NAFLD : Diagnosis and Risk Stratification

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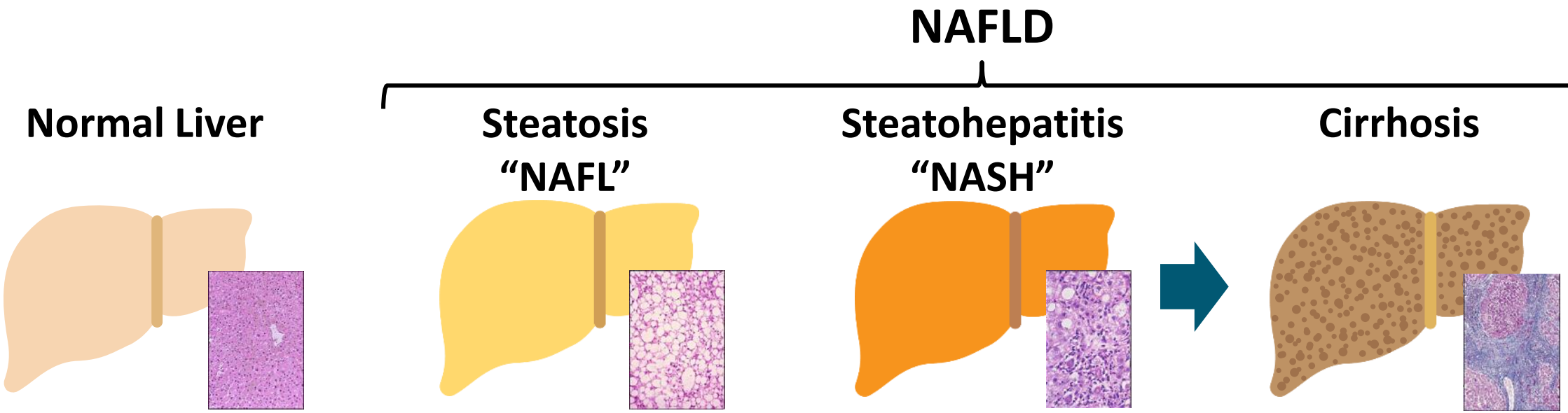
Prevalence and incidence

- NAFLD is the most common liver disorder in Western countries.
- The prevalence of NAFLD in the general population is about 25%, peaking at more than 30% in the Middle East and South America and as low as 13% in Africa.
- Parallels the prevalence of metabolic syndrome and its components, which also increase the risk of more advanced disease.
- NAFLD is also present in 7% of normal-weight (lean) individuals.

1. Vernon G, et al. Aliment Pharmacol Ther 2011;34:274–85; 2. Younossi ZM, et al. Medicine 2012;91:319–27;
EASL–EASD–EASO CPG NAFLD. J Hepatol 2016;64:1388–402

Worldwide Prevalence of NAFLD and NASH

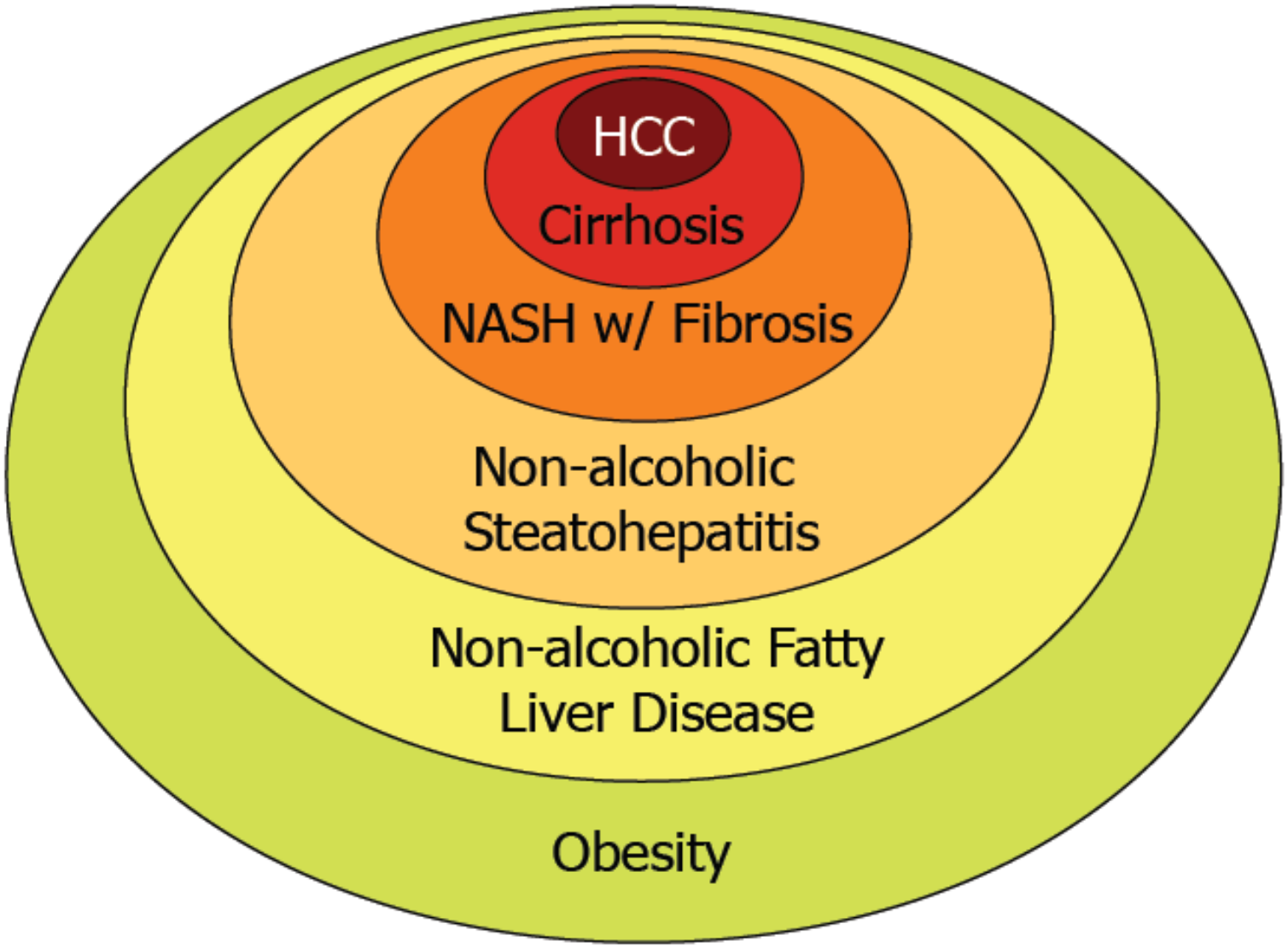


Worldwide prevalence:	25%[1]	3% to 5%[1]	1% to 2% at risk*

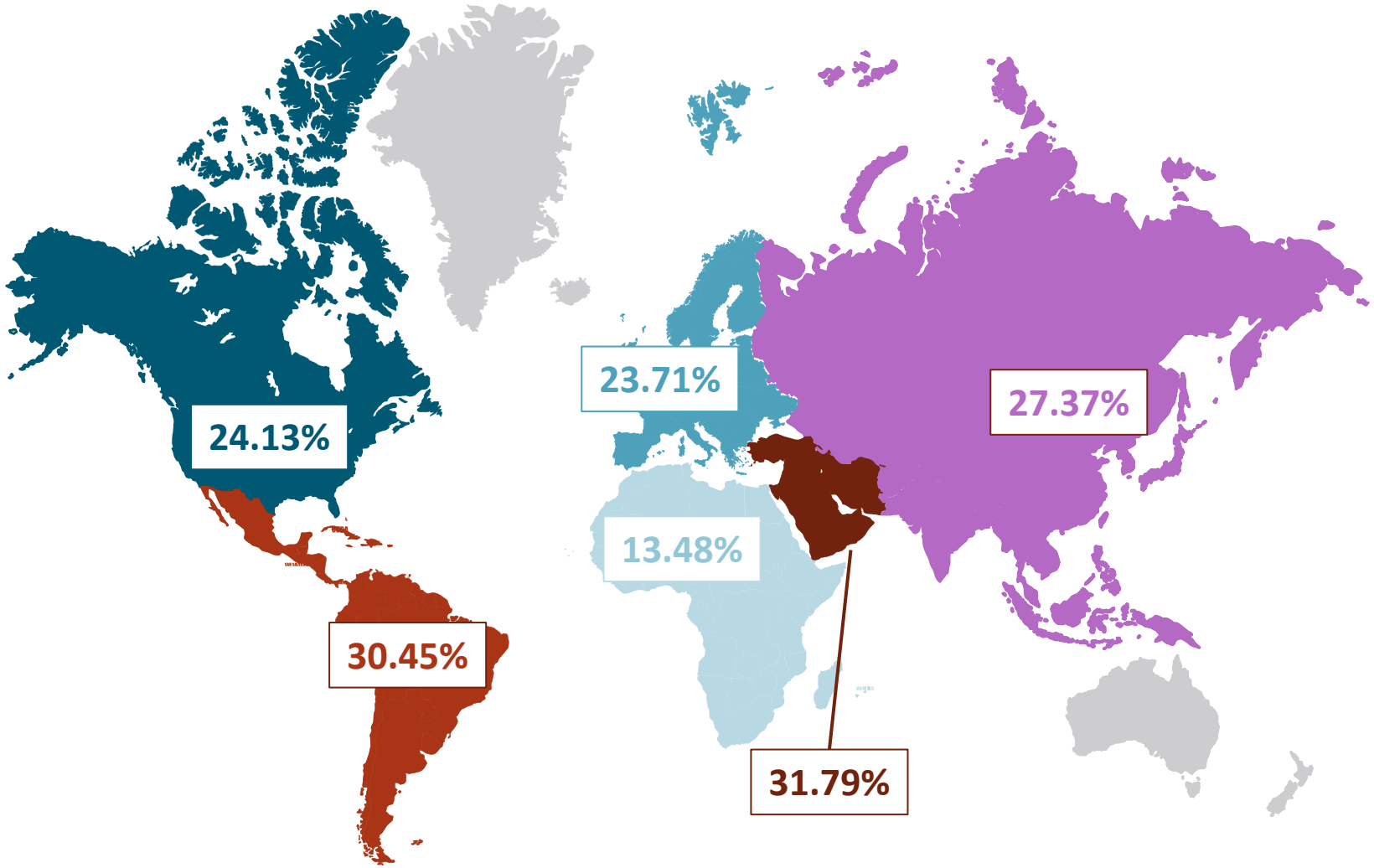
*Based on analysis of NHANES data estimating 1.74% prevalence of NASH with advanced fibrosis[2]

1. Younossi. J Hepatol. 2019;70:351. 2. Kabbany. Am J Hepatol. 2017;112:581.

Spectrum of NAFLD
Public Health/Primary Care Perspective



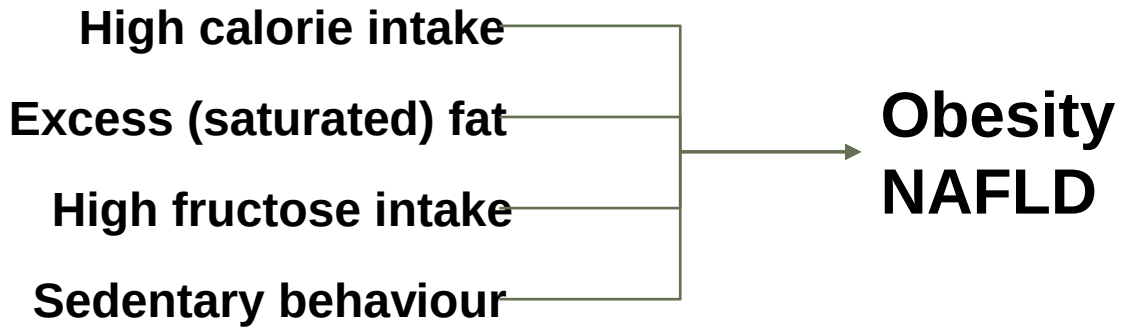
Prevalence of NAFLD



Younossi. Hepatology. 2016;64:73

Pathogenesis: lifestyle and genes

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



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

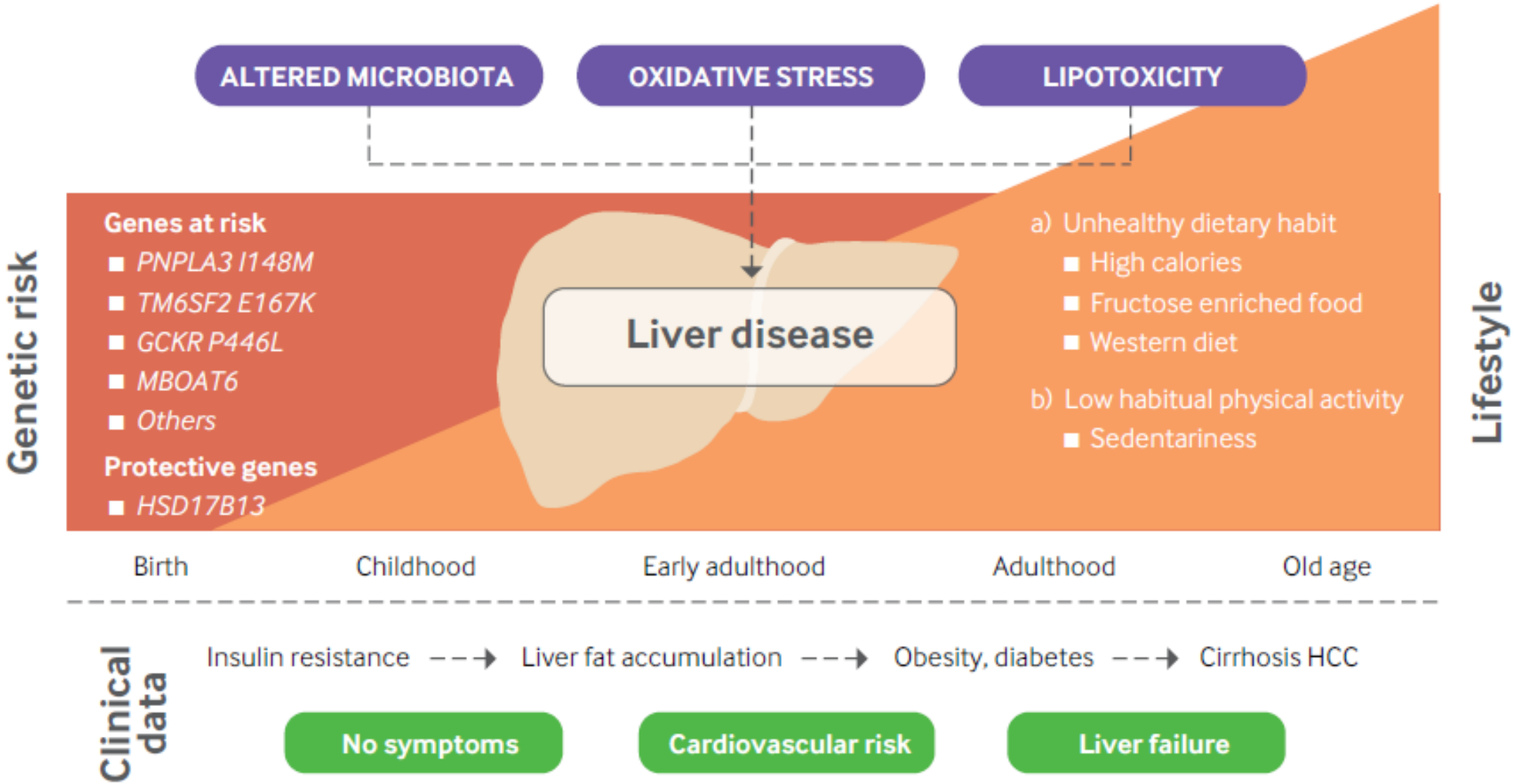
Pathogenesis: lifestyle and **genes**

Several genetic modifiers of NAFLD have been identified:

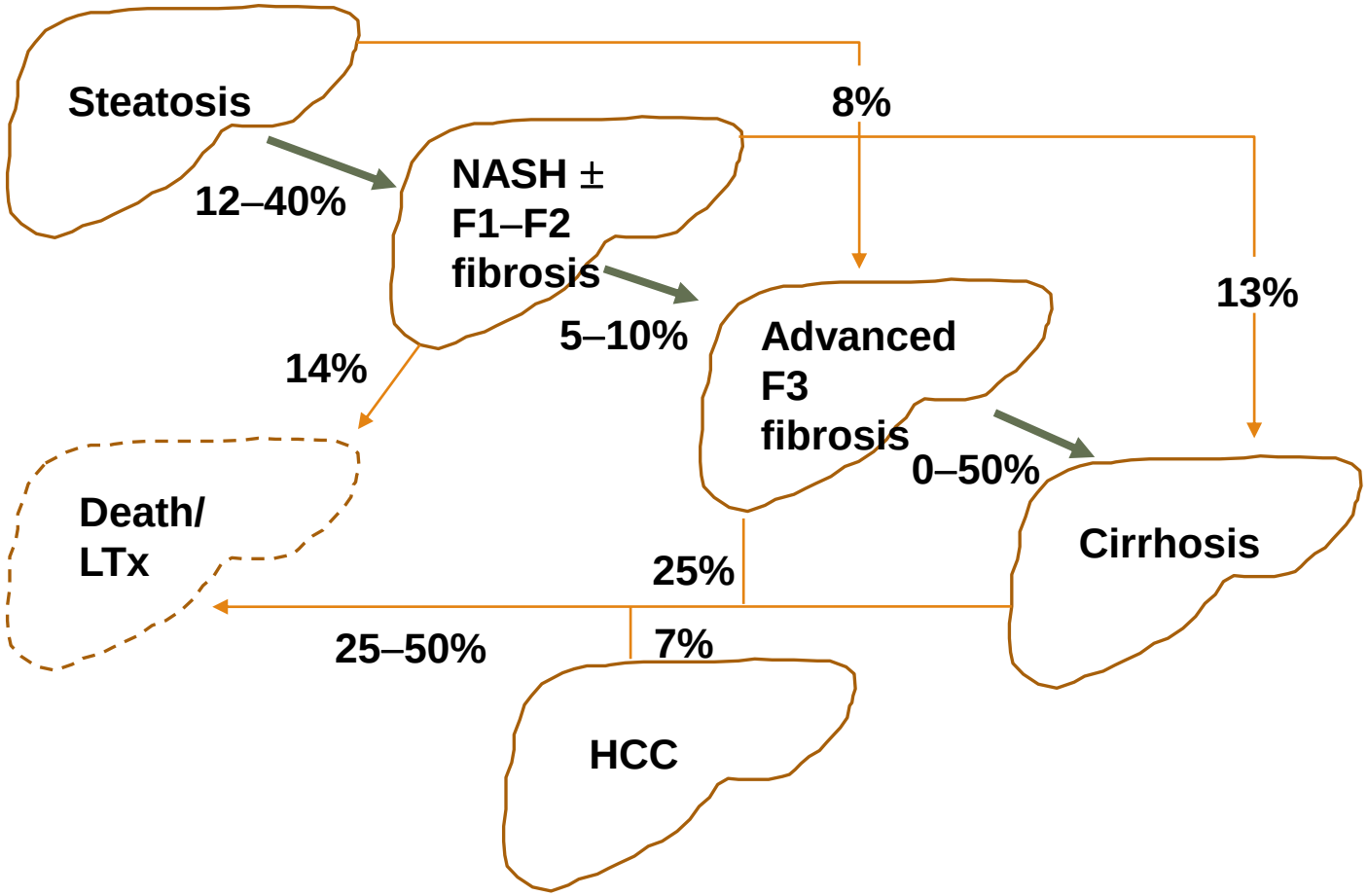
- PNPLA3/148M and TM6SF2 E167K carriers have a higher liver fat content
- Increased risk of NASH

*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


ALTERED MICROBIOTA
OXIDATIVE STRESS
LIPOTOXICITY
Genetic risk
Genes at risk
PNPLA3 I148M
TM6SF2 E167K
GCKR P446L
MBOAT6
Others
Protective genes
HSD17B13
Liver disease
a) Unhealthy dietary habit
High calories
Fructose enriched food
Western diet
b) Low habitual physical activity
Sedentariness
Lifestyle
Birth
Childhood
Early adulthood
Adulthood
Old age
Clinical data
Insulin resistance
Liver fat accumulation
Obesity, diabetes
Cirrhosis HCC
No symptoms
Cardiovascular risk
Liver failure

Natural history of NAFLD over 8–13 years



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

Identifying Individuals With NAFLD

NAFLD Presentation

Symptoms

- Usually asymptomatic; majority discovered by chance
- Fatigue frequently present
- Right upper quadrant discomfort

Often an “incidental finding”

- Incidental abnormal LFTs
- Incidental “bright liver” on imaging
- Incidental hepatomegaly

De Alwis. Dig Dis. 2016;34:19.

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

Liver Enzymes: Inadequate in Assessing NAFLD/NASH

- ALT can be normal in > 50% of individuals with NASH, 80% of individuals with NAFLD
- ALT can be elevated in > 50% of individuals with NAFLD but without NASH
- In NAFLD, ALT is neither indicative nor predictive of NASH or fibrosis stage:
  - Normal ALT does not preclude NASH/progressive disease
  - Elevated ALT cannot predict NASH or fibrosis
  - **ALT or AST not sensitive for NAFLD/NASH**

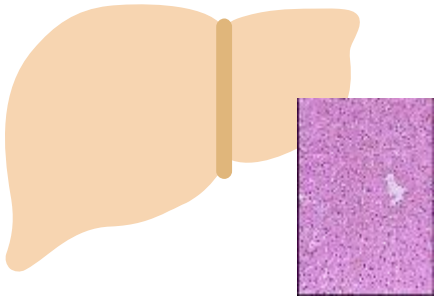
Abnormal ALT may warrant workup for NAFLD,
but is not sensitive to confirm, rule out, or characterize NAFLD

1. Browning. Hepatology. 2004;40:1387. 2. Dyson. Frontline Gastroenterol. 2014;5:211.
3. Mofrad. Hepatology. 2003;37:1286. 4. Younossi. Am J Gastroenterol. 2020;00:1.

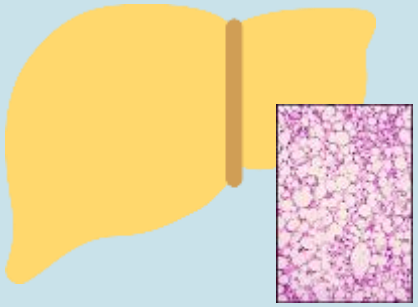
Identifying NAFL: Ultrasound

NAFLD

Normal Liver

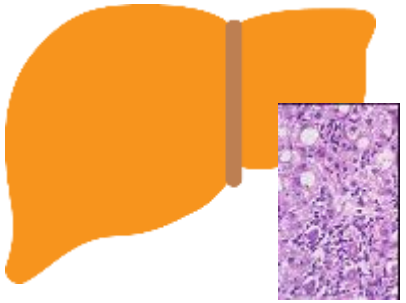


Steatosis
"NAFL"



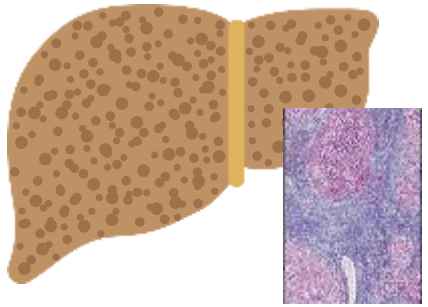
Fatty liver with trivial or no inflammation and no hepatocyte ballooning

Steatohepatitis
"NASH"



Fatty liver with significant inflammation and hepatocyte ballooning

Cirrhosis



Increasing fibrosis leading to cirrhosis, hepatocellular carcinoma

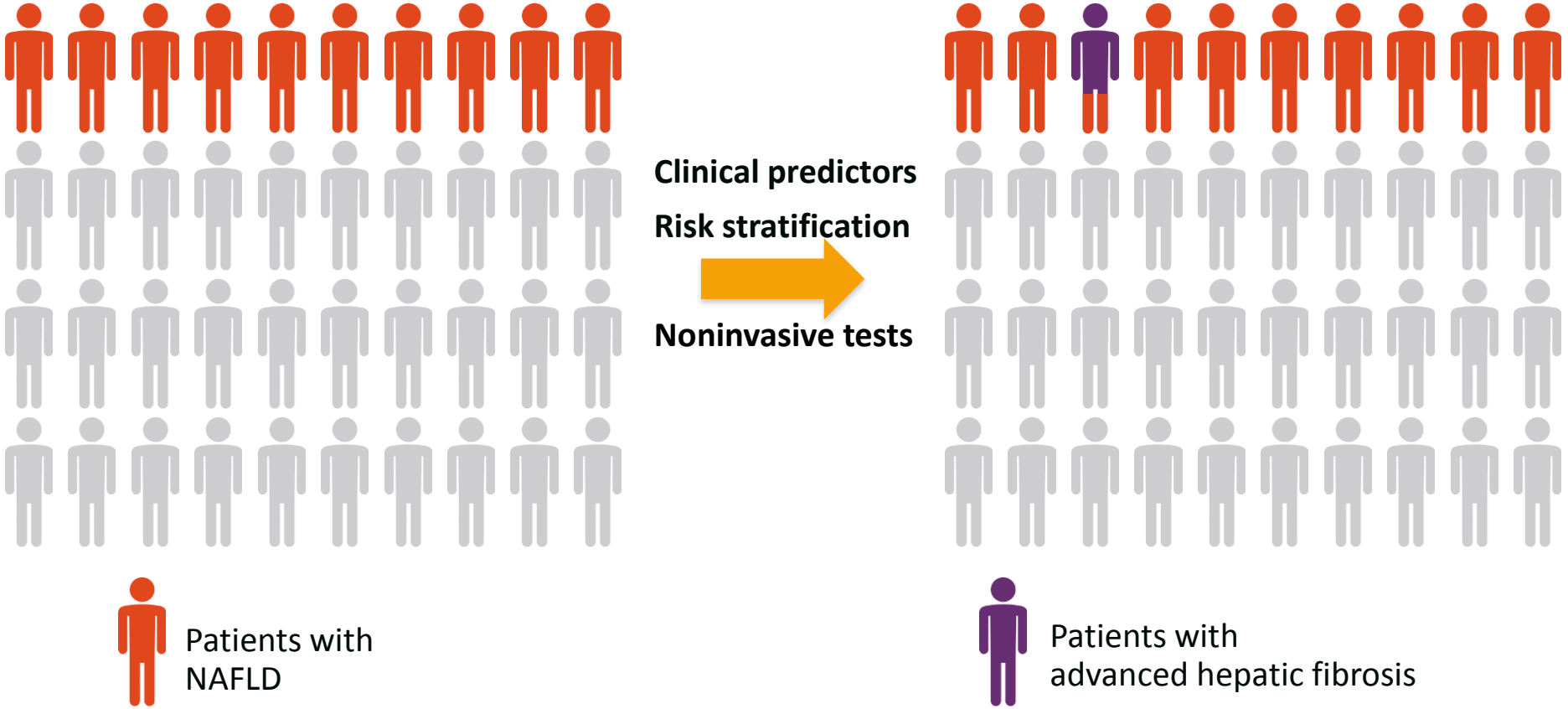
Ultrasound can identify fatty liver (steatosis),
but cannot distinguish steatosis vs NASH vs fibrosis/early cirrhosis

1. Younossi. J Hepatol. 2019;70:351. 2. Kabbany. Am J Hepatol. 2017;112:581.

Risk Stratifying NAFLD:
Tools to Identify Significant or Advanced Hepatic Fibrosis

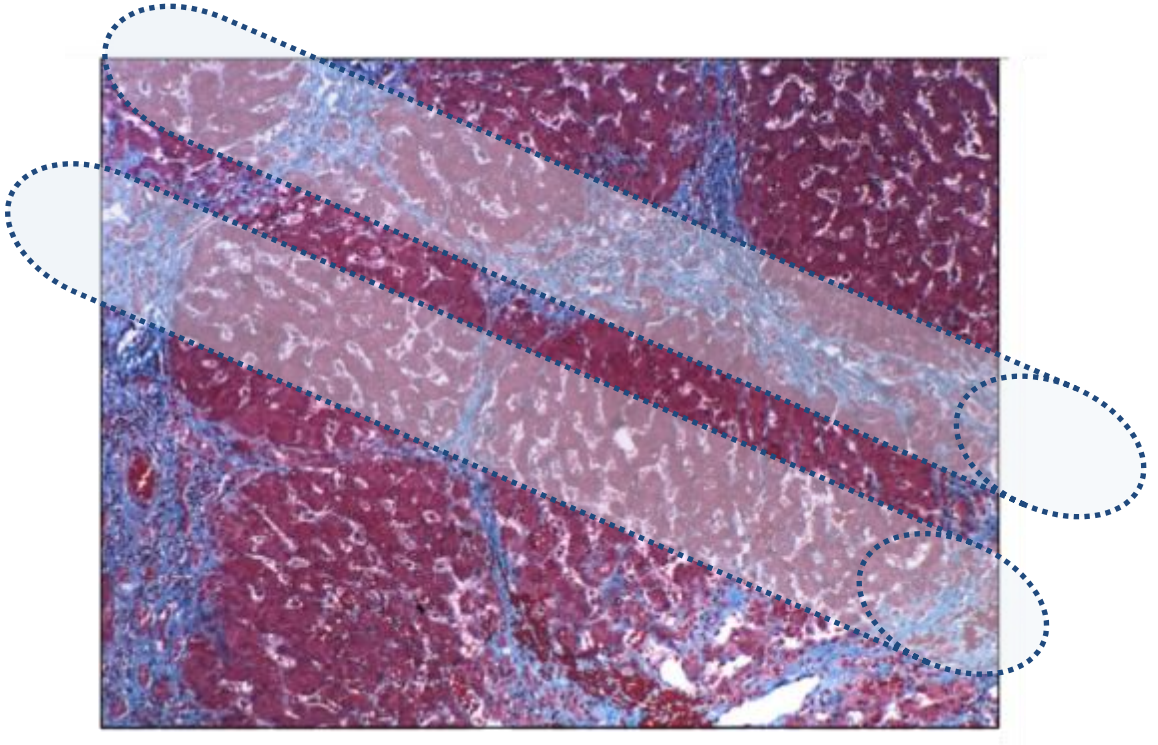
Identifying Advanced Hepatic Fibrosis

Need to identify individuals at risk of progression BEFORE bad outcomes occur



Liver Biopsy: The Imperfect Gold Standard

- **Limitations**
  - Invasive
  - Painful
  - Expensive
  - Morbidity/mortality
  - Sampling variability
  - Observer variability
  - Expertise to perform
  - Impractical for population screening



Sampling variability:
Same biopsy may give
2 different grades of liver fibrosis

Rockey. Hepatology. 2009;49:1017. Kleiner. Hepatology 2005;41:1313.

Liver biopsy

Liver biopsy is essential for the diagnosis of NASH

- Clinical, biochemical or imaging measures cannot distinguish NASH from steatosis

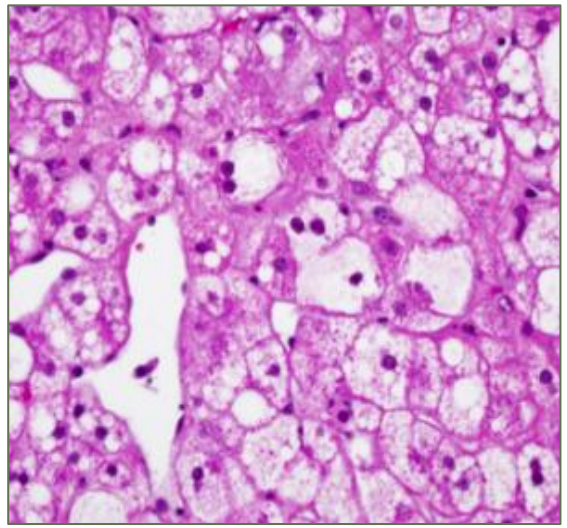
NAFL encompasses

- 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

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

Commonly Used Noninvasive Tests

Clinical or Laboratory Scores

Simple

- Fibrosis-4 (FIB-4)[1,2]
- NAFLD fibrosis score[1,2]
- AST/platelet ratio index[1]

Proprietary

- Enhanced Liver Fibrosis Test[1] (not available in US)
- NIS4
- ADAPT/Pro-C3[3] (not available in US)
- *FibroSure*[1]
- Hepascore

Imaging

Elastography

- Transient elastography (eg, *FibroScan*)[1,2]
- 2D shear wave elastography[4]
- Magnetic resonance elastography[1]
- Corrected T1 (*Liver MultiScan*)[5,6]
- MRI-PDFF[7]
- FAST score[8]

1. EASL. J Hepatol. 2015;63:237. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Daniels. Hepatology. 2019;69:1075.
4. Sigrist. Theranostics 2017;7:1303. 5. Jayaswal. AASLD 2018. Abstr. 1042. 6. Jayaswal. Liver Int. 2020;40:3071.
7. Idilman. Radiology. 2013;267:767. 8. Newsome. Lancet Gastroenterol Hepatol. 2019;[Epub].

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

Non-invasive assessment of **steatosis**

- ✓ Steatosis should be documented whenever NAFLD is suspected
- ✓ **Ultrasound is the preferred first-line diagnostic procedure** for imaging of NAFLD
- ✓ Whenever imaging tools are not available or feasible, serum biomarkers and scores are an acceptable alternative for the diagnosis of steatosis
- ✓ A quantitative estimation of liver fat can only be obtained by **H-MRS**. This technique is of value in clinical trials and experimental studies, but is expensive and not recommended in the clinical setting

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

Clinical or Laboratory Scores

Commonly Used Noninvasive Tests

Clinical or Laboratory Scores

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- Transient elastography (eg, *FibroScan*)[1,2]
- 2D shear wave elastography[4]
- Magnetic resonance elastography[1]
- Corrected T1(*Liver MultiScan*)[5,6]
- MRI-PDFF[7]
- FAST score[8]

- Good negative predictive value for **ruling out** fibrosis
- Calculators freely available on the Internet

1. EASL. J Hepatol. 2015;63:237. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Daniels. Hepatology. 2019;69:1075.
4. Sigrist. Theranostics 2017;7:1303. 5. Jayaswal. AASLD 2018. Abstr. 1042. 6. Jayaswal. Liver Int. 2020;40:3071.
7. Idilman. Radiology. 2013;267:767. 8. Newsome. Lancet Gastroenterol Hepatol. 2019;[Epub].

NAFLD Fibrosis Score and FIB-4 Score: Online Calculators Easily Interpret Noninvasive Tests

- Based on age, platelet count, AST, ALT ± other lab values

Available at: https://www.mdcalc.com.

Noninvasive Tests Exclude or Determine Advanced Hepatic Fibrosis

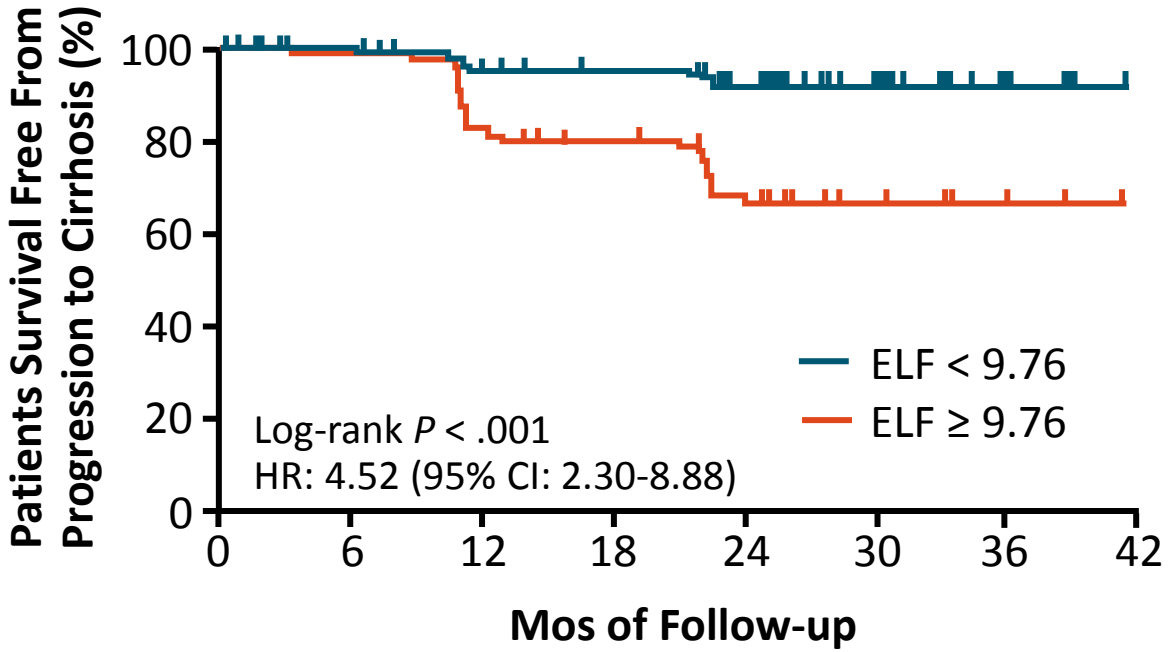
- **FIB-4** recognized by AASLD as useful in identifying patients with a higher likelihood of F3 or F3-F4

Cutoff Scores for Measurement of Advanced Hepatic Fibrosis[1]

1. Vallet-Pichard. Hepatology. 2007;46:32. 2. Alkhouri. Gastroenterol Hepatol (N Y). 2012:8:661. 3. Shah. Clin Gastroenterol Hepatol. 2009;7:1104.

ELF Test in NASH Predicts Progression to Cirrhosis More Accurately Than Biopsy

Progression to Cirrhosis by Baseline ELF



Predictors of Progression to Cirrhosis

Parameter	Adjusted HR (95% CI)	*P* Value
Baseline ELF	3.20 (2.33-4.39)	< .001
Change in ELF	1.60 (1.19-2.16)	< .01
Ishak stage 4 vs 3	0.87 (0.47-1.59)	.64

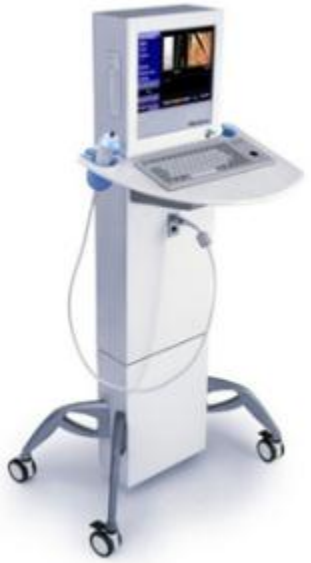
- Optimal threshold of baseline ELF: 9.76 (sensitivity 77%, specificity 66%)
- Higher baseline, greater change in ELF associated with increased risk of progression to cirrhosis

Harrison. AASLD 2017. Abstr 2122.

Imaging

Vibration-Controlled Transient Elastography

- Measures 1D velocity of low-frequency shear wave
- Directly related to tissue stiffness (fibrosis)
  - The stiffer the liver, the faster the shear wave propagates
- Quick, bedside test (~ 5 mins)
- Limited by obesity, food intake, operator experience

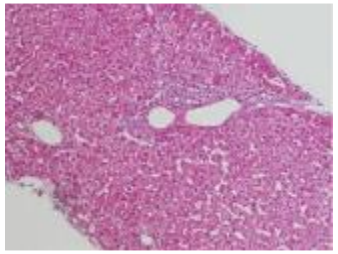


Sigrist. Theranostics 2017;7:1303.

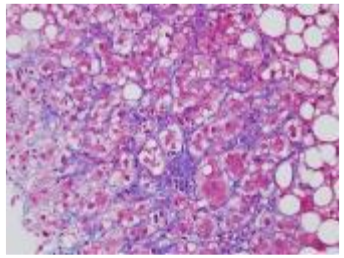
VCTE for NASH Fibrosis

Fibrosis Stage

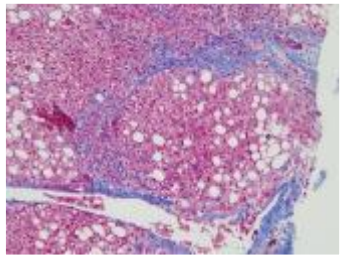
F0: Normal



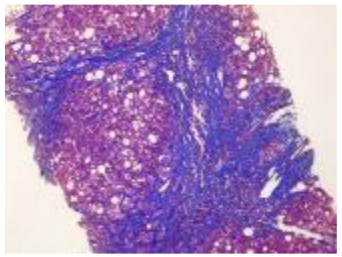
F1/2: Perisinusoidal ± Portal



F3: Bridging Fibrosis



F4: Cirrhosis



***FibroScan* Liver Stiffness (kPa)[1,2]**

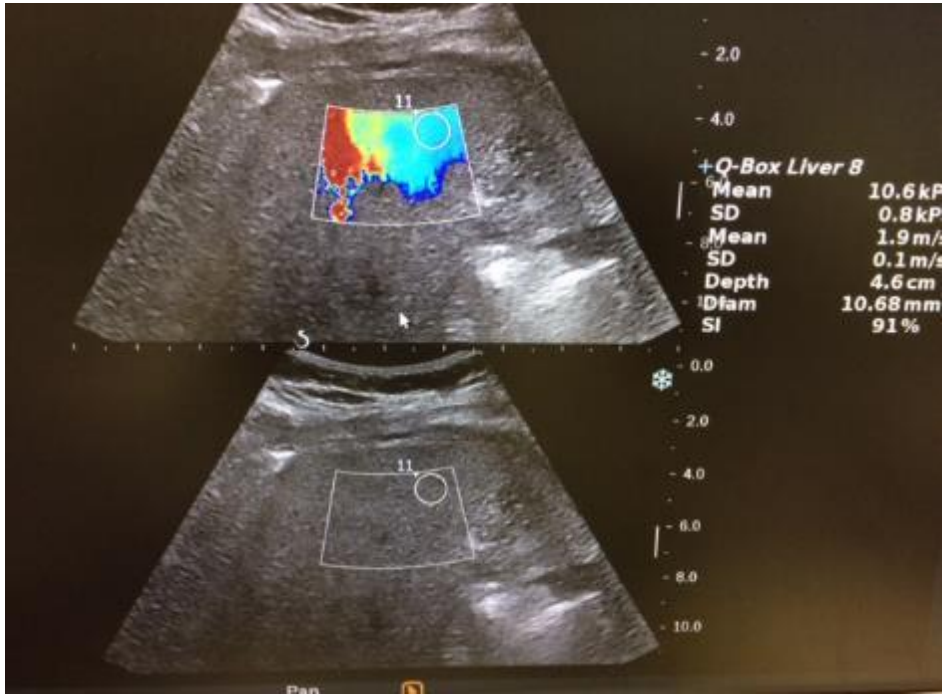
Increasing liver stiffness

- Most reliable in **ruling out advanced hepatic fibrosis (NPV > PPV)**
  - Fibrosis unlikely with low value (< 6 kPa)
- Higher values increase likelihood of more severe fibrosis, predicts risk of decompensation and complications
- **Overestimation of fibrosis can occur** in cases of hepatitis, cholestasis, liver congestion, obesity, and if mass lesions are present in the liver
- Correlates well with portal pressure (20+ kPa)

1. Vuppalanchi. Hepatology. 2018;67:134. 2. Hashemi. Caspian J Intern Med. 2016;7:242.
3. Kemp. Australian Family Physician. 2013;42:468. 4. Robic. J Hepatol. 2011;55:1017.

2D Shear Wave Elastography

- Ultrasound system, using real-time SWE map of liver elasticity to determine liver stiffness
  - 2D SWE color-coded map superimposed on B-mode image confirms readings are in liver, not in nearby vessels or kidneys
- May require radiologist/sonographer
- Liver elasticity measurements can be obtained in challenging cases of obesity

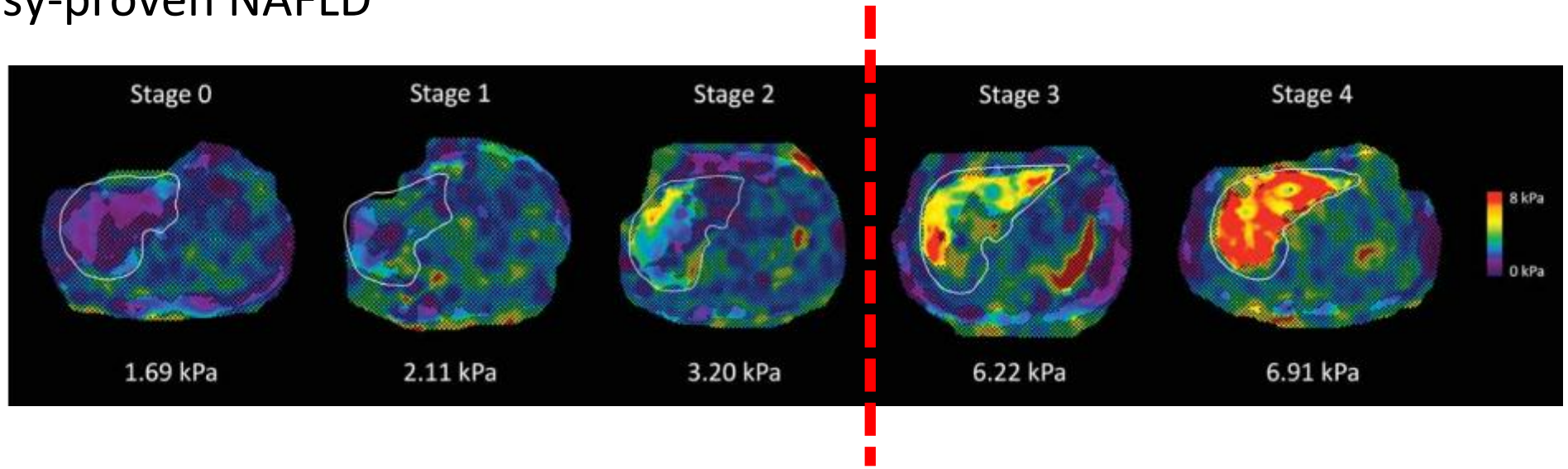


Cutoff for Detecting Advanced Hepatic Fibrosis ≥ F3 in HCV[2]	Sensitivity	Specificity	AUROC
2D-SWE stiffness > 8.7 kPa	.973	.951	.98

1. Sigrist. Theranostics 2017;7:1303. 2. Ferraiolo. Hepatology 2012;56:2125.

MRE: Detecting Advanced Hepatic Fibrosis in NAFLD

- Prospective, cross-sectional analysis of 2D MRE in N = 117 patients with biopsy-proven NAFLD



Cutoff for Detecting Advanced Hepatic Fibrosis ≥ F3	Sensitivity	Specificity	AUROC
MRE stiffness > 3.63 kPa	.86	.91	.924

Loomba. Hepatology. 2014;60:1920.

Common Imaging Tests for Hepatic Fibrosis: Summary

Imaging	Comments
Vibration-controlled transient elastography – *FibroScan*	▪ Can be point of care ▪ **Most reliable in ruling out advanced hepatic fibrosis (great NPV)**
MR elastography/MR spectroscopy/ *LiverMultiScan*	▪ Requires radiology referral ▪ Most accurate of the imaging modalities
2D shear wave elastography	▪ May require radiology referral but can be point of care with minimal training

These imaging tests measure liver stiffness, which is an indirect measure of hepatic fibrosis and not hepatic fat content

Summary

1. **Identify** NAFLD
2. If NAFLD/NASH is present, **stratify** according to **hepatic fibrosis**
   - A mix of approaches and sequential tests may help rule out or even rule in significant or advanced hepatic fibrosis

- Different approaches to assessing hepatic fibrosis
  - Simple and proprietary predictive scores quantify **biomarkers** in serum samples that have been shown to be associated with fibrosis stage
  - **Imaging** techniques measure liver stiffness

Thank You for your attention

22 July 2021