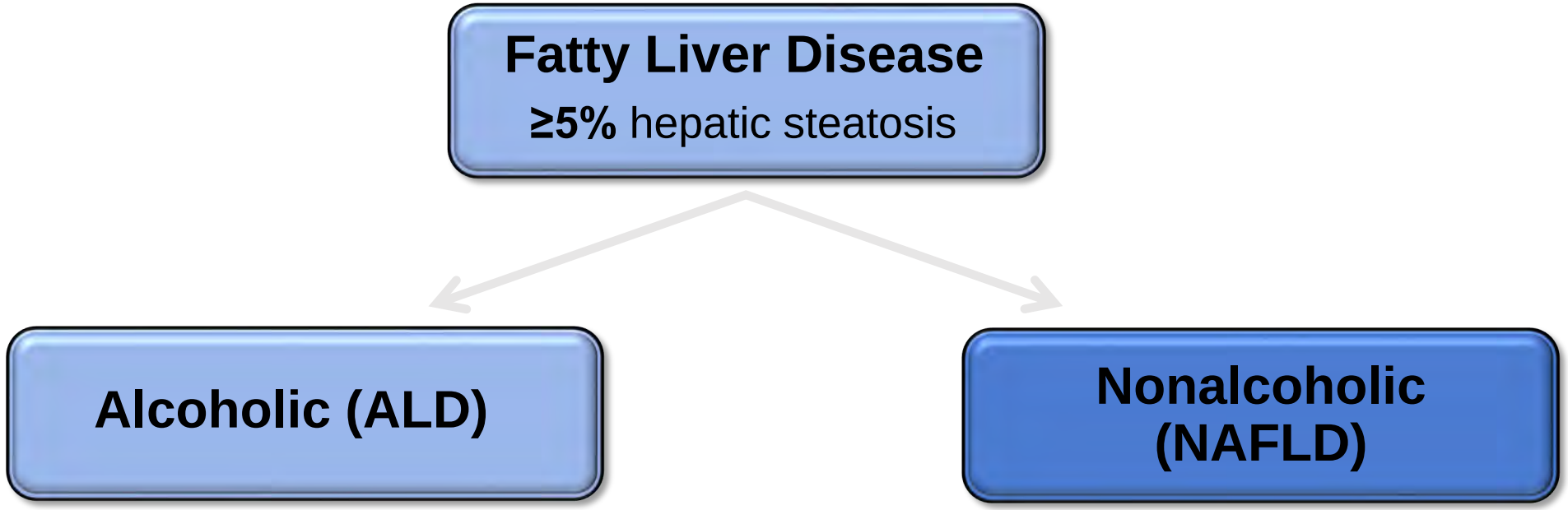
Update on NAFLD/ NASH And HCV

Anita Kohli, MD
Arizona Liver Health

Fatty Liver Disease: Alcoholic and Nonalcoholic



ALD or NAFLD: How **Do You Know?**

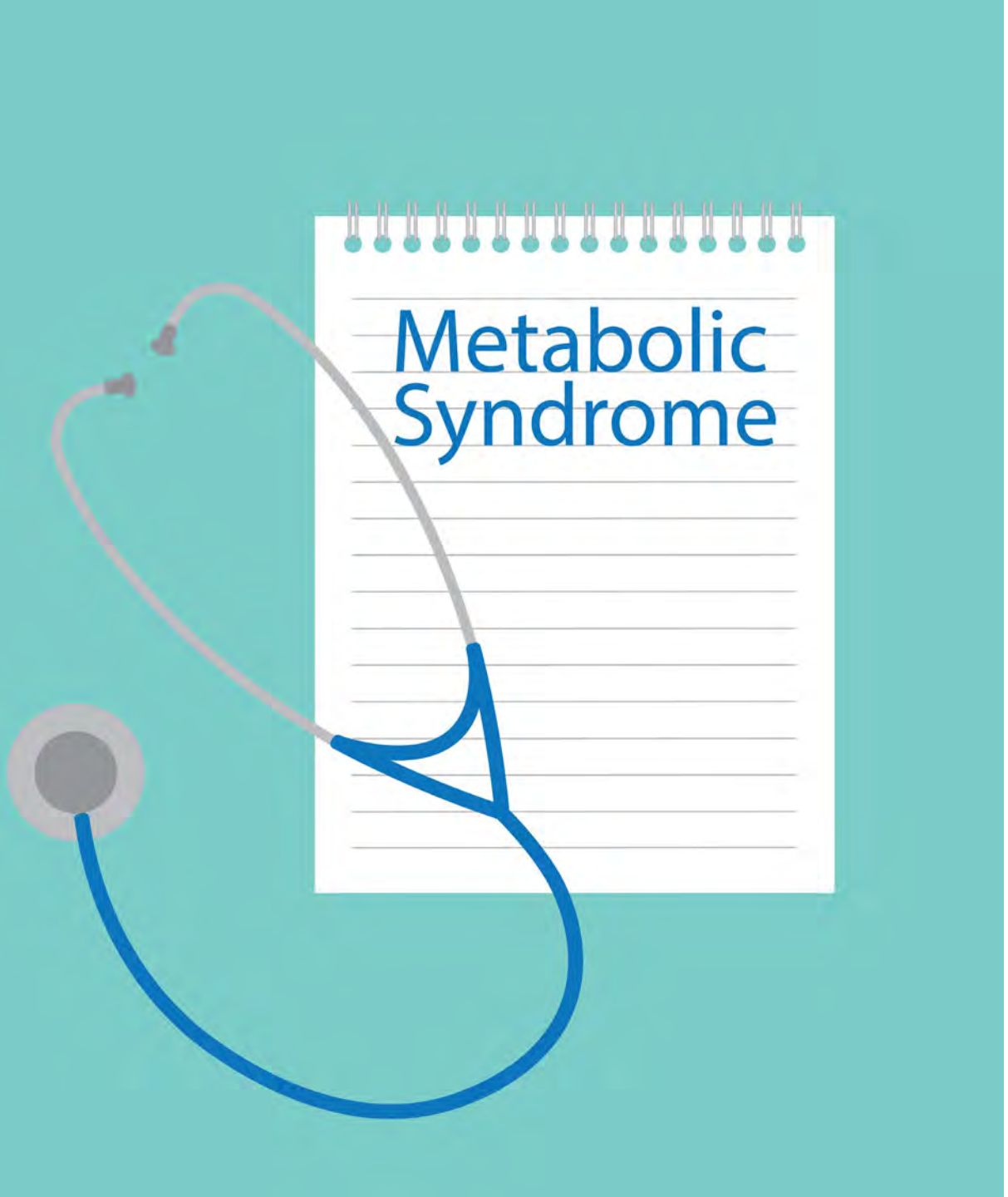
Dose of Alcohol

Excessive amounts of alcohol is defined as:

- **≥ 3 drinks/day for men (21 drinks/week)**
  ≥ 2 drinks/day for women (14 drinks/week)

A standard drink of beer, distilled spirits, and wine each contain the same amount of alcohol.

Standard Alcoholic Drink = 10 g of alcohol

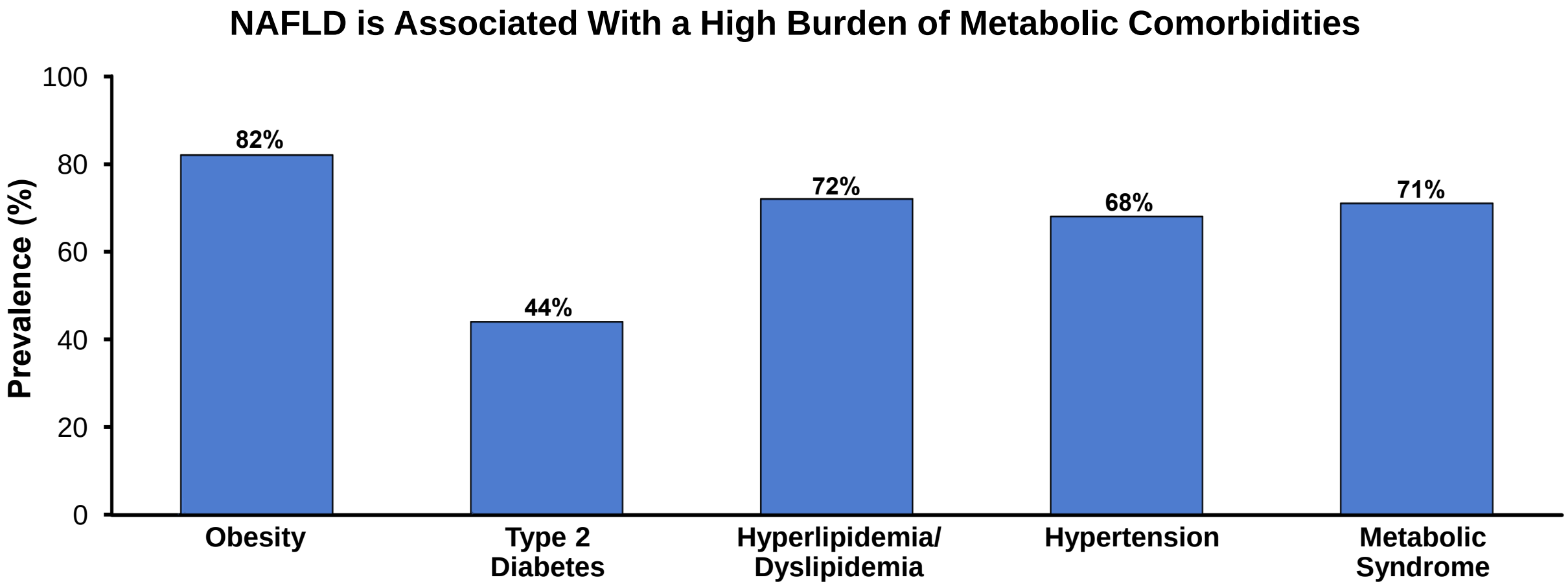


Metabolic Syndrome

- Insulin Resistance
- Dyslipidemia
- Hypertension

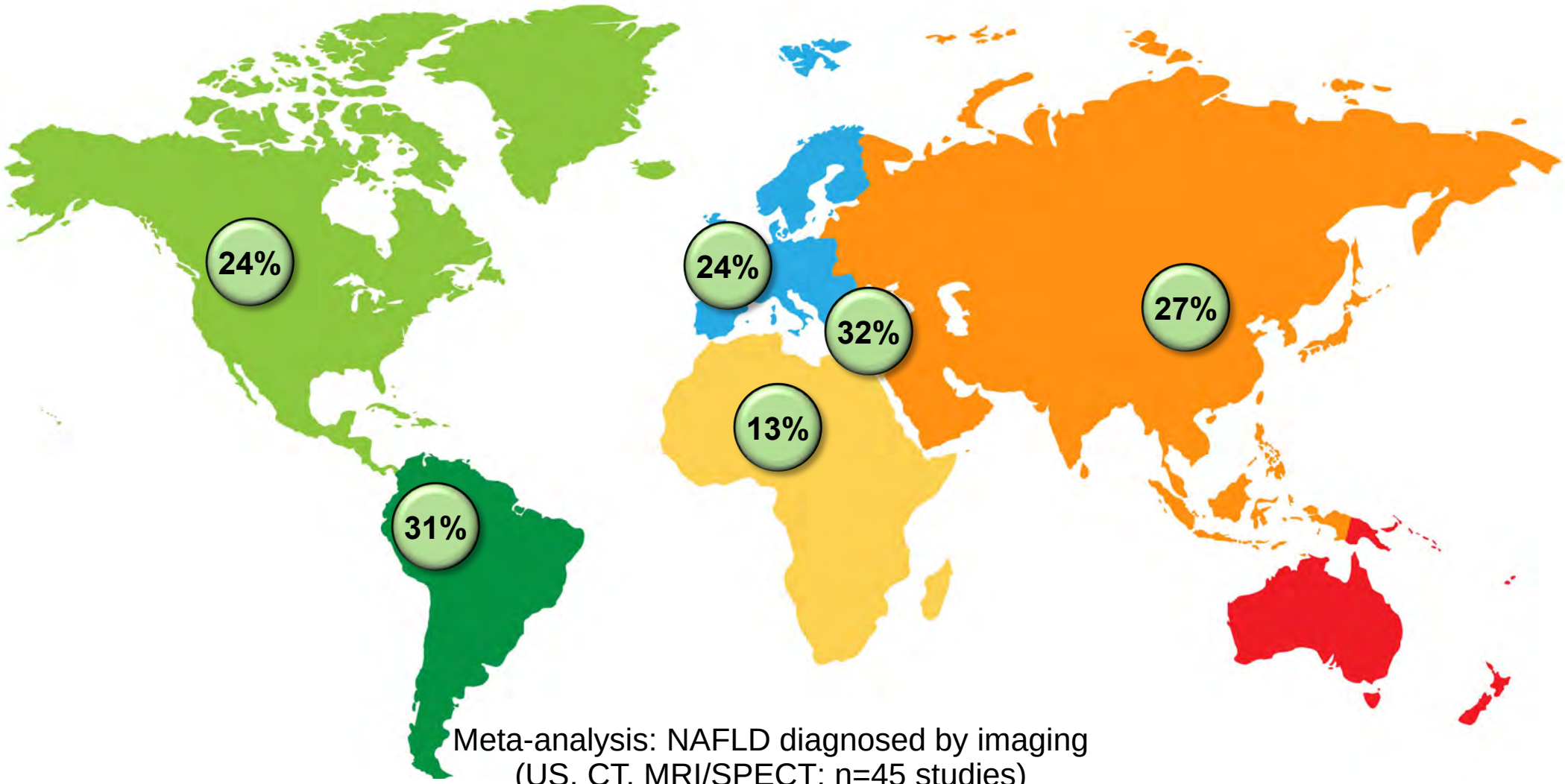
NAFLD

Comorbidities Associated With NAFLD: Global Prevalence Among NAFLD Patients



Adapted from Younossi ZM, et al. *Hepatology.* 2016;64:73-84.

Estimated Global Prevalence of NAFLD: 25%

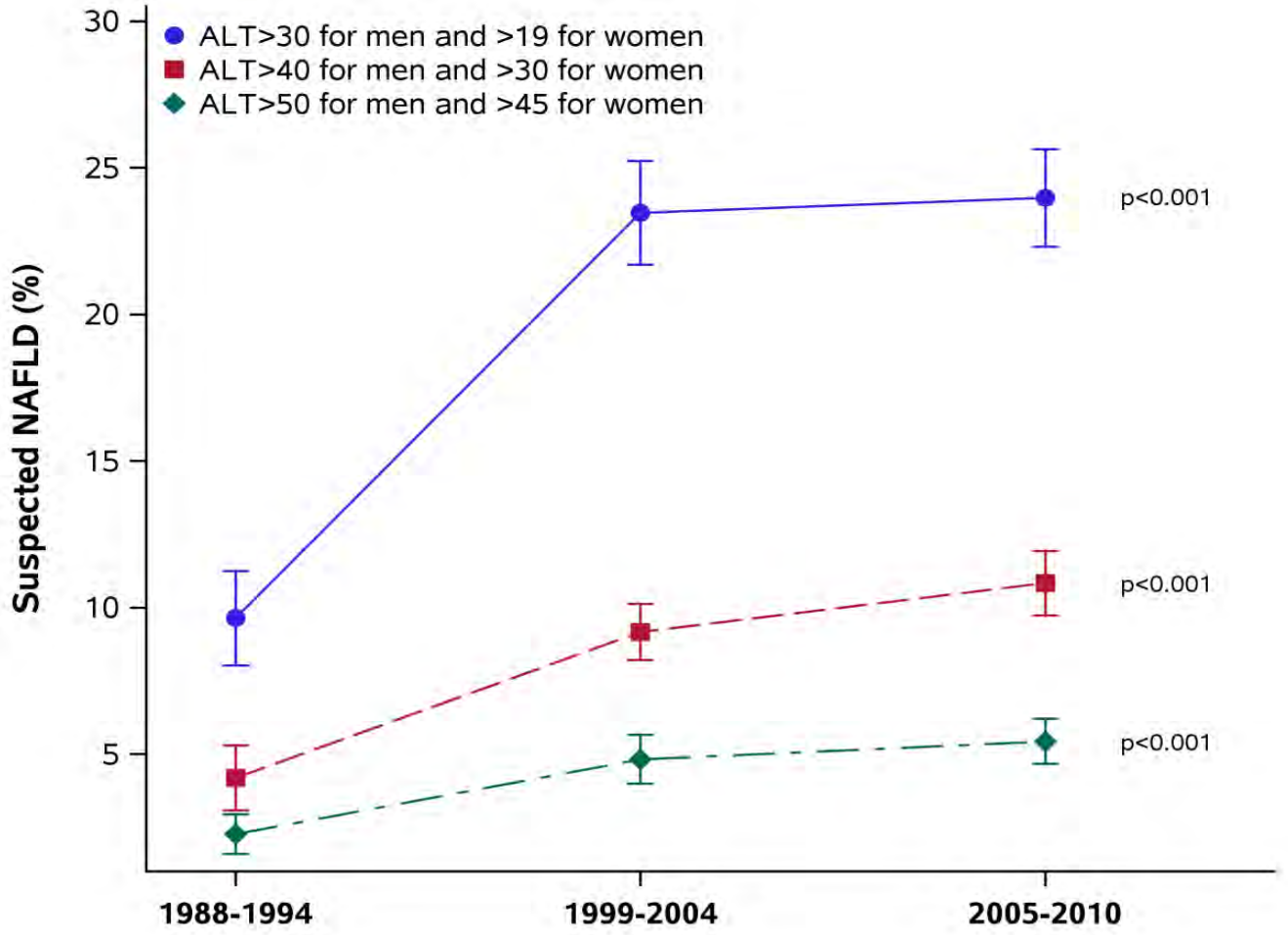


Meta-analysis: NAFLD diagnosed by imaging
(US, CT, MRI/SPECT; n=45 studies)

Younossi ZM, et al. *Hepatology.* 2016;64:73-84.

Burden of NAFLD Among Young Adults in the US

- National Health And Nutrition Examination Survey (NHANES) database
- 14,371 subjects
- Age 18-35
- Three study periods:
  - 1988-1994
  - 1999-2004
  - 2005-2010

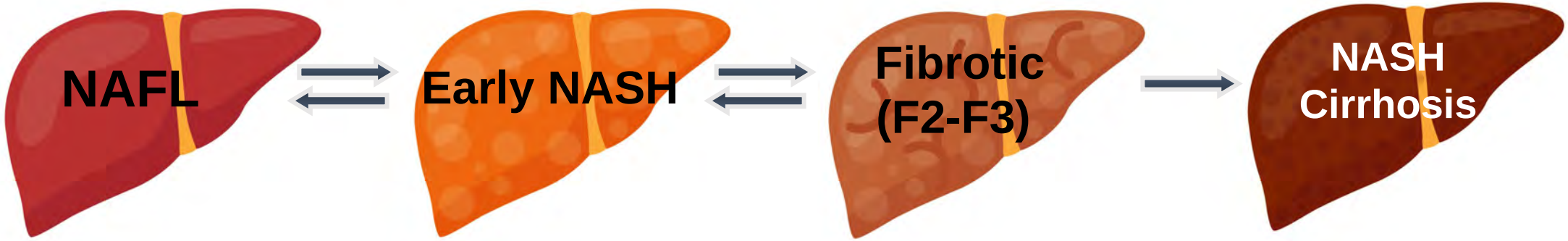


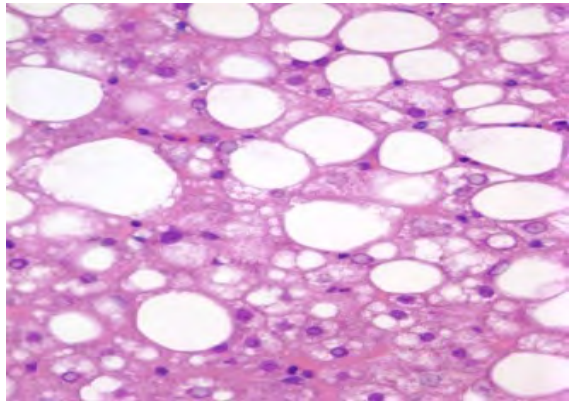
Abou Mrad R., Alkhouri N., et. al. *Hepatology.* 2016.

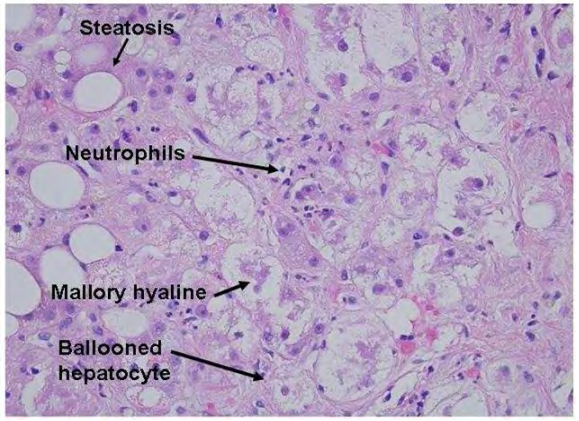
Young Kids, Old Bodies

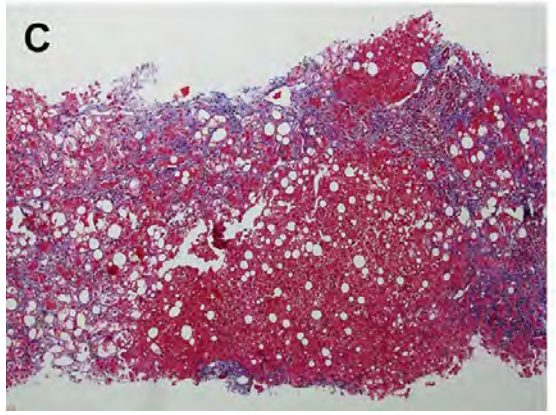
Obesity is turning a generation of children into biological adults, ageing them before their time

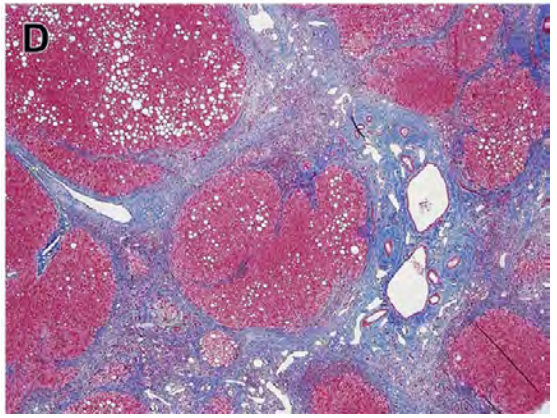
The NAFLD Spectrum



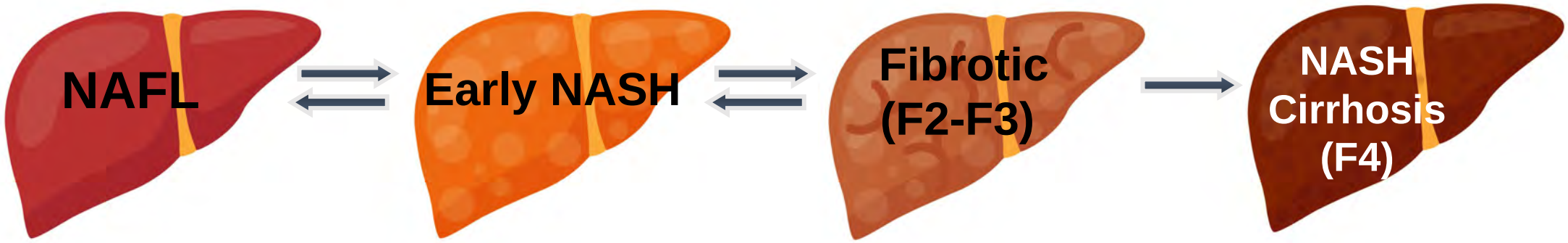


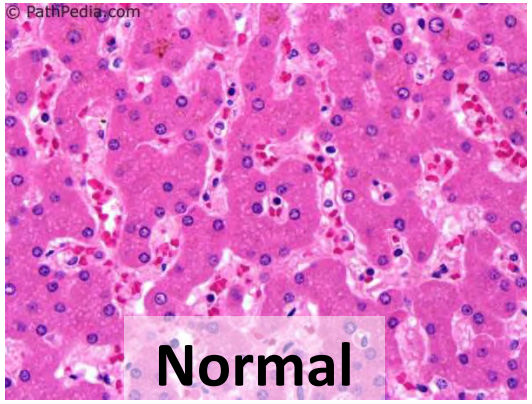


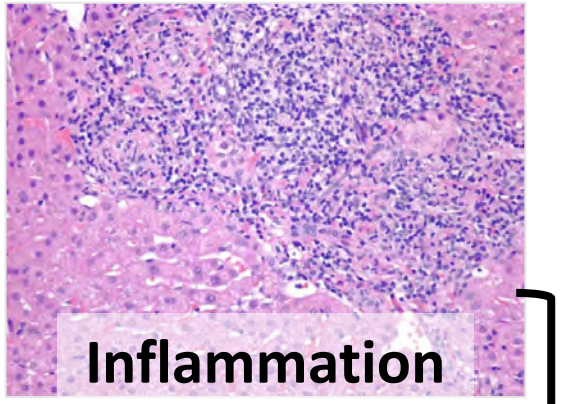


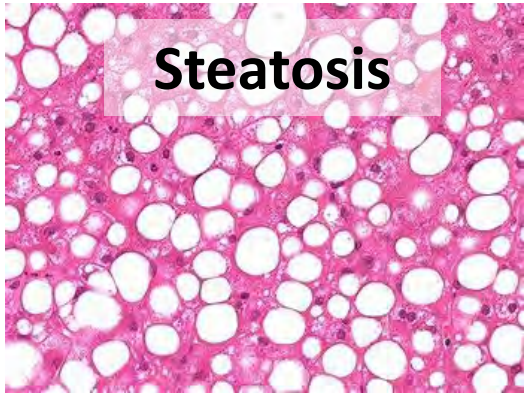


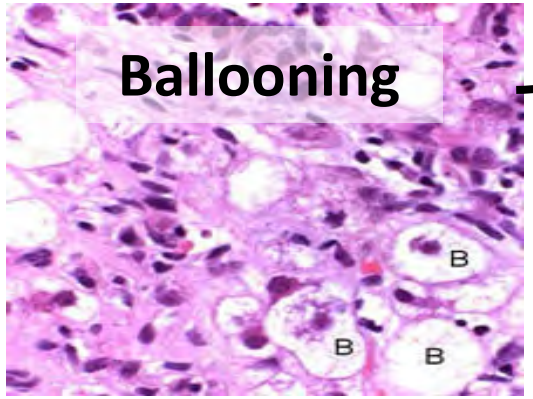
The NAFLD Spectrum (con't)









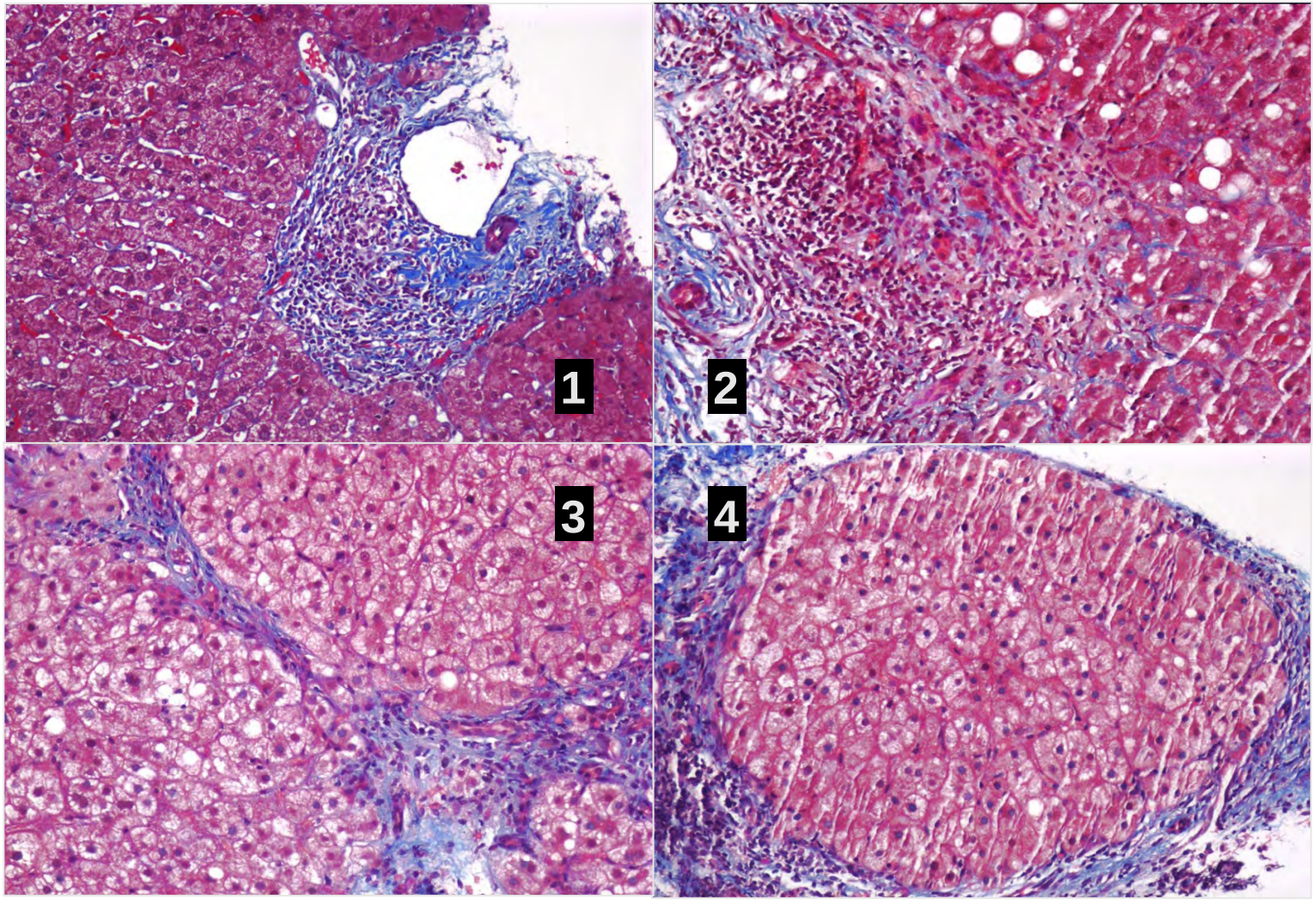


Activity

NAFLD Activity Score	
Steatosis (0-3)	
5-33%	1
34-65%	2
≥66%	3
Inflammation (0-3)	
<2 under 20x	1
2-4 under 20x	2
>4 under 20x	3
Ballooning (0-2)	
Few	1
Many	2

Four Stages of Fibrosis

Periportal OR Perisinusoidal

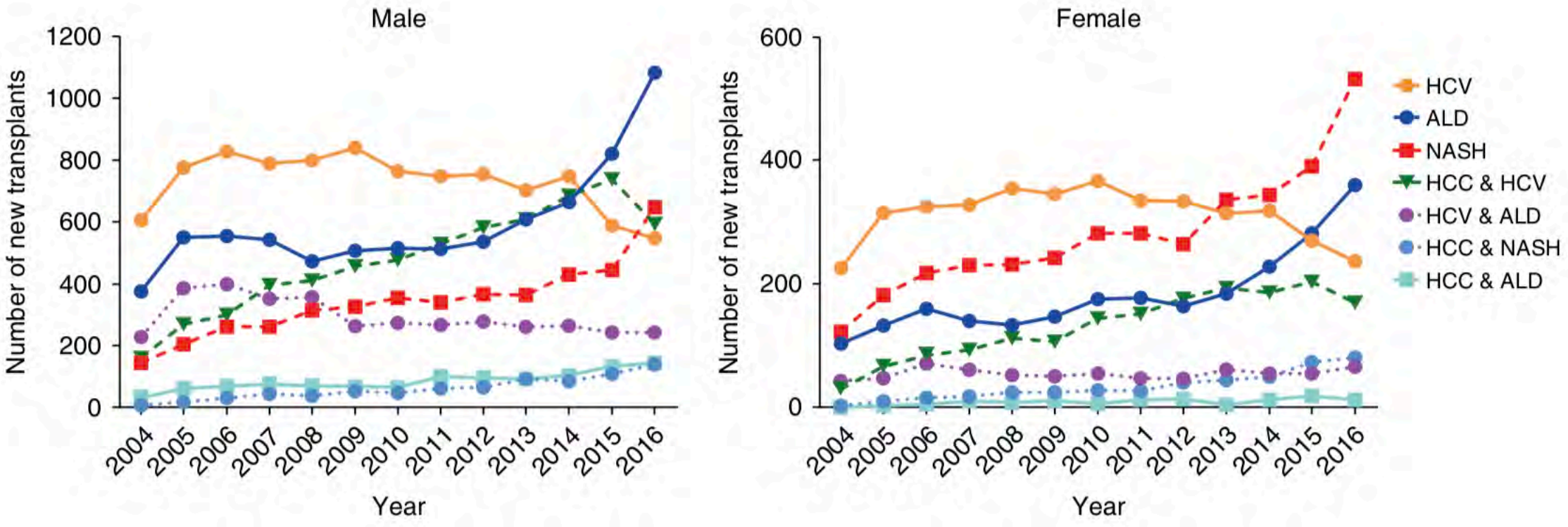


Periportal AND Perisinusoidal

Bridging Fibrosis

Cirrhosis

NASH is the Most Common Indication for Liver Transplantation (LT) in Women in the U.S.



Noureddin M, Alkhouri N et al. AJG. 2018

Weight Loss Through Lifestyle Modification in NAFLD

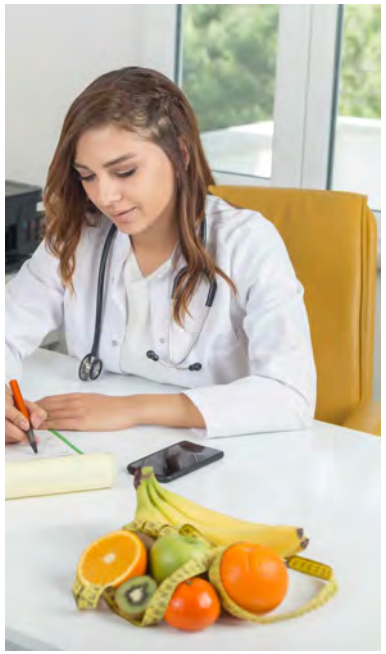
Weight Loss	Outcome Among Patients Achieving Weight Loss	Patients Sustaining Weight Loss at 1 Yr[1]
≥ 10%	Fibrosis regression (45% of patients)[1]	< 10%
≥ 7%	NASH resolution (64% to 90% of patients)*	18%
≥ 5%	Ballooning/inflammation improvement (41% to 100% of patients)*	30%
≥ 3%	Steatosis improvement (35% to 100% of patients)*	Not reported

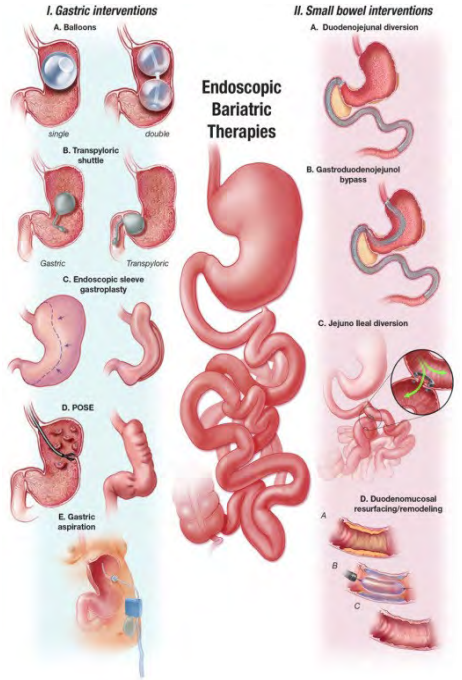
*Depending on degree of weight loss.

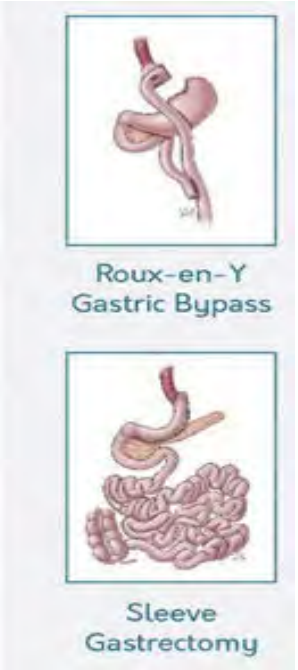
Vilar-Gomez. Gastroenterology. 2015;149:367.

Weight Management Spectrum for NAFLD

Traditional Lifestyle Intervention	PDT for Weight Loss	AOMs - Oral - Injectable	EndoBariatric Procedures	Bariatric Surgery

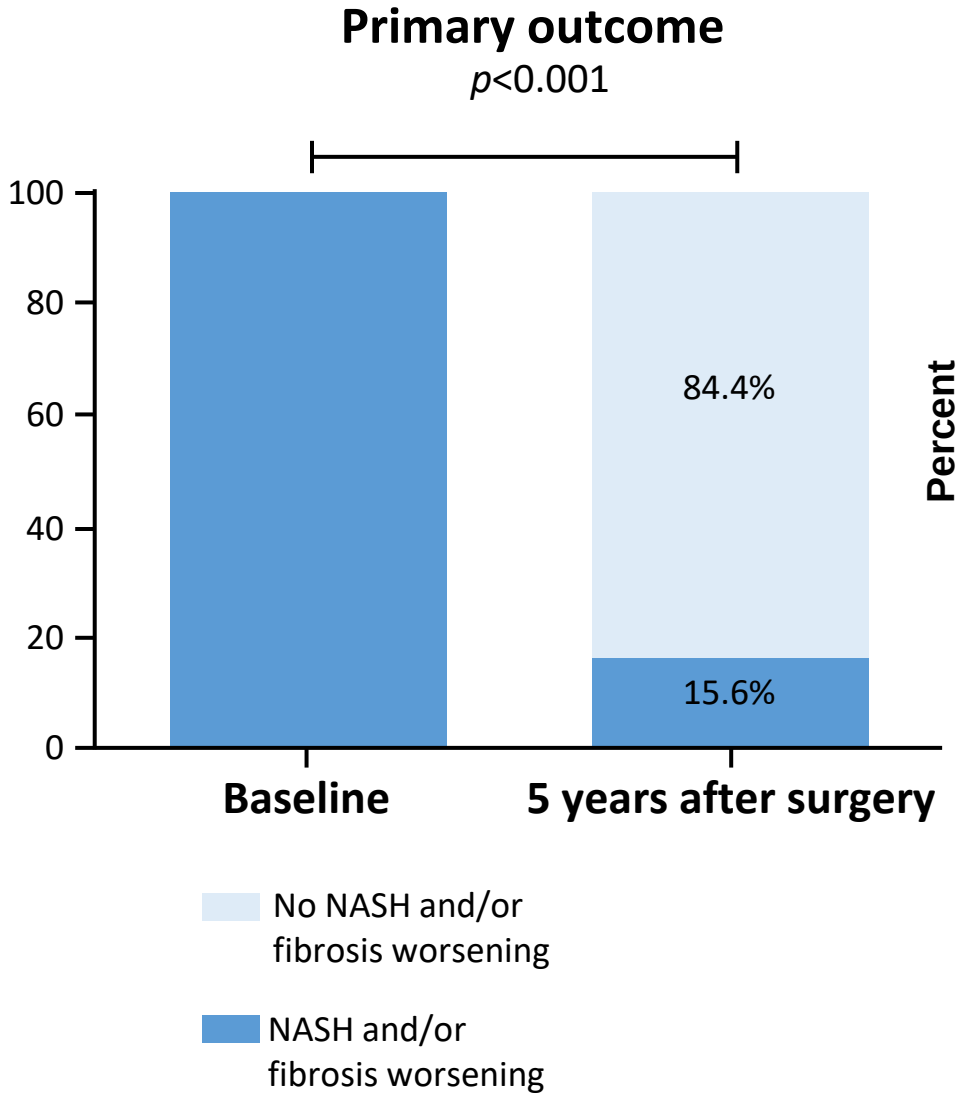


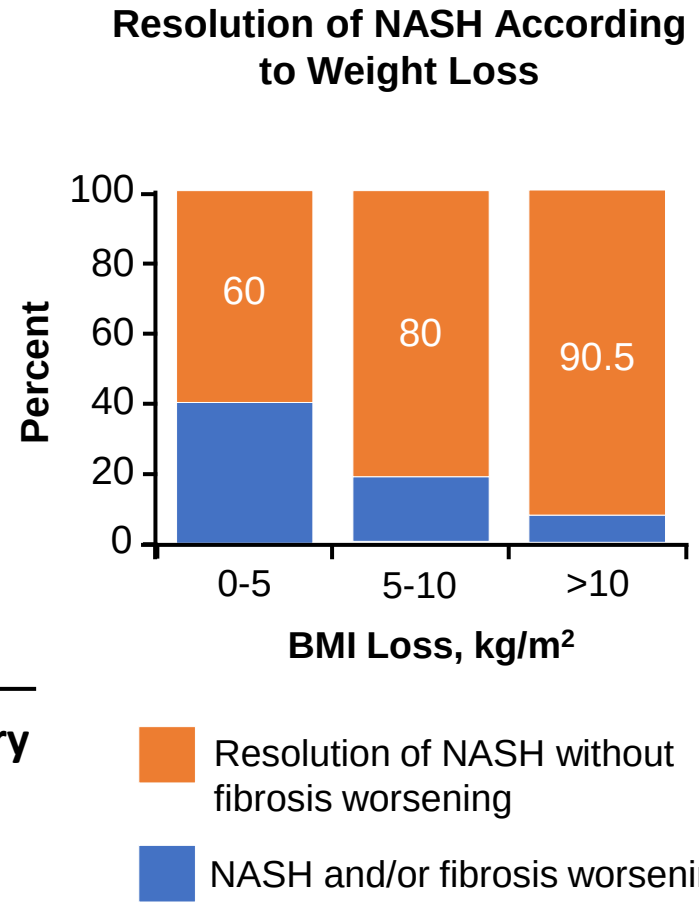




Is NASH Reversible with Bariatric Surgery?

- French single-center study of **bariatric surgery** in severely obese patients with biopsy-confirmed NASH (N = 180)
- At 5 yrs. post surgery, 64 of 94 patients (84%) had NASH resolution with no worsening of fibrosis
  - NASH improvement correlated with weight loss.





Lassailly. *Gastroenterology*. 2020;159:1290.

Current Pharmacologic Treatments for NASH

ORIGINAL ARTICLE

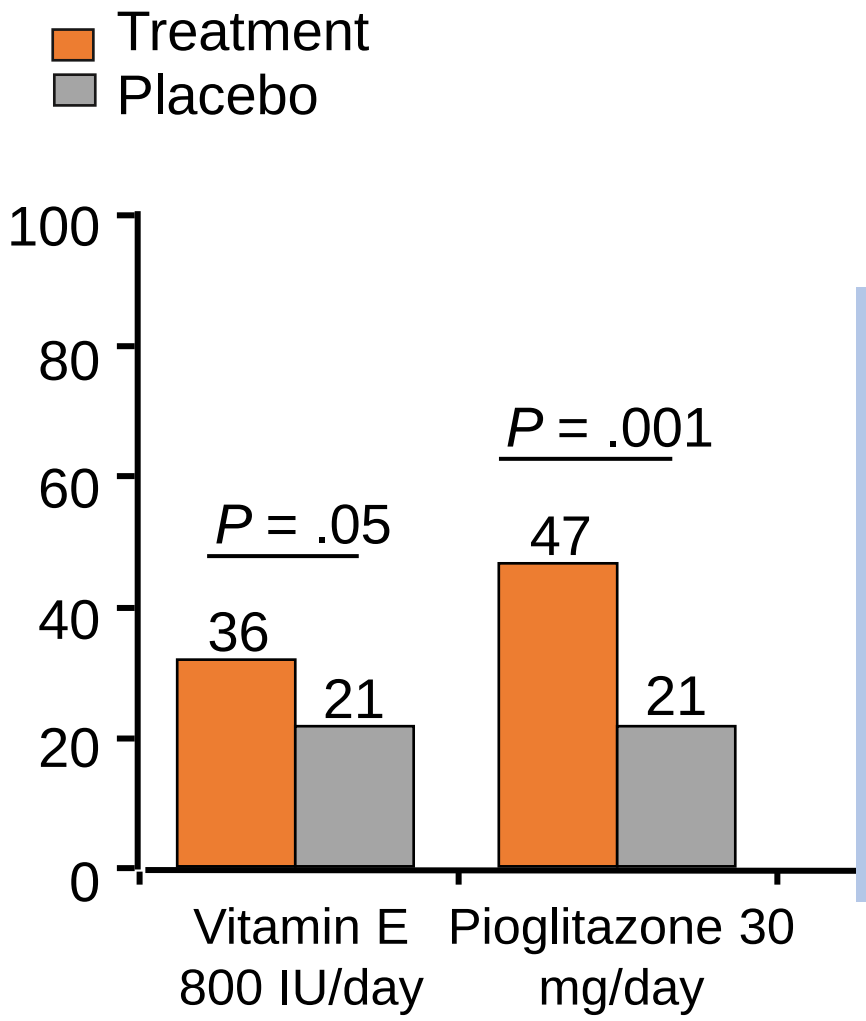
Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis

- 247 **non-diabetic** patients with NASH
  - Pioglitazone: 30 mg/d
  - Vitamin E: 800 IU/d
  - Placebo

- Primary outcome: Improvement in histologic features of NASH

Sanyal AJ et al. *N Engl J Med.* 2010

Resolution of NASH with Vitamin E and Pioglitazone



- **Vitamin E: Increased overall mortality/ hemorrhagic stroke/prostate cancer**
- **Pioglitazone: Weight gain, fluid retention- HF?/ Increased risk of bladder cancer/ osteoporosis/**

WE DON'T USE PIOGLITAZONE

Sanyal A et al. *NEJM* 2010

AASLD: Current Pharmacologic Treatment for NASH

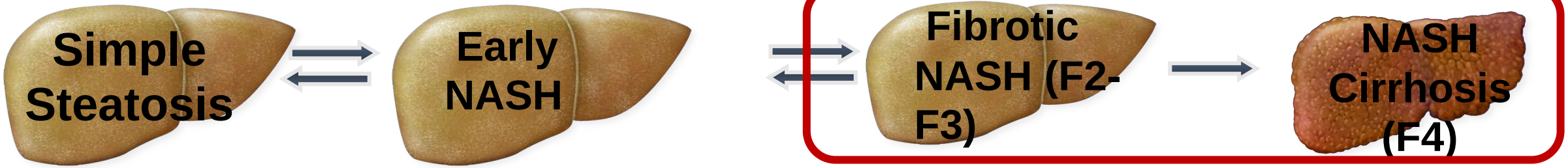
Drug	Mechanism of Action	Study	Primary Endpoint(s)	AASLD Recommendation
Metformin	Multiple	Multiple studies	Various	Not recommended
Pioglitazone	PPARγ agonist	PIVENS Multiple studies	Improvement in NAS ≥ 2 without fibrosis worsening	May be used in patients with biopsy-proven NASH
Liraglutide	GLP-1 receptor agonist	LEAN	Resolution of NASH without fibrosis worsening	Premature to consider GLP-1 receptor agonists
Vitamin E	Targeting oxidative stress	PIVENS	Improvement in NAS ≥ 2 without fibrosis worsening	May be used in **nondiabetic** adults with biopsy-proven NASH

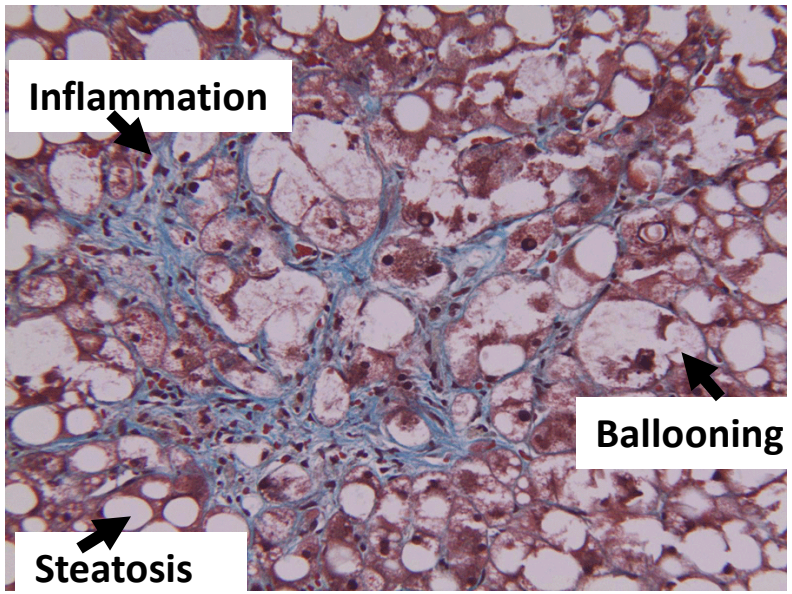
***NOT FDA-APPROVED**

Chalasani. Hepatology. 2018;67:328.

Future Treatments for NASH

The Adult NAFLD Spectrum and Target Population





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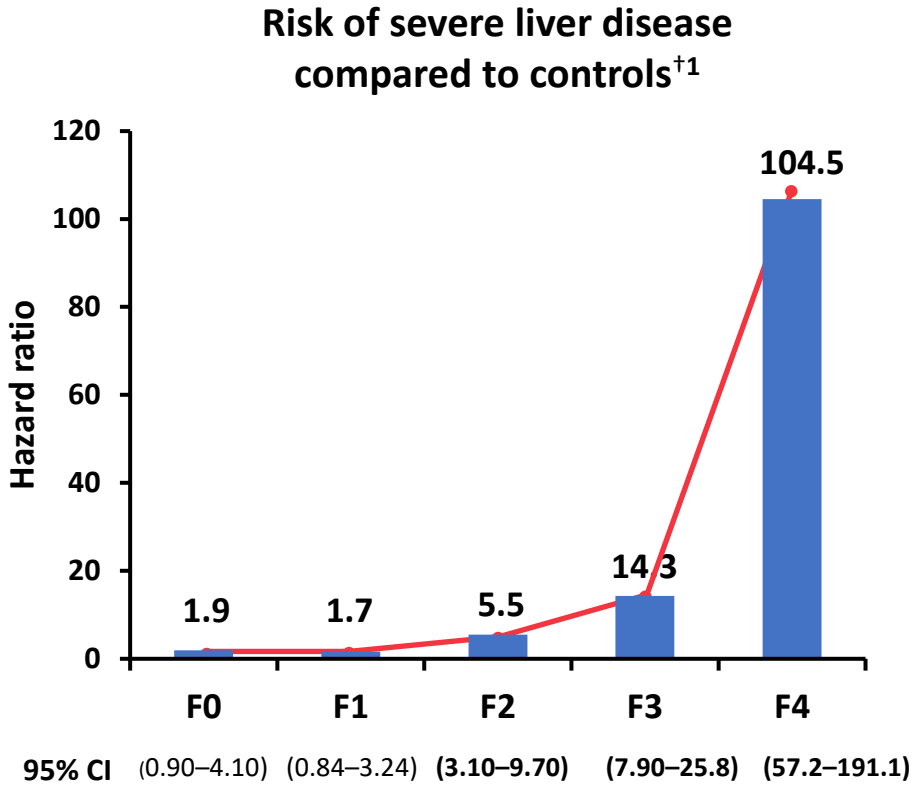


Fibrotic NASH = NAS of 4 or higher + F2 or higher

Hagström H et al. *J Hepatol* 2017;67:1265

FDA Efficacy Endpoints for Phase 3 Trials: Liver Histologic Improvement

NASH Resolution

- Resolution of steatohepatitis on overall histopathologic reading

and

- No worsening of liver fibrosis

OR BOTH

Fibrosis Improvement

- Improvement ≥ 1 fibrosis stage

and

- No worsening of steatohepatitis

1. US FDA. Draft Guidance. Noncirrhotic NASH With Liver Fibrosis. December 2018.

Noninvasive Tests (NITs) to Assess Treatment Response

Liver Fat Fraction (MRI-PDFF)

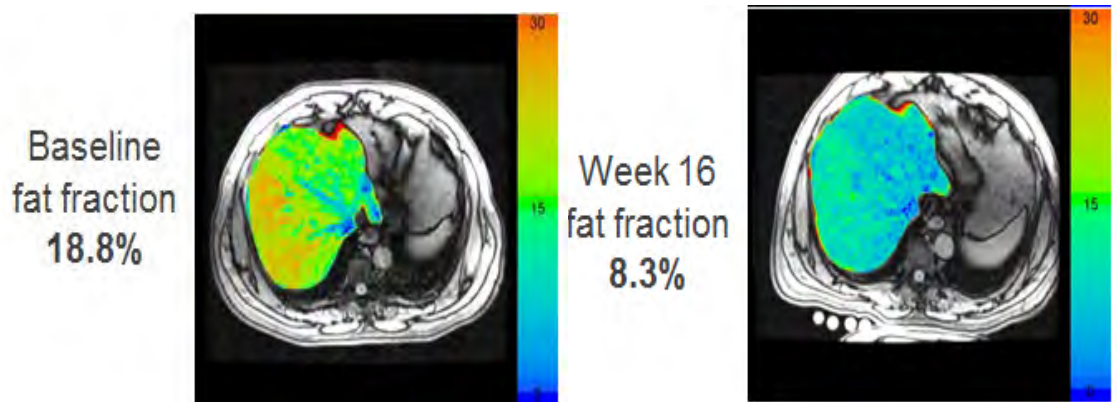
- ≥ 5% absolute/ ≥ 30% relative reduction associated with improvement in NAS

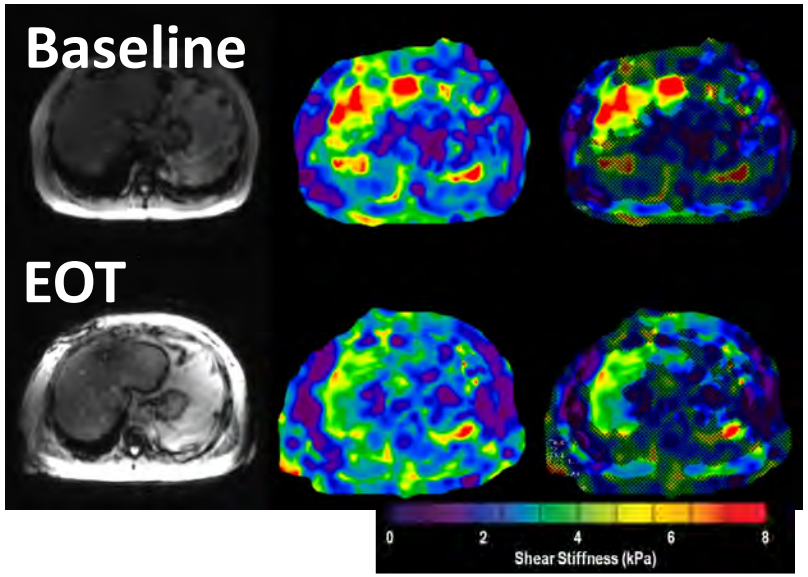
ALT/ AST

- ≥ 17 U/L reduction predicts histologic response

MRE/ cT1/ LSM?

- MRE: ≥ 15% relative reduction from BL?
- cT1: > 88 ms reduction from BL or change in category?
- LSM decrease by 20-25% from BL ?

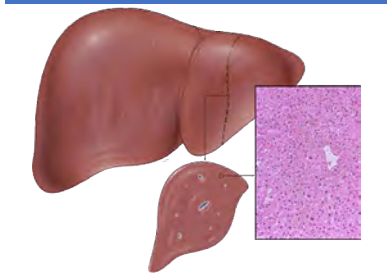




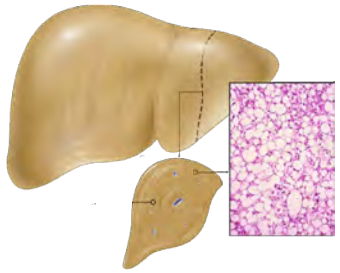
Loomba. Gastroenterology. 2019;156:88.
Patel. Therap Adv Gastro 2016;9:692.

Targeting Pathophysiological Processes

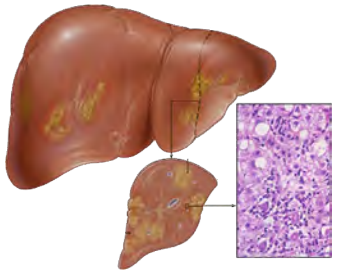
NORMAL LIVER



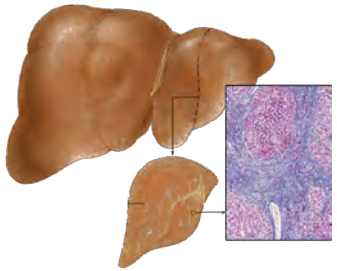
STEATOSIS



Fibrotic NASH



CIRRHOSIS



Targets related to insulin resistance and/or lipid metabolism

GLP-1:	**Semaglutide**
GLP-1/GR/GIP	MEDI0382, BI456906, Tirzepatide, Cotadutide, HM15211
SCD1:	Aramchol
SGLT1/2:	Licogliflozin
FGF21:	Efruxifermin, BIO89-100
THR-β:	**Resmetirom**, VK2809
FGFR1/KLB	BFKB8488A, MK-3655
MPC	MSDC-0602K, PXL065
Mixed ag-antag GR and antag MR	Miricorilant
Fatty acid	Icosabutate
FASN Inh	TVB-2640
GHRH analog	Tesamorelin
Berberine/UDCA	HTD1801
DGAT2 Inhib./ACCi	Ervogastat/Clesacostat
DGAT2 Inhib.	ION224
AAs	AXA1125

Targets related to lipotoxicity & oxidative stress

PPARα/∂/γ:	**Lanifibranor**
PPARα/γ:	Saroglitazar
MPC	MSDC-0602K, PXL065
FXR:	**OCA**, EYP001, TERN-101
FGF19:	Aldafermin
Testosterone prodrug	LPCN 1144

Targets related to inflammation and immune activation

Cyclo Inh	CRV431

Targets related to cell death (apoptosis and necrosis)

Cyclo Inh	CRV431

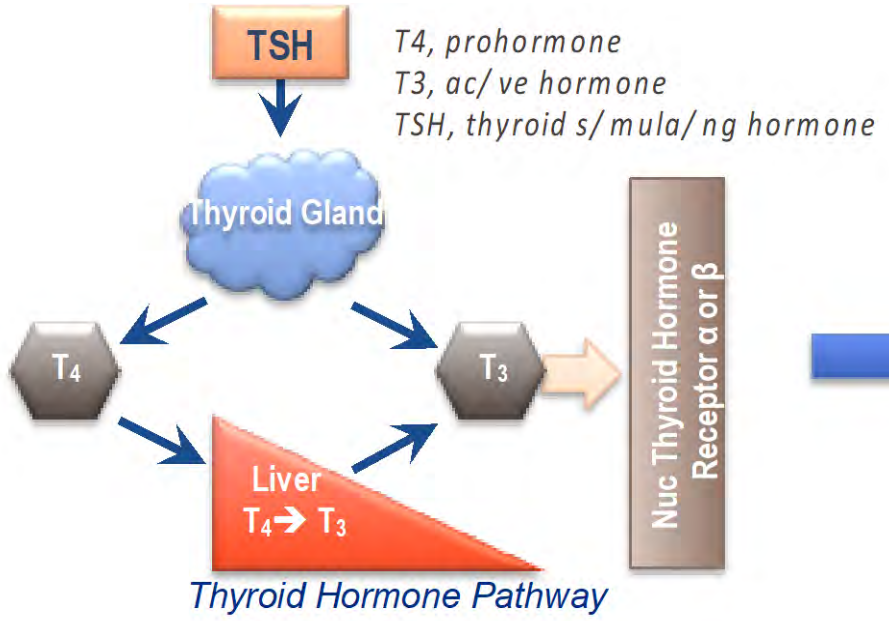
Targets related to fibrogenesis & collagen turnover

Galectin	Belapectin
Cyclo Inh	CRV431
JNK Inh.	CC-90001
GLP1 ag + ACCi + FXR	Semaglutide + Firsocostat + Cilofexor

Phase 3 drugs in red

Some drugs have pleiotropic effects

Resmetirom (MGL-3196): selective thyroid hormone receptor-beta agonist



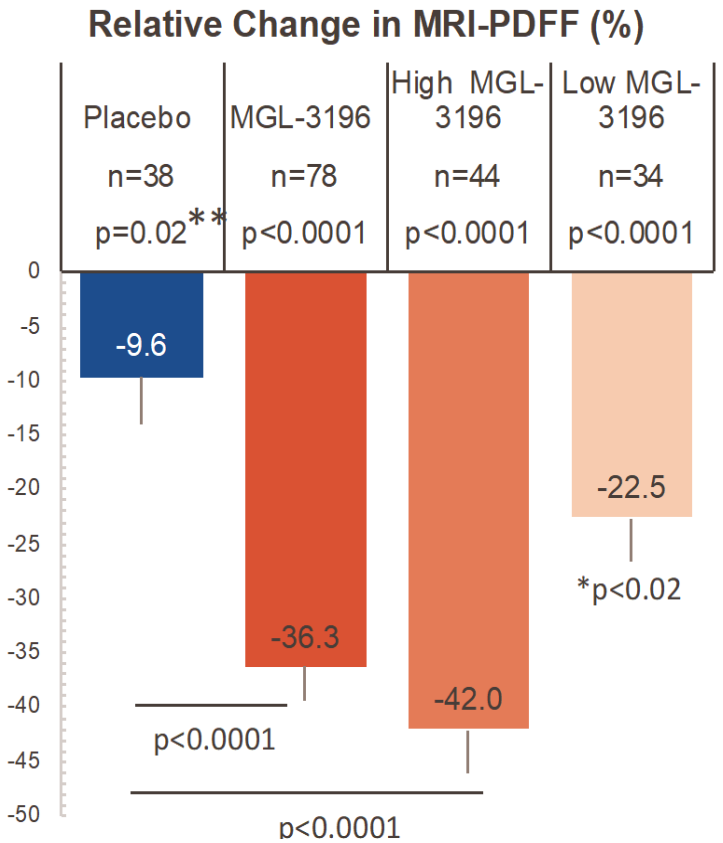
In humans THR-β agonism:

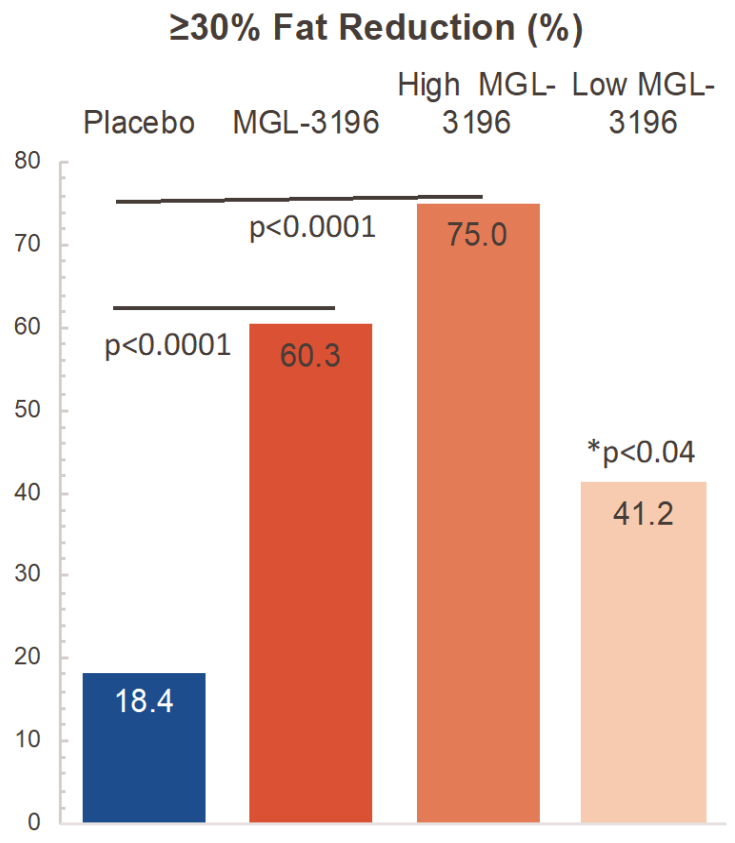
- Lowers LDL-cholesterol
- Lowers triglycerides
- Lowers liver fat, potentially reducing lipotoxicity, NASH

No thyrotoxicosis (THR-α effect)

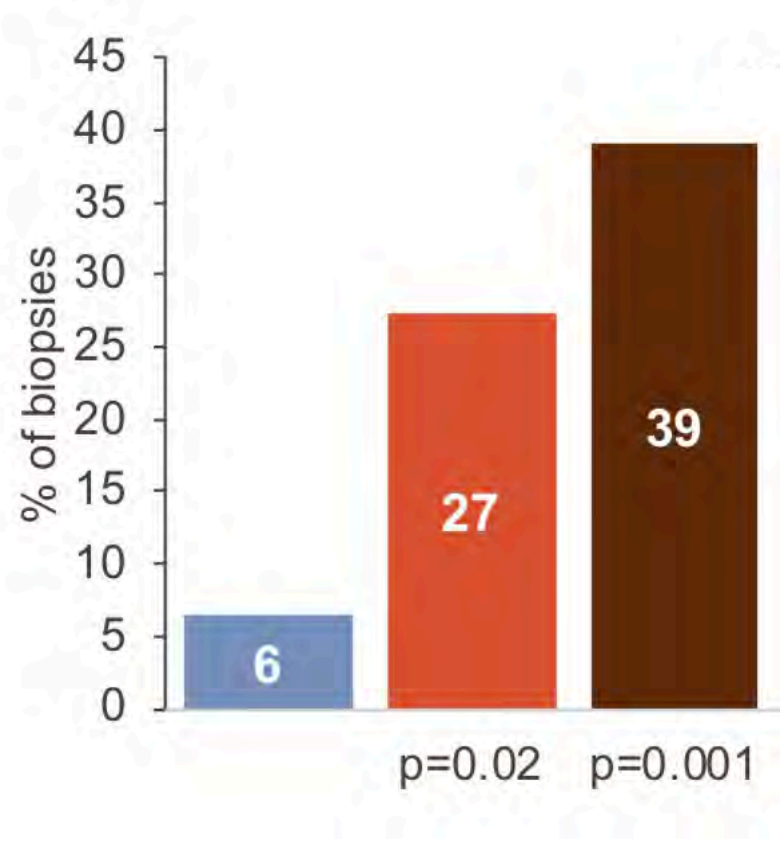
Resmetirom significantly decreases hepatic fat in NASH patients at week 12 MRI-PDFF, and was associated with NASH resolution at week 36 biopsy

Fat Reduction at week 12 MRI-PDFF



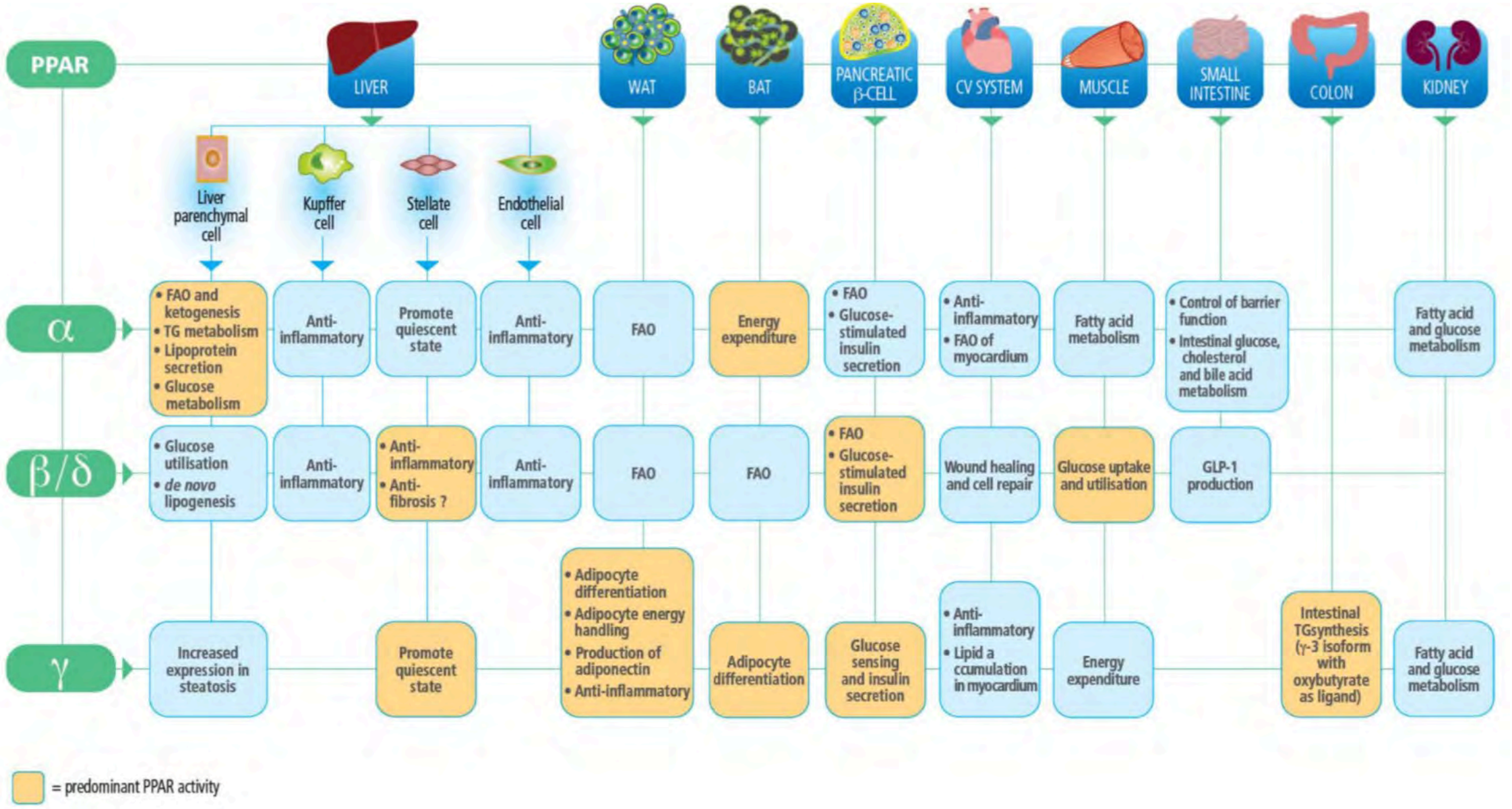


NASH Resolution at week 36 biopsy



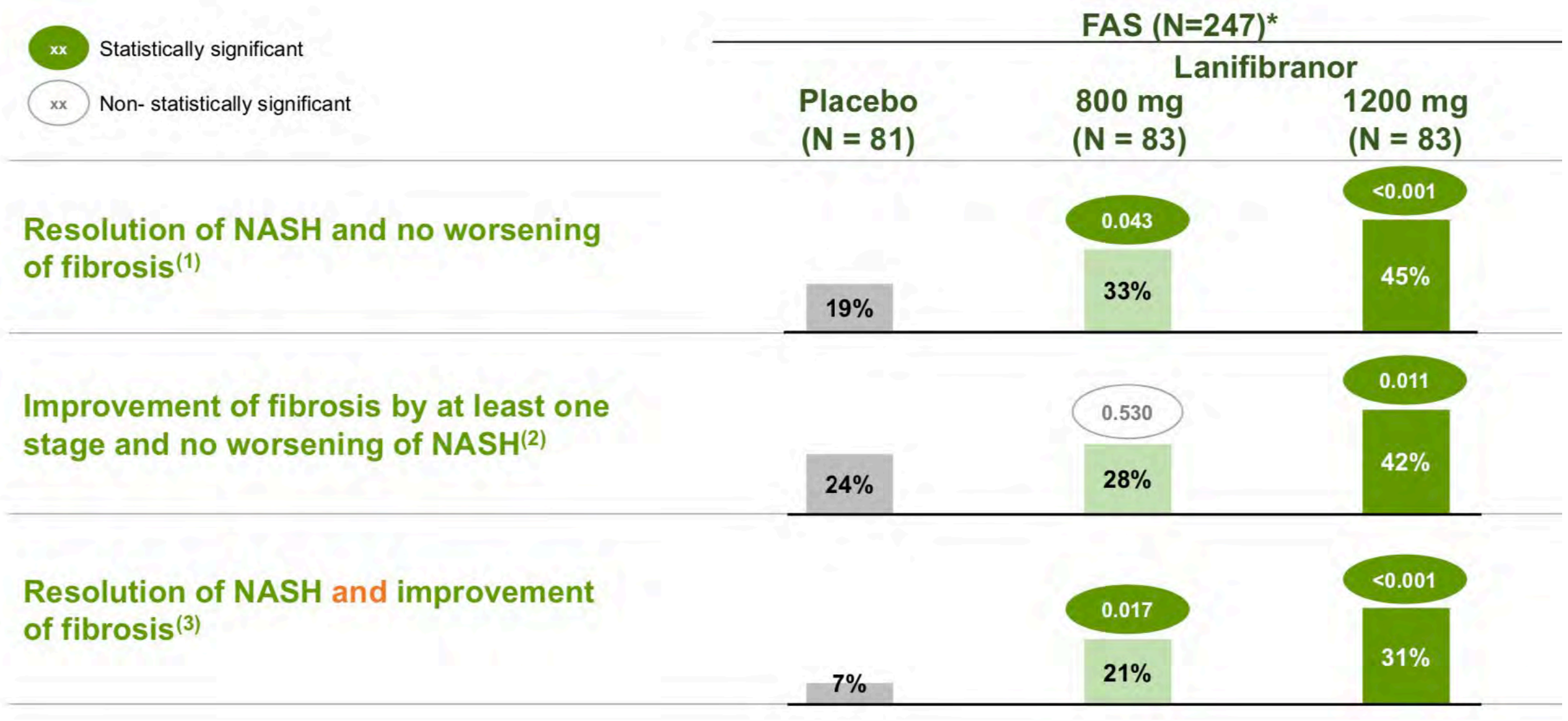
Harrison SA, ... Alkhouri N et al. Lancet 2019. 2012-2024

Lanifibranor: A pan-PPAR agonist



Francque S et al. Nature Rev Gastroenterol Hepatol 2020

Lanifibranor: Significant improvements in both resolution of NASH and regression of fibrosis



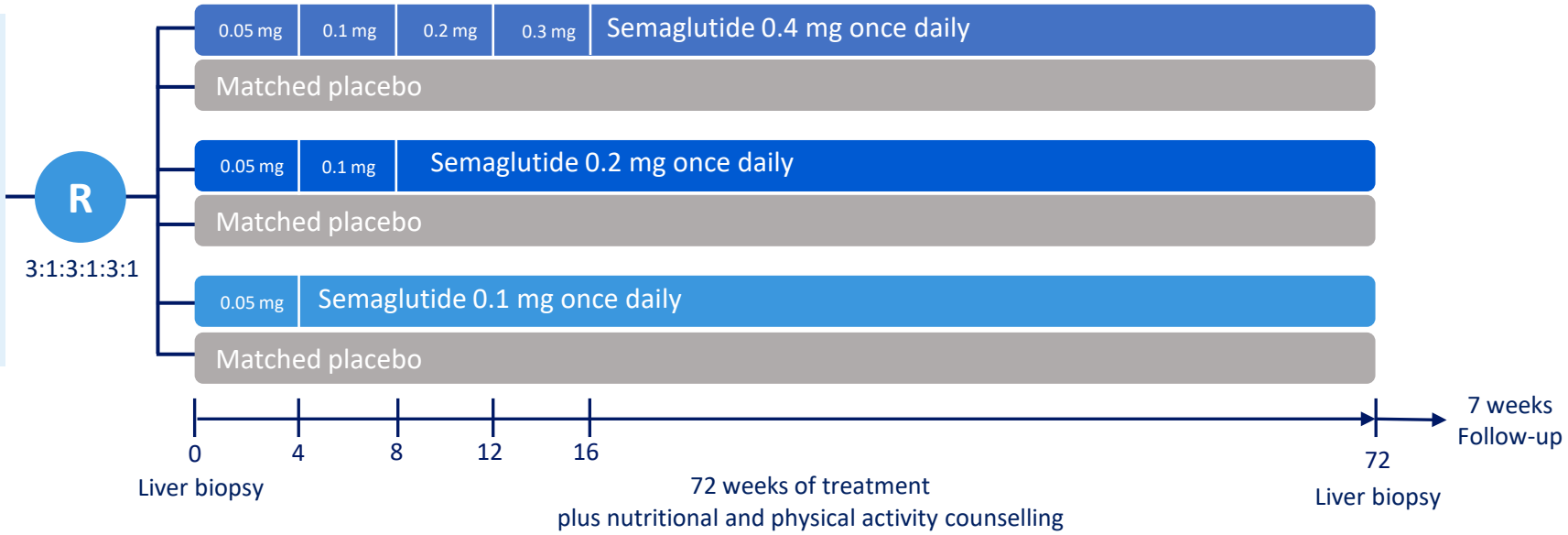
Francque S, … Alkhouri N, et al. AASLD 2020

Semaglutide (GLP1 agonist): Efficacy and safety of once-daily SQ

Trial objective: To compare the effect of three different doses of semaglutide subcutaneous (s.c.) once daily versus placebo on histological resolution of NASH

Eligible patients

Biopsy confirmed NASH
NAS ≥ 4
Fibrosis stage 1, 2 or 3
BMI > 25 kg/m^2
HbA_{1c} ≤ 10%



Primary endpoint:

Resolution of steatohepatitis and no worsening in liver fibrosis in patients with baseline fibrosis stage 2 or 3

Confirmatory secondary endpoint:

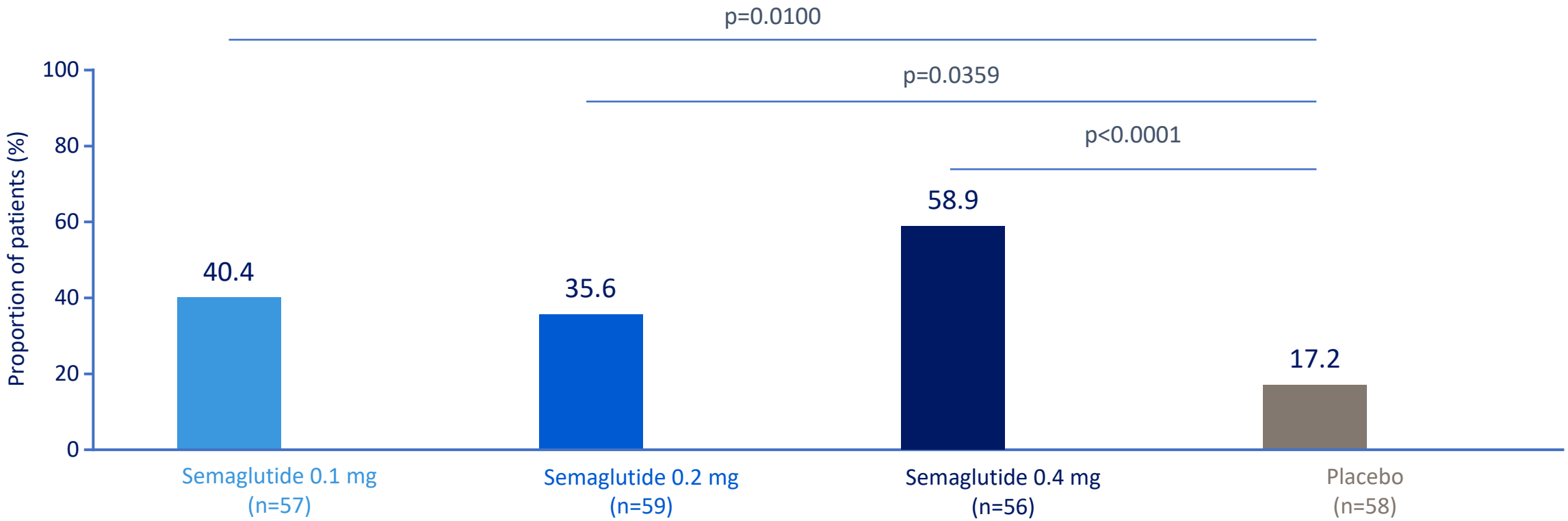
Improvement in liver fibrosis and no worsening in steatohepatitis with baseline fibrosis stage 2 or 3

BMI, body mass index; HbA_{1c}, glycated hemoglobin; NAS, non-alcoholic fatty liver disease activity score; NASH, non-alcoholic steatohepatitis.

Newsome P et al. NEJM 2021

Resolution of steatohepatitis and no worsening in liver fibrosis

Patients with fibrosis stage 2 or 3 at baseline



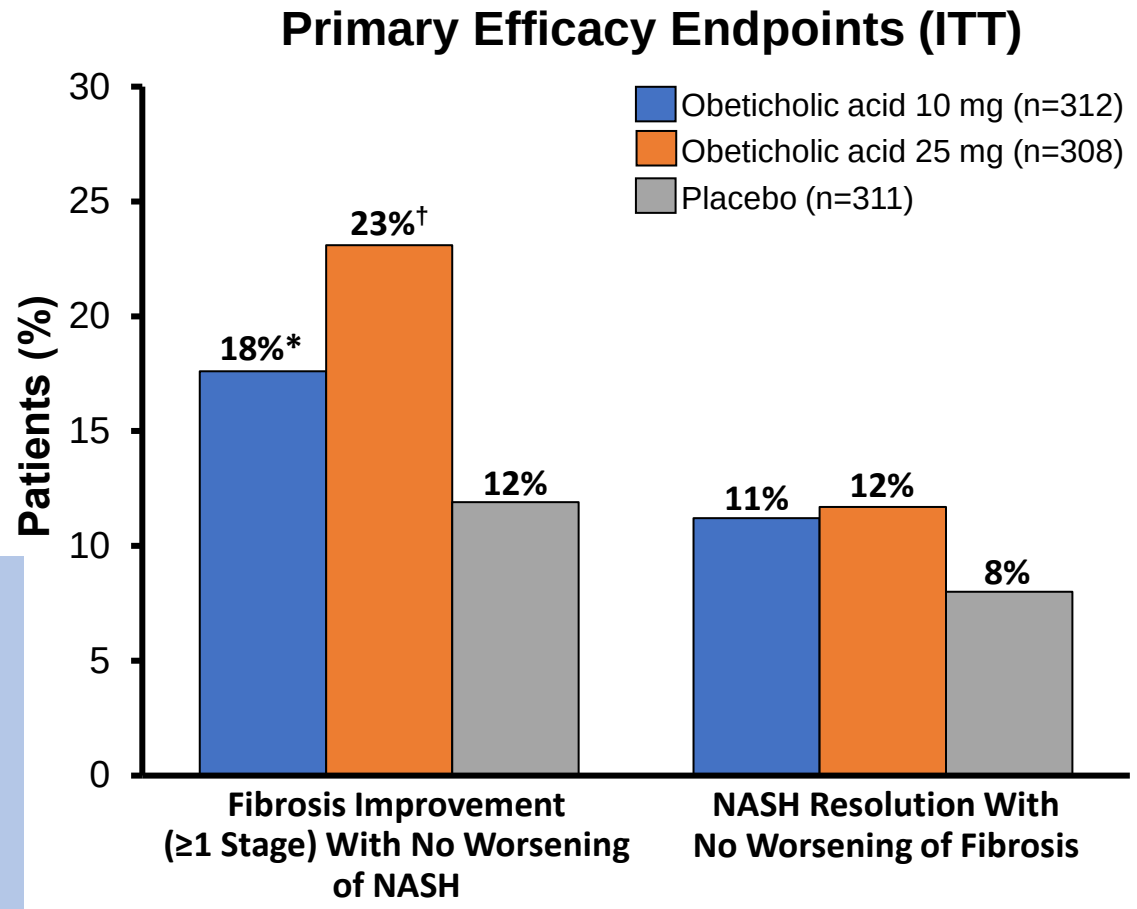
Data based on in-trial period. Two-sided p-values from a Cochran-Mantel-Haenszel test. Patients with missing data handled as non-responders. p<0.05 signifies statistical significance.

Newsome P et al. NEJM 2021

REGENERATE Study: Interim Efficacy Analysis at 18 Months

- **Fibrosis improvement** (≥1 stage) and no worsening of NASH in patients (obeticholic acid versus placebo)
  10 mg: 18% versus 12% (*P*<0.05)
  25 mg: 23% versus 12% (*P*=0.0002) versus placebo

- **Pruritus: 50% in the OCA 25 mg arm**
- **Worsening lipid profile: Increase in LDL and decrease in HDL**
- **Cholecystitis/ ?Hepatotoxicity**

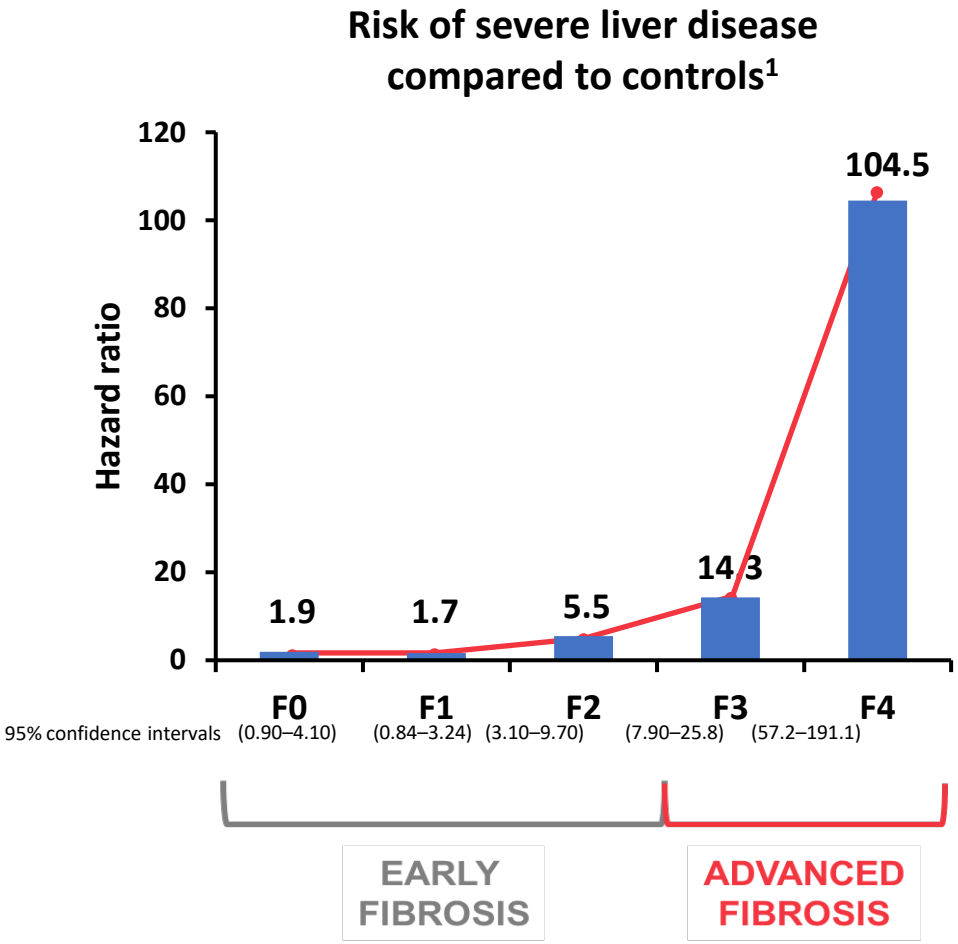


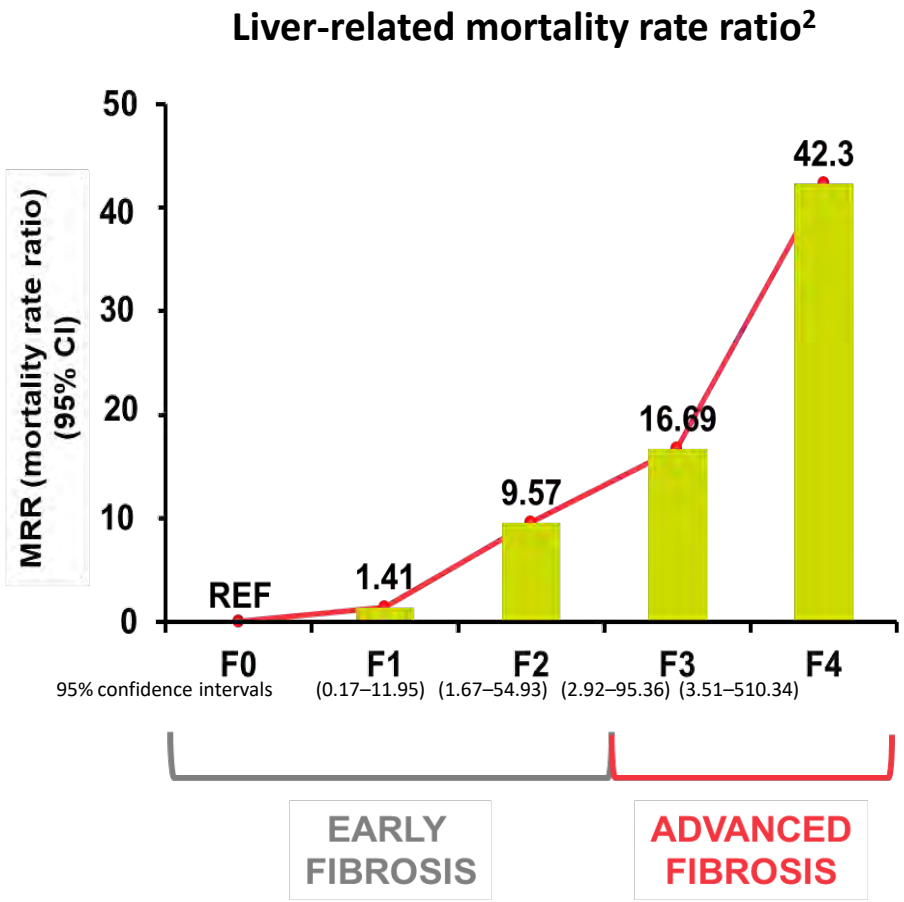
Younossi Z, et al. *Lancet 2019. 2184-2196*

Ruling Out the Presence of Advanced Disease **by PCPs**

ARIZONA LIVER HEALTH™

Advanced **Fibrosis (F3-F4) Increases the Risk of Liver-Related Morbidity and Mortality**





1. Hagström H et al. *J Hepatol* 2017;67:1265 –1273; 2. Dulai PS et al. *Hepatology* 2017;65(5):1557–1565.

Simple NITs to Rule Out Advanced Disease (F3-F4)

Serologic

- **Simple Scores**
  - FIB-4 Index
  - NAFLD Fibrosis Score (NFS)
  - AST/ ALT ratio
  - APRI
- **Proprietary predictive Scores**
  - FibroSURE™, Liver FASt™
  - ELF

Imaging

- **Elastography**
  - VCTE (Fibroscan)
  - ARFI
  - SWE
  - Velacur

Alkhouri N et al. *Gastroenterol Hepatol* 2012;8(10):661-668

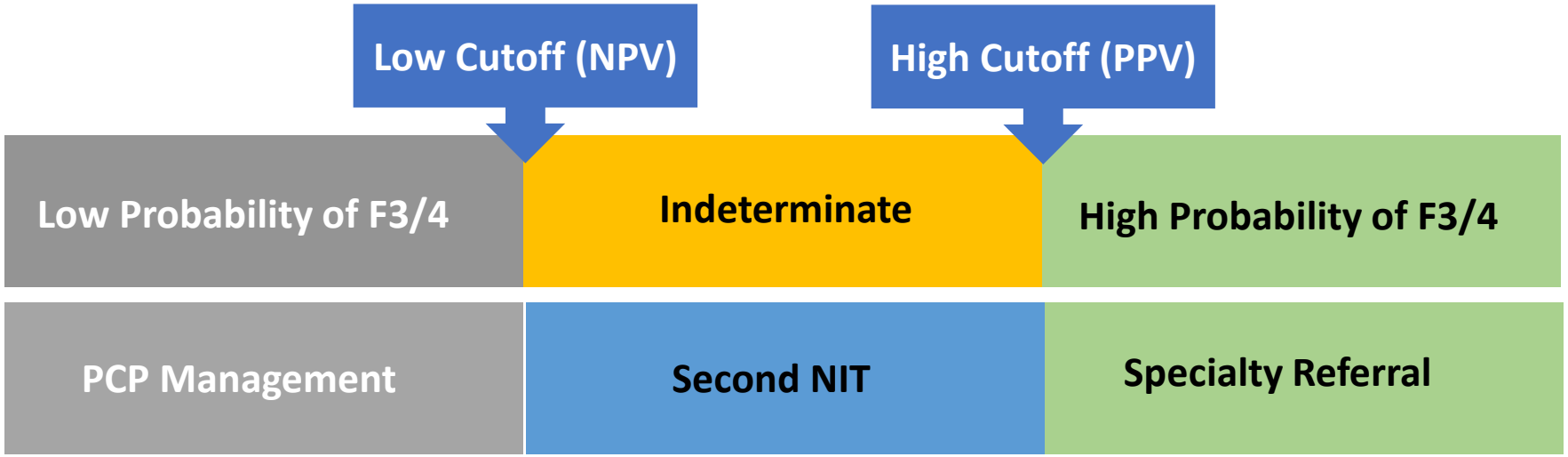
“Simple Scores” for Predicting Advanced (F3-4) Fibrosis

NAFLD Fibrosis Score

- = -1.675 + 0.037 x **Age** + 0.094 x **BMI** + 1.13 x **IFG/diabetes** + 0.99 x **AST/ALT ratio** - 0.013 x **Platelets** - 0.66 x **Albumin**.
- A score of less than -1.455 excludes fibrosis (NPV 88-93%).
- A score of greater than 0.676 predicts fibrosis (PPV 82-90%).

FIB-4 Score

- = (**Age** * **AST**) / (**Platelets** * Sqrt (**ALT**))
- A score of less than 1.3 excludes fibrosis (NPV 95%)
- A score greater than 3.25 predicts fibrosis (PPV ~70%)



Angulo et al. Hepatology. 2007; Sterling et al. Hepatology. 2006; McPherson et al. Gut. 2010

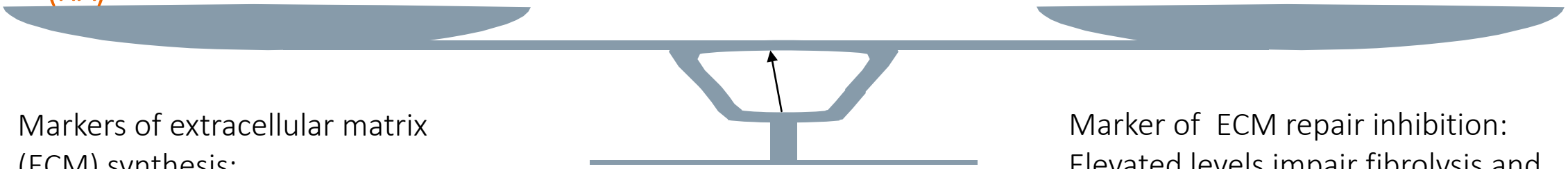
Enhanced Liver Fibrosis (ELF™) Test for prognosis in advanced NASH

SIEMENS Healthineers

Hyaluronic acid (HA)

Procollagen III amino terminal peptide (PIIINP)

Tissue inhibitor metalloproteinase-1 (TIMP-1)



Markers of extracellular matrix (ECM) synthesis:
Elevated levels associated with increased ECM deposition and fibrogenesis

Marker of ECM repair inhibition:
Elevated levels impair fibrolysis and increase fibrosis

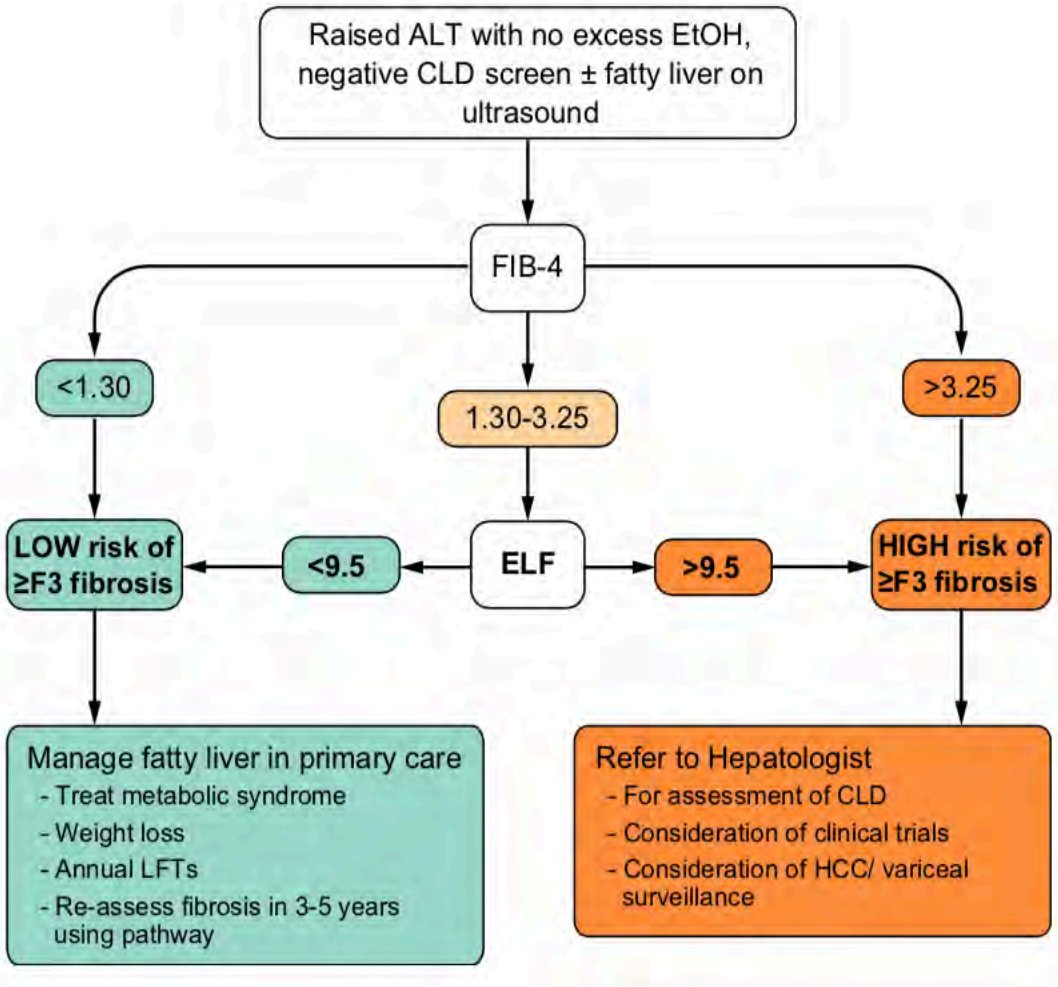
Fully Automated: ELF Score Calculated and Reported

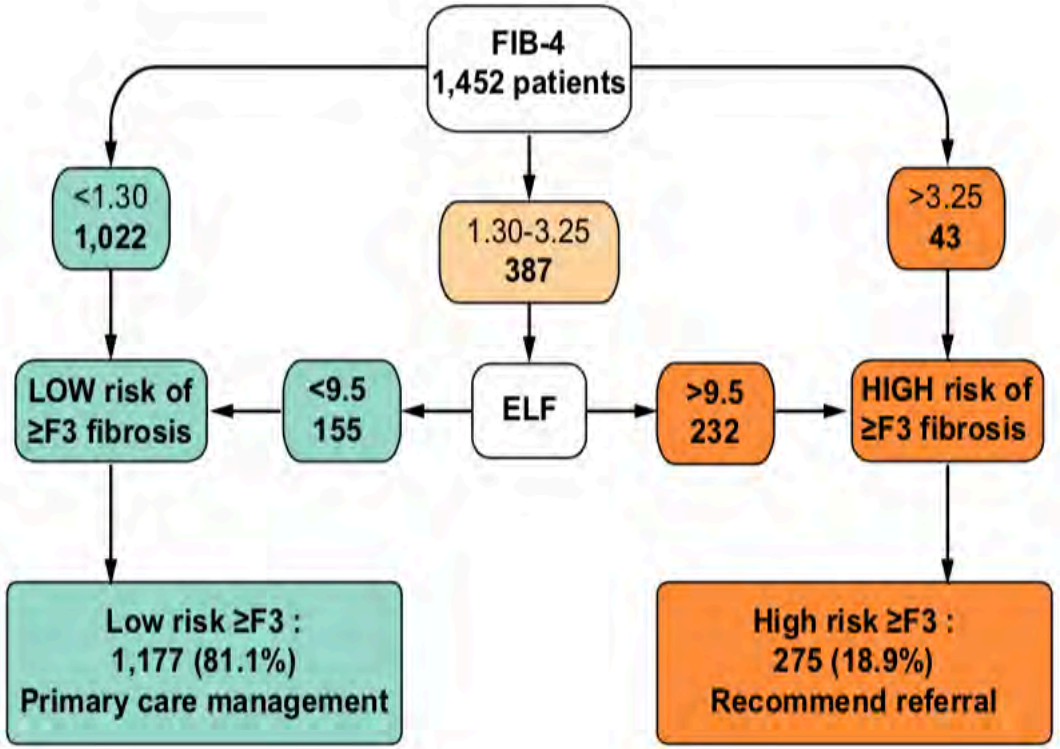
$$\text{ELF score}^{*\dagger} = 2.278 + 0.851 \ln (C_{HA}) + 0.751 \ln (C_{PIIINP}) + 0.394 \ln (C_{TIMP\text{-}1})$$

None to Mild | Moderate | Severe | Cirrhosis

- Score shown is for the test run on the ADVIA Centaur XP system.
- Arpino V, Brock M, Gill SE. The role of TIMPs in regulation of extracellular matrix proteolysis. Matrix Biol 2015;44-46:247-54.
- Rosenberg WM, Voelker M, Thiel R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. Gastroenterology 2004;127:1704-13.

Prospective Evaluation of a Primary Care Referral Pathway





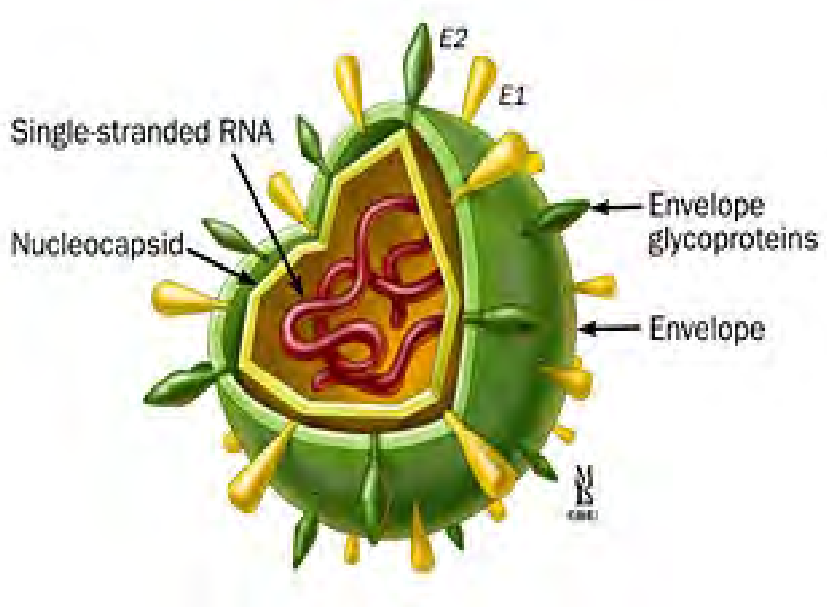
Srivastava A, … Rosenberg W. J of Hepatol 2019. 71: 371–378

HCV Overview

- Virology
- Epidemiology
- Transmission
- Natural History
- Testing
- Treatment

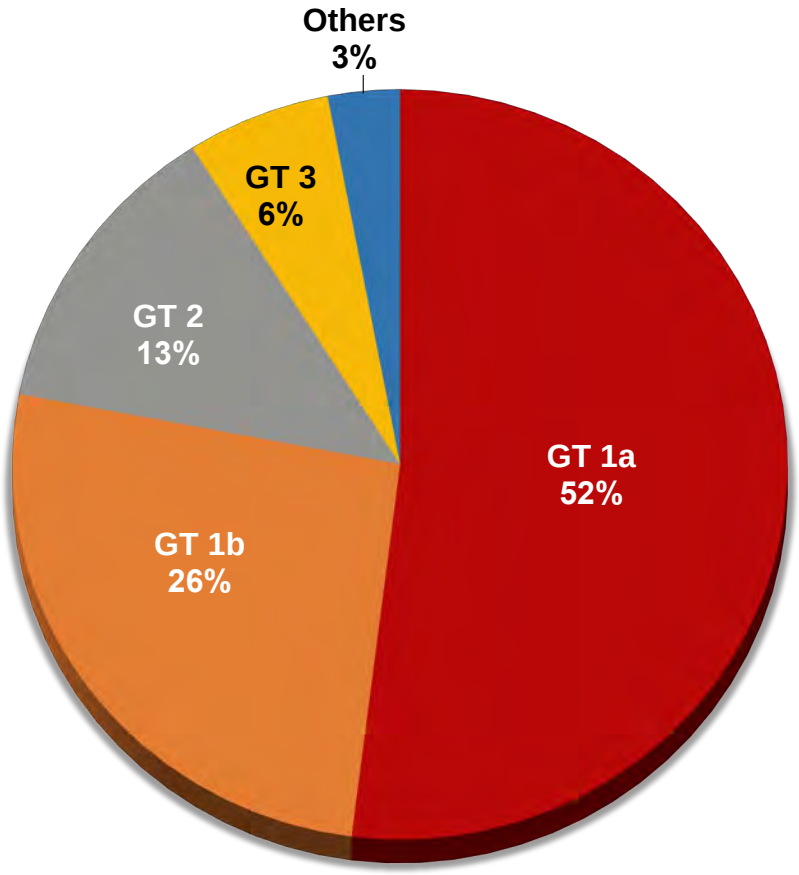
Hepatitis C Virus (HCV)

- Single-stranded RNA virus
- Result in both acute and chronic hepatitis
- HCV is a blood-borne infection



6 HCV Genotypes

GT 1 accounts for 78% of HCV infections



Hepatitis C- The Numbers

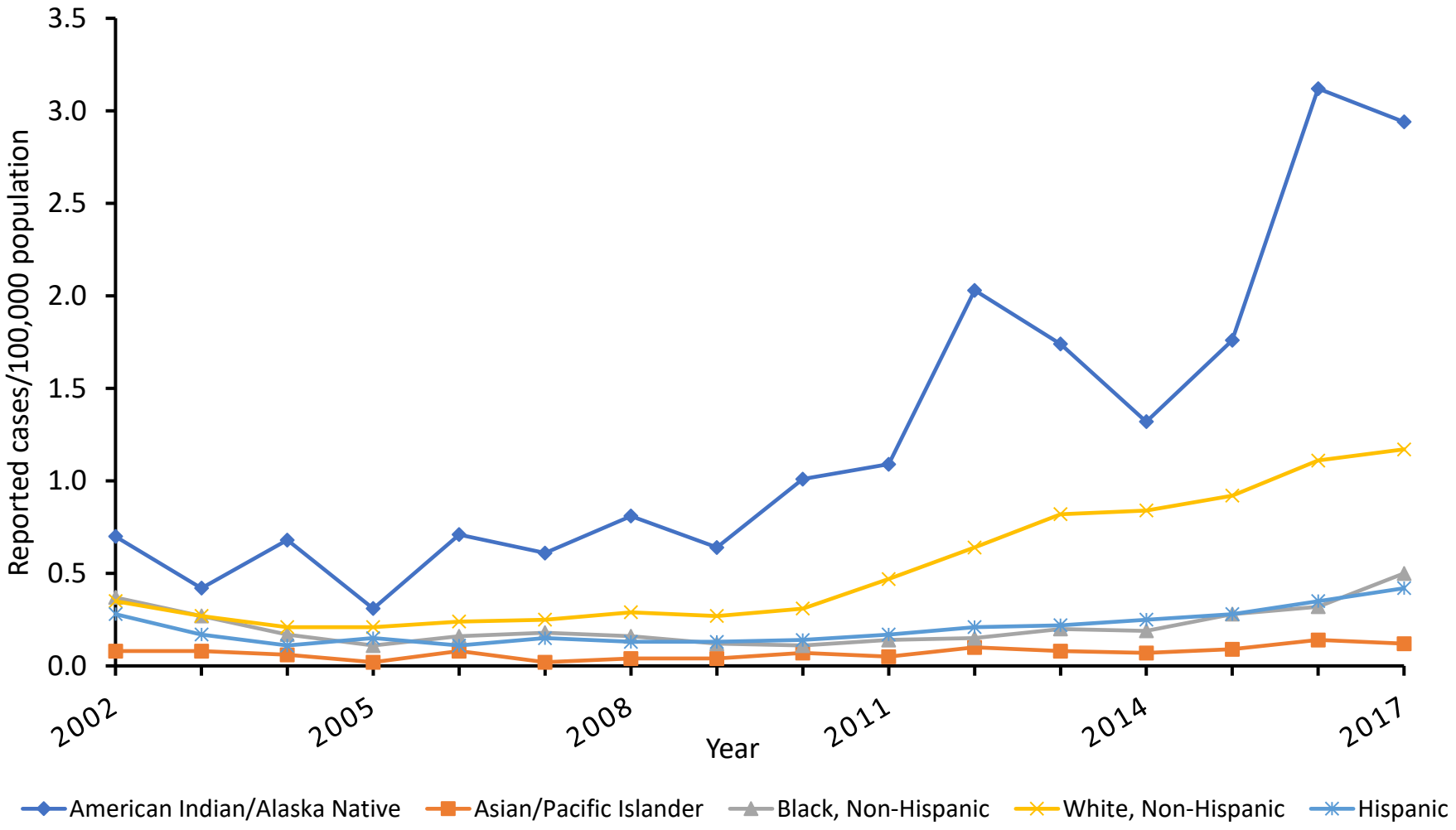
71 million
people worldwide

#1
blood-borne infection in US
indication for liver transplantation
cause of liver cancer in US

2.2 million
people in US

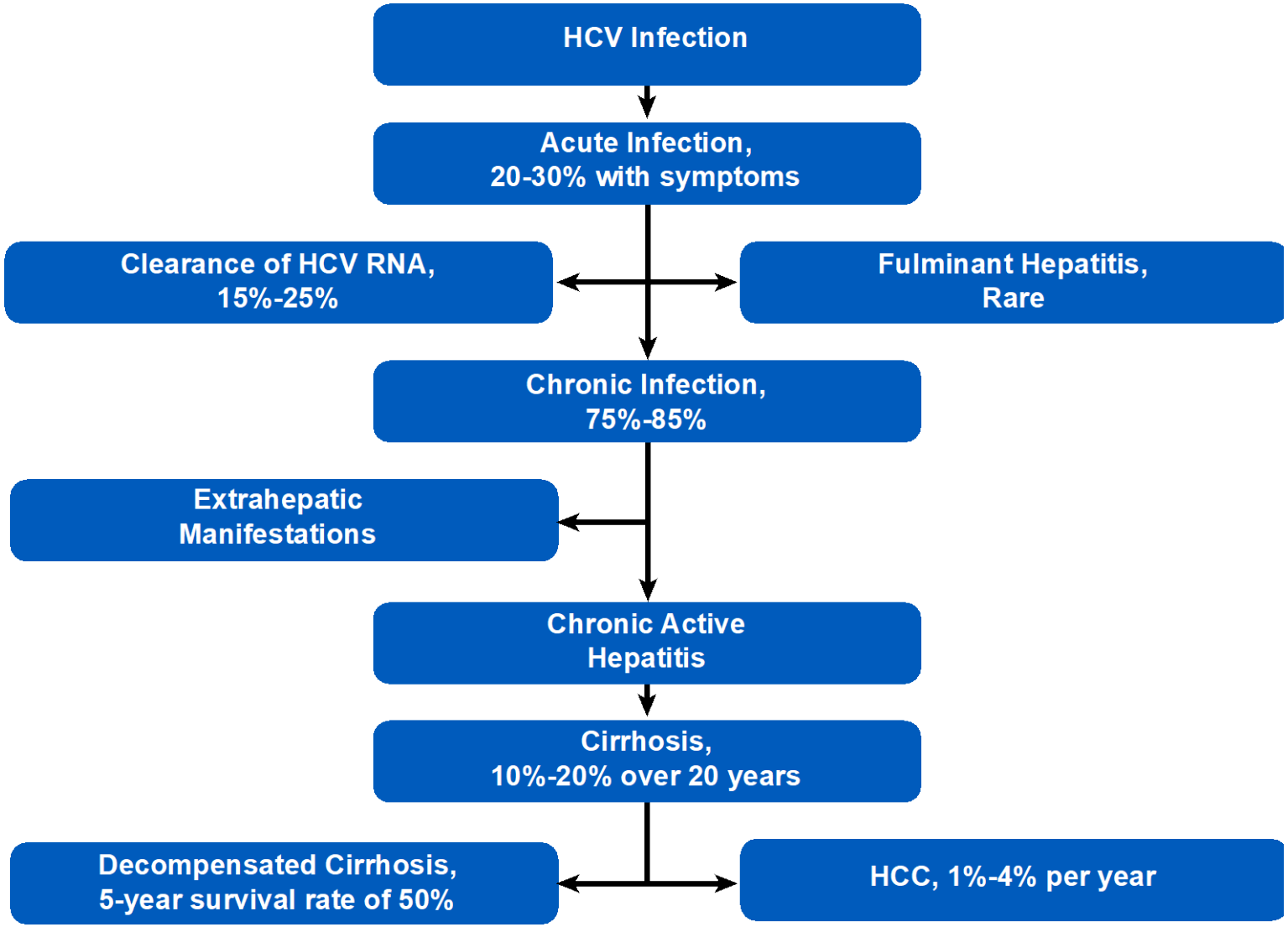
0 FDA-approved vaccines

Rates of Reported Acute Hepatitis C, by Race/Ethnicity — United States, 2002–2017



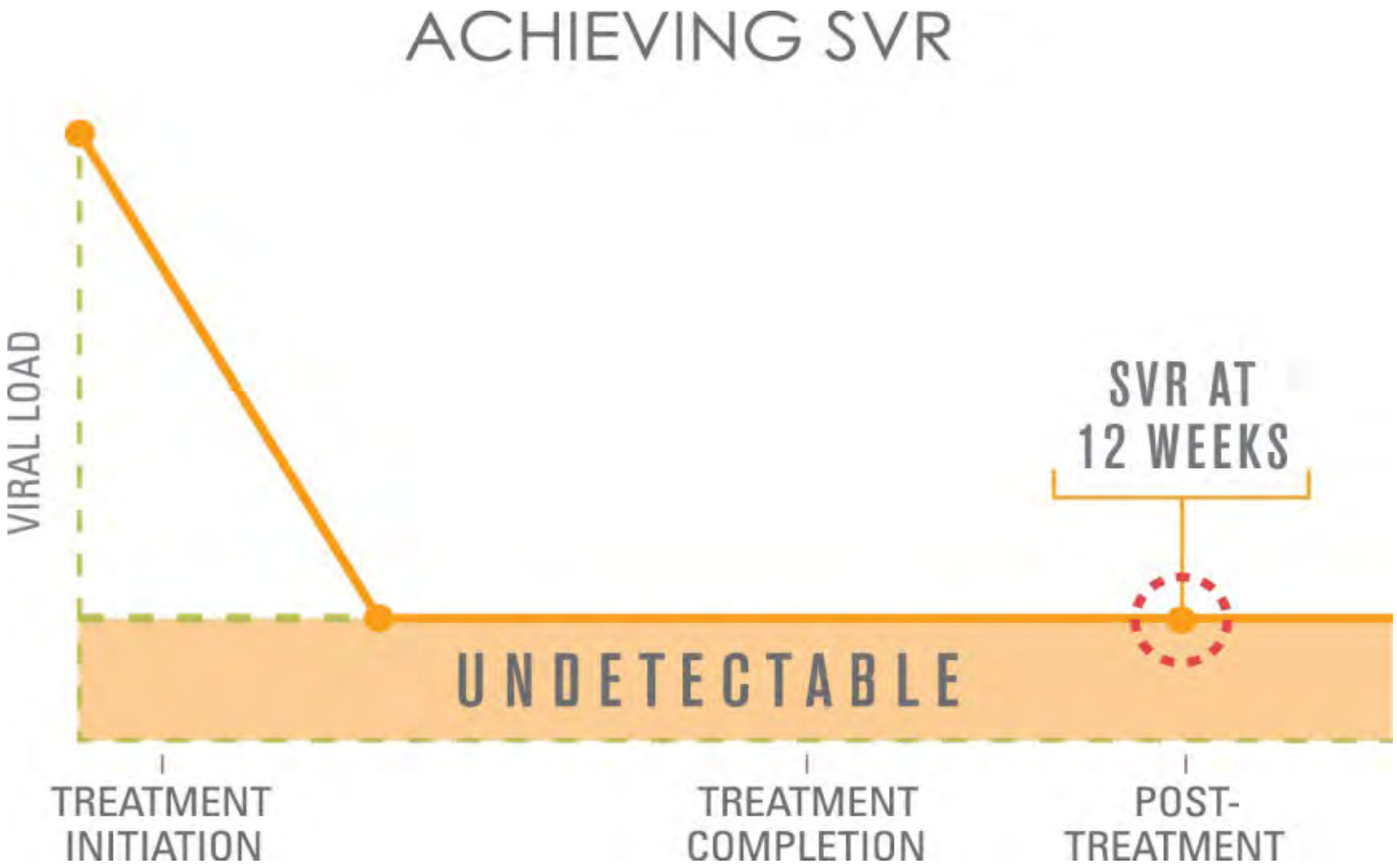
Source: CDC, National Notifiable Diseases Surveillance System.

Natural History of HCV



Chen & Morgan. 2006.

HCV Can Be Cured in Most Patients: SVR



1. Soriano V, et al. *J Antimicrob Chemother*. 2008;62:1-4;
2. Swain MG, et al. *Gastroenterology.* 2010;139:1593–1601.

Which Patients Should We Screen?

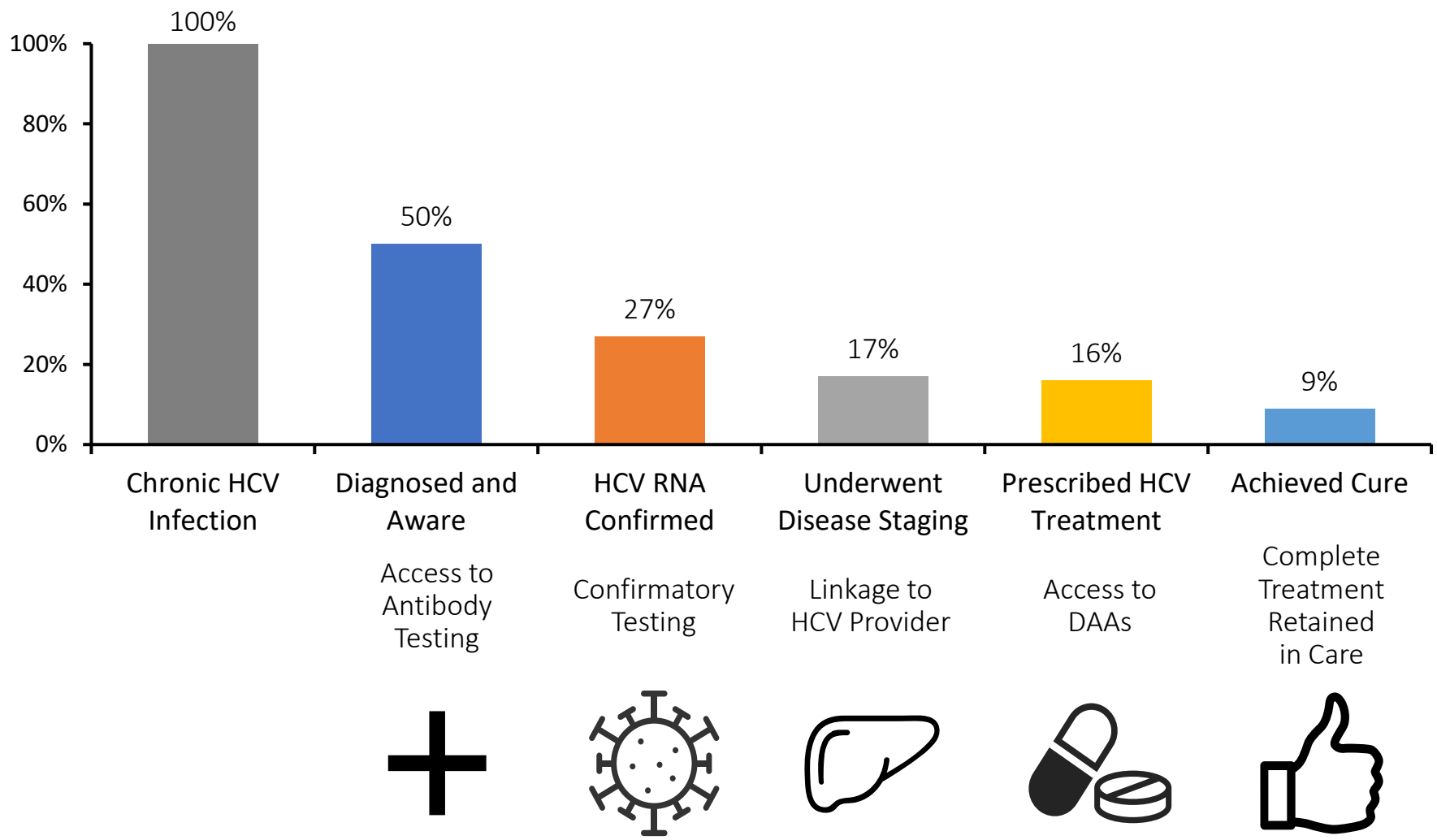
AASLD/IDSA HCV Guidance Document Recommendations for Screening

- One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years and older.
- One-time HCV testing should be performed for all persons less than 18 years old with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV infection (e.g. injection drug use).
- *Annual* HCV testing is recommended for all persons who inject drugs and for HIV-infected men who have unprotected sex with men.

Available at: www.hcvguidelines.org. Accessed January 21, 2020.

Linkage to Care

Under-Diagnosis: The Largest Gap in the Cascade of Care



Terrault NA. Hepatitis C elimination: challenges with under-diagnosis and under-treatment [version 1; peer review: 2 approved]. F1000Research 2019, 8(F1000 Faculty Rev):54 (https://doi.org/10.12688/f1000research.15892.1)

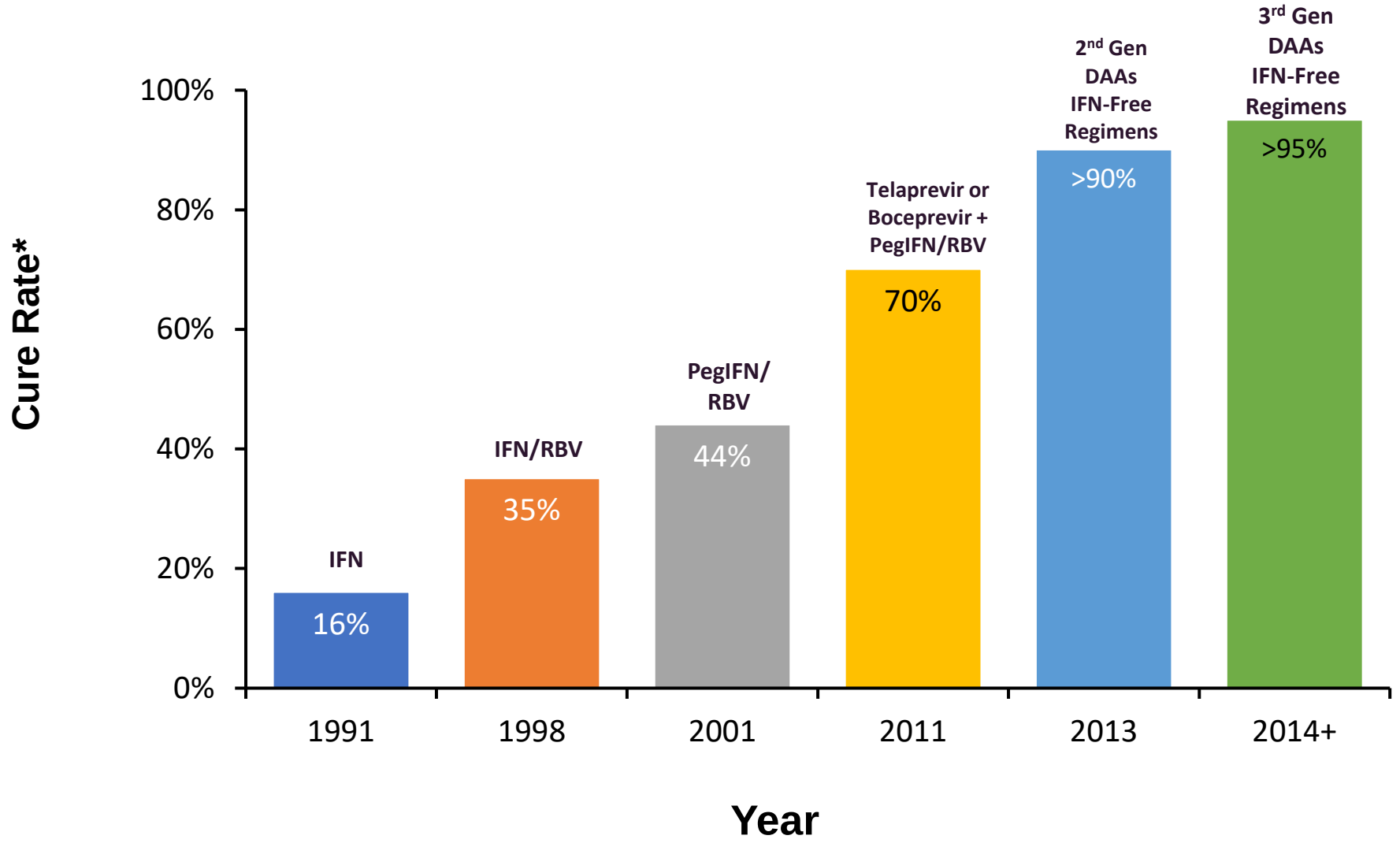
The AASLD/IDSA Recommendation for Linkage to Care

All persons with current active HCV infection should be linked to a practitioner who is prepared to provide comprehensive management

Available at: www.hcvguidelines.org. Accessed March 13, 2018.

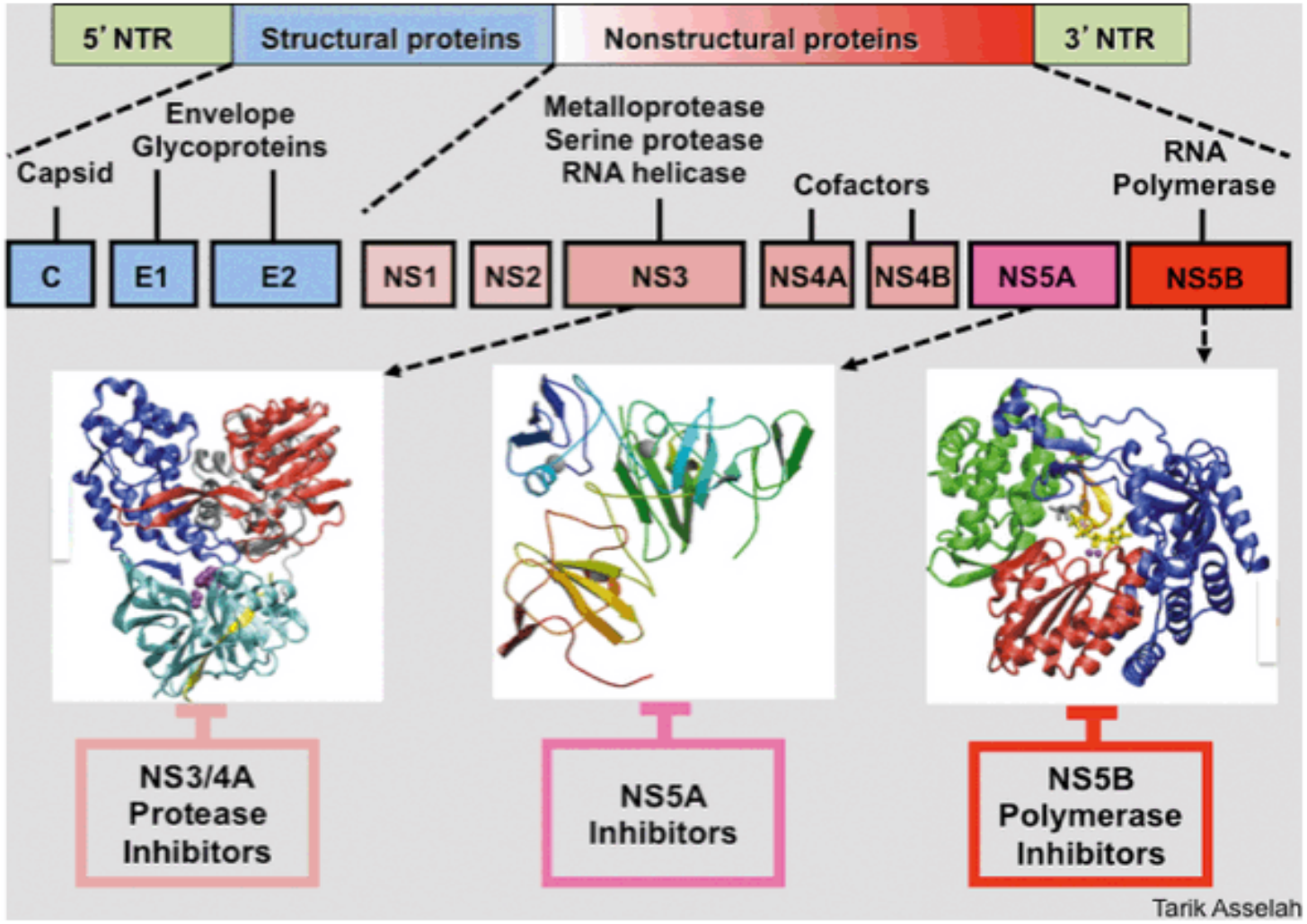
HCV Management and Treatment Update

HCV Cure Rates Now Exceed 95%



*Cure rates based on data from clinical trials

Approved DAAs from Multiple Classes: Combination All-oral Regimens for HCV



-previr
Grazoprevir

-asvir
Ledipasvir

-buvir
Sofosbuvir

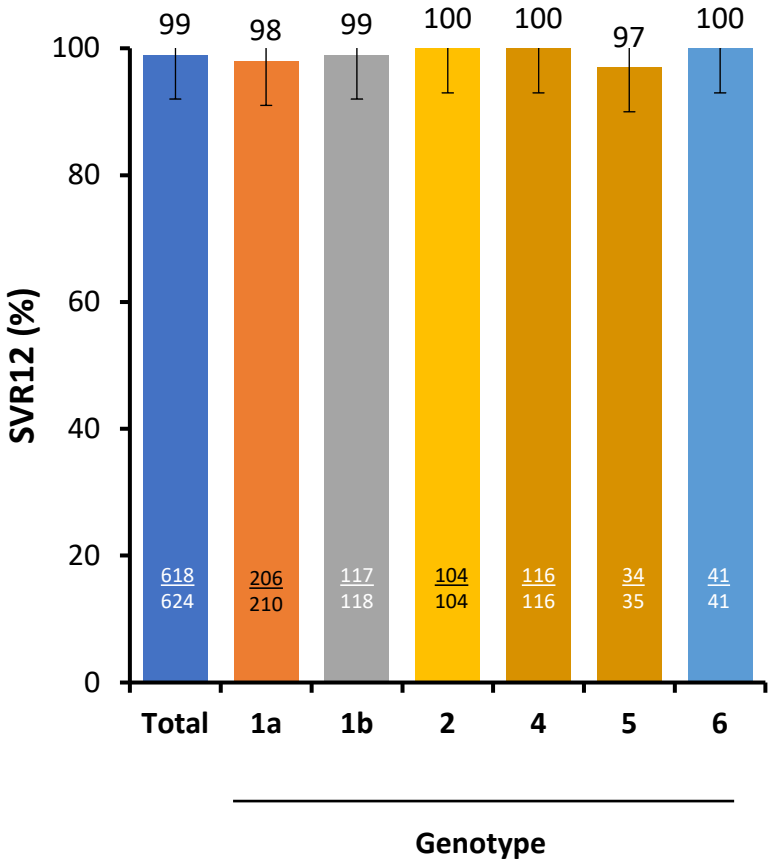
HCV Drugs You Need To Know About in 2023

Brand Name	Protease inhibitors	Polymerase inhibitors	NS5A inhibitors	Genotypes	Contra-indications
Harvoni ®		Sofosbuvir	Ledipasvir	1, 4, 5, 6	
Epclusa ®		Sofosbuvir	Velpatasvir	1-6 (2,3)	
Vosevi ®	Voxilaprevir	Sofosbuvir	Velpatasvir	1-6	CTP C
Mavyret ®	Glecaprevir		Pibrentasvir	1-6	CTP C
Zepatier ®	Grazoprevir		Elbasvir	1, 4	CTP C

Data on Approved Therapies

Velpatasvir (NS5A)/Sofosbuvir (NS5B) x 12 Weeks (ASTRAL 1): GT1-6

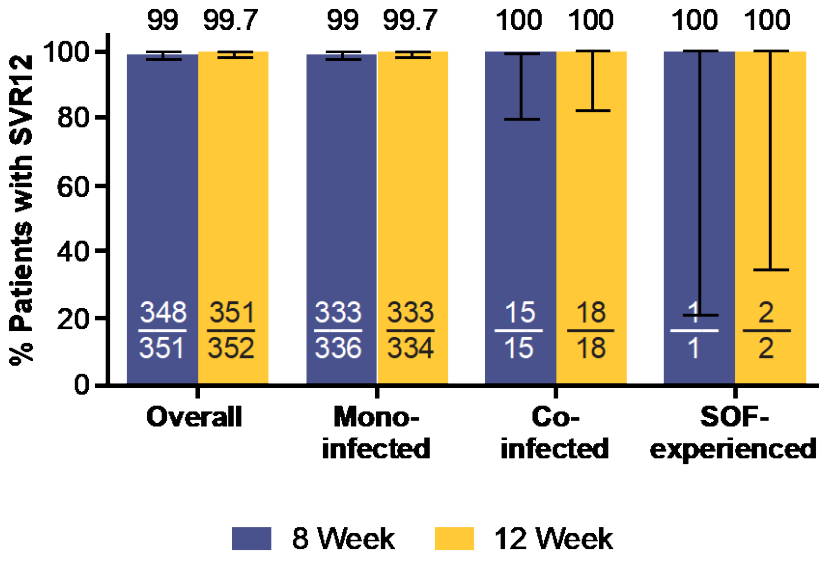
- 68% treatment-naïve; 32% TE (IFN based +/- RBV +/- PI)
- 79% White, 10% Asian, 8% Black
- 34% GT1a, 19% GT1b
- 19% cirrhotic
- Considerations
  - DDIs (eg, amiodarone, PPIs)
  - Renal impairment



Feld et al. *N Engl J Med.* 2015; 373: 2599-607.

Glecaprevir (PI)/Pibrentasvir (NS5A) x 8 or 12 Weeks (ENDURANCE-1): GT1

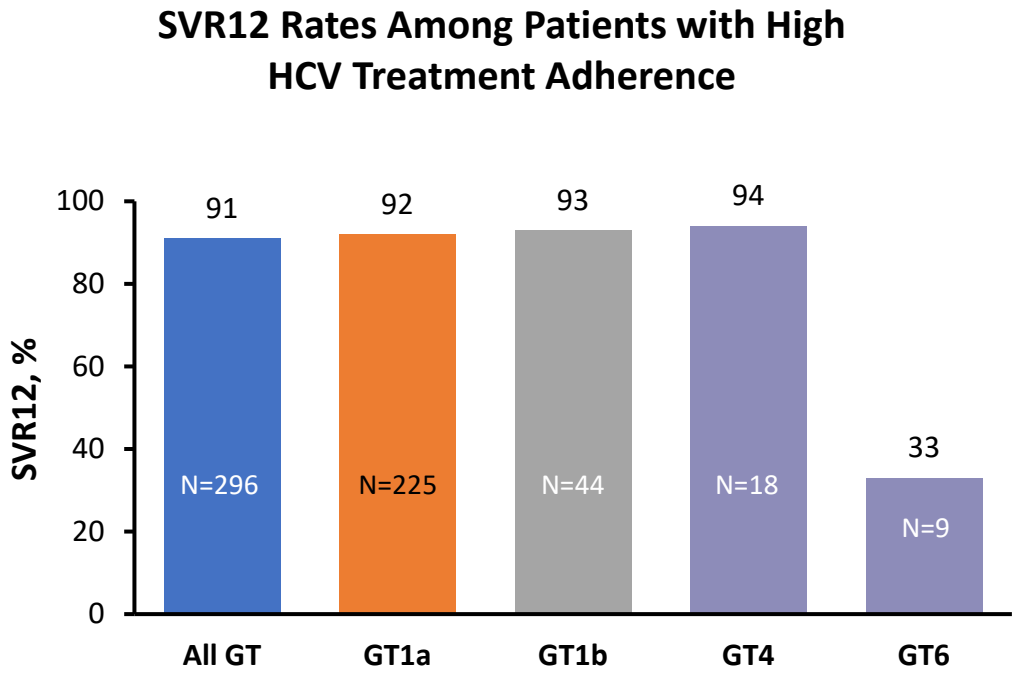
- 62% treatment-naïve
- 38% treatment-experienced
  - Previously failed PEG +/- RBV or PEG/RBV +/- SOF
- 5% HIV coinfected
- 79% White, 10% Asian, 8% Black
- 43% GT1a
- 15% F2-F3
- Considerations
  - DDIs (e.g., atazanavir, rifampin)
  - Hepatic impairment (Child-Pugh C)



Zeuzem et al. *N Engl J Med.* 2018 Jan 25;378(4):354-369. doi: 10.1056/NEJMoa1702417.

HCV Treatment and Drug Use

- Prospective RCT in patients with high HCV treatment adherence despite drug use
- ~60% of patients had positive urine test for ≥1 of 8 drug classes
  - Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, phencyclidine, propoxyphene
- 6/18 (2%) with recurrent viremia had evidence of reinfection



GT, genotype; RCT, randomized controlled trial.
Dore G, et al. *Ann Int Med.* 2016;165(9):625-634.

Antiviral Therapy Guidelines in PWUD

AASLD/IDSA

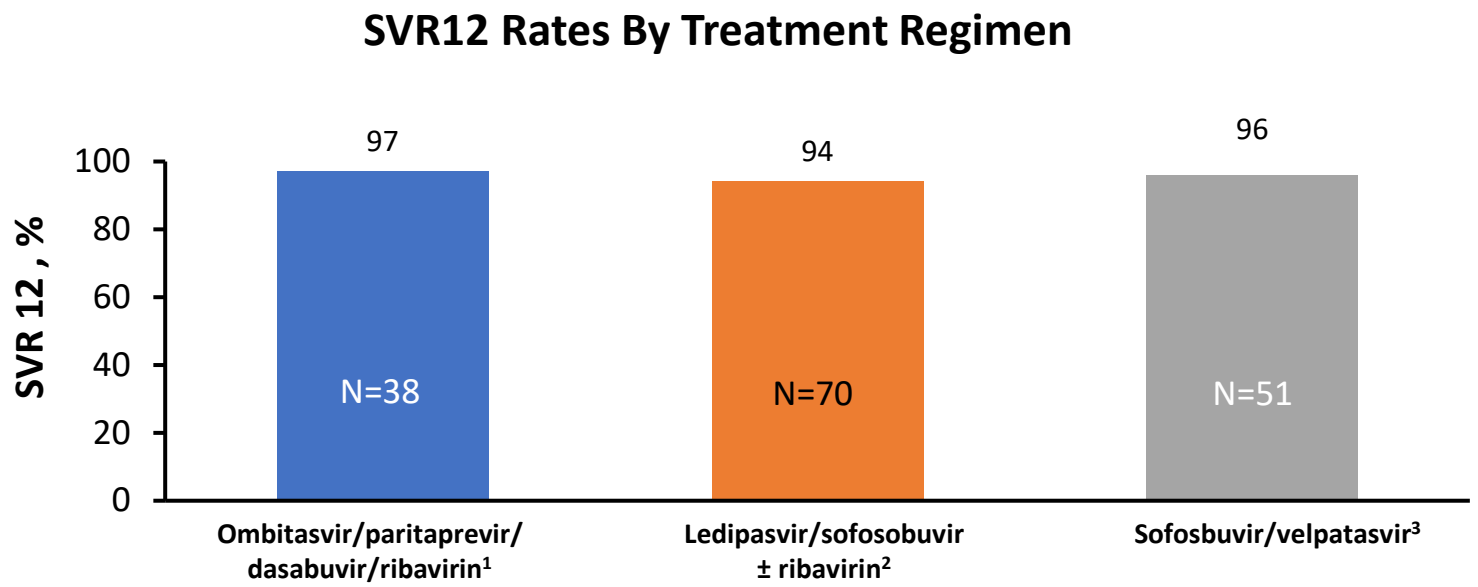
Recent/active IDU should *not* be seen as contraindication to HCV therapy[1]

EASL

Treatment should be prioritized in those at risk of transmitting HCV *including* active PWUD[2]

1. www.hcvguidelines.org; 2. EASL. *J Hepatol.* 2015.

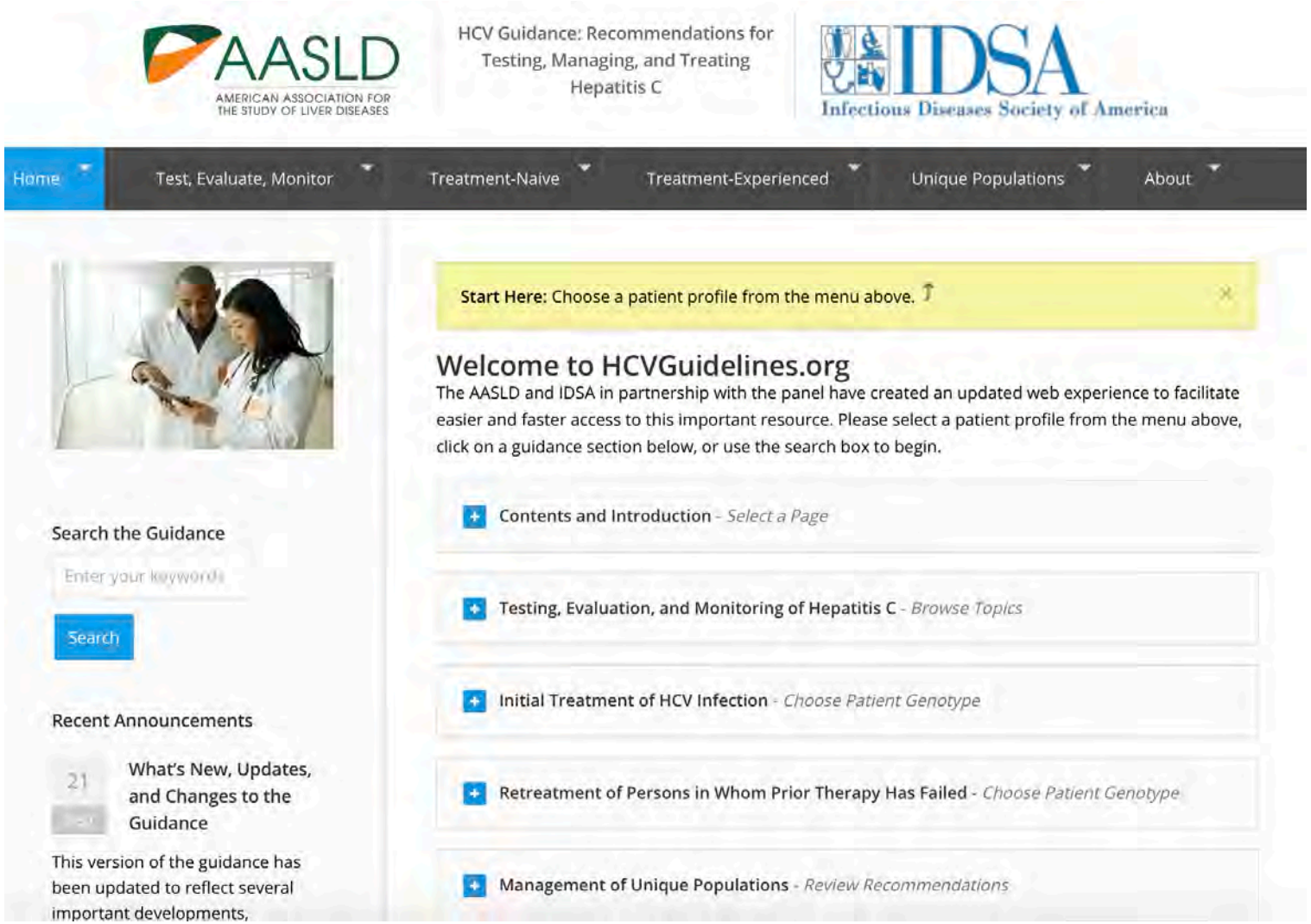
HCV Treatment and ORT



- **Patients on stable regimen of ORT**
- **Methadone vs. buprenorphine: No difference in antiviral efficacy, pharmacokinetics, no dose adjustments[1]**
- **No difference in efficacy, adherence, adverse events vs. non-ORT[2,3]**

1. Lalezari. *J Hepatol* 2015; 2. Grebely. *Clin Inf Dis*. 2016; 3. Grebely. *Clin Inf Dis*. 2016.

IDSA/AASLD Guidance Document Remains Current and Best Resource (www.hcvguidelines.org)



Thank You!