Improving People's Lives Through Innovations in Personalized Health Care

Updates on Non-Alcoholic Fatty Liver Disease

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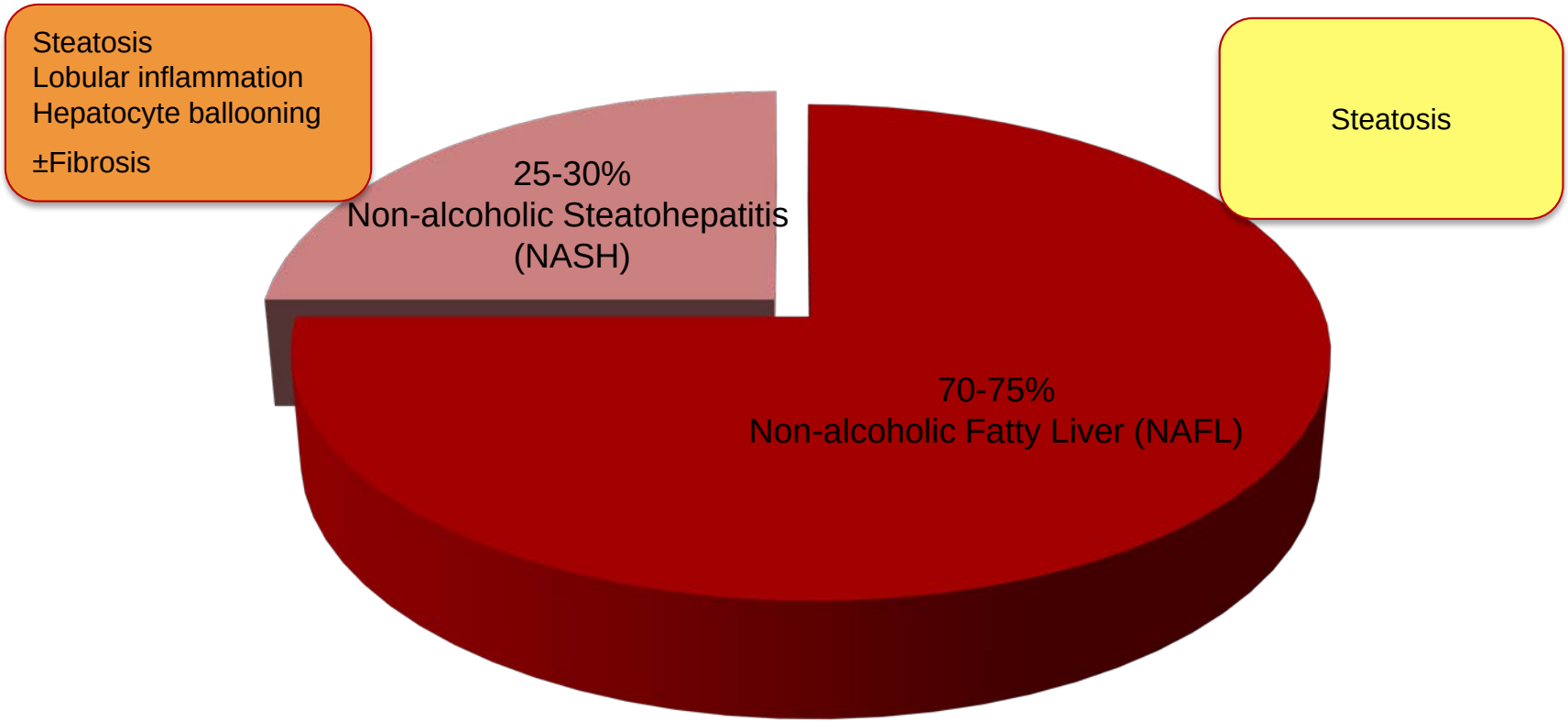
Disclosure

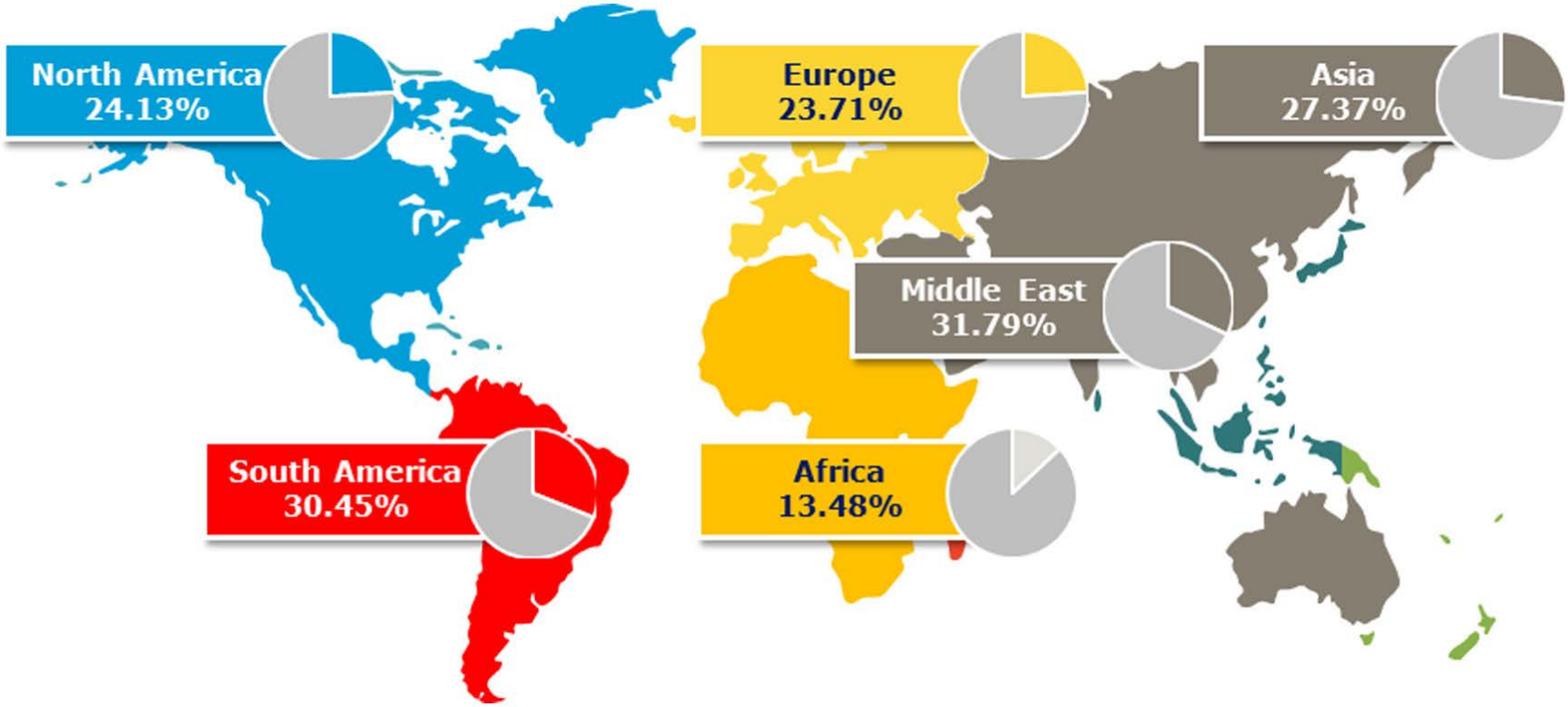
- None

Non-alcoholic Fatty Liver Disease (NAFLD)



Rinella ME, et al. JAMA 2015;313:2263-73

Prevalence of NAFLD



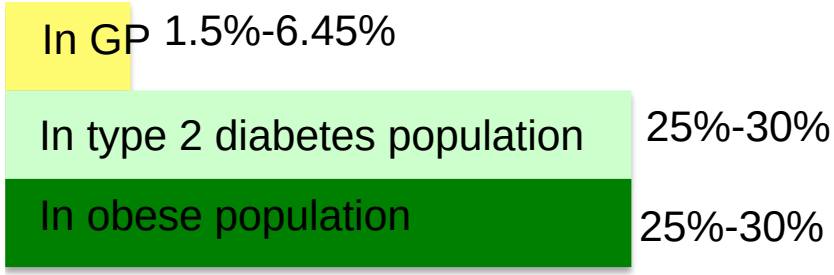
- Prevalence of NASH is estimated 1.5-6.45% in the United States
- Projected NAFLD prevalence 76 million in the United States, 52 million in the Europeans

Younossi ZM, et al. Hepatology 2019;69:2672-82

High prevalence of NAFLD/NASH in high-risk population

NAFLD prevalence among adult population

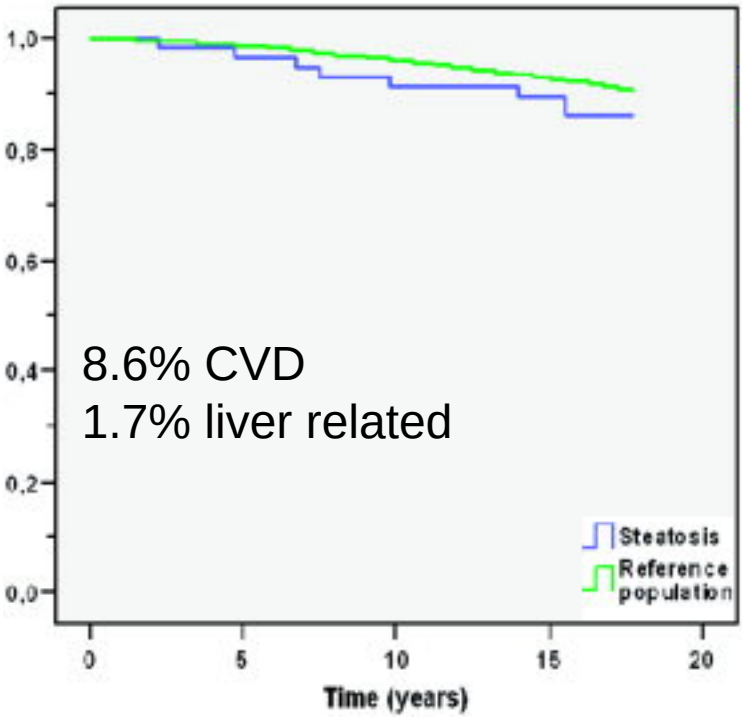
NASH prevalence among adult population



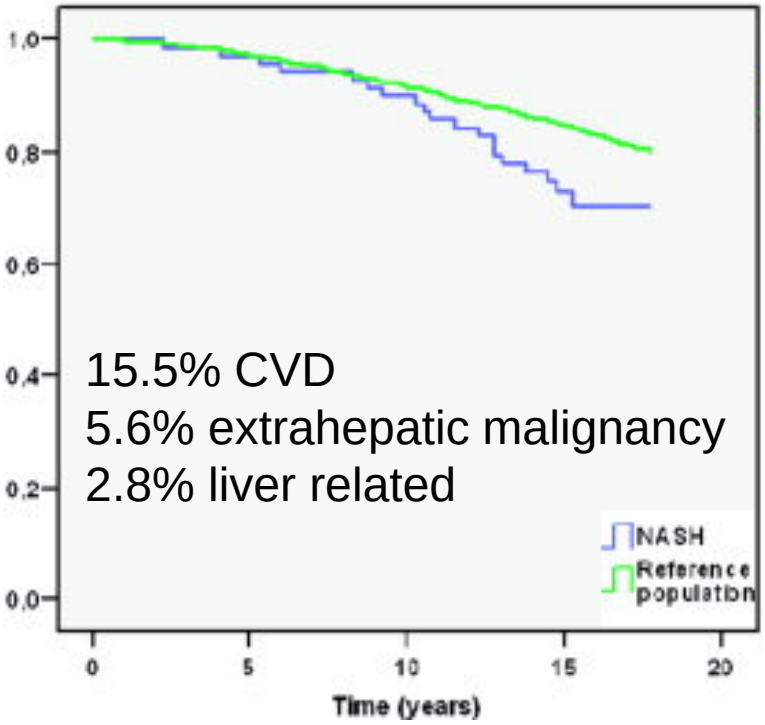
Younossi Z, et al. Hepatology;2016;64:73-84; Bril F, et al. Diabetes Care 2017;40:419-30; Anstee QM, et al. Nat Rev Gastroenterol Hepatol 2013;10:330-44

NASH increases all-cause mortality

Isolated hepatic steatosis



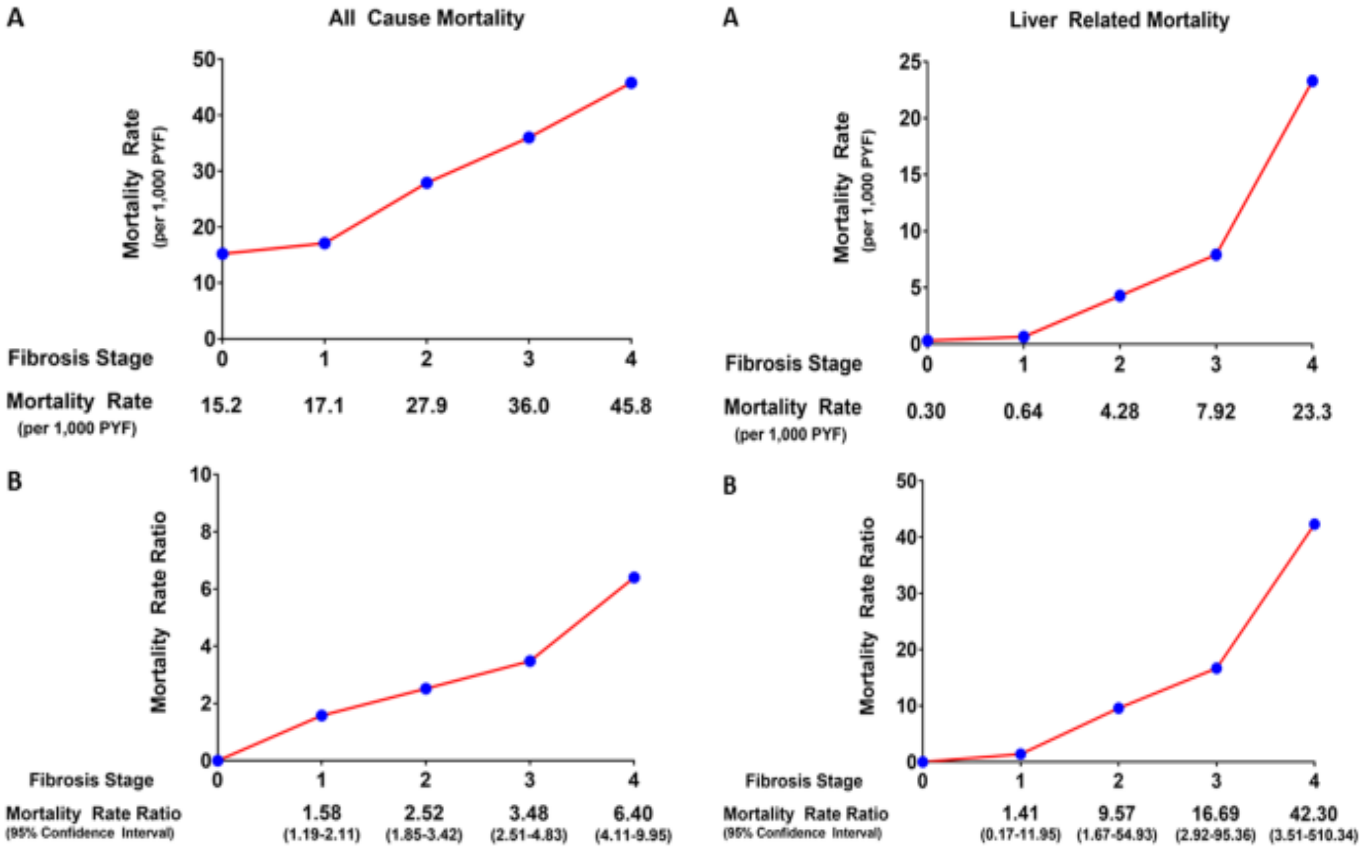
NASH



Ekstedt M, et al. Hepatology 2006;44:865-873

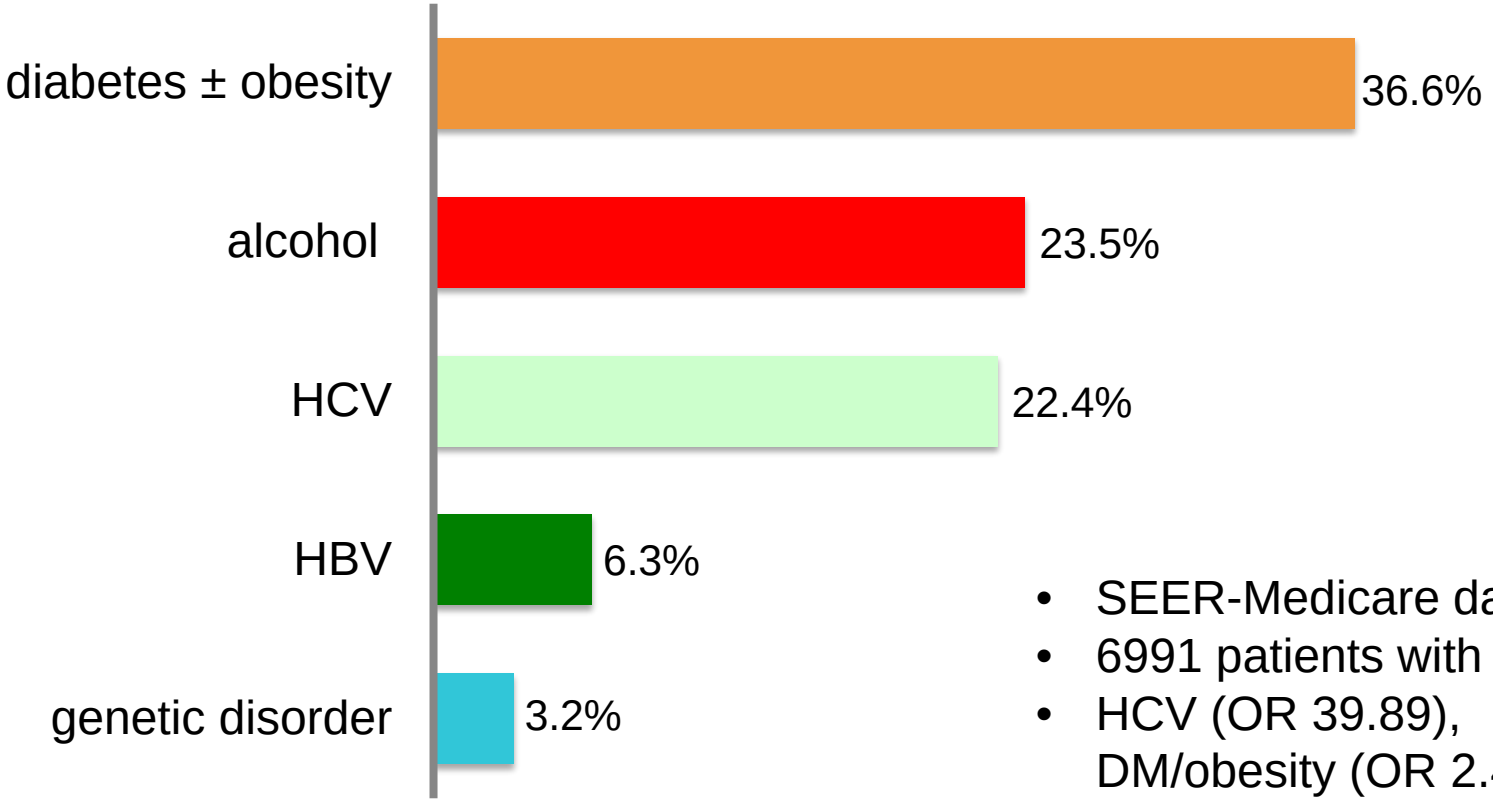
Fibrosis stage correlates with mortality

- Meta-analysis
- 5 adult NAFLD cohorts
- 1495 patients with 17452 patient years of follow up



Dulai PS, et al. Hepatology 2017;65:1557-1565

Population attributable fractions for HCC

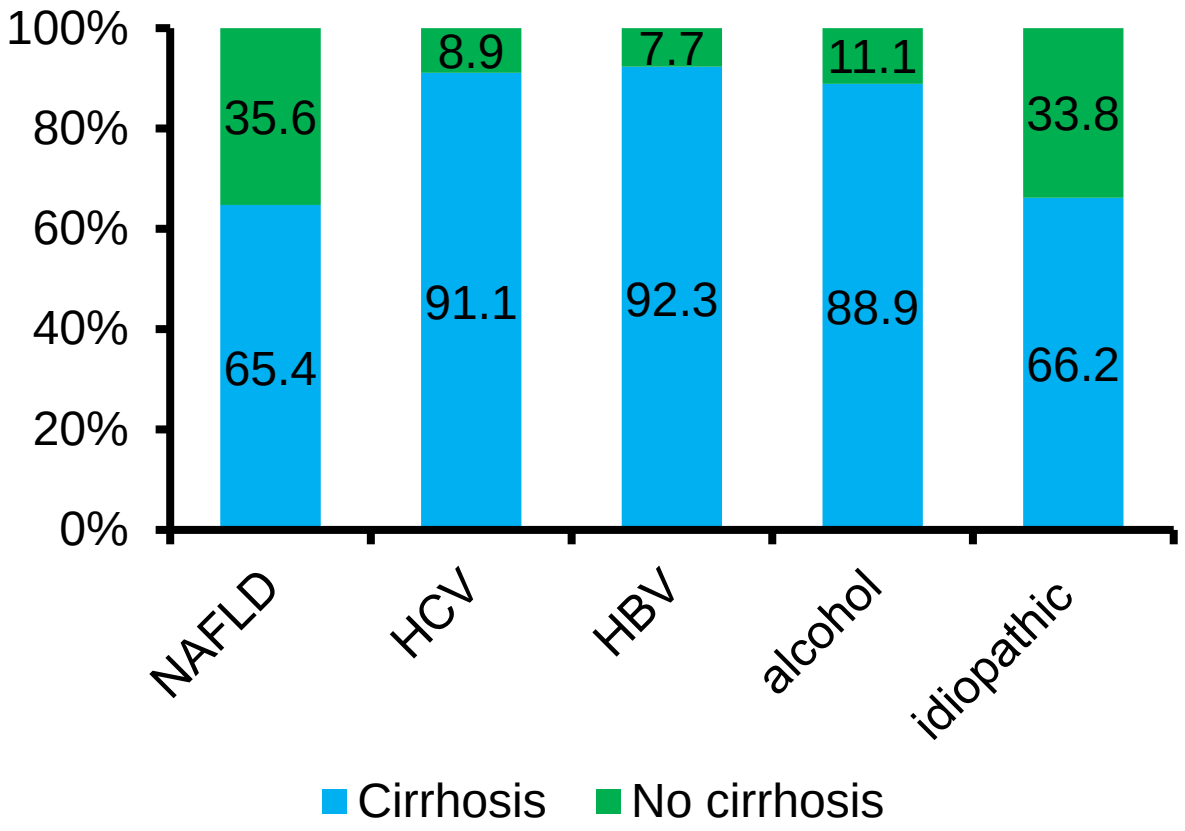


- SEER-Medicare database
- 6991 patients with HCC
- HCV (OR 39.89), DM/obesity (OR 2.47)

Welzel TM, et al. Am J Gastroenterol 2013;108:1314-21

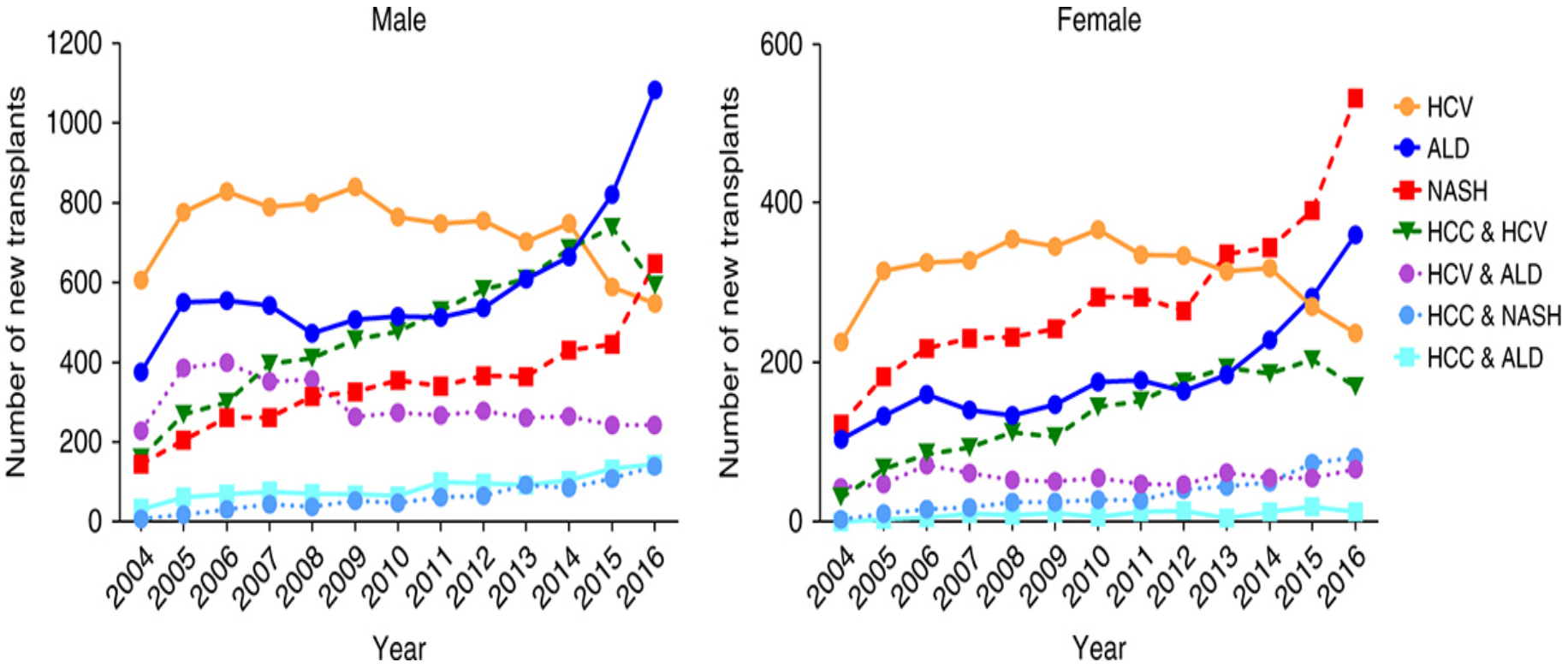
Occurrence of HCC with or without cirrhosis

- 1500 VA patients with HCC (2005-2010)
- 13% of patients with HCC do not have cirrhosis
- Risk of HCC in absence of cirrhosis: NAFLD (OR 5.4), metabolic syndrome (OR 5.0)



Mittal et al. Clin Gastroenterol Hepatol 2016;14:124

NASH is the leading cause for liver transplant in females and the second leading cause in males



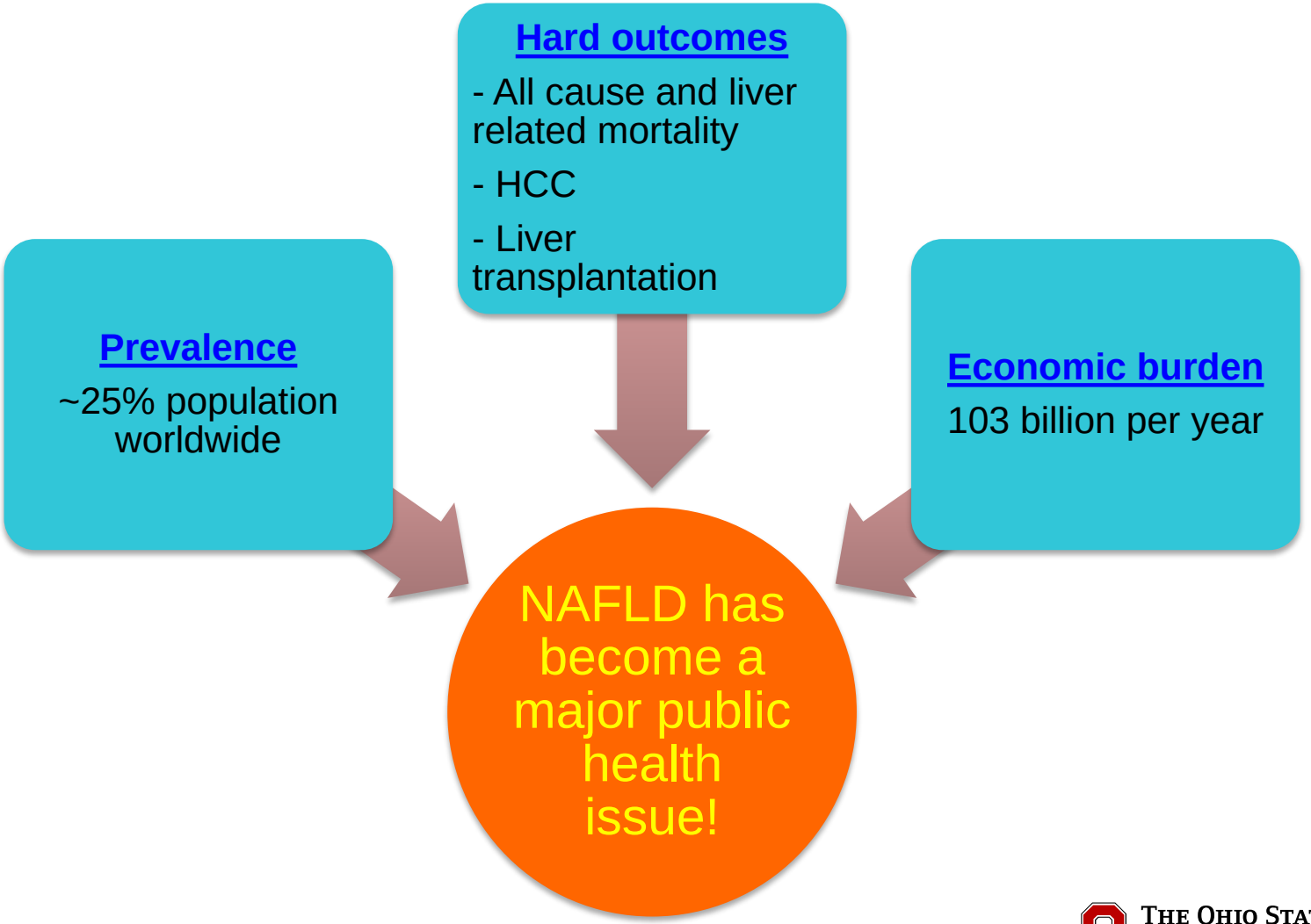
Noureddin M, et al. Am J Gastro 2018;113:1649-59

Economic burden of NAFLD related care

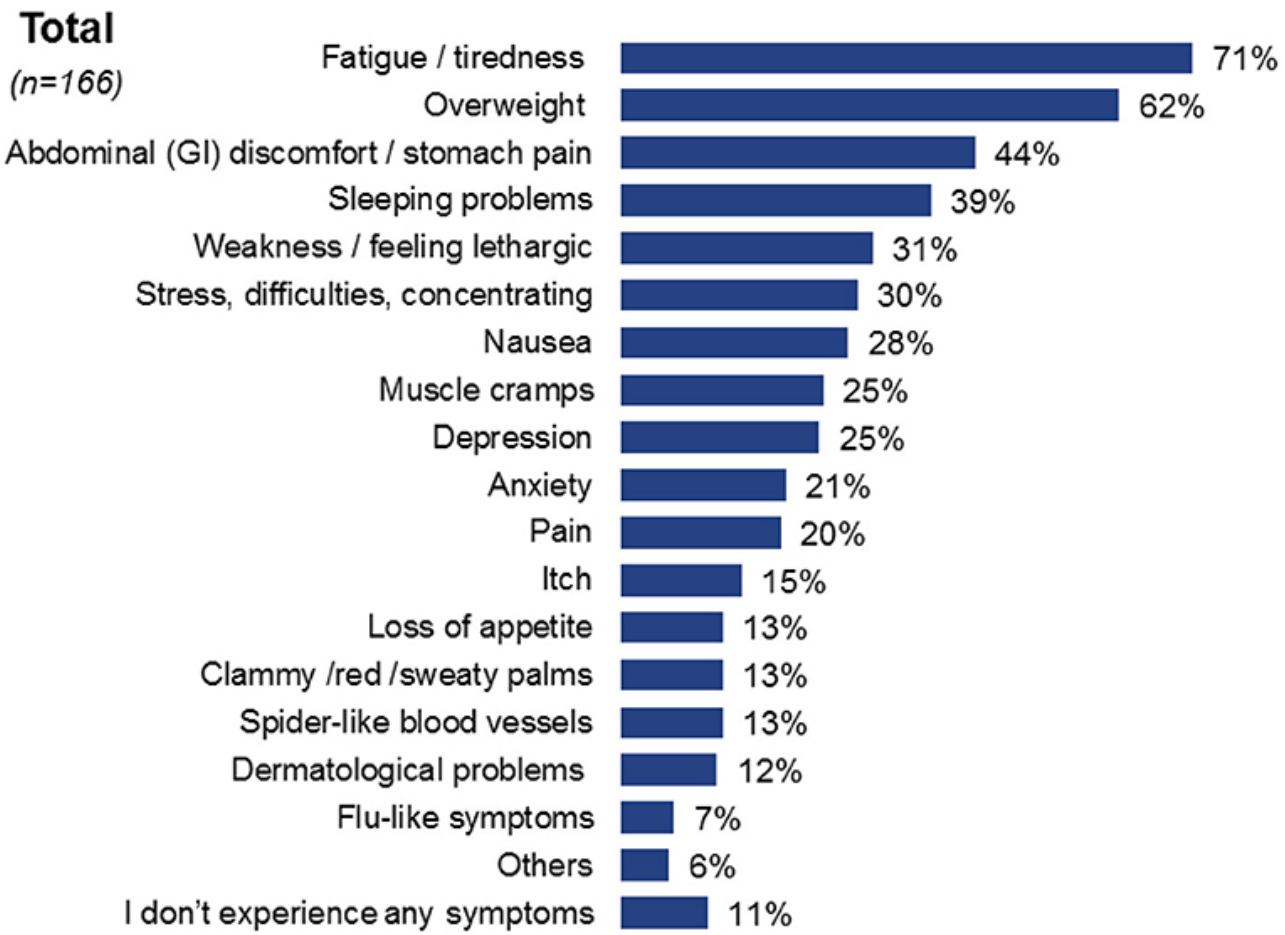
	United States	Germany	France	Italy	United Kingdom
Total costs (in billions)					
Direct costs	$103.31	€4.33	€11.40	€11.95	£5.24
Societal costs	$188.88	€51.94	€64.31	€44.14	£26.03
Total costs	$292.19	€56.27	€75.72	€56.09	£31.26
Costs (in millions) due to					
NAFL	$86,564.2	€3,492.43	€9,163.92	€9,776.54	£4,326.86
NASH no FB	$5,483.6	€244.07	€759.79	€701.42	£301.79
NASH FB	$1,866.3	€87.86	€242.90	€250.94	£110.21
CC	$6,573.3	€312.74	€916.78	€900.07	£362.66
DCC	$1,765.5	€90.33	€268.63	€260.60	£103.06
HCC	$522.7	€31.30	€25.78	€15.50	£17.60
LT	$161.6	€30.09	€18.24	€15.25	£11.09
PLT	$375.7	€43.97	€8.08	€30.35	£4.26

Younossi ZM, et al. Hepatology 2016;64:1577-86

Clinical significance of NAFLD



Symptoms related to NASH

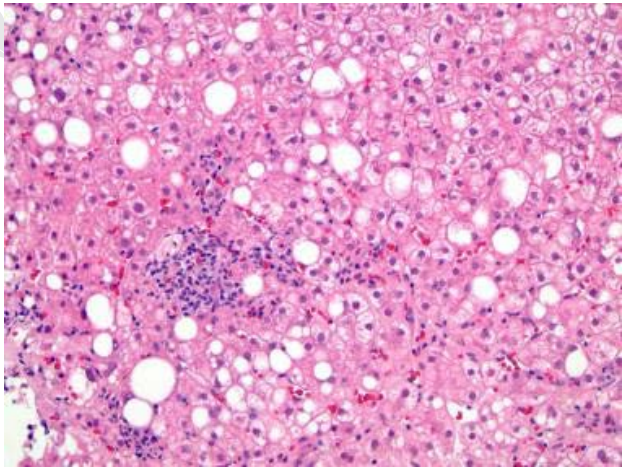


Cook N, et al. Front Med 2019;6:61

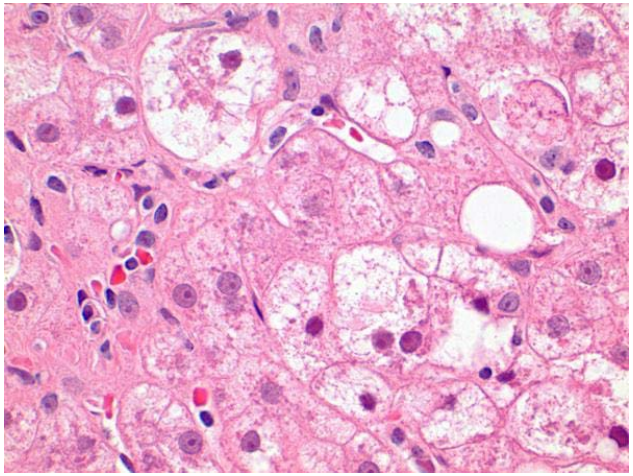
Diagnosis of NAFLD

Steatosis	NASH	Fibrosis
>5% fat in the liver	NAFLD activity score (NAS): • Steatosis (0-3) • Lobular inflammation (0-3) • Hepatocyte ballooning (0-2) 0-2: Non-NASH 3-4: Possible NASH 5-8: NASH	F1: Perisinusoidal or periportal fibrosis F2: Perisinusoidal and portal/periportal fibrosis F3: Bridging fibrosis F4: Cirrhosis

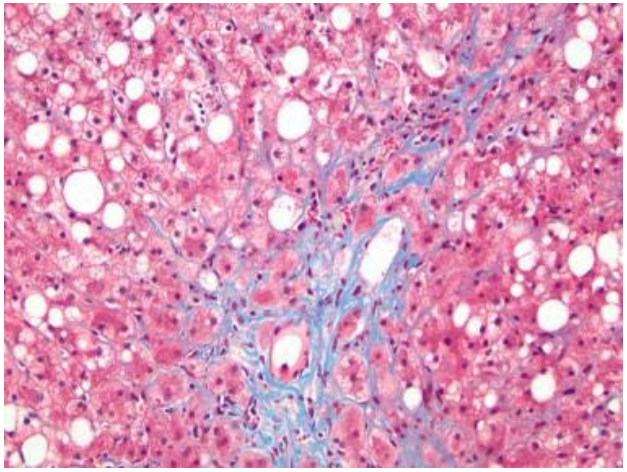
Liver biopsy – “gold standard”



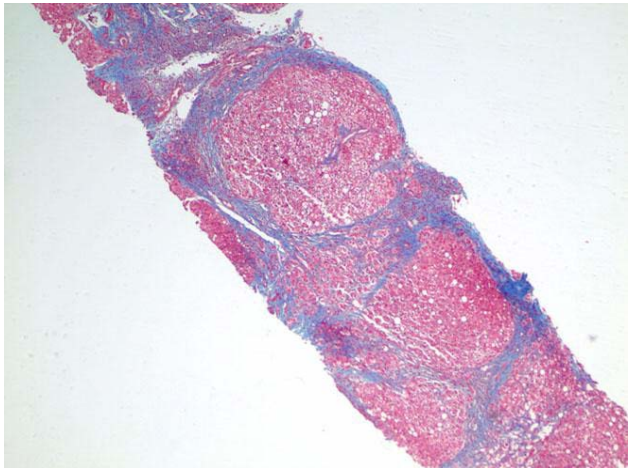
Macrovesicular steatosis
Lobular inflammation



Hepatocyte ballooning
Mallory-Denk body



Perivenular/pericell
ular (chicken wire)
fibrosis



cirrhosis

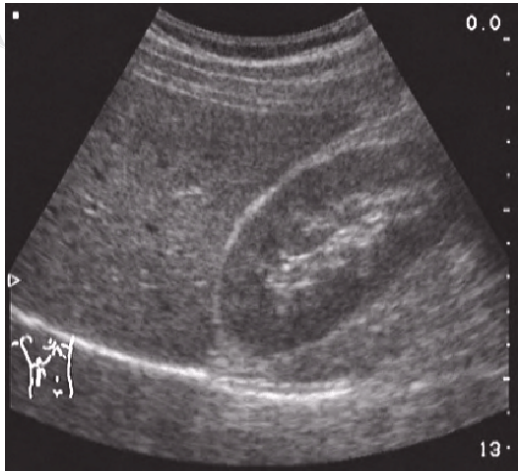
Yeh MM. http://emedicine.medscape.com/article/2038493-overview

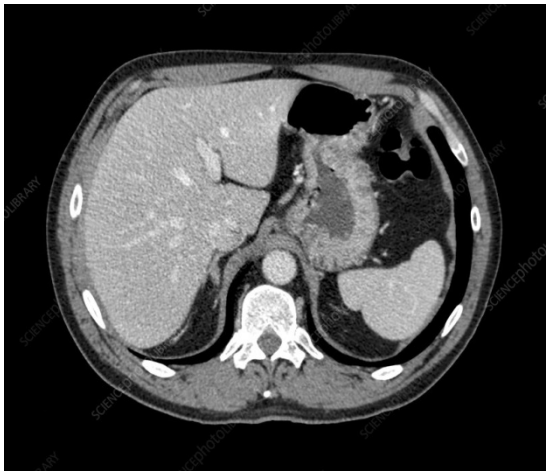
Non-invasive tests (NITs) - Steatosis

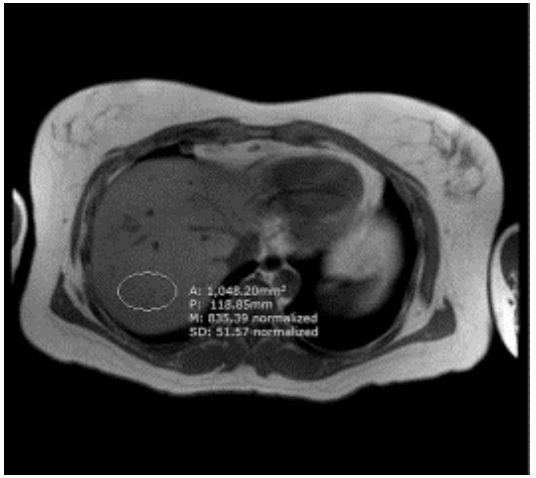
Test	Components	Accuracy (AUC)
Fatty liver index (FLI)	BMI, WC, TG, GGT	0.85
Hepatic steatosis index (HSI)	Sex, diabetes, BMI, ALT, AST	0.82
NALFD liver fat score	Metabolic syndrome, diabetes, insulin, AST, ALT	0.86
SteatoTest	ALT, α2 macroglobulin, apo-A1, haptoglobin, sex, BMI, bili, GGT, cholesterol, TG, glucose, age	0.70

WC=waist circumference; TG=triglyceride;

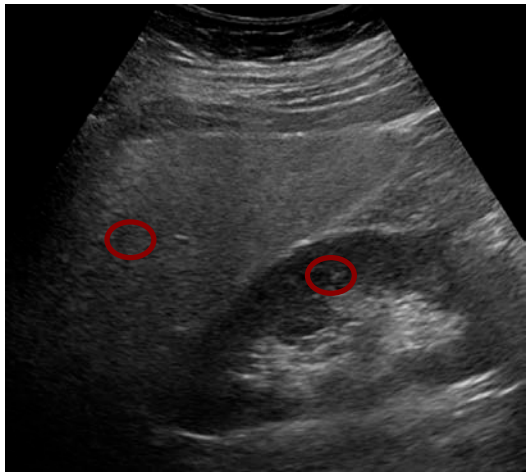
Steatosis on imaging

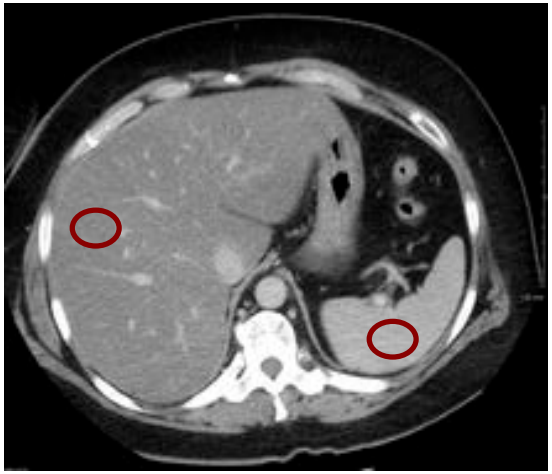


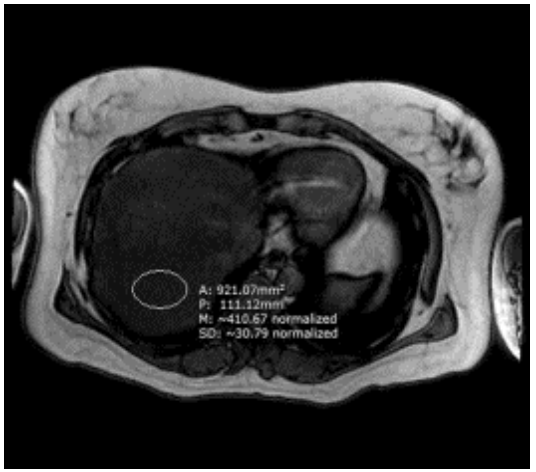




Normal liver







steatosis

Ultrasound

CT

MRI

Steatosis on imaging

- Controlled Attenuation Parameter (CAP)
  - Point of care technique
  - Quantification
  - Needs more validation
- MRI Proton Density Fat Fraction (MRI-PDFF)
  - High diagnostic accuracy
  - Quantify steatosis of the entire liver
  - Not widely available

Non-invasive tests (NITs) - Steatohepatitis

Test	Components	Accuracy (AUC)
NashTest	Age, sex, height, weight, TG, cholesterol, α2 macroglobulin, apo-A1, haptoglobin, total bilirubin, GGT, AST, ALT	0.84

Biochemistry:

- Mildly raised ALT >AST
- ALT < 250 usually

- 40-60% patients normal range ALT
- ALT value does not correlate with histological findings

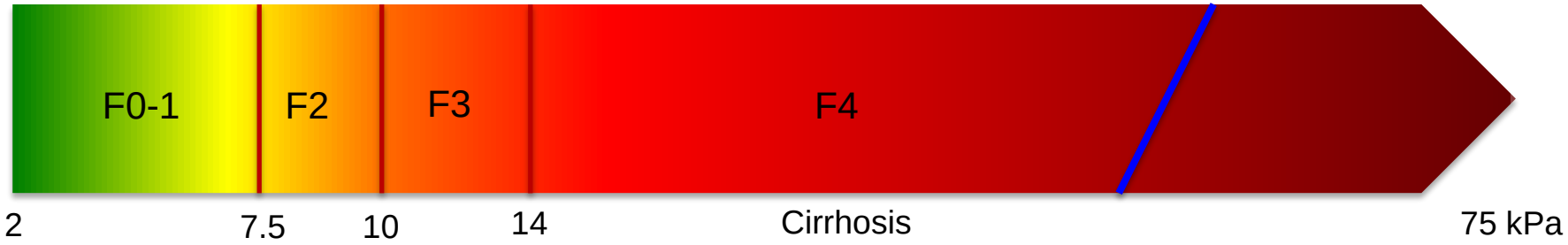
Non-invasive tests (NITs) - Fibrosis

- Routine labs (thrombocytopenia, low albumin, prolonged INR)
- ALT/AST ratio (AAR) <0.8

Test	Components	AUROC
	Simple	
FIB4	Age, platelet, AST, ALT	0.80
NFS	age, BMI, diabetes, platelet, AST/ALT ratio, albumin	0.77
APRI	platelet, AST	0.73
BARD score	BMI, diabetes, AST/ALT ratio	0.70
	Proprietary	
FibroTest	Age, sex, BMI, α2 macroglobulin, apo-A1, haptoglobin, total bilirubin, GGT	0.81
FibroMeter	Age, platelet, AST, ALT, glucose, ferritin, weight	0.81
ELF	Hyaluronic acid, PIIINP, TIMP-1	0.87

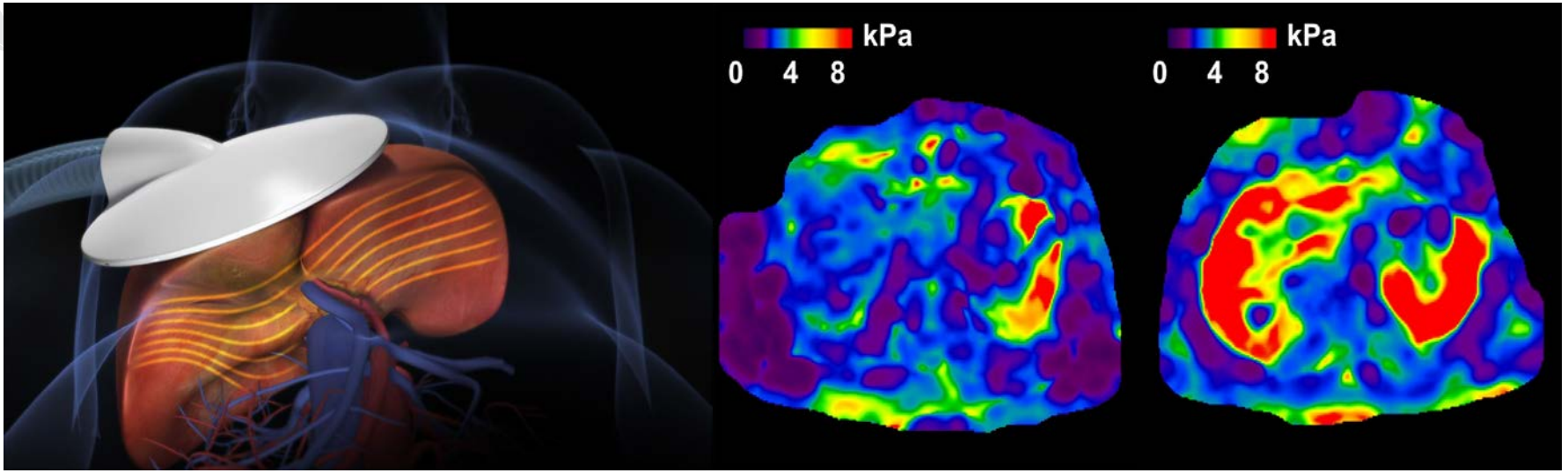
Vibration Controlled Transient Elastography (VCTE) – FibroScan®

VCTE Cutoff	NPV	PPV	Sensitivity	Specificity
7.6kPa	**92.5%**	43.2%	84.2%	63.8%
14.6kPa	**96.8%**	64.3%	81.8%	92.4%



Chen J, et al. Radiology 2017;283:418

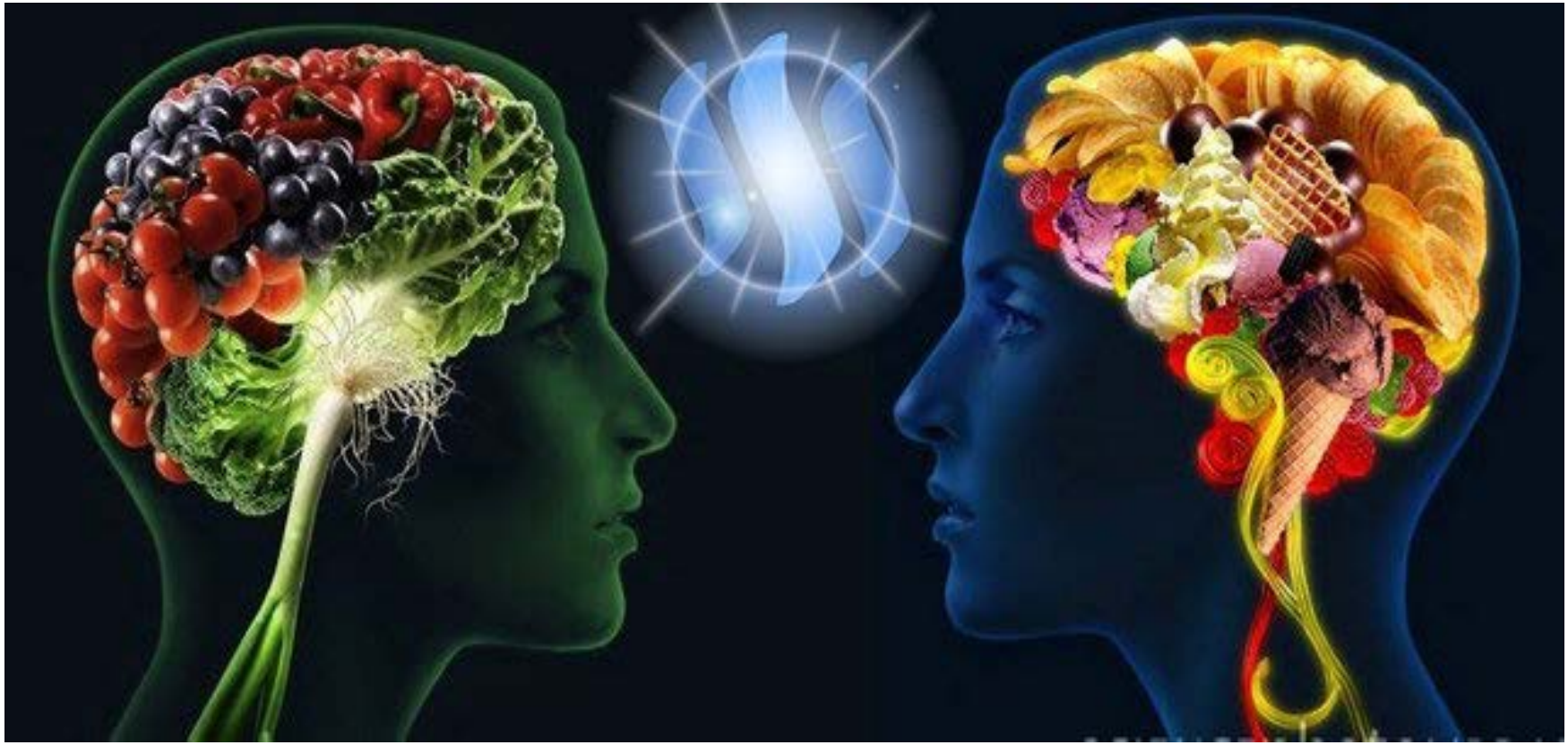
MR Elastography (MRE)



MRE cutoff	NPV	PPV	Sensitivity	Specificity
3.60kPa	**94.1%**	61.5%	84.2%	82.8%
4.52kPa	**96.8%**	60.0%	81.8%	90.9%

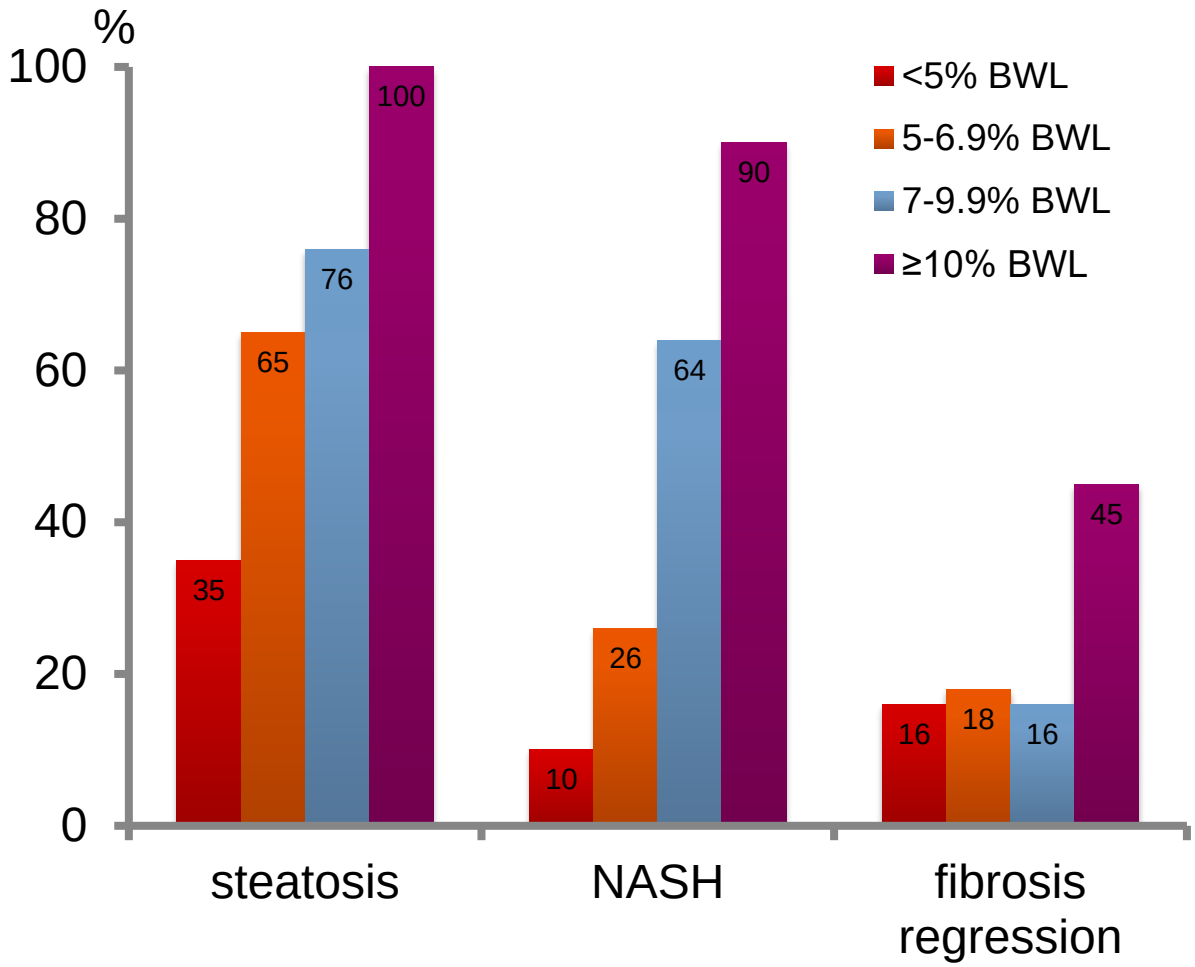
Chen J, et al. Radiology 2017;283:418

We are what we eat



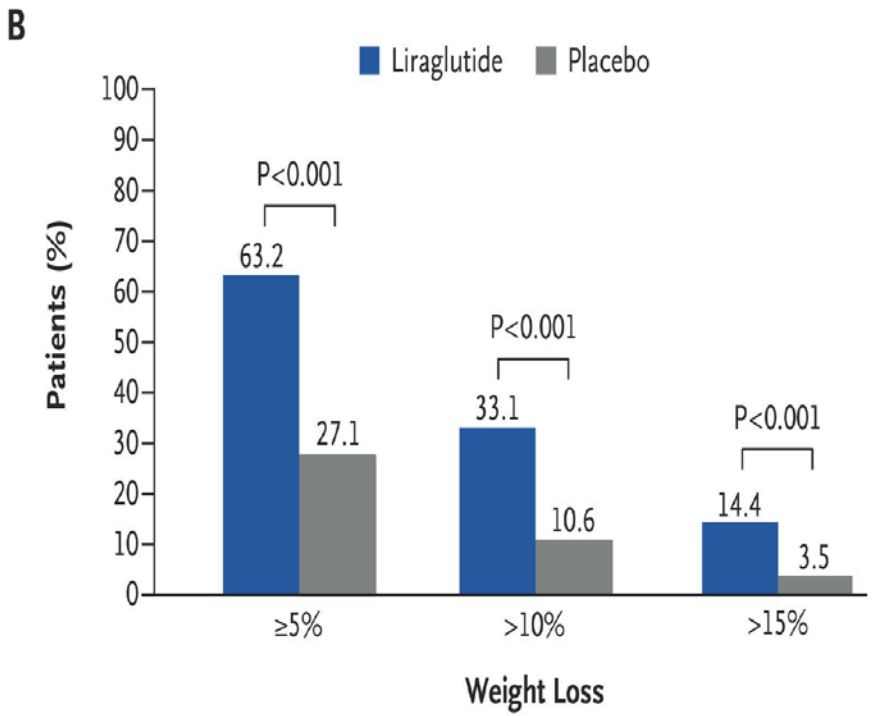
Weight loss improves NASH and fibrosis

- Biopsy proven NASH
- 52 weeks lifestyle change (low fat 22% hypocaloric diet and walk 200 min/week
- N=261 paired biopsy



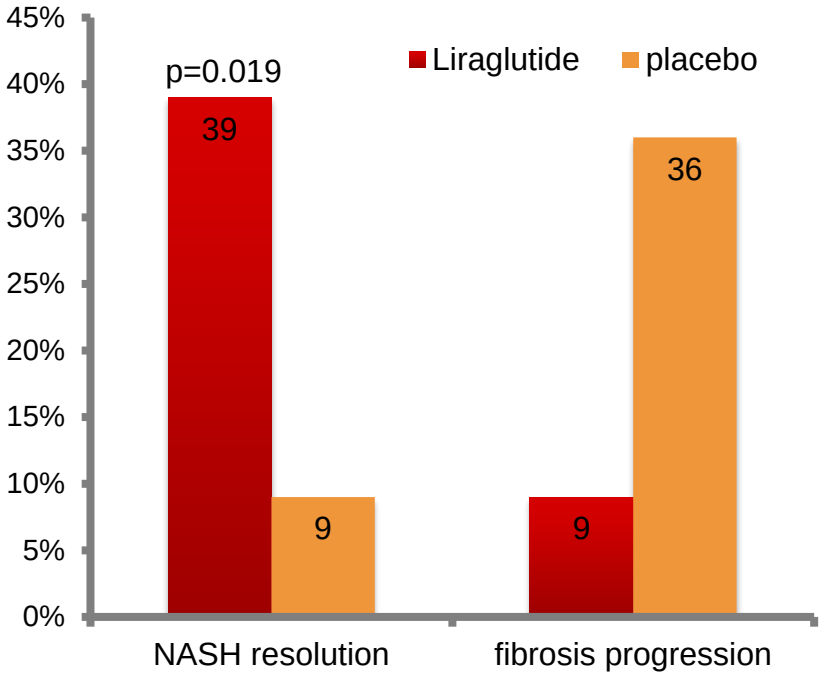
Vilar-Gomez E, et al. Gastroenterology 2015;149:367

Effect of Liraglutide on body weight and liver pathology



N=373, BMI>30, non-DM, 3.0mg

Pi-Sunyer X, et al. NEJM 2015;373:11-22

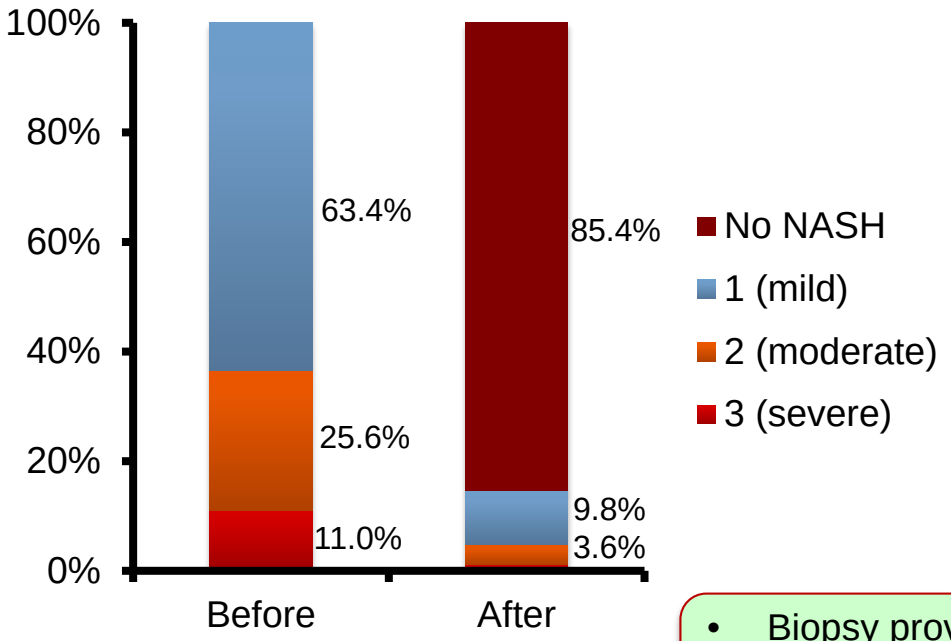


LEAN-phase 2 trial: n=52, non-cirrhotic NASH, 1.8mg, 48 weeks

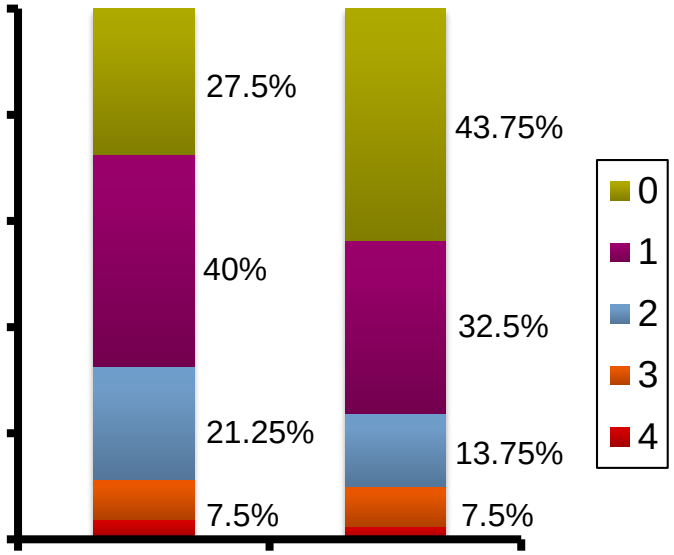
Armstrong MJ, et al. Lancet 2016;387:679

Bariatric surgery improves NASH and fibrosis

Distribution of NASH inflammatory activity grade before and 1 year after surgery



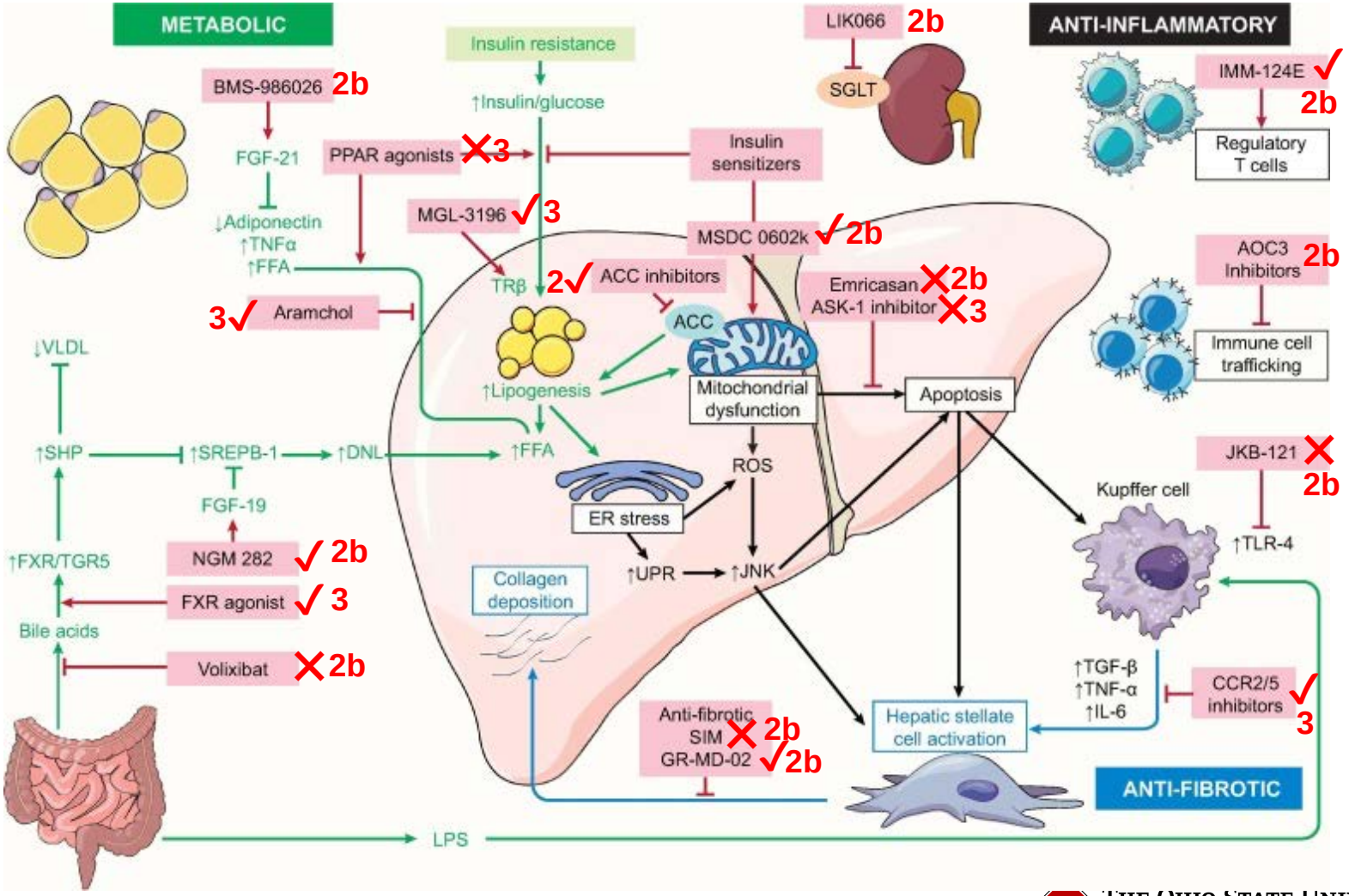
Distribution of fibrosis stage before and 1 year after surgery



- Biopsy proven NASH
- n=109

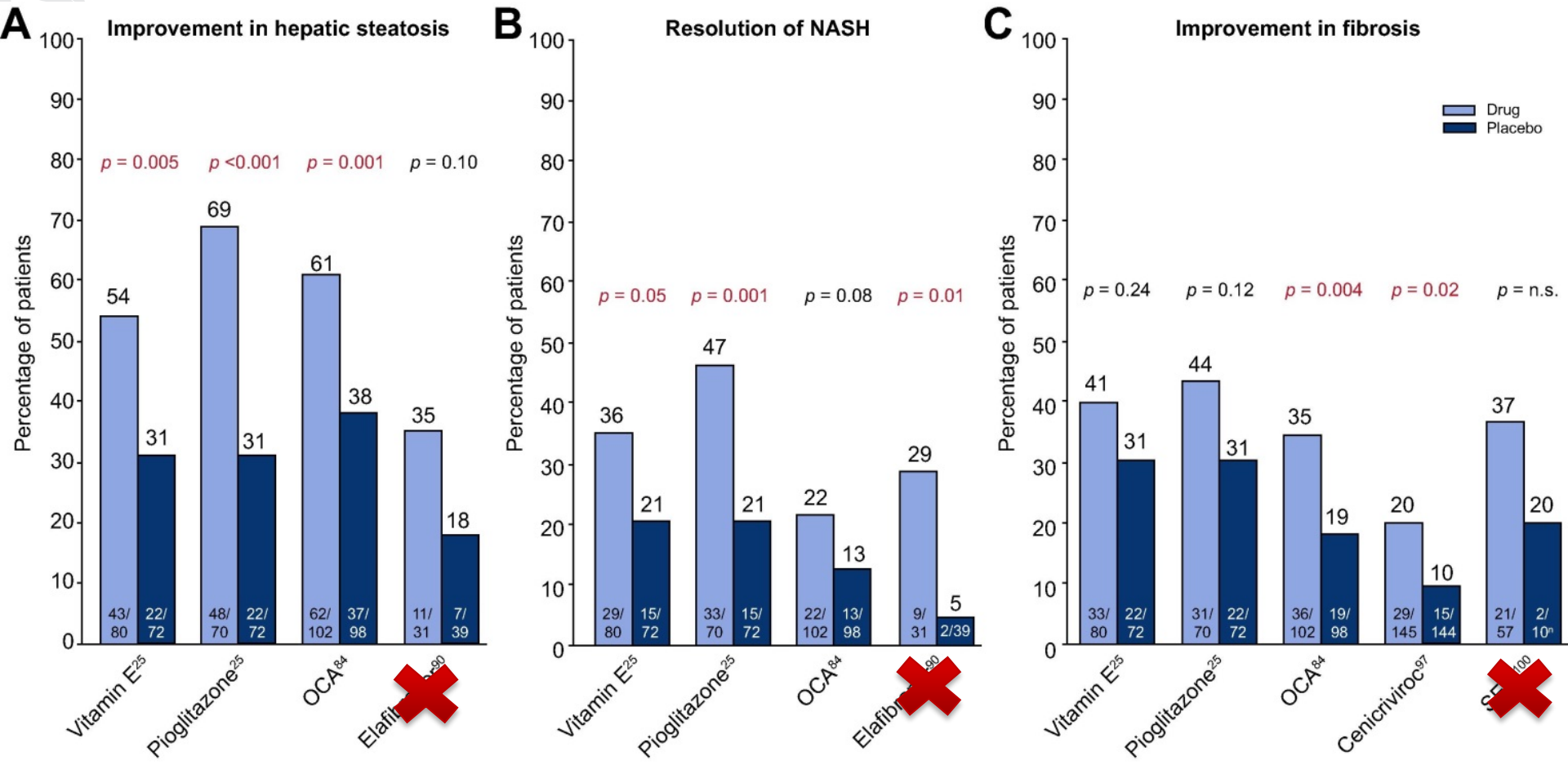
Lassailly G, et al. Gastroenterology 2015;149:379

Mechanism of action of pharmacologic treatments for NAFLD and NASH



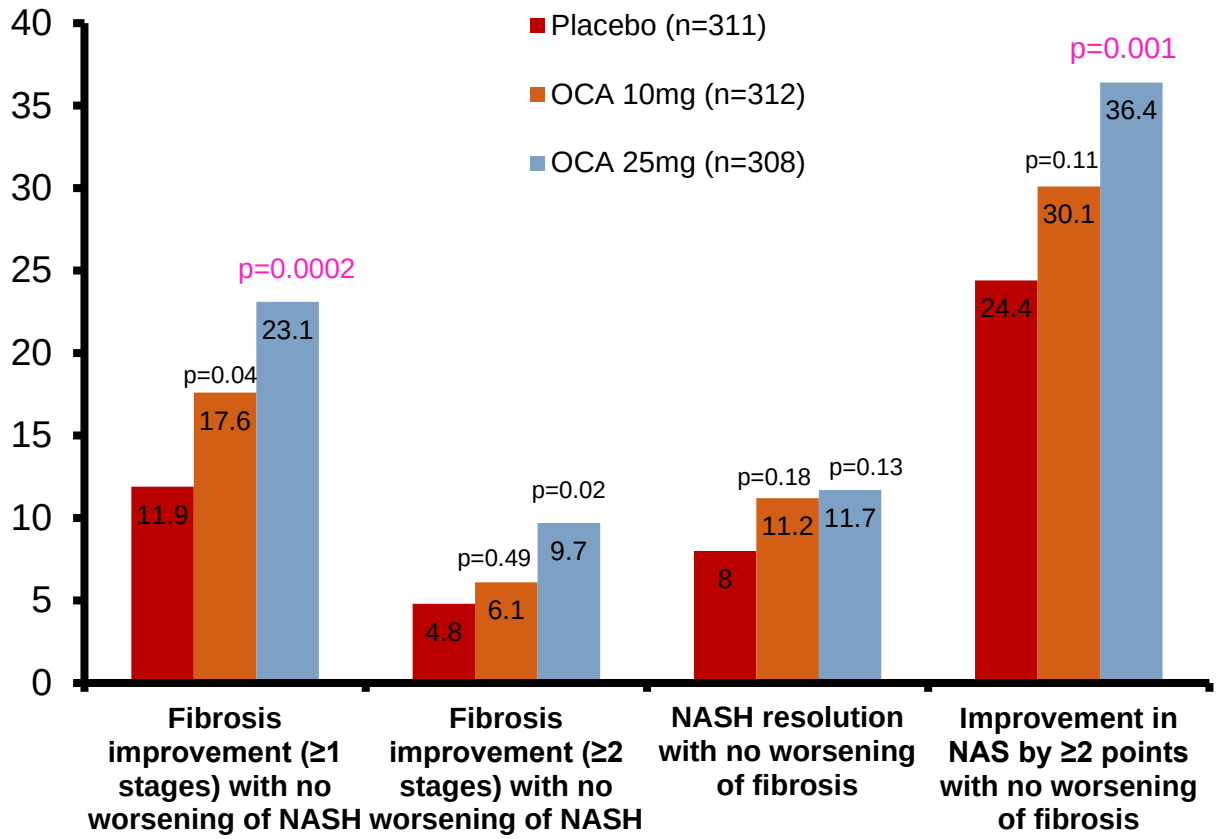
Konerman MA, et al. 2018;68:362

Effects of pharmacotherapy on NASH and fibrosis



Konerman MA, et al. 2018;68:362

REGENERATE Trial (Phase 3 study of OCA on NASH)- Interim Efficacy Analysis at 18 months

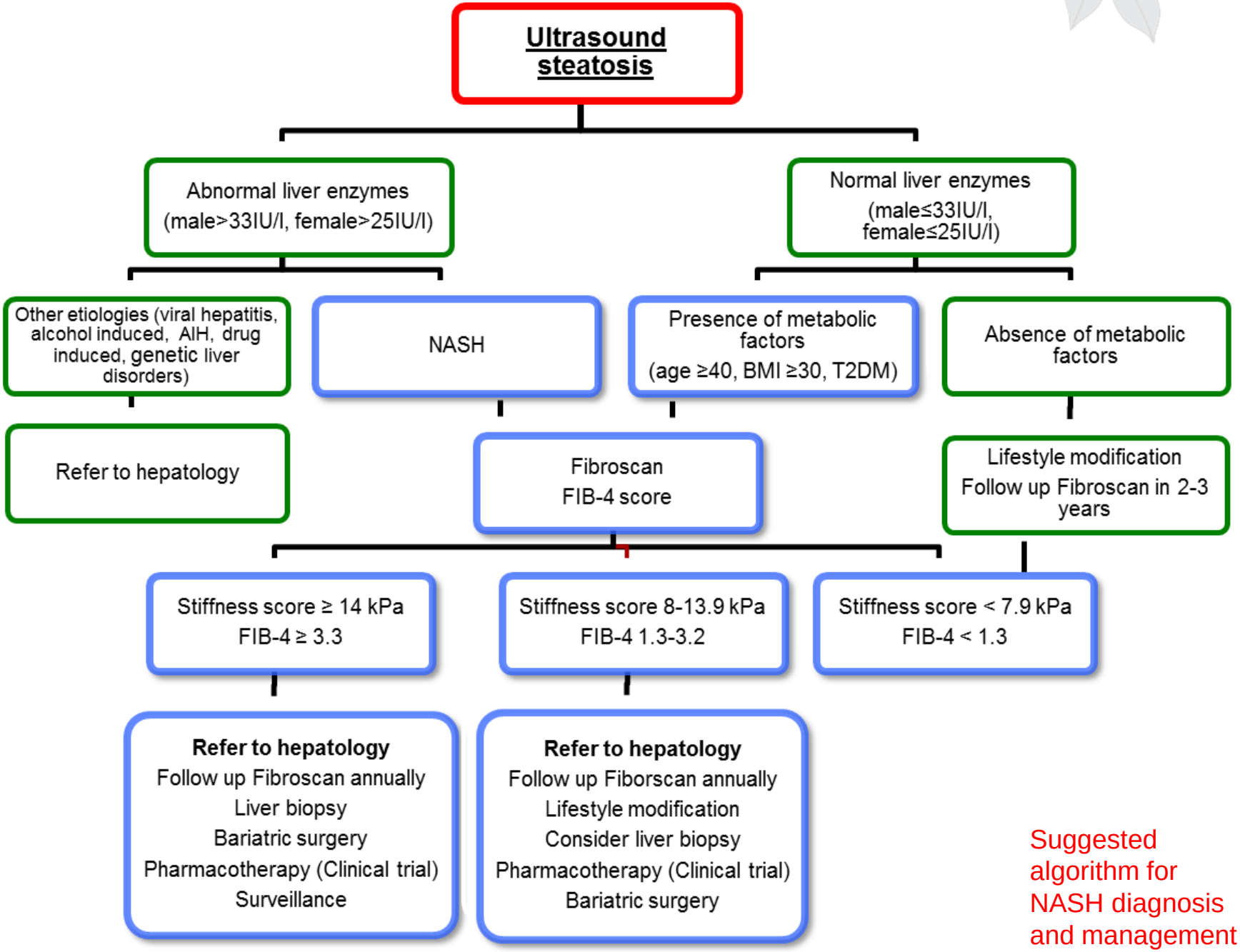


- 51% patients reported pruritus, 9% discontinued medication due to pruritus
- The first medication showed histological benefit in a phase 3 study

Younossi Z et al. Lancet 2019;384:2184-96

Other clinical trials for NASH

Drug	MOA	Phase	Results	Reference
NGM282	FGF 19	2	Improves NAS, fibrosis score	Harrison SA, et al. Lancet 2018
Pegbelfermin	FGF21	2	Reduce liver fat (6.8% vs. 1.3%)	Sanyal AJ, et al. Lancet 2019
Resemtirom	Thyroid receptor β agonist	2 to 3	Reduces liver fat; NASH resolution (27% vs 6%)	Harrison SA, et al. Hepatology 2018
Semaglutide	GLP-1 agonist	2	NASH resolution (59% vs 17%)	Just released in May,2020
Aramchol	Stearoyl CoA desaturase modulator	2 to 3	Reduce liver fat (47% vs. 24%)	AASLD 2018
Cilofexor	FXR agonist	2	pending	
Tropifexor	FXR agnoist	2	pending	



Suggested algorithm for NASH diagnosis and management

NAFLD care at OSU

Diagnostic modality	NASH treatment	Care for advanced liver disease
Steatosis • US, **CAP, MRI-PDFF** Fibrosis • **Fibroscan, USE, MRE,** biopsy	**Multispecialty care** Pharmacotherapy • **Multiple Phase 2 & 3 Clinical Trials**	HCC Liver transplant

Summary

- NAFLD has become a major health issue due to high prevalence, increased mortality, and hard outcomes
- NAFLD is a hepatic component of metabolic disorders
- Presence of fibrosis and NASH are key factors associated with mortality
- Combination of non-invasive tests including labs and elastography improves diagnostic accuracy
- Liver biopsy remains the definitive diagnosis and staging for NASH and required for clinical trials
- Lifestyle change with a goal of >10% weight loss should be encouraged
- Pharmacotherapy for NASH with fibrosis likely will be available in the near future and combined medical therapy is likely required
- Primary care centered multispecialty care model