Metabolic Dysfunction-Associated Fatty Liver Disease (Formerly NAFLD)

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13TH ANNUAL RICHARD C. STAAB MEMORIAL SYMPOSIUM

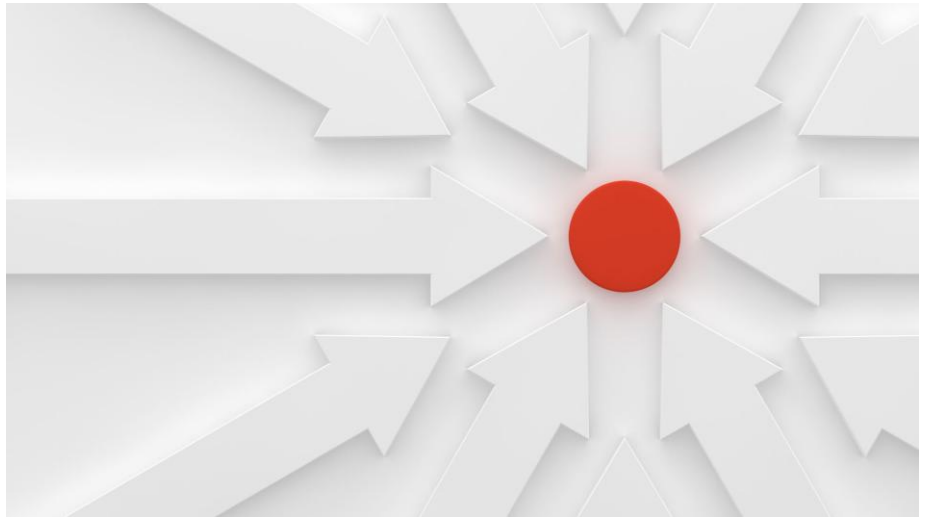
4-5-2025

Disclosures

Speakers Bureau for Gilead Sciences

Speakers Bureau for Abbvie

Objectives



- WHAT IS IT?
- HOW DO WE IDENTIFY IT?
  - Who gets screened and how?
- HOW DO WE MAKE THE DIAGNOSIS?
  - What tests do we order?
- HOW DO WE TREAT IT?
  - What is currently available?

What is This?
FOIE GRAS

Nonalcoholic Steatohepatitis: Mayo Clinic Experiences With a Hitherto Unnamed Disease

- Jurgen Ludwig, M.D., Dept. Pathology and Anatomy
- Thomas Viggiano, M.D., Resident in Gastroenterology
- Douglas McGill, M.D., Division of GI and IM
- Beverly Ott, M.D., Division of GI and IM

- Mayo Clinic Proceedings, 55; 434-438, 1980

Clinical Vignette #1

- 68 y/o morbidly obese presents with GERD and heartburn not improved with PPI/H2 therapy
- EGD performed

Grade 4 Varices Are Noted (Endoscopy Campus)

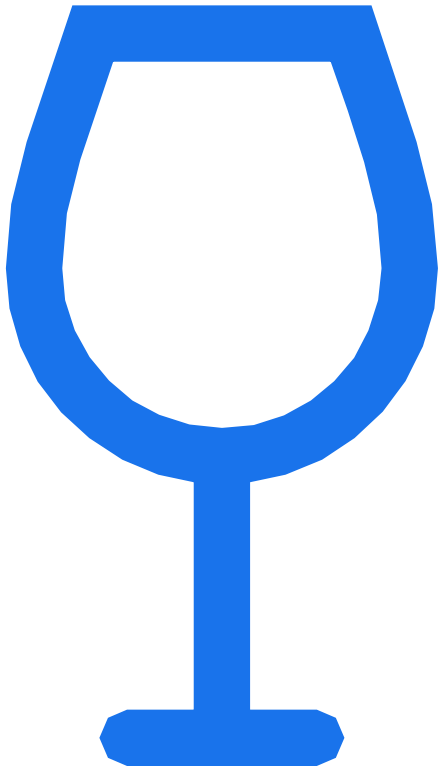
SOMETIMES I DRINK WATER JUST TO SURPRISE MY LIVER

What is Metabolic Dysfunction-Associated Fatty Liver Disease?

- Presence of fat in the liver NOT due to ETOH, viral hepatitis or medications (other causes ruled out)
- Associated conditions include obesity, diabetes, dyslipidemia, hypothyroidism, PCOS, sleep apnea
- Patients at increased risk of CVD and cirrhosis
- Increasing with about 25%-30% of world population with MDAFLD (HCC and cirrhosis also increasing)
- 6% will get inflammation/hepatitis that can lead to cirrhosis

Definitions

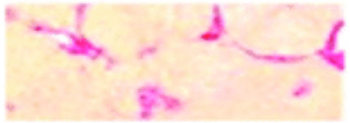
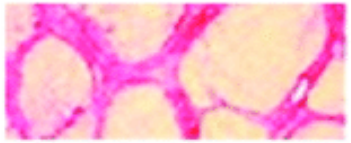
- MAFLD: Includes all stages of this disease process
  - See >/=5% of hepatocytes showing MACROVESICULAR STEATOSIS in the absence of other etiologies and little or no alcohol
- MAFL: Macrovesicular steatotosis seen (as above) with no, or mild, inflammation
- MASH: Inflammation seen and balloon degeneration noted on histology
- MASH/Cirrhosis: Inflammation seen and balloon degeneration noted on histology



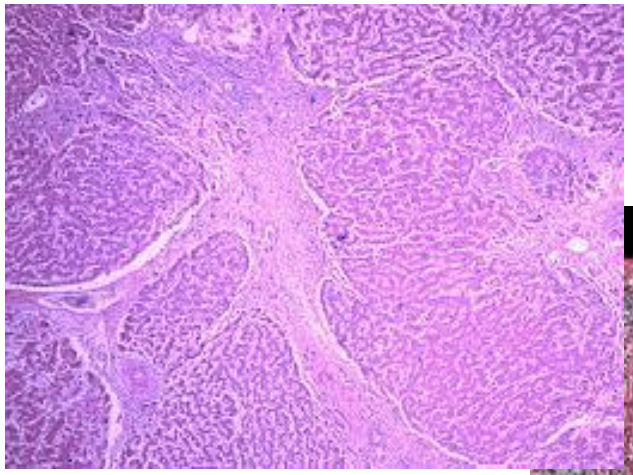
KEY POINTS

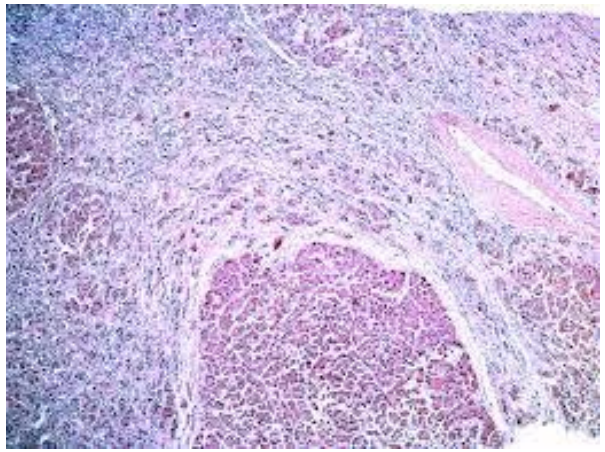
- GOAL IS TO IDENTIFY HIGH RISK PATIENTS AND PREVENT PROGRESSION TO CIRRHOSIS
- IF HAVE CIRRHOSIS GOAL IS TO SURVEY THEM APPROPRIATELY TO PREVENT VARICEAL BLEEDING AND LIVER CANCER (IDENTIFY DECOMPENSATED LIVER DISEASE)

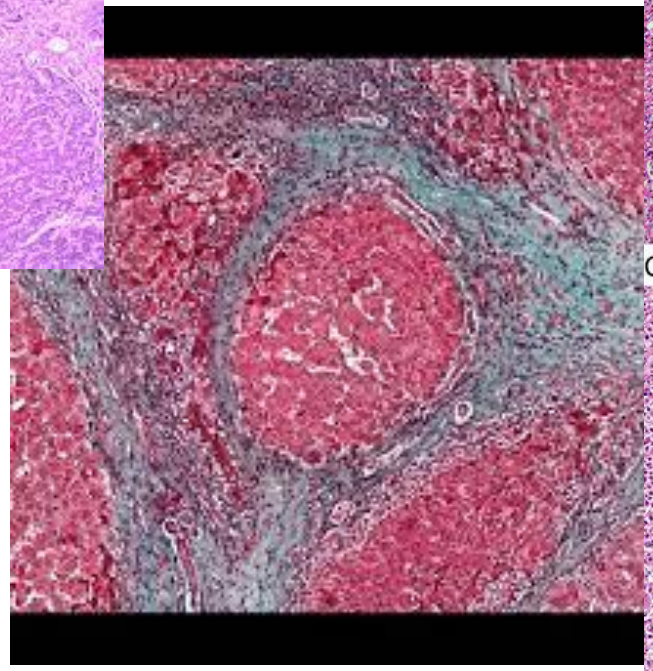
Stages of Fibrosis, Ishak and Metavir Staging

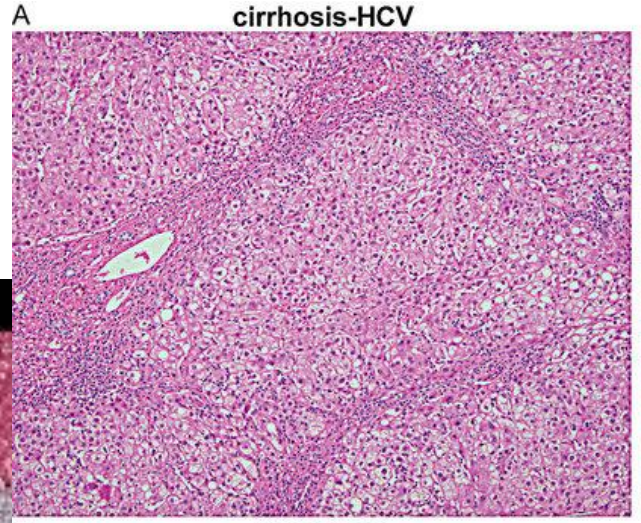
Appearance	Ishak stage: categorical description	Ishak	Metavir
	No fibrosis (normal)	0	F0
	Fibrosis expansion of some portal areas ± short fibrous septa	1	F1
	Fibrosis expansion of portal areas ± short fibrous septa	2	F2
	Fibrosis expansion of most portal areas with occasional portal to portal (P-P) bridging	3	
	Fibrosis expansion of portal areas with marked portal to portal (P-P) bridging as well as portal to central (P-C)	4	F3
	Marked bridging (P-P and / or P-C) with occasional nodules (incomplete cirrhosis)	5	
	Cirrhosis, probable or definite	6	F4

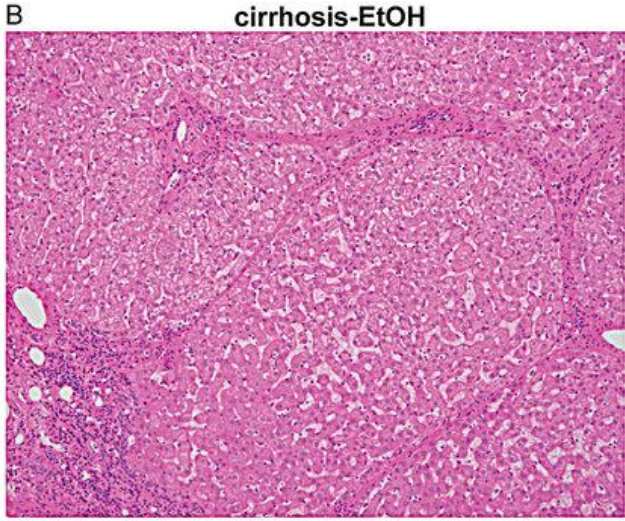
Cirrhosis

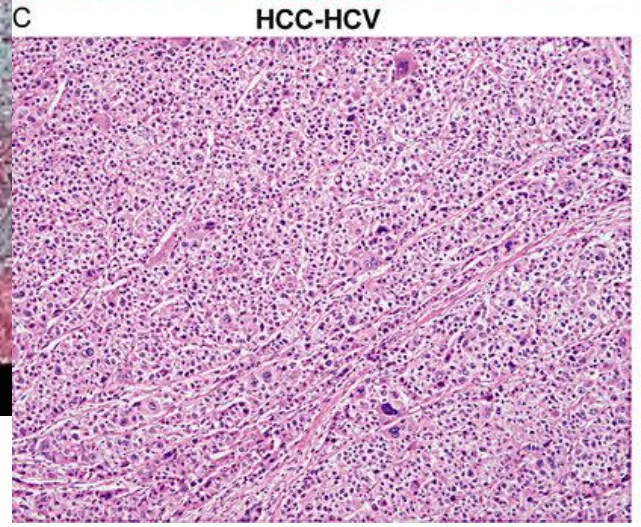


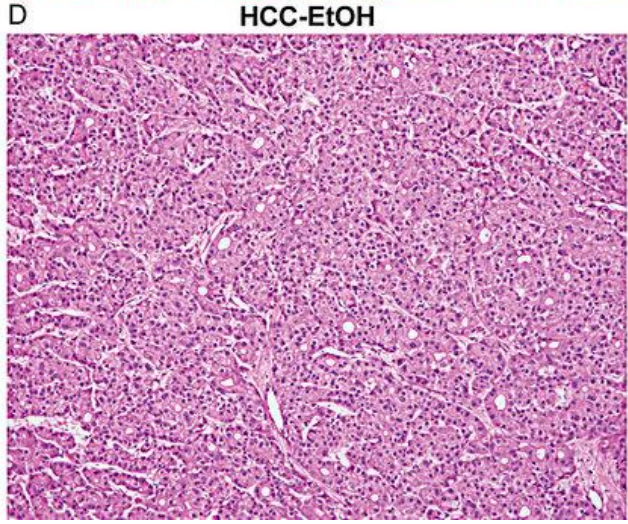




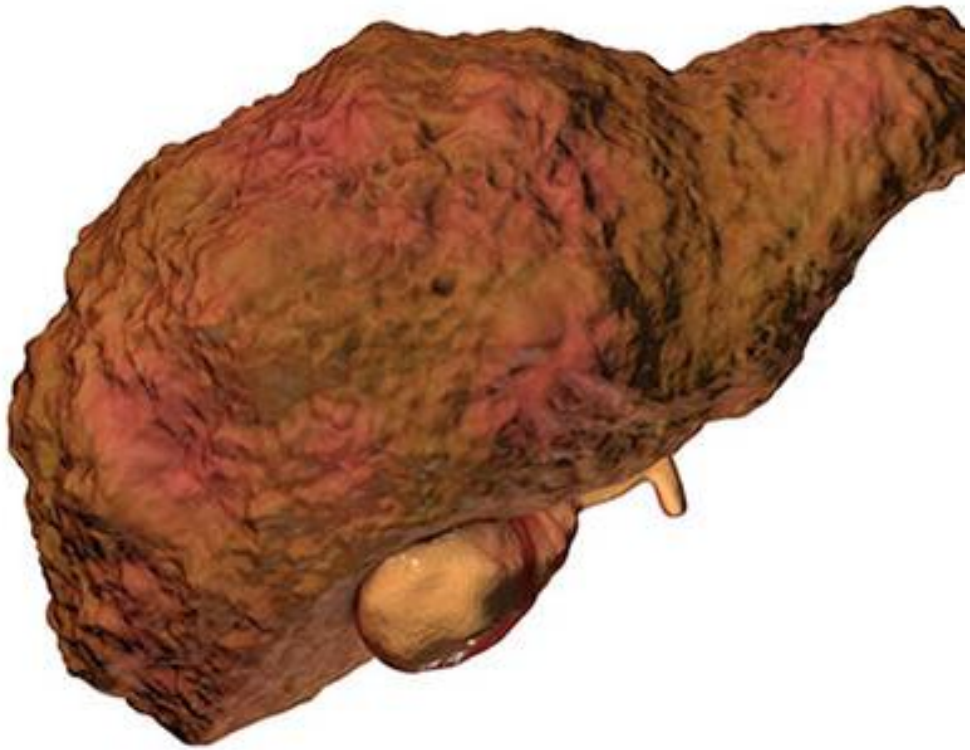








Healthy liver



Cirrhotic liver

DIAGNOSING MDAFLD

- HEPATIC STEATOSIS ON IMAGING
- ELEVATED ALT/AST/BILIRUBIN
- DECREASING PLATELET COUNTS
- METABOLIC DISEASES SUCH AS T2DM, HTN, OBESITY, DL, PCOS, OSA, HYPOTHYROID, CKD

EXLUDE OTHER CAUSES OF HEPATIC STEATOSIS

- ONGOING OR RECENT ETOH, >21 DRINKS/WK IN MEN, 14 DRINKS/WK IN WOMEN
- R/O OTHER CAUSES OF HEPATITIS
  - AUTOIMMUNE (ANA, AMA, ASMA,GGT, sp100/gp200)
  - VIRAL HEPATITIS
  - HEMOCHROMATOTIS
  - WILSON'S DISEASE
  - MEDICATIONS (AMIODARONE, MTX, 5 FU, Irinotecan, Tamoxifen, Steroids)
  - GENETIC DISEASES

Who Do We Screen?

General Population-Based Screening for NAFLD is NOT Advised, UNLESS…

Patients have hepatic steatosis on imaging or clinically suspected NAFLD based on presence of obesity/metabolic risk factors, undergo risk assessment with FIB-4

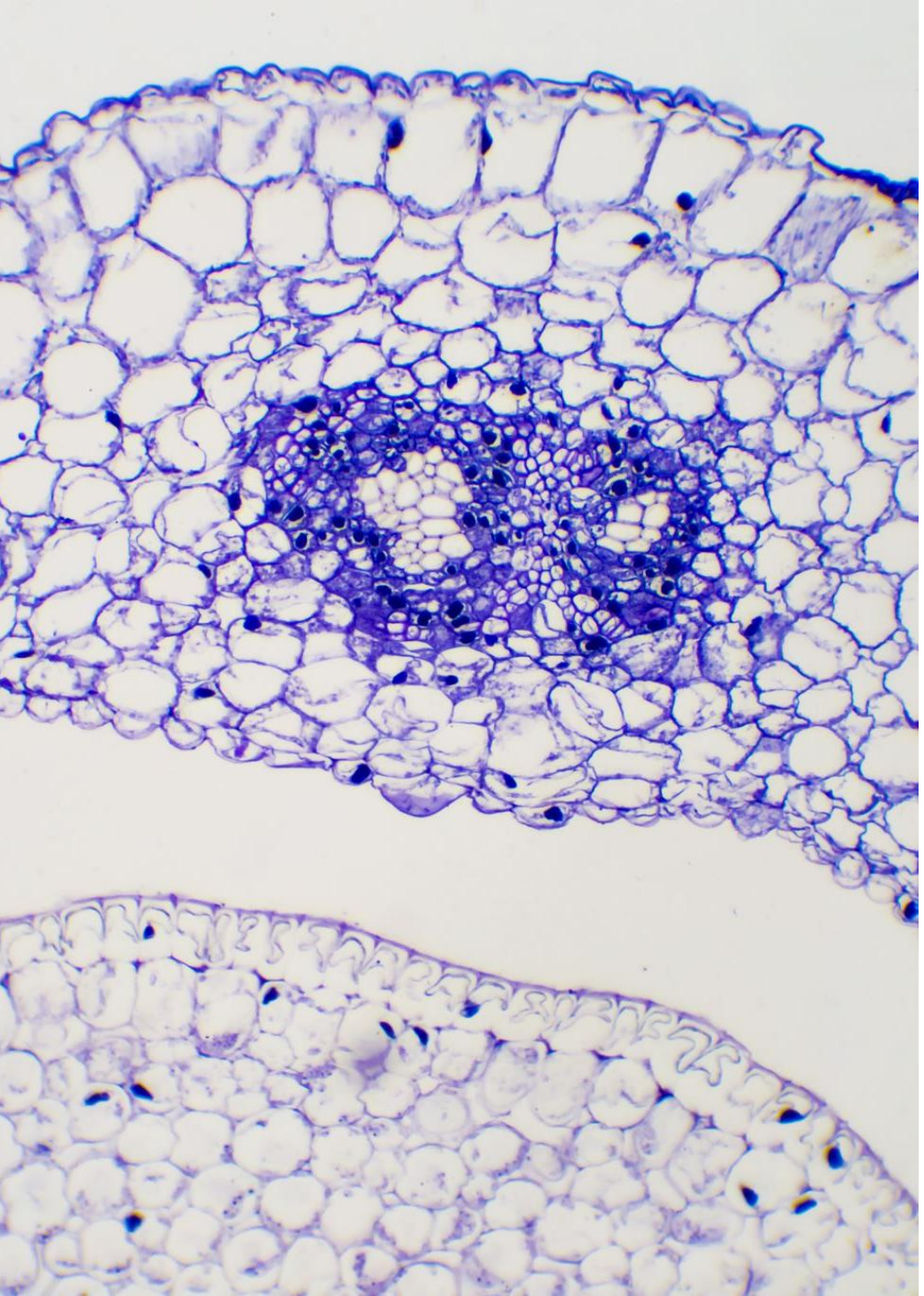
Patients with T2DM, medically complicated obesity, FH ofNAFLD or cirrhosis, more than mild ETOH consumption should be screened for advanced fibrosis

LOOK AT TRENDED PLATELET COUNTS (LOW), ALBUMIN (LOW) AND LIVER CHEMISTRIES (HIGH). If these have been trending to abnormal levels over extended time (NO MATTER PTS BMI) I would do some calculation to look for advanced fibrosis/cirrhosis

SHIFTING AWAY FROM LIVER BIOPSY

- RISK OF BLEEDING: 1-2%
- RISK OF DEATH: 1 IN 10,000

- NOW MOSTLY USING **NON-INVASIVE** TESTS FOR MDAFLD
  - US, ***FIBROSCAN***, MRI-PDFF, FAST, MAST, MEFIB, cT1, ***FIB-4***, NFS, ***ELF***, FibroSpect II, VCTE, ARFI, SWE, MRE



Clinical Suspicion for Fatty Liver Disease

- **GOAL OF PCPS**: EXCLUDE ADVANCED FIBROSIS IN LOW PREVALENCE POPULATIONS
- Primary Risk Assessment
- FIB-4 >/= 1.3
  - YES. Is FIB-4 > 2.67, refer to GI/Hepatology.
  - Persistent ALT or AST elevation, refer to GI/Hepatology
  - NO. Check FIB-4 every 1-2 years if T2DM/pre T2DM or >/= 2 metabolic risk factors. Can do FIB-4 every 2-3 years if no T2DM and <2 metabolic risk factors. Follow/trend AST/ALT, platelets, albumin

Clinical Suspicion for Fatty Liver Disease

- Secondary Risk Assessment

Risk Level	Elastography	ELF (or equivalent test like Fibrosure)
LOW	8	<7.7
MID	8-12	7.7-9.8
HIGH	>12	>9.8

(ELF = enhanced liver fibrosis; looks at 3 extracellular matrix metabolism markers/turnover)

Tests/Calculations to Look for Cirrhosis

- APRI (AST to Platelet Ratio Index)

$$\frac{\text{AST Level/ULN AST Level}}{\text{Platelet count}} \times 100$$

- In 40 studies APRI > 1 had sensitivity of 76% and specificity 72% for predicting cirrhosis, F4.
- APRI > 0.7 had sensitivity of 77% and specificity of 72% for predicting significant fibrosis (advanced fibrosis, F2 or >)
- APRI > 2 was 91% specific for detection of cirrhosis but less sensitive, 46%

Tests/Calculations to Look for Cirrhosis

- **Fibrosis-4 (FIB-4) Calculator**

$$\text{FIB-4} = \frac{\text{AGE (YEARS)} \times \text{AST}}{\text{PLATELETS} \times \sqrt{\text{ALT}}}$$

- FIB-4 > 3.25 has 97% specificity and positive predictive value of 65% for advanced fibrosis
- FIB-4 < 1.45 had 90% negative predictive value for advanced fibrosis

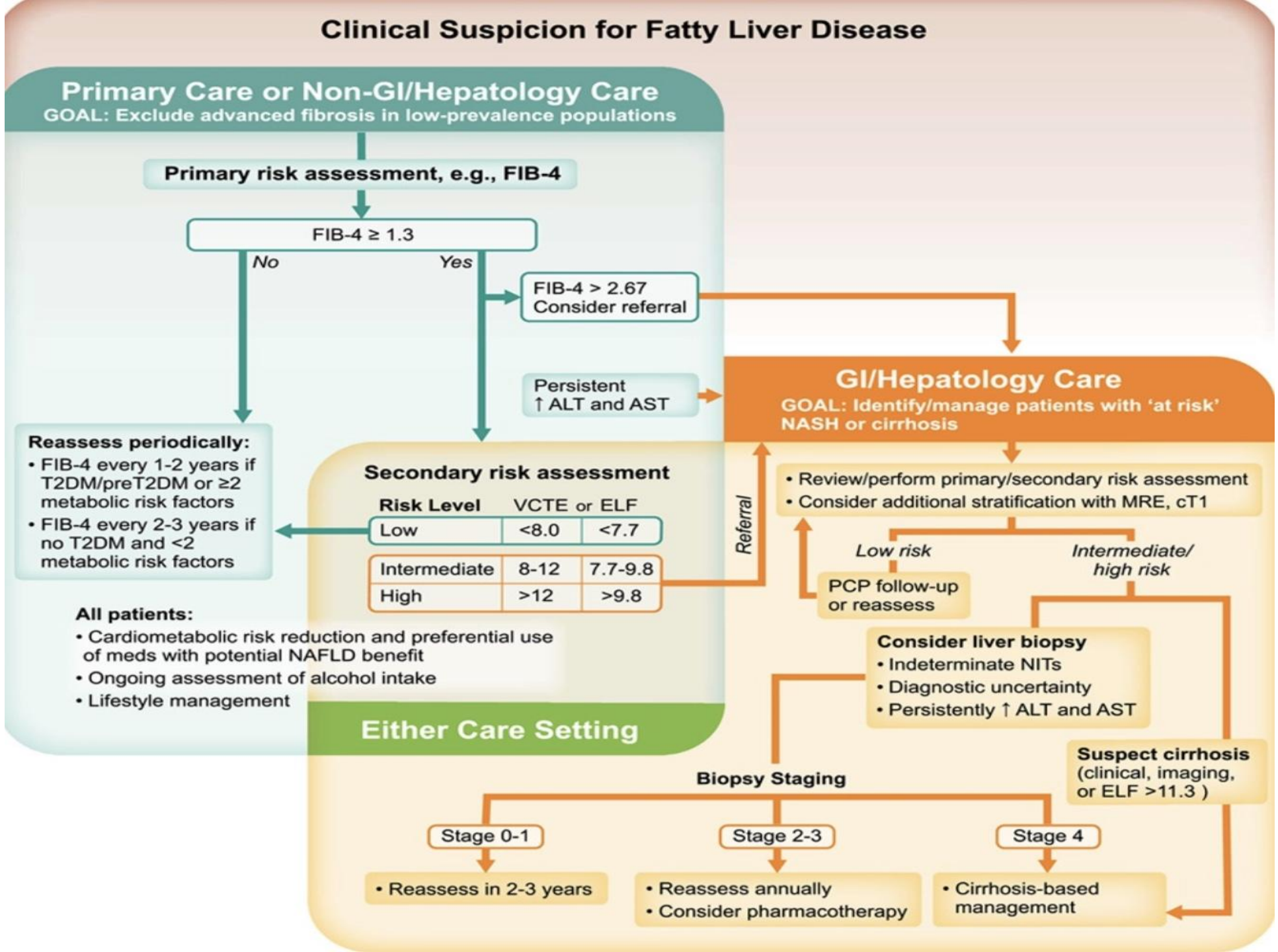
Other Calculators to Look for NAFLD Fibrosis

NAFLD FIBROSIS SCORE

- Uses Age, BMI, Impaired fasting glucose/DM, AST, ALT, Platelets, Albumin
- Results in # Points that correlates to fibrosis severity

Fibrotic NASH Index (FNI). Screens for fibrotic NASH in pts at high risk for NAFLD

- AST, HbA1c, HDL
- Number given is a % predicted probability of fibrotic NASH


Clinical Suspicion for Fatty Liver Disease
Primary Care or Non-GI/Hepatology Care
GOAL: Exclude advanced fibrosis in low-prevalence populations
Primary risk assessment, e.g., FIB-4
FIB-4 ≥ 1.3
No
Yes
FIB-4 > 2.67
Consider referral
Persistent
↑ ALT and AST
GI/Hepatology Care
GOAL: Identify/manage patients with 'at risk' NASH or cirrhosis
Reassess periodically:
• FIB-4 every 1-2 years if T2DM/preT2DM or ≥2 metabolic risk factors
• FIB-4 every 2-3 years if no T2DM and <2 metabolic risk factors
Secondary risk assessment
Risk Level
VCTE or ELF
Low
<8.0
<7.7
Intermediate
8-12
7.7-9.8
High
>12
>9.8
Referral
• Review/perform primary/secondary risk assessment
• Consider additional stratification with MRE, cT1
Low risk
Intermediate/ high risk
PCP follow-up or reassess
Consider liver biopsy
• Indeterminate NITs
• Diagnostic uncertainty
• Persistently ↑ ALT and AST
All patients:
• Cardiometabolic risk reduction and preferential use of meds with potential NAFLD benefit
• Ongoing assessment of alcohol intake
• Lifestyle management
Either Care Setting
Suspect cirrhosis
(clinical, imaging, or ELF >11.3)
Biopsy Staging
Stage 0-1
Stage 2-3
Stage 4
• Reassess in 2-3 years
• Reassess annually
• Consider pharmacotherapy
• Cirrhosis-based management

TREATMENT FOR MAFLD

- DRUGS THAT HAVE BEEN STUDIED THAT SHOWED **NO** SIGNIFICANT IMPROVEMENT IN HISTOLOGY
  - Metformin
  - Silymarin
  - Statins
  - DPP-4
  - Ursodiol

TREATMENT FOR MAFLD

- Healthy Diet and Exercise
- Weight Loss
  - 3-5% decreases steatosis
  - 7-10% can stop inflammation (hepatitis) and even REVERSE FIBROSIS
- Control of other comorbid metabolic conditions

TREATMENT FOR MAFLD

- BARIATRIC SURGERY
  - Risk of having undiagnosed cirrhosis in pts undergoing bariatric surgery is 1-3%
  - Reduces fat accumulation in the liver, which decreases inflammation and can even reverse fibrosis
  - High rate of SH resolution, up to 80% have improved liver histology
  - Roux en Y gastric bypass, gastric sleeve, duodenal switch
  - After 5 years from bariatric surgery, NASH was resolved, with no worsening fibrosis (and in some reversal of fibrosis) in 84% of patients both seen within 1 year post surgery.

Bariatric Surgery Is More Cost Effective Than Newer Weight Loss Drugs Alone

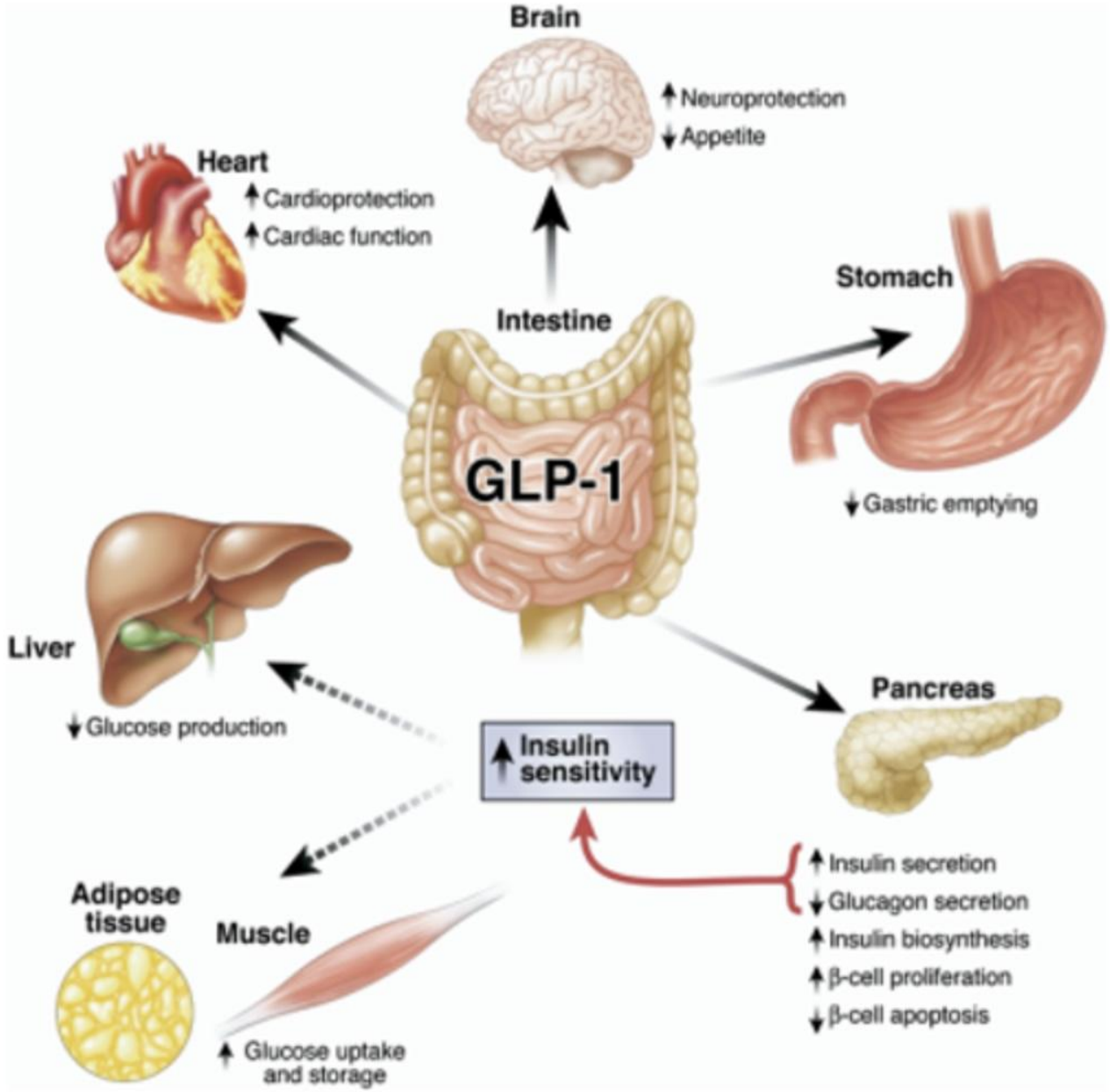
- “GLP-1 Ras are life long medications for obesity management”
- GLP-1 Ras have increased in use for weight loss more than 3 fold from 8 to 24% in 3 years
- Increased use by 40 fold from 2017 to 2021, 2-3% of US population on GLP-1s
- 1/3 of patients on GLP-1s don’t even have dx of T2DM; 70% semaglutide Rxs given to Caucasians
- Can cost $500-$1200/month
- Cost-Effectiveness
  - Bariatric Surgery Cost: $17,400-$22,850
  - GLP-A RA cost/year: $9360-$16,200
- 1.5 to 2 years of drug cost would equal the cost of a single bariatric surgery

TREATMENT FOR MAFLD

- Vitamin E
  - Pivens trial in NEJM 2010
    - 800 IU daily for 96 weeks
      - Improved steatosis and inflammation but NOT fibrosis
      - Retrospective study showed lower rate of decompensation (37% vs 62%, p=0.04) and higher transplant free survival (78% vs 49%, p,0.01)
      - Controversial data suggesting Vit E and increased prostate cancer risk?

TREATMENT FOR MAFLD

- Pioglitazone
  - Improvement in steatosis and inflammation but not fibrosis
  - Gained more weight than with Vit E or placebo
  - Osteoporosis risk in women
  - Bladder cancer risk?
  - Worsens CHF?



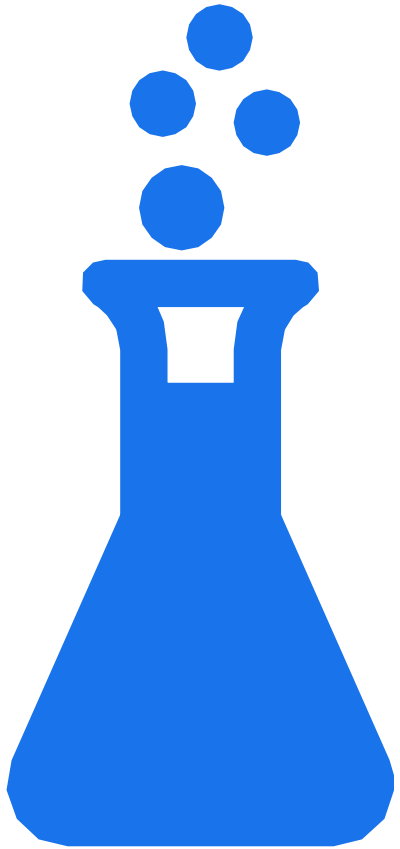
https://pubmed.ncbi.nlm.nih.gov/17498508/

TREATMENT FOR MAFLD

- GLP-1 Receptor Agonists Liraglutide and Semaglutide
  - NEJM 2021, double blind, phase 2b study
  - Randomized to 0.1 mg, 0.2 mg, 0.4 mg Semaglutide or placebo
  - Steatohepatitis resolution was dose-dependent
    - 59% in 0.4 mg group vs. 17% placebo experienced steatohepatitis resolution ($p<0.001$)
  - Improvement in fibrosis did occur in 0.4 mg group more than placebo (43% vs 33%, $p=0.48$) but no statistically significant
  - Mean % weight loss was 13% in 0.4 mg group and only 1% in placebo
  - Phase 3 trial in progress

TREATMENT FOR MAFLD

- Obeticholic Acid (farnesoid X receptor agonist)
  - FDA approved and used in PBC already. MASH?
  - REGENERATE TRIAL, 2500 patients
  - Hepatoprotective and anti-cholestatic, 10 mg, 25 mg and placebo
  - OCA 25 mg showed improvement in fibrosis by 1 stage with no worsening in inflammation
  - Pruritis in 51% of the 25 mg arm and 28% in 10 mg arm. 19% in placebo arm
  - Gallbladder and gallstone adverse events
  - NOT CURRENTLY APPROVED



TREATMENT FOR MAFLD

- MAESTRO-NASH TRIAL (randomized, double-blind, placebo controlled)
  - Resmetirom 80 and 100 mg
  - Thyroid hormone receptor beta agonist (THR-B): improves lipid metabolism, decreases intrahepatic TG
  - N=888: Placebo 294, 80 mg 298, 100 mg 296. Bx confirmed NASH, F2-F3
  - Resmetirom along with diet and exercise in
  - 52 week dual primary endpoints.
    - NASH resolution: 0-1 score for inflammation
    - Fibrosis improvement: >/= 1 stage improvement

Clinical Vignette #2

70 F with hx stage 1 R breast cancer s/p lumpectomy, XRT, hormone tx

Elevated AST/ALT intermittently since 2016

Decreasing platelets since 2016

Imaging with fatty liver, splenomegaly, varices, mild ascites, new liver lesions (#5)

Not a surgical or transplant candidate

Y-90 treatment only

Don’t Forget About…

Lipids, must treat if TG over 500 or could get TG induced pancreatitis

Vacinate for HBV, HAV, peurmonia, shingles, Covid-19, HPV, Influenza, RSV, Tdap/Td booster,

Following Patients with MAFLD/Cirrhosis

- Refer to GI and to transplant center (if appropriate)
- Endocrinologist (if available)
- EGD for variceal screening
- Liver imaging every 6 months for HCC screening
- 6 month labs to include CBC, CMP, PT/INR, AFP

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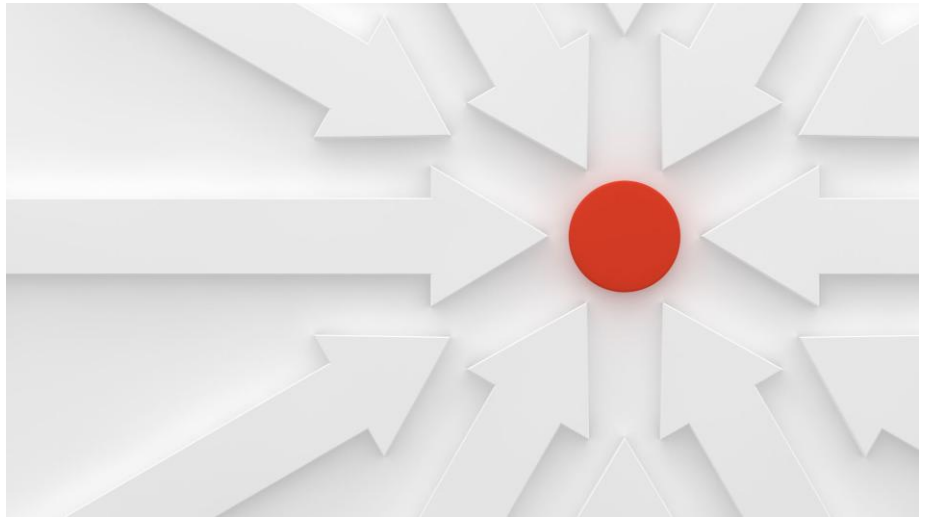

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Maybe not the best abbreviation for "ASSORTED"

Thank You!

REFERENCES

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- Comparative cost-effectiveness analysis of bariatric surgery and GLP-1RA for the management of obesity, Sanchez J, et all. Scientific Forum, American College of Surgeons Clinical Congress 2024
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