

**INTENSIVE  
OSTEOPATHIC  
UPDATE  
VIRTUAL**

**THE VIRTUAL EXPERIENCE:**  
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# Elevated Liver Enzymes: Interpretation & Management

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# Goals & Objectives

- Recognize liver function test (LFT) elevations
- Review common causes of LFT elevation
- Understand the work up of LFT elevations both via laboratory and imaging modalities
- Understand the management of common causes of LFT elevation
- Recognize when to refer to a specialist

# Agenda

- Review definition and epidemiology of elevated LFTs
- Discuss the common causes of elevated LFTs
- Work through the evaluation of LFT elevation
- Discuss use of NAFLD fibrosis scoring
- Discuss when to refer to specialist

# Why do we care?

- Data from 2016:
  - Cirrhosis related complications resulted in 40,000 US deaths = 12<sup>th</sup> leading cause of death in US
  - Projections of growth suggest 630,000 US patients have Cirrhosis
    - Only 1 in 3 is aware
- Annual US costs of Cirrhosis and advanced liver disease = \$12 billion-\$23 billion healthcare dollars
- Liver function tests often checked by PCP for various reasons
  - Screen for liver infections, such as hepatitis
  - Monitor the progression of a disease
  - As part of a work up a particular symptom (ex. Fatigue)
  - Monitor possible side effects of medications



# Definition

- ALT (Alanine aminotransferase) - somewhat more specific for liver disease
  - Normal = 7-55 units per liter (U/L)
- AST (Aspartate aminotransferase) - can be elevated by other extra hepatic causes
  - Normal = 8-48 units per liter (U/L)

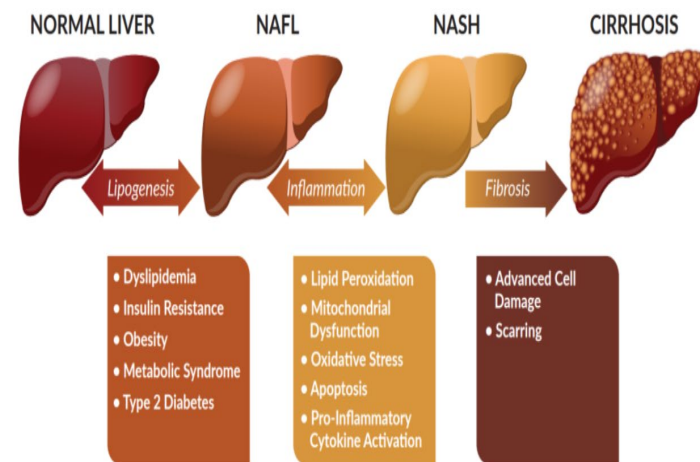
# Epidemiology

- Mild elevations of LFTs in asx patients common
  - 10% prevalence
  - 5% with serious liver disease
- Presence of NASH estimated at 3-5% of adult population

\*\*\* In an asx otherwise healthy patient we need to discover/rule out early liver disease without doing unnecessary extensive work ups on everyone

# ETIOLOGY: COMMON HEPATIC

- NAFLD: Non-alcoholic fatty liver disease = most common cause of asx elevations of transaminase levels (25-51%)
  - NAFL: Non alcoholic fatty liver - hepatic steatosis w/o inflammation
  - NASH: Non alcoholic steatohepatitis: hepatocyte injury with inflammation
    - Can lead to fibrosis → cirrhosis → Hepatocellular CA
- **\*\*\*Key is to determine which NAFLD patients are at risk for progression to more severe disease**
- Alcoholic Liver Disease: primary cause of liver-related mortality in western countries





# ETIOLOGY: UNCOMMON HEPATIC

- Medication induced liver injury
  - OTC meds, supplements, abx, etc
  - Statin induced is RARE
  - <http://www.livertox.nih.gov>
- Viral hepatitis
  - Hepatitis C: 3.5 million people
  - Hepatitis B: 2.2 million people
- Hereditary hemochromatosis
  - Autosomal recessive disease —>increased iron absorption
  - 1/150-250 persons but only about 10% people phenotypically express

**Table 4. Selected Medications Commonly Associated with Elevated Liver Transaminase Levels**

|  |   |
|--|---|
| <b>Antihypertensive</b><br>Lisinopril<br>Losartan (Cozaar)   | <b>Psychiatric</b><br>Bupropion (Wellbutrin)<br>Risperidone (Risperdal)<br>Selective serotonin reuptake inhibitors<br>Trazodone<br>Valproic acid (Depakene)     |
| <b>Antimicrobial</b><br>Ciprofloxacin<br>Isoniazid<br>Ketoconazole<br>Pyrazinamide<br>Rifampin<br>Tetracycline             | <b>Other</b><br>Acarbose (Precose)<br>Amiodarone<br>Baclofen<br>Herbal and dietary supplements<br>Highly active antiretroviral therapy<br>Omeprazole (Prilosec) |
| <b>Chemotherapeutics</b><br>Imatinib (Gleevec)<br>Methotrexate   |   |
| <b>Pain relievers/anti-inflammatory</b><br>Acetaminophen<br>Allopurinol<br>Aspirin<br>Nonsteroidal anti-inflammatory drugs |   |

*Information from references 25 and 28.*

# ETIOLOGY: RARE CAUSES

- Alpha1 Antitrypsin Deficiency: Genetic condition causing lung and liver disease
  - 1/3000-5000 persons
    - 10% those with disease diagnosed
  - Suspect in early onset emphysema with elevated liver enzymes
- Autoimmune Hepatitis:
  - 11-17/100,000 persons
  - Often present with other autoimmune condition
- Wilson disease: Autosomal recessive – ineffective copper metabolism
  - 1/30,000 persons
- Extrahepatic causes:
  - Celiac, thyroid disorders, polymyositis/rhabdomyositis

# WORK UP: STEP 1

- Thorough H&P
- Repeat AST, ALT
- Check Alk Phos, Bilirubin, GGT

Note: If +ETOH abuse or use of drugs or liver toxic meds – stop and recheck enzymes 6 weeks later before instituting a full work up

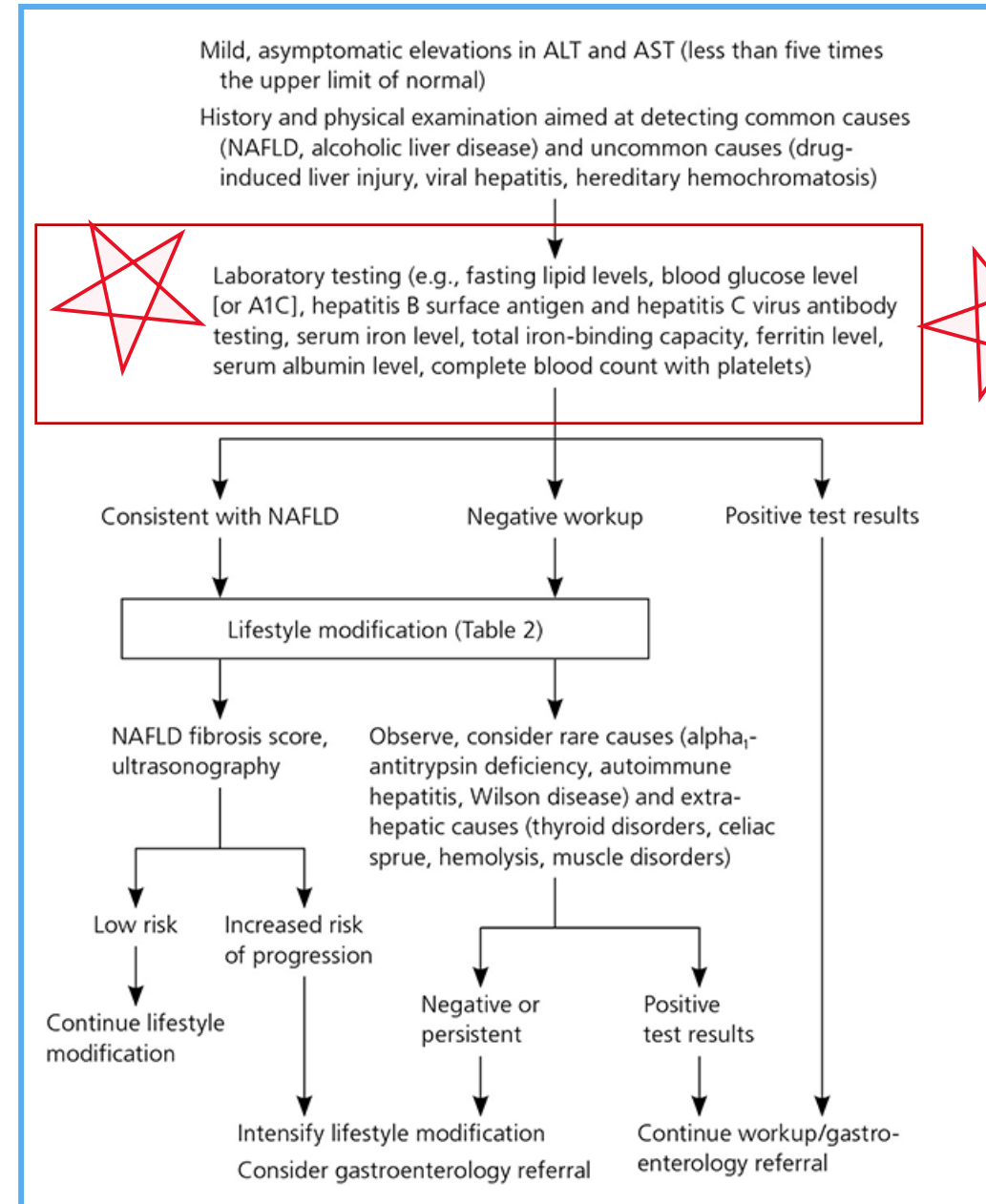
| Symptoms        | Signs                           | History                    |
|-----------------|---------------------------------|----------------------------|
| Pain in abdomen | Jaundice                        | FHx liver disease          |
| Nausea/vomiting | Dark urine                      | Obesity                    |
| Weakness        | Pale colored stools             | Diabetes                   |
| Fatigue         | Edema                           | ETOH abuse                 |
| Poor appetite   | Hepatosplenomegaly              | Drug abuse                 |
| Pruritus        | Ascites                         | Liver toxic meds           |
|                 | Gynecomastia/testicular atrophy | Hx chronic diarrhea or IBD |

# OTHER LIVER STUDIES

- Alk Phos – Elevated levels indicate either bone, liver or biliary disease
- GGT – Marker of hepatobiliary disease
  - Not very specific
- Bilirubin – Conjugated in the liver
  
- When levels of the above are elevated in conjunction with elevated ALT or AST the likelihood of liver/biliary pathology is higher

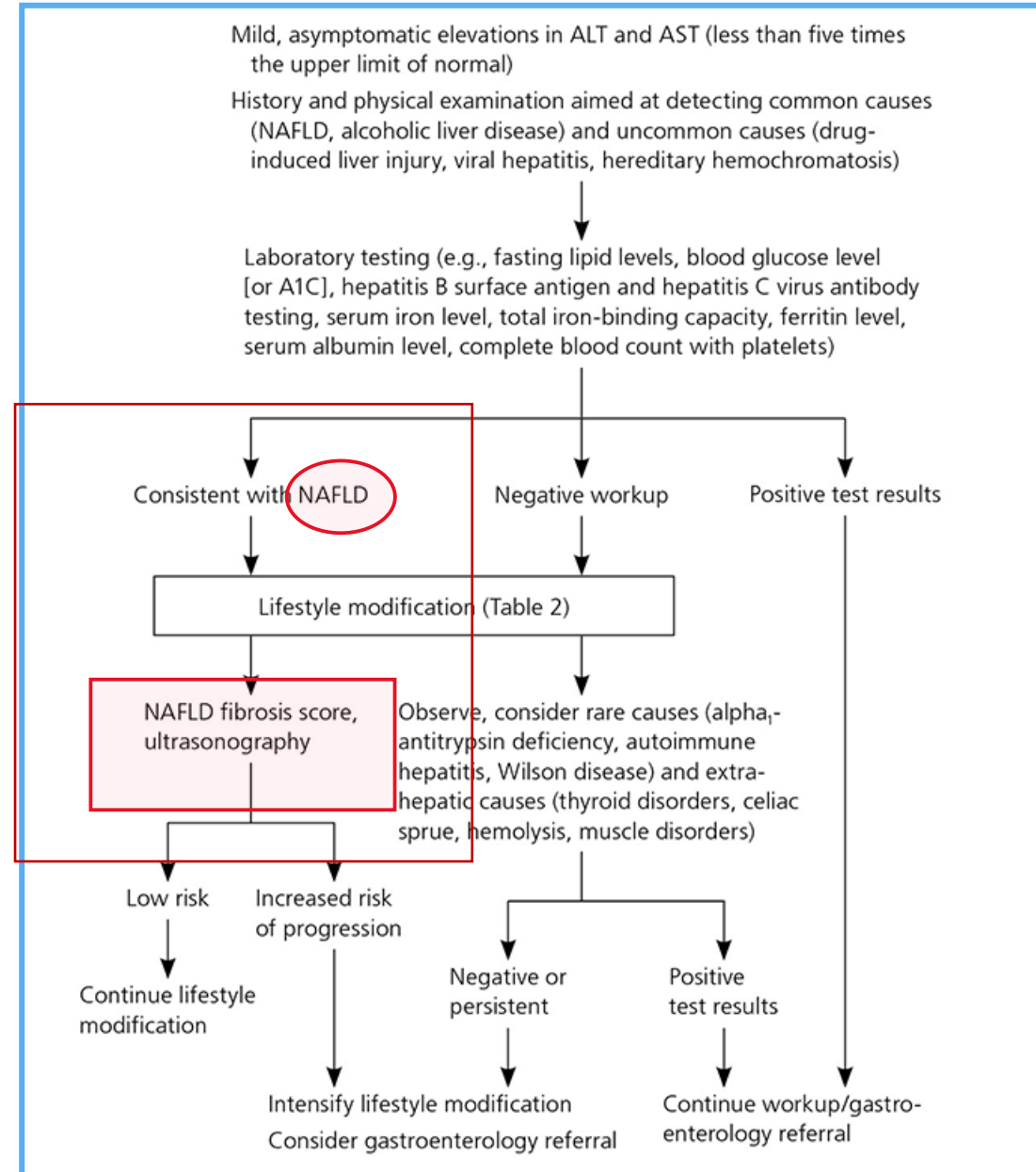
# WORK UP: STEP 2

- Stratify severity of elevation and presence of any pattern
  - AST:ALT ratio
    - **ETOH** liver disease is suggested AST:ALT >2
    - **NAFLD** associated with AST:ALT <1
- Obtain further lab evaluation
  - NAFLD/Metabolic syndrome
    - Lipids
    - BG or HgbA1c
  - Hepatitis
    - HepB panel, HepCAb
  - Hemochromatosis:
    - Iron, TIBC, Ferritin
  - Liver function:
    - CBC w/plts, Albumin, PT



# STEP 3A: CONSISTENT WITH NAFLD

- May attempt lifestyle modifications
- Liver US
- NAFLD fibrosis score



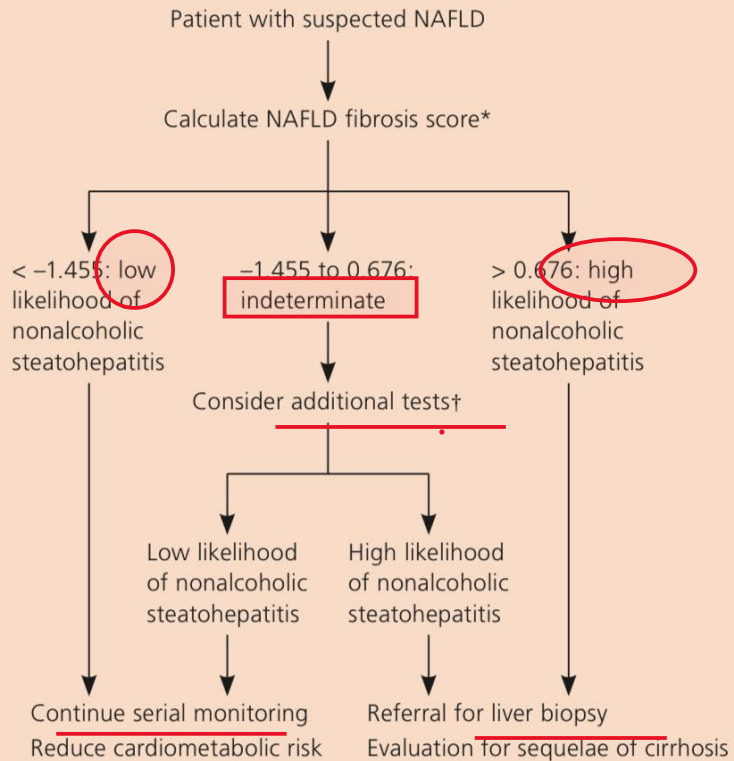




## NAFLD FIBROSIS SCORE

- Tool used to identify patient likely to have fibrosis
- Includes age, BMI, blood glucose levels, transferase levels, platelets, and albumin levels.
- Can reduce number of liver biopsies in lower risk patients
- <http://nafldscore.com>
  - Low risk: score  $< -1.455$
  - High risk: score  $> 0.676$
  - “Indeterminate”: scores between  $-1.455$  &  $0.676$

## Evaluating NAFLD in Primary Care



\*—The NAFLD fibrosis score is available as an online calculator at <http://www.naflscore.com>, or it can be calculated using the following equation:  $-1.675 + 0.037 \times \text{age (year)} + 0.094 \times \text{BMI (kg per m}^2) + 1.13 \times \text{impaired fasting glucose/diabetes mellitus (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet count (} \times 10^9 \text{ per L)} - 0.66 \times \text{albumin (g per dL)}$ .

†—Additional tests such as transient elastography (Fibroscan) and fibrosis biomarker measurements may be useful to further stratify patients with an indeterminate NAFLD fibrosis score.

- Low risk: Serial monitoring; Lifestyle modifications
- High risk: Liver biopsy
- Indeterminate: Additional testing – i.e. Liver elastography

**Figure 1.** Evaluating NAFLD in primary care. (ALT = alanine transferase; AST = aspartate transferase; BMI = body mass index; NAFLD = nonalcoholic fatty liver disease.)

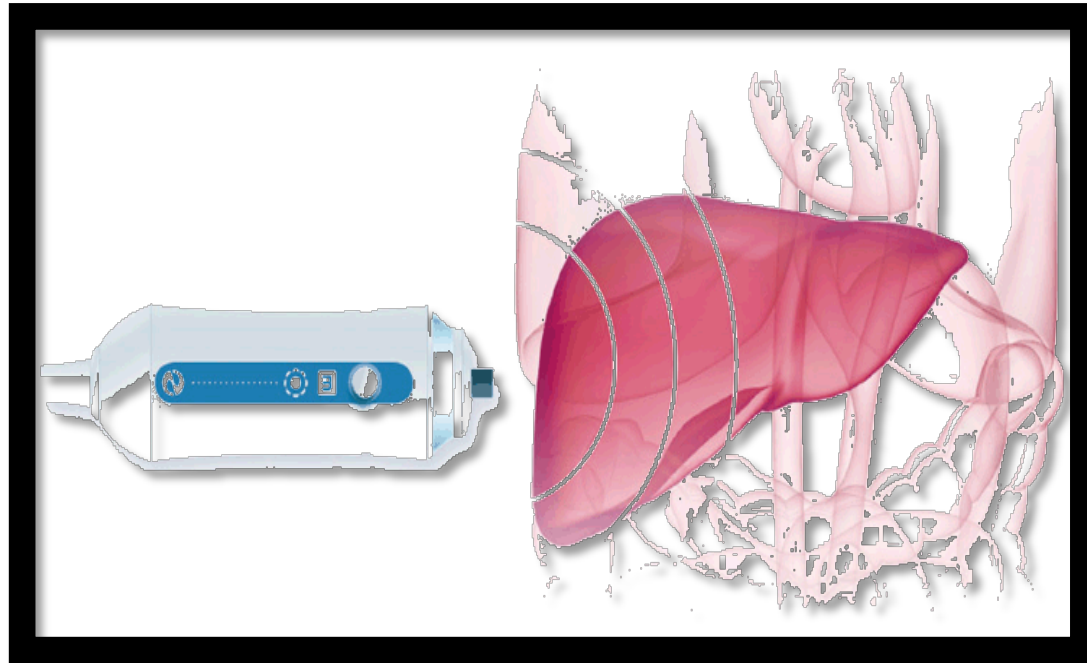


# LIFESTYLE MODIFICATIONS FOR NAFLD

- Weight loss: 7-10% body weight
- Low fat, low carb/Mediterranean diet
- Avoid sugar sweetened beverages
- ETOH <30g men = about 2 drinks; <20g women = about 1-1.5drink
- Activity: 150-200 min per week mod-vigorous exercise
- \*\*\*Coffee drinking may lower risk of NAFLD\*\*\*

# Liver Elastography

- Imaging modality of choice to evaluate degree of fibrosis
- Determines liver stiffness
- Meta-analysis indicates sensitivity 81% and specificity 88% for detecting liver fibrosis and cirrhosis

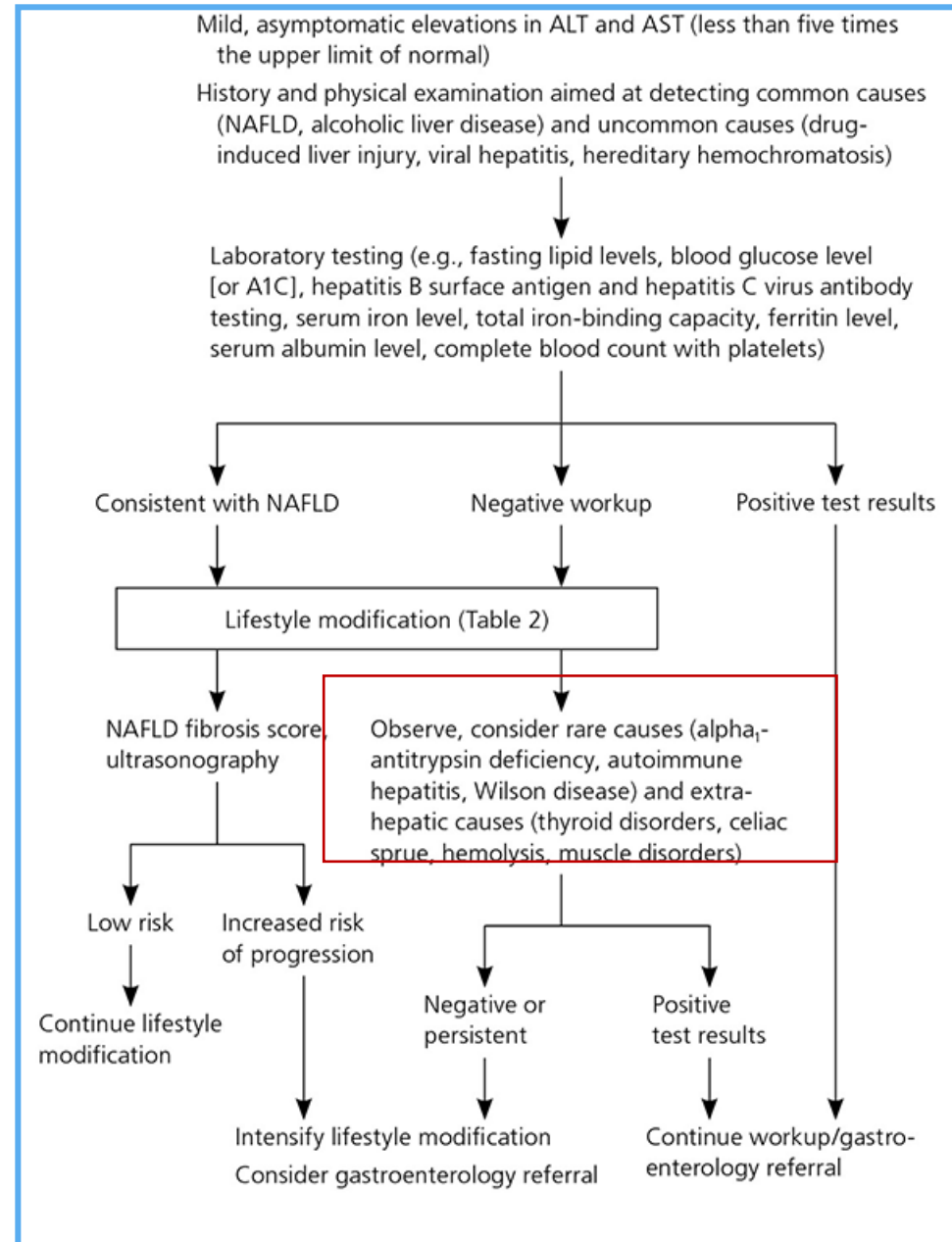




# WORK UP: STEP 3B - NEGATIVE

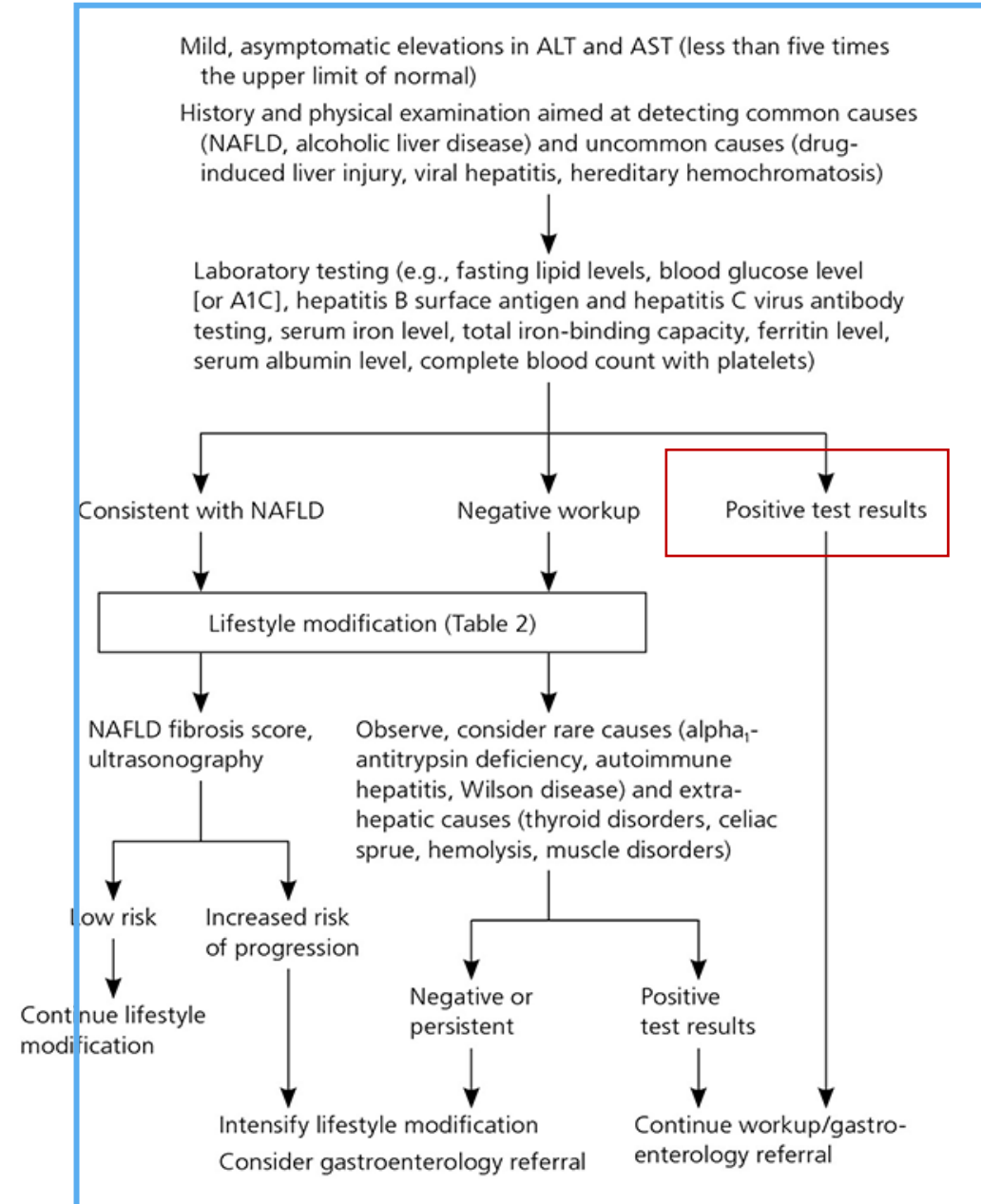
## INITIAL WORK UP

- Lifestyle modifications
- Labs for rare causes:
  - Alpha1 antitrypsin def:
    - A1a level
  - Autoimmune hepatitis:
    - Anti KLM antibody
    - Anti smooth musc antibody
    - Serum protein electrophoresis
  - Wilson's disease:
    - Ceruloplasmin
  - Thyroid disorder:
    - TSH
  - Celiac spree:
    - Total IGA
    - Anti TTG
  - Muscle injury:
    - CPK



# WORK UP: STEP 3 – POSITIVE RESULTS ON INITIAL SCREEN

- HepB+ or HepC+ treat accordingly
- Hemochromatosis: Ferritin levels >200ng/ml women or >250 ng/ml in men OR Transferrin saturation >45%
  - Check for HFE gene
- Low albumin or low Plts indicate liver disease





# WHEN TO REFER?

- NAFLD Score high risk or indeterminate
- Enzymes > 2x upper limit of normal chronically without known cause
- Fibrosis on US
- Lab findings consistent with liver damage/disease
- Lab findings consistent with rare causes of LFT elevations (i.e. Wilsons, A1A def, etc)

# CASE #1

- 42 y/o Caucasian male with history of DM2, HTN, Hypertriglyceridemia, and Obesity (BMI 41.9) is found to have elevated transaminase level of ALT of 56 with normal AST of 26 when checked due to complaints of fatigue.

What is the next step in work up for this patient?

# CASE #1...

- Next step: repeat levels, H&P, check liver studies:
  - Elevated ALT of 49, AST 20
  - Elevated alk phos 135
  - No s/sx of liver disease
  - No additional information on history indicates increased risk of liver disease

Now what?

# CASE #1...

- Next step: Determine pattern, additional labs (Lipids, HgbA1c, Iron studies, Hepatitis panel, CBC, Albumin, PT)
  - Pattern AST:ALT <1 – consistent with NAFLD
  - Labs: Lipids with TG of 345, HgbA1c of 10.9, normal iron studies/CBC/Albumin & PT, negative Hepatitis panel
- Findings consistent with suspected NAFLD – move to step 3A

Now what?

# CASE #1

- Next step = 3A - Liver US and NAFLD fibrosis score
  - Liver US: Diffusely echogenic echotexture of the hepatic parenchyma suggestive of hepatic steatosis or hepatocellular disease
  - NAFLD Fibrosis score: 1.519
  - High risk for fibrosis/liver disease

Next step would be referral to GI for liver biopsy to delineate degree of liver disease present.

## CASE #2

- 36 year old Caucasian female with history of hyperlipidemia, obesity, fibromyalgia, and depression is found to have elevated liver transaminases when checked before starting statin therapy.
  - ALT = 83 AST = 48.

What is the next step in evaluation of this patient?



# CASE #2...

- Next step: Determine pattern, additional labs (Lipids, HgbA1c, Iron studies, Hepatitis panel, CBC, Albumin, PT)
  - Pattern AST:ALT <1 – consistent with NAFLD
  - Labs: Lipids with LDL 143, HgbA1c 5.3, Iron level elevated with Ferritin of 290 and Transferrin saturation calculated at >45%, CBC, Albumin & PT normal, negative Hepatitis panel

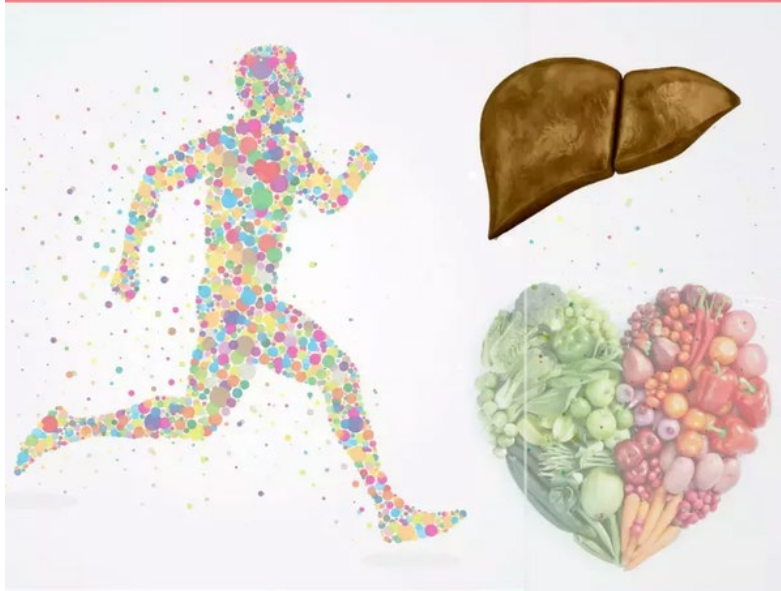
Now what?

# CASE #2...

- Findings are consistent with both NAFLD as well as possible Hemochromatosis....therefore, we have to be creative....
  - 1<sup>st</sup> – rule out Hemochromatosis by checking HFE gene
    - This patient was Heterozygous for the C282Y mutation – will not express the disease
  - 2<sup>nd</sup> – further work up NAFLD with Liver US & NAFLD fibrosis score
    - Liver US: Fatty infiltration of liver
    - NAFLD fibrosis score: **-2.98**
      - LOW risk for NASH

Now what?

## LIFESTYLE APPROACH for Fatty Liver (NAFLD)



### WEIGHT REDUCTION

Target: > 7-10% of  
body weight

### EXERCISE

- 150-220 min/week  
of moderately  
intense aerobic  
activity
- Resistance training

### DIET

- 500 kcal deficit/ day
- Omega-3 fatty acids
- Moderate carbohydrate,  
high protein
- Avoid fructose
- Avoid alcohol

DR ABHINAV JAIN, GASTROENTEROLOGIST

## CASE #2...

- Patient with elevated LFTs due to NAFL.
  - Next step would be serial monitoring and lifestyle modifications.
  - Patient encouraged to lose weight, exercise, avoid pop and other sugar sweetened beverages, avoid excess ETOH.

- Step 1:
  - H&P
  - Repeat AST, ALT
  - Check liver studies: Alk Phos, GGT, Bilirubin

- Step 2:
  - Determine pattern
  - Further labs: Lipids, HgbA1c, Iron studies, Hepatitis panel, CBC, Albumin, PT

- Step 3A: NAFLD
  - Liver US
  - NAFLD fibrosis score

- Step 3B: Initial neg w/u
  - Labs for rare causes: A1a level, Anti KLM antibody, Anti smooth musc antibody, Serum protein electrophoresis, Ceruloplasmin, TSH, Total IGA, Anti TTG, CPK

- Step 3C: Initial pos w/u
  - Continue appropriate w/u
  - Treat underlying condition


# SUMMARY

- Elevated LFT levels are a common occurrence in the primary care patient
- There are many causes for LFT elevations with the most common being NAFLD
- Early diagnosis of inflammation/fibrosis of the liver are critical, therefore, a systematic approach to the work up of elevated LFTs is crucial
- The NAFLD fibrosis score has helped to decrease the number of unnecessary liver biopsies

# REFERENCES

- <https://www.aafp.org/afp/2017/1201/p709.html>
- <https://www.mayoclinic.org/tests-procedures/liver-function-tests/about/pac-20394595https://>
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