NASH- IS IT REVERSIBLE?

Introduction

- NonAlcoholic Fatty Liver Disease (NAFLD) is one of the growing epidemic world wide due to obesity and insulin resistance.
- NAFLD encompasses Non Alcoholic Fatty Liver, NonAlcoholic Steatohepatitis(NASH), NASH-related cirrhosis, and NASH-related hepatocellular carcinoma (HCC).
- NAFLD patients are at increased risk of liver-related as well as cardiovascular mortality, and NAFLD is rapidly becoming the leading indication for liver transplantation.

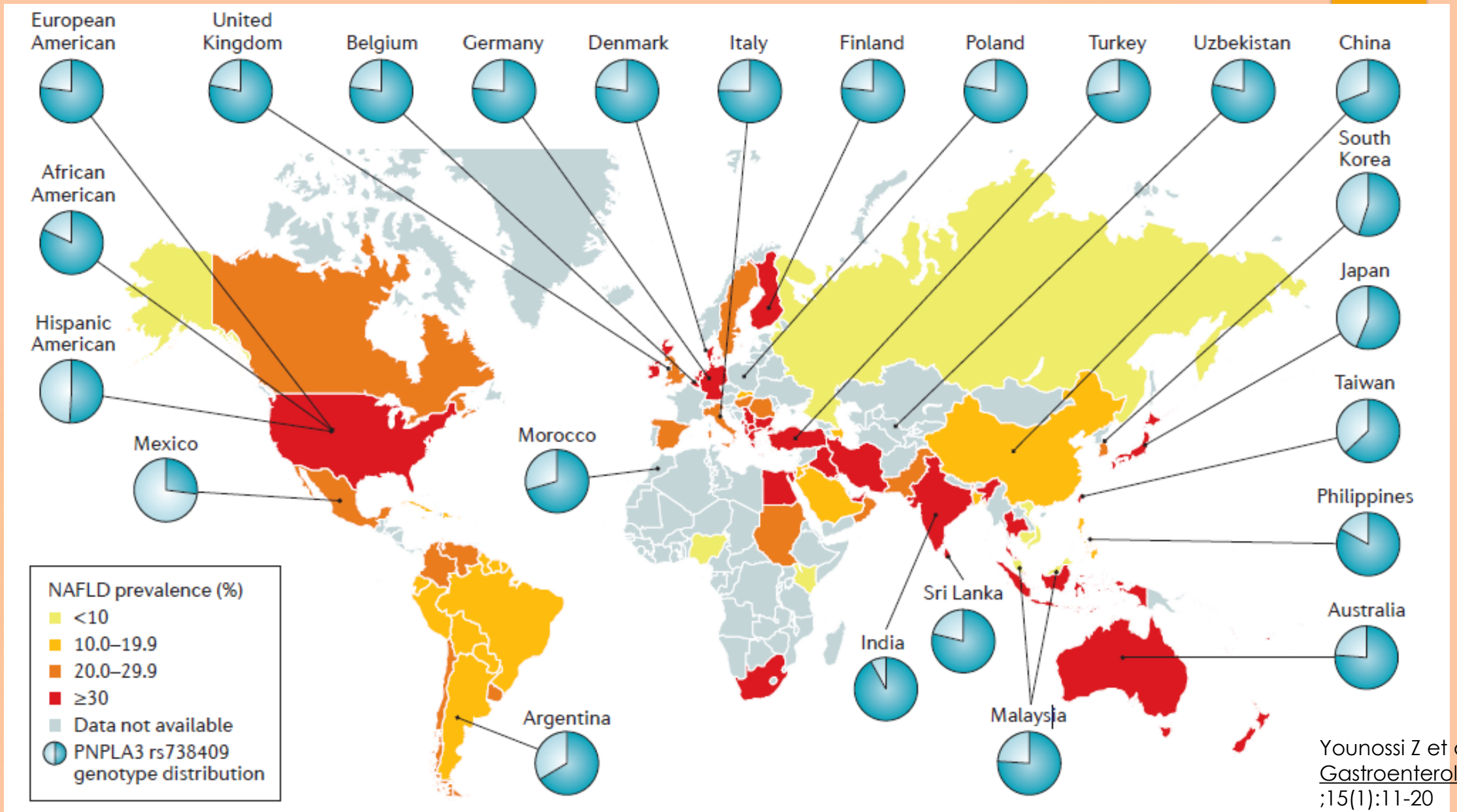
Benedict M et al. World J Hepatol 2017 June 8; 9(16): 715-732

Prevalence of NAFLD, NASH

- The global prevalence of NAFLD is currently estimated to be 24%.
- The prevalence of NAFLD is constantly increasing and similarly the rate of NASH in the same timeframe has almost doubled.
- NASH is estimated to affect 3–5% of the global population, most suffering from several comorbidities.
- Advancing fibrosis drives clinical outcomes, with approximately 20% of patients developing cirrhosis and/or HCC.

Younossi Z et al. Nat Rev Gastroenterol Hepatol. 2018 ;15(1):11-20
Povsik M et al. Adv Ther (2019) 36:1574–1594

Prevalence of NAFLD world wide



Worldwide estimated prevalence of NAFLD and distribution of *PNPLA3* genotypes. *PNPLA3* is presented as minor allele frequency (light blue section of the pie chart).

Younossi Z et al. Nat Rev Gastroenterol Hepatol. 20 ;15(1):11-20

Prevalence of NAFLD, NASH in india

- In India, the NAFLD prevalence ranged from 8.7% to 32.6%.
- The prevalence of hyperlipidemia/dyslipidemia was observed to be on the higher side at 69% in patients with NAFLD and 72% in patients with NASH.
- Higher prevalence of obesity (51% of individuals with NAFLD and 82% of NASH patients) and diabetes mellitus (23% of NAFLD patients and 47% of NASH patients) was observed.
- About 3-15 per cent cases of the obese NASH progress to cirrhosis and about 4-27 per cent of NASH with cirrhosis cases transform to HCC.

Hande V et al. J Mar Med Soc 2018;20:57-62..
Younossi ZM et al. J Hepatol. 2019 Mar;70(3):531-544

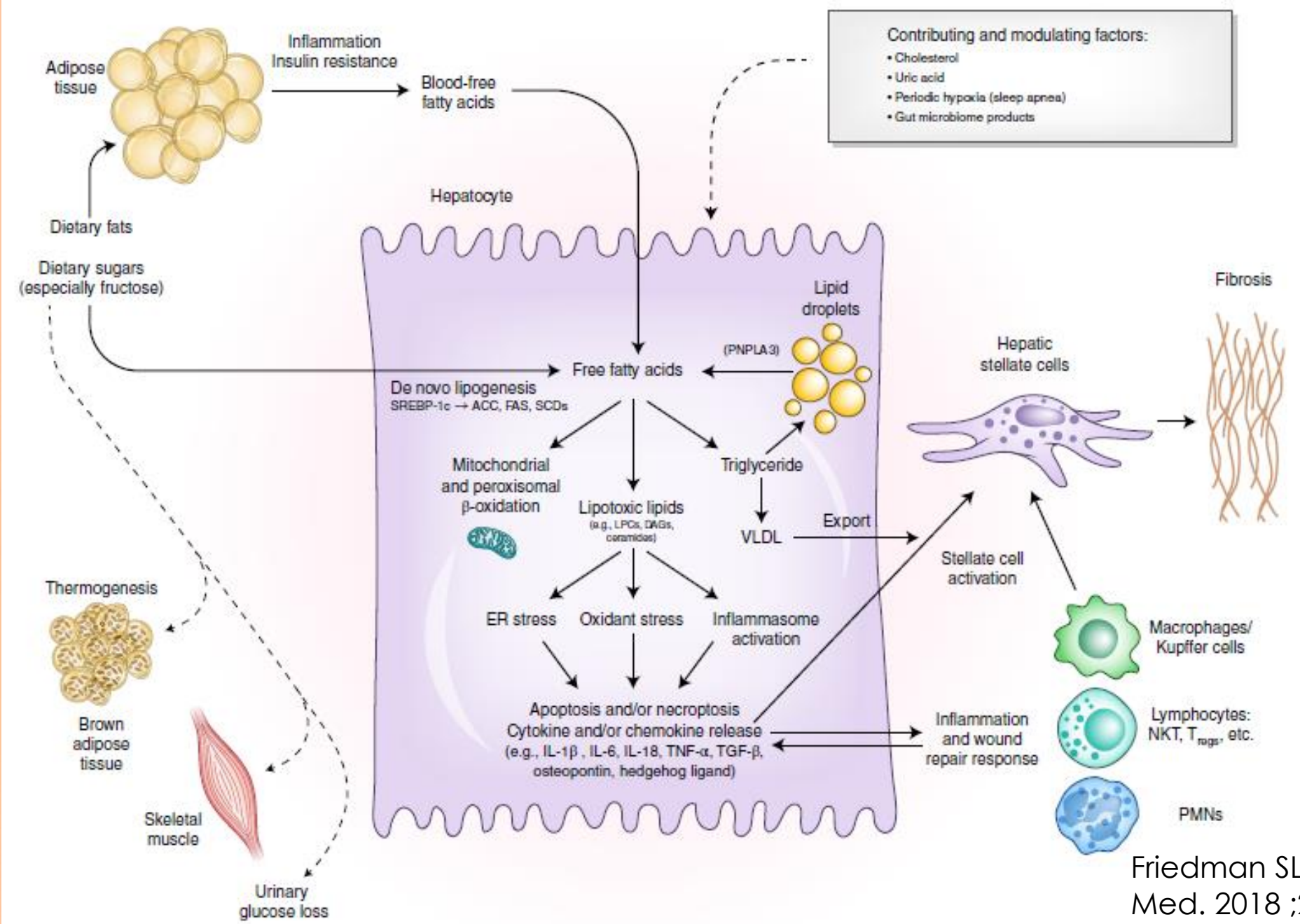
Spectrum of NAFLD and concurrent disease

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

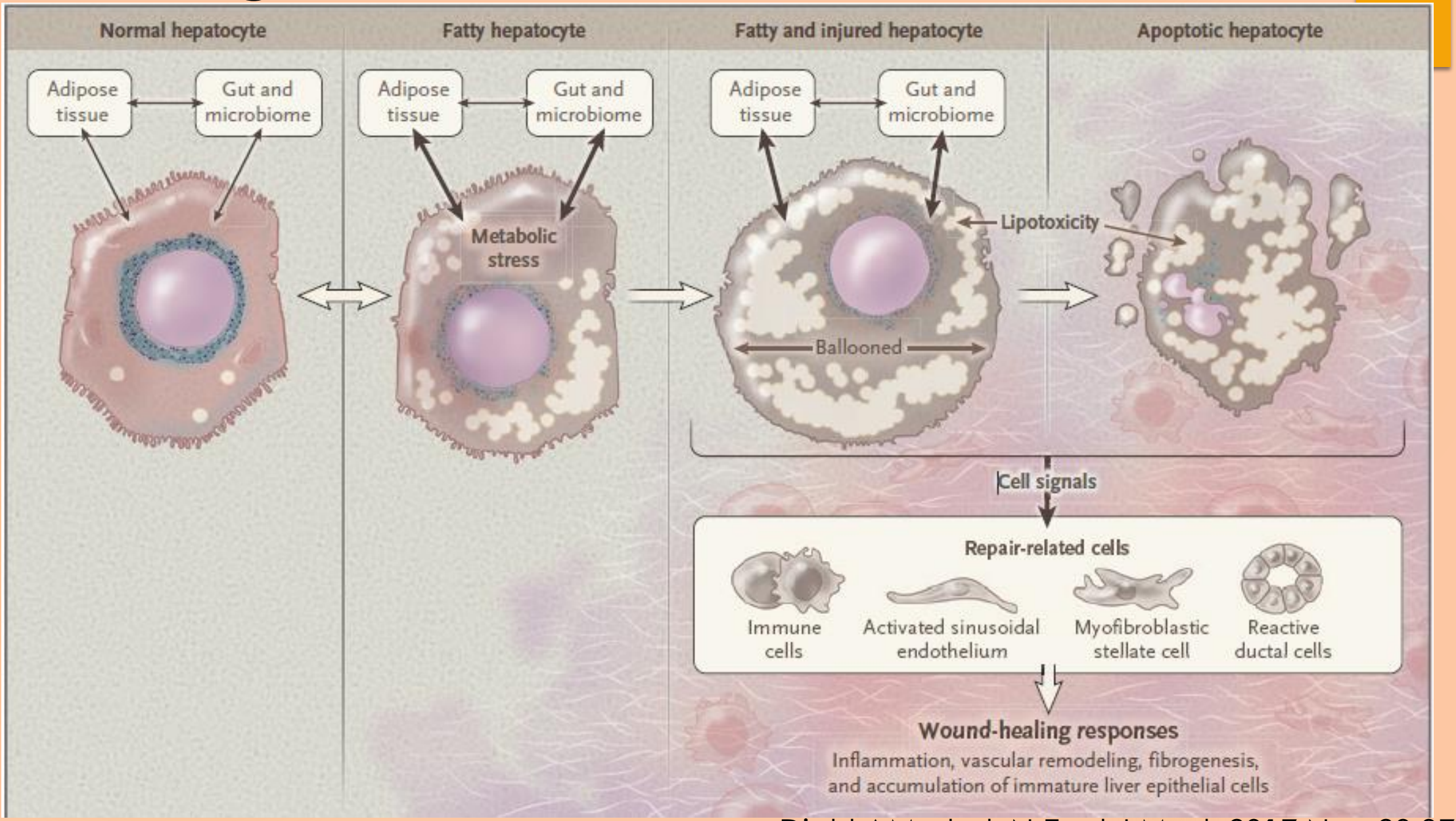
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Pathogenesis



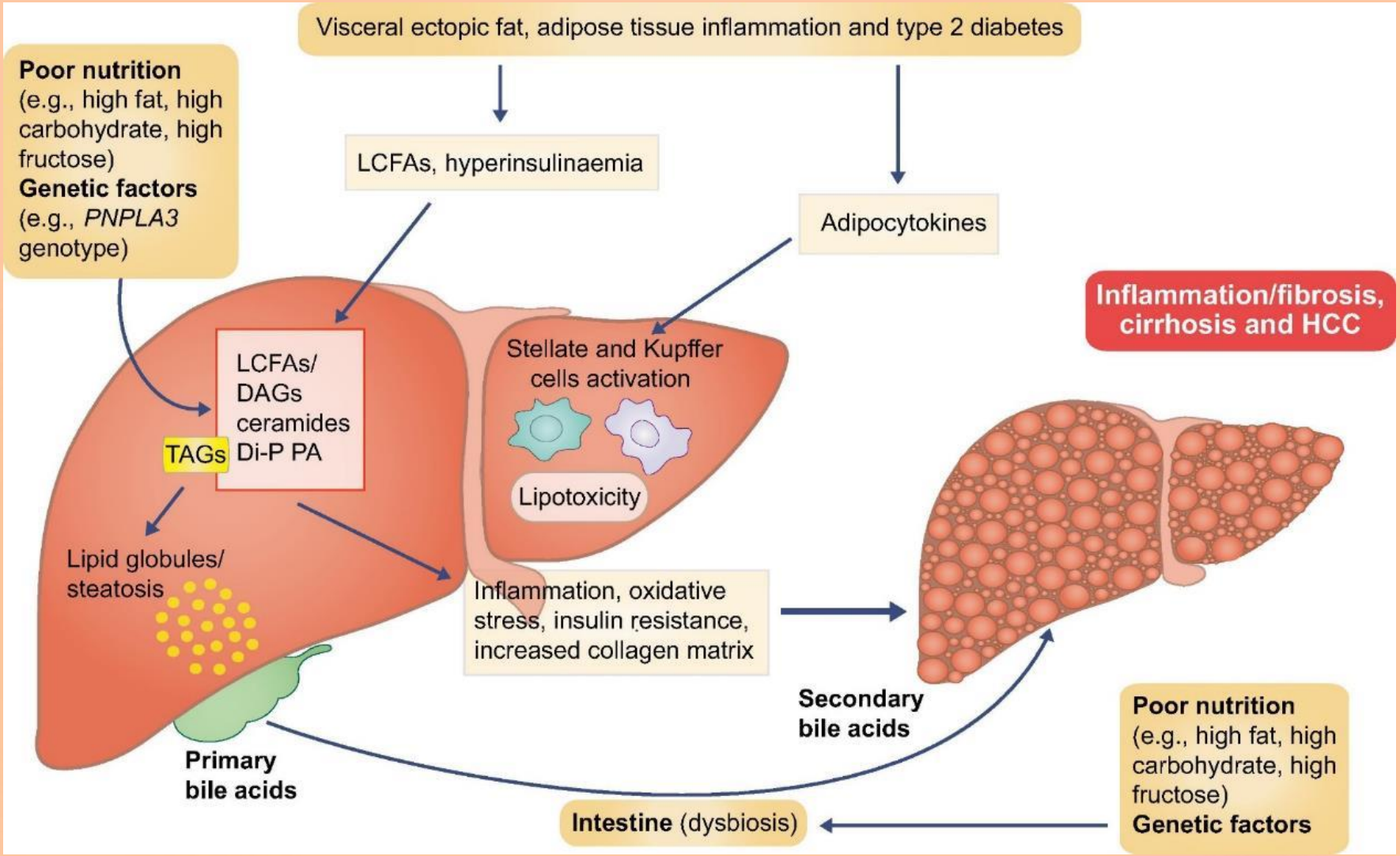
Friedman SL et al Nat Med. 2018 ;24(7):908-922.

Pathogenesis of NASH



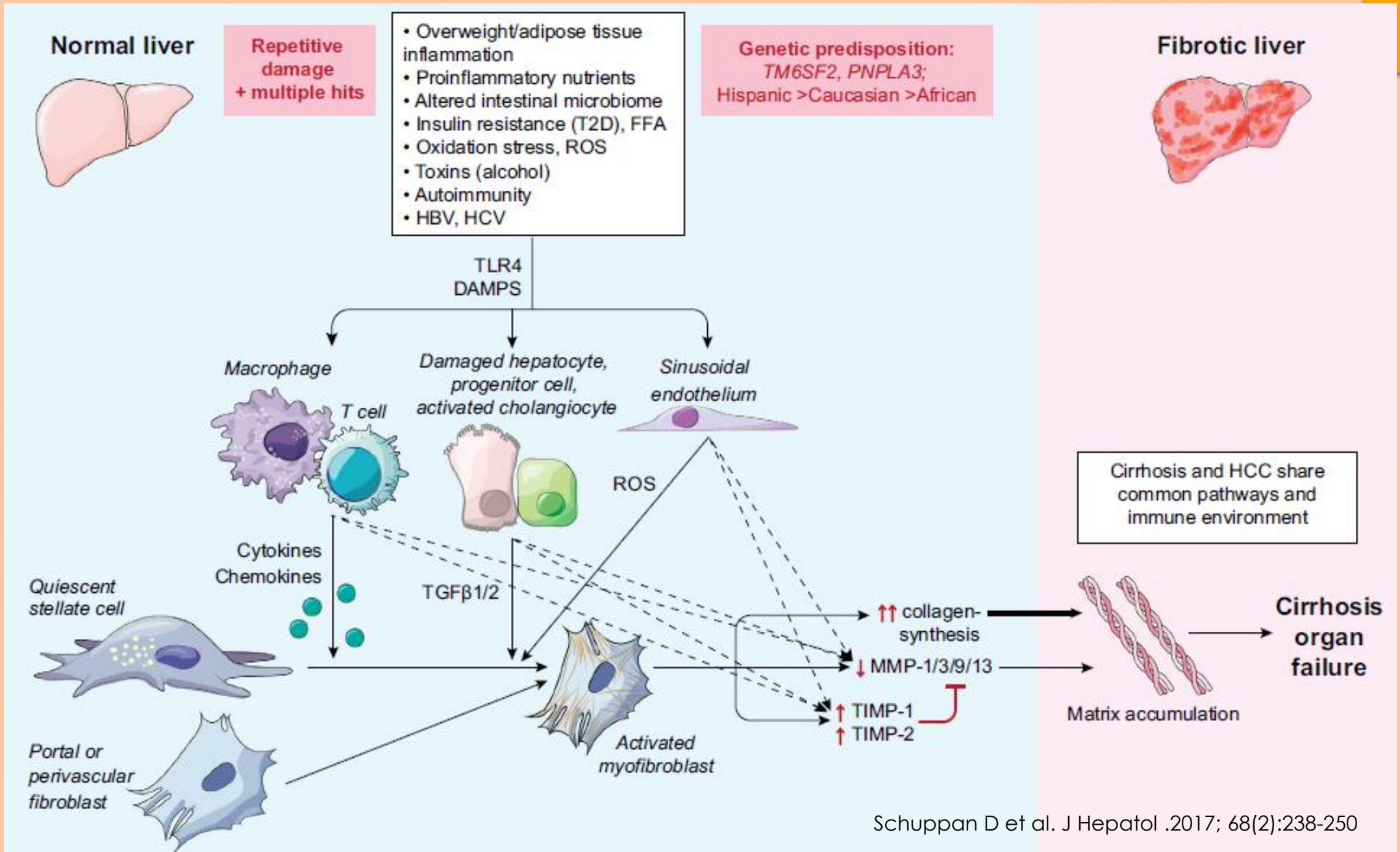
Diehl AM et al. N Engl J Med. 2017 Nov 23;377(21):206

Progressive liver disease in NAFLD



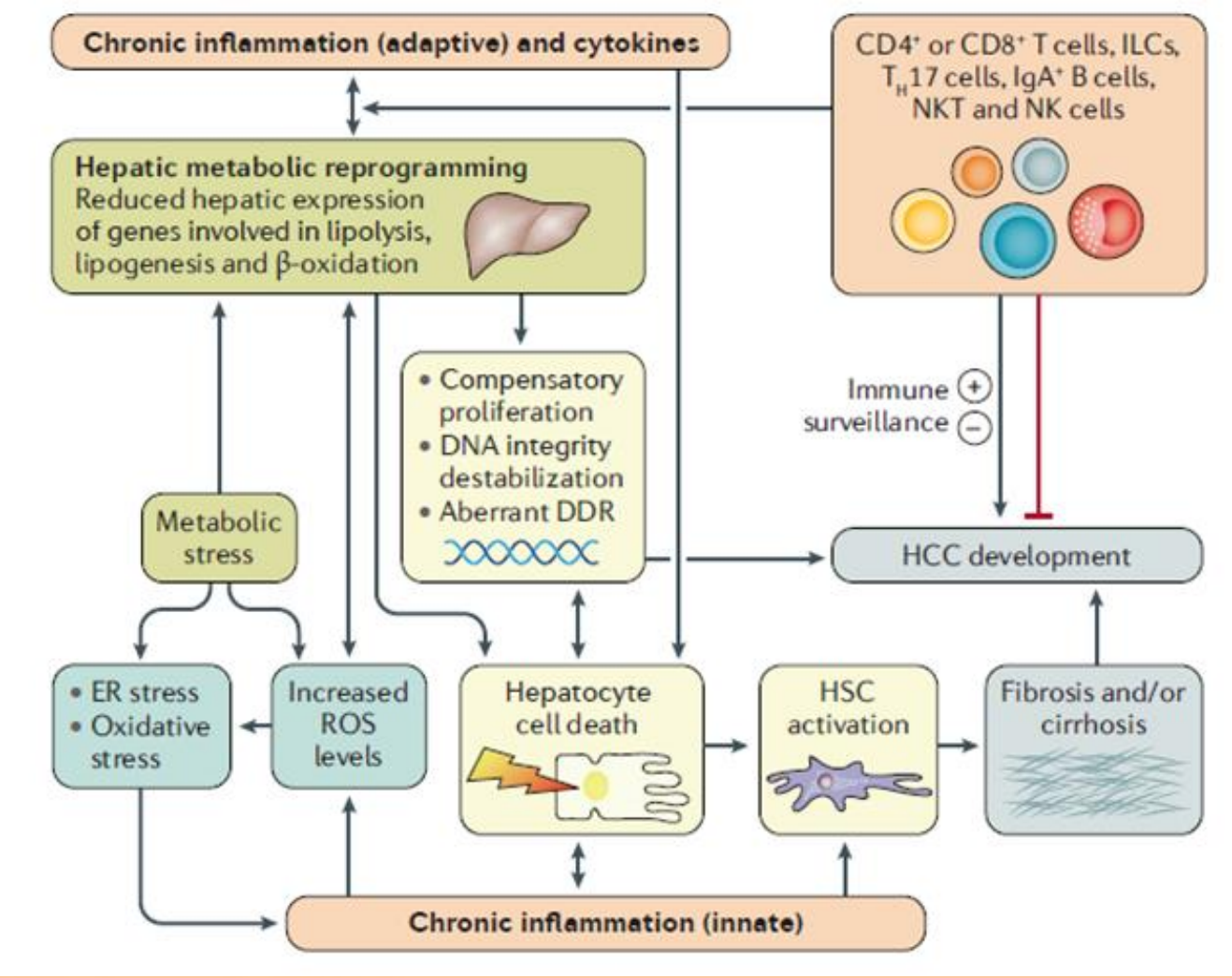
Byrne CD et al. J Hepatol. 2015;62(1): 47-64

Mechanisms of liver fibrogenesis in NASH



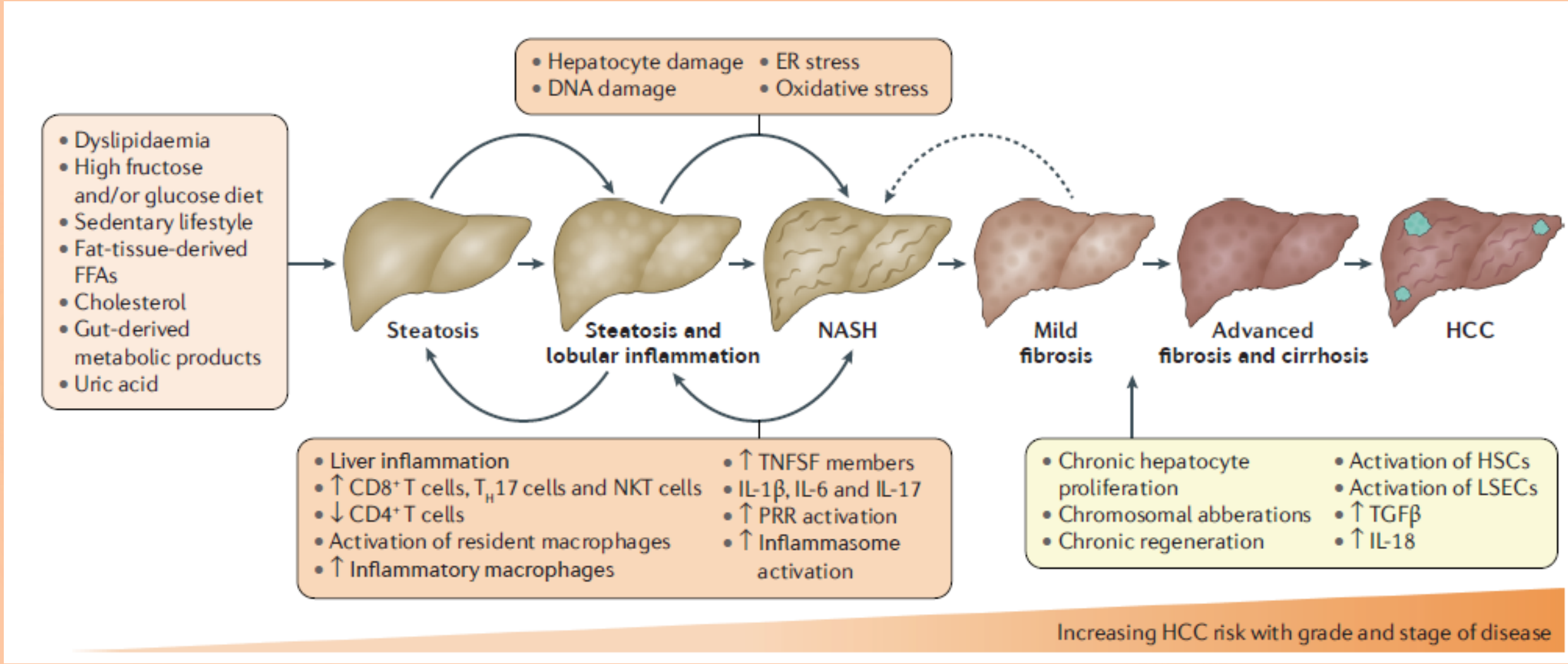
Schuppan D et al. J Hepatol .2017; 68(2):238-250

Metabolic reprogramming,tumorigenesis induced by adaptive and innate chronic inflammation of the liver



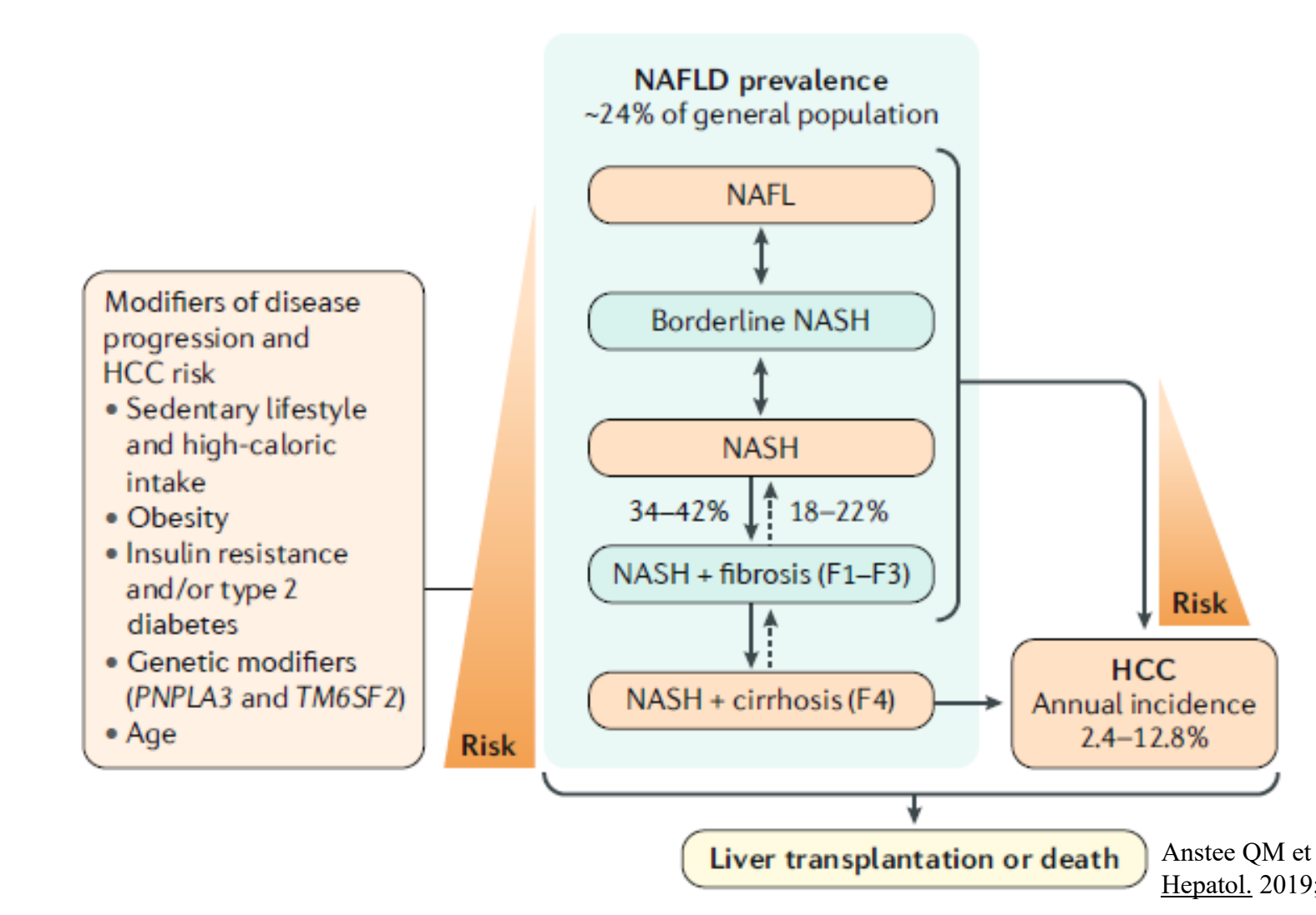
Anstee QM et al. Nat Rev Gastroenterol Hepatol. 2019;16(7):411-428.

Factors in NASH pathogenesis and the increased risk of liver tumorigenesis



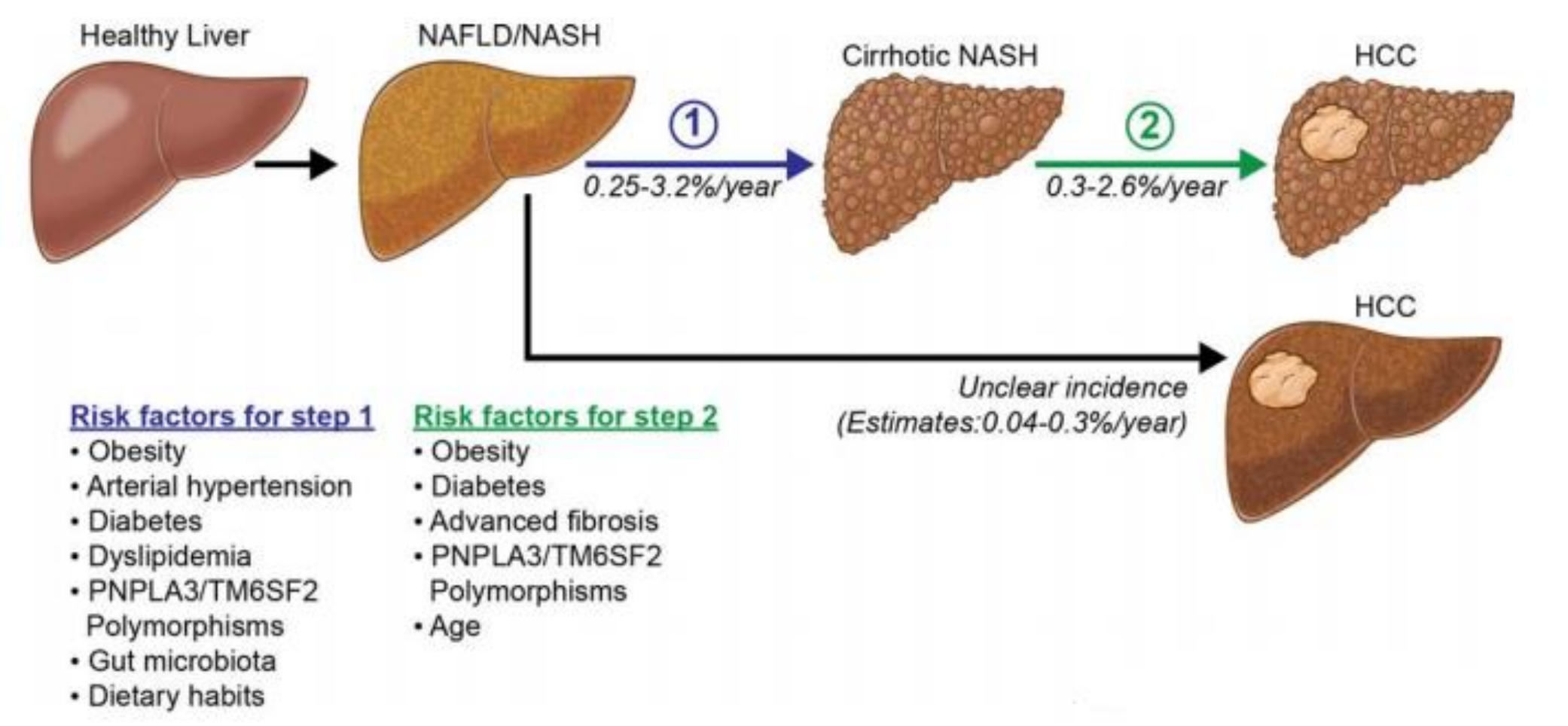
Anstee QM et al. Nat Rev Gastroenterol Hepatol. 2019;16(7):411-428.

The sequential pathophysiological states of NAFLD and HCC



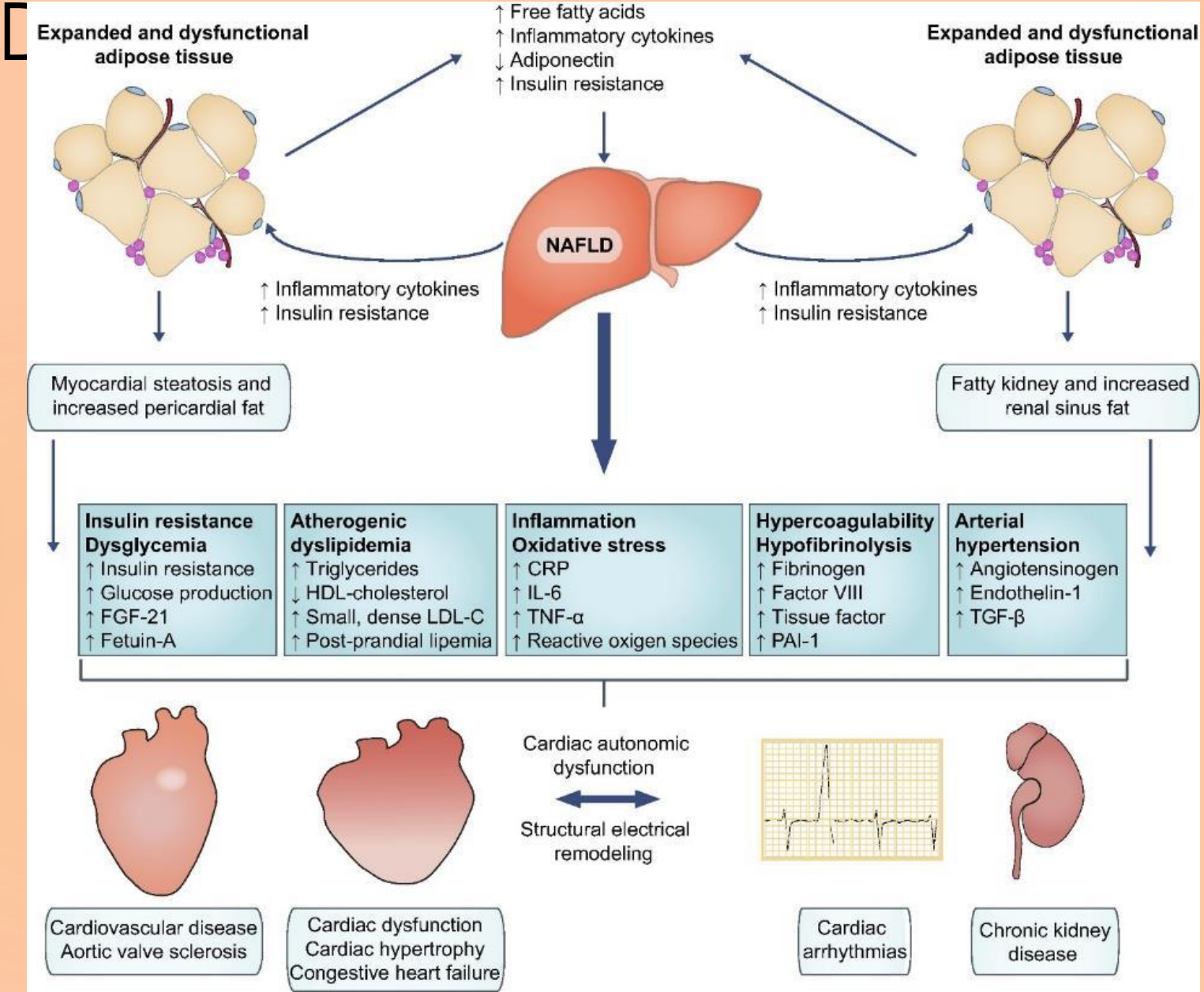
Anstee QM et al. Nat Rev Gastroenterol Hepatol. 2019;16(7):411-428.

Natural history of NASH/NAFLD-related HCC



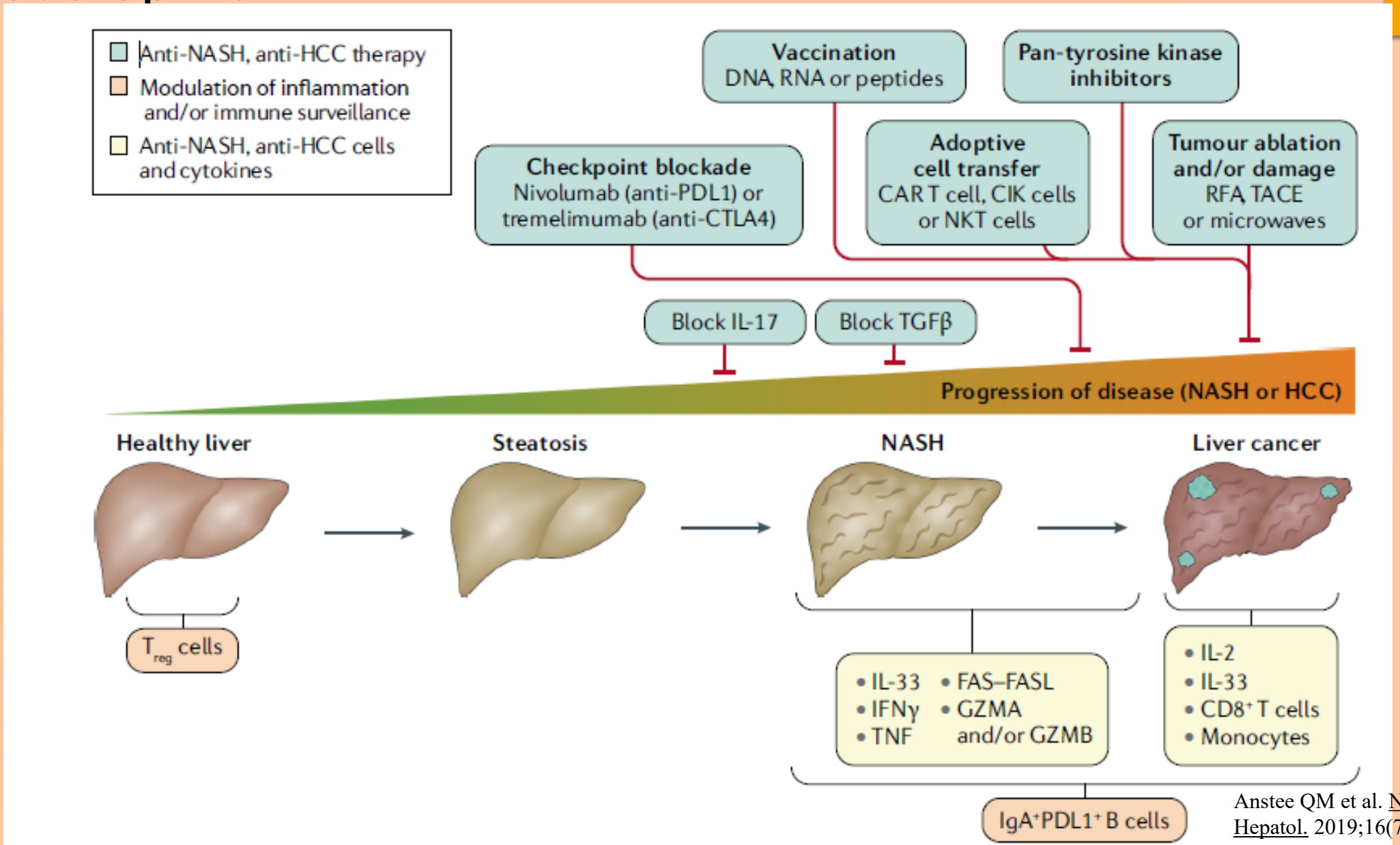
D' Avola D et al . Clin Liver Dis (Hoboken). 2016;8(4):100-104

Correlation between NAFLD, CVD and CKD



Byrne CD et al. J Hepatol. 2015;62(1): 47-64

Different treatment options for NASH- associated liver cancer development



Anstee QM et al. Nat Rev Gastroenterol Hepatol. 2019;16(7):411-428.

Brunt Grading and Staging for Non alcoholic Steatohepatitis

Grading	Staging
Mild (Grade 1)	Stage 1
Steatosis (mostly macrovesicular)	Zone 3 perisinusoidal/pericellular fibrosis (focal or extensive)
Involves up to 66% of biopsy	
Occasional ballooned zone 3 hepatocytes	Stage 2
Scattered rare intra-acinar neutrophils with/without associated lymphocytes	Zone 3 perisinusoidal/pericellular fibrosis with associated focal
No/mild portal chronic inflammation	or extensive periportal fibrosis
Moderate (Grade 2)	
Steatosis-any degree	
Ballooning hepatocytes-zone 3	
Intra-acinar neutrophils-may be associated with zone 3 pericellular fibrosis	Stage 3
Portal and intra-acinar chronic inflammation	Zone 3 perisinusoidal/pericellular fibrosis and portal fibrosis
Severe (Grade 3)	with associated focal or extensive bridging fibrosis
Panacinar steatosis	
Ballooning-zone 3	
Intra-acinar inflammation with scattered neutrophils	Stage 4
Neutrophils associated with ballooned hepatocytes with/without chronic inflammation	Cirrhosis
Chronic portal inflammation-mild or moderate	

Benedict M et al. World J Hepatol 2017 June 8; 9(16): 715-732

Steatosis, activity, and fibrosis scoring system

Steatosis score (S): Assessed the quantities of large or medium-sized lipid droplets (0-3)
- S0: < 5%
- S1: 5%-33%
- S2: 34%-66%
- S3: > 67%

Activity grade (0-4): Sum of scores for ballooning and lobular inflammation
- A1: Mild activity
- A2: Moderate activity
- A3 and A4: Severe activity

Hepatocyte ballooning (0-2)
- 0: None
- 1: Foci of hepatocytes with rounded shape, pale or reticulated cytoplasm
- 2: Foci of hepatocytes with rounded shape, pale or reticulated cytoplasm and enlargement (> 2 × normal size)

Lobular inflammation (0-2)
- 0: None
- 1: < 2 foci per 20 × field
- 2: > 2 foci per 20 × field

Fibrosis stage (F)
- F0: No relevant fibrosis
- F1: 1a - mild zone 3 perisinusoidal fibrosis
  - 1b - moderate zone 3 perisinusoidal fibrosis
  - 1c - portal fibrosis
- F2: Zone 3 perisinusoidal fibrosis with periportal fibrosis
- F3: Bridging fibrosis
- F4: Cirrhosis

Benedict M et al. World J Hepatol 2017 ; 9(16): 715-

Biochemical markers to detect NASH

- Liver function tests
- soluble Fas and intact CK-18 (cytokeratin-18 fragments)
- Adipokines (e.g., adiponectin, t umor necrosis factor-alpha [TNF-a], interleukin-6, and adipocyte fatty acid-binding protein)
- Metabolic markers (HOMA-IR and growth factor receptor 21)
- Inflammatory markers (e.g., C-reactive protein [CRP]

Dharmalingam M et al. Indian J Endocr Metab

Markers of fibrogenesis and fibrolysis

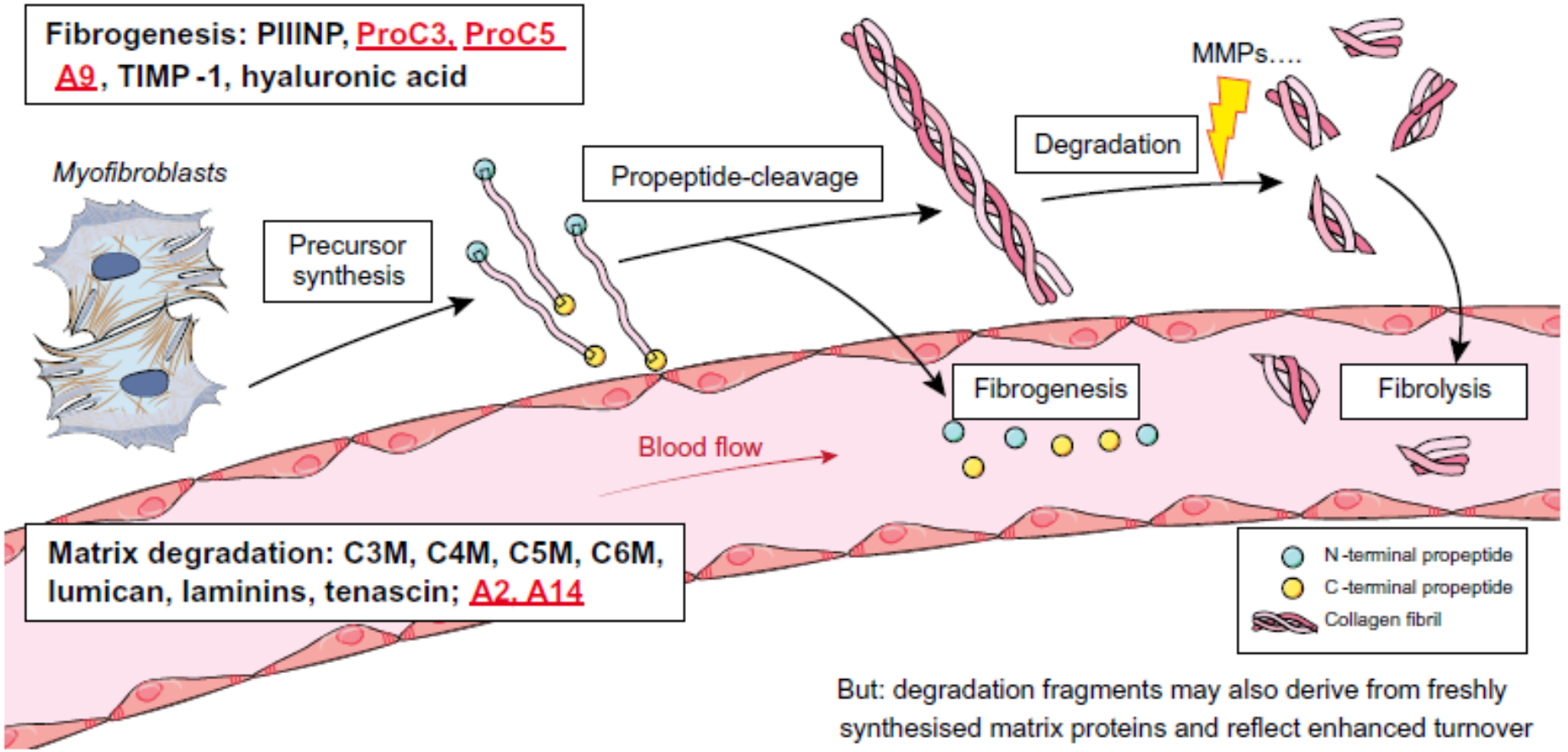
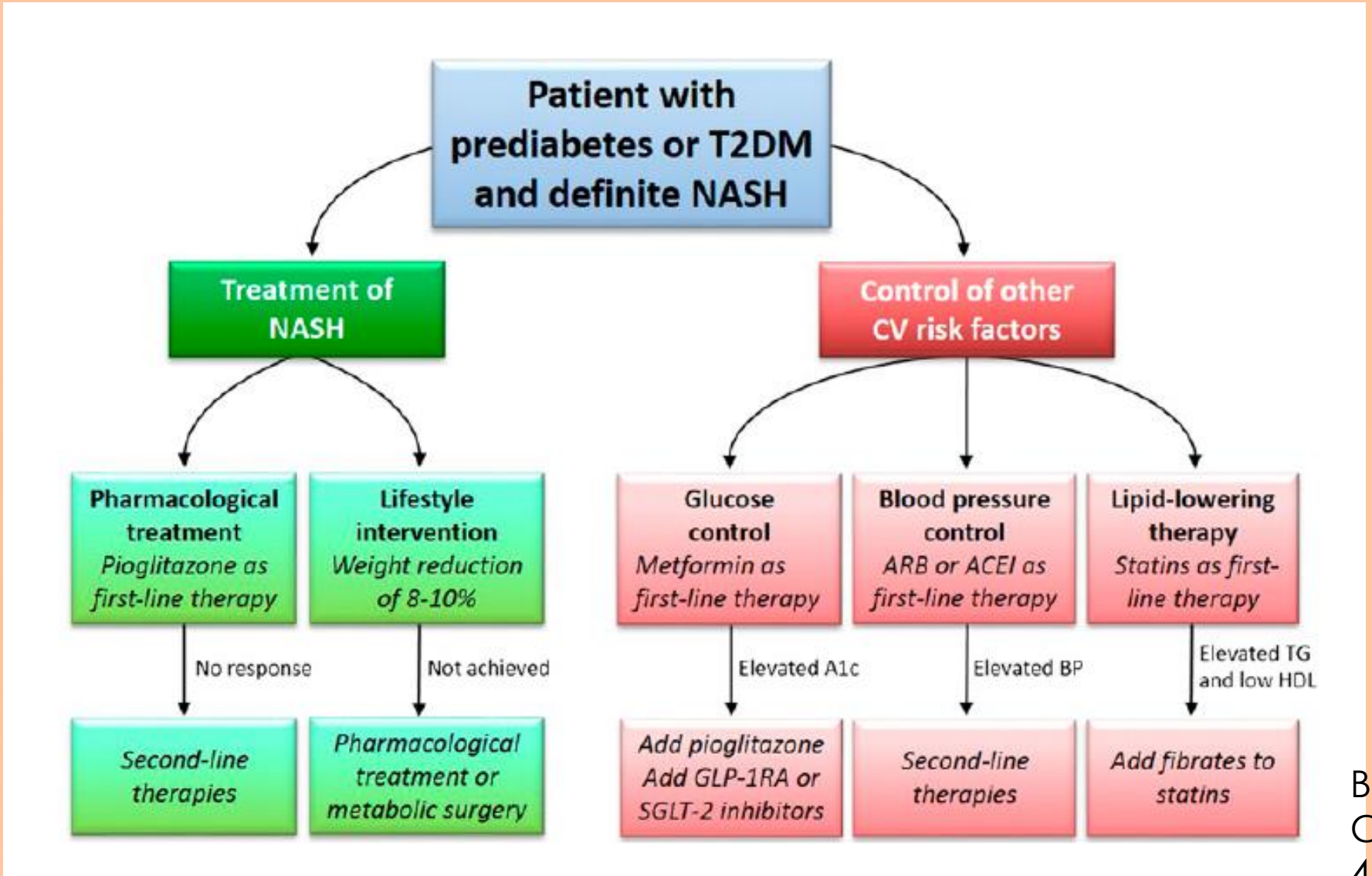


Fig. Direct serum markers of fibrogenesis and fibrolysis. Direct markers stem from the ECM and have the highest plausibility to mirror ECM turnover in liver fibrosis. The underlined markers are currently in clinical validation for fibrogenesis and fibrolysis. A2, A9, A14: ECM associated molecules. C3M, C4M, C5M, C6M: degradation epitopes of collagens type III, IV, V and VI. ECM, extracellular matrix; PIIINP, aminoterminal propeptide of type III procollagen; Pro-C3 (Pro-C5), C-terminal cleavage site of the aminoterminal propeptide of type III (V) procollagen; MMP, matrix metalloproteinase; TIMP-1, tissue inhibitor of metalloproteinase-1.

Schuppan D et al. J Hepatol .2017; 68(2):238-250

Management of patients with prediabetes or T2DM and definite NASH.



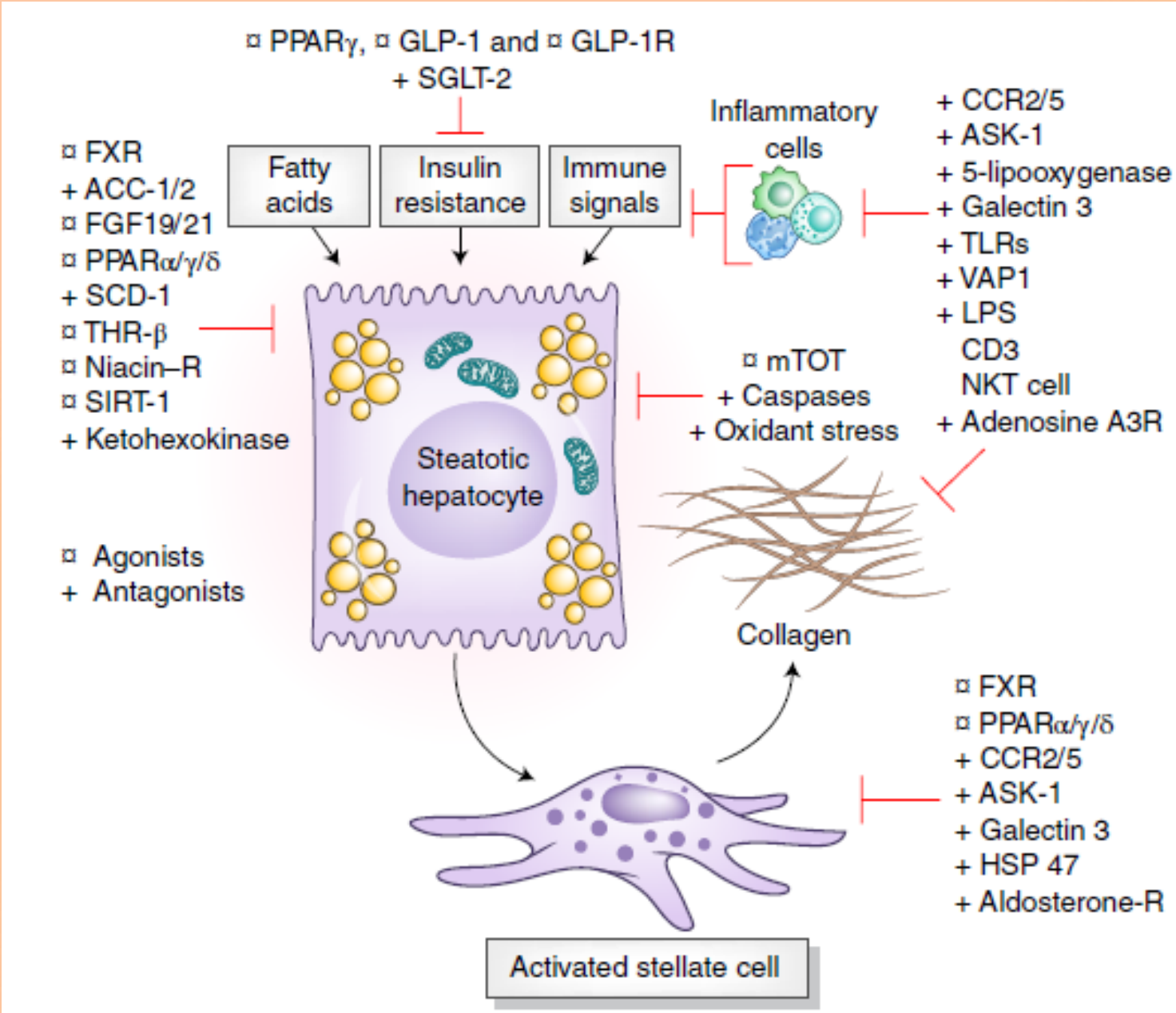
Bril F et al. Diabetes Care 2017;40:419–430

Recommendations about pharmacological treatment of non-alcoholic fatty liver disease

	EASL	NICE	ASIA-PACIFIC	AISF	AASLD
Metformin	Insufficient evidence	Not beneficial	Not beneficial	Not mentioned	Not beneficial
Vitamin E	Insufficient evidence	Consider use regardless of diabetes	Not beneficial	Insufficient evidence	Consider use in non-diabetic, biopsy-proven NASH
PPAR-gamma agonists	Consider use in selected diabetic patients	Consider pioglitazone in adults regardless of diabetes	Insufficient evidence in Asian	Insufficient evidence, potentially useful	Pioglitazone indicated in biopsy-proven NASH (regardless of diabetes)
PUFA	Not beneficial	Insufficient evidence	Not beneficial	Not mentioned	Not beneficial
Pentoxifylline	Insufficient evidence	Not mentioned	Not beneficial	Not mentioned	Not mentioned
GLP-1 analogues	Insufficient evidence, potentially useful	Insufficient evidence	Insufficient evidence in Asian patients	Insufficient evidence, potentially useful	Insufficient evidence
UDCA	Not beneficial	Not beneficial	Not mentioned	Not mentioned	Not beneficial
Obetycolic acid	Scarce evidence	Not mentioned	waiting for ongoing RCT results	Waiting for ongoing RCT results	Insufficient evidence
Silymarin	Not mentioned	Not mentioned	insufficient evidence, potentially useful	Not mentioned	Not mentioned
Statins	Safe but not beneficial	Safe but not beneficial	Safe but not beneficial	Safe but not beneficial	Safe but not beneficial

Leoni S et al. *World J Gastroenterol* 2018 ; 24(30): 3361-3373

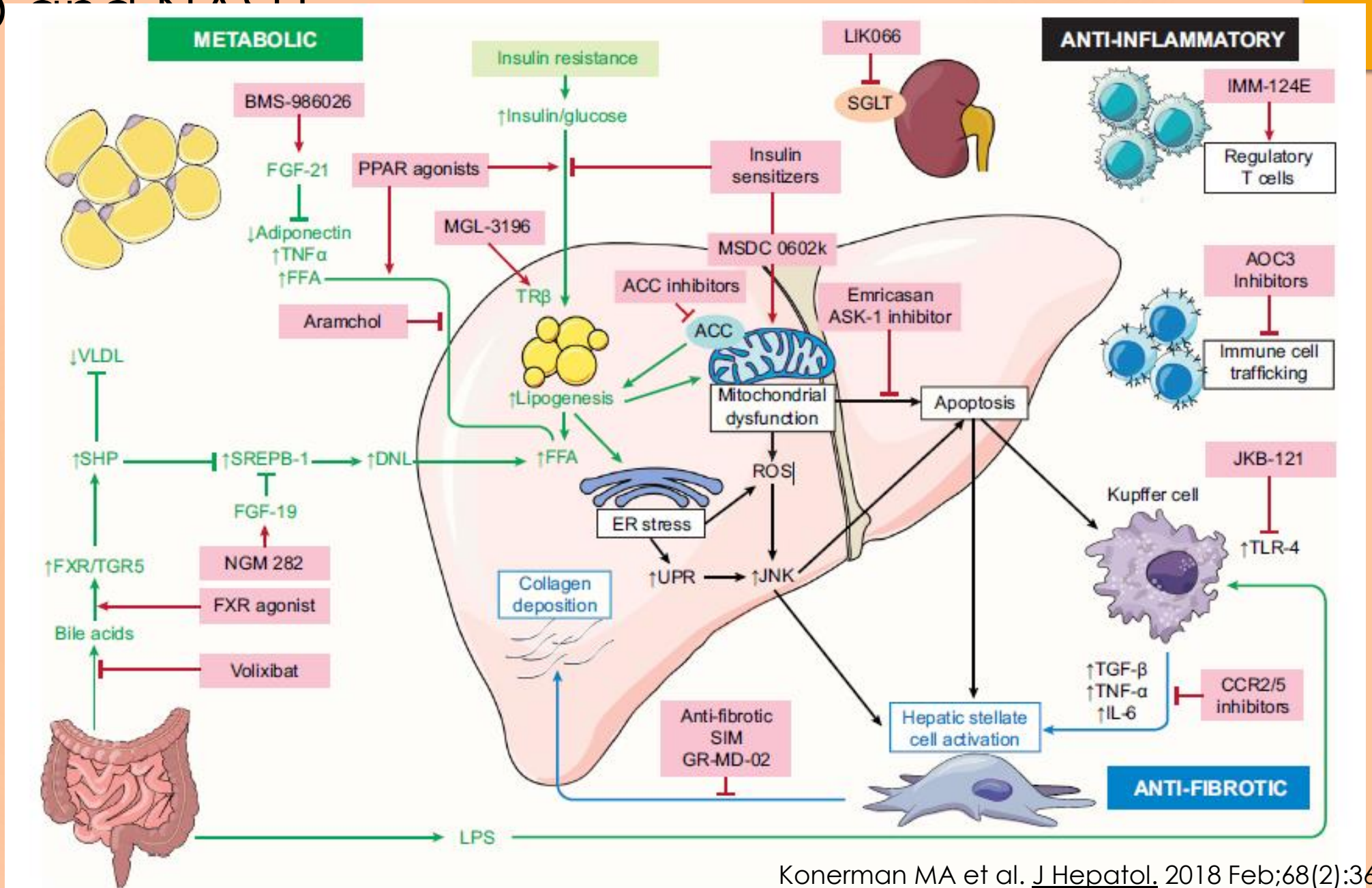
Intrahepatic drug targets for NASH



DGAT, Diacylglycerol O-acyltransferase; SCD, steroyl CoA-desaturase;
THR, thyroid hormone receptor;
SIRT, sirtuin;
GLP, glucagon-like peptide;
SGLT, sodium–glucose cotransporter;
VAP, vascular adhesion protein; LPS, lipopolysaccharide;
PPARa /δ /γ , peroxisome proliferator–activated receptors

Friedman SL et al Nat Med. 2018 Jul;24(7):908-922.

Mechanism of action of pharmacologic treatments for NAFLD and NASH



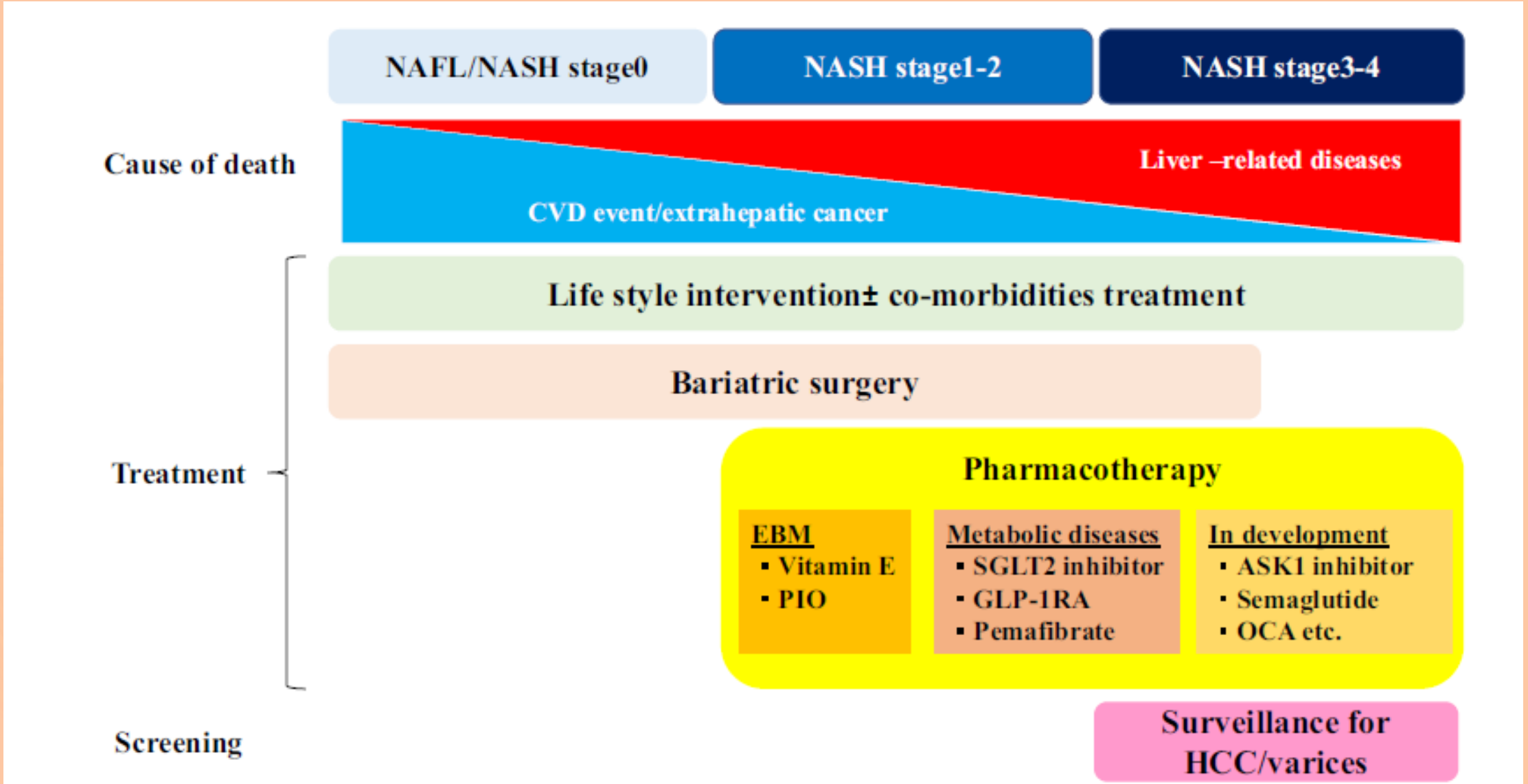
Konerman MA et al. J Hepatol. 2018 Feb;68(2):362-375

Recommended pharmacotherapies for NASH/NAFLD in guic

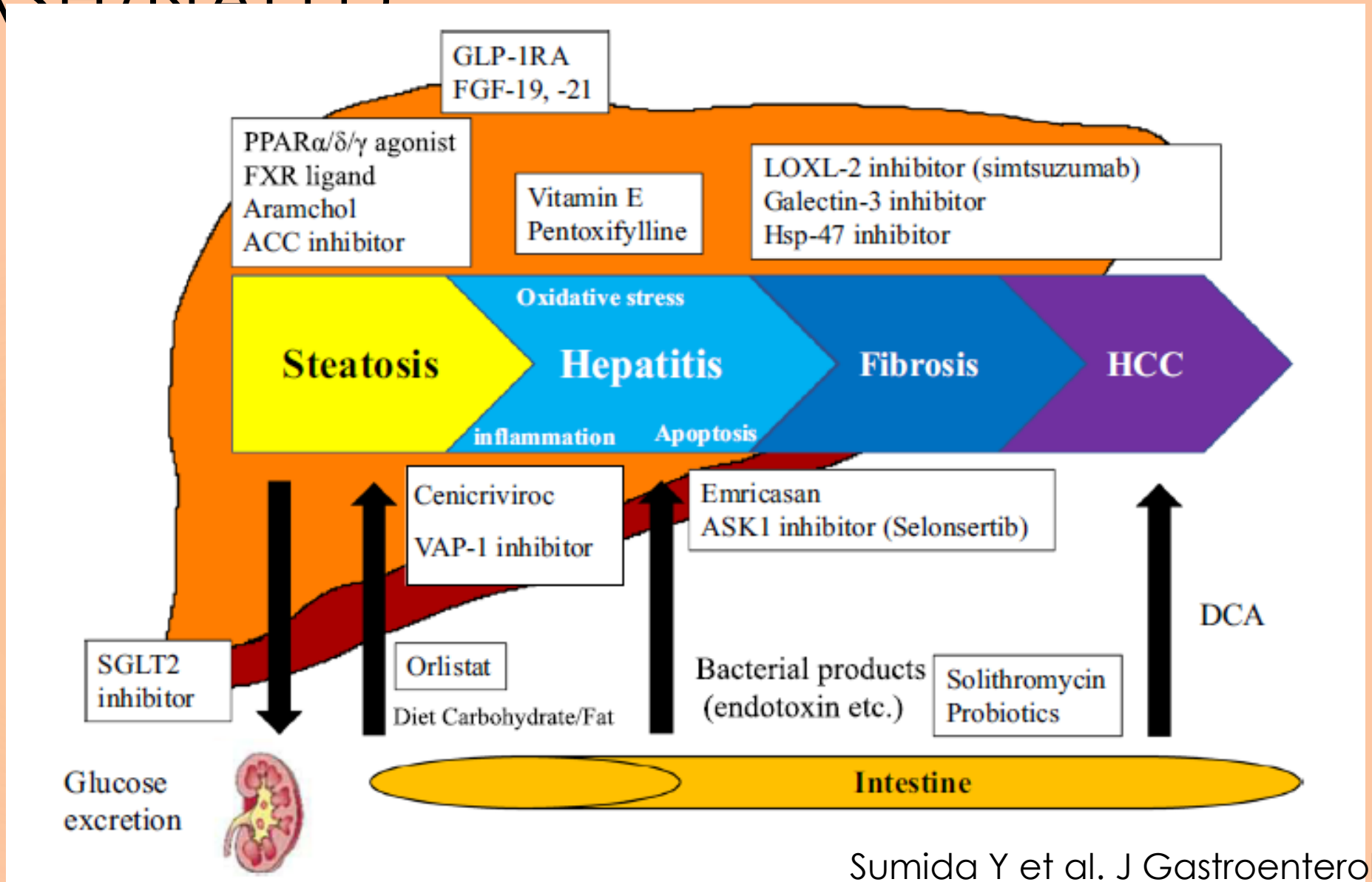
	AGA/AALSLD (2012)	JSG/JSH (2014)	EASL/EASD/EAO (2016)	AASLD guidance (2017)
Vitamin E	First-line therapy for biopsy-proven NASH without diabetes and cirrhosis (800 mg/day)	Recommended	Not firmly recommended, but could be used	May be considered in biopsy-proven NASH without diabetes and cirrhosis (800 mg/day) Discuss benefit and risk with patients
UDCA	Not recommended	Not recommended	Not mentioned in detail	Not recommended
Pioglitazone	Can be used in patients with biopsy-proven NASH	Recommended in NASH with insulin resistance	Not firmly recommended, but could be used	Can be used in patients with biopsy-proven NASH Discuss benefit and risk with patients
Metformin	Not recommended as a specific treatment for NASH	Not recommended as a specific treatment for NASH	Insufficient evidence	Not recommended as a specific treatment for NASH
GLP-1RA	Not mentioned	Not mentioned	Not mentioned	Premature as a specific treatment for NASH
ω3 fatty acid	May be considered in NAFLD with hypertriglyceridemia	Not mentioned	Reduced lipid in plasma and liver, but no evidence related to NASH	Not recommended as a specific treatment for NASH May be considered in NAFLD with hypertriglyceridemia
Statin	Can be used to treat dyslipidemia	Recommended for hypercholesterolemia	Can be used to reduce LDL-C and prevent cardiovascular risk	Can be used to treat dyslipidemia Should be avoided in decompensated cirrhosis
Pentoxifylline	Not mentioned	Recommended, but commercially unavailable in Japan	Not mentioned	Not mentioned
OCA	Not mentioned	Not mentioned	Not mentioned	Off-label use not recommended (approved for PBC in USA)

Sumida Y et al. J Gastroenterol .2018; 53:362–376

Fibrosis stage-based treatment



Targets of upcoming therapies for NASH/NAFLD



Sumida Y et al. J Gastroenterol .2018;

Phase 2 placebo-controlled trials with histology as a primary endpoint

Drug	Mode of action	Mode of administration	Primary endpoint	Treatment period to primary endpoint	Remarks
Semaglutide	GLP-1 Receptor agonist	SC	NASH resolution without worsening of fibrosis	72 w	
Lanifibranor (IVA337)	PanPPAR	PO	≥ 2 points decrease from baseline in activity score (SAF)	24 w	
MSDC 0602K	PPARγ-independent (?) regulator of mitochondrial pyruvate entry	PO	≥ 2 points decrease in NAS without worsening of fibrosis	12 w	
Emricasan	Pan-caspase inhibitor	PO	≥ 1 stage improvement in fibrosis without worsening of steatohepatitis	72 w	Also in phase 2 with composite clinical endpoint without histology and trial in cirrhotic patients with effect on HVPG as outcome measure

Francque S et al. Adv Ther .2019; 36:1052–1074

Drug	Mode of action	Mode of administration	Primary endpoint	Treatment period to primary endpoint	Remarks
BI 1467335	AOC3 (VAP1) inhibitor	PO	AOC3 activity relative to baseline	12 w	ALT change from baseline as a secondary outcome measure
Foralumab	Oral anti-CD3 antibody	PO	Safety	30 d	Change in ALT as a secondary outcome measure
SNP-610	Enzyme modulator at several steps of TG metabolism and lipid peroxidation (CYP2E1 pathways)	PO	Absolute change from baseline in serum ALT	12 w	
Emricasan	Pan-caspase inhibitor	PO	Event-free survival based on composite clinical endpoint	48–120 w	In patients with decompensated cirrhosis. Compound also phase 2 with histological endpoint
Emricasan	Pan-caspase inhibitor	PO	Mean change in HVPG	28 d	In cirrhotic patients

Francque S et al. Adv Ther .2019; 36:1052–1074

Drug	Mode of action	Mode of administration	Primary endpoint	Treatment period to primary endpoint	Remarks
Saroglitazar	Dual PPARαγ agonist	PO	% change in ALT levels	16 w	Also trial of 24 w in women with PCOS and with changes in liver fat by MRI-PDFF as primary outcome
Pemafibrate	PPARα agonist	PO	% change in liver fat measured by MRI-PDFF	24 w	
HTD1801	Lipid modulator (2 moities)	PO	% change in liver fat content measured by MRI	18 w	
PF-5521304	ACC inhibitor	PO	% change in liver fat content measured by MRI PDFF	16 w	

Francque S et al. Adv Ther .2019; 36:1052–1074

Drug	Mode of action	Mode of administration	Primary endpoint	Treatment period to primary endpoint	Remarks
BMS-986036	Pegylated FGF21 analogue	SC	≥ 1 stage improvement in fibrosis without worsening of steatohepatitis or NASH improvement without worsening of fibrosis	24 w	
SAR 425899	Dual GLP-1 receptor/ GCGR agonist	SC	Resolution of NASH	52 w	

Francque S et al. Adv Ther .2019; 36:1052–1074

Drug	Mode of action	Mode of administration	Primary endpoint	Treatment period to primary endpoint	Remarks
SGM-1019	Small molecule modulator of inflammasome activity	PO	Safety	12 w	Monitoring of ALT as secondary outcome measure
EDP-305	Non-steroidal FXR agonist	PO	Change in ALT	12 w	
Tesamorelin	Growth hormone releasing hormone analogue	SC	Liver fat content by MR spectroscopy	12 months	
MGL-3196	TRHβ agonist	PO	Change from baseline in hepatic fat fraction measured by MRI-PDFF	12 w	Study continues for a total of 36 weeks with histology as secondary outcome measures; study has been completed and results presented (EASL 2018, AASLD 2018). Will enter Phase 3

Francque S et al. Adv Ther .2019; 36:1052–1074

Drug	Mode of action	Mode of administration	Primary endpoint	Treatment period to primary endpoint	Remarks
Aparenone (MT-3995)	Non-steroidal mineralocorticoid receptor antagonist	PO	ALT change	24 w	
Tropifexor (LNJ452)	Non-steroidal FXR agonist	PO	Change in transaminase levels Change in liver fat (MRI)	12 w	
Seladelpar (MBX-8025)	Selective PPARδ agonist	PO	Relative change in MRI-PDFF	12 w	Study continues for 52 weeks including histology as secondary outcome measure
Namodenoson (CF102)	A3 adenosin receptor inhibitor	PO	Mean % change in ALT levels	12 w	
LIK 066	Dual SGLT1/2 inhibitor	PO	Change from baseline ALT	12 w	

Francque S et al. Adv Ther .2019; 36:1052–1074

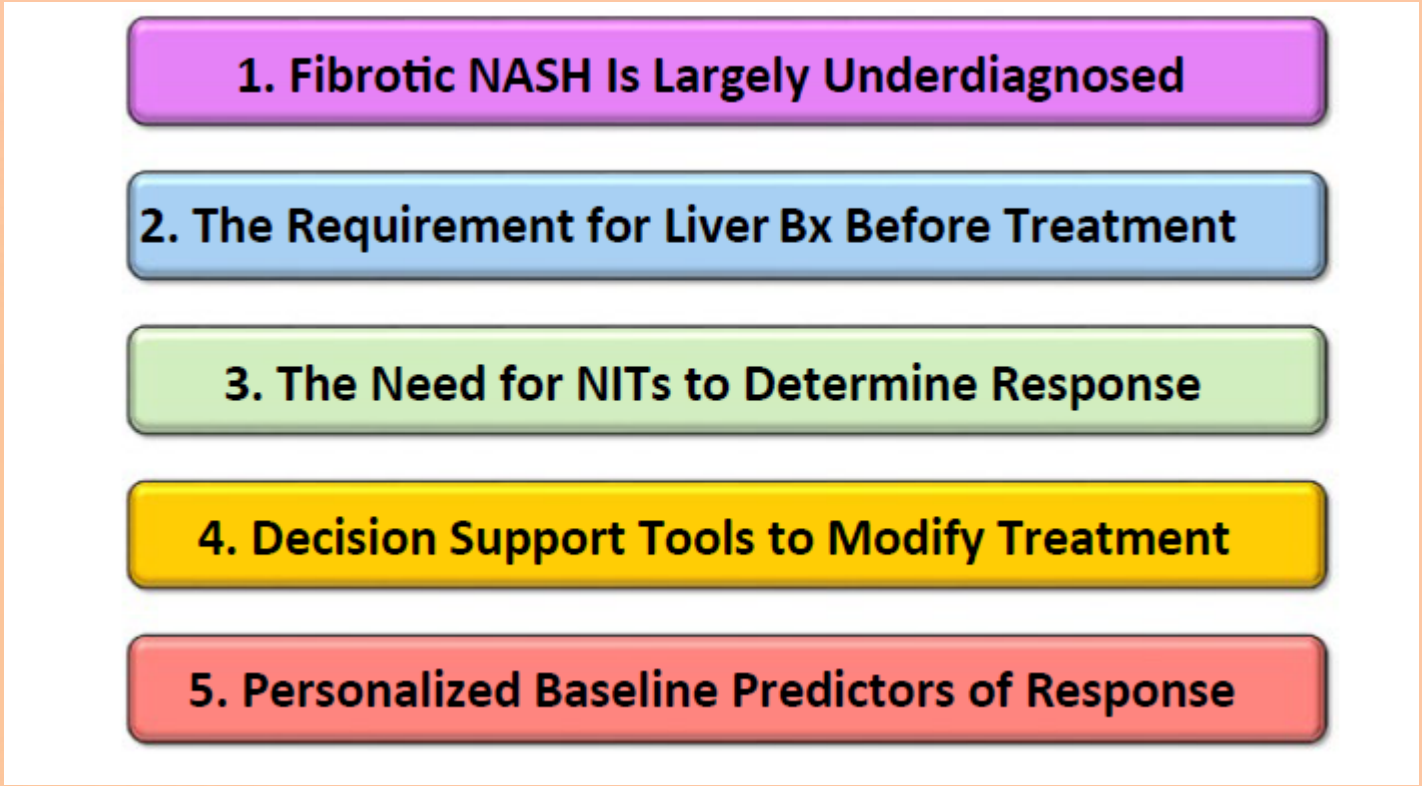
Follow-up of nonalcoholic fatty liver disease

Condition	Frequency of monitoring
NAFL patients without worsening of metabolic risk factors	Once in every 2-3 years
NASH and/or those with fibrosis	Annually
NASH with cirrhosis	Once in 6 months
NASH with high risk of progression	Liver biopsy after 5-year follow-up
NASH patients with fibrosis and hypertension	Closer monitoring because of a higher risk of disease progression
NASH cirrhosis	Screen for gastroesophageal varices and HCC

NASH: Nonalcoholic steatohepatitis, NAFL: Nonalcoholic fatty liver,
HCC: Hepatocellular carcinoma

Dharmalingam M et al. Indian J Endocr Metab

Future challenges in treating fibrotic NASH



NIT- Non Invasive Tests

Alkhouri N et al. Hepatol Commun. 2019; 3(5): 605–613

Summary

- NASH will continue to be the most common liver-related health problem in the future.
- NASH is increasing ,connected to the increase in obesity, visceral obesity, T2DM, and arterial hypertension.
- Numerous medications have been added to the pipeline of novel therapies, increasing the promise of successful treatment of NASH in the future.