Treatment Disparities in NASH

Stephen A. Harrison, MD, COL (Ret.), FAASLD
Visiting Professor of Hepatology
Radcliffe Department of Medicine, University of Oxford
Medical Director, Pinnacle Clinical Research
President, Summit Clinical Research

Disclosures

Stephen A. Harrison

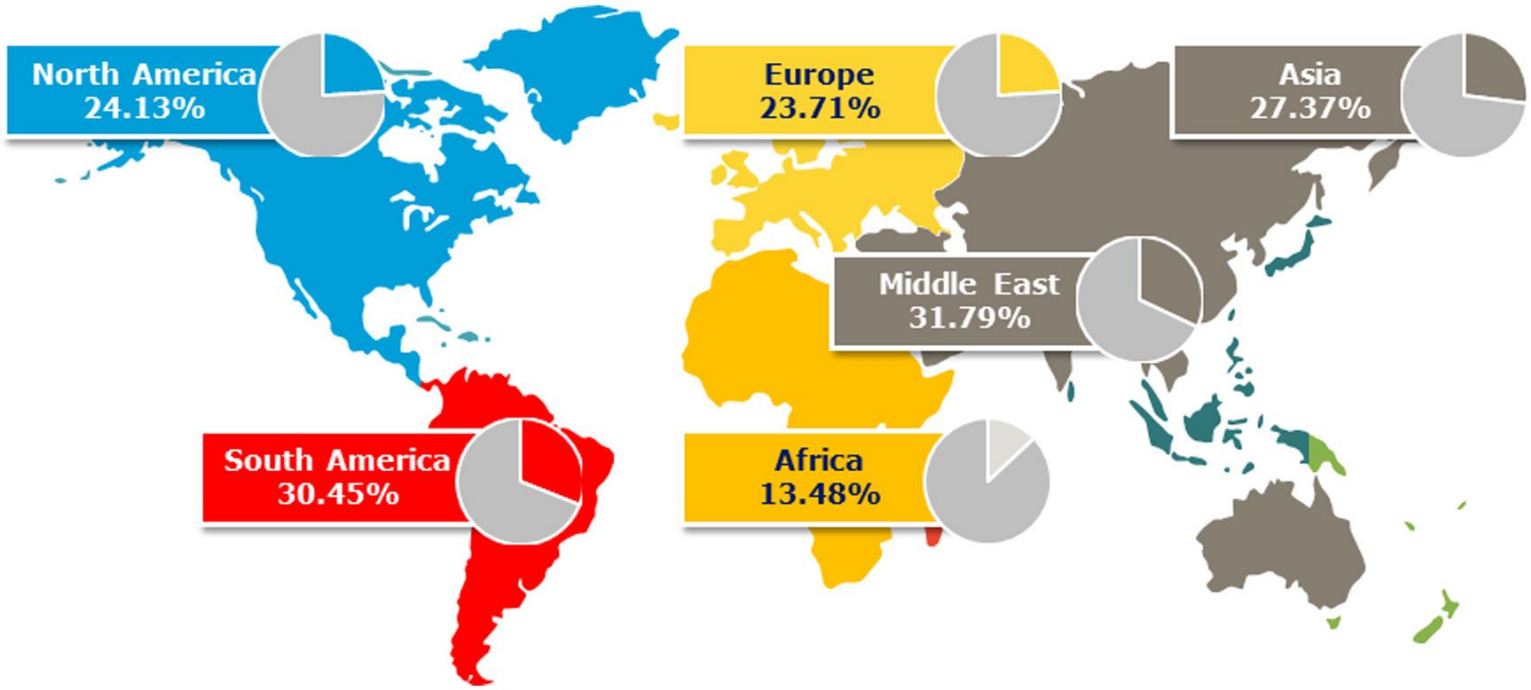
I disclose the following financial relationship(s) with a commercial interest:

Scientific advisor or consultant for Akero, Alentis, Altimmune, Arrowhead, Axcella, BMS, Echosens, Fibronostics, Forest Labs, Galectin, Gilead, Hepion, Hepagene, HistoIndex, Intercept, Madrigal, Medpace, Metacrine, NGM Bio, Northsea, Novartis, Novo Nordisk, PathAI, Poxel, Liminal, Sagimet, Terns, Viking.

Stock options: Akero, Cirius, Galectin, Genfit, Hepion, HistoIndex, PathAI, Metacrine, NGM Bio, Northsea.

Grant/Research support: Akero, Axcella, BMS, Cirius, CiVi Biopharma, Conatus, Cymabay, Enyo, Galectin, Genentech, Genfit, Gilead, Hepion, Hightide, Intercept, Madrigal, Metacrine, NGM Bio, Novartis, Novo Nordisk, Northsea, Pfizer, Sagimet, Viking, 89 Bio.

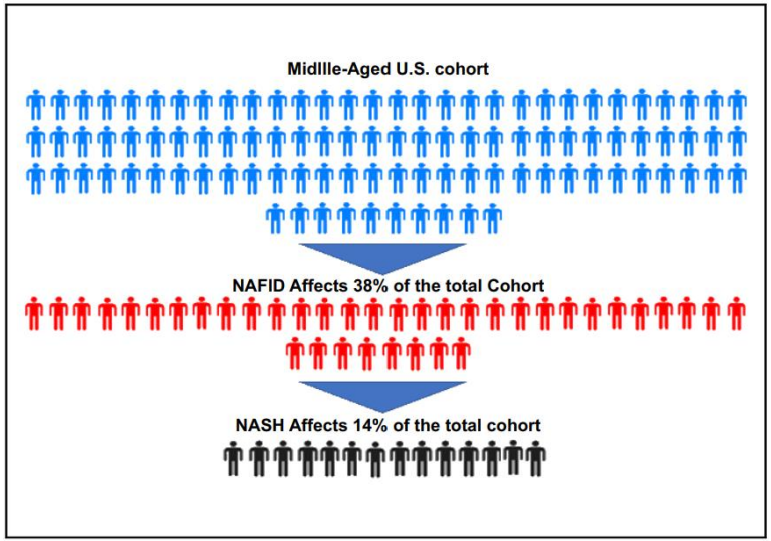
NAFLD Prevalence Worldwide



Younossi ZM et al. Global epidemiology of nonalcoholic fatty liver disease–meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology.* 64, 73–84 (2016).

CLDF
Chronic Liver Disease Foundation

NAFLD and NASH Prevalence in USA



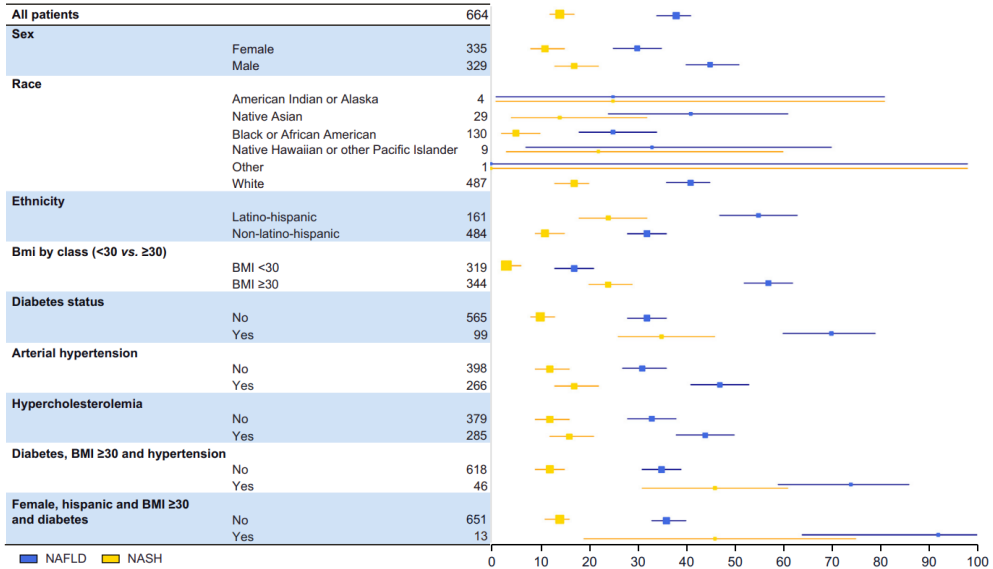
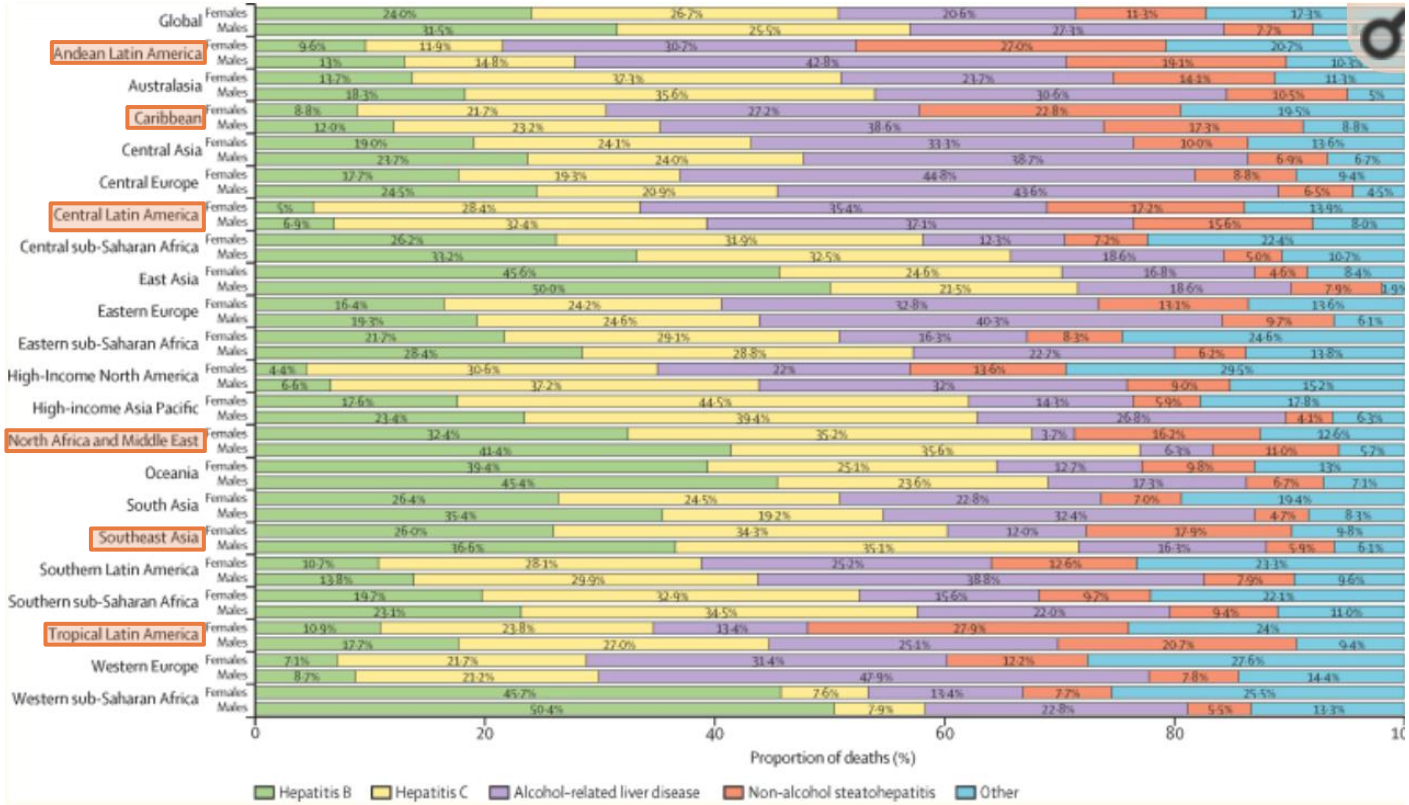


Fig. 2. The prevalence of NAFLD and NASH in the entire cohort and different racial/ethnic groups. NAFLD was present in 38% and NASH was present in 14%. Both entities were most common in Latino-Hispanics. NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis. Differences between rates and proportions of occurrences were assessed with use of the Fisher exact test. The 95% CIs were computed with the Clopper-Pearson method. (This figure appears in color on the web.)

Harrison SA et al. *J Hepatol*. 2021.

CLDF
Chronic Liver Disease Foundation

Global Deaths Due to NASH



Lancet Gastroenterol Hepatol. 2020 Mar; 5(3): 245–266,

CLDF
Chronic Liver Disease Foundation

Target Topics for Treatment Disparity

- Knowledge Gaps in Diagnosis/Work Up
- Access to Care/Resources
- Lifestyle Modification and Current Therapy
- Clinical Trial Demographics and Genetic Influences

CLDF
Chronic Liver Disease Foundation

Lack of Knowledge

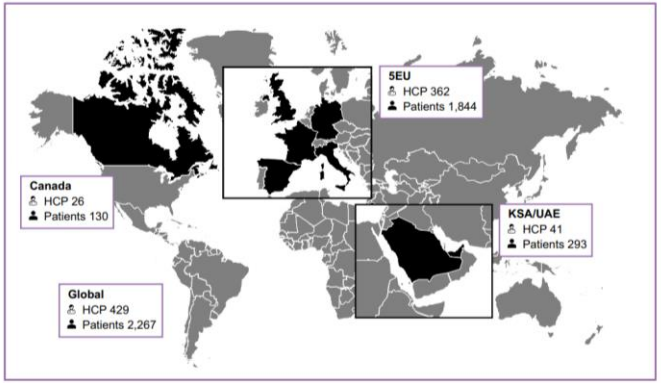
- Under-Investigation of abnormal liver chemistry tests and/or imaging
- Unclear who “at risk” populations are
- Substantial variation in practice patterns around the globe
- Lack of confidence to make appropriate diagnosis

Gracen L et al. *Diabetes Medicine*. 2022; Anstee Q et al. *J Hep Reports.* 2022.

CLDF
Chronic Liver Disease Foundation

Real World Management of NASH

Real-world NASH data were analyzed to identify the degree of disconnect between reference guidelines[1] and real-world clinical practice in the 5EU, Canada, and the Middle East

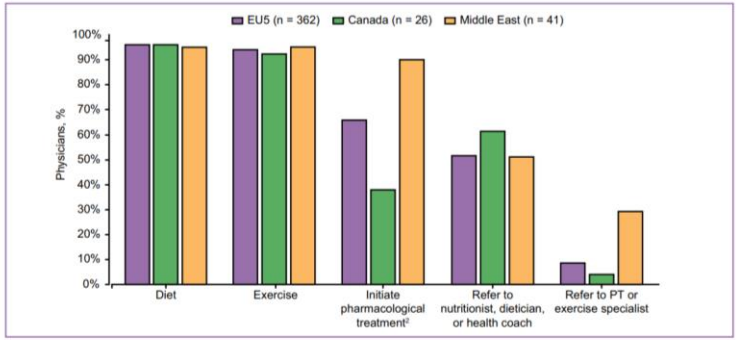


Real-world NASH management differs across region/specialty:

- ✓ Liver biopsy at diagnosis varies:
  EU5 48%; Canada 35%; Middle East 20%
- ✓ Specialist variation in diagnostic VCTE use:
  Hepatologists 80%; gastroenterologists 69%;
  diabetologists 63%
- ✓ Initiation of pharmacological treatment[2] to address NASH varies:
  Middle East 90%; EU5 66%; Canada 38%

Substantial disconnects between reference guidelines and real-world practice were observed:

- ✓ 82% of obese/metabolic patients received liver ultrasound
- ✓ 68% of patients received non-invasive tests conducted at diagnosis
- ✓ 70% of patients received lifestyle advice
  - ✓ 52% were referred to nutritionist/dietician/health coach
  - ✓ 10% were referred to personal trainer (PT)/exercise specialist
- ✓ 67% of patients received treatment for NASH,[2] most commonly statins, metformin, and vitamin E



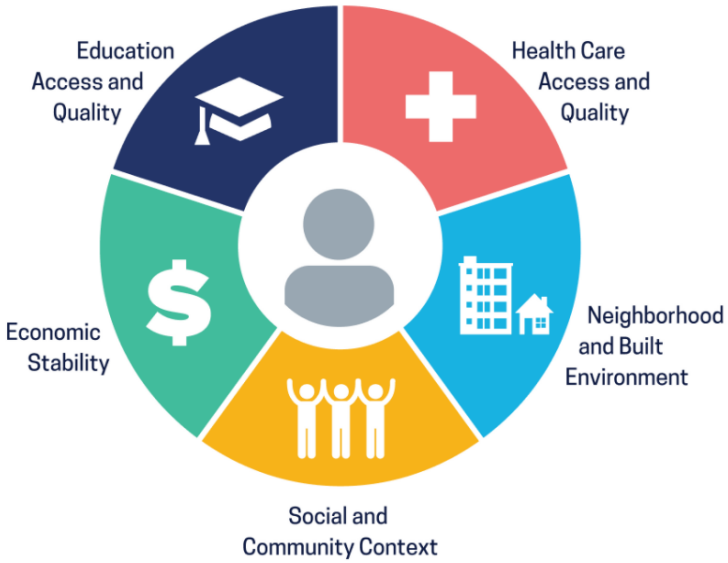
Establishment, awareness, and adherence to regional and national guidelines may improve outcomes for patients with NASH

[1] European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), and European Association for the Study of Obesity (EASO) jointly developed management guidelines
[2] Initiating pharmacological treatment includes initiating drug to control underlying cause of disease, initiating off-label NASH drug, and prescribing a weight-loss drug

CLDF
Chronic Liver Disease Foundation

Anstee Q et al. *J Hep Reports.* 2022.

Access to Care/Resources



- There is a need for implementation of a NAFLD care pathway
  - Integrated into standard practice care for diabetes
- Geographic Influences
- Socio-economical Influences

Gracen L et al. *Diabetes Medicine*. 2022.

CLDF
Chronic Liver Disease Foundation

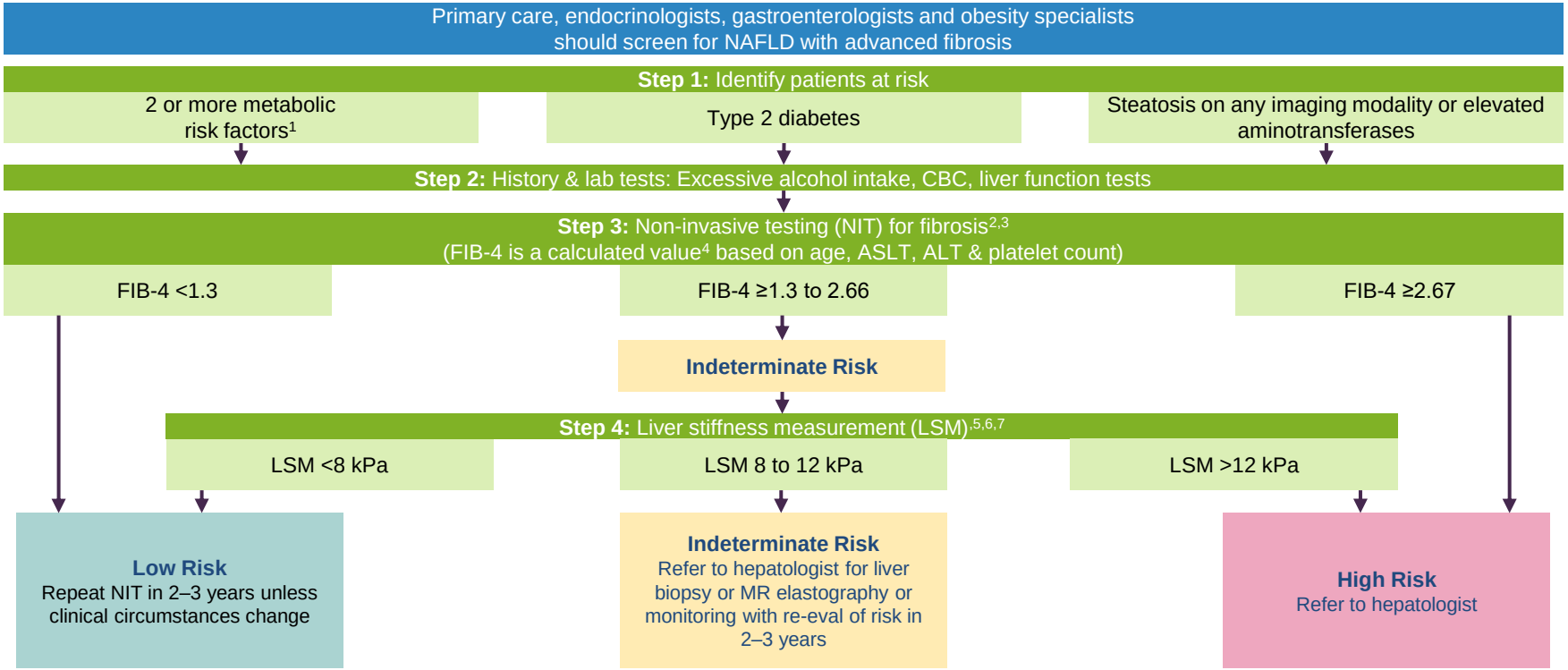
Access to Care/Resources

The European Association for the Study of the Liver (EASL) European Association for the Study of Diabetes (EASD) European Association for the Study of Obesity (EASO)	Recommends Screening for NAFLD in people with obesity, metabolic syndrome and in particular T2DM
Latin American Association for the Study of the Liver (ALEH) Asian Pacific Association for the Study of the Liver (APASL) Asia-Pacific Working Party on NAFLD	Recommends considering screening in certain high-risk population, including those with obesity and T2DM
American Diabetes Association	Recommends screening for NASH and advanced fibrosis in patients with elevated liver enzymes or hepatic steatosis on US
American Association of the Study of Liver Disease (AASLD)	Does not recommend systematic screening in these groups, given the lack of cost-effectiveness data for such efforts

Lazarus JV et al. *Nat Rev Gastroenterol Hepatol*. 2022 Jan;19(1):60-78.

Chronic Liver Disease Foundation

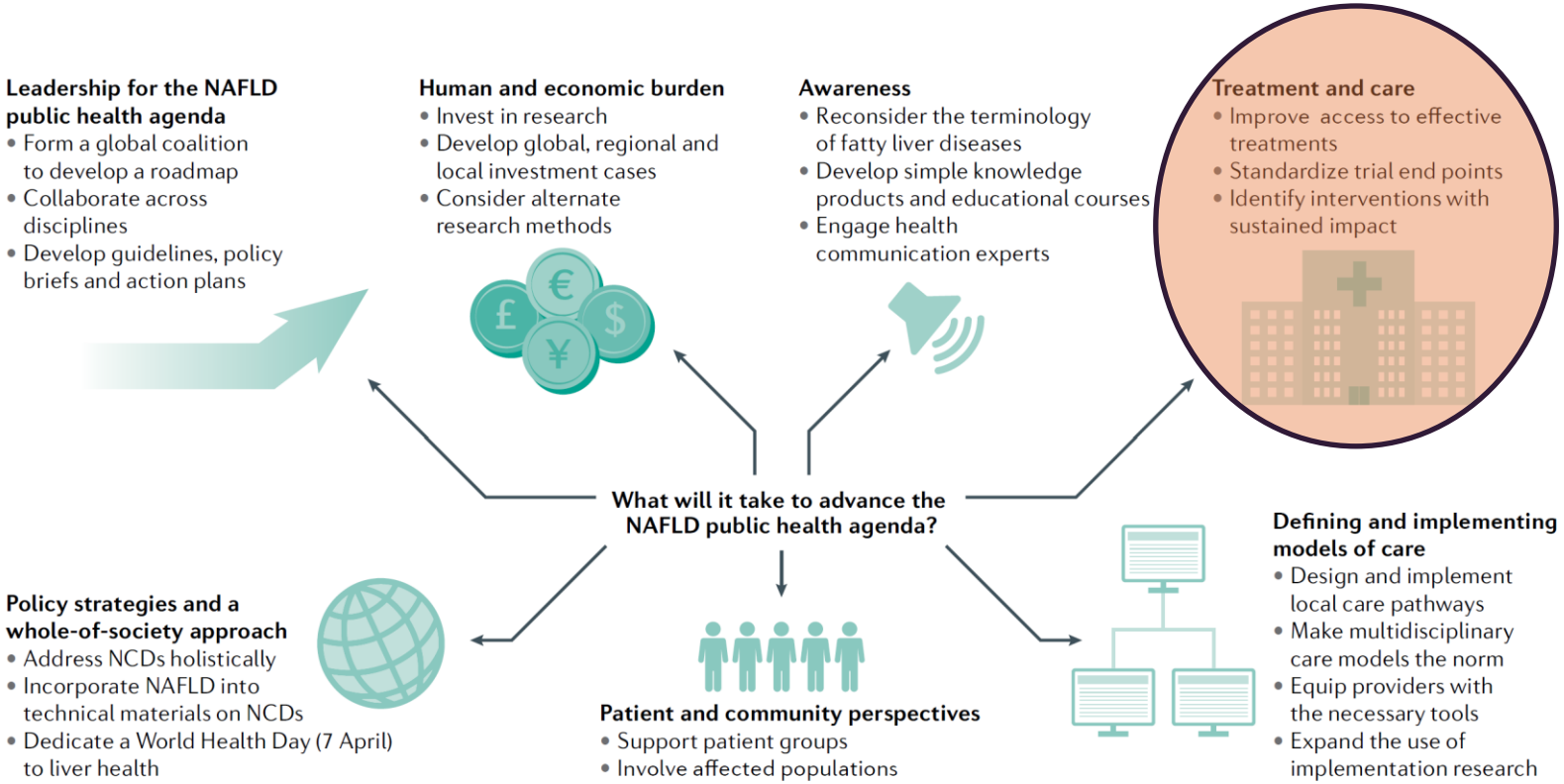
AGA NAFLD Care Pathway



CLDF
Chronic Liver Disease Foundation

Kanwal F et al. *Gastroenterol*. 2021.

Advancing the Global Public Health Agenda for NAFLD: A Consensus Statement



Lazarus JV et al. *Nat Rev Gastroenterol Hepatol*. 2022 Jan;19(1):60-78.

Lifestyle Modification

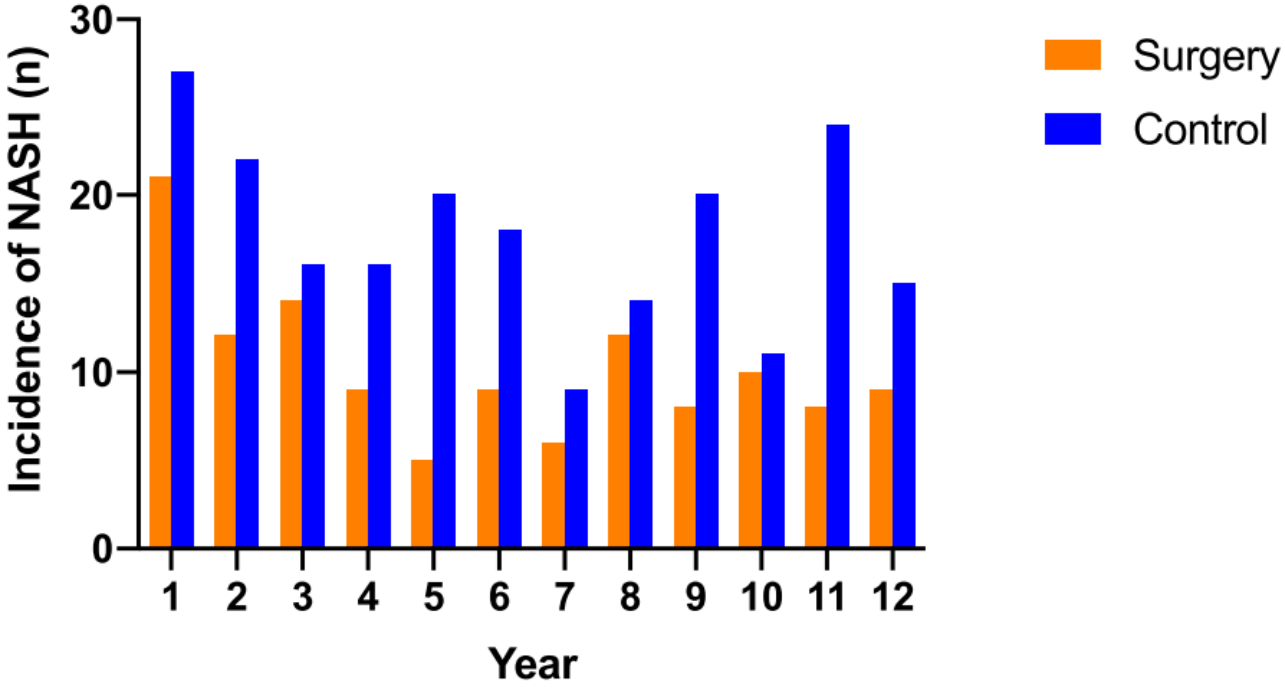
- Socioeconomic Factors
  - Prevent access to nutritionally healthy food choices
  - Impact ability to obtain proper exercise advice and the opportunity to access exercise equipment or even have time to exercise

Bariatric Surgery

506

Table 1
Comparison of basel

	p value
Age (years)	0.83
Female	0.19
White	0.52
Initial BMI (kg/m^2	0.04
Government insur	0.14
DM Type II	0.28
Viral Hepatitis	0.88
NASH	0.29
Hypertension	0.82
GERD	0.66
Current alcohol us	0.55
Current smoker	0.82
CHF/CAD	0.66
COPD	0.5
OSA	0.62
Degenerative Joint	0.15



Kwak M et al. *Am J Surgery*. 2020;219: 504-507.

CLDF
Chronic Liver Disease Foundation

Geographic Disparities in NAFLD Treatment

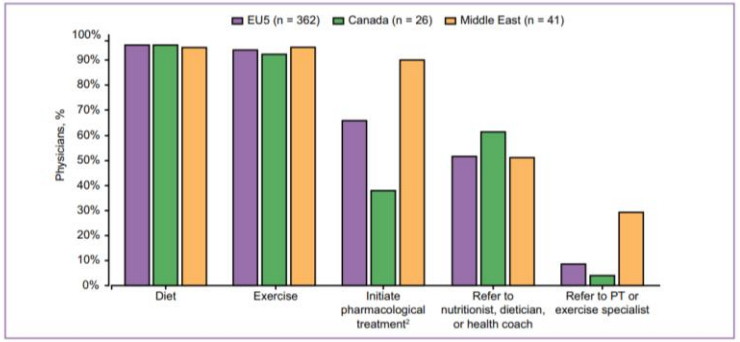
Real-world NASH data were analyzed to identify the degree of disconnect between reference guidelines[1] and real-world clinical practice in the 5EU, Canada, and the Middle East

Real-world NASH management differs across region/specialty:

- ✓ Liver biopsy at diagnosis varies:
  EU5 48%; Canada 35%; Middle East 20%
- ✓ Specialist variation in diagnostic VCTE use:
  Hepatologists 80%; gastroenterologists 69%; diabetologists 63%
- ✓ Initiation of pharmacological treatment[2] to address NASH varies:
  Middle East 90%; EU5 66%; Canada 38%

Substantial disconnects between reference guidelines and real-world practice were observed:

- ✓ 82% of obese/metabolic patients received liver ultrasound
- ✓ 68% of patients received non-invasive tests conducted at diagnosis
- ✓ 70% of patients received lifestyle advice
  - ✓ 52% were referred to nutritionist/dietician/health coach
  - ✓ 10% were referred to personal trainer (PT)/exercise specialist
- ✓ 67% of patients received treatment for NASH,[2] most commonly statins, metformin, and vitamin E



Establishment, awareness, and adherence to regional and national guidelines may improve outcomes for patients with NASH

[1] European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), and European Association for the Study of Obesity (EASO) jointly developed management guidelines
[2] Initiating pharmacological treatment includes initiating drug to control underlying cause of disease, initiating off-label NASH drug, and prescribing a weight-loss drug

CLDF
Chronic Liver Disease Foundation

Anstee Q et al. *J Hep Reports*. 2022.

Geographic Disparities in NAFLD Treatment

Survey of 102 Romanian Gastroenterologists

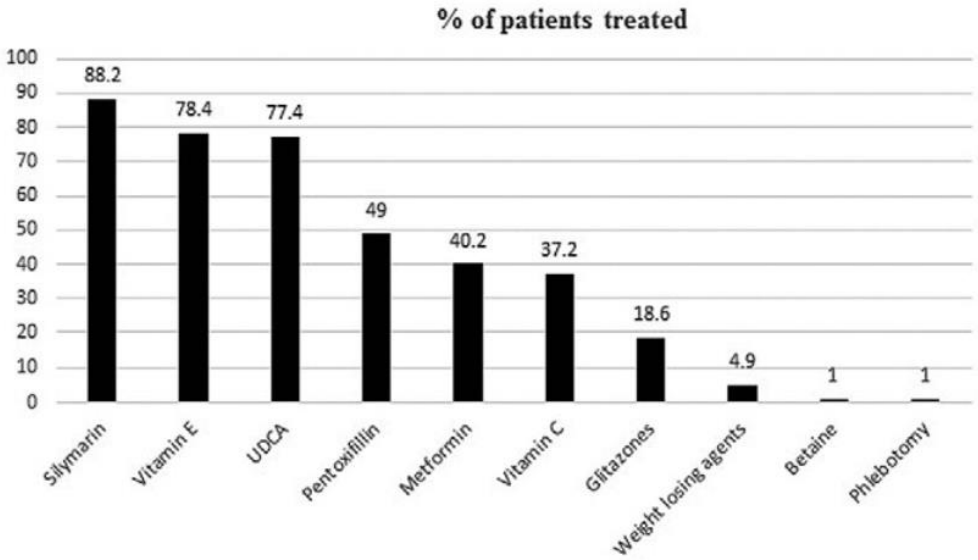


Fig. 1. Proportion of patients treated with different pharmacological agents.

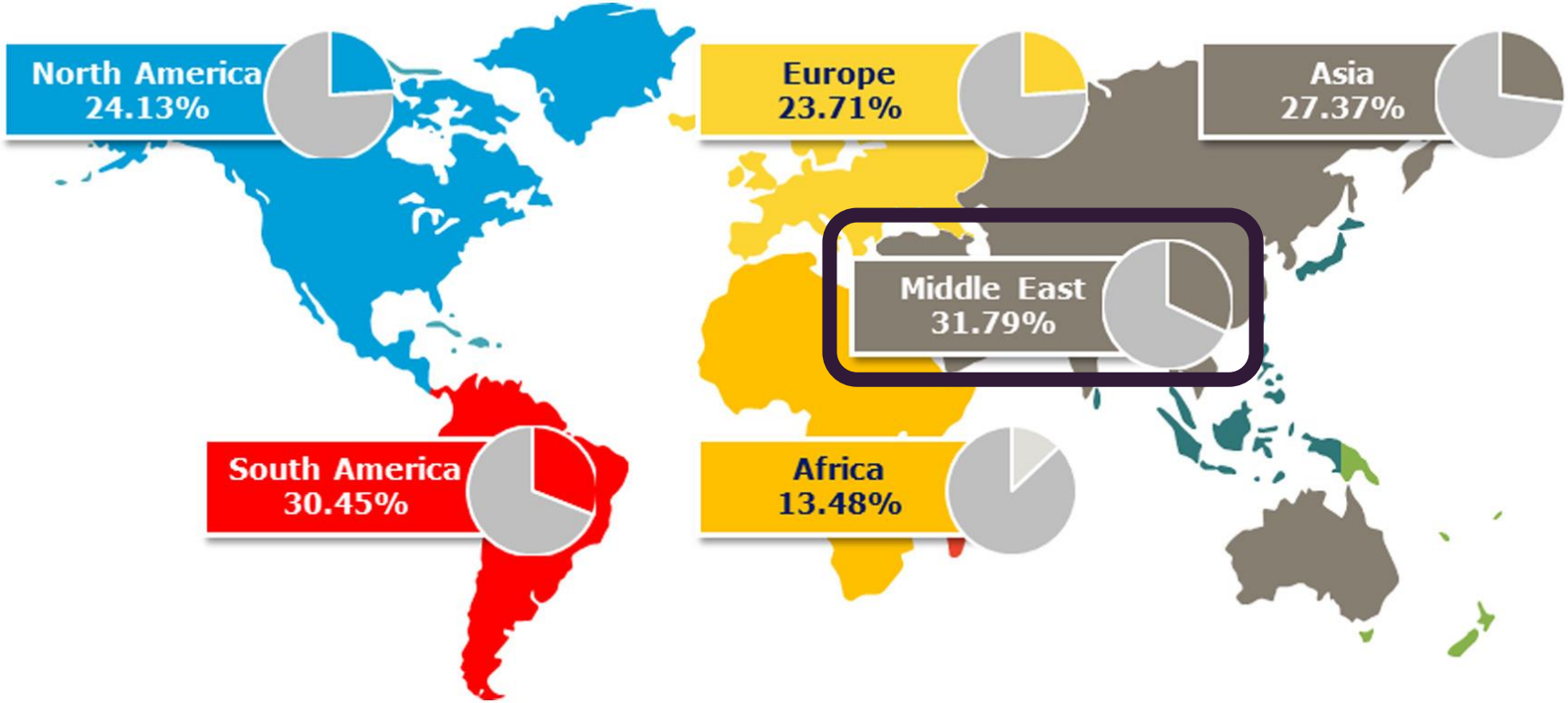
Iacob S et al. *J Gastrointestin Liver Dis*. 2016;25:183-189.

CLDF
Chronic Liver Disease Foundation

Disparities in Drug Development in NASH

- Lack of diversity in enrollment in late-stage clinical trials
- Potential differences in response to mechanism
  - Genetic influences
  - Epigenetic influences
  - Microbiome impact

NAFLD Prevalence Worldwide



Younossi ZM et al. Global epidemiology of nonalcoholic fatty liver disease–meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology.* 64, 73–84 (2016).

Ethnic Variation in Large Phase 2b and 3 NASH Trials

Semaglutide Study

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Full Analysis Population).*

Stellar Studies

	Lanifibran 1200 mg	800 mg	Placebo	Overall
NAS††	5.9±0.9	5.9±1.0	5.9±1.1	5.9±1.0
NAS ≥6 — no. (%)	61 (73)	63 (76)	56 (69)	180 (73)
Alanine aminotransferase level — IU/liter	63.6±43.4	64.1±41.4	56.9±31.6	61.6±39.2
Aspartate aminotransferase level — IU/liter	43.9±24.8	53.9±43.4	43.3±24.1	47.1±32.3

Table 1. Baseline demographic and clinical characteristics.

	STELLAR-3			STELLAR-4		
Characteristic	**SEL 18 mg (n = 322)**	**SEL 6 mg (n = 321)**	**Placebo (n = 159)**	**SEL 18 mg (n = 354)**	**SEL 6 mg (n = 351)**	**Placebo (n = 172)**
Demographics						
Age (years)	59 (51–64)	59 (53–64)	59 (51–63)	59 (53–66)	59 (52–64)	61 (55–67)
Female sex	181 (56)	196 (61)	76 (48)	216 (61)	230 (66)	101 (59)
Race						
White	219 (68)	227 (71)	113 (71)	261 (74)	279 (79)	136 (79)
Asian	88 (27)	84 (26)	41 (26)	73 (21)	59 (17)	33 (19)
Black	8 (2)	5 (2)	2 (1)	5 (1)	4 (1)	1 (1)
Ethnicity						
Hispanic or Latino	52 (16)	48 (15)	22 (14)	49 (14)	51 (15)	22 (13)
Not Hispanic or Latino	269 (84)	269 (84)	137 (86)	300 (85)	297 (85)	149 (87)
Metabolic factors						
Diabetes mellitus	224 (70)	223 (69)	116 (73)	270 (76)	269 (77)	135 (78)
Body mass index (kg/m^2)	32.4 (29.5–37.1)	32.4 (28.4–36.1)	32.2 (27.5–37.5)	32.4 (28.5–37.4)	33.6 (29.5–37.9)	32.9 (27.9–37.5)

Continuous variables are median (interquartile range) and categorical variables are n (%).
SEL, selonsertib.

CLDF
Chronic Liver Disease Foundation

Pooled Prevalence of Hispanic Patients in NAFLD Trials

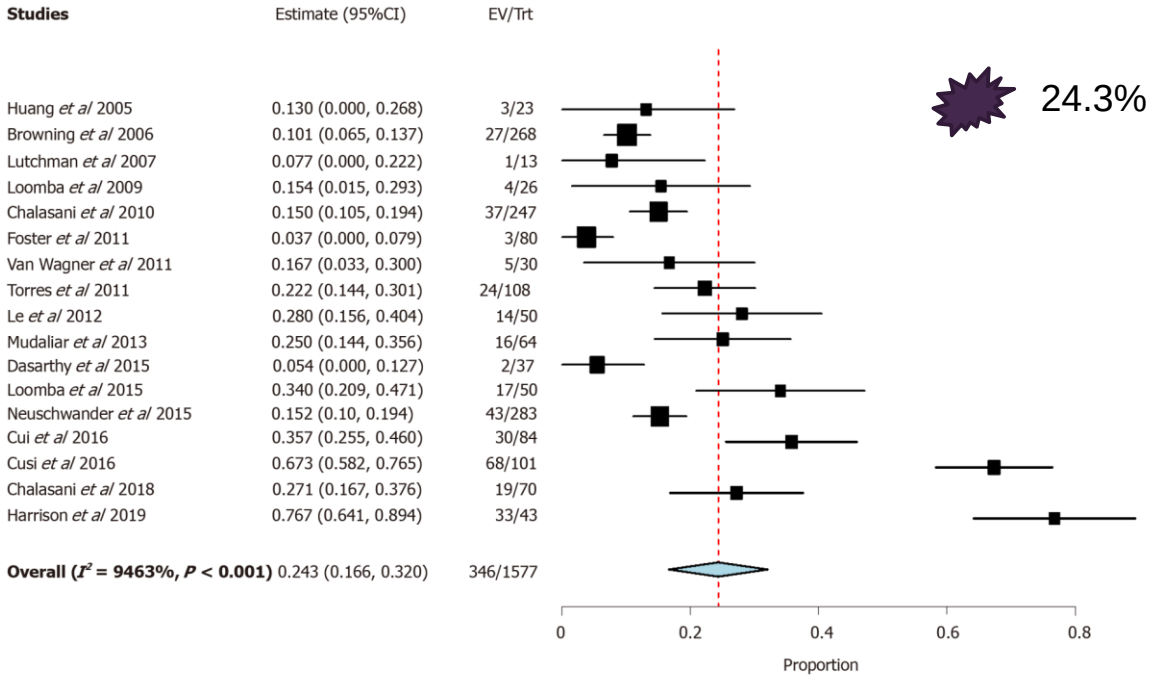
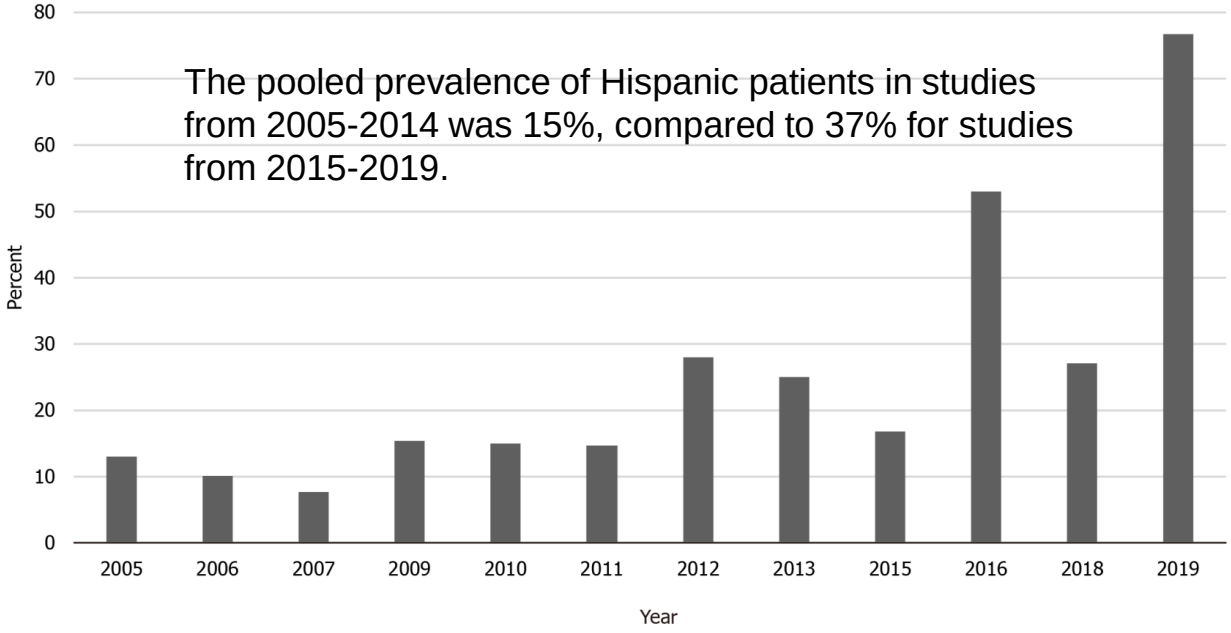


Figure 2 Pooled prevalence of Hispanic patients among studies reporting ethnicity.

Patel P et al. Racial disparities in NAFLD trials. *World J Hepatol.* 2020 August 27; 12(8): 506-518.

CLDF
Chronic Liver Disease Foundation

Percentage of Hispanic Enrollment in NAFLD Trials Grouped by Year



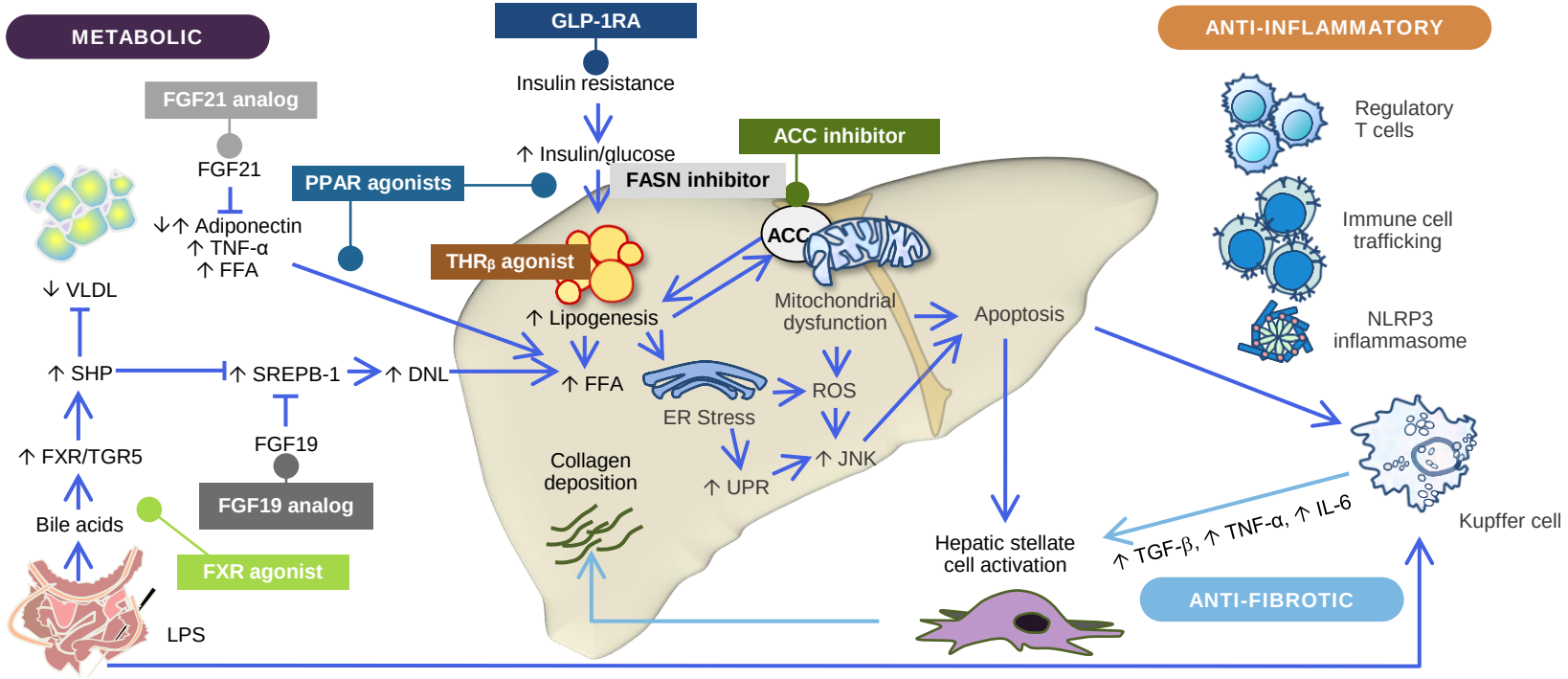
Patel P et al. Racial disparities in NAFLD trials. *World J Hepatol.* 2020 August 27; 12(8): 506-518.

CLDF
Chronic Liver Disease Foundation

Disparities in Drug Development in NASH

- Lack of diversity in enrollment in late-stage clinical trials
- Potential differences in response to mechanism
  - Genetic influences
  - Epigenetic influences
  - Microbiome impact

NASH: Potential Therapeutic Targets

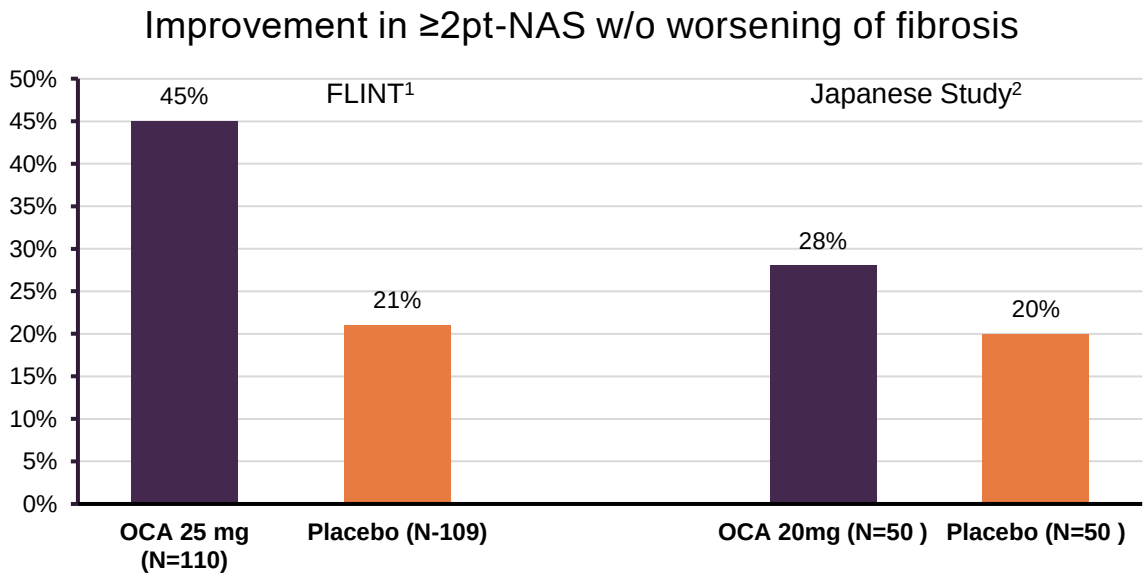


Adapted from: Konerman MA et al. *J Hepatol*. 2018;68:362–375.

CLDF
Chronic Liver Disease Foundation

Difference in Response to Treatment

- Lower response in Japanese study for OCA

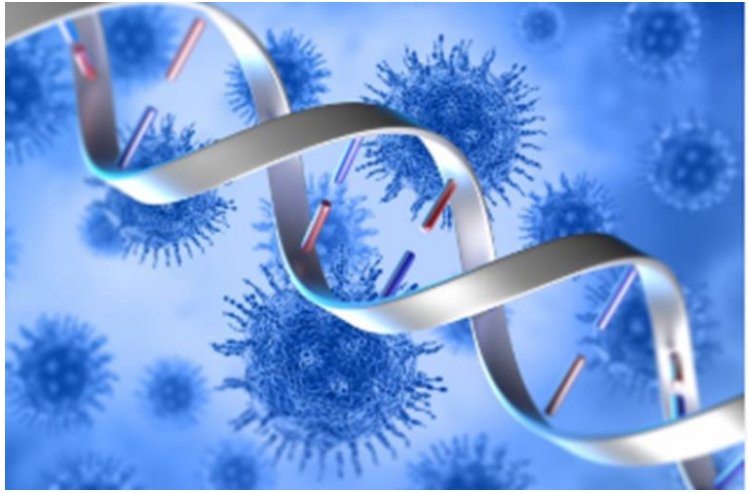


1. Neuschwander-Tetri et al. *Lancet*. 2015; 2. Press Release Oct 28, 2015 - ICPTNews.

CLDF
Chronic Liver Disease Foundation

Genetic Influences – Linked to Fatty Liver

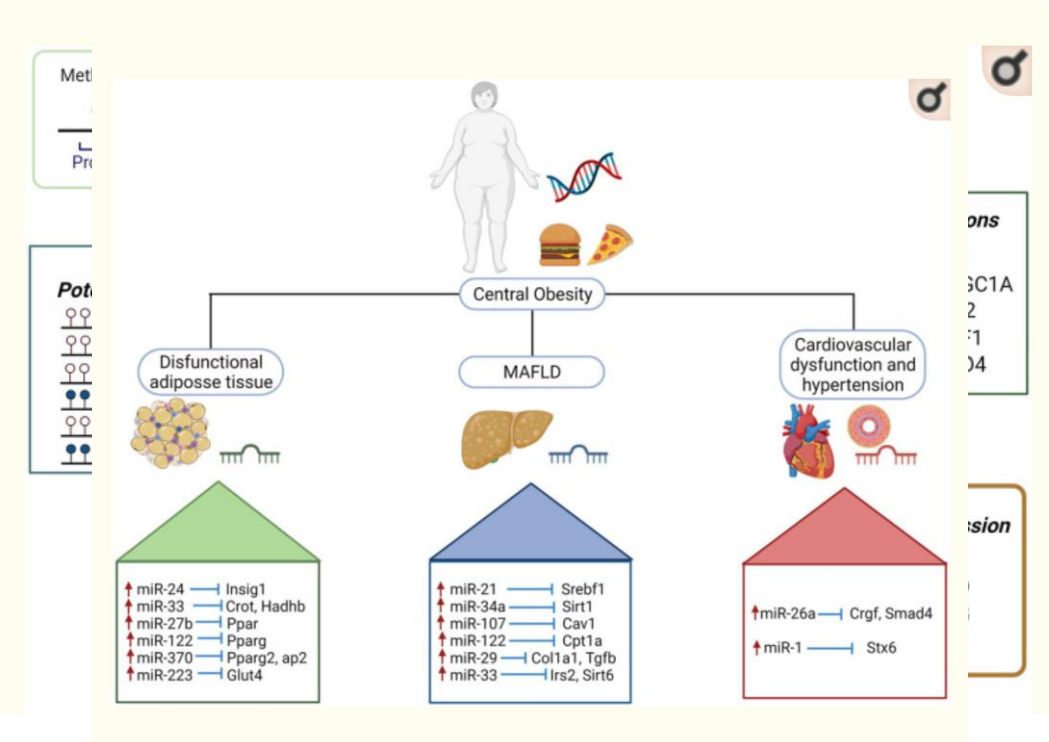
- PNPLA3 I148M variant
  - Hispanics – 49%
  - Non-Hispanic Whites – 23%
  - African Americans – 17%



Romeo S, et al. Genetic variation in PNPLA3 confers susceptibility to n.nalcoholic fatty liver disease. *Nat Genet.* 2008; 40: 1461-1465.

CLDF
Chronic Liver Disease Foundation

Epigenetic Influences- Linked to Fatty Liver



Rodriguez-Sanabria JS et al. *Frontier Medicine*. 2021.

CLDF
Chronic Liver Disease Foundation

Nutrition and Gut Microbiome

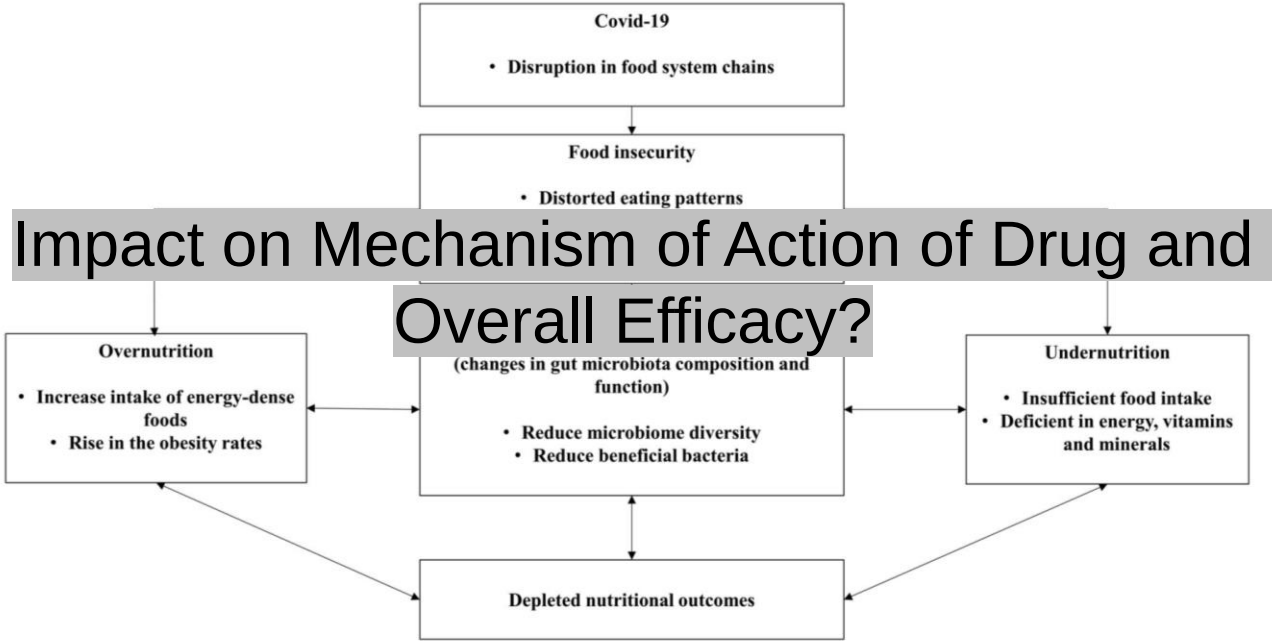


Figure 2 Potential mechanism interlinked food insecurity, malnutrition, and gut microbial changes.

Impact on Mechanism of Action of Drug and Overall Efficacy?

Shafiee NH et al. *JGH Open*. 2022;6:112–119.

CLDF
Chronic Liver Disease Foundation

Summary

- There is a clear, broad based, lack of understanding about identification of “at risk” NASH patients
- Access to care and resources are disparate and generally limited
- Standard of care treatment is not uniform
- Clinical trials in NASH under-represent ethnic minorities such as Hispanic and African-American
  - Barriers may include mistrust, reduced access to healthcare, financial/time constraints, lack of education about trials, cultural or language impediments
- Racial and Ethnic influences may impact response to treatment and should be evaluated carefully

CLDF
Chronic Liver Disease Foundation