American Gastroenterological Association
Preparing for the NASH Epidemic
Call to Action Virtual
July 10th 2020

Future Directions: What Are We Expecting? Screening, Risk Stratification and Treatment

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Future projections on the epidemic of NAFLD worldwide by 2030

United States: faste
of decompens
Estimated 56% incr
cases in 2016 to 27

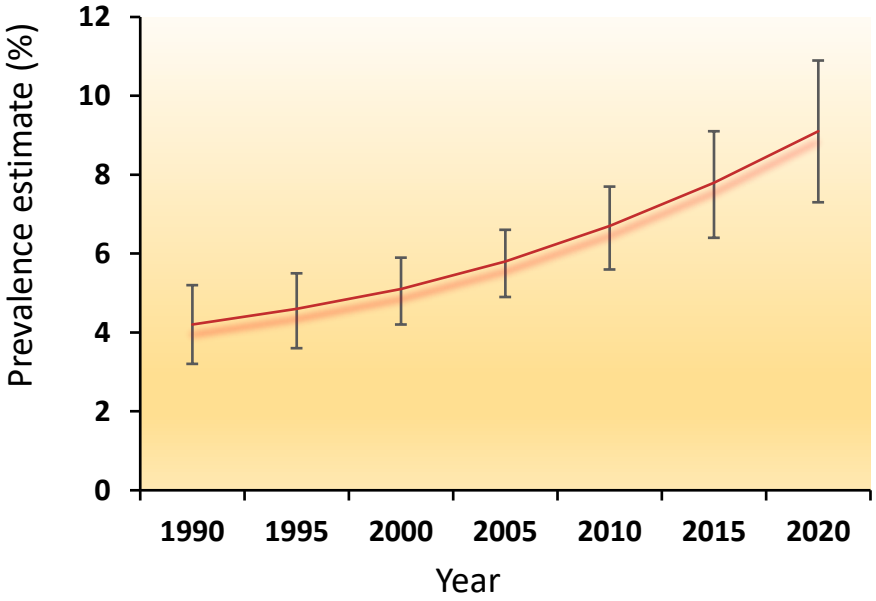
est overall increase in
nts with NAFLD
29% increase from
016 to 314.6 million in
2030

- Modelling s
- **advanced c**
- **NASH preva**
- **Liver-relate**

increase in

louble

Rising prevalence of overweight in children aged 0–5 years (144 countries)



Overweight/obesity in childhood/young adulthood increase risk of liver-related mortality later in life

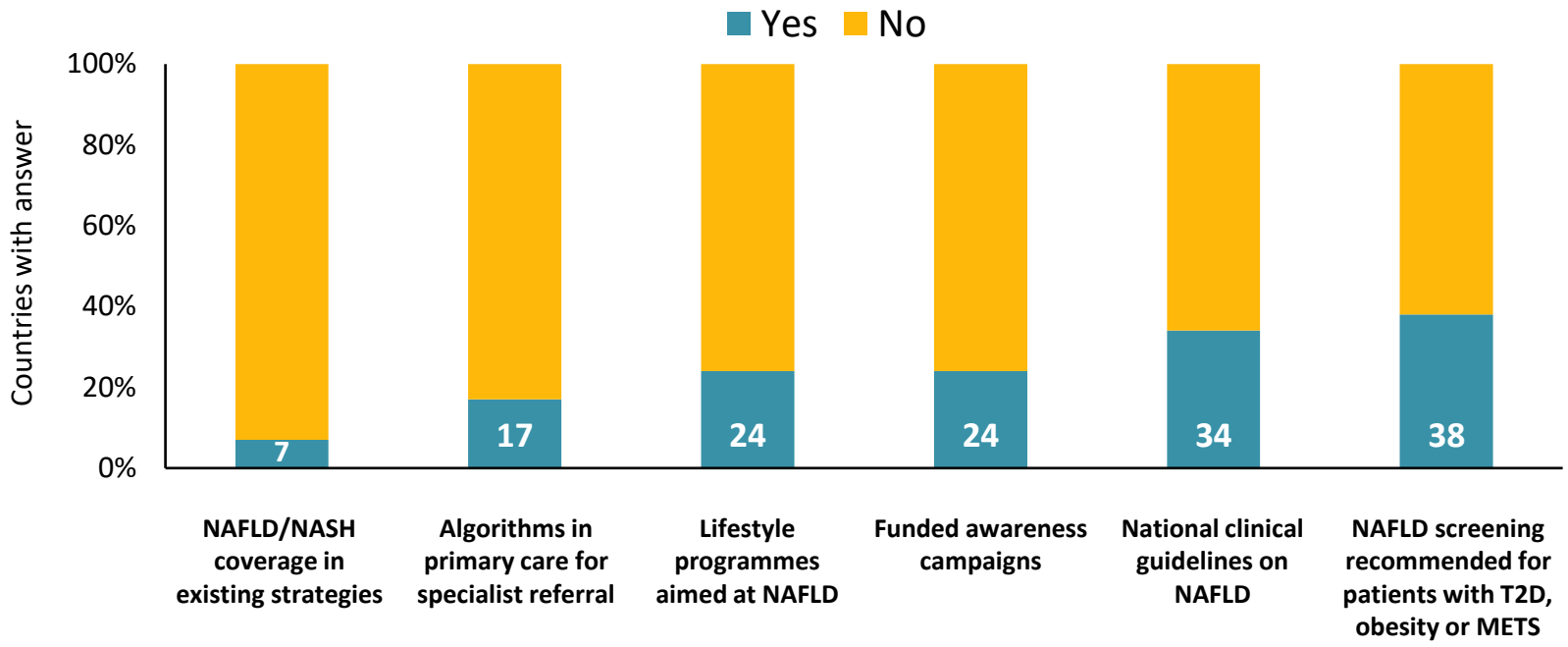
Onis M et al. Am J Clin Nutr 2010, Hagström H et al. J Hepatol 2016

M, million; NAFLD, non-alcoholic fatty liver disease
*China, France, Germany, Italy, Japan, Spain, UK, and US modelled from 2016 to 2010
Estes C et al. J Hepatol 2018;67:896–904

The public health response to NAFLD in 29 European countries is insufficient

Does your country have any written national NAFLD/NASH strategy/action plan?

100% NO

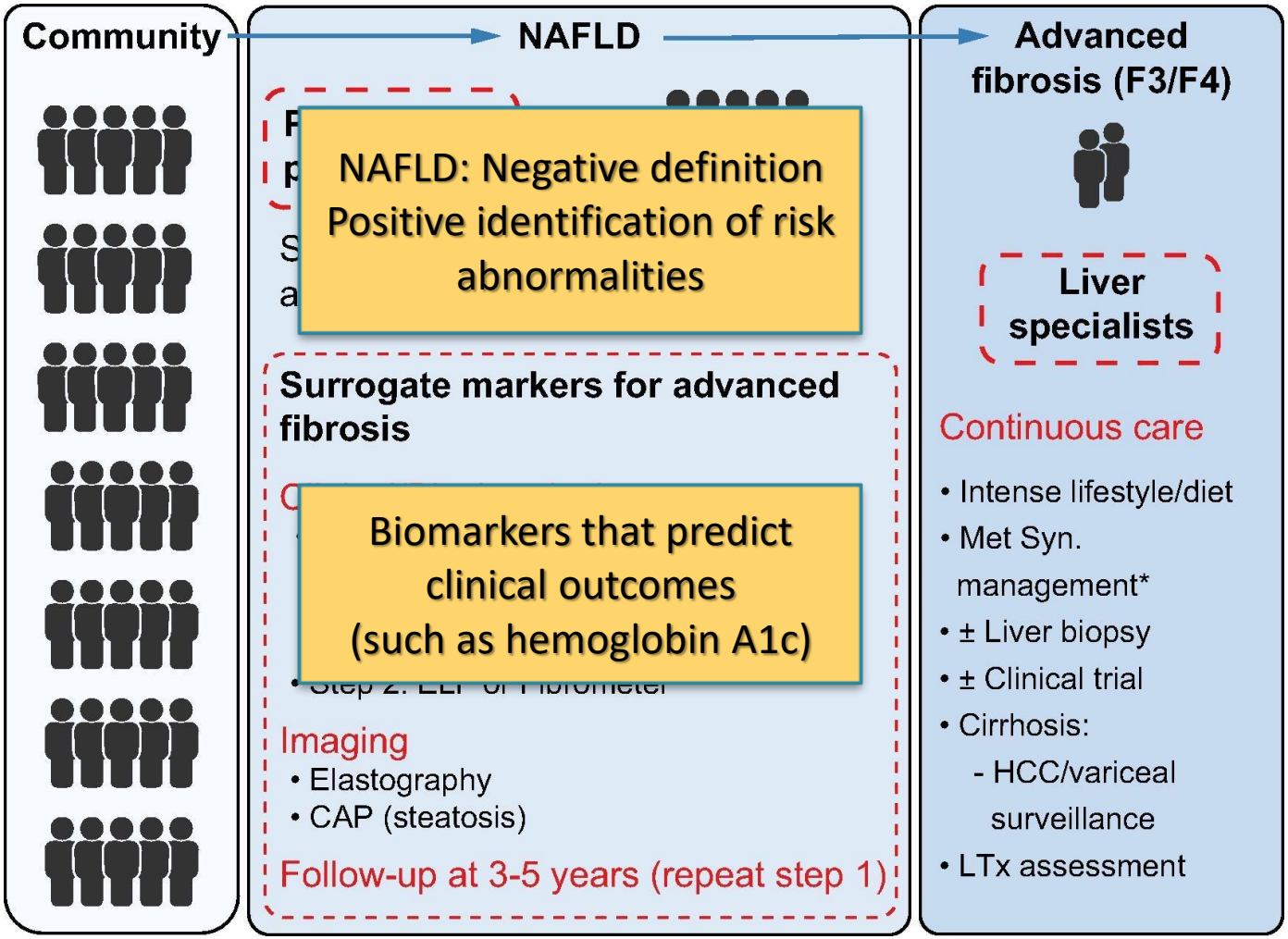


Lazarus JV et al J Hepatol 2020

NAFLD Guidelines

CPG	Fist line diagnosis-test	When GPs refer patients to hepatologist?	Non invasive Tests
AASLD (US)	• **Not clear in the guideline** • Routine screening for NAFLD in high-risk group in not recommended.	• **Not clear in the guideline**	• Diagnosis for NASH: Liver biopsy • Assessment for fibrosis: **NFS or FIB-4**
EASL (EU)	• Ultrasound + Liver enzymes for patients with risk factors	• Refer to specialist when patient with abnormal liver enzymes or medium/high risk fibrosis markers	• Diagnosis for NASH: Liver biopsy • Assessment for fibrosis: **NFS or FIB-4**
World Gastro Organisation J Clin Gastroenterol. 2014	• Ultrasound + Liver enzymes for patients with risk factors	• **Not clear in the guideline**	• Diagnosis for NASH: Liver biopsy
NICE (UK)	• Ultrasound + Liver enzymes for patients with risk factors • But routine liver function blood tests are not sensitive and US is not cost effective	• Refer adults with advanced liver fibrosis to a hepatologist. • Refer children with suspected NAFLD to a pediatric specialist in hepatology.	• Assessment for advanced fibrosis: **Enhanced liver fibrosis (ELF)** (every 2-3 year)

Primary to secondary care interface in patients with NAFLD



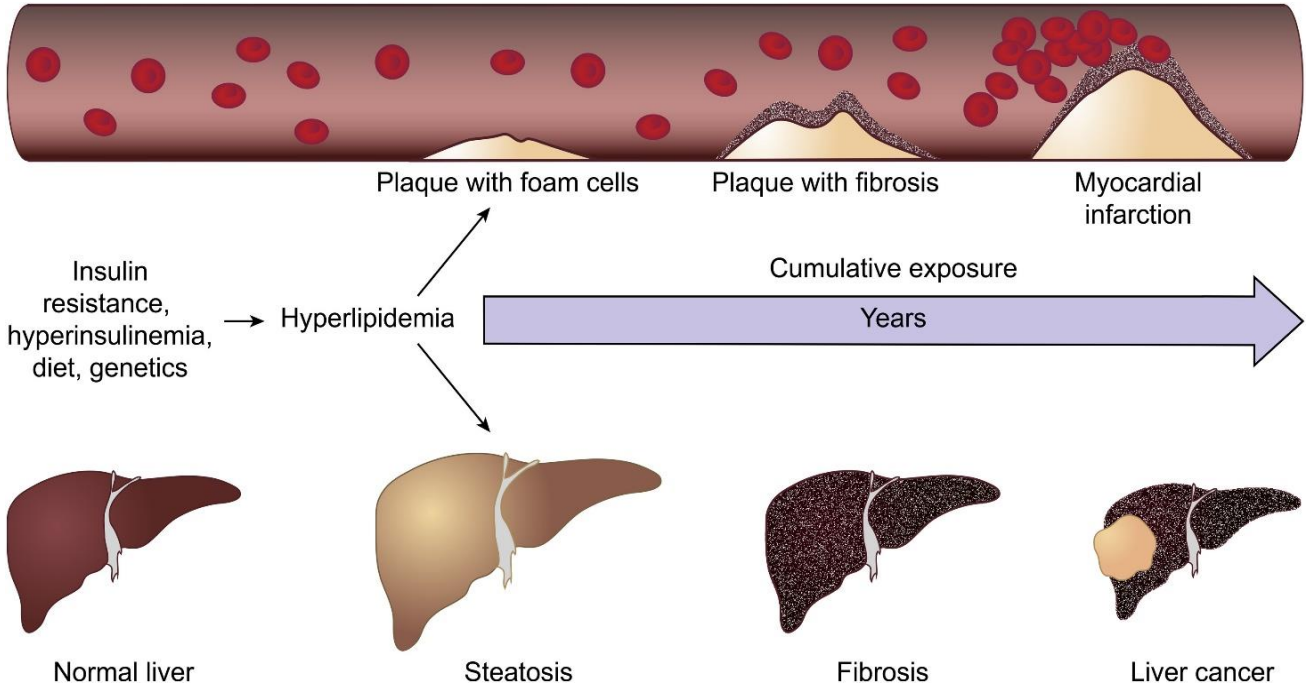
Marchesini&Armstrong J Hepatol 2019

Risk stratification: biomarkers

- **Main barriers to the identification of a reliable biomarker:**
  - disease heterogeneity
  - dynamic nature of liver damage

- **Main needs for effective risk stratification:**
  - Large human cohorts to provide longitudinal data on clinical course of patients and outcomes, particularly in the transition from childhood through adolescence to adulthood
  - Extending research on the dynamic range of disease (eg fibrosis stage) and clarifying the bidirectional changes
  - Establishing collinearity in organ status (liver, heart and pancreas) with disease progression

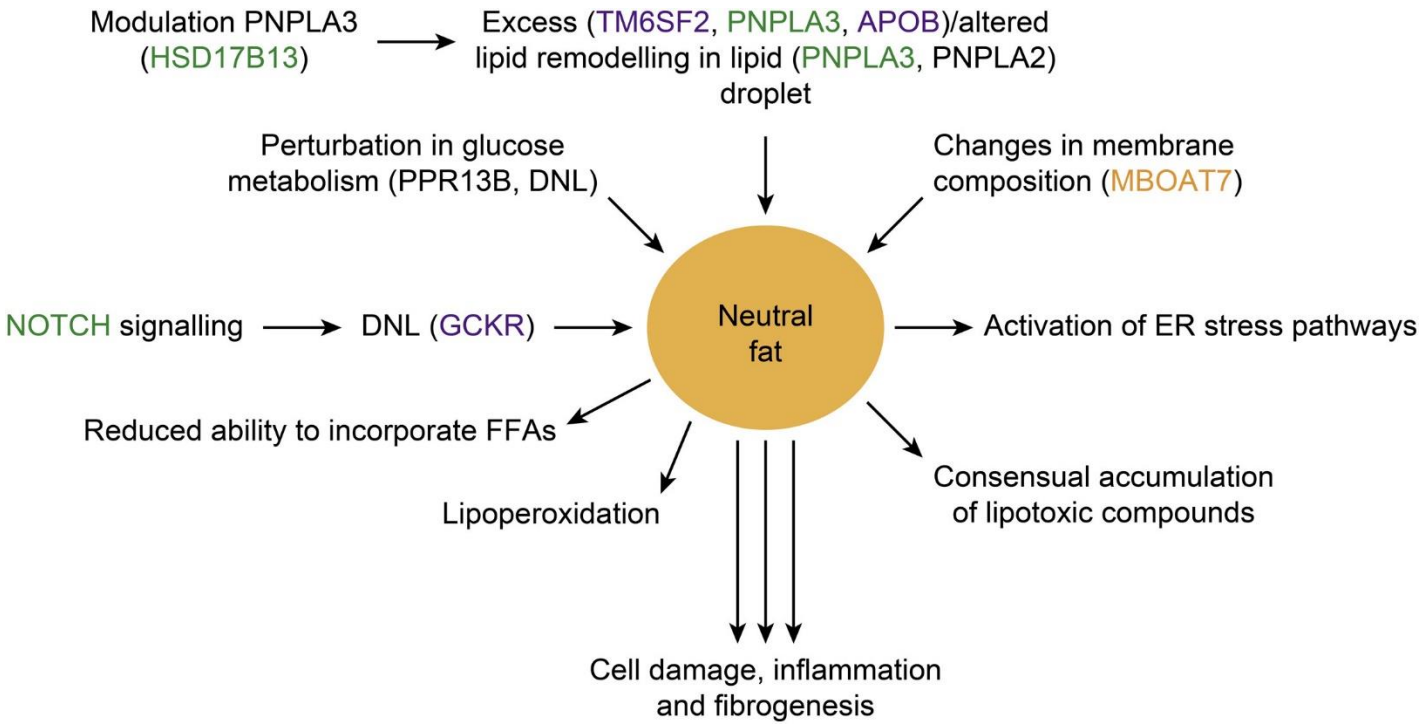
Parallel between the Development and Progression of Atherosclerosis and NAFLD



- NASH, atherosclerosis and T2DM share many common pathogenic features which are expected to drive common diagnostic tools
- Therapies that will beneficially affect all of these end- organ diseases will emerge as the first- line treatments

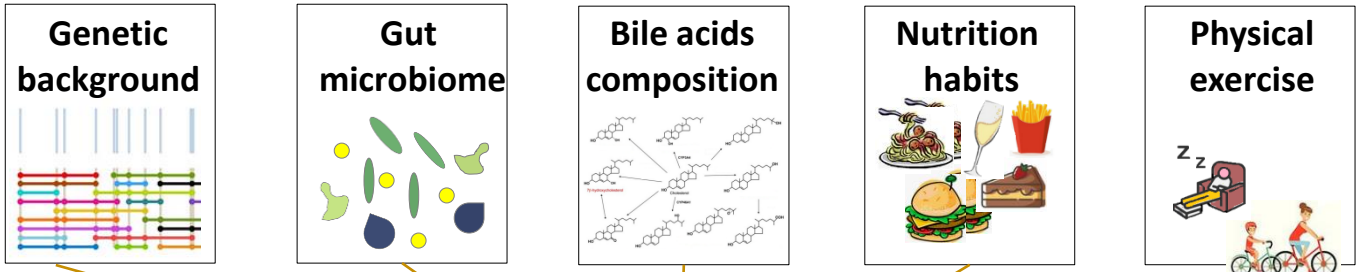
Romeo et al Cell Metab 2020

Genetic risk variants in risk stratification

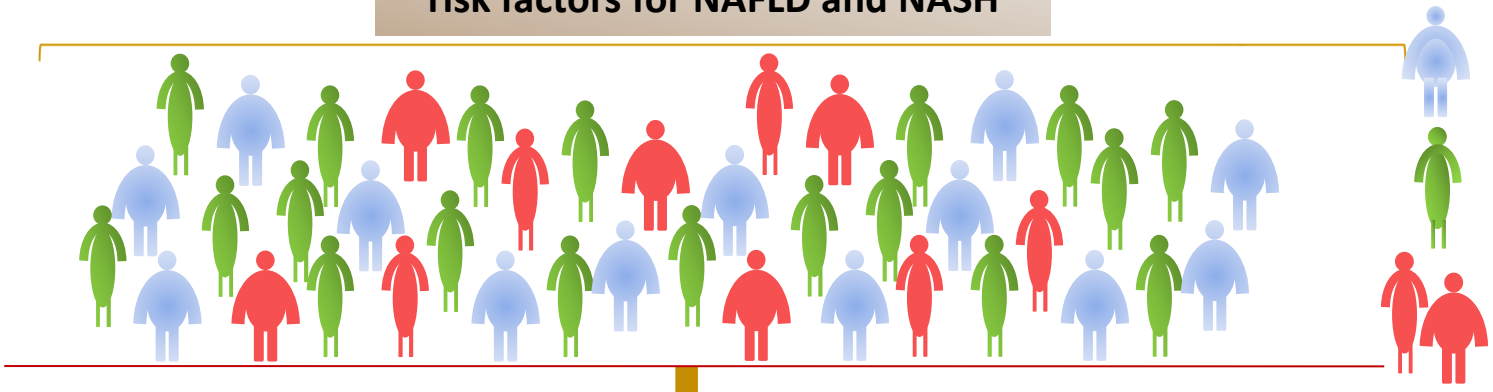


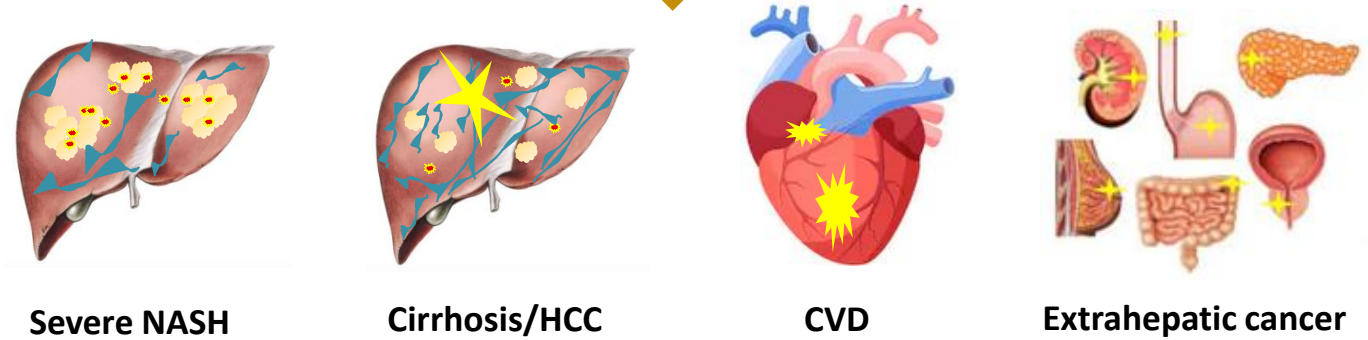
- Genetic scores may be able to help stratify patients at risk of progressive liver disease independently of fibrosis staging
- Modulation of the expression of PNPLA3 may become the first precision-based approached for the treatment of a chronic disorder.

Romeo et al Cell Metab 2020



Integrative approaches: risk factors for NAFLD and NASH



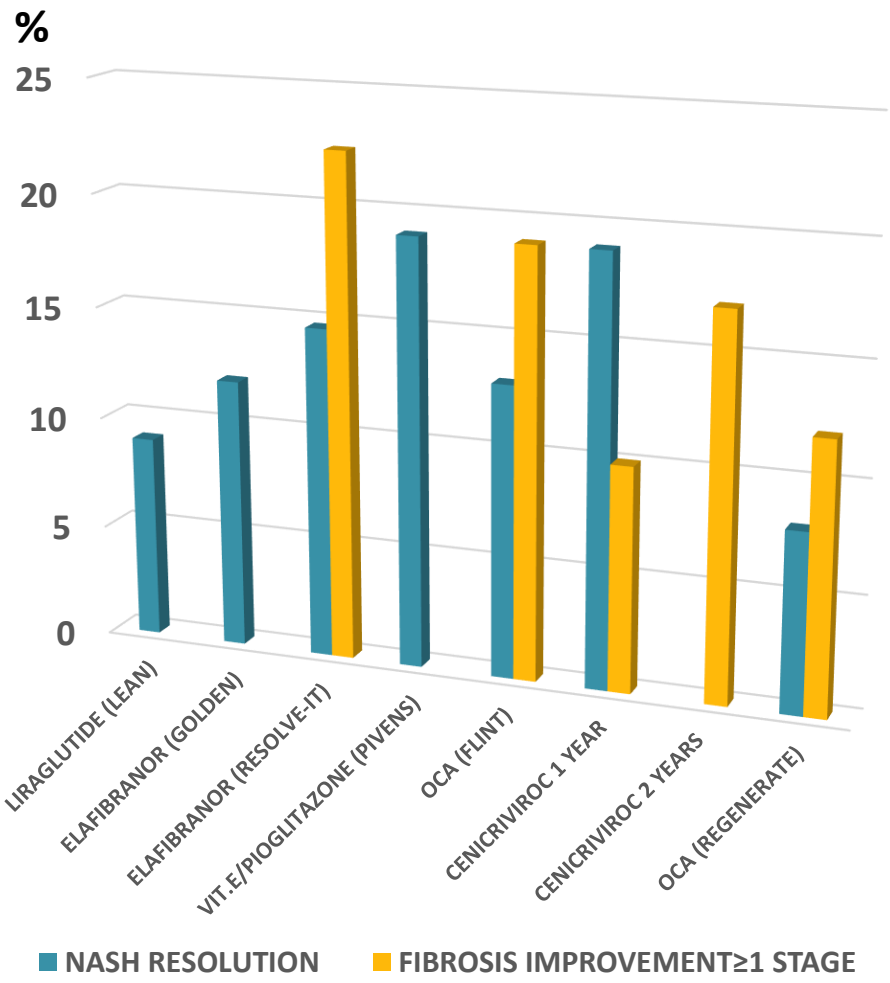


Severe NASH | Cirrhosis/HCC | CVD | Extrahepatic cancer

Clinical trials for treatment of NASH

- Need for common case definitions, genotype/phenotype risk stratification and harmonization of assessments
- Better insight into “placebo effect”
- Innovations in trial designs
  - Development of a **virtual placebo arm cohort analysis**, to eventually replace need for placebo- controlled trials
  - **Master protocols** that enable multiple agents to be tested sequentially in the context of a single longitudinal study to accelerate assessment of combination therapies
- Increased use of efficacy-to-effectiveness trials to demonstrate the value of therapies in real-world settings
- Increasing use of patient-centred outcomes assessment

Placebo effect in NAFLD trials



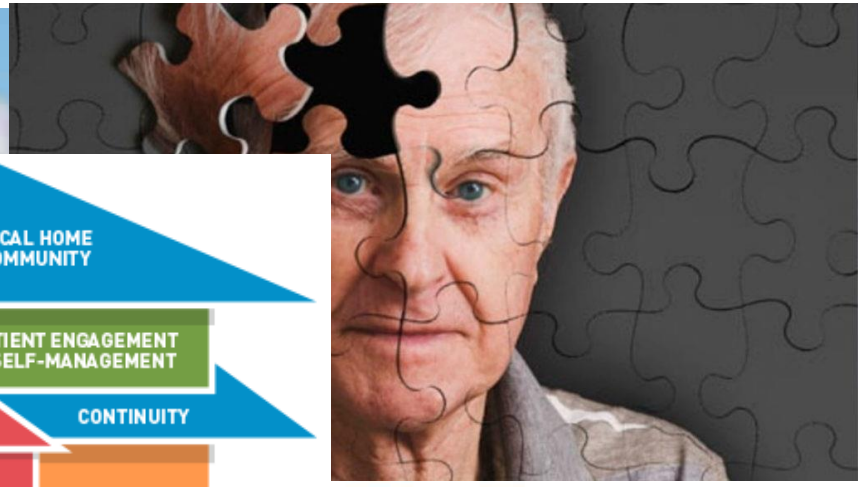
- Mild disease is more likely to improve spontaneously
- *Hawthorne effect:* patients may modify their behavior either consciously or unconsciously in response to their awareness of being observed
- *See-saw effect*: substantial variability over time in fibrosis stage
- Need for improved delivery, adherence and reporting of lifestyle recommendations in RCTs

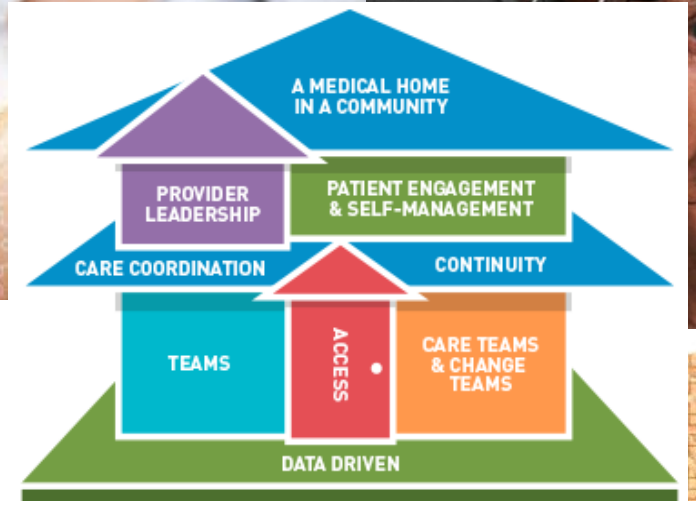
The Liver Forum, J Hepatol 2020

Future directions: summary

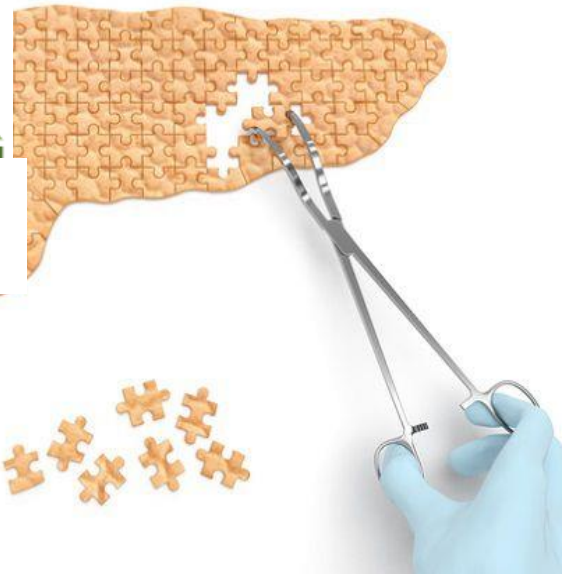
- NAFLD is
  - A widely spread liver disease that significantly contribute to morbidity and mortality
  - A component of MetS with important metabolic and CVD clinical implication
- Identification of distinct phenotypes based on integrated models of disease development (genetics, clinical history, histology and metabolome, proteome and microbiome)
- Timely diagnosis of NAFLD to reduce lifetime burden and costs
  - inter-society collaborations for armonization of guidelines, optimization of screening and therapy
  - programs for disease awareness
  - novel regulatory endpoints for drug development and biomarker approval
- Societal change is needed to address social determinants of health and failing food systems.

A patient is not a sum of organs





A Medical Home for patients with metabolic diseases



Thank you for your attention!

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Horizon 2020 EPoS GA : 634413
IMI2 Litmus GA:777377
Progetto di Eccellenza Dipartimentale
Project n. D15D18000410001

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