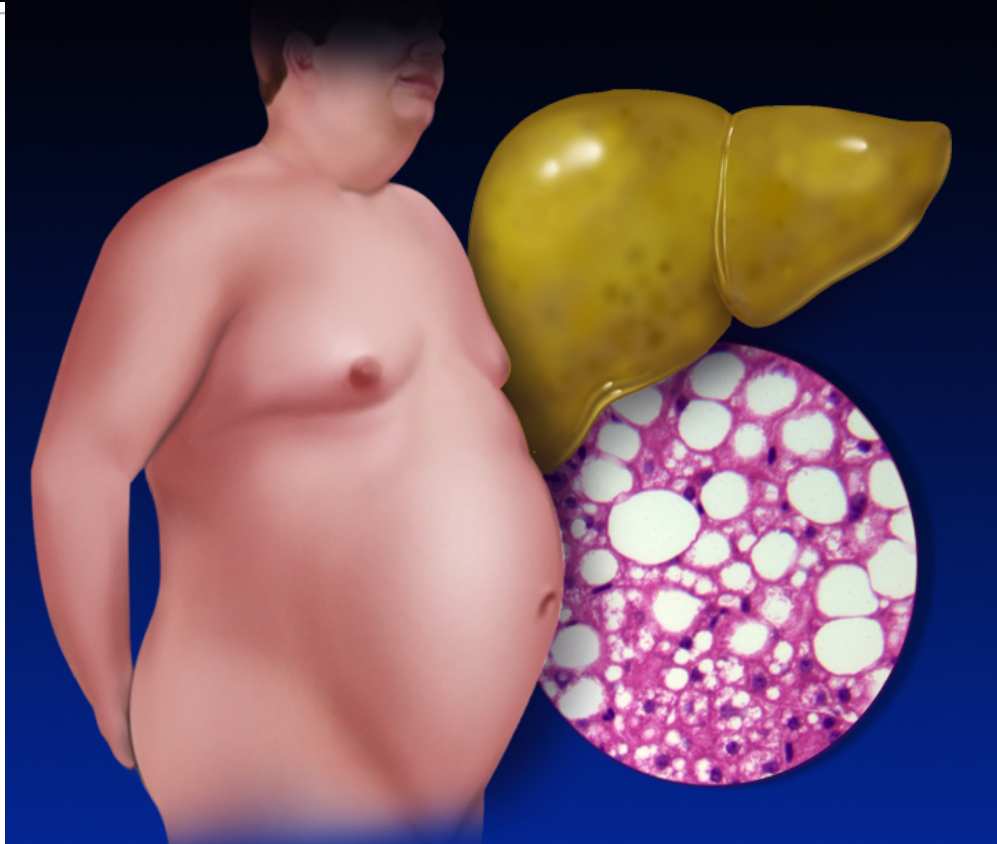


The Diagnosis and Management of NAFLD



“At the end of this program participants should know”:

Take home message!!



■ OBJECTIVES

1. the factors playing a role in the pathogenesis of NAFLD
2. how to diagnose and stage NAFLD
3. how to provide specific advice regarding diet and exercise
4. what and when to use supplements and drugs

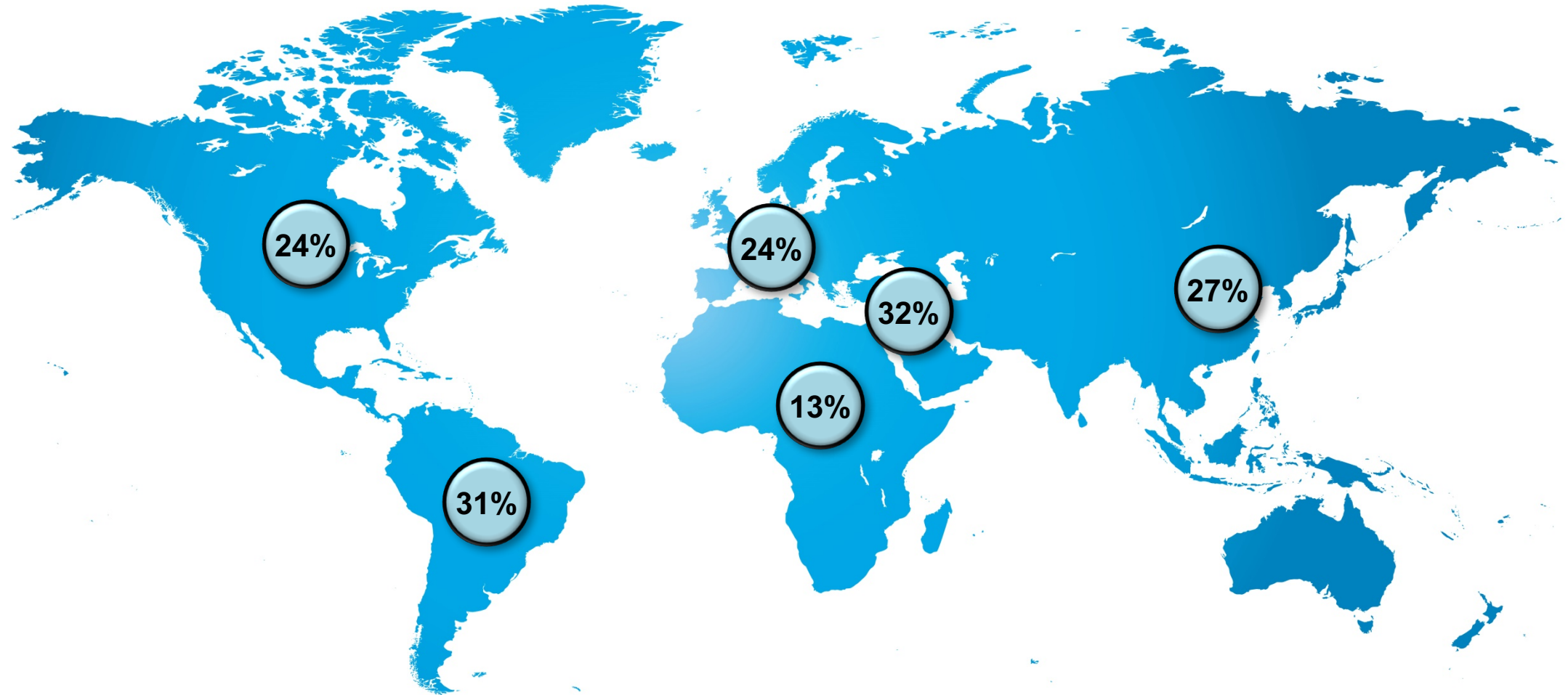
Financial Interest Disclosure & CANMEDS Roles

Commercial Interest	Relationship*
Janssen	Consultant



✓	Medical Expert (as <i>Medical Experts</i> , physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care. <i>Medical Expert</i> is the central physician Role in the CanMEDS framework.)
✓	Communicator (as <i>Communicators</i> , physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.)
✓	Collaborator (as <i>Collaborators</i> , physicians effectively work within a healthcare team to achieve optimal patient care.)
✓	Manager (as <i>Managers</i> , physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system.)
✓	Health Advocate (as <i>Health Advocates</i> , physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.)
	Scholar (as <i>Scholars</i> , physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge.)
✓	Professional (as <i>Professionals</i> , physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour.)

The Estimated Prevalence of NAFLD worldwide is 25%



Meta-analysis: NAFLD diagnosed by imaging (US, CT, MRI/SPECT; n=45 studies).
Younossi, Hepatology, 2016, 64, 73-84.
Younossi ZM, et al. Hepatology. 2016;64:73-84.



Modified from: clinicaloptions.com

NAFLD is the most common liver disease in Western Countries

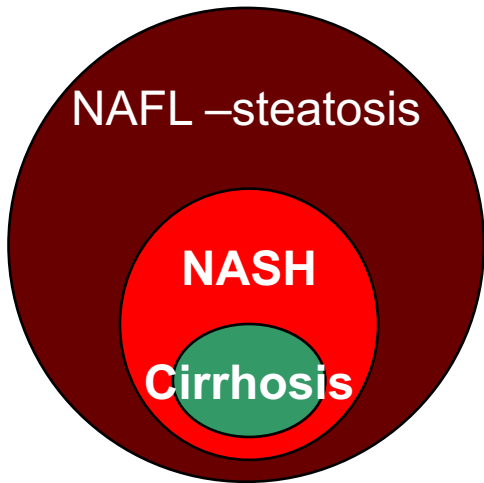
	NAFLD	NASH
GENERAL POPN	25-46%	3%
DIABETICS	70%	22%
OBESE	90%	14-37%

Ratziu et al, J Hepatol 2010

- affecting 17–46% of adults¹
- Parallels the prevalence of metabolic syndrome (MetS) and its components, which also increase the risk of more advanced disease
- NAFLD is also present in 7% of normal-weight (lean) individuals²

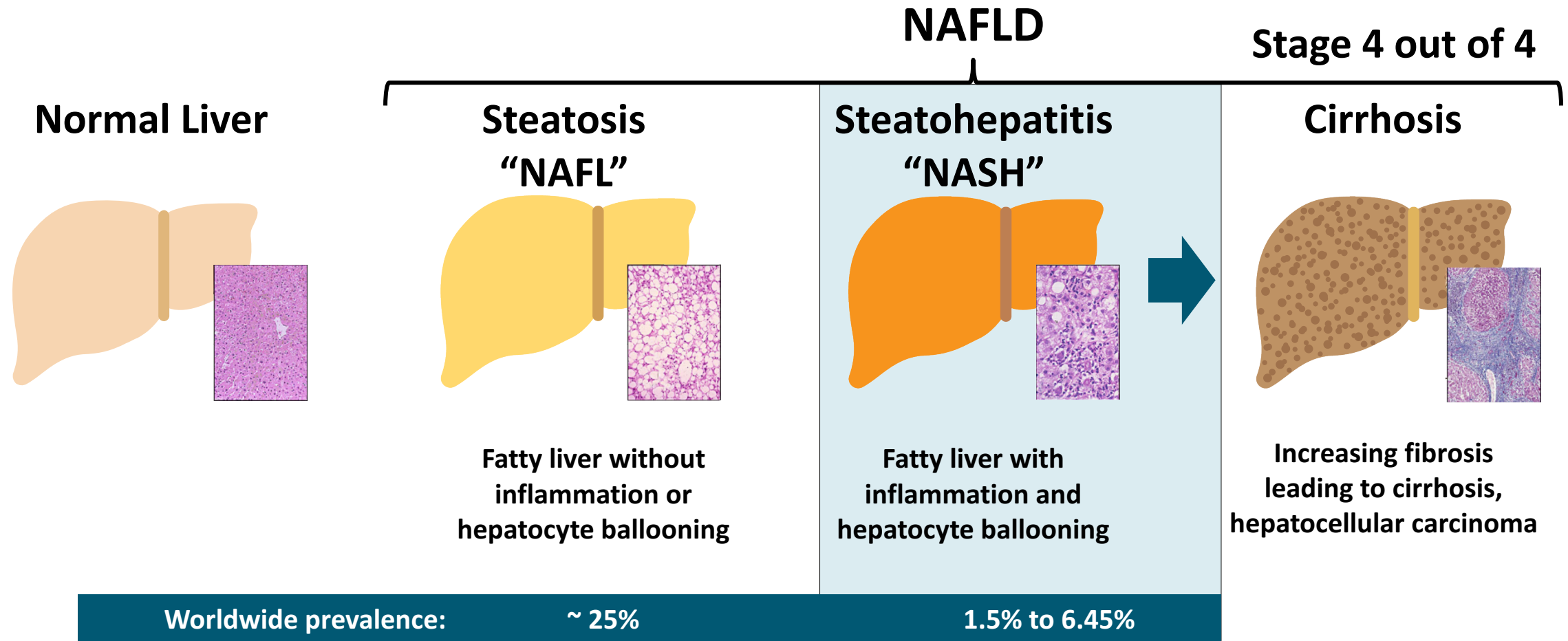
1. Vernon G, et al. Aliment Pharmacol Ther 2011;34:274–85
2. Younossi ZM, et al. Medicine 2012;91:319–27; EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Non-Alcoholic Fatty Liver Disease (NAFLD)



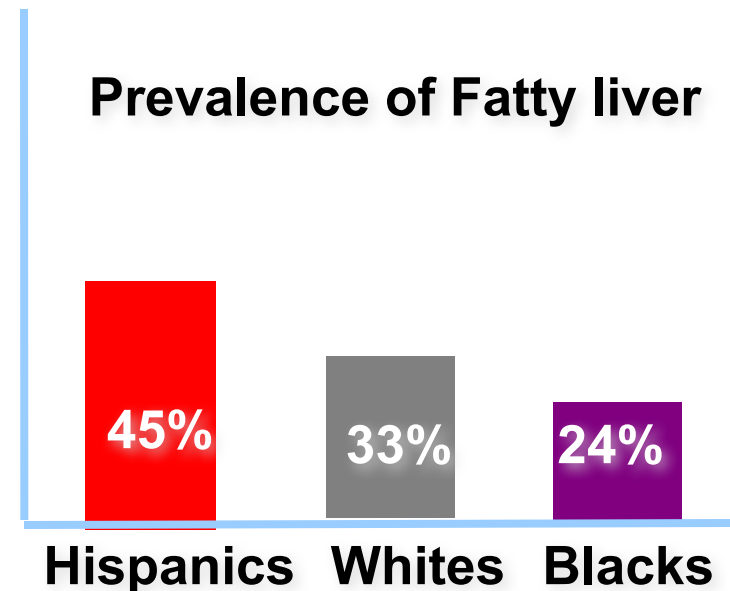
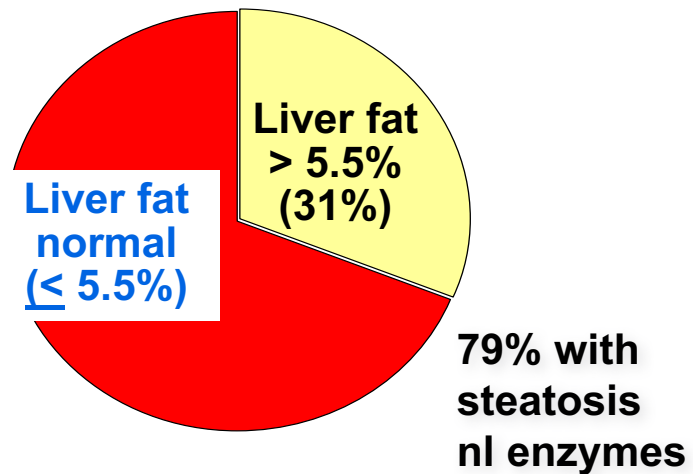
- Steatosis by imaging or histology in the absence of secondary causes (alcohol, other drugs, etc)
- Histologic spectrum of liver damage
- At the cirrhotic stage often “burnt out” or “cryptogenic”

Rate of fibrosis corresponds to 1 stage every 14 years in NAFL and every 7 years in NASH, is doubled by arterial hypertension



NAFLD is common and commonly asymptomatic

- Dallas heart study (n=2200)
- Liver fat assessed by MR spectroscopy



Met synd > in hispanics than whites
Met Synd also common in blacks

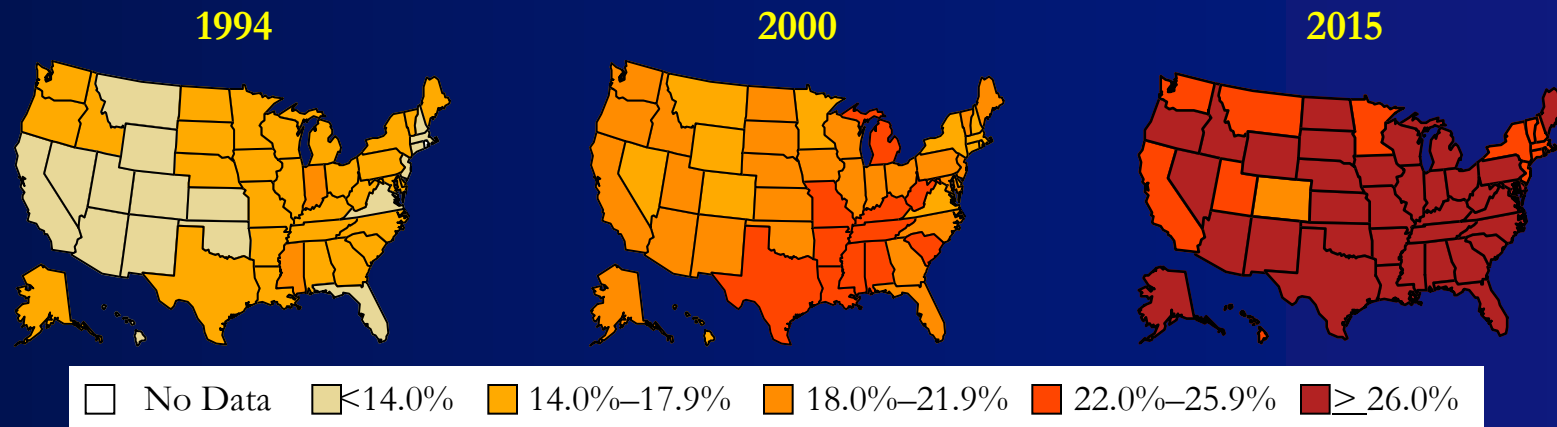
D Browning et al. Hepatology 2004;40:1387-1395

NAFLD is commonly associated with obesity and the metabolic syndrome

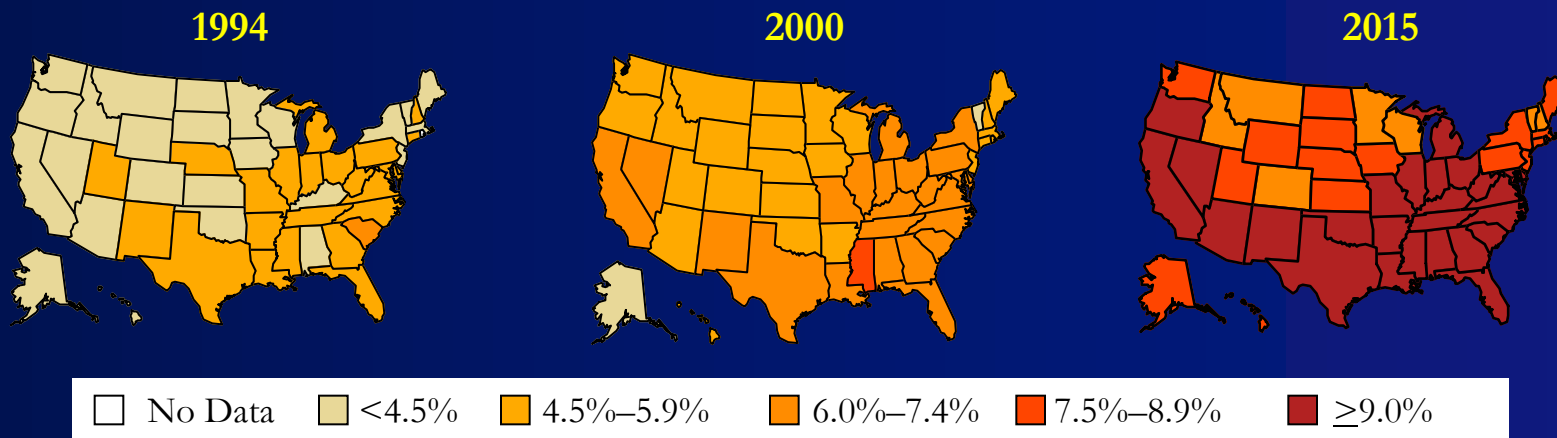
- NAFLD is closely associated with:
 - Insulin Resistance in the liver as well as adipose and muscle tissue
 - Metabolic Syndrome: 3 of:
 1. impaired fasting glucose or T2DM
 2. Hypertriglyceridemia
 3. low HDL-C
 4. * increased waist circumference
 5. † high blood pressure
- BMI and waist circumference are positively related to NAFLD
 - Predictors of advanced disease, particularly in the elderly

Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

Obesity (BMI ≥ 30 kg/m²)



Diabetes



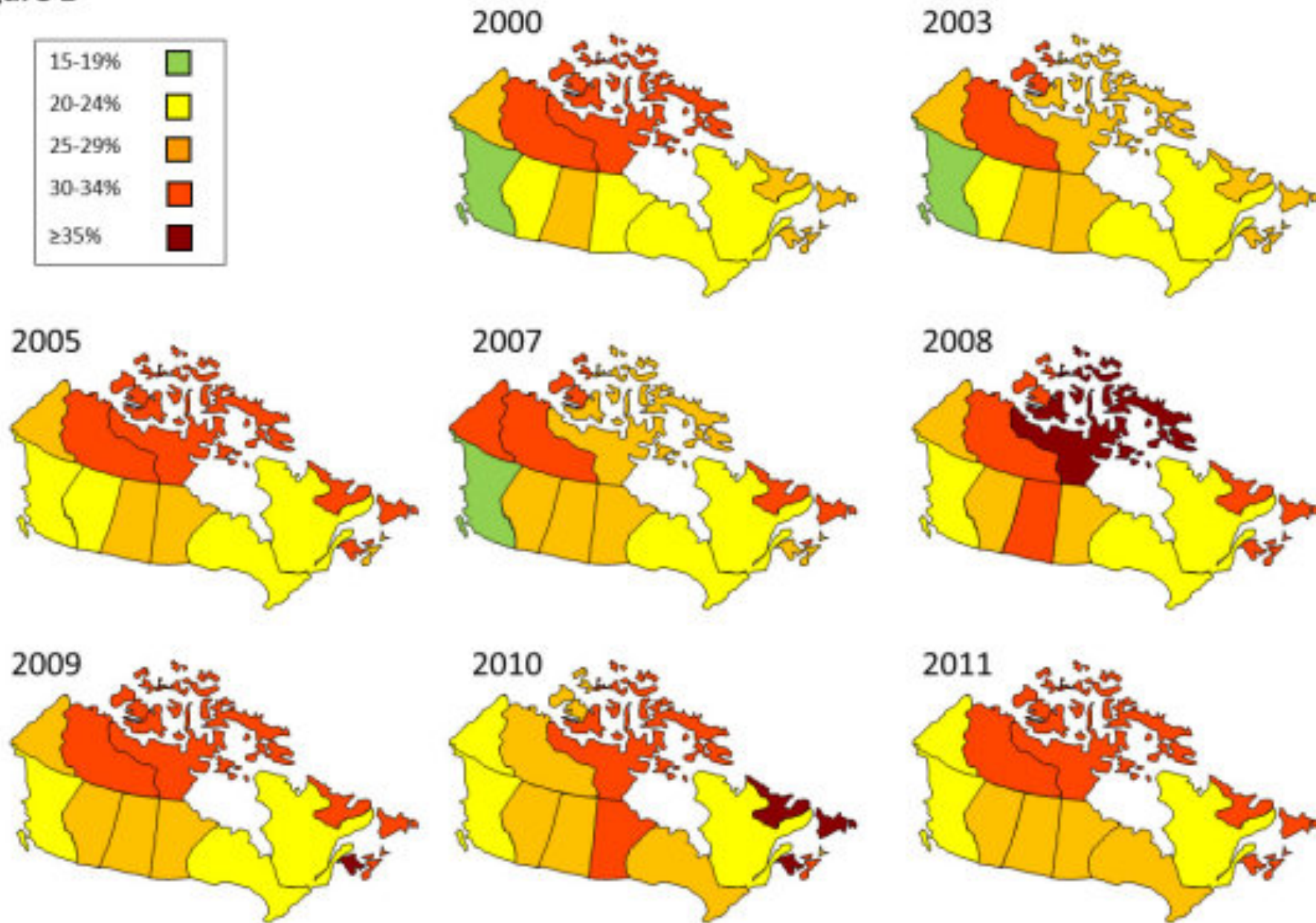
CDC's Division of Diabetes Translation. United States Surveillance System available at <http://www.cdc.gov/diabetes/data>



Obesity map by total population

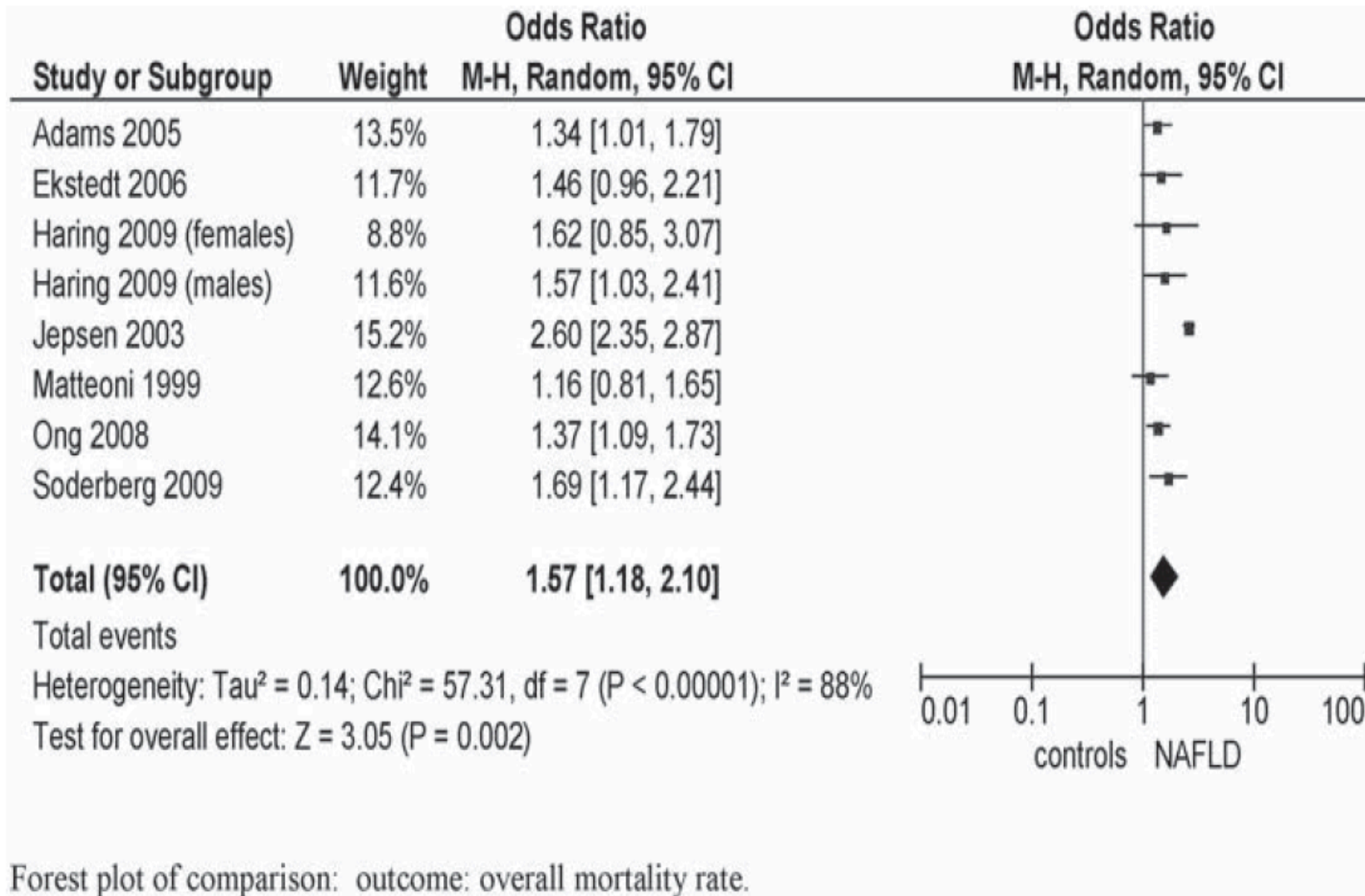
Gotay, C. *Can J Public Health* 2013

Figure 1



What risks to my health does NAFLD pose?

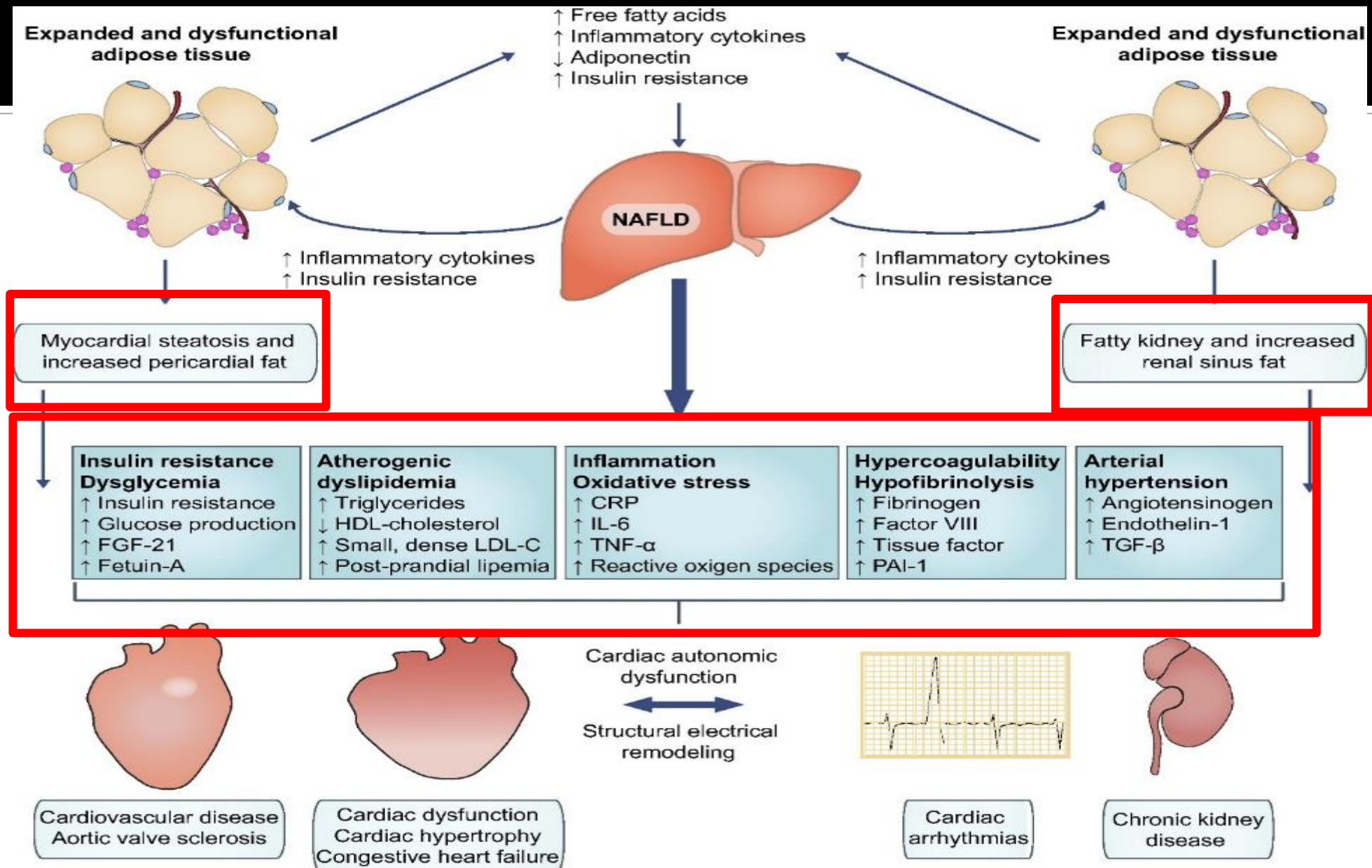
NAFLD has higher overall mortality...



Liver Disease is not the Major Cause Of Death

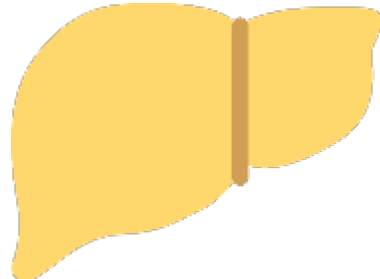
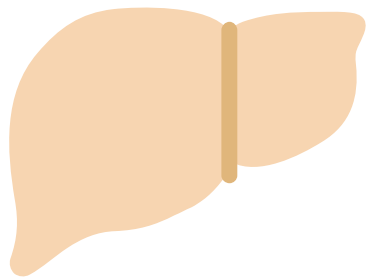
- Cause of Death:
 - Malignancy 28%
 - Cardiovascular 25%
 - Liver 13%
- For 45 – 54 yr old group CV causes most significant
 - Standardized mortality ratio all causes: 4.4 (1.2 -13.2)
 - SMR for CV disease: 8.15 (2 – 33.2)
- Prevalence and incidence of CVD is higher in NAFLD than in matched controls
 - Driven by the association between NAFLD and MetS components
- CVD should be identified in NAFLD, regardless of traditional risk factors

Connection between NAFLD, CVD and CKD



NAFLD Progression: Stratifying Risk Remains a Challenge; Cirrhosis is an IMPORTANT Milestone...

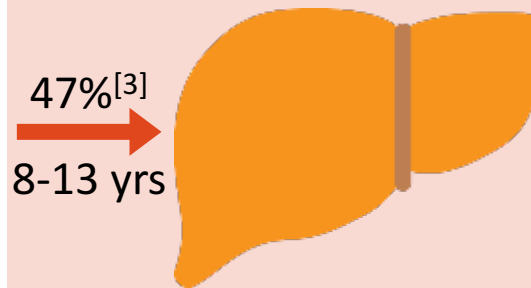
Normal Liver^[1,2] Steatosis (NAFL)^[1,2]



- Risk factors (metabolic syndrome, genetic factors)
- Hepatocytes are less responsive to insulin
- Increased fat storage
- Decreased fatty acid oxidation
- Fat droplets in cells
- Steatosis

- Majority asymptomatic^[4]
- Minority have bad clinical outcome^[4]

Steatohepatitis (NASH)^[1,2]



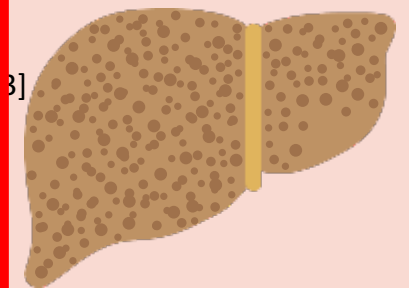
47%^[3]
8-13 yrs

- Oxidative and ER stress
- Mitochondrial dysfunction
- Lipotoxicity
- Inflammation, apoptosis

25% to 50%^[3]
8-13 yrs

- Variable rates of disease progression^[4]

Cirrhosis^[1,2]



- Hepatic stellate cells produce extracellular matrix deposits

5% HCC
50% OLT
20% liver-related mortality

10 yrs^[3]

1. Machado. Gastroenterology. 2016;150:1769. 2. Schuppan. J Gastroenterol Hepatol. 2013;28:68.
3. Moore. Proc Nutr Soc. 2010;69:211. 4. Spengler. Mayo Clin Proc. 2015;90:1233.

Screening for NAFLD is recommended if these Risk Factors are present

Risk Factor for NAFLD ^[1]
Type 2 diabetes
Obesity
Dyslipidemia
Metabolic syndrome
Polycystic ovary syndrome

Commonest Concurrent Liver diseases

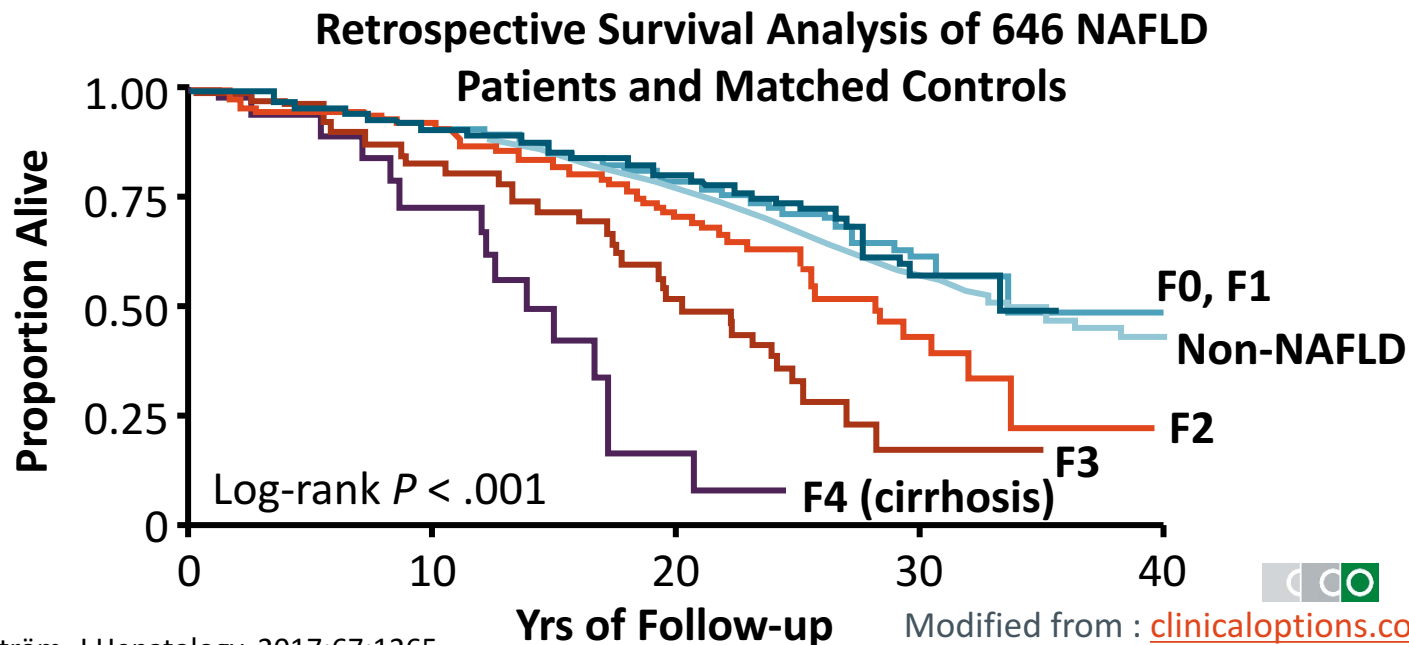
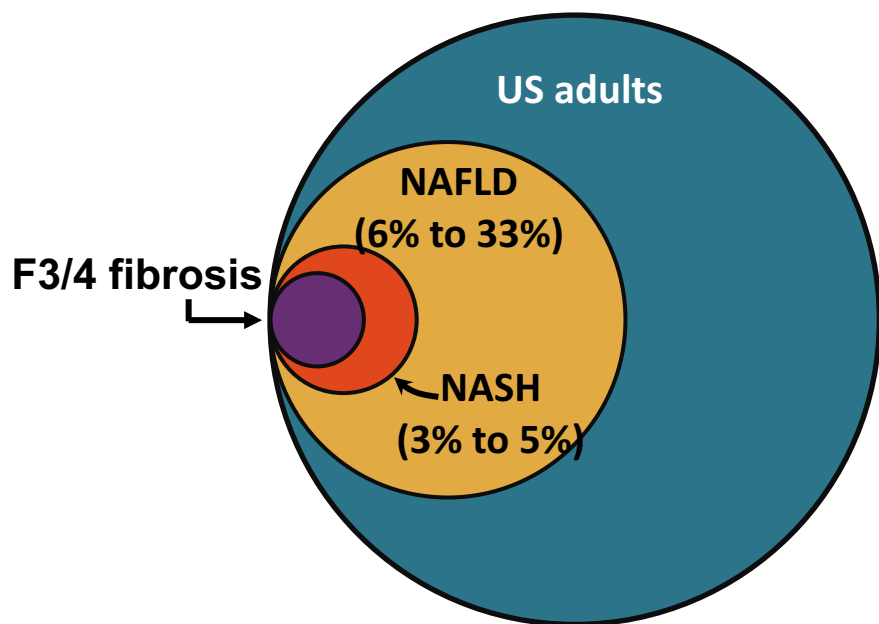
- Alcoholic Fatty Liver Disease (AFLD) or Drug-induced fatty liver disease (secondary cause)
- HCV-associated fatty liver disease (GT 3)⁺
- Others⁺
 - Haemochromatosis
 - Autoimmune hepatitis
 - Coeliac disease
 - Wilson disease
 - A/hypo-betalipoproteinaemia lipomatrophy
 - Hypopituitarism, hypothyroidism
 - Starvation, parenteral nutrition
 - Inborn errors of metabolism
 - Wolman disease (lysosomal acid lipase deficiency)

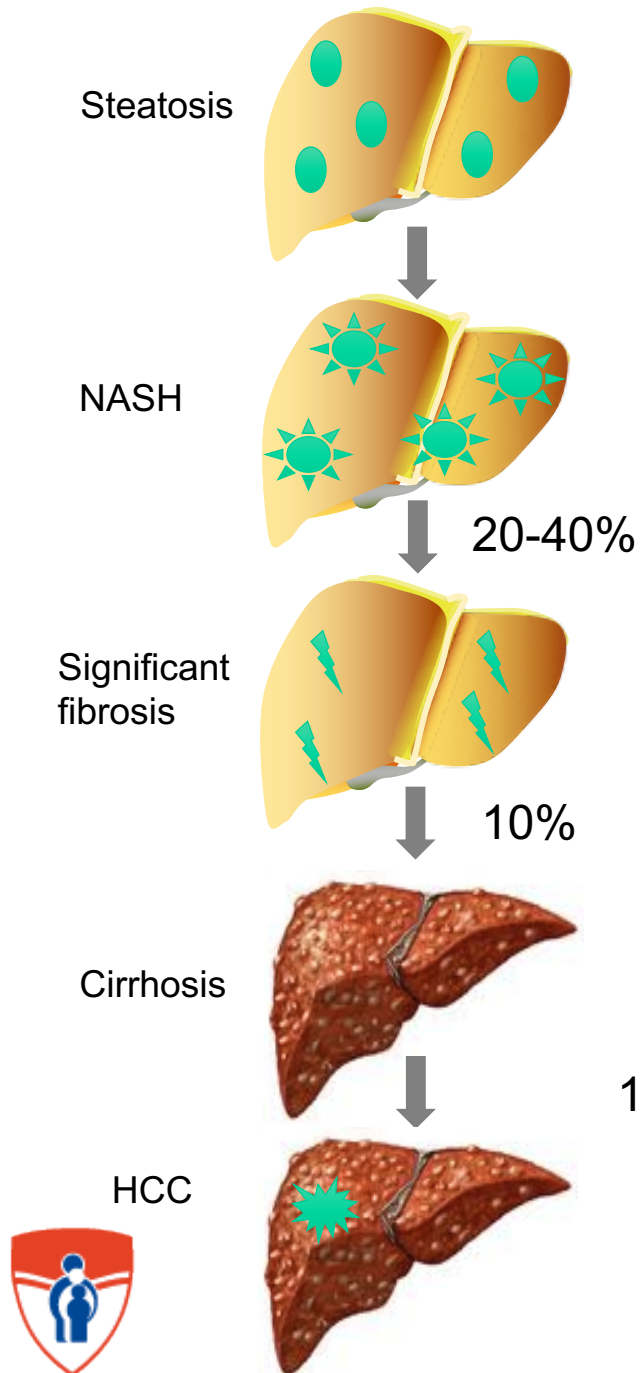
1. Chalasani. Hepatology. 2018;67:328. 2. EASL, EASD, EASO. J Hepatol. 2016;64:1388.

Fibrosis is the most important prognostic factor in NAFLD

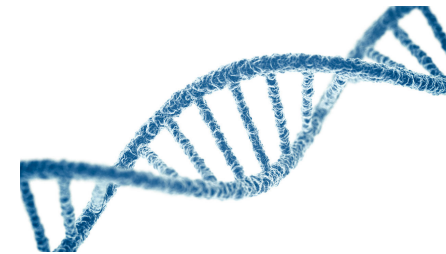
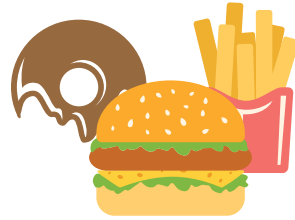
Correlates with liver-related outcomes and mortality

- Goal 1: Identify those with NASH
 - Having NASH increases the risk of **progression of fibrosis**
 - Identify treatment candidates
- Goal 2: Identify those at risk for progressing to cirrhosis
 - Having **any fibrosis, and particularly those with significant fibrosis \geq F2** associated with increased mortality





Multifactorial progression (environment + genes)



- Sedentary lifestyle
- Snacking, fast food
- Saturated fats
- Trans fats
- Processed red meat
- Hepatotoxic drugs
- Gut dysbiosis

PNPLA3*
(*PNPLA3* rs738409
C>G gene
polymorphism is
associated with
incr. HCC risk)

TM6SF2
GCKR
SOD2
MBOAT7

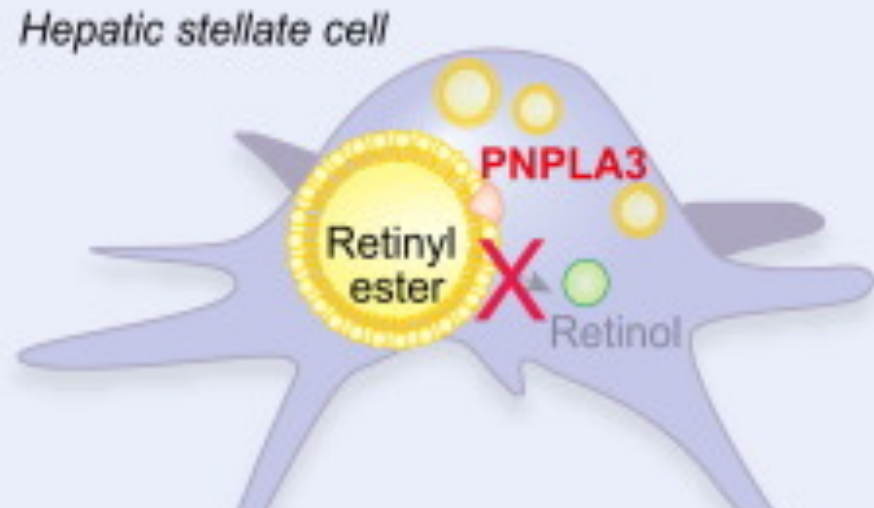
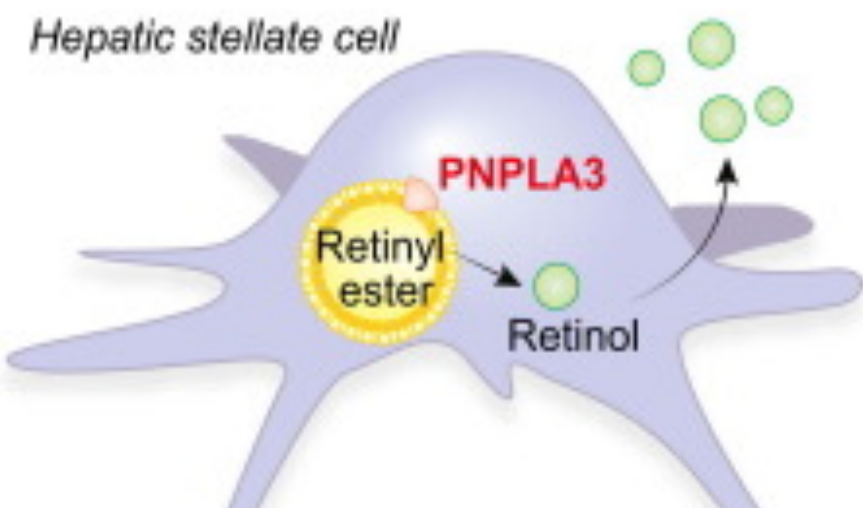
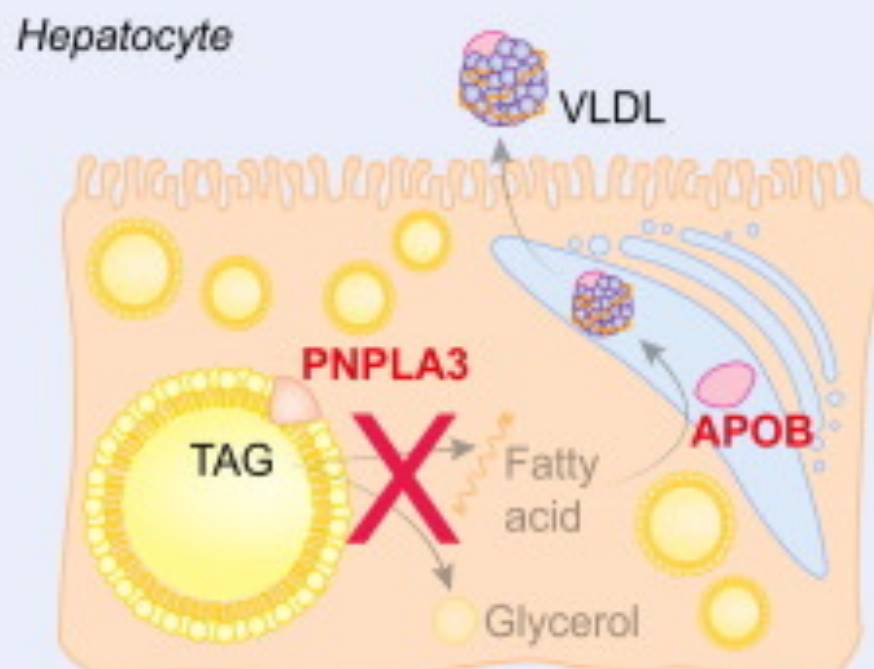
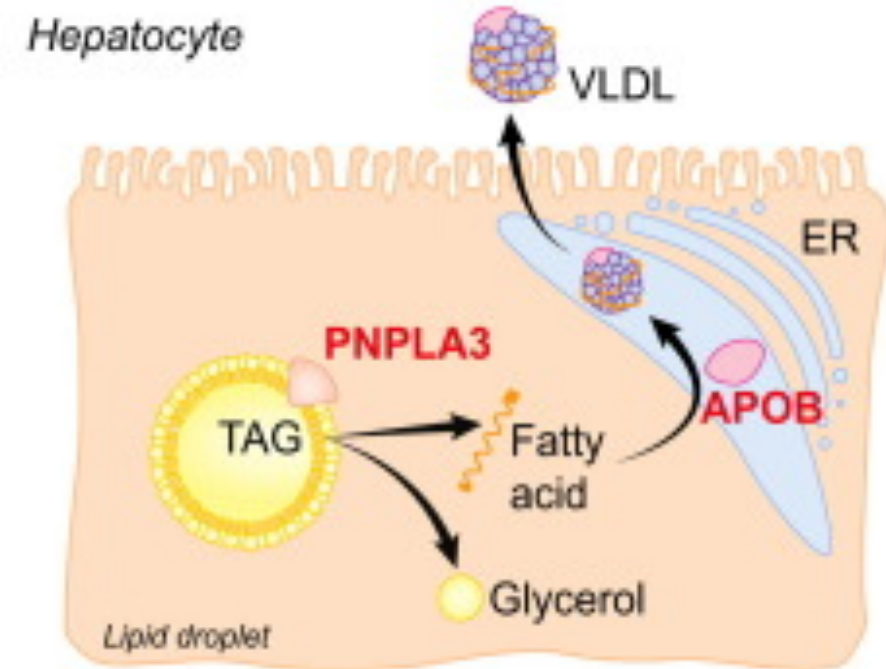
*thanks to G.
Sebastiani



NORMAL

PNPLA3 (p.148M)

The PNPLA3 protein has lipase activity towards triglycerides in hepatocytes and retinyl esters in hepatic stellate cells and the I148M substitution leads to a loss of function.



Normal Liver Enzymes Do Not Rule Out NASH

AST/ALT are not sensitive for NASH/NAFLD

- NAFLD a common diagnosis in patients with “incidental” abnormal liver enzymes such as ALT, AST^[1-3]

However:

- Liver enzymes may be normal in > 50% of individuals with NASH, and ~ 80% of NAFLD patients^[4,5]
 - Poor correlation between ALT and histology in NAFLD (ie. High values poorly predict fibrosis)
 - ALT typically decreases with advanced fibrosis
 - As NASH progresses, AST/ALT ratio may increase (ie, ALT < AST)
- Histology severity similar in NAFLD patients with normal vs abnormal liver enzymes^[6-8]

Blood tests: Be careful when working up “a diagnosis of exclusion”

- Elevated serum autoantibodies are common in patients with NAFLD and are generally considered to be an epiphenomenon

Vuppalanchi. Hepatology 2009

- NASH Clinical Research Network
 - +ANA > 1:160 or SMA > 1:40 in 21 % of NAFLD patients without more advanced histologic features

Vuppalanchi R. Hepatol Int. 2011

Ultrasound or CT: Inadequate in Assessing NAFLD and detects only **ADVANCED FIBROSIS** cases (too late!)

- **US or CT cannot identify most NAFLD stages/severity**

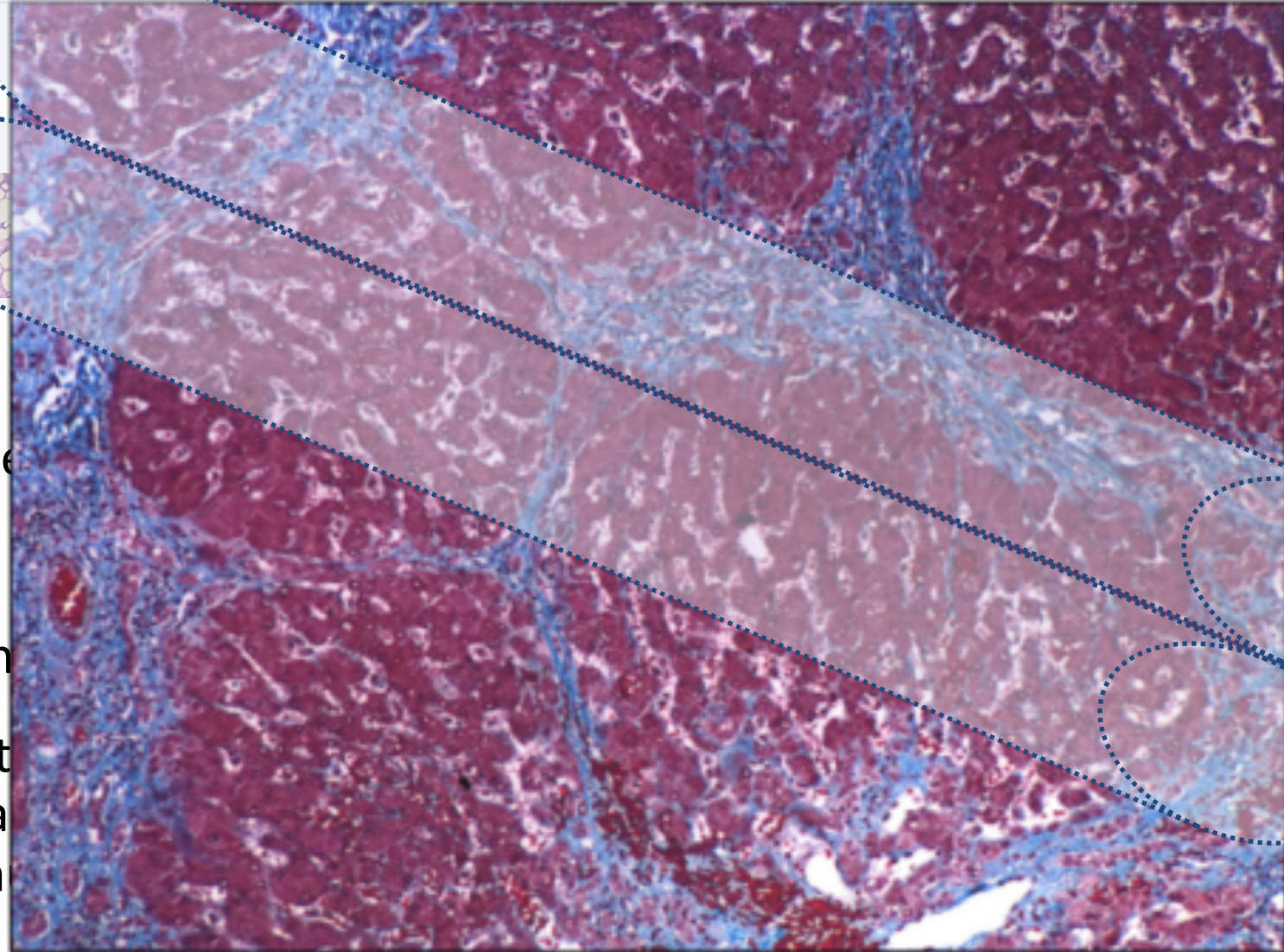
- Cannot distinguish steatosis vs NASH or NASH fibrosis/early cirrhosis

- **US or CT may identify advanced cirrhosis**

- Portal hypertensive changes such as varices, ascites, splenomegaly

Method for Identifying Steatosis	Sensitivity, %	Specificity, %	Comments
Ultrasound ^[1] <ul style="list-style-type: none"> ▪ Any degree ▪ ≥ 20% 	61 100	100 90	Inexpensive and accessible; cannot distinguish fibrosis/steatosis
CT without contrast ^[2] <ul style="list-style-type: none"> ▪ > 30% 	79	97	Also useful in morbidly obese; affected by iron, fibrosis; reduced accuracy with minimal steatosis

Li-



■ Benefits

- Establishes
- Assesses
- Determin
- Rules out alpha-1 and autoimmune

leath

n and

serial biopsies
gression,
pulations

especially with

IR biopsies if they are small)



Commonly Used Noninvasive Tests include: NFS, Fib-4, APRI, Fibroscan

- Different approaches to determine liver fibrosis^[1]
 - Simple and proprietary predictive scores quantify biomarkers in serum samples that have been shown to be associated with fibrosis stage
 - Imaging techniques measure liver stiffness

Clinical or Laboratory Scores

Simple

- NAFLD fibrosis score^[1,2]
- Fibrosis-4 (FIB-4)^[1,2]
- AST/platelet ratio index (APRI)^[1]

Proprietary

- *FibroSure*^[1]
- *FibroSpect*^[3]
- *Enhanced Liver Fibrosis Test (ELF)*^[1] (not commercially available in the US)

Imaging

Elastography

- Transient elastography (eg, *FibroScan*)^[1,2] \$\$\$
- Magnetic resonance elastography (MRE)^[1] \$\$\$\$

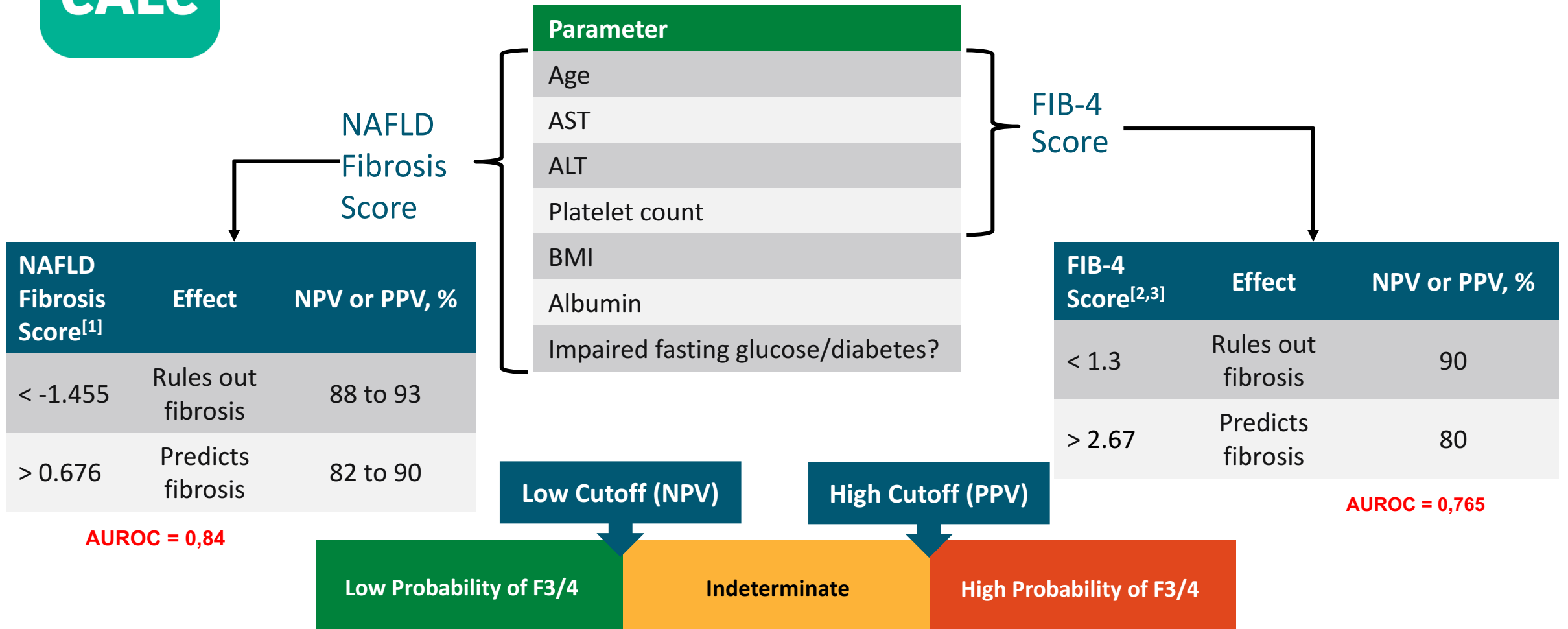
1. EASL. J Hepatol. 2015;63:237.

2. Alkhoury. Gastroenterol Hepatol (N Y). 2012;8:661. 3. Loomba. Clin Gastroenterol Hepatol. 2019;17:1867.



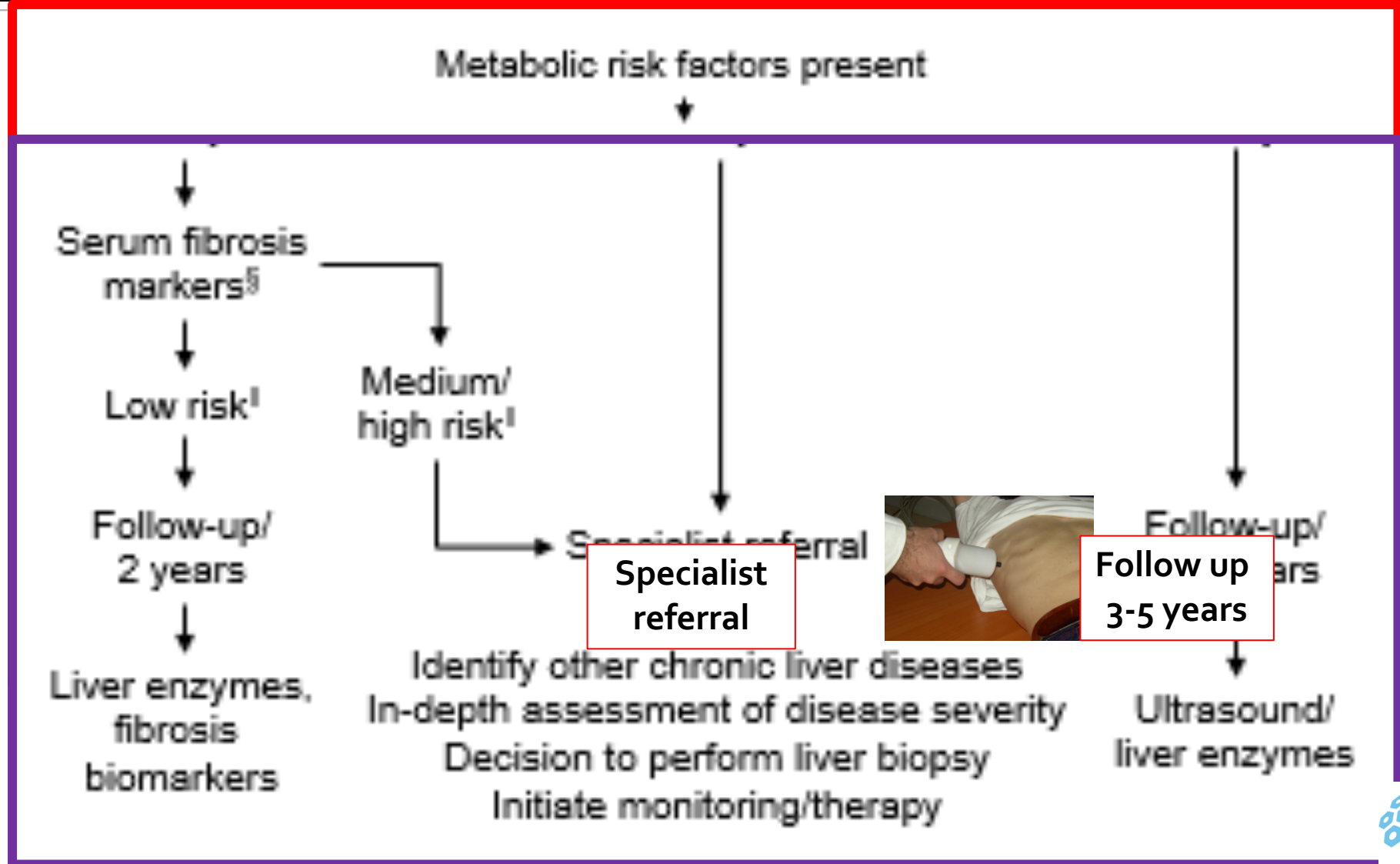
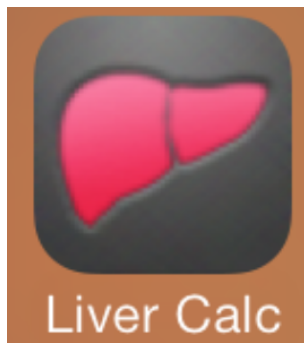


NAFLD Fibrosis Score and FIB-4



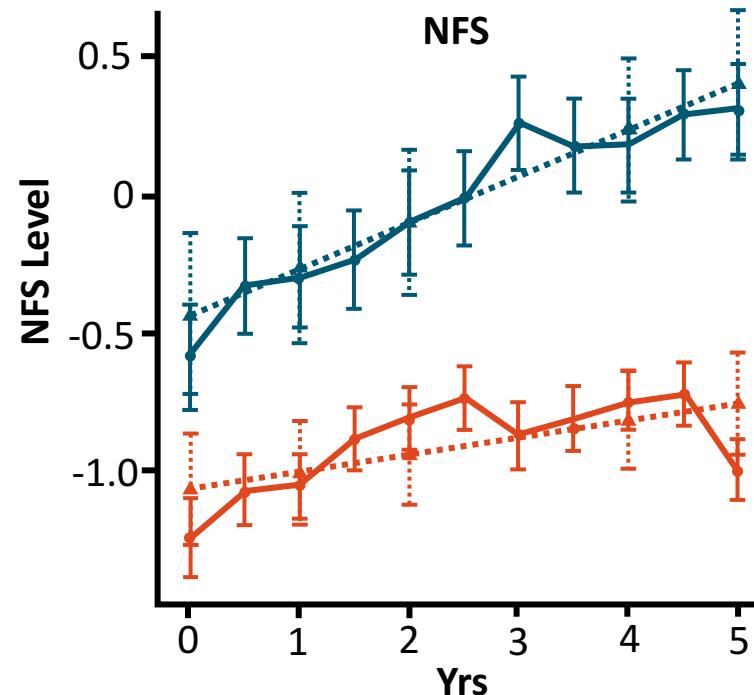
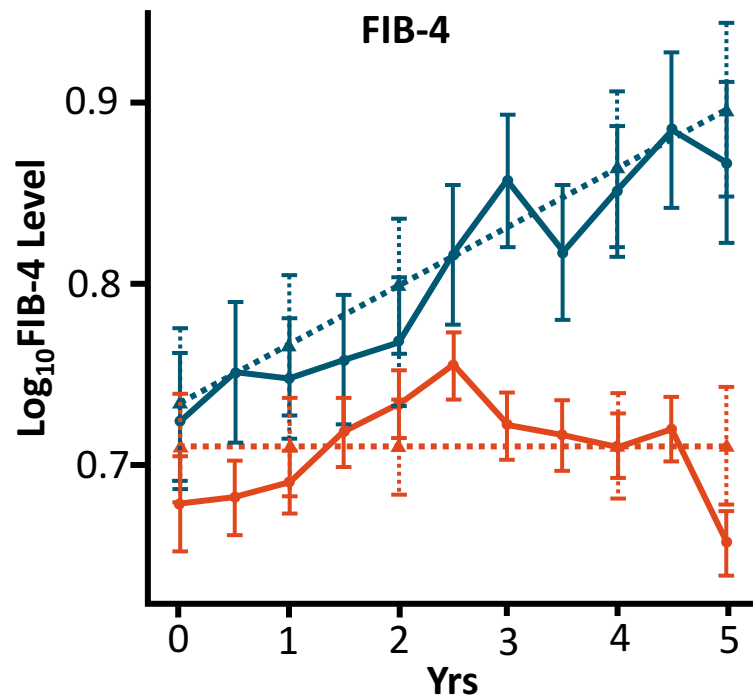
1. Angulo. Hepatology. 2007;45:846. 2. Shah. Clin Gastroenterol Hepatol. 2009;7:1104. 3. McPherson. Gut. 2010;59:1265.

Non-invasive tests are simple to use, reproducible, available and cheap (apps)



Longitudinal Increases in FIB-4 and NAFLD Fibrosis Scores Predict Clinically Significant Fibrosis

- Retrospective study assessing clinical and laboratory records of patients with NAFLD (N = 230) to calculate FIB-4 and NFS scores during 5 yrs prior to hepatology assessment of clinically significant fibrosis (\geq stage 2)



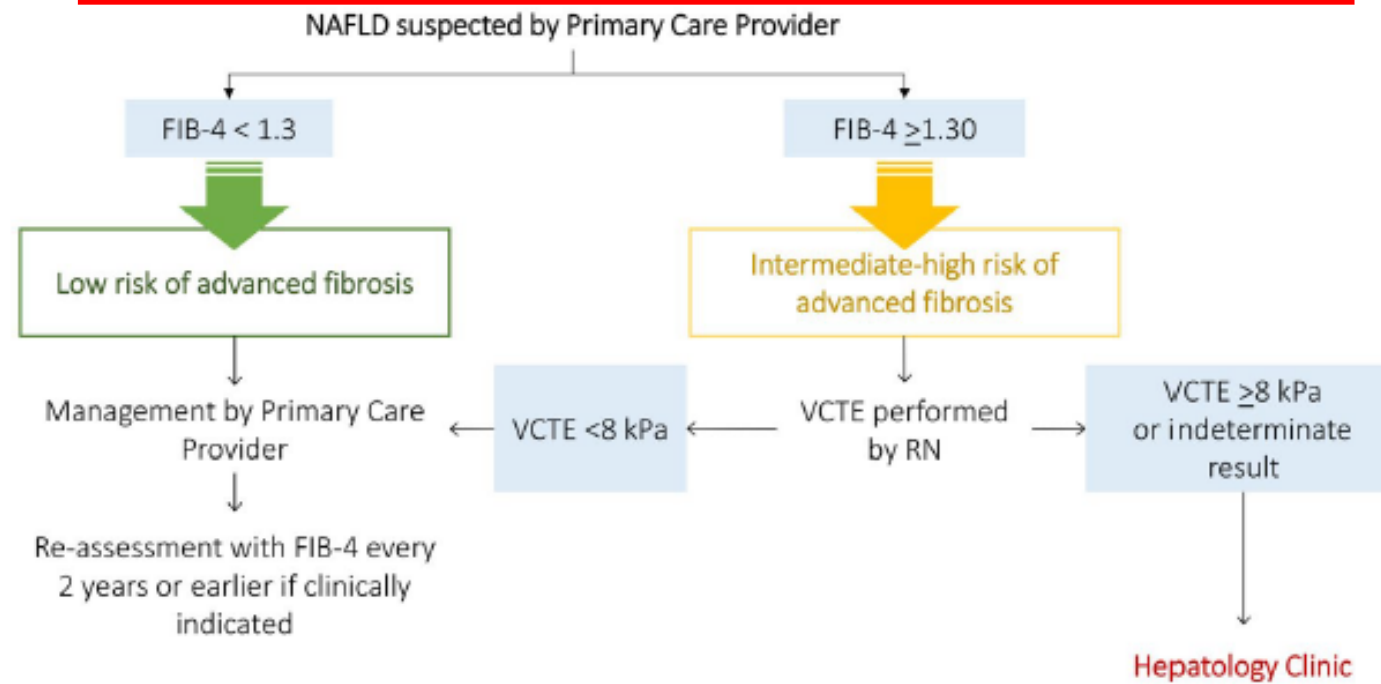
No clin signif fibrosis 77 105 122 124 123 125 127 133 142 149 158
 Clin signif fibrosis 54 55 60 62 60 58 62 64 70 69 72

No clin signif fibrosis 76 103 121 124 123 125 127 133 142 149 158
 Clin signif fibrosis 54 55 60 62 60 58 62 64 70 69 72



Impact of Implementing a “FIB-4 First” Strategy on a Pathway for Patients With NAFLD Referred From Primary Care

N=565 patients at risk for NAFLD identified by GPs
Up to 87% further specialistic assessment saved



*thanks to G. Sebastiani

FibroScan is “physical technology” – convenient, fast, BUT \$\$\$ to start-up



- Painless
- Rapid (5 min) – point of care
- Bedside/Outpatient

- Measures 1D velocity of low-frequency shear wave
- Directly related to tissue stiffness (fibrosis) – the stiffer the liver, the faster the shear wave propagates
- Limited by obesity, food intake, operator experience

How do you know if it's a "Good" Fibroscan?

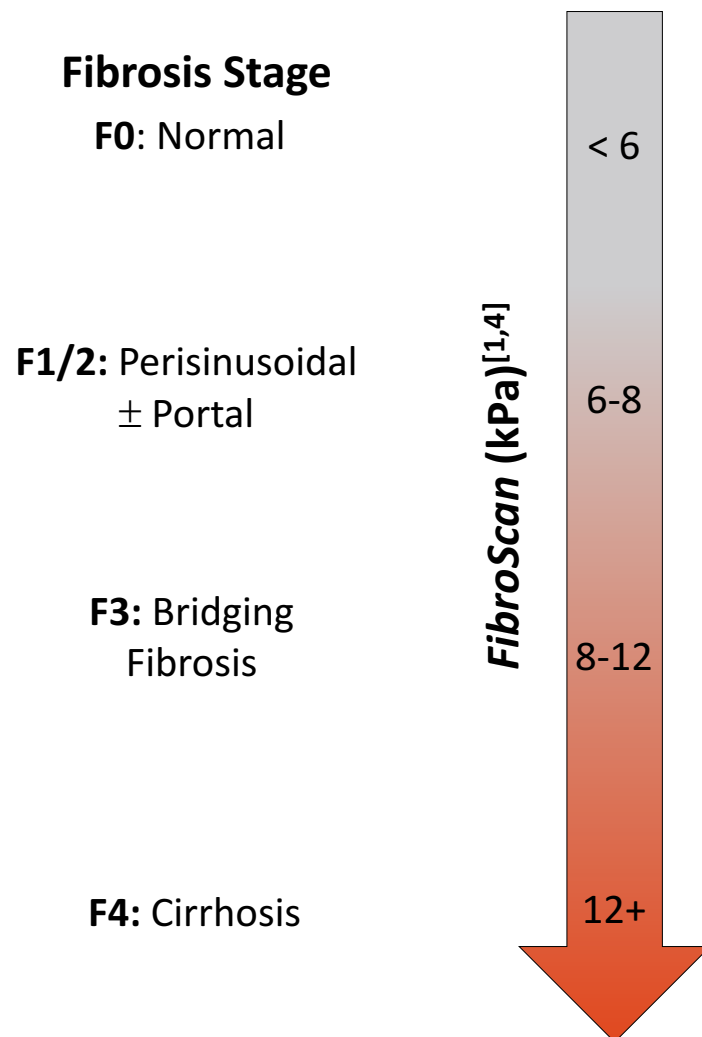
Stiffness (kPa)
Median value of 10 shots
3.9 Kilo Pascals



③ IQR * (kPa)
Interval around median
Contains 50% of valid shots
 $\leq 25\%$ of median value

- ① At least 10 shots
- ② Success Rate: $\geq 60\%$

FibroScan for NASH Fibrosis



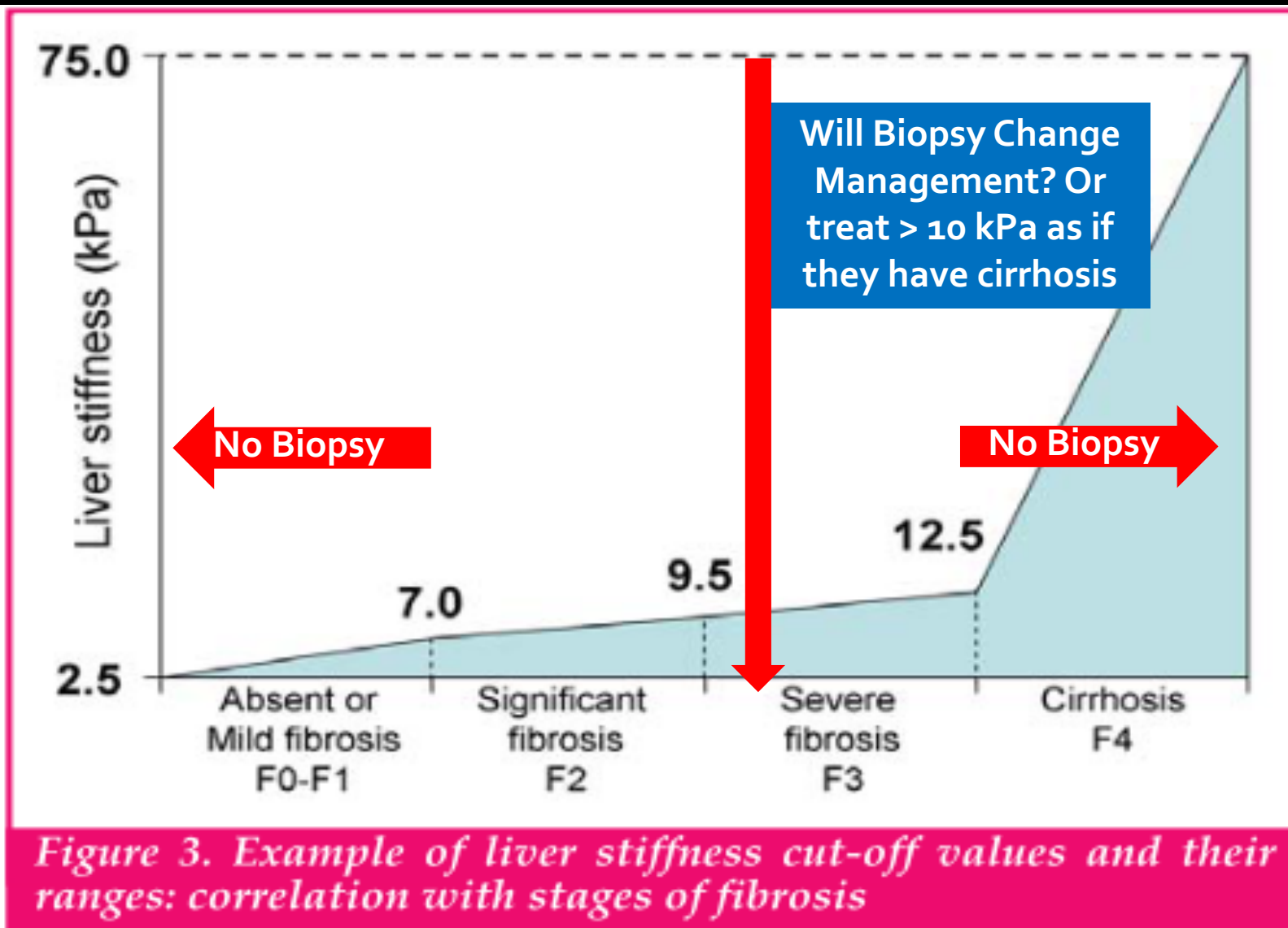
- Most reliable in **ruling out advanced hepatic fibrosis (NPV > PPV)**^[4]
 - Fibrosis unlikely with low value (< 6 kPa)
 - 12+ kPa predicts advanced fibrosis
- Higher values increase likelihood of more severe fibrosis, predicts risk of decompensation and complications^[2]
- **Overestimation of fibrosis can occur** in cases of hepatitis, cholestasis, liver congestion and if mass lesions are present in the liver^[2]
- Correlates well with portal pressure (20+ kPa)^[3]

Different Cut-off Values Exist For Different Diseases

Table 1.

Aetiology	F2	AUROC	F3	AUROC	F=4	AUROC	Ref
HBV ⁷	7.2	0.81	8.1	0.93	11.0	0.93	6
HCV ³⁰	7.1	0.83	9.5	0.90	12.5	0.95	
HCV ⁶	8.8	0.79	9.6	0.91	14.6	0.97	5
HCV/HIV ⁸	4.5	0.72	-	-	11.8	0.97	7
PBC or PSC ¹⁰	7.3	0.92	9.8	0.95	17.3	0.96	9
NAFLD ⁹	6.6	0.87	9.8	0.90	17.5	0.99	8

Using cut-off ranges instead of specific values for each disease is the “quick and dirty” method



Controlled Attenuation Parameter – “CAP” has a high accuracy for fat detection

- Steatosis should be documented whenever NAFLD is suspected
 - Predicts future T2DM, cardiovascular events and arterial hypertension
 - Quantification of fat content is of limited clinical relevance
 - Except as a surrogate of treatment effectiveness
 - **US is the preferred first-line diagnostic procedure for imaging of NAFLD, as it provides additional diagnostic information (EASL Grade A, Level 1)**
- A module developed to quantify hepatic steatosis with Fibroscan machine
- Result is expressed in decibel/m (dB/m) and interpreted according to cut-off values

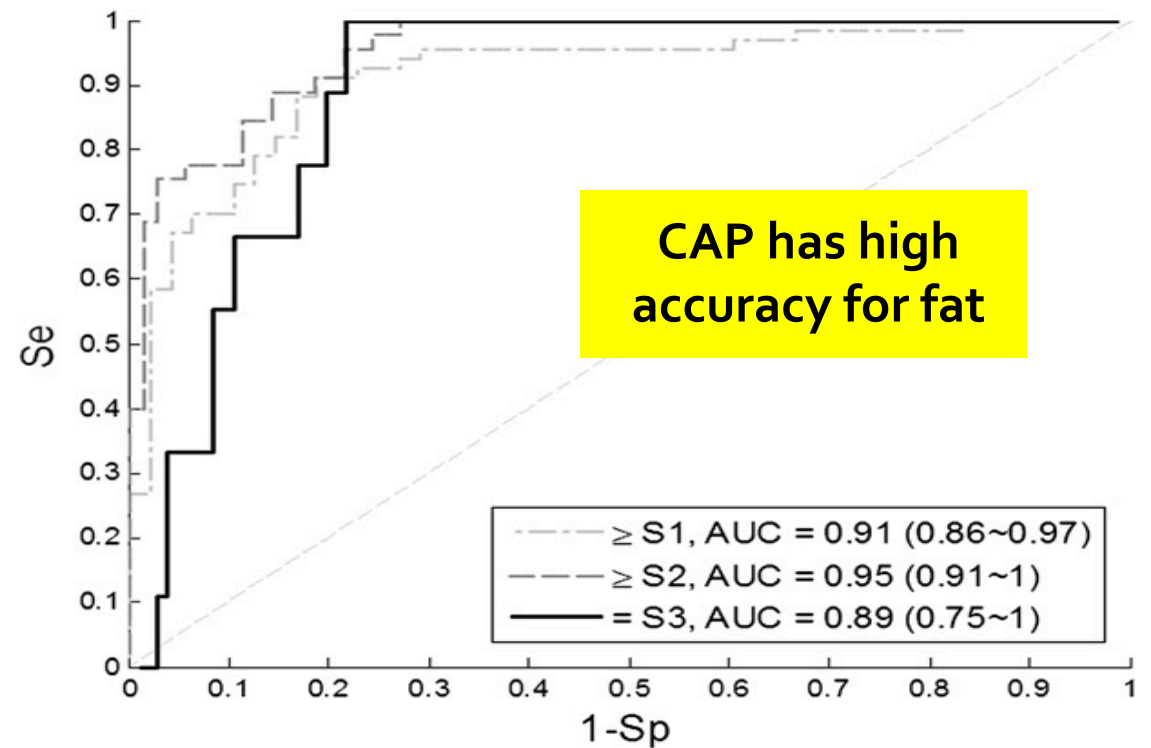
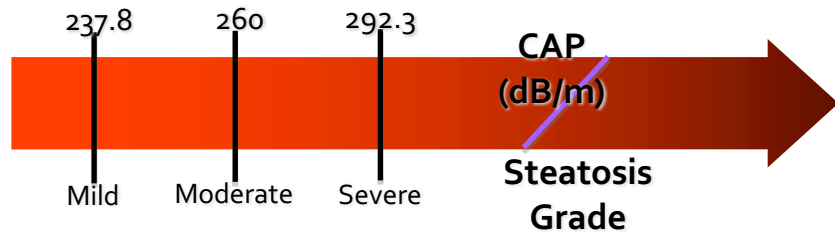


Fig. 5. ROC curves and AUC for the detection of steatosis grades $S_G \geq S1$, $S_G \geq S2$ and $S_G = 3$.

Use All Available Resources: No Single Test Accurately Assesses Hepatic Fibrosis in the Setting of NAFLD

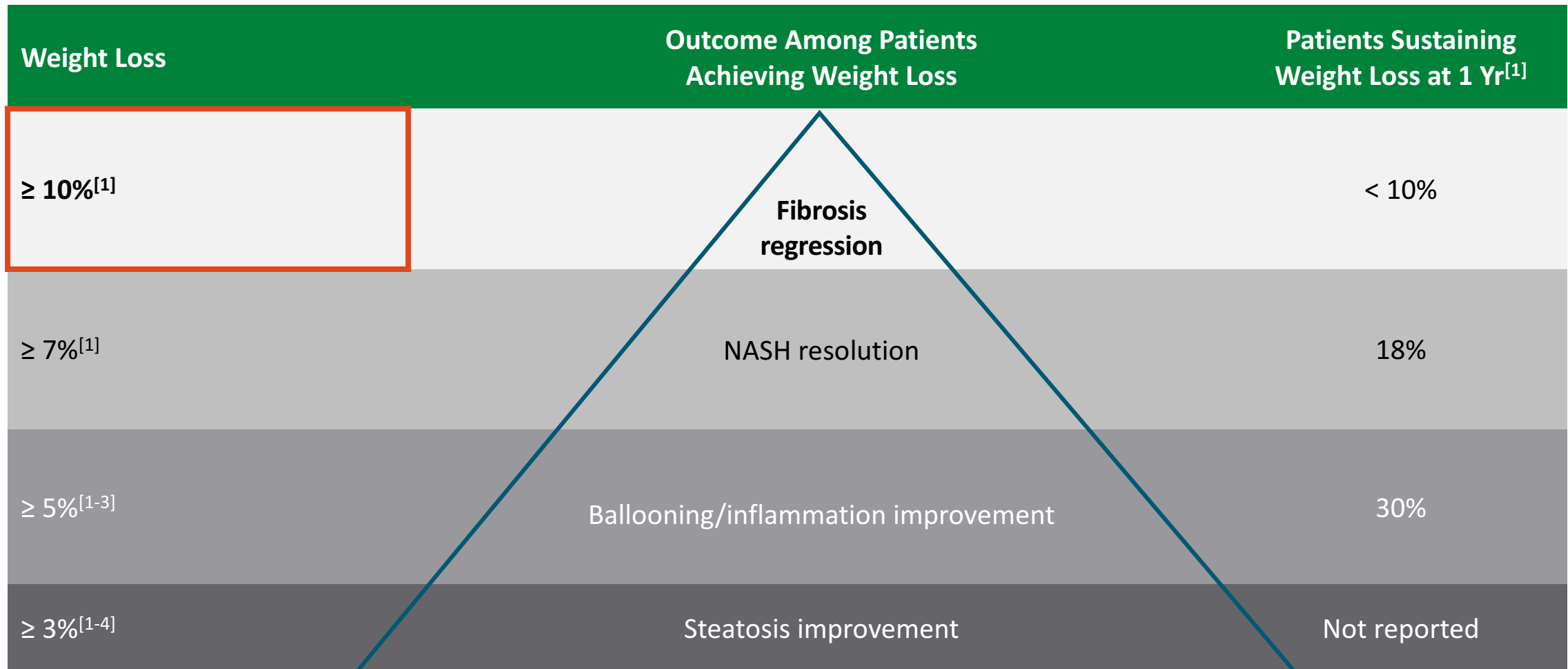
- AST/ALT ratio
 - > 1 suggests advanced fibrosis if no alcohol (F3/F4)
 - < 0.8 rules out advanced fibrosis
- APRI (AST/ULN divided by platelet count x 100)
 - $[(AST/ULN) / \text{platelet count}] \times 100$
 - > 2 suggests cirrhosis
- Platelet count
 - < 150,000 suggests portal hypertension
- Serum markers of fibrosis
- CT/MRI/ultrasound
 - Splenomegaly or PV diameter > 11 mm suggests portal hypertension
- Elastography; no consensus for NAFLD, but studies suggest the following cutoffs:
 - ≥ 7.5 to < 9.5 kPa suggests moderate fibrosis (F2)
 - ≥ 9.5 to < 12 kPa suggests precirrhosis (F3)
 - ≥ 12 kPa suggests cirrhosis (F4)

Family physicians are the front line MDs for NAFLD and referral for advanced therapies

- **F0-1 (minimal to mild fibrosis)**
 - Primary care, Lifestyle advice and dietitian referral, Treat metabolic risk factors, and Restage in 3 yrs
- **F2-3 (moderate fibrosis)**
 - Co-manage with family medicine, provide Lifestyle advice, Treat metabolic risk factors, refer or manage NAFLD-directed therapy
- **F4 (cirrhosis)**
 - Co-manage with family medicine, provide Lifestyle advice, Treat metabolic risk factors, refer or manage NAFLD-directed therapy and apply U/S screening for Hepatocellular cancer and refer for varices screening

7-10% BW loss may reverse fibrosis and NASH

3-5% BW loss may normalize blood tests



1. Vilar-Gomez. Gastroenterology. 2015;149:367. 2. Promrat. Hepatology. 2010;51:121.
3. Harrison. Hepatology. 2009;49:80. 4. Wong. J Hepatol. 2013;59:536.

Fat Matters, But Calories Count

Read the nutrition labels and compare the calories

1 Fig Cookie

- ◆ Fat free 51 calories
- ◆ Regular 56 calories

◆ 1/2 cup Vanilla Frozen Yogurt

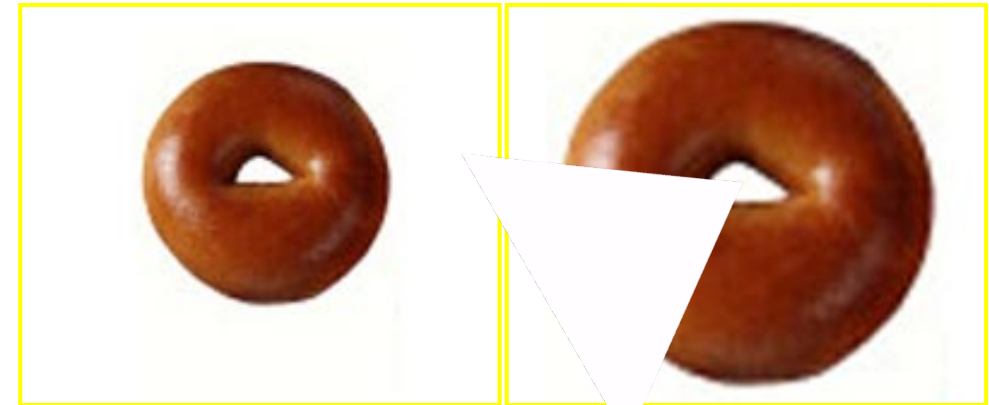
- ◆ Nonfat 100 calories
- ◆ Regular 104 calories

◆ 2 Tbsp. Peanut Butter

- ◆ Reduced Fat 187 calories
- ◆ Regular 191 calories

20 Years Ago

Today



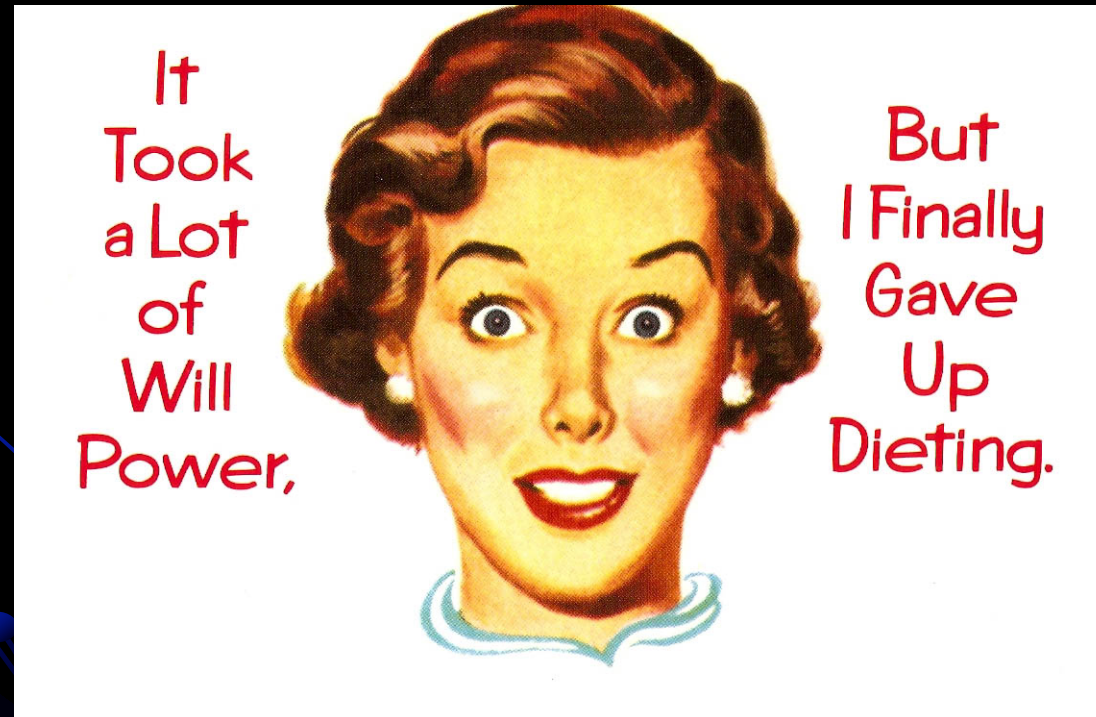
140 calories
3-inch diameter

350 calories
6-inch diameter

Calorie Difference: 210 calories

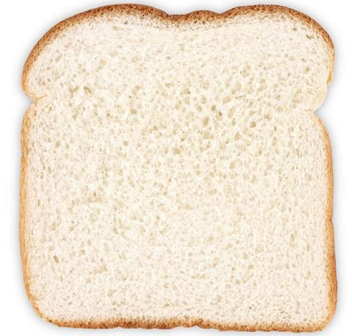
A Dietician and Exercise Therapy May Delay Decompensation

- Is realistic only in Stages 1-2 for weight loss (before ascites)
- Preservation of muscle mass** improves outcomes, especially if headed to transplantation



Diet changes are often more efficient than exercise

- 1 lb weight = 3500 cal
- Reduce calories by 500 cal/day x 7 days = 3500 cal/week
- = 1 lb loss/week
- 30 minutes exercise
 - Stationary bike
 - Elliptical trainer
 - Walking
- = 250-350 cal/session
- = 10+ hours/wk gym



**-100 calories
a day may =
10 lbs in a
year**

**Dietitian referrals are effective
? Exercise therapists?**

Vigorous, but not moderate exercise, correlates with less NASH (accept ANY!)

- Intensity may be more important than duration
- It is unknown the amount of exercise needed to decrease the progressive severity of NASH
 - Federal US guidelines: ≥ 150 min/wk moderate or ≥ 75 min/wk vigorous exercise
- N=609 bx'd NAFLD (232 M: 377F)
 - Patients meeting moderate exercise had same progression and fibrosis as the sedentary patients.
 - Vigorous exercise group had a significantly reduced OR of having NASH (OR 0.58 [0.35-0.97])
 - Doubling the recommended time of vigorous exercise to ≥ 150 min/week was better (OR 0.39 [0.18-0.88])





Energy restriction

- Calorie restriction (500–1,000/day)
- 7–10% weight loss target
- Long-term maintenance approach

Fructose intake

- Avoid fructose-containing food and drink

Coffee consumption

- No liver-related limitations

Comprehensive
lifestyle approach

Daily alcohol intake

- Strictly below 30 g men and 20 g women

Macronutrient composition

- Low-to-moderate fat
- Moderate-to-high carbohydrate
- Low-carbohydrate ketogenic diets or high protein

Physical activity

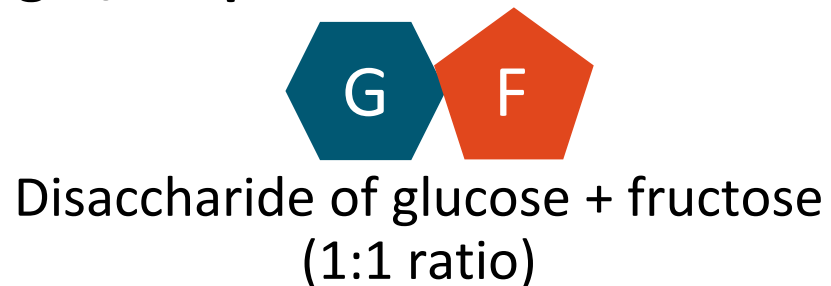
- 150–200 min/week moderate intensity in 3–5 sessions
- Resistance training to promote musculoskeletal fitness and improve metabolic factors

Starch vs Sugar vs High-Fructose Corn Syrup: Is Fructose the Problem? (Yes)

- **Starch/complex carb**



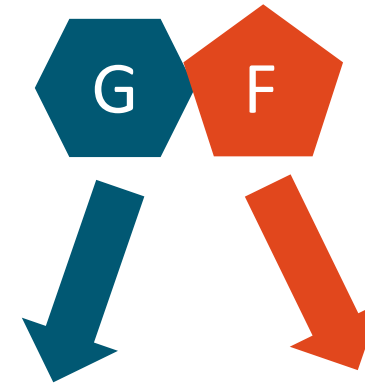
- **Sugar/simple carb**



- **High-fructose corn syrup**

Typically 55% fructose

Liver Metabolism Differs for Glucose vs Fructose



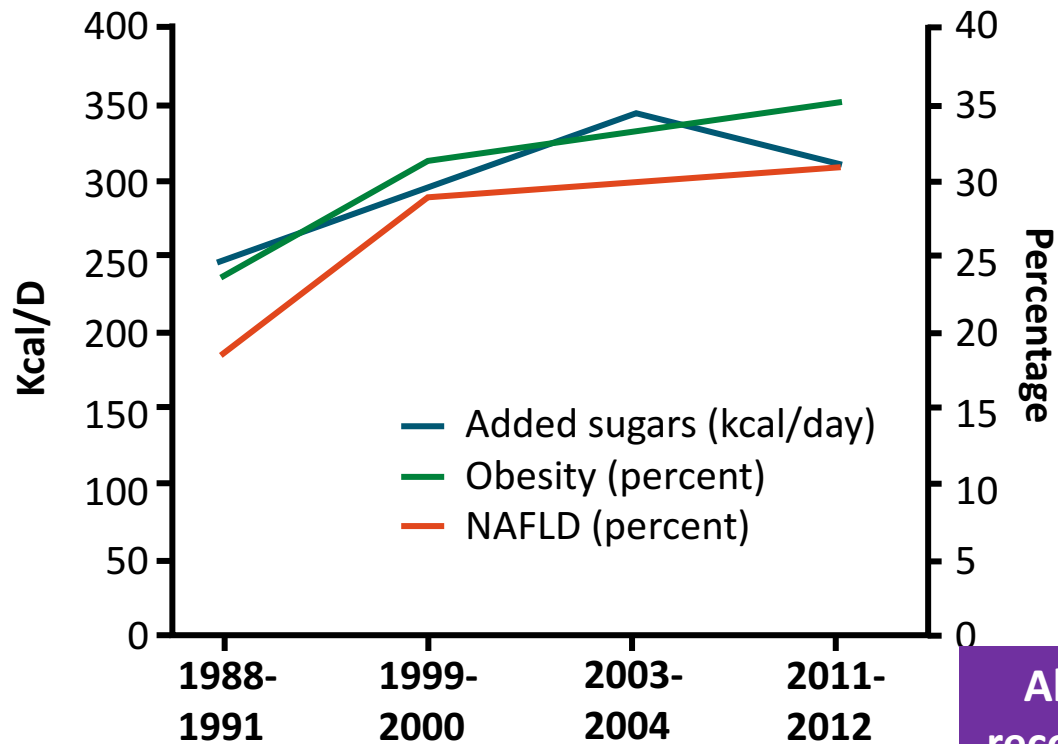
Mainly generates
liver glycogen
or passes to other tissue

Mainly contributes to
de novo lipogenesis,
generates uric acid

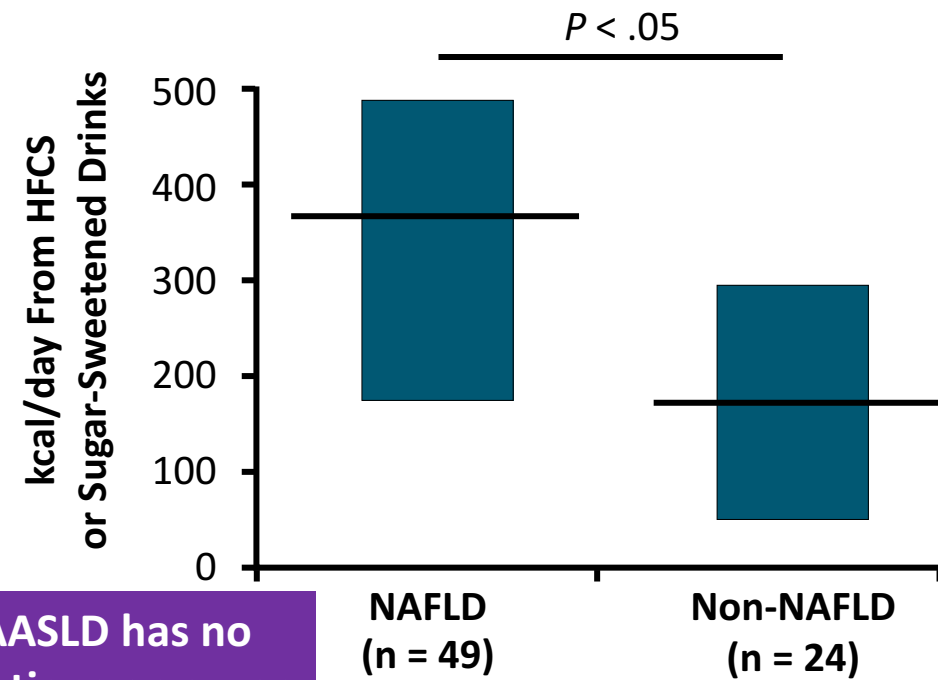
Case-Control Studies: High sugar = more NAFLD

Sugar Raises Insulin Levels, Which Correlates With NASH Histology

- Higher NAFLD prevalence correlates with rates of **added sugar consumption**^[1]



- Higher NAFLD prevalence correlates with **sugar-sweetened beverages or total fructose**^[2]



Although AASLD has no recommendations on sugar restriction, it makes sense to do so

Nonnutritive Sweeteners and Metabolic Disease

Obesity

- Positive correlation between **NNS consumption and obesity/T2D** in epidemiologic studies^[1]
 - Major issue of reverse causality, residual confounding
- Yet NNS **neutral or beneficial for weight loss** in controlled dietary intervention studies^[1]

ALT

- In Framingham Heart Study cohorts^[2]
 - **Diet soda not associated** with elevated ALT (after adjusting for BMI)
 - **Sugar-sweetened beverages significantly associated** with elevated ALT in dose-dependent manner (including after adjusting for BMI)

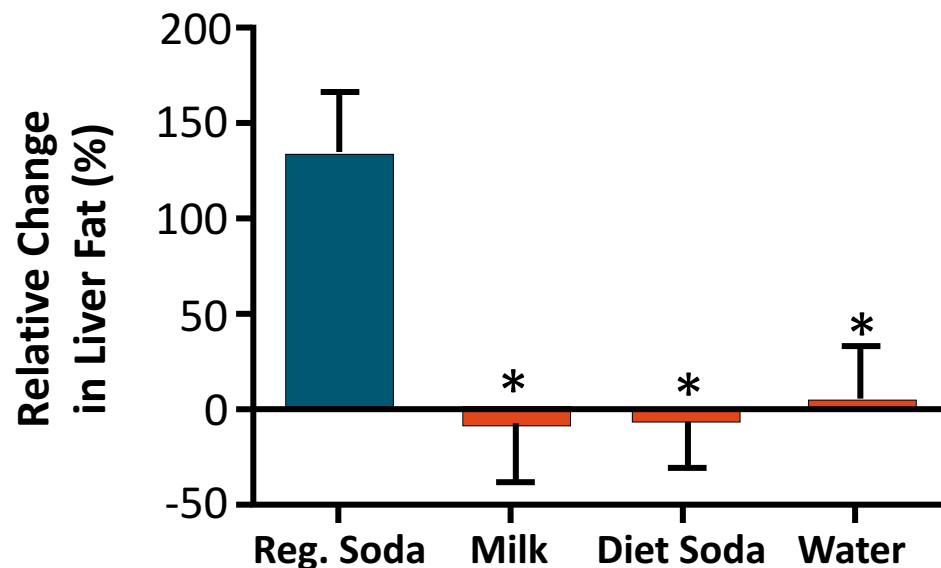
Potential Mechanisms of NNS-Induced Metabolic Dysfunction

- Activation of sweet taste receptors at both oral and extraoral sites (intestinal cells, pancreatic β cells)
 - Change in taste preference?
 - Increased insulin secretion?
 - Increased appetite?
- Alterations to microbiome
- Specific effects of particular sweeteners (ie, aspartame vs sucralose)
- Particular populations (ie, greater appetite increases in obese people?)
- Findings from human and animal studies are inconsistent

Sugar-Sweetened Beverages vs Nonnutritive Sweetener Beverages: Liver Fat Studies

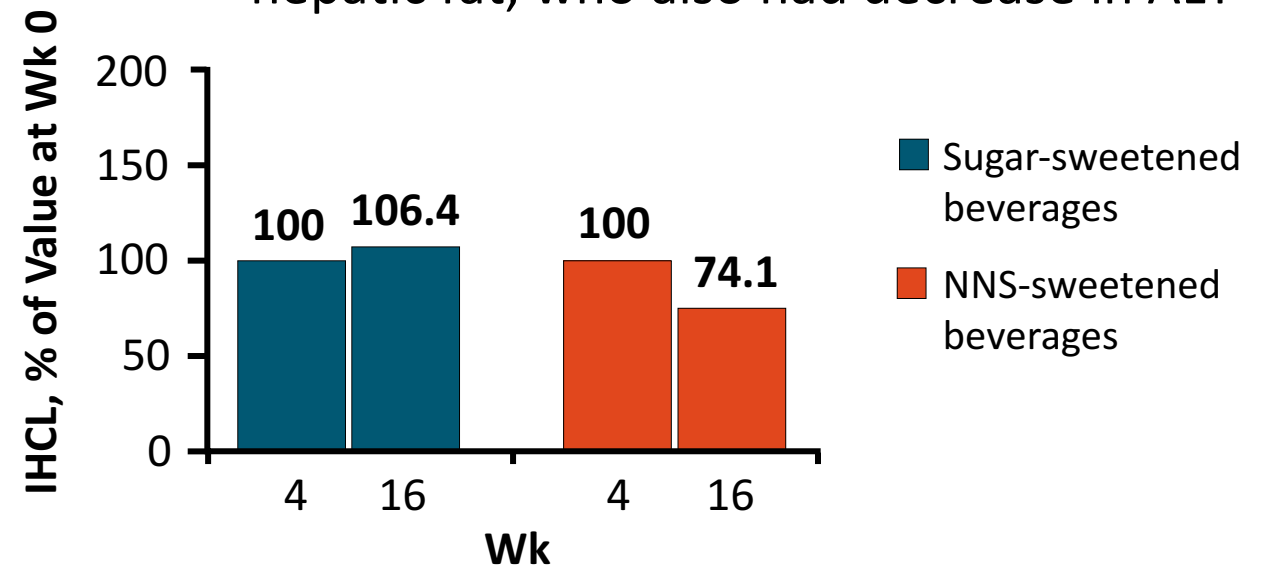
- **6-mo study^[1]:**
N = 60 overweight or obese participants given different drinks

- Regular soda increased liver fat; diet soda with NNS did not



- **12-wk study^[2]:**
N = 31 overweight participants (27 completed) replacing sugar with NNS

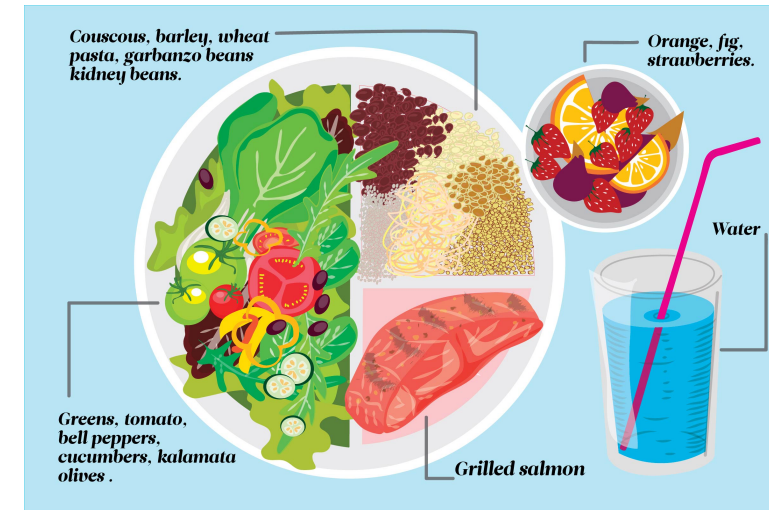
- Biggest effect in those with higher hepatic fat, who also had decrease in ALT



The Mediterranean Diet: A proportionally high consumption of olive oil, legumes, unrefined cereals, fruits and vegetables, moderate to high consumption of fish, moderate consumption of dairy products (mostly as cheese and yogurt), moderate wine consumption, and low consumption of non-fish meat products

- Patients with NAFLD more likely to have morbidity and mortality from **CVD** than from liver cause.

	Type of fat	Energy content
Mediterranean diet	↑ monounsaturated fatty acids and polyunsaturated fatty acids $\Omega 3$	40% fatty acids 40% glucids 20% proteins
Diet high in carbohydrates / low in fat	↓ acids saturated and unsaturated fatty acids especially $\Omega 6$	30% fatty acids 50% glucids 20% proteins



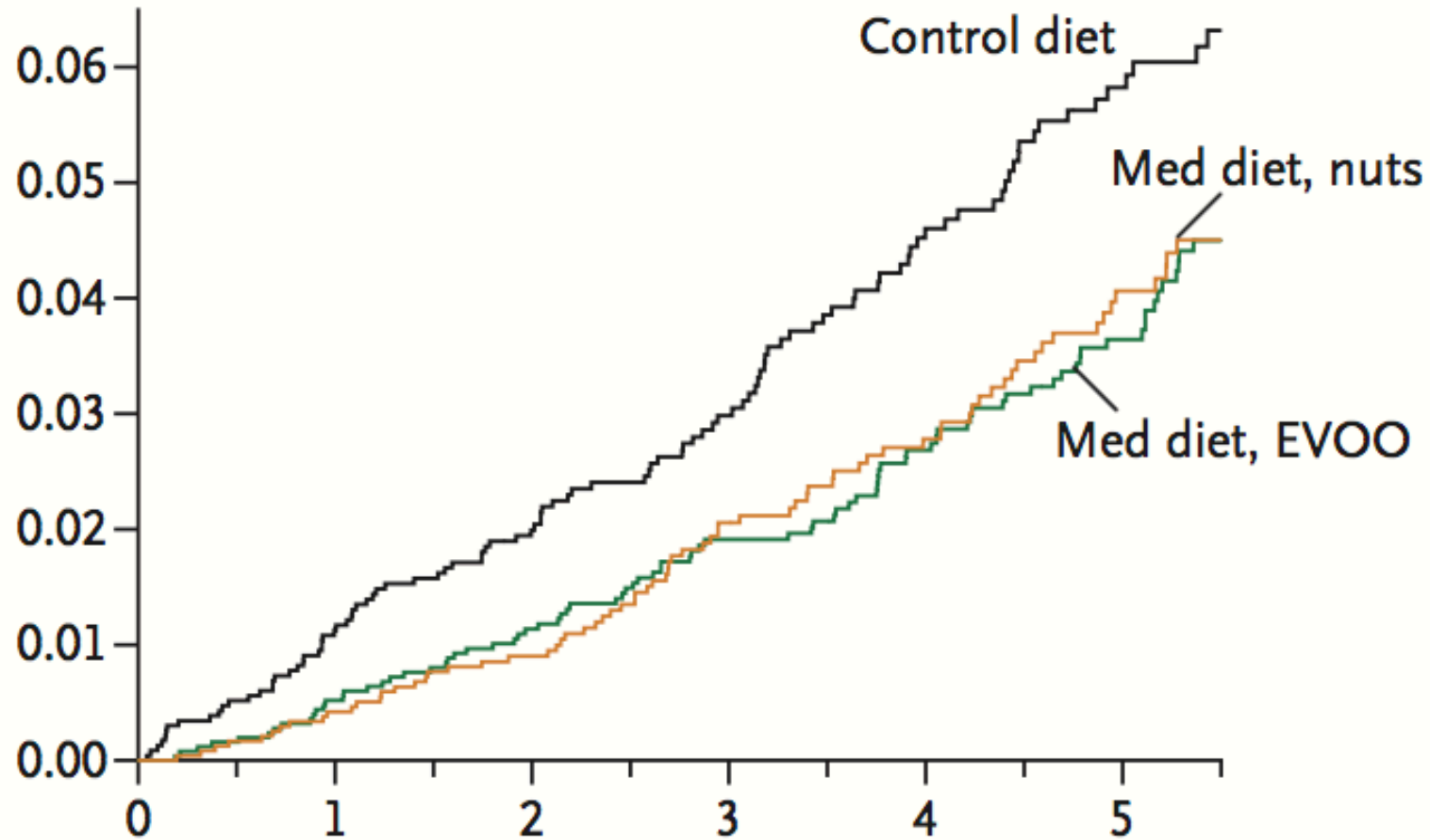
Mediterranean diet: A heart-healthy eating plan

Courtesy of Dr JM Giard, CHUM





Mediterranean Diet and Cardiovascular Disease



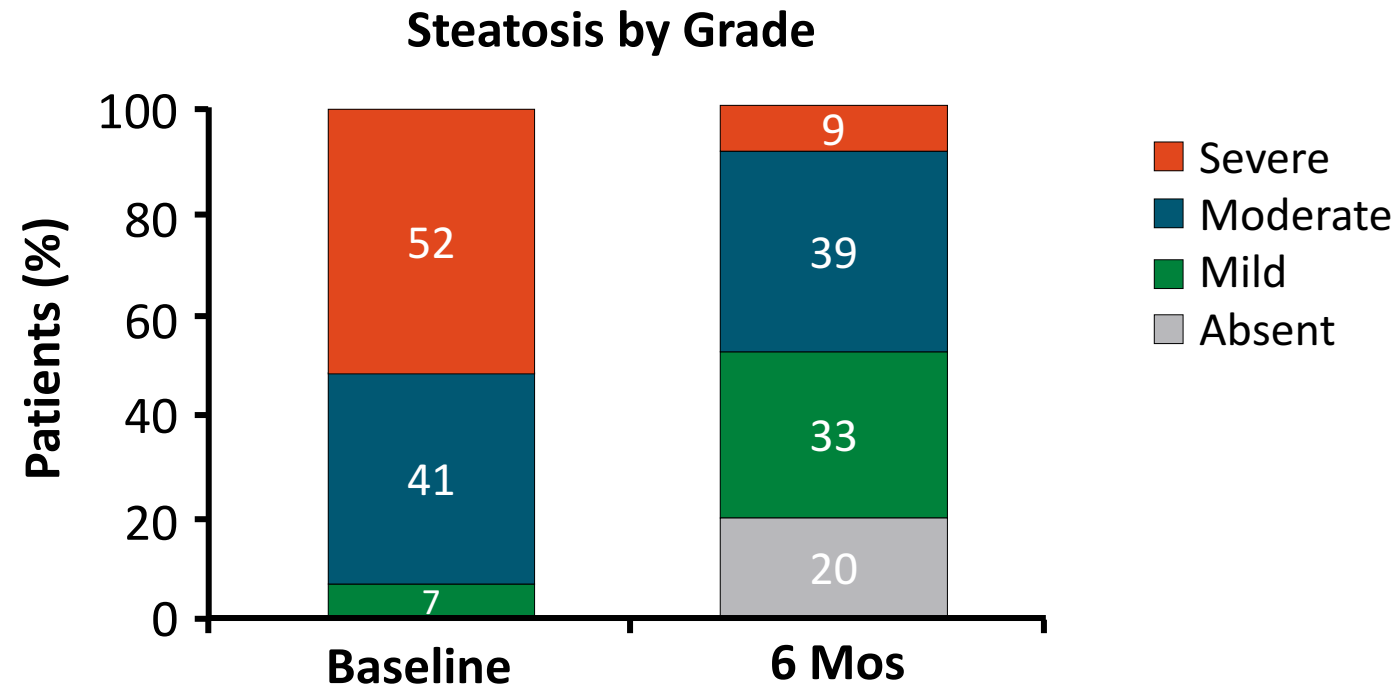
Mediterranean Diet in NAFLD: Observational Study Shows Reduction in liver fat

Design

- 6-mo observational study of **Mediterranean diet** intervention with monthly nutrition counseling in patients with NAFLD (N = 46)

Results

- Frequency of grade ≥ 2 steatosis decreased in > 80%, with resolution in 20%



Meta-analysis of Low-Carbohydrate Diets in NAFLD

Studies

- Meta-analysis of 10 international clinical trials of **low-carbohydrate (< 50%) diets** in patients **with NAFLD**
 - 10 evaluated ALT (n = 238)
 - 9 evaluated AST (n = 216)
 - 5 evaluated GGT (n = 91)
 - 4 evaluated intrahepatic lipid content (n = 50)

Results

- Low-carbohydrate diets associated with **significant reduction in intrahepatic lipid content** by -11.53% (95% CI: -18.10% to -4.96%; $I^2 = 83.2%$)
- Nonsignificant reductions in serum ALT, AST, GGT

Mediterranean Diet in NAFLD: Comparison to Low-Fat/High-Carb Diet

Design

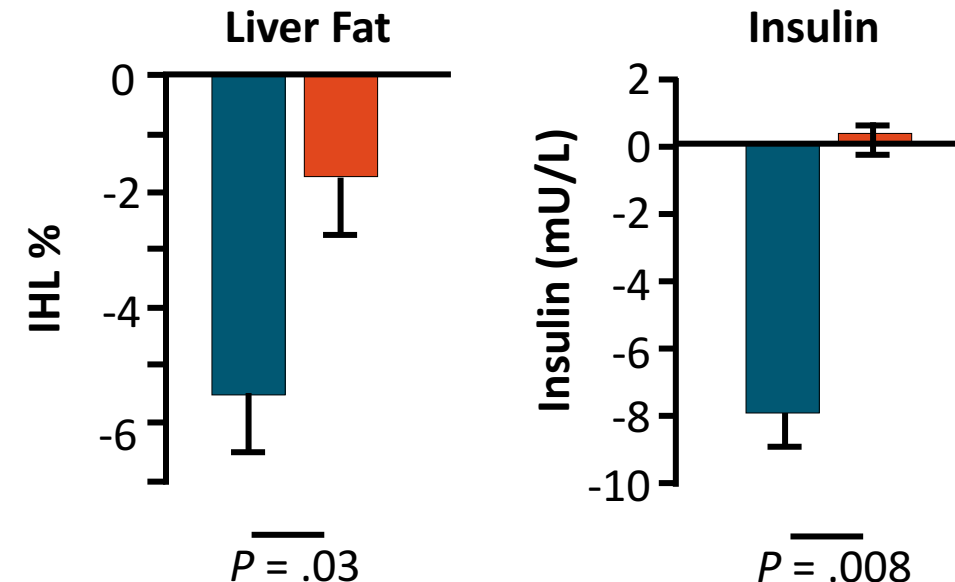
- 6-wk cross-over study in nondiabetic patients with biopsy-proven NAFLD (N = 12)
- Mediterranean diet (higher in monounsaturated fatty acids)* vs low-fat/high-carb diet**

*Fresh fruits and vegetables, whole grains; less meat and dairy than a typical Western diet; very little red meat.

Results

- Comparable minor weight loss, significantly **greater decreases in liver fat and serum insulin with Mediterranean diet**

■ Mediterranean diet ■ Low-fat/high-carb diet



Head-to-Head Comparisons of Low-Carb vs Low-Fat Diets are INCONSISTENT

Study Population	N	Mos	Comparison	Results	Difference Between Diets?
Obese with insulin resistance ^[1]	52	4	60% carb + 25% fat vs 40% carb + 45% fat	<ul style="list-style-type: none"> Significant reductions in weight, SSPG, circulating insulin, serum ALT ALT reductions greater with 40% carb diet 	Yes
Overweight and obese, otherwise healthy ^[2]	170	6	Reduced carb vs reduced fat	<ul style="list-style-type: none"> Similar reductions in weight, body fat, visceral fat, ALT, intrahepatic lipids 	No
Obese with or without NAFLD ^[3]	162	3	Low fat vs low carb	<ul style="list-style-type: none"> Reductions in weight, BP, cholesterol In patients with NAFLD, similar reductions in glucose, triglycerides, transaminases 	No

**Initial promise, inconsistent results:
Losing weight is key; unclear whether type of diet is important**

Do Low-Fat Diets Better Protect From CVD? (maybe)

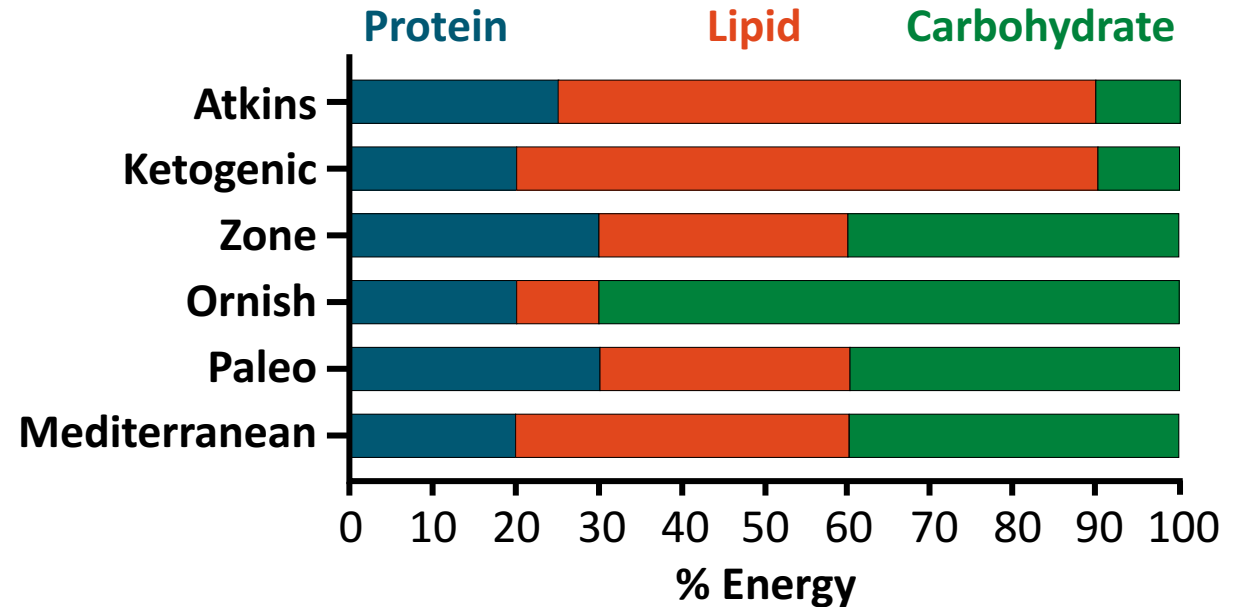
- Meta-analysis of randomized, controlled trials comparing **low-carb** vs **low-fat** diets in overweight and obese subjects for ~ 1 yr (17 trials; N = 1797)
- **Low-carb** diets superior for metabolic syndrome components (weight loss, HDL, TG, and BP); **low-fat** diets superior for lowering LDL and total cholesterol
 - ASCVD risk reduced by both diets but more by **low carb**

	Low Carb		Low Fat		Between Group Differences*	
	Mean (95% CI)	P Value	Mean (95% CI)	P Value	Mean (95% CI)	P Value
BMI, kg/m ²	-2.8 (-3.3 to -2.2)	< .0001	-2.1 (-2.5 to -1.7)	< .0001	-0.7 (-1.1 to -0.3)	.0016
Cholesterol, mg/dL	-4.2 (-9.4 to 1.1)	.11	-13.8 (-21.6 to -5.9)	.002	9.1 (2.6 to 15.7)	.006
HDL, mg/dL	4.4 (2.3 to 6.5)	.0004	-1.0 (-3.2 to 1.2)	.35	5.1 (3.5 to 6.7)	< .0001
LDL, mg/dL	-1.8 (-6.1 to 2.6)	.39	-10.9 (-17.3 to -4.4)	.0025	8.6 (3.6 to 13.7)	.0008
TG, mg/dL	-41.1 (-54.7 to -27.5)	< .0001	-11.3 (-18.8 to -3.7)	.006	-28.8 (-39.1 to -18.5)	< .0001
Systolic BP, mm Hg	-6.7 (-9.0 to -4.3)	< .0001	-4.4 (-7.2 to -1.5)	.006	-1.7 (-3.5 to 0.2)	.08

*Positive mean value denotes greater drop with low fat; negative mean value denotes greater drop with low carb.

Popular Diet Strategies

- Popular diets employ different strategies:
 - **Macronutrient** manipulation
 - High protein or low carb
 - **Timing** manipulation
 - Intermittent fasting
 - **Food/food group** restrictions
 - Gluten free, paleo



- Factors for successful weight loss
 - Adherence
 - Negative energy balance
 - High-quality foods

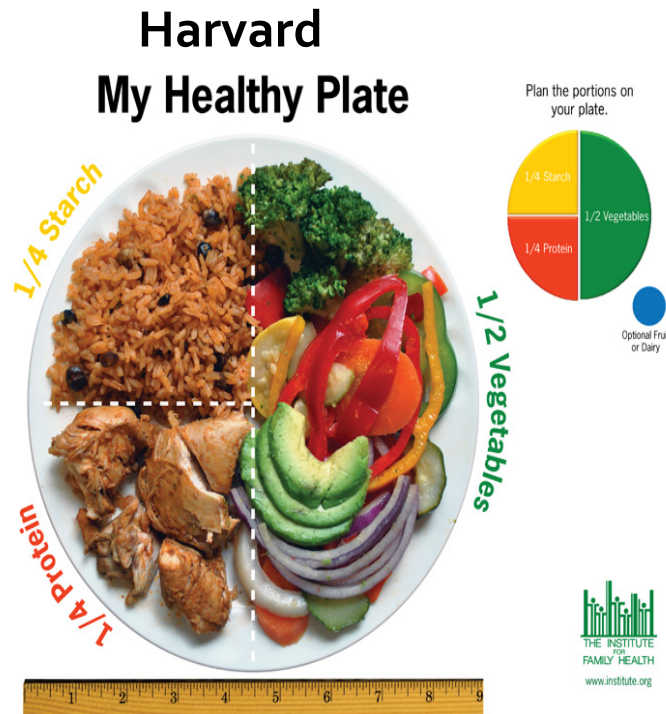
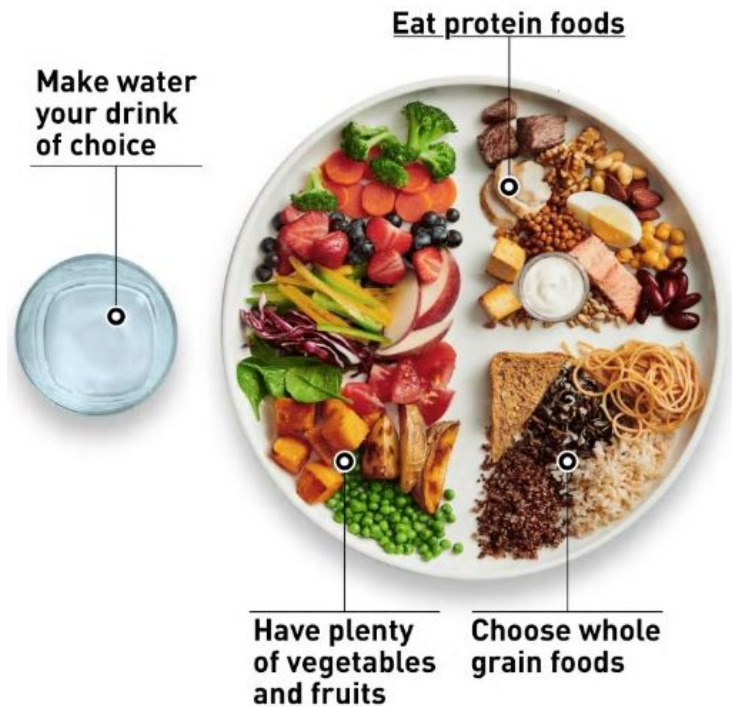
No Diet has proven* superior, and weight loss is the key

The Mediterranean and DASH diets have lower NAFLD

- Low dietary sugar? } ■ Theoretical reasons to limit sugar (esp fructose)
- Nonnutritive sweeteners? } ■ Theoretical reasons to avoid; practical reasons to use in moderation to limit sugar
- Low-caloric, low-fat, or low-carbohydrate diet? } ■ No diet has consistent superiority: Provided **simple sugars** and **total calories** are reduced, key is **weight loss**
- Popular diets? } – **Individualize** to patient preference
- Weight watchers or Jenny Craig lack data but work
- Vitamin supplementation? } ■ Vitamin E recommended for nondiabetic adults with NASH, but consider risks

Canada Food Guide 2019

Canada's food guide recommendations



- “Healthy eating” (instead of “dieting”)
- Mediterranean diet
- Harvard Healthy Eating Plate
- Eliminate sugar-sweetened beverages and drink water/tea
- Use healthy oils (olive, canola)
- Minimize restaurants or split portions
- Avoid fast food - Calorie dense (1300 cal and more fat than a stick of butter in some commonly marketed burgers)
- Avoid eating at night
- Portion control – 9” plate



Coffee reduces enzymes, fibrosis progression and improves response rates (to PEG IFN)



- Lower AST/ALT and GGT

Arnesen E. Scand J Clin Lab Invest. 1986, Casiglia E. Eur J Epidemiol. 1993

Honjo S. J Clin Epidemiol. 2001, Klatsky AL. Arch Intern Med. 2006

Ruhl CE. Gastroenterology. 2005, Tanaka K. Int J Epidemiol. 1998

- Slower progression of liver disease in NASH or HCV

Molloy JW. Hepatology 2012, Freedman ND. Hepatology. 2009

- Reduces liver fibrosis in a number of liver diseases

Torres DM. Gastroenterology 2013

- Reduces risk of HCC (meta-analysis)

Larsson SC, Wolk A. Gastroenterology 2007

- Improved response to PEG IFN based therapy

- * > 3 cups coffee/day in the HALT-C trial

Freedman Gastro 2011

≥ 2 cups of coffee/day (not espresso) may reduce all-cause mortality



- N=229,119 men and 173,141 women (NIH-AARP Diet and Health Study)
- 50 to 71 yo, Coffee consumption was assessed once at baseline.
- 5,148,760 person-years of follow-up between 1995 and 2008

HR Death	Men	Women
<1 cup	0.99	1.01
1 cup	0.94*	0.95
2-3 cups	0.90*	0.87*
4-5 cups	0.88*	0.84*
6+ cups	0.90*	0.85*

- * Less deaths due to heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infections, but not for deaths due to cancer.



Coffee may be protective in NAFLD



Reference	Year	Design	n	Country	Details
Anty et al.	2012	Cross-sectional	195	France	Filter coffee protects against fibrosis (not espresso)
Birerdinc et al.	2011	Cross-sectional	1782	USA	↓ risk of NAFLD
Catalano et al.	2010	Case-control	157/ 153	Italie	↓ steatosis on US
Gutierrez-Grobe et al.	2012	Case-control	57/73	Mexico	↓ risk of NAFLD
Molloy et al.	2012	Cross-sectional	306	USA	↓ risk of fibrosis



Moderate alcohol consumption (1 drink/d) may be protective in NAFLD



- NAFLD is a CV risk factor
- Moderate alcohol consumption reduces CV risk
- Do patients with NAFLD have to abstain from alcohol or can they consume moderately?
- 7211 non-life drinkers vs 4543 modest drinkers - cross-sectional study; follow-up study with histology n = 483
- Moderate = 1 drink / day

Note: most of the benefits seem to be through the wine

Histology	OR (95% CI)
Steatohepatitis	0.52 [0.36-0.76]
Fibrosis	0.56 [0.41-0.78]
Ballooning	0.62 [0.45-0.87]
Portal inflammation	0.69 [0.48-1.00]

Vitamin D and NAFLD

- Patients with NAFLD often obese, high risk for vitamin D deficiency
 - Endocrine Society guidelines: screen for vitamin D deficiency if BMI ≥ 30 mg/m², treat if vitamin D < 20 ng/mL^[1]
- Vitamin D receptor highly expressed in hepatic stellate cells, where it is antifibrogenic in preclinical studies

Lack of data in NAFLD/fibrosis

- But studies underway^[2]

Data in PCOS

- Randomized, double-blind, placebo-controlled study of vitamin D supplementation in women with PCOS (N = 40) for 3 mos^[3]
- Vitamin D significantly decreased ALT

Vitamin E > pioglitazone in improving histology and liver enzymes (PIVENS Trial)

- PIVENS (Pioglitazone, Vitamin E therapy in Non-alcoholic steatohepatitis) trial
- RCT trial of (n=247) NASH patients without DM for 96 wks
 - Pioglitazone 30 mg/d (n=80)
 - Vit. E 800 IU/d (n=84)
 - Placebo (n=83)
 - All had bx proven NASH, and >90% had post treatment bx's
- primary end point — an improvement in histology (decrease in NAFLD activity score ≥ 2 points (with a decrease of at least 1 point in cytologic ballooning) and no worsening of fibrosis

Vitamin E improves liver histology and liver enzymes in nondiabetic patients with NASH

- Primary endpoint met:
 - Vitamin E 43% > pioglitazone 34% > placebo 19%
 - Vitamin E (vs. Placebo) had improved steatosis ($P = .005$), inflammation ($P = .02$), ballooning scores ($P = .01$), and serum ALT ($P = .001$), but no improvement in fibrosis scores
- **Pioglitazone did not meet the primary endpoint (improvement in fibrosis scores)**
 - Side effect of weight gain
 - Secondary endpoints: was superior to placebo in improving steatosis ($P < .001$), inflammation ($P = .004$), ballooning scores ($P = .08$), and serum ALT ($P < .001$).

All therapies currently are “Off Label” for NAFLD

Reported Safety Profile

Vitamin E (800 IU/day)

- Possible increased all-cause mortality risk at > 800 IU/day^[1]
- Increased hemorrhagic stroke risk^[2]
 - Also shows reduced ischemic stroke risk
- Increased prostate carcinoma risk (HR vs placebo: 1.17; 99% CI: 1.004-1.36; $P = .008$)^[3]

Pioglitazone

- Edema, weight gain (~ 2-3 kg over 2-4 yrs)^[4]
- Risk of osteoporosis in women^[5]
- Equivocal bladder cancer risk
 - Increased in some studies^[6]
 - No association in most studies^[7,8]

Vitamin E is not recommended for NASH in diabetic patients, NAFLD without a liver biopsy, NASH cirrhosis, or cryptogenic cirrhosis

1. Miller. Ann Intern Med. 2005;142:37. 2. Schurks. BMJ. 2010;341:c5702. 3. Klein. JAMA. 2011;306:1549.
4. Bril. Diabetes Care. 2017;40:419. 5. Yau. Curr Diab Rep. 2013;13:329. 6. Tuccori. BMJ. 2016;352:i1541.
7. Lewis. JAMA. 2015;314:265. 8. Davidson. Diabetes Complications. 2016;30:981.



Treatment should be indicated in patients with Progressive NASH, Early-stage NASH with risk of fibrosis progression and Active NASH with high necroinflammatory activity



*NAFLD does not increase statin risk of drug-induced liver injury.^[6]

1. Promrat. Hepatology. 2010;51:121. 2. Vilar-Gomez. Gastroenterology. 2015;149:367. 3. Lassailly. Gastroenterology. 2015;149:379. 4. Musso. Hepatology. 2010;52:79. 5. Ratziu. J Hepatol. 2010;53:372. 6. Bril. J Clin Endocrinol Metab. 2017;102:2950. 7. Zhang. Scand J Gastroenterol. 2013;48:78. 8. Chen. Medicine (Baltimore). 2015;94:e1013. 9. Sanyal. NEJM. 2010;362:1675. 10. Cusi. Ann Intern Med. 2016;165:305. 11. Armstrong. Lancet. 2016;387:679.

All therapies currently are “Off Label” for NAFLD

Targeting Insulin Resistance

Compound	Mechanism of Action	Trial	Primary Endpoint(s)	AASLD Recommendation as NASH Treatment
Metformin	Multiple	Multiple studies	Various	Not recommended
Pioglitazone	PPAR γ agonist	PIVENS Multiple studies	Improvement in NAS \geq 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

Targeting Oxidative Stress

Compound	Mechanism of Action	Trial Name	Primary Endpoint(s)	AASLD Recommendation as NASH Treatment
Vitamin E	Antioxidant	PIVENS TONIC	Improvement in NAS \geq 2 without fibrosis worsening	May be used in nondiabetic adults with biopsy-proven NASH

Lipid-lowering agents: Statins have not been adequately tested in NASH

*Phase IIb.

NASH Treatments Currently in Phase III Investigations

Agent	MoA	Trial	N	Primary Endpoint(s)	Time Point
Cenicriviroc	CCR2/5 antagonist	AURORA ^[1]	2000	≥ 1 stage fibrosis improvement with no NASH worsening	12 mos
Elafibranor	PPARα/σ agonist	RESOLVE-IT ^[2]	2000	Resolution of NASH with no fibrosis worsening	72 wks
Obeticholic acid	FXR agonist	REGENERATE ^[3]	2370	≥ 1 stage fibrosis improvement with no NASH worsening; resolution of NASH with no fibrosis worsening	18 mos
		REVERSE ^[4]	540	≥ 1 stage fibrosis improvement with no NASH worsening	12 mos
Selonsertib	ASK1 inhibitor	STELLAR 3 ^[5]	808	≥ 1 stage fibrosis improvement with no NASH worsening; event-free survival	48 wks
		STELLAR 4 ^[6]	883	NASH with compensated cirrhosis	240 wks

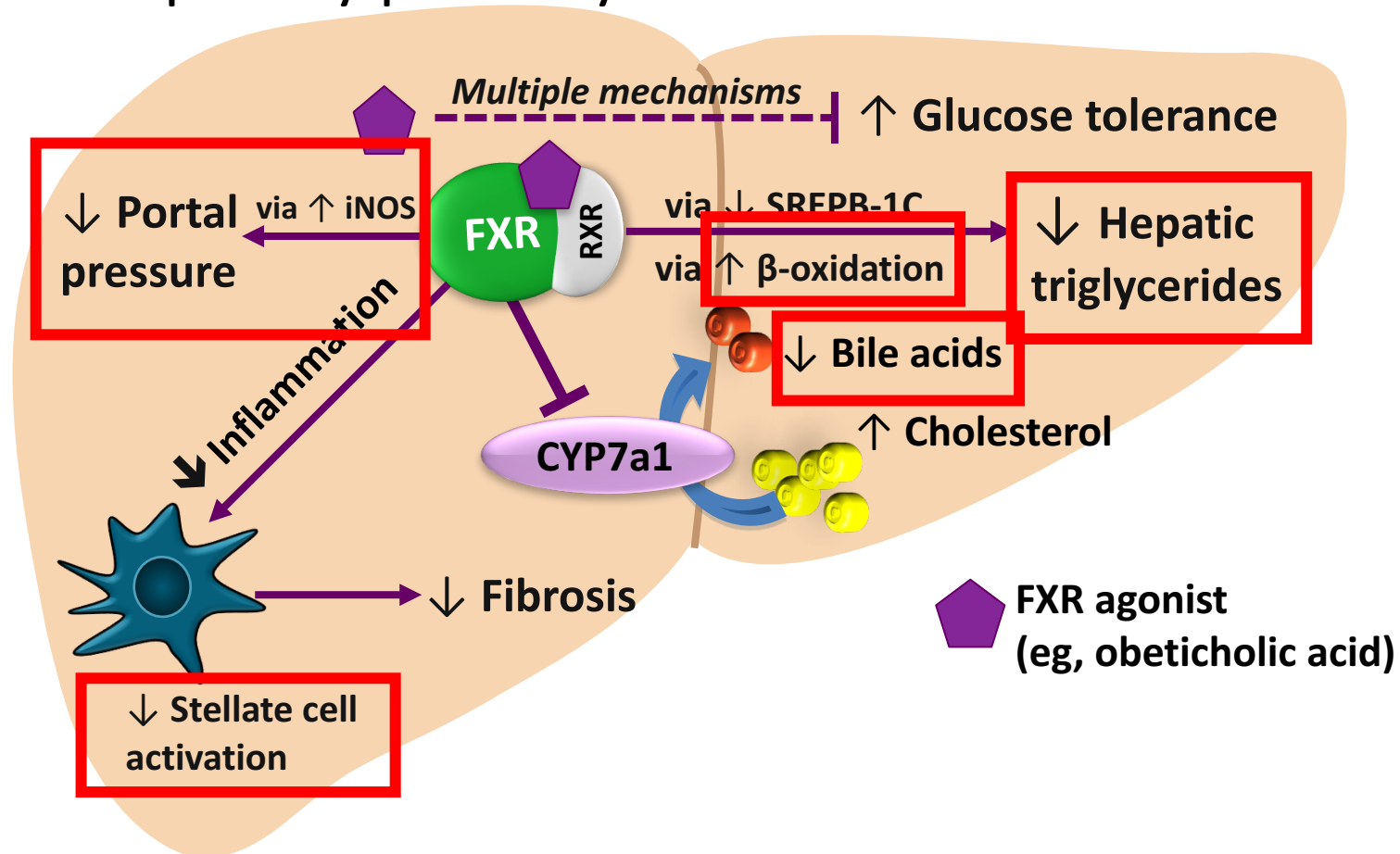


Phase III/IV studies use adaptive design

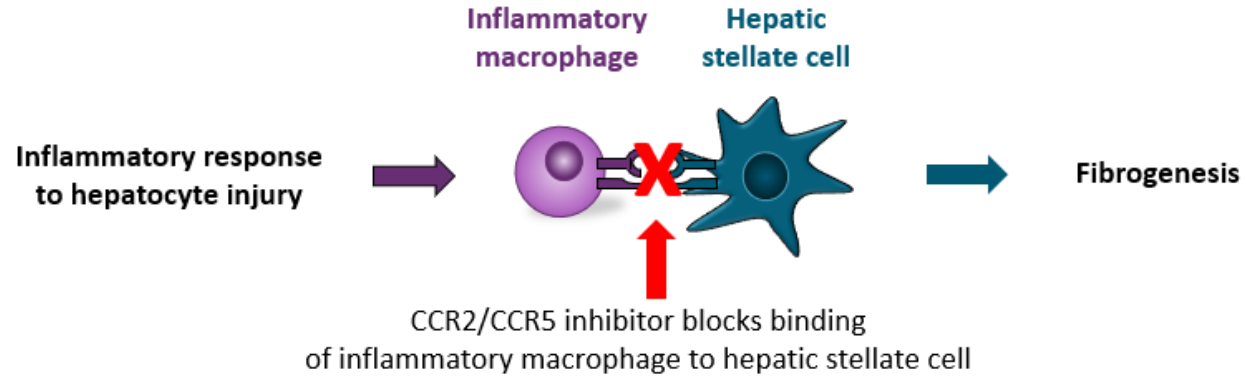
- Histologic endpoints for Subpart H conditional approval
 - Clinical endpoints for full approval

Obeticholic Acid: FXR Agonist

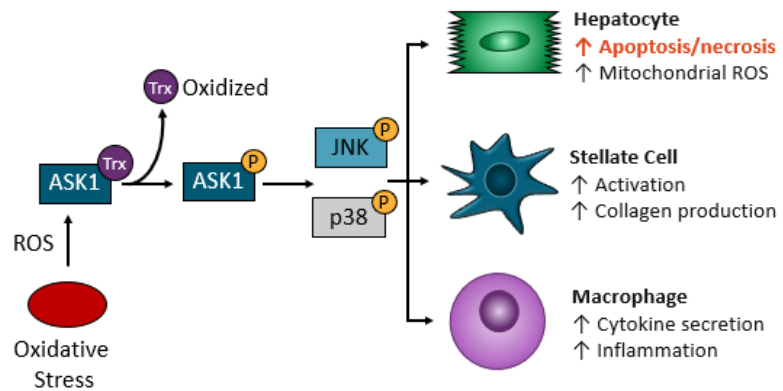
- FXR central to multiple key pathways in animal models



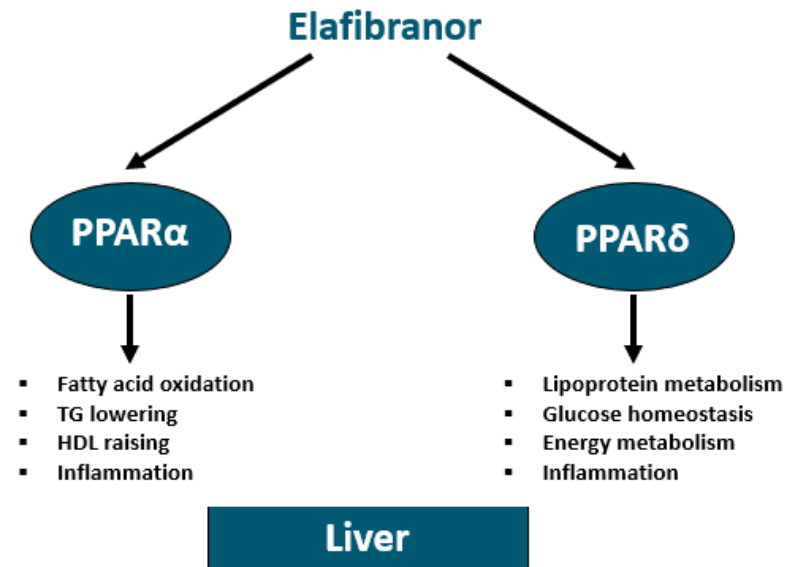
Cenicriviroc: CCR2/CCR5 Inhibitor



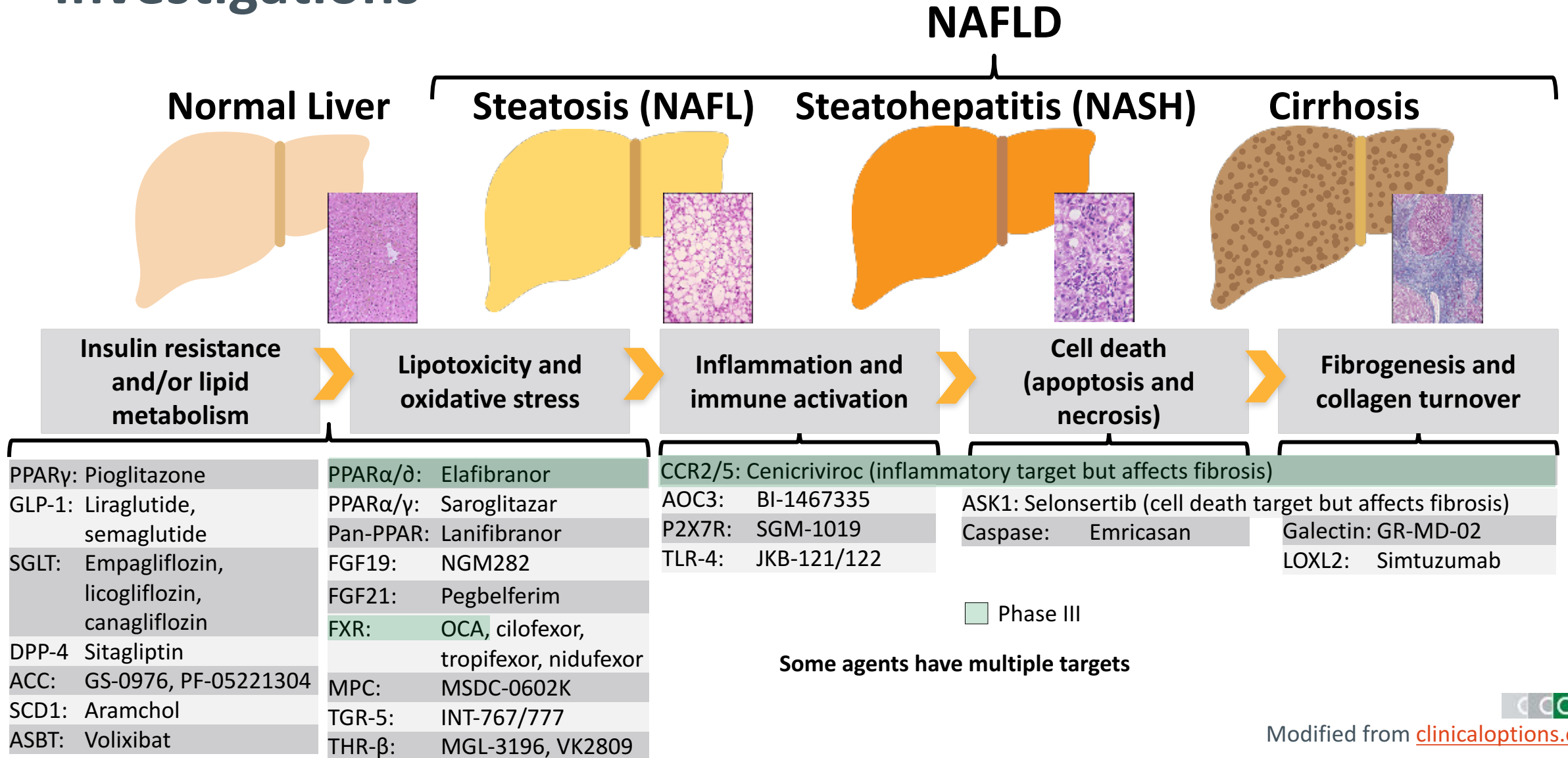
Selonsertib: ASK1 Inhibitor



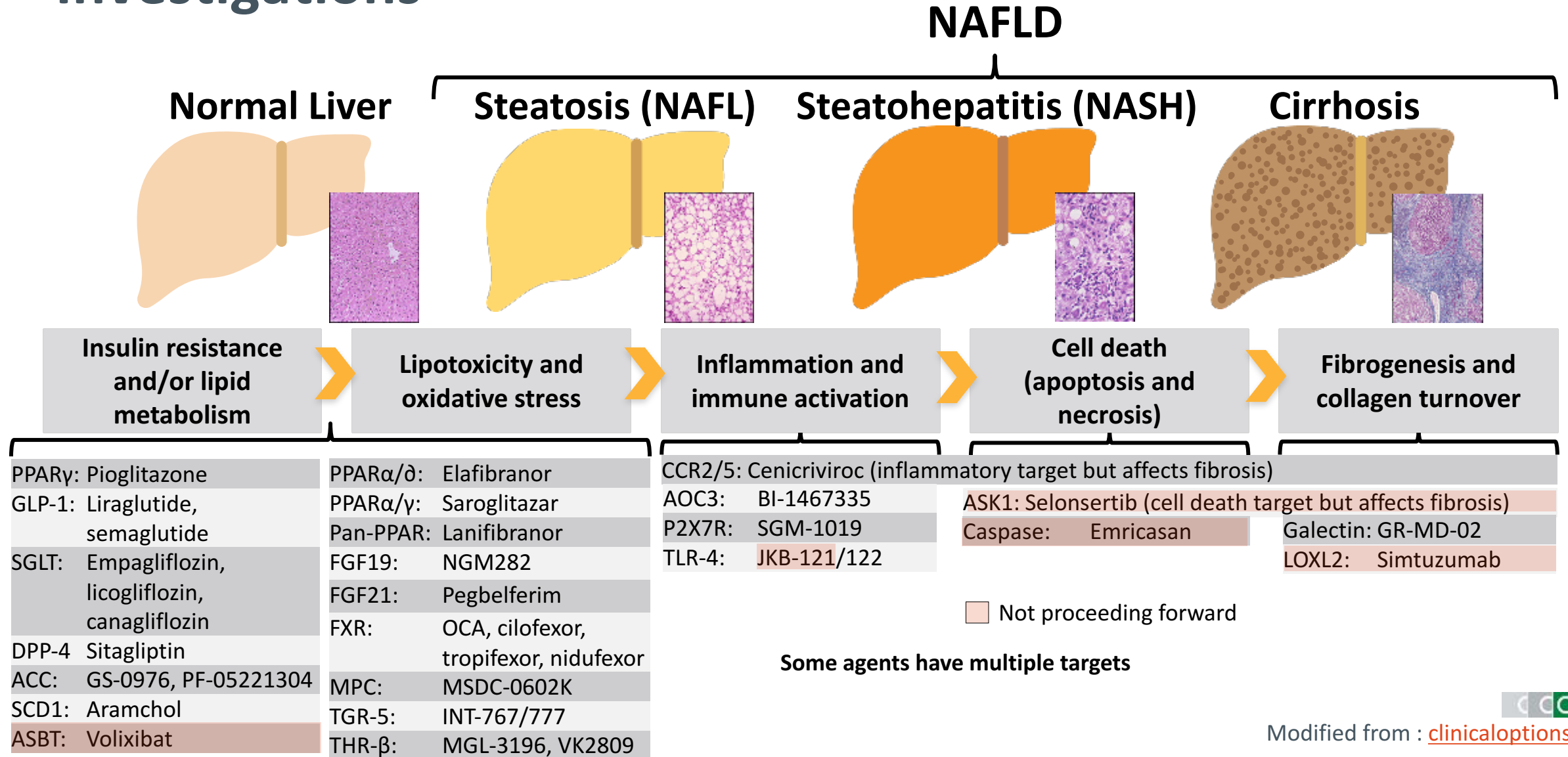
Elafibranor: PPARα/δ Agonist



Examples of NASH Treatments in Phase II or III Investigations



Examples of NASH Treatments in Phase II or III Investigations



Bariatric surgery improves steatosis, steatohepatitis (?fibrosis) after weight loss

- A meta-analysis with 15 studies showed these positive outcomes
- The steatosis and lobular inflammation usually improves but fibrosis may not regress
- Too rapid weight loss may worsen liver disease
- Cautious surgery in compensated cirrhosis – may make them decompensate

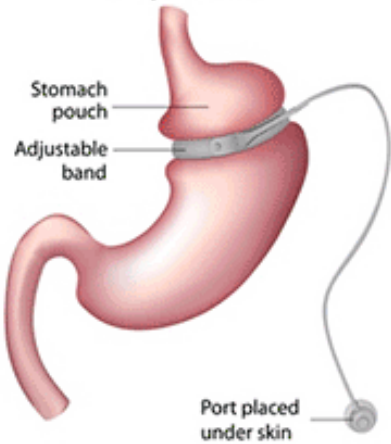
Younossi, Z. M. Ali Phcol & Ther, 2014
Mummadi RR. Clin Gastroenterol Hepatol 2008

Recommendations for bariatric surgery	Grade of evidence	Grade of recommendation
Bariatric surgery reduces liver fat and is likely to reduce NASH progression; prospective data have shown an improvement in all histological lesions of NASH, including fibrosis	B	1

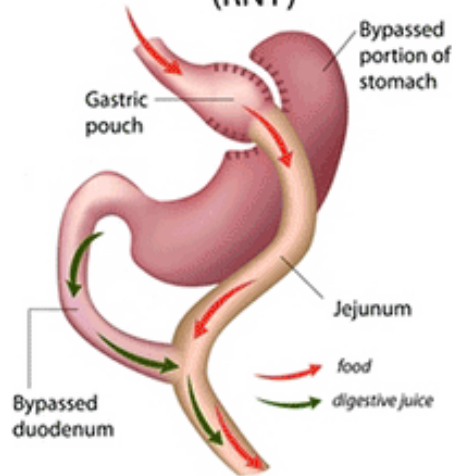
4 Most Common Weight Loss Surgery Procedures in the United States

Bariatric surgery is effective for durable weight loss, diabetes and dyslipidemia

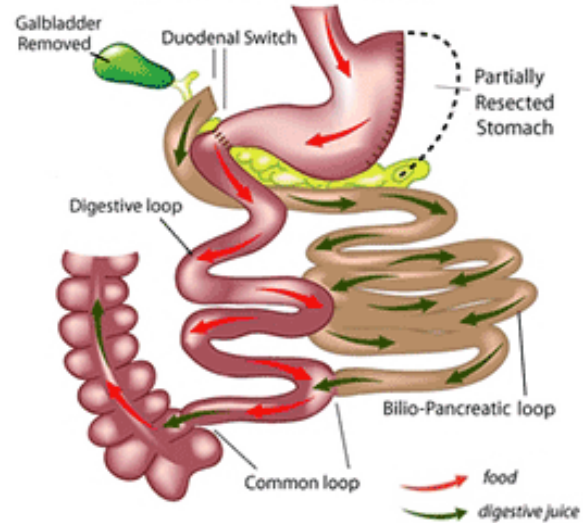
Adjustable Gastric Band (Lap Band)



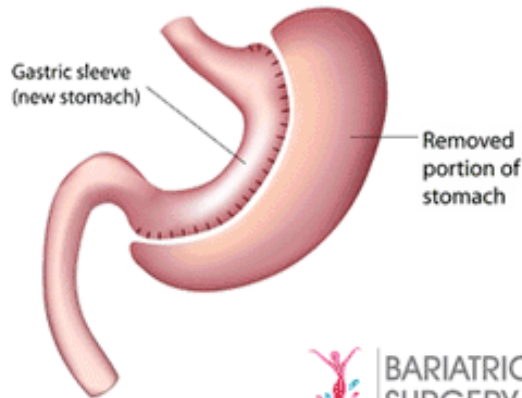
Roux-en-Y Gastric Bypass (RNY)



Duodenal Switch (DS)



Vertical Sleeve Gastrectomy (Gastric Sleeve)



Surgery	Mean BMI decrease	% DM resolved	% improved DLP
Duodenal switch	17.99	98.9	99.1
Gastric bypass	16.70	83.7	96.9
Gastroplasty	14.20	71.6	73.6
Gastric banding	10.43	47.9	58.9

JAMA 292(14):1724-1737

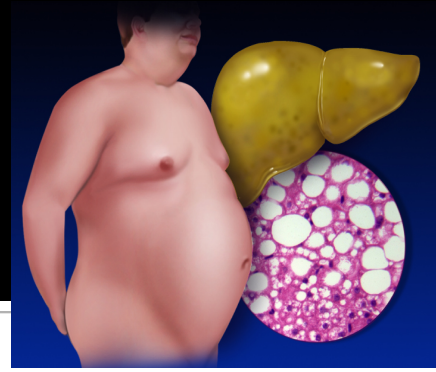
Overall resolution:
76.8% (n=1846)

Overall resolution:
79.3% (n=1019)



www.bariatric-surgery-source.com

Summary: Fatty Liver Disease



1. NAFLD is becoming the most common liver disease
2. Type 2 diabetes is the main risk factor for disease severity and progression
3. Non-invasive diagnostic tools (NFS, Fib-4, APRI) can be used in primary care to identify high risk patients who may need referral to specialist clinics
4. Dietary and lifestyle advice is essential
5. There are currently no drugs that have indication to treat NAFLD