Update on Non-Alcoholic Fatty Liver Disease

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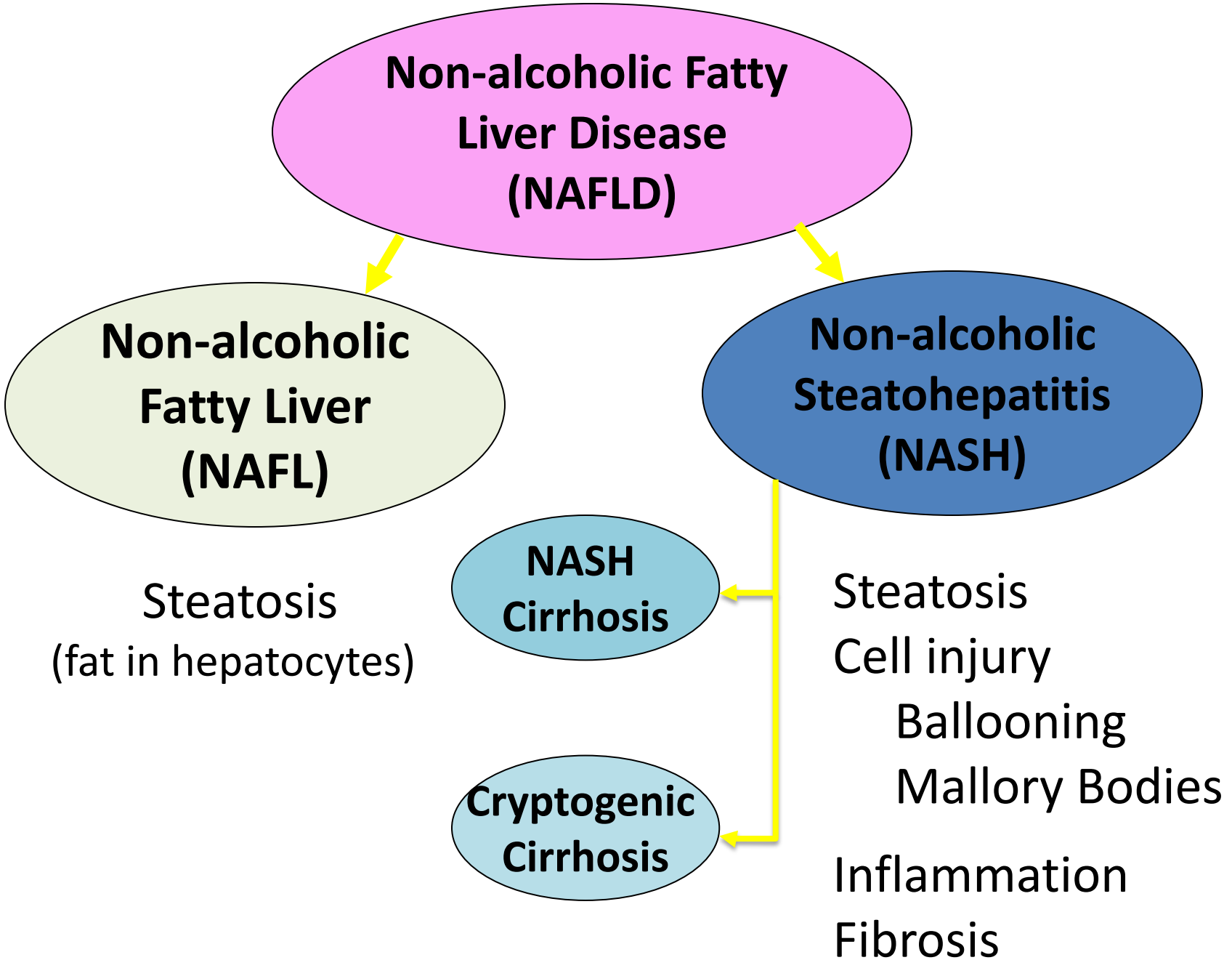
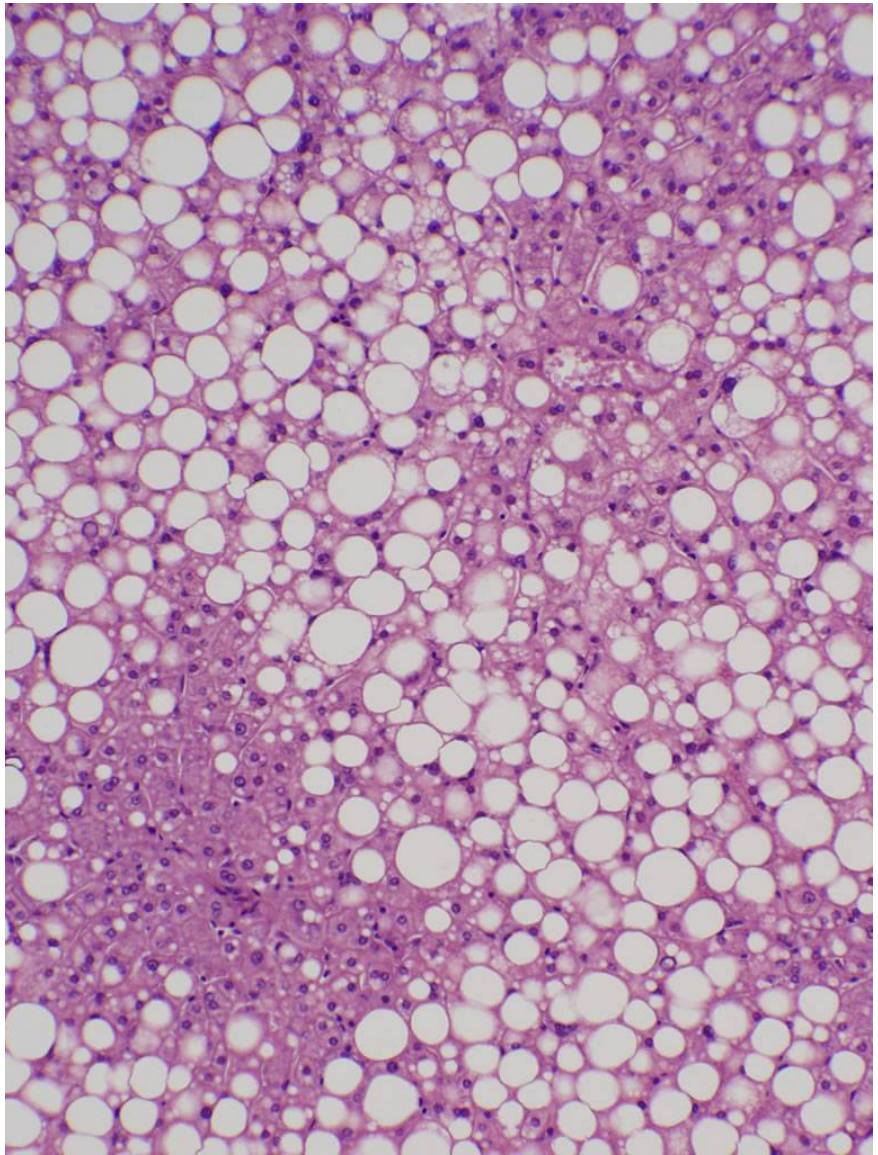
Disclosure

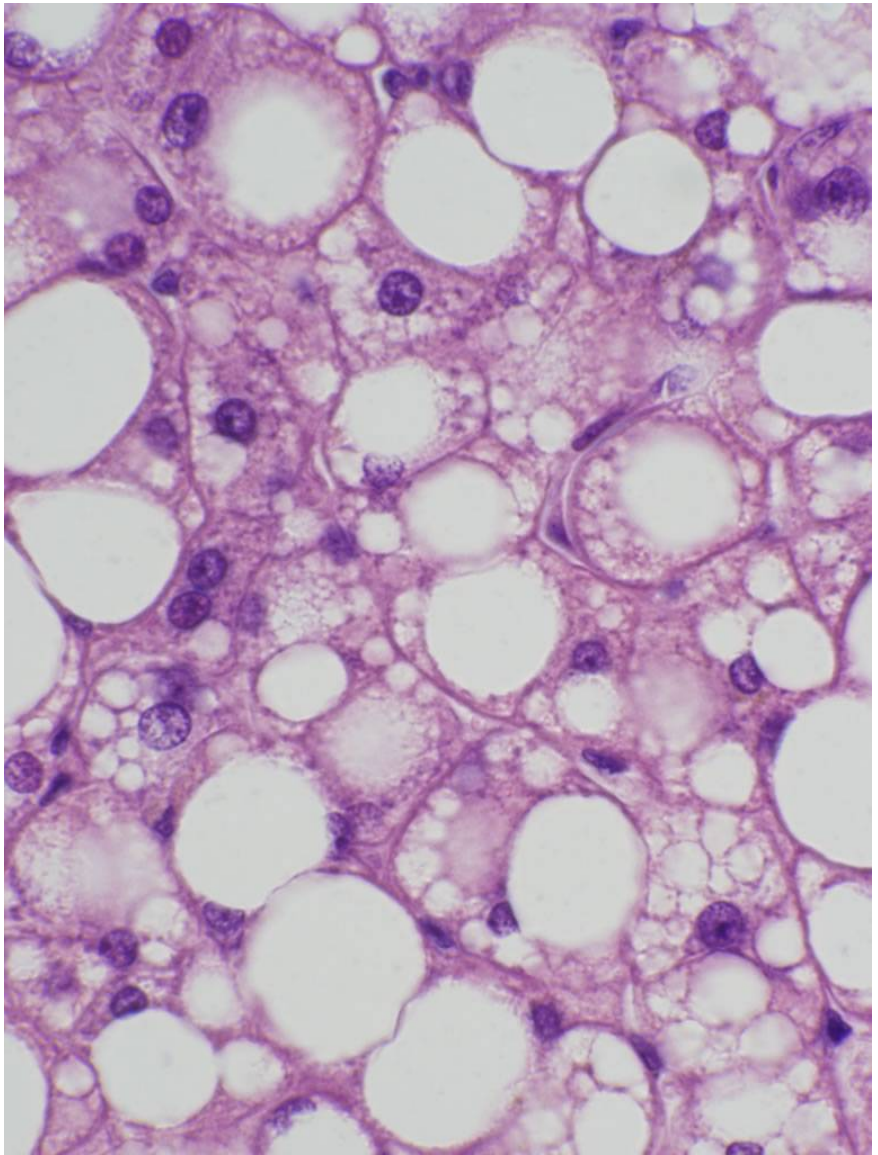
- Clinical trials: Genfit
- Speaker's Bureau: none
- Advisory Board: none


Non-alcoholic Fatty Liver Disease (NAFLD)
Non-alcoholic Fatty Liver (NAFL)
Non-alcoholic Steatohepatitis (NASH)
Steatosis
(fat in hepatocytes)
NASH Cirrhosis
Cryptogenic Cirrhosis
Steatosis
Cell injury
Ballooning
Mallory Bodies
Inflammation
Fibrosis

Non-Alcoholic Fatty Liver

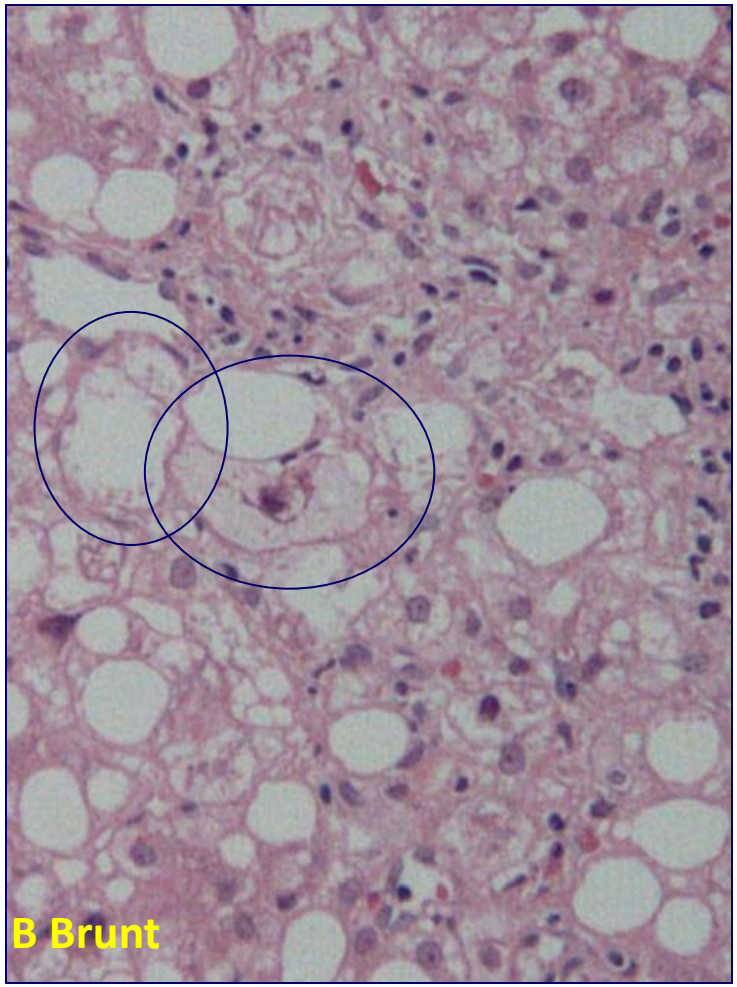
("Simple" Steatosis)



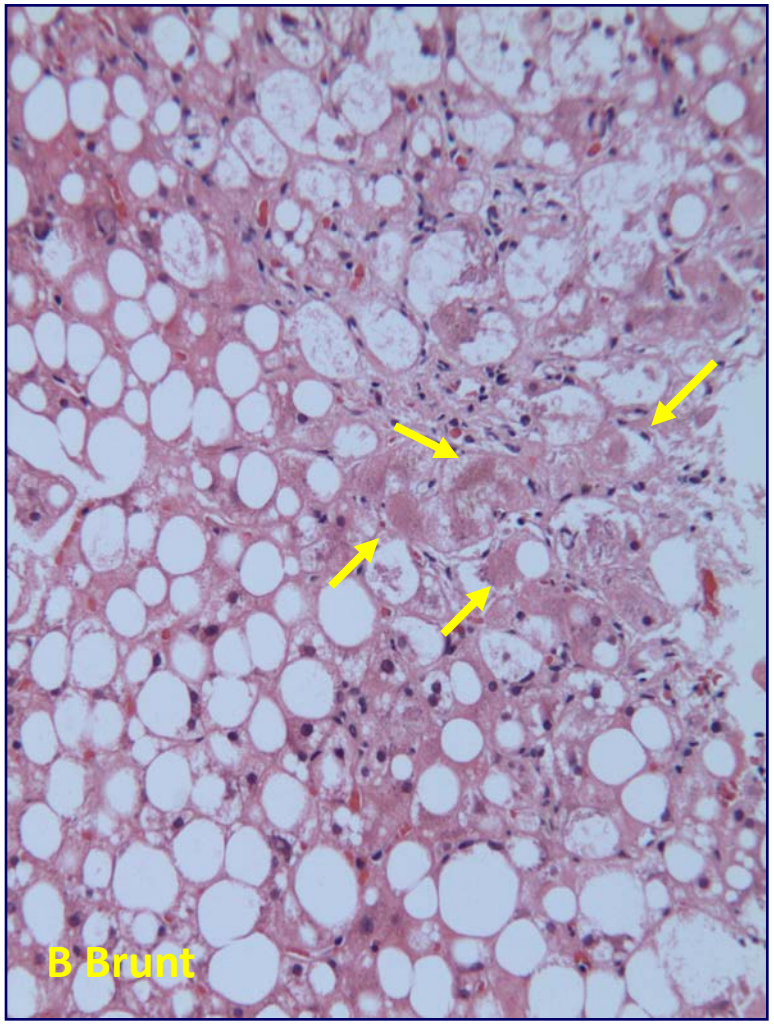


Steatohepatitis (NASH): Hepatocyte Injury

Ballooning (swelling)

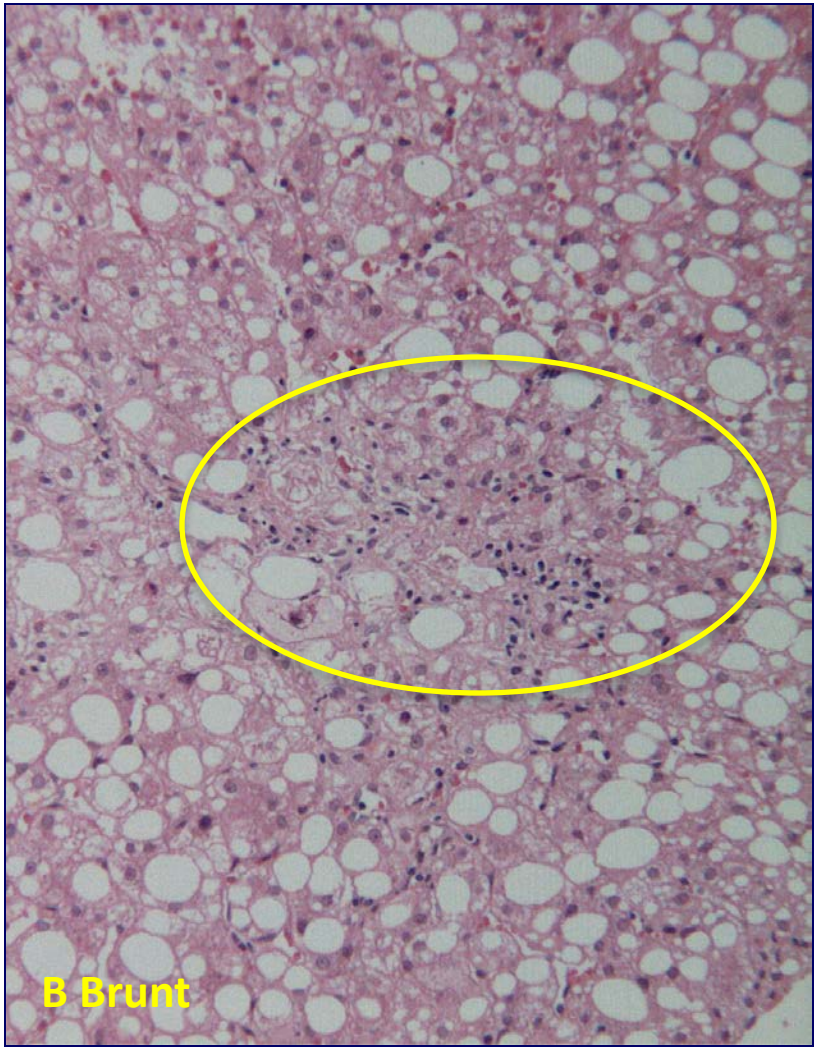


Mallory Bodies (inclusions)

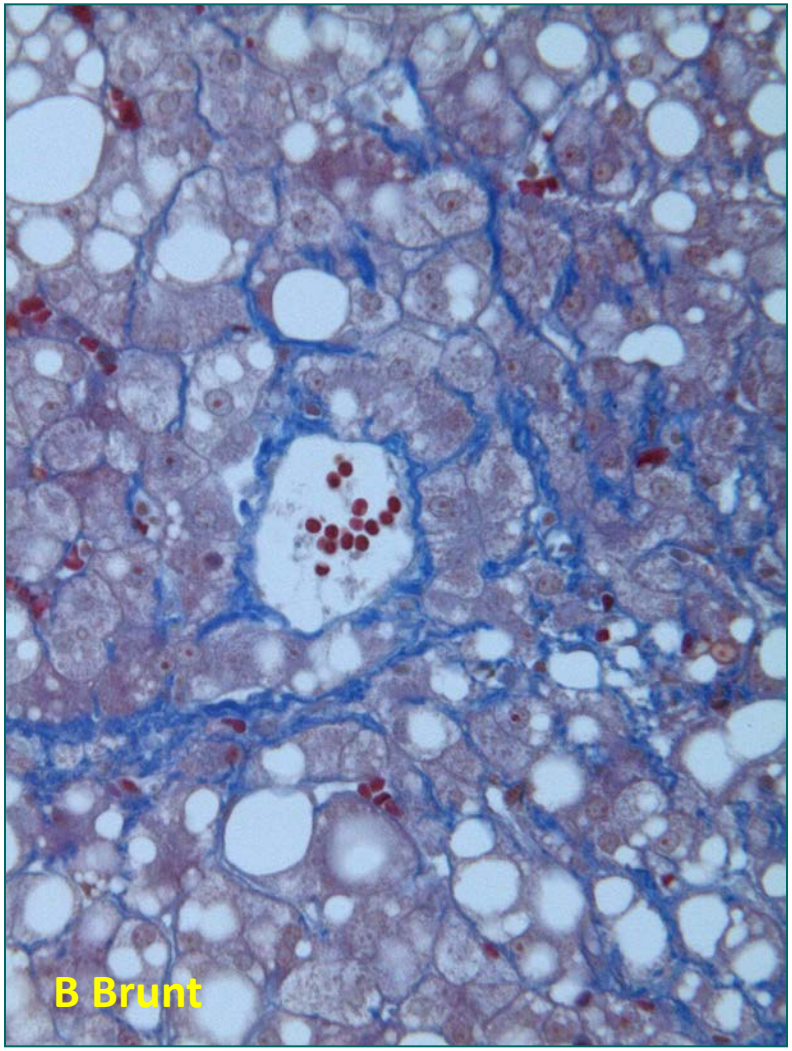


Steatohepatitis (NASH)

Inflammation



Pericellular Fibrosis



NAFLD Activity Score (NAS) and Fibrosis

NAFLD Activity Score (NAS)

Feature	Points	Criteria
Steatosis	0	<5%
	1	5-33%
	2	>33 to 66%
	3	>66%
Lobular Inflammation	0	None
	1	<2 foci per 200x field
	2	2-4 foci per 200x field
	3	>4 foci per 200x field
Ballooning	0	None
	1	Few ballooning cells
	2	Many/prominent ballooning

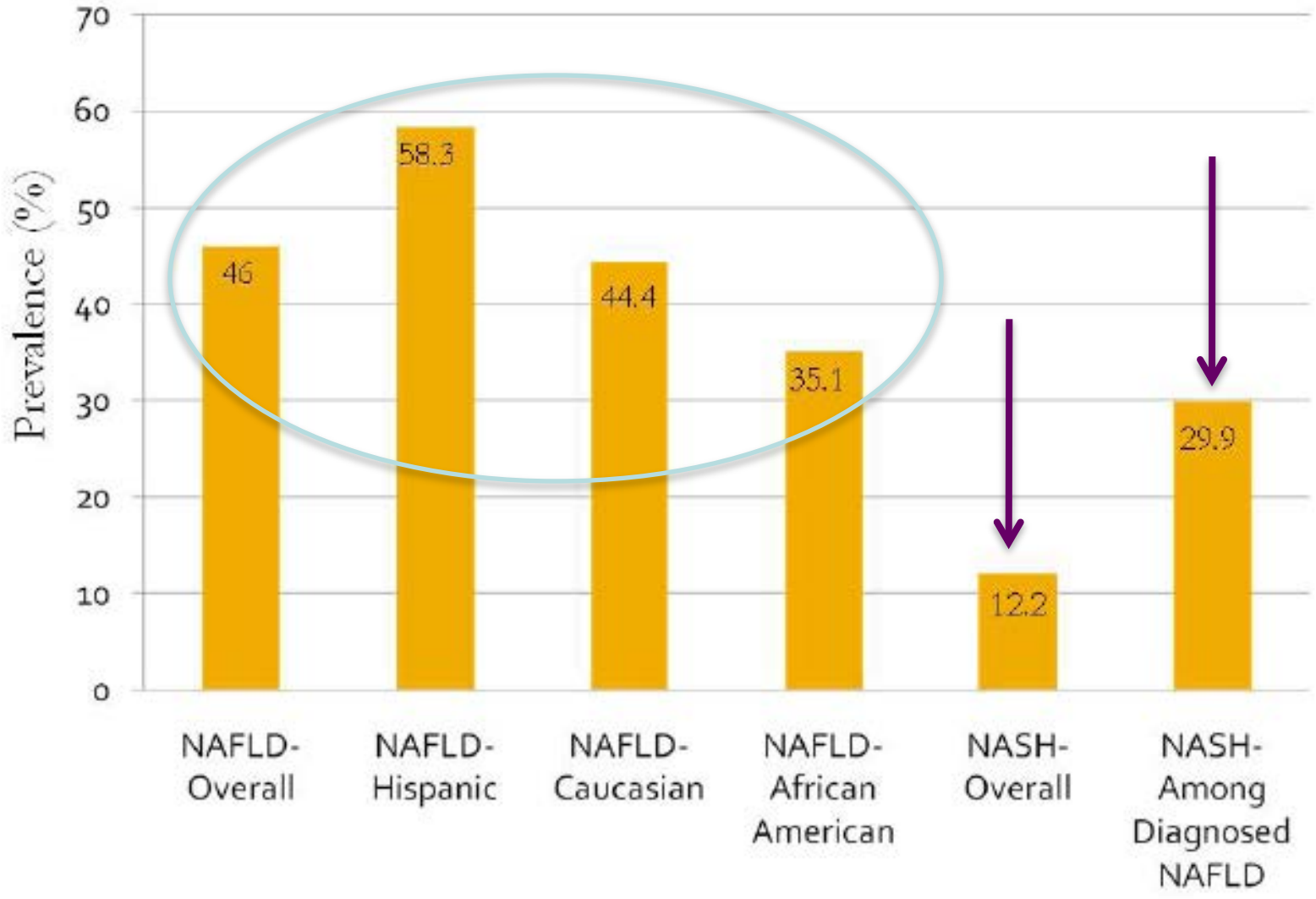
NAS Score
0-2 Likely not NASH
3-4 Indeterminate
5-8 Likely NASH

Fibrosis stage

	Criteria
I	Zone 3 pericellular, focal or extensive
II	Zone 3 pericellular, With periportal fibrosis
III	Zone 3 pericellular, With portal bridging
IV	Cirrhosis

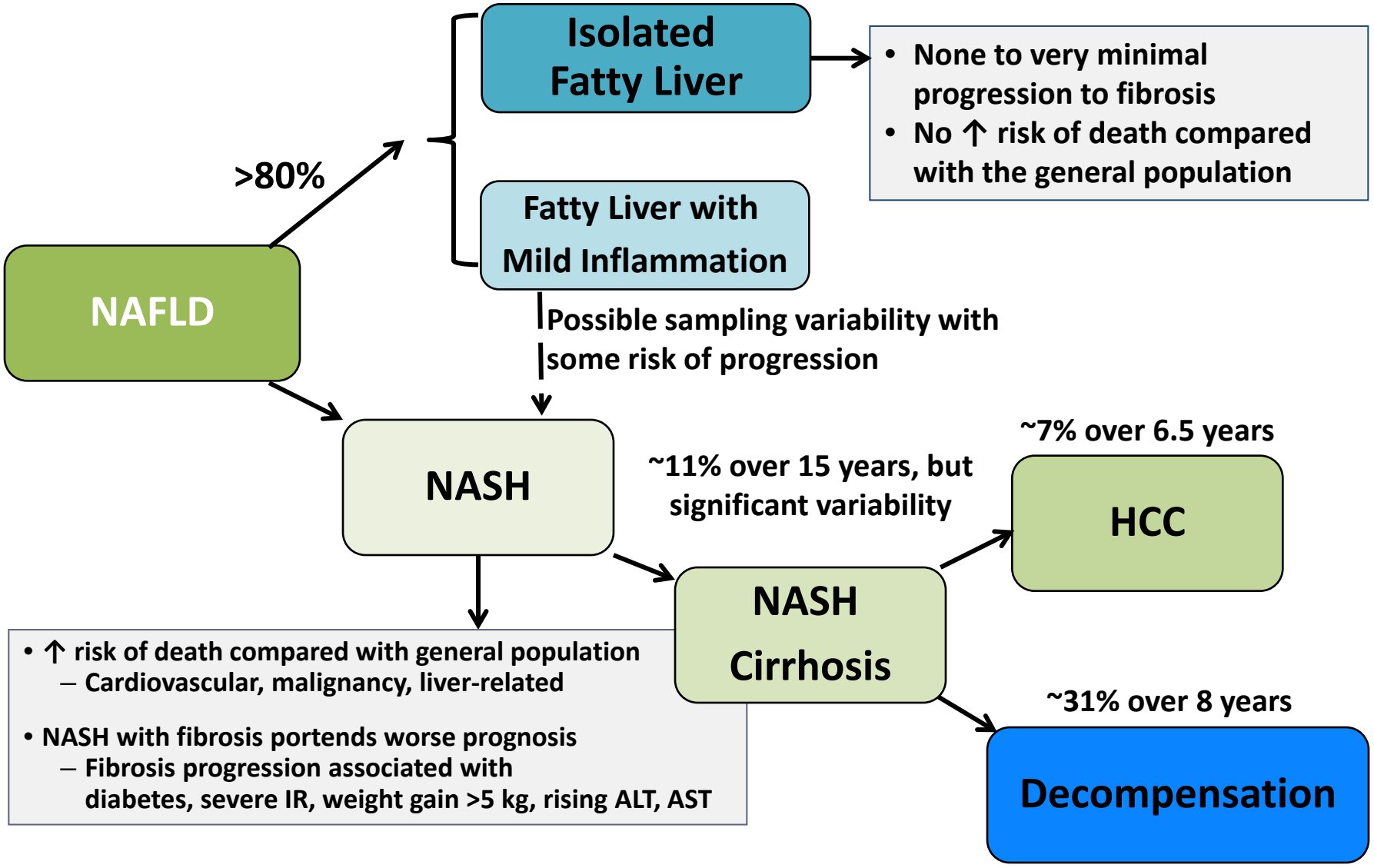
Kleiner et al. Hepatology 2005;41:1313

NAFLD Prevalence in US:
Ethnicity



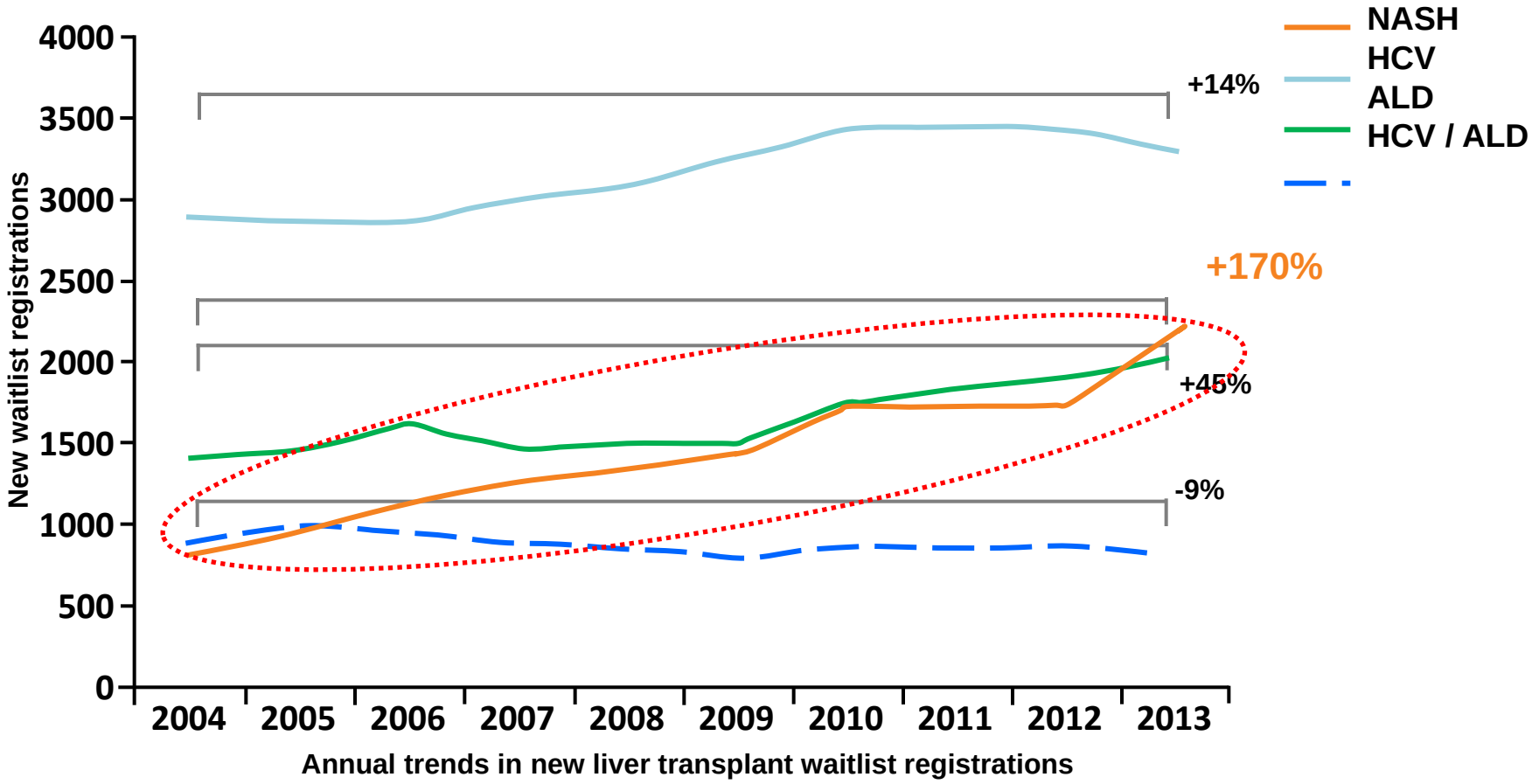
Williams Gastro 2011

Natural History of NAFLD



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

NAFLD and Liver Transplantation



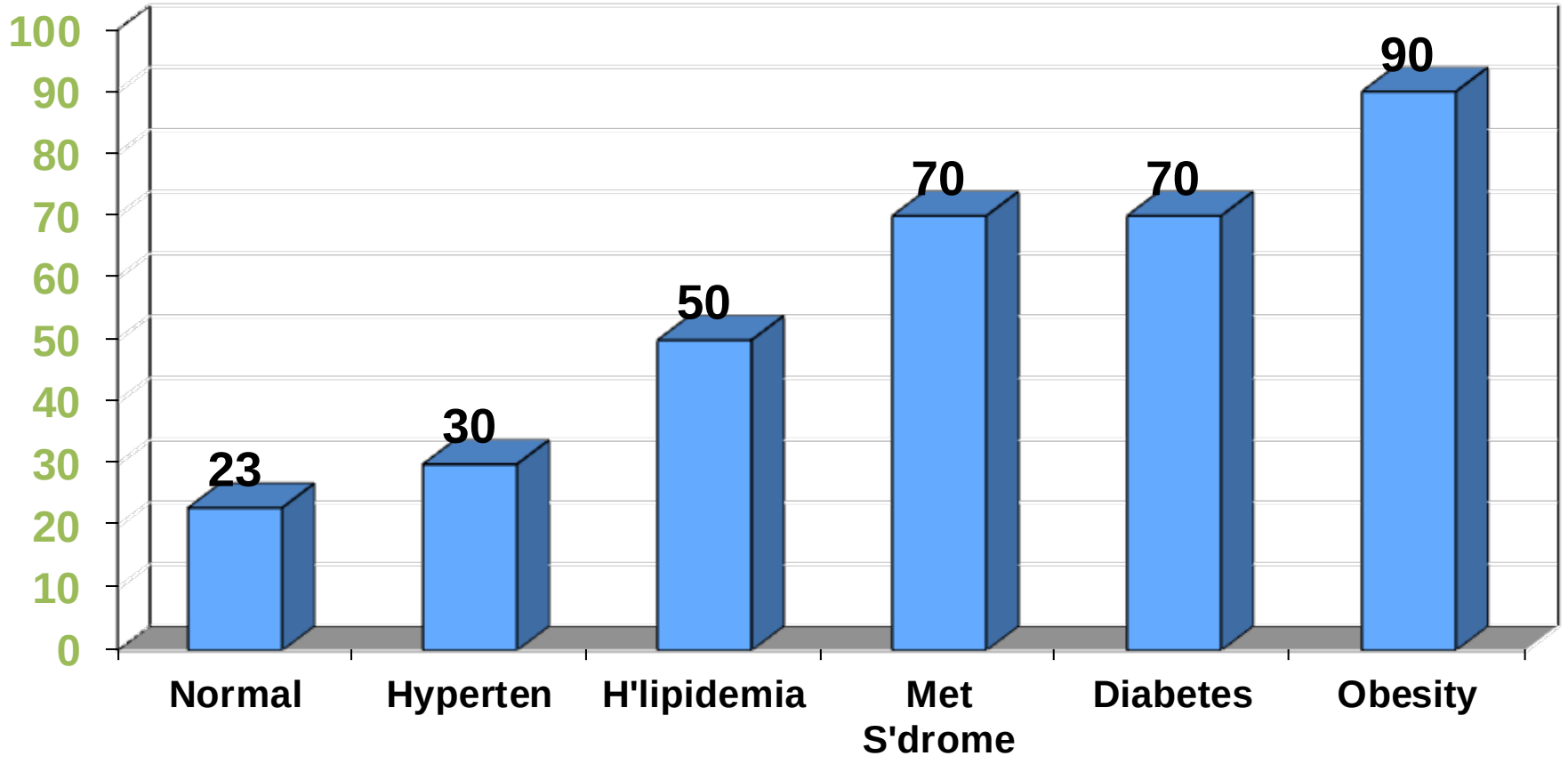
Wong RJ, et al. Gastroenterology. 2015;148:547-55

NAFLD Diagnosis

- Requires:
  - Hepatic steatosis on imaging or histology
  - Exclusion of other causes of hepatic steatosis / liver injury
- Lack of significant alcohol use
  - <21 drinks/week for men, <14 drinks/week for women
- Typically associated with metabolic risk factors:
  - DM
  - Obesity
  - Hyperlipidemia/triglyceridemia
- **NASH diagnosis requires Liver Biopsy**

Joint AGA, AASLD, ACG Guidelines on NAFLD 2012

Prevalence of NAFLD in patients with features of the metabolic syndrome



Predictive Value of Aminotransferases in NAFLD

Serum ALT can be normal in up to nearly 60% 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

Abbreviations: ALT, alanine aminotransferase; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

1. Fracanzani AL, et al. *Hepatology.* 2008;48:792-798. 2. Verma S, et al. *Liver Int.* 2013;33:1398-1405.
3. Torres DM, et al. *Nat Rev Gastroenterol Hepatol.* 2013;10:510-511.

Noninvasive Tests for Liver Fibrosis & Fat

- Clinical or laboratory tests
  - NAFLD Fibrosis Score (www.nafldscore.com)
  - FIB-4 index
  - Enhanced Liver Fibrosis (ELF) (not in US)
- Imaging modalities
  - Shear-wave elastography
    - Fibroscan, supersonic imaging, ARFI
  - MRI-based
    - Magnetic Resonance Elastrography (MRE)
    - Liver MultiScan
- Fat in liver
  - Controlled Attenuation Paramater (Fibroscan-based)
  - MRI – Proton Derived Fat Fraction (PDFF)

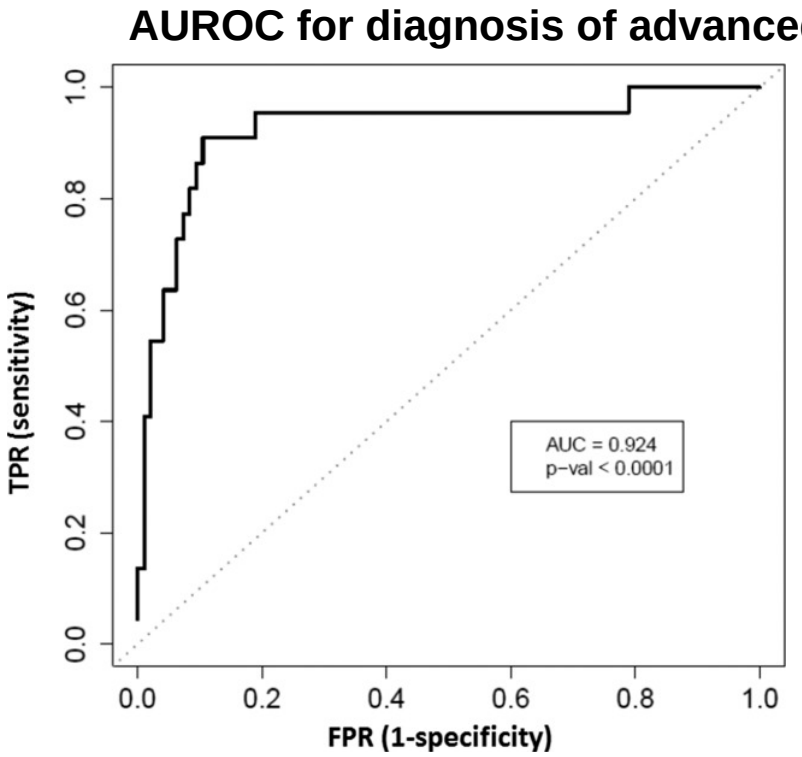
Abbreviations: ALT, alanine aminotransferase; ARFI, acoustic radiation force impulse; AST, aspartate aminotransferase; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease.

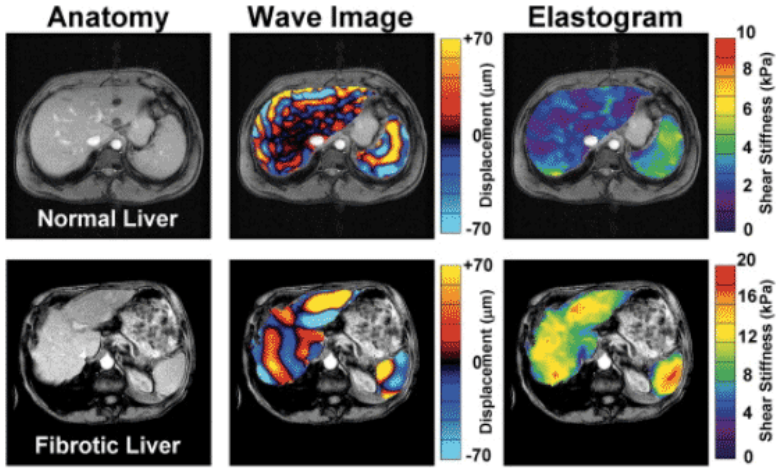
Transient Elastography

- FibroScan® is based on patented technology: **V**ibration **C**ontrolled **T**ransient **E**lastography (VCTE™)
- Allows painless and simultaneous measurement of two quantitative parameters:
  - Liver stiffness expressed in kPa
    - ➔ Correlated to liver fibrosis [1]
  - Controlled Attenuation Parameter (CAP™) expressed in dB/meter
    - ➔ Correlated to liver steatosis [2]
- Both quantitative parameters are assessed on the same volume of liver tissue (3cm^3)
  - 100 times bigger than liver biopsy

FibroScan® 502 TOUCH

MR Elastography in NAFLD

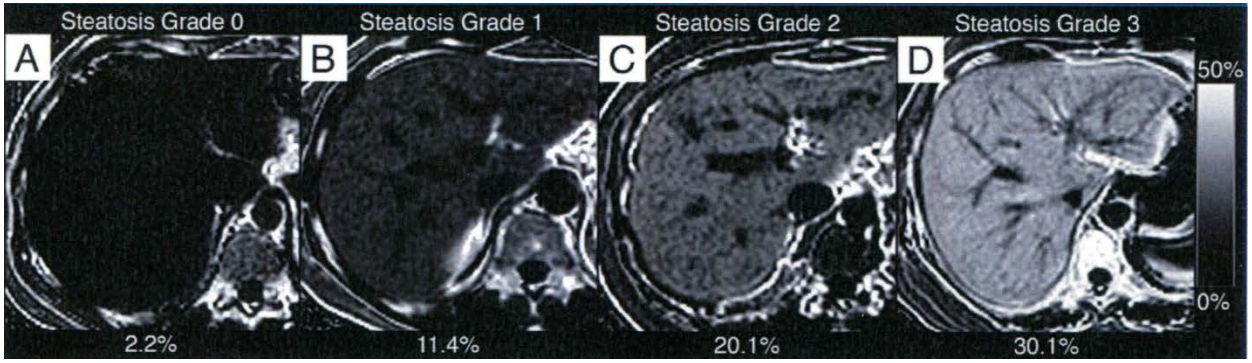


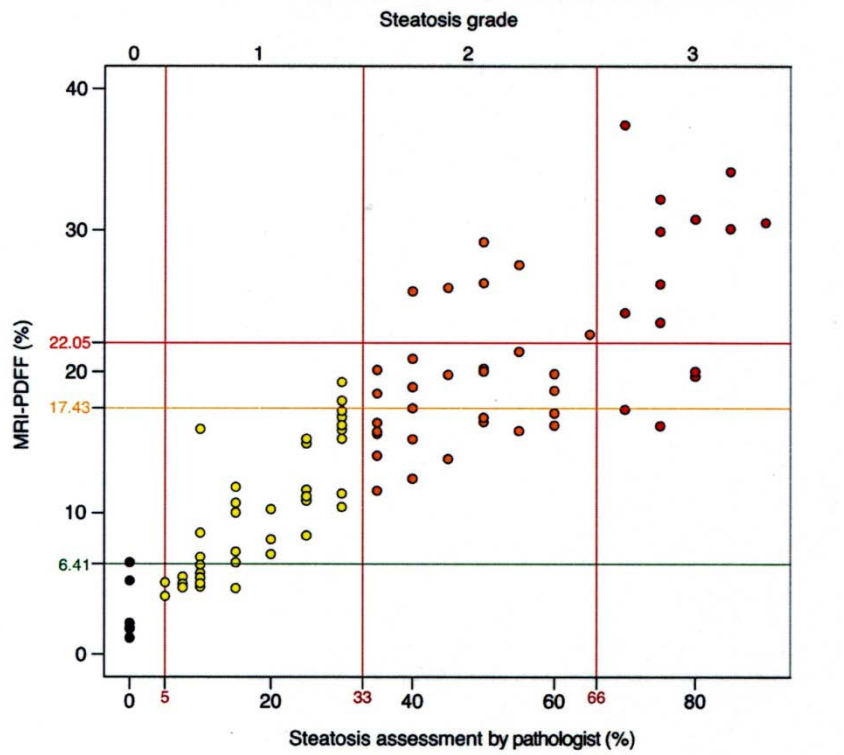


For Stage 3-4 fibrosis: >3.63 kPa
86% sensitivity and 91% specificity

Loomba R et al Hepatology 2014 60 1920-8 Meng Y et al Clin Gastroenterol Hepatol 2007 10 1207-1213

MRI Proton Density Fat Fraction



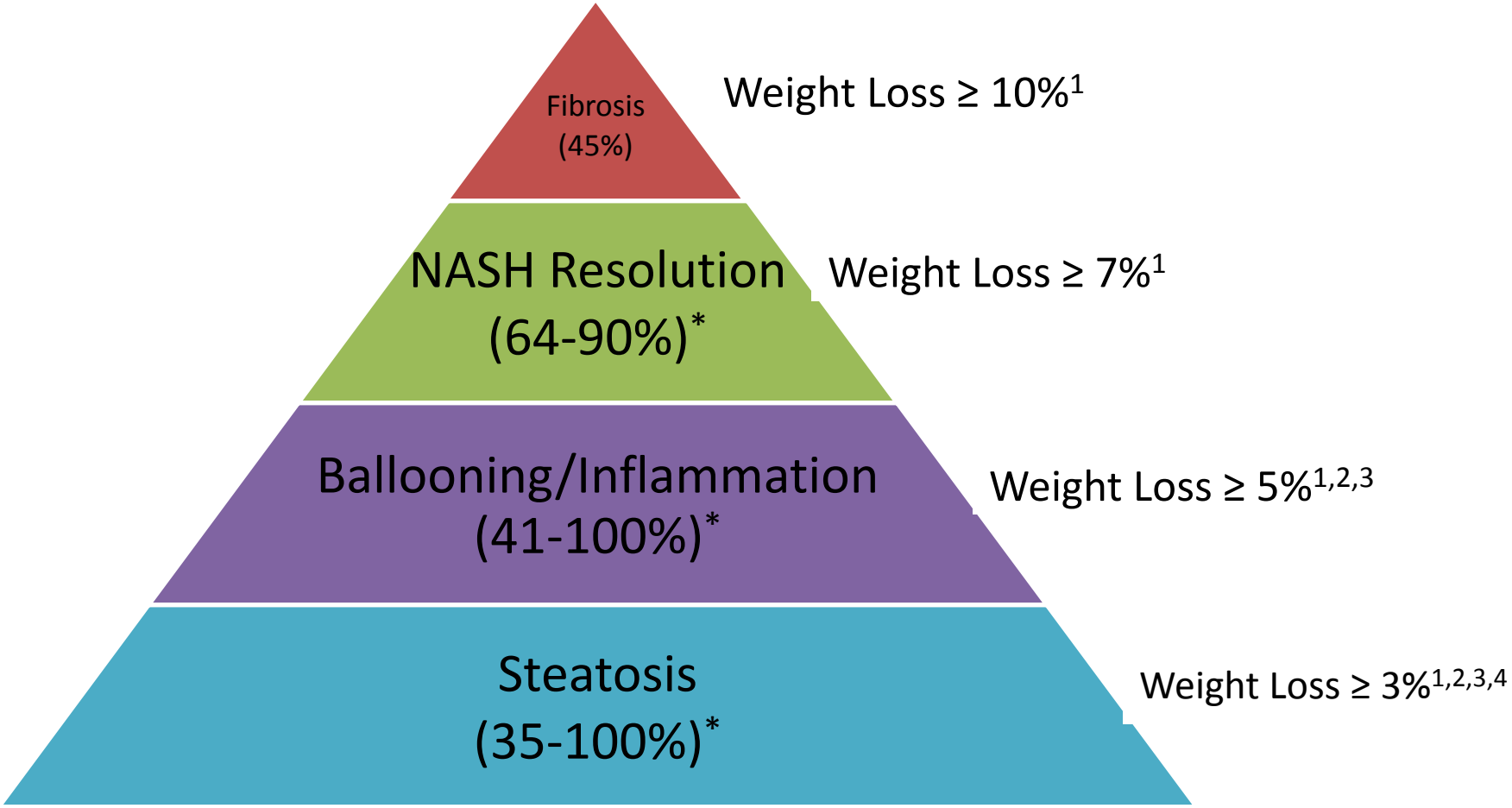


Tang A, Radiology 2015

Treatment

- Lifestyle
  - Diet
  - Exercise
- Pharmacology
  - Vitamin E, pioglitazone
  - Liraglutide, obetacholic acid (OCA); elafibranor
- Bariatric surgery

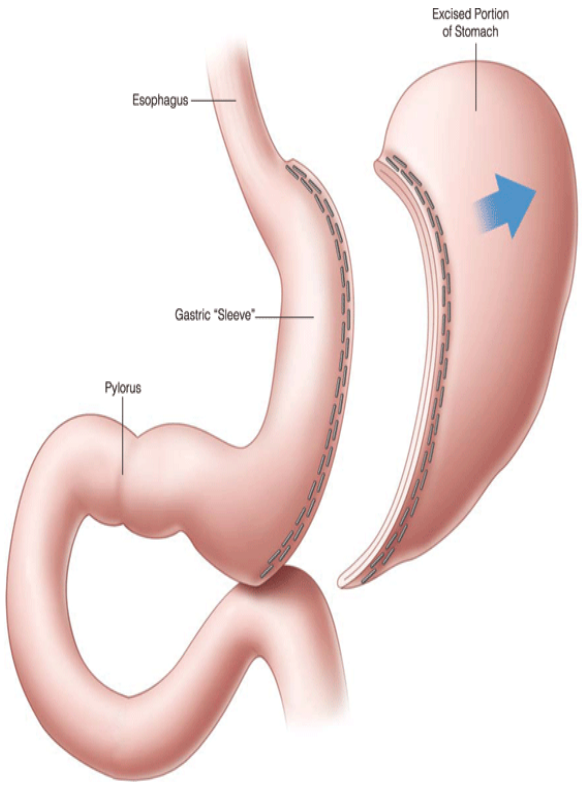
Weight Loss Pyramid



1 Vilar-Gomez. Gastroenterology 2015; 2 Promrat. Hepatology 2010; 3 Harrison. Hepatology 2009; 4 Wong. J Hepatol 2013

*Depending on degree of weight loss

Bariatric Surgery



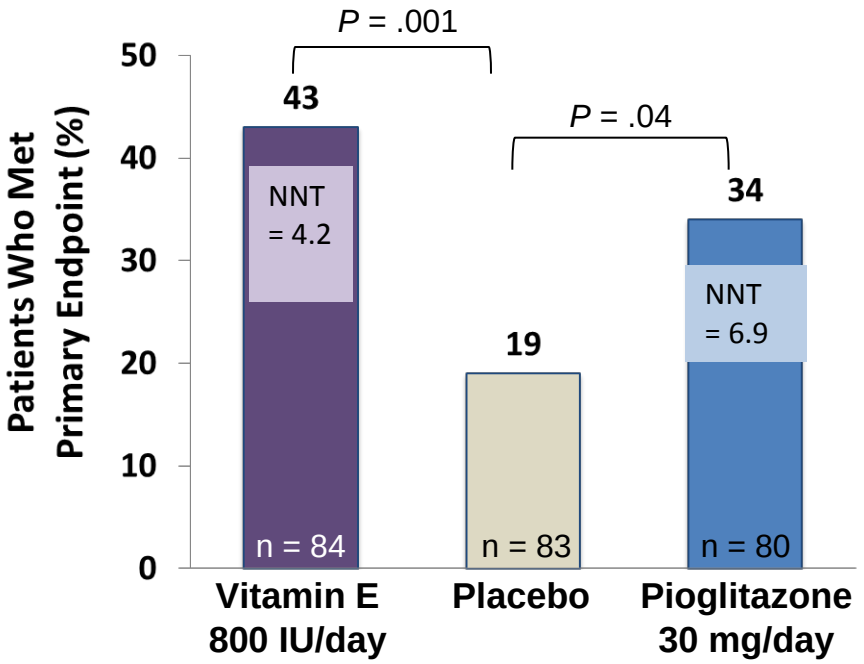
- Decreases Steatosis
- Decreases Inflammation / NASH
- No clear evidence of improvement in fibrosis
- Current Indication
  - BMI >40
  - >35 with comorbidity (DM, OSA, HTN, CHF)
- NAFLD currently not an indication for bariatric surgery but NASH is not contraindication
- Consider if multiple failed attempts at wt loss
- Acceptable surgical risk

Dixon Hepatology 2004
Furuya J Gastroenterol Hepatol 2007
Barker Am J Gastroenterol 2006
Chavez-Tapia Cochrane Database Sys Rev 2010

PIVENS Trial of Vitamin E or Pioglitazone in NASH: *Primary Endpoint: histologic improvement (↓in NAS)*

Primary endpoint = histologic improvement

Defined as: ≥1-point improvement in hepatocellular ballooning score, no increase in fibrosis score, and either a decrease in NAS to ≤3 or a ≥2-point decrease in NAS plus ≥1-point decrease in either the lobular inflammation or steatosis score



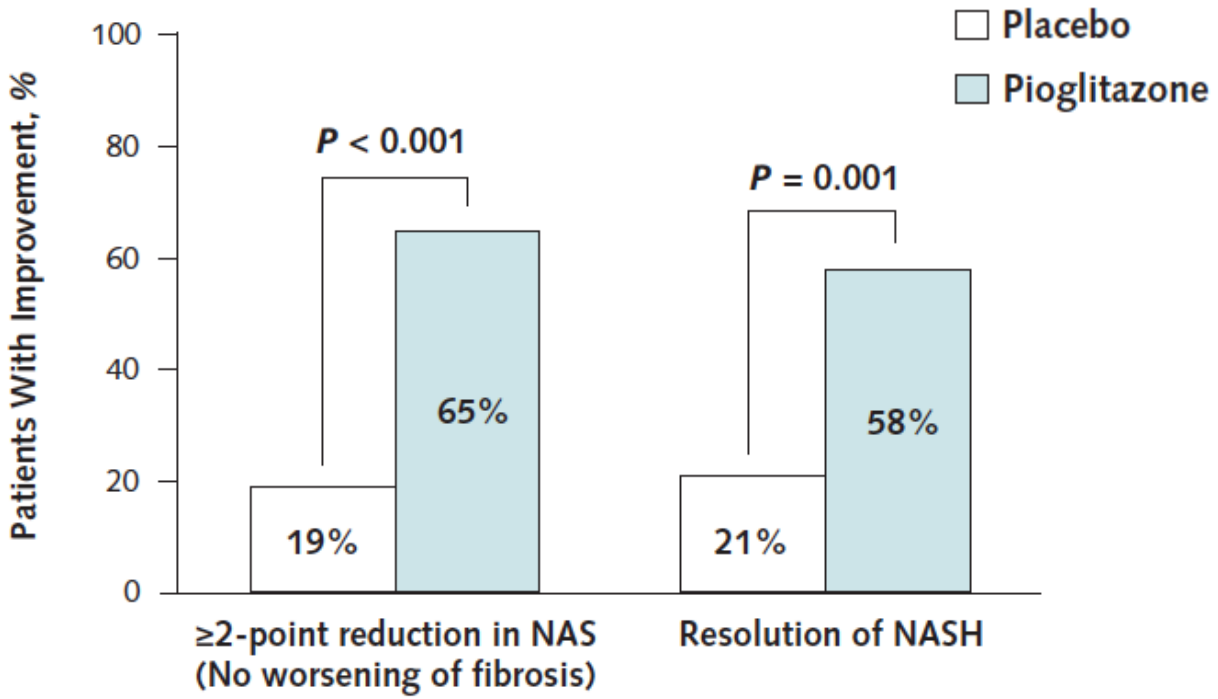
Abbreviations: NAS, nonalcoholic fatty liver disease score; NASH, nonalcoholic steatohepatitis, NNT, number needed to treat.

Sanyal AJ, et al. *N Engl J Med.* 2010;362:1675-1685.

Effect of Pioglitazone on Liver Histology at 18 months*

Primary: ≥2 point reduction in NAS without worsening fibrosis

Secondary: resolution of NASH

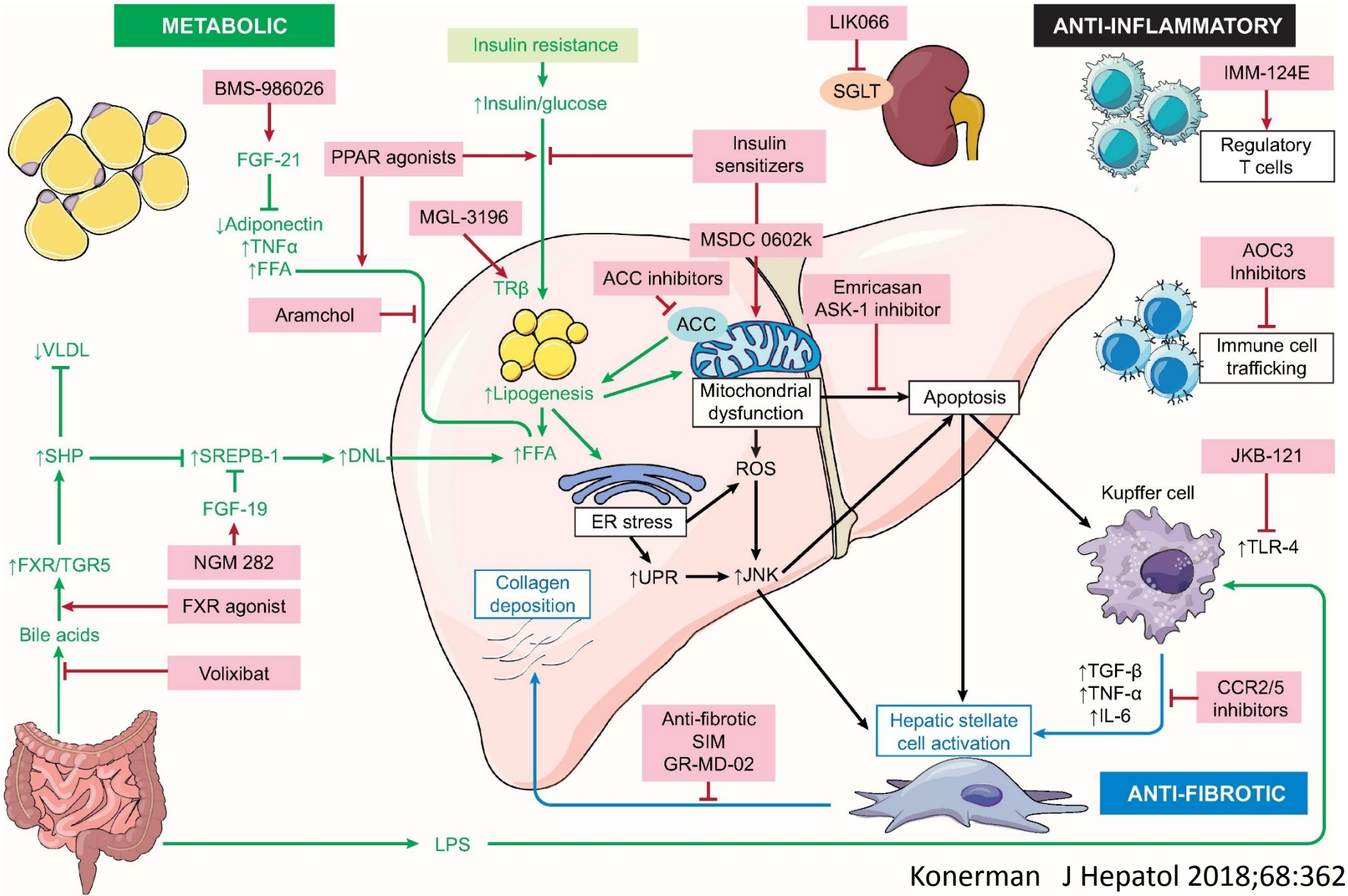


* In patients with paired biopsies (n = 82)

Resolution of NASH defined as absence of NASH after 18 mo of therapy with definite NASH at baseline

Cusi et al, Ann Intern Med June 21, 2016. [Epub].

Phase II and III NASH Agents



Konerman J Hepatol 2018;68:362

Liraglutide for NASH (LEAN Trial)

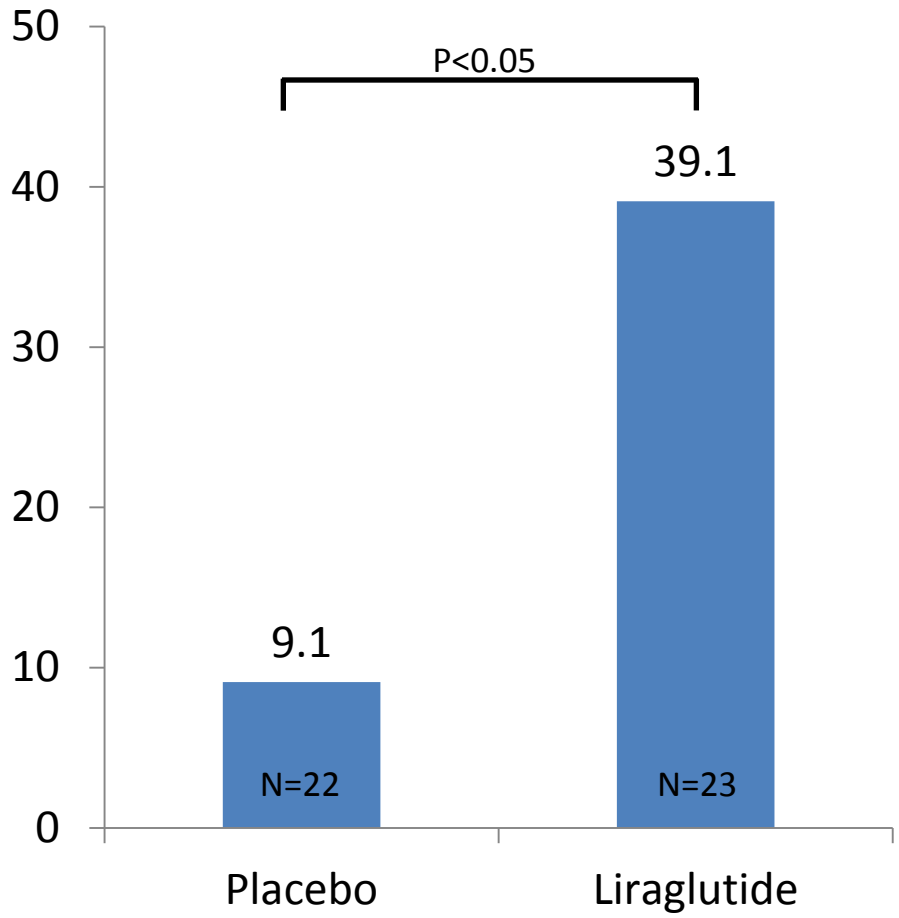
Primary Outcome (per protocol analysis)

NASH on Biopsy
Non-DM or DM (not on insulin)

~33% had T2DM
HbA1c ~6.0
ALT ~70
~50% F0-2
~50% F3-4

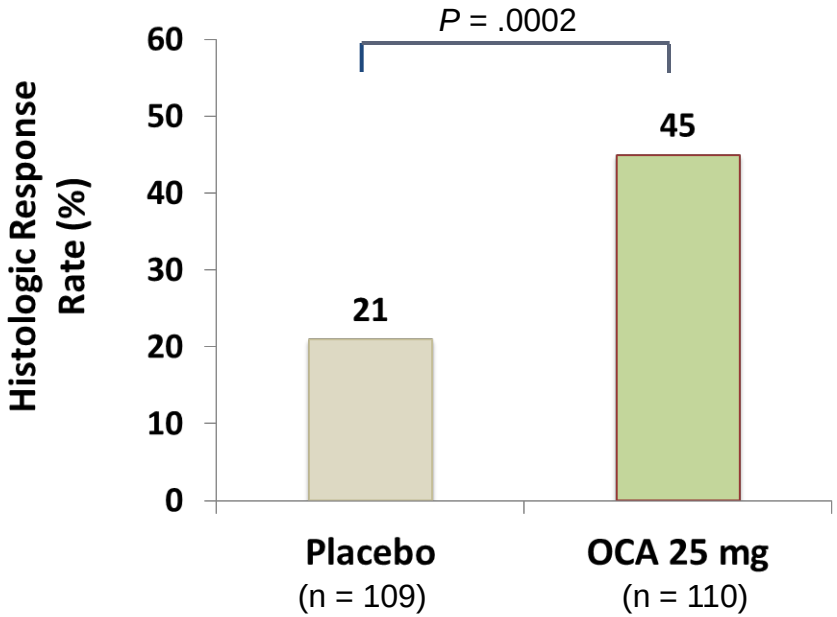
Primary Outcome:
Histology at week 48

Resolution of NASH
+ no worsening in fibrosis



Armstrong Lancet 2016;387:679

Obetacholic Acid: FLINT Primary Endpoint—*Improved Liver Histology at Week 72*



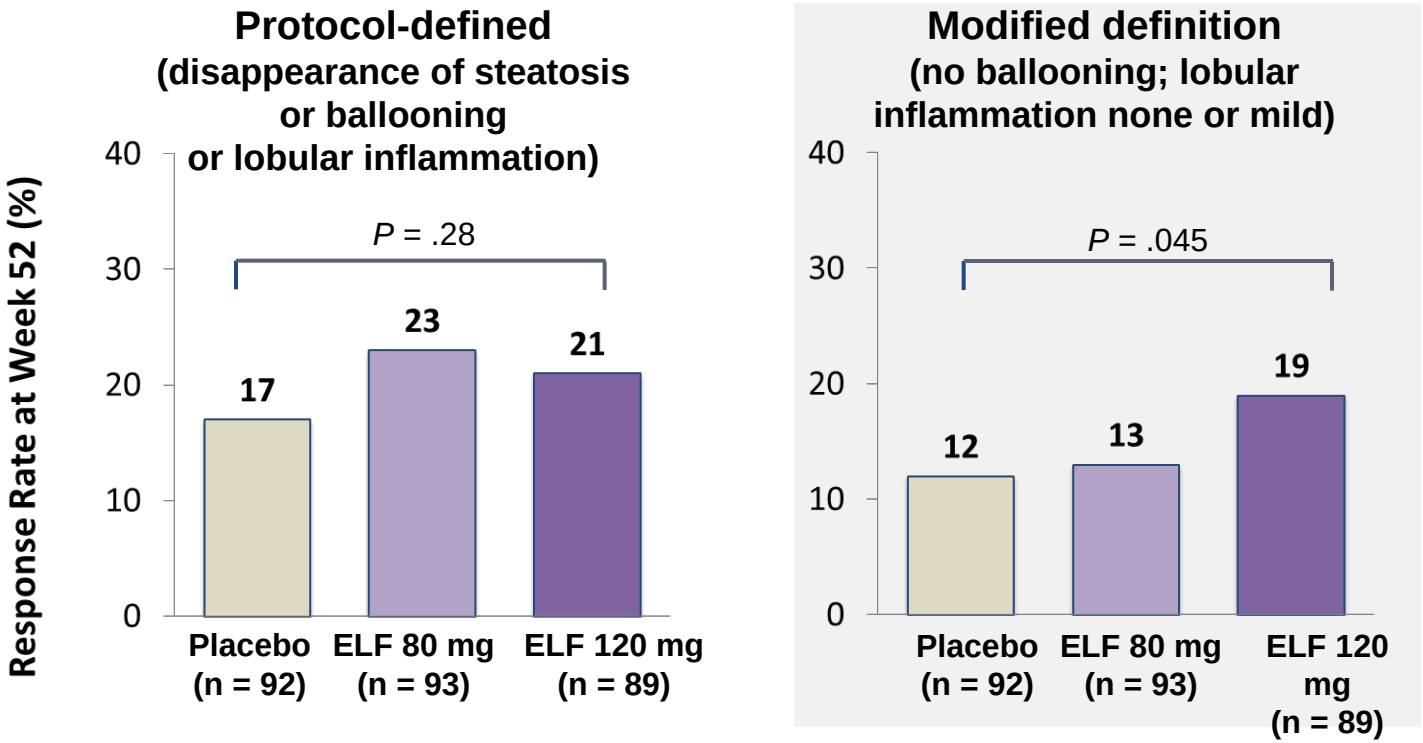
Histologic response: ≥2-point improvement in NAS without worsening of fibrosis

Abbreviations: NAS, nonalcoholic fatty liver disease activity score; OCA, obeticholic acid.

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

Elfibrinor: Primary Endpoint in ITT Population

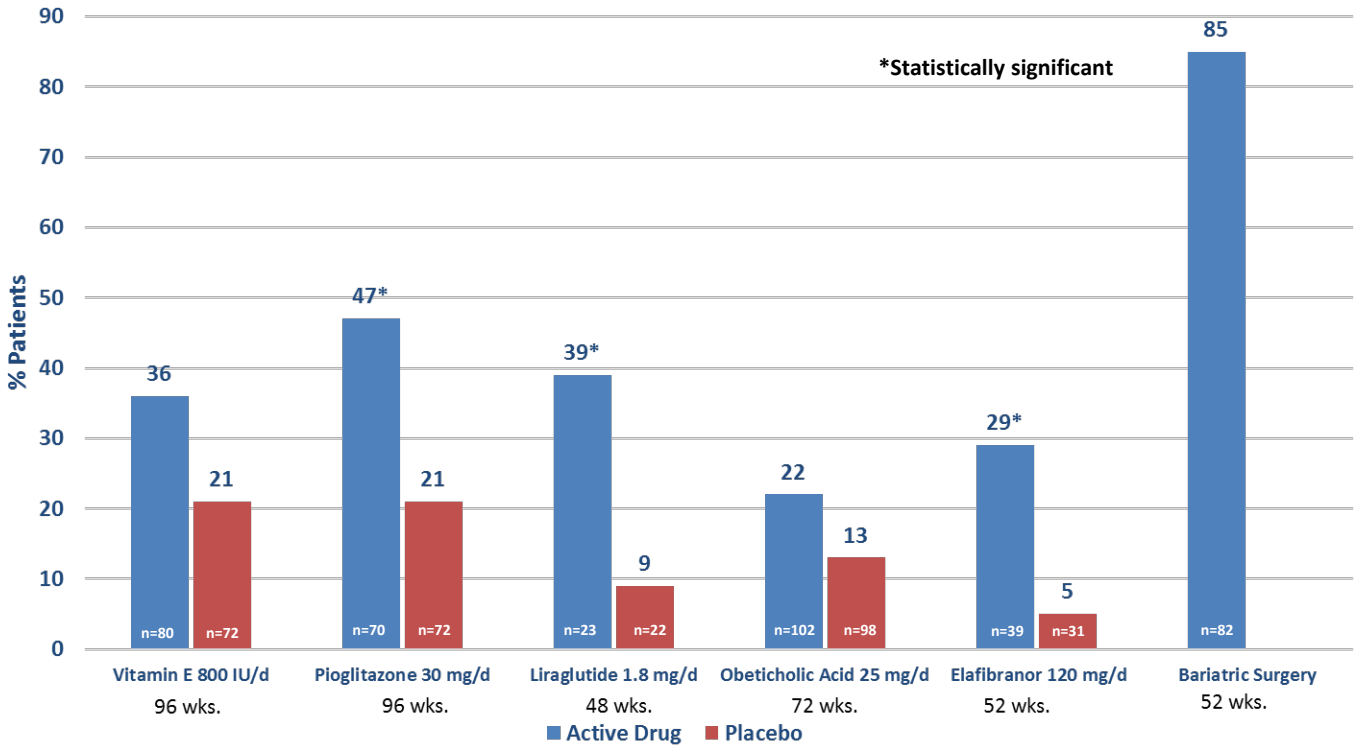
Resolution of NASH Without Fibrosis Worsening



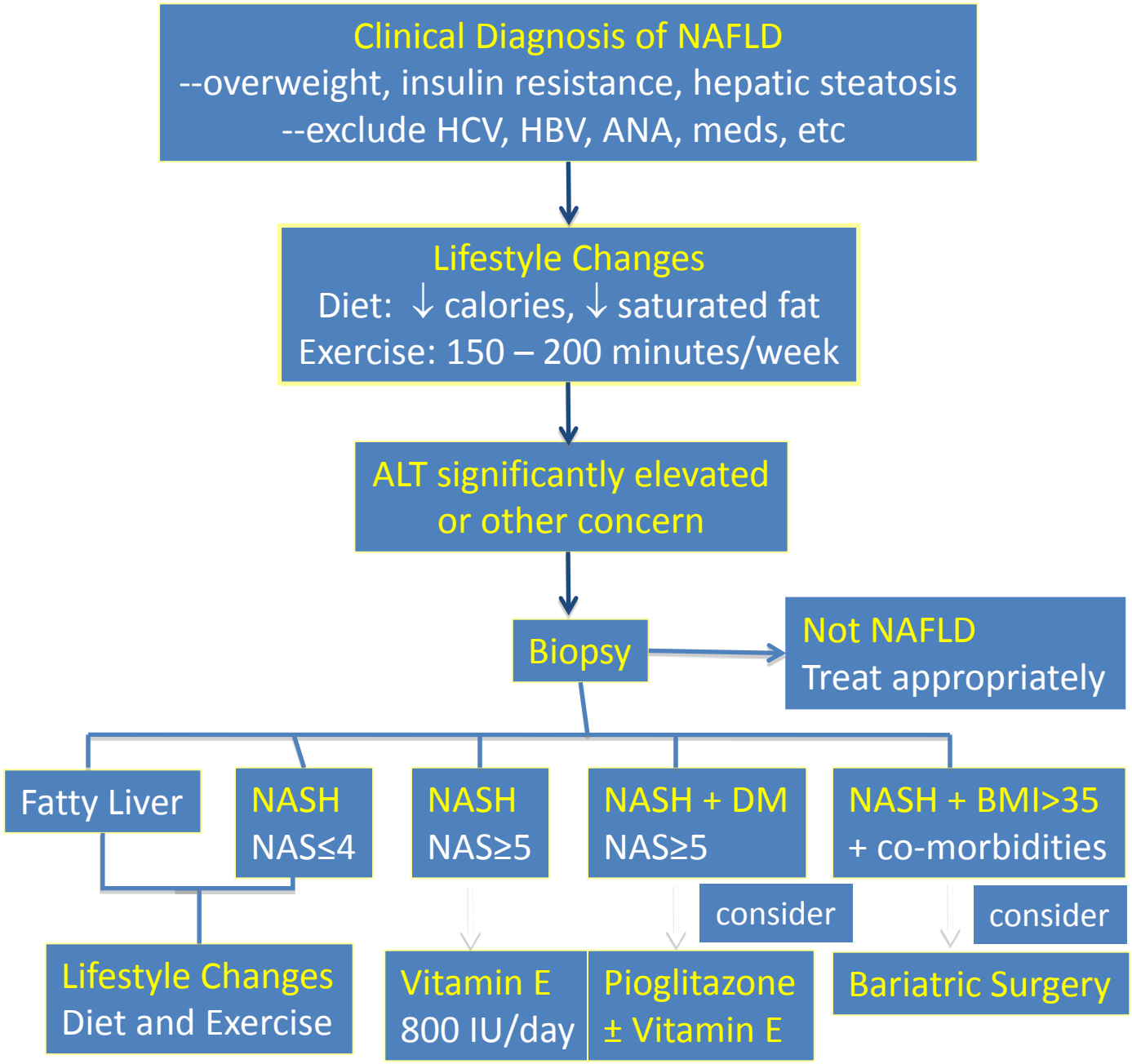
Abbreviations: EASL, European Association for the Study of the Liver; ELF, elafibranor; ITT, intent-to-treat; NASH, nonalcoholic steatohepatitis.

Ratziu V, et al. *Gastroenterology.* 2016 Feb 11. [Epub ahead of print]

Resolution of NASH:
Comparison of Key NASH Therapies



- ***Rates of resolution of NASH not available from cenicriviroc Phase 2* study (CENTAUR Trial); reported as no significant difference between treatment arms**


Clinical Diagnosis of NAFLD
--overweight, insulin resistance, hepatic steatosis
--exclude HCV, HBV, ANA, meds, etc
Lifestyle Changes
Diet: ↓ calories, ↓ saturated fat
Exercise: 150 – 200 minutes/week
ALT significantly elevated
or other concern
Biopsy
Not NAFLD
Treat appropriately
Fatty Liver
NASH
NAS≤4
NASH
NAS≥5
NASH + DM
NAS≥5
NASH + BMI>35
+ co-morbidities
consider
consider
Lifestyle Changes
Diet and Exercise
Vitamin E
800 IU/day
Pioglitazone
± Vitamin E
Bariatric Surgery