Non-alcoholic steatohepatitis (NASH): Definition, natural history and current therapeutic interventions

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Disclosures Frank Tacke

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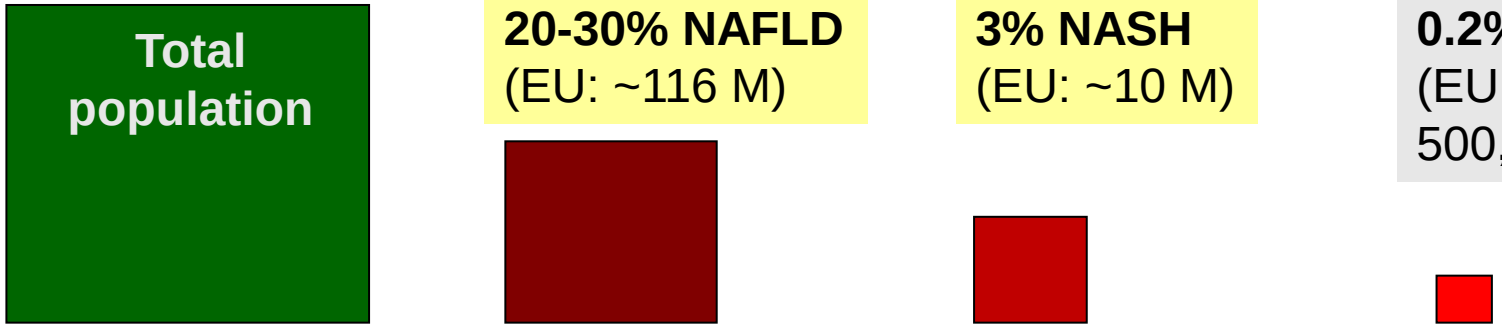
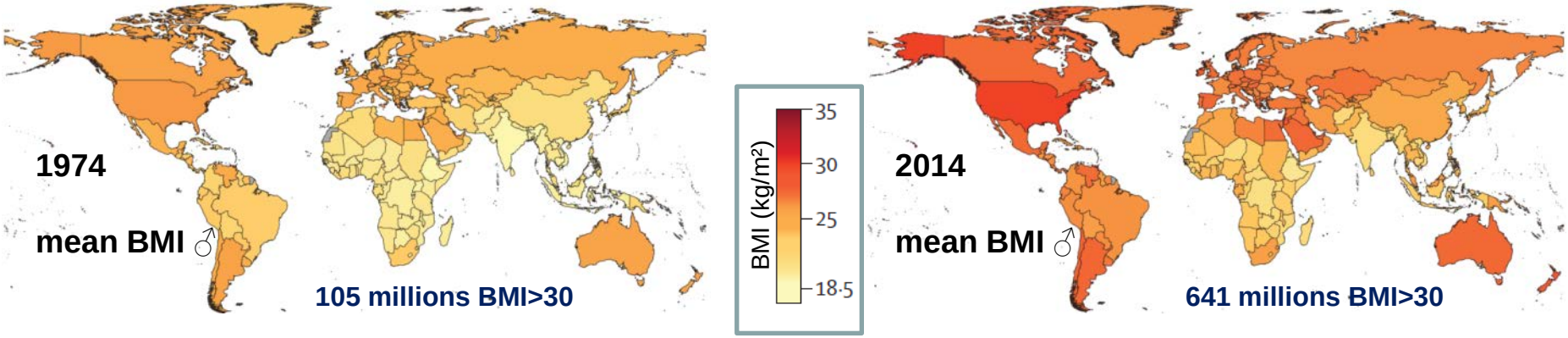
  Tobira/Allergan, Galapagos, Inventiva, BMS
- *Speaker/Consulting:*
  Tobira/Allergan, Gilead, AbbVie, BMS, Falk, Boehringer, Galapagos, Intercept, Inventiva

Non-alcoholic Fatty Liver Disease: The epidemiological challenge

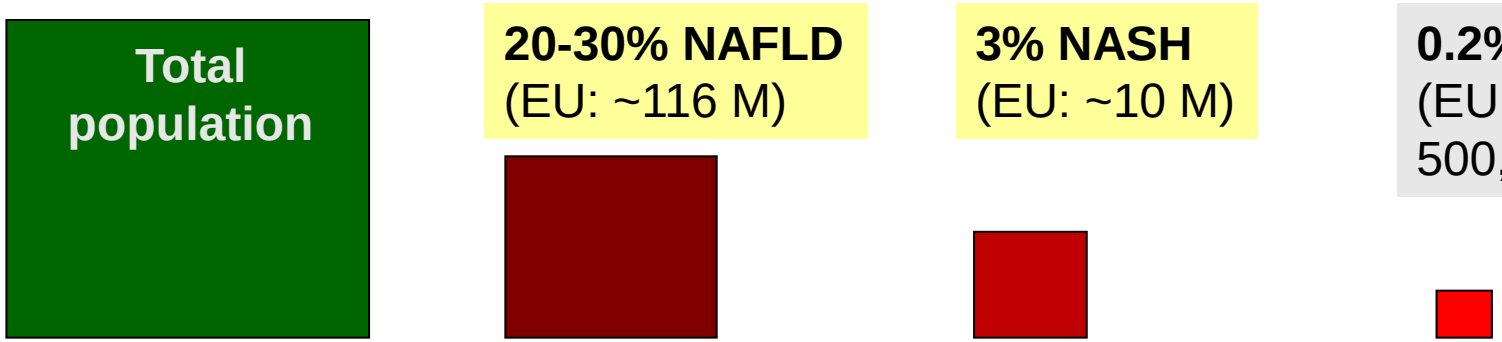


HEPAMAP. A roadmap for hepatology research in Europe: An overview for policy makers. *EASL* 2015



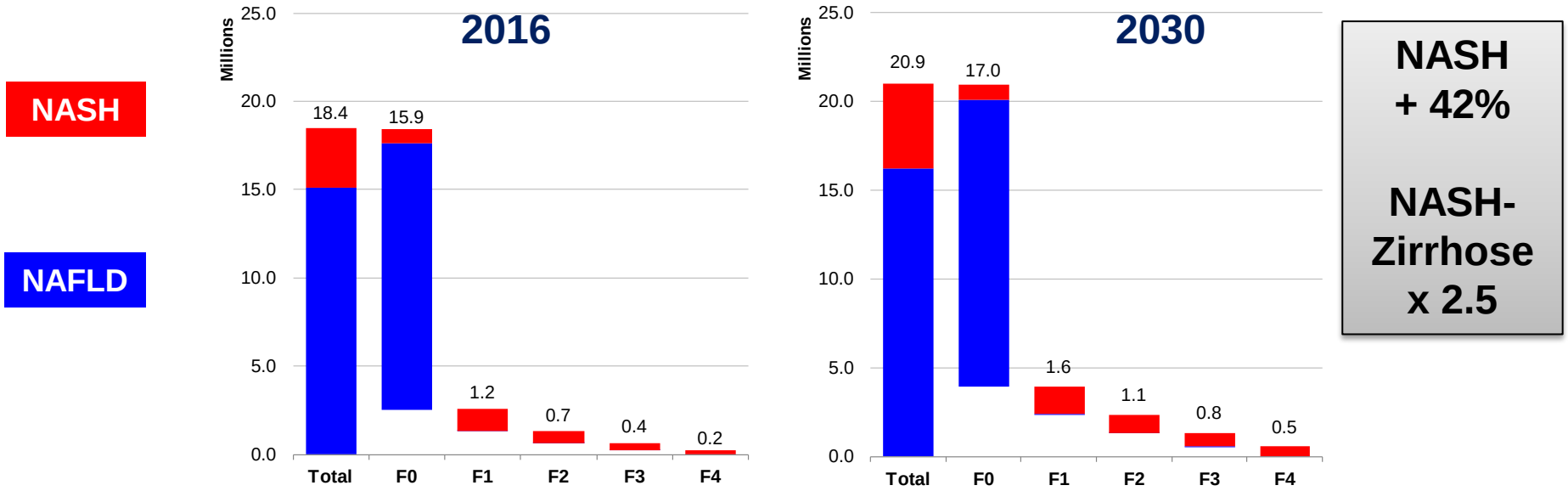
NCD Risk Factor Collaboration, Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet. 2016; 387(10026):1377-96*

Non-alcoholic Fatty Liver Disease: The epidemiological challenge



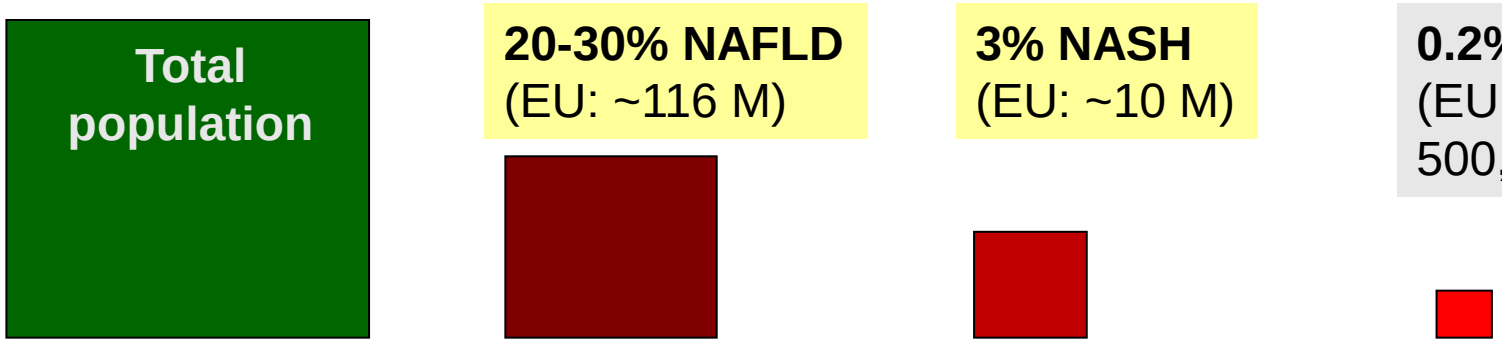
HEPAMAP. A roadmap for hepatology research in Europe: An overview for policy makers. *EASL* 2015

Projection for Germany



Estes C, et al. *J Hepatol.* 2018; 69(4):896-904

Non-alcoholic Fatty Liver Disease: The epidemiological challenge



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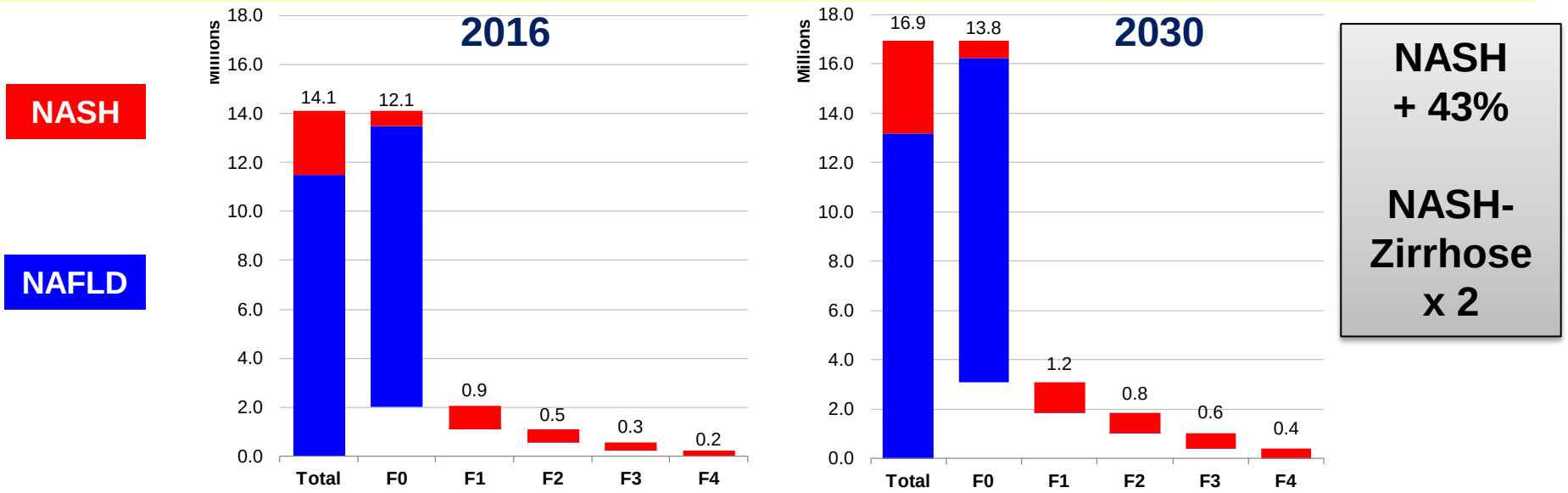
Projection for UK



Estes C, et al. *J Hepatol.* 2018; 69(4):896-904

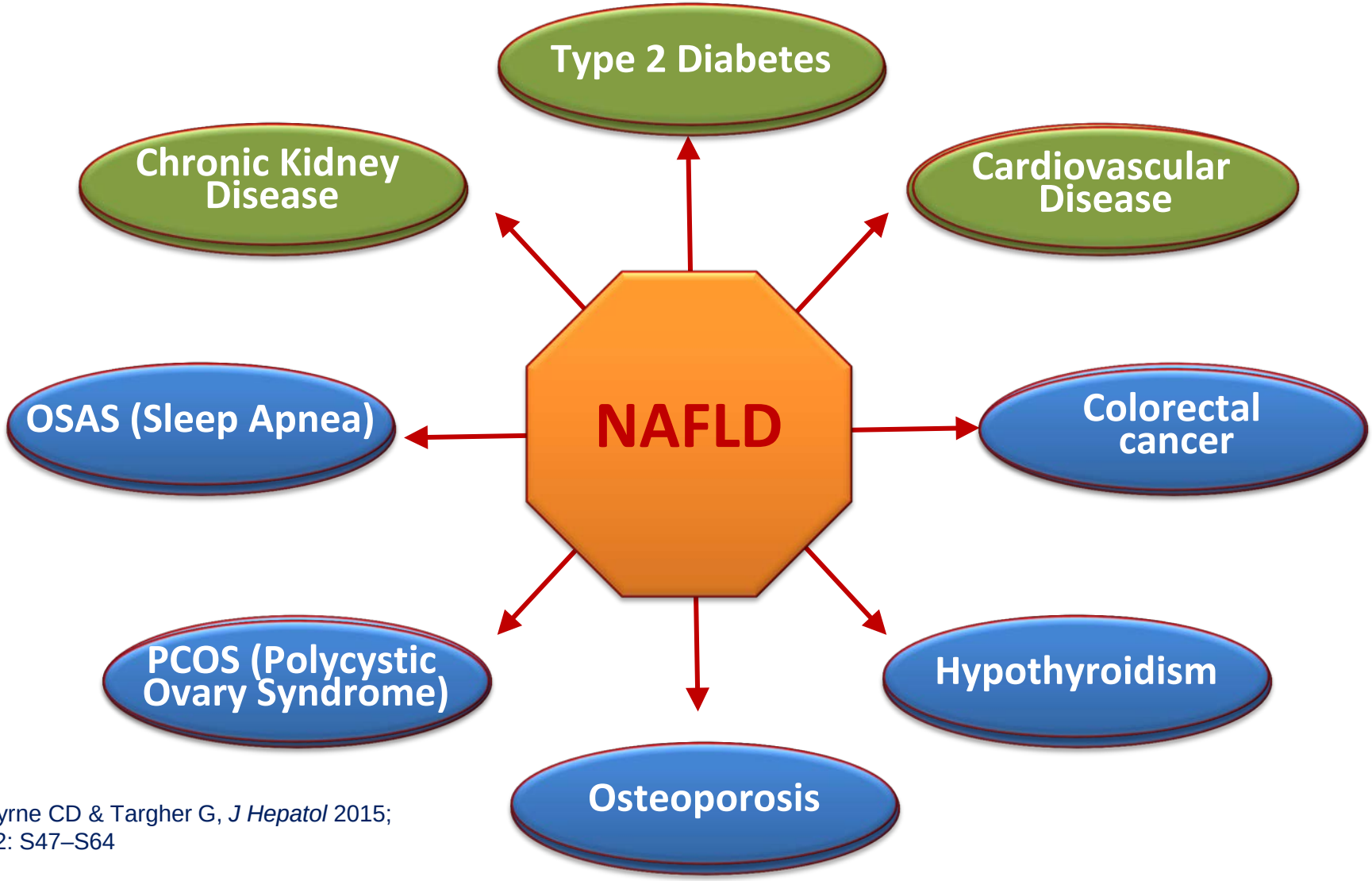
Non-alcoholic Fatty Liver Disease: The clinical challenge

- Old(er) age, high(er) body-mass index
- Many comorbidities (diabetes, kidney, cardiovascular…)
- Substantial proportion unaware of their liver condition
- High(er) rate of malignancies

Non-alcoholic Fatty Liver Disease: The clinical challenge

https://broadly.vice.com

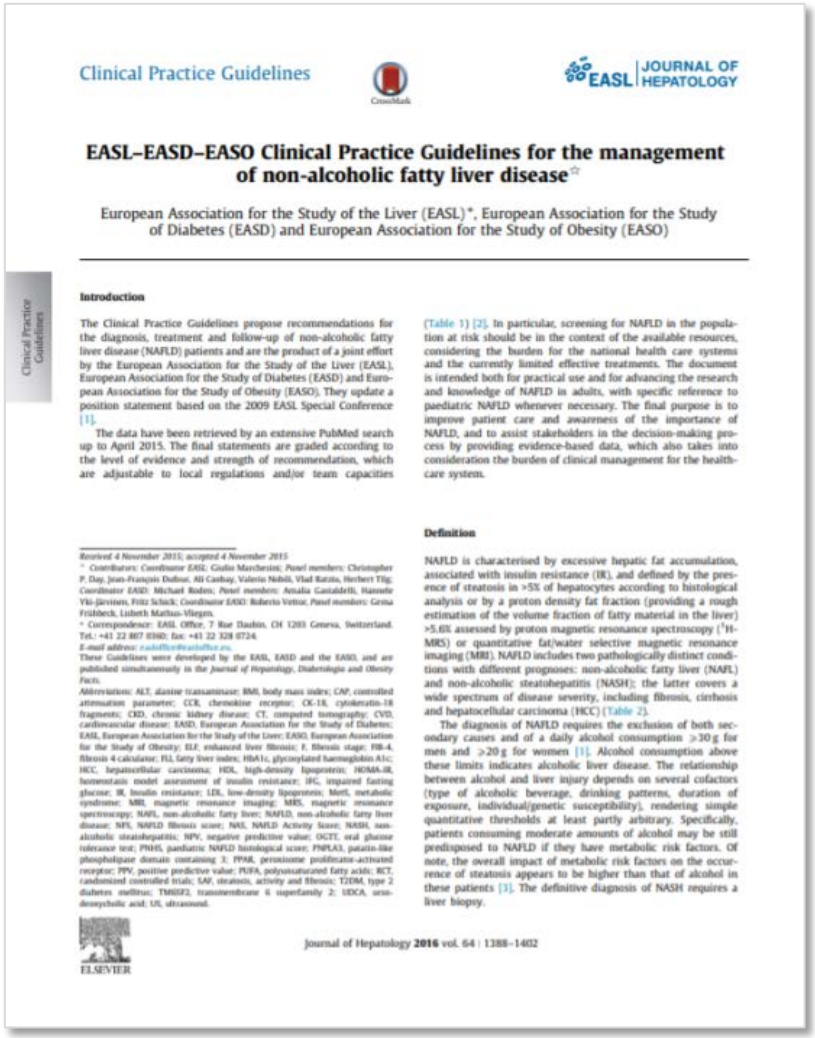
Extrahepatic complications of non-alcoholic fatty liver disease



Byrne CD & Targher G, *J Hepatol* 2015; 62: S47–S64

Management of fatty liver disease: EASL multidisciplinary Clinical Practice Guideline

- **Chairs**
  - EASL: Giulio Marchesini
  - EASD: Michael Roden
  - EASO: Roberto Vettor
- **Panel members**
  - EASL: Christopher P Day, Jean-François Dufour, Ali Canbay, Valerio Nobili, Vlad Ratziu, Herbert Tilg
  - EASD: Amalia Gastaldelli, Hannele Yki-Järvinen, Fritz Schick
  - EASO: Gema Frühbeck, Lisbeth Mathus-Vliegen
- **Reviewers**
  - Elisabetta Bugianesi, Helena Cortez-Pinto, Stephen Harrison



Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease☆

European Association for the Study of the Liver (EASL)*, European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO)

Clinical Practice Guidelines

Introduction

The Clinical Practice Guidelines propose recommendations for the diagnosis, treatment and follow-up of non-alcoholic fatty liver disease (NAFLD) patients and are the product of a joint effort by the European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO). They update a position statement based on the 2009 EASL Special Conference [1].

The data have been retrieved by an extensive PubMed search up to April 2015. The final statements are graded according to the level of evidence and strength of recommendation, which are adjustable to local regulations and/or team capacities (Table 1) [2]. In particular, screening for NAFLD in the population at risk should be in the context of the available resources, considering the burden for the national health care systems and the currently limited effective treatments. The document is intended both for practical use and for advancing the research and knowledge of NAFLD in adults, with specific reference to paediatric NAFLD whenever necessary. The final purpose is to improve patient care and awareness of the importance of NAFLD, and to assist stakeholders in the decision-making process by providing evidence-based data, which also takes into consideration the burden of clinical management for the health-care system.

Definition

NAFLD is characterised by excessive hepatic fat accumulation, associated with insulin resistance (IR), and defined by the presence of steatosis in >5% of hepatocytes according to histological analysis or by a proton density fat fraction (providing a rough estimation of the volume fraction of fatty material in the liver) >5.6% assessed by proton magnetic resonance spectroscopy (^{1}H-MRS) or quantitative fat/water selective magnetic resonance imaging (MRI). NAFLD includes two pathologically distinct conditions with different prognoses: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH); the latter covers a wide spectrum of disease severity, including fibrosis, cirrhosis and hepatocellular carcinoma (HCC) (Table 2).

The diagnosis of NAFLD requires the exclusion of both secondary causes and of a daily alcohol consumption ⩾30 g for men and ⩾20 g for women [1]. Alcohol consumption above these limits indicates alcoholic liver disease. The relationship between alcohol and liver injury depends on several cofactors (type of alcoholic beverage, drinking patterns, duration of exposure, individual/genetic susceptibility), rendering simple quantitative thresholds at least partly arbitrary. Specifically, patients consuming moderate amounts of alcohol may be still predisposed to NAFLD if they have metabolic risk factors. Of note, the overall impact of metabolic risk factors on the occurrence of steatosis appears to be higher than that of alcohol in these patients [3]. The definitive diagnosis of NASH requires a liver biopsy.

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* Contributors: Coordinator EASL: Giulio Marchesini; Panel members: Christopher P. Day, Jean-François Dufour, Ali Canbay, Valerio Nobili, Vlad Ratziu, Herbert Tilg; Coordinator EASD: Michael Roden; Panel members: Amalia Gastaldelli, Hannele Yki-Järvinen, Fritz Schick; Coordinator EASO: Roberto Vettor, Panel members: Gema Frühbeck, Lisbeth Mathus-Vliegen.
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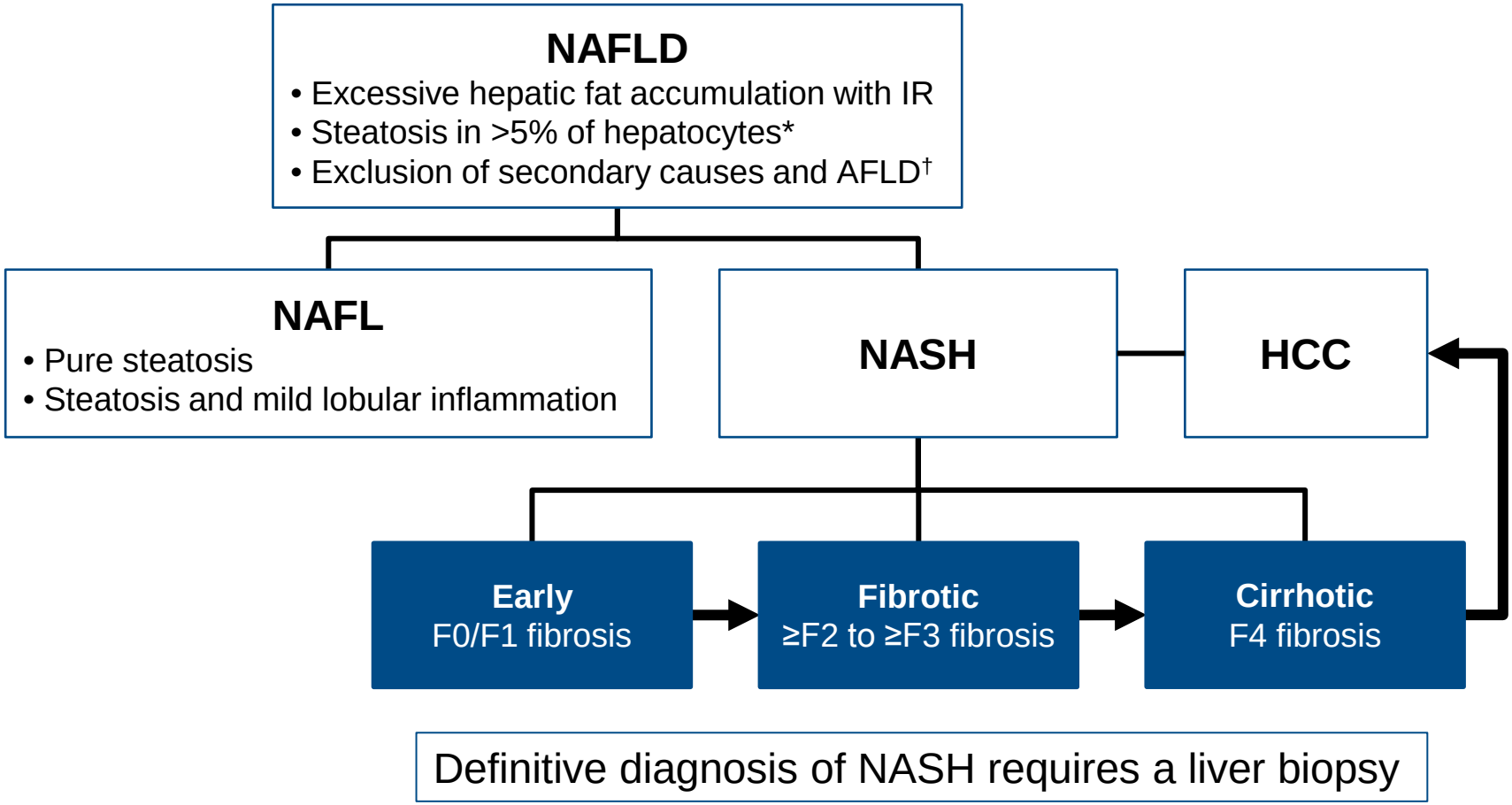
These Guidelines were developed by the EASL, EASD and the EASO, and are published simultaneously in the Journal of Hepatology, Diabetologia and Obesity Facts.

Abbreviations: ALT, alanine transaminase; BMI, body mass index; CAP, controlled attenuation parameter; CCR, chemokine receptor; CK-18, cytokeratin-18 fragments; CKD, chronic kidney disease; CT, computed tomography; CVD, cardiovascular disease; EASD, European Association for the Study of Diabetes; EASL, European Association for the Study of the Liver; EASO, European Association for the Study of Obesity; ELF, enhanced liver fibrosis; F, fibrosis stage; FIB-4, fibrosis 4 calculator; FLI, fatty liver index; HbA1c, glycosylated haemoglobin A1c; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IR, insulin resistance; LDL, low-density lipoprotein; MetS, metabolic syndrome; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NAFL, non-alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; NAS, NAFLD Activity Score; NASH, non-alcoholic steatohepatitis; NPV, negative predictive value; OGTT, oral glucose tolerance test; PNPLA3, patatin-like phospholipase domain containing 3; PPAR, peroxisome proliferator-activated receptor; PPV, positive predictive value; PUFA, polyunsaturated fatty acids; RCT, randomized controlled trials; SAF, steatosis, activity and fibrosis; T2DM, type 2 diabetes mellitus; TM6SF2, transmembrane 6 superfamily 2; UDCA, ursodeoxycholic acid; US, ultrasound.

ELSEVIER

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

Natural history of fatty liver disease: Definitions of NAFLD, NAFL and NASH



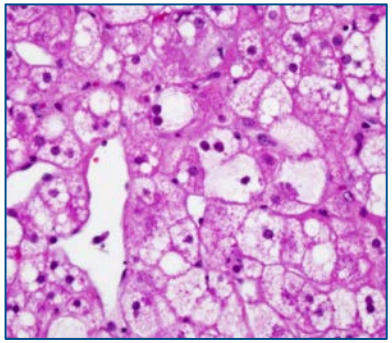
*According to histological analysis or proton density fat fraction or >5.6% by proton MRS or quantitative fat/water-selective MRI;
†Daily alcohol consumption of ≥30 g for men and ≥20 g for women

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

Diagnosis and staging of fatty liver disease: Role of 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*

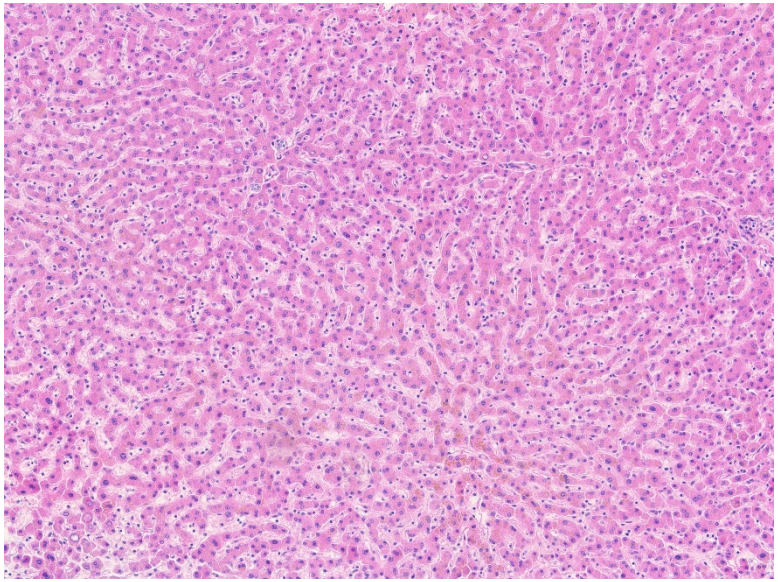
*Should not be used for initial diagnosis

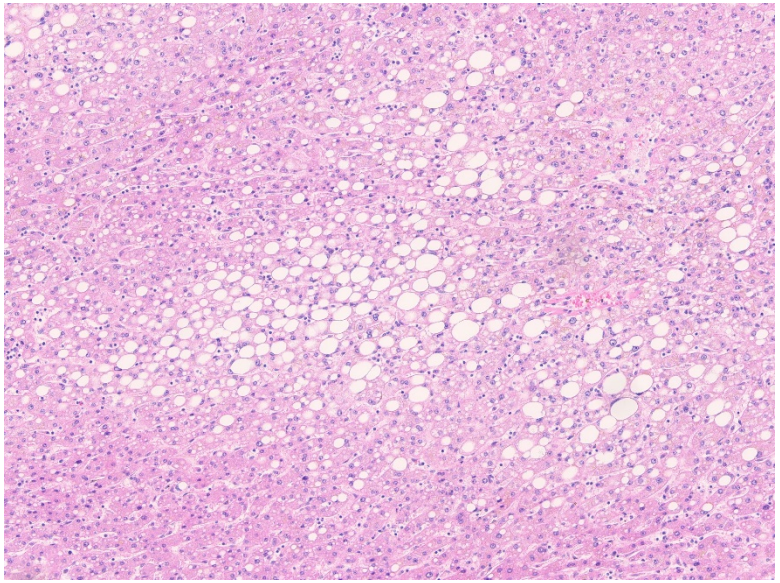


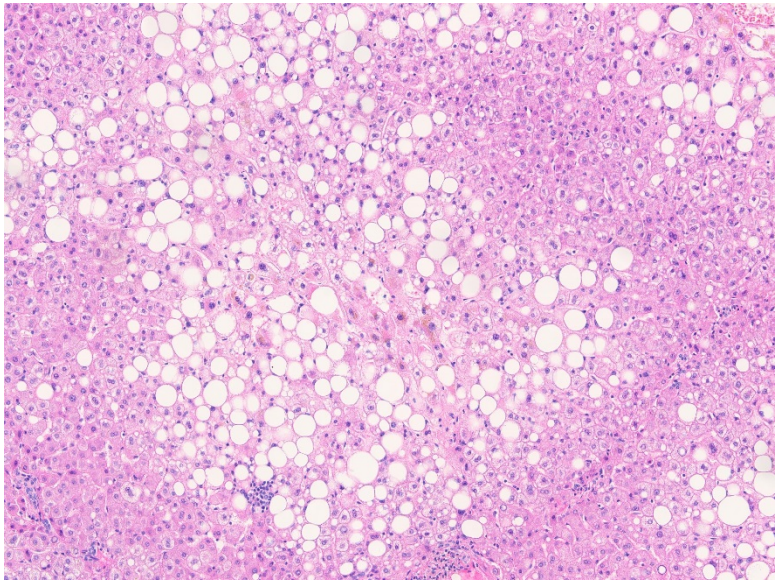
Recommendations	Grade of evidence	Grade of recommendation
NASH has to be diagnosed by a liver biopsy showing **steatosis, hepatocyte ballooning and lobular inflammation**	A	1

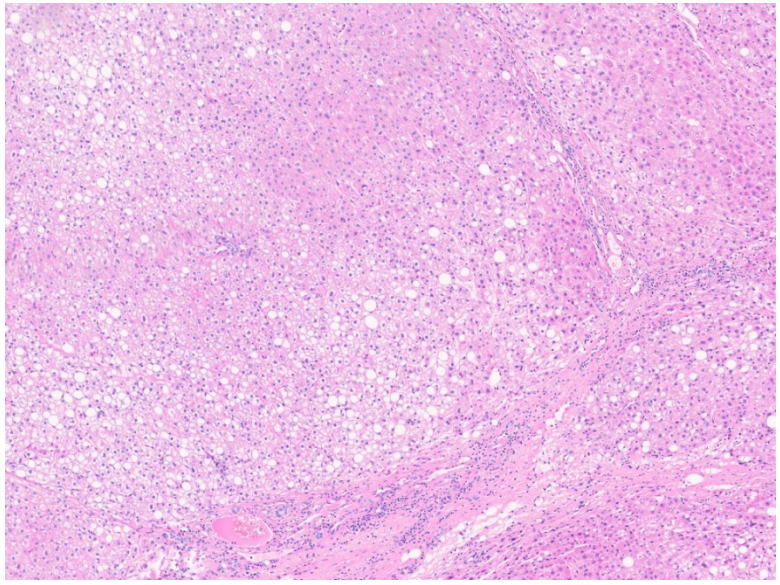
EASL–EASD–EASO CPG NAFLD. *J Hepatol* 2016; 64:1388–402

Diagnosis and staging of fatty liver disease: Role of liver biopsy



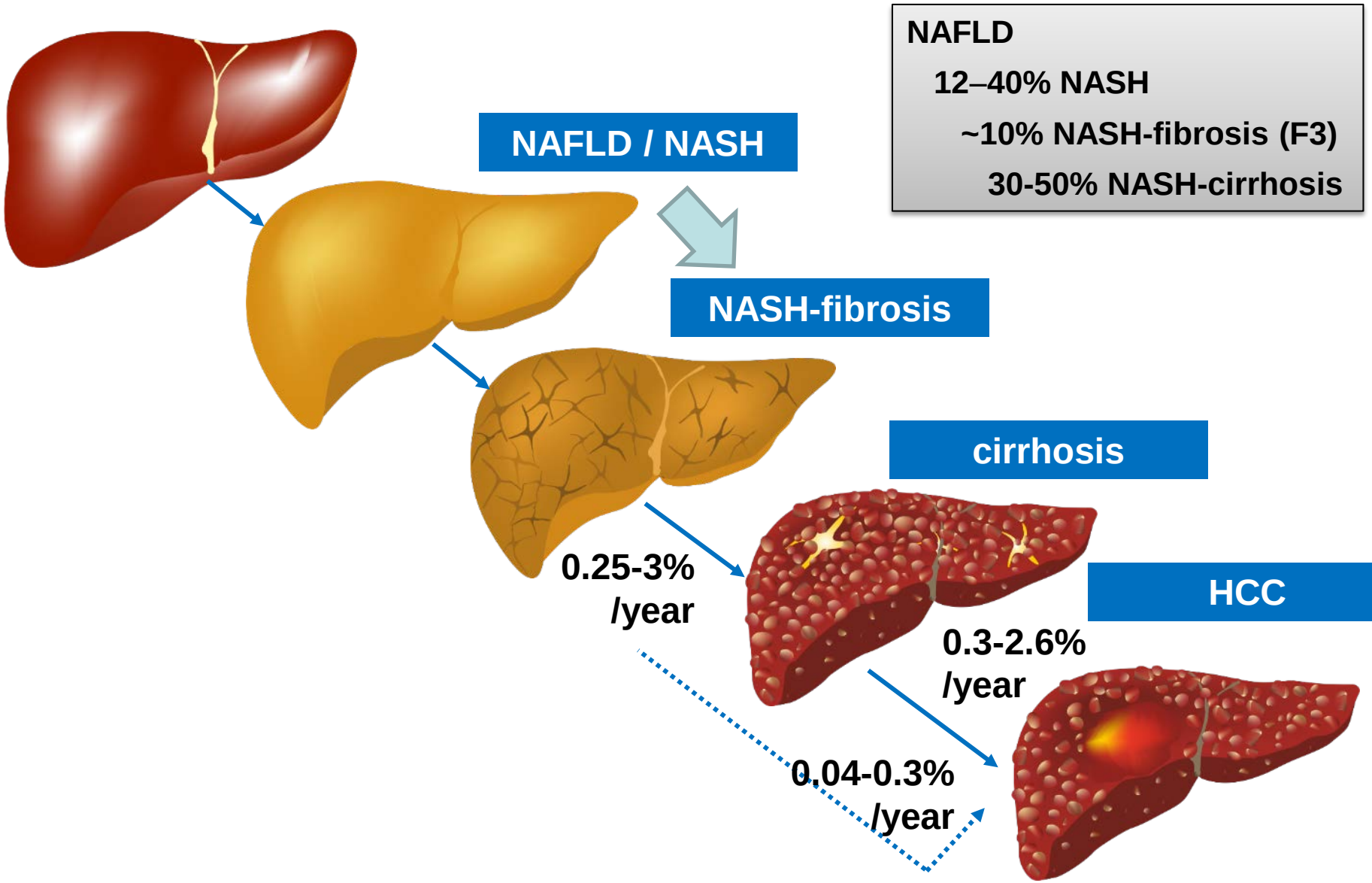






Courtesy of Dr. Thomas Ritz, Institute of Pathology, University Hospital Aachen

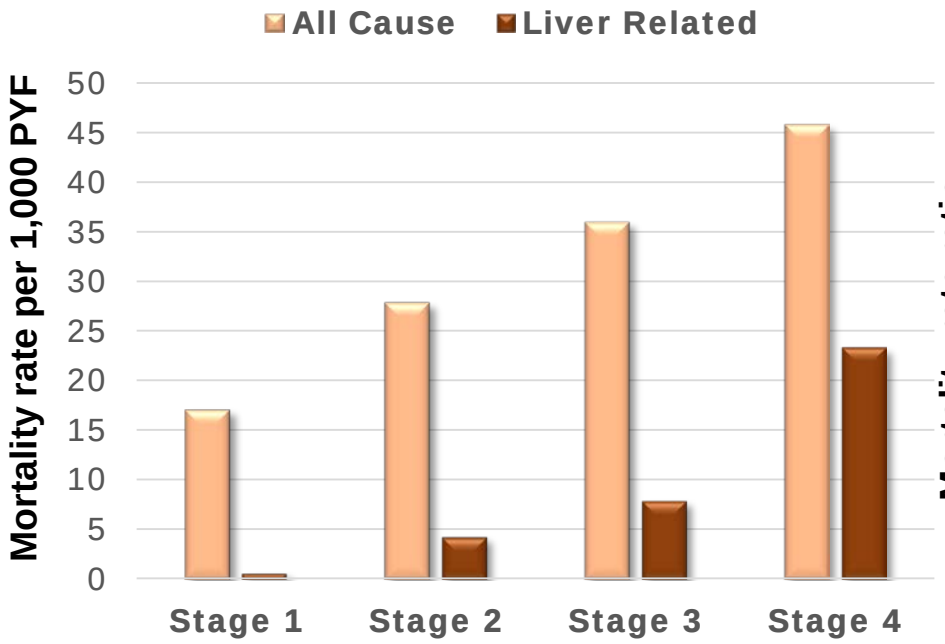
Natural history of fatty liver disease: Estimated progression rates



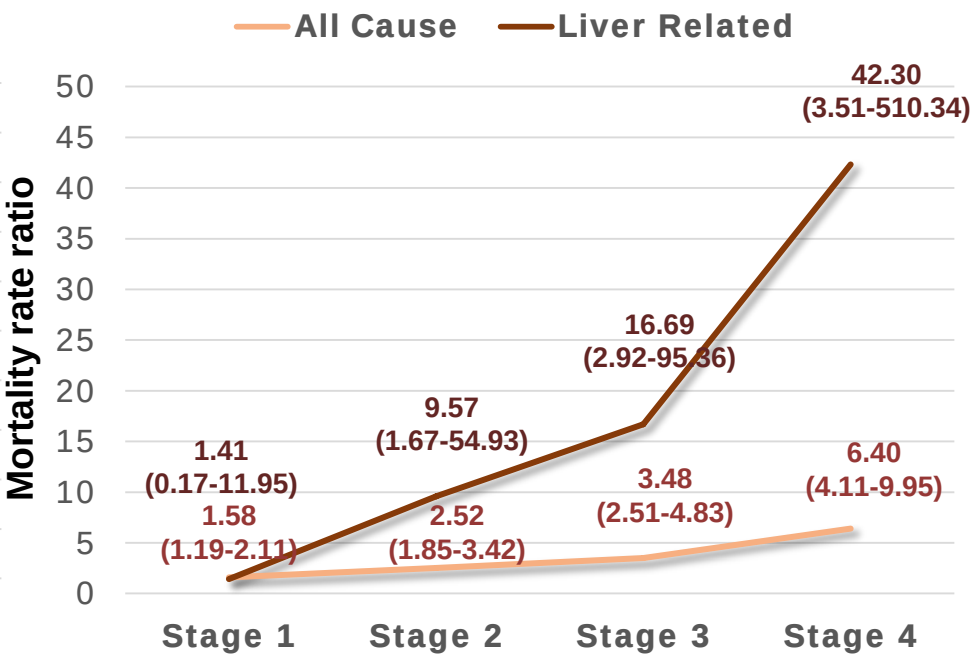
Fibrosis determines the prognosis of non-alcoholic fatty liver disease

- Meta-analysis of 5 studies on fibrosis-related mortality
- 1,495 NAFLD patients with 17,452 patient years of follow-up

Mortality rate by fibrosis stage



Mortality rate ratio by fibrosis stage

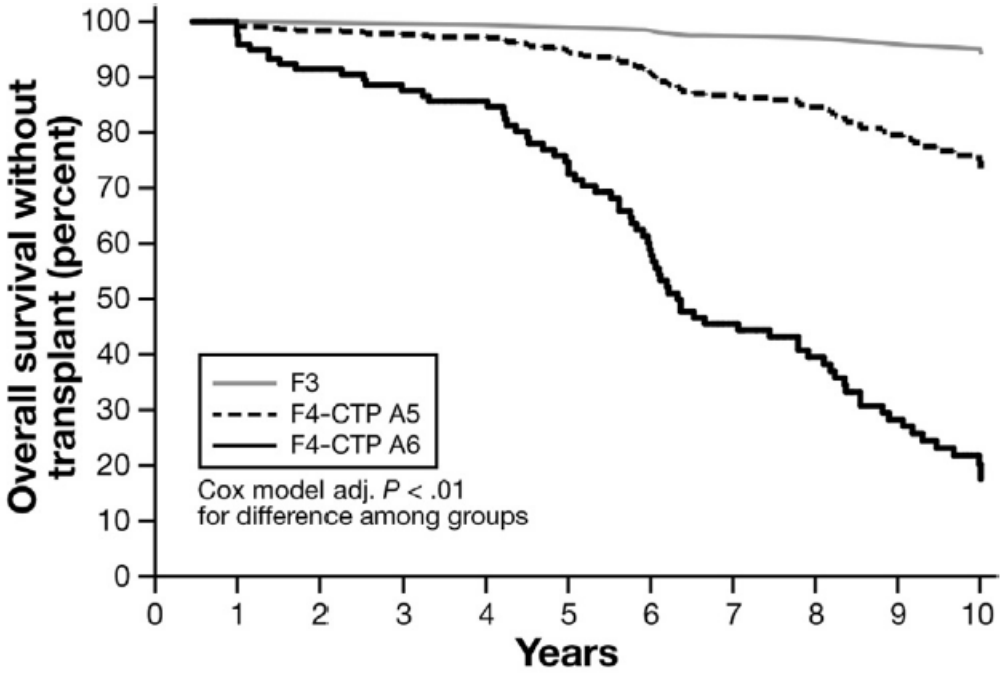


PYF, patients years of follow-up
Mortality rate ratio = actual mortality versus expected mortality

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

Fibrosis determines the prognosis of non-alcoholic fatty liver disease

- 458 NAFLD patients (bridging fibrosis, F3, n=159; Child A5 cirrhosis, n=222; Child A6 cirrhosis, n=77); 4 tertiary centers, mean follow-up 5.5 years
- Deaths: n=37, Liver Transplant: n=37, decompensation: n=88, Liver Cancer (HCC): n=41, Cardiovascular events: n=14, non-liver cancer: n=30



No. at risk											
F3	159	157	144	155	102	81	72	54	41	31	20
F4-CTP A5	222	212	191	155	129	112	96	77	63	56	43
F4-CTP A6	77	74	58	55	53	44	30	24	18	11	5

Vilar-Gomez E, et al. *Gastroenterology*. 2018; 155(2):443-457.

Fibrosis determines the prognosis of non-alcoholic fatty liver disease

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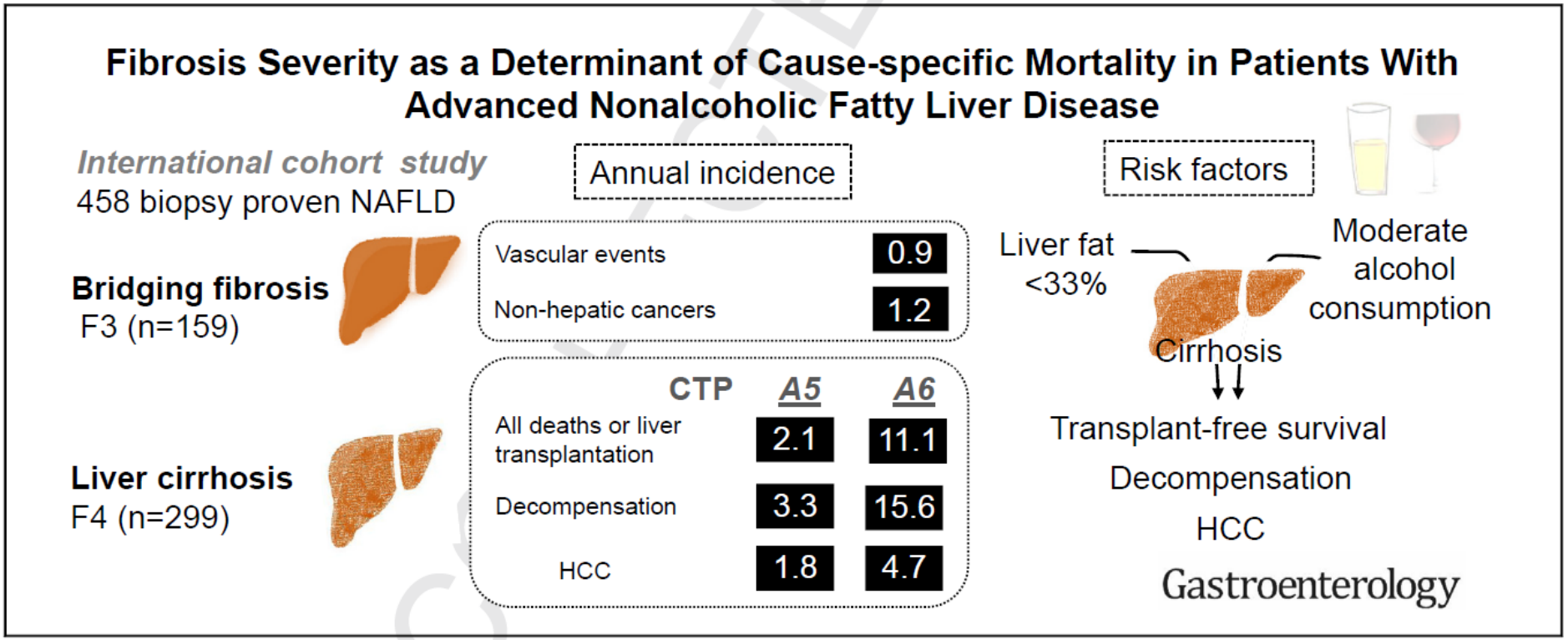
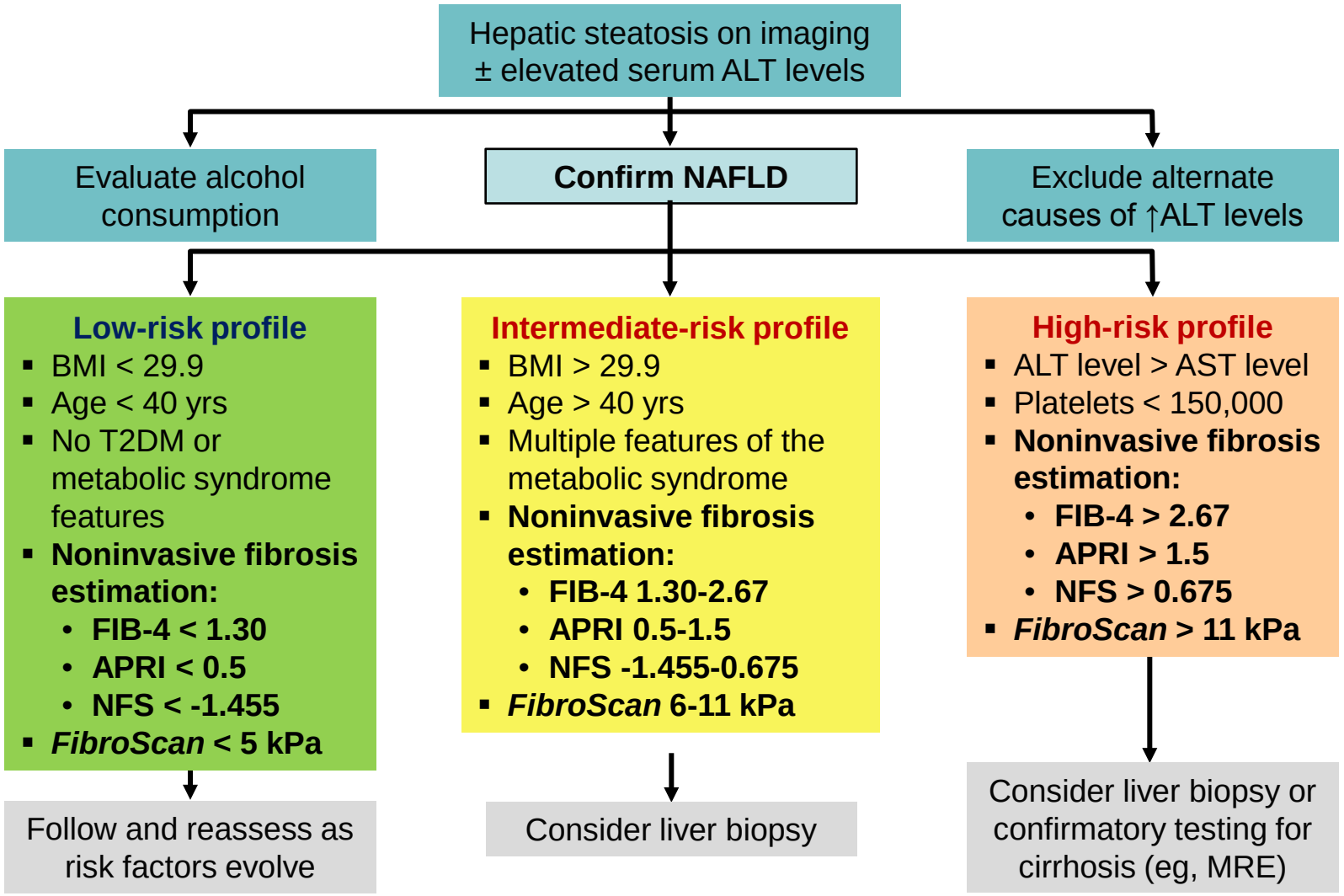


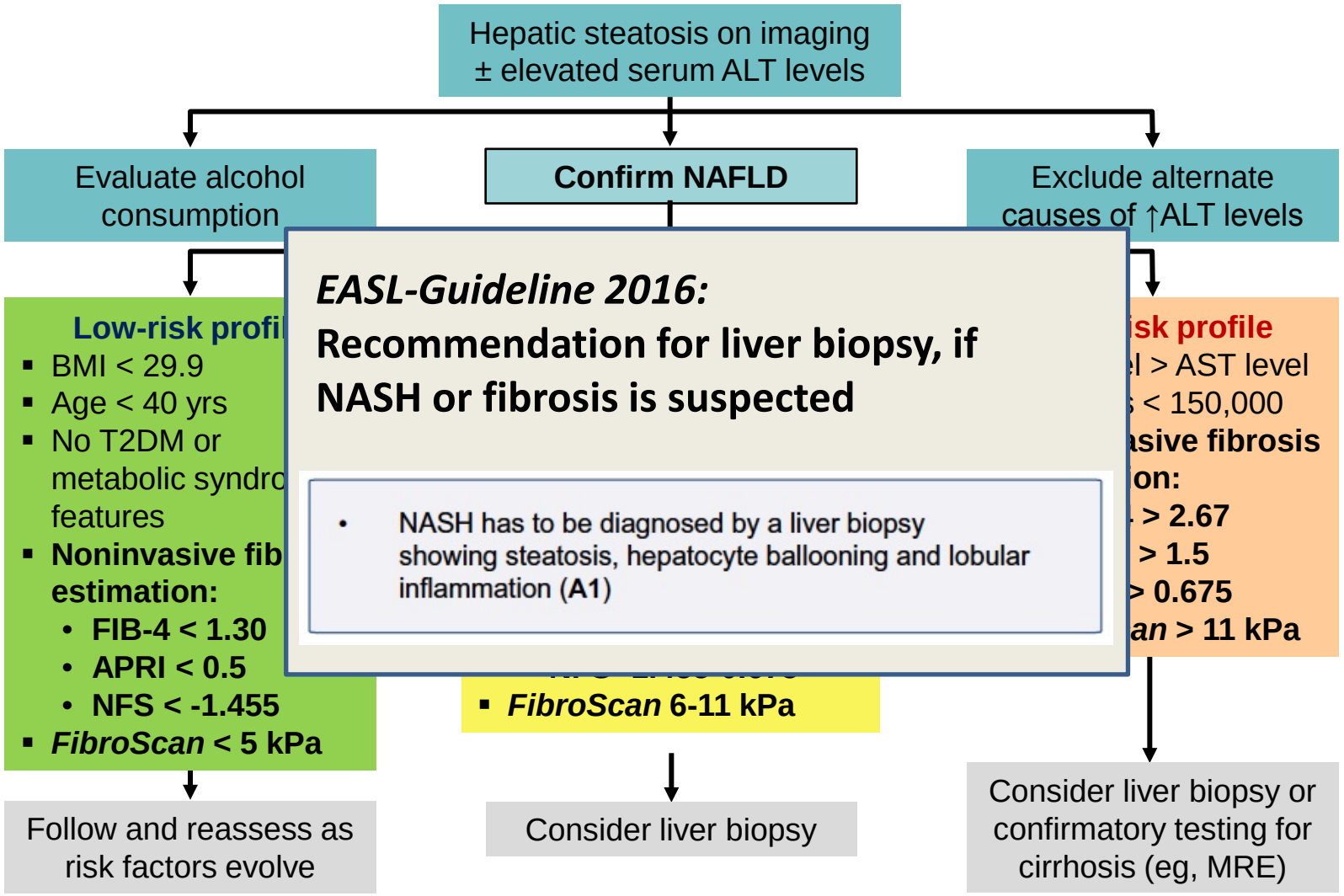
Vilar-Gomez E, et al. *Gastroenterology*. 2018; 155(2):443-457.

A potential algorithm for risk assessment in non-alcoholic fatty liver disease



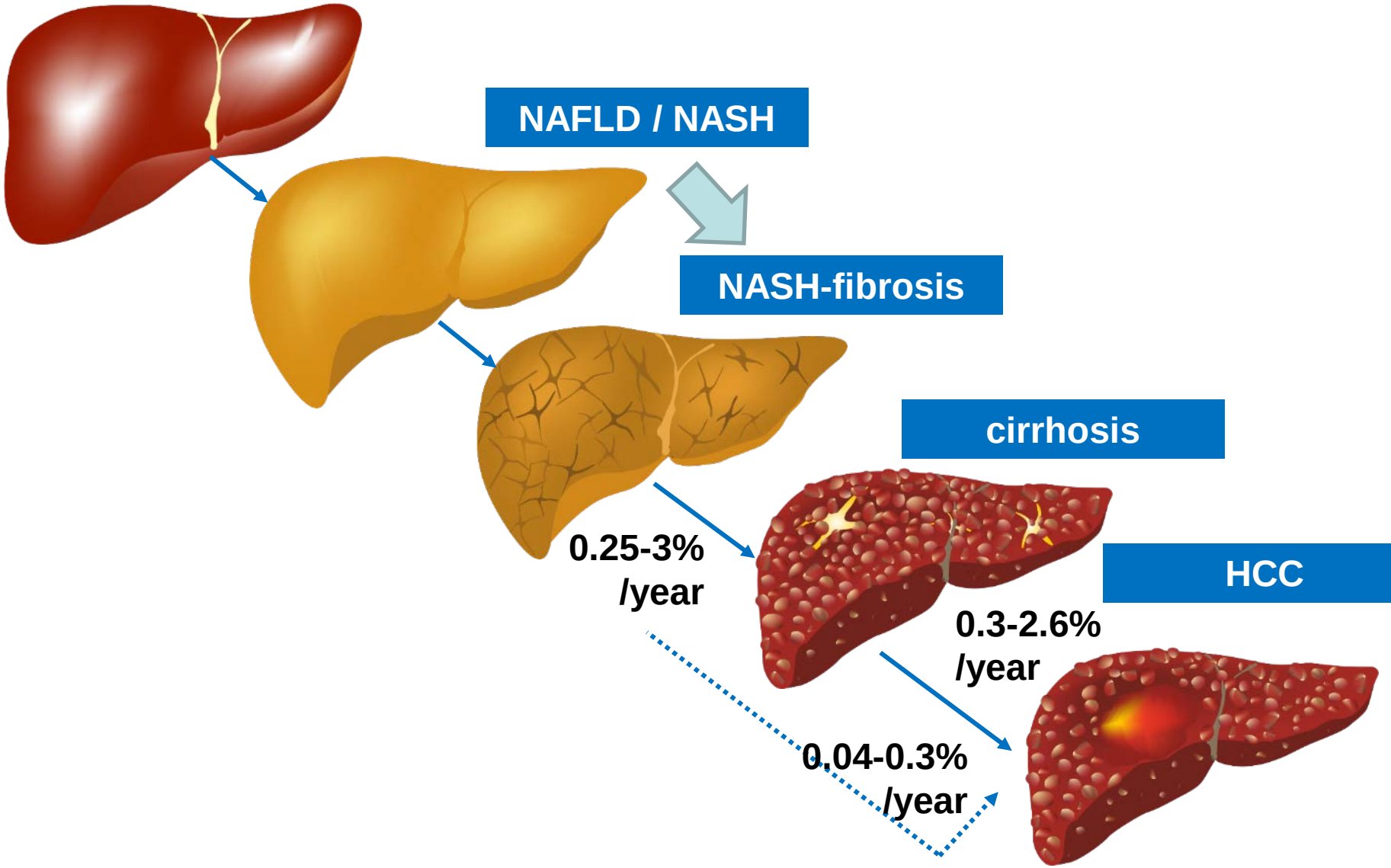
Rinella ME, Sanyal AJ. *Nat Rev Gastroenterol Hepatol*. 2016; 13:196-205.

A potential algorithm for risk assessment in non-alcoholic fatty liver disease

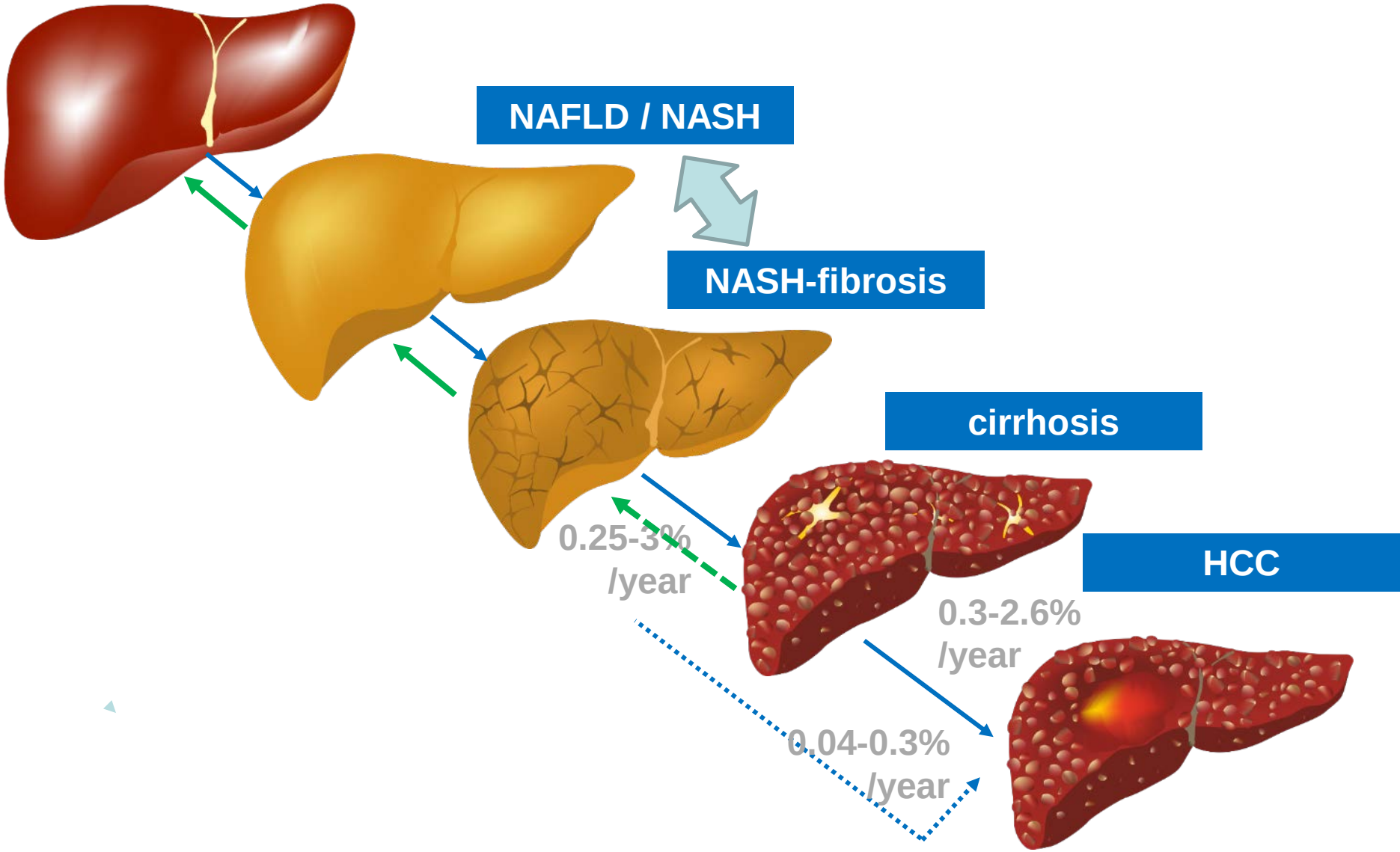


Rinella ME, Sanyal AJ. *Nat Rev Gastroenterol Hepatol*. 2016; 13:196-205.

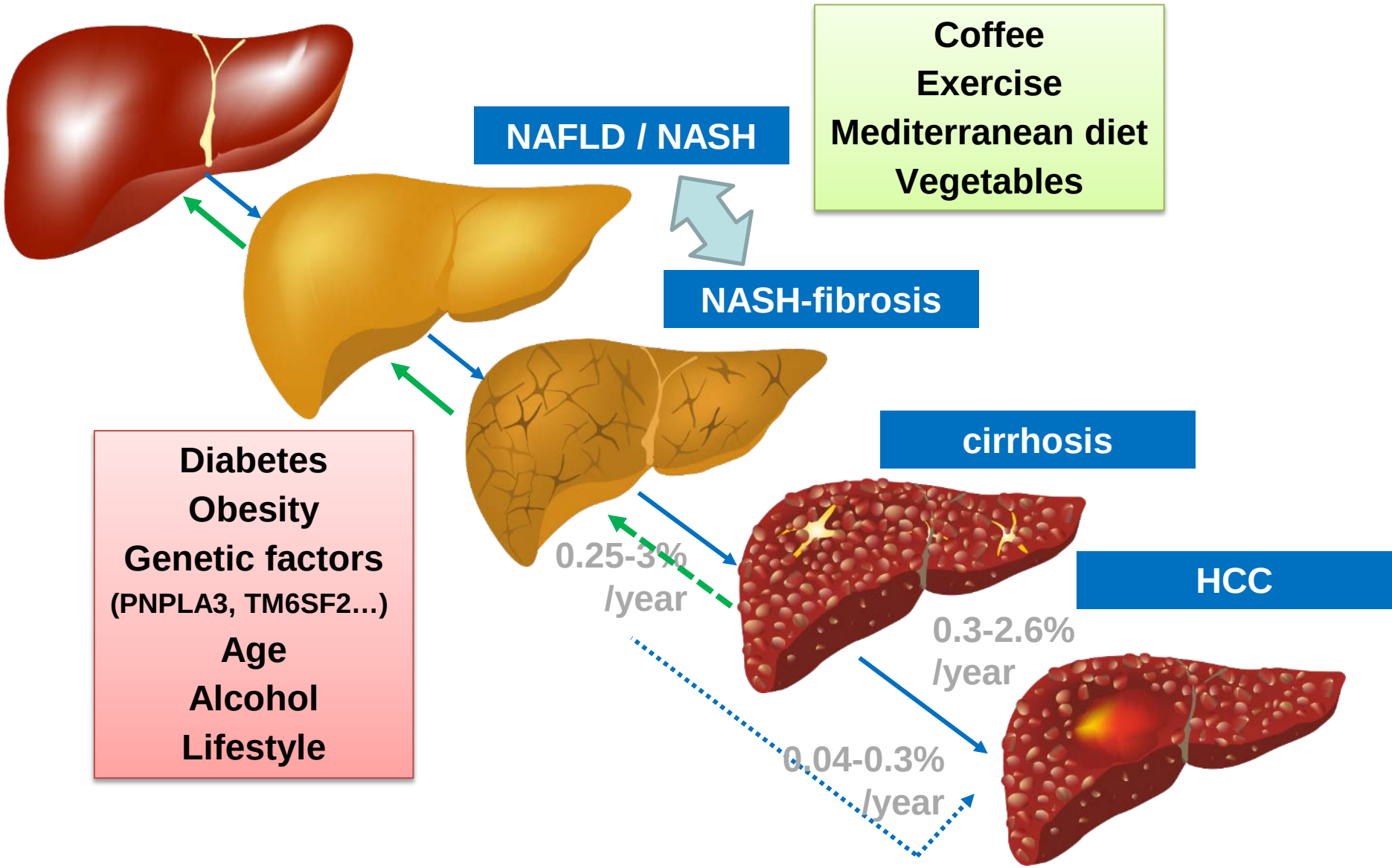
Natural history of fatty liver disease: Estimated progression rates



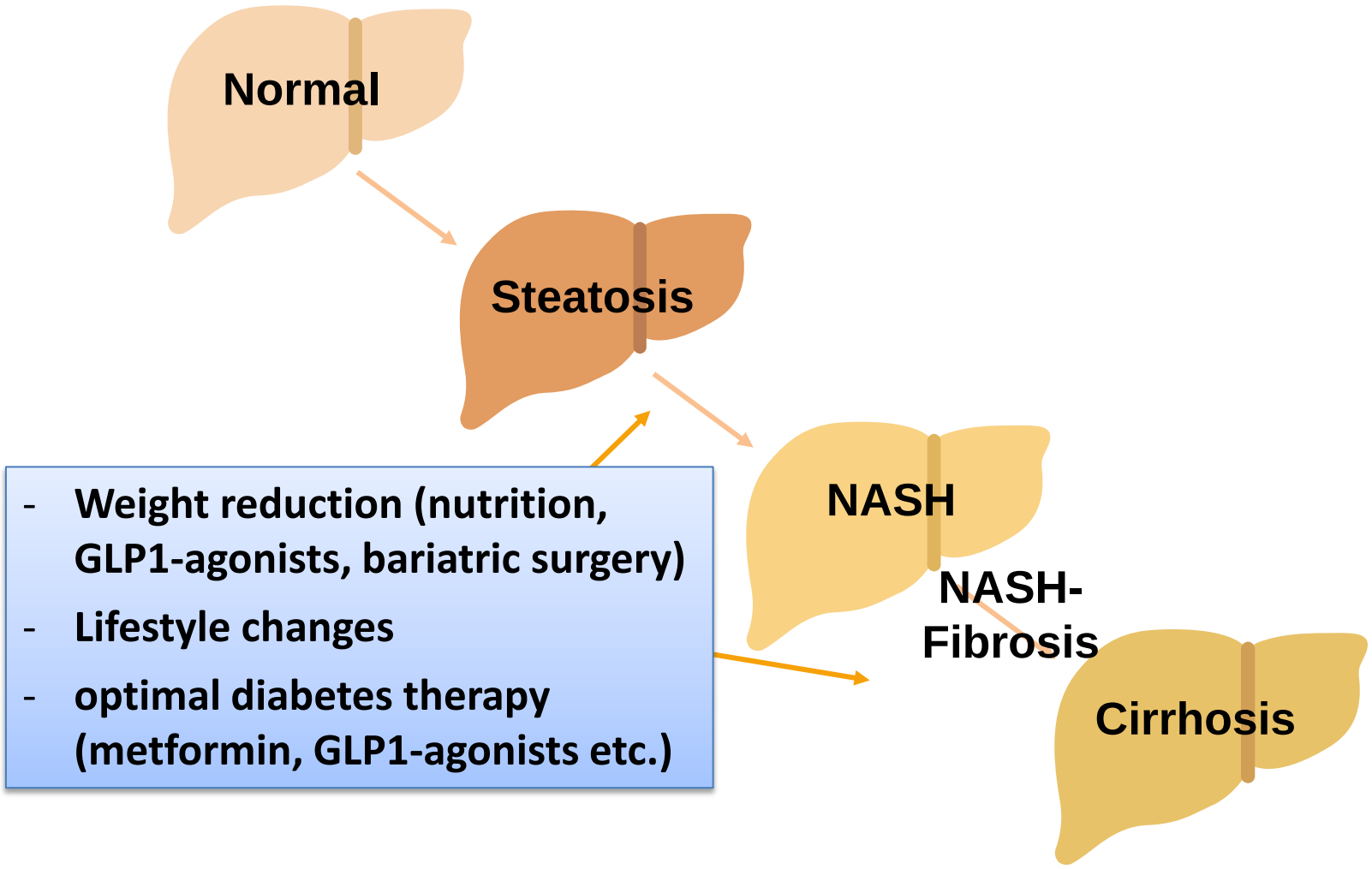
Natural history of fatty liver disease: Progression and Regression



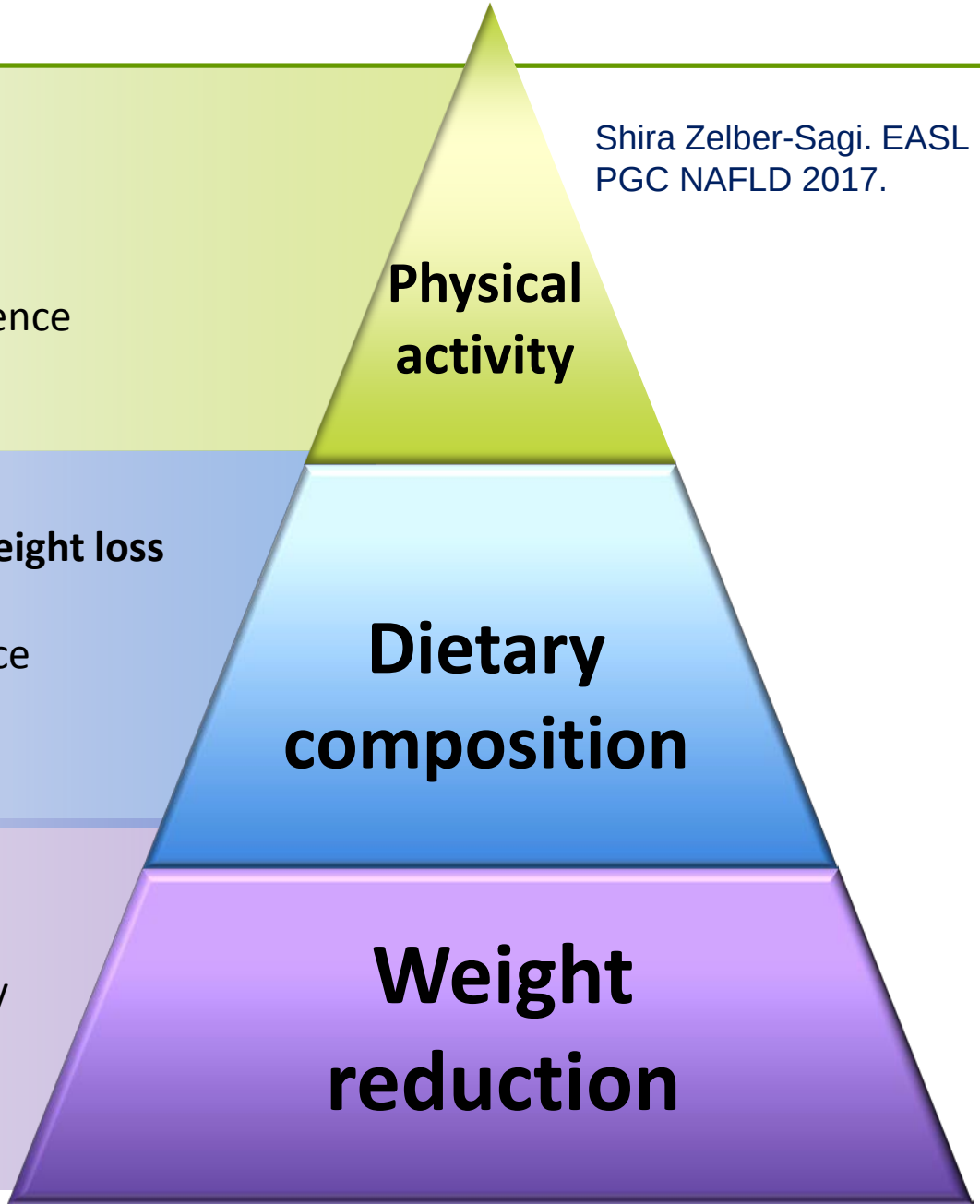
Progression of fatty liver disease: Relevance of cofactors and lifestyle



Current therapeutic strategies in non-alcoholic fatty liver disease



NAFLD Lifestyle Treatment Pyramid



✓ **Aerobic & Resistance activity independently**:
- Reduce liver fat
- NASH and fibrosis – little evidence

✓ **Modifications of diet without weight loss**
- reduce liver fat
- NASH and fibrosis – less evidence
- Reduce risk for HCC ?

✓ **Consistently beneficial**
- **Steatosis** ≥ 5%
- Few studies with histopathology
- **NASH** ≥ 7%
- **Fibrosis** ≥ 10%

Shira Zelber-Sagi. EASL PGC NAFLD 2017.

Lifestyle Modification in Fatty Liver Disease: EASL multidisciplinary Clinical Practice Guideline

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

Pharmacological Options in Fatty Liver Disease: EASL multidisciplinary Clinical Practice Guideline

- 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

Pharmacological Options in Fatty Liver Disease: EASL multidisciplinary Clinical Practice Guideline

- Insulin sensitizers
  - Little evidence of histological efficacy with metformin
  - PPARγ agonist pioglitazone better than placebo
    -
    -
- Antiox
  - Vita g and resolve NASH in some patients
    - Concerns about long-term safety exist

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
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

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‡No recommendations can be made in patients with normal baseline ALT

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

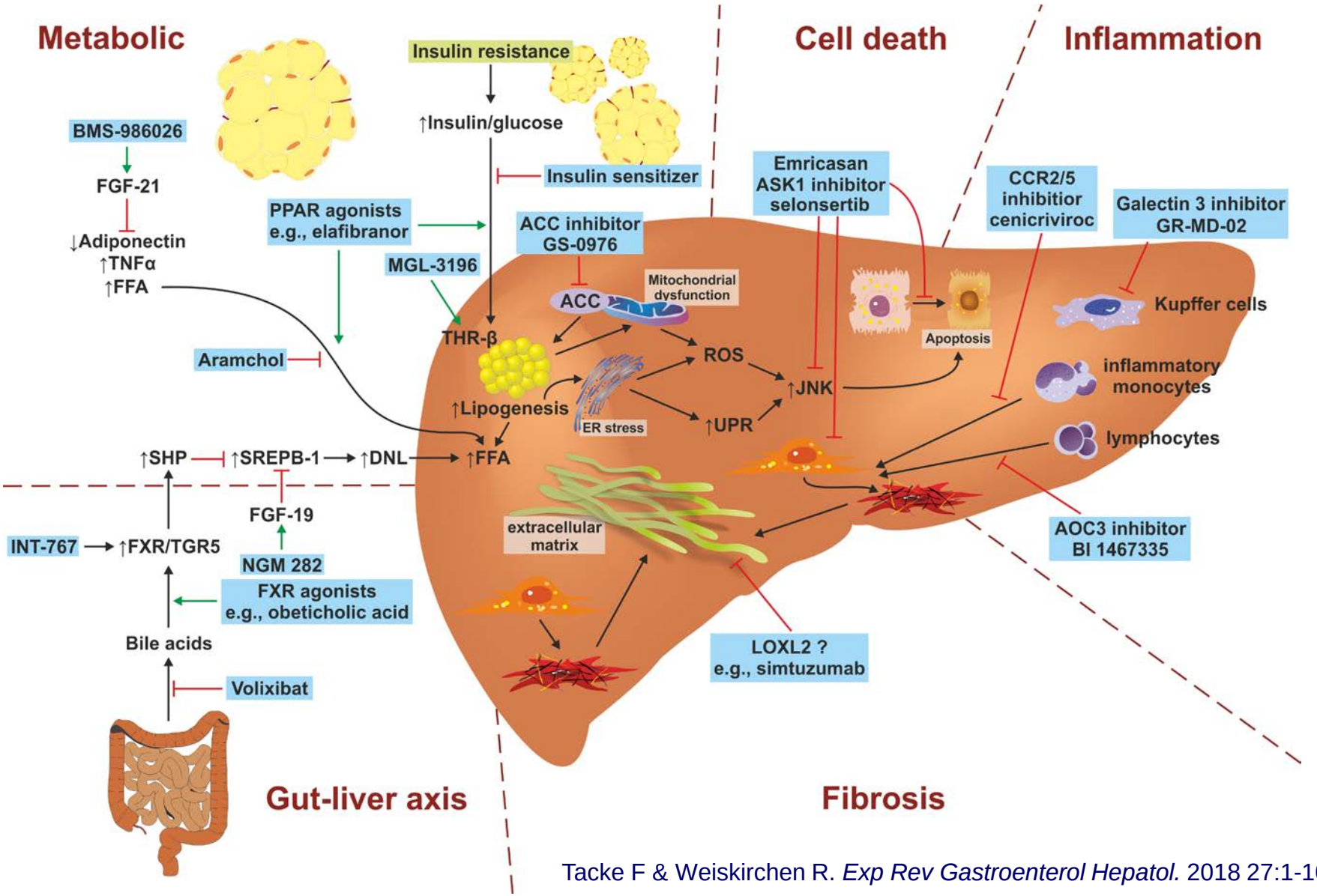
Surgical Treatment Options in Fatty Liver Disease: EASL multidisciplinary Clinical Practice Guideline

- 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

Therapeutic Targets in Steatohepatitis und Fibrose



Tacke F & Weiskirchen R. *Exp Rev Gastroenterol Hepatol.* 2018 27:1-10.

NASH: Definition, natural history and current therapeutic interventions

- **Metabolic liver diseases** increase tremendously and will become the main cause for **cirrhosis**, liver **transplantation** and liver **cancer**
- **Fibrosis** is considered the key mechanism for prognosis – can be assessed by non-invasive tests, risk scores and (if needed) liver biopsy
- effective **lifestyle changes or bariatric surgery** can improve liver histology - no general recommendation for vitamin E, pioglitazone, UDCA, silymarin
- surveillance for **liver-related complications** (cirrhosis, portal hypertension, HCC) and **comorbidities** (cardiovascular, metabolic, renal, malignancies) is needed in high-risk patients

Thank you for your attention!

Prof. Dr. Frank Tacke

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ftacke@ukaachen.de