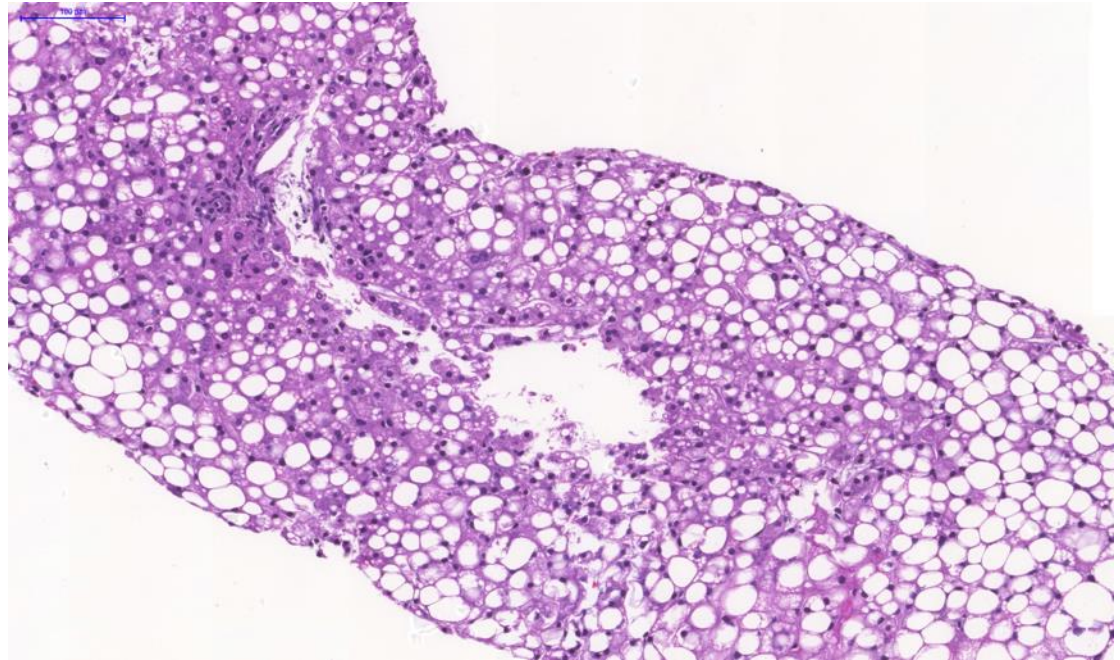# Recent Advances in the Management of NAFLD
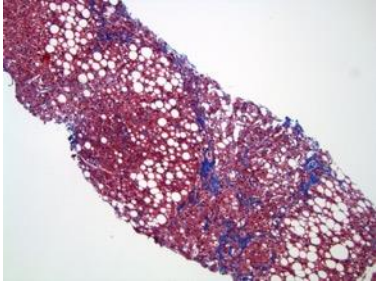
Jaideep Behari, MD, PhD

UPMC FLOW® Clinic

Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh
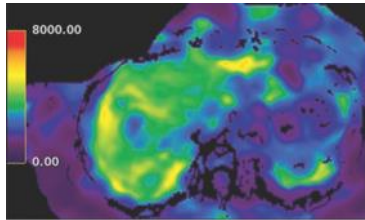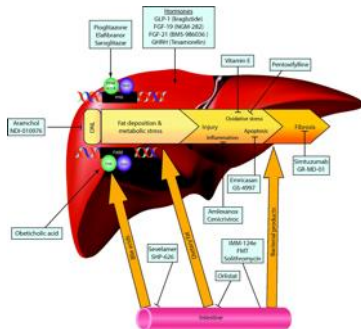
December 7, 2019

This presentation focuses on the following three topics

Update on the pathogenesis and natural history of NAFLD

Update on strategies for risk stratification of NAFLD

Update on management of NAFLD

Liver fibrosis is the most important prognostic factor for clinical outcomes in NAFLD

Image source: The AURORA study, Tobira Therapeutics
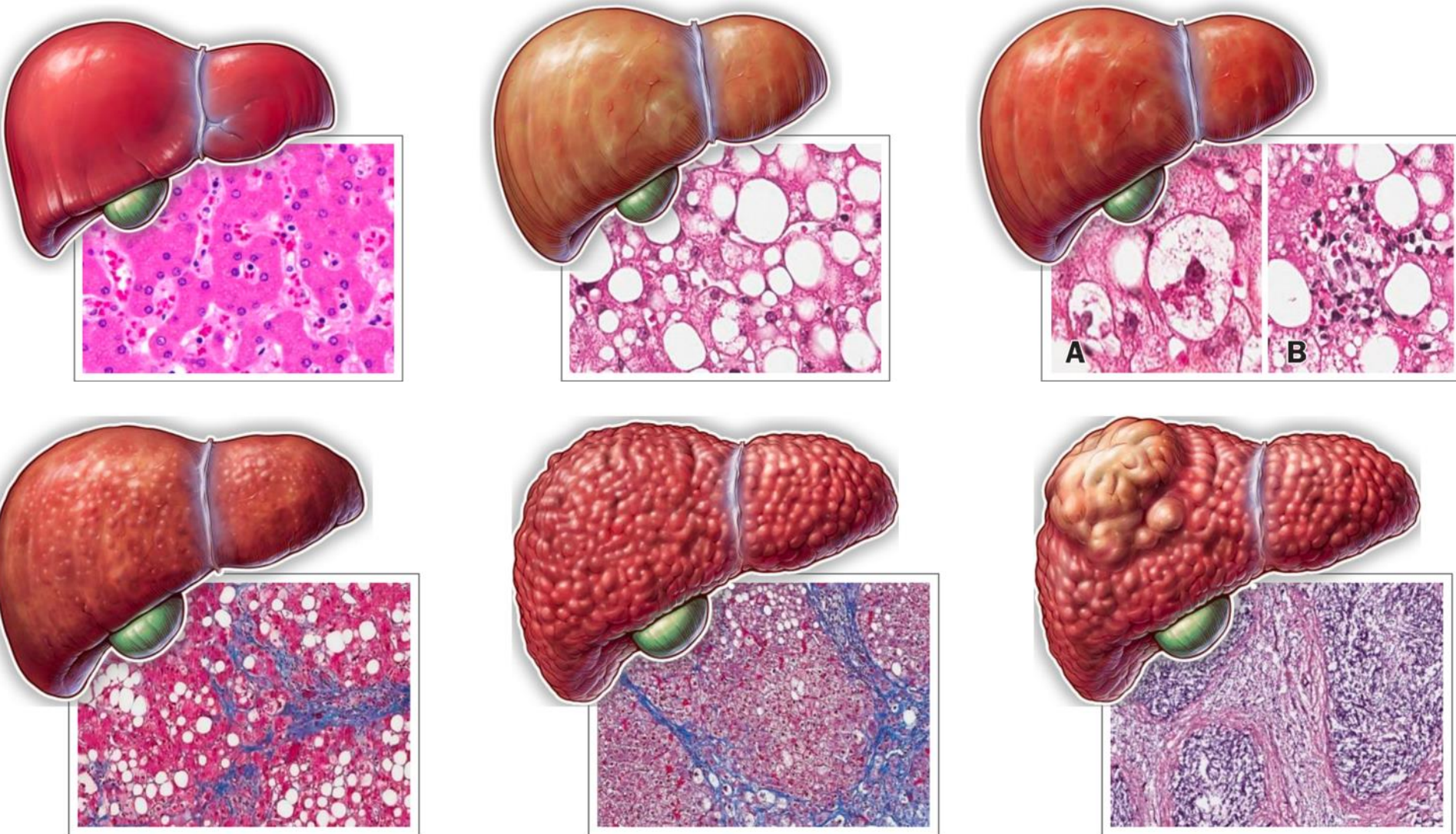
High-risk genetic polymorphisms are associated with the prevalence of NAFLD
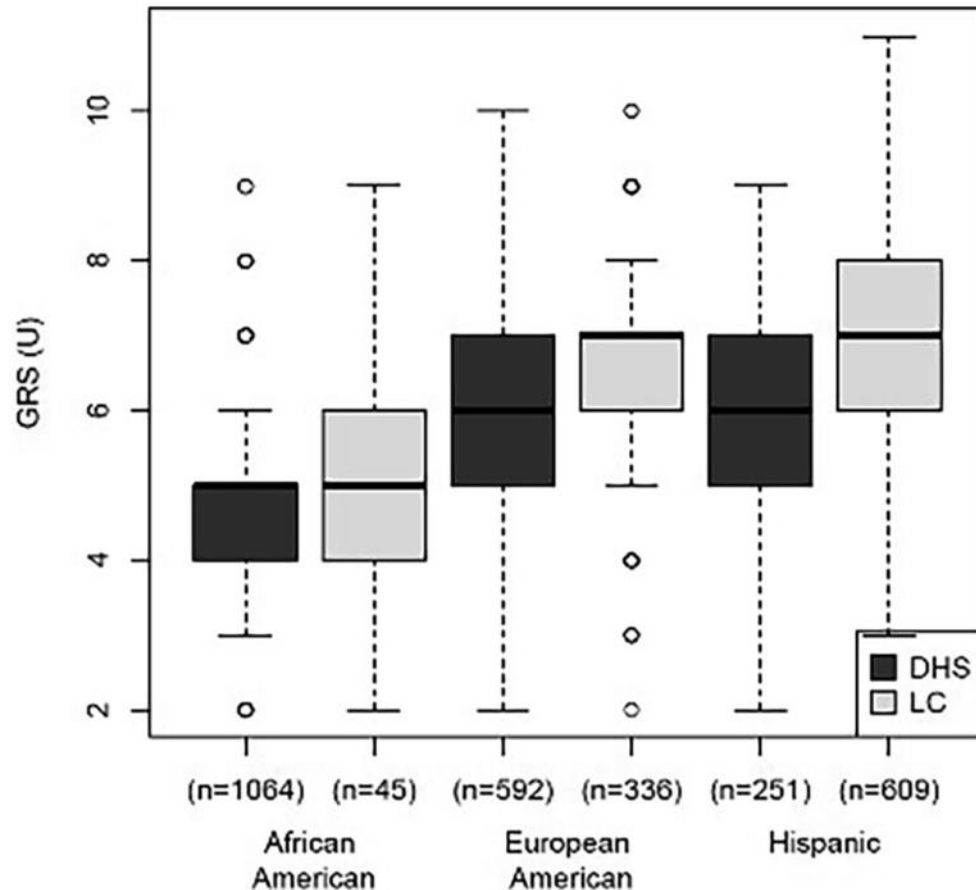
GCKR rs1260326
TM6SF2 rs58542926
TMC4- MBOAT7 rs641738,
PNPLA3 rs738409
HSD17B13 rs72613567
HSD17B13 rs80182459

Kubilian et al, Liver Meeting 2019

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Liver-related as well as non-liver related complications increase with advancing fibrosis
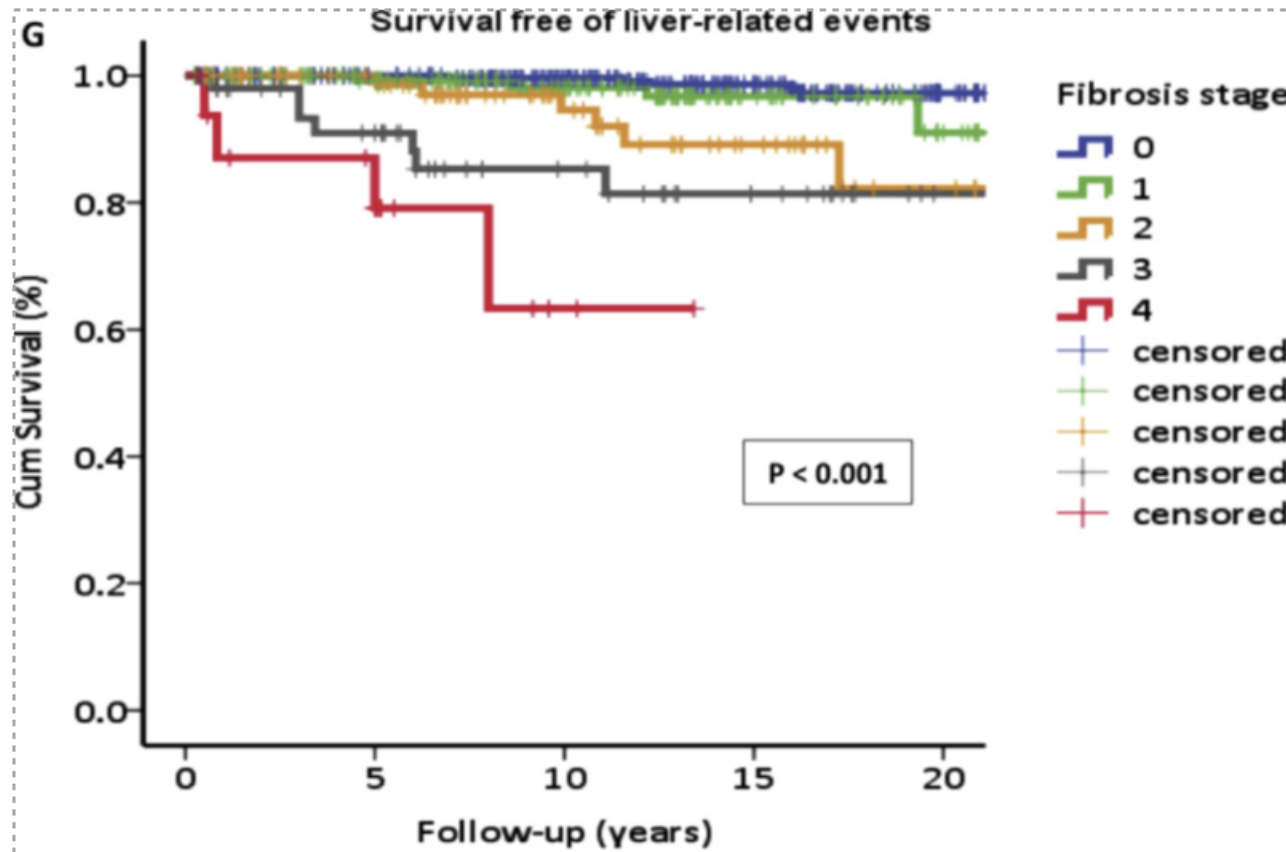
Angulo et al. Gastro 2015
Eksted et al. Hepatology 2015
Vilar-Gomez et al. Gastro 2018.
Hagstrom et al. J Hepatology 2017

Cardiovascular disease and extra-hepatic cancers are common causes of death in patients with NAFLD
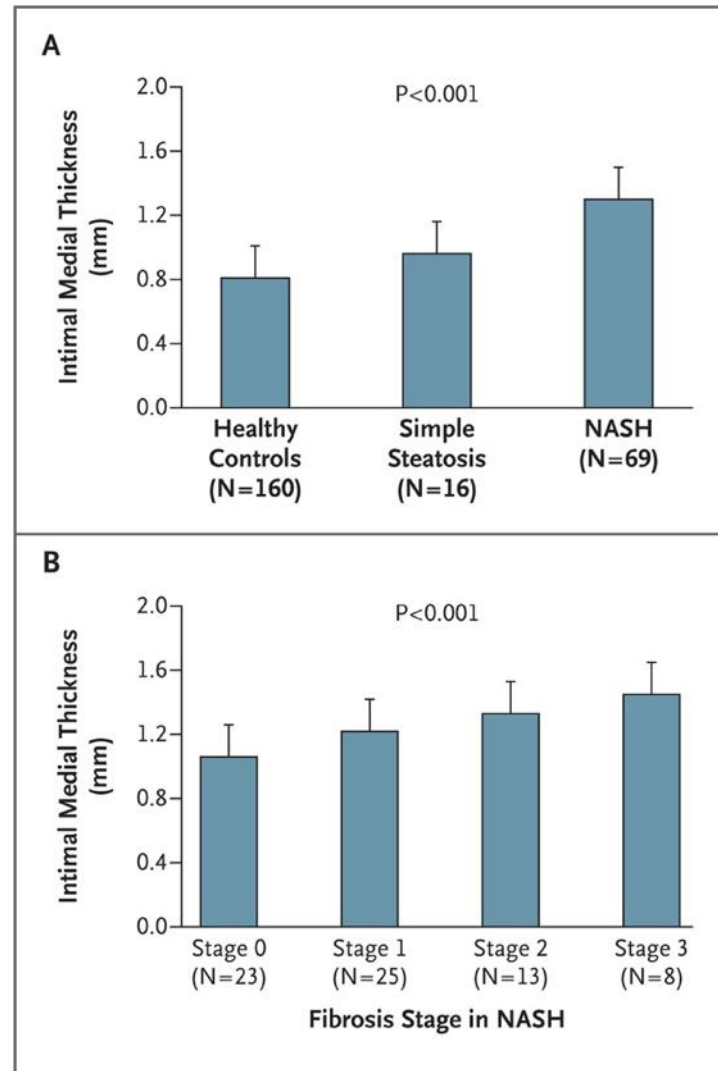
The NAFLD Simulator is a helpful tool to facilitate conversations with patients about risk stratification
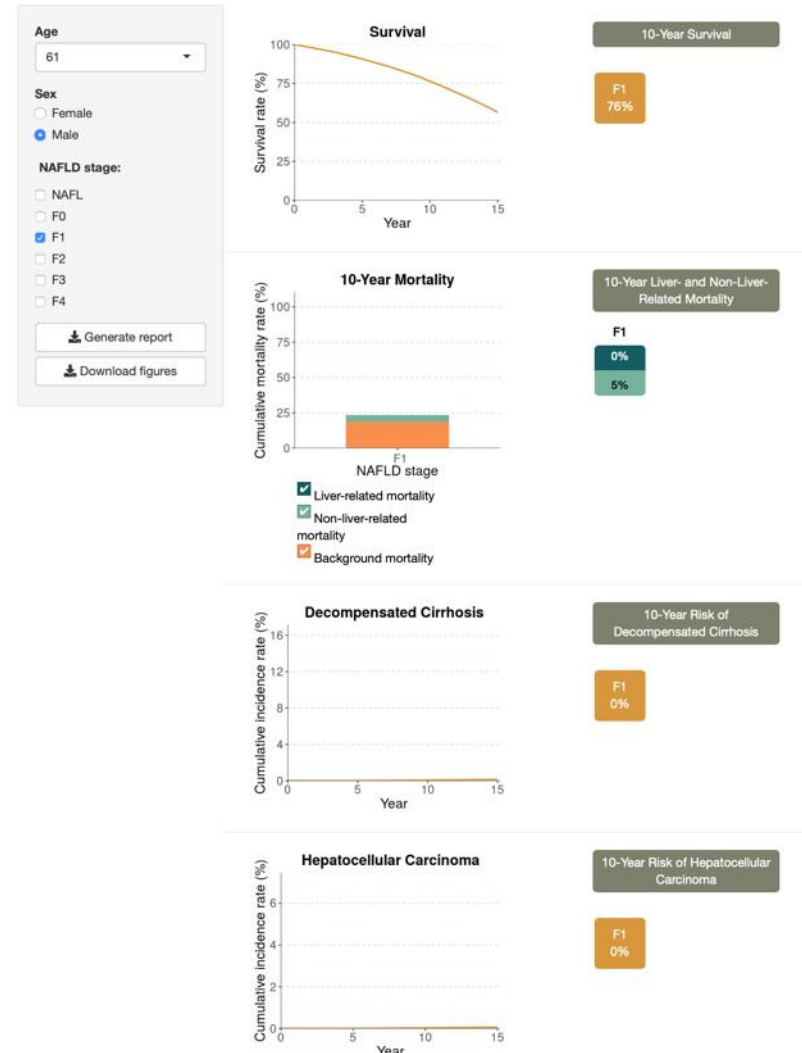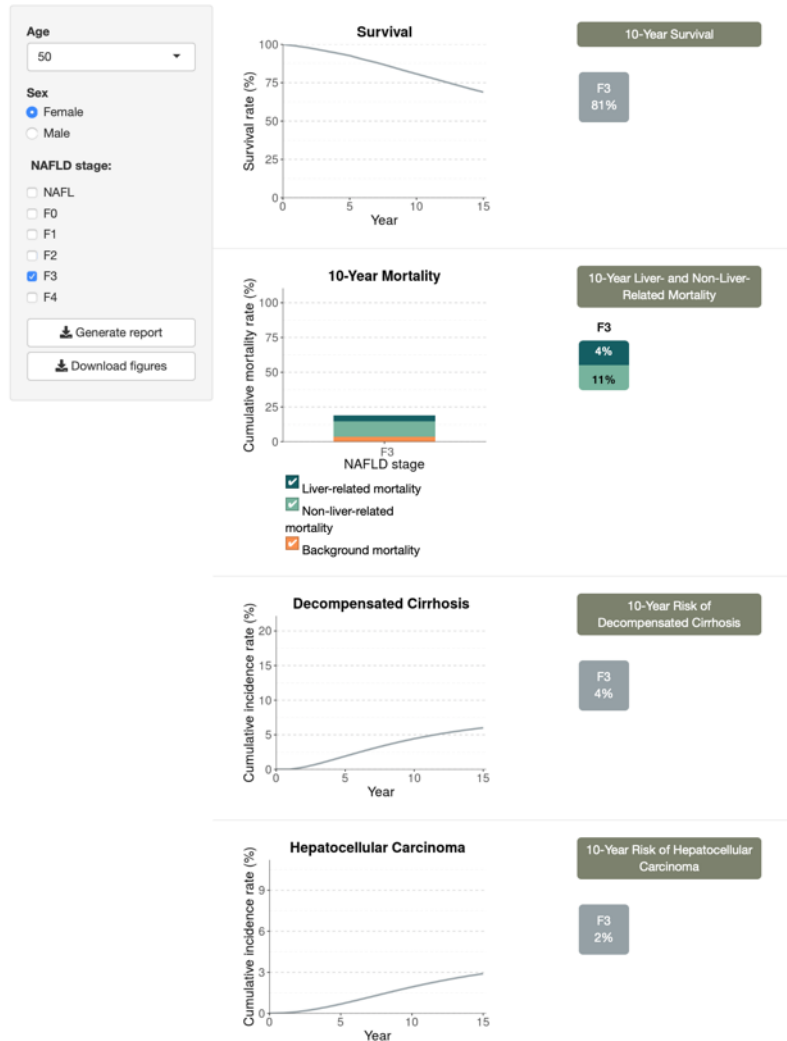
NAFLDsimulator.org

Chhatwal et al, 2019 Liver Meeting

Vibration Controlled Transient Elastography (Fibroscan®) is very useful for point-of-care risk stratification

Steatosis cutoff: 274 dB/m for grade ≥1 steatosis [sensitivity of .90 (95% CI .87-.93)]
Fibrosis: liver stiffness measurement cutoff values of 8.2 kPa for ≥F2, 9.7 kPa for ≥F3 and 13.6 kPa for F4.

LSM: Assessment of liver fibrosis (kPa)

CAP: Assessment of liver fat (dB/m)

Image source: Echosens

Eddowes, Gastroenterol, 2019

Ultrasound Shear Wave Elastography is equivalent to VCTE/Fibroscan for noninvasive fibrosis assessment
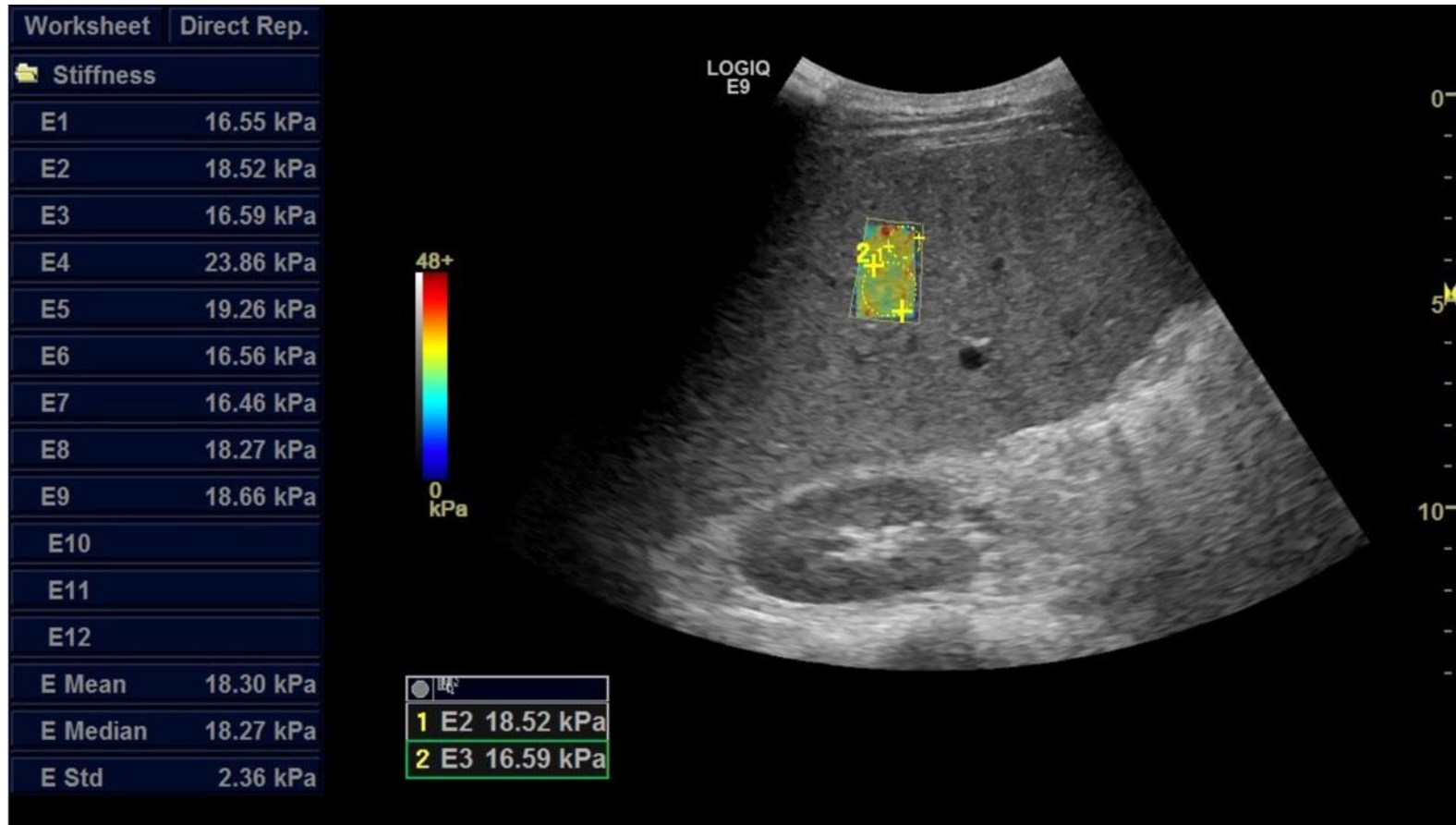
Image source: GE Healthcare

Furlan...Behari, 2019, Am J Roent.

MR Elastography and proton density fat fraction (PDFF) can accurately measure liver fibrosis and steatosis

Furlan, 2019, Am J Roent.
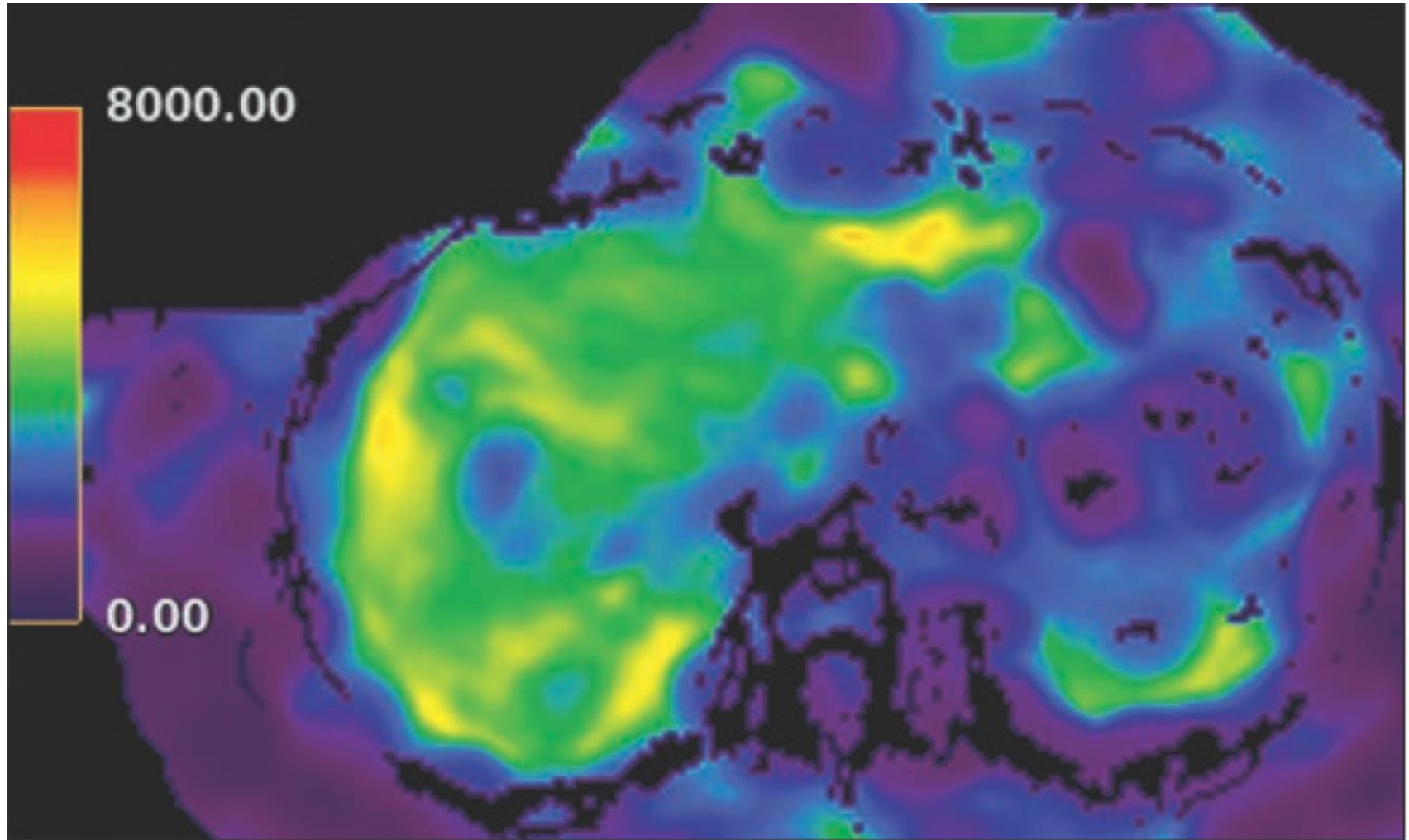
Noninvasive approaches to fibrosis assessment can avoid liver biopsy in a large percentage of patients
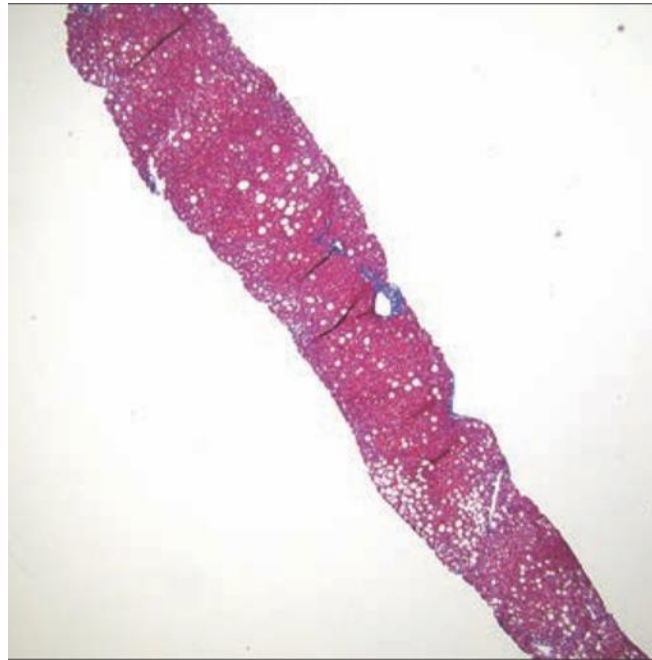
35 year old male
NAFLD Fibrosis Score: -2.15

5.7 kPa

2.35 kPa

Furlan, 2019, Am J Roent.
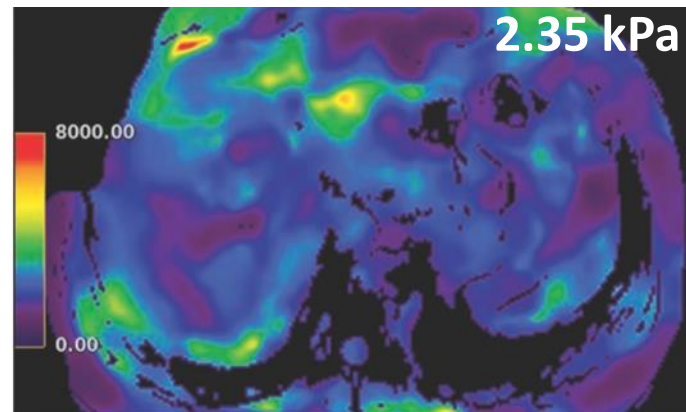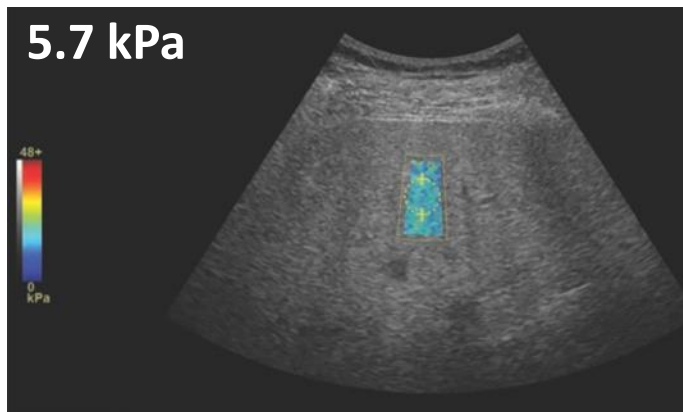
Several new technologies are on the horizon for imaging-based assessment of liver fat and fibrosis

Multiparametric three-dimensional magnetic resonance elastography (3D-MRE)

Allen et al, 2019, Hepatol Comm
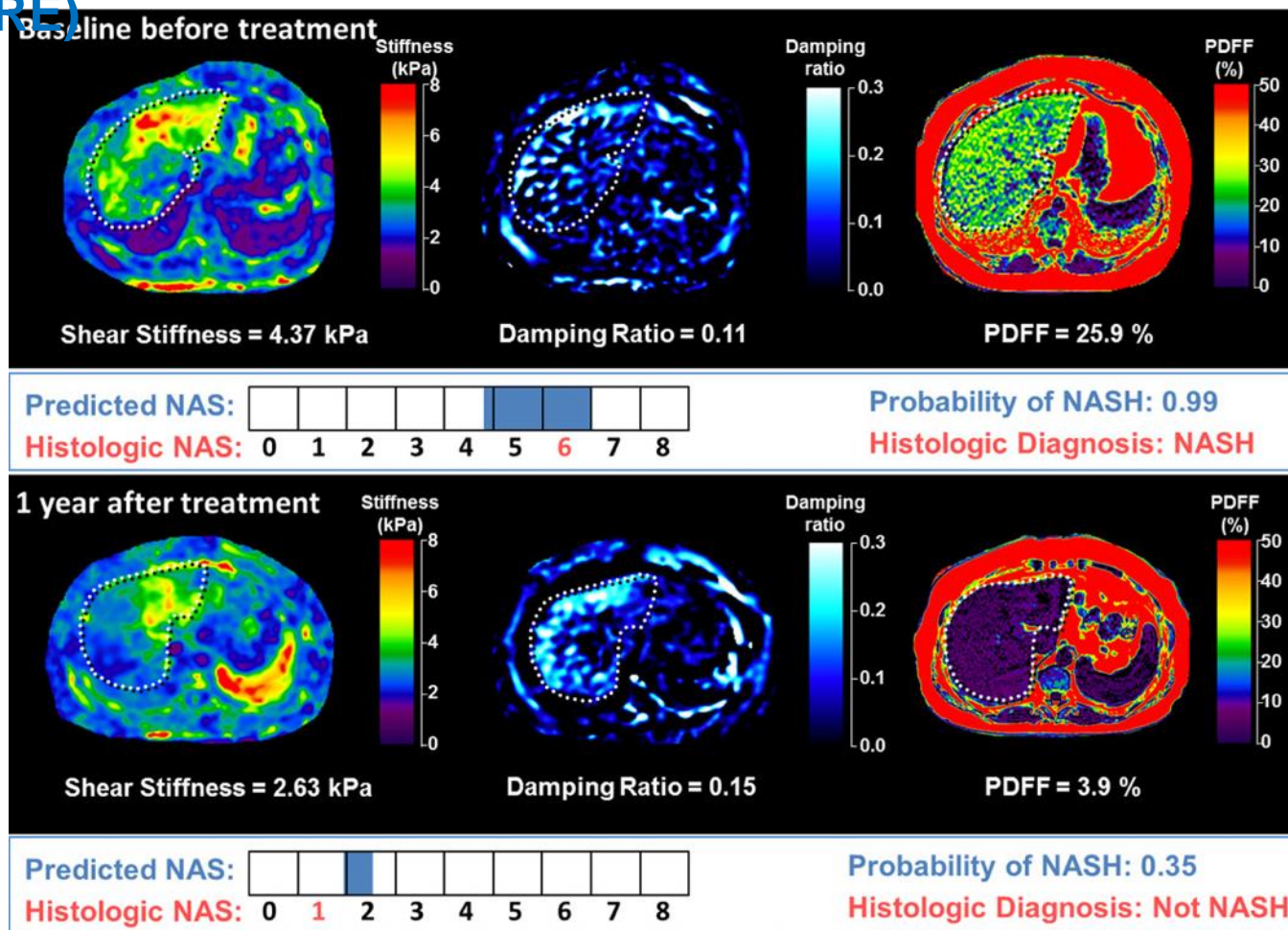
Imaging-based technologies will allow rapid noninvasive assessment of liver fat and inflammation

Multiparametric magnetic resonance imaging (Liver Multiscan)

57 yo overweight female with 6 months of lifestyle intervention
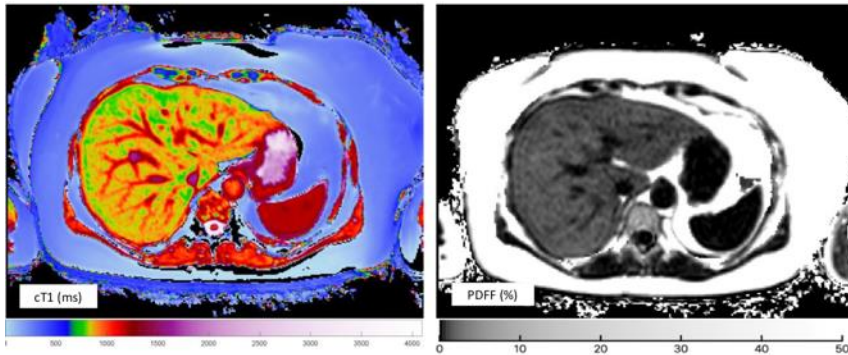
MONTH 0

PDFF: 16.5%
Normal range: <5.6%

T2*: 14.5ms
Normal range: >12.5ms

cT1: 878.4ms
Reference interval: 633ms – 794ms
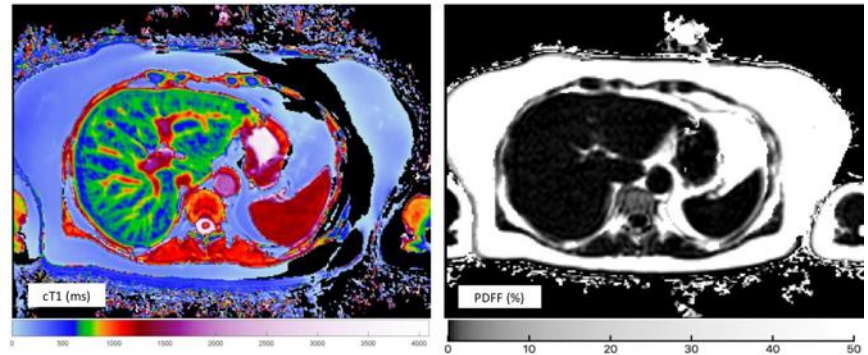
MONTH 6

PDFF: 2.4%
Normal range: <5.6%

T2*: 16.2ms
Normal range: >12.5ms

cT1: 738.3ms
Reference interval: 633ms – 794ms

Image source: Perspectum Diagnostics

Consider a systematic risk-stratified approach to NAFLD management

M: ALT>30; F > 19
Repeat labs; Risk factors

Alcohol history, HBsAg, HCV Ab, ferritin/iron sat, ANA, ASMA, ASMA, AIAT level, ceruloplasmin

Treat as appropriate

Abd US echobright
Liver screen negative

Abd US normal
Liver screen negative

NAFLD

Alternate diagnosis?
Mild steatosis?

NAFLD Fibrosis score
VCTE/2D-SWE/MRE

Low risk:
NFS<-1.455 (NPV 93%)
VCTE < 7 kPa*

High risk
NFS > 0.676 (PPV 90%)
VCTE > 13.5 (+/-1) kPa*

<-2.5
<5 kPa

PCP follow up/3 years

Indeterminate
NFS -1.455-0.676
VCTE 8.2-13.5*
OR Discordant NFS/VCTE

Manage as cirrhosis

-1.45 to -2.5
5-7 kPa

Reassess in 1 year
Lifestyle mod.

Liver biopsy
Treat if F2-3 fibrosis

*Cutoffs not validated

It is helpful to consider a risk-stratified management strategy for NAFLD

Rinella, 2016
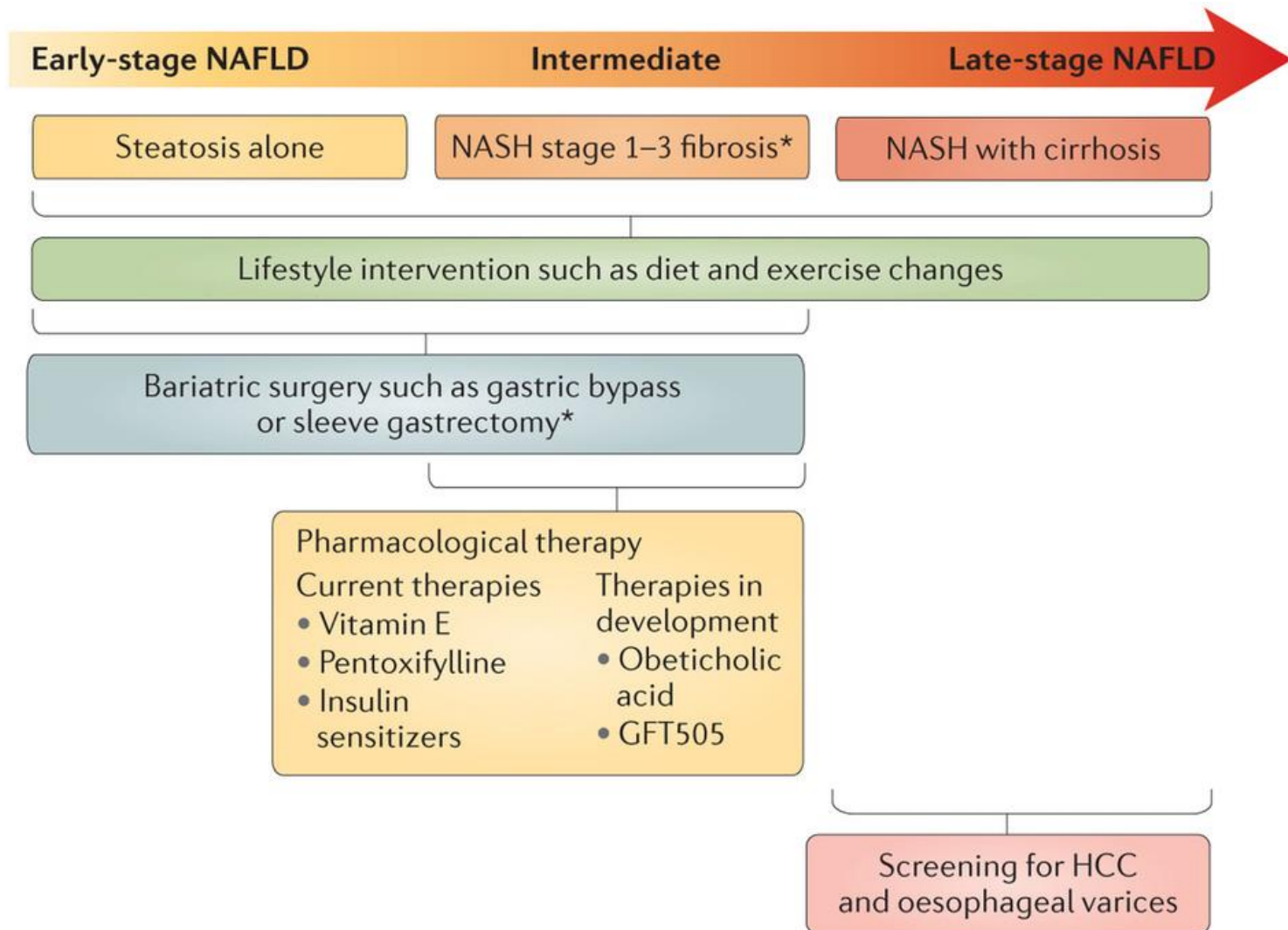
Despite relatively low probability of long-term success, weight loss is an excellent treatment option for NAFLD

52 weeks of lifestyle intervention

	5%	7%	10%
% Weight loss (WL)	5%	7%	10%
NASH-resolution	10%	26%	64%	90%
FIBROSIS-regression	45%	38%	50%	81%
STEATOSIS improvement	35%	65%	76%	100%
% Patients achieving WL	70%	12%	9%	10%

Romero-Gomez, J Hepatol, 2017

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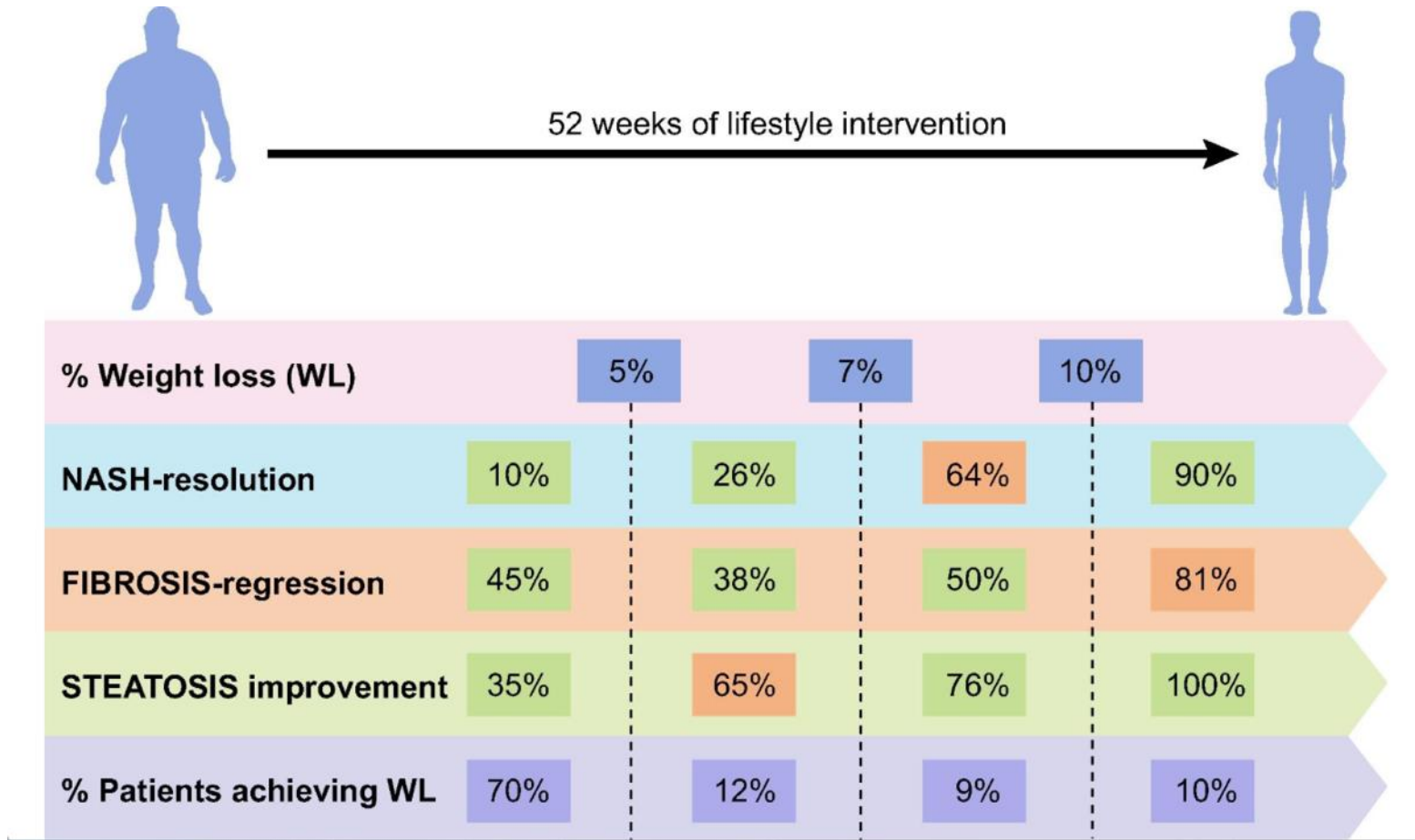
Weight loss surgery is effective in resolving NASH but liver fibrosis may not regress in some patients

NASH grade
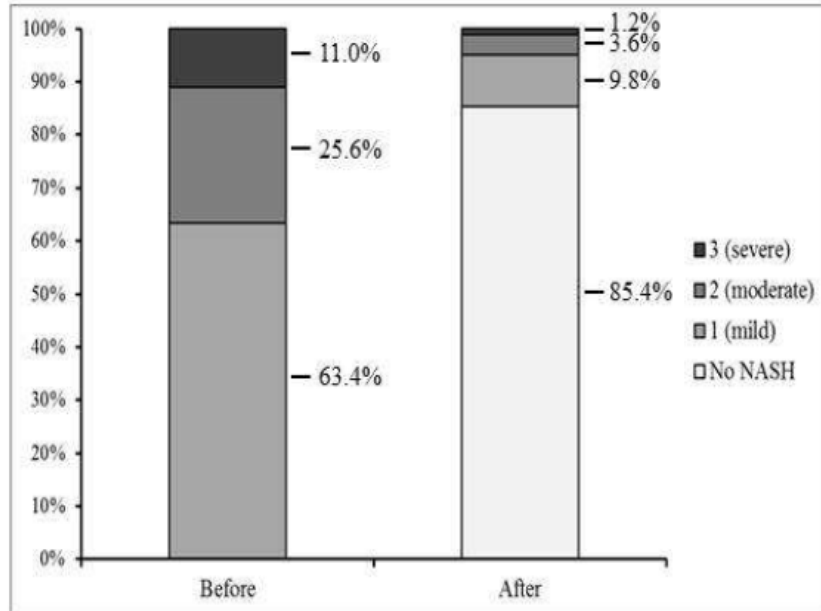
Fibrosis stage

82 patients at 1 year after surgery

Despite weight loss >20 kg and NASH resolution, 45% of patients did not achieve resolution of advanced fibrosis (F/4) after 6 years*

Lassailly, 2015, Gastroenterology

*Pais, 2019 Liver Meeting

Vitamin E (with modest weight loss) is effective in improving NASH in NAFLD patients without diabetes

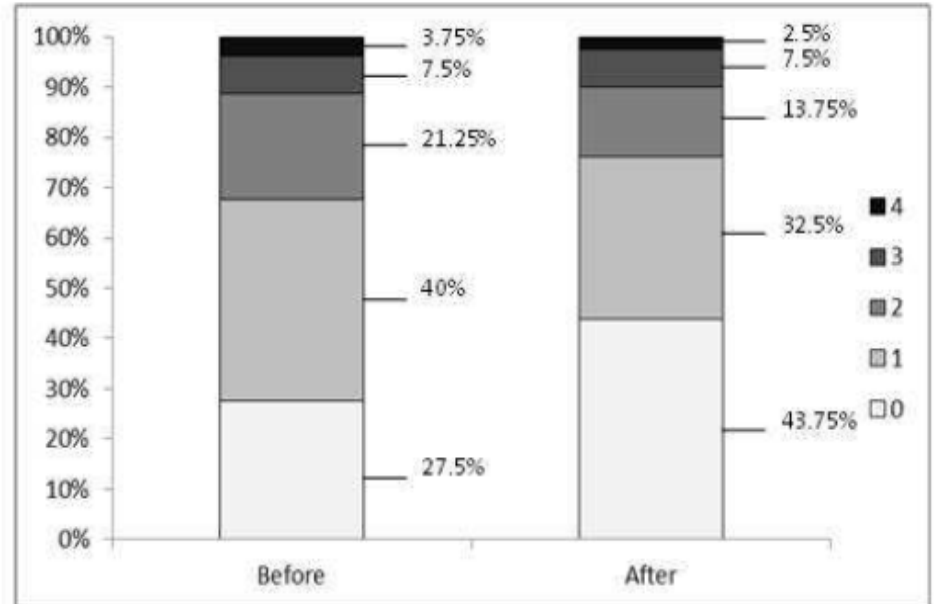| Variable	Placebo	Vitamin E	Pioglitazone	Vitamin E vs. Placebo	Pioglitazone vs. Placebo
				P Value*	
Primary outcome†					
No. of subjects randomly assigned	83	84	80		
Subjects with improvement (%)	19	43	34	0.001	0.04
Changes from baseline in histologic features					
No. of subjects with biopsy specimens at baseline and 96 wk	72	80	70		
Steatosis					
Subjects with improvement (%)	31	54	69	0.005	<0.001
Mean change in score	−0.1	−0.7	−0.8	<0.001	<0.001
Lobular inflammation					
Subjects with improvement (%)	35	54	60	0.02	0.004
Mean change in score	−0.2	−0.6	−0.7	0.008	<0.001
Hepatocellular ballooning					
Subjects with improvement (%)	29	50	44	0.01	0.08
Mean change in score	−0.2	−0.5	−0.4	0.03	0.01
Total NAFLD activity score (mean change)	−0.5	−1.9	−1.9	<0.001	<0.001
Fibrosis‡					
Subjects with improvement (%)	31	41	44	0.24	0.12
Mean change in score	−0.1	−0.3	−0.4	0.19	0.10
Resolution of definite nonalcoholic steatohepatitis (% of subjects)	21	36	47	0.05	0.001

Vitamin E 800 international units/d

Sanyal, 2010, NEJM

Pioglitazone is an option to treat NASH with fibrosis in patients with NASH and T2DM or prediabetes
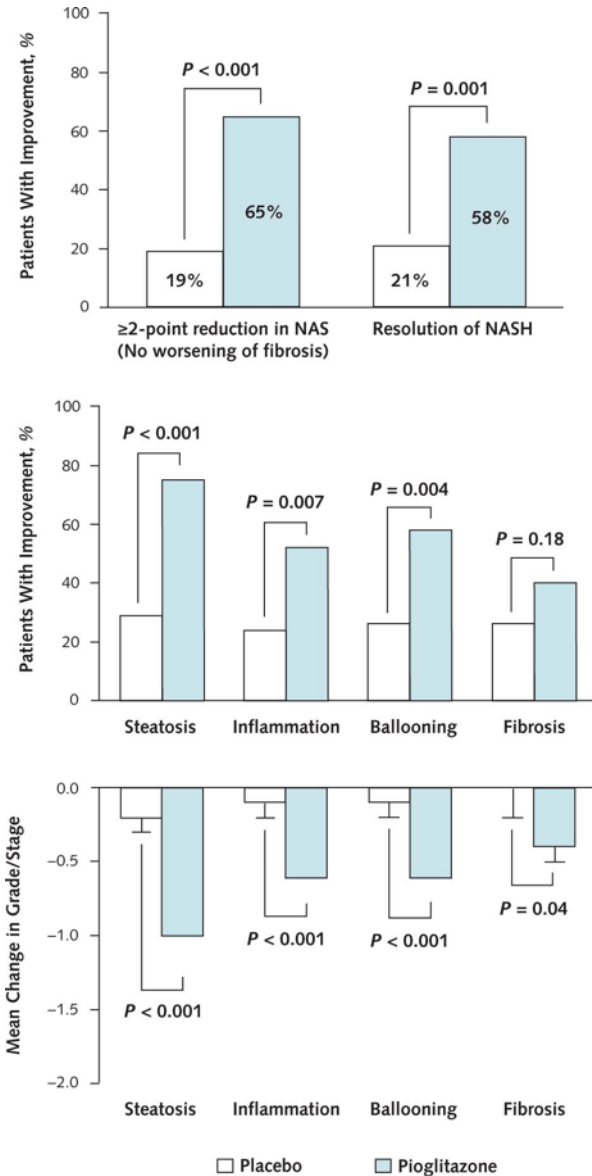
45 mg/d x 18 months

2.5 kg weight gain vs placebo

Cusi, 2018, Ann Int Med

Several new therapies are in advanced stages of testing and have shown promising results in treating NASH

Oseini and Sanyal, 2017, Liver Int
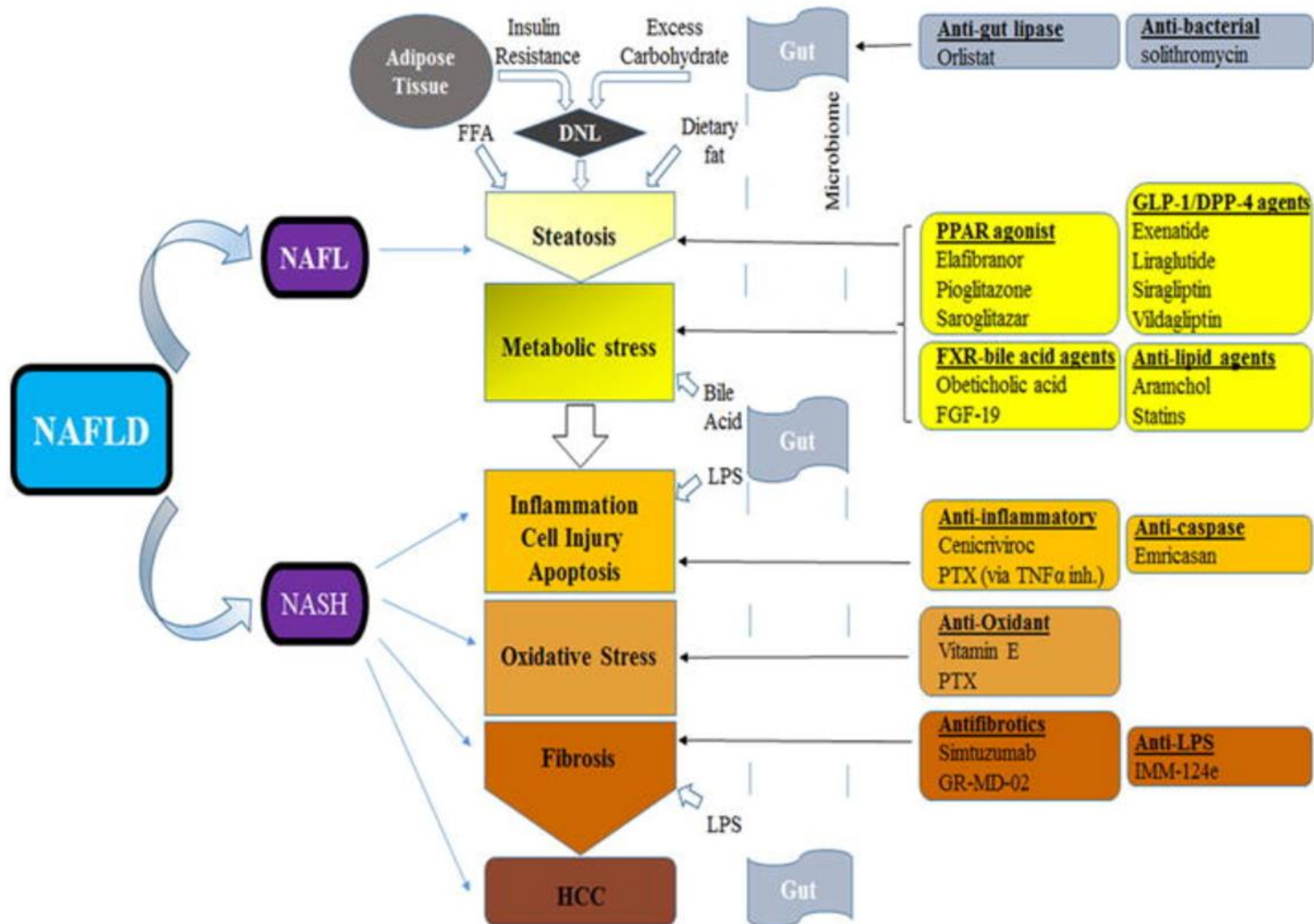
Obeticholic acid (OCA) has shown promising results in treatment of NASH and fibrosis but can cause itching

	Placebo	OCA 10 mg	OCA 25
Population with F1-F3 fibrosis	**n=407**	**n=407**	**n=404**
Fibrosis improvement + no worsening of NASH	**10.6%**	**15.7% p<0.029**	**21% p<0.0001**
NASH resolution + no worsening of fibrosis	**7.9%**	**11.3% p=0.09**	**14.9% p=0.001**
Pruritus	**19%**	**28%**	**51%**

Phase 3 REGENERATE trial: Interim analysis at 18 months based on surrogate endpoints (impact on clinical outcomes not yet established)

Adapted from Sanyal, 2019 Liver Meeting

A multidisciplinary approach is needed to manage NAFLD-associated comorbid metabolic problems

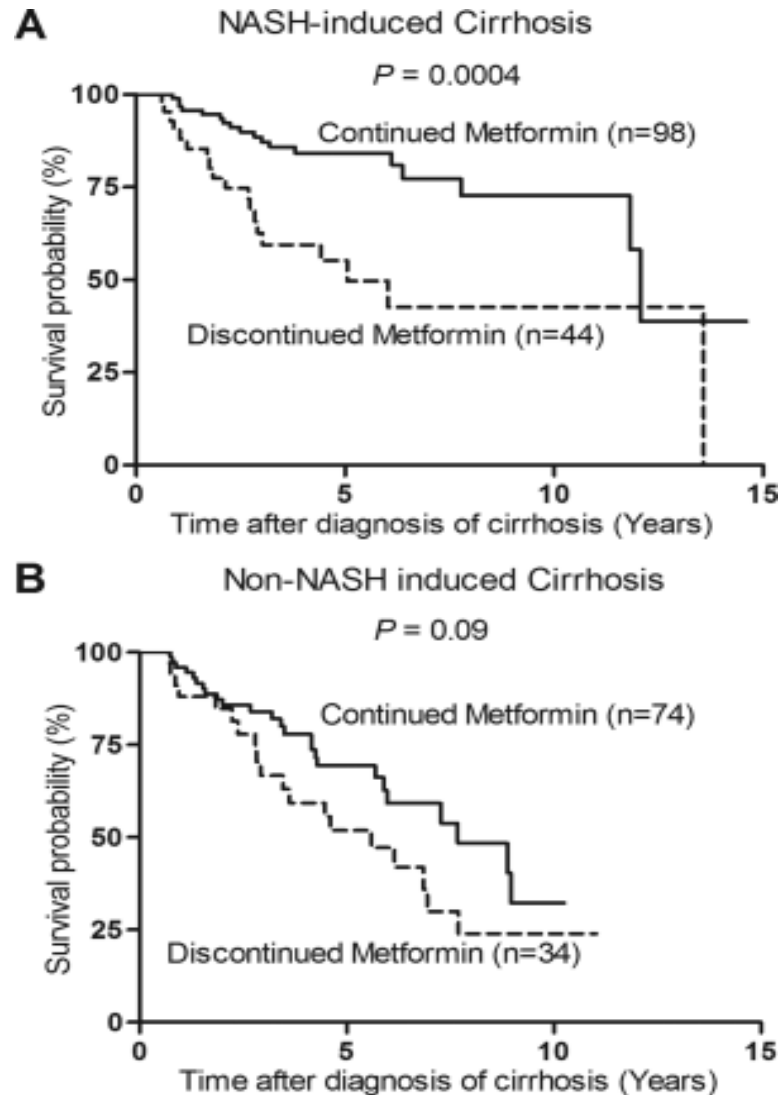|		
Diagnosis of NAFLD →	**Screen for Metabolic Risk Factors** →	**Management Goals of Metabolic Risk Factors**
	Obesity Body mass index >30 →	Weight loss of 7%-10% over 48%-52 weeks
	Diabetes Mellitus Hemoglobin A1c >6.5%, random glucose >200 mg/dL, or fasting glucose >126 mg/dL on 2 separate occasions →	Hemoglobin A1c <7.0% with lifestyle modifications +/• antiglycemic agent(s)
	Dyslipidemia 10-year atherosclerotic cardiovascular disease risk score •7.5%, LDL • 190 mg/dL, or LDL • 70-189 mg/dL with diabetes →	Treat using a moderate- to high-intensity statin. Expect •50% reduction in LDL from baseline using high-intensity statin. Expect 30%-50% reduction in LDL from baseline using moderate-intensity statin.
	Hypertension Blood pressure >140/90 mm Hg on at least 2 separate measurements →	Systolic blood pressure <150 or <140 mm Hg depending on age, presence of diabetes, and/or chronic kidney disease; diastolic blood pressure <90 mm Hg

Wong and Lim, 2018, Clin Liv Dis

Metformin may decreasing overall mortality and statin therapy is safe in NAFLD

Zhang, 2014, Hepatology

In summary, systematic risk stratification with weight loss and pharmacotherapy is recommended for NAFLD

UPMC FLOW Clinic

- **Noninvasive fibrosis assessment**
- **NASH clinical trials**
- **Endocrinology, nutrition**
- **Weight loss programs (dietary and pharmacotherapy)**

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