M Khoshbaten, M.D.
Professor of Gastroenterology & Hepatology
Tabriz university of medicale siencese

Non Alcoholic Fatty Liver Disease

History

- Since the initial descriptions in the early 1980s by Dr. Ludwig et al. and Drs. Schaner and Thaler, who firstly coined the terms nonalcoholic steatohepatitis (NASH) and nonalcoholicfatty liver disease (NAFLD), this liver disease has become a global health problem worldwide, causing
  - Considerable liver-related and extra-hepatic
    - Morbidity
    - Mortality

Metabolites **2020**, 10, 397; doi:10.3390/metabo10100397

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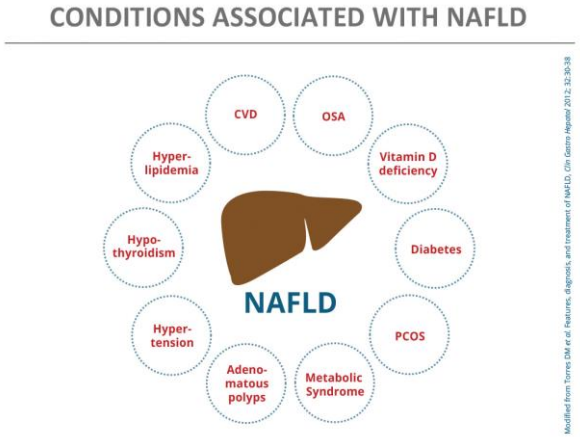
History

- Over the last two decades, NAFLD has reached epidemic proportions and is now recognized as a public health problem that a acts up to
  - Nearly a third of the world's adult population
  - has gone
    - From an obscure liver disorder to
    - Most prominent chronic liver disease worldwide



- The burden of NAFLD is strongly influenced by
  - Global epidemics of obesity and type 2 diabetes mellitus
    - Prevalence of these conditions is expected to dramatically increase in the forth coming decades
- Thus, NAFLD is
  - An important cause of a poor quality of life for many patients
  - In a considerable global health and economic burden for healthcare providers

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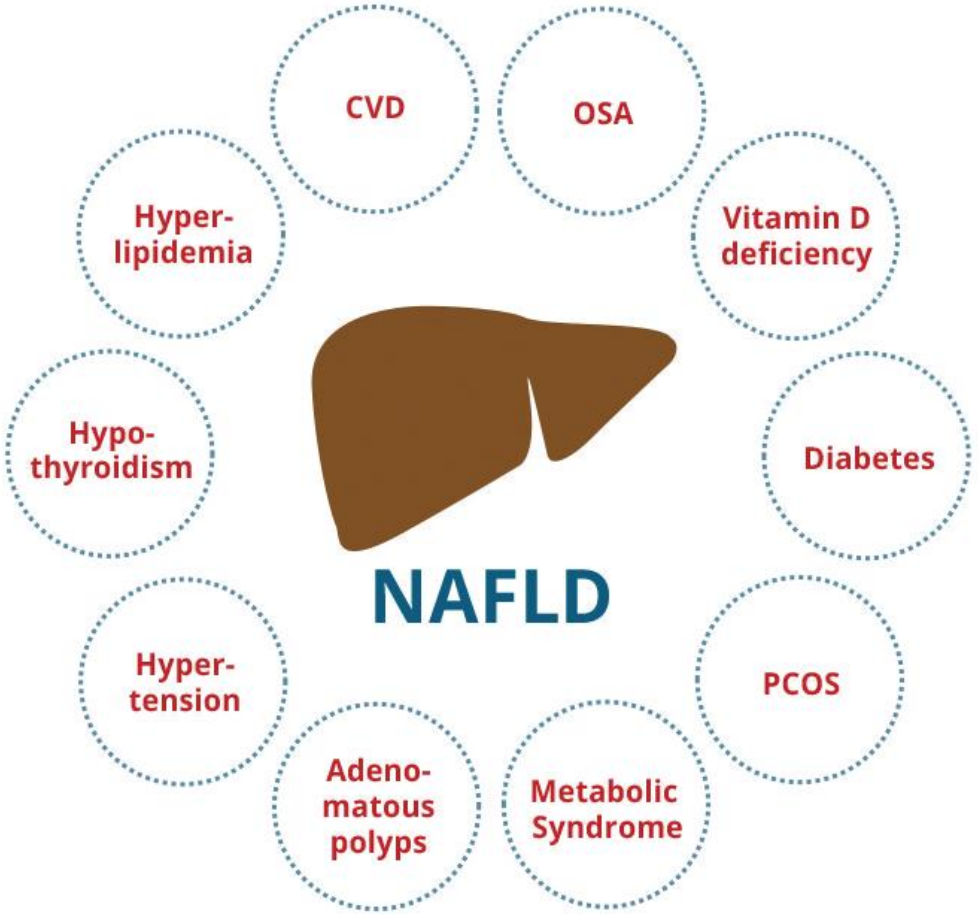
Conditions Associated with NAFLD



Modified from Torres DM *et al.* Features, diagnosis, and treatment of NAFLD, *Clin Gastro Hepatol* 2012; 32:30-38

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NAFLD Publications

- Since the initial descriptions in the early 1980s by Dr. Ludwig et al. and Dr. Schaner et al. ,who firstly coined the terms nonalcoholic steatohepatitis (NASH) and NAFLD, respectively
  - Number of published papers on NAFLD has increased exponentially over time, principally over the last decade

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nonalcoholic fatty liver disea

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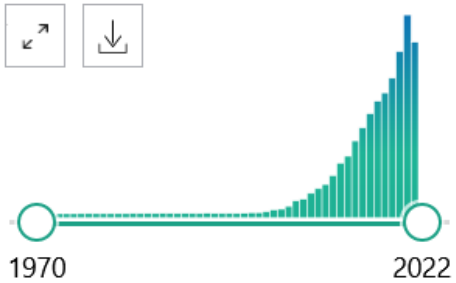
RESULTS BY YEAR



TEXT AVAILABILITY

Abstract

1 Cite Share

Nonalcoholic fatty liver disease: a systematic review.

Rinella ME.

JAMA. 2015 Jun 9;313(22):2263-73. doi: 10.1001/jama.2015.5370.

PMID: 26057287 Review.

IMPORTANCE: **Nonalcoholic fatty liver disease** and its subtype **nonalcoholic** steatohepatitis affect approximately 30% and 5%, respectively, of the US population. ...OBJECTIVES: To illustrate how to identify patients with **nonalcoholic fatt** ...

2

Nonalcoholic Fatty Liver Disease.

Wang XJ, Malhi H.

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NAFLD Publications

- Looking at this timeline of publications carefully, it appears that the number of published papers per year on NAFLD has
  - Remained very low for over two decades, with
    - Much fewer than 100 papers published per year until about the mid-2000s
  - Then began to grow exponentially starting in 2010–2011
    - With nearly 1000 papers published per year
- Notably, 3561 papers were published on PubMed in 2019 and over 4000 papers are expected to be published in 2020

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Epidemiology

- Over the past years, the global burden of chronic liver diseases (CLDs) has been steadily increasing, irrespective of
  - Age
  - Sex
  - Region
  - Race

- The European Union (EU) countries have the highest CLDs burden in the world, with
  - Almost 30 million people suffering from CLDs

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Epidemiology

- Unrecognized and often untreated, CLDs may progress to more advanced stages, such as
  - Cirrhosis
  - Liver failure
  - Hepatocellular carcinoma (HCC)

- Global and country-specific estimates of the disability-adjusted life years and years of life lost place cirrhosis within the
  - Top 20 causes

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Epidemiology

- In EU countries, the most common causes of cirrhosis and the most frequent indications for liver transplantation in 2013 were
  - Alcoholic liver disease (ALD, 25%-45%)
  - Chronic hepatitis C (HCV, 30%-35%)
  - Chronic hepatitis B (HBV, 10%-20%)

- However, with the implementation of prevention, screening, and treatment (direct antiviral agents) programs for chronic viral hepatitis, in most countries ALD and nonalcoholic fatty liver disease (NAFLD) have overtaken viral hepatitis as the primary causes of cirrhosis

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Epidemiology

- NAFLD is highly prevalent across nearly all continents and is geographically heterogeneous in its prevalence from country to country, with the highest rates, for example
  - Being reported in South America and the Middle East, followed by Asia, the USA, and Europe
  - NAFLD is less common in Africa

Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology 2019;69:2672–82.doi:10.1002/hep.30251
Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology 2018;67:123–33

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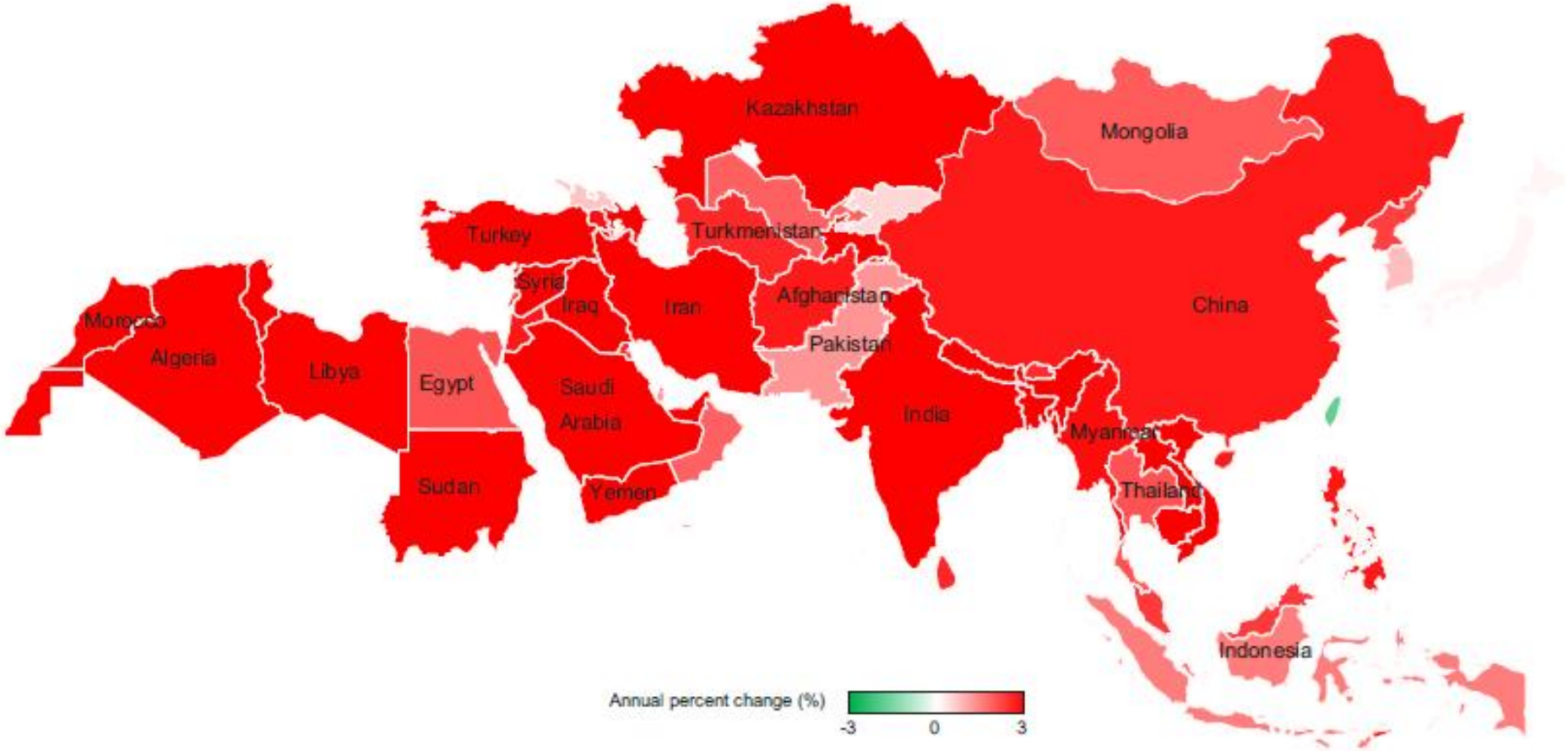

Fig. 1. Changes in incidence rate of LC-NAFLD from 2009 to 2019: Data from Global Burden of Disease. LC-NAFLD, liver complications due to NAFLD; NAFLD, non-alcoholic fatty liver disease.

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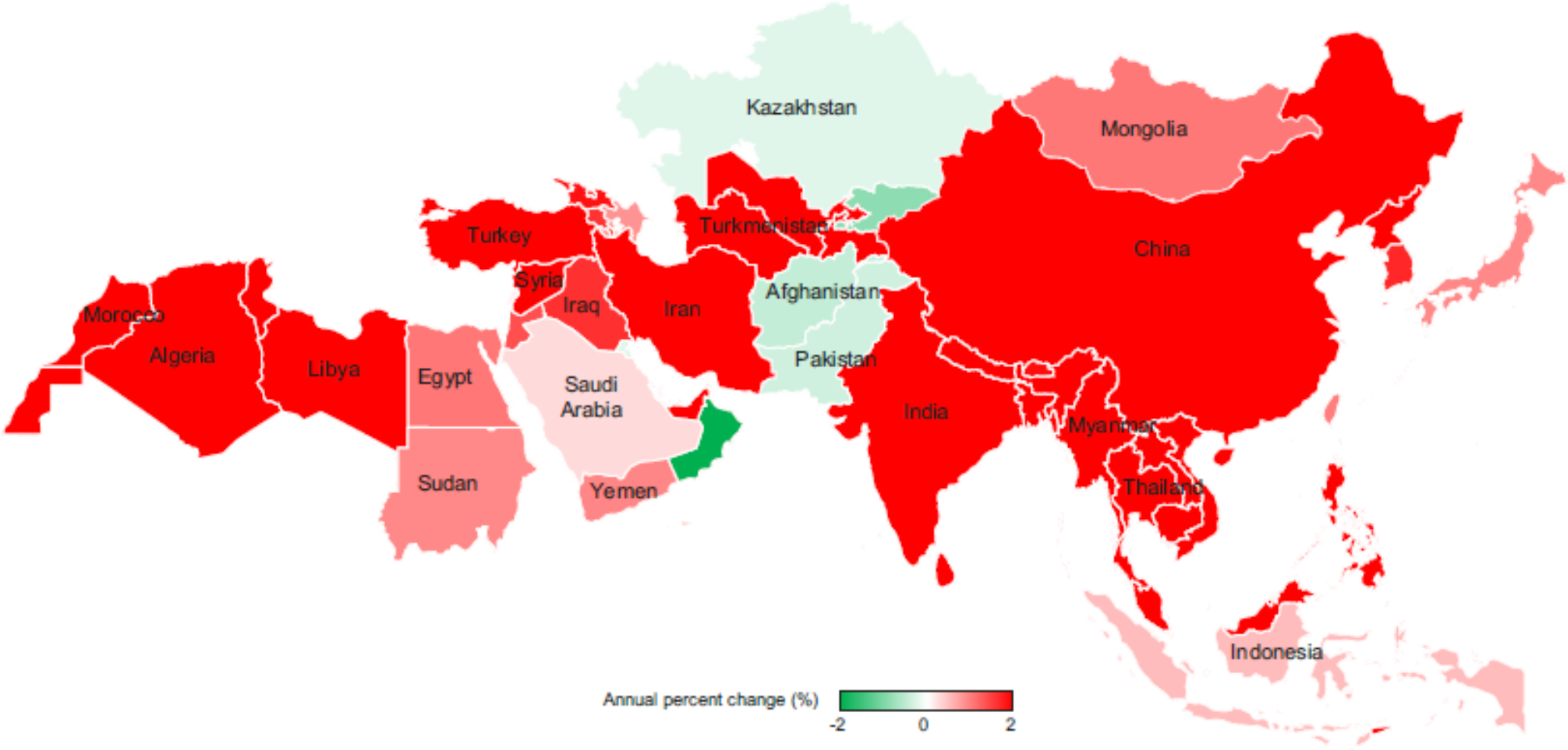

Fig. 2. Changes in death rate attributable to LC-NAFLD from 2009 to 2019: Data from Global Burden of Disease. LC-NAFLD, liver complications due to NAFLD; NAFLD, non-alcoholic fatty liver disease.

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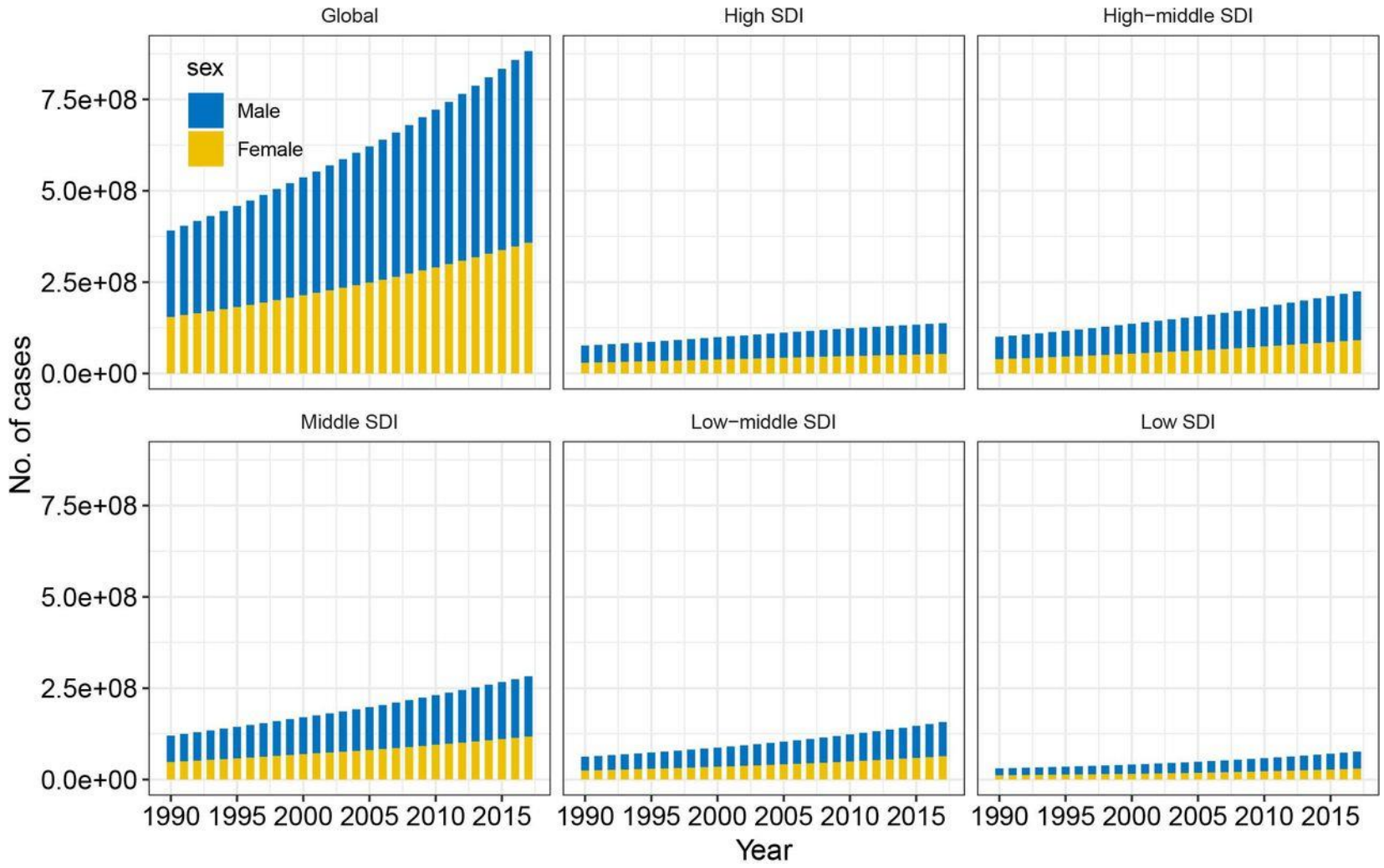
Changing trends in case numbers for non-alcoholic fatty liver disease between 1990 and 2017, by sex and SDI. SDI, Sociodemographic Index.



Xiaojun Ge et al. BMJ Open 2020;10:e036663

BMJ Open

NAFLD Epidemiology

- An updated meta-analysis of 86 observational studies from 22 countries (involving more than 8.5 million individuals) reported that the
  - Global prevalence of NAFLD in the general adult population was around 25%
  - with the highest prevalence in
    - Middle East
    - South America

Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64:73-84.

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HCC and NAFLD

- Over half a million individuals worldwide every year develop
  - Incident HCC
- The global incidence of this liver cancer has been steadily rising, making HCC
  - Fifth most frequently diagnosed cancer
- Similarly, NAFLD is the fastest growing cause of HCC in liver transplant candidates both in
  - European Liver Transplant Registry
  - United Network for Organ Sharing databases

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HCC and NAFLD

- A further important clinical problem when it comes to NAFLD is that
  - HCC may develop also in patients with non-cirrhotic NAFLD
- In fact, some studies demonstrated that HCC could develop in NAFLD patients who do not have cirrhosis, especially in those with
  - Nonalcoholic steatohepatitis with or without fibrosis
  - It is one of the most worry-aspects of HCC in NAFLD

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HCC and NAFLD

- Given the epidemic proportions of NAFLD in the general population worldwide
  - HCC screening in all people with NAFLD (especially in those without cirrhosis) is unfeasible

- As it has been discussed above, there are several open questions about HCC in NAFLD, such as
  - Timing of carcinogenesis in non-cirrhotic patients with NAFLD
  - Best diagnostic approaches that will detect high-risk patients

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NAFLD and MetS

- Many authors believe that NAFLD will in the foreseeable future overtake ALD as the leading
  - Indication for liver transplantation in CLD patients

- This finding is not surprising, because today NAFLD is the most common cause of CLD worldwide
  - Its prevalence parallels the increasing global prevalence of obesity, metabolic syndrome (MetS), and type 2 diabetes (T2DM)

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NAFLD and MetS

- NAFLD is also strongly associated with MetS and its individual components, such as
  - Central obesity
  - T2DM
  - Hypertension
  - Iatrogenic dyslipidemia
- One of the largest cohort studies on the clinical course and progression of NAFLD conducted in Sweden has reported that the liver fibrosis stage is the strongest histologic risk factor for
  - Liver-related morbidity and mortality in NAFLD
- Thus, we need patient-friendly, easy-to-use, and inexpensive non-invasive tests for the detection of
  - Significant and advanced liver fibrosis

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NAFLD and Pediatric

- Worryingly, NAFLD is a growing cause of CLDs also in
  - Pediatric population
- The pediatric population with NAFLD will face an
  - Increased risk of liver-related morbidity and mortality in adulthood
- These observations indicate the need for a global policy for the prevention of obesity and its chronic complications
  - Starting from childhood

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NAFLD & Extrahepatic Diseases

- Another important issue in the context of NAFLD is its strong association with the risk of
  - Many extrahepatic diseases
- In the past decade, strong evidence has been provided of adverse effects of NAFLD extending beyond the liver, and of
  - NAFLD being not just a liver disease but a multisystem disease
- Cardiovascular diseases are a well documented predominant cause of death in
  - Patients with NAFLD

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NAFLD & Extrahepatic Diseases

- However, growing evidence also indicates that NAFLD is associated with an increased risk of developing
  - T2DM
  - Chronic kidney disease
  - Polycystic ovary syndrome
  - Psoriasis
  - Obstructive sleep apnea
  - Some types of extra-hepatic malignancies (eg, colorectal and breast cancers)
- These associations could be simply a consequence of the shared cardiometabolic risk factors
  - Insulin resistance, MetS and its individual components
- A growing body of evidence, however, suggests that NAFLD is related to many of these extra-hepatic diseases independently of the shared cardiometabolic risk factors

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NAFLD & Extrahepatic Diseases

- Coexistence of T2DM and NAFLD is
  - Not only associated with the risk of NAFLD progression
  - But also with the risk of chronic vascular complications of diabetes
- Based on all these considerations, all patients with NAFLD would benefit from a periodical screening for
  - T2DM
  - Cardiovascular diseases
  - Chronic kidney disease
- Further research is needed to address the cost-effectiveness of screening for
  - Extrahepatic diseases in all patients with NAFLD

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NAFLD & Extrahepatic Diseases

- Knowing that most CLDs, including NAFLD
  - Are preventable and treatable
  - Urgent need arises for action plans on
    - Preventive measures
    - Screening
    - Pharmacological treatment options of this very common and burdensome liver disease

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MAFLD

- For many years, NAFLD has been considered as a consequence of the
  - Metabolic syndrome
- Deleterious effects of NAFLD extend far beyond the liver, with an accumulating body of clinical evidence now supporting the notion that NAFLD may precede and/or promote the development of
  - Cardiovascular disease
  - Type 2 diabetes mellitus

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MAFLD

- For many years, NAFLD has been considered as a consequence of the
  - Metabolic syndrome

- Based on pathophysiological insights gained from the past decades and to further emphasize the strong link between NAFLD and cardio-metabolic diseases
  - An international panel of experts has recently proposed a new name and definition for NAFLD in adults, i.e.,
    - Metabolic dysfunction-Associated Fatty Liver Disease (MAFLD)

A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J. Hepatol. 2020, 73, 202–209.

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MAFLD

- Proposal to change the terminology from NAFLD to ***MAFLD*** is still under intense discussion

- This newly proposed definition might also promote
  - Establishment of MAFLD clinics run jointly by
    - Diabetologists and hepatologists to
      - Further improve patient care
  - Further research is required to better establish
    - Other extra-hepatic diseases associated with NAFLD
    - Has fostered the development of entirely new drug classes

History of nonalcoholic fatty liver disease. Int. J. Mol. Sci. 2020, 21, 5888

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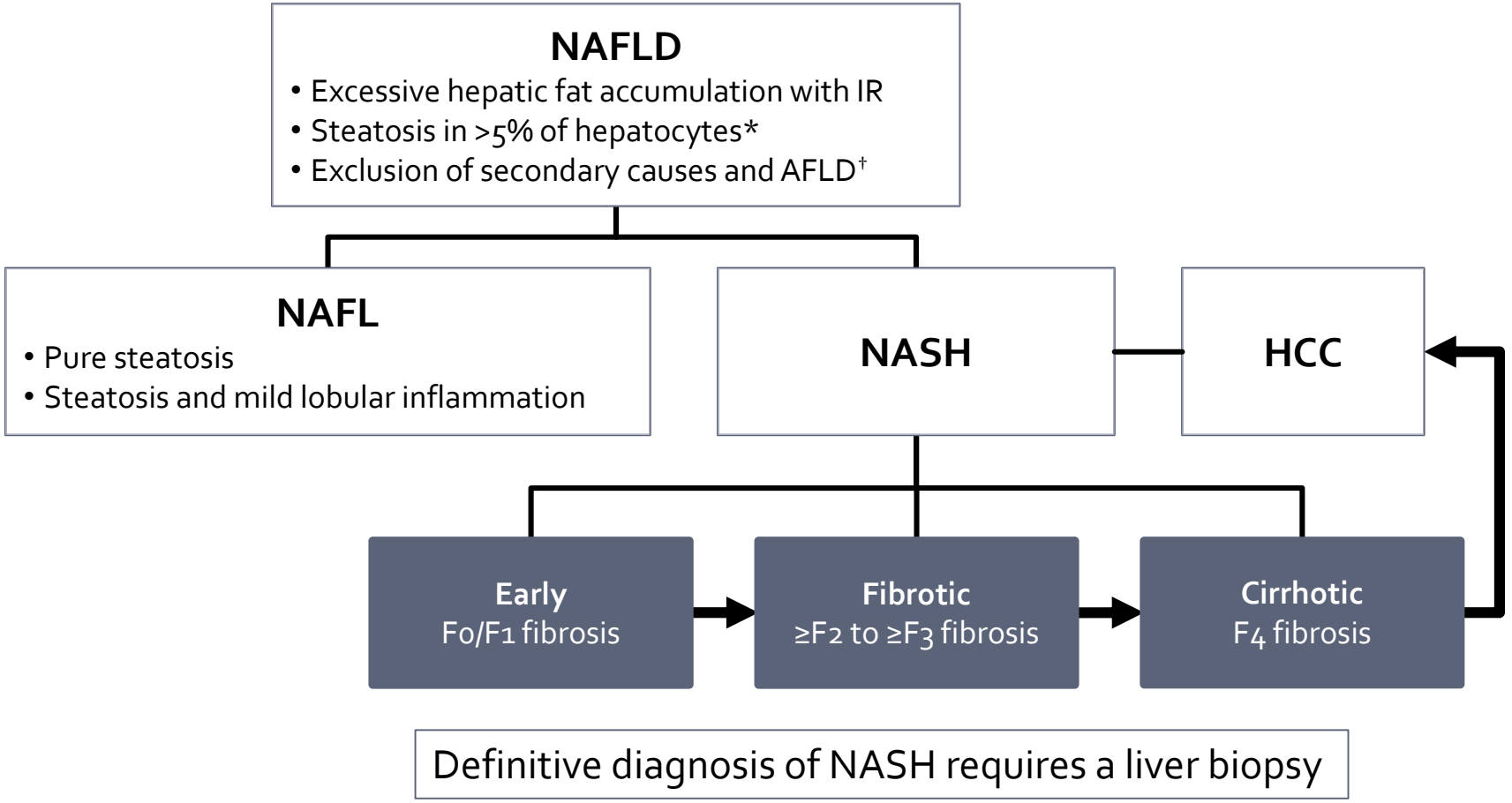
Definitions of NAFLD, NAFL and NASH



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

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

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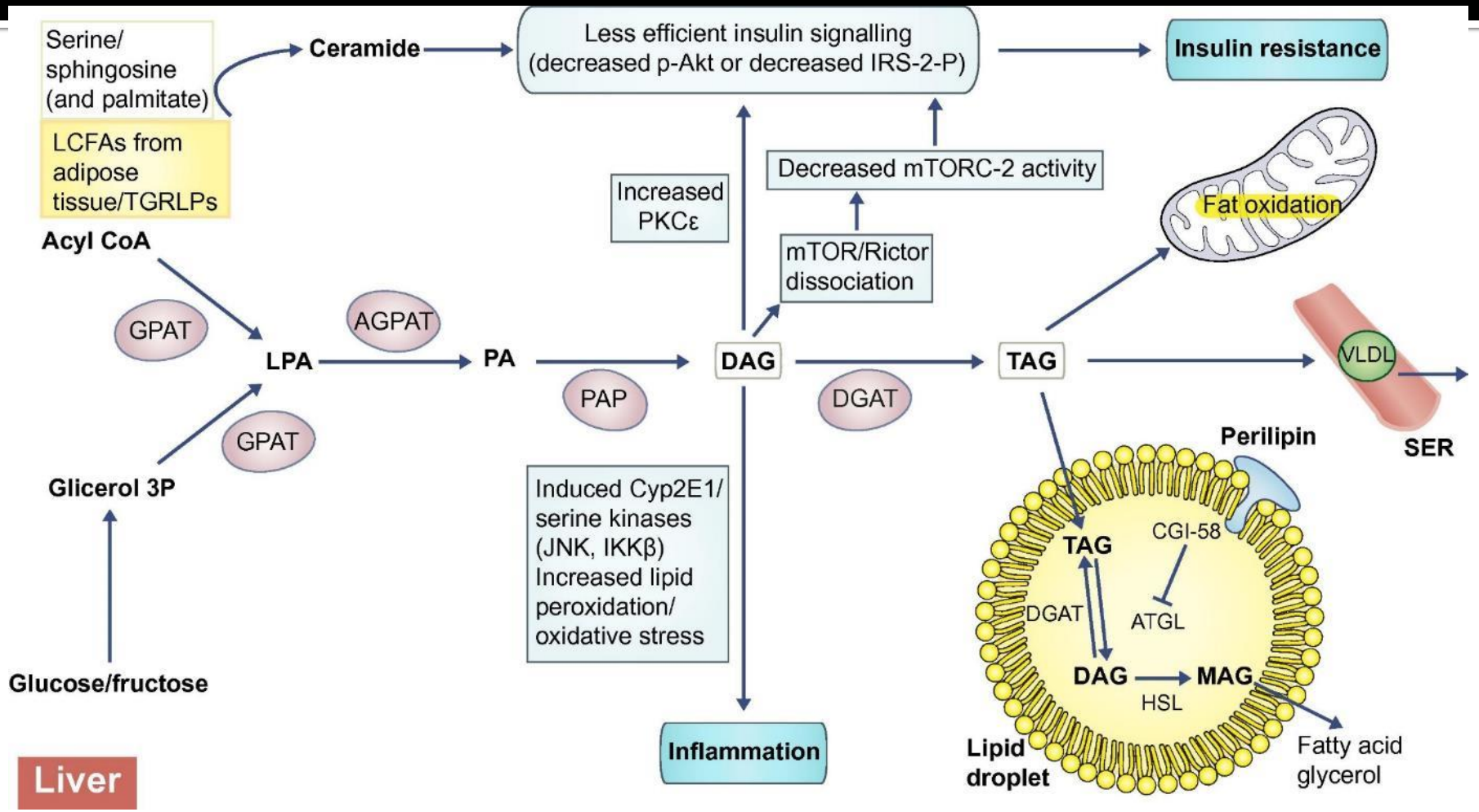
Lipids induce hepatic IR and inflammation



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

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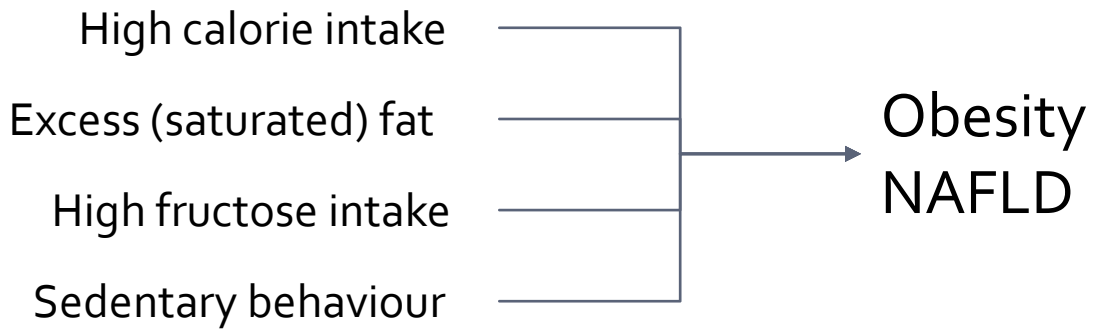
Pathogenesis: lifestyle and genes

- **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

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

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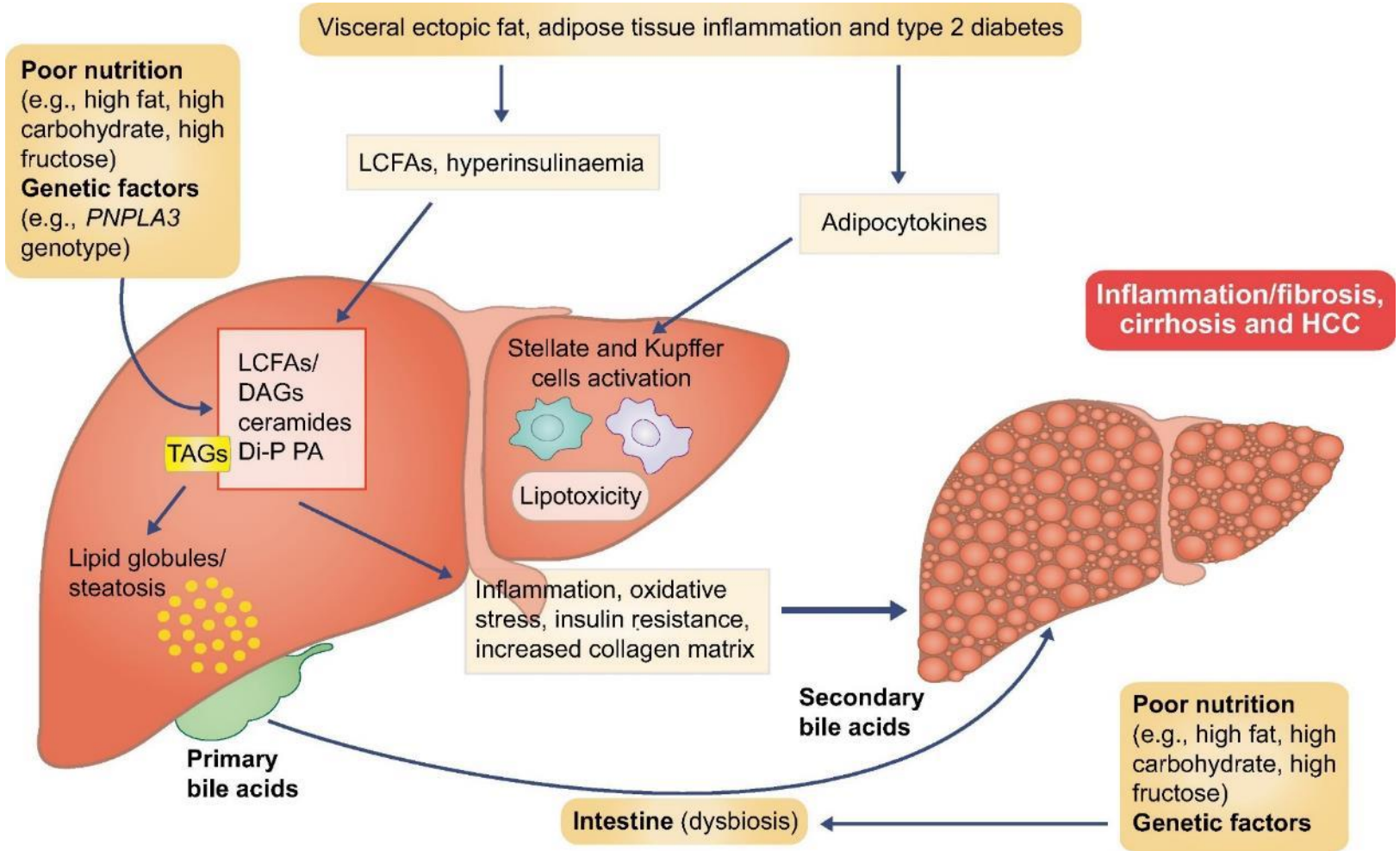
Progressive liver disease in NAFLD



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

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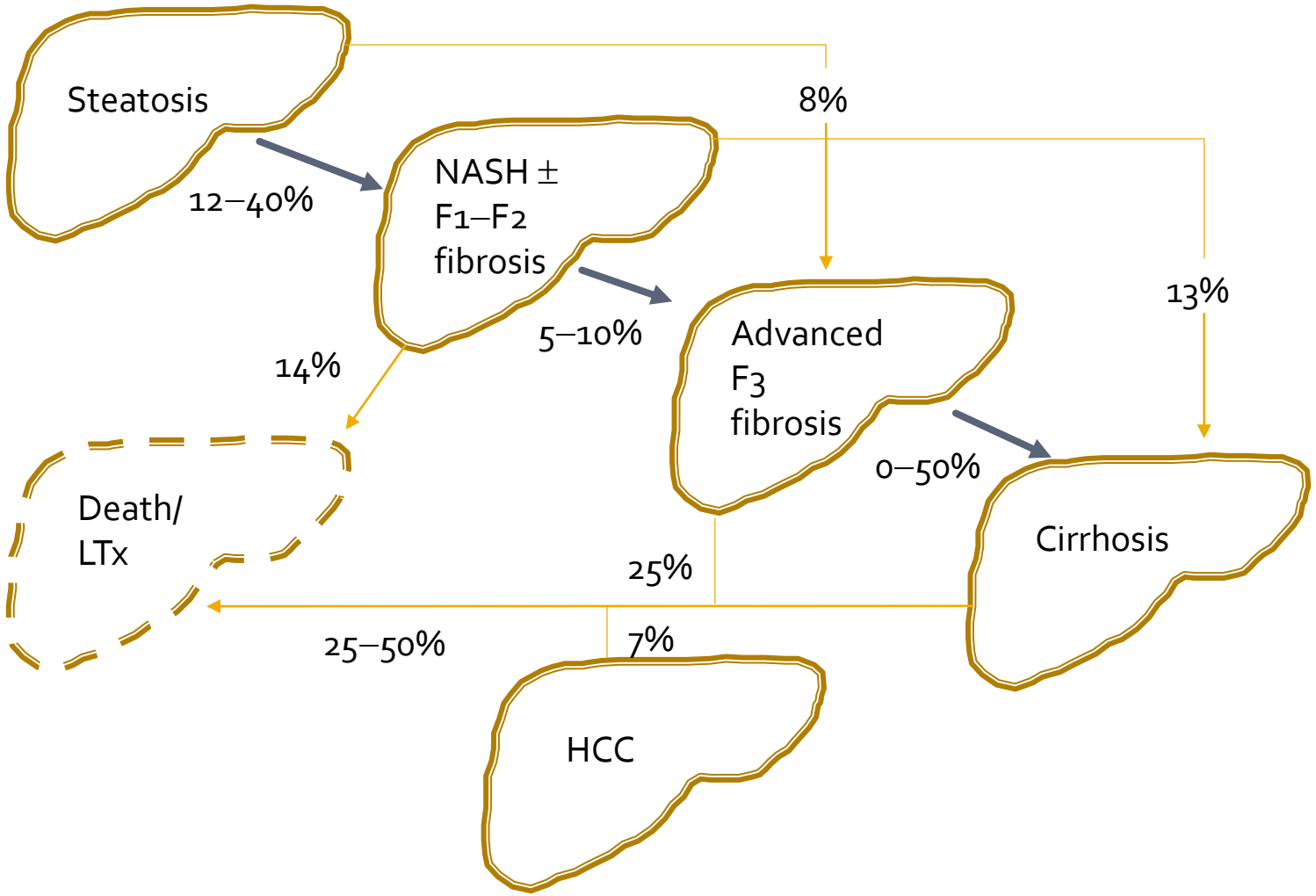
Natural history of NAFLD over 8–13 years



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

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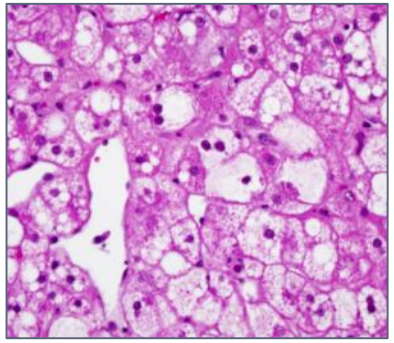
Liver biopsy

- 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

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

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Role of non-invasive assessments

- **Non-invasive markers should aim to:**
  - **Identify the risk of NAFLD among individuals with increased metabolic risk in primary care**
  - **Identify those with a worse prognosis in secondary and tertiary care**
    - **E.g. severe NASH**
  - **Monitor disease progression**
  - **Predict response to therapeutic interventions**

Achieving these aims could reduce the need for liver biopsy

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

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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

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

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Non-invasive assessment of fibrosis

- **Fibrosis is the most important prognostic factor in NAFLD**
  - **Correlates with liver-related outcomes and mortality**
  - **Advanced fibrosis indicates thorough investigation**

Recommendations	Grade of evidence	Grade of recommendation
Biomarkers, fibrosis scores, and transient elastography, are acceptable non-invasive procedures to identify those at low risk of advanced fibrosis/cirrhosis	A	2
Biomarkers/scores PLUS transient elastography might confer additional diagnostic accuracy and reduce need for liver biopsy	B	2
Monitoring of fibrosis progression may rely on biomarkers/scores and transient elastography, although this strategy requires validation	C	2
The identification of advanced fibrosis or cirrhosis by serum biomarkers/scores and/or elastography is less accurate and needs to be confirmed by liver biopsy, according to the clinical context	B	2
In selected patients at high risk of liver disease progression, monitoring should include a repeat biopsy after ≥5-year follow-up	C	2

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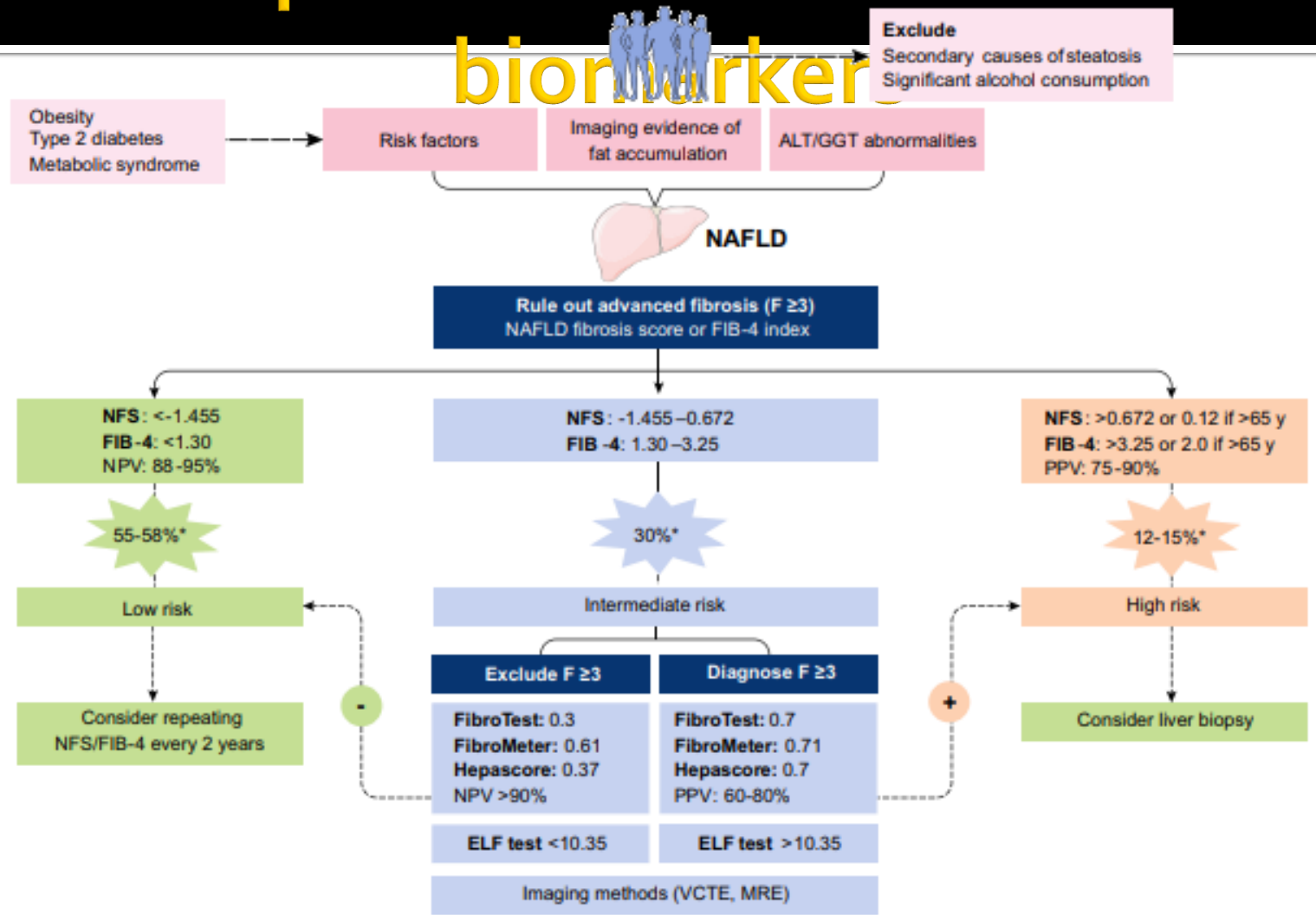
Potential algorithm for non-invasive assessment: prediction rules and blood-based biomarkers



*Estimated prevalence for low-, intermediate- and high-risk groups

Vilar-Gomez E, Chalasani N. J Hepatol 2018;68:305–15

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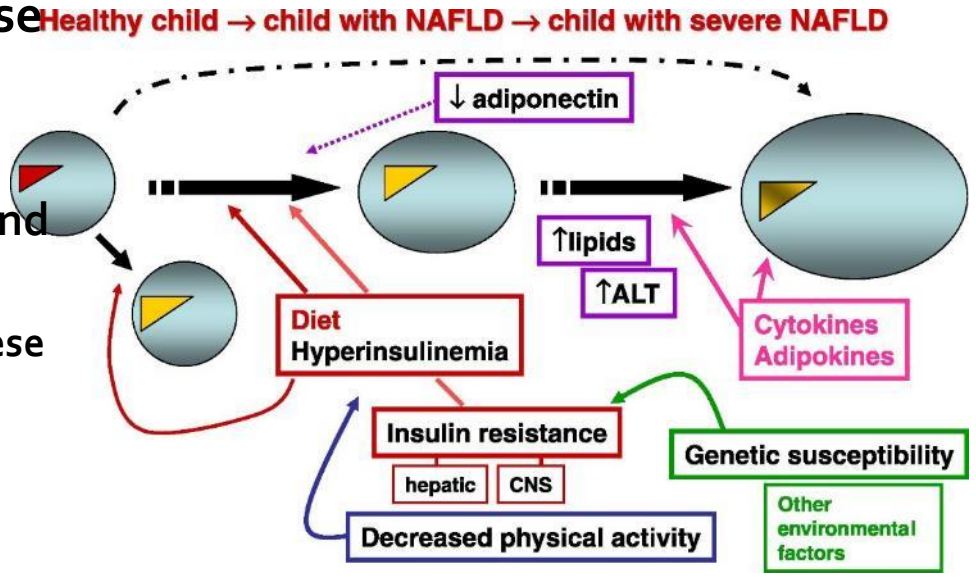
Non-invasive assessment of paediatric NAFLD

- 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

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Common related metabolic disorders

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

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

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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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**

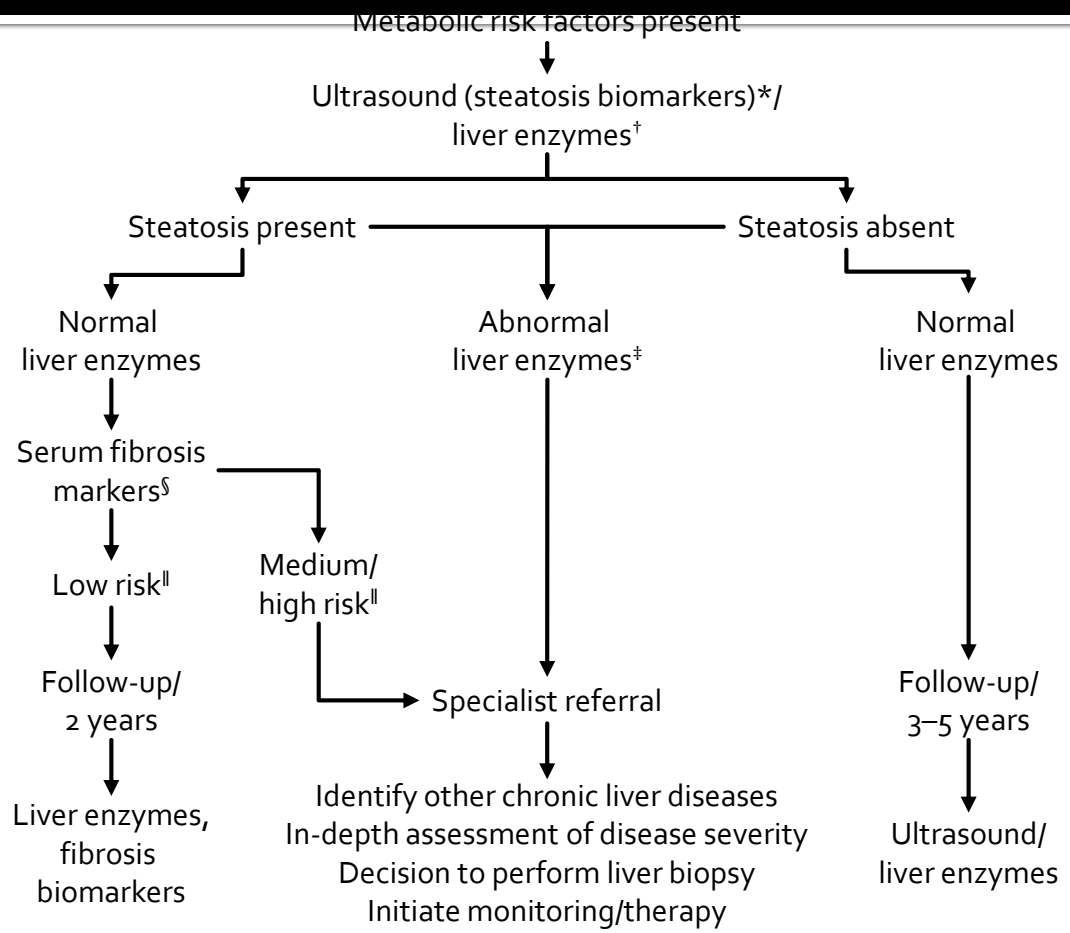
Level	Variable
Initial evaluation	1. Alcohol intake: <20 g/day (women), <30 g/day (men) 2. Personal and family history of diabetes, hypertension and CVD 3. BMI, waist circumference, change in body weight 4. Hepatitis B/hepatitis C virus infection 5. History of steatosis-associated drugs 6. Liver enzymes (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
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

M Khoshbaten, M.D.
Professor of Gastroenterology & Hepatology

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

M Khoshbaten, M.D.
Professor of Gastroenterology & Hepatology

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

M Khoshbaten, M.D.
Professor of Gastroenterology & Hepatology

Treatment: diet and lifestyle changes

- **A pragmatic, individually tailored approach is required**
  - **Dietary restriction PLUS**
  - **Progressive increase in aerobic exercise/resistance training**

Recommendations	Grade of evidence	Grade of recommendation
Dietary recommendations should consider energy restriction and exclusion of NAFLD-promoting components (processed food, and food and beverages high in added fructose). The macronutrient composition should be adjusted according to the Mediterranean diet	B	1
Both aerobic exercise and resistance training effectively reduce liver fat. The choice of training should be tailored based on patients' preferences to be maintained in the long-term	B	2

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M Khoshbaten, M.D.
Professor of Gastroenterology & Hepatology

Components of a lifestyle approach to NAFLD

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

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

M Khoshbaten, M.D.
Professor of Gastroenterology & Hepatology

Treatment: pharmacotherapy

- Treatment should be indicated in:
  - Progressive NASH
  - Early-stage NASH with risk of fibrosis progression*
  - Active NASH with high necroinflammatory activity
- Treatment should reduce NASH-related mortality and progression to cirrhosis or HCC
  - Resolution of NASH-defining lesions accepted as surrogate endpoint
- Safety and tolerability are prerequisites
  - Extensive comorbidities associated with significant polypharmacy and increased likelihood of DDIs

Recommendations	Grade of evidence	Grade of recommendation
Pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis (stage F2 and higher). Patients with less severe disease, but at high risk of disease progression could also be candidates for treatment	B	1

*Age > 50 years, diabetes, MetS, increased ALT

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M Khoshbaten, M.D.
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  - Active NASH with high necroinflammatory activity
- Treatment should reduce NASH-related mortality and progression to cirrhosis or HCC
  - Resolution of NASH
- Safety and tolerabilit
  - Extensive comorbidi ased likelihood of DDIs

No drugs are approved for NASH

No specific therapy can be recommended

Any drug treatment is off label

Recommendations	Grade of evidence	Grade of recommendation
Pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis (stage F2 and higher). Patients with less severe disease, but at high risk of disease progression could also be candidates for treatment	B	1

*Age > 50 years, diabetes, MetS, increased ALT

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

M Khoshbaten, M.D.
Professor of Gastroenterology & Hepatology

Treatment: pharmacotherapy

- **Insulin sensitizers**
  - **Little evidence of histological efficacy with metformin**
  - **PPARγ agonist pioglitazone better than placebo**
    - **Improved all histological features except fibrosis**
    - **Achieved resolution of NASH more often**
- **Antioxidants**
  - **Vitamin E may improve steatosis, inflammation and ballooning and resolve NASH in some patients**
    - **Concerns about long-term safety exist**

Recommendations	Grade of evidence	Grade of recommendation
While no firm recommendations can be made, pioglitazone* or vitamin E† or their combination could be used for NASH	B	2
The optimal duration of therapy is unknown; in patients with increased ALT at baseline, treatment should be stopped if there is no reduction in aminotransferases after 6 months of therapy‡	C	2

*Most efficacy data, but off-label outside T2DM; †Better safety and tolerability than pioglitazone in the short-term;
‡No recommendations can be made in patients with normal baseline ALT
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

M Khoshbaten, M.D.
Professor of Gastroenterology & Hepatology

Treatment: pharmacotherapy

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

Recommendations	Grade of evidence	Grade of recommendation
Statins may be confidently used to reduce LDL cholesterol and prevent cardiovascular risk, with no benefits or harm to liver disease. Similarly, n-3 polyunsaturated fatty acids reduce both plasma and liver lipids, but there are no data to support their use specifically for NASH	B	1

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

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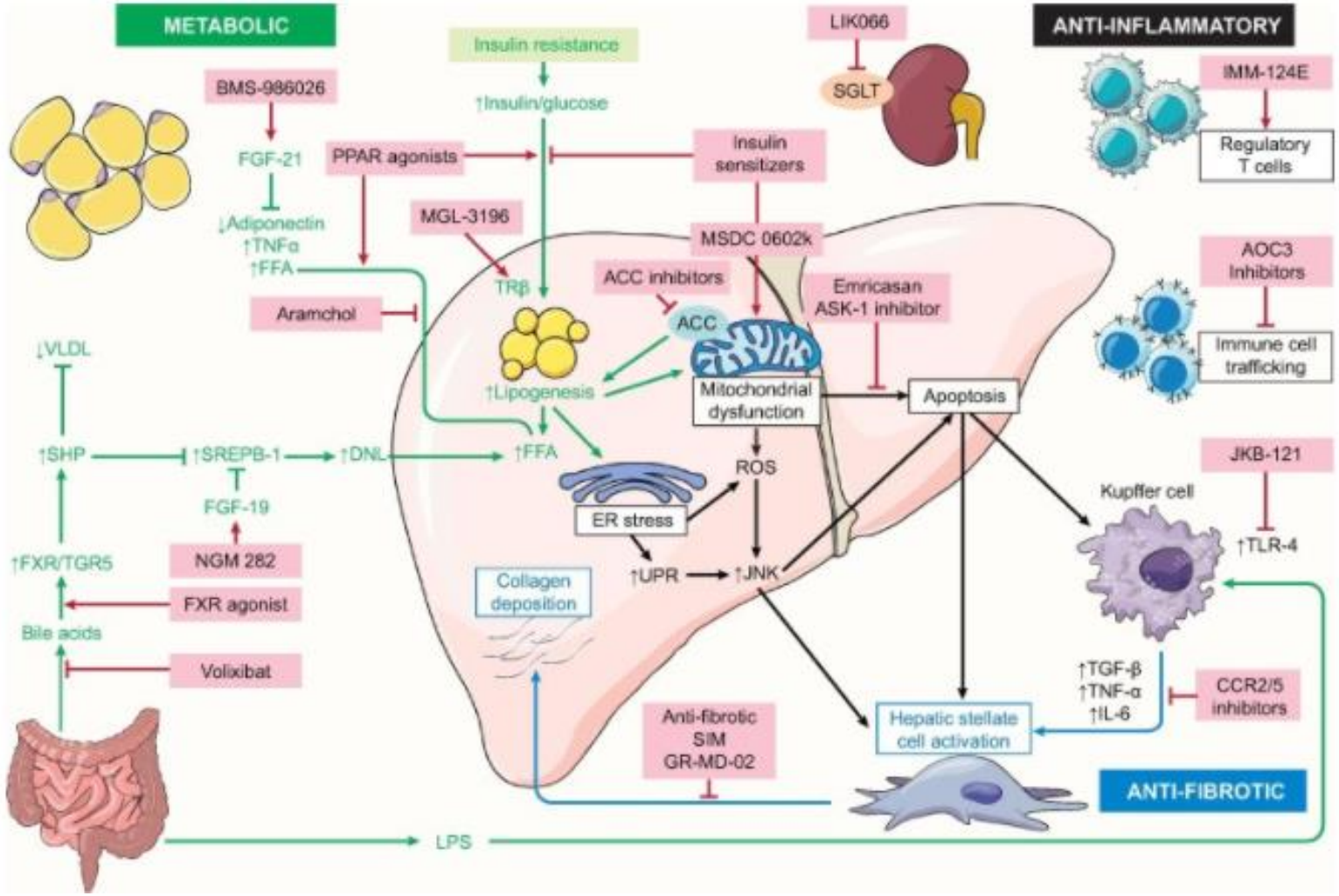
MOA of pharmacological treatments for NAFLD



Konerman MA, et al. J Hepatol 2018;68:362–75

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Professor of Gastroenterology & Hepatology

Treatment: paediatric NAFLD

- Diet and exercise training reduce steatosis, but do not affect ballooning, inflammation, and fibrosis
- The long-term outcome of paediatric NASH remains poor
  - Drugs have shown beneficial effects but fibrotic lesions are refractory to treatment

Recommendations	Grade of evidence	Grade of recommendation
Diet and physical activity improve steatosis and hepatic inflammation in paediatric NAFLD, but no beneficial effects on fibrosis have ever been demonstrated. **No safe drug treatment has proven effective on fibrosis in paediatric NAFLD**	B	1

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

M Khoshbaten, M.D.
Professor of Gastroenterology & Hepatology

Treatment: surgery

- **Bariatric surgery is an option in patients unresponsive to lifestyle changes and pharmacotherapy**
  - **Reduces weight and metabolic complications**
  - **Stable results in the long term**
- **NAFLD-associated cirrhosis is one of the top three indications for LTx**

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
Recommendations for liver transplant		
LTx is an accepted procedure in patients with NASH and end-stage liver disease. Overall survival is comparable to other indications, despite a higher cardiovascular mortality. **Patients with NASH and liver failure and/or HCC are candidates for liver transplantation**	A	1

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

M Khoshbaten, M.D.
Professor of Gastroenterology & Hepatology

Treatment

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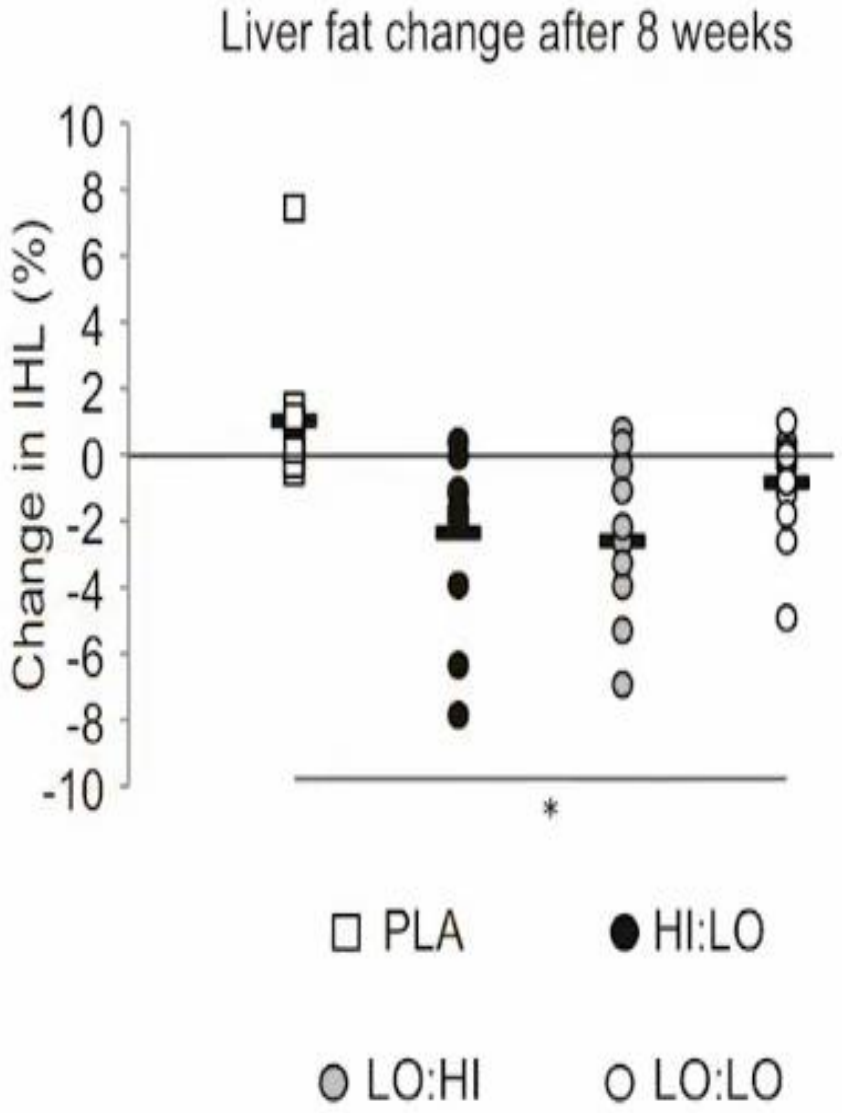
Weight loss with hypocaloric diet improves liver histology

Physical exercice improves steatosis

- 48 overweight/obese
- Aerobic exercises vs placebo
  - Continuous cycling
  - 45 to 60 mn, 3 to 4 days/week
  - 8 weeks duration
- Liver fat content by spectroscopy



Keating SE et al, J Hepatol 2015

Guidelines *(EASL)*

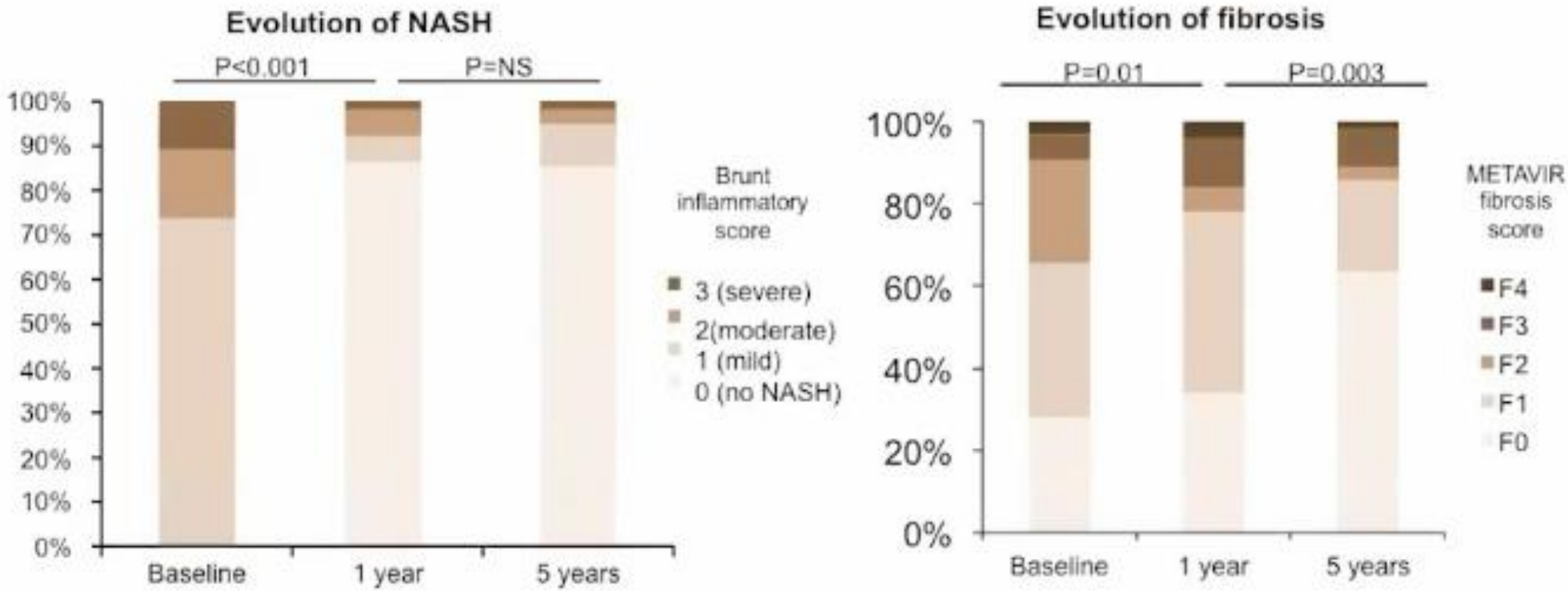
- Weight loss, physical exercise, dietary change: first-line therapy.
- Indication: NAFLD patient without NASH or fibrosis
- Efficacy assessed after 6-month period
- Weight loss : 7-10%
- Soft drink should be avoided
- Mediterranean diet
- Aerobic exercise: > 150 mn/w

J Hepatol 2016;64:1388–402

Bariatric surgery

Guidelines:

- To be considered in absence of cirrhosis to reduce obesity
- BMI cutoffs not provided



Lassailly G, et al. Gastroenterology 2020

Pharmacological treatment *(EASL guidelines)*

Who to treat ?

- Pharmacotherapy should be reserved for patients with NASH, particularly for those with significant fibrosis (stage F2 and higher). Patients with less severe disease, but at high risk of disease progression (i.e. with diabetes, MetS, persistently increased ALT, high necroinflammation) could also be candidates to prevent disease progression (**B1**)

How to treat ?

- While no firm recommendations can be made, pioglitazone (most efficacy data, but off-label outside T2DM) or vitamin E (better safety and tolerability in the short-term) or their combination could be used for NASH (**B2**)

Monitoring

- The optimal duration of therapy is unknown; in patients with increased ALT at baseline, treatment should be stopped if there is no reduction in aminotransferases after 6 months of therapy; in patients with normal ALT at baseline, no recommendations can be made (**C2**)

Statins use

- Statins may be confidently used to reduce LDL-cholesterol and prevent cardiovascular risk, with no benefits or harm on liver disease. Similarly *n*-3 polyunsaturated fatty acids reduce both plasma and liver lipids, but there are no data to support their use specifically for NASH (**B1**)

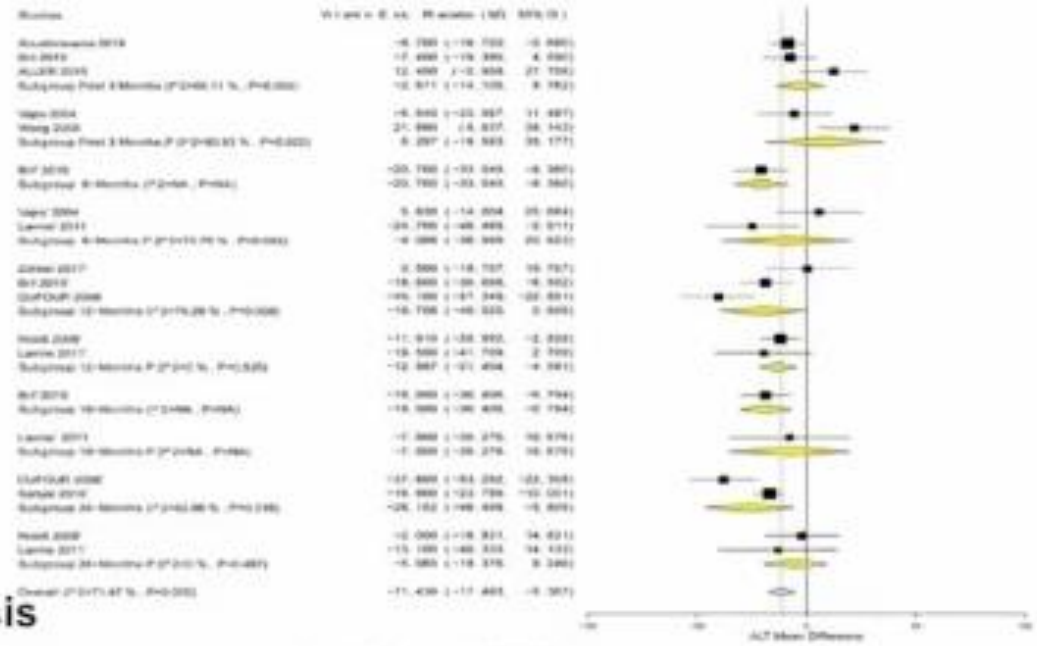
Consensus

J Hepatol 2016;64:1388–402

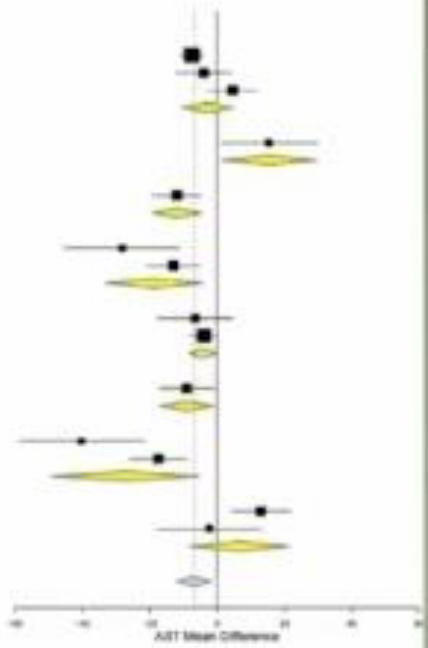
Vitamine E: meta-analysis

(15 controlled studies, n=1317)

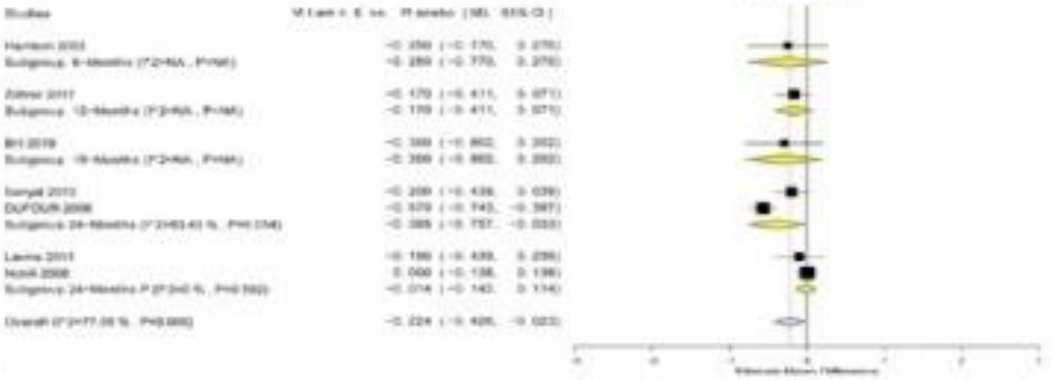
ALT



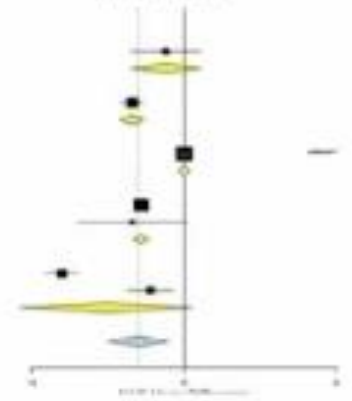
AST



Fibrosis

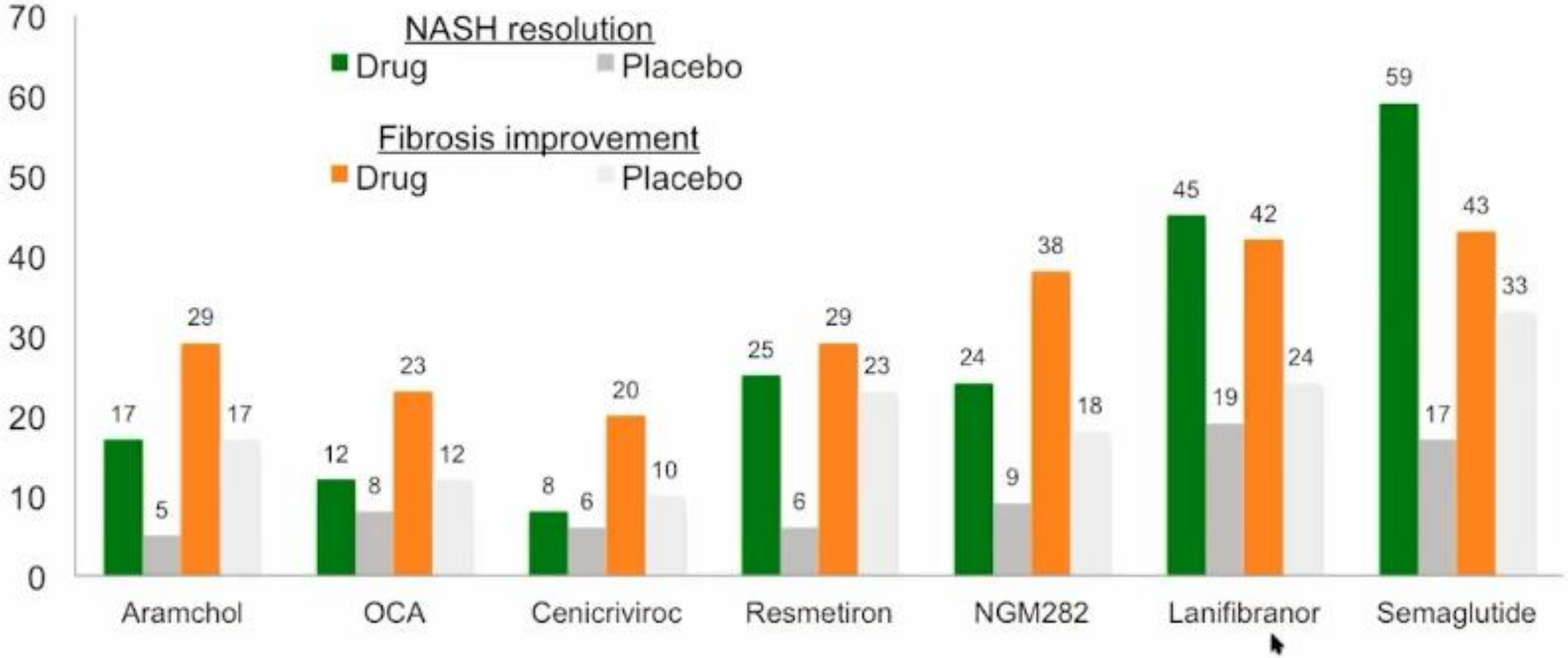


NAS score



Abdel-Maboud M. et al. Therap Adv Gastroenterol 2020

New molecules: histological efficacy

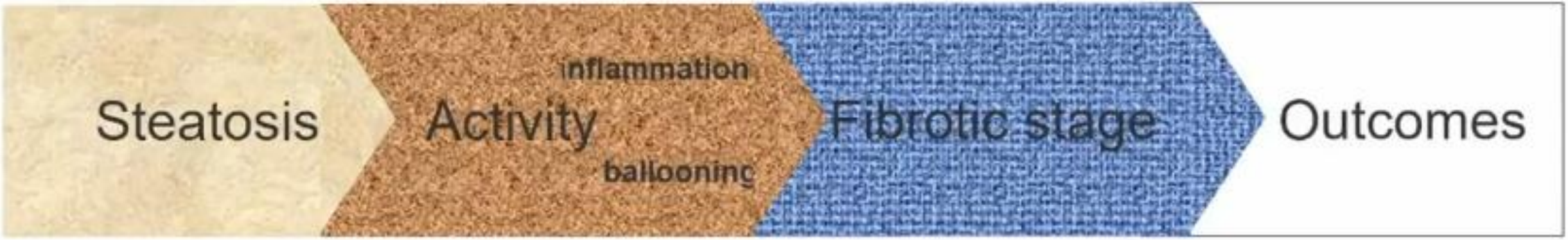


Ratziu V et al, AASLD 2018-Younossi ZM and al, Lancet 2019- Friedman S et al, Hepatology 2018-Press release Madrigal-Press release NGM-Press release Inventiva-Newsome P et al, NEJM 2020

NASH Treatment
New Drugs

M Khoshbaten, M.D.
Professor of Gastroenterology & Hepatology

Framework for NASH Drug Therapy

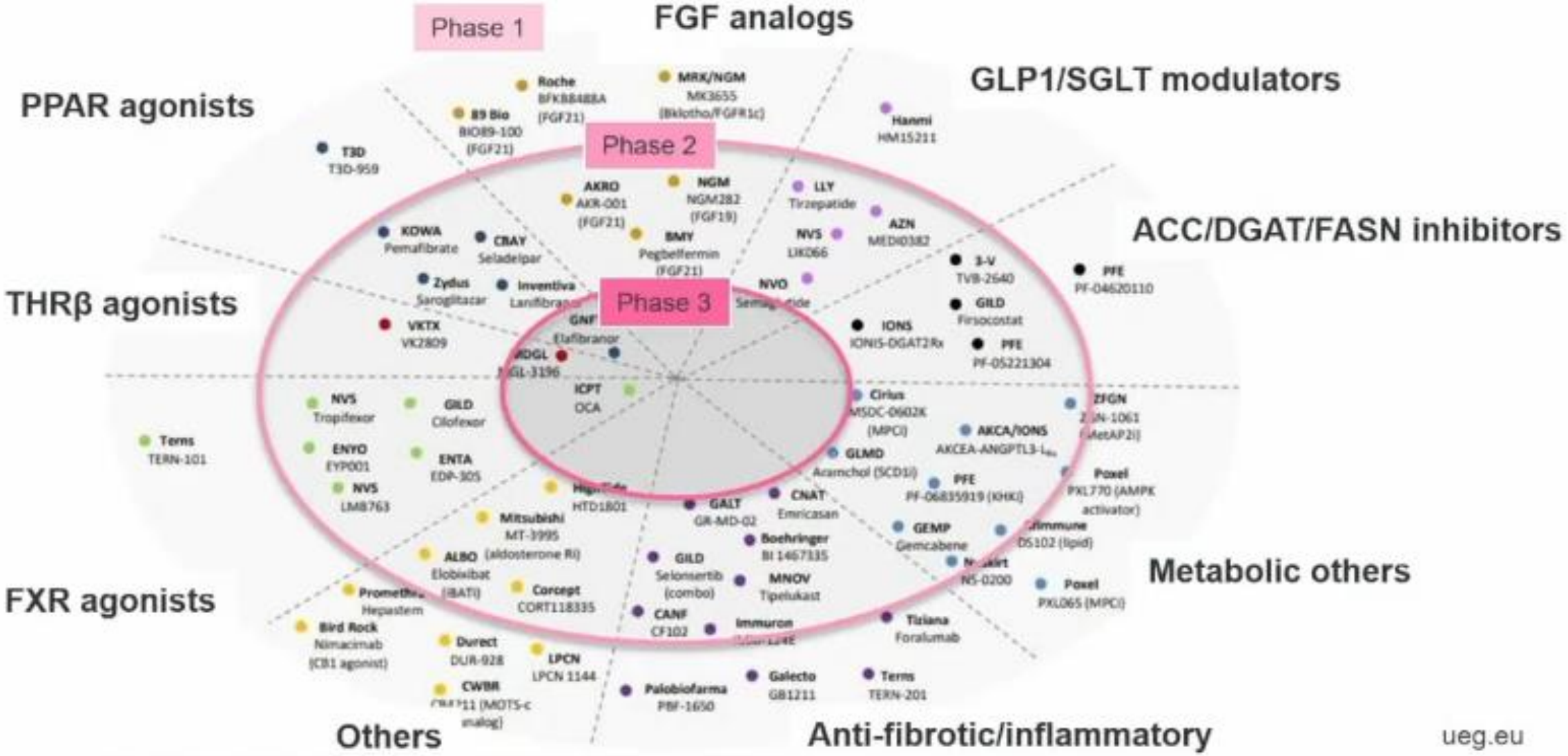


Regulatory endpoints for conditional approval

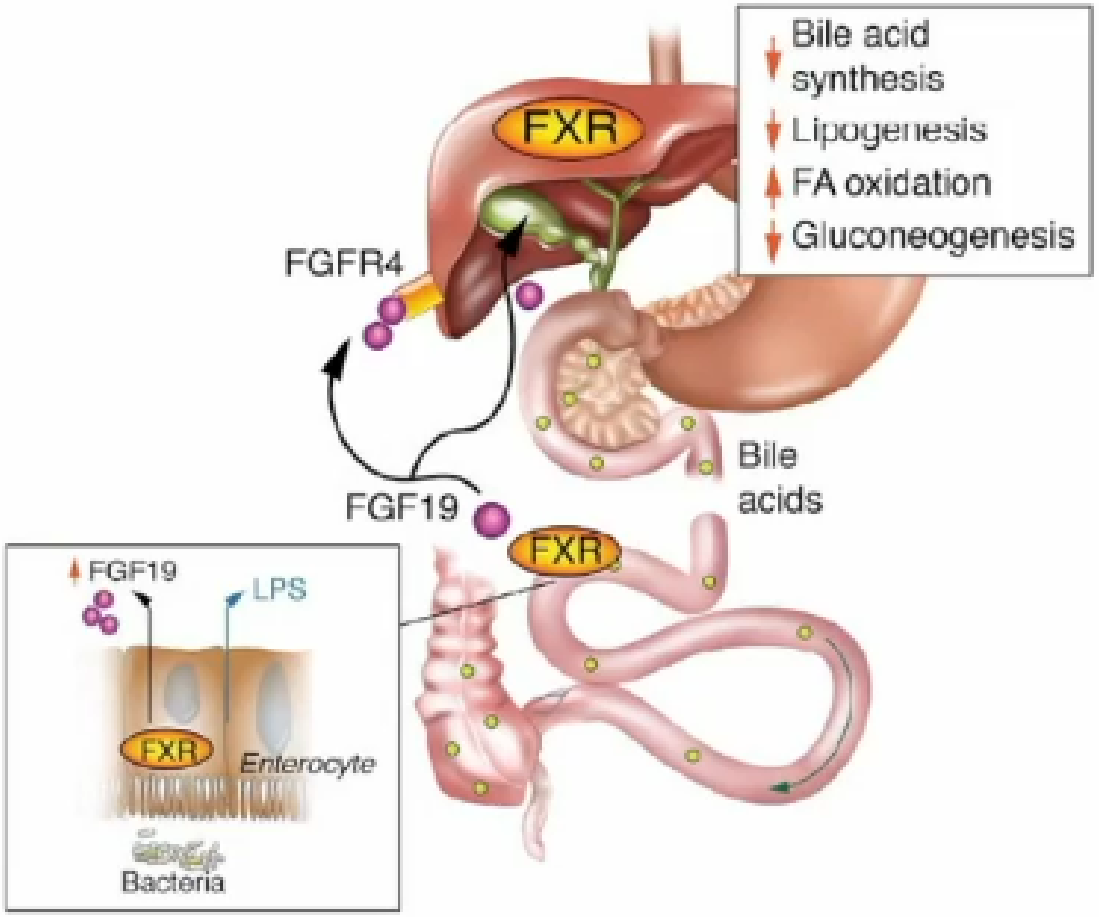
Resolution of NASH without worsening of fibrosis

Improvement of fibrosis without worsening of NASH

Busy NASH Landscape



FXR – FGF19 – FXR Axis

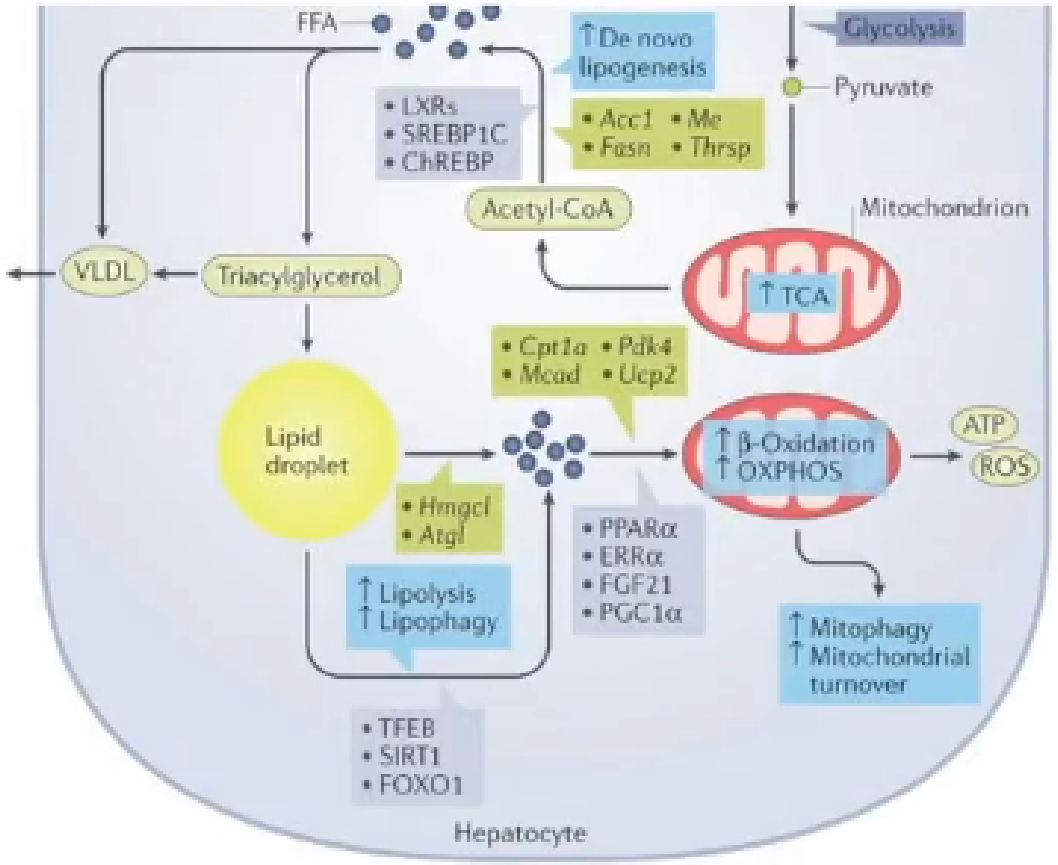


FXR agonists	Phase	Resolution NASH	Improvement fibrosis
Obeticholic acid	3*	n.s.	✓
		Dose/duration	**MRI-PDFF responder rate (%) with relative liver fat change from baseline >30%**
Obeticholic acid	3*	25 mg/W 72	26%
Tropifexor	2	200 ug/W 12	69%
Cilofexor	2	100 mg/W 12	31%
Vonafexor	2	100 mg/W 12	50%
EDP-305	2	2.5 mg/W 12	45%
MET409	2	80 mg/W 12	93%
TERN-101	2	10 mg/W 12	20%
* Interim Analysis			

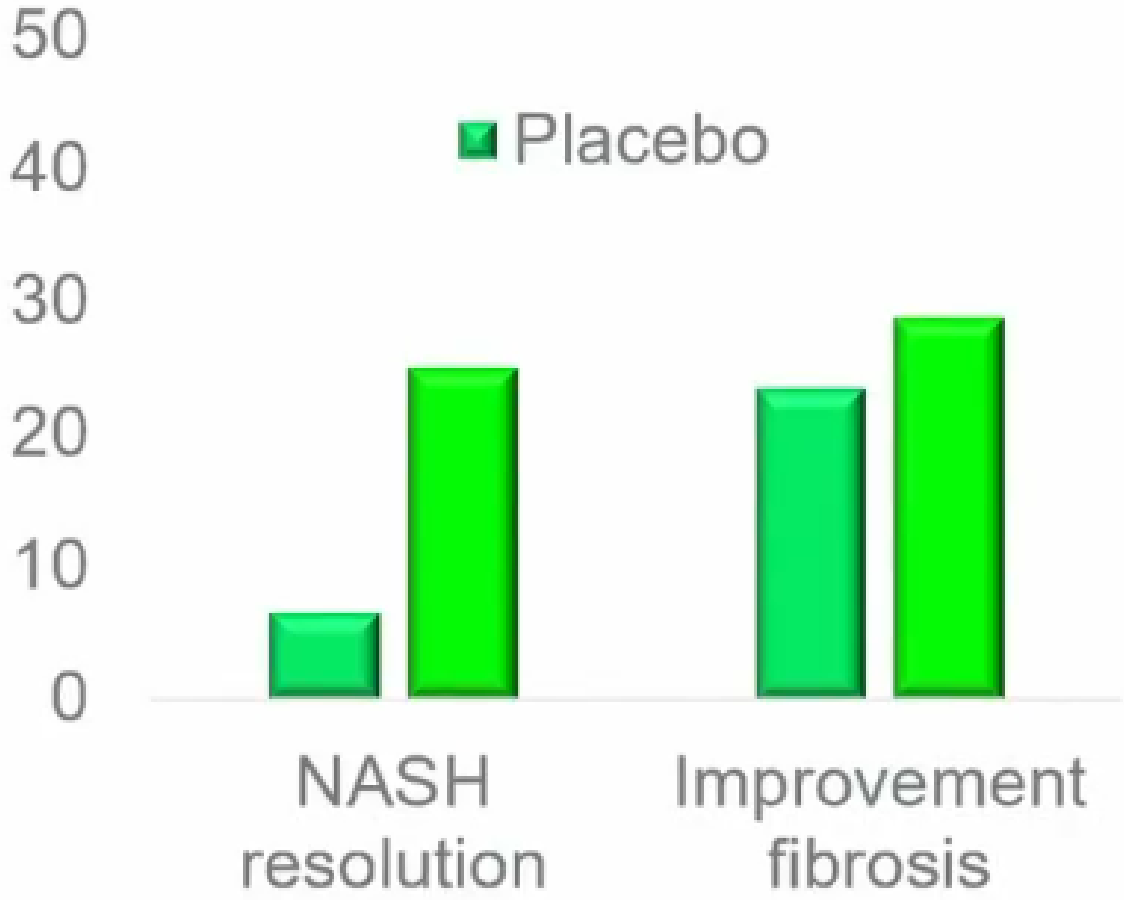
FGF19 – FGF21

FGF21	**Phase**	**Dose/duration**	**MRI-PDFF responder rate (%) with relative liver fat change from baseline >30%**	**Reference**
Pegbelfermin	2	10 mg/W 16	56% vs 24%	Sanyal et al. Lancet 2018
Efruxifermin	2	50 mg/W 12	85% vs 10%	Harrison et al. Nature Med 2021
BIO89-100	2	36 mgQ2W/W 13	88% vs 0%	Loomba et al. ILC 2021
FGF19		**Resolution NASH**	**Improvement fibrosis**	
Aldafermin	2b*	✓	n.s.	
* ALPINE 2/3 3mg				

Thyroxine beta receptor agonist: resmetirom

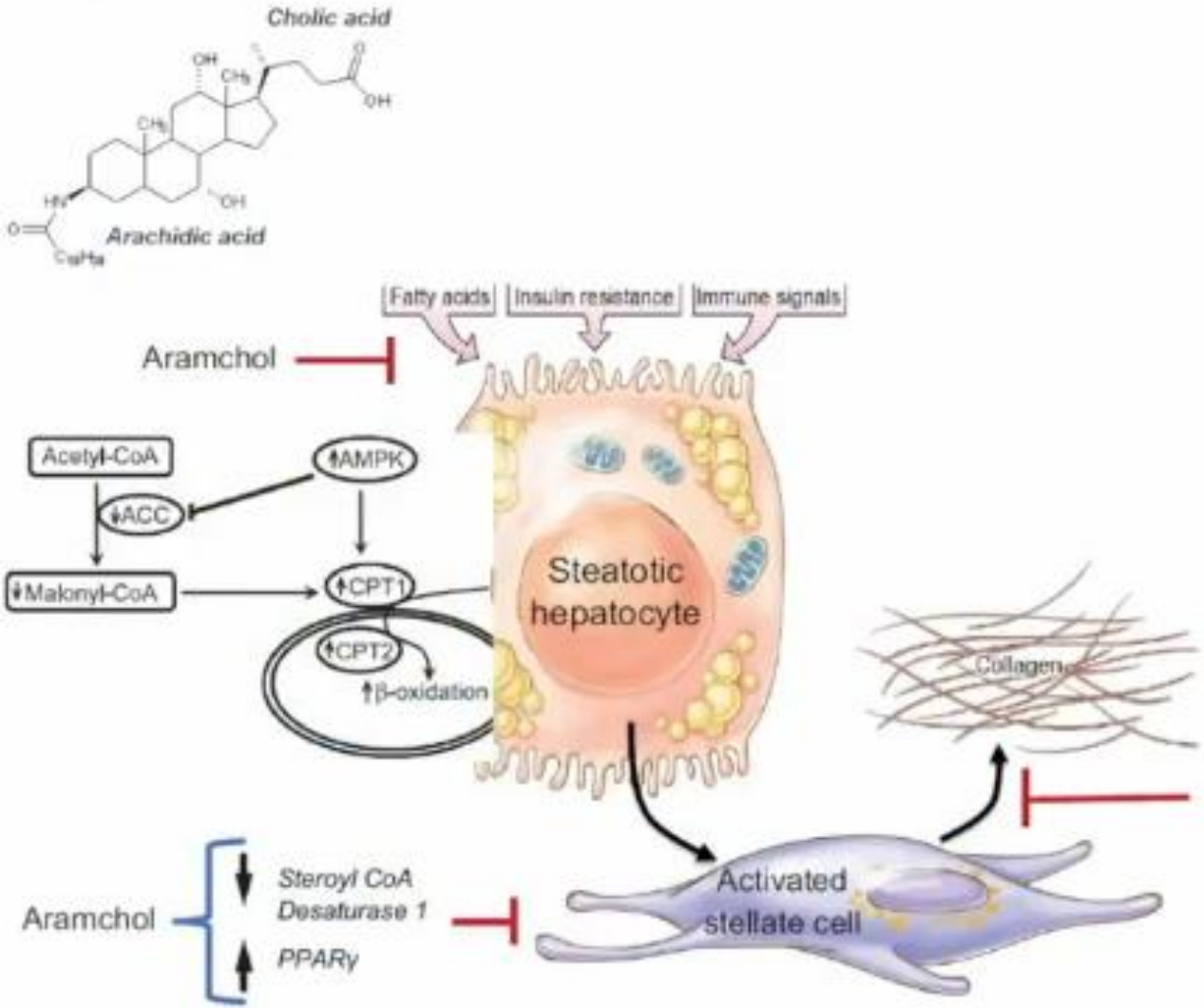


Sinha et al. Nat Rev Endocrinol 2018

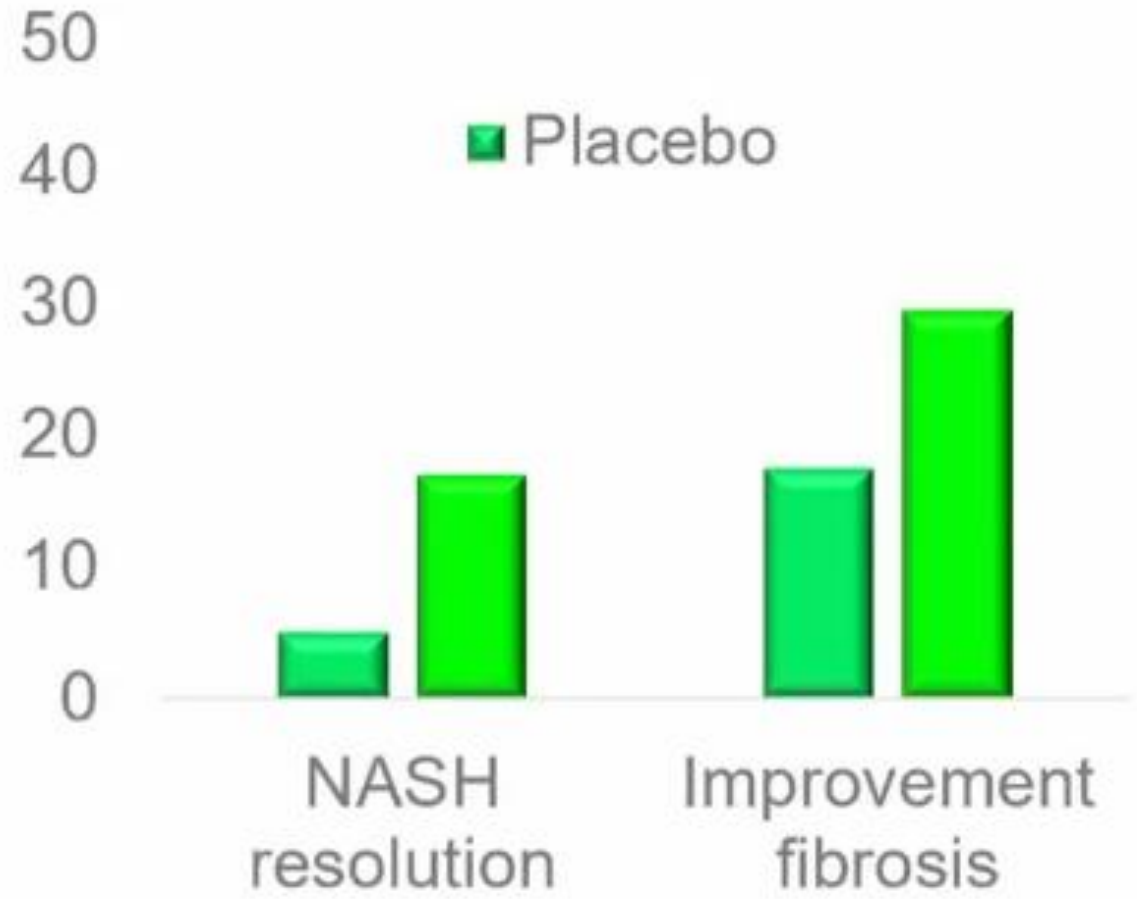


Harrison et al. Lancet 2019

Fatty acid–bile acid conjugate: aramchol



Bhattacharya et al. JHEP Reports 2021



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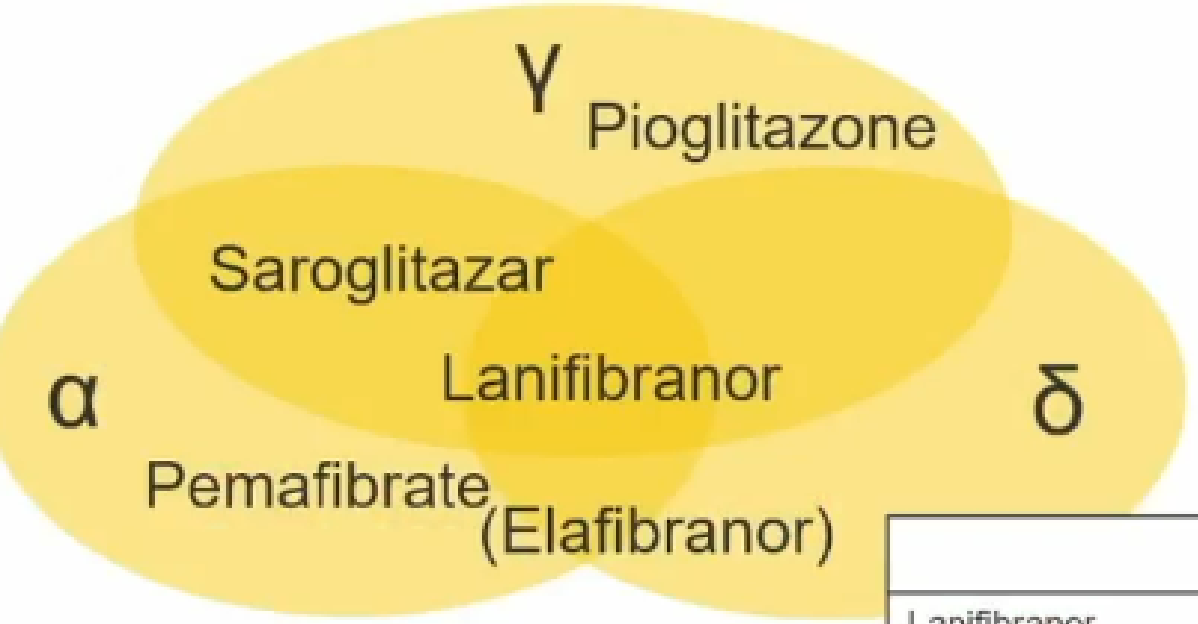
Ratziu et al. AASLD 2018

PPARs Agonists



	Phase	Resolution NASH	Improvement fibrosis
Lanifibranor	2→3	✓	✓
Saroglitazar	2→3	(✓)	(✓)
Pemafibrate	2	No histo data	No histo data
Pioglitazone	2*	✓	n.s.
Pioglitazone	**	✓	✓
* PIVENS RCT in non-diabetics ** Meta-analysis in diabetics			

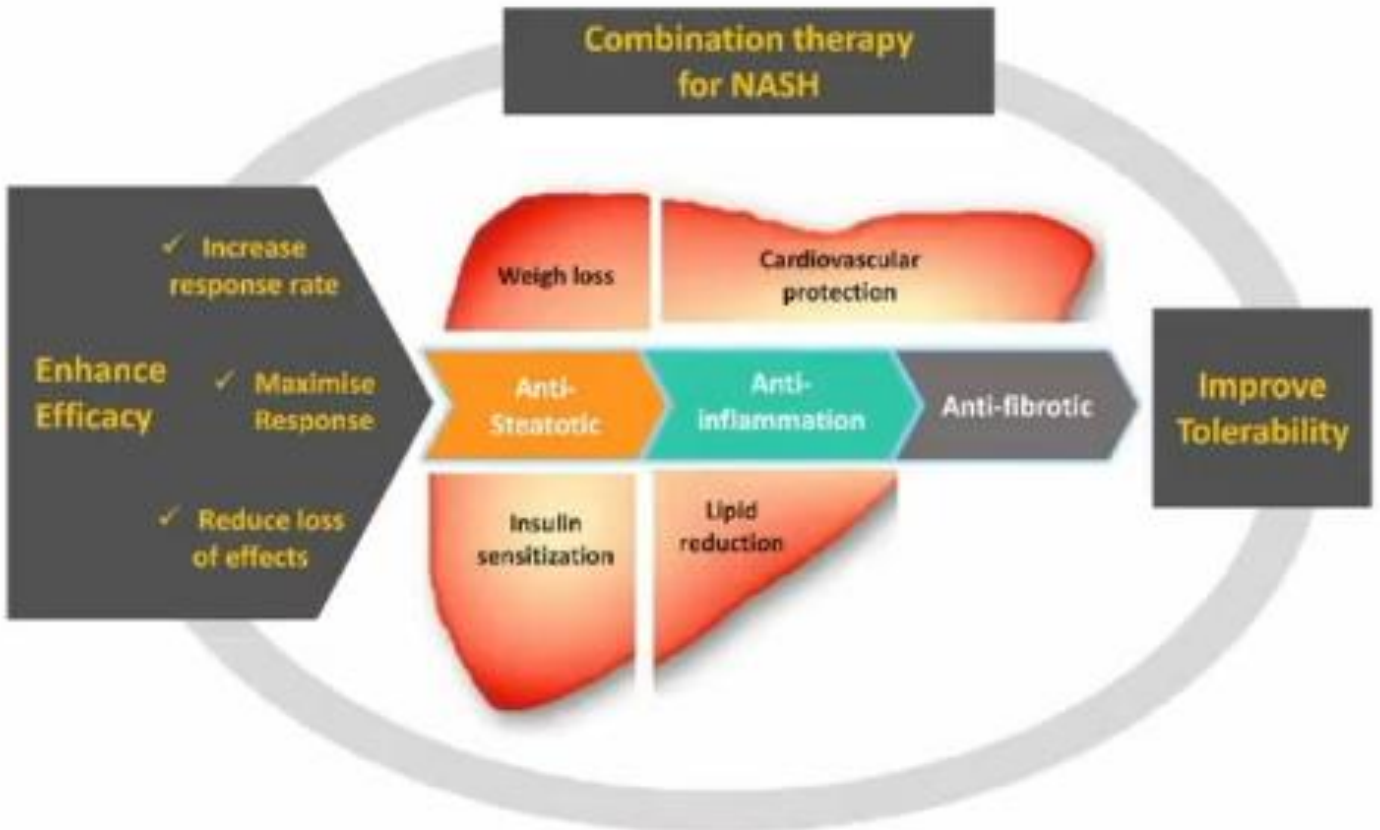
GLP1 Agonists

GLP1 Agonists	Phase	Resolution NASH	Improvement fibrosis
Semaglutide	2→3	✓	n.s.
Liraglutide	2→3	✓	n.s.
Oral formulation			
Beyond GLP1 Agonists			
Tirzepatide[1]	2	Ongoing	Ongoing
Cotadutide[2]	2	Ongoing	Ongoing
HM15211[3]	2	Ongoing	Ongoing
[1]Dual agonist GIP/GLP1 [2]Dual agonist Glucagon/GLP1 [3]Triple agonist Glucagon/GIP/GLP1 triple agonist			

Metabolic drugs

Drug	MoA	Phase	Dose/duration	MRI-PDFF responder rate (%) with relative liver fat change from baseline >30%	
Firsocostat	ACC inhibitor	2	20 mg/W 16	48% vs. 15%	Loomba et al. Gastro 2018
TVB-2640	FASN inhibitor	2	50 mg/W 12	61% vs 11%	Loomba et al. Gastro 2021
Icosabutate	Liver –targeted engineered fatty acid decreasing production of inflammatory lipids	2	600 mg/W 16	No change [expected given MoA]	Harrison et al. NAFLD Summit 2021

Combination therapies



Rationale

- Combining different mechanisms of action
- Targeting steatosis, inflammation and fibrosis
- Positive effects beyond the liver (e.g. weight loss, cardiovascular protection)

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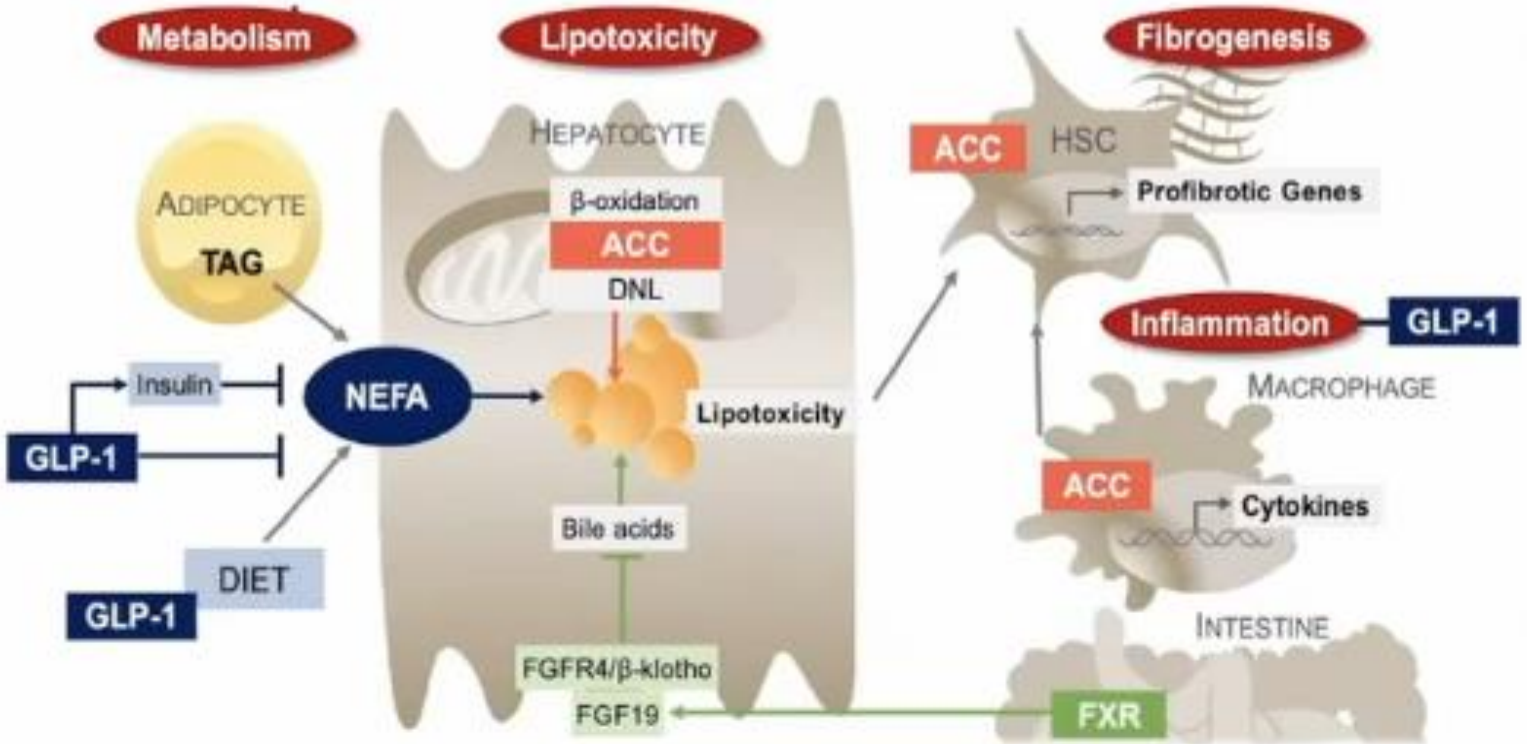
Dufour et al. GUT 2020

Combination therapies

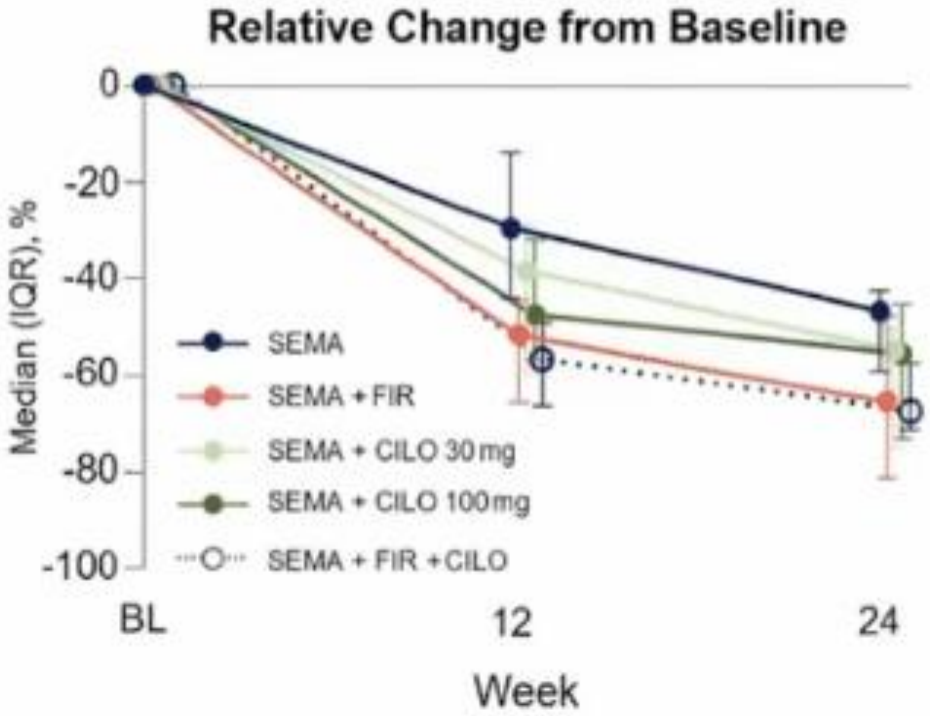
GLP-1 **Semaglutide (SEMA)**
Metabolic (weight loss, insulin sensitivity, glucose), anti-inflammatory effects, CV risk reduction*[1,2]

ACC **Firsocostat (FIR)**
DNL & β-oxidation

FXR **Cilofexor (CILO)**
Bile acid signaling



MRI-PDFF



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Alkhoury et al. AASLD 2020

Whom to treat with what ?

2021 no drug approved

Enroll patients in clinical trials

Emphasize lifestyle changes

Keep in mind the cardiovascular and cancer risk