Non-Alcoholic Steatohepatitis: Challenges and Opportunities

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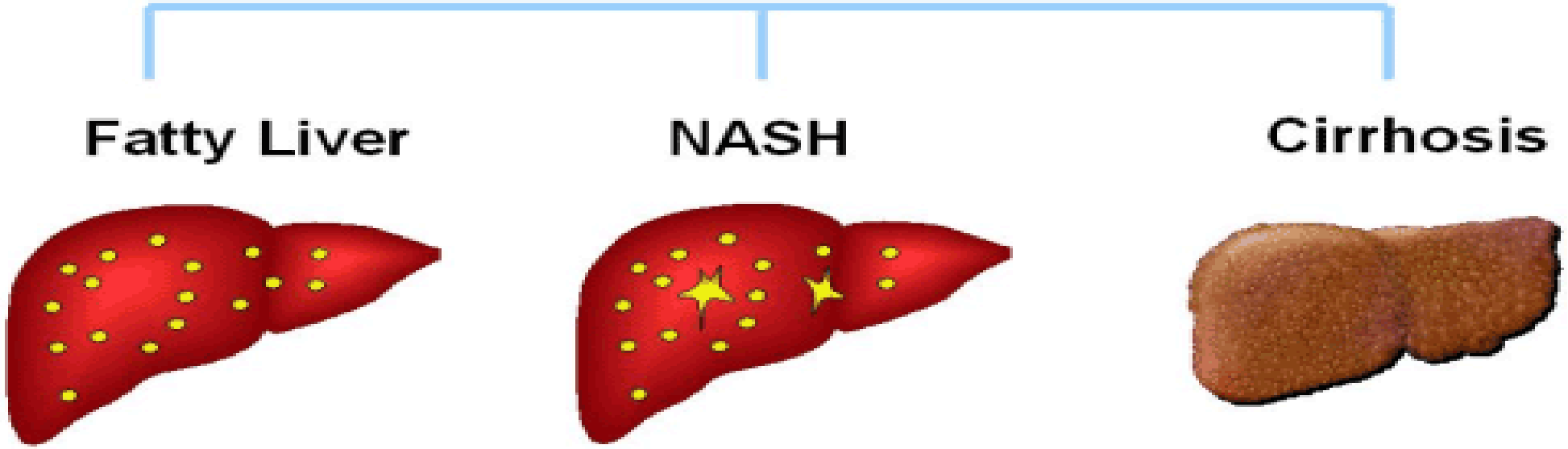
Outline

- Introduction- Definition and Epidemiology
- Challenges
- Opportunities

Definition: NAFLD and NASH

- **Nonalcoholic Fatty Liver Disease (NAFLD)** = Spectrum of disorders characterized by hepatic steatosis in the absence of alcohol consumption (<20g/day)
- **Nonalcoholic Steatohepatitis (NASH)** = more severe end of the spectrum characterized by steatosis, inflammation and fibrosis
- Causes: obesity, metabolic syndrome (Type 2 diabetes), PCOS, medications, malnutrition, celiac disease, Wilson's, mitochondrial disorders, TPN, cystic fibrosis

The Spectrum of NAFLD

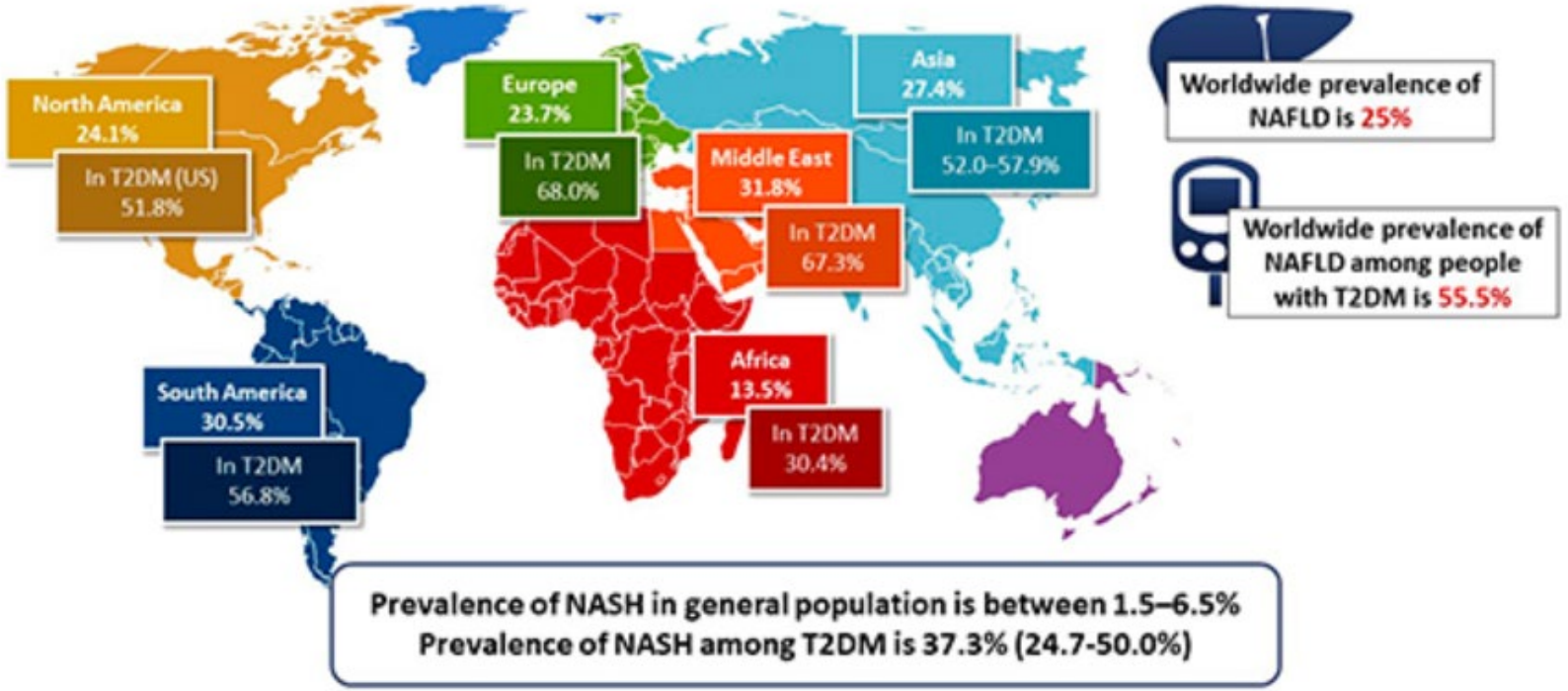


70%
Relatively benign

30%
Can progress to cirrhosis and HCC

Prevalence of NAFLD and NASH

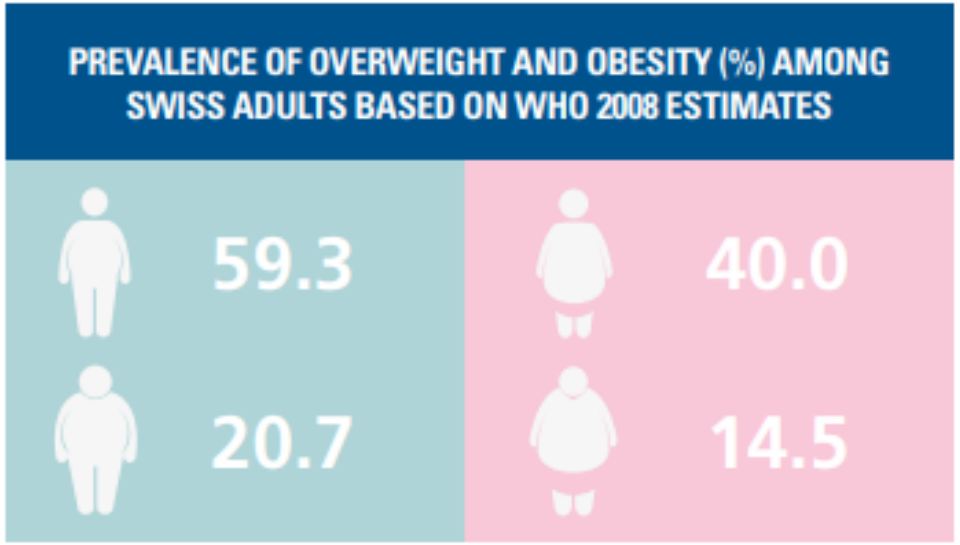
-the other Pandemic



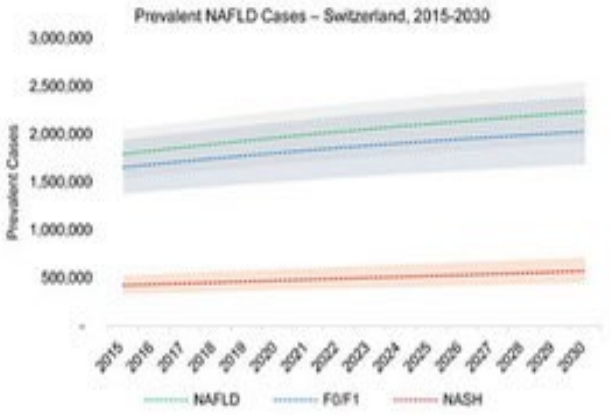
Font: Younossi ZM et al. *Hepatology*. 2016;64:73-84, Younossi ZM. *J Hepatol*. 2019;70:531-544.

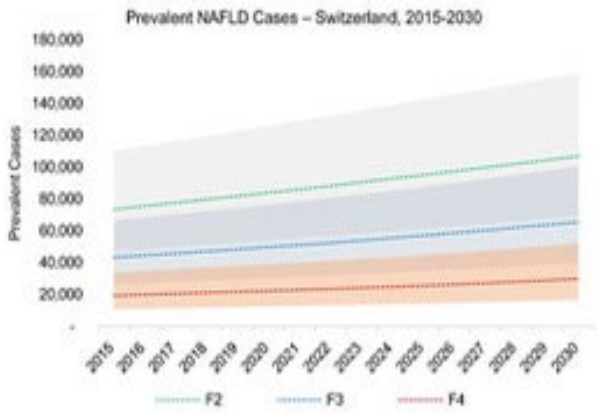
Switzerland

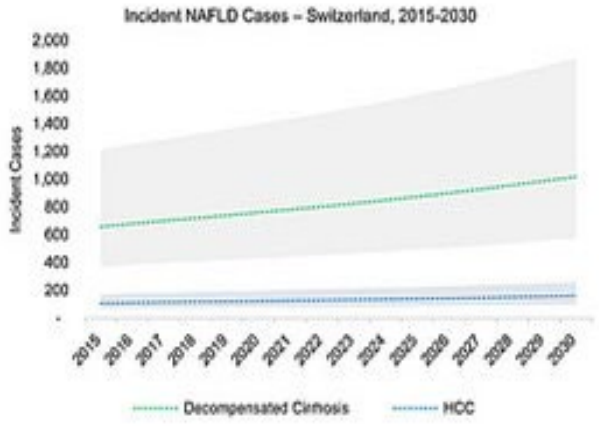
-following global trend



Source: WHO Global Health Observatory Data Repository *(1)*.





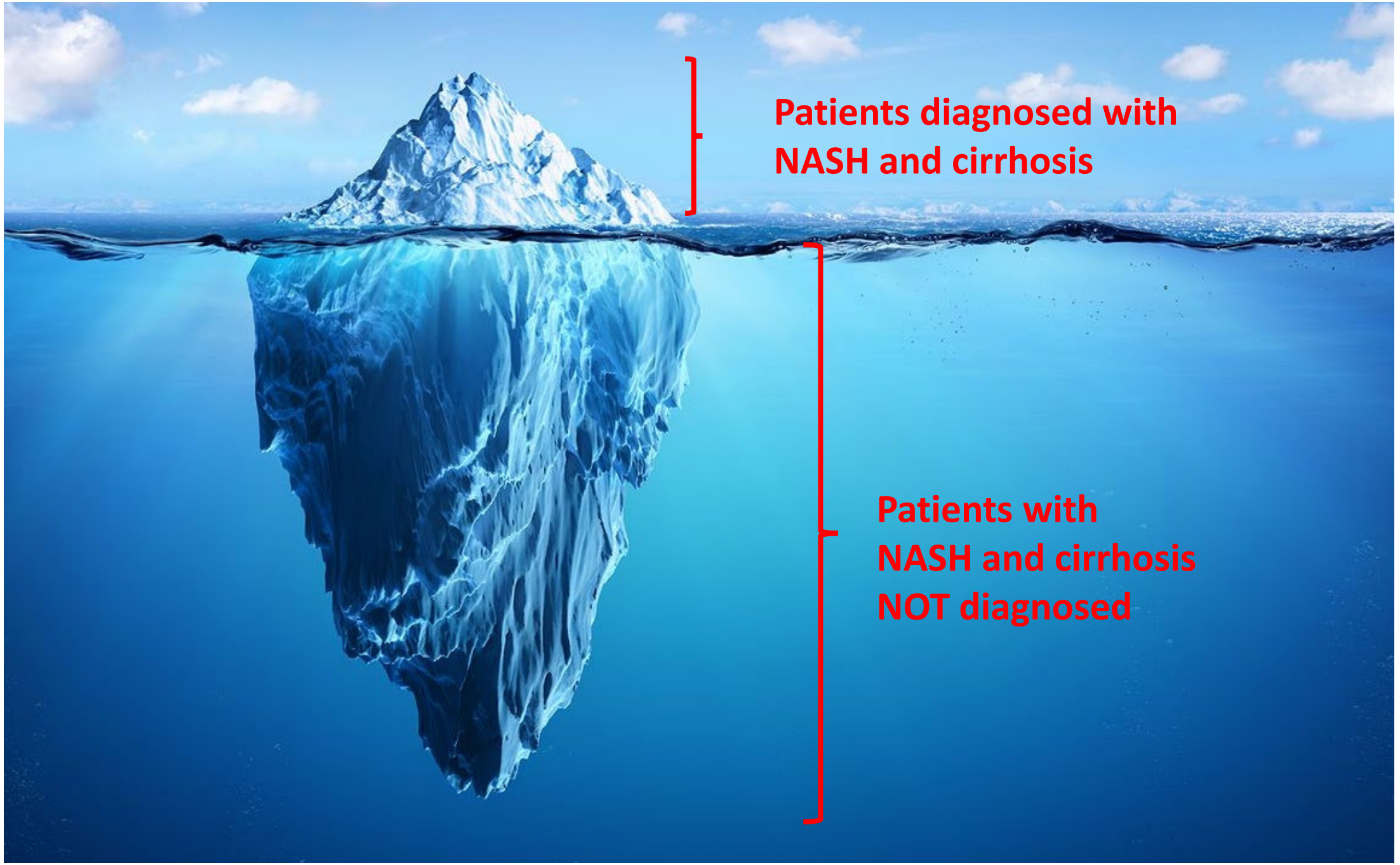


Goossens et al. Swiss Med Wkly. 2019;149:w20152

Challenges

Identification of patients with NASH and fibrosis

- NAFLD Highly prevalent disease- need to be identified by primary care doctors (GPs)
- Only 1/3 of them have NASH- need an easy way to screen and triage patients
- Asymptomatic until very late stage.- presenting to specialists too late


Patients diagnosed with
NASH and cirrhosis
Patients with
NASH and cirrhosis
NOT diagnosed

Opportunities

This is a preventable and reversible disease.

Opportunities

I. Prevention

II. Early Diagnosis and Intervention

III. Screening for complications of late disease

Prevention

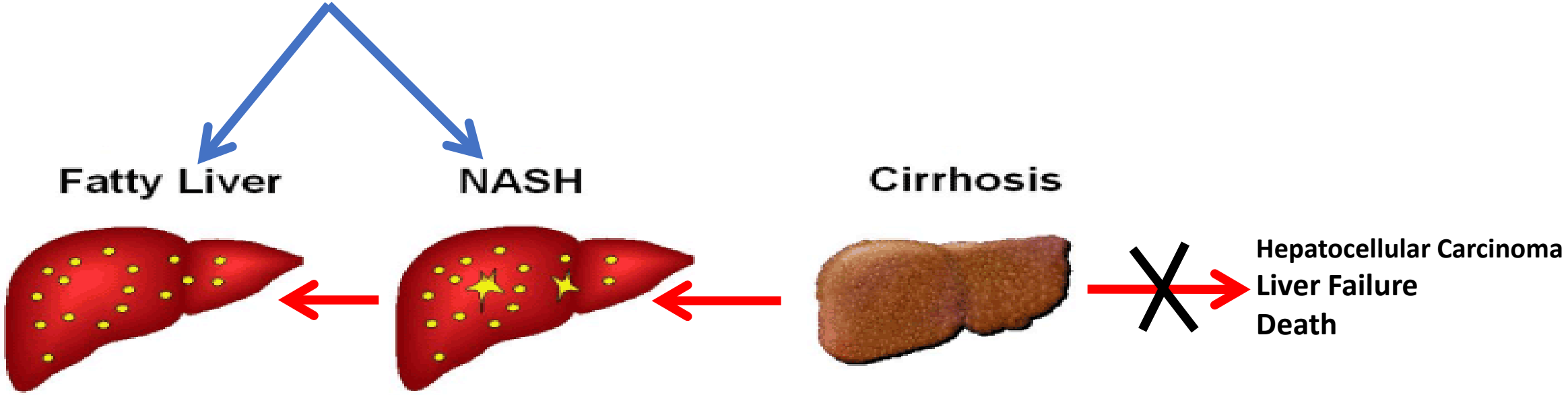
- Public Health Measures to combat both adult and childhood obesity
- Across EU countries, mean childhood obesity rates: 14% boys and 10% of girls aged 7-8 years old.
- These children will go on to develop metabolic syndrome including NASH
- Public Health Measures in Europe to combat childhood obesity have shown signs of decrease in rate of obesity in recent years.

Prevention

- A lot more work needs to be done
- You (doctors and other health professionals) are the strongest voices to advocate for more sweeping public health measures.

Early Diagnosis and Intervention

- To reverse disease or
- To prevent progression
- Ideally we want to diagnose the patient before cirrhosis



Late diagnosis= high mortality

- ~50% of cases of advanced fibrosis from NAFLD are not discovered until presentation for first episode of decompensated cirrhosis
- at which point their five year transplant-free mortality rate is as high as 85%
- Across the world, NASH has emerged as one of the leading indication for liver transplantation.

Tanajewski et al. *BMJ Open*. 2017.
Ratib S et al. *J Hepatol*. 2014.
Schuppan D, NH A. *Lancet*. 2008;371(9615):838-851.

How do we identify patients with NASH early when this disease is asymptomatic?

Answer:

By screening high risk populations

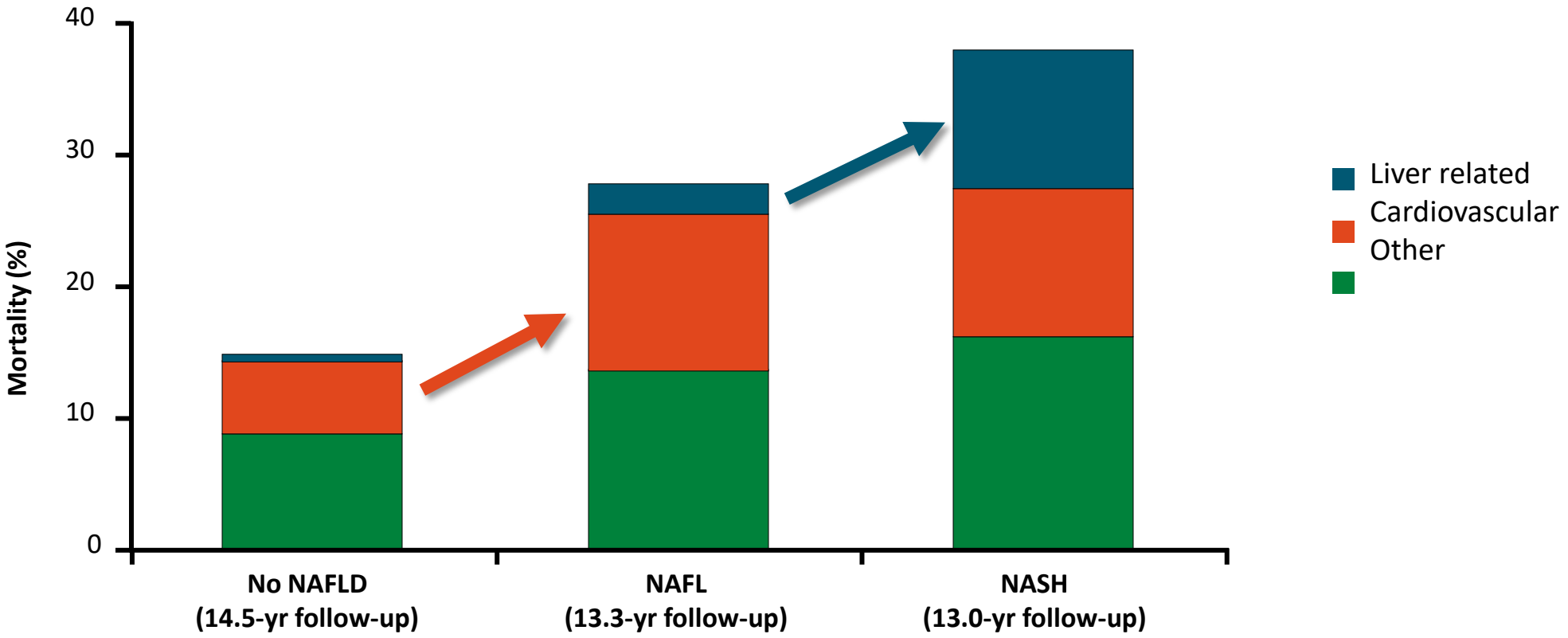
DM2: Strongest Risk Predictor

- strongest risk factor for the development of NASH, advanced fibrosis/cirrhosis, Hepatocellular Carcinoma (HCC) and mortality.
- ~70% of DM2 patients have underlying NAFLD
  - Among those, 37% have NASH and 17% will develop advanced fibrosis.
- NAFLD associated with more retinopathy and nephropathy
- Higher hgb A1C associated with more liver fibrosis
- NASH associated with more nephropathy and retinopathy

Koehler et al. Hepatology 2016;63:138-147
McPherson et al. J Hepatol 2015;62:1148-1155
Younossi et al. Hepatology 2015;62:1723-1730
Stepanova M et al. Dig Dis Sci 2013;58:3017-3023

Anstee et al. Nat Rev Gastroenterol Hepatol 2013;10:330-344
Williamson et al. Diabetes Care 2011;34:1139-1144
Targher et al. Diabetes Care 2007;30:1212-1218
Younossi ZM et al. J Hepatol 2019;71:793-801

All-Cause Mortality Risk for DM2 Associated With NAFL and NASH



Bril. Endocrinol Metab Clin N Am. 2016;45:765.

European Association for the Study of Diabetes

- All individuals with steatosis should be screened for features of MetS, independent of liver enzymes.
- In subjects with obesity or MetS, screening for NAFLD by liver enzymes and/or ultrasound should be part of routine work-up.
- In high-risk individuals (age >50 years, T2D, MetS) case finding of advanced disease (i.e. NASH with fibrosis) is advisable

EASL-EASD-EASO. Diabetologia. 2016 Jun;59(6):1121-40.

Screening Patients with DM2 SUMMARY

- Patients with DM2 are at high risk for NASH and advanced fibrosis and HCC as well as cardiovascular and liver-related morbidity and mortality
- EASD guideline recommends that patients with DM2 should be screened for NASH and advanced fibrosis

Assessing NAFLD-How?

- Liver biopsy- too invasive, not practical
- Fibrosis staging- many commercially available non-invasive markers of fibrosis
  - Serum (usually combined with some clinical variables)
  - Elastography (ultrasound, vibration-controlled transient elastography, MR)
  - These markers do not make biopsies obsolete but does save a lot of patients from biopsies

Problem with ALT

- Most lab “normal” ALT range inaccurate
- True normal ALT≤19 for women, ≤30 for men
- “Normal” ALT does NOT preclude NAFLD or severe disease
- Also, ALT can normalize after progression to cirrhosis (“burnt out” liver)

Portillo-Sanchez et al. J Clin Endocrinol Metab, June 2015, 100(6):2231–2238

Clinical Scoring Systems

- Free formulas using readily available variables (clinical variables and labs such as AST, ALT, platelets)
  - NFS, FIB-4, APRI
- Give you a low risk cut off, high risk cut off and indeterminate range
- Problem is a low negative predictive value in high risk groups like DM2 (NPV for DM2 in our data 63.5% vs. 84.8% in non-DM2)

Elastography (Ultrasound, MRI, vibration controlled

- Many different modalities- MRI, ultrasound, vibrations controlled (Fibroscan), Velacur, etc.
- All assess liver stiffness as a marker of liver fibrosis
- Some are point of care- to aid same day clinical management

Screening all DM2 patients

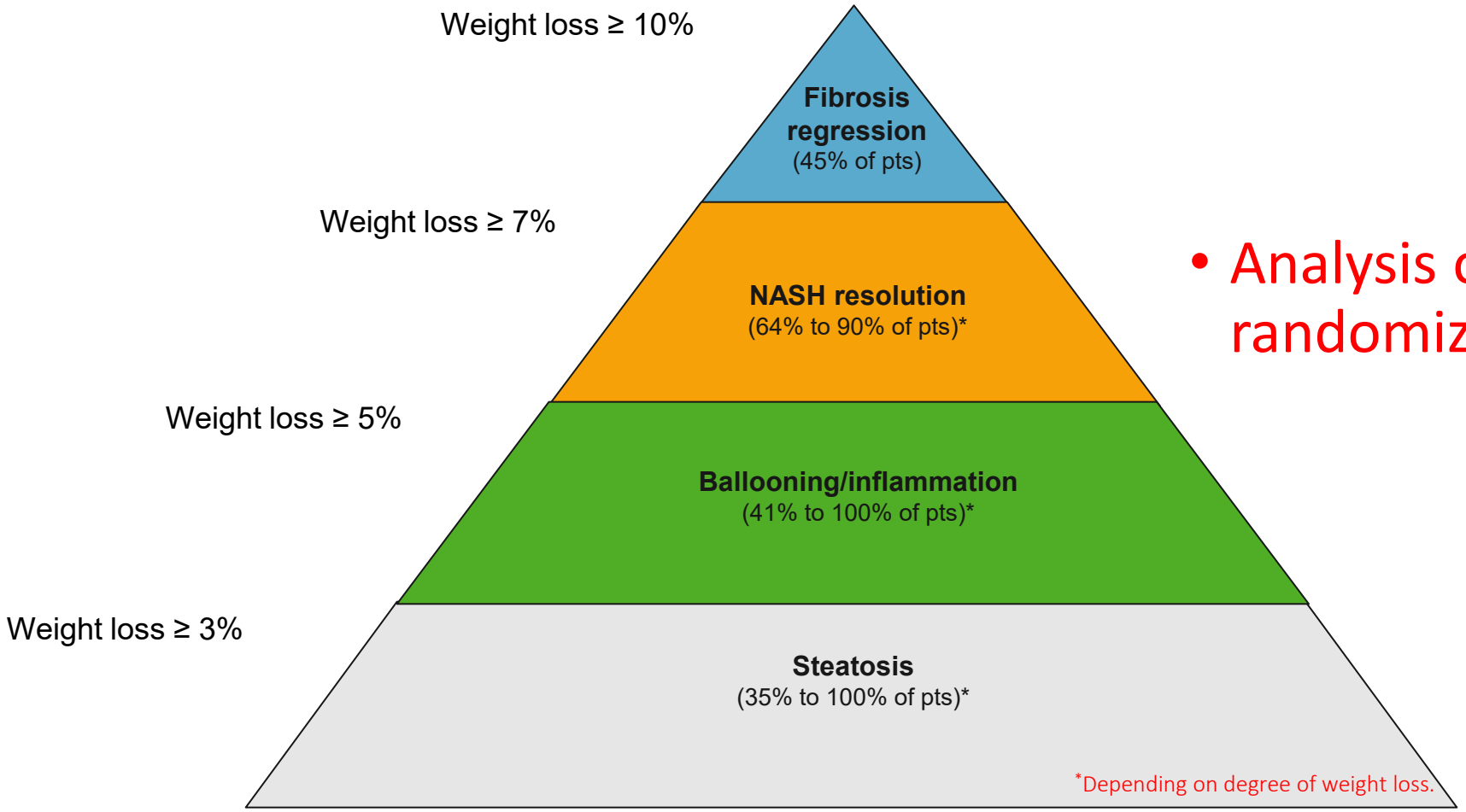
- Either with elastography-based modality if readily available

- If not, then can use a stepwise algorithm with a clinical scoring system like FIB-4, followed by elastography in patients with high or indeterminate risk score

Interventions

- Weight loss leads to reversal of NASH, NAFLD and fibrosis regression
- More aggressive cardiovascular risk reduction (e.g. statin)
- Tighter glycemic control
- Emerging data on GLP-1 agonists as promising treatment for NASH, but awaiting more data from many clinical trials
- A large number of drugs in development

Weight Loss Is Still the Best Treatment



- Analysis of data from 4 randomized studies

Hannah WN, et al. Clin Liver Dis. 2016;20:339-350.

Screening for Complications of Late Disease

- Patients with advanced fibrosis (Stage 3-4)
- Screen for Hepatocellular carcinoma (HCC) to identify HCC at earlier, curable stages
- Screen for varices as can treat patients with Beta blockers to prophylax against variceal hemorrhage

Hepatocellular carcinoma (HCC)

- NASH-2nd most common cause of HCC
- Incidence in the US has increased over threefold in the past few decades
- Most present at an advanced stage and receive either no treatment or only palliative treatment
- One of the most lethal cancer with an overall 5-year survival of ~15%

Stepanova M, Younossi ZM. Clin Gastroenterol Hepatol 2012; 10:646.

NAFLD and HCC

- NAFLD patients less likely to receive surveillance for HCC.
- NAFLD HCC present at more advanced stages (less treatable)
- Obesity and diabetes mellitus are independent risk factors of HCC
- Screen with liver imaging every 6 months (+ AFP)

Mittal et al. *Clin Gastroenterol Hepatol*. 2015; 13(3): 594–601

Variceal hemorrhage

- In the past, the mortality rate of a single variceal hemorrhage was 30%
- Survival has improved with modern techniques for controlling variceal hemorrhage, mortality rates remain high (15 – 20% 30-day mortality)
- Screen with endoscopy and prophylaxis with beta blockers or band ligation if high risk.

Key Learning Points

- There is a pandemic of NAFLD with 1 in every 4 people affected worldwide
- NASH is the more severe form which can progress to cirrhosis, hepatocellular carcinoma and liver failure.
- The challenge is identifying patients with NASH and cirrhosis early in a very prevalent disease.
- Opportunies exist for us to improve on: prevention, early diagnosis and intervention as well as preventing late complications.

Key Learning Points

- Prevention requires a global public health approach
- Early diagnosis and intervention requires screening high risk patients such as patients with DM2 for NASH and advanced fibrosis (regardless of ALT)
- Weight loss and glycemic control are cornerstones of treatment currently.
- Screening for HCC and varices in patients with advanced fibrosis can decrease mortality.