

NASH Update 2024

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A multi-society Delphi consensus statement on new Fatty Liver Disease nomenclature

- A modified Delphi process was led by three large pan-national liver associations. Consensus was defined *a priori* as a supermajority (67%) vote. An independent committee of experts external to the nomenclature process made the final recommendation on the acronym and its diagnostic criteria.
- A total of 236 panelists from 56 countries participated in four online surveys and two hybrid meetings. Response rates across the 4 survey rounds were 87%, 83%, 83% and 78%, respectively.

Steatotic Liver Disease (SLD)

Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD)

MetALD
(MASLD and increased alcohol intake*)

MASLD predominant		ALD predominant	
140/210	210	280	350/420
Weekly alcohol intake (g)			

20/30	30	40	50/60
Average daily alcohol intake (g)			

MASLD predominant		ALD predominant	
20/30	30	40	50/60
Average daily alcohol intake (g)			

20/30	30	40	50/60
Average daily alcohol intake (g)			

Average daily alcohol intake (g)

Alcohol-Associated (Alcohol-related) Liver Disease (ALD)

Specific aetiology SLD

Drug-Induced Liver Injury (DILI)

Monogenic diseases**

Miscellaneous***

Cryptogenic SLD

*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)

**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism

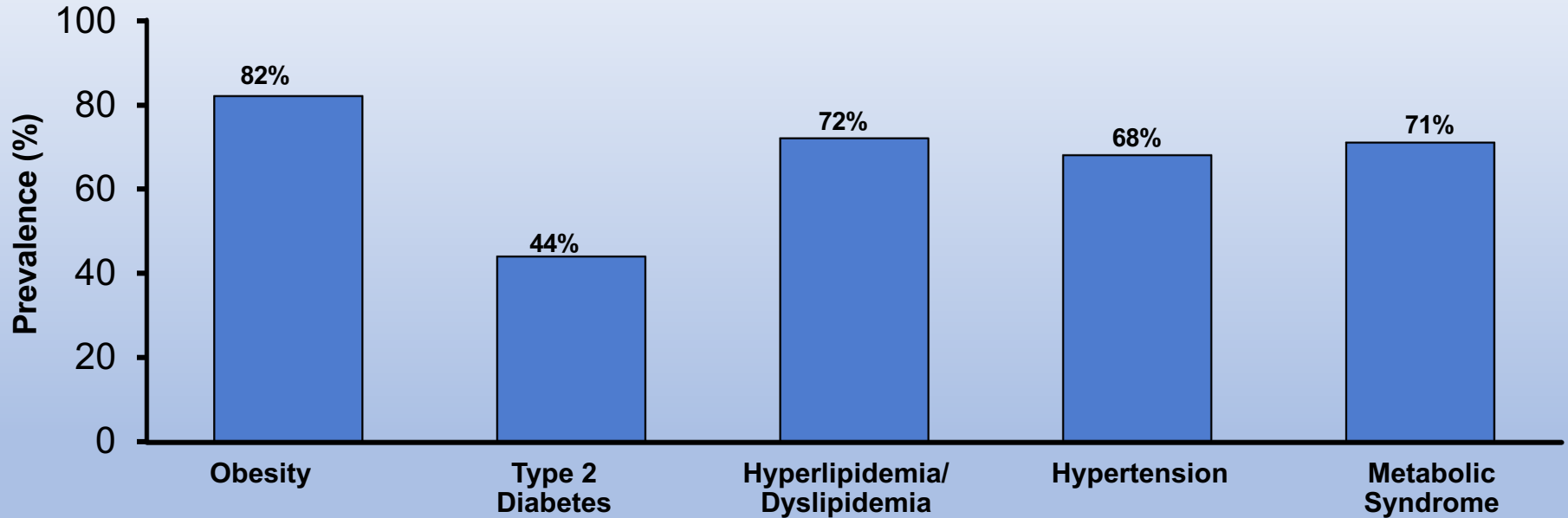
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

The 1st FDA-Approved Pharmacotherapy for MASH

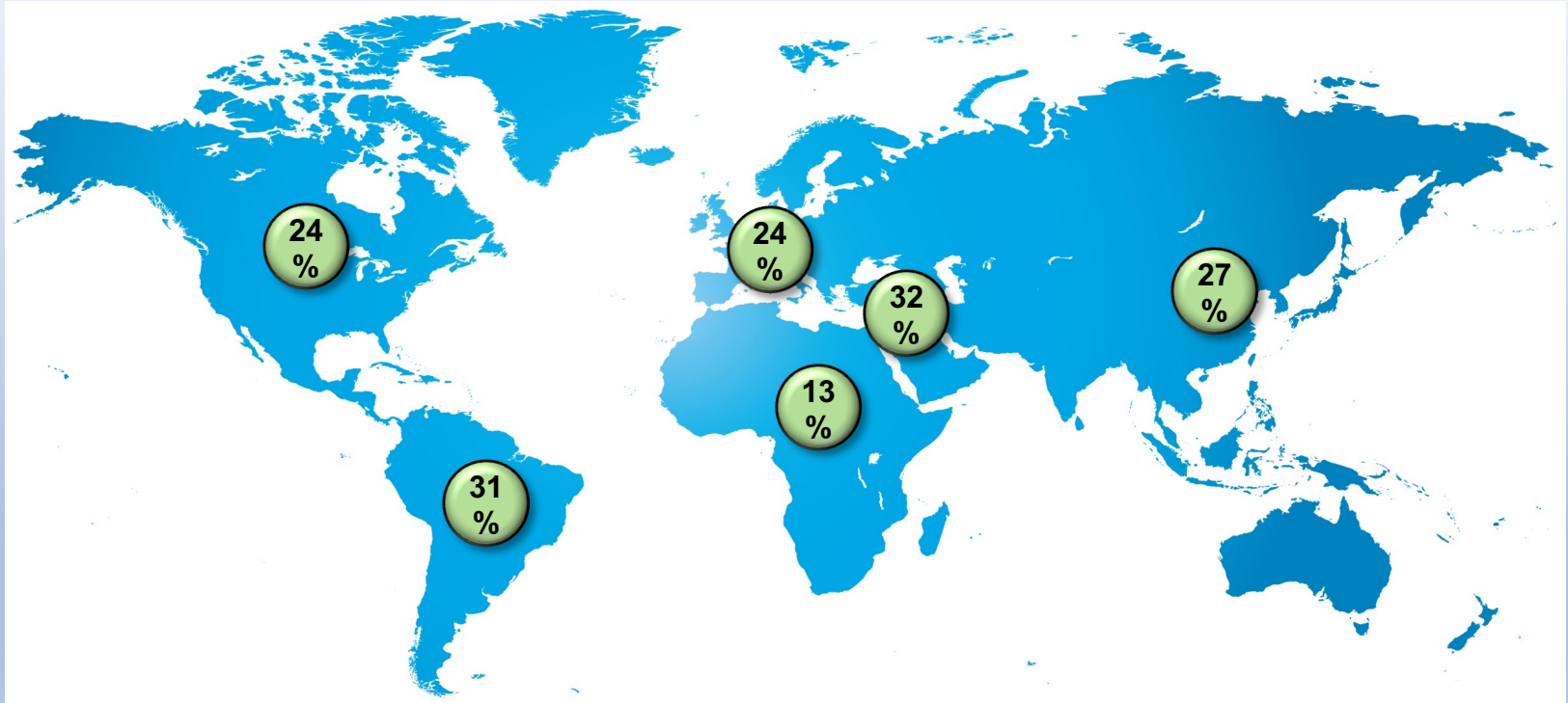
- **Resmetirom** now approved!
 - Decreases fat in the liver, improves inflammation and fibrosis
 - Improves LDL
 - Well tolerated
 - Nausea, diarrhea usually resolves early
- Focus on F2-F3
- Payers may follow established treatment guidelines (AASLD)
- Non-Invasive Tests (NIT's) replace Liver Biopsy for diagnosis

Comorbidities Associated With NAFLD: Global Prevalence Among NAFLD Patients

NAFLD is Associated With a High Burden of Metabolic Comorbidities



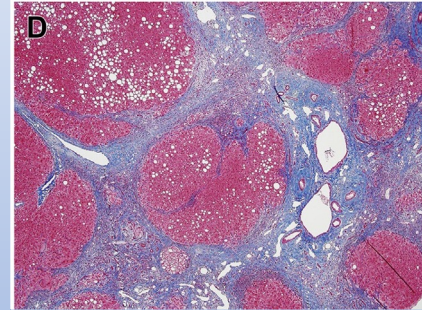
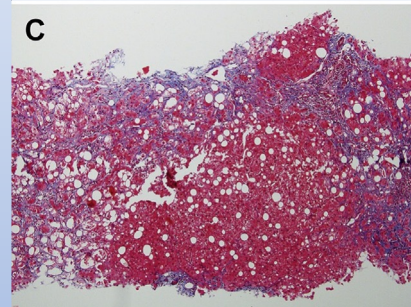
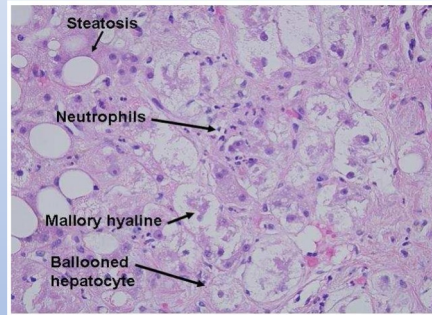
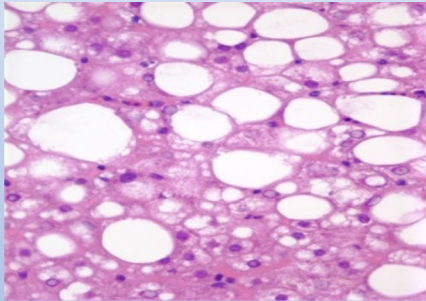
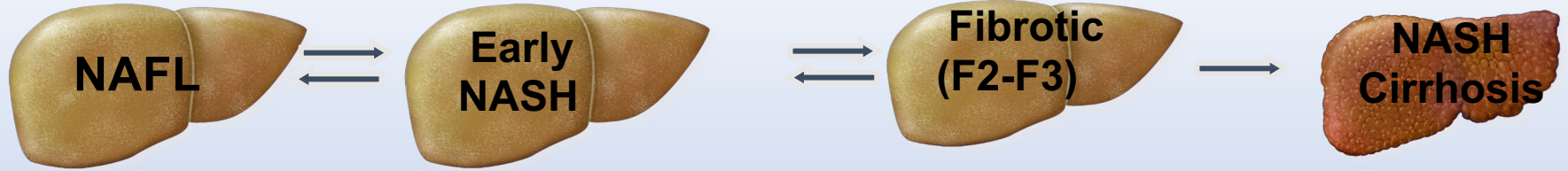
Estimated Global Prevalence of MASLD: 25%



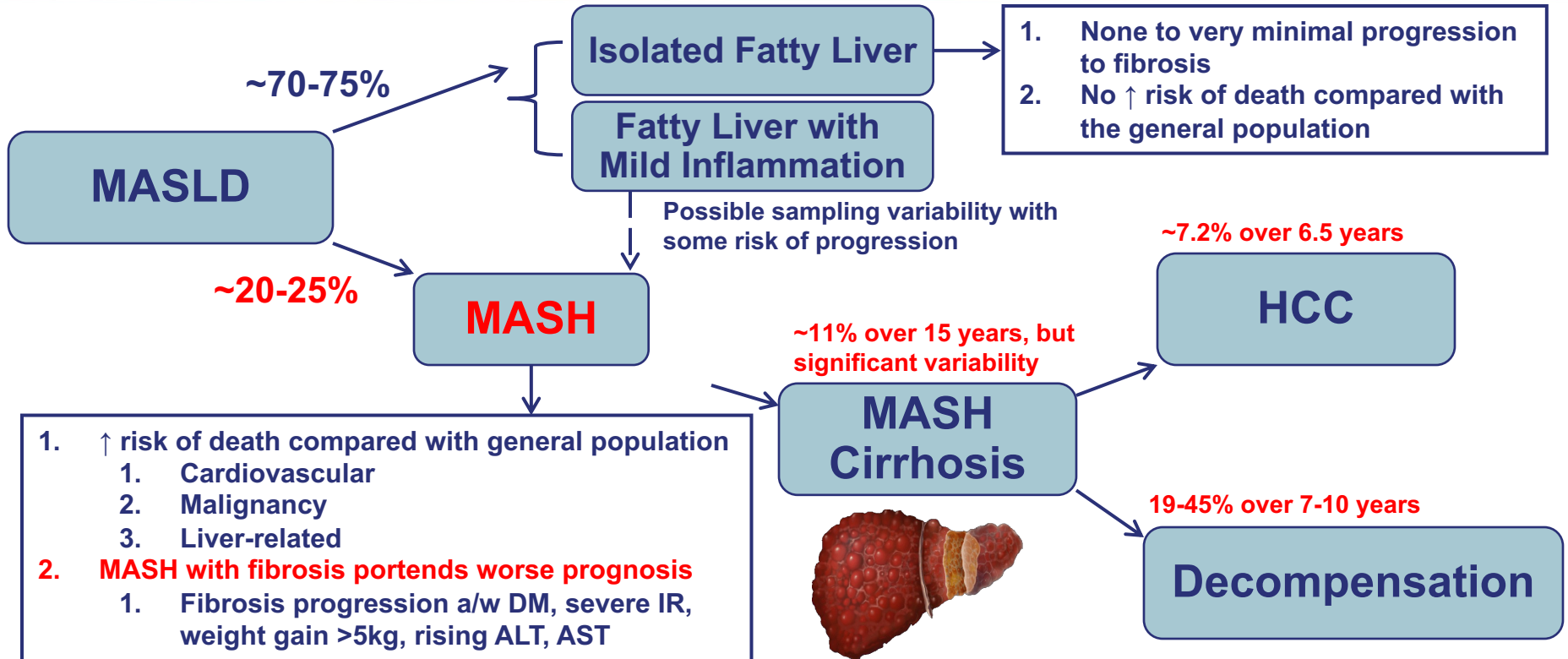
Meta-analysis: NAFLD diagnosed by imaging (US, CT, MRI/SPECT; n=45 studies).

Younossi ZM, et al. *Hepatology*. 2016;64:73-84.

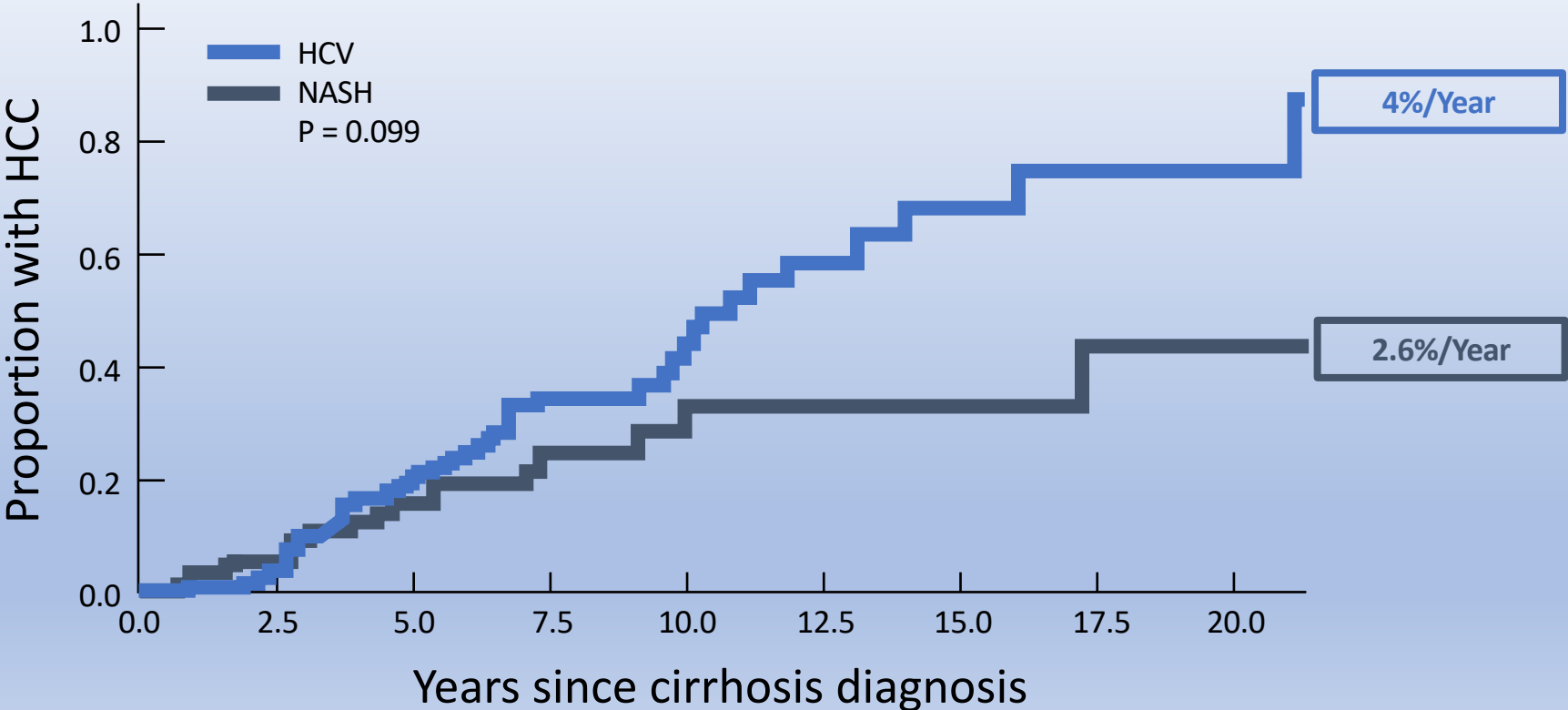
The MASLD Spectrum



Natural History of MASLD

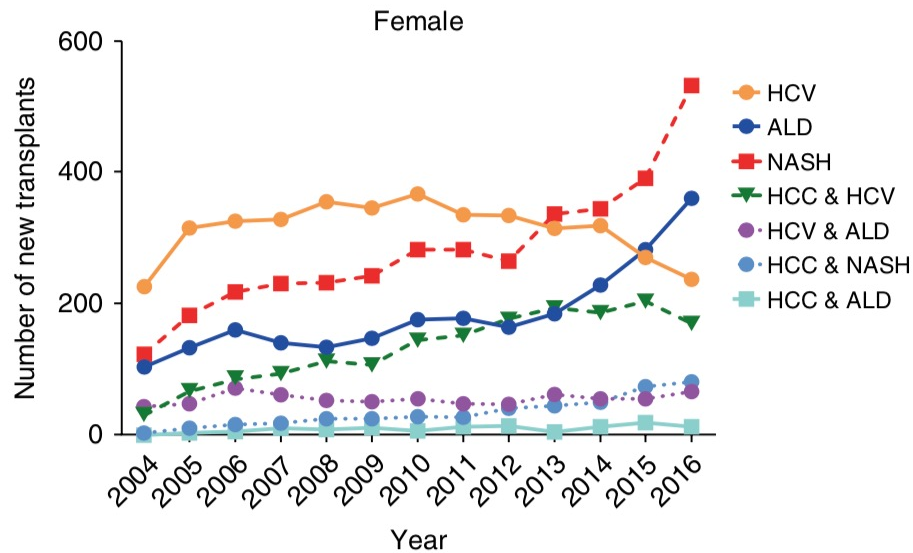
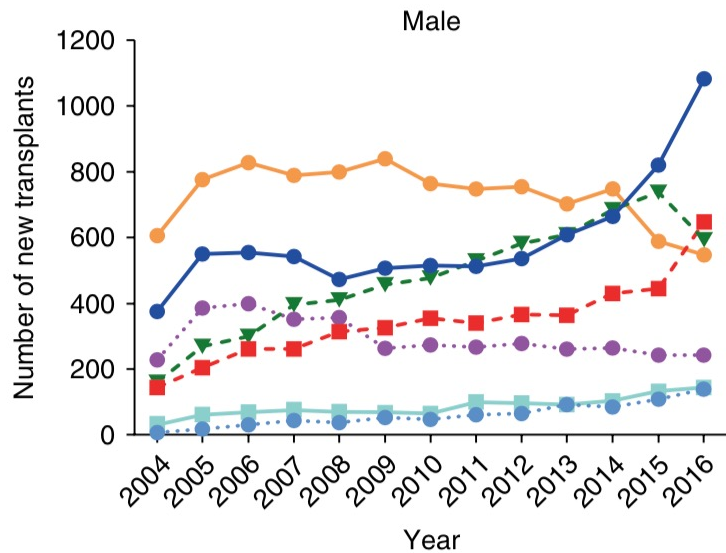


Annual Cumulative Incidence of HCC in NASH Cirrhosis



Ascha MS et al. *Hepatology*. 2010.

NASH is becoming the Most Common Indication for Liver Transplantation in the U.S.



Red Flags for NASH

- Age
- Gender
- Hispanic
- Hypertension
- Obesity
- Dyslipidemia
- Type 2 Diabetes
- ALT and AST level
- AST/ALT ratio
- Metabolic Syndrome
- Various genetic markers



No lab test or imaging study will be able to predict NASH with 100% accuracy



The more risk factors... the more concern



Treatment and Intervention

Lifestyle Management of NAFLD

Mediterranean Diet

HIGH IN:



MUFA



PUFA



Folate

Fiber

Antioxidants

LOW IN:






**Saturated
Fat**



The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease

NAFLD Dietary Patterns

	 NAFLD	 Healthy	 Healthy
Dietary patterns	Western Diet	Mediterranean Diet (MD)	Dietary Approach to Stop Hypertension (DASH)
Foods intake	<ul style="list-style-type: none"> ❖ Processed foods ❖ Red meats ❖ Processed meats ❖ Sugary beverages ❖ Snacks ❖ cakes and biscuits ❖ eggs ❖ butter 	<ul style="list-style-type: none"> ❖ Extra virgin olive oil ❖ Vegetables and Fruits ❖ Cereals, legumes, nuts ❖ Moderate intakes of fish and other meat, dairy products and red wine ❖ Low intakes of eggs and sweets. 	<ul style="list-style-type: none"> ❖ Fruits and vegetables ❖ whole grains, ❖ fish, poultry, nuts, ❖ legumes ❖ low-fat dairy products ❖ reduced sodium ❖ Fresh food ❖ Minimally processed food
Nutrients	<ul style="list-style-type: none"> ↑Energy intake ↑SFA ↓PUFA ↑protein animal ↑sugar, fructose ↑cholesterol ↑Salt ↓fiber 	<ul style="list-style-type: none"> ↓SFA ↑MUFA ↑PUFA ↑protein vegetables ↓sugar fructose ↓cholesterol ↑fiber ↑polyphenols, ↑carotenoids 	<ul style="list-style-type: none"> ↓ total fat ↓Salt ↑protein vegetables ↓sugar fructose ↓cholesterol ↑fiber ↑polyphenols, ↑carotenoids

Reported Outcomes in NAFLD Lifestyle Intervention Trials

Type of Diet	Weight Loss	Lower ALT	Improved IR	Lower Glucose Levels	Improved NAFLD (US)	Improved Hepatic TG (MRS)	Improved NAFLD (biopsy)	Improved NASH (biopsy)
Low calorie (~1 200-1 500 kcal/day)	✓	✓			✓	✓	✓	✓
VLCD (450 kcal/day)	✓				✓			
VLCD (800 kcal/day)	✓				✓			
Low carbohydrates (<20%-45%)	✓	✓	✓	✓	✓	✓	✓	
Low fat (20%-27%)	✓	✓		✓		✓	✓	✓
DASH diet (fruits, vegetables, whole grains, low-fat dairy, low in saturated fats, cholesterol, refined grains, and sweets)	✓	✓	✓		✓		✓	
Mediterranean diet	✓		✓		✓			
IF	✓		✓					

Exercise and Activity in NAFLD

Moderate-intensity exercise:

- Moderate effort
- Noticeable acceleration of heart rate
- Increased rate of breathing
- Able to hold a conversation

Examples:

- Brisk walking
- Taking stairs
- Using a cross trainer
- Gardening
- Vigorous housework

High-intensity exercise:

- Large effort
- Substantial increase in heart rate
- Rapid breathing
- Less able to hold a conversation

Examples:

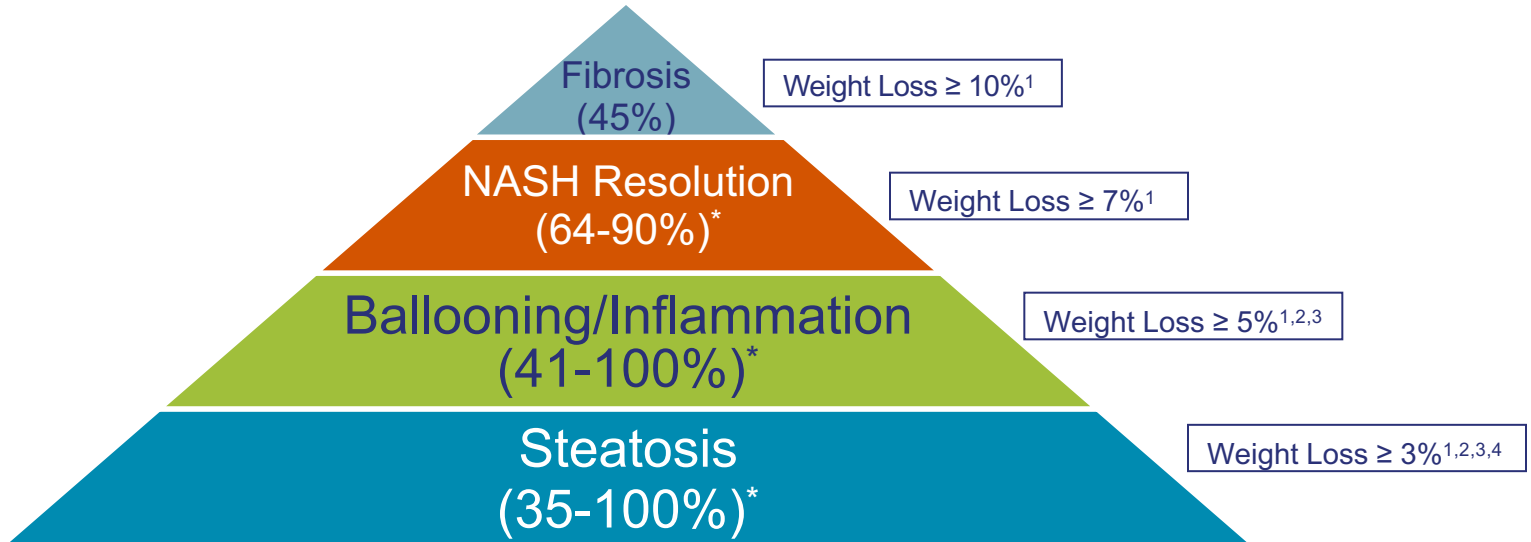
- Running
- Fast cycling

***Activity recommendations for NAFLD:
30-60 minutes of moderate-intensity
exercise 3-5 days per week***

Lifestyle recommendations for NAFLD

	NAFLD	NASH	NAFLD Cirrhosis
Weight loss goal	>5% at minimum	7-10% at minimum	5-10% if compensated
Dietary Recommendations	<ul style="list-style-type: none"> No Snacks Regular meals Reduce sugar, fructose sweetened beverages, refined carbs and processed foods Consider Intermittent Fasting Consider Mediterranean or DASH diet Minimize alcohol 	<ul style="list-style-type: none"> No Snacks Regular meals Reduce sugar, fructose sweetened beverages, refined carbs and processed foods Consider Intermittent Fasting Consider Mediterranean or DASH diet Minimize alcohol 	<ul style="list-style-type: none"> Consider bedtime snack Regular meals Reduce sugar, fructose sweetened beverages, refined carbs and processed foods Protein intake 1.2-1.5 g/kg/day Consider Mediterranean or DASH diet Avoid alcohol
General Health Recommendations	<ul style="list-style-type: none"> Moderate physical activity for 30-60 min on 3-5 days per week or increase baseline activity by 60 min per week Resistance training for 20-30 min, 2-3 times per week (in addition to or instead of moderate physical activity) Decrease sedentary time and increase movement throughout the day Stress reduction through exercise when possible Avoid cigarette smoking Adequate restful sleep goal of >6 hours per night 		

Weight Loss Pyramid



1. Vilar-Gomez. *Gastroenterology* 2015; 2. Promrat. *Hepatology* 2010; 3. Harrison. *Hepatology* 2009; 4. Wong. *J Hepatol* 2013

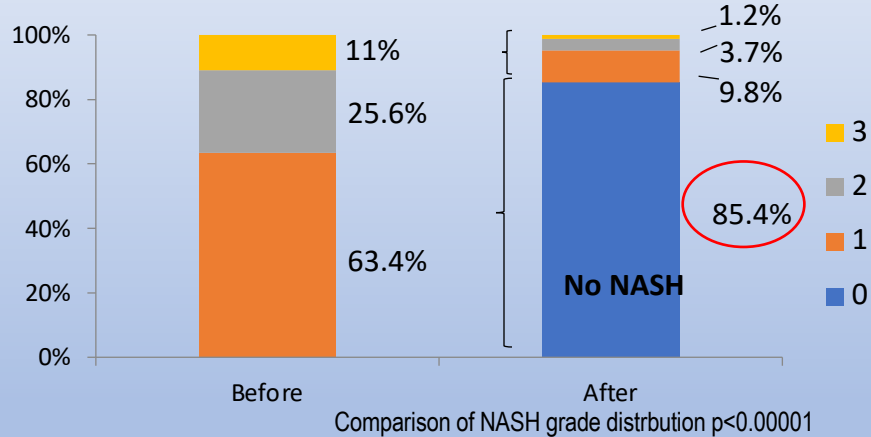
*Depending on degree of weight loss

Bariatric Surgery and Liver Histology

Prospective study in morbidly obese patients with **biopsy-validated NASH**, ≥ 1 comorbidity factor for > 5 yrs, no chronic liver disease (N = 109)^[1]

NASH disappearance

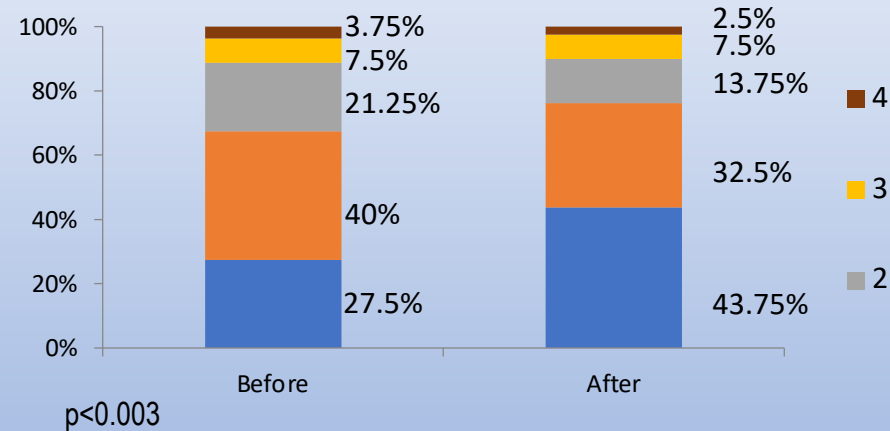
NASH grade evolution (Brunt score)



85% of NASH disappearance, 1 year after Bariatric surgery

Fibrosis Improvement

Fibrosis evolution



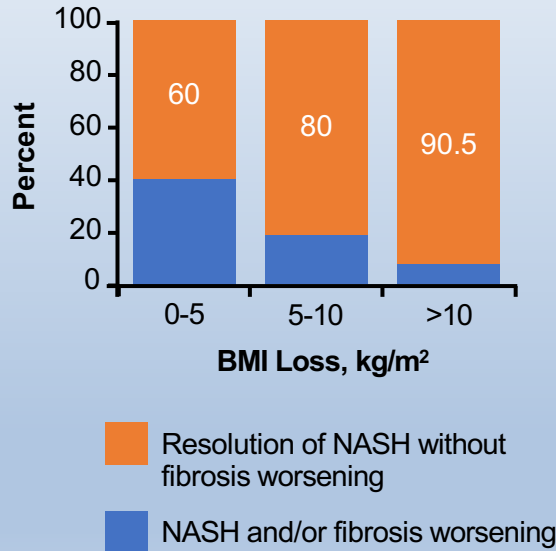
*Metavir scale.

Significant improvement of Fibrosis lesions 1 year after bariatric surgery.

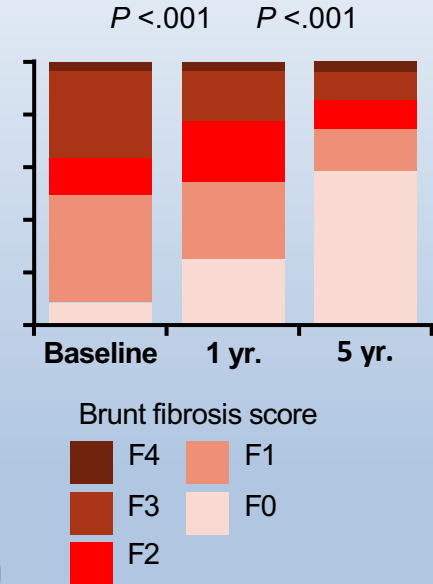
Is NASH Reversible?

- French single-center study of **bariatric surgery** in severely obese patients with biopsy-confirmed NASH (N = 180)
- At 5 yrs. post surgery, 64 of 94 patients (84%) had NASH resolution with no worsening of fibrosis
 - NASH improvement correlated with weight loss

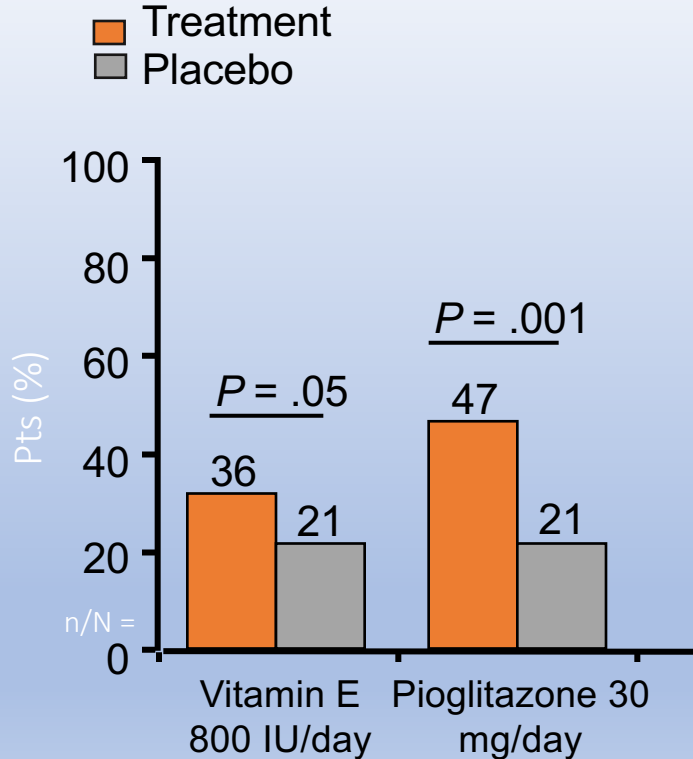
Resolution of NASH According to Weight Loss



Evolution of Fibrosis After Bariatric Surgery



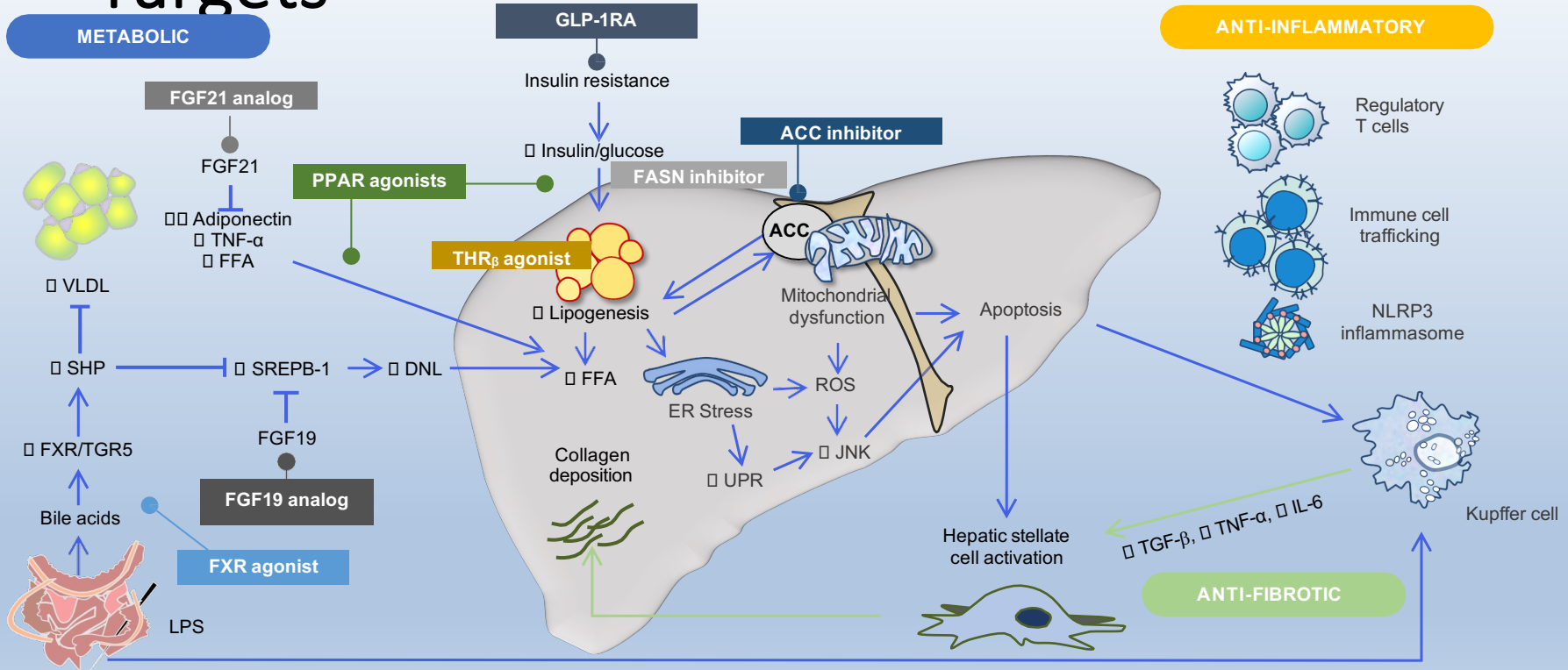
Resolution of NASH with Vitamin E and Pioglitazone



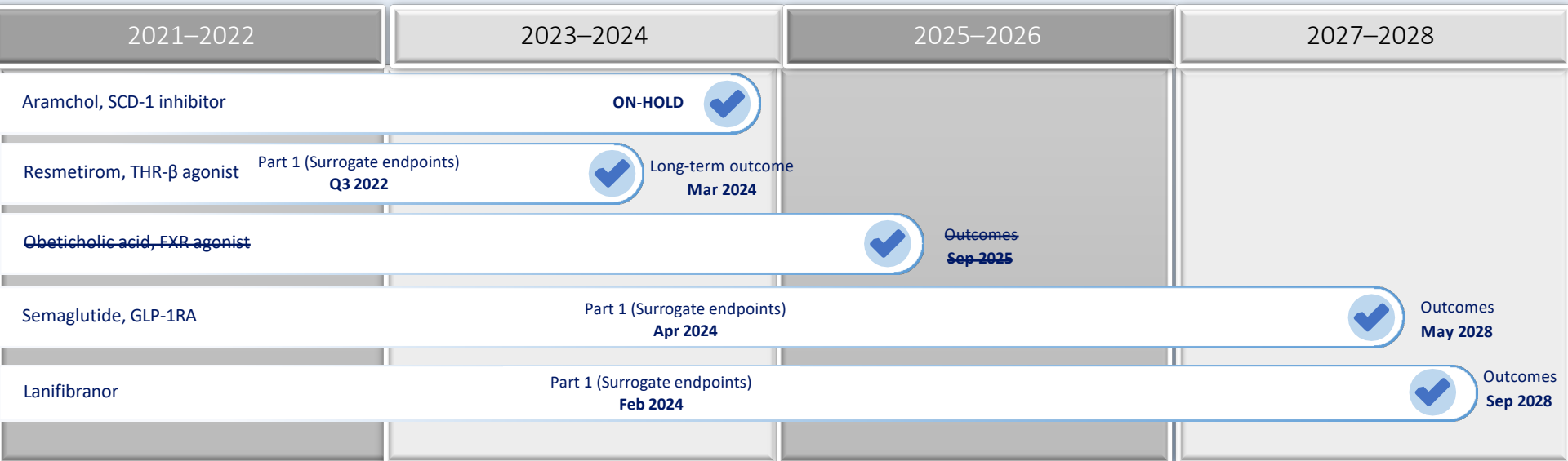
- **Vitamin E: Increased overall mortality/ hemorrhagic stroke/prostate cancer**
- **Pioglitazone: Weight gain, fluid retention-HF?/ Increased risk of bladder cancer/ osteoporosis/**

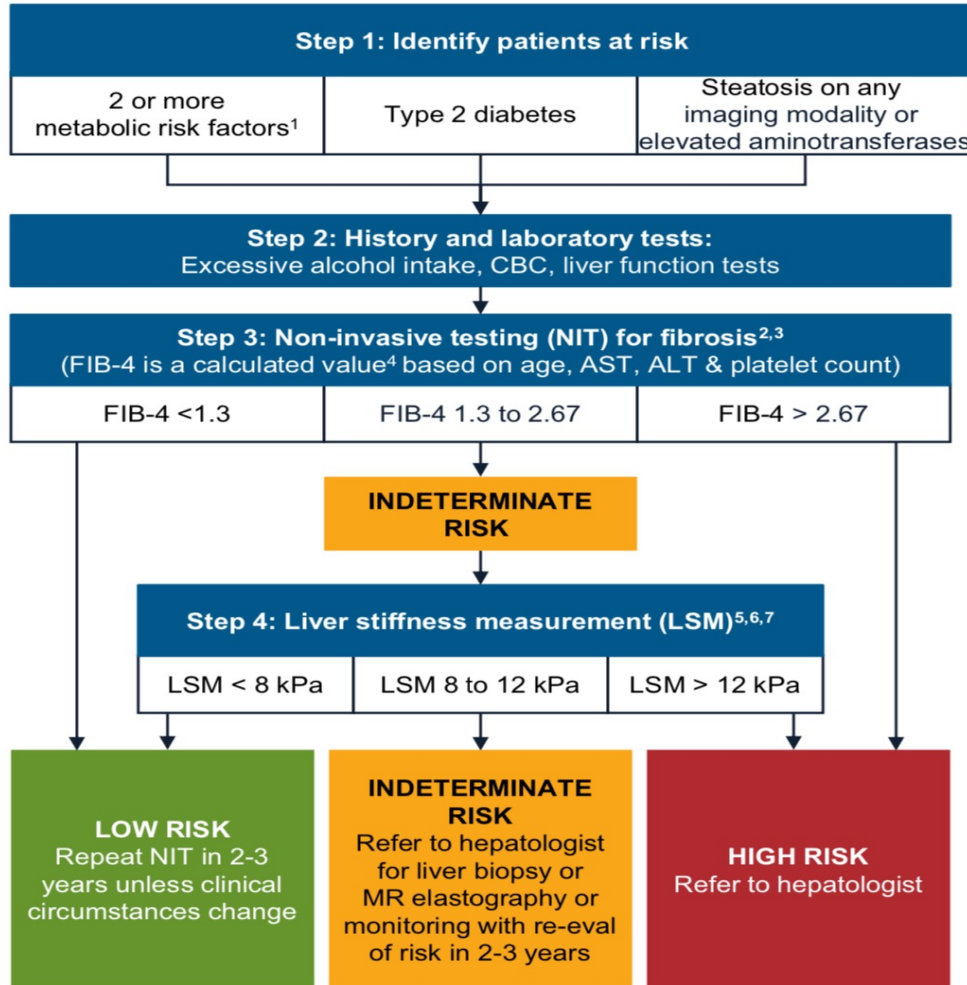
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NASH: Potential Therapeutic Targets

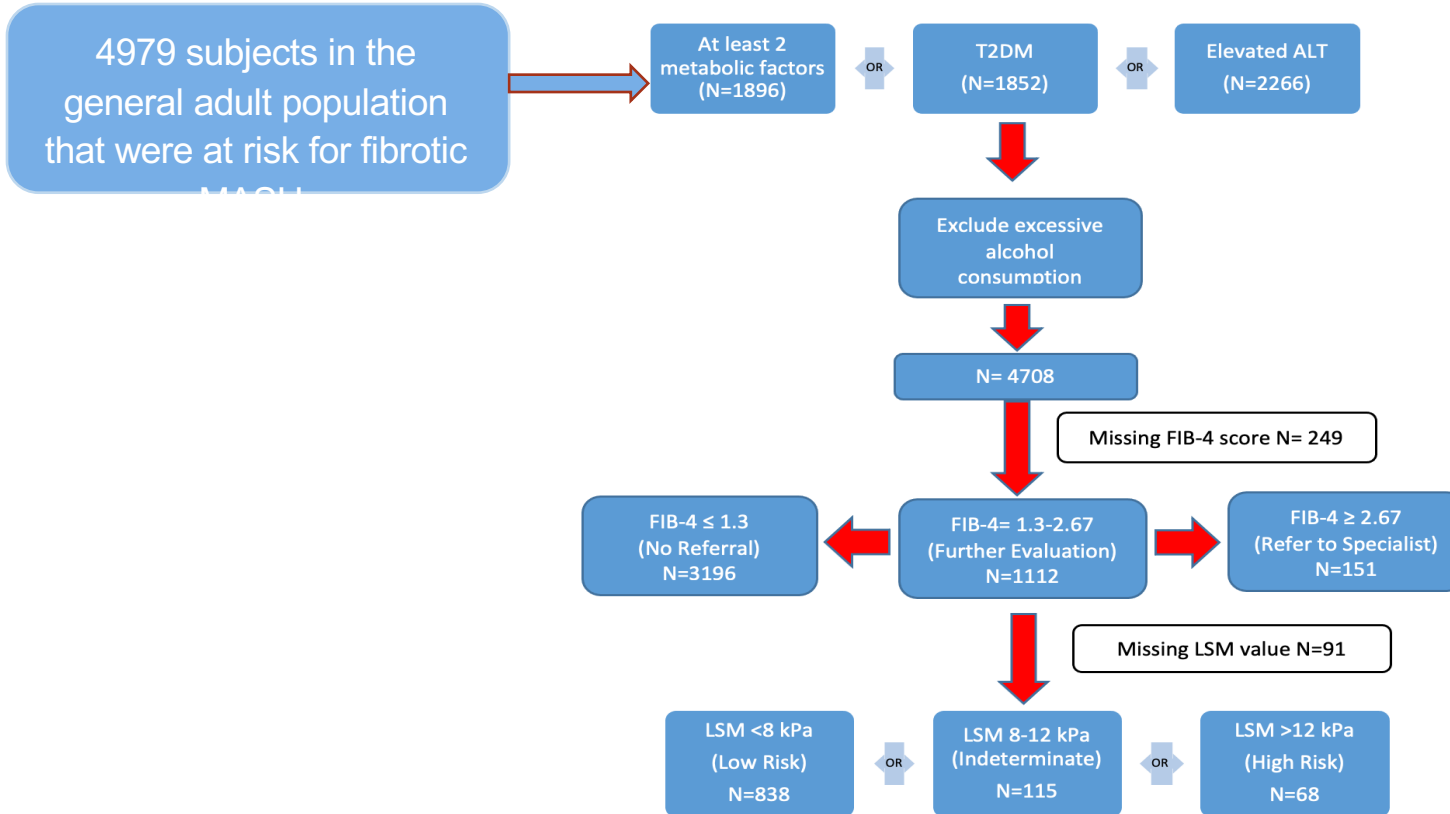


The future of NASH therapeutics Ongoing phase 3 trials

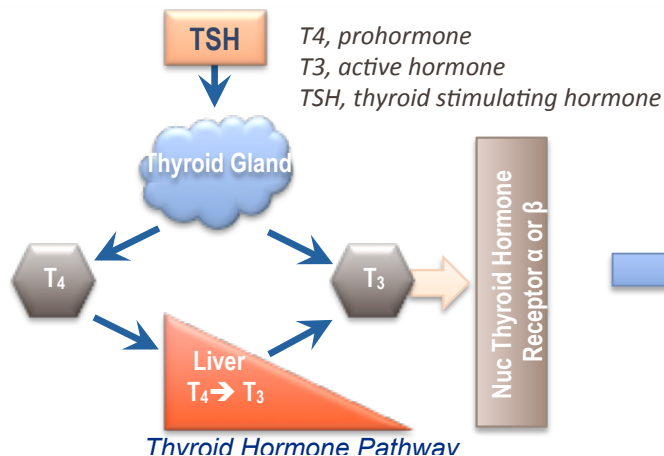




Flowchart: AGA Algorithm For Risk Stratification



Resmetirom (MGL-3196): selective thyroid hormone receptor-beta agonist



In humans THR-β agonism:

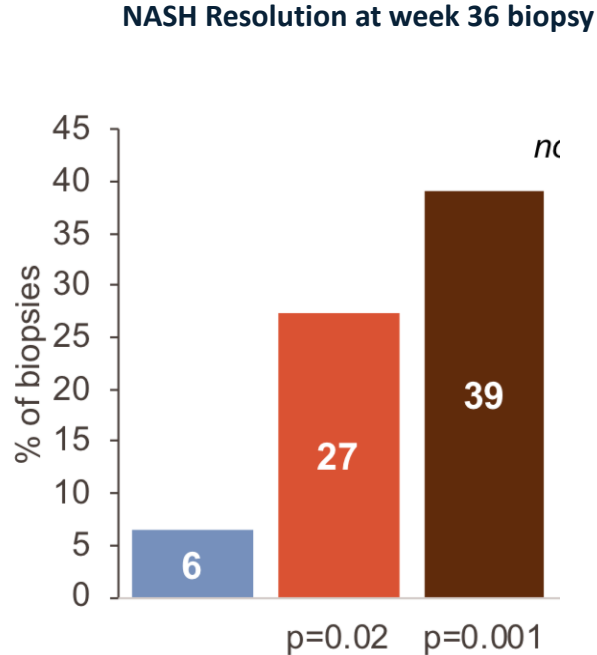
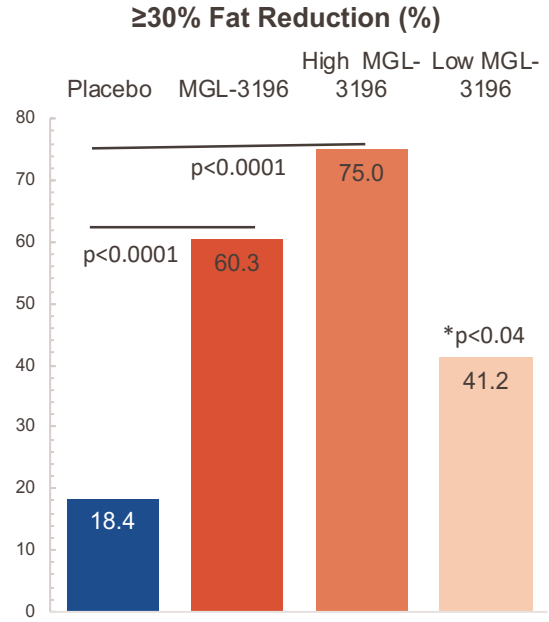
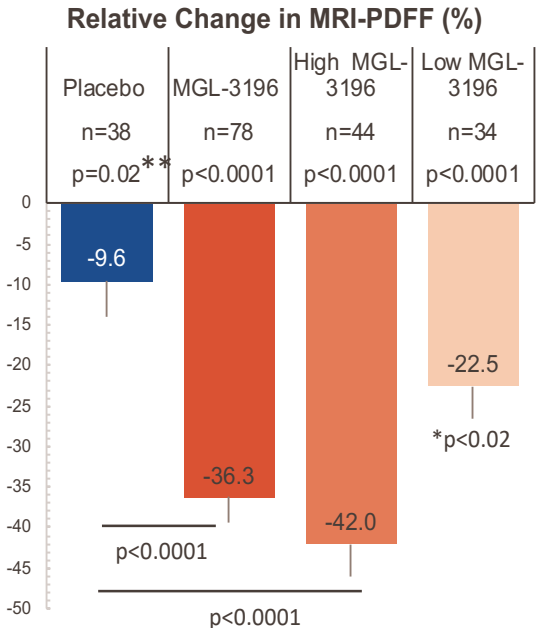
- ↓ Lowers LDL-cholesterol
- ↓ Lowers triglycerides
- ↓ Lowers liver fat, potentially reducing lipotoxicity, NASH

No thyrotoxicosis (THR-α effect)

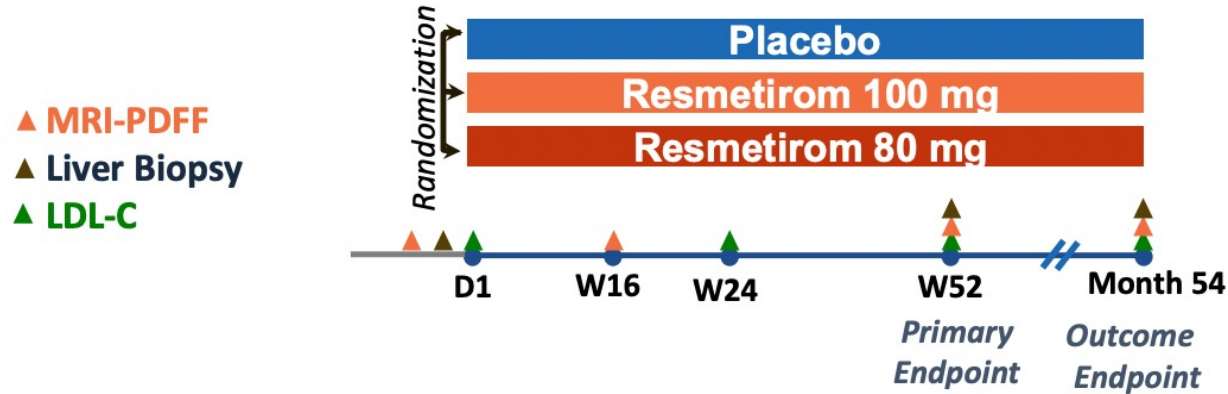


Resmetirom significantly decreases hepatic fat in MASH patients at week 12 MRI-PDFF, and was associated with MASH resolution at week 36 biopsy

Fat Reduction at week 12 MRI-PDFF



Phase 3 MAESTRO-NASH Study Design

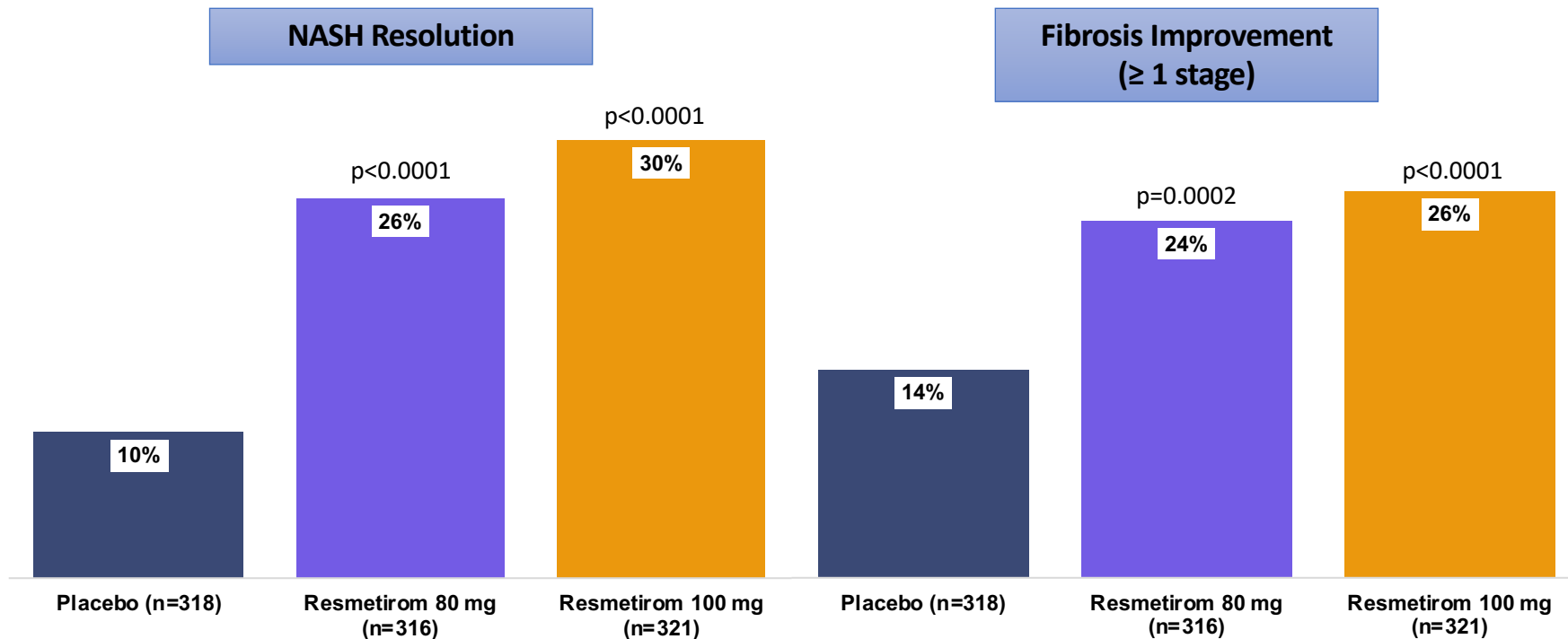


- Key Inclusion/Exclusion:

- Requires 3 metabolic risk factors (Metabolic Syndrome)
- FibroScan kPa consistent with F2-F3, CAP \geq 280
- NASH on liver biopsy: NAS \geq 4 with fibrosis stage 1-3
- \geq 8% liver fat on MRI-PDFF

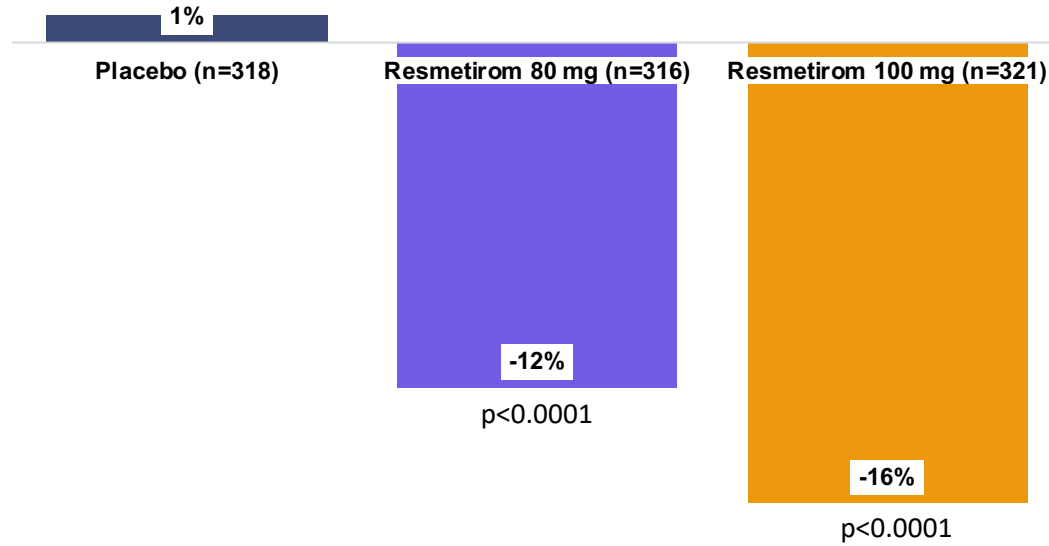
MAESTRO-NASH (Primary Statistical Model)

Liver Biopsy (ITT) at Week 52



MAESTRO-NASH

Key Secondary Endpoint LDL-c at Week 24 (ITT)



MAESTRO-NASH

Safety Summary

AE Term	Resmetirom 80 mg (n=316)	Resmetirom 100 mg (n=321)	Placebo (n=318)
SAEs	11.8%	12.7%	12.1%
Study discontinuation for AEs	2.8%	7.7%	3.7%
Diarrhea	28%	34%	16%
Nausea	22%	19%	13%

- Resmetirom was **safe and well-tolerated**
- Consistent with previous Phase 2 and Phase 3 data, the most common adverse events reported with greater frequency in the resmetirom groups vs placebo were an excess of generally mild and transient diarrhea and generally mild nausea at the beginning of therapy

Resmetirom – Phase 3 Program



MAESTRO NAFLD-1

Safety and tolerability as measured by incidence of AEs over 52 weeks in >1200 patients



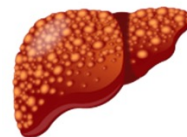
MAESTRO NAFLD-OLE

52-week extension to MAESTRO-NAFLD-1 in >700 patients: Safety & tolerability by incidence of AEs over 52 weeks



MAESTRO NASH

Subpart H:
NASH resolution or fibrosis improvement on serial liver biopsy at Week 52
Outcomes
(54 months – ongoing)



MAESTRO NASH OUTCOMES

Event-driven clinical outcome to decompensated cirrhosis in patients with well-compensated NASH cirrhosis



A total of > 1500 patients at the top dose of 100 mg and > 2000 patients on at least 80 mg to support accelerated approval

The background is a dark blue gradient with a pattern of lighter blue hexagons and dashed white lines. The hexagons are arranged in a grid-like pattern, some overlapping, and the dashed lines form a series of concentric, irregular shapes that resemble a stylized 'S' or a path.

THANK YOU!

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