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LIVER
FOUNDATION

كلنا نستحق كبد صحي
每个人都值得拥有一颗健康的肝脏
JEDER BRAUCHT EINE GESUNDE LEBER
TOUT LE MONDE MÉRITE UN FOIE SAIN
TODOS MERECEMOS UM FÍGADO SAUDÁVEL
КАЖДЫЙ ЗАСЛУЖИВАЕТ ИМЕТЬ ЗДОРОВУЮ ПЕЧЕНЬ

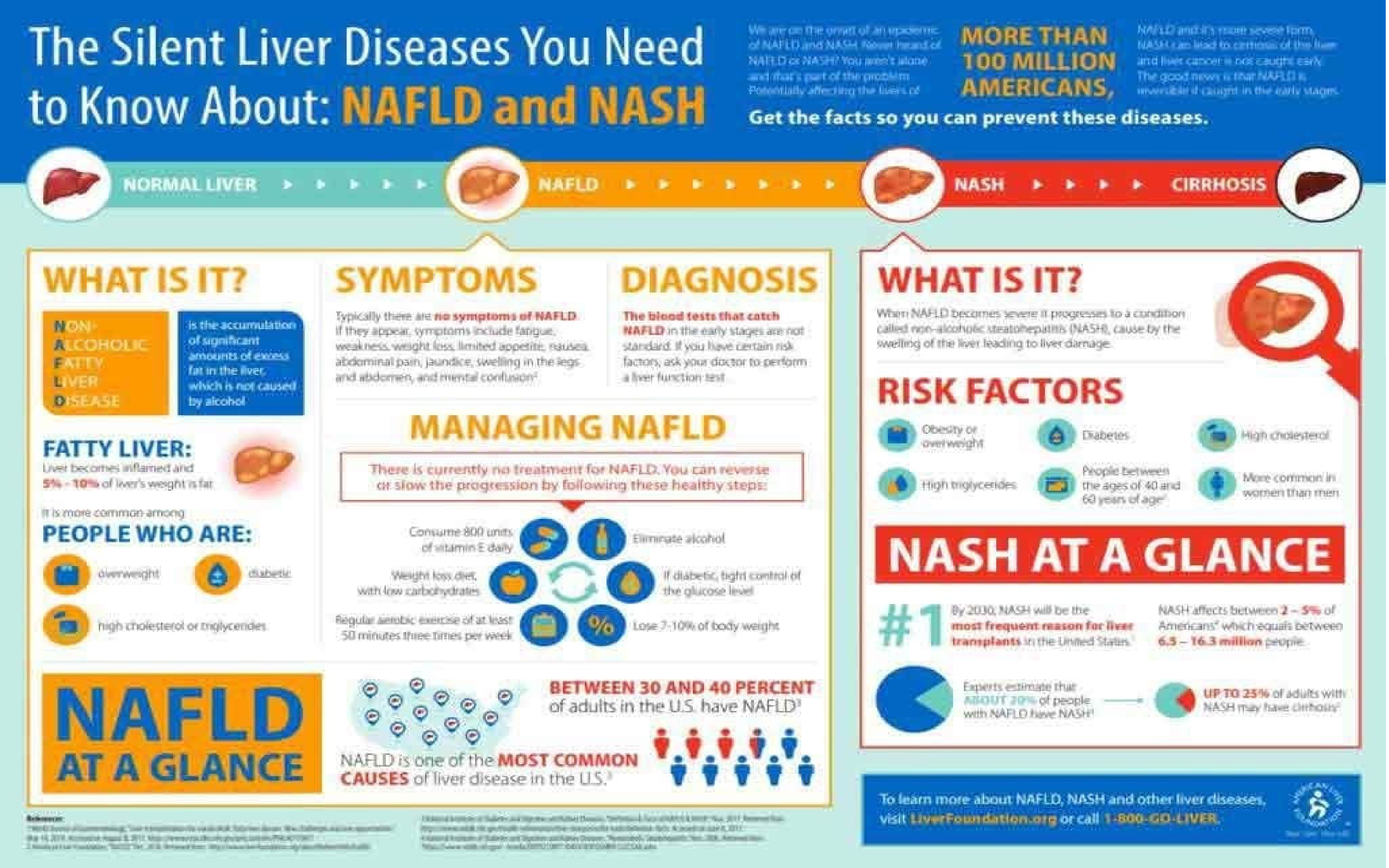
EVERYONE DESERVES A HEALTHY LIVER

Fatty Liver; An Update for Primary Physicians

Clinical Gastroenterology Update for Primary Care Physicians".

En Memoria Dr. Carlos Rubio Amador
Wilfredo Pagani M.D. FACG

9/12/2020


The Silent Liver Diseases You Need to Know About: NAFLD and NASH
We are on the onset of an epidemic of NAFLD and NASH. Never heard of NAFLD or NASH? You aren't alone and that's part of the problem. Potentially affecting the livers of
MORE THAN 100 MILLION AMERICANS,
NAFLD and it's more severe form, NASH can lead to cirrhosis of the liver and liver cancer if not caught early. The good news is that NAFLD is reversible if caught in the early stages.
Get the facts so you can prevent these diseases.
NORMAL LIVER
NAFLD
NASH
CIRRHOSIS
WHAT IS IT?
NON-ALCOHOLIC FATTY LIVER DISEASE
is the accumulation of significant amounts of excess fat in the liver, which is not caused by alcohol
FATTY LIVER:
Liver becomes inflamed and 5% - 10% of liver's weight is fat
It is more common among
PEOPLE WHO ARE:
overweight
diabetic
high cholesterol or triglycerides
SYMPTOMS
Typically there are no symptoms of NAFLD. If they appear, symptoms include fatigue, weakness, weight loss, limited appetite, nausea, abdominal pain, jaundice, swelling in the legs and abdomen, and mental confusion
DIAGNOSIS
The blood tests that catch NAFLD in the early stages are not standard. If you have certain risk factors, ask your doctor to perform a liver function test.
MANAGING NAFLD
There is currently no treatment for NAFLD. You can reverse or slow the progression by following these healthy steps:
Consume 800 units of vitamin E daily
Eliminate alcohol
Weight loss diet, with low carbohydrates
If diabetic, tight control of the glucose level
Regular aerobic exercise of at least 30 minutes three times per week
Lose 7-10% of body weight
NAFLD AT A GLANCE
BETWEEN 30 AND 40 PERCENT of adults in the U.S. have NAFLD
NAFLD is one of the MOST COMMON CAUSES of liver disease in the U.S.
WHAT IS IT?
When NAFLD becomes severe it progresses to a condition called non-alcoholic steatohepatitis (NASH), cause by the swelling of the liver leading to liver damage.
RISK FACTORS
Obesity or overweight
Diabetes
High cholesterol
High triglycerides
People between the ages of 40 and 60 years of age
More common in women than men
NASH AT A GLANCE
#1
By 2030, NASH will be the most frequent reason for liver transplants in the United States.
NASH affects between 2 – 5% of Americans which equals between 6.5 – 16.3 million people.
Experts estimate that ABOUT 20% of people with NAFLD have NASH
UP TO 25% of adults with NASH may have cirrhosis
To learn more about NAFLD, NASH and other liver diseases, visit LiverFoundation.org or call 1-800-GO-LIVER.

NAFLD Presentation

Symptoms

Usually asymptomatic; majority discovered by chance

Fatigue frequently present

Often an "incidental finding"

Incidental abnormal LFTs

Incidental "bright liver" on imaging

Incidental hepatomegaly

Common scenarios

Statin monitoring

"Annual reviews" in T2D/lipid/ hypertension clinics

Medical insurance/occupational health checks

What is nonalcoholic fatty liver disease (NAFLD)?

NAFLD is a general term for a range of conditions characterized by extra fat in liver cells that is not caused by alcohol. It's normal for the liver to contain some fat. However, if more than 5 percent of the liver's weight is fat, it's considered a fatty liver (steatosis). There are two different types of nonalcoholic fatty liver disease:

•Simple fatty liver

In this form of NAFLD you have fat in your liver, but little or no inflammation of the liver or damage to liver cells. Your healthcare provider may refer to this as nonalcoholic fatty liver (NAFL). Typically, this form does not progress to cause liver damage.

•Nonalcoholic steatohepatitis (NASH)

This is the more severe form of NAFLD in which you have hepatitis – meaning swelling or inflammation of the liver — and liver cell damage, in addition to fat in your liver. Inflammation and liver cell damage can cause fibrosis, or scarring, of the liver.

- **Fibrosis**
  This **fibrosis** can progress to **cirrhosis**, where hard scar tissue replaces an increasingly larger amount of soft healthy liver tissue. Cirrhosis from NASH typically takes years of damage to develop.

TABLE 2.

NAFLD and Related Definitions

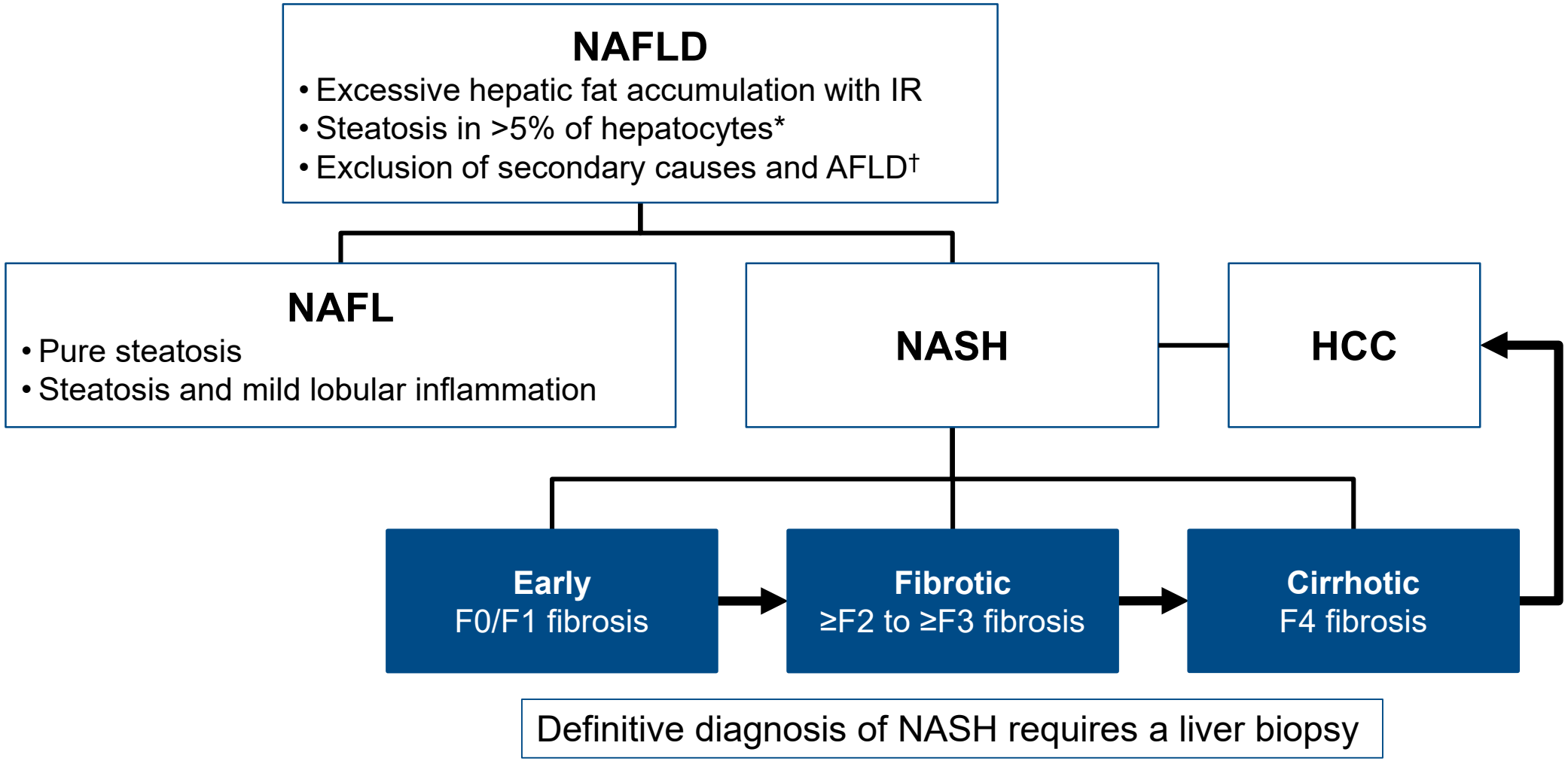
NAFLD Encompasses the entire spectrum of FLD in individuals without significant alcohol consumption, ranging from fatty liver to SH to cirrhosis

NAFL Presence of 5% HS without evidence of hepatocellular injury in the form of ballooning of the hepatocytes or evidence of fibrosis. The risk of progression to cirrhosis and liver failure is considered minimal.

NASH Presence of 5% HS with inflammation and hepatocyte injury (ballooning) with or without fibrosis. This can progress to cirrhosis, liver failure, and rarely liver cancer.

NASH cirrhosis Presence of cirrhosis with current or previous histological evidence of steatosis

Definitions of NAFLD, NAFL and NASH



*According to histological analysis or proton density fat fraction or >5.6% by proton MRS or quantitative fat/water-selective MRI;
†Daily alcohol consumption of ≥30 g for men and ≥20 g for women
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Spectrum of NAFLD and concurrent disease

Sub-classification of NAFLD*	Most common concurrent diseases
NAFL • Pure steatosis • Steatosis and mild lobular inflammation	**AFLD†** **Drug-induced fatty liver disease†** **HCV-associated fatty liver disease (GT 3)†** **Others†** • Haemochromatosis • Autoimmune hepatitis • Coeliac disease • Wilson disease • A/hypo-betalipoproteinaemia lipoatrophy • Hypopituitarism, hypothyroidism • Starvation, parenteral nutrition • Inborn errors of metabolism – Wolman disease (lysosomal acid lipase deficiency)
NASH • Early NASH (no or mild fibrosis) • Fibrotic NASH (significant/advanced fibrosis) • NASH cirrhosis	
HCC‡	

*Also called primary NAFLD and associated with metabolic risk factors/components of MetS: 1. Waist circumference ≥94/≥80 cm for Europid men/women; 2. Arterial pressure ≥130/85 mmHg or treated for hypertension; 3. Fasting glucose ≥100 mg/dl (5.6 mmol/L) or treated for T2DM; 4. Serum triacylglycerols >150 mg/dl (>1.7 mmol/L); 5. HDL cholesterol <40/50 mg/dl for men/women (<1.0/<1.3 mmol/L); †Also called secondary NAFLD. Note that primary and secondary NAFLD may coexist in individual patients. Also NAFLD and AFLD may coexist in subjects with metabolic risk factors and drinking habits above safe limits; ‡Can occur in the absence of cirrhosis and histological evidence of NASH, but with metabolic risk factors suggestive of "burned-out" NASH

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TABLE 1.

Common Causes of Secondary HS

Macrovesicular steatosis

- **Excessive alcohol consumption**
- **Hepatitis C (genotype 3)**
- WD
- Lipodystrophy
- Starvation
- Parenteral nutrition
- Abetalipoproteinemia
- **Medications** (e.g., mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, corticosteroids)

Microvesicular steatosis

- Reye's syndrome
- Medications (valproate, antiretroviral medicines)
- Acute fatty liver of pregnancy
- HELLP syndrome
- Inborn errors of metabolism (e.g., lecithin-cholesterol acyltransferase deficiency, cholesterol ester storage disease, Wolman's disease)

There are also some less common reasons why you may get NAFLD or NASH, including…

- Rapid excessive weight loss
- Certain infections like hepatitis C
- Medical conditions that cause your body to use or store fat improperly
- Taking certain medications, such as:
  - Glucocorticoids
  - Synthetic estrogens
  - Amiodarone (Cordarone, Pacerone)
  - Methotrexate (Rheumatrex, Trexall)
  - Tamoxifen (Nolvadex, Soltamox)
- Exposure to certain toxins
- Polycystic ovarian Syndrome (PCOS) a health condition that can affect a woman's menstrual cycle, fertility and hormones

Diagnosis: protocol for evaluation of NAFLD

- Incidental discovery of steatosis indicates comprehensive evaluation
  - Family and personal history of NAFLD-associated diseases
  - Exclusion of secondary causes of steatosis

Level	Variable
Initial evaluation	1. Alcohol intake: <20 g/day (women), <30 g/day (men) 2. Personal and family history of diabetes, hypertension and CVD 3. BMI, waist circumference, change in body weight 4. Hepatitis B/hepatitis C virus infection 5. History of steatosis-associated drugs 6. Liver enzymes (ALT, AST, GGT) 7. Fasting blood glucose, HbA1c, OGTT, (fasting insulin [HOMA-IR]) 8. Complete blood count 9. Serum total and HDL cholesterol, triacylglycerol, uric acid 10. Ultrasonography (if suspected for raised liver enzymes)
Extended* evaluation	1. Ferritin and transferrin saturation 2. Tests for coeliac and thyroid diseases, polycystic ovary syndrome 3. Tests for rare liver diseases (Wilson, autoimmune disease, AATD)

*According to *a priori* probability or clinical evaluation

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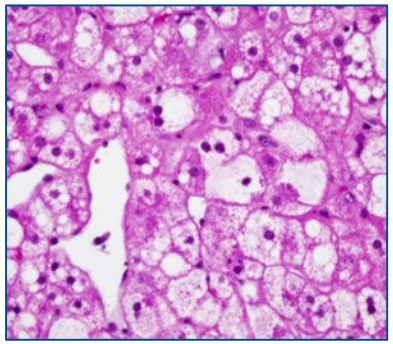
Liver biopsy

- Liver biopsy is essential for the diagnosis of NASH
  - Clinical, biochemical or imaging measures cannot distinguish NASH from steatosis
- NAFL encompasses
  - Steatosis alone plus **ONE** of lobular or portal inflammation **OR** ballooning
- NASH requires
  - Steatosis **AND**
  - Lobular or portal inflammation **AND**
  - Ballooning
- NAS scoring indicates disease severity*



Recommendations	Grade of evidence	Grade of recommendation
NASH has to be diagnosed by a liver biopsy showing **steatosis, hepatocyte ballooning and lobular inflammation**	A	1

*Should not be used for initial diagnosis

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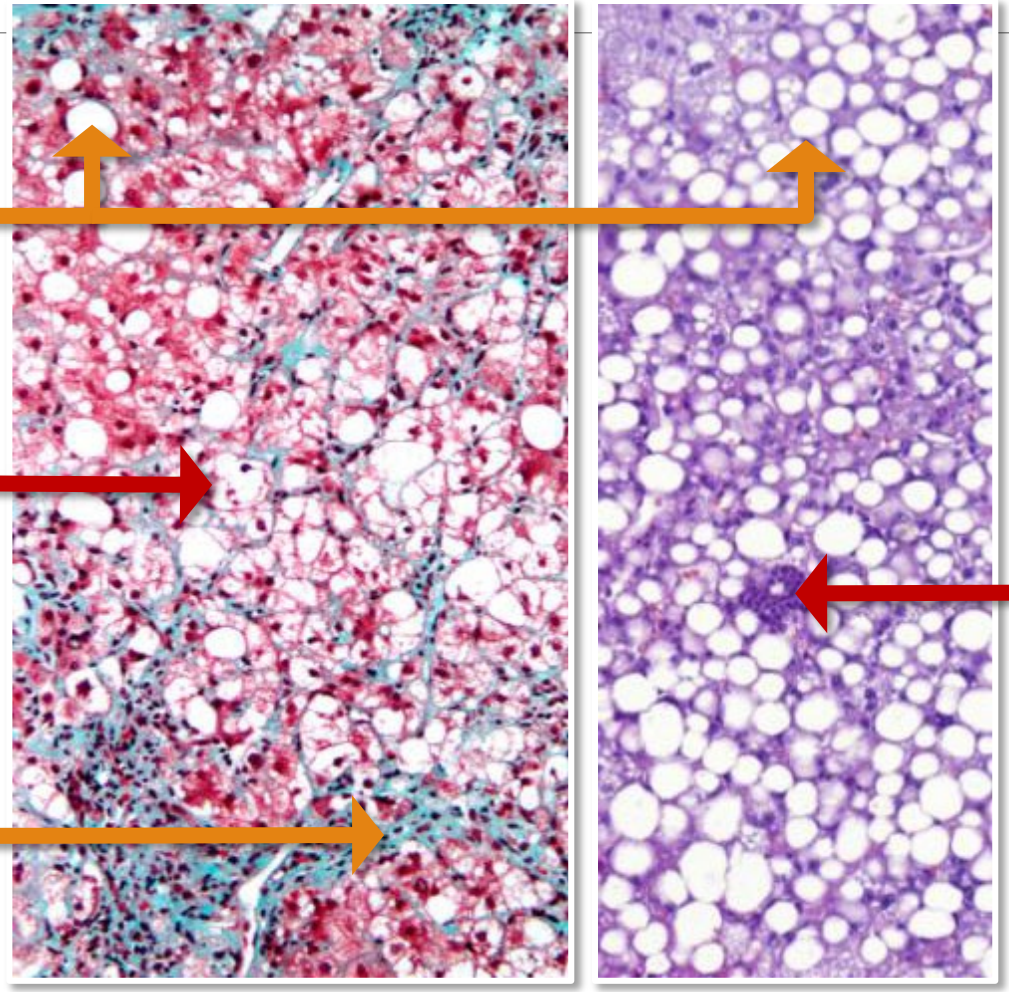
Histological Features of NAFLD and NASH



Steatosis

Hepatocyte Ballooning

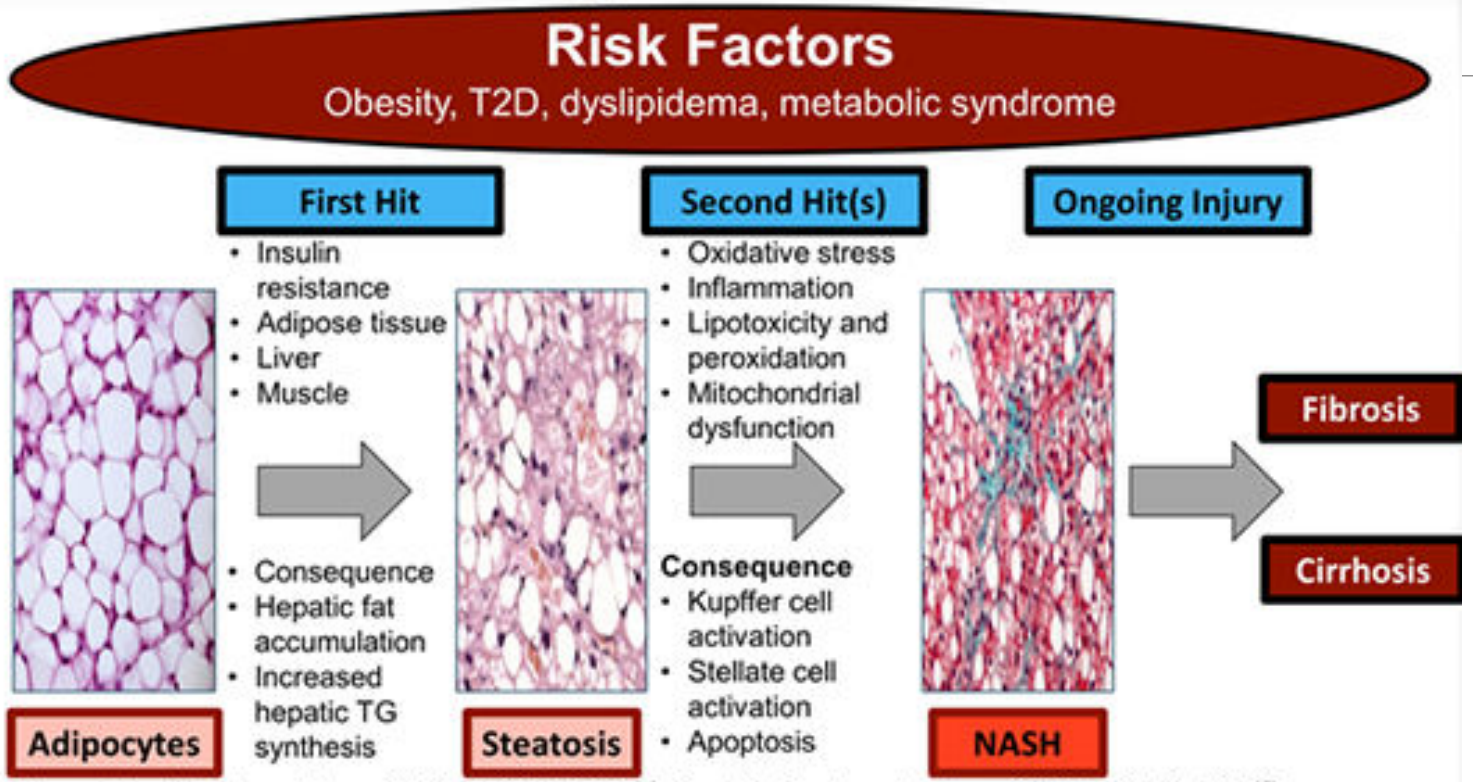
Fibrosis

Lobular Inflammation

Slide courtesy of Quentin Anstee, PhD, FRCP.

Slide credit: clinicaloptions.com

NAFLD/NASH Closely Associated With Visceral Obesity, Insulin Resistance



Chalasani N, et al. *Hepatology.* 2012;55:2005-2023[4]; Cusi K. *Gastroenterology.* 2012;142:711-725.[5]
"Non-alcoholic fatty liver disease1" by Nephron - Own work. CC-SA-3.0 via Wikimedia Commons.
"Liver steatosis fatty change" by Laboratory of Experimental Pathology, Division of Intramural Research, NIEHS (NIH) via Wikimedia Commons.

Non-invasive assessment of **steatosis**

- 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

Recommendations	Grade of evidence	Grade of recommendation
US is the preferred first-line diagnostic procedure for imaging of NAFLD, **as it provides additional diagnostic information**	A	1
Whenever imaging tools are not available or feasible serum biomarkers and scores are an acceptable alternative for the diagnosis of steatosis	B	2
A quantitative estimation of liver fat can only be obtained by ^{1}H-MRS. This technique is of value in clinical trials and experimental studies, but is expensive and not recommended in the clinical setting	A	1

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Transient elastography - Fibroscan

- First quantitative method – introduced in 2003
- The technique has been inspired from a device used to measure the Camembert cheese elasticity

Elastography indications for chronic hepatitis

- Initial staging (indication for treatment or not)
- Estimation of the complications (EV, HCC)
- Monitoring of the fibrosis (natural history or treated patients)
- Estimating the risk of developing complications

Serum-Based Single Tests for Identifying Patients With NAFLD at Increased Risk for Worse Outcomes

Algorithms Coming →

Test	Variables Included
FIB-4[a]	Age, ALT, AST, platelet count
APRI[b]	AST, platelet count
NAFLD fibrosis score[c,d]	Age, ALT, AST, platelet count, BMI, albumin, impaired fasting glucose/diabetes
BARD[e]	ALT, AST (AST/ALT ratio), BMI, T2D
ELF™[a]	TIMP-1, PIIINP, HA

Screening, prevalence and incidence

- NAFLD is the most common liver disorder in Western countries, affecting 17–46% of adults[1]
  - 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) individuals[2]

Recommendations	Grade of evidence	Grade of recommendation
Patients with IR and/or metabolic risk factors (i.e. obesity or MetS) should undergo procedures for the diagnosis of NAFLD	A	1
Screen individuals with steatosis for secondary causes of NAFLD, including a careful assessment of alcohol intake. Always consider the interaction between moderate amounts of alcohol and metabolic factors in fatty liver	A	1
Identify other chronic liver diseases that may coexist with NAFLD as these might result in more severe liver injury	B	1

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

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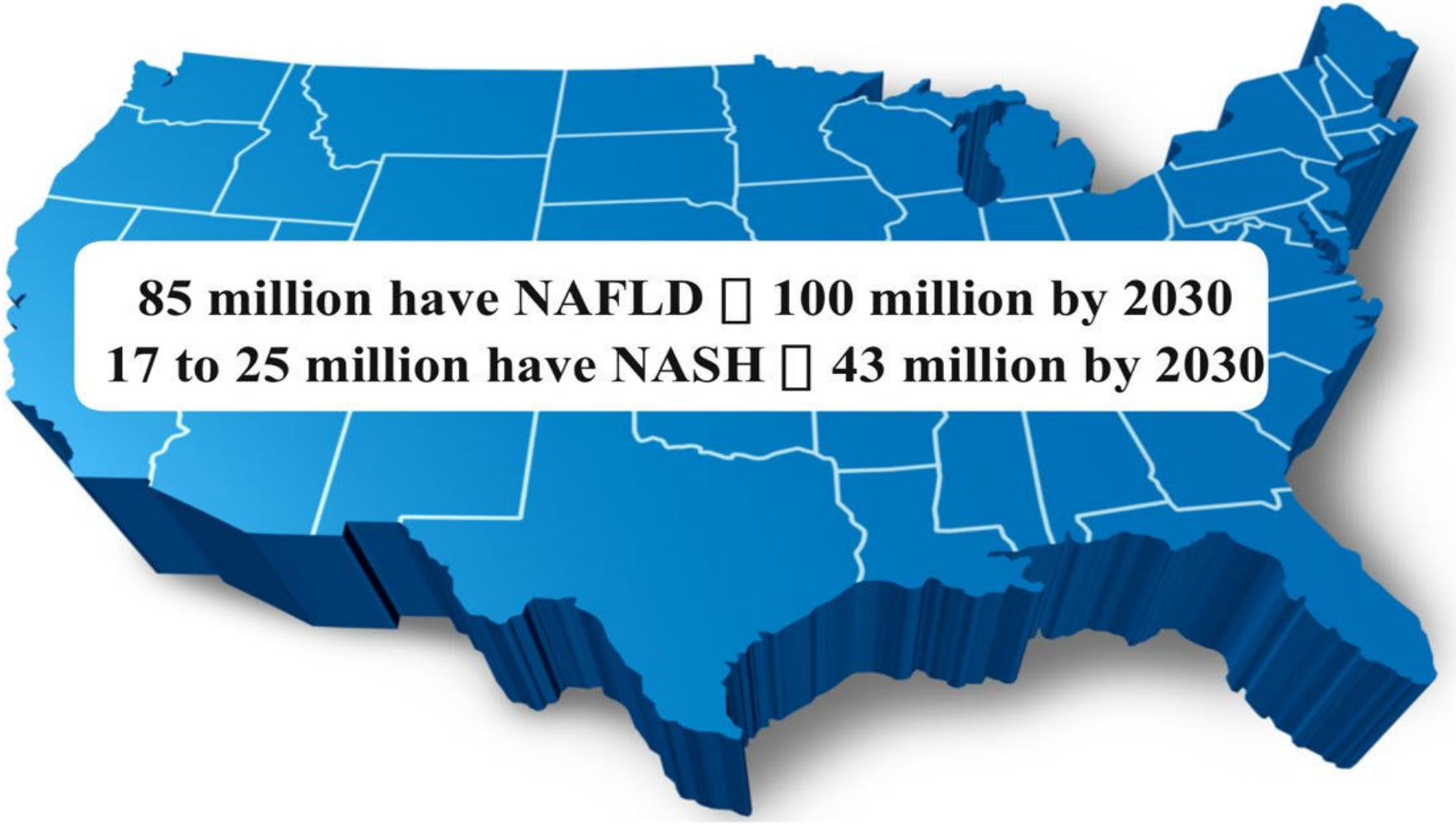
How common is NAFLD and NASH?

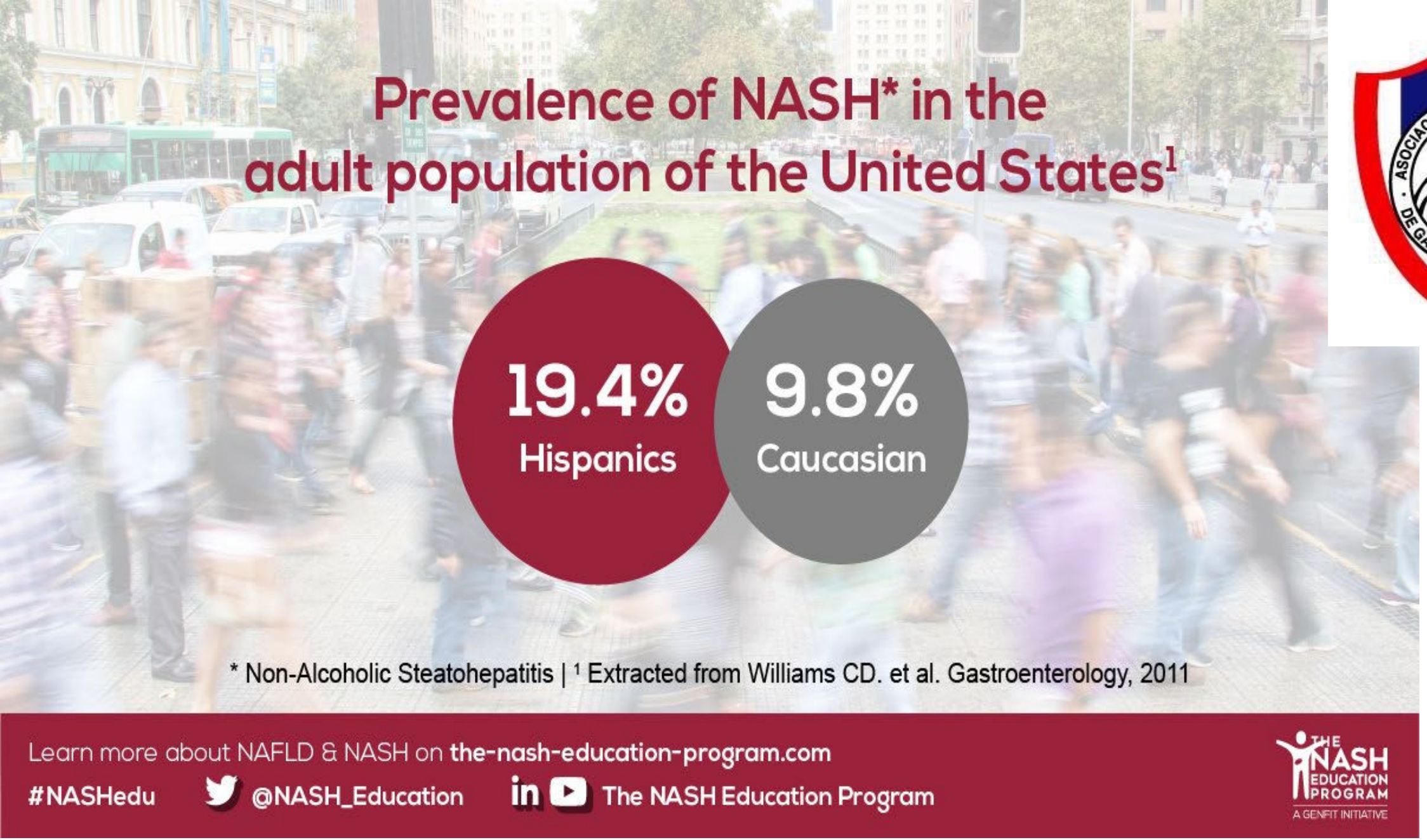
NAFLD is the most common chronic liver condition in the United States. It's estimated that about 25 percent of adults in the U.S. have NAFLD. Of those with NAFLD, about 20 percent have NASH (5% of adults in the U.S.). Most people with NAFLD have simply fatty liver.

The reason some people with NAFLD have simple fatty liver and others get NASH isn't known, although research suggests that certain genes may play a role.

The Burden of NAFLD Among Americans



Shetty A, Syn W-K. *Fed Practitioner.* 2019;36:14-19.


Prevalence of NASH* in the adult population of the United States[1]
19.4%
Hispanics
9.8%
Caucasian
* Non-Alcoholic Steatohepatitis | [1] Extracted from Williams CD. et al. Gastroenterology, 2011
Learn more about NAFLD & NASH on the-nash-education-program.com
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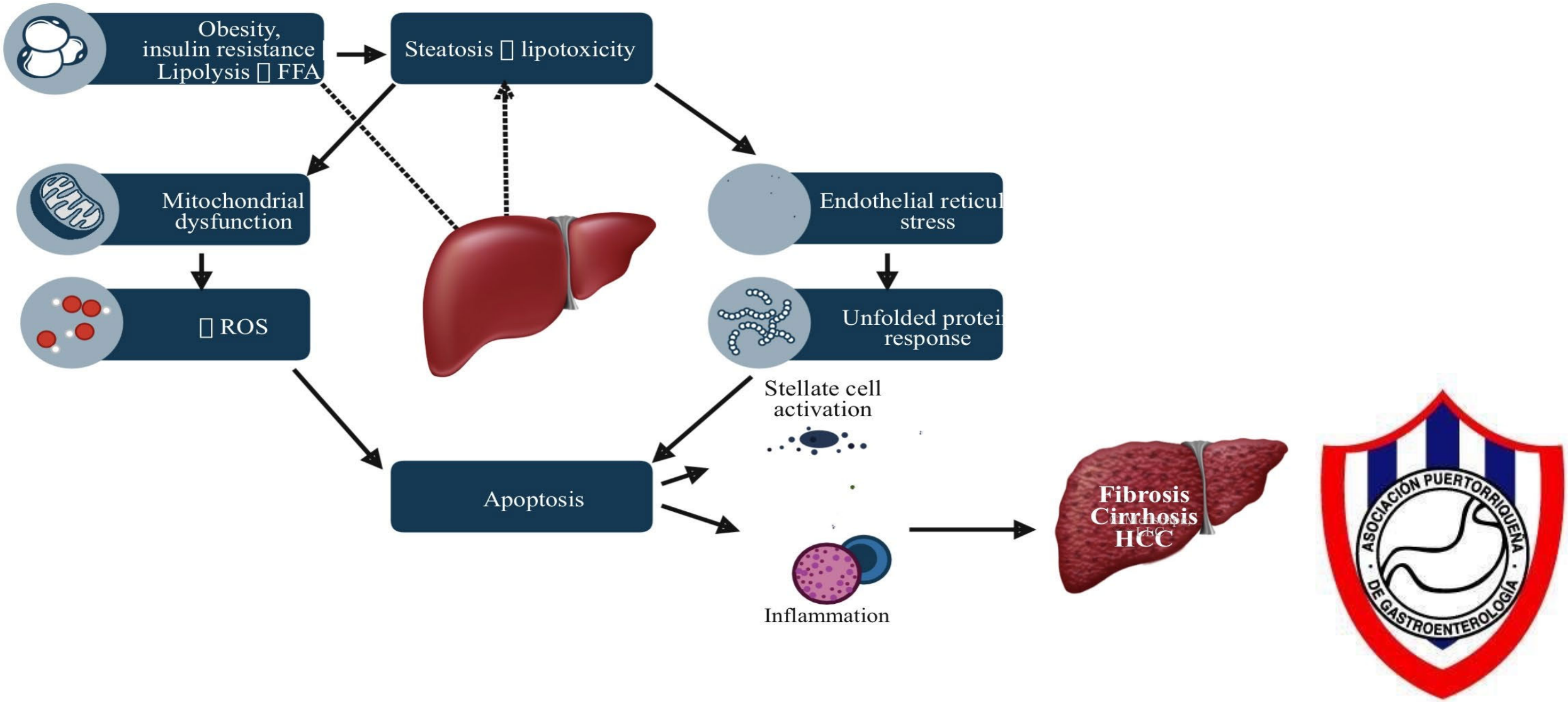
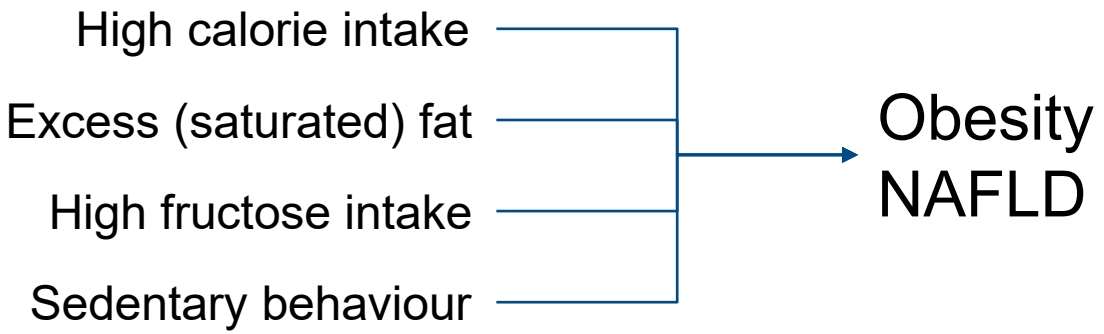
THE NASH EDUCATION PROGRAM
A GENFIT INITIATIVE

Pathogenesis of NAFLD and NASH



Pathogenesis: **lifestyle** and genes

- A Western diet/lifestyle has been associated with weight gain and obesity, and NAFLD[1]



Recommendation	Grade of evidence	Grade of recommendation
Unhealthy lifestyles play a role in the development and progression of NAFLD. The assessment of dietary and physical activity habits is part of comprehensive NAFLD screening	A	1

1. Barrera F, George J. Clin Liver Dis 2014;18:91–112;
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Pathogenesis: lifestyle and **genes**

- Several genetic modifiers of NAFLD have been identified[1]
  - A minority have been robustly validated
- *PNPLA3 I148M* and *TM6SF2 E167K* carriers have a higher liver fat content*
  - Increased risk of NASH
  - NAFLD not systematically associated with features of IR

Recommendation	Grade of evidence	Grade of recommendation
Genotyping may be considered in selected patients and clinical studies but **is not recommended routinely**	B	2

*Grade of evidence B, grade of recommendation 2

1. Anstee QM, et al. Nat Rev Gastroenterol Hepatol 2013;10:330–44;
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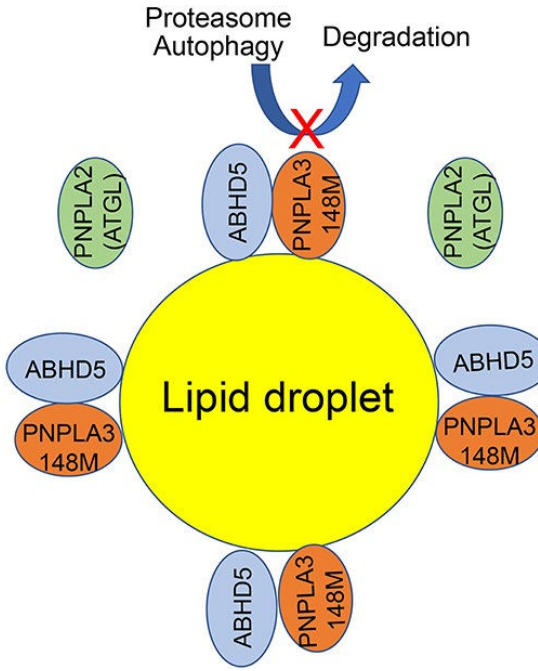
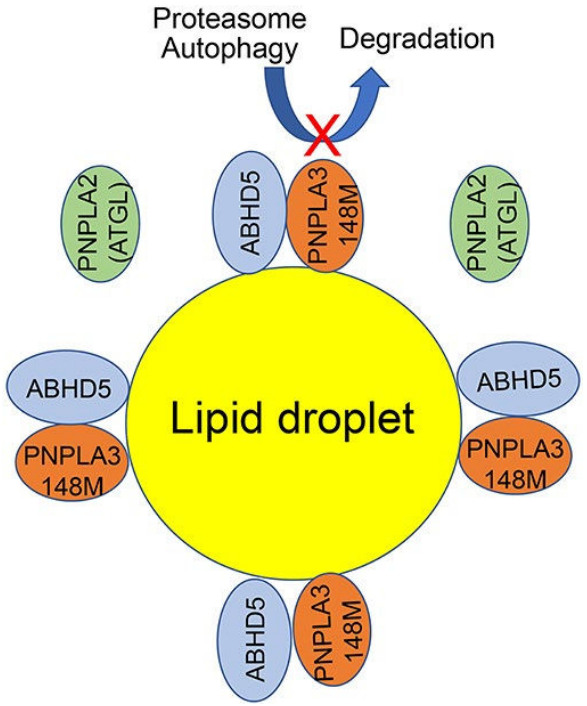
The frequency of PNPLA3(148M) variant ranges from 17% in African Americans, 23% in European Americans, **to 49% in Hispanics** in the Dallas Heart Study. Due to high prevalence of obesity and alcohol consumption in modern societies, the PNPLA3(148M) gene variant and environment interaction poses a serious concern for public health, especially chronic liver diseases including alcohol-related liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD).

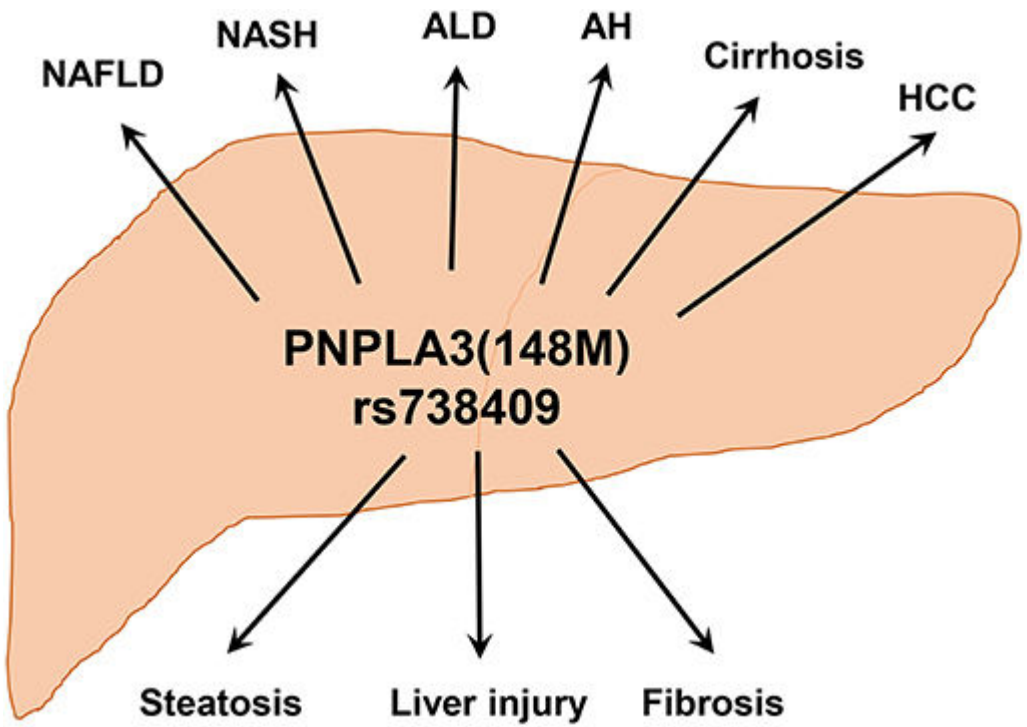


PNPLA3—A Potential Therapeutic Target for Personalized Treatment of Chronic Liver Disease

Xiaocheng Charlie Dong*
Center for Diabetes and Metabolic Diseases, Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, United States

Patatin-like phospholipase domain-containing protein 3 (PNPLA3) is a lipid droplet-associated protein that has been shown to have hydrolase activity toward triglycerides and retinyl esters. The first evidence of PNPLA3 being associated with fatty liver disease was revealed by a genome-wide association study (GWAS) of Hispanic, African American, and European American individuals in the Dallas Heart Study back in 2008. Since then, numerous GWAS reports have shown that PNPLA3 rs738409[G] (148M) variant is associated with hepatic triglyceride accumulation (steatosis), inflammation, fibrosis, cirrhosis, and even hepatocellular carcinoma regardless of etiologies including alcohol- or obesity-related and others.

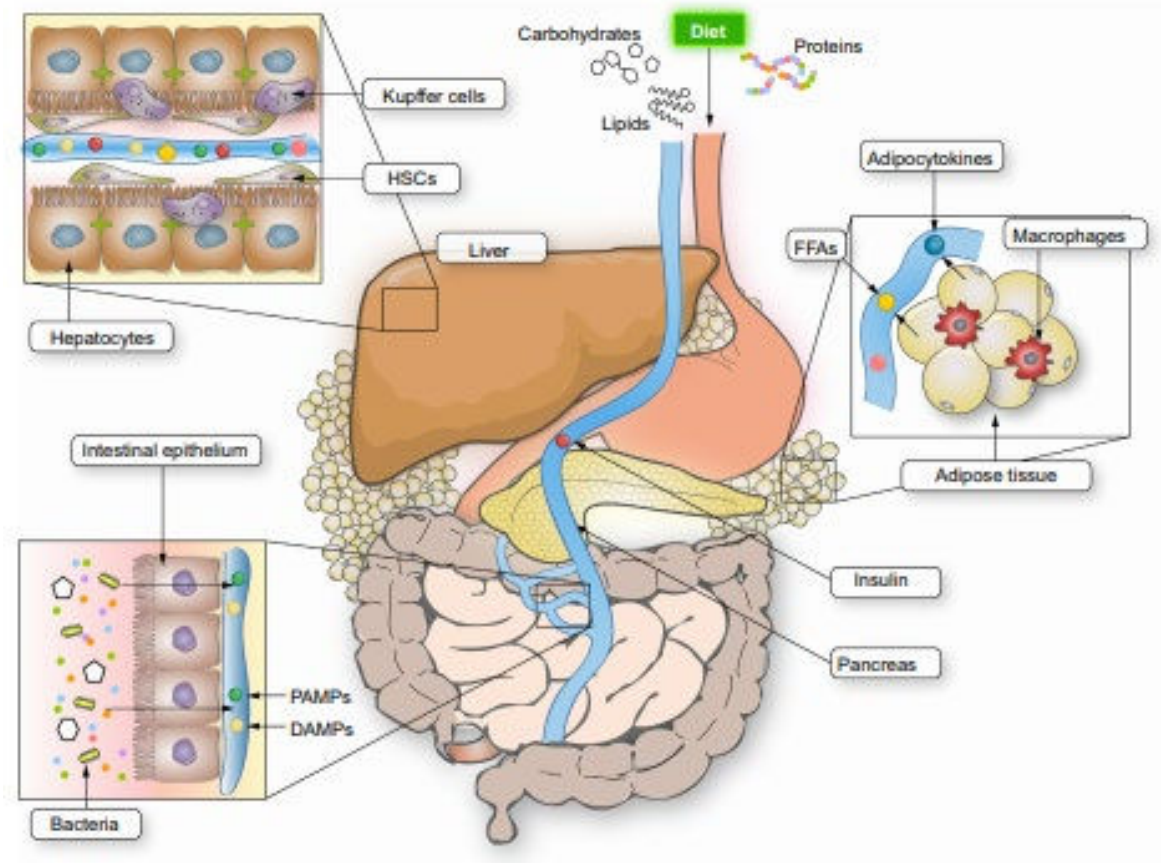




PNPLA3(148M) is associated with a wide-spectrum of chronic liver diseases. **Hepatic accumulation of PNPLA3(148M) protein leads to triglyceride accumulation, liver injury, and fibrosis.** With different etiologies, this may lead to the development of various liver disorders including NAFLD, NASH, ALD, alcoholic hepatitis (AH), cirrhosis, and HCC.

Multiple organs are likely to be involved in NAFLD

- Pathogenesis of NAFLD probably involves inter-organ crosstalk
  - Adipose tissue, pancreas, gut, and liver



Nobili, V et al. J Hepatol 2013;58:1218–29

Who is at risk for developing NAFLD and NASH?

Researchers do not know the exact cause of nonalcoholic fatty liver disease. They do know that you're more likely to develop NAFLD – either simple fatty liver or NASH – if you:

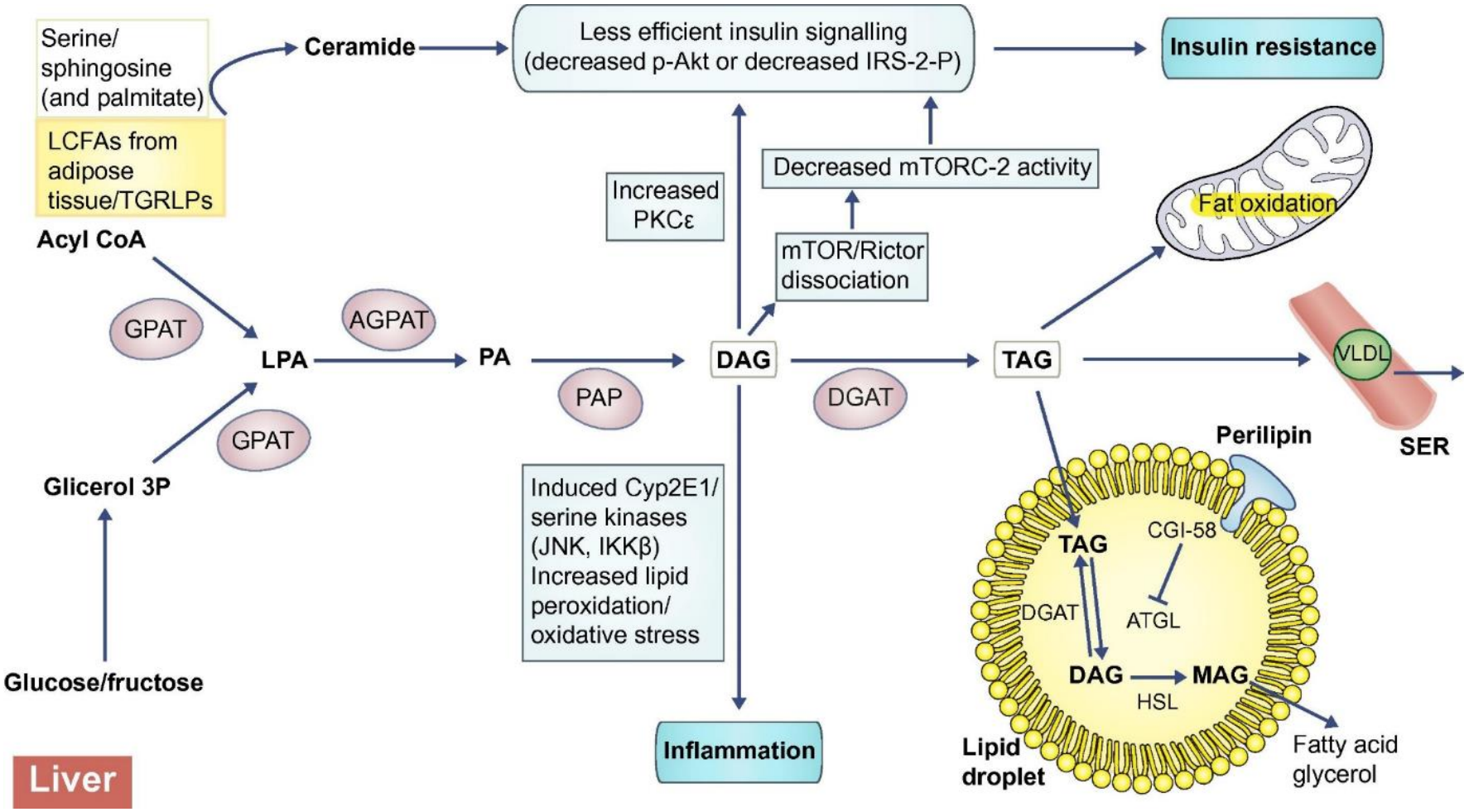
Are overweight or obese
Have type 2 diabetes or pre-diabetes
Have abnormal levels of fats in your blood, which may include high levels of triglycerides, high levels of "bad" (LDL) cholesterol, or low levels of "good" (HDL) cholesterol
Have metabolic syndrome. This is a mix of conditions linked to being overweight or obese, and makes you more likely to get type 2 diabetes and heart disease. In order to be diagnosed with metabolic syndrome, any three of the following conditions must be present:
Large waist size
High blood pressure
High blood sugar (glucose)
High levels of triglycerides in your blood
Low levels of "good" (HDL) cholesterol in your blood

List of well-established risk factors for NAFLD*:[1]

- Ethnicity
- Genetic variation related to PNPLA3
- Obesity
- Type 2 Diabetes
- Dyslipidemia
- Hypertension
- Insulin resistance
- ALT and AST level
- Metabolic syndrome (any three of the five features):
  - Impaired fasting glucose
  - Raised triglyceride level
  - Low HDL
  - Increased waist circumference
  - High blood pressure

*Non-Alcoholic Fatty Liver Disease | [1] Extracted from AASLD Practice Guidance. Hepatology, 2018 and Younossi Z. et al. Nat Rev Gastroenterol Hepatol. 2018

Lipids induce hepatic IR and inflammation



Byrne CD, Targher G. J Hepatol 2015;62:S47–64

Common related metabolic disorders

- NAFLD is closely associated with:
  - IR in the liver as well as adipose and muscle tissue
  - MetS
    - Three of: impaired fasting glucose or T2DM, hypertriglyceridaemia, low HDL-C,* increased waist circumference,† high blood pressure

All components of MetS correlate with liver fat content:

Evaluate risk of NAFLD in patients with MetS
Evaluate MetS in patients with NAFLD

*Gender-adjusted; †ethnicity-adjusted

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Common related metabolic disorders

- In individuals without diabetes, HOMA-IR can be considered as a surrogate for IR

$$\text{HOMA-IR:}\ \frac{\text{Fasting glucose (mmol/L)} + \text{insulin (mU/ml)}}{22.5}$$

Recommendations	Grade of evidence	Grade of recommendation
HOMA-IR can be recommended if proper reference values have been established	A	1
HOMA-IR is of limited use for NAFLD diagnosis in patients with metabolic risk factors. It could confirm altered insulin sensitivity, thereby favouring a diagnosis of IR-associated NAFLD in cases of diagnostic uncertainty*	B	2
During follow-up, HOMA-IR might help identify patients at risk of NASH or fibrosis progression in selected cases. Improvement of HOMA-IR during weight loss may indicate metabolic improvement	C	2

*E.g. US-defined steatosis with normal body weight

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HOMA-IR

- HOMA-IR stands for Homeostatic Model Assessment of Insulin Resistance. The meaningful part of the acronym is the IR “Insulin Resistance” part. This calculation marks for both the presence and extent of any insulin resistance that you might currently express. You can visit TheBloodCode.com to plug in your values and get the calculation. It is a terrific way to reveal the dynamic between your baseline (fasting) blood sugar and the responsive hormone insulin.
- **Low HOMA-IR** means that you are sensitive to insulin. A small amount of the hormone insulin is doing the trick to keep your blood sugars in good balance.
- **High HOMA-IR** relates to your level of insulin resistance. The higher the number, the more resistant you are to the message of insulin. If you are above 2, your self-prescribed diet and fitness habits will bring your number down into the lower insulin-sensitive range.[i]

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*E.g. US-defined steatosis with normal body weight

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Common related metabolic disorders: T2DM

- Irrespective of liver enzymes, diabetes risk and T2DM are closely associated with:
  - Severity of NAFLD
  - Progression to NASH
  - Presence of advanced fibrosis
  - Development of HCC

Recommendations	Grade of evidence	Grade of recommendation
In individuals with NAFLD, screening for diabetes is mandatory, by fasting or random blood glucose or HbA1c…	A	1
…and if available, by the standardized 75 g OGTT in high-risk groups	B	1
Look for NAFLD in patients with T2DM, irrespective of liver enzyme levels, due to high risk of disease progression	A	2

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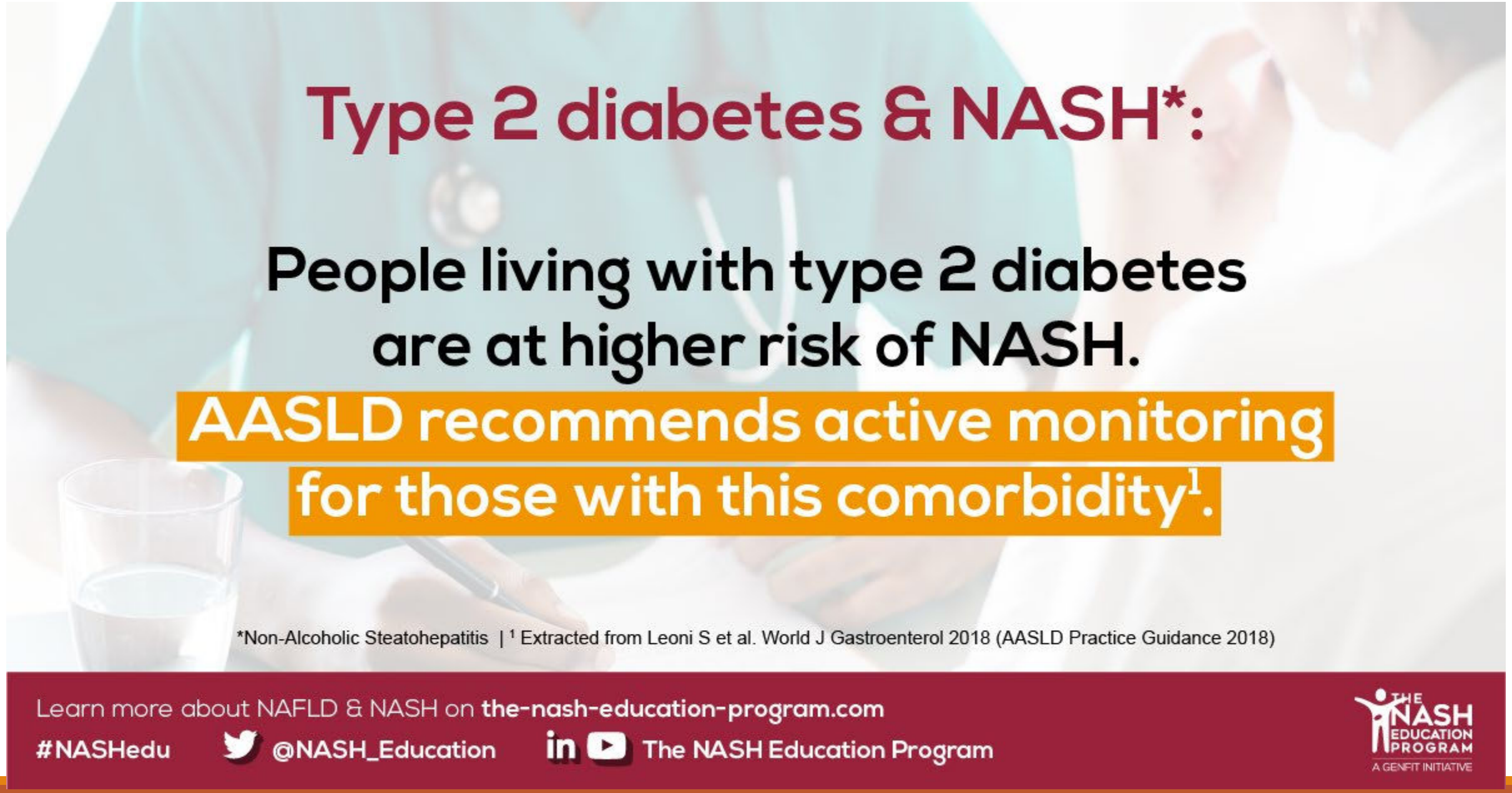
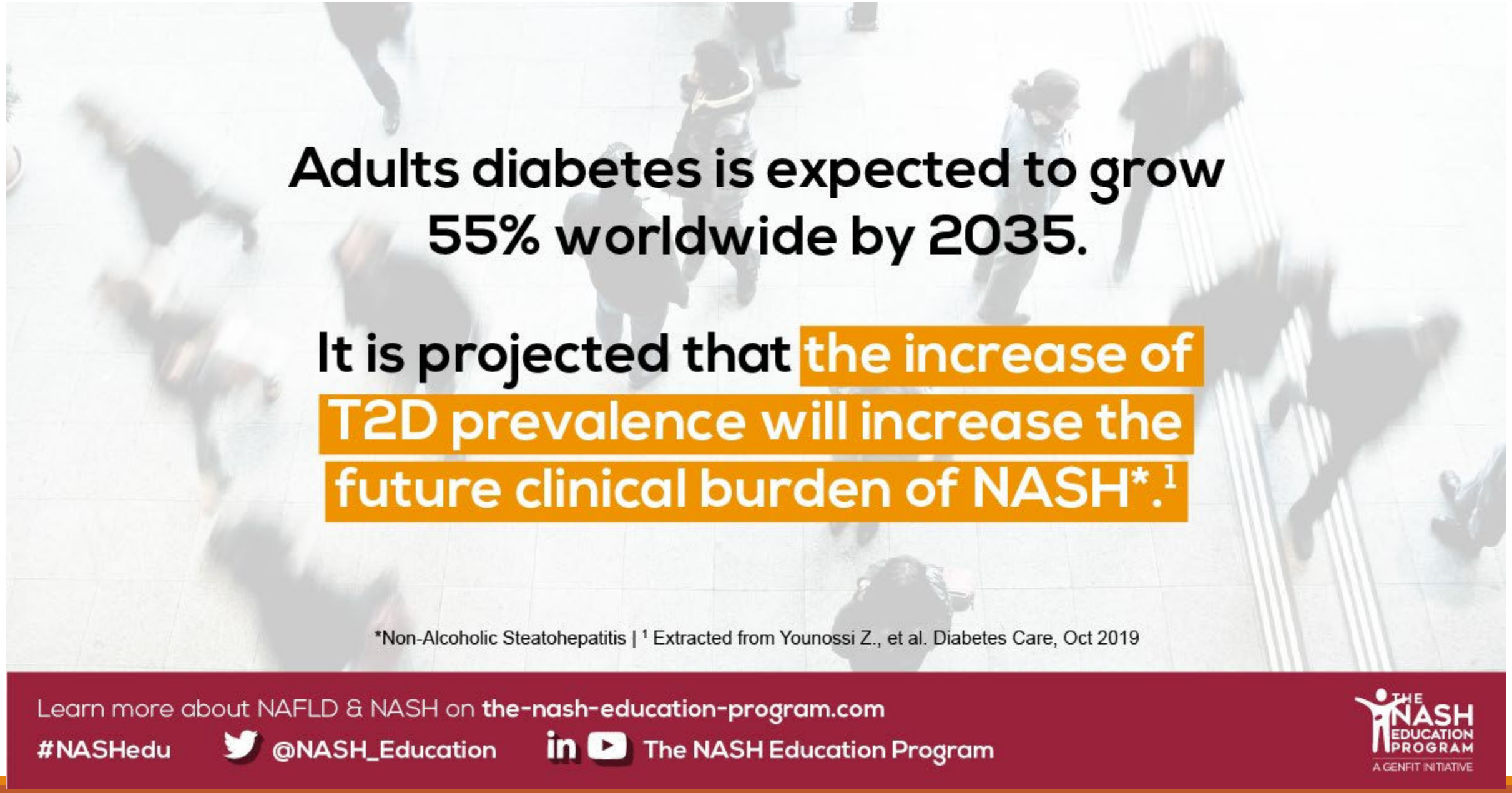
Metabolic Syndrome

Criterion	Definition
Abdominal obesity	• Waistline ≥35 in (89 cm) for women or 40 in (102 cm) for men
Dyslipidemia	• Serum TG level ≥150 mg/dL (1.7 mmol/L) • Serum HDL-C level <40 mg/dL (men) or <50 mg/dL (women)
Elevated FBS*	• ≥100 mg/dL (5.6 mmol/L)
Hypertension	• ≥130/85 mm Hg

*Or being on medicine to treat high blood sugar.
NIH website. Metabolic syndrome. 2019.


Type 2 diabetes & NASH*:
People living with type 2 diabetes are at higher risk of NASH.
AASLD recommends active monitoring for those with this comorbidity[1].
*Non-Alcoholic Steatohepatitis | [1] Extracted from Leoni S et al. World J Gastroenterol 2018 (AASLD Practice Guidance 2018)
Learn more about NAFLD & NASH on the-nash-education-program.com
#NASHedu
@NASH_Education
The NASH Education Program
THE NASH EDUCATION PROGRAM
A GENFIT INITIATIVE


Adults diabetes is expected to grow
55% worldwide by 2035.
It is projected that the increase of
T2D prevalence will increase the
future clinical burden of NASH*.[1]
*Non-Alcoholic Steatohepatitis | [1] Extracted from Younossi Z., et al. Diabetes Care, Oct 2019
Learn more about NAFLD & NASH on the-nash-education-program.com
#NASHedu
@NASH_Education
The NASH Education Program
THE NASH EDUCATION PROGRAM
A GENFIT INITIATIVE

Natural history and complications: progression

- In general, NAFLD is a slowly progressive disease, both in adults and in children
  - Rate of progression corresponds to 1 fibrosis stage every 14 years in NAFL and every 7 years in NASH
  - Rate of progression is doubled by arterial hypertension[1]
  - Progression of fibrosis is more rapid in about 20% of cases[1]

Recommendations	Grade of evidence	Grade of recommendation
NASH patients with fibrosis associated with hypertension should receive closer monitoring because of a higher risk of disease progression	B	1

- Paediatric NAFLD is of concern
  - Potential for severe liver-related complications later in life
  - NASH-related cirrhosis has been reported as early as 8 years of age

1. Sing S et al. Clin Gastroenterol Hepatol 2015;13:643–54;
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Natural history and complications: CVD

- 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
- CVD and metabolic risk factors are also reported in adolescents and children with NAFLD

Recommendations	Grade of evidence	Grade of recommendation
Screening of the cardiovascular system is mandatory in all individuals with NAFLD because CV complications frequently dictate the outcome	A	1

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

NAFLD and CV Mortality

- Twice as likely to die of CVD than liver disease[a]
- >65% increased risk of developing both fatal and nonfatal CV events[b]

Cardiovascular Disease/Type 2 Diabetes

The association between NAFLD and NASH with both cardiovascular disease and type 2 diabetes is bidirectional. This means that people with cardiovascular disease and/or type 2 diabetes are more likely to have NAFLD and NASH. And conversely, people with NAFLD or NASH are more likely to have cardiovascular disease and/or type 2 diabetes. In fact, cardiovascular disease is the most common cause of death in people who have either form of NAFLD.

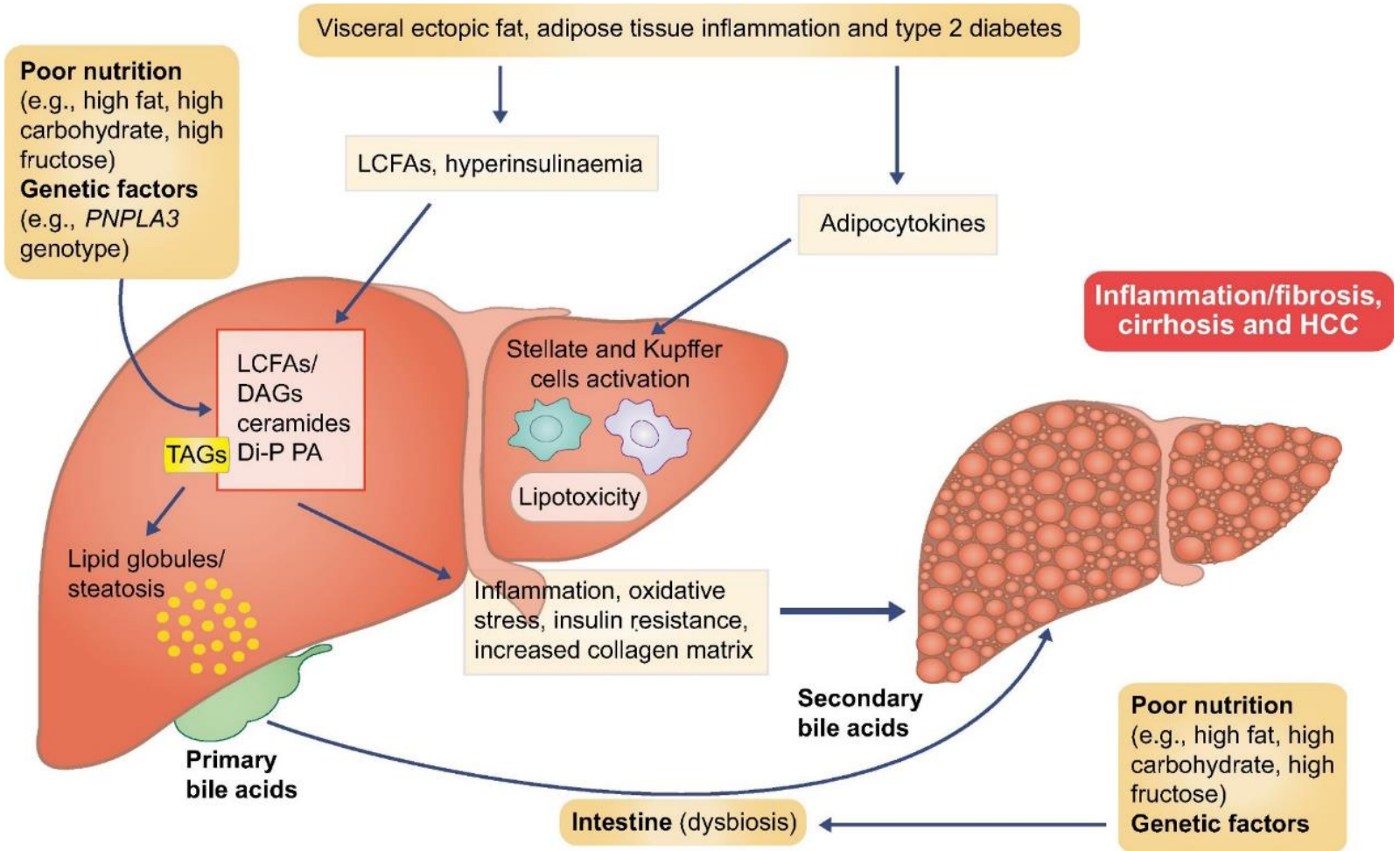
Natural history and complications: HCC

- Cumulative incidence of NAFLD-associated HCC varies according to study population
- Large number of NAFLD cases at risk of HCC makes systematic surveillance largely impracticable
  - *PNPLA3* rs738409 C>G gene polymorphism is associated with increased HCC risk
  - However, HCC surveillance in NAFLD is not yet considered cost effective

Recommendations	Grade of evidence	Grade of recommendation
Although NAFLD is a risk factor for HCC, which may also develop in the pre-cirrhotic stage, and the risk is further increased by the presence of the *PNPLA3* rs738409 C>G polymorphism, no recommendation can be currently made on the timing of surveillance and its cost effectiveness	B	1

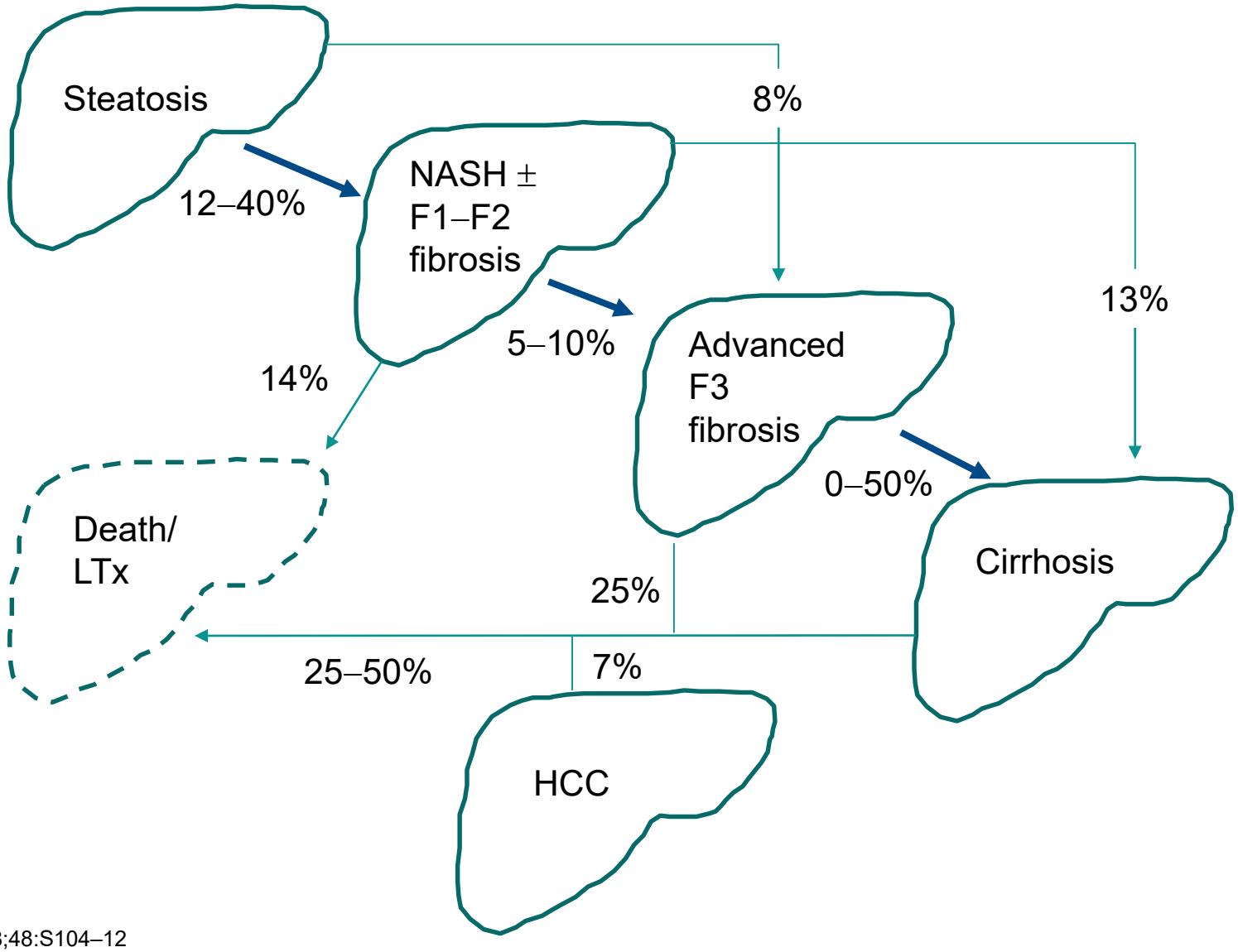
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Progressive liver disease in NAFLD



Byrne CD, Targher G. J Hepatol 2015;62:S47–64

Natural history of NAFLD over 8–13 years



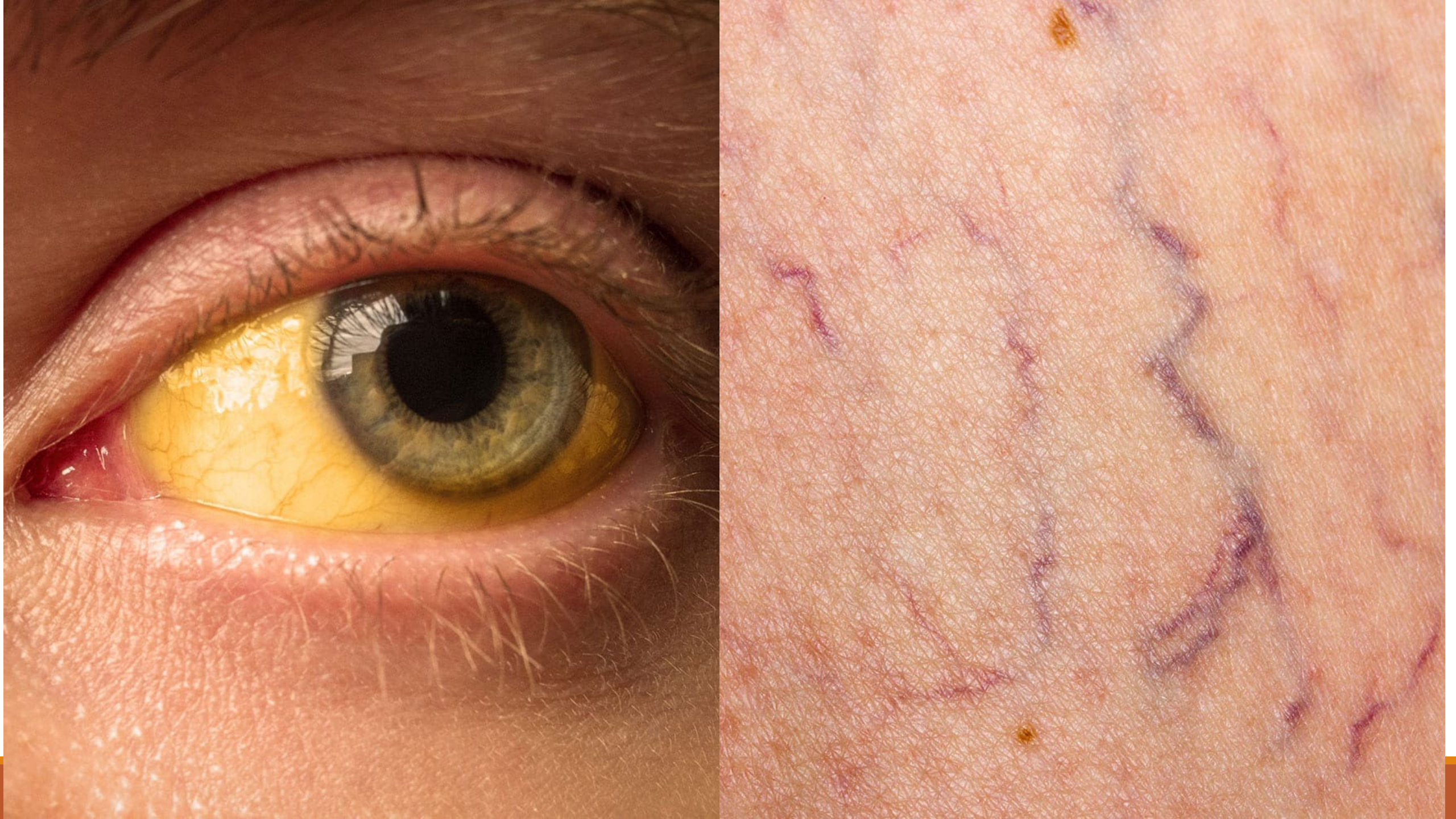
de Alwis NMW, Day CP. J Hepatol 2008;48:S104–12

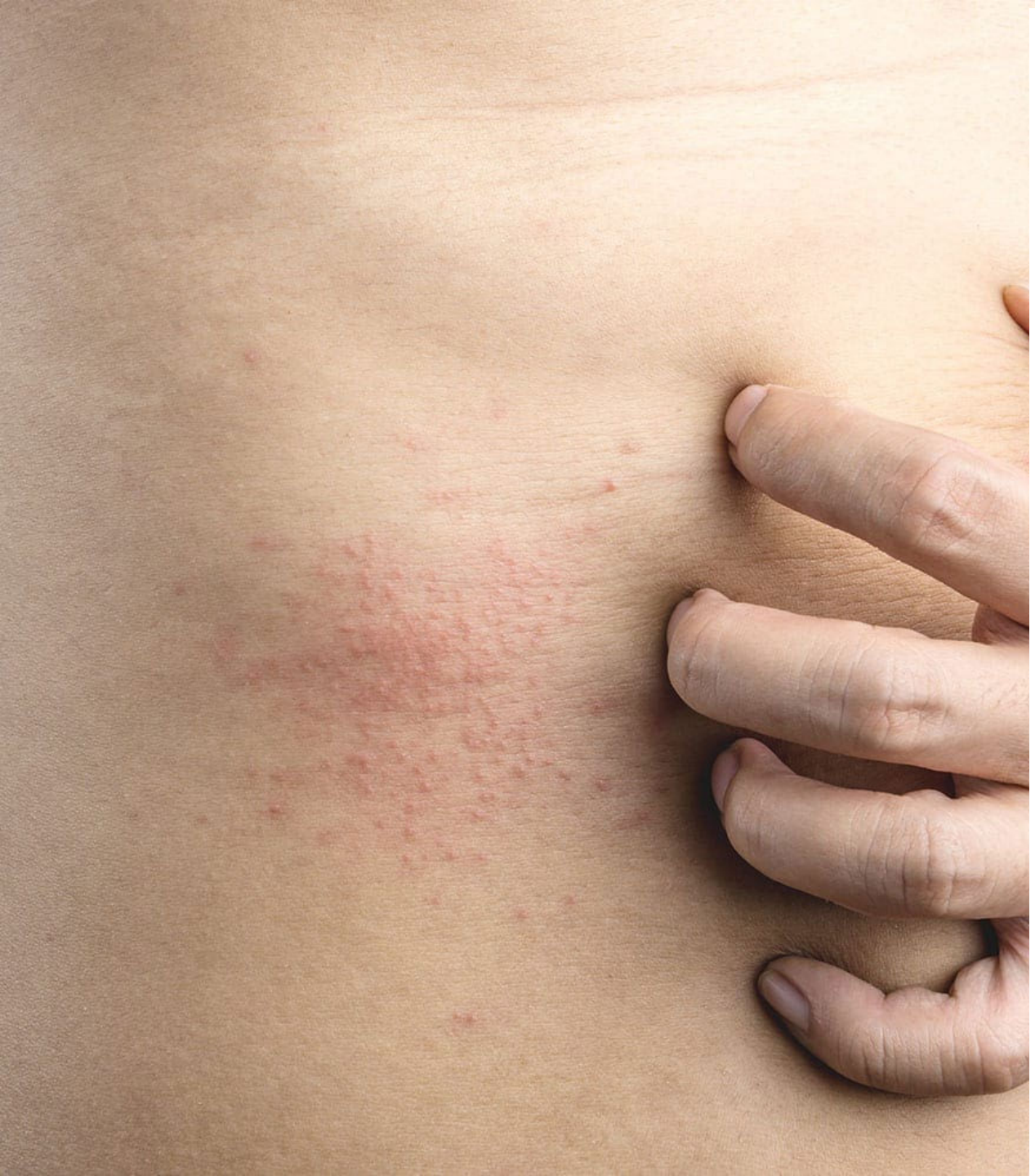
What are the symptoms of NAFLD and NASH?

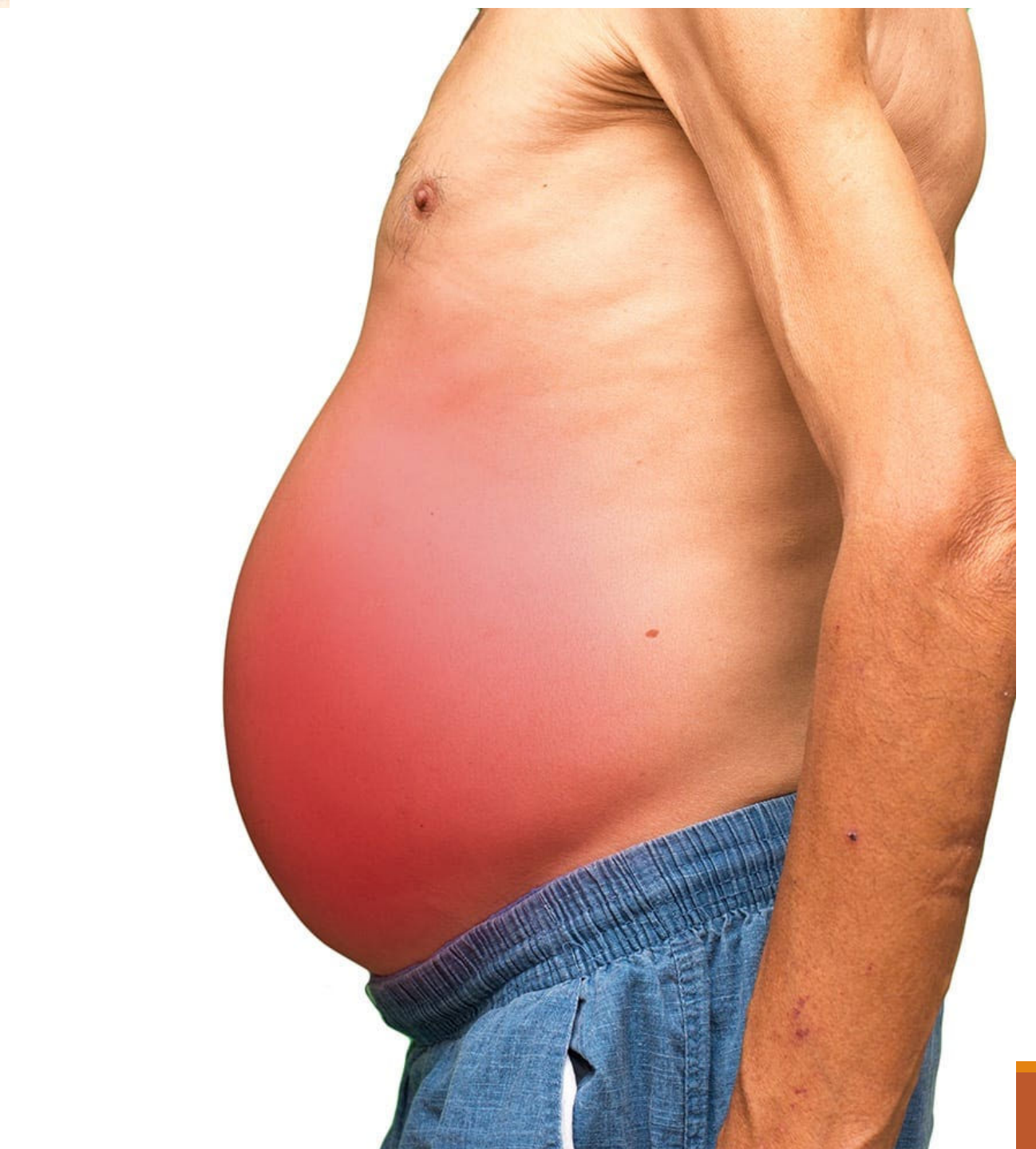
Usually NAFLD and NASH do not cause symptoms. If you do have symptoms, you may feel tired or have pain in the upper right side of your abdomen, where your liver is.

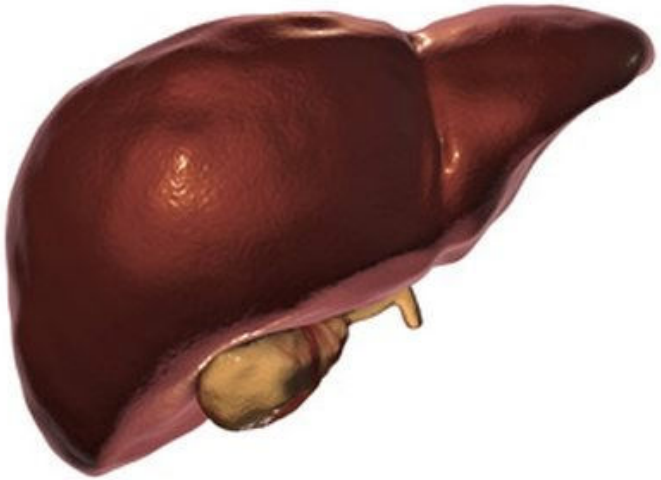
Often the first sign of liver disease occurs when cirrhosis has developed typically after many years of having NAFLD. If you have NASH and severe scarring of your liver, you may have some of the following signs and symptoms of cirrhosis:

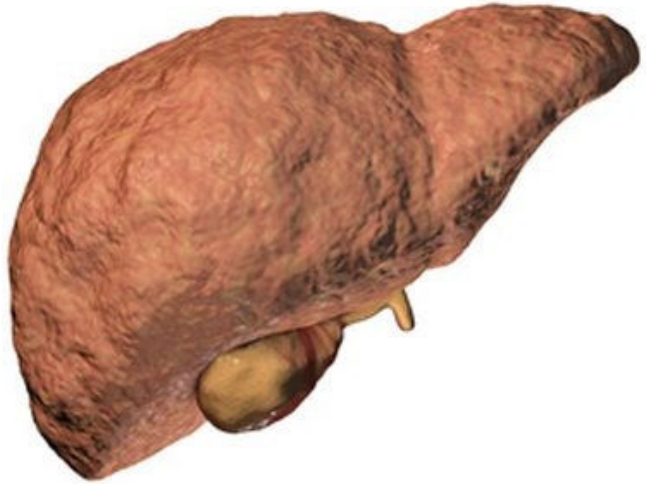
Intense itching
A swollen belly (ascites)
Bruising and bleeding easily
Yellowing of the skin and eyes (jaundice)
Spider-like blood vessels just beneath your skin's surface
Behavior changes, slurred speech, and confusion (hepatic encephalopathy)
If someone with NAFLD/NASH develops cirrhosis they are also at some risk of developing a common type of liver cancer called hepatocellular carcinoma.



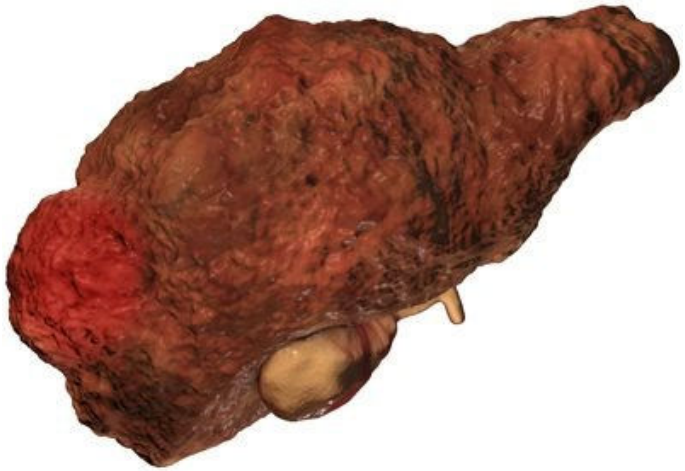


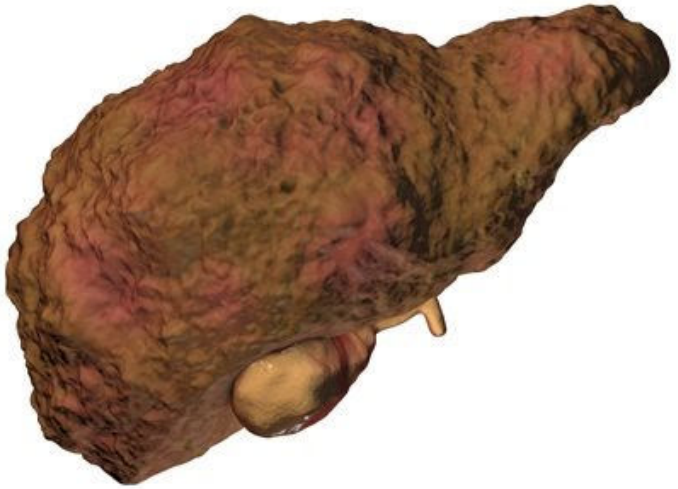






ASOCIACIÓN PUERTORRIQUEÑA DE GASTROENTEROLOGÍA





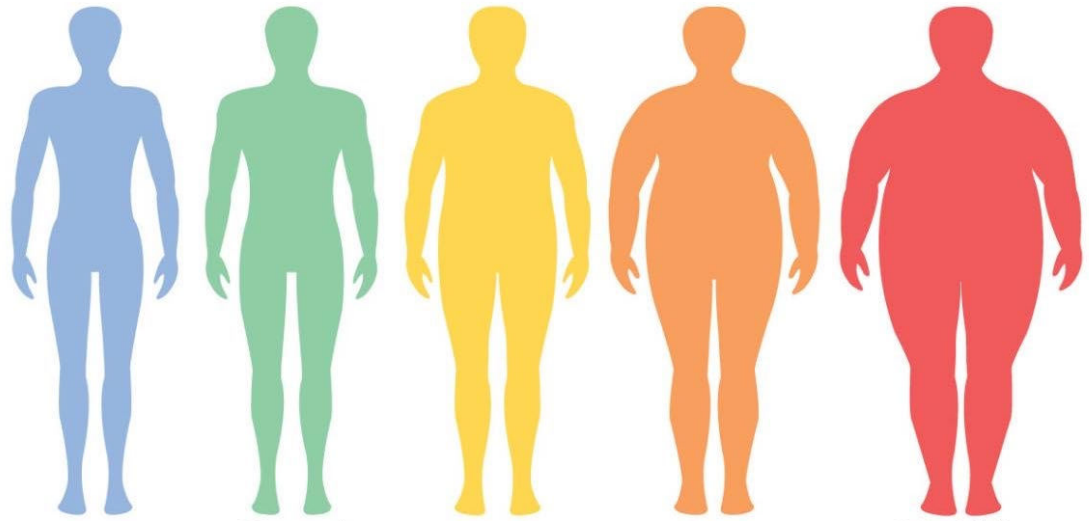
World Health Organization

OBESITY INCREASES THE RISK OF THESE CANCERS

When am I obese?

The easiest way to determine whether a person is overweight or obese is through measuring their body mass index (BMI).

$$BMI = \frac{\text{Weight in kg}}{(\text{Height in m})^2}$$



Underweight	Normal weight	Overweight	Obese	Morbidly obese
Asians				
<18.5	18.5-22.9	23-27.5	27.6-39.9	40 and above
Non-Asians				

Treatment: diet and lifestyle changes

- Epidemiology suggests a close relationship between an unhealthy lifestyle and NAFLD
- Diet and lifestyle changes are mandatory in all patients
  - Modest weight loss reduces liver fat, improves hepatic IR, and can result in NASH regression
  - Weight loss of ≥7% is associated with histological improvement

Recommendations	Grade of evidence	Grade of recommendation
Structured programmes aimed at lifestyle changes towards healthy diet and habitual physical activity are advisable in NAFLD	C	2
Patients without NASH or fibrosis should receive counselling for healthy diet and physical activity but no pharmacotherapy	B	2
In overweight/obese NAFLD, a 7–10% weight loss is the target of most lifestyle interventions, and results in improvement of liver enzymes and histology	B	1

EASL™ The Home of Hepatology

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

What are the treatments for NAFLD and NASH?

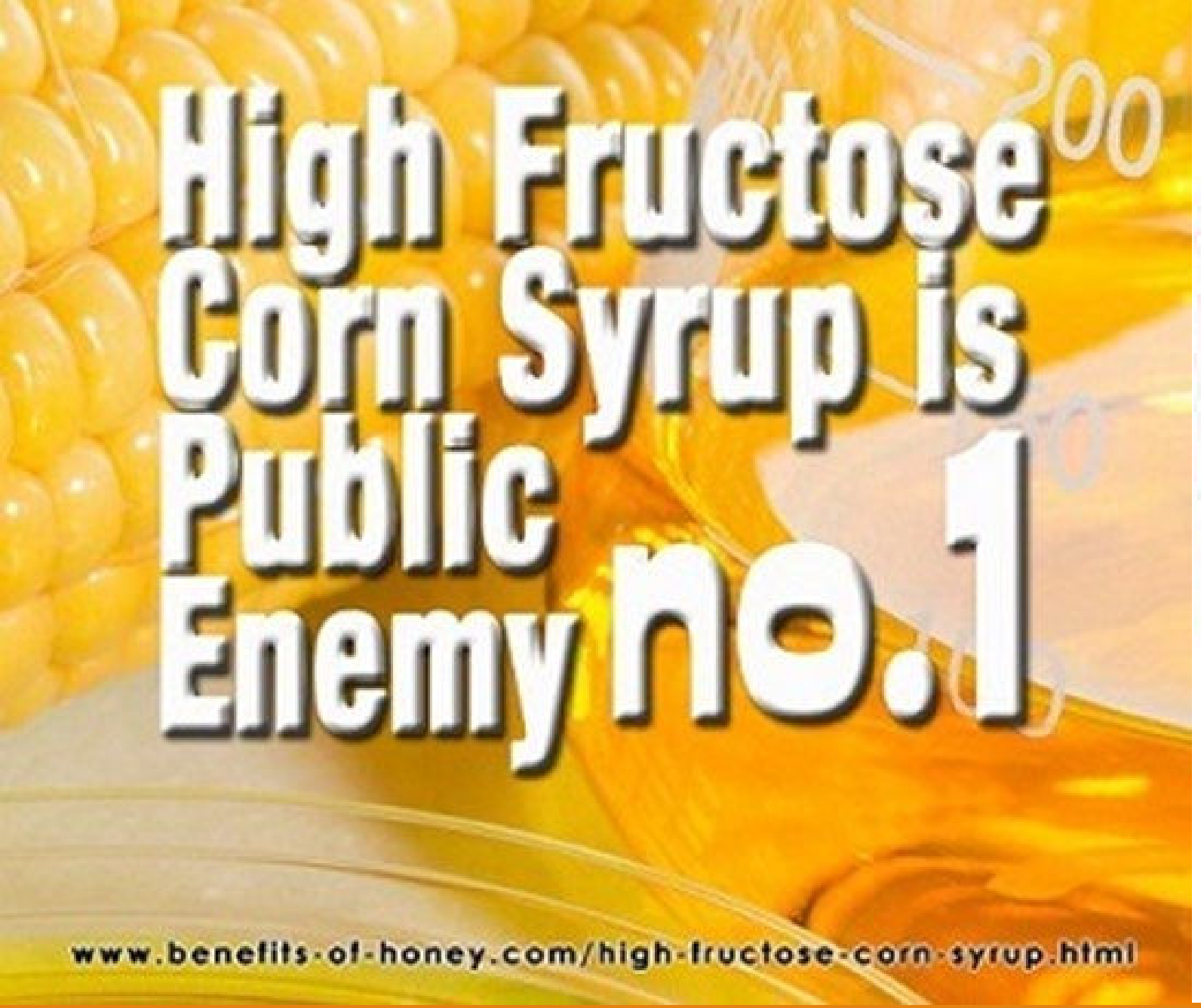
The first line of treatment for **NAFLD** and NASH is **weight loss**, done through a combination of calorie reduction,
exercise, and healthy eating. Weight loss can reduce fat and inflammation in the liver. The following lifestyle changes are important in managing your disease.

NAFLD DIET

- **limit alcohol consumption,**
- **limit saturated fat to less than 7% of calories and go easy on red meat**
- **when possible use low fat or skim dairy products**
- **eliminate trans-fat and all hydrogenated oils**
- **eliminate all high fructose corn syrup**
- **cut way down on salt -- the goal is 1500 mg/day**
- **minimize added dietary sugar**
- **limit the use of processed grains**
- **be aware that there are unknown health consequences for many chemicals**

DIET NAFLD 2

- Use extra virgin olive oil for cooking and try avocado oil
- Don't buy prepared foods without reading the label, there isn't actually much that you can buy
- Eat lots of fruits and vegetables but watch the salt
- Learn to like kale, lima beans, brussel sprouts, etc.
- Look for fiber like whole wheat bread no white breads and use brown rice
- Eat fatty fish like salmon at least a few times a week
- East skinless chicken or turkey and lean pork
- Minimize processed meats like ham
- Explore new foods like quinoa as a grain
- Eat plenty of vegetable protein like beans.
- Keep in mind that eating out is mostly unhealthy so be thoughtful


High Fructose Corn Syrup is Public Enemy no.1
www.benefits-of-honey.com/high-fructose-corn-syrup.html


SWEET'N LOW
SKIPPY
Welch's
Grape Jelly
HEINZ
TOMATO KETCHUP
HIGH FRUCTOSE
CORN SYRUP

CONSUMPTION OF HIGH-FRUCTOSE CORN SYRUP IN THE U.S. HAS GROWN TO **60 POUNDS** PER PERSON PER YEAR

HOW MUCH IS **60 POUNDS**?...ROUGHLY **5.3 GALLONS**:

HIGH-FRUCTOSE CORN SYRUP CONSUMPTION IN THE U.S. PER PERSON PER YEAR

Source: Census Bureau

WHY SHOULD YOU LIMIT HIGH-FRUCTOSE CORN SYRUP CONSUMPTION?

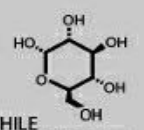
RESEARCH INDICATES THAT HFCS IS LINKED TO **OBESITY**:

- ABNORMAL INCREASE IN BODY FAT
- RISING BLOOD LEVELS OF ***TRIGLYCERIDES***

"Animals with access to high-fructose corn syrup gained 48% more weight than those eating a normal diet."

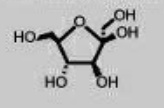
Source:
Princeton University study Feb. 26 2010
Pharmacology, Biochemistry and Behavior

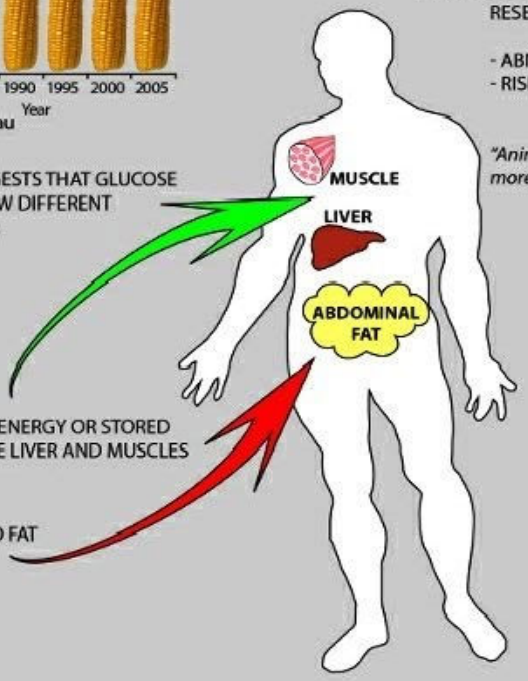
EARLY RESEARCH SUGGESTS THAT GLUCOSE AND FRUCTOSE FOLLOW DIFFERENT METABOLIC PATHWAYS:



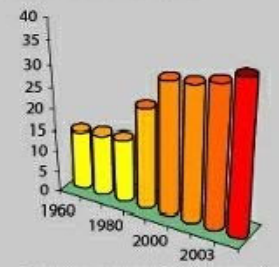
WHILE
GLUCOSE
IS PROCESSED INTO ENERGY OR STORED AS GLYCOGEN IN THE LIVER AND MUSCLES

FRUCTOSE
IS METABOLIZED INTO FAT





PERCENTAGE OF THE U.S.POPULATION CONSIDERED ***OBESE*** BETWEEN 20-74 YEARS OLD

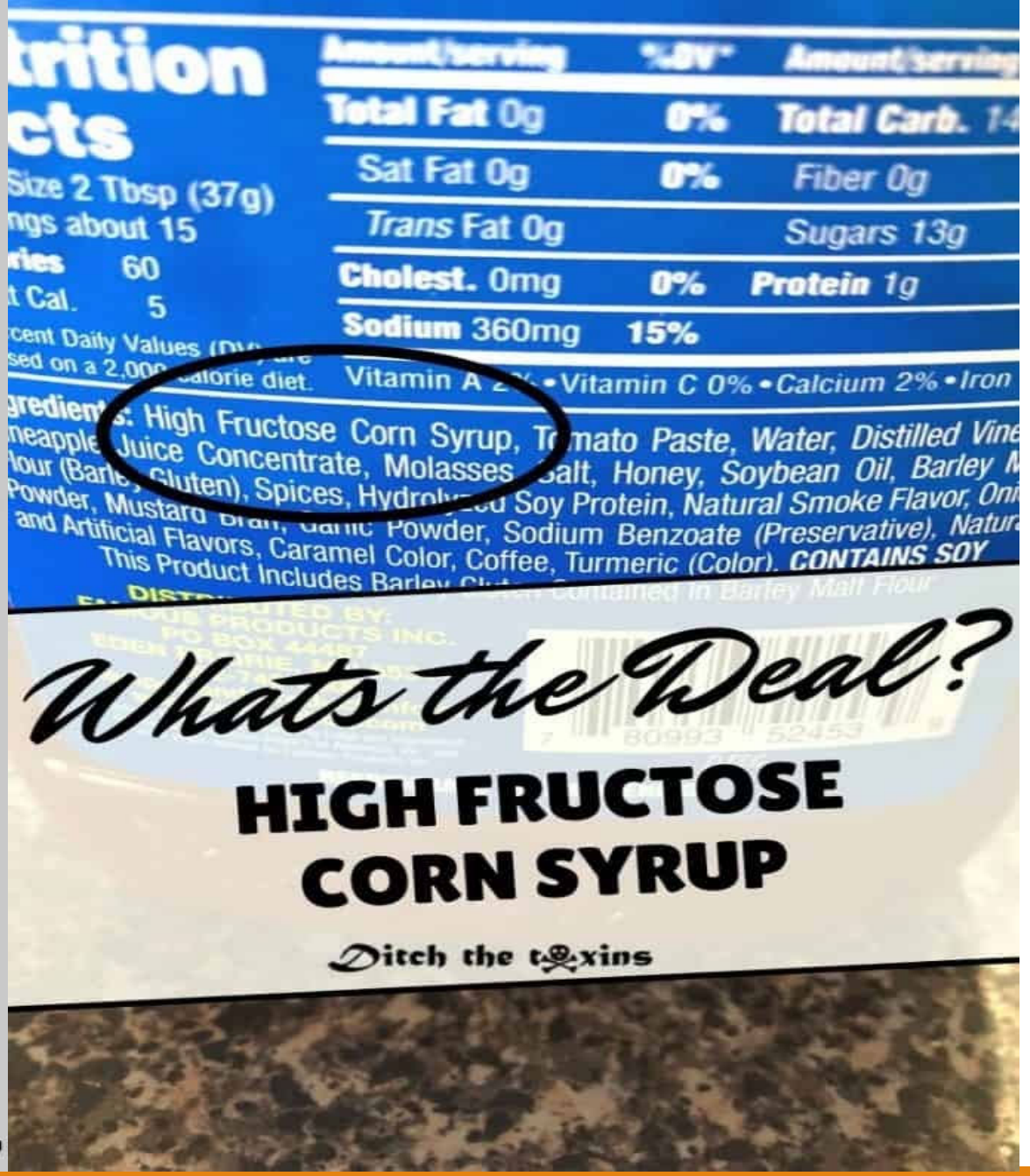


Source: Center for Disease Control

HIGH-FRUCTOSE CORN SYRUP ACCOUNTS FOR **40%** THE SWEETENERS USED IN THE U.S.
MOST OF THE PROCESSED PACKAGED FOOD...AND OTHER PLACES WHERE YOU WOULD NOT SUSPECT IT!!

BOTTLED DRINKS | CANDY BARS AND SPORT BARS | ICECREAM | SALAD DRESSING | CEREALS | CANNED SOUPS | YOGURT | CONDIMENTS AND SAUCES | ***. . . AND MORE !***

...COOK YOUR OWN MEALS!!
...READ THE LABELS!!



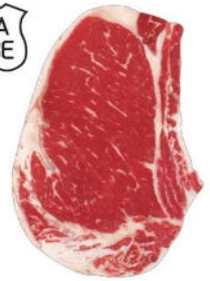
USDA BEEF QUALITY GRADING

UNDERSTANDING BEEF QUALITY GRADES

USDA PRIME

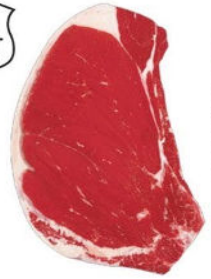
Prime beef is produced from young, well-fed cattle. It has the most marbling, is produced in smaller quantities than other grades, and is often sold in hotels and restaurants. Prime roasts and steaks are excellent for roasting, grilling or broiling.

USDA CHOICE



Choice beef is high quality and produced in highest quantity, but has less marbling than Prime. Choice roast and steaks, especially from the rib and loin, will be very tender, juicy and flavorful. They are suited for roasting, grilling or broiling. Less tender cuts are perfect for slow-cooking.

USDA SELECT



Select beef is slightly leaner than Prime and Choice because it has less marbling. It can lack some tenderness, flavor and juiciness as compared to the higher grades. Select grade beef often benefits from slow-cooking or from marination prior to grilling or broiling.

NO ROLL Standard and Commercial grades of beef are frequently sold as ungraded "No Roll" beef. Because No Roll does not carry a grade designation, there is a risk it will not be as tender, flavorful and juicy as products graded Prime, Choice or Select.

FACTORS IN DETERMINING A QUALITY GRADE:

Distribution of Marbling within Lean Muscle at 12th/13th Rib

Age/Maturity of Carcass

Color, Texture & Firmness of Lean Muscle

WHAT IS MARBLING?

Marbling, also known as intramuscular fat, is the fat intermingled with the beef muscle. Marbling is the primary factor in determining the quality grade of a beef carcass. When determining the amount of marbling, a grader will look at the ribeye where the carcass is cut at the 12th & 13th rib juncture. Marbling helps ensure and is a strong visual predictor of beef tenderness, flavor and juiciness and improves the overall palatability of beef.

BEEF

Funded by Beef Farmers and Ranchers

ASOCIACIÓN PUERTORRIQUEÑA DE GASTROENTEROLOGÍA


What's Your Beef?
A guide to understanding USDA's beef grades.
USDA PRIME
USDA PRIME
USDA PRIME
Prime beef is produced from young, well-fed beef cattle. It has abundant marbling, and is generally sold in hotels and restaurants. Prime roasts and steaks are excellent for broiling, roasting or grilling.
USDA CHOICE
USDA CHOICE
USDA CHOICE
USDA CHOICE
Choice beef is high quality, but has less marbling than Prime. Choice roasts and steaks from the loin and rib will be very tender, juicy, and flavorful and are suited for broiling, roasting or grilling. Less tender cuts are perfect for braising, roasting or simmering on the stovetop with a small amount of liquid.
USDA SELECT
USDA SELECT
Select beef is very uniform in quality and normally leaner than Prime or Choice. It is fairly tender, but, because it has less marbling, it may not have as much juiciness or flavor. Select beef is great for marinating or braising.
USDA
Produced by the U.S. Department of Agriculture
Agricultural Marketing Service
www.ams.usda.gov/grading
background photo courtesy Kyle Wirth


GRADES OF STEAK
Prime
Choice
Select
Biteseez


FURIOUS GRILL
Full Comparison Guide on
WAGYU VS KOBE BEEF
Everything You Need to Know


ASOCIACIÓN PUERTORRIQUEÑA
DE GASTROENTEROLOGÍA

No therapies have yet been approved by the US Food and Drug Administration (FDA) for the treatment of nonalcoholic steatohepatitis (NASH). Thus, therapy has mostly been lifestyle-based, often directed at achieving weight loss with exercise and a diet that is low in cholesterol, saturated fats, and fructose, such as the Mediterranean diet. However, most patients find lifestyle interventions difficult to sustain long term.

Besides lifestyle interventions, have pioglitazone and vitamin E been used much?

Exercise Mobilizes Hepatic Fat Mobilization in Patients With NAFLD

Systematic review (8 RCTs and prospective cohort studies) in adults (N = 433)

- Dietary interventions plus exercise augment hepatic fat reduction
- Moderate-intensity exercise mobilizes intrahepatic triglycerides (30.2% in the exercise-only group and 49.8% in diet plus exercise group)

Exercise 3-4 times/wk, 20-30 min/sessions

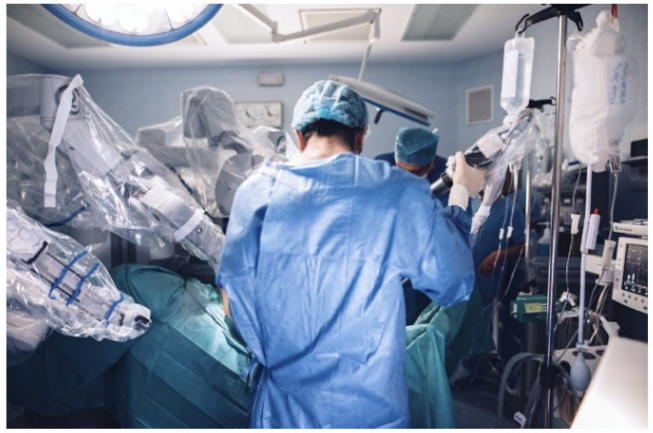
Bariatric Surgery: An Option for Patients With NASH

Morbid obesity and cirrhosis[a]

- Compared with noncirrhotic and nonobese patients with cirrhosis, severely obese patients with cirrhosis have highest risk of mortality

Bariatric surgery may be considered for severely obese persons (BMI >40 or >35 with comorbidity) who clearly wish to lose weight[a]

- Induces long-term weight loss; decreases morbidity, incidence of cancer, and mortality
- Improves steatosis in 90% of cases
- Resolves steatohepatitis in >80% of cases
- Mortality rates increased 2-fold in compensated cirrhosis, 21-fold in decompensated cirrhosis



"Foregut bariatric surgery can be considered in otherwise eligible obese individuals with NAFLD or NASH - Premature to consider it an established option to treat NASH specifically".[b]

ASOCIACIÓN PUERTORRIQUEÑA DE GASTROENTEROLOGÍA

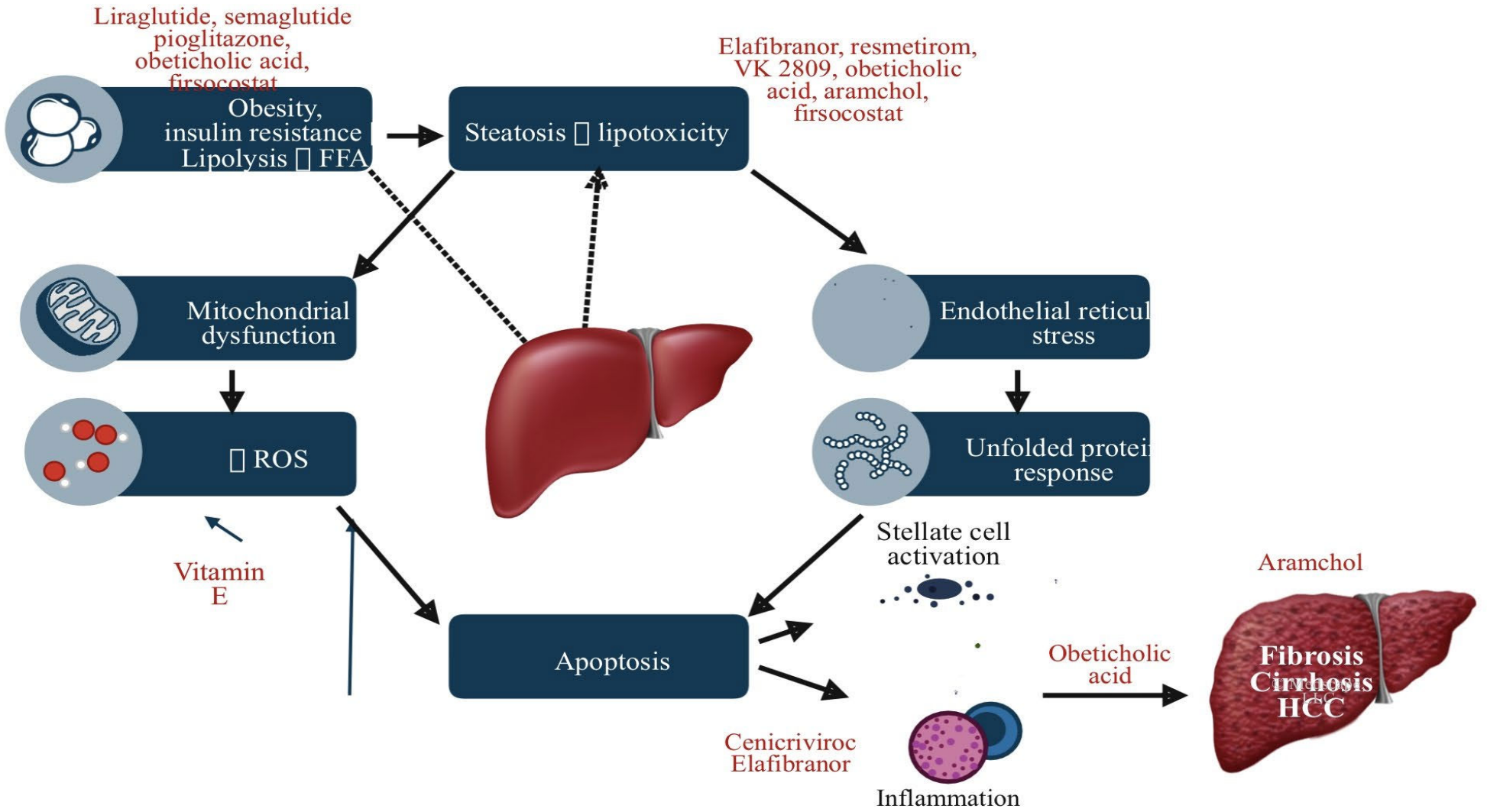
Vitamin E for NASH: AASLD Guidance

AASLD Guidance[a]

- 800 IU/d (D-alpha-tocopherol) improves liver histology in nondiabetic adults with biopsy-proven NASH; may be considered for this population
- Not yet recommended for:
  - NASH in patients with T2D
  - NAFLD without liver biopsy
  - NASH cirrhosis
  - Cryptogenic cirrhosis

Chalasani N, et al. *Hepatology*. 2018;67:328-357.

Targets for Treatment



Partial List of Drugs in Phase 2 Trials for NASH

Drug	MOA	Primary Endpoint*
GR-MD-02[a]	Galectin-3 inhibitor	Reduction of HVPG at 1 y
NGM282[b]	FGF19 analogue	Change in hepatic fat fraction assessed by MRI-PDFF at 12 wk
VK2809[c]	THR-β agonist	Change in hepatic fat: absolute change in liver fat from baseline, median relative change in liver fat from baseline, ≥30% relative reduction in liver fat
Fircosostat[d]	Acetyl-CoA carboxylase inhibitor	Relative reduction in liver fat from baseline
Semaglutide[e]	GLP-1 receptor agonist	Change in ALT level

*Biopsy data from paired liver biopsies
Note: Since the time of the recording, resmetirom moved into a phase 3 clinical trial
a. Harrison SA, et al. *Aliment Pharmacol Ther*. 2016;44:1183-1198; b. Harrison SA, et al. *Lancet*. 2018;391:1174-

What are some of the most promising drugs in development for the treatment of NASH?

There are many promising drugs, but the most important ones to consider are those in phase 3 development. As previously mentioned, **obeticholic acid** is the furthest along in development and could, theoretically, receive approval by the FDA soon.

Also promising is the peroxisome proliferator–activated receptor (PPAR) agonist **elafibranor** (GFT505, Genfit), which will soon report interim phase 3 results. This drug has very broad effects involving both lipid and glucose metabolism, as well as downstream effects on inflammation and fibrosis.

Other promising drugs in phase 3 trials are aramchol (Galmed Pharmaceuticals), which is a stearoyl-CoA desaturase 1 inhibitor, and cenicriviroc (Allergan), which likely has primarily anti-inflammatory effects.

Among thyroid hormone receptor β agonists, MGL-3196 (Madrigal Pharmaceuticals) is furthest along and looks promising. However, there are no data on longer-term safety or the impact on clinical endpoints, such as liver failure, involving any of the drugs in advanced development.

Current Ongoing Phase 3 Trials for NASH

Drug	MOA	Trial	Primary Endpoint
Obeticholic acid	FXR agonist	REGENERATE[a] REVERSE[b]	≥1 stage fibrosis improvement with no NASH worsening OR resolution of NASH with no fibrosis worsening ≥1 stage fibrosis improvement AND no worsening of steatohepatitis
Cenicriviroc	CCR2/CCR5 antagonist	AURORA[c]	≥1 stage fibrosis improvement AND no worsening of steatohepatitis
Elafibranor	PPARα/σ agonist	RESOLVE-IT[d]	Resolution of NASH without fibrosis worsening
Resmetirom	Selective THR-β agonist	MAESTRO-NASH[e]	Resolution of NASH Composite long-term outcome: all-cause mortality, cirrhosis, and liver-related clinical outcomes
Aramchol	Fatty acid bile acid conjugate	ARMOR[f]	Resolution of NASH without fibrosis worsening or ≥1 stage fibrosis improvement AND no worsening of steatohepatitis

Note: Since the time of the recording, resmetirom and aramchol moved into phase 3 clinical trials
a. Sanyal AJ, et al. *Hepatology*. 2019;70:23A; b. ClinicalTrials.gov. NCT0303439254; c. ClinicalTrials.gov. NCT03028740; d. ClinicalTrials.gov. NCT02704403; e. ClinicalTrials.gov. NCT03900429; f. ClinicalTrials.gov. NCT04104321.

Obeticholic Acid for NASH: Revolution or Just a Ripple?

OCA might improve fibrosis in a portion of patients affected by NASH. In this multicenter, double-blind study conducted across 332 centers in 20 countries, patients were randomly assigned to receive placebo, OCA 10 mg/d, or OCA 25 mg/d. Liver biopsies were obtained at baseline and at month 18 or at the end of treatment.

Liver fibrosis improvement was reached more frequently and with statistical significance in the groups taking OCA. Improvement in fibrosis was seen in 23% of patients taking 25 mg OCA, 18% taking 10 mg OCA, and 12% in the placebo group.

OCA

Despite OCA being well tolerated across all groups, pruritus (most of which occurred during the first 3 months) led to treatment discontinuation in 9% of the 25-mg OCA group,

In addition, OCA can elevate low-density lipoprotein (LDL) cholesterol levels. Patients receiving OCA in the phase 3 trial were more likely to require a statin compared with placebo,

FDA adds Boxed Warning to highlight correct dosing of Ocaliva (obeticholic acid) for patients with PBC

OCA 3

In addition, on June 29, 2020, the FDA issued a Complete Response Letter to Intercept Pharmaceuticals that requested additional post-interim analysis to support the accelerated approval of OCA. Despite the improvement in liver fibrosis, the FDA did not feel the existing data demonstrated adequate benefit to outweigh potential risk and emphasized the importance of long-term outcome. This decision not only is a setback to Intercept Pharmaceuticals but also sends a message to other pharmaceutical companies with therapeutic agents in development that there will be a high bar for a surrogate endpoint to gain FDA approval.

Cenicriviroc (CVC)

is a CCR2/5 dual antagonist under evaluation for treating liver fibrosis in adults with nonalcoholic steatohepatitis (NASH).

Year 1 primary analysis of the 2-year CENTAUR study showed that CVC had an antifibrotic effect without impacting steatohepatitis.

The 2-year data suggest no further improvement in fibrosis beyond that observed after a year. Furthermore, patients who switched from placebo to CVC after 1 year had similar improvement in fibrosis (without worsening of steatohepatitis) compared with those on placebo for 2 years (24% vs. 17%; *P*=0.37).

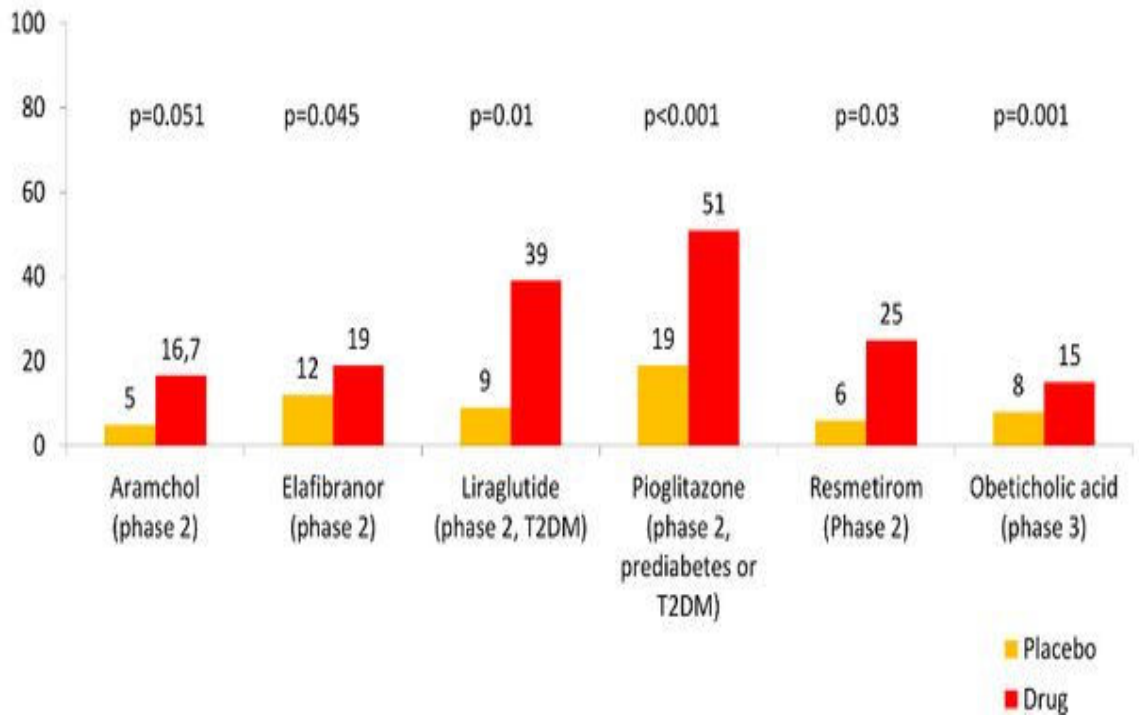
These 2-year results suggest that CVC mainly improves fibrosis in NASH, especially in cases with advanced fibrosis, and that most of the improvement occurs within the first year. The current results have prompted a phase III study (the AURORA study) that will focus on fibrosis improvement as the primary endpoint — and only in those with advanced fibrosis; this appears to be a reasonable approach since morbidity and mortality are mainly driven by fibrosis in NASH.

Genfit's elafibranor en route to NASH graveyard with phase 3 flop

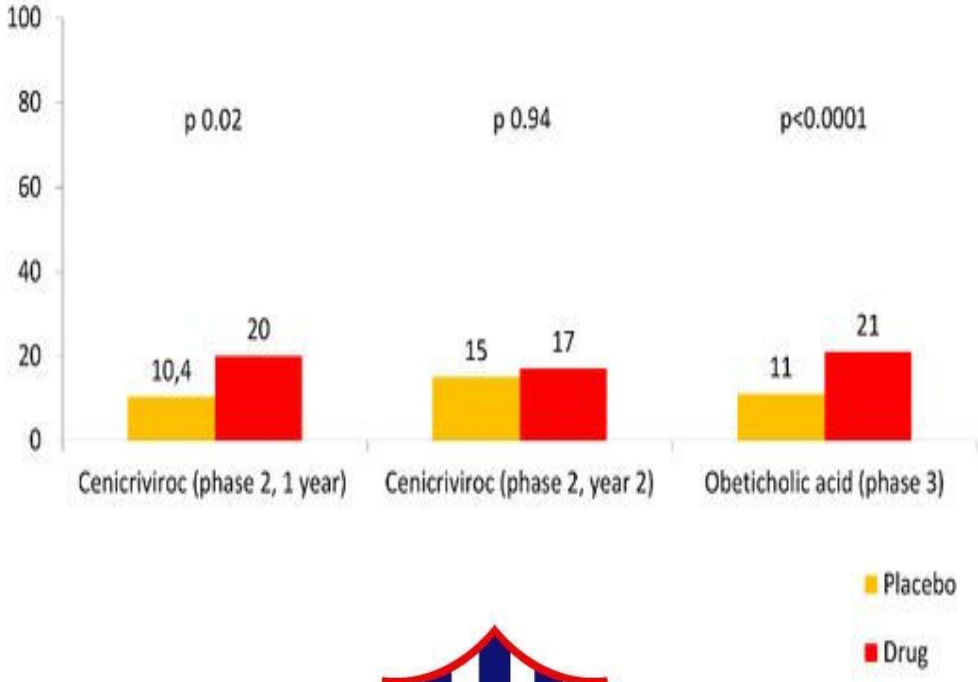
Genfit's leading drug has failed a key phase 3 study in nonalcoholic steatohepatitis (NASH), **joining a growing number of fatty liver prospects that have bitten the dust** and putting the biotech's future on a knife-edge. The drug, elafibranor, **did not beat placebo** at improving NASH symptoms without making liver scarring worse, interim data show.

The study pitted elafibranor against placebo in 1,070 adults with a form of fatty liver disease known as NASH with stage 2 or stage 3 scarring (fibrosis). After 72 weeks of treatment, the study missed its primary endpoint, with 19% of patients in the treatment arm achieving NASH resolution—improvements in liver inflammation and liver cell ballooning—without their scarring getting worse, compared to 15% of patients in the placebo group.

A Resolution of NASH without worsening of fibrosis



B >1 stage fibrosis reversal without worsening of NASH



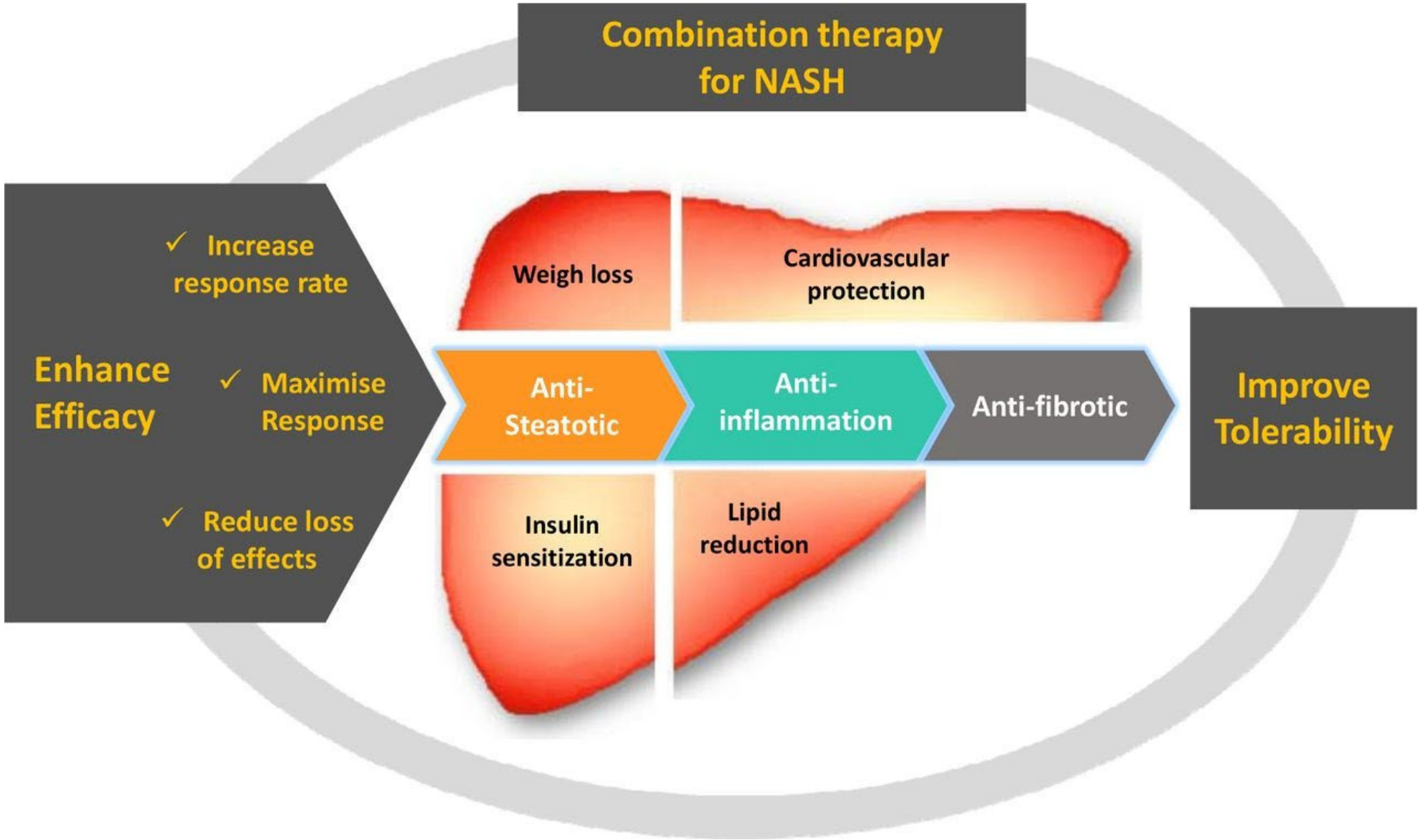
Poxel Initiates Phase 2 NASH Trial for PXL065 (DESTINY 1) in Biopsy-Proven Patients

Phase 2 trial will include approximately 120 noncirrhotic biopsy-proven NASH patients and is designed to identify optimal dose or doses for Phase 3 registration trial

Streamlined development with a single Phase 2 trial given knowledge of pioglitazone, including data in NASH, and 505(b)(2) regulatory pathway, which offers the opportunity for an efficient and lower risk development program

The primary endpoint of DESTINY 1 will measure the relative change in the percentage of liver fat as measured by MRI-PDFF

PXL065 is a new chemical entity derived from pioglitazone, which has shown to retain NASH efficacy without triggering peroxisome proliferator-activated receptor (PPAR)-g-related side effects in preclinical studies


Combination therapy for NASH
Enhance Efficacy
✓ Increase response rate
✓ Maximise Response
✓ Reduce loss of effects
Weigh loss
Cardiovascular protection
Anti-Steatotic
Anti-inflammation
Anti-fibrotic
Insulin sensitization
Lipid reduction
Improve Tolerability

How common are NAFLD and NASH in children?

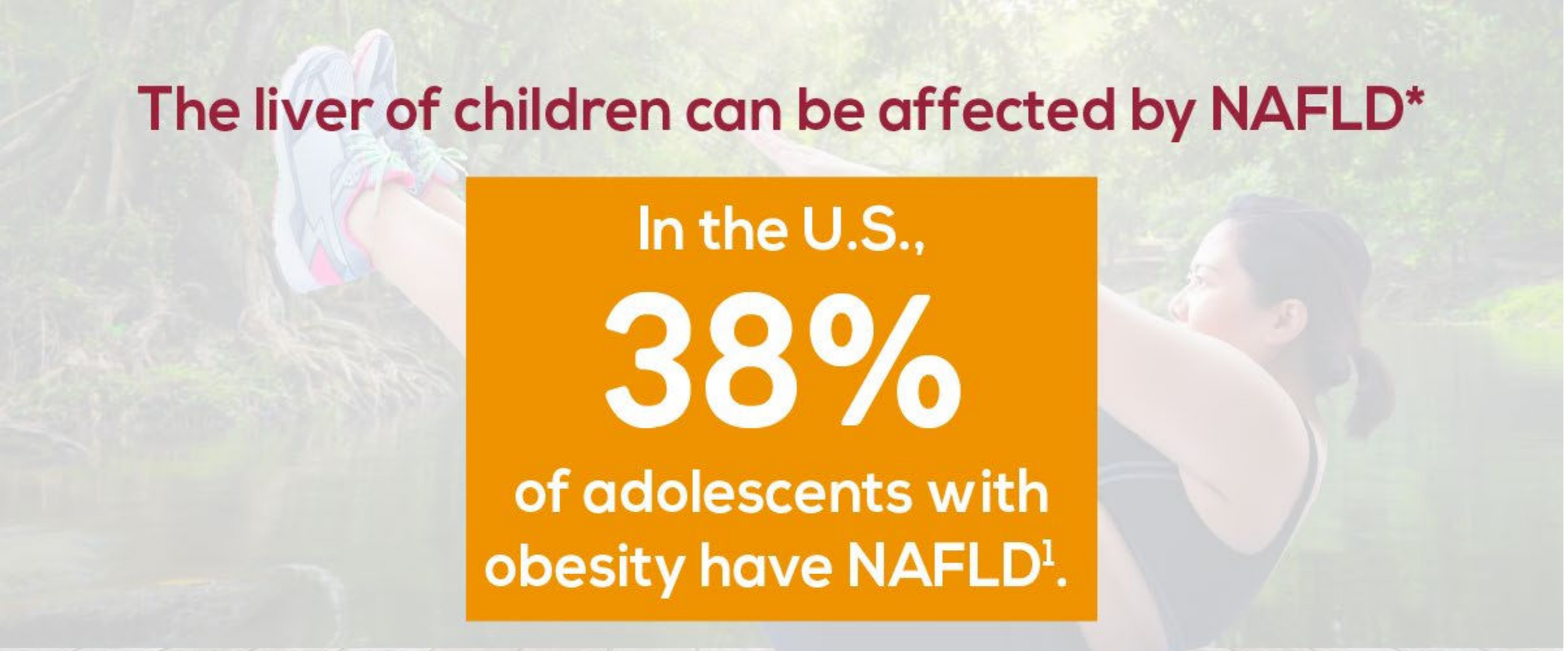
NAFLD is the most common cause of chronic liver disease in children in the United States. Researchers estimate that close to 10 percent of U.S. children ages 2 to 19 – about six million children – have NAFLD. It's become more common in children in recent decades, in part due to the growing epidemic of childhood obesity.

NAFLD is more common in…
Older children than in younger children
Hispanic and Asian American children, followed by Non-Hispanic White children (and less likely in African American children)
NAFLD is more common in boys than in girls; however, among children with NAFLD, boys and girls are equally likely to have NASH.

The majority of children with NAFLD have simple fatty liver. Children with simple fatty liver typically don't develop liver complications. However, compared with adults who develop NAFLD, children with NAFLD more likely to have NASH and related complications or liver disease as adults.

NAFLD and NASH in Children in the United States: A Serious Threat (cont)

- Prevalence of NAFLD in US children is as high as 17.3%[a]
  - More common in Hispanic boys
- Risk factors: family history
  - Gestational diabetes
  - T2D



*Non-Alcoholic Fatty Liver Disease | [1] Extracted from Liver Forum Pediatric Working Group. Factors to Consider in Development of Drugs for Pediatric Nonalcoholic Fatty Liver Disease. Volume 157, Issue 6, December 2019, Pages 1448-1456.e1

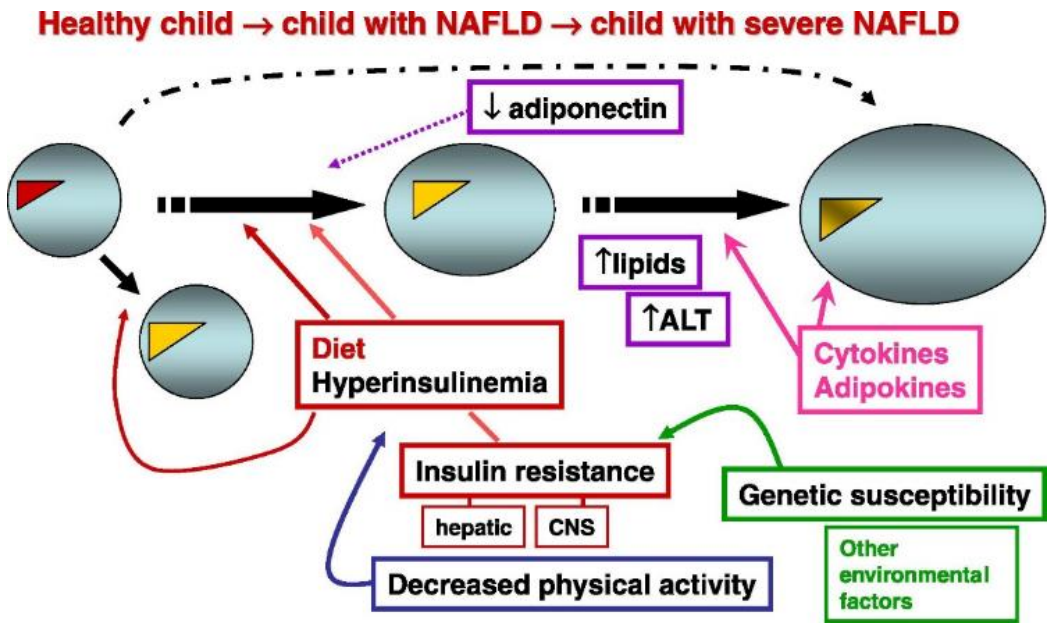
Learn more about NAFLD & NASH on **the-nash-education-program.com**

#NASHedu **@NASH_Education** **The NASH Education Program**

THE NASH EDUCATION PROGRAM
A GENFIT INITIATIVE

Non-invasive assessment of paediatric NAFLD

- NAFLD should always be suspected in obese children
  - Exclude other causes
  - Evaluate elevated aminotransferase levels and liver hyperechogenicity
    - Due to the poor sensitivity in overweight/obese children, non-invasive markers and imaging techniques are the first diagnostic step



Recommendations	Grade of evidence	Grade of recommendation
In children, predictors of fibrosis, including elastometry, ARFI imaging and serum biomarkers might help reduce the number of biopsies	B	2

Roberts EA. J Hepatol 2007;46:1133–42

EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Recommended interventions in pediatric NAFLD*:[1]

Lifestyle changes

- Avoidance of sugar-sweetened beverages
- Consumption of healthy, well balanced diet
- Moderate to high intensity exercise daily
- Less than 2 hours/day of screen time

Medications for NAFLD

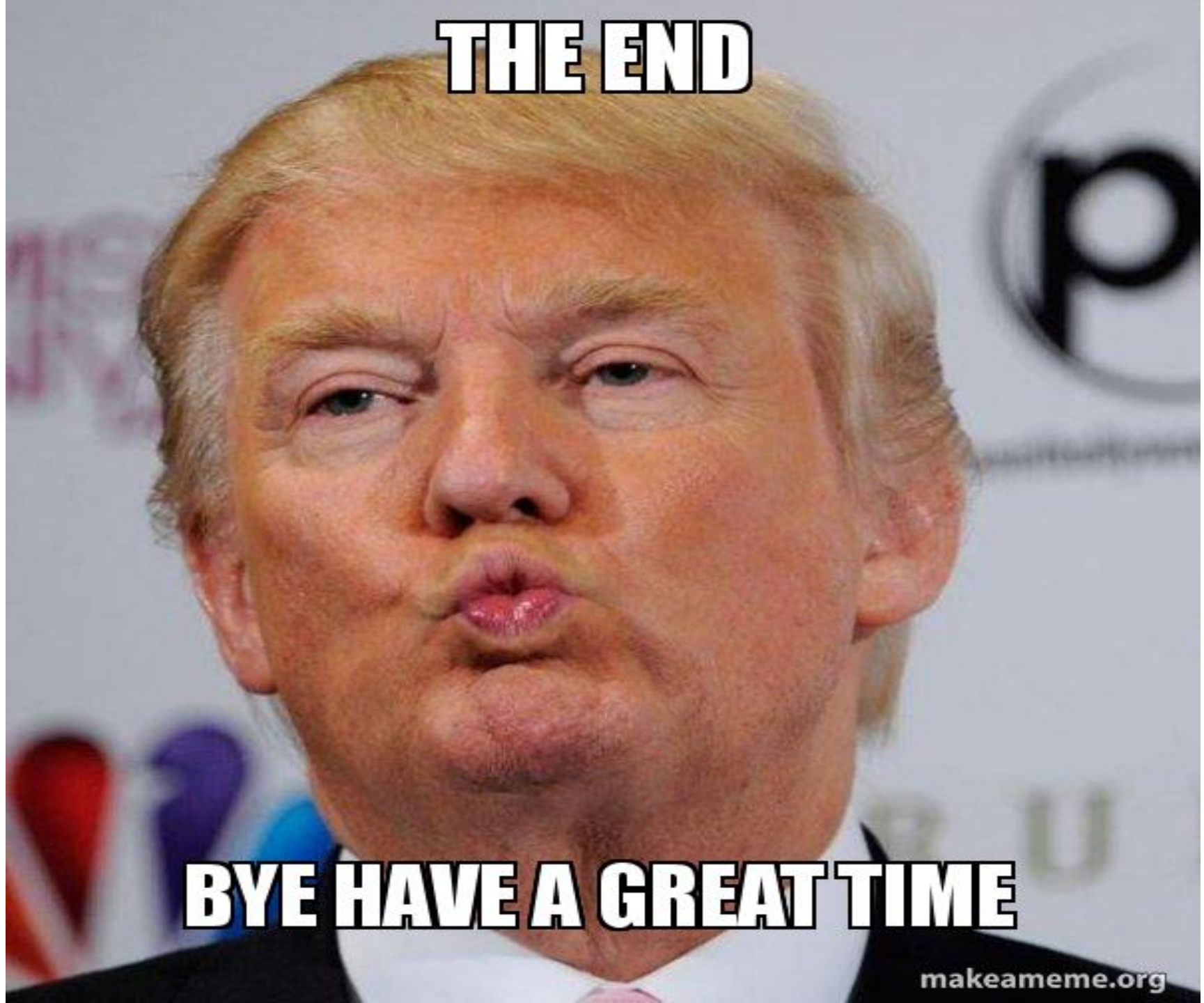
- No currently available medications have been proven to benefit the majority of patients with NAFLD

*Non-Alcoholic Fatty Liver Disease | [1]Extracted from NASPGHAN Clinical Practice Guideline (Copyright ESPGHAL and NASPGHAN. JPGN, 2017)

Ni el amor ni el tiempo sanan...
Lo único que sana es la colita de rana.

–Tate quieto, hombre. Que es una pruebita de nada.

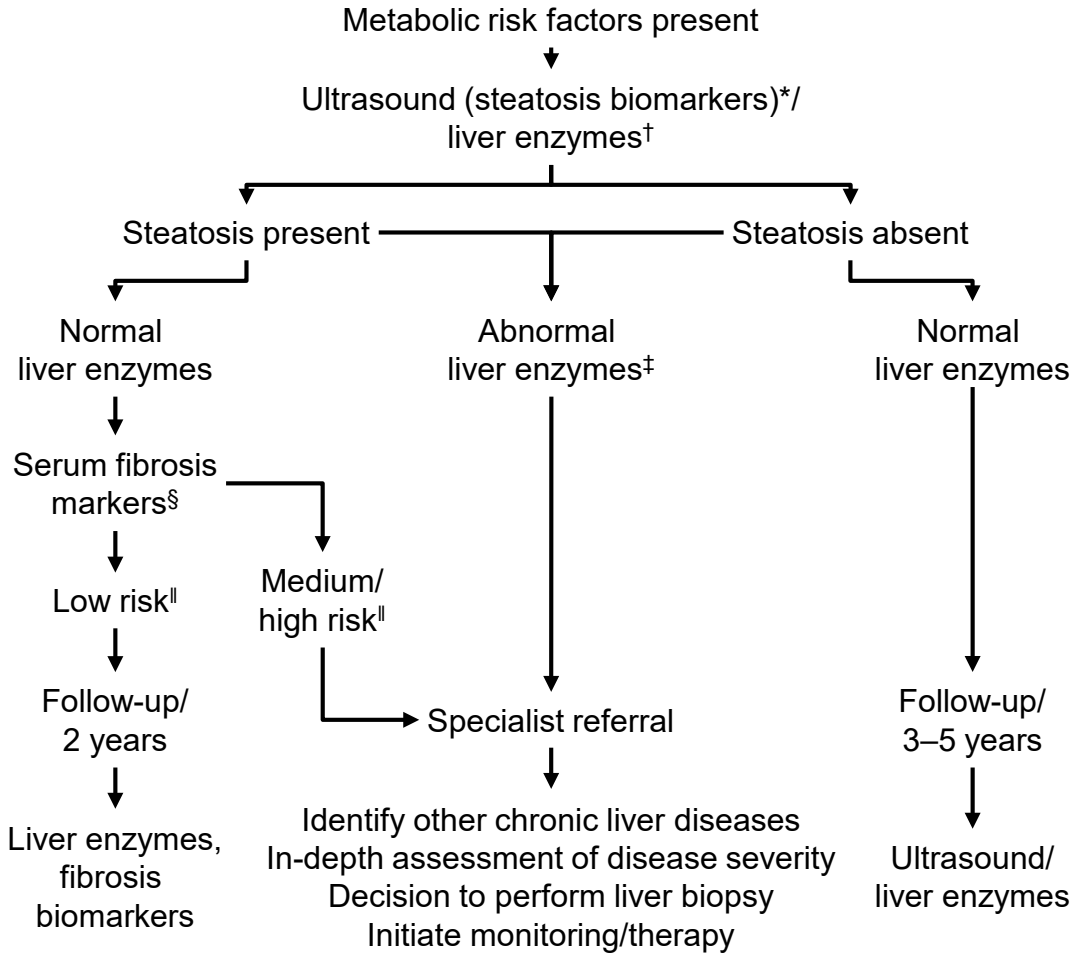

THE END
NOW CLAP
ICANHASCHEEZBURGER.COM


THE END
BYE HAVE A GREAT TIME
makeameme.org

ASOCIACIÓN PUERTORRIQUEÑA DE GASTROENTEROLOGÍA

Diagnosis: diagnostic flow-chart

- Metabolic work-up must carefully assess all components of MetS
- Obesity/T2DM or raised liver enzymes in patients with metabolic risk factors should prompt non-invasive screening to predict steatosis, NASH and fibrosis



*Steatosis biomarkers: Fatty Liver Index, SteatoTest, NAFLD Fat score;
†Liver tests: ALT AST, GGT; ‡Any increase in ALT, AST or GGT;
§Serum fibrosis markers: NAFLD Fibrosis Score, FIB-4, Commercial tests (FibroTest, FibroMeter, ELF);
‖Low risk: indicative of no/mild fibrosis; medium/high risk: indicative of significant fibrosis or cirrhosis
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

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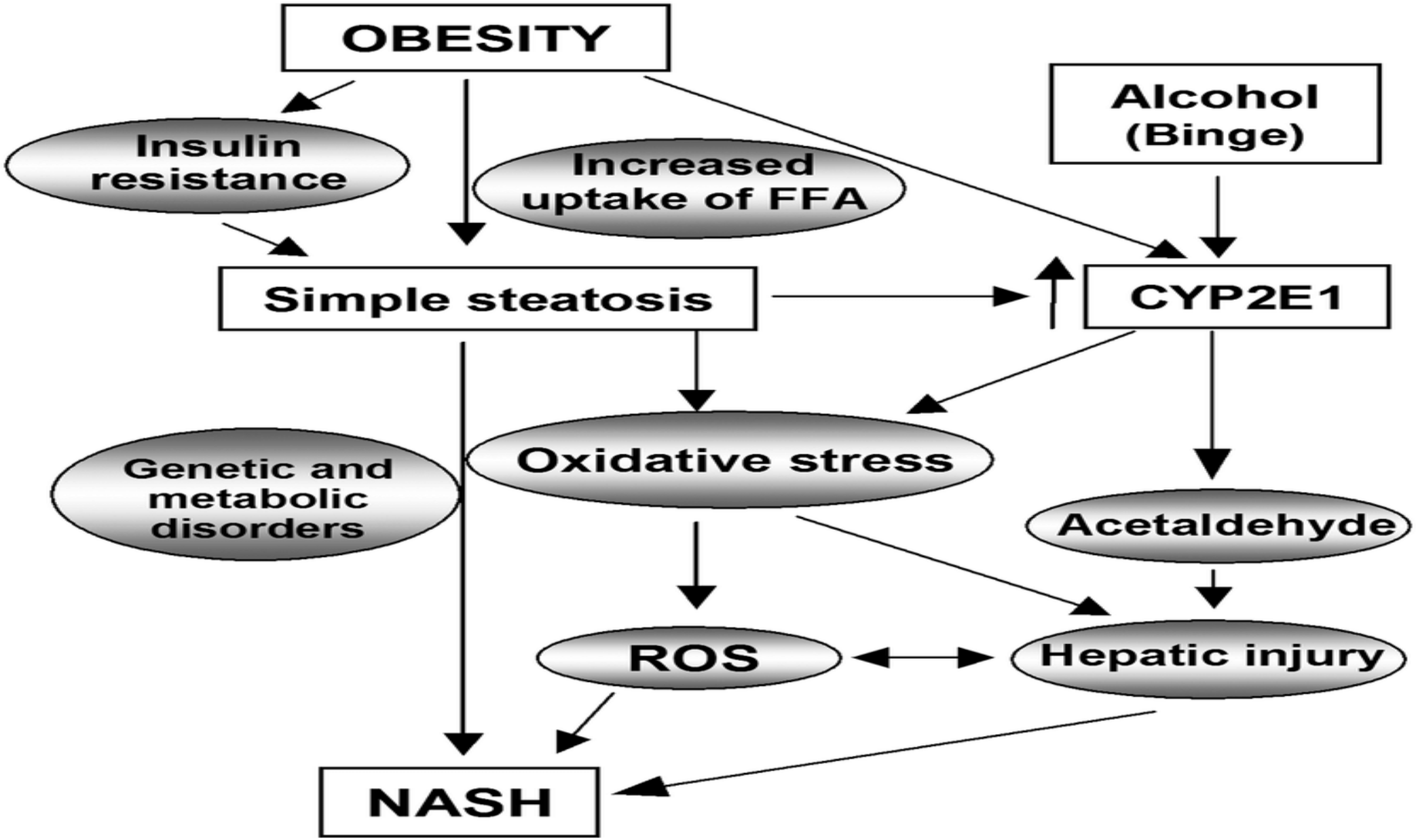
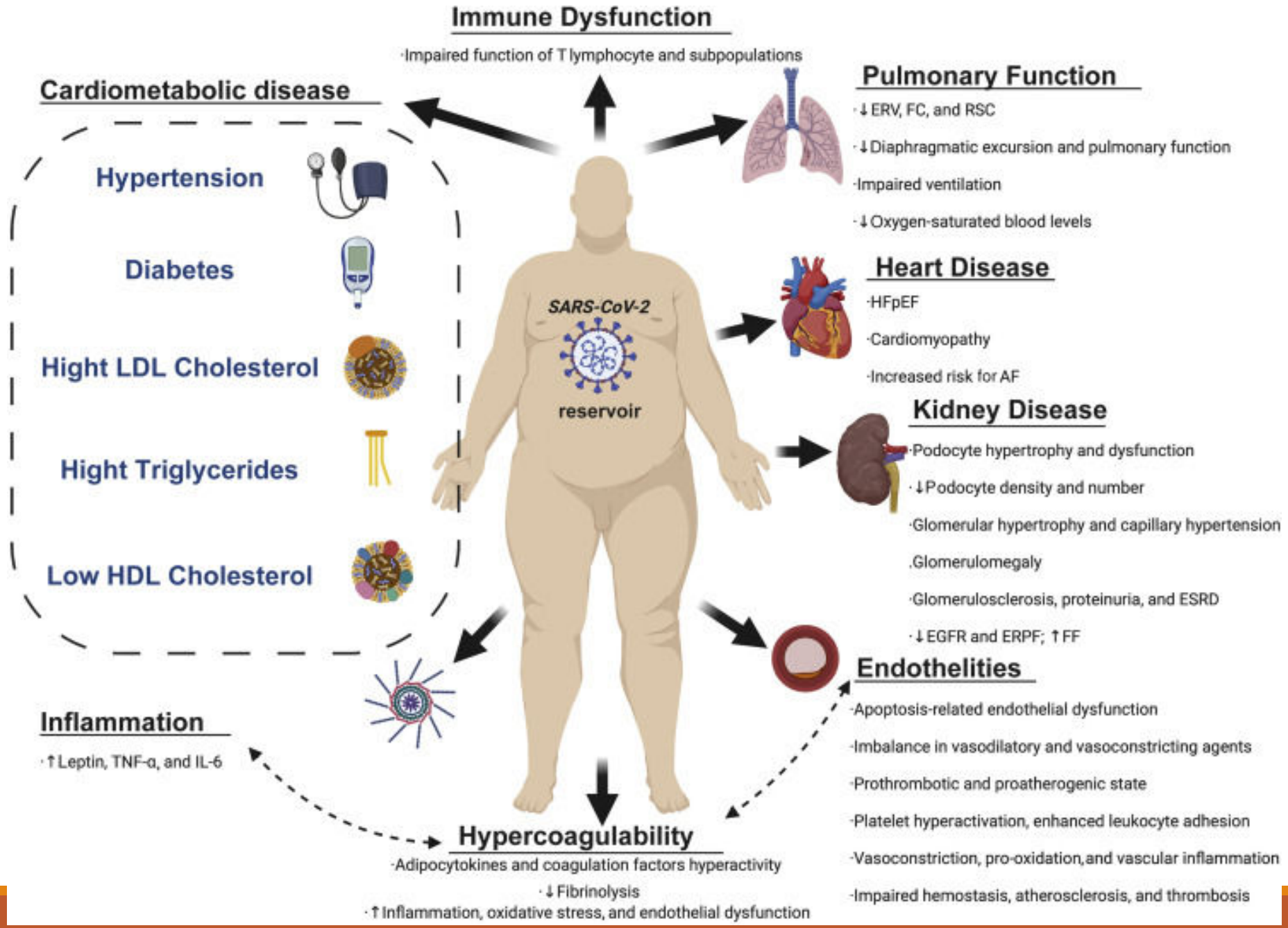

OBESITY
Alcohol (Binge)
Insulin resistance
Increased uptake of FFA
Simple steatosis
CYP2E1
Genetic and metabolic disorders
Oxidative stress
Acetaldehyde
ROS
Hepatic injury
NASH


Immune Dysfunction
·Impaired function of T lymphocyte and subpopulations
Cardiometabolic disease
Hypertension
Diabetes
Hight LDL Cholesterol
Hight Triglycerides
Low HDL Cholesterol
Pulmonary Function
·↓ERV, FC, and RSC
·↓Diaphragmatic excursion and pulmonary function
·Impaired ventilation
·↓Oxygen-saturated blood levels
SARS-CoV-2
reservoir
Heart Disease
·HFpEF
·Cardiomyopathy
·Increased risk for AF
Kidney Disease
·Podocyte hypertrophy and dysfunction
·↓Podocyte density and number
·Glomerular hypertrophy and capillary hypertension
.Glomerulomegaly
·Glomerulosclerosis, proteinuria, and ESRD
·↓EGFR and ERPF; ↑FF
Endothelities
·Apoptosis-related endothelial dysfunction
·Imbalance in vasodilatory and vasoconstricting agents
·Prothrombotic and proatherogenic state
·Platelet hyperactivation, enhanced leukocyte adhesion
·Vasoconstriction, pro-oxidation,and vascular inflammation
·Impaired hemostasis, atherosclerosis, and thrombosis
Inflammation
·↑Leptin, TNF-α, and IL-6
Hypercoagulability
·Adipocytokines and coagulation factors hyperactivity
·↓Fibrinolysis
·↑Inflammation, oxidative stress, and endothelial dysfunction