NEW YORK SOCIETY FOR GASTROENTEROLOGY & ENDOSCOPY
48th Annual
NEW YORK COURSE
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NYSGE
New York Society for Gastroenterology and Endoscopy

Update on Steatotic Liver Disease

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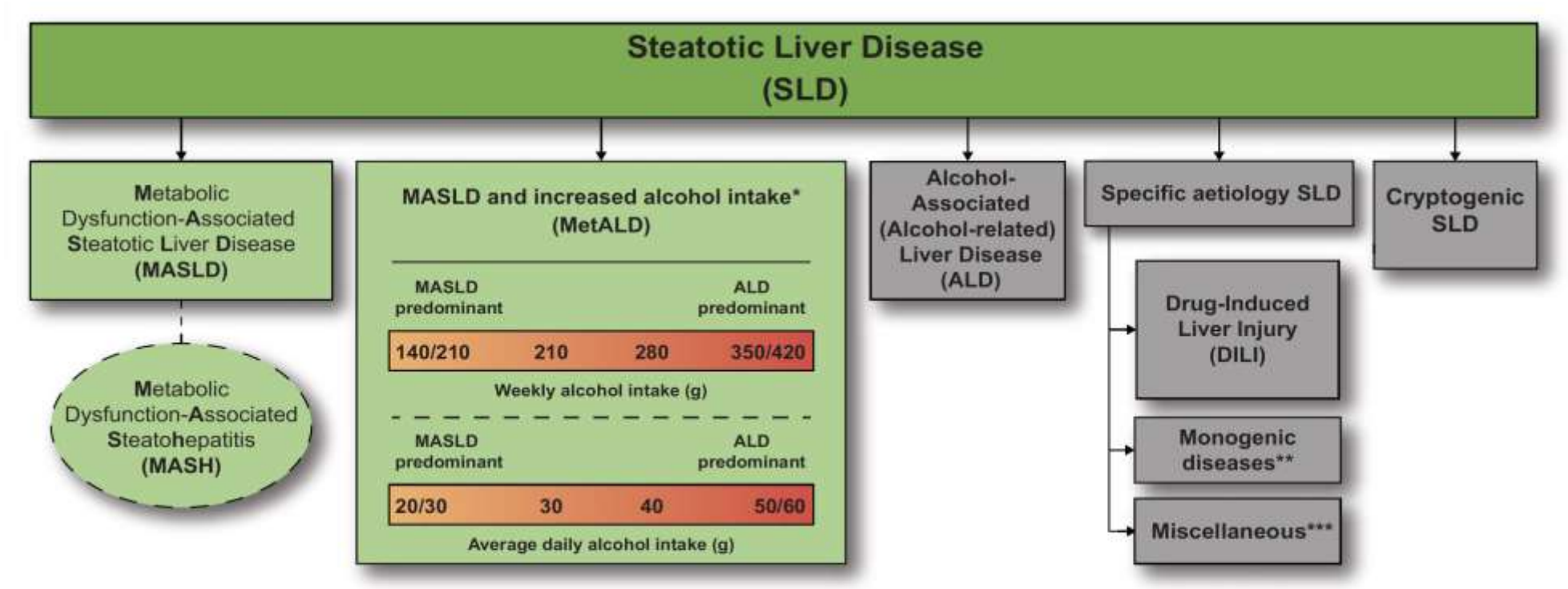
Disclosures

Speakers Bureau: Gilead Sciences, Madrigal Pharmaceuticals

Objectives

- Understand new nomenclature: NAFLD-> MASLD
- How to approach a patient with incidental finding of fatty liver
  - Significance of fatty liver
  - Risk Stratification
  - Treatment Options
- Future Direction

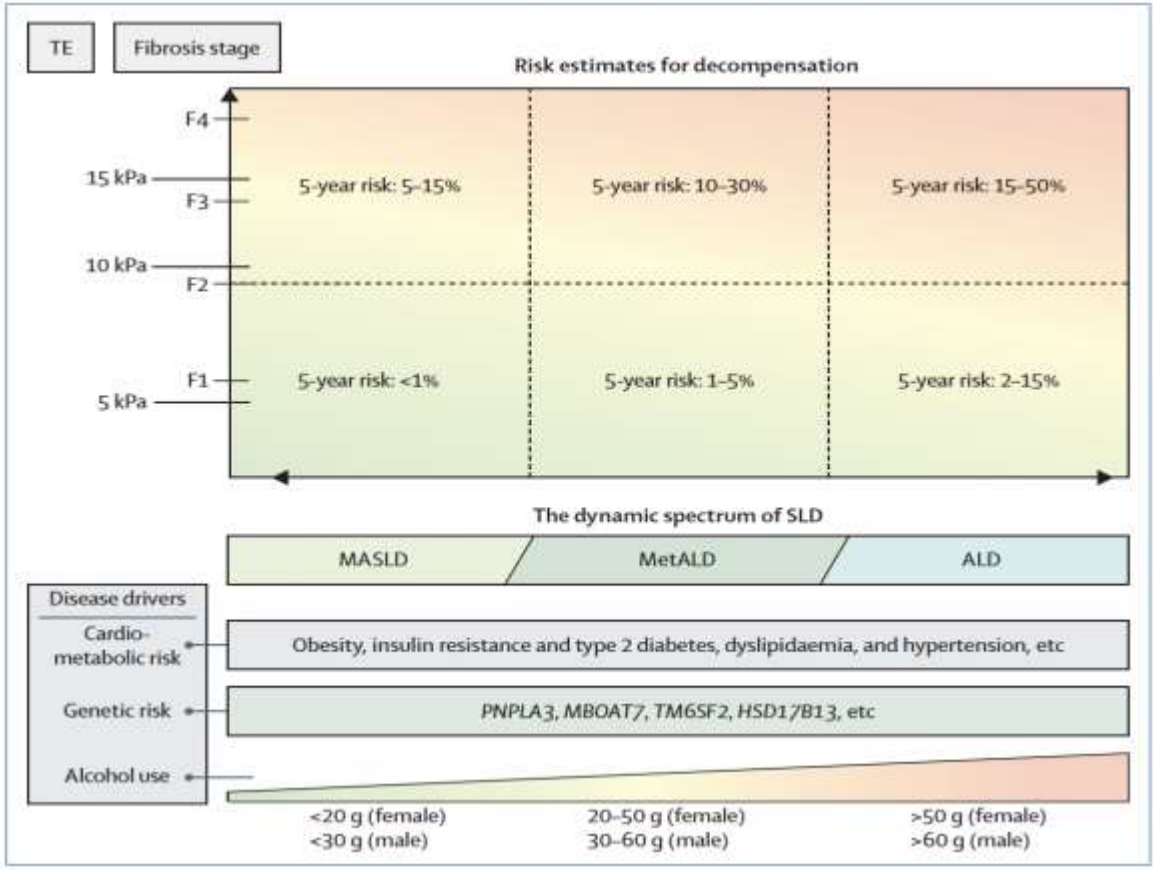
Change in Nomenclature: Clarity in Pathophysiology



*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, human immunodeficiency virus (HIV)

Kanwal, Tetri, Loomba, Rinella. Metabolic dysfunction-associated steatotic liver disease (MASLD) in context: Implications for the AASLD clinical practice guidance on nonalcoholic fatty liver disease. Hepatology 2023, *in press; Adapted from* Rinella, Lazarus, Ratziu…Newsome, on behalf of the NAFLD Nomenclature consensus group. A multi-society Delphi consensus statement on new fatty liver disease nomenclature *Hepatology* 2023; Rinella et al. *Journal of Hepatology* 2023; Rinella et al. *Annals of Hepatology* 2023 Hepatology79(5):1212-1219, May 2024

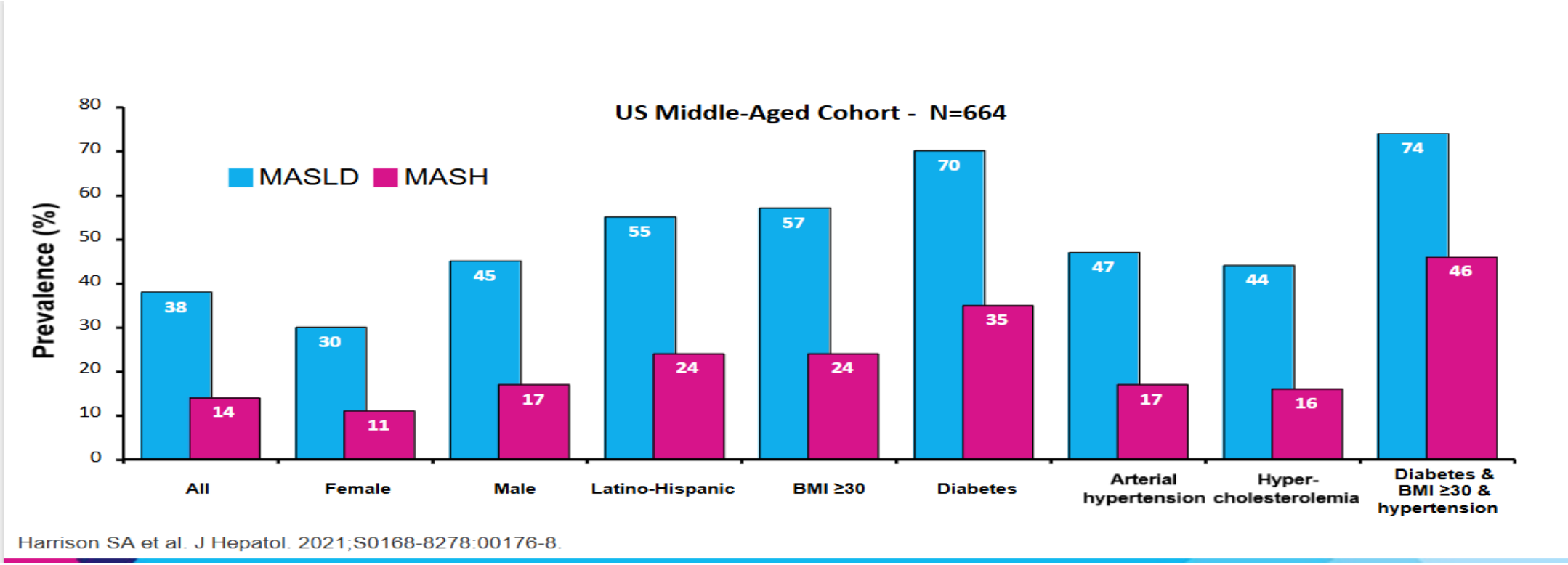
Dynamic Spectrum of MASLD-MetALD-ALD



- Addresses the role of stigma
- ‘Elevates’ mutual importance of BOTH harmful alcohol use AND cardiometabolic risk as drivers of liver disease
- Opportunities for research
- Inclusion into clinical trials
- Personalized understanding of drivers of fibrosis progression rates

Slide borrowed: https://www.aasld.org/new-masld-nomenclature?check_logged_in=1 & Meena Bansal MD.
Israelsen et al. MetALD: new opportunities to understand the role of alcohol in steatotic liver disease. Lancet GI Hep 2023

MASLD and MASH Prevalence US Cohort



Harrison SA et al. J Hepatol. 2021;S0168-8278:00176-8.

Slide Courtesy of Meena Bansal MD

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Case

42yo Hispanic woman referred by PCP for incidental finding of fatty liver on Ultrasound

- **Exam:** Vitals notable for BP: 147/90, BMI 40, No stigmata of cirrhosis
- **Labs:**
  - AST 35, ALT 30, Tbil 0.6, AP 175
  - Hgb 15 g/dl, MCV 96, Platelets 130K
  - Negative viral and autoimmune serologies
  - Ferritin 250 ng/dL; iron saturation 17%
- **Social:** computer based work, alcohol use: 2-3 wine glasses/day over weeknd

Case

- What does this patient have?

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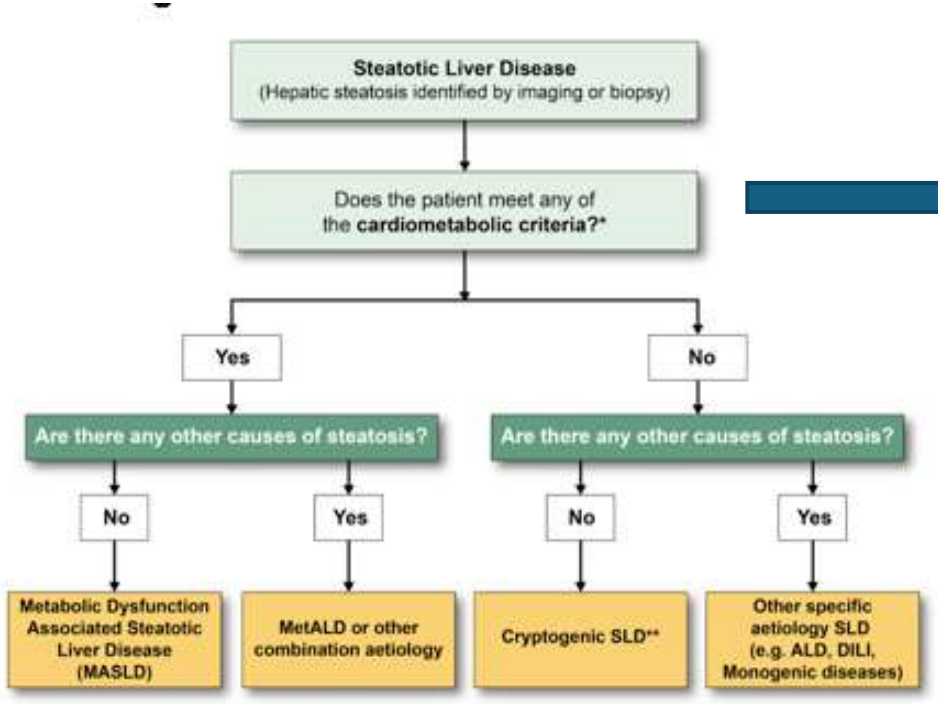
MASLD Diagnostic Criteria



Metabolic Risk Factors

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 equivalent
- ☐ 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

Hepatology79(5):1212-1219, May 2024.

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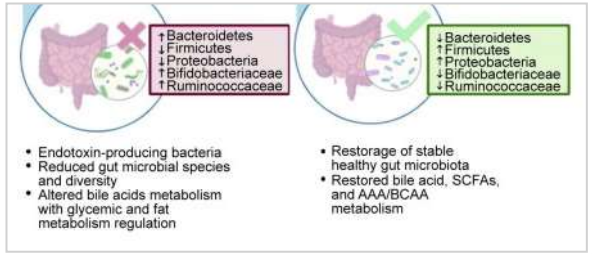
Risk Factors

>/= Class 2 Obesity: 90% MASLD, 25% MASH
Body fat distribution:
Android: increased truncal subcutaneous & and visceral fat confers -> insulin resistance/CVD/hepatic fibrosis, irrespective of body mass index (BMI)

Gynoid: increased subcutaneous fat predominantly in the hips or buttocks, appears to be protective against NAFLD.



Most impactful risk factor for the development of NAFLD, fibrosis progression, and HCC.

Upto 67% T2DM have MASLD, 30% have MASH, 20% advanced fibrosis

Relationship between NAFLD and T2DM is bidirectional

Patients with NAFLD should be screened for the presence of T2DM

The *PNPLA3 rs738409 C/G* polymorphism is strongly associated with:

- Fibrosis progression and HCC risk in MASLD and ALD
- May increase the risk of cirrhosis in HCV patients

HSD17B13 rs72613567:TA is a common splice variant (loss of function) and is associated with:

- Decreased transaminases
- Reduced risk of alcoholic and non-alcoholic liver disease and cirrhosis
- Protection from MASH in individuals with fatty liver

Pts with NAFLD 2x more likely to have DL

More atherogenic lipid sub fraction

Management of dyslipidemia in NAFLD should include moderate- to high-intensity statins as first-line therapy

Add on fibrates for elevations in TGs

CVD is an important cause of death in patients with NAFLD (extent of rltnshp unclear)

Harrison et al. EASL 2019. Lindén, Daniel et al. Journal of Hepatology,October 2023 Volume 79, Issue 4, 1056 – 1064. Ernesto Saenz et la, Engineering, Volume 40, 2024, Pages 51-60

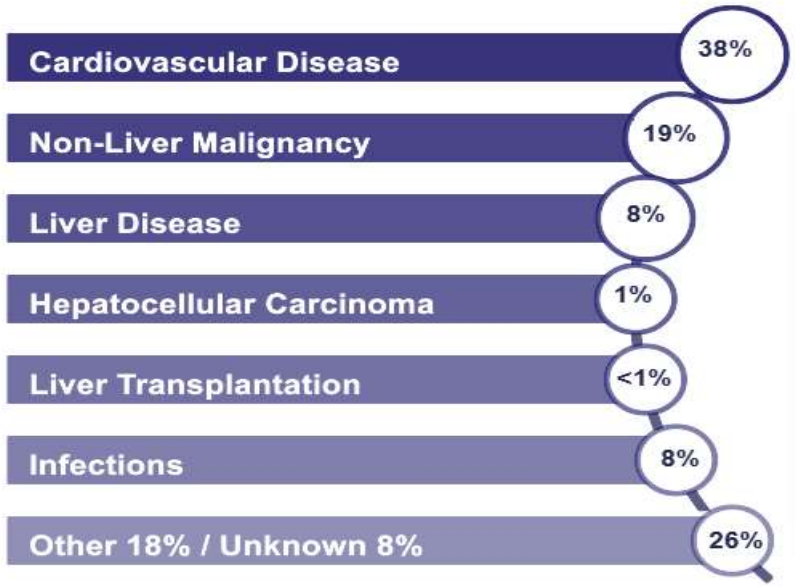
Case

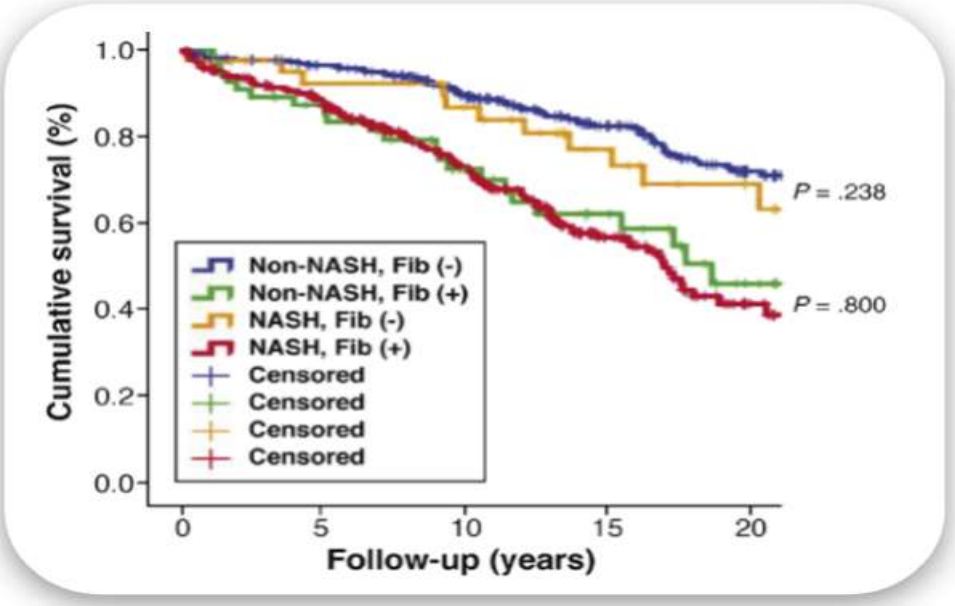
- What is patient’s prognosis?

Mortality in MASLD Patients

Leading Causes of Mortality in MASLD

PRELHIN Study: 619 MASLD Cases (median follow-up 12.6 [0.3-35.1] years)





Fib: fibrosis; NASH: nonalcoholic steatohepatitis.
Angulo P, et al. *Gastroenterology*. 2015;149:389-397.e10.
Reproduced for educational purposes only.

Slide Courtesy of Meena Bansal MD

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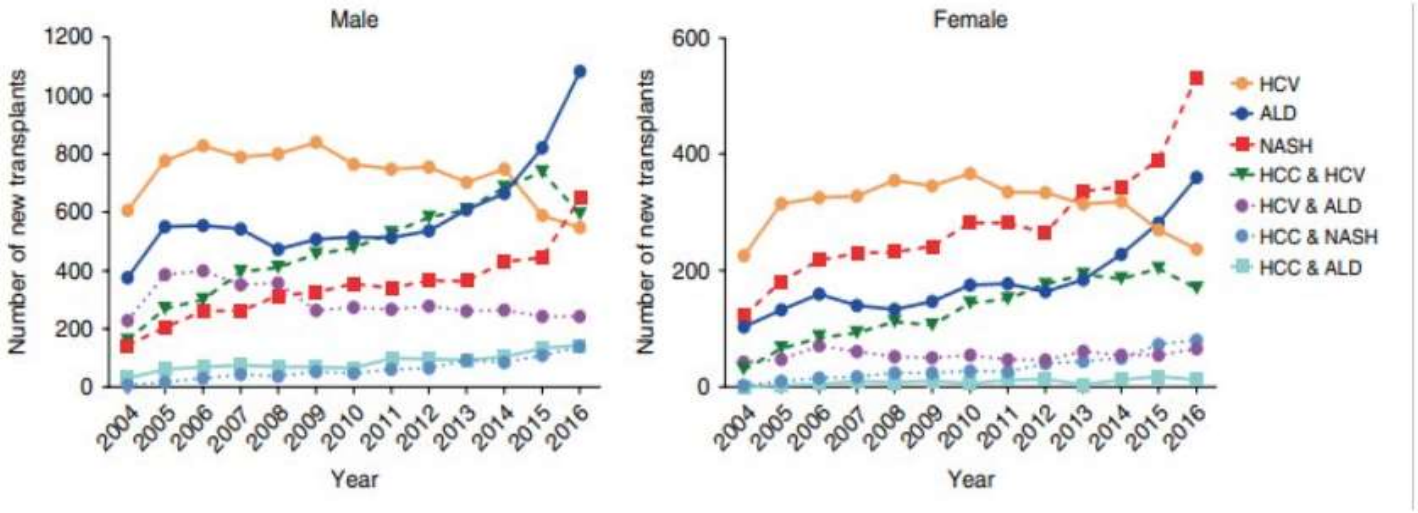
MASLD and Liver Transplantation

MASH now leading cause of transplants in women and second to alcohol overall

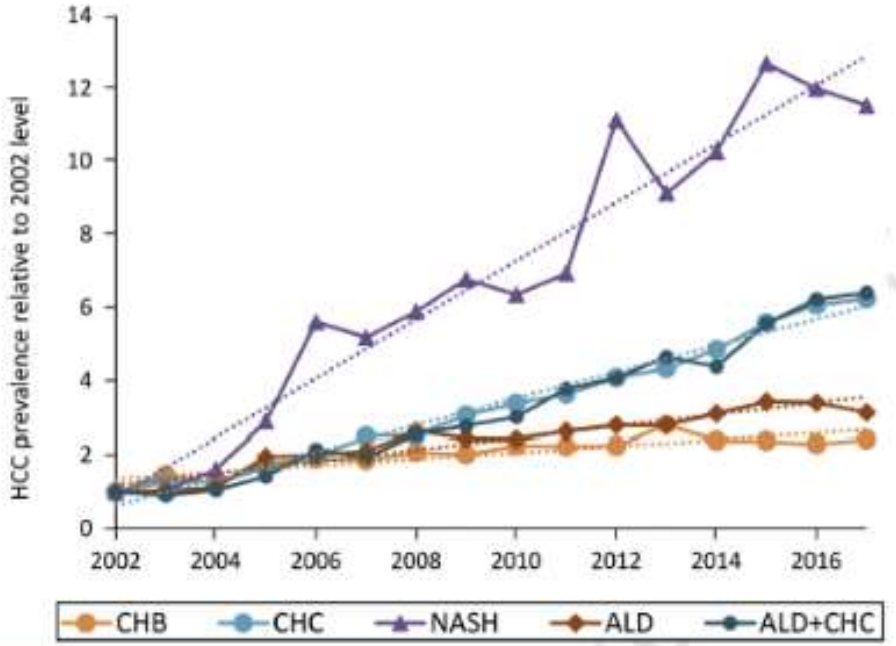


Noureddin et al, American Journal of Gastroenterology, 2018

Slide Courtesy of Meena Bansal MD

MASLD and HCC

NASH is the fastest growing cause of HCC in LT candidates



11.5–fold increase in prevalence of HCC from 2002 to 2016

Younossi ZM et al. CGH. 2018

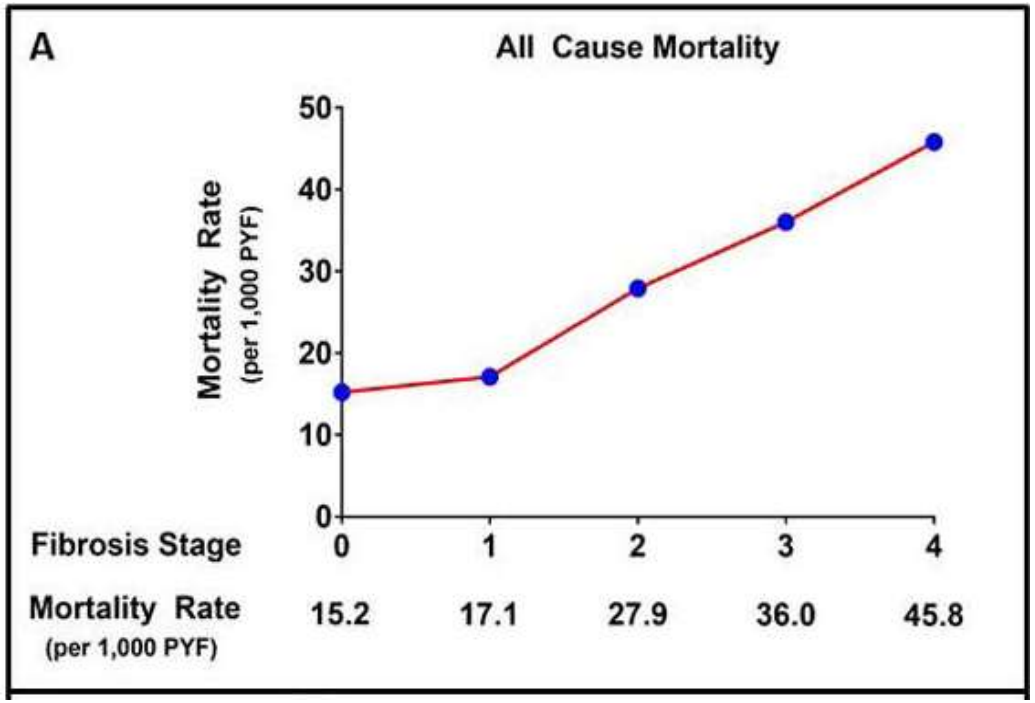
Case

- Does this patient need a GI/hepatologist?

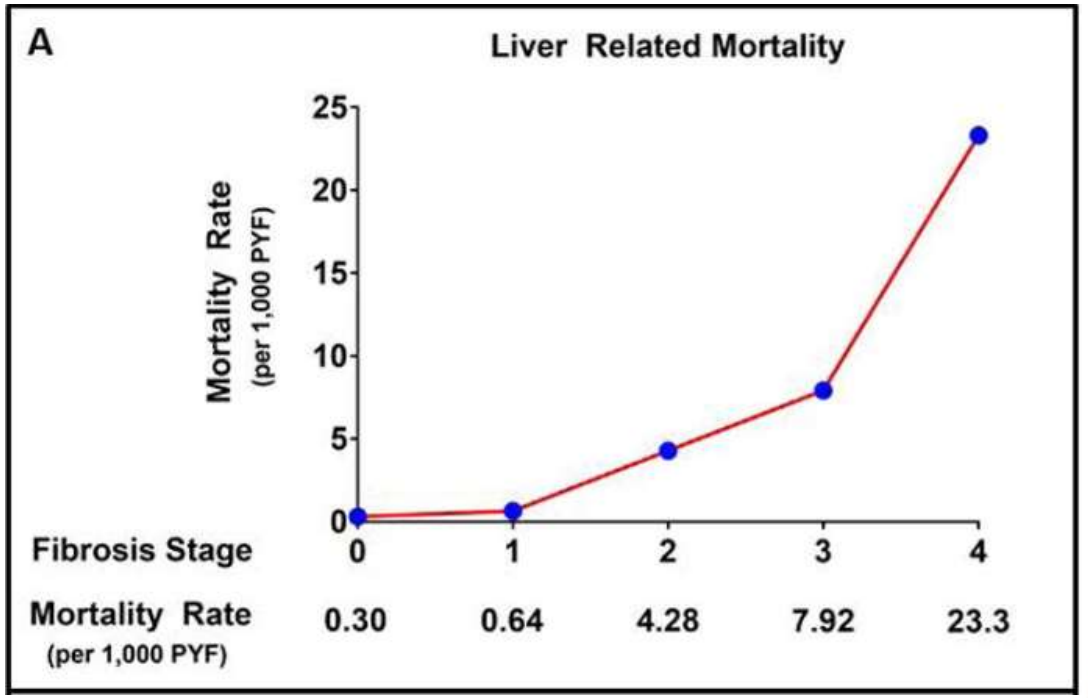
Fibrosis is the most important predictor for Mortality in MASLD

Systemic Review: 1,495 NAFLD pts with 17,452 patient years of follow-up

Fibrosis Stage Specific All-Cause Mortality Rate and Mortality Rate Ratio



Fibrosis Stage Specific Liver-Related Mortality Rate and Mortality Rate Ratio



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Dulai PS, et al.Hepatology. 2017 May;65(5):1557-1565. doi: 10.1002/hep.29085.

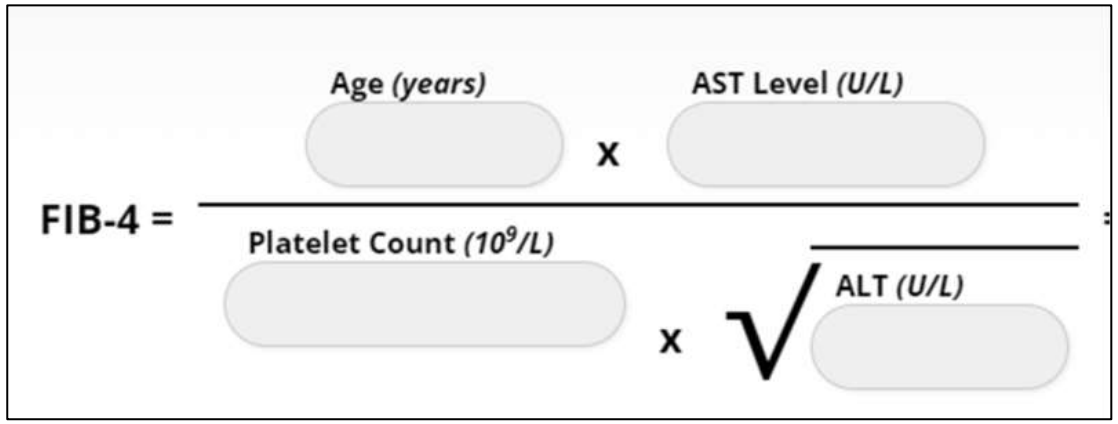
How Do We Stage Fibrosis

- Given the large scale of cases, liver biopsy is not practical (invasive, cost and access)
- Non-invasive liver fibrosis tests have been developed
  - Scores using blood tests (NASH, Fibrosure, Fib-4, APRI, etc)
  - Elastography devices (US, Fibroscan, MR)
  - Serum markers (ie ELF)

Modality type	Cut point: Likely	Cut point: Unlikely	Strengths/limitations, references/caveats
Detection of advanced fibrosis			
Serum			
FIB-4	≥2.67	<1.3	No added cost[117,329,330]; not accurate in age <35 y and lower rule-out threshold among high-risk individuals who have high pretest probability
NFS	≥0.672	<−1.44	No added cost; not accurate in age <35 y, people with obesity and/or type 2 diabetes[117,329,330]
ELF	≥9.8	<7.7	Blood test sent to a reference laboratory[331]; cost
FIBROSpect II	≥17	<17	Blood test sent to a reference laboratory[332]; cost
Imaging			
VCTE	≥12 kPa	<8 kPa	Point of care[4]
ARFI	≥1.34	<1.3	Cut points not well validated[333]
SWE	≥12 kPa	<8 kPa	Cut points not well validated[488]
MRE	≥3.63 kPa	<2.55 kPa	MRE LSM ≥3.63 kPa (associated with advanced fibrosis, AUROC of 0.93)[334]
Diagnosis of cirrhosis (rule-in or rule-out)	Rule-in	Rule-out	
CPR			
FIB-4	≥3.48	<1.67	90% specificity cut point for ruling-in and 90% sensitivity for ruling out cirrhosis, respectively[4,335]
ELF	≥11.3	<7.7	ELF ≥11.3 is associated with increased risk of hepatic decompensation among patients with cirrhosis[331]
Imaging			
VCTE	≥20 kPa	<8 kPa	LSM by VCTE ≥20 kPa is associated with cirrhosis, but for ruling out, cirrhosis optimal cut point is <8 kPa[4]
MRE	≥5 kPa	<3 kPa	LSM by MRE ≥5 kPa has a very good (approaches 95%) specificity for diagnosis of cirrhosis and is also associated with increased risk of incident hepatic decompensation[334,336]

Rinella, et al, Hepatology 77(5):p 1797-1835, May 2023.

To Start: FIB-4



FIB-4 status category:
Low risk (<1.3)
Intermediate risk (1.3–2.67)
High risk (>2.67)

- Easy and essentially free assessment of liver fibrosis
- Developed in a cohort of subjects that did not include the young or very old (age is numerator)
- Different cut-offs for varying liver disease
- AST is numerator – alcohol may over-estimate

Rinella, et al, Hepatology 77(5):p 1797-1835, May 2023.

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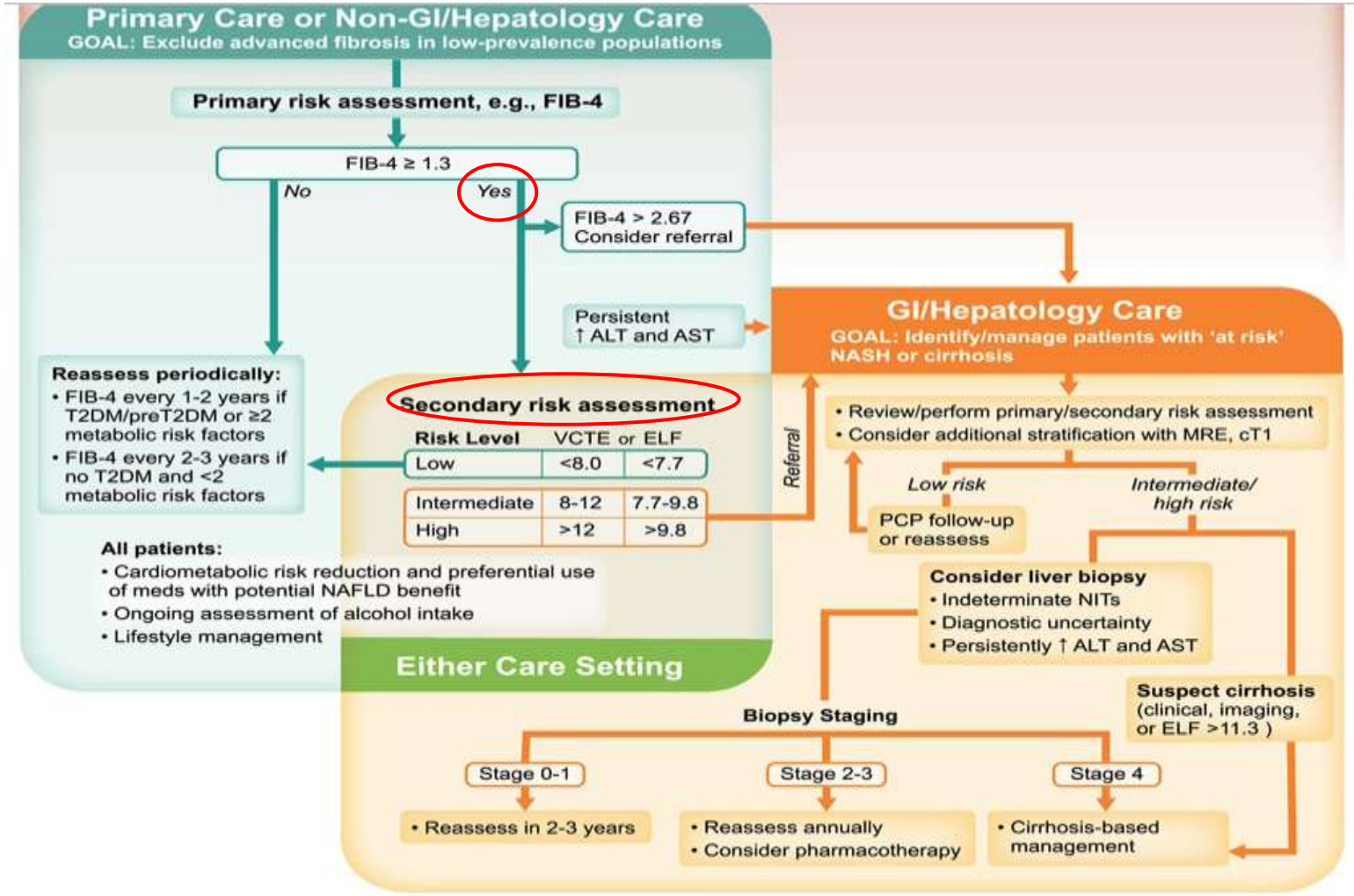
Algorithm for Evaluation



Case:
FIB-4 = 2.06

Rinella, et al, Hepatology 77(5):p 1797-1835, May 2023.

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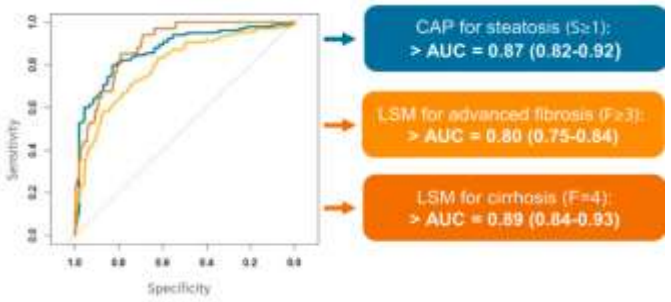
Secondary NIT Fibrosis Assessment

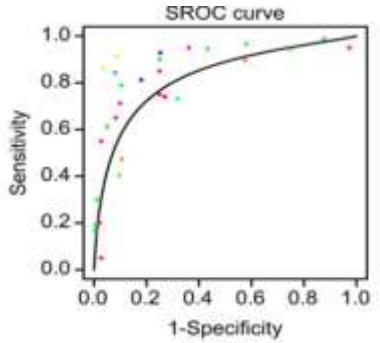
VCTE

- Most commonly used method to assess liver stiffness, more available data
- LSM<8 kPa can be used to rule out advanced fibrosis
- Non-invasive, bedside, 2minutes
- Limited by obesity & inflammation
- May over-estimate fibrosis



ELF

- Proprietary blood test consisting of three elements involved in matrix turnover
  - Validated for liver fibrosis
  - Prognostic for complications of liver disease
- ELF score of ≥9.8 reliably identifies patients with NAFLD at increased risk of progression to cirrhosis



11 studies were included in the meta-analysis of advanced fibrosis
AUC: 0.83 (0.71, 0.90)
Sensitivity: 0.73 (0.60, 0.83)
Specificity: 0.80 (0.68, 0.88)

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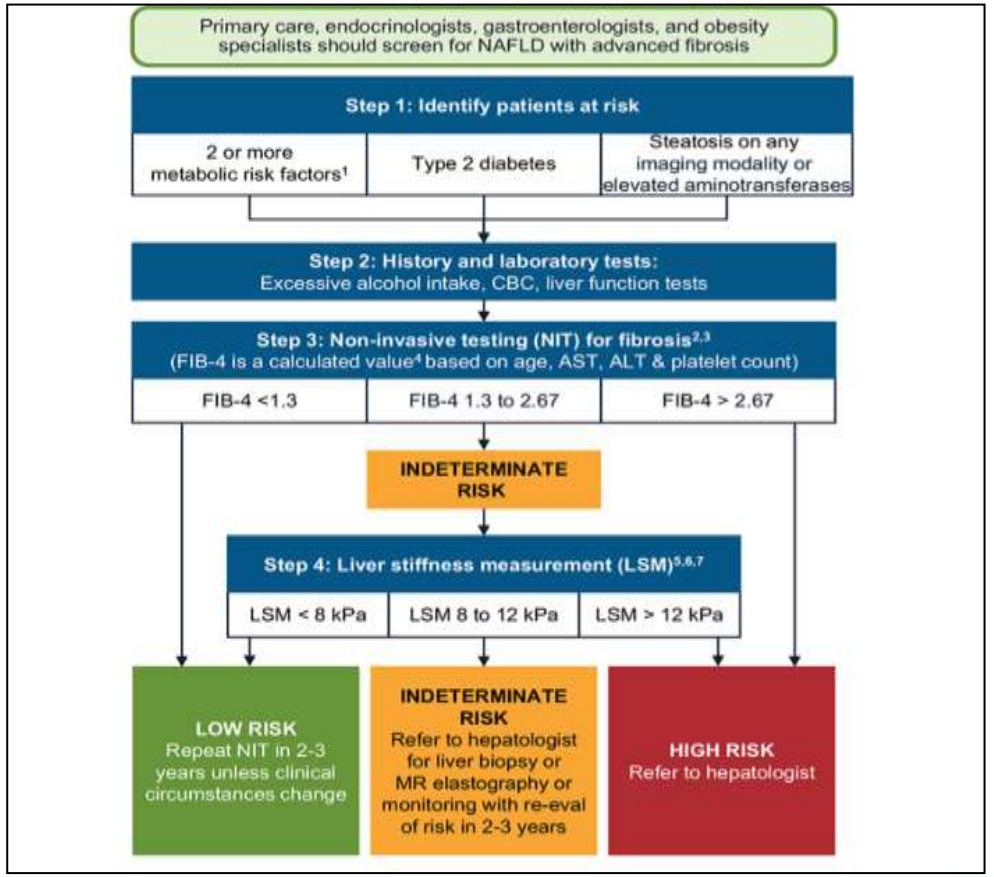
Rinella, et al, Hepatology 77(5):p 1797-1835, May 2023. Vali Y, et al, J Hepatol. 2020 Aug;73(2):252-262

Final Step in Fibrosis Assessment

- Liver Biopsy vs. MRE
- MRE:
  - More sensitive than VCTE in the detection of fibrosis stage ≥2
  - Most accurate NIT
  - Expensive and Access issues

Cutoff for Detecting Advanced Fibrosis	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
MRE stiffness ≥ 3.64 kPa	0.86 (0.65-0.97)	0.91 (0.83-0.96)	0.68 (0.48-0.84)	0.97 (0.91-0.99)

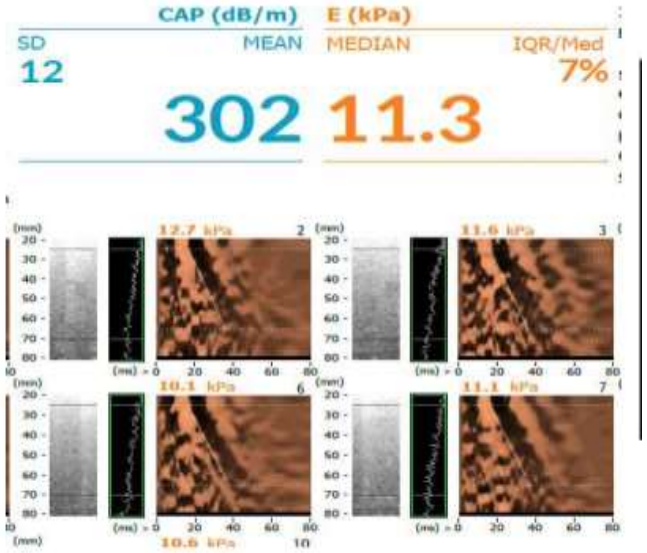
AUC for diagnosis of advanced fibrosis: 0.924



Rinella et al., Hepatology 77(5):p 1797-1835, May 2023. Kanwal F, et al.Gastroenterology. 2021 Nov;161(5):1657-1669.

Case

Fibroscan:



Intermediate Fibrosis

- What are goals of treatment?
- What are treatment options?

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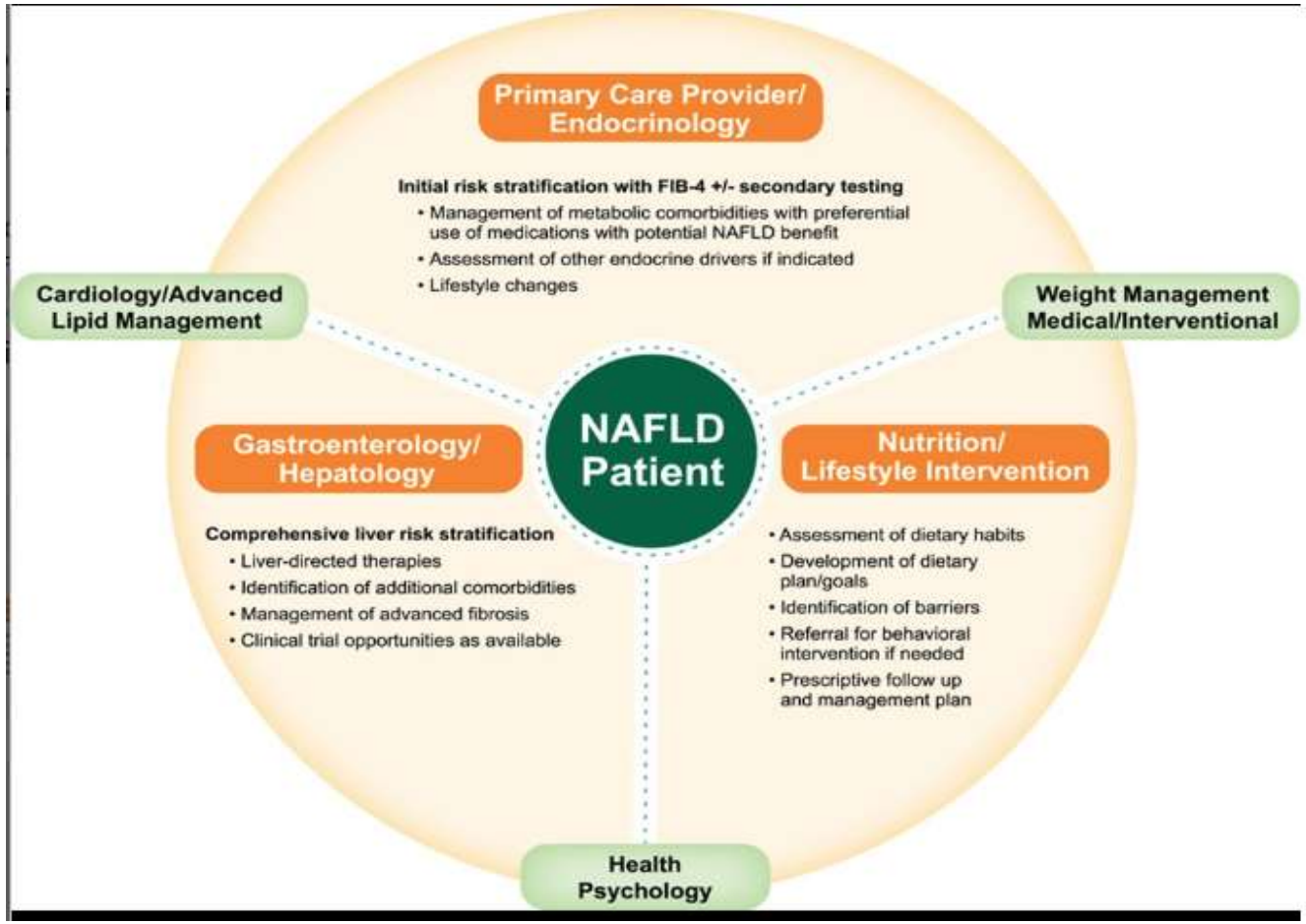
Treatment Goals



Layla A. et al., Clinical Gastroenterology and Hepatology, Volume 22, Issue 8,2024, Pages 1565-1574. Created with BioRender.com

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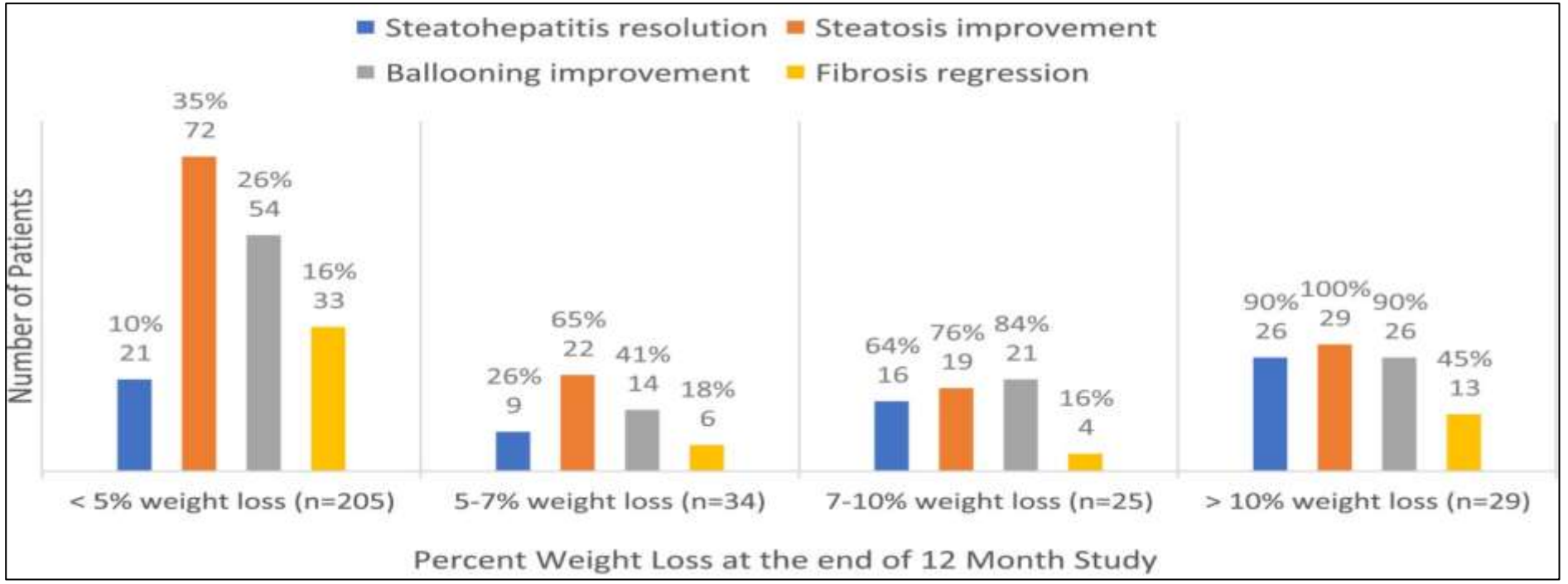
Treatment: Weight Loss

Prospective Trial Impact of Weight loss on Liver Histology



Vilar-Gomez et la., *Gastroenterology* 2015;**149**:367-378.e5.

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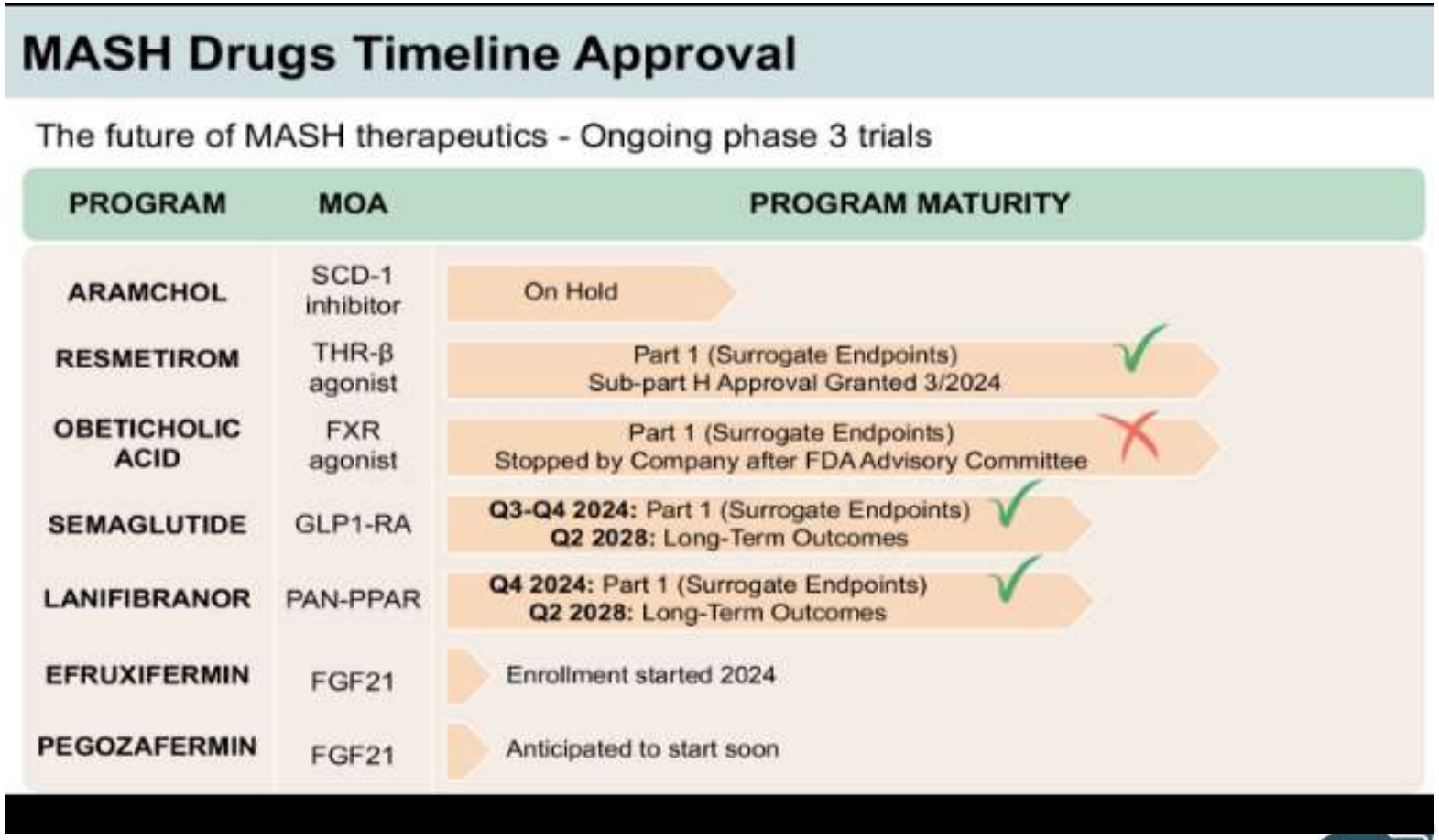
Pipeline of MASLD Rx

FDA APPROVAL:

- Conditional- based on surrogate endpoints, reasonably likely to improve clinical benefit

  MASH resolution with no worsening of fibrosis AND/OR >/= 1 stage fibrosis improvement without worsening of MASH

- Full- based on Major Adverse Liver Outcomes



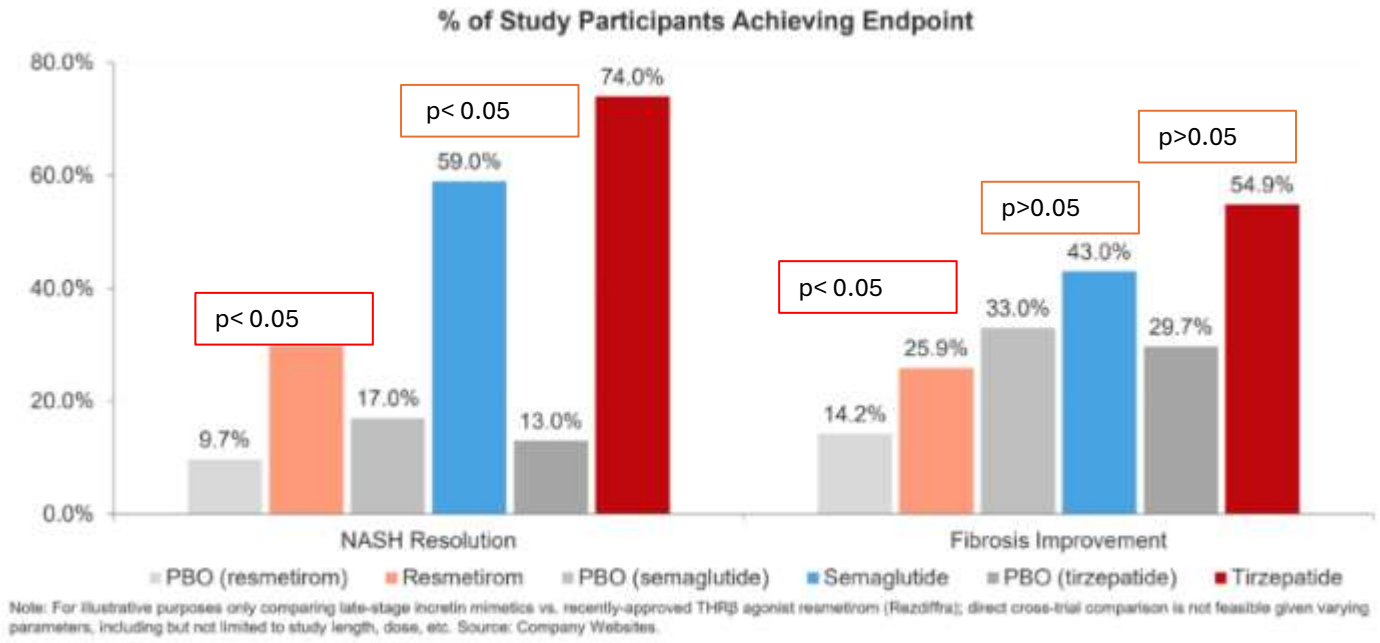
Noureddin M. MASH clinical trials and drugs pipeline: An impending tsunami. Hepatology. 2024 Mar 19.

Repurposed Rx:

DRUG	POPULATION	DURATION	PRIMARY END POINT
Therapies recommended for NASH by International Societies			
Vitamin E (800IU/day) – anti-oxidant	NASH w/o Cirrhosis	96 weeks	Improvement in NAS by 2 pts
Pioglitazone (45mg/day) - PPARγ	NASH w/o cirrhosis Pre-DM or DM	18 months	Improvement in NAS by 2 pts
Therapies for Obesity/MetSyndr with initial efficacy evidence			
Liraglutide (1.8mg/day)	NASH w/o cirrhosis	48 weeks	Resolution of NASH w/o worsening of fibrosis
Semaglutide	NASH F1-F3	72 weeks	Resolution of NASH w/o worsening of fibrosis

Noureddin M, et al. Clin Liver Dis. 2023 May;27(2):397-412

Metabolic Agents: Incretin Mimetics



PHASE 2 DATA:

Semaglutide- not statistically significant improvement in fibrosis

Tirzepatide – not adequately powered for fibrosis, no dose-response seen

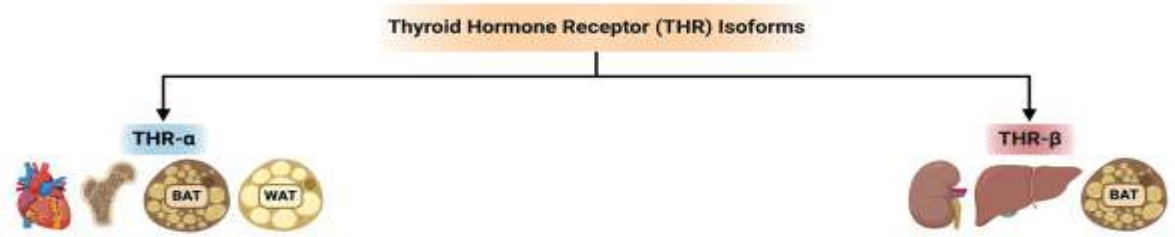
Survodutide – dual glucagon/GLP-1 – steatosis improved.

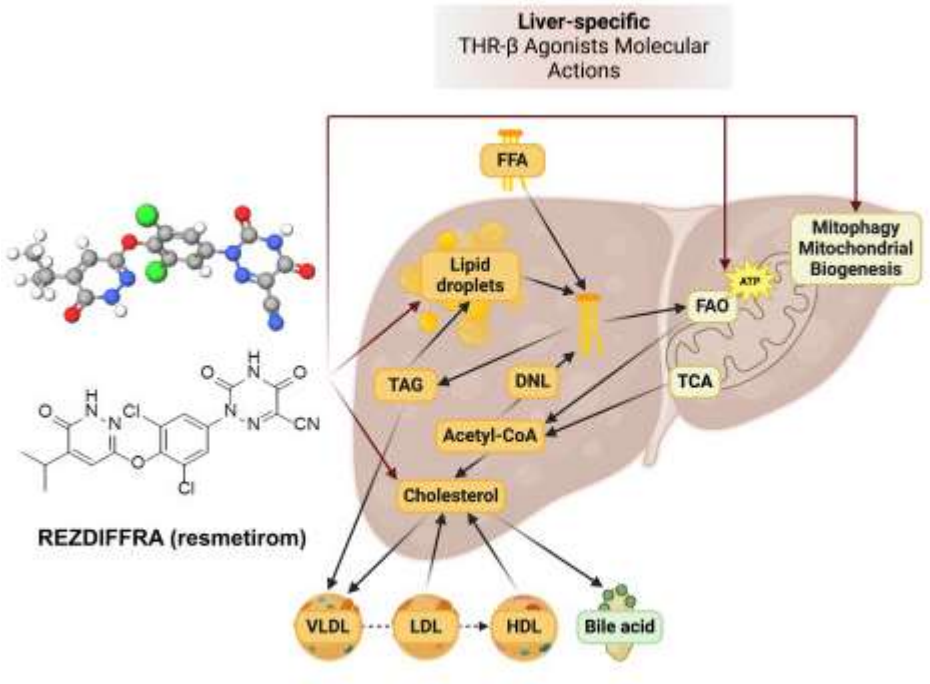
May need to do combination therapy with anti-fibrotic if Phase 3 data does not show statistical significance

Loomba R et al. N Engl J Med. 2024 Jul 25;391(4):299-310. Harrison SA et al. N Engl J Med. 2024 Feb 8;390(6):497-509. Newsome PN, et al. N Engl J Med. 2021 Mar 25;384(12):1113-1124
https://bluematterconsulting.com/mash-in-2024-catalyst-year/.

Metabolic Agent: Thyroid Receptor–B agonists

Resmetirom
Accelerated FDA Conditional Approval March 2024





LATE BREAKER ABSTRACT: AASLD Meeting Nov 2024
Voyage Trial - 52 Week, Placebo Control
Positive phase 2b THRβ agonist (VK2809)
NASH resolution (75% Txt vs. 29% Placebo) P<0.05
Fibrosis improvement (57% Txt vs. 34% Placebo) P<0.05

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Kokkorakis, Michail et al. Metabolism - Clinical and Experimental, Volume 154, 155835. Harrison SA et al. N Engl J Med. 2024 Feb 8;390(6):497-509

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

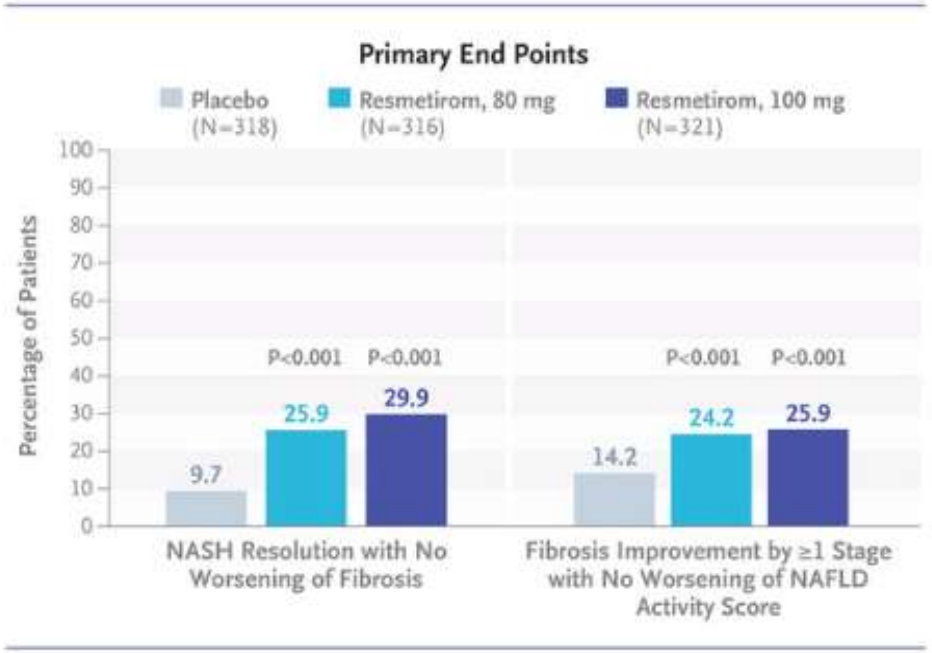
A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis

Harrison SA et al. DOI: 10.1056/NEJMoa2309000

MAESTRO TRIAL

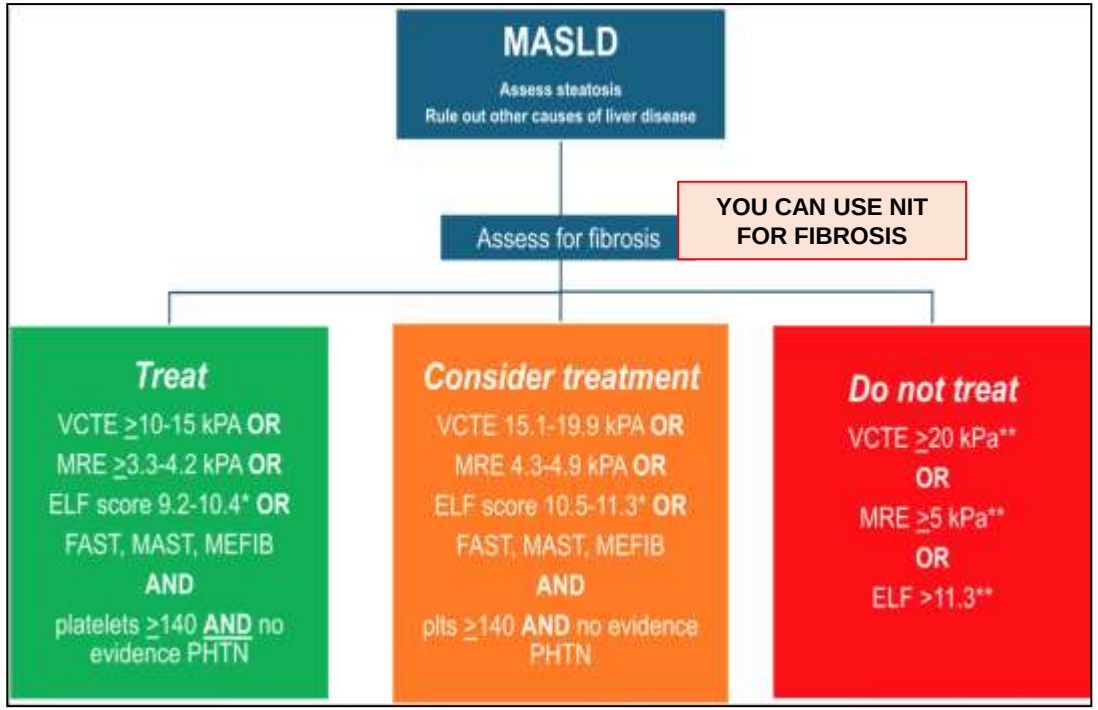
Biopsy-confirmed NASH with F1B, F2 or F3 fibrosis

- Resmetirom 80mg, 100mg or Placebo for 52 weeks
- 2 Primary End points:
  - Improve NASH w/o worsening fibrosis
  - Improve Fibrosis 1 stage w/o worsening NASH
- SE: diarrhea, nausea. No SS in serious adverse events when compared to placebo

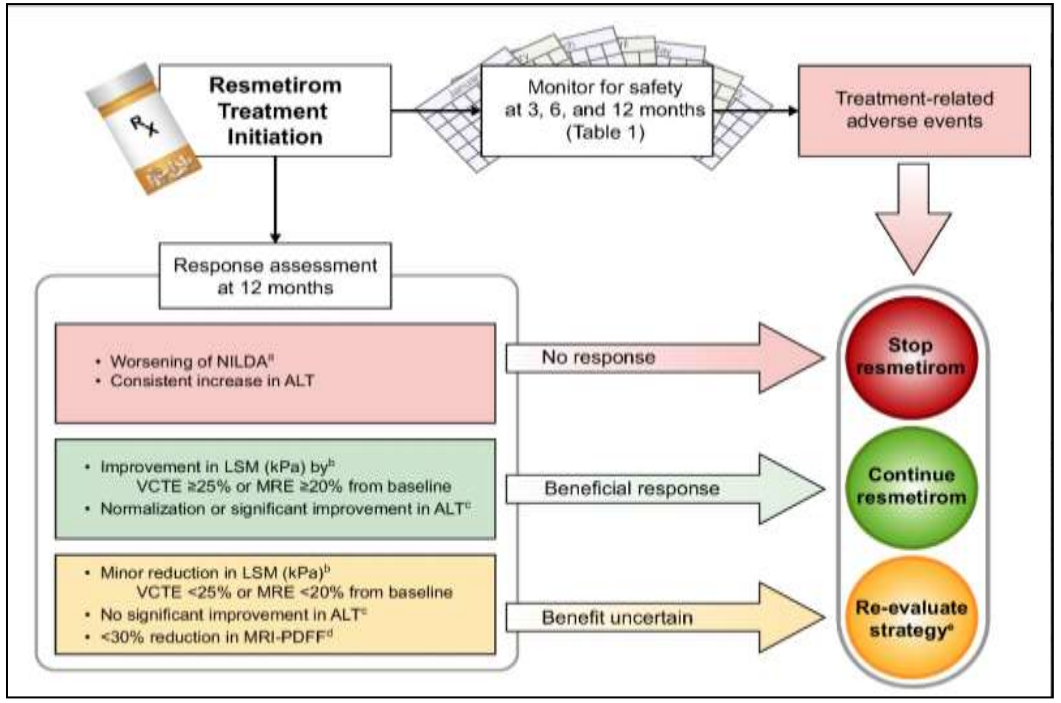


Practice Guidelines: Resmetirom

Who To Treat



Assessment on Treatment



The FDA-approved label does not require liver biopsy to confirm the diagnosis of fibrotic MASH.
While MASH can only be definitively diagnosed by histologic examination, patient selection in practice is based on evidence of steatosis and fibrosis as determined by NILDA methodologies among persons with cardiometabolic risk factors without other causes of steatosis, notably alcohol consumption of more than 20 g/d for women and more than 30 g/d for men.[10]

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Noureddin, Mazen et al. Clinical Gastroenterology and Hepatology, Volume 22, Issue 12, 2367 – 2377. Chen et al., October 2024 updates to AASLD Practice Guidance. Hepatology

Practice Guidelines: Resmetirom

	Safety/Efficacy assessments	Safety assessments		Efficacy assessments	
Timeframe	Hepatic function panel[a]	Thyroid function[b]	Lipid profile[c]	Noninvasive measurement of liver stiffness[d]	MRI-PDFF[e]
Before treatment initiation	✓	✓	✓	✓	Consider
3 months	✓				
6 months	✓	✓	✓		
12 months	✓	✓	✓	Repeat if imaging NILDA was used at baseline	Consider repeating if baseline data are available

- Comprehensive lifestyle modification (nutrition, exercise, and behavior modification) & optimal control of comorbid metabolic conditions
- Trial did not include patients on GLP1, Vit E or pioglitazone. For those already on these Rx, not enough data on when and if to introduce resmetirom
- DDI: Resmetirom is a substrate for cytochrome P450 enzyme 2C8 and organic anion transporting polypeptides 1B1 and 1B3
  - Plavix -> 60 mg dose
  - Statin -> max. dose rosuvastatin and simvastatin is 20 mg/d; atorvastatin and pravastatin is 40 mg/d
- Elevated liver enzymes common, but most resolve at 2 months. Stop Txt if: AST/ALT > 5xULN or AP > 2xULN
- One case jaundice-> biopsy showed interface hepatitis (but patient had AMA positive at enrollment).
- Most common side effects: diarrhea, nausea
- FDA Review: Thyroid Axis function maintained during remetirom therapy

Case

- Lifestyle counseling: reduce alcohol to 1-2drinks on occasion, desk job- recommend 150 min of aerobic exercise, reduce sweetened drinks and add more vegetables

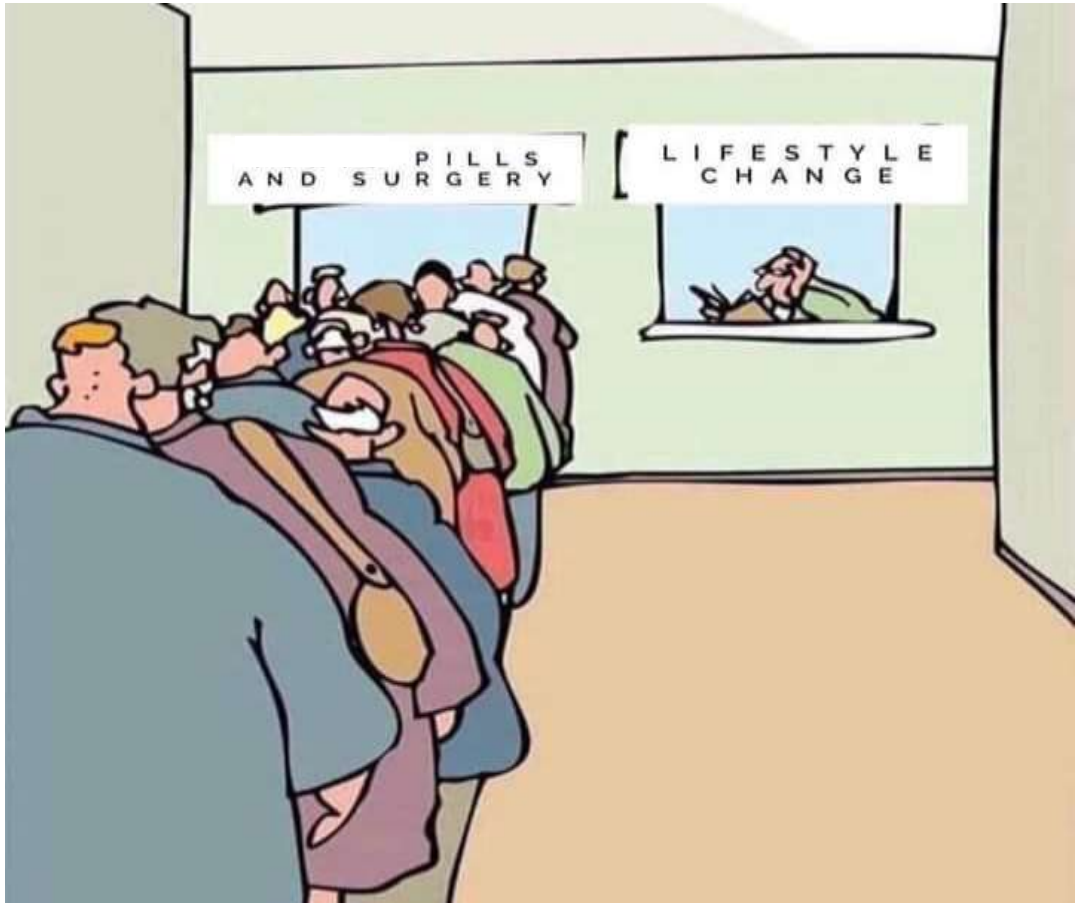
- Patient was offered resmetirom 80mg

- Lipid and A1c optimization with PCP

Summary: Tip of the Iceberg

- Change in name – change in game. Takes into account metabolic risk factors and alcohol
- Foundation of treatment must include diet/exercise: improve metabolic risk factors and reduce cardiovascular disease. CV disease is frequent cause of death in this population.
- Advance Fibrosis associated with increased liver morbidity & mortality. These patient require liver directed therapy
- Resmetirom first conditional approved agent for MASH
- Weight loss from ESG +/- GLP may help MASLD
- Numerous drugs in pipeline

Thank you!



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