MASLD: Overview from sub-Saharan Africa
New Nomenclature and screening for MASLD

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MASLD Advisory Group: 1 December 2023

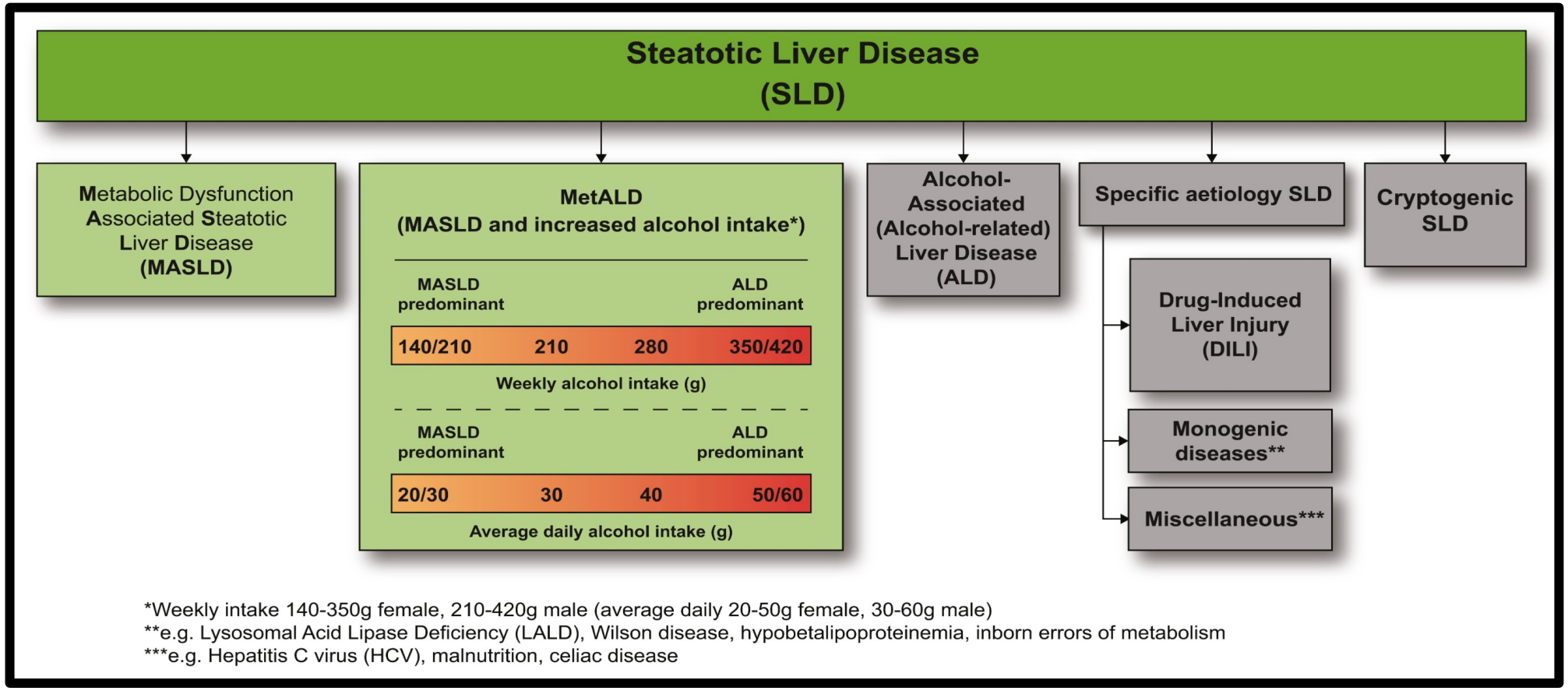
MASLD in AFRICA

Outline of Talk

- New nomenclature
- Global epidemiology
- Epidemiology in SSA
- Risk factors for MASLD
- Social determinants of MASLD
- Risk stratification for MASH and advanced fibrosis

Multi-society Delphi Consensus Statement on New Fatty Liver Disease Nomenclature

Hepatology June 2023; doi: 10.1097/HEP.0000000000000520



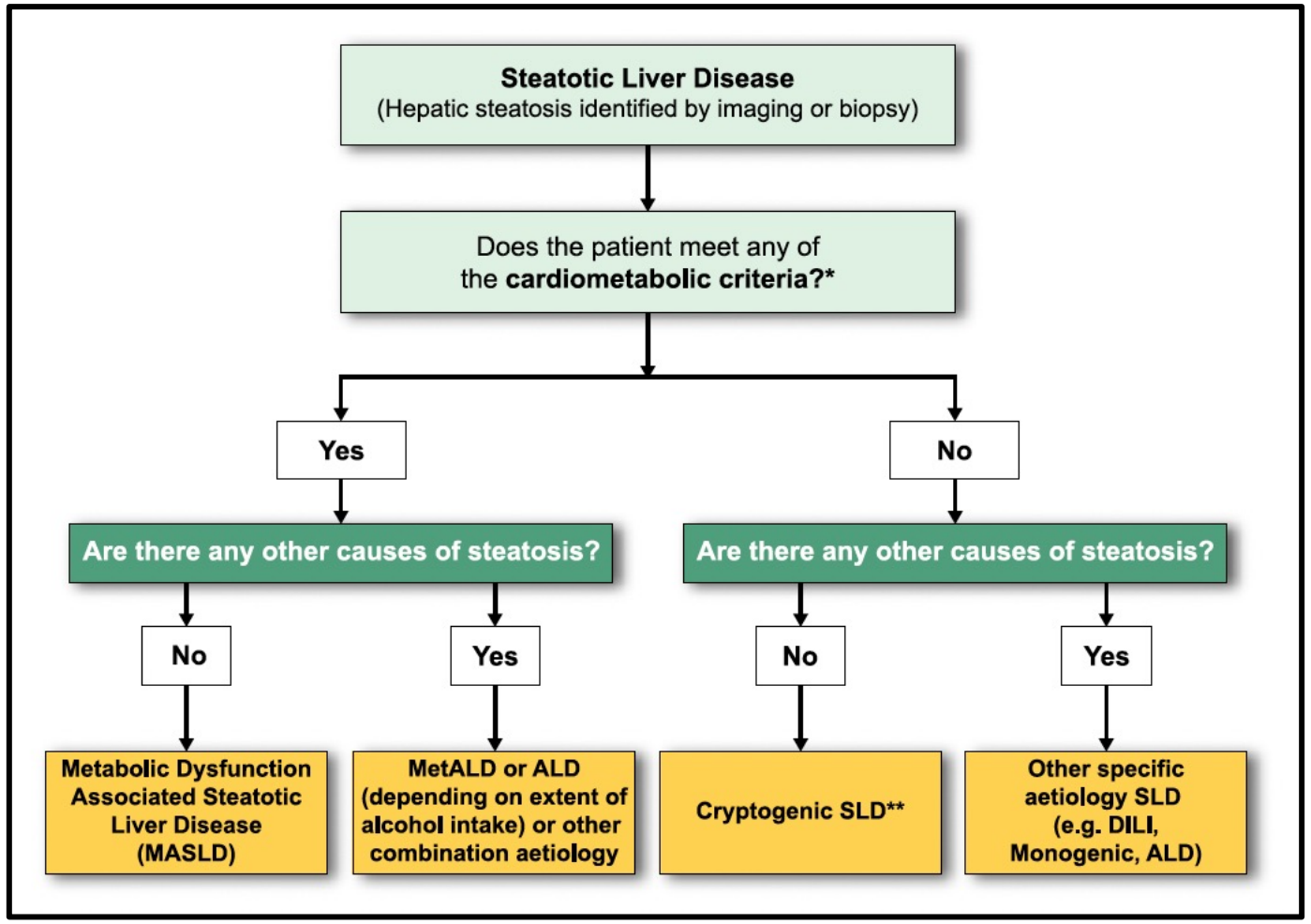
Steatotic Liver Disease diagnosed histologically or by imaging

MASLD: Defined as presence of hepatic steatosis in conjunction with one CMRF and no other discernible cause

MetALD: There is a continuum across which the contribution of MASLD and ALD will vary

Multiple aetiologies of steatosis can coexist: MASLD + autoimmune hepatitis or viral hepatitis

Changes in Nomenclature: MASLD & MASH



Adult Criteria

At least 1 out of 5:

- ☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment

Global Epidemiology of NAFLD

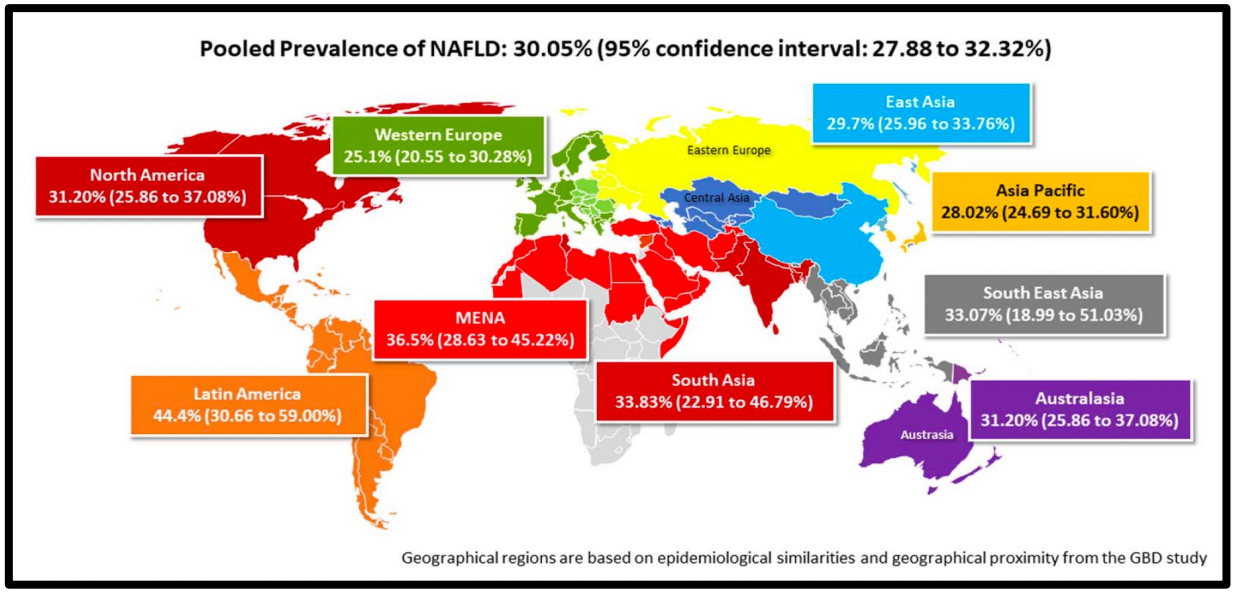
NAFLD is the leading global cause of chronic liver disease

Estimated to **affect approximately 38.0% (33.71-42.49) of world's population: 1.66 billion (0.95–2.59)**

- Global NASH prevalence is 5.27% (SE: 2.63)
- Prevalence of **NASH among NAFLD patients is 16.02% (3.24% - 52.08%)**

Data for the prevalence and incidence of NAFLD in Africa are scarce

- **Earlier meta-analysis reported NAFLD prevalence of 13.5% (95% CI 5.67–28.7)**
  - Ranging from 9% in Nigeria to 20% in Sudan – did not meet criteria for inclusion in recent meta-analyses
- Underestimate considering **increasing burden of NCDs**, esp rising prevalence of obesity & type 2 diabetes



NAFLD Prevalence: 2019 GBD

- **Latin America: 44.4%**
- **MENA: 36.5%**
- **South Asia: 33.8%**
- **South-East Asia: 33.1%**
- **North America 31.2%**
- **East Asia: 29.7%**
- **Asia Pacific: 28.0%**
- **Western Europe: 25.1%**

Hepatology 2023;77:1335; Nat Rev Gastroenterol Hepatol 2018; 15: 11
Lancet Gastroenterol Hepatol 2022;7:851

MASLD: SPECTRUM OF DISEASE

NAFL
- Pure steatosis
- Steatosis and mild lobular inflammation

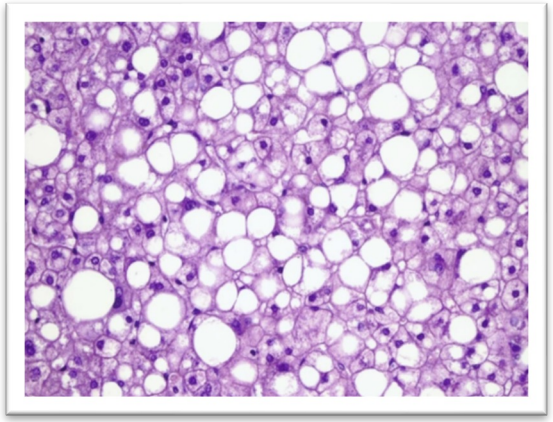
NASH

HCC

Early
F0/F1 fibrosis

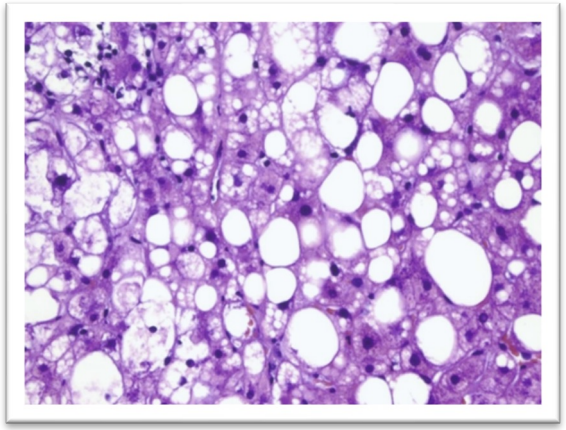
Fibrotic
≥F2 to ≥F3 fibrosis

Cirrhotic
F4 fibrosis



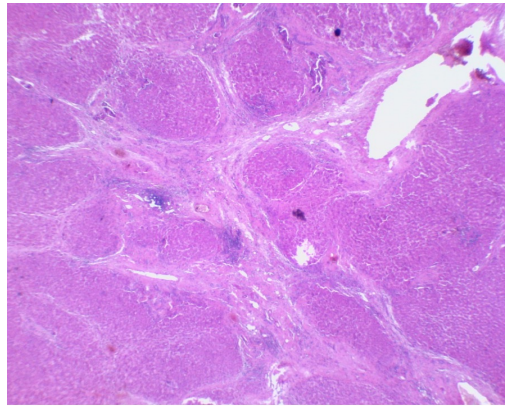
MAFL

Diffuse macro-vesicular steatosis >5% of hepatocytes



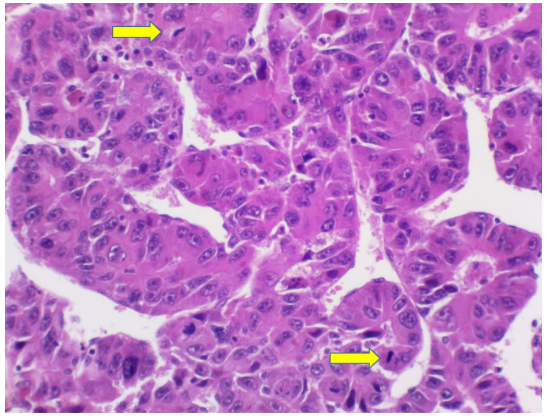
MASH

NAFL + lobular inflammation, hepatocyte ballooning, necrosis



Cirrhosis

Variably sized regenerative nodules surrounded by fibrous septa
Loss of steatosis

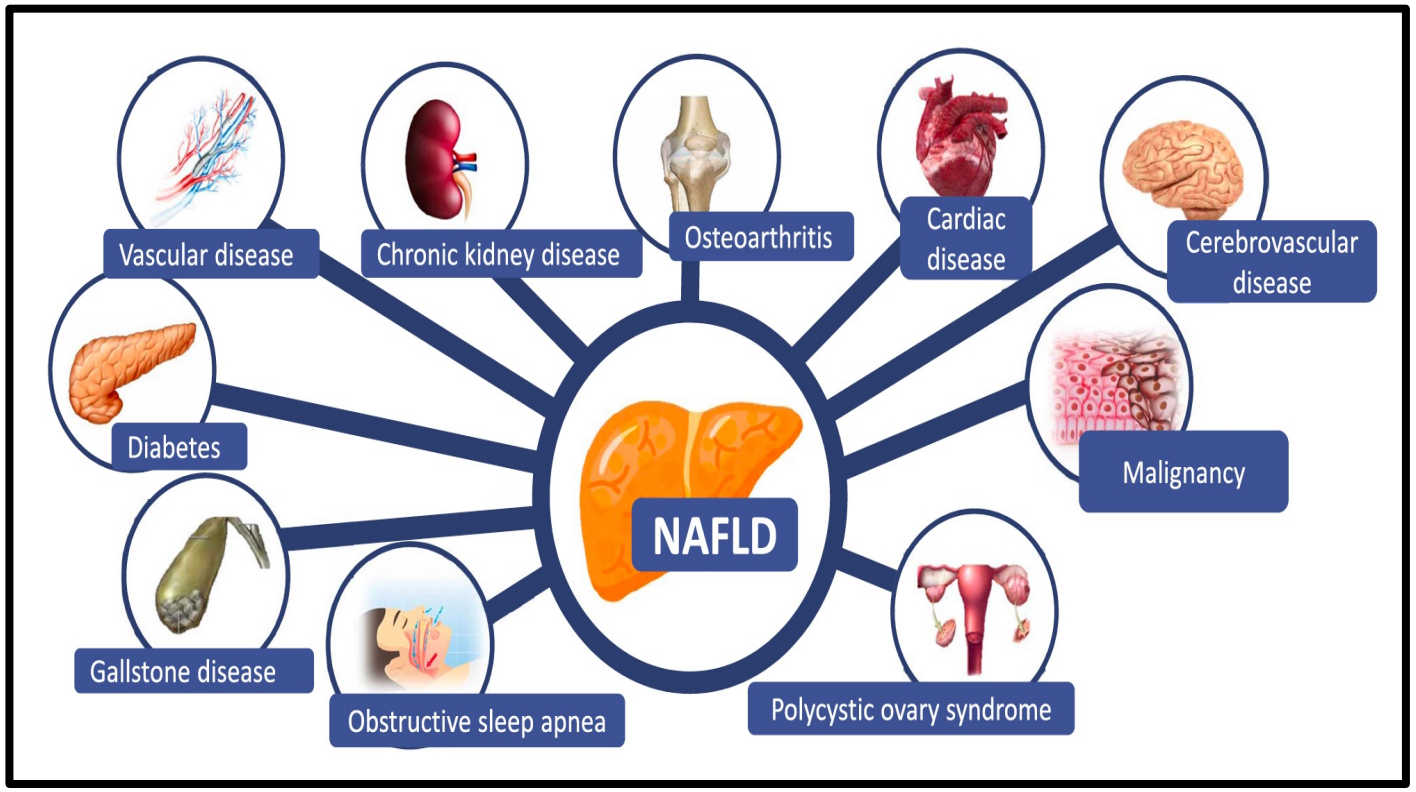


HCC

Thickened trabeculae of pleomorphic hepatocytes
Large irregular nuclei with conspicuous mitotic activity

J Hepatol 2016; 64:1388

Extrahepatic Manifestations of MASLD



Pooled mortality rates per 1000 PY for NAFLD: US or FLI

- **12.60 for all-cause mortality**
- **4.20 for cardiac-specific mortality**
- 2.83 for extrahepatic cancer-specific mortality
- 0.92 for liver-specific mortality

- Although liver-related mortality is increased**, cardiovascular disease remains the leading cause of death** in patients with MASLD and liver fibrosis stages F3 or F4
- **HCC can occur in the absence of cirrhosis**

Lancet Gastroenterol Hepatol 2021; 6: 578; Hepatology 2023;77:1335

Global prevalence of MASLD among T2DM patients: 55.5% (95% CI: 47.3-63.7)

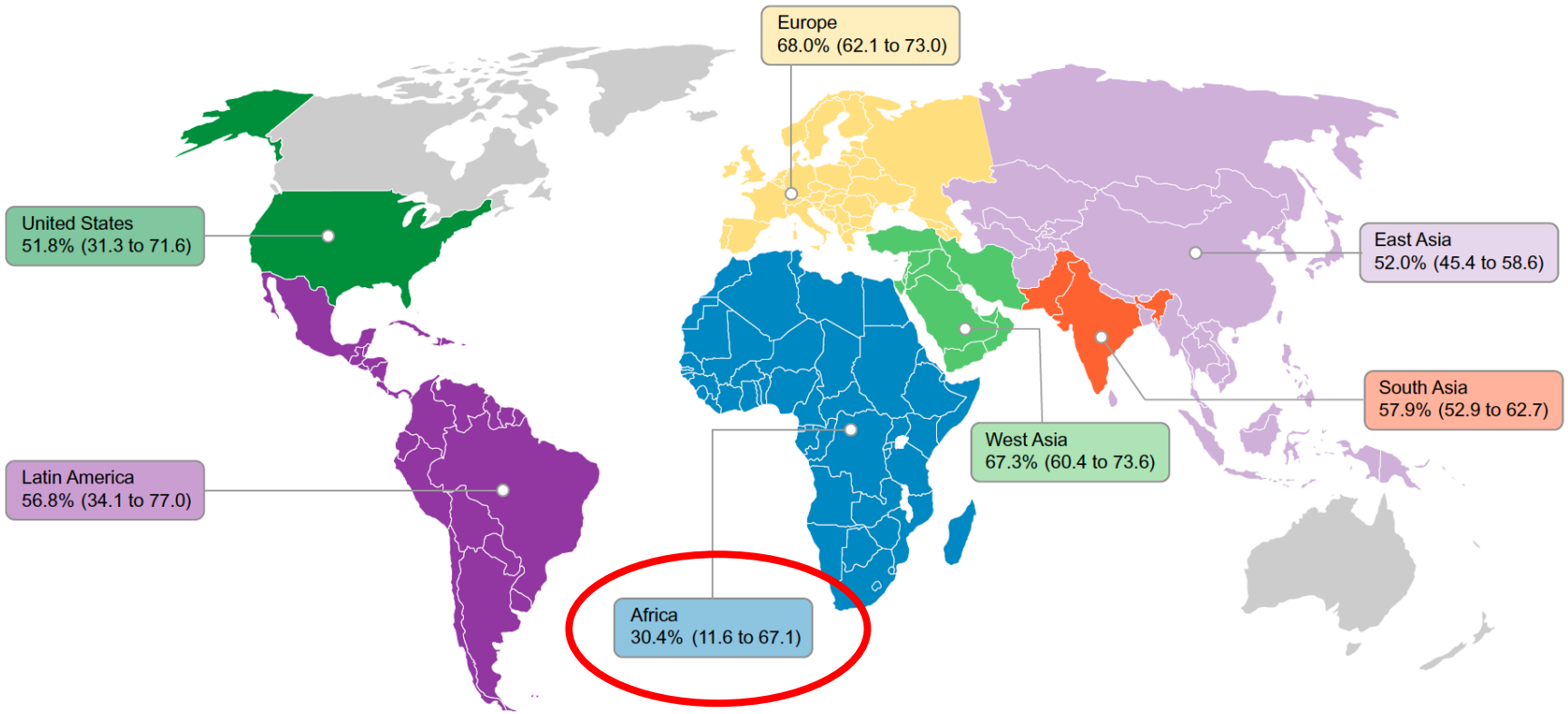


Fig. 2. Global and regional prevalence of NAFLD among patients with T2DM. H-MRS, proton magnetic resonance spectroscopy; NAFLD, non-alcoholic fatty liver disease; T2DM, type 2 diabetes mellitus. NAFLD diagnosed by ultrasound or H-MRS. Data are displayed as prevalence (95% CI).

Prevalence of MASLD in patients with type 2 DM is >2-fold higher than in general population

- Global prevalence of MASH among patients with type 2 DM is 37.3%
- Patients with MASLD and type 2 DM undergoing liver biopsy, 17% have advanced fibrosis

J Hepatol 2019;71:793

Epidemiology of NAFLD in sub-Saharan Africa

NAFLD cases in SAA

Western SSA

- **1990:** 8·4 per million
- **2017:** 23·2 per million

Central SSA

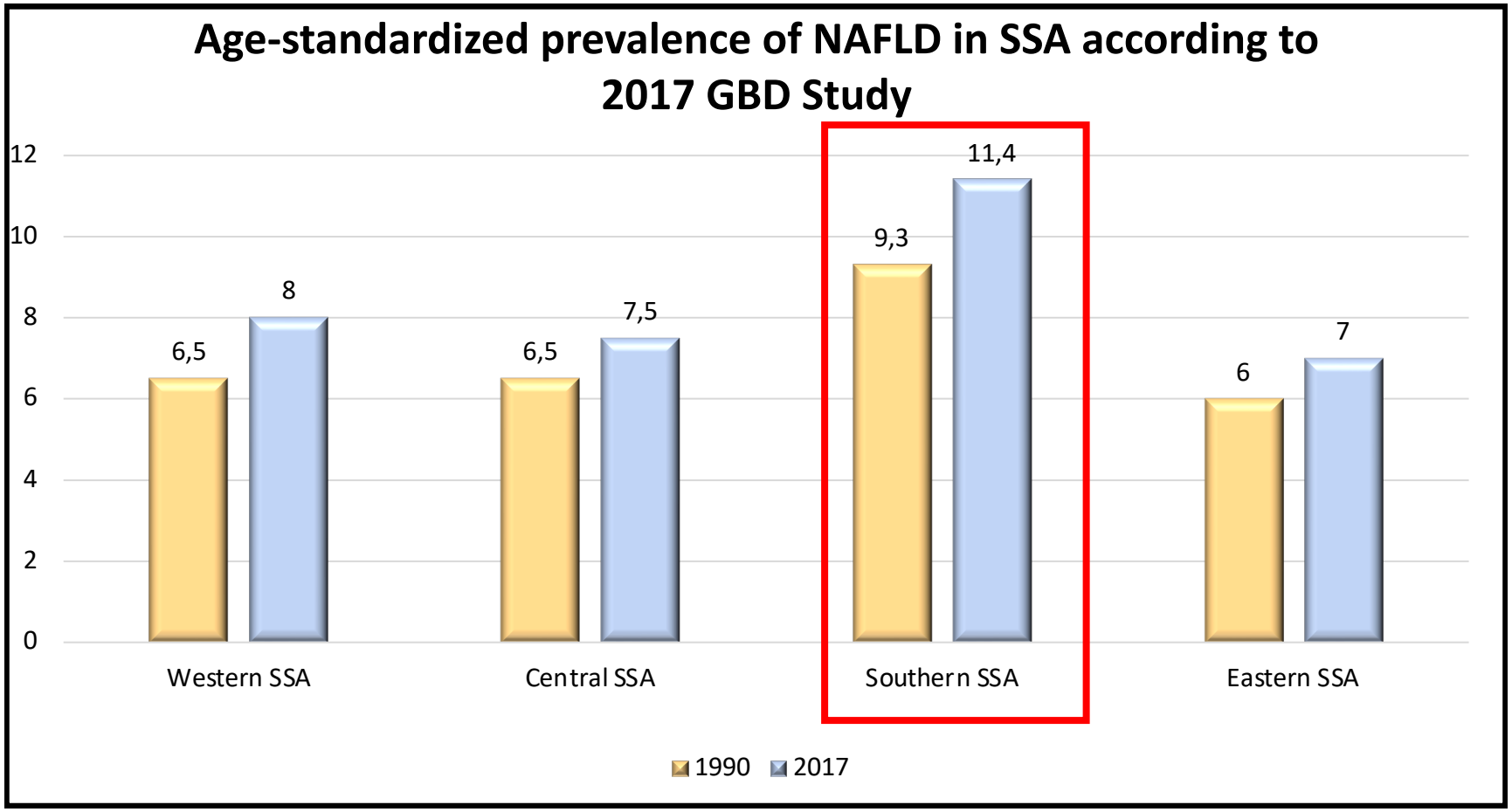
- **1990:** 2.3 per million
- **2017:** 6.2 per million

Southern SSA

- **1990:** 3.7 per million
- **2017:** 8.1 per million

Eastern SSA

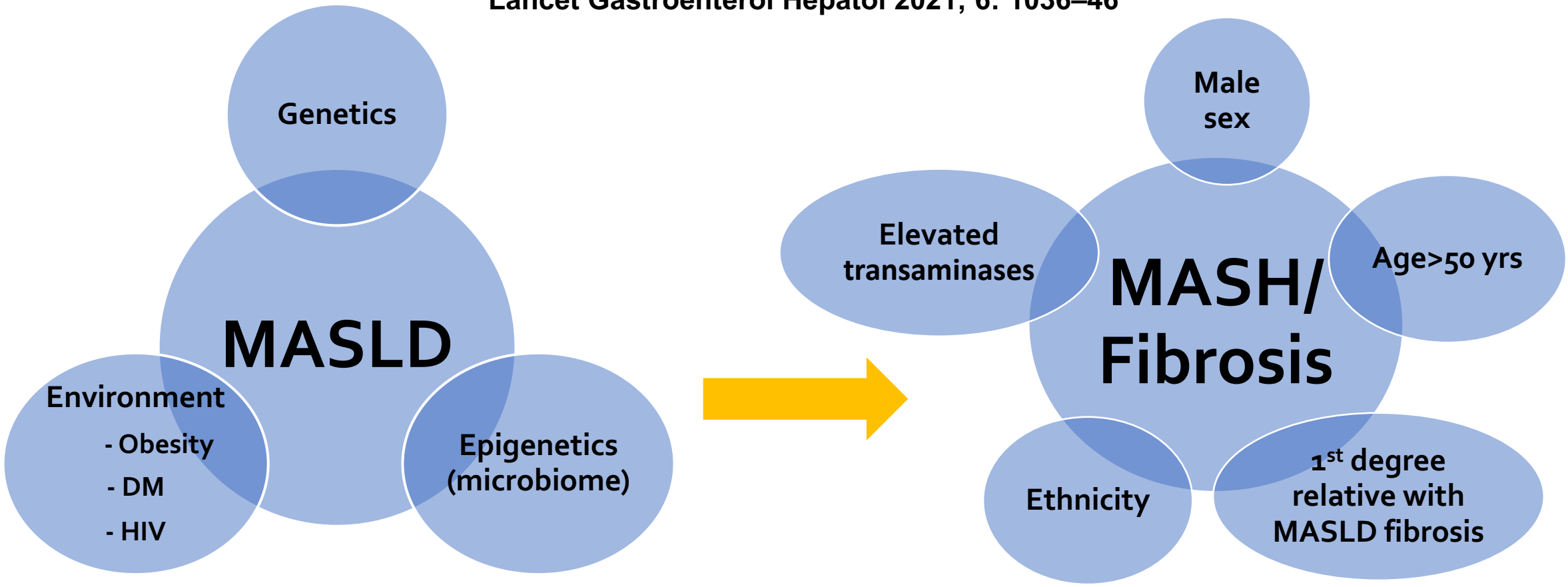
- **1990:** 7.1 per million
- **2017:** 18 per million



BMJ Open 2020; 10: e036663

Risk Factors for MASLD

Lancet Gastroenterol Hepatol 2021; 6: 1036–46



Non-linear disease progression

- Fibrosis progression rate: 1 stage/7years (NASH); 1 stage/14years (NAFLD)

Hepatocellular Carcinoma can develop in MASH without cirrhosis: 0.59%/year

MASLD: Genetic factors

- Risk alleles in PNPLA3, TM6SF2, and MBOAT7
- Protective HSD17B13 and PNPLA3 rs6006460[T] variants

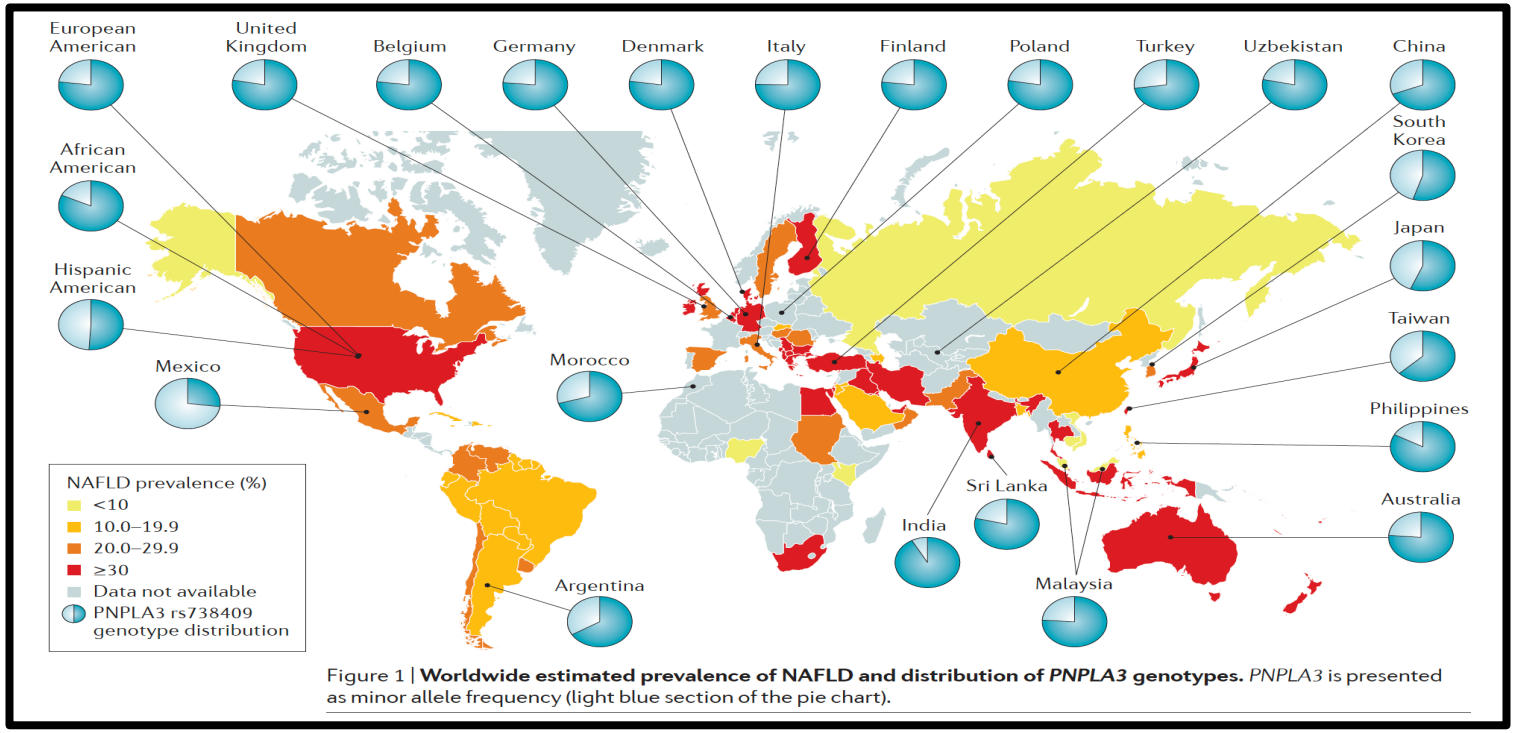


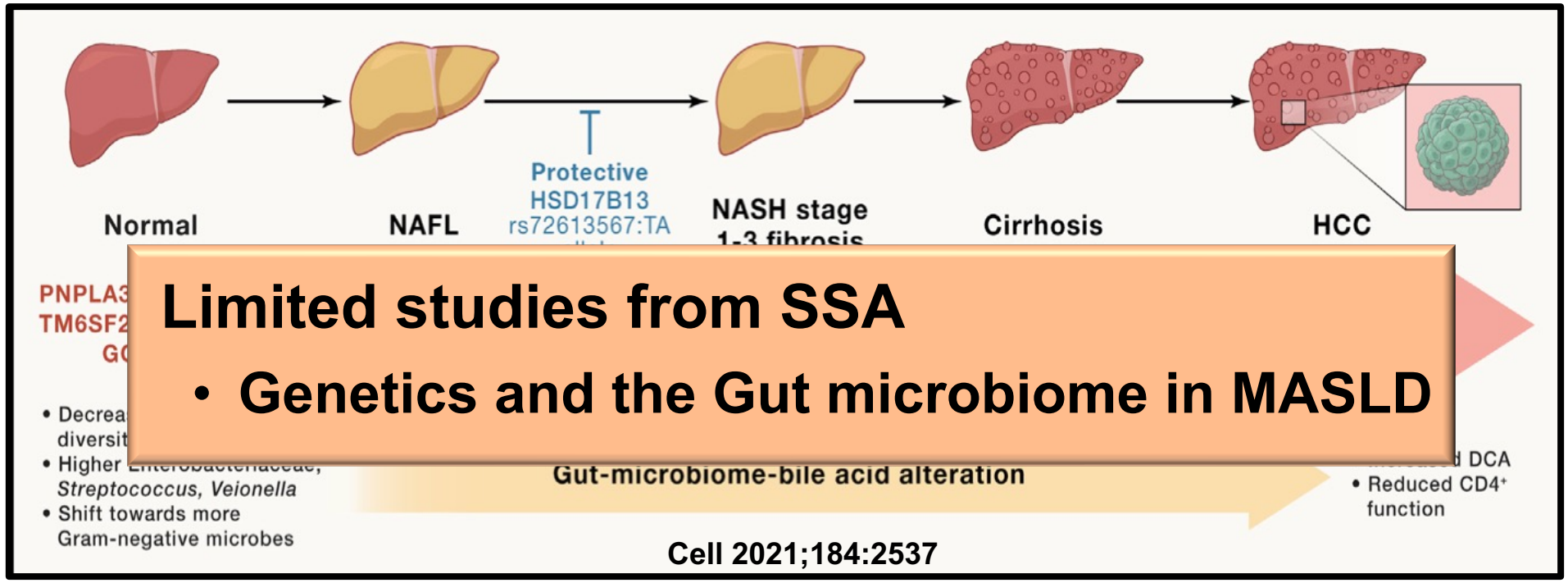
Figure 1 | **Worldwide estimated prevalence of NAFLD and distribution of *PNPLA3* genotypes.** *PNPLA3* is presented as minor allele frequency (light blue section of the pie chart).

No studies from sub-Saharan Africa

NATURE REVIEWS GASTROENTEROLOGY & HEPATOLOGY 2018; 15: 11

Clin Mol Hepatol 2021; 27(3): 486 Nat Genet 2008; 40: 1461

Gene-environment nexus drives the risk of cirrhosis and HCC in MASH



PNPLA3 gene is a major driver of MASLD, MASH, cirrhosis, and HCC risk in individuals who have metabolic risk factors such as obesity, diabetes, and metabolic syndrome

- **Most genetic factors** manifest in setting of **metabolic risk factors**, including obesity, diabetes, and metabolic syndrome, as well as other **environmental factors**, such as alcohol and smoking

Gut microbiome is **altered by diet and alcohol** and together with **changes in bile acids and metabolic dysfunction**, including lipotoxicity **promote disease progression** to cirrhosis and HCC in susceptible hosts

SSA: MASLD and Non-Communicable Diseases

Sub-Saharan Africa, a middle-to-lower-income region, has varied evolving economies and increasing urbanization with pro-MASLD dietary and behavioural changes

Transition from infectious diseases of TB, malaria, and HIV to an increasing burden of non-communicable diseases

- Rising prevalence of obesity and type 2 diabetes
- Driven by overlapping challenges of food insecurity, nutritional transition, and associated increased consumption of calorie-dense foods and more sedentary urban lifestyles
- Africans with NCDs are younger by 10 years or more compared with people in other world regions with twice the risk of NCD-related mortality
- Burden of NCDs in all 4 SSA regions is higher than the global average
- SSA anticipated to experience largest global increase in NCD-related mortality

Lancet Glob Health 2019; 7: e1375; Lancet 2006;367: 1747; Nature 2018; 559: 507

SSA: MASLD and Non-communicable Diseases

2017 GBD study, all-age total DALYs due to NCDs increased by 67% in SSA

- **1990: 90.6 million** (95% UI 81.0–101.9) **2017: 151.3 million** (133.4–171.8)

NCD	Prevalence in SSA
Metabolic syndrome	11.1- 23.9%
Hypertension	30% (95% CI 27–34)
Dyslipidaemia	25.5% (95% CI 20·0–31·4)
Diabetes	8.5% (6·5–10·8) in men and 8.9% (6·9–11·2) in women
NAFLD	30.4% (95% CI 11.6–67.1)
Chronic kidney disease	15.8% (95% CI 12·1–19·9)

Increasing number of metabolic diseases are associated with increased risk of progressive liver disease and reduced survival:

Odds ratios for development of moderate-to-severe fibrosis for metabolic risk factors:

- **1.72 (1.13–2.31; p=0.0205) for type 2 diabetes, hypertension, and visceral obesity**

Int J Epidemiol 2017; 46: 1421; J Hepatol 2019; 71: 793; Clin Gastroenterol Hepatol 2009; 7: 1224

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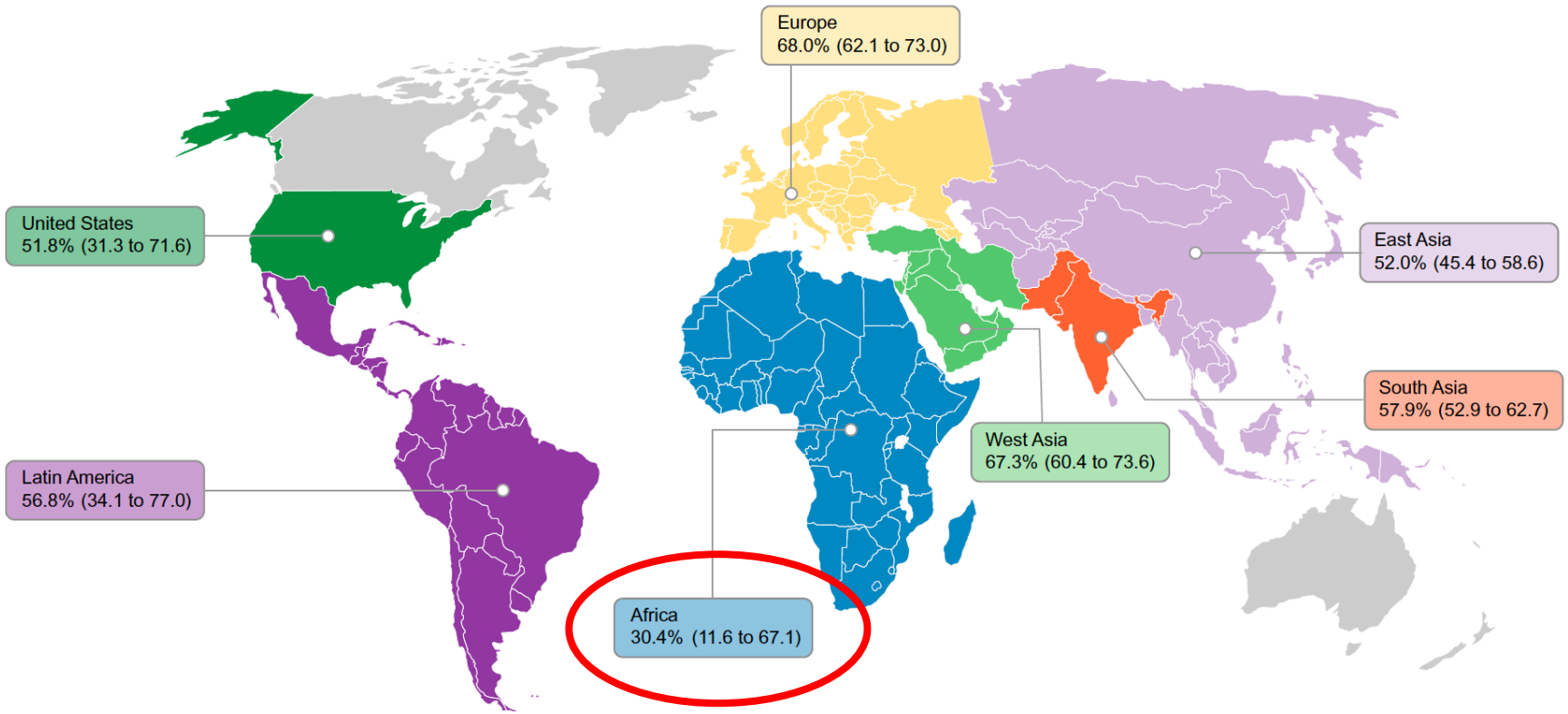

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J Hepatol 2019;71:793

SSA: Social & other Determinants of MASLD

Rapid epidemiological transition driven by fast urbanisation

- 41.3% population living in urban areas in 2020 compared with 27.4% in 1990

Nutritional transition

- Traditional diets, high in fibre, low in fat, substituted by more calorie-dense diets with increased intake of sugar-sweetened beverages & fast foods and increased fat & protein consumption
- Steady increase in daily caloric intake in Africa
- Obesity and type 2 DM associated with soft drink consumption, which is often higher in patients with MASLD than in those without MASLD
    - South Africa has high soft-drink consumption correlating with highest obesity prevalence in SSA

https://data.worldbank.org/country/ZA; https://ourworldindata.org/food-supply ; Ann N Y Acad Sci 2014; 1311: 88; Nutrients 2011; 3: 429; Am J Public Health 2013; 103: 2071; Int J Obes 2019; 43: 603; Lancet Gastroenterol Hepatol 2021;6:1036

SSA: MASLD and Non-Communicable Diseases

Food insecurity and the Metabolic syndrome

Food insecurity in SSA is associated with transition to increased use of inexpensive, low nutritional value, higher calorie options driving obesity and metabolic syndrome

Meta-analysis: Relationship between food insecurity & metabolic risk factors in SSA

- **High pooled prevalence estimate of key metabolic risk factors** among food-insecure participants: **41.8%** [95% CI 33.2–50.8, I.=99.5%]
- **Most prevalent metabolic risk factors**
  - Dyslipidaemia: 27.6% [6.5–54.9]
  - Hypertension: 24.7% [15.6–35.1]
  - Overweight: 15.8% [10.6–21.7]

Sci Rep 2021; 11: 5178

SSA: Social & other Determinants of MASLD

Reduced physical activity / poor aerobic fitness: Increased risk of MAFLD/MASH

- **Meta-analysis: 10 SSA countries: 26 022 participants**
  - 18.9% (95% CI 14.3–24.1) adults ≥18 years participated in leisure-time physical activity: M > F
  - Age inversely associated with exercise
  - Higher levels of education: Increased participation in leisure-time physical activity
  - Rural-living or self-employed less likely to participate

Subcutaneous fat stores: South African study: 106 female volunteers

- Black African women had lower hepatic fat content on Liver CT scan than their Indian and White counterparts
  - Despite higher level of total body fat, subcutaneous body fat, BMI & waist circumference
- **Subcutaneous fat was a significant negative determinant of hepatic fat content**

BMC Public Health 2020; 20: 927; PLoS One 2018; 13: e0191388

SSA: Social & other Determinants of MASLD

HIV

2022: Globally, 39 million people were living with HIV

- **67% reside in sub-Saharan Africa with the majority in Southern SSA**
- 689,000 new HIV infections
- 76% [60–92%] of people living with HIV in SSA had access to ART

Increased risk for MASLD/MASH

- More likely to have metabolic syndrome (>40%) than non-HIV
- Pro-inflammatory state
- Role of the gut microbiome and bacterial translocation
- ART toxicity: NRTI, Protease inhibitors, and INSTIs

South African prospective study: 301 HIV-positive patients undergoing liver biopsy

- NAFLD in 58 (19%) patients
- 16 (28%) had steatohepatitis

MASLD: Risk Stratification: MASH and Fibrosis: NITs

	Components and calculation	Rule out cut-point	Rule in cut-point	Limitations	Strengths
Indirect serum fibrosis biomarkers					
FIB-4	Age × AST (IU/L)/platelet count (× 10^9/L) × √ALT (IU/L)	<1·3	>2·67	Low PPV (40%); less accurate performance when age >65 years and <35 years; 30% indeterminate	Minimal data required; routine clinical data; high NPV
Direct serum fibrosis biomarkers					
FibroSpect NASH	Proprietary algorithm combining HA, TIMP-1, and α2-macroglobulin	<16	Not reported	Proprietary test; lower NPV	Easy to interpret results
FIB-C3	−5·939 + (0·053 × age) + (0·076 × BMI) + (1·614 × T2DM) − (0·009 × platelet count) + (0·071 × PRO-C3)	<−0·4	>−0·4	Requires non-routine clinical data; lower NPV	Uses a single threshold for risk stratification
ELF	−7·412 + [ln(HA) × 0·681) + [ln(PIINP) × 0·775] + [ln(TIMP) × 0·494)	<7·7	>9·8	Send-out testing; cost	High NPV
Imaging fibrosis biomarkers					
VCTE	kPa	<8	>12	Multiple potential confounders; requires experienced operator	Point of care; high NPV
MRE	kPa	<2·5	>3·6	High cost; not widely available	Highly accurate; few confounders

NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis. FIB-4=Fibrosis-4 index. AST=aspartate aminotransferase. ALT=alanine aminotransferase. PPV=positive predictive value. NPV=negative predictive value. HA=hyaluronic acid. TIMP-1=tissue inhibitor of metalloproteinase-1. T2DM=type 2 diabetes. PIIINP=procollagen III-peptide. ELF=enhanced liver fibrosis. VCTE=vibration controlled transient elastography. MRE=magnetic resonance elastography.

Table 1: **Non-invasive biomarkers of advanced fibrosis in NAFLD and NASH**

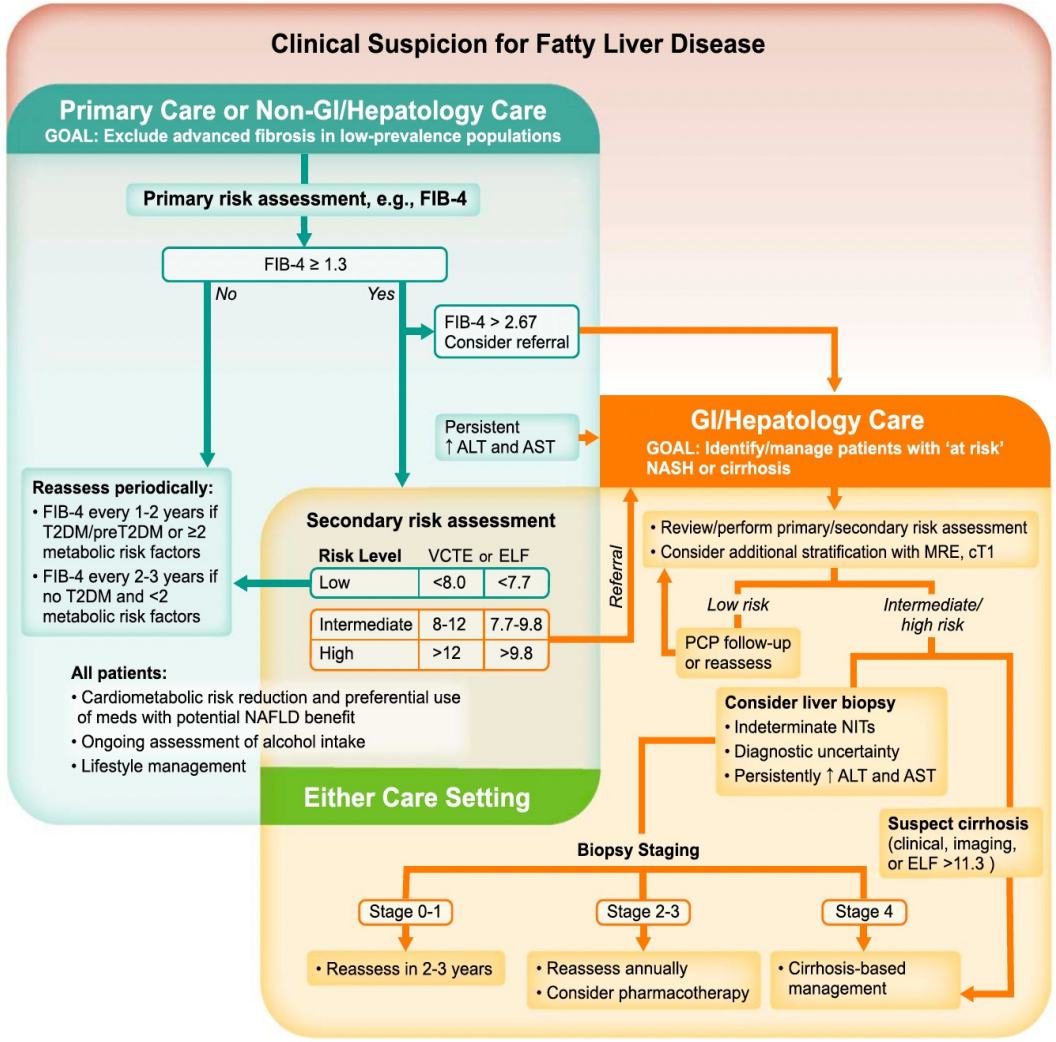
Lancet Gastroenterol Hepatol 2023; 8: 660

	Components	Rule out cut-point (sensitivity)	Rule-in cut-point (specificity)	AUROC
Circulating biomarkers				
Fibrotic NASH index	AST, HDL, $HbA1_c$	0·1 (89%)	0·33 (90%)	0·78*
NIS-4	α2-macroglobulin, YKL-40, HbA_{1c}, miR34a	<0·36 (82%)	>0·63 (87%)	0·80*
Imaging biomarkers				
MRI cT1	MRI based calculation	<825 ms (78%)	≥875 ms (90%)	0·78*
Combination serologic and imaging biomarkers				
FAST score	VCTE kPa and CAP, AST	<0·35 (80%)	≥0·67 (88%)	0·69
MAST score	MRE kPa and PDFF, AST	0·165 (65%)	0·242 (84%)	0·72
MEFIB index	MRE kPa, FIB-4	FIB-4 <1·6 and MRE <3·3 kPa (91%)	FIB-4 ≥1·6 and MRE ≥3·3 kPa (78%)	0·76

NASH=non-alcoholic steatohepatitis. FAST=Fibroscan-AST. MRE=magnetic resonance elastography. MAST=MRI-AST. MEFIB=MRE combined with FIB-4. ELF=Enhanced Liver Fibrosis. VCTE=vibration controlled transient elastography. AST=aspartate aminotransferase. CAP=controlled attenuation parameter. PDFF=proton density fat fraction. FIB-4=Fibrosis-4 Index. AUROC=area under the receiver operator curve. *Requires further validation as data derived only from a single study.

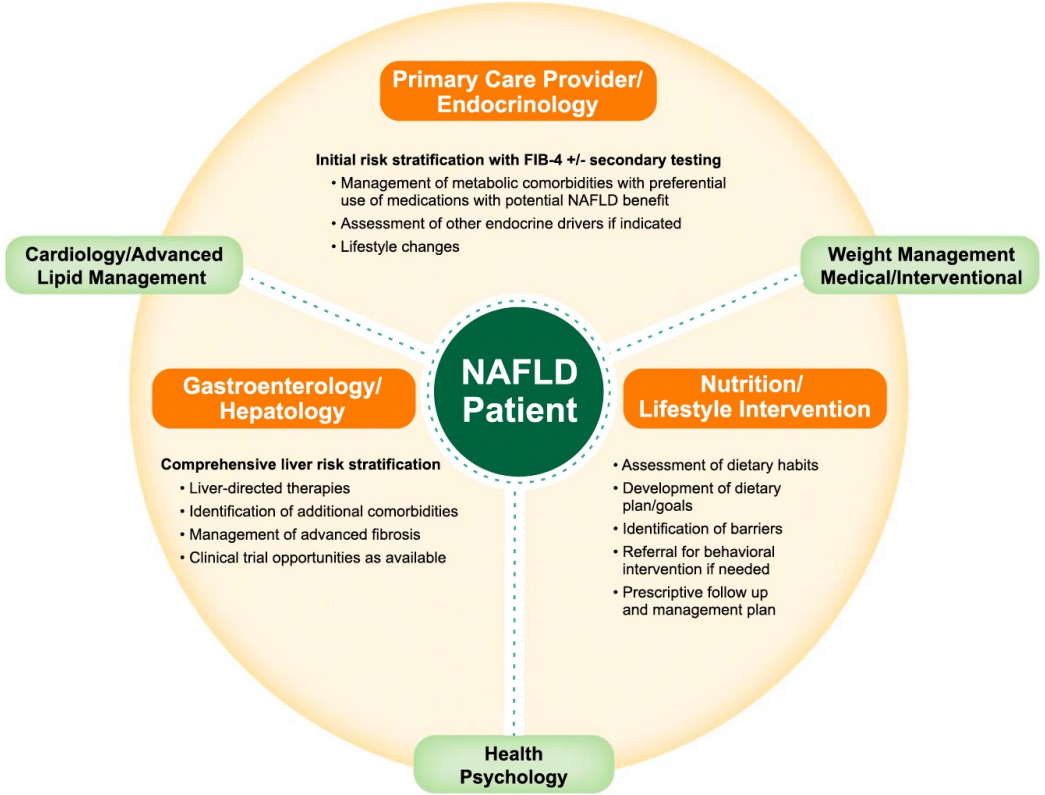
Table 2: **Non-invasive biomarkers to detect at risk NASH**

Management of MASLD: Multidisciplinary approach



Hepatology 2023;77:1797

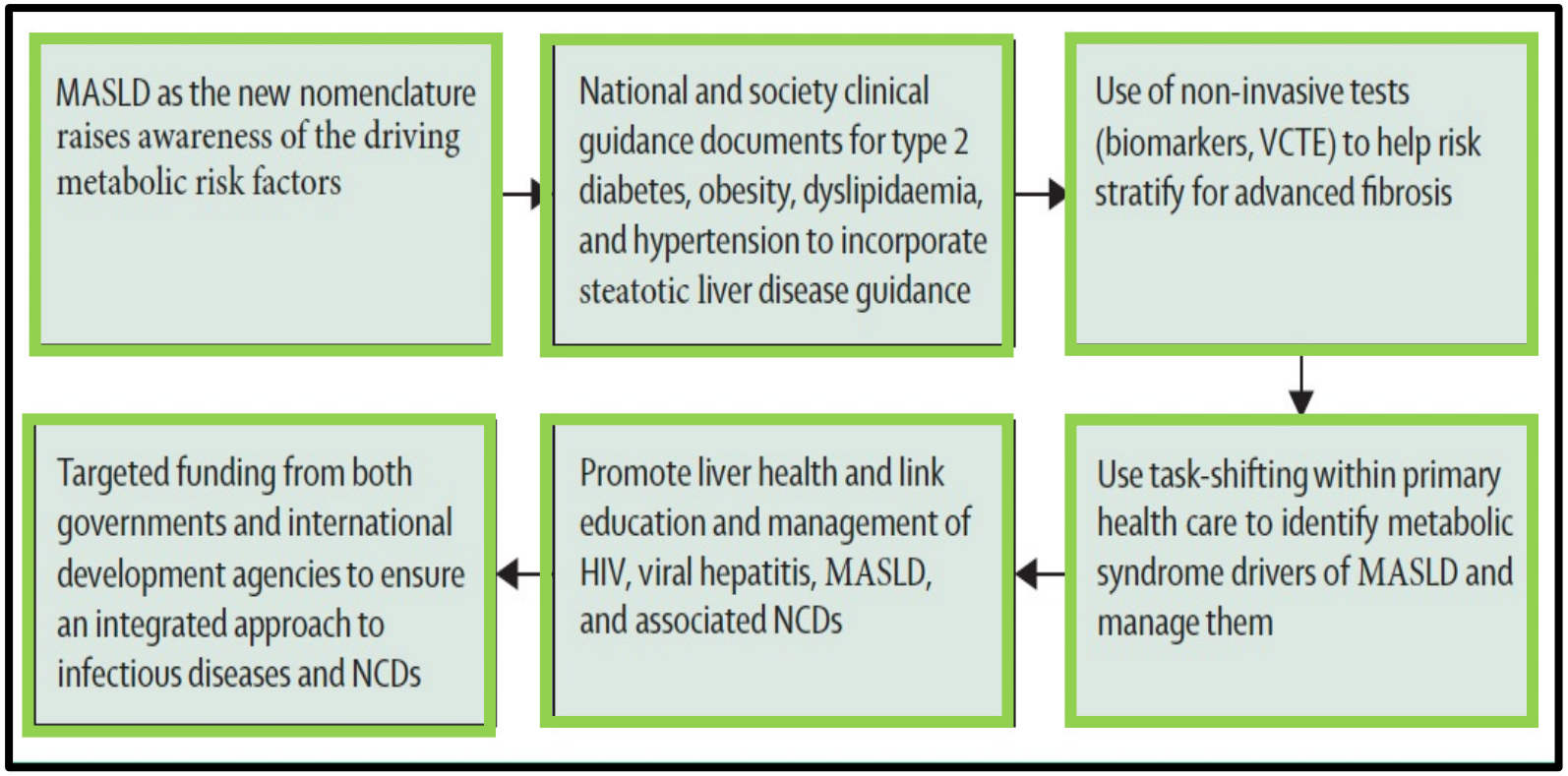
- Majority of patients are in primary care/endocrine settings
- Management of medical comorbidities optimised
  - Type 2 diabetes, hypertension & obesity:
    Further beneficial effects on MASLD



Management of MASLD in SSA

Management must be centred on prevention and primary care strategies

- Diagnosis of MASLD and screening at-risk individuals for MASH / F2 Fibrosis
- Lifestyle changes and aggressive management of associated NCDs



Challenges: MASLD in SSA

- Failure to recognise MASLD as the hepatic component of metabolic syndrome
- No published national clinical guidelines on MASLD in sub-Saharan Africa
- Guidance documents on type 2 diabetes, obesity, dyslipidaemia and hypertension do not include guidance on MASLD
- Dismantle silos of health-care management: Communicable vs Non-communicable
- Limited therapeutic options: Costs of pioglitazone & GLP-1-receptor agonists prohibitive
- Limited access to therapeutic trials – access often based on liver biopsies that makes recruitment challenging

Need to adopt a multidisciplinary & multisectoral approach to MASLD at all levels of care to address this major public health threat