NAFLD and metabolic comorbidities – current understanding and perspectives

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Learning objectives

1. Explore the relationship between **metabolic comorbidities**, such as type 2 diabetes and obesity, and **NAFLD severity**
2. Understand the importance of **early diagnosis of NAFLD** and consider how this may impact patient outcomes
3. Review the available **diagnostic techniques** in screening and staging NAFLD

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

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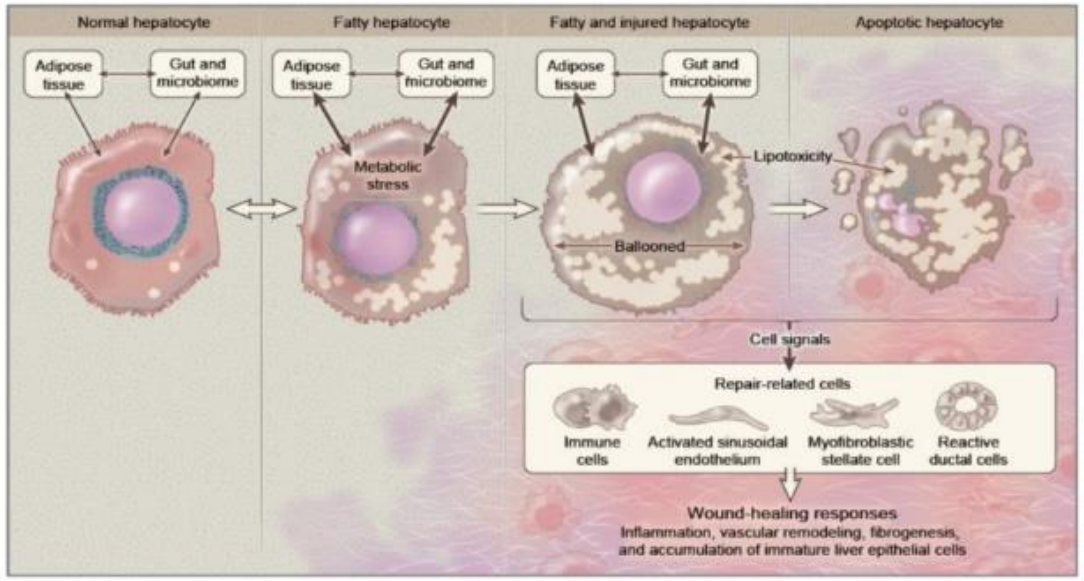
Spectrum of the disease: NAFLD includes NAFL and NASH

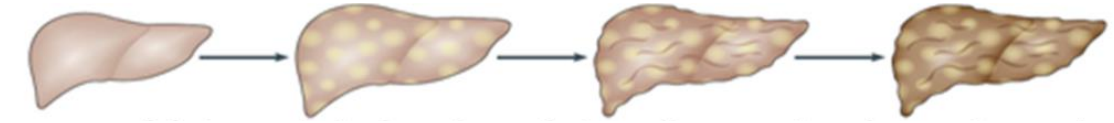
Activity



NAFL | **NASH**

NAFLD

Stage



Normal liver — Deposits of fat — Fibrosis — Cirrhosis

NAFLD, non-alcoholic fatty liver disease; NAFL, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis

Diehl AM, et al. N Engl J Med 2017; 377:2063–72

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Increasing prevalence of risk factors of NAFLD

The prevalence of NAFLD parallels that of diabetes [1]

- The worldwide prevalence of type 2 diabetes has been increasing rapidly over the past 2 decades[2]
- Diabetes is one of the largest global health emergencies of the 21st century[3]
- Diabetes is among the top 10 causes of death globally[3]
  - According to WHO, diabetes was estimated to be the 7th leading cause of death in 2016[4]

NAFLD, non-acoholic fatty liver disease; WHO, World Health Organisation

1. Bertot LC. Int J Mol Sci. 2016;17:774; 2. Dai W, et al. Medicine (Baltimore). 2017; 96:e8179; 3. IDF Diabetes atlas. Eighth edition 2017; 4. Diabetes. WHO.15 November 2017. 23 July 2018. Available from: http://www.who.int/news-room/fact-sheets/detail/diabetes. (Last accessed: October 2020)

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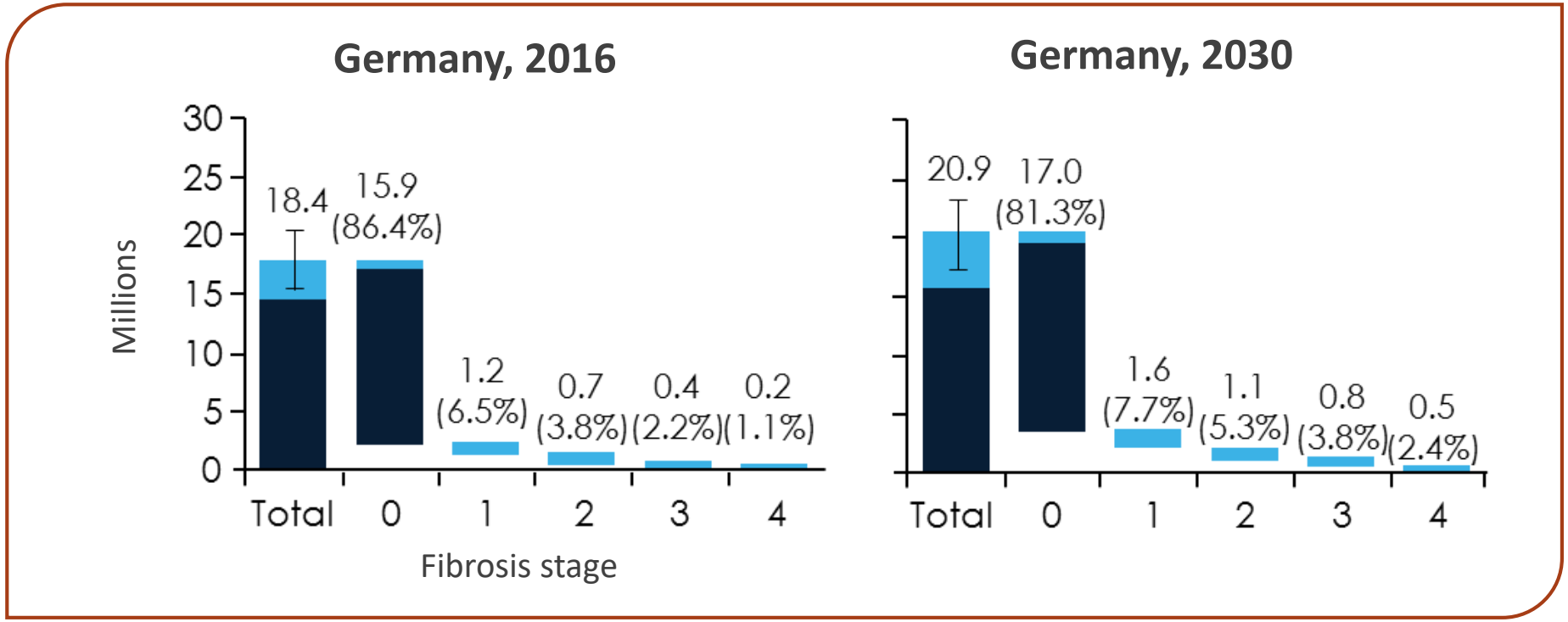
NAFLD and fibrosis stages in Germany



In Germany, the burden of Stage 3 and 4 fibrosis is projected to increase from 600,000 cases in 2016 to 1.3 million in 2030

NAFLD, non-acoholic fatty liver disease

Estes C, et al. J Hepatol 2018;69:896–904

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Which of these risk factors do you think is most strongly associated with the development of NAFLD/NASH?

1. Age
2. Gender
3. BMI
4. Ethnicity
5. Diabetes
6. Hypercholesterolemia
7. Hypertension

BMI, body mass index; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

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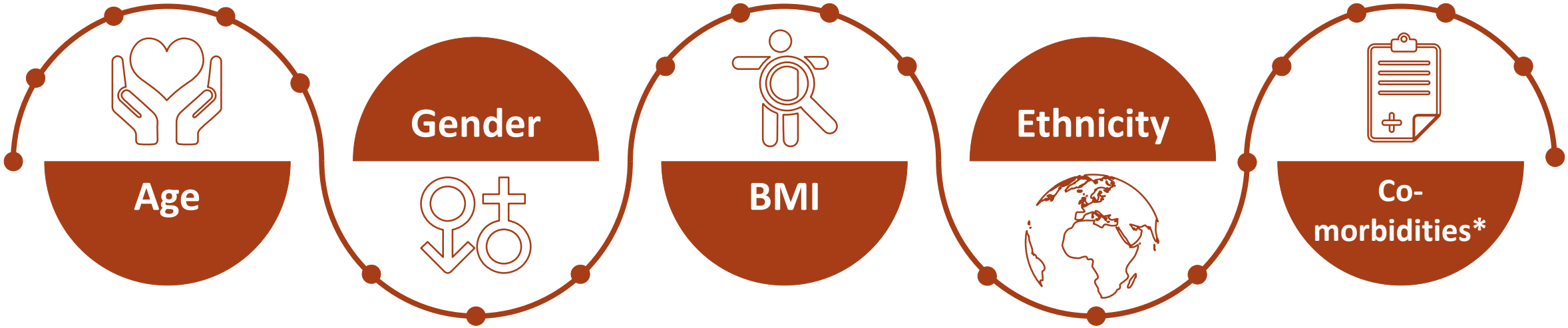
Risk factors for NAFLD

The development and progression of NAFLD is associated with a number of risk factors, including:



*Co-morbidities include type 2 diabetes, hypercholestrolemia and hypertension. BMI, body mass index; NAFLD, non-alcoholic fatty liver disease

Younossi Z et al. Gut 2020;69:564–68

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Risk stratification

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Personalization through clinical risk stratification

Diabetes as a predictor of advanced fibrosis

BMI, body mass index; CI, confidence interval; NFS NAFLD fibrosis score, NHANES, National Health and Nutrition Examination Survey

1. Wong RJ, et al. Aliment Pharmacol Ther 2017;46:974–80; 2. Labenz C, et al. Aliment Pharmacol Ther 2018;48:1109–16

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Relationship between metabolic comorbidities and NAFLD severity

Variable	Fibrosis 0–2	Advanced fibrosis	P value
n	220	41	
Age in years	50 (20; 93)	57 (19; 74)	0003*
Male gender	118 (53.6%)	19 (46.3%)	0.390
Education			
Blue collar worker	132 (60%)	24 (58.5%)	0.599
BMI (kg/m^2)	30.5 (22.8; 50.4)	32.2 (23.3; 42.6)	0.032*
Hypertension	110 (50%)	32 (78%)	0.001*
Diabetes Mellitus	53 (24.1%)	25 (61%)	<0.001*
Dyslipidemia			
High TG	57 (25.9%)	11 (26.8%)	0.858
High cholestrol	61 (27.7%)	15 (36.6%)	0.225
Bilirubin (mg/dL)	0.68 (0.2; 3.4)	0.72 (0.2; 1.8)	0.244
AST (U/L)	45 (16; 238)	63 (21; 209)	0.006*
ALT (U/L)	72 (10; 720)	82 (5; 218)	0.606

Variable	Fibrosis 0–2	Advanced fibrosis	P value
Albumin (g/L)	41 (31; 48)	40 (32; 48)	0.011*
INR	1.0 (0.9; 9.0)	1.0 (0.9; 1.5)	0.892
Platelet count (/nL)	239 (98; 473)	219 (55; 358)	0.022*
HDL (mg/dL)	45 (16; 85)	47 (22; 85)	0.903
LDL (mg/dL)	136 (35; 257)	109 (24; 182)	0.001*
HbA1c (%)	5.6 (3.5; 11.5)	6.5 (4.8; 10.8)	0.001*
Ferritin (µg/L)	191.5 (7.1; 6540)	277.5 (8.5; 2734)	0.449
Serum urate (mg/dL)	6.1 (2.8; 15.0)	6.0 (2.9; 8.9)	0.584
Statins	24 (10.9%)	10 (24.4%)	0.017*
Insulin users	15 (6.8%)	10 (24.4%)	<0.001*
Metformin	30 (13.6%)	11 (26.8%)	0.033*
AR2 blocker	18 (18.2%)	6 (14.6%)	0.189
Presence of NASH	96 (43.6%)	31 (75.6%)	<0.001*

*Significance at a level of P<0.05. Study investigating predictors of advanced fibrosis in non-cirrhotic non-alcoholic fatty liver disease in Germany (N=261). AR2B, Angiotensin receptor 2; ALT, alanine aminotransferase; AST, aspartate transaminase; BMI, body mass index; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; INR, International Normalized Ratio; LDL, low-density lipoprotein; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; TG, triglyceride. Labenz C, et al. Aliment Pharmacol Ther. 2018 Nov;48:1109–6

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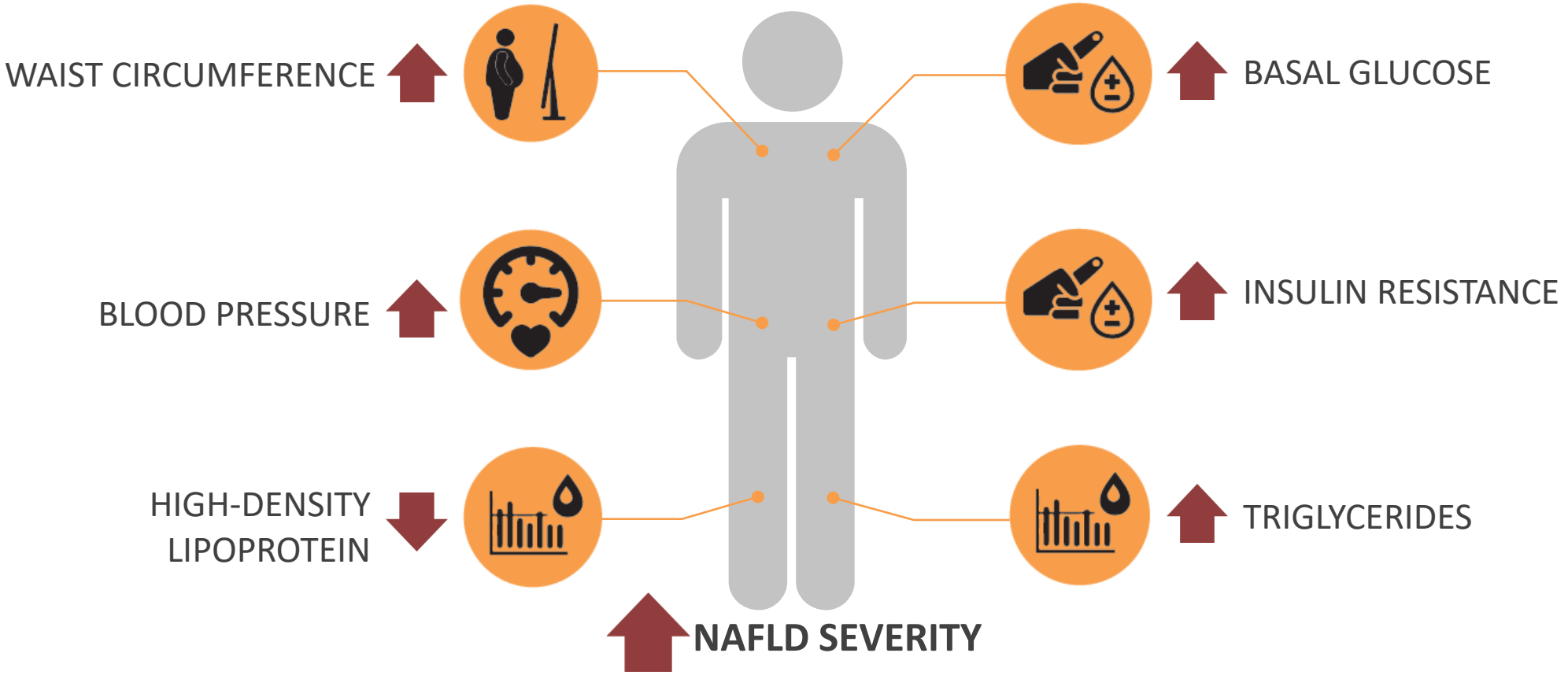
Metabolic burden is associated with higher risk of NAFLD



For patients with mild NAFLD, the OR of having metabolic burden was **3.64 (95% CI: 1.5–8.8)** vs no NAFLD

For patients with moderate-to-severe NAFLD, the OR was **9.4 (95% CI: 3.5–25.0)** vs no NAFLD

CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio. Yang, K. C. et al. Sci. Rep. 6, 27034; doi: 10.1038/srep27034 (2016)

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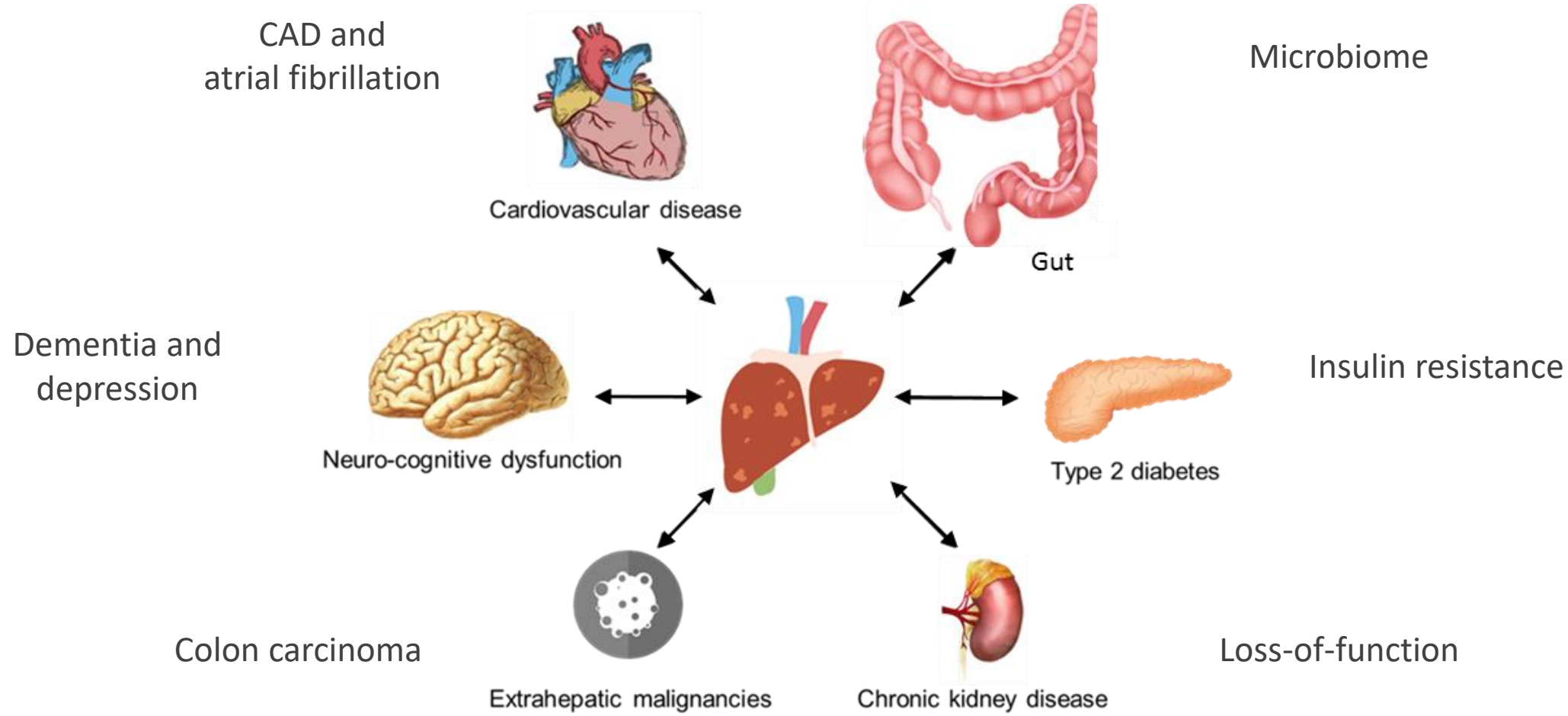
The liver interacts with other organs in the context of metabolically-ill patients



CAD, coronary artery disease
Schattenberg & Straub Der Gastroenterologe 2020 – slide provided by speaker

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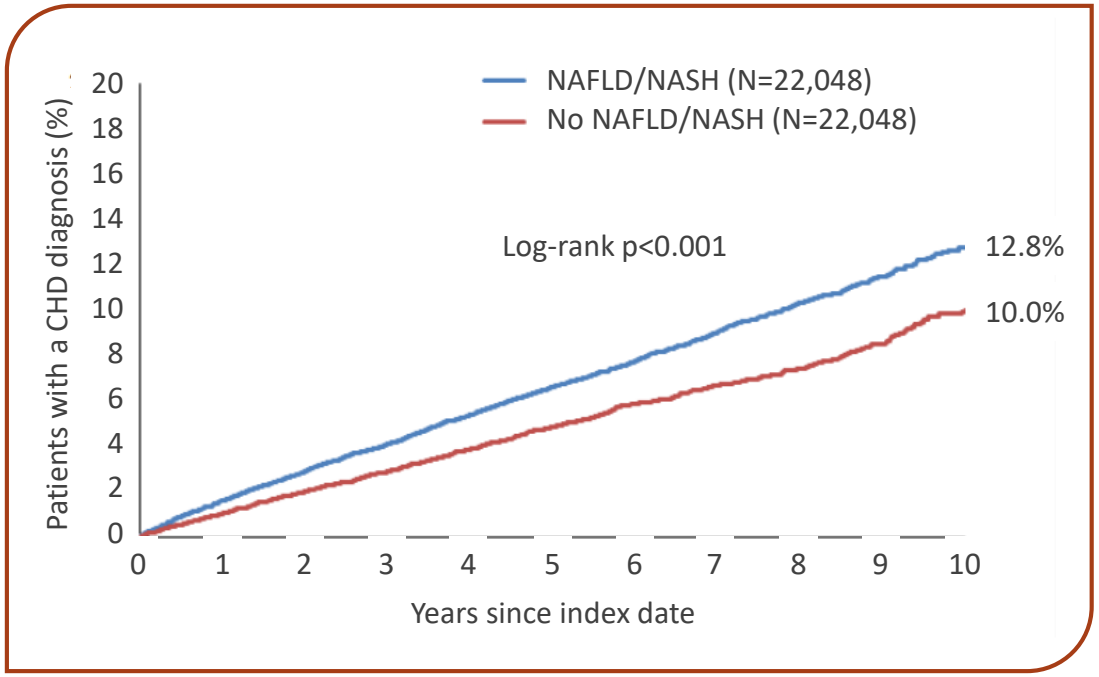
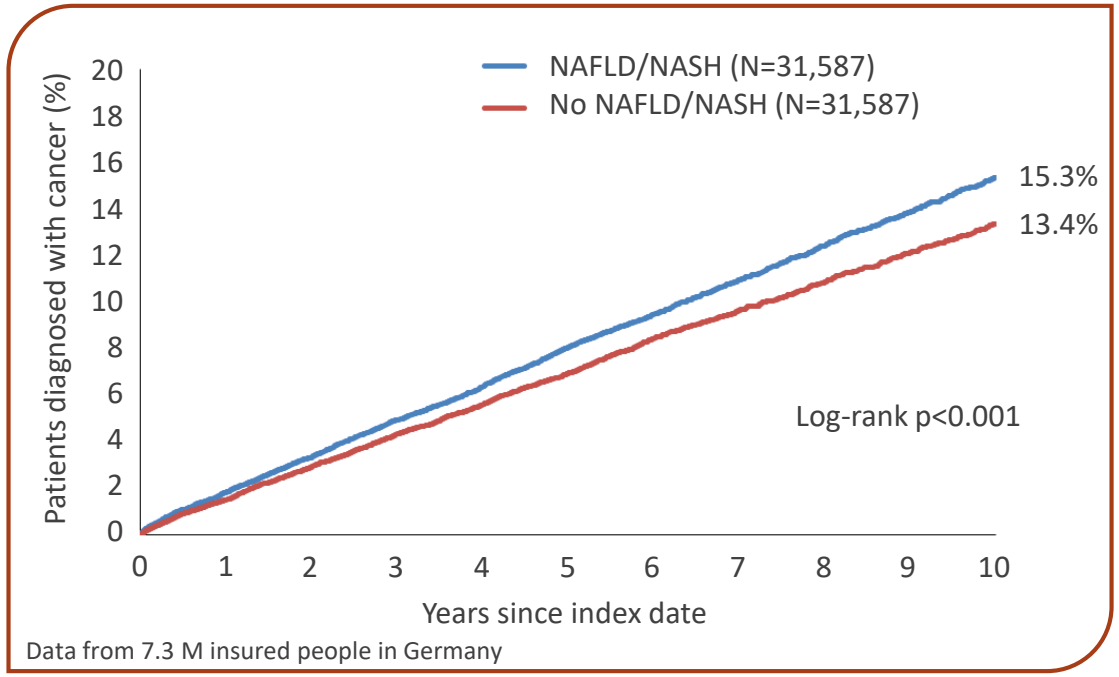
Does NAFLD contribute to extrahepatic diseases
Population-based analyses in Germany

1. Primary care patients in Germany



2. Disease Analyzer Database



Data from 7.3 M insured people in Germany

The German Disease Analyzer database combines data from primary and secondary care in Germany and is adjusted to represent outpatient practice and thus provides a representative database

CHD, congenital heart disease; NAFLD, non-alcoholic fatty liver disease

1. Labenz C, et al. Dig Dis Sci 2020. 65:2112–19; 2. Huber et al. DAEB 2020 – in press *[data provided by speaker]*

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Disease progression and importance of early diagnosis

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Steatosis may be a risk factor not only for NAFLD progression but also for cardiometabolic disorders

1. True
2. False

NAFLD, non-alcoholic fatty liver disease

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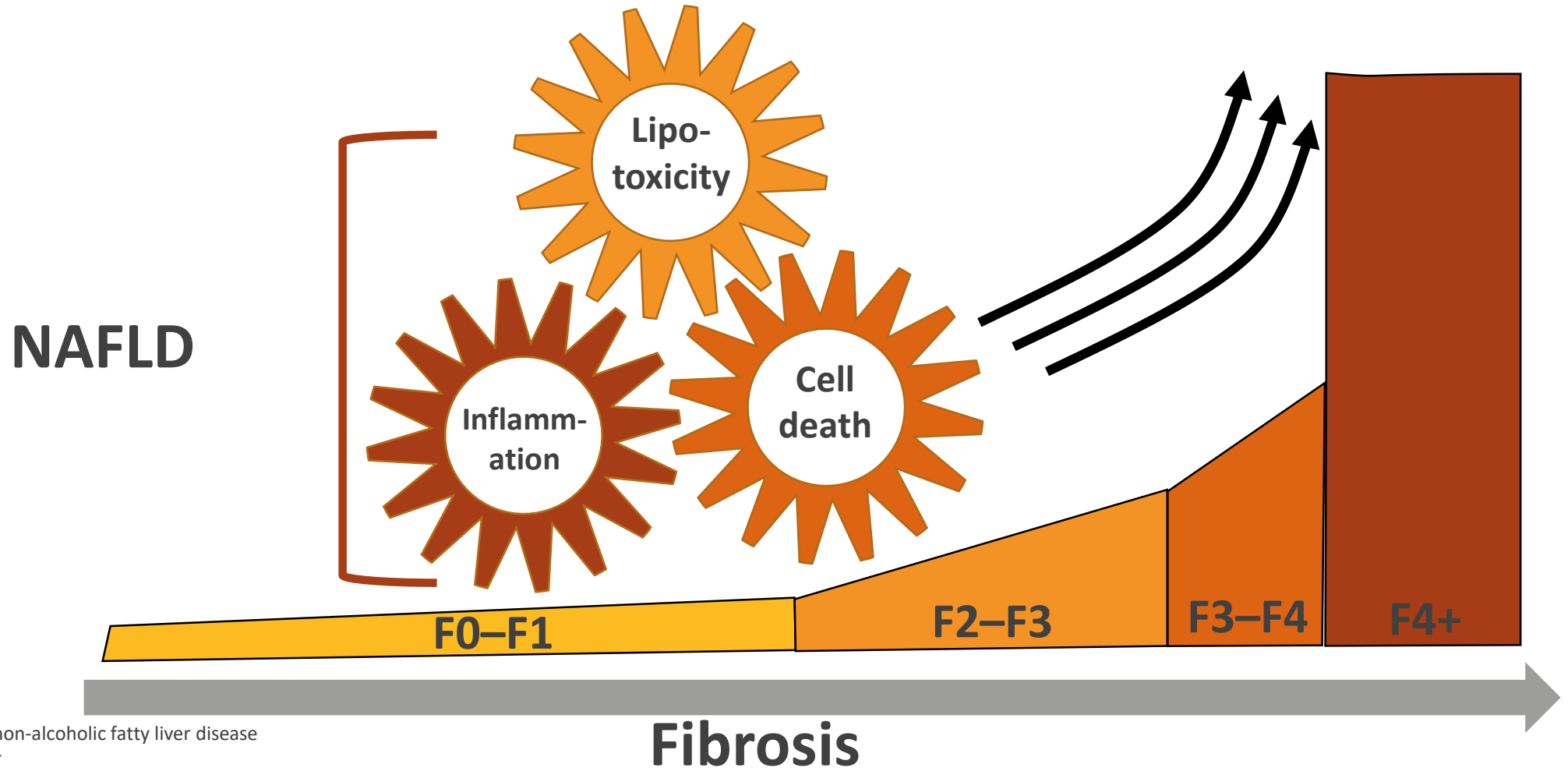
NAFLD is a multifactorial, progressive disease



F, fibrosis stage; NAFLD, non-alcoholic fatty liver disease
Slide provided by speaker

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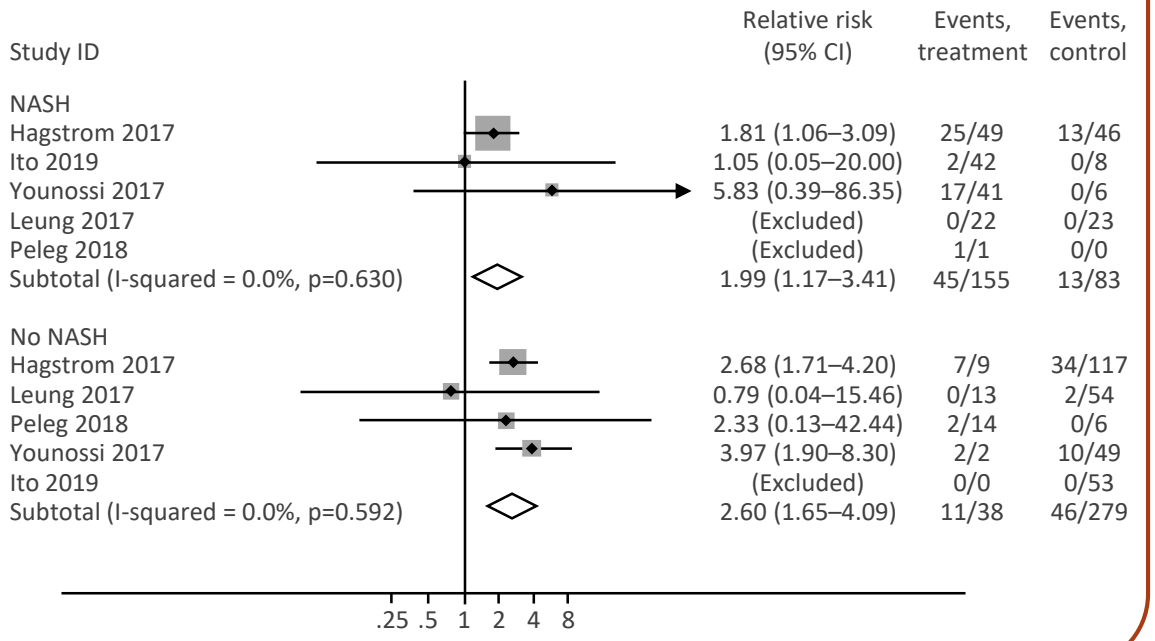
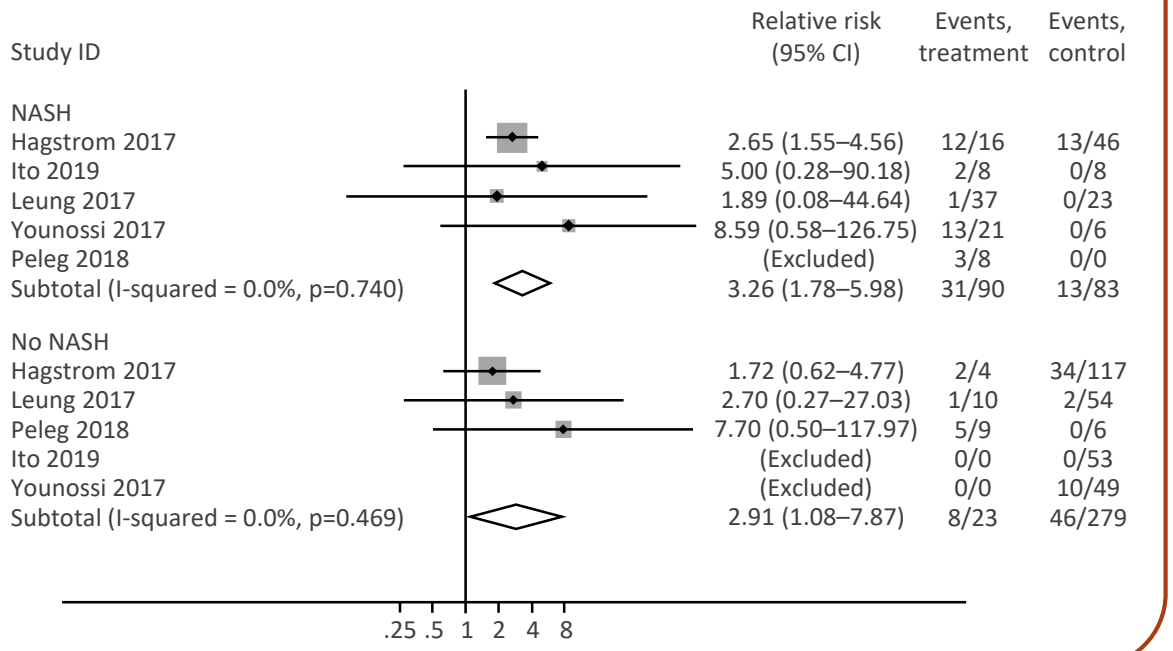
Fibrosis stage and mortality risk

Meta-analysis: 13 studies; 4428 patients with liver histology, 65% of whom had NASH

All-cause mortality NAFLD stage 0 vs stage 3



All-cause mortality NAFLD stage 0 vs stage 4



CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis

Taylor RS, et al. Gastroenterology 2020;158:1611–25

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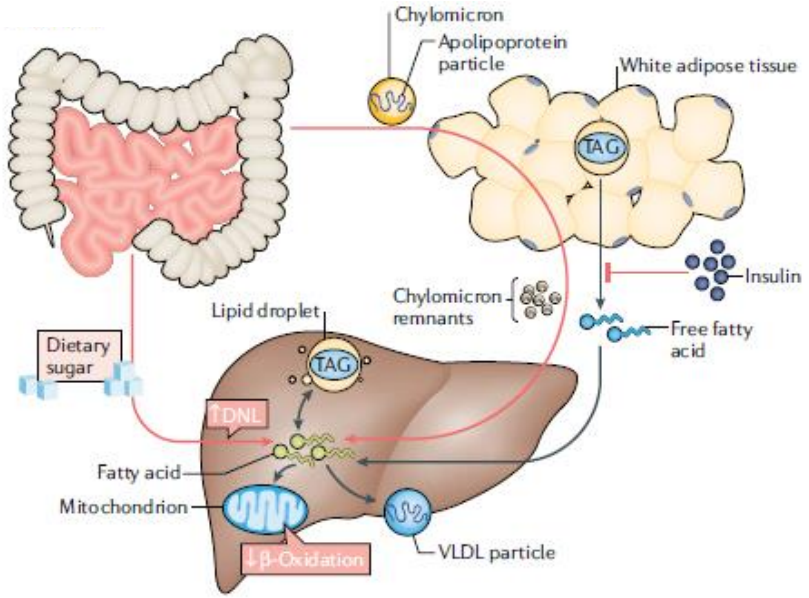
Pathogenesis of hepatic steatosis

Fasting state

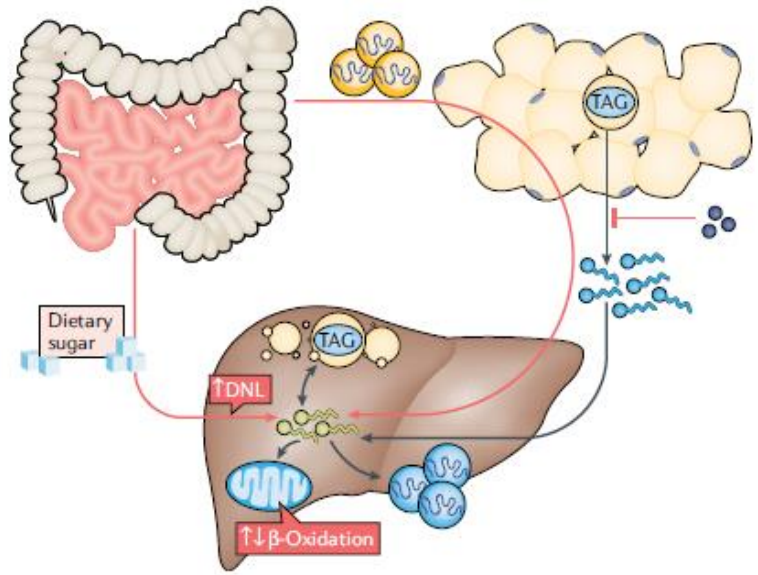
Postprandial

‘Healthy’ phenotype



FAs are liberated by TAG hydrolysis. Postprandial increase in insulin suppresses TAG hydrolysis, upregulates DNL and promotes esterification

‘Unhealthy’ phenotype



Metabolic pathways are disrupted. The DNL pathway is promoted and β–oxidation is impaired

DNL, de novo lipogenesis; FA, fatty acid; TAG, triacylglycerol

Hodson L and Gunn PJ. Nat Rev Endocrinol 2019;15:689–700; Postic C and Girard J. J Clin Invest 2008;118:829–38

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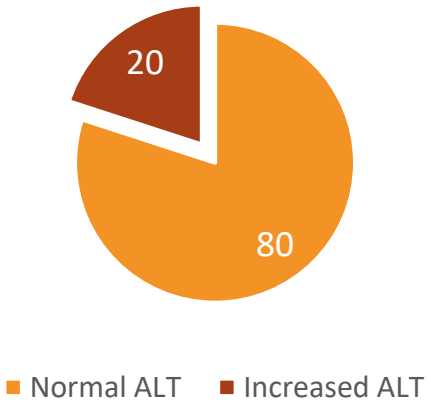
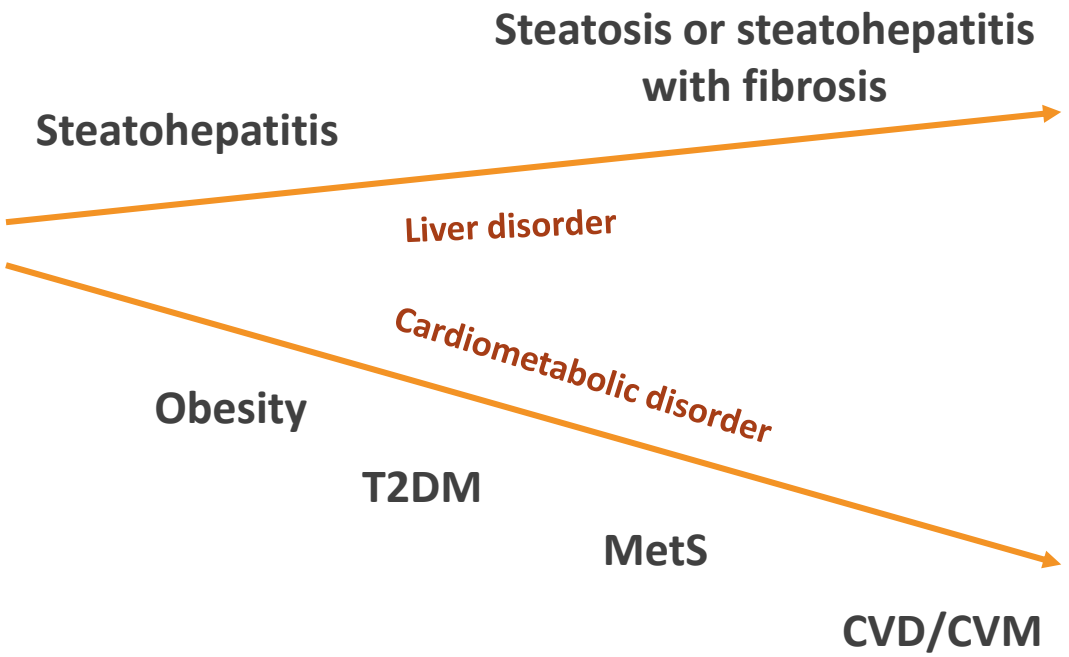
Correlation of steatosis progression and metabolic comorbidities

80% patients with NAFLD have normal-range transaminases

Transaminases



Steatosis as an early change may be a risk factor not only for NAFLD progression but also for other cardiometabolic disorders



ALT, alanine aminotransferase; CVD, cardiovascular disease; CVM, cardiovascular medicine; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus

Masihur RA, et al. Indian Heart Journal 2014; 66:574–9; Dyson JK, et al. Frontline Gastroenterology 2014;5:211–8; Yang, KC, et al. Sci. Rep. 6:27034

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Screening and diagnostics

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NAFLD screening: review of guidelines

Table 2 Comparative analysis of the recommendations regarding the screening for non-alcoholic fatty liver disease

	EASL	NICE	Asia-Pacific	AISF	AASLD
Systematic screening	No	No	No	No	No
Screening in high-risk groups	Yes Obesity Metabolic syndrome Abnormal liver enzymes	Yes Obesity Type II Diabetes	Yes Obesity Type II Diabetes	Not mentioned	No[1]
Screening modality	Yes liver enzymes	No ~~liver enzymes~~ Yes ultrasonography	No ~~liver enzymes~~ Yes ultrasonography Yes transient elastography		

[1]"Active surveillance" (but not screening) suggested for patients with type II diabetes mellitus. EASL: European Association for the Study of the Liver; NICE: National Institute for Health and Care Excellence; AISF: Italian Association for the Study of the Liver; AASLD: American Association for the Study of Liver Diseases.

- Screening is recommended in high-risk NAFLD groups[1]
- Ultrasound should be performed for screening purposes[1]
- Enzyme levels do not reflect steatosis and NAFLD severity/stage since ALT is not elevated in 80% of NAFLD patients[2]

- Recent guidance from the ADA recommends that people with T2DM or pre-diabetes and elevated liver enzymes or fatty liver on ultrasound should be evaluated for the presence of NASH and liver fibrosis[3]
- Consideration of NAFLD/NASH should now be included in the management of people with T2DM[4]

ADA, American Diabetes association; ALT, alanine aminotransferase; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, type 2 diabetes mellitus

1. Leoni S, et al. World J Gastroentero 2018;24:3361–73; 2. Kotronen A, et al. Arterioscler Thromb Vasc Biol 2008;28:27–38; 3. ADA. Diabetes Care 2019;42(Suppl 1):S34–S45; 4. Cusi K. Diabetes Care 2020;43:275–9

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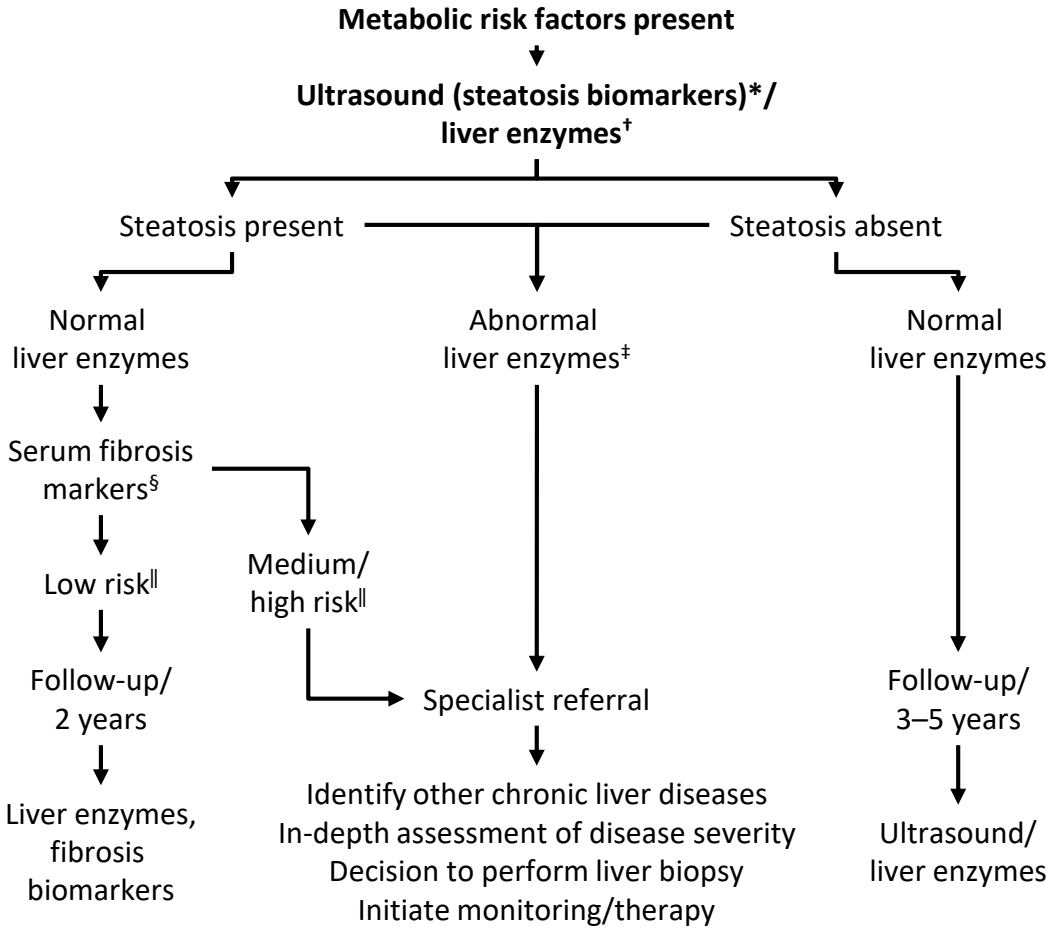
EASL: Diagnostic flow-chart

- 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. ALT, alanine aminotransferase; AST, aspartate transaminase;
EASL, European Association for the Study of the Liver; MetS, metabolic syndrome; NAFLD, non-acoholic fatty liver disease; T2DM, type 2 diabetes mellitus. EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

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How is NAFLD diagnosed?

Ultrasonography:

- First line imaging technique for diagnosing hepatic steatosis
- Good sensitivity (~85%) and specificity (~95%) for detecting moderate steatosis
- Confirms hepatic steatosis and excludes other causes of liver disease (gall stones or metastasis)

- Computed tomography
- Magnetic resonance imaging (MRI)
- Magnetic resonance spectroscopy (MRS)

More expensive and less readily available

NAFLD, non-alcoholic fatty liver disease

Byrne C et al. BMJ 2018;362:k2734

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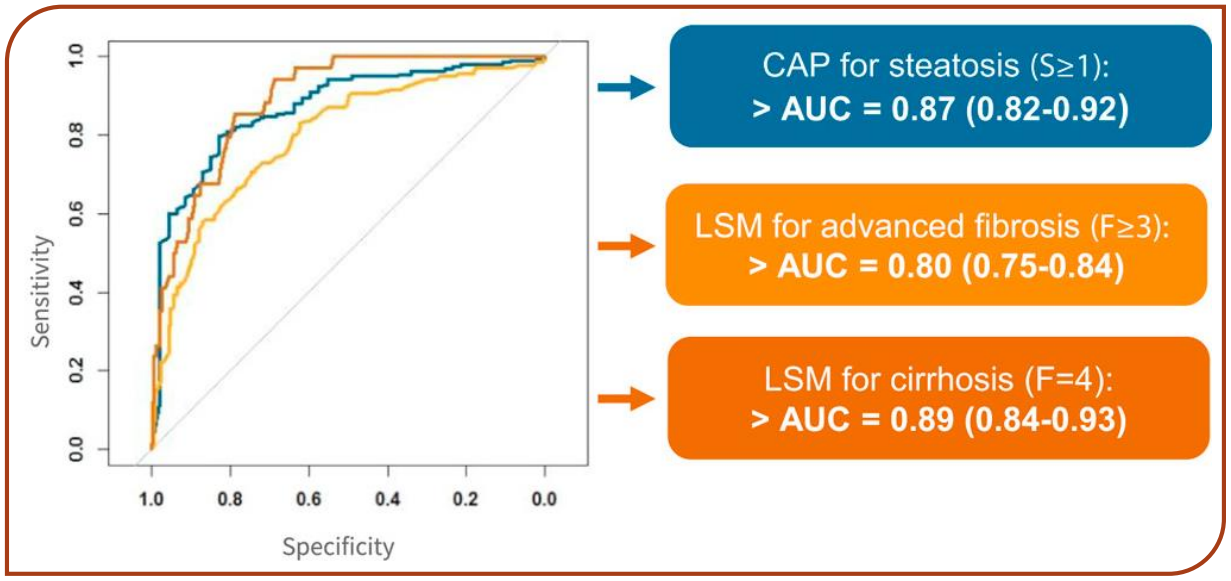
Transient elastography

Liver-stiffness measurement (LSM) und controlled attenuation parameter (CAP)

- 450 patients analyzed for suspected NAFLD at 7 centers in the United Kingdom from March 2014 through January 2017
- Approximately **10%** (46/450) had **invalid measurements** (M- and XL-Probe)



Steatosis or probe type had no impact on LSM (multivariable analysis)

CAP and LSM by FibroScan are reliable biomarkers to non-invasively assess liver steatosis and fibrosis respectively in NAFLD

AUC, area under the curve; NAFLD, non-alcoholic fatty liver disease
Eddowes PJ, et al. Gastroenterology 2019;156:1717–30

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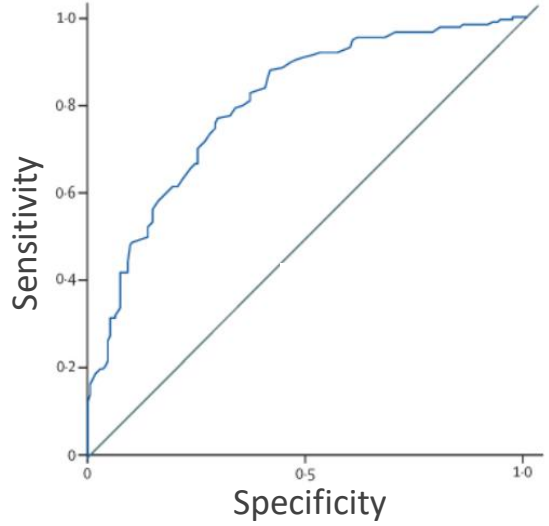
FibroScan-AST (FAST) score

Predictive model combining LSM, CAP and AST

- A prospective study to develop a score to identify patients with NASH, elevated NAFLD activity score (NAS≥4), and advanced fibrosis (stage 2 or higher [F≥2]) (N=350) found:
  - Predictive performance of FAST score indicated an AUROC of 0·80 (95% CI: 0·76–0·85) with satisfactory calibration of predicted probabilitiesand AST



Diagnostic performance for NASH + NAS≥4 + F≥2:
AUROC = 0·80 (95% CI 0·76–0·85)

Calibration of the score was satisfactory and discrimination was good across the full range of validation cohorts **(AUROC range: 0·74–0·95)**

The FAST score provides an efficient way to non-invasively identify patients at risk of progressive NASH

AST, aspartate transaminase; ; AUROC, area under the receiver operating characteristic curve; CAP, controlled attenuation parameter; CI, confidence interval; F, fibrosis stage; LSM, liver-stiffness measurement; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis. Newsome PN, et al. Lancet Gastroenterol Hepatol. 2020;5:362–73

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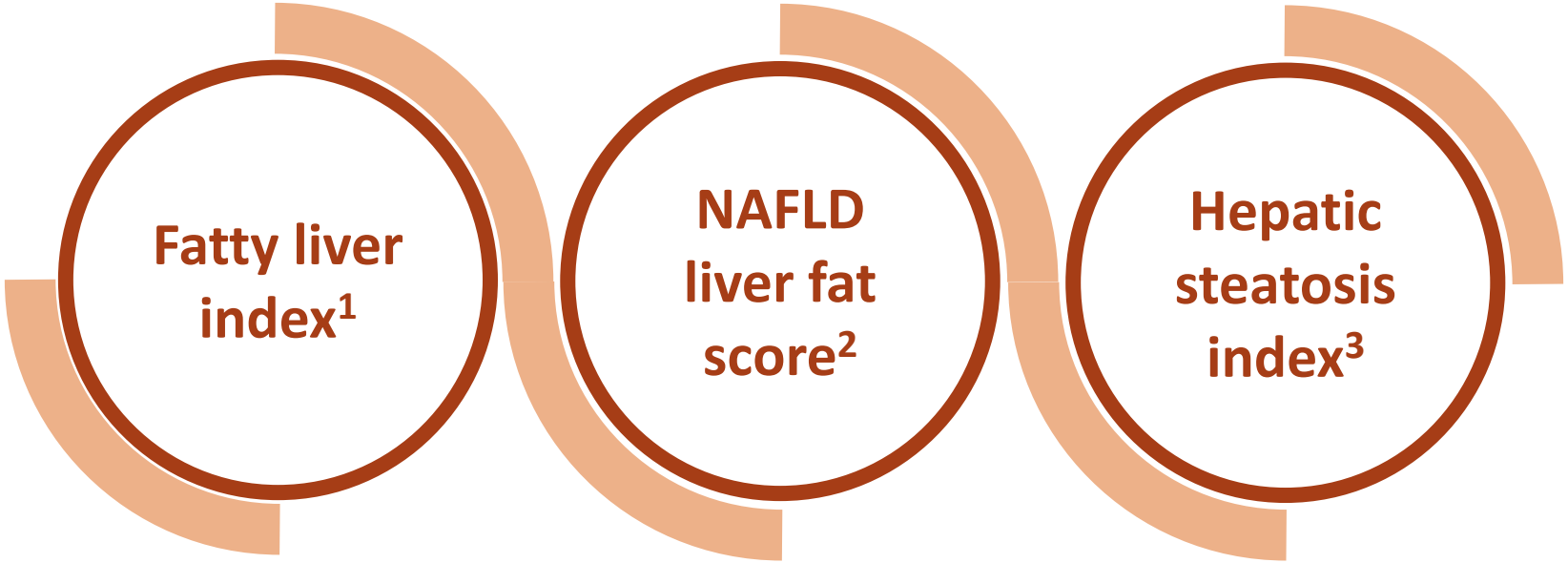
Additional non-invasive techniques



1. The **fatty liver index** is an algorithm based on waist circumference, body mass **index** (BMI), triglyceride, and gamma-glutamyl-transferase
2. The **NAFLD Liver Fat Score** is calculated using the presence of the metabolic syndrome, type 2 diabetes, fasting serum insulin, fasting serum AST and the AST/ALT ratio
3. The **hepatic steatosis index** is calculated using the patients gender, BMI, ALT and AST levels and diagnosis of type 2 diabetes

ALT, alanine aminotransferase; AST, aspartate transaminase; NAFLD, non-alcoholic fatty liver disease

Bugianesi E et al. J Hepatol. 2016;65:643–4

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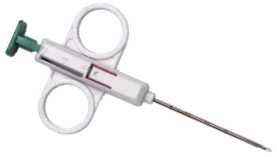
Use and applicability in clinical trials

Clinical trials utilize these different diagnostic techniques to quantify outcomes

Primary Outcomes

MRI-PDFF

Liver Biopsy



1

2

Secondary Outcomes

Liver enzymes

Transient elastography

MRE

Multiparametric MRI

Biomarkers

Metabolomics and proteomics

MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; MRI-PDFF, magnetic resonance imaging derived proton density fat fraction

Noureddin N, et al. Hepatol Commun 2020;4:141–4

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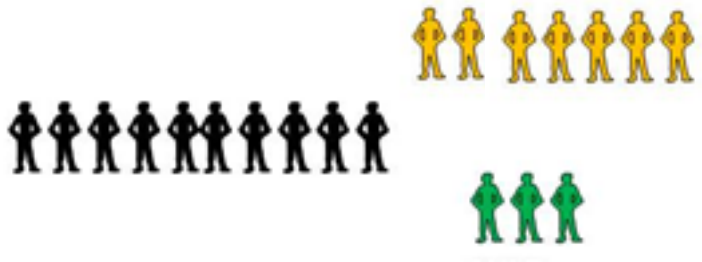
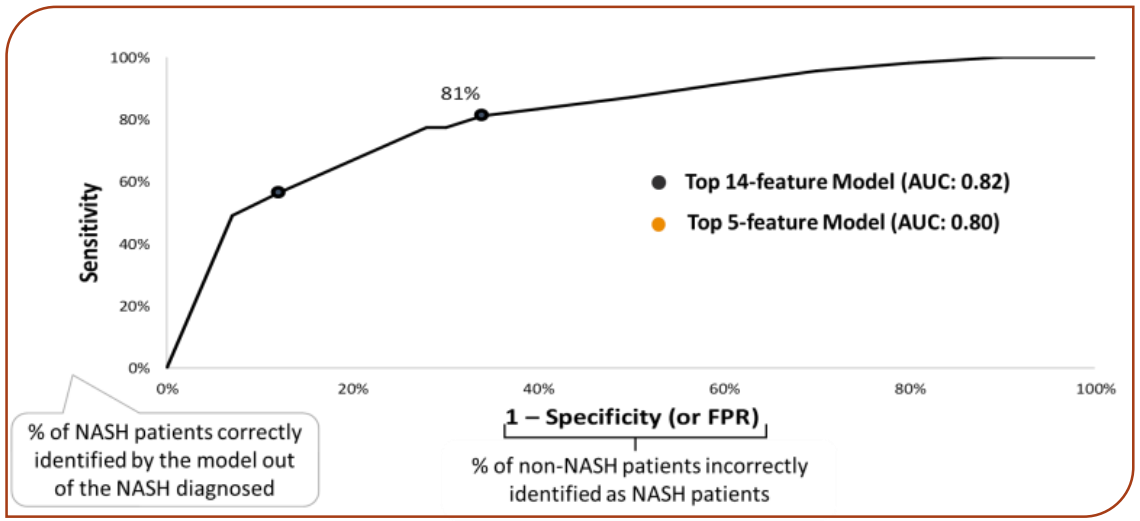
Artificial intelligence in precision medicine





Importance rank	Feature	Importance rank	Feature
1	HbA1c	**8**	Height
2	AST	**9**	Platelets
3	ALT	**10**	**WBC**
4	Total protein	**11**	**Hematocrit**
5	AST/ALT	**12**	Albumin
6	BMI	**13**	**Hypertension**
7	Triglycerides	**14**	Gender

AI identifies 14 parameters which discriminate NASH from non-NASH

AI, artifical intelligence; ALT, alanine aminotransferase; AST, aspartate transaminase AUC, area under the curve; BMI, body mass index; HbA1c, glycated hemoglobin; NASH, non-alcoholic steatohepatitis; WBC, white blood cells. Schattenberg JM, et al. AASLD 2019

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Conclusions

1. NAFLD severity is linked to metabolic comorbidities – diabetes and high BMI
2. Early stage NAFLD exhibits lower mortality and morbidity versus advanced disease – early diagnosis could allow for improved disease management and outcomes for patients
3. Screening is necessary for high-risk NAFLD patients, including those with diabetes or obesity – non-invasive tests are increasingly available

BMI, body mass index; NAFLD, non-alcoholic fatty liver disease

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