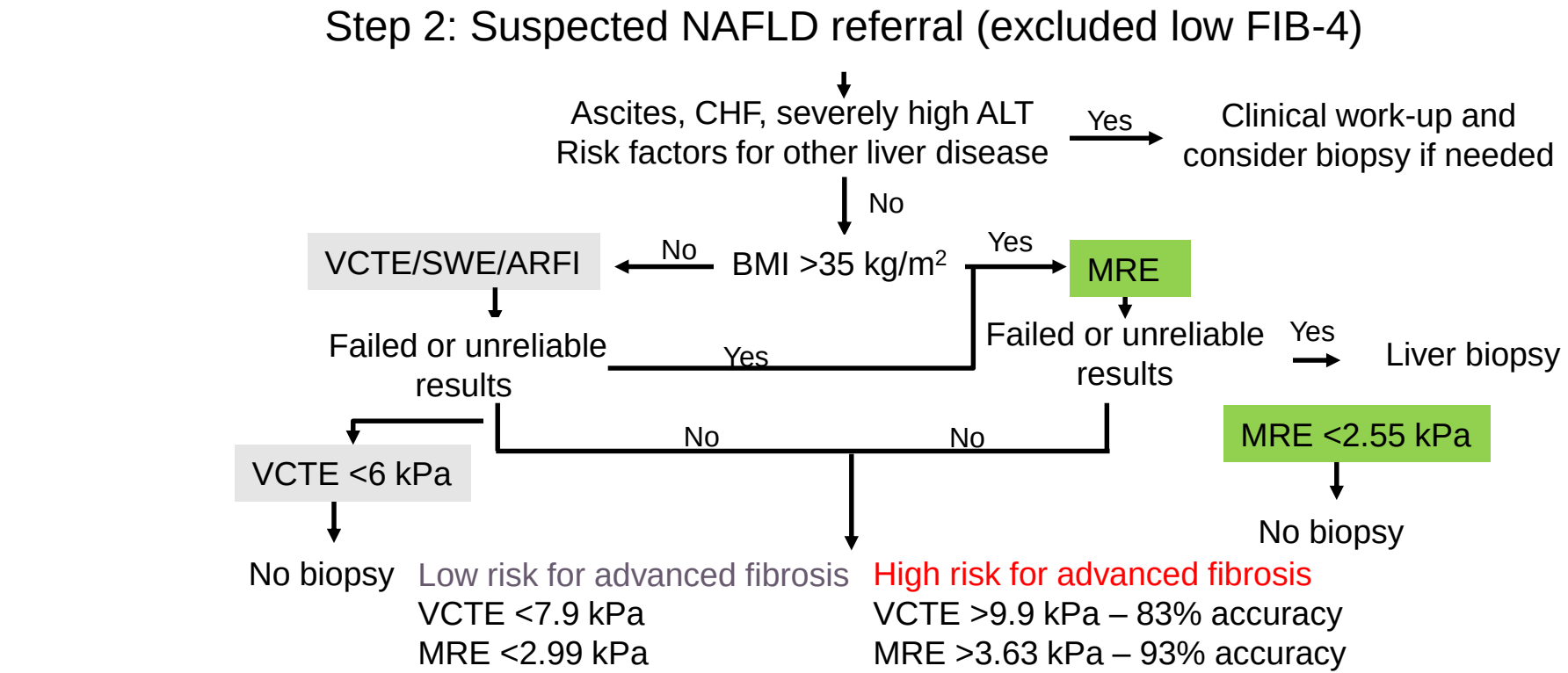
Optimizing Risk Management



NPV = negative predictive value.

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

Elastography in Assessing Advanced Fibrosis



CHF = congestive heart failure.

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

Caveats Associated with Available Modalities

- Transient elastography, ARFI, and other ultrasound-based test have limitations:
  - Obesity
  - Ascites
  - Acute inflammation
  - Cirrhosis
- MRE improves upon all except
  - Iron overload
  - Acute inflammation

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

Audience Q&A

Learning Objective 3

Evaluate the efficacy of emerging therapies for improving fibrosis in patients with NASH.

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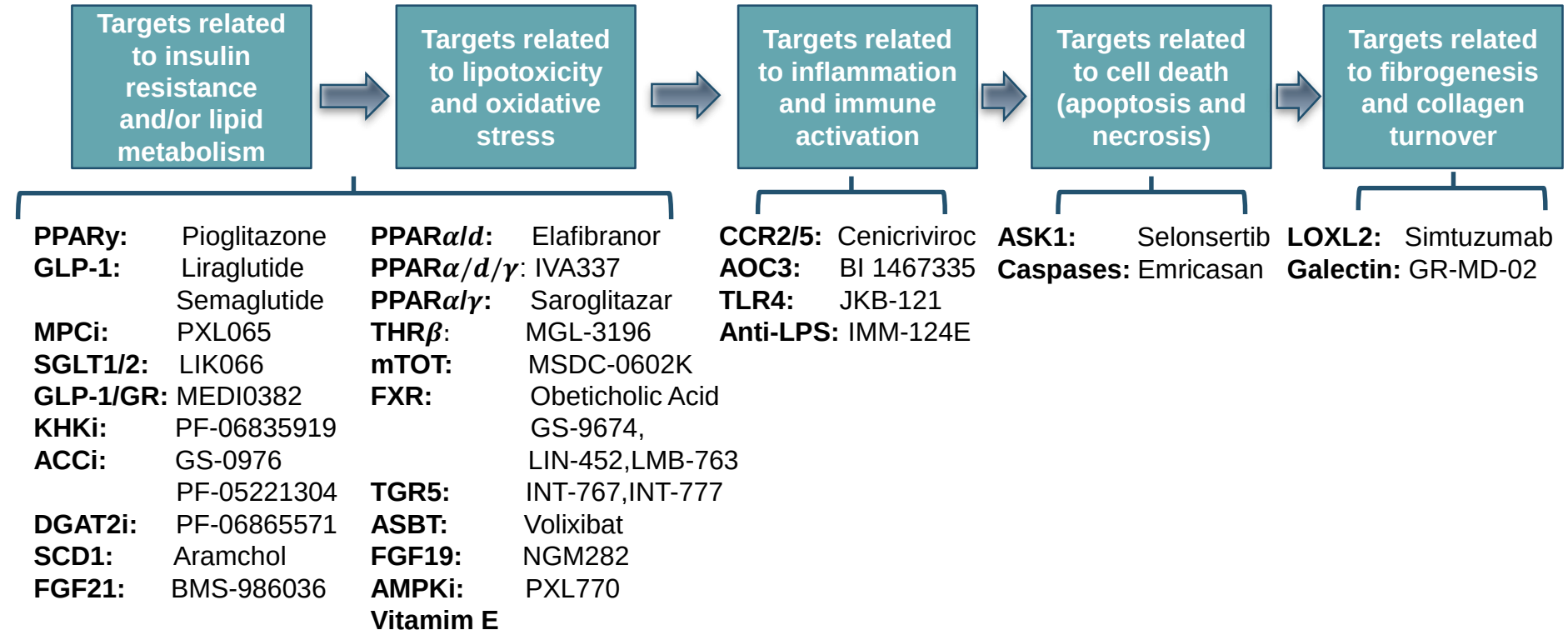
If Standard Treatment is Unsuccessful, What Future Options Exist?



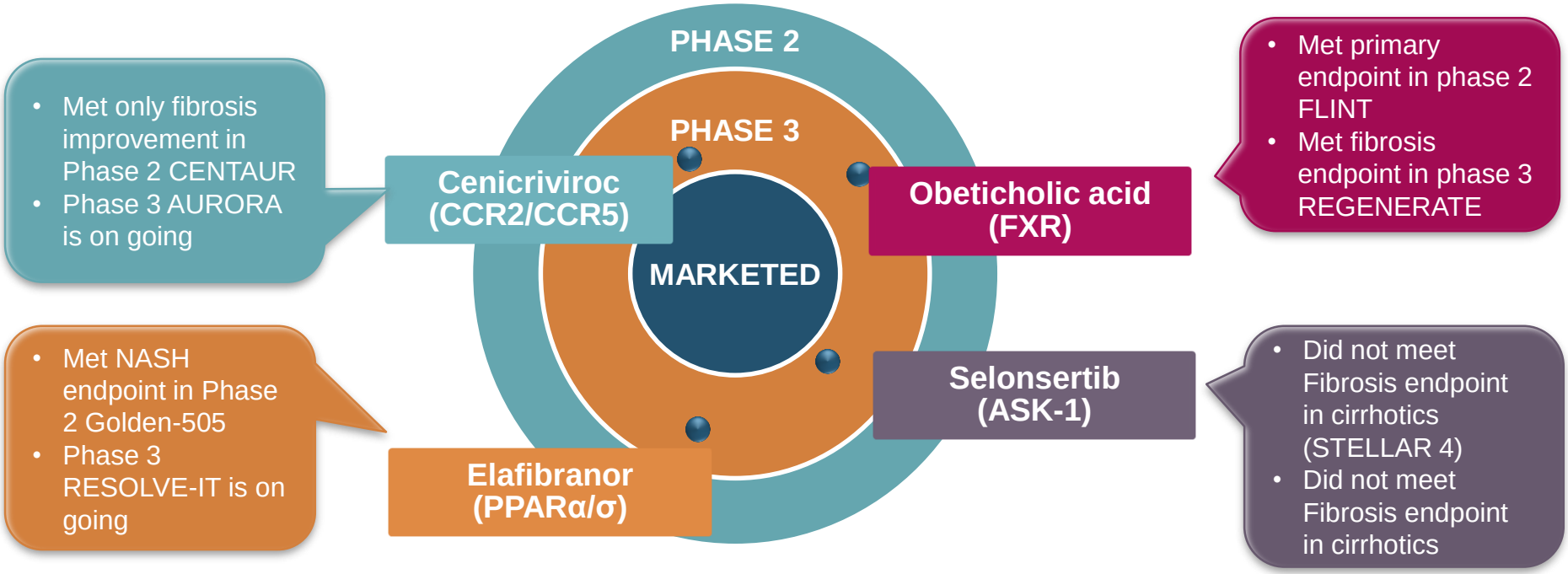
Younossi ZM, et al. *Hepatology.* 2018;68(1):361-371.

Audience Response

How often do you enroll patients with NASH in clinical trials?

A. Never
B. 1-25% of the time
C. 26-50% of the time
D. 51-75% of the time
E. 76-100% of the time

Regimens in Phase 3 Clinical Trials for Treatment of NASH



ASK-1 = apoptosis signal-regulating kinase 1; CCR = chemokine (C-C motif) receptor; PPAR = peroxisome proliferator-activated receptors; FXR = farnesoid X receptor.

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

Augmented Reality

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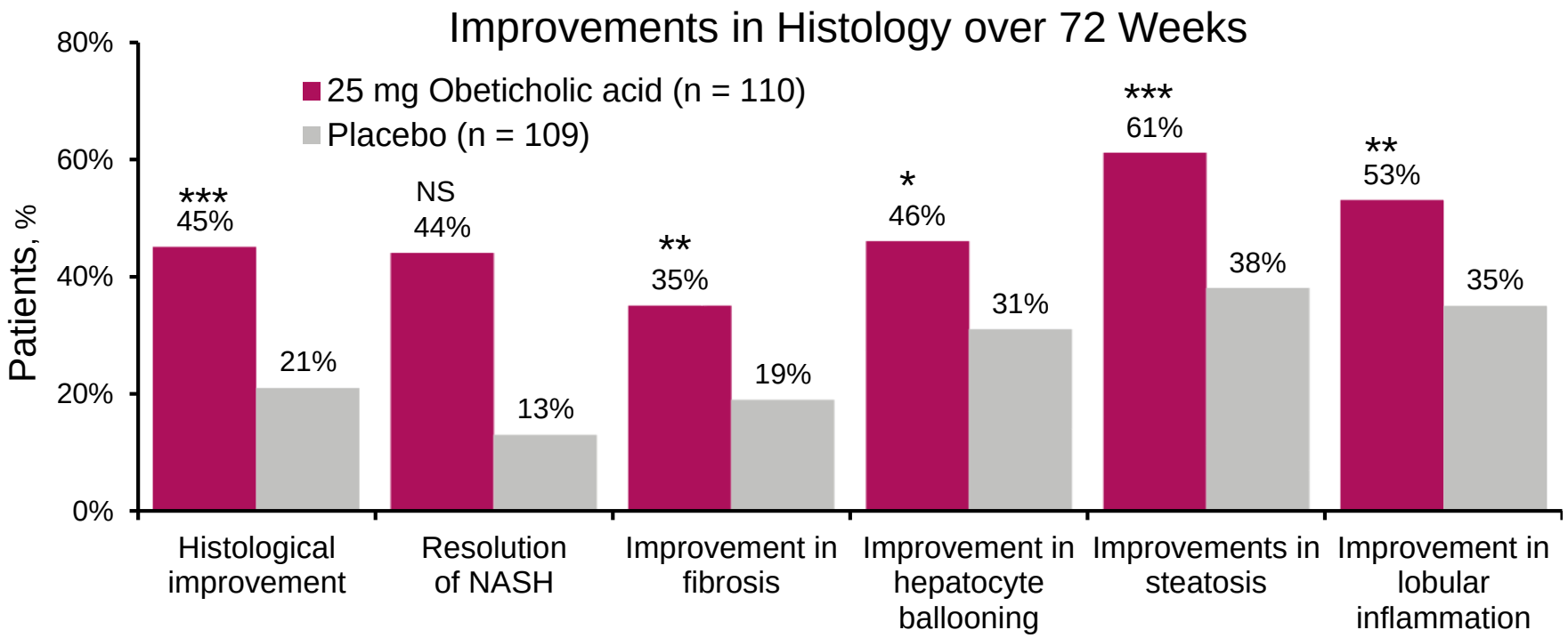
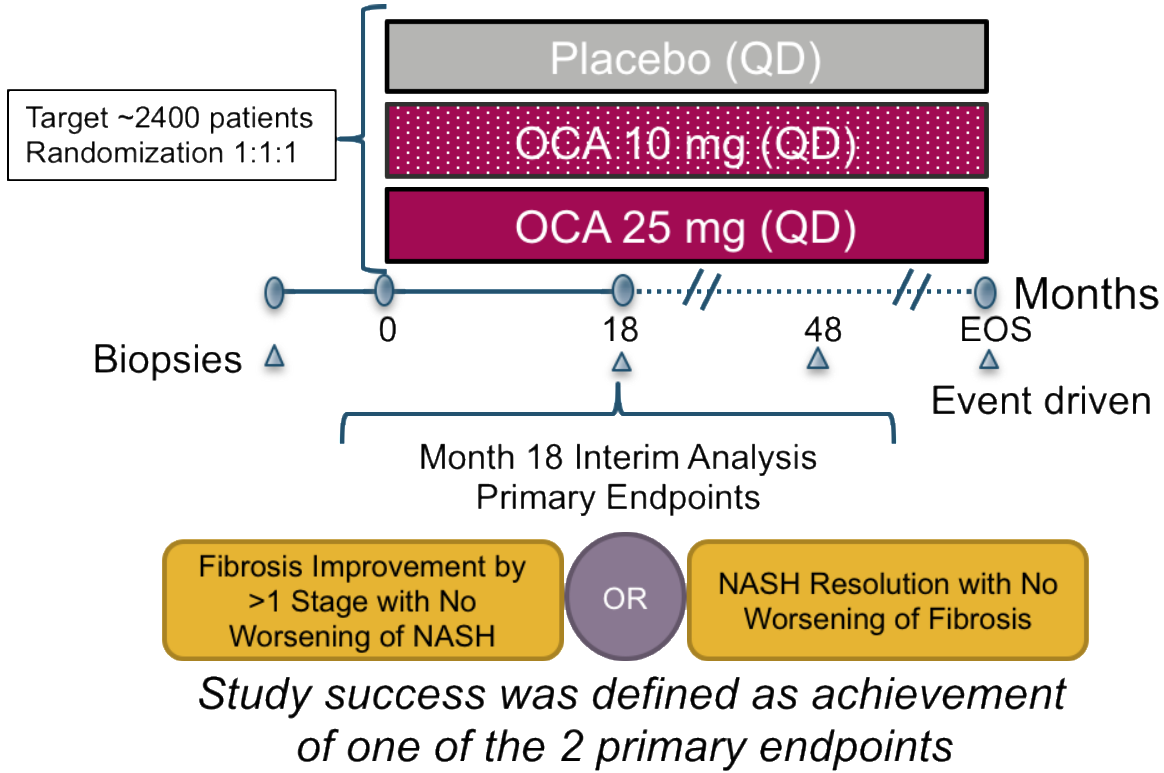
Obeticholic Acid: FLINT Study



NS = not significant; *P value ≤ 0.05; ** P value ≤ 0.01; *** P value ≤ 0.001.

Neuschwander-Tetri BA, et al. *Lancet*. 2015;385(9972):956-965; Younossi Z, et al. International Liver Congress 2019; April 10-14, 2019. Vienna, Austria. Abstract No. GS-06.

Obeticholic Acid: REGENERATE Design

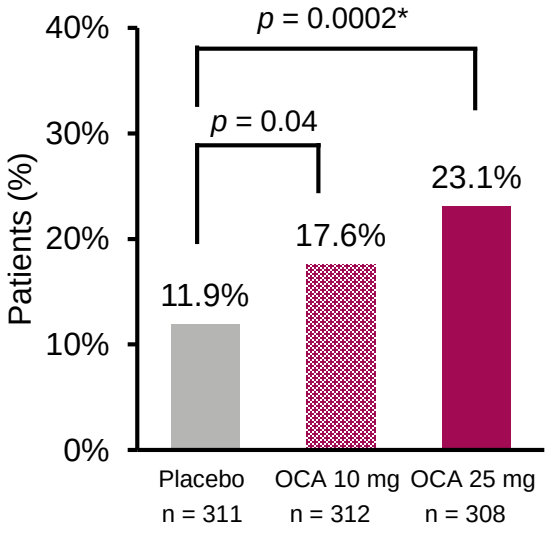


Study success was defined as achievement of one of the 2 primary endpoints

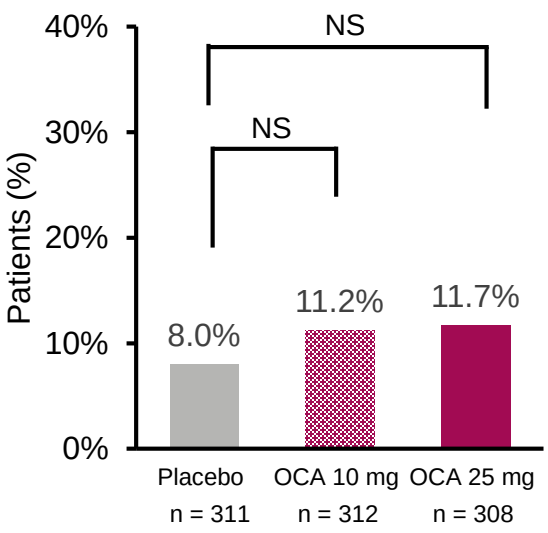
Ratziu V, et al. *Contemp Clini Trials* 019 Sep;84:105803. doi: 10.1016/j.cct.2019.06.017. Epub 2019 Jun 29.; Younossi Z, et al. International Liver Congress 2019; April 10-14, 2019. Vienna, Austria. Abstract No. GS-06.

Obeticholic Acid: REGENERATE Results

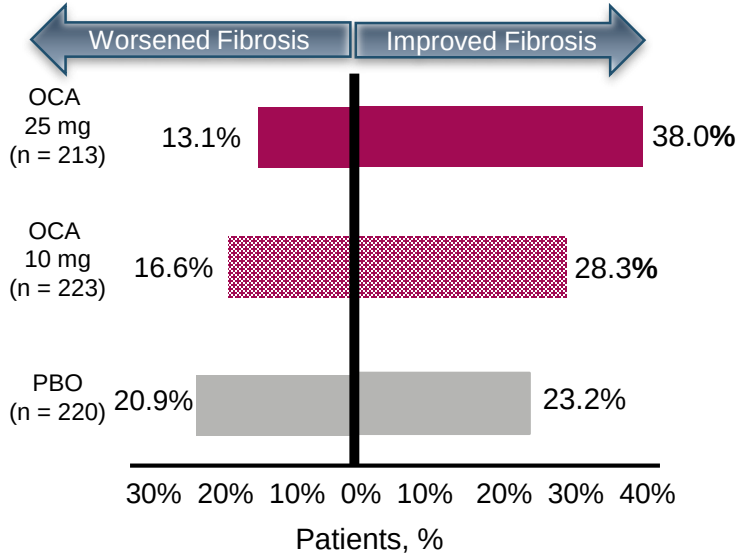
Primary Endpoint (ITT): Fibrosis Improvement by ≥1 Stage With No Worsening of NASH



NASH Resolution With No Worsening of Liver Fibrosis



Regression or Progression of Fibrosis by ≥1 Stage (Per Protocol With Post-Baseline Biopsy)

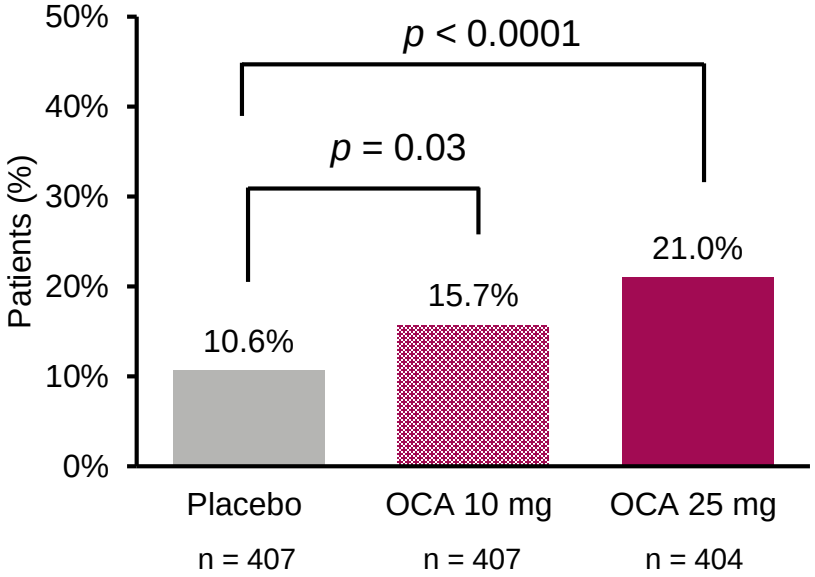


*Statistically significant in accordance with the statistical analysis plan agreed with the FDA

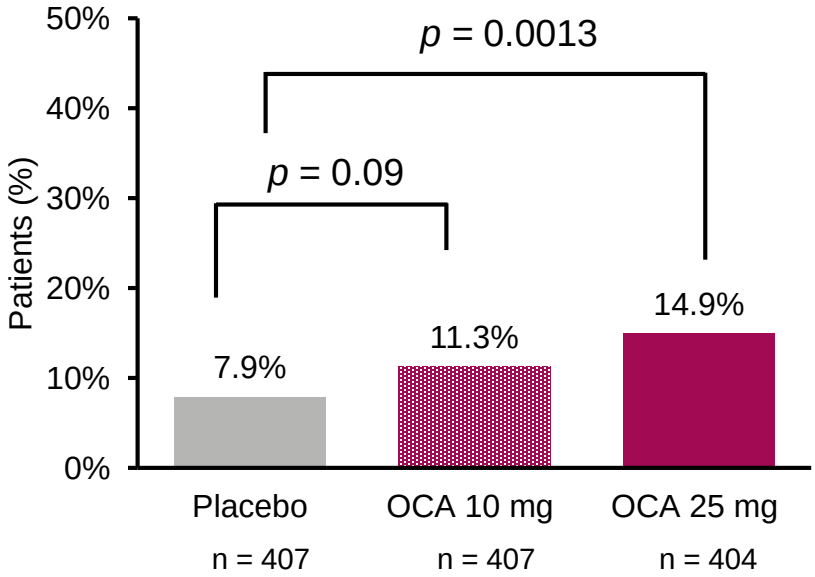
Younossi Z, et al. International Liver Congress 2019; April 10-14, 2019. Vienna, Austria. Abstract No. GS-06.

Obeticholic Acid: EXPAND-IT ITT

Fibrosis Improvement ≥1 Stage With No Worsening of NASH: Expanded ITT Population



NASH Resolution With No Worsening of NASH: Expanded ITT Population

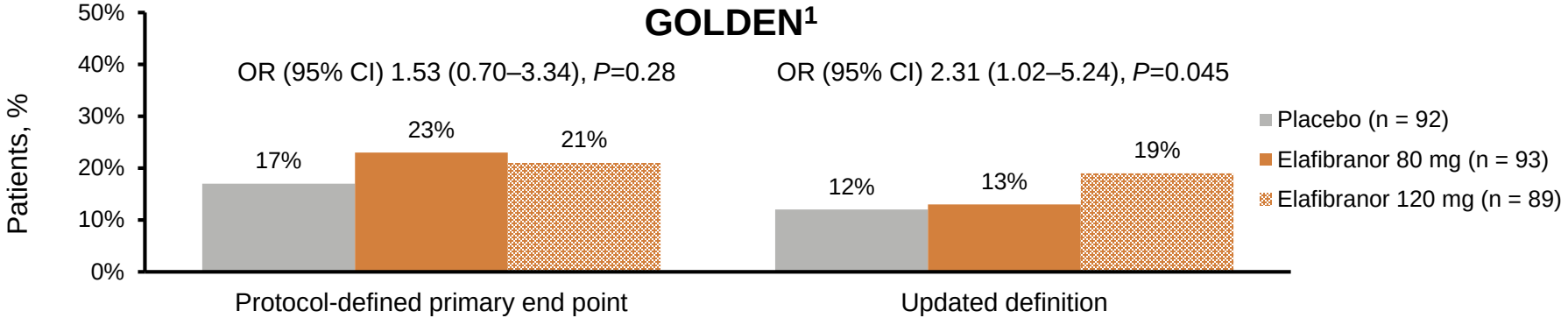


Sanyal A, et al. Abstract #34 Presented at The Liver Meeting 2019, November 8-12, 2019, Boston, MA.

Elafibranor: GOLDEN and RESOLVE-IT

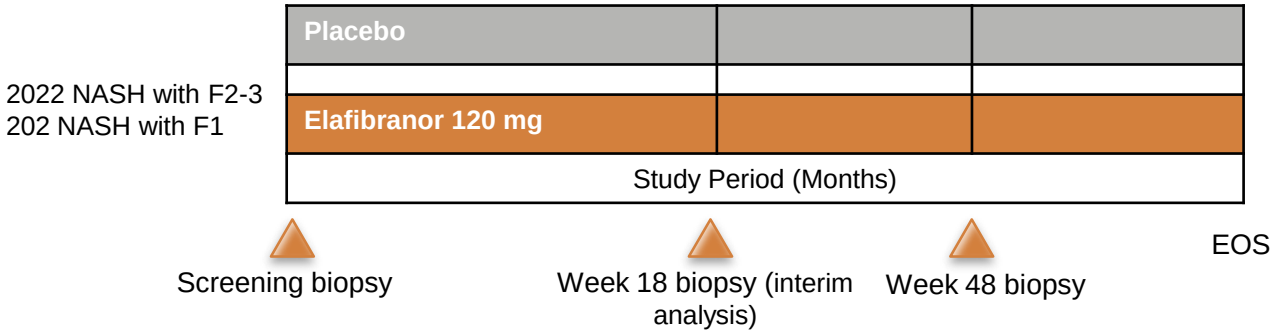
505-Peroxisome Proliferator-Activated Receptors (PPAR α/δ Pathways)

GOLDEN[1]



RESOLVE-IT[2]

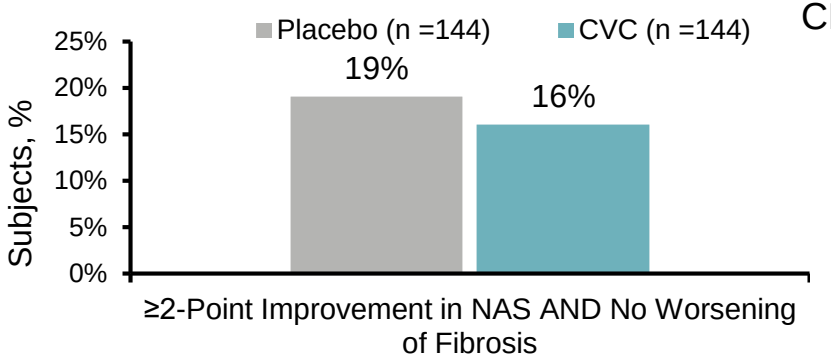
Primary Endpoint at Year 1: Resolution of NASH no worsening fibrosis

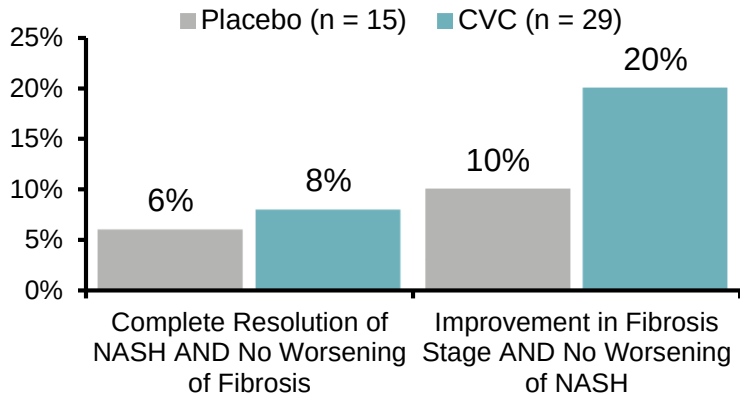


Ratziu V, et al. *Gastroenterology.* 2016;150(5):1147-1159.e5.; Birman P. Phase 3 Study to Evaluate the Efficacy and Safety of Elafibranor Versus Placebo in Patients With Nonalcoholic Steatohepatitis (NASH) (RESOLVE-IT). ClinicalTrials.gov Identifier: NCT02704403. 2016.

Cenicriviroc: CENTAUR and NASH-AURORA

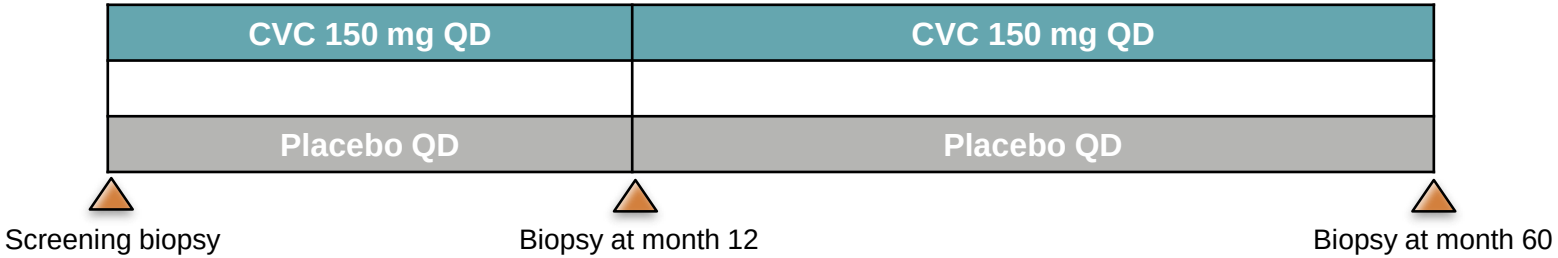
CENTAUR





NASH-AURORA Study

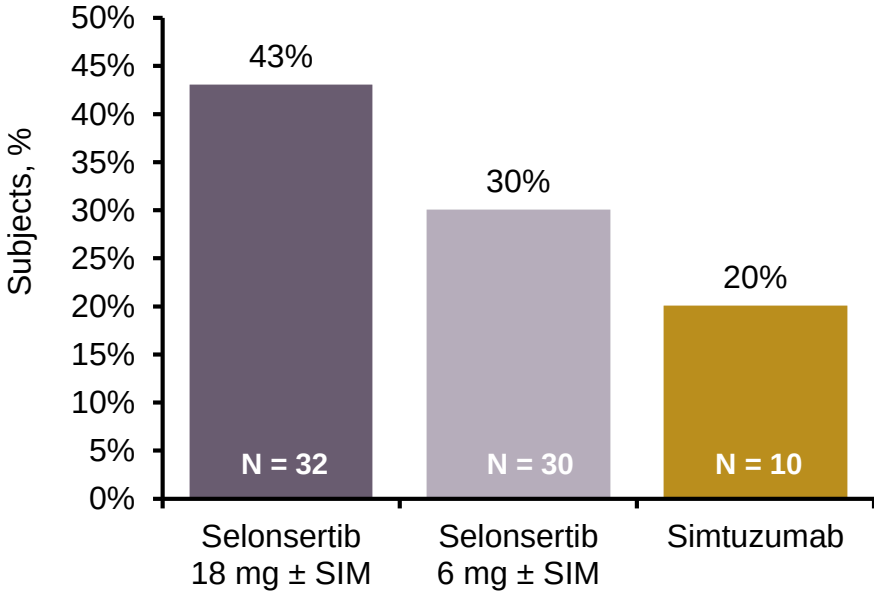
Primary Endpoint at Year 1: improvement in fibrosis AND no worsening of NASH (N ≅ 1000)



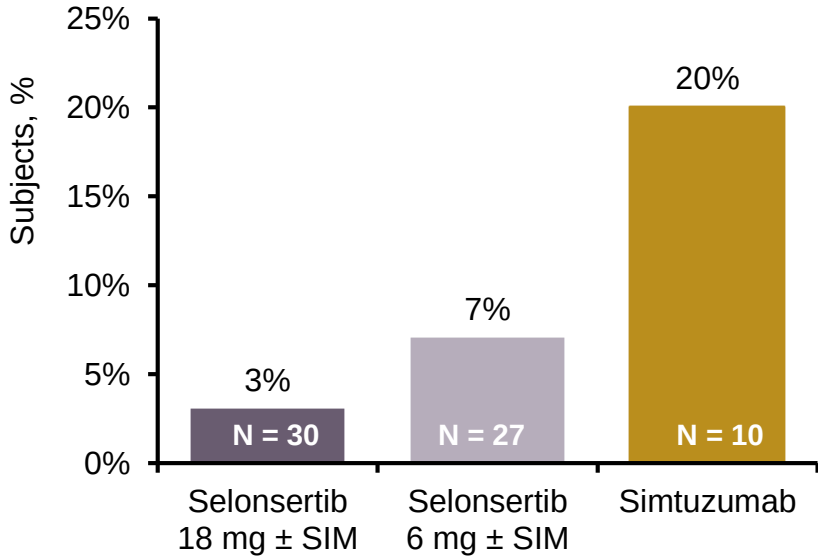
Ratziu V, et al. The International Liver Conference 2018; April 11-15, 2018. Paris, France. Abstract No. GS-002; Friedman SL, et al. *Hepatology.* 2018;67(5):1754-1767; Martins EB. AURORA: Phase 3 Study for the Efficacy and Safety of CVC for the Treatment of Liver Fibrosis in Adults With NASH. Clinical Trials.gov Identifier: NCT03028740.

Selonsertib: Phase 2 Study

Fibrosis Improvement (≥1 stage from baseline)



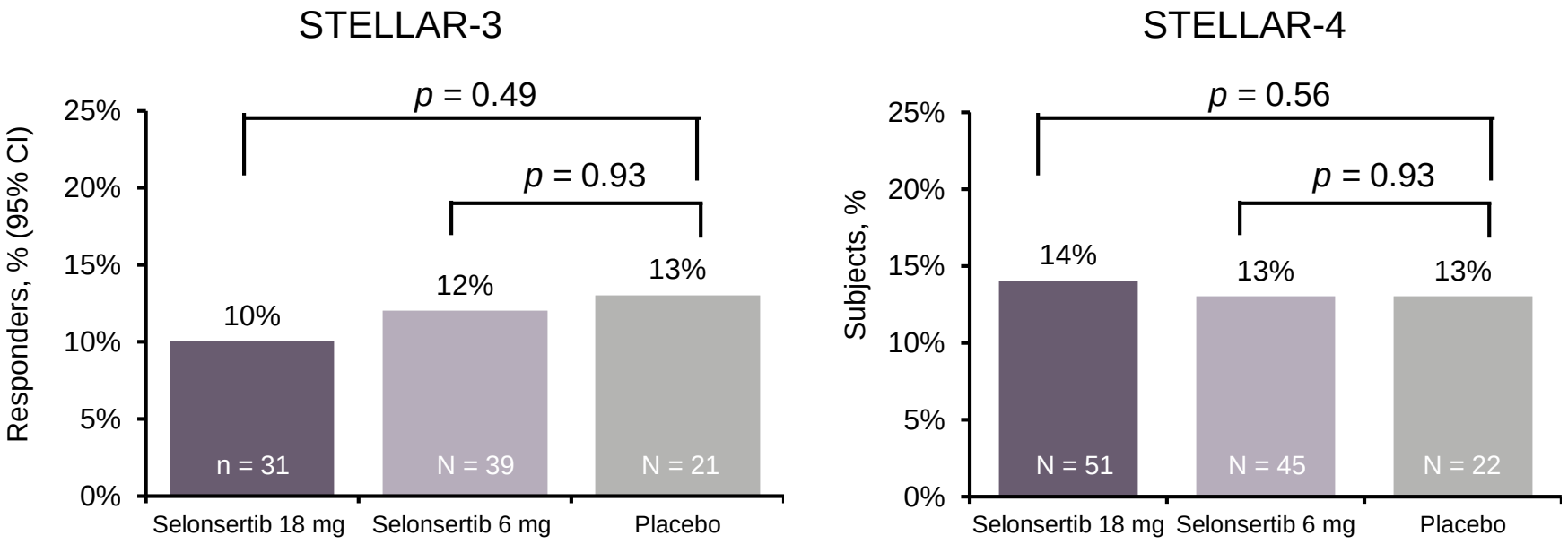
Progression to Cirrhosis at Week 24



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

Selonsertib: STELLAR-3 and STELLAR-4

Fibrosis Improvement Without Worsening of NASH



Harrison SA, et al. Abstract #64 Presented at The Liver Meeting 2019, November 8-12, 2019, Boston, MA.

Liver Fat Changes in Early Phase Trials

#futureofNASH

Liver Fat-Mapping Before and After Treatment

Why do we need to co-localize?

Heterogeneity in distribution
More comprehensive assessment

↓

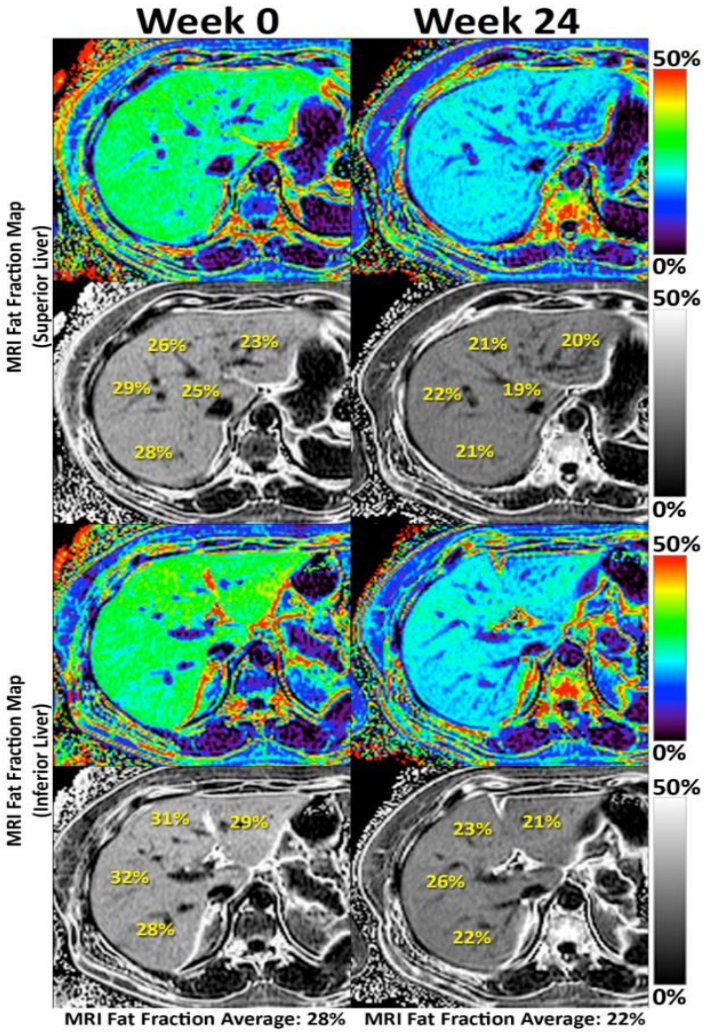
Higher precision and accuracy

↓

Enhanced responsiveness

↓

Efficiency in clinical trial

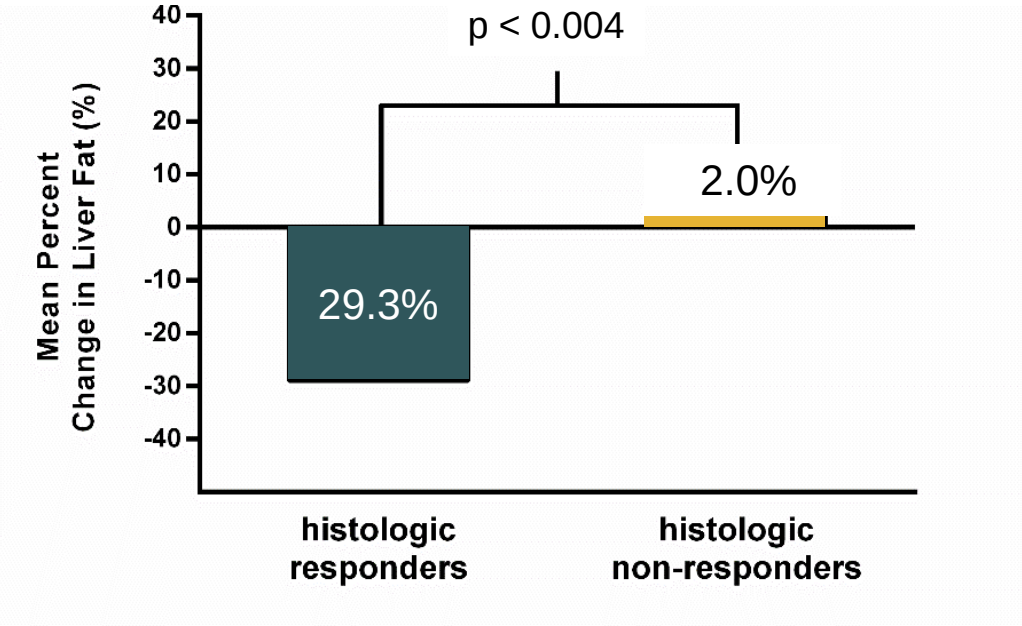


Loomba R, et al. *Hepatology*. 2015;63(1):10-12.

What is a clinically significant reduction in MRI-PDFF?

#futureofNASH

Change in MRI-PDFF Estimated Liver Fat Content by Histologic Response



30% reduction in MRI-PDFF may be associated with a 2-point improvement in NAFLD Activity Score (NAS): FLINT Trial

Patel J, Loomba R, et al. *Therapeutic Advances in Gastro.* 2016;9(5):692-701.

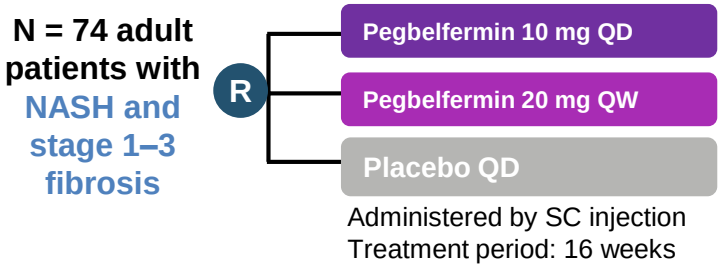
Pegbelfermin: Phase 2 Study

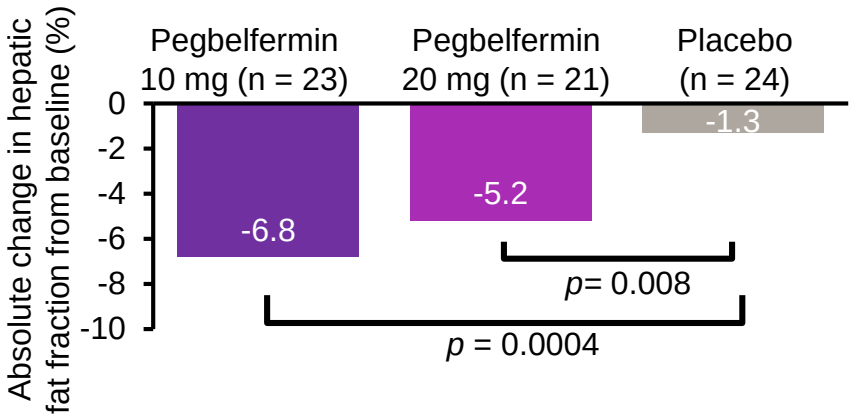
Pegbelfermin

- Pegylated FGF21 analogue
- Reduces steatosis and piotoxicity
- Improved lipid profiles
- Reduces hepatic inflammation and pro-C3, a marker of fibrosis

Primary outcomes

- Change in hepatic fat fraction (%) from baseline to Week 16

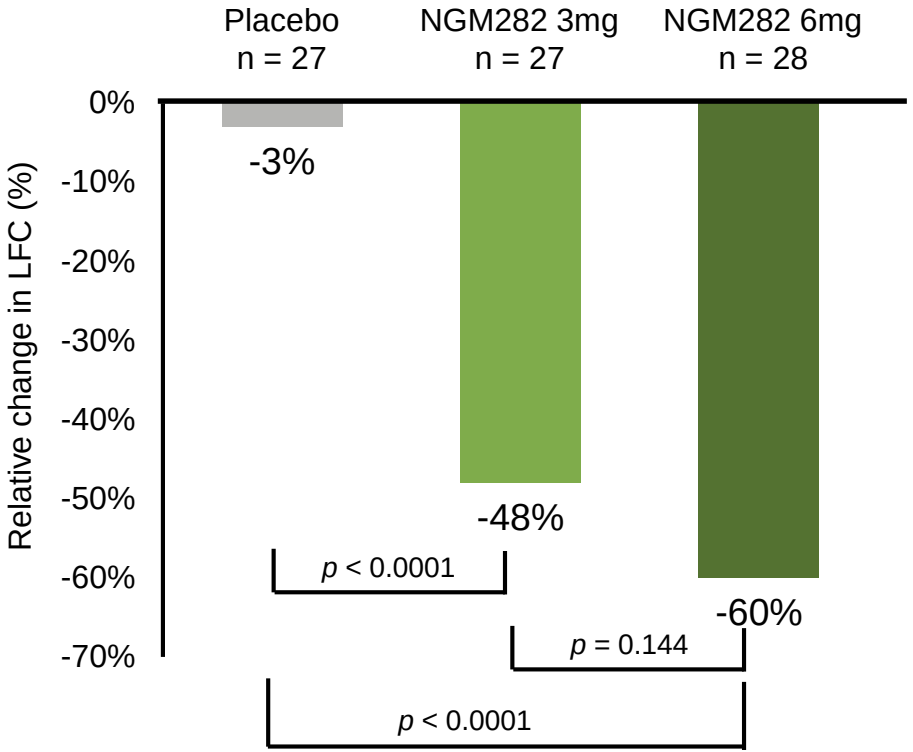




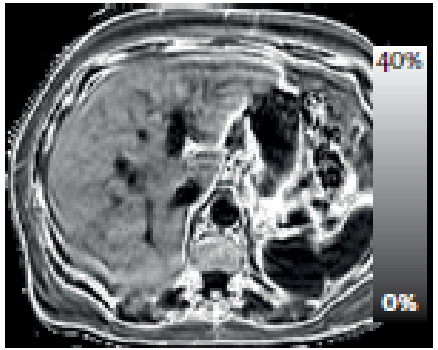
FGF, fibroblast growth factor

Sanyal AJ, et al. *Lancet*. 2019; 392(10165):2705-2717.

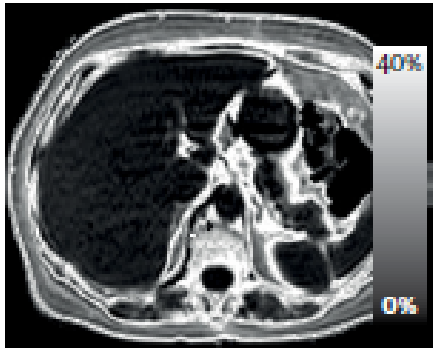
NGM282: Phase 2 Study



Baseline
MRI-PDFF = 24.1%



12 weeks
MRI-PDFF = 3.6%



Harrison SA, et al. *Lancet.* 2018;391(10126):1174-1185.

Resmetirom: Phase 2 Study

Enrolled
N=125 adult patients with NASH and stage 1–3 fibrosis

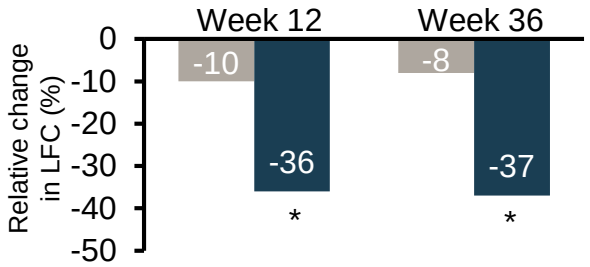
R

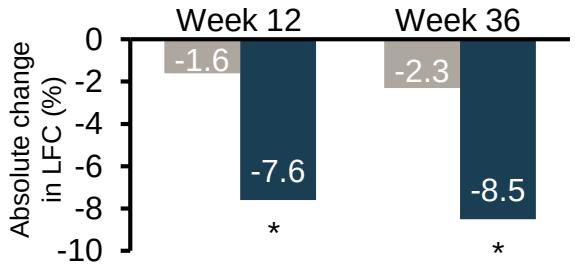
- MGL-3196 80 mg†
- Placebo

Administered orally once daily
Treatment period: 36 weeks, followed by 36-week open-label extension

Primary outcomes

- Change from baseline in hepatic fat fraction assessed by MRI-PDFF at week 12





Results

- More patients achieved a 2-point NAS improvement (56% vs 32%; *P* = .02)
- More patients achieved NASH resolution (27% vs 6%; *P* = .02)

*$p < 0.0001$ vs placebo.
MRI-PDFF, magnetic resonance imagine-proton density fat fraction.
Harrison SA et al. Presented at AASLD 2019, available at: https://www.madrigalpharma.com/wp-content/uploads/2018/11/MGL-3196-Plenary-presentation-Nov-10-NASDAQ.pdf

Combinations with Complementary MOA

Future: Targeting Multiple Pathways

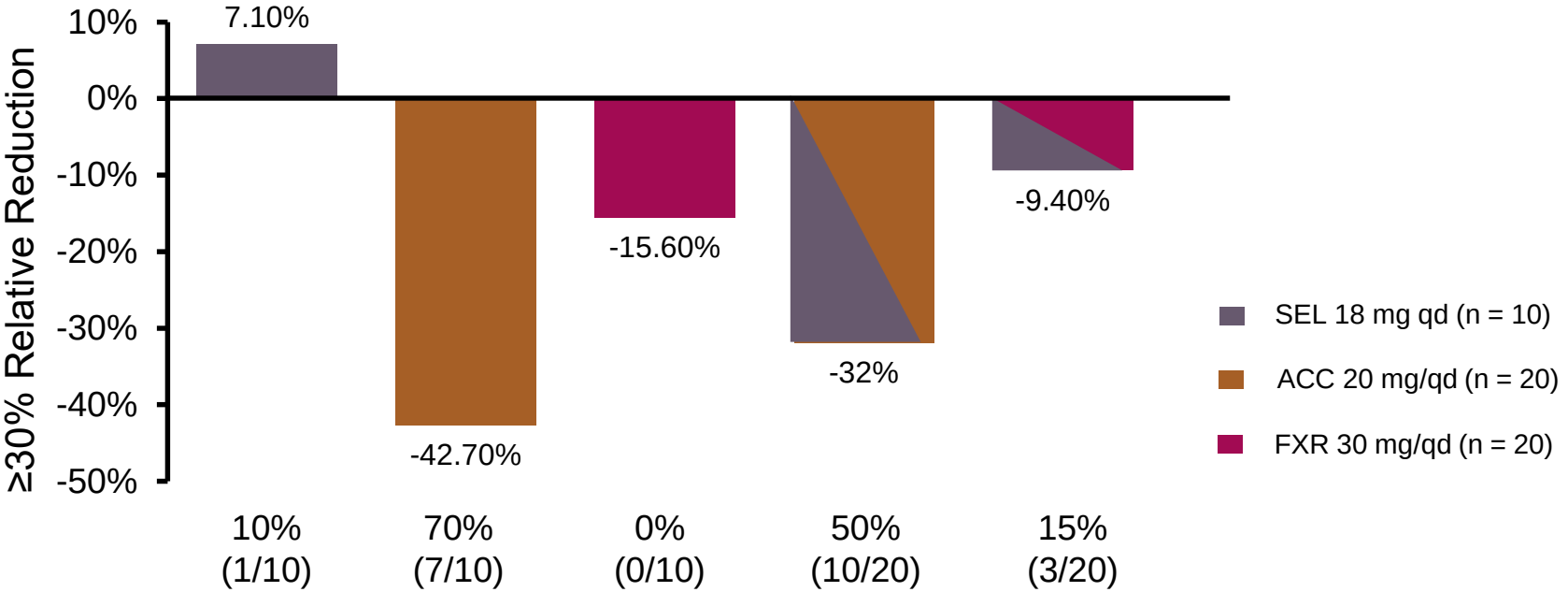
Mechanism of Action (MOA)	Disease Process/ Pathway Target(s)
ASK1 inhibitor (selonsertib) and non-steroidal FXR agonist (GS-9674) and/or ACC inhibitor (GS-0976)[1]	Inflammation, fibrosis, and lipogenesis
Combined PPAR alpha and delta agonist (elafibranor) and an FXR agonist[2]	Inflammation, fibrosis,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

Combinations with Complementary MOA

Combination of Selonsertib (SEL) with GS-0976 (ACC) or GS-9674 (FXR)



ACC = acetyl-CoA carboxylase; FXR = farnesoid X receptor.

Lawitz E, et al. ILC. April 11-15, 2018; Paris, France. Abstract PS105.

SMART Goals

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

- Identify the risk factors and the markers of disease progression in patients with NAFLD
- Apply the latest data to choose appropriate non-invasive diagnostic and prognostic tools
- Stay current on the latest clinical trial evidence on novel emerging therapies for NASH

Questions & Answers

#futureofNASH