NAFLD MAFLD

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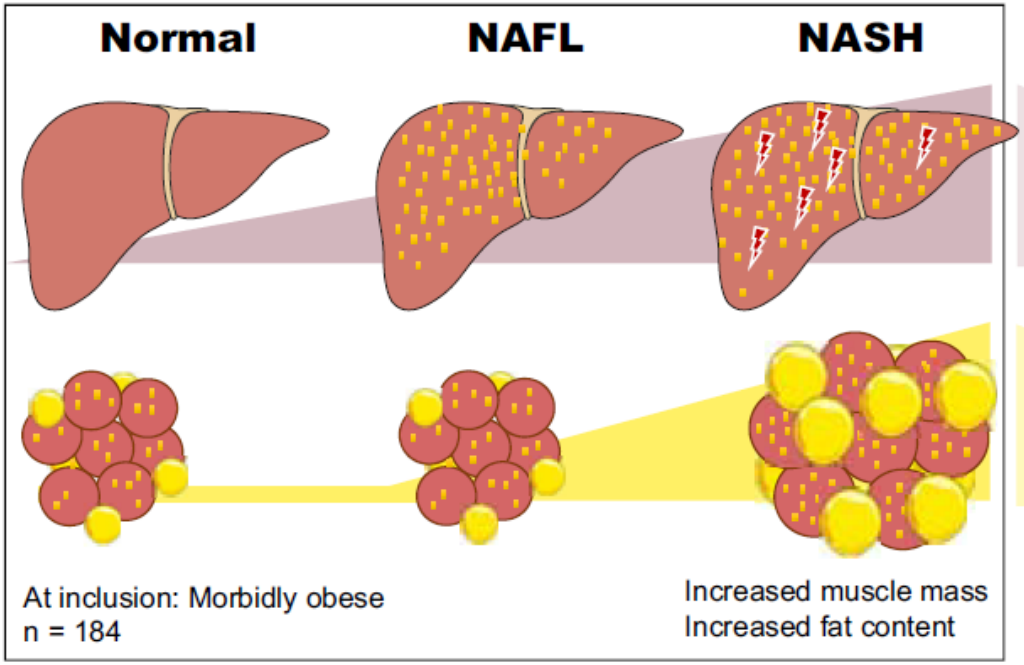

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Bible Class Gastroenterolgy

Definitions

A) NAFLD

NAFLD is characterised by

- excessive hepatic fat accumulation,
- associated with insulin resistance (IR),
- and defined by the presence of steatosis in >5% of hepatocytes

The diagnosis of NAFLD requires the **exclusion** of both secondary causes and of a daily alcohol consumption >30 g for men and >20 g for women.

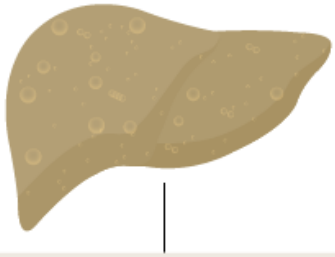
Definitions

Which pathologically distinct conditions with different prognoses does NAFLD include?

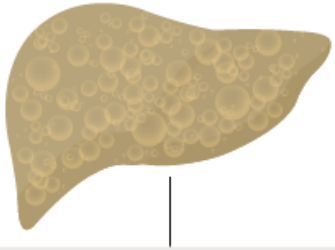
- non-alcoholic fatty liver (NAFL)
- non-alcoholic steatohepatitis (NASH)

What are the different NASH subclasses?

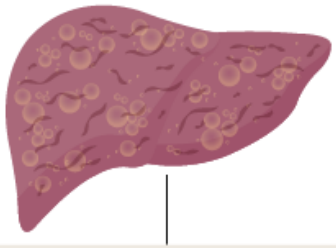
And which risks are associated with which subclass?



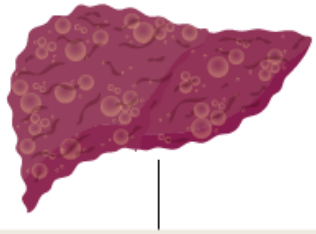
NAFL
- Cardiovascular
- Non-hepatic malignancies
- Renal disease
- Cerebrovascular disease



NASH without fibrosis
- Cardiovascular
- Non-hepatic malignancies
- Liver disease
- Renal disease



NASH with F1 and F2
- Liver disease
- Cardiovascular disease
- Hepatic and non-hepatic malignancies
- Renal disease



NASH with F3 and F4
- Liver disease
- Cardiovascular disease
- Hepatic and non-hepatic malignancies
- Renal disease

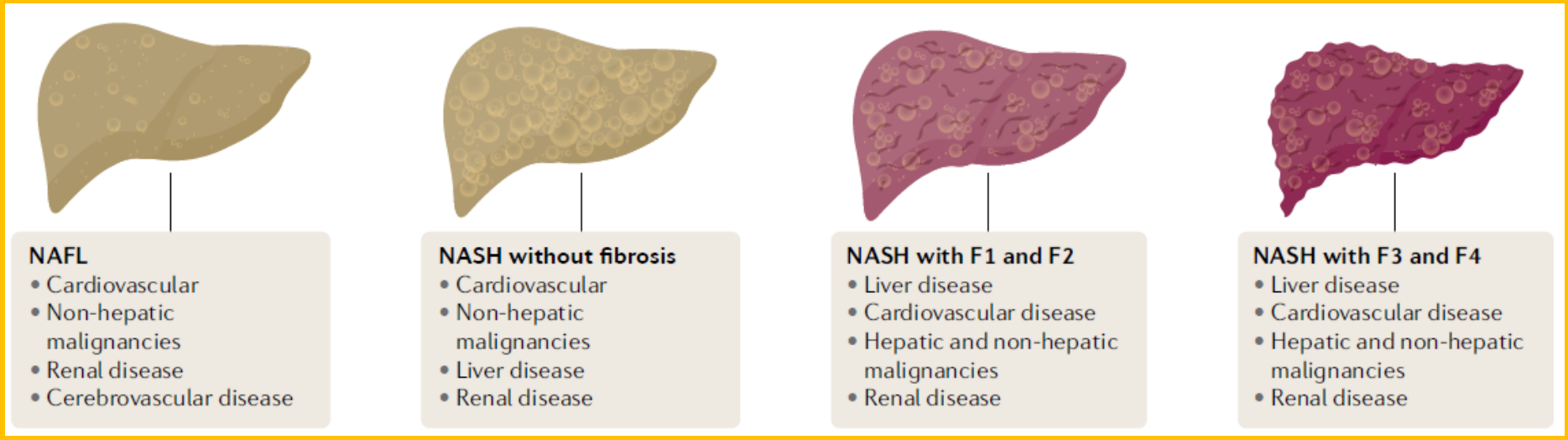
Which other diseases can present similar to NAFLD?

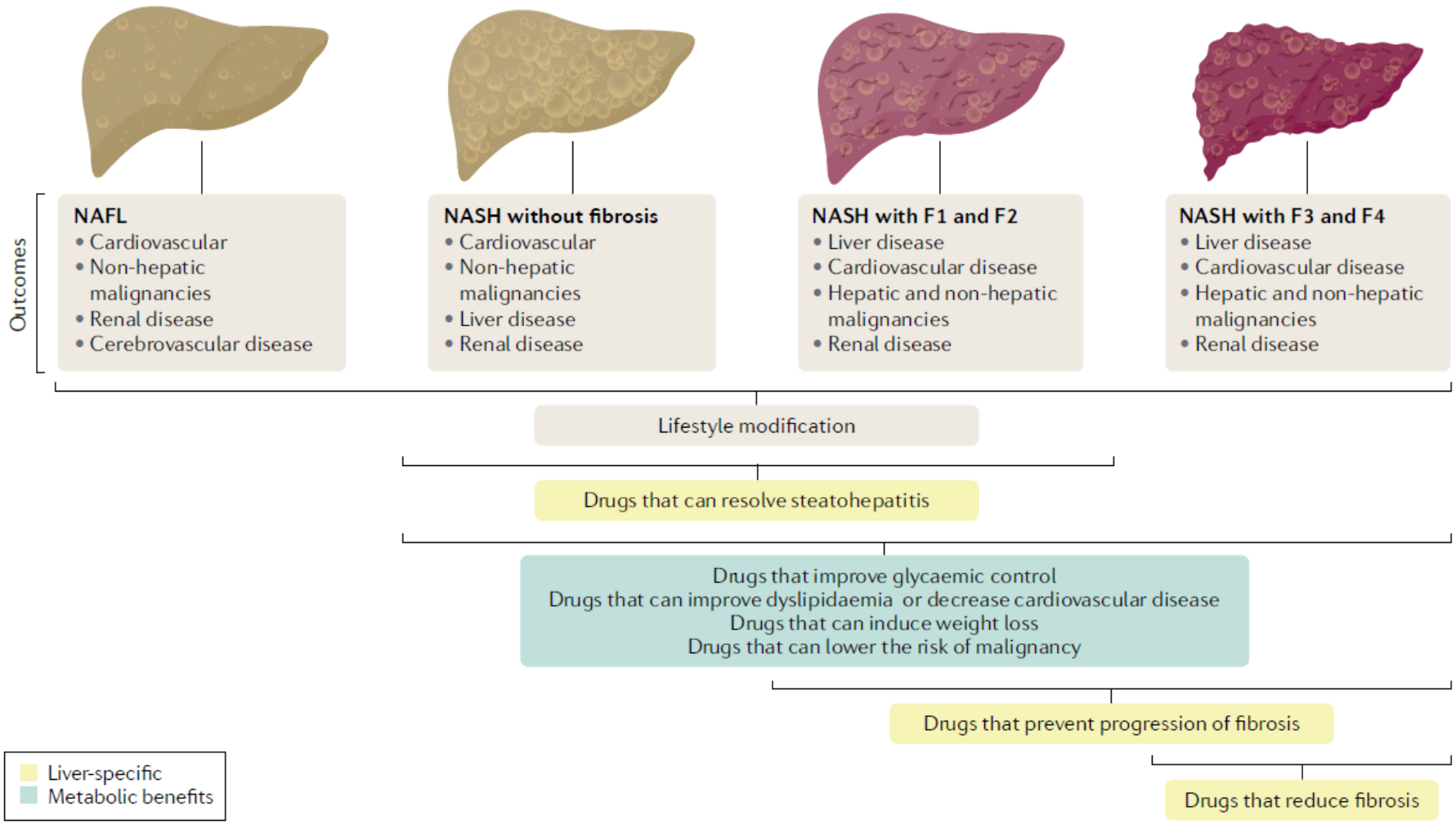
Table 2. The spectrum of NAFLD and concurrent diseases.

Disease	Subclassification	Most common concurrent diseases
NAFLD*	NAFL • Pure steatosis • Steatosis and mild lobular inflammation NASH • Early NASH: no or mild (F0-F1) fibrosis • Fibrotic NASH: significant (≥F2) or advanced (≥F3, bridging) fibrosis • NASH-Cirrhosis (F4) Hepatocellular carcinoma^	° AFLD-Alcoholic fatty liver disease ° Drug-induced fatty liver disease ° Hepatitis C virus-associated fatty liver (genotype 3) ° Others • Haemochromatosis • Autoimmune hepatitis • Coeliac disease • Wilson's disease • A/hypo-betalipoproteinaemia lipoatrophy • Hypopituitarism, hypothyroidism • Starvation, parenteral nutrition • Inborn errors of metabolism (Wolman disease [lysosomal acid lipase deficiency])

When should which treatment strategy be applied?

- **Lifestyle**
- **Liver specific: steatitis**
- **Liver specific: fibrosis**
- **Metabolic benefits**

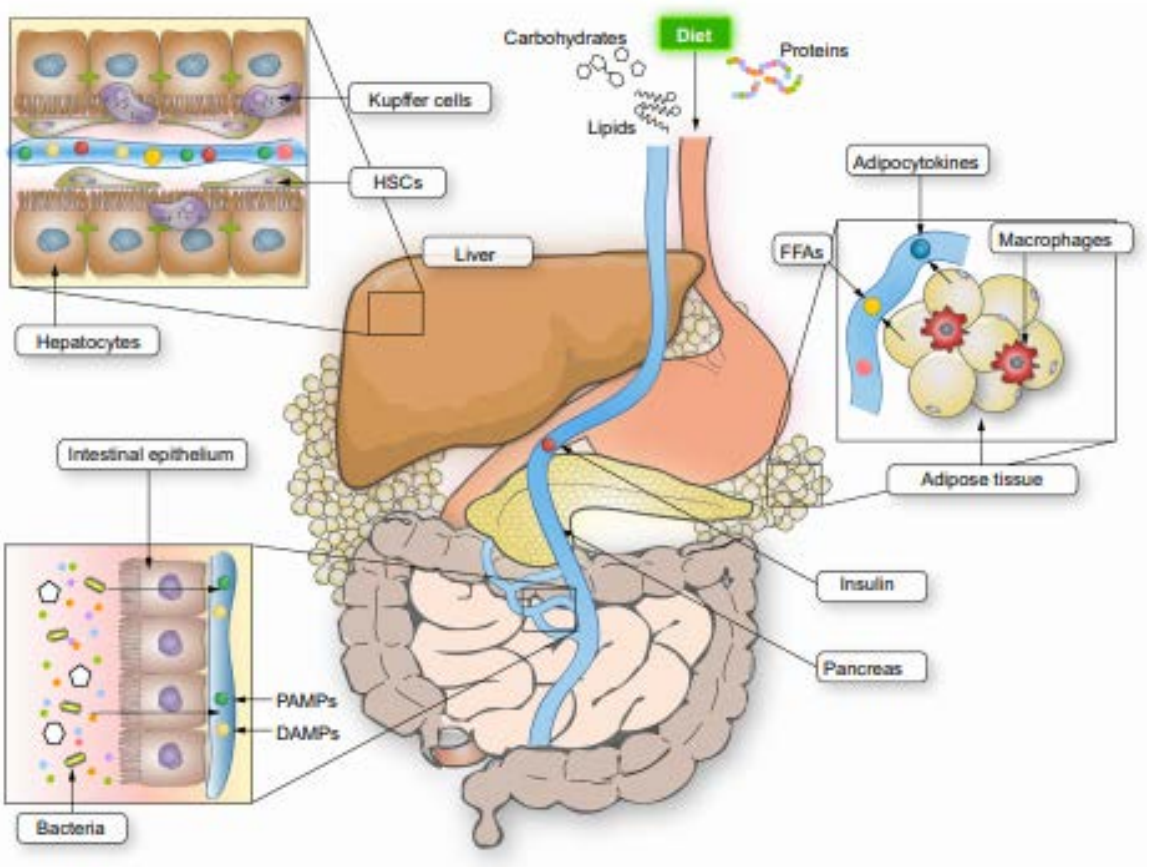



Outcomes
NAFL
• Cardiovascular
• Non-hepatic malignancies
• Renal disease
• Cerebrovascular disease
NASH without fibrosis
• Cardiovascular
• Non-hepatic malignancies
• Liver disease
• Renal disease
NASH with F1 and F2
• Liver disease
• Cardiovascular disease
• Hepatic and non-hepatic malignancies
• Renal disease
NASH with F3 and F4
• Liver disease
• Cardiovascular disease
• Hepatic and non-hepatic malignancies
• Renal disease
Lifestyle modification
Drugs that can resolve steatohepatitis
Drugs that improve glycaemic control
Drugs that can improve dyslipidaemia or decrease cardiovascular disease
Drugs that can induce weight loss
Drugs that can lower the risk of malignancy
Drugs that prevent progression of fibrosis
Drugs that reduce fibrosis
Liver-specific
Metabolic benefits

Which mechanisms and organ systems are important in the pathophysiology of NAFLD?

Pathogenesis of NAFLD probably involves inter-organ crosstalk

Adipose tissue, pancreas, gut, and liver

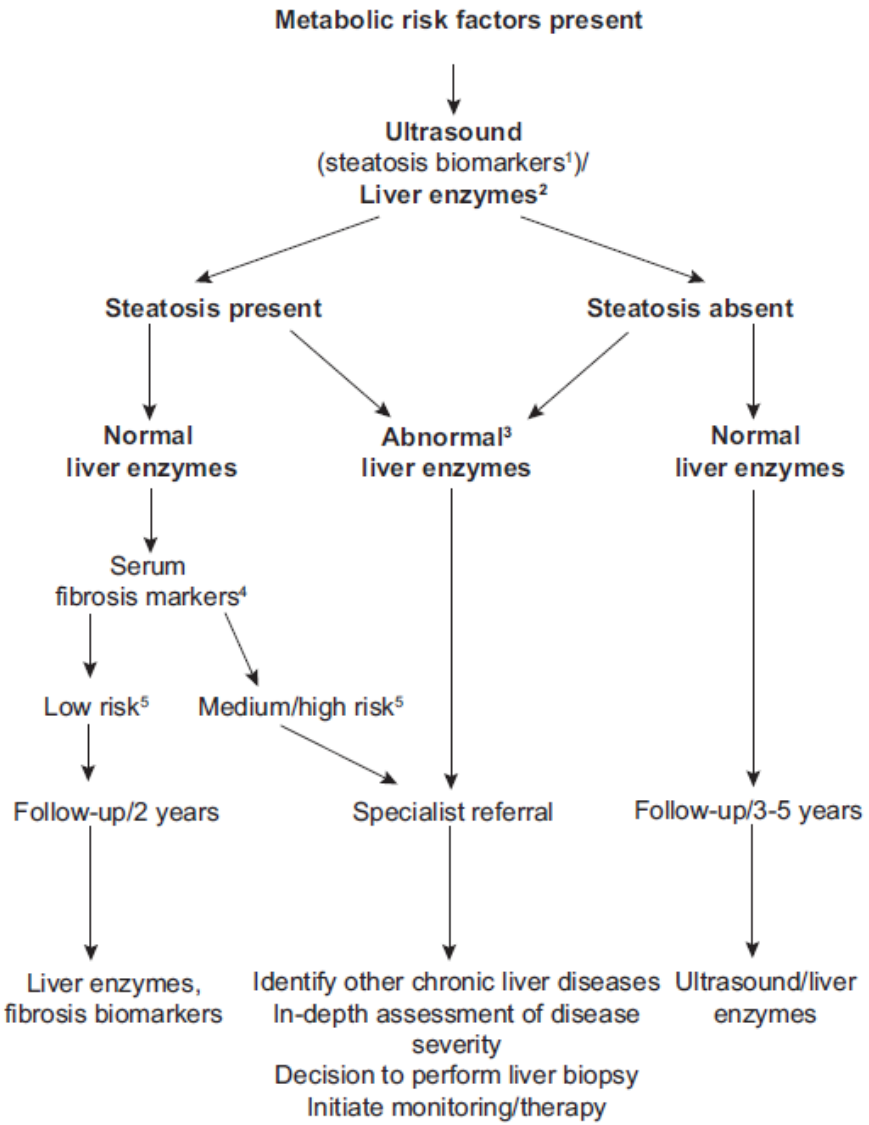


Nobili, V et al. J Hepatol 2013;58:1218–29

Which patients should be screened for NAFLD?

Which methods should be applied?

How often should a follow-up be performed?


Metabolic risk factors present
Ultrasound
(steatosis biomarkers[1])/
Liver enzymes[2]
Steatosis present
Steatosis absent
Normal liver enzymes
Abnormal[3] liver enzymes
Normal liver enzymes
Serum fibrosis markers[4]
Low risk[5]
Medium/high risk[5]
Follow-up/2 years
Specialist referral
Follow-up/3-5 years
Liver enzymes, fibrosis biomarkers
Identify other chronic liver diseases
In-depth assessment of disease severity
Decision to perform liver biopsy
Initiate monitoring/therapy
Ultrasound/liver enzymes

What should a comprehensive evaluation of a NAFLD patient look like?

Table 3. Protocol for a comprehensive evaluation of suspected NAFLD patients.

Level	Variable	
Initial	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 (aspartate and alanine transaminases (γ-glutamyl-trans-peptidase))
	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 *	1.	Ferritin and transferrin saturation
	2.	Tests for coeliac and thyroid diseases, polycystic ovary syndrome
	3.	Tests for rare liver diseases (Wilson, autoimmune disease, α1-antitrypsin deficiency)

*According to a priori probability or clinical evaluation.

What are the components of a comprehensive lifestyle intervention?

Table 5. Elements of a comprehensive lifestyle approach to NAFLD treatment.

Area	Suggested intervention
Energy restriction	• 500-1000 kcal energy defect, to induce a weight loss of 500-1000 g/week
	• 7-10% total weight loss target
	• Long-term maintenance approach, combining physical activity according to the principles of cognitive-behavioural treatment
Macronutrient composition	• Low-to-moderate fat and moderate-to-high carbohydrate intake • Low-carbohydrate ketogenic diets or high-protein
Fructose intake	• Avoid fructose-containing beverages and foods
Alcohol intake	• Strictly keep alcohol below the risk threshold (30 g, men; 20 g, women)
Coffee drinking	• No liver-related limitations
Exercise/physical activity	• 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions are generally preferred (brisk walking, stationery cycling) • Resistance training is also effective and promotes musculoskeletal fitness, with effects on metabolic risk factors • High rates of inactivity-promoting fatigue and daytime sleepiness reduce compliance with exercise

Which are the two main goals of NASH treatment in clinical trials?

The are two important histological end points in the ongoing clinical trials are

- Resolution of steatohepatitis and
- reversal of fibrosis

- **Which is the most advanced NASH trial (non-cirrhotic with fibrosis)?**
- **What is the name of the molecule used in this trial?**
- **What is the mechanism of action of this molecule?**
- **For which disease is this molecule already on the market?**

Table 2 | **Therapies currently beyond phase II for the treatment of non-cirrhotic NASH with fibrosis**

Medication	Mechanism of action	Effective dose	Phase II efficacy data		Phase III RCT	Planned interim analysis duration (weeks)	Comments
			Resolution of NASH	Decrease in fibrosis			
Obeticholic acid	FXR agonist	25 mg per day	No	Yes	REGENERATE (NCT02548351)	72	Interim analysis data submitted to FDA and received a CRL for additional post-interim data
Elafibranor	PPARα/δ agonist	120 mg per day	Yes	No	RESOLVE-IT (NCT02704403)	72	Interim analysis failed to show any treatment effect; the programme has been terminated
Resmetirom	THRβ agonist	80–100 mg per day	Yes	No	MAESTRO (NCT03900429)	52	Recruiting
Aramchol	SCD1 inhibitor	300 mg twice daily	Yes	No	ARMOR (NCT04104321)	52	Recruiting
Cenicriviroc	CCR2–CCR5 antagonist	150 mg per day	No	Yes	AURORA (NCT03028740)	52	Terminated due to lack of efficacy

CCR, CC-chemokine receptor; CRL, complete response letter; FXR, farnesoid X receptor; NASH, nonalcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; RCT, randomized controlled trial; SCD1, stearoyl-CoA desaturase 1; THRβ, thyroid hormone receptor-β.

What is the difference between OCA (ocaliva) and other FXR agonists tested for NASH?

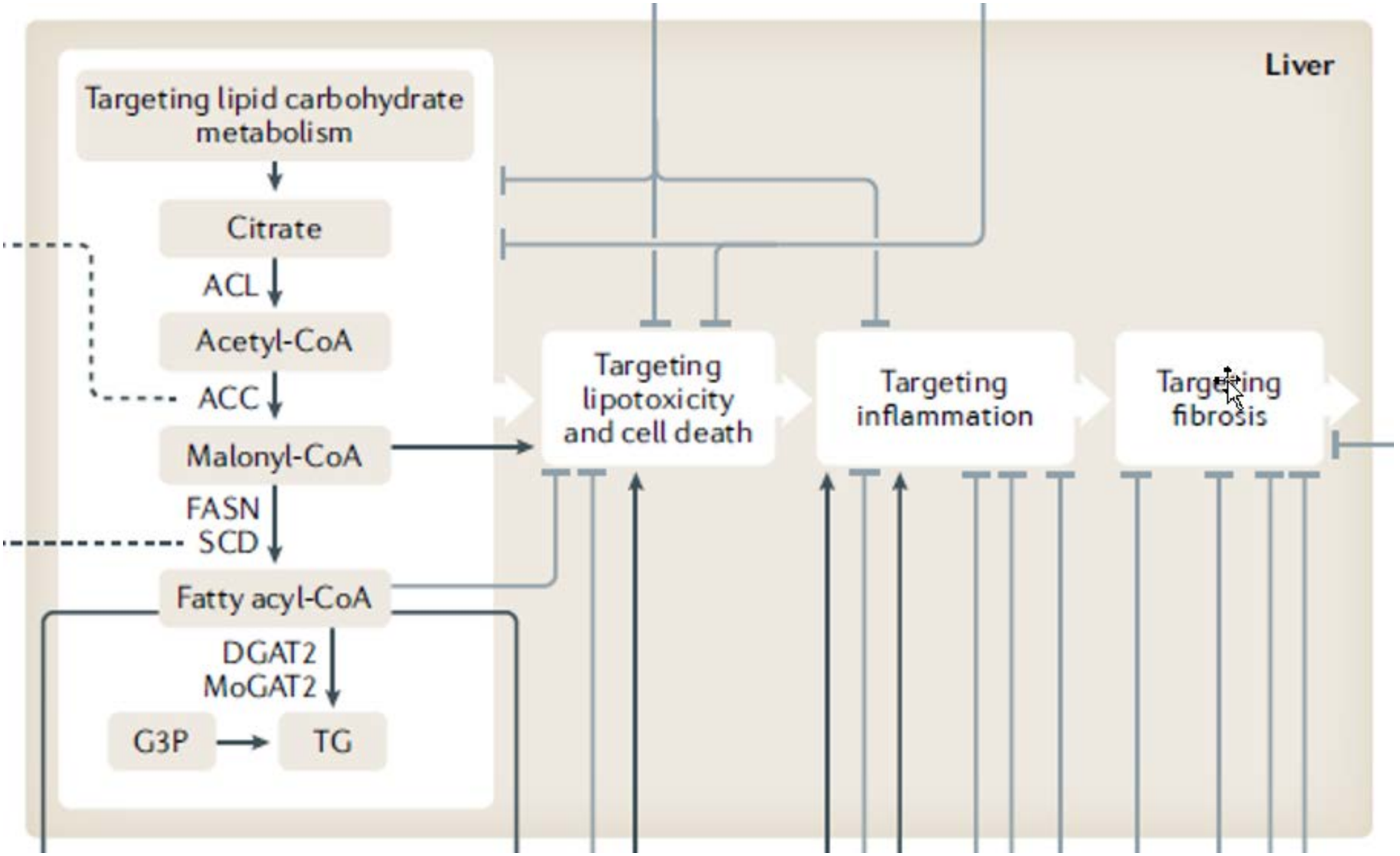
What is the main adverse drug reaction of these drugs?

Table 3 | **Summary of FXR agonists with clinical trial results in non-cirrhotic NASH**

FXR agonist	Phase	Sample size	Daily dose	Duration (weeks)	Main efficacy end point	Main safety end point
Semi-synthetic steroidal FXR agonist						
OCA (bile acid analogue)[59]	III	933	10 mg or 25 mg	72	Fibrosis regression by one stage: placebo 12%, 10 mg 18%, 25 mg 23%	Pruritus (any grade): 28% at 10 mg, 51% at 25 mg
Synthetic non-steroidal FXR agonist						
Cilofexor[128]	II	140	30 mg or 100 mg	24	Relative HFF reduction: placebo +1.9%, 30 mg −1.8%, 100 mg −22.7%	Grade 2–4 pruritus: 4% at 30 mg, 14% at 100 mg
Tropifexor[131–133]	II	152	140 µg or 200 µg	12	Relative HFF reduction: placebo −10%, 140 µg −17%, 200 µg −34%	Pruritus leading to discontinuation: 2% at 140 µg, 6% at 200 µg
EDP-305 (REF.[135])	II	134	1 mg or 2.5 mg	12	ALT reduction: placebo −15 U/l, 2.5 mg −28 U/l	Pruritus (any grade): 10% at 1 mg, 51% at 2.5 mg
MET-409 (REF.[136])	II	58	50 mg or 80 mg	12	Relative HFF reduction: placebo −6%, 50 mg −38%, 80 mg −55%	Pruritus (any grade): 10% at 50 mg, 35% at 80 mg

Only phase II and III results listed. ALT, alanine amino transferase; FXR, farnesoid X receptor; HFF, hepatic fat fraction; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid.

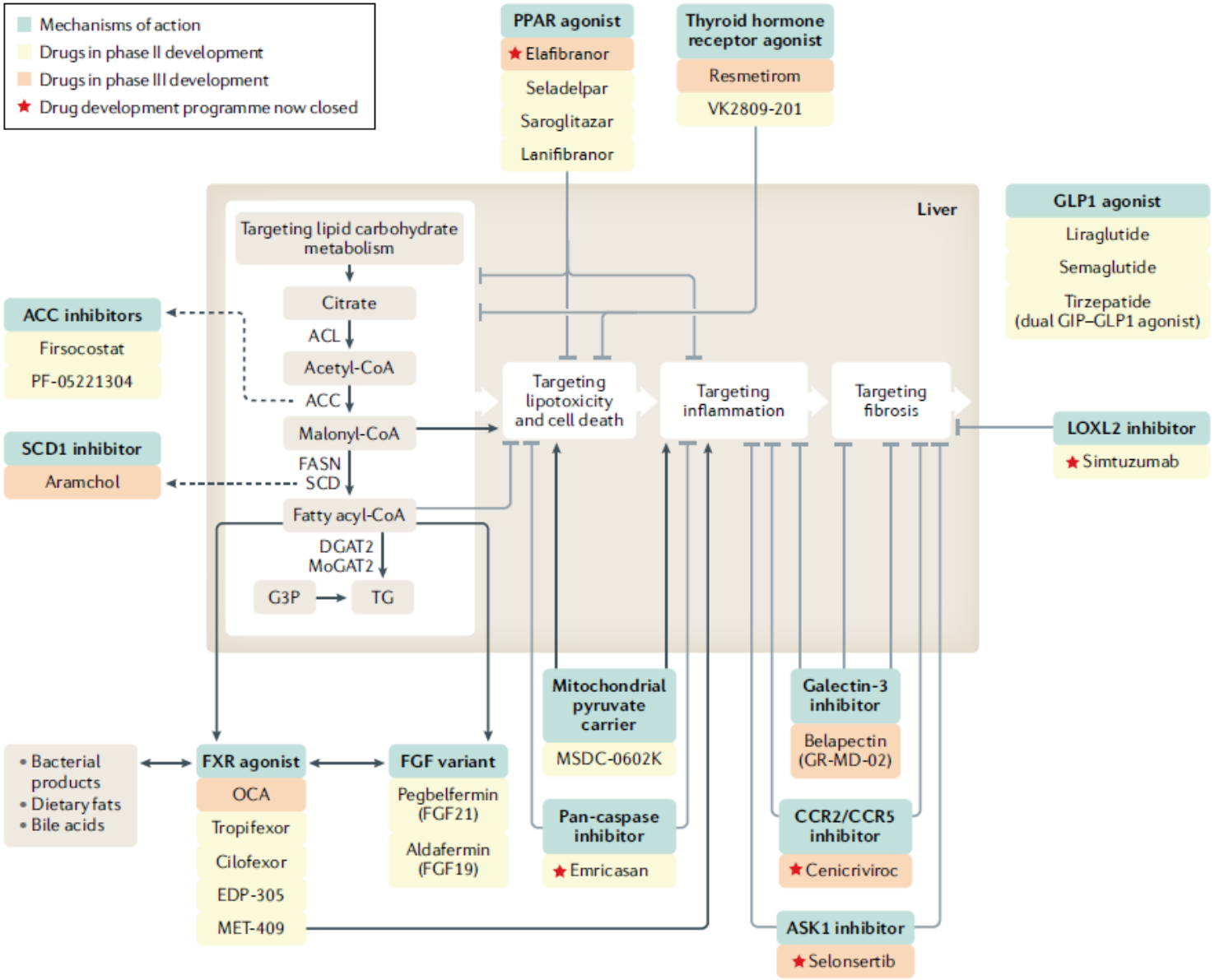
What are the main therapeutic targets for NASH in the liver?


Liver
Targeting lipid carbohydrate metabolism
Citrate
ACL
Acetyl-CoA
ACC
Malonyl-CoA
FASN
SCD
Fatty acyl-CoA
DGAT2
MoGAT2
G3P
TG
Targeting lipotoxicity and cell death
Targeting inflammation
Targeting fibrosis

Which drugs are promising candidates?

What is the mechanism of action fo these drugs?

Which drugs/mechanisms failed in clinical trials?


Mechanisms of action
Drugs in phase II development
Drugs in phase III development
Drug development programme now closed
PPAR agonist
Elafibranor
Seladelpar
Saroglitazar
Lanifibranor
Thyroid hormone receptor agonist
Resmetirom
VK2809-201
Liver
Targeting lipid carbohydrate metabolism
Citrate
ACL
Acetyl-CoA
ACC
Malonyl-CoA
FASN
SCD
Fatty acyl-CoA
DGAT2
MoGAT2
G3P
TG
ACC inhibitors
Firsocostat
PF-05221304
SCD1 inhibitor
Aramchol
Targeting lipotoxicity and cell death
Targeting inflammation
Targeting fibrosis
GLP1 agonist
Liraglutide
Semaglutide
Tirzepatide (dual GIP–GLP1 agonist)
LOXL2 inhibitor
Simtuzumab
Bacterial products
Dietary fats
Bile acids
FXR agonist
OCA
Tropifexor
Cilofexor
EDP-305
MET-409
FGF variant
Pegbelfermin (FGF21)
Aldafermin (FGF19)
Mitochondrial pyruvate carrier
MSDC-0602K
Pan-caspase inhibitor
Emricasan
Galectin-3 inhibitor
Belapectin (GR-MD-02)
CCR2/CCR5 inhibitor
Cenicriviroc
ASK1 inhibitor
Selonsertib

What is MAFLD?

Gastroenterology 2020;158:1999–2014

MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease



Mohammed Eslam[1] *Arun J. Sanyal*[2] *Jacob George*[1], *on behalf of the International Consensus Panel*

[1]*Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, NSW, Australia; and* [2]*Virginia Commonwealth University School of Medicine, Richmond, Virginia*

Experts reached consensus that NAFLD does not reflect current knowledge, and metabolic (dysfunction) associated fatty liver disease "MAFLD" was suggested as a more appropriate overarching term.

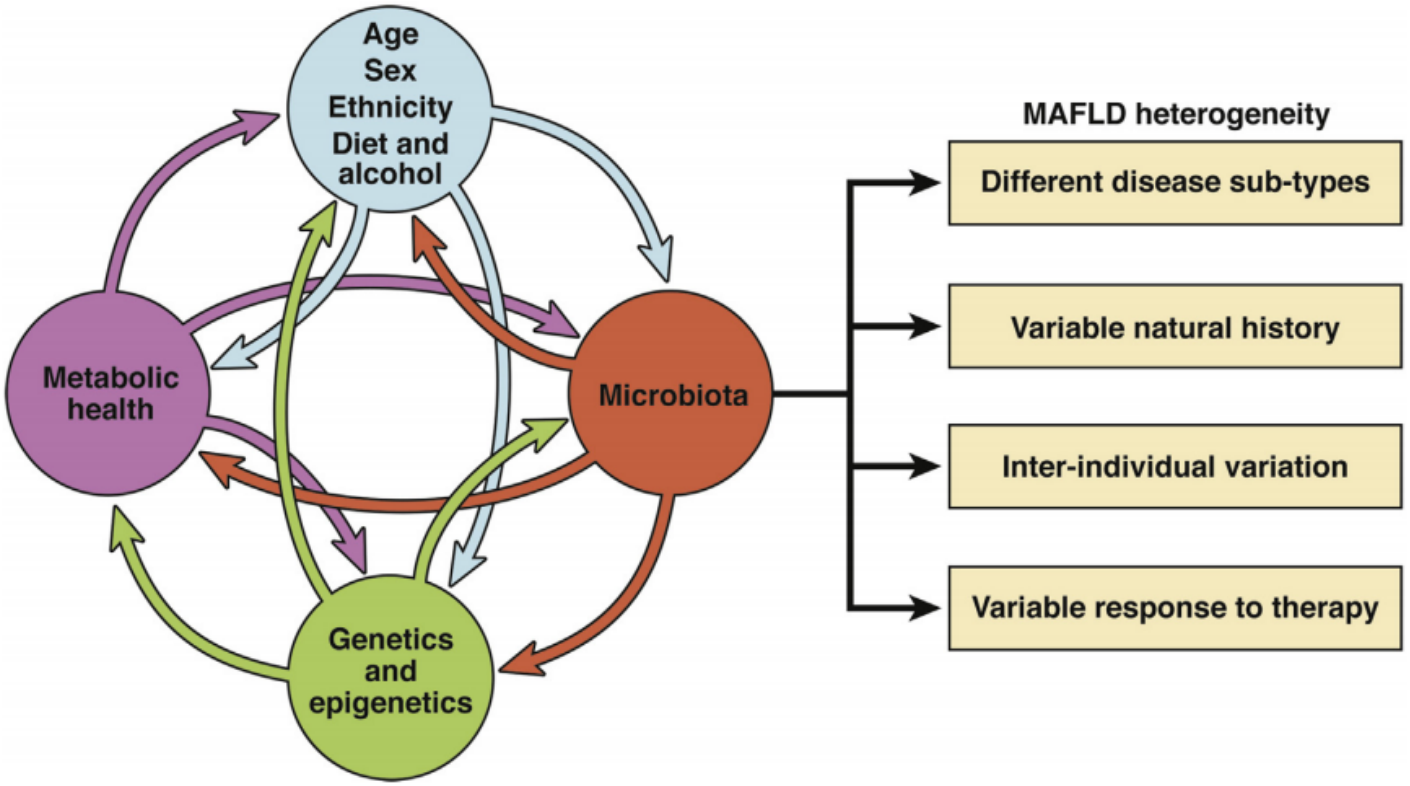


Figure 1. Heterogeneity of MAFLD. The heterogeneity in clinical presentation and course of fatty liver disease is influenced by a multitude of factors, including age, sex, ethnicity, alcohol intake, dietary habits, hormonal status, genetic predisposition, and epigenetic factors, the microbiota, and metabolic status. It is likely that there is a differential impact in the contribution of the various factors in any individual over time and among individuals that then shapes disease phenotype and course.

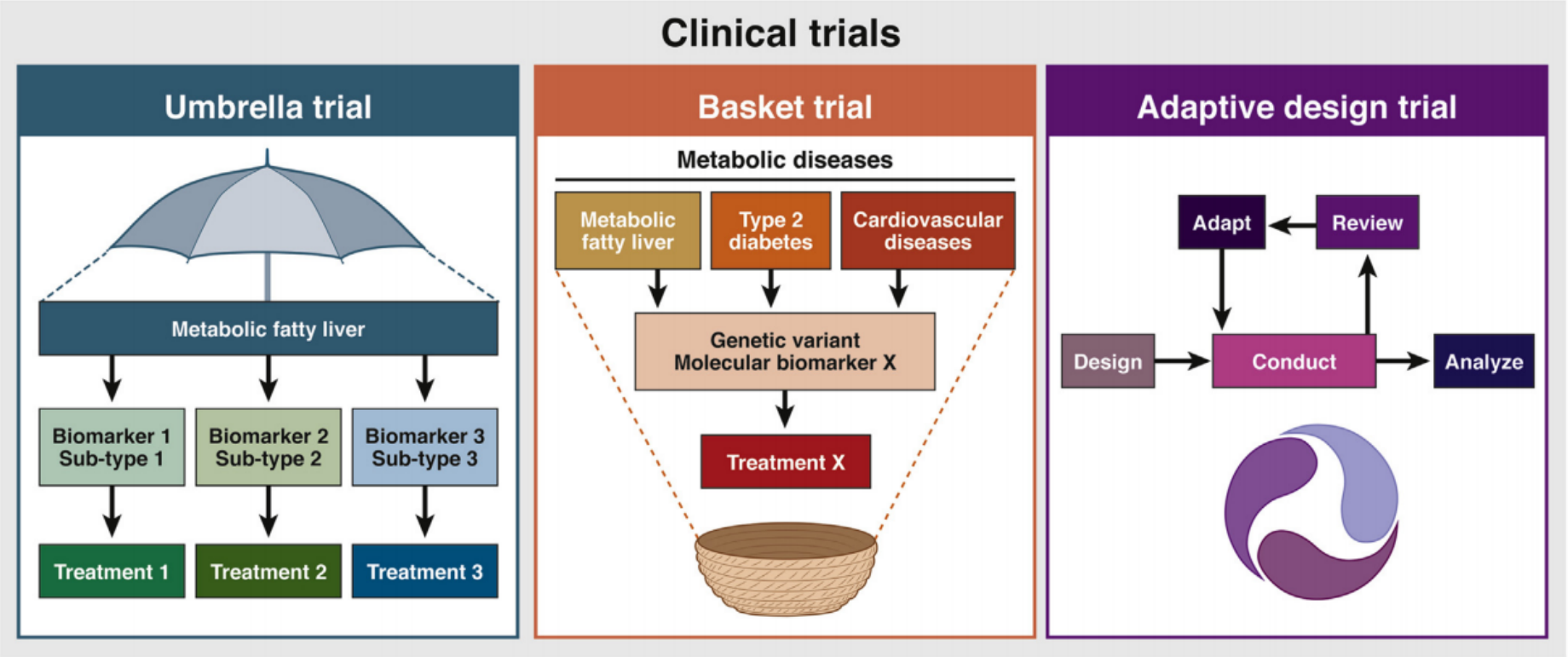


Figure 3. Innovative clinical trials for MAFLD. The substantial heterogeneity of patients with MAFLD and the limited responses to investigational targets in current clinical trials imply that innovative trial designs are required. Trial designs such as umbrella, basket, and adaptive designs have been suggested to overcome the challenges; however, such designs add complexity to the trial analysis.