Liver Fibrosis

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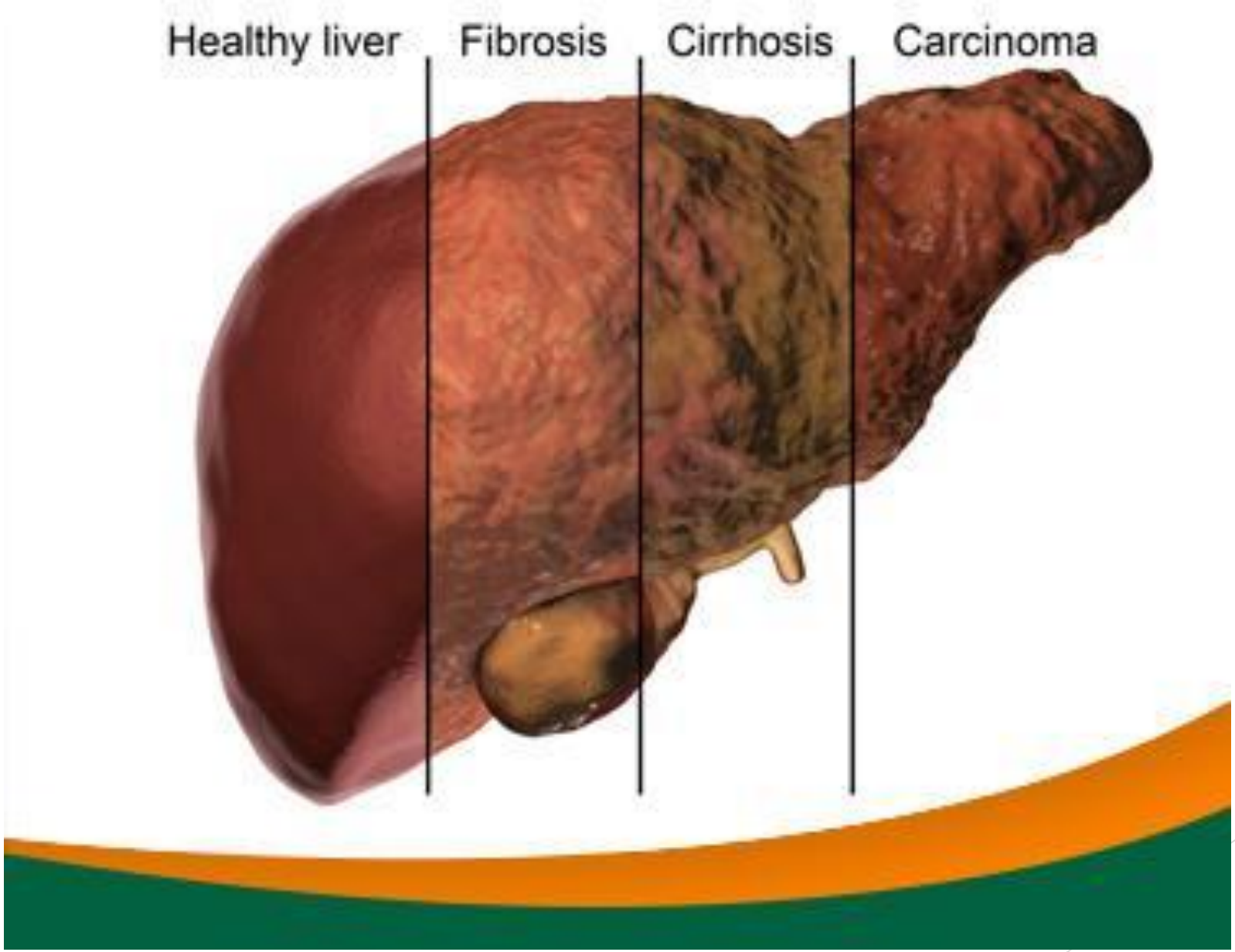
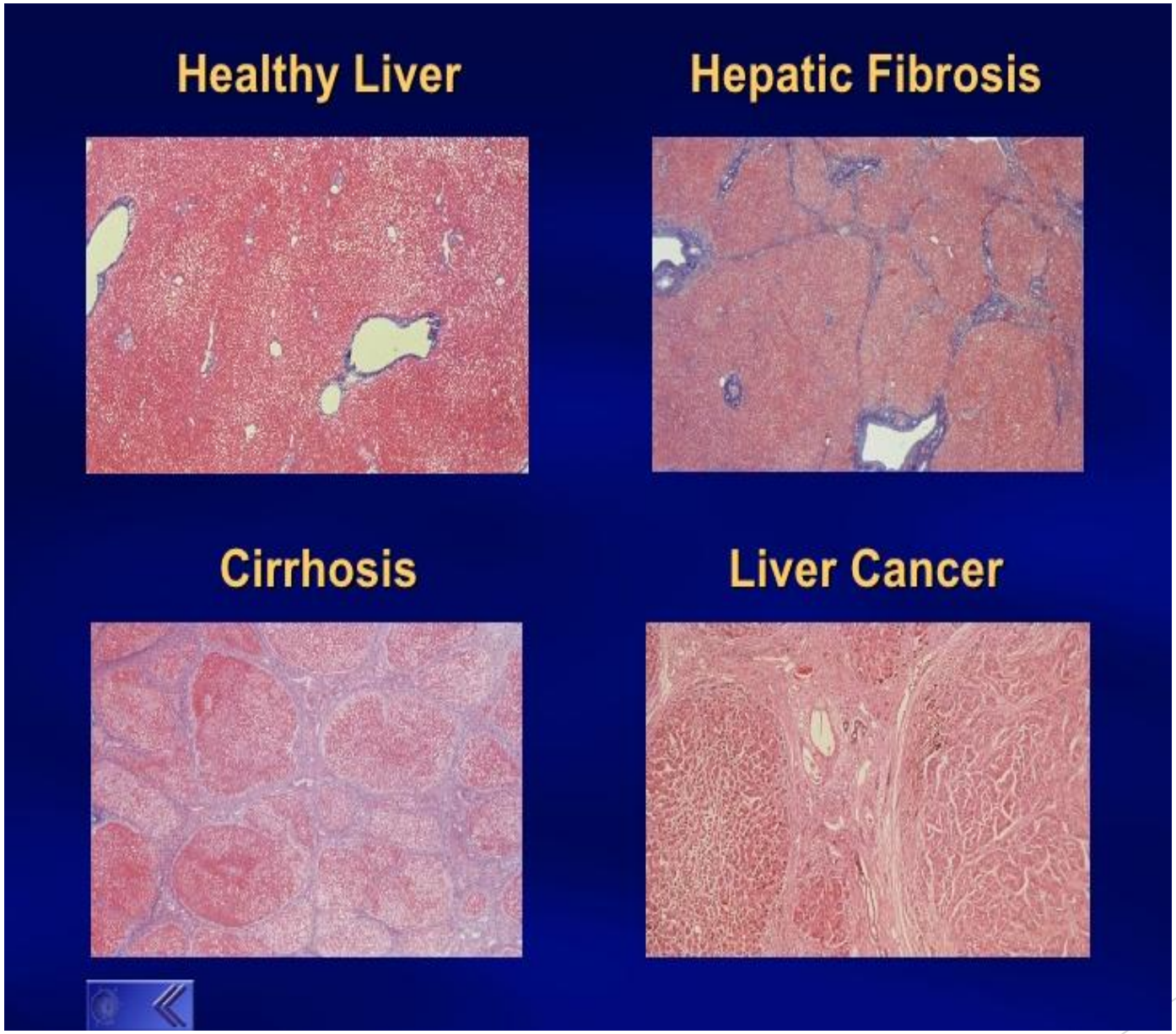

Healthy liver
Fibrosis
Cirrhosis
Carcinoma

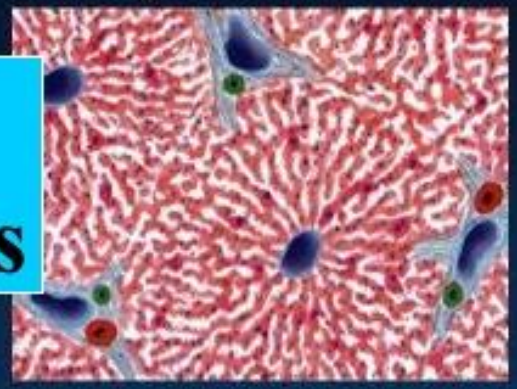
Liver Fibrosis

- A response generated as a result of chronic liver injury due to various factors, such as alcohol consumption, non-alcoholic steatohepatitis, viral hepatitis (B and C), autoimmune hepatitis, non-alcoholic fatty liver disease, and cholestatic liver disease.
- The common effects of all of these factors on the liver is the generation of a chronic inflammation resulting in an abnormal wound healing response
- The end result is the accumulation of extracellular matrix (ECM) components, leading to fibrous scar formation
- Liver fibrosis is a reversible process.

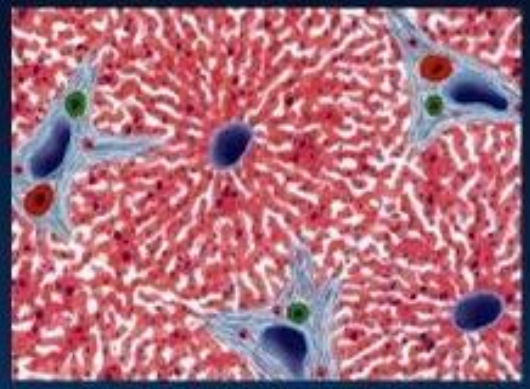

Healthy Liver
Hepatic Fibrosis
Cirrhosis
Liver Cancer

Liver Biopsy by Stage

Stage 1

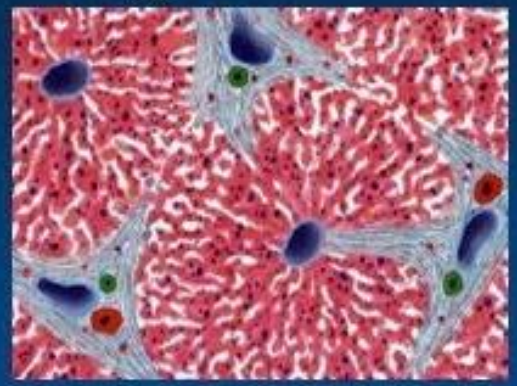


Stage 2

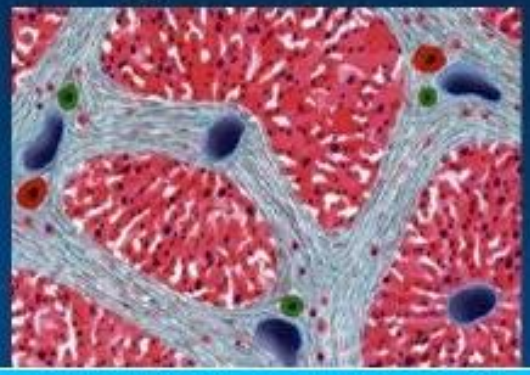


Mild Fibrosis

Stage 3



Stage 4



Cirrhosis

A Stepwise Approach to Fibrosis Evaluation

Hepatitisc.uw.edu
or
MD Calc App

- Start with indirect, non-invasive markers
  - Calculate APRI & FIB-4. If both are low, generally no further testing needed.
- If indeterminate or high, correlate those results with one of the following:
  - -Serum fibrosis test (e.g. Fibrotest, FibroSure)
  - -Transient Elastography (e.g. FibroScan)
- Ultrasound at baseline on those who've had HCV for some time and whenever other tests suggest advanced fibrosis
- Consult hepatologist re: further testing if test results are discordant
  - MRE
  - Liver biopsy

Score [References]	Serum markers/Fibroscan	Cut-off	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
FIB-4 [51,141]	Age, ALT, AST, platelets	1.3	74-85	65-71	73-96	22-72
		2.67	34	98	59-93	60-93
		3.25	26	98	85	75
*BAAT [134]	Age, BMI, ALT, triglycerides	2	71	80	86	61
NAFLD fibrosis score [51,136]	Age, BMI, platelets, albumin, AST/ALT, IFG/diabetes	-1.455	78-82	58-77	88-93	30-56
		0.676	33-51	98	85-86	82-90
BARD [51,136,139,142]	BMI, AST/ALT, diabetes	2-4	NA	NA	96	43
		2	51-89	44-77	45-95	27-81
ELF® [135]	N-terminal propeptide of collagen type III, hyaluronate, TIMP-1	-1.0281	90	75	96	52
		0.2112	80	90	94	71
Fibrotest® [121]	Alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, bilirubin, γ-GT	0.30	92	71	98	33
		0.70	25	97	89	60
*Fibrometer® [137]	Platelets, prothrombin time, macroglobulin, AST, hyaluronate, age, urea	NA	79	96	92	88
Fibroscan® [122]	Transient elastography	7.9	91	75	52	79

**Performance characteristics for the detection of significant (≥F2) fibrosis*
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; IFG, impaired fasting glycaemia; TIMP, tissue inhibitor metalloproteinases; γ-GT, gamma glutamyl transpeptidase; NA, not available; NPV, negative predictive value; PPV, positive predictive value

APRI

AST to Platelet Ratio Index:

AST ÷ ULN of AST (40) ÷ Platelets (k/mL) x 100

- The lower the APRI score < 0.5 the greater the negative predictive value to rule out cirrhosis.
- The higher the APRI > 1.5 the greater the positive predictive value to rule in cirrhosis. APRI > 2.0 is 91% specific for cirrhosis.

FIB-4

Fibrosis-4 score

- Age (years) x AST ÷ Platelets (k/mL) x √ALT
- Score < 1.45 has a negative predictive value of 90% for advanced fibrosis
- Score > 3.25 has a 97% specificity and 65% positive predictive value for advanced fibrosis

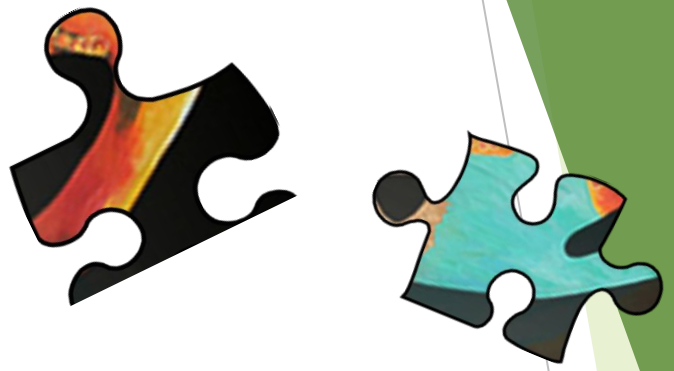
Interpretation of APRI and FIB-4

APRI Result	Fibrosis Interpretation
< 0.5	No – Moderate Fibrosis
≥ 1.5	Advanced fibrosis (bridging fibrosis to cirrhosis)
> 2	Cirrhosis
> 0.5 < 1.5	Indeterminate

FIB-4 Result	Fibrosis Interpretation
< 1.45	No-Moderate Fibrosis
> 3.25	Advanced Fibrosis
1.45 – 3.25	Indeterminate

The use of multiple indices in combination may result in higher diagnostic accuracy than APRI or FIB-4 alone.

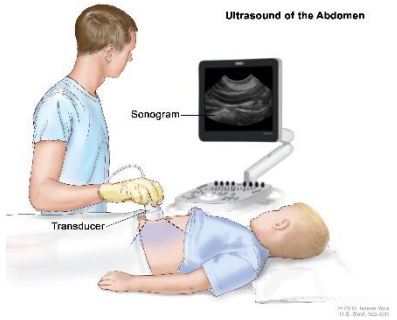
Serum Fibrosis Tests

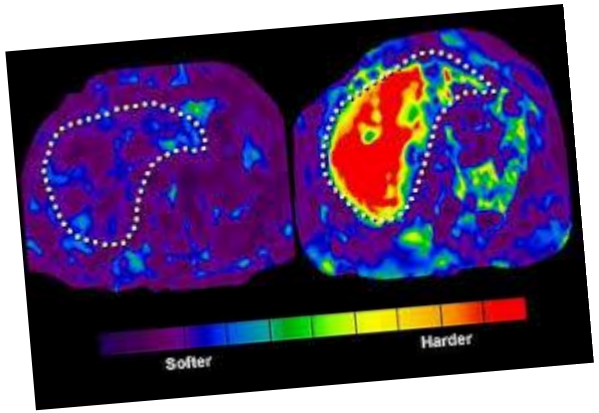


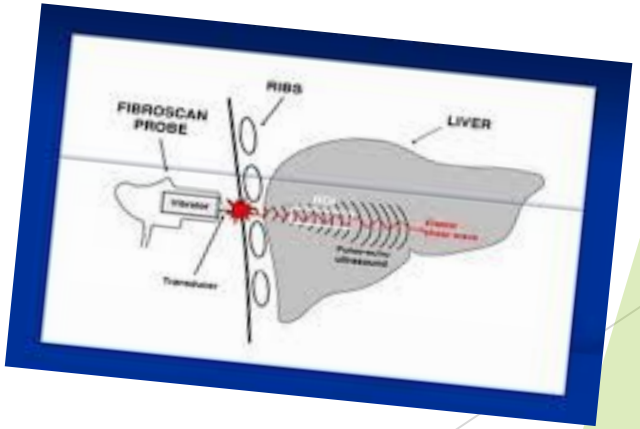
- FibroTest/Quest
- Fibrosure/LabCorp
- FibroSpect II/Prometheus
  - These use proprietary algorithms that includes age, gender, and biochemical markers associated with hepatic fibrosis
    - Will give estimate of fibrosis stage
  - Contraindications to these tests: Gilbert's disease, acute hemolysis, extrahepatic cholestasis, post-transplant, and renal failure
  - FibroSure - 8-hour fast recommended
  - Like APRI and FIB-4, good at estimating low fibrosis and significant fibrosis but not so good in between

Imaging to Estimate Fibrosis

- Abdominal U/S
- Transient U/S Elastography
- Magnetic Resonance Elastography







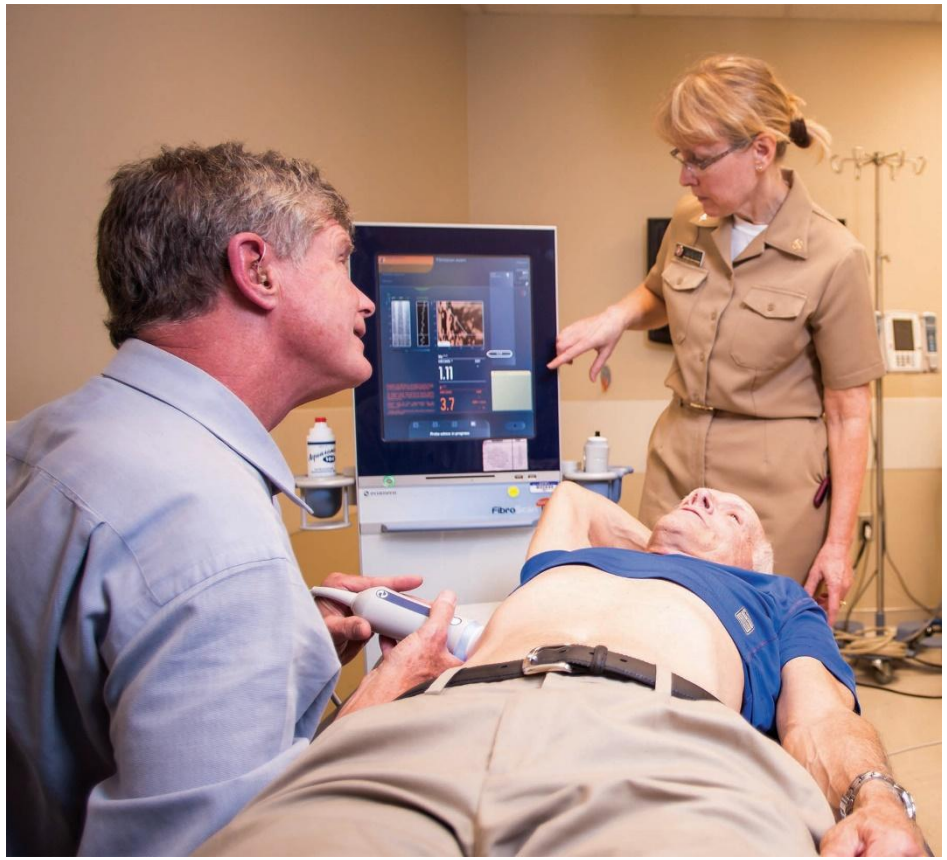
Abdominal U/S

- Readily available
- Potential to identify useful factors
  - Nodularity, ascites, spleen size
  - Coarseness of the liver parenchyma
  - Patency and flow of veins and arteries
  - Lesions suspicious for HCC
- Consider RUQ vs full abdominal U/S
- Not sufficient alone to rule out cirrhosis

Transient U/S Elastography

- Advantages
  - Painless, quick, easy to perform, reasonably accurate
  - Measures liver stiffness with decent correlation with pathology
  - Available at local imaging centers
  - Relatively inexpensive test
- FibroScan®
  - Is a specific branded vibration controlled transient U/S elastography (VCTE) for measuring fibrosis, steatosis with limited availability in AK
  - Has been studied for nearly 2 decades, several hundred studies back its use
  - Available at ANTHC and portable machine taken to field clinics

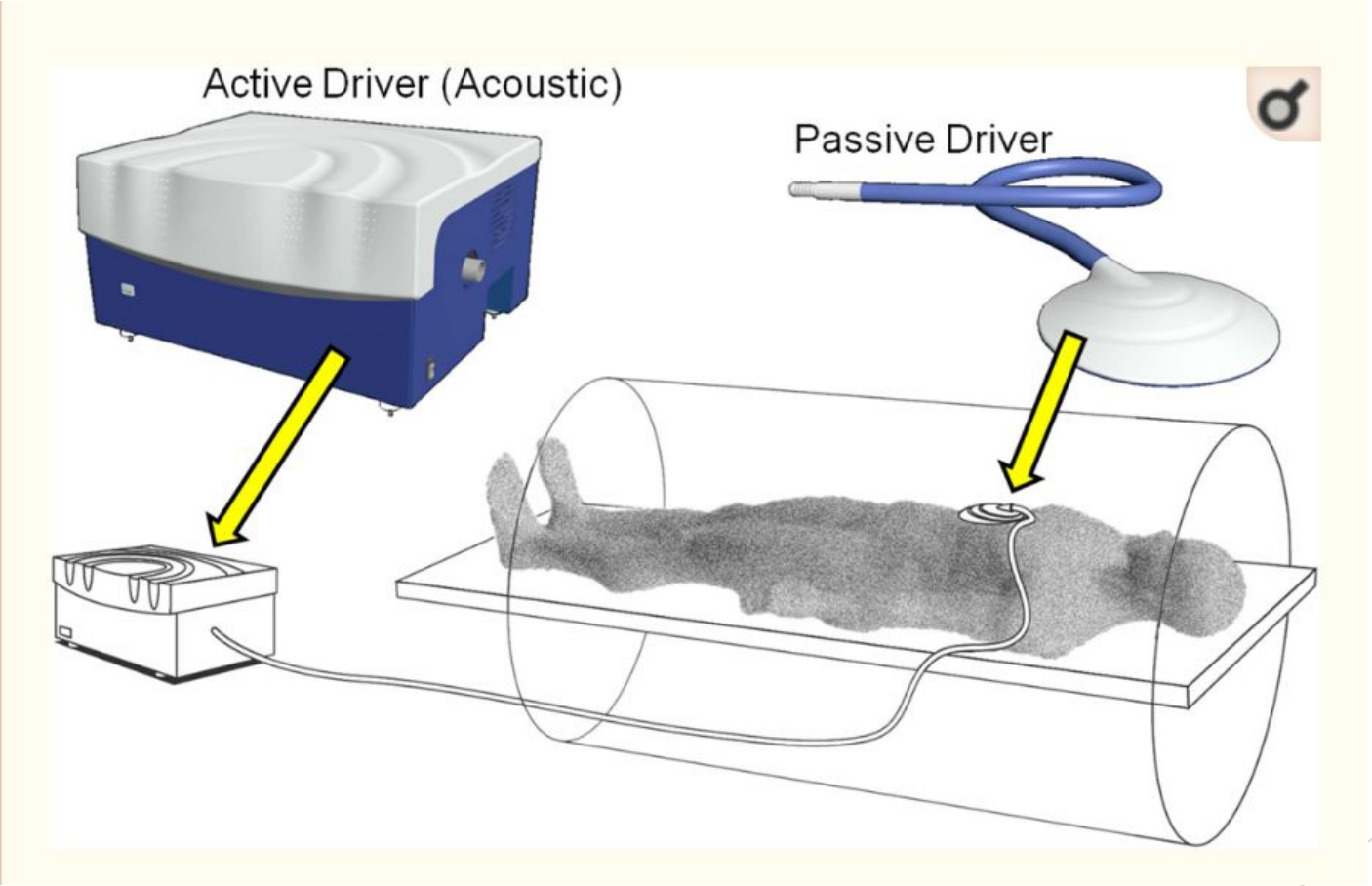
FibroScan®



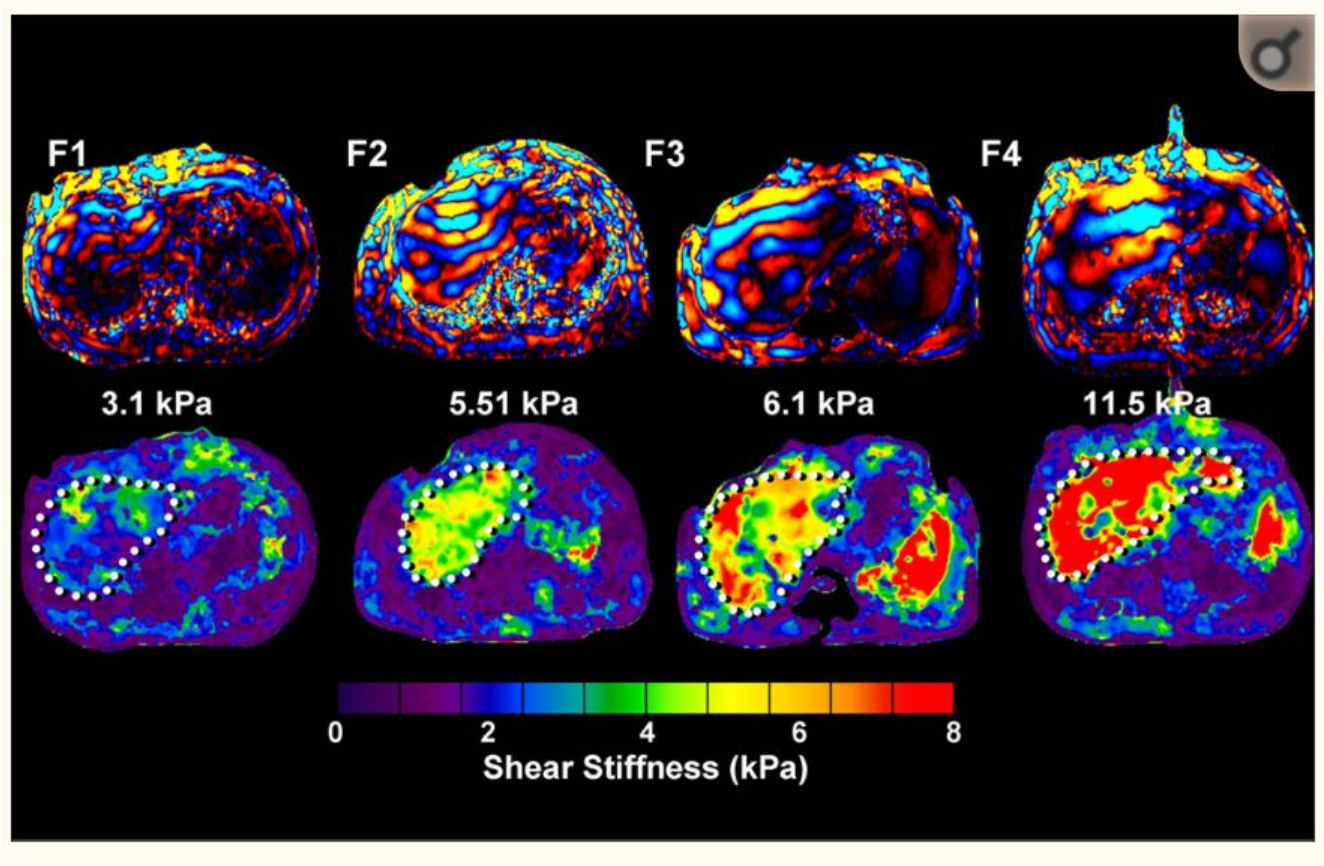
Transient U/S Elastography

- Disadvantages
  - Operator dependent
  - Can be difficult on patient's with significant central adiposity
  - Not meant to diagnose liver mass

Magnetic Resonance Elastography



Magnetic Resonance Elastography

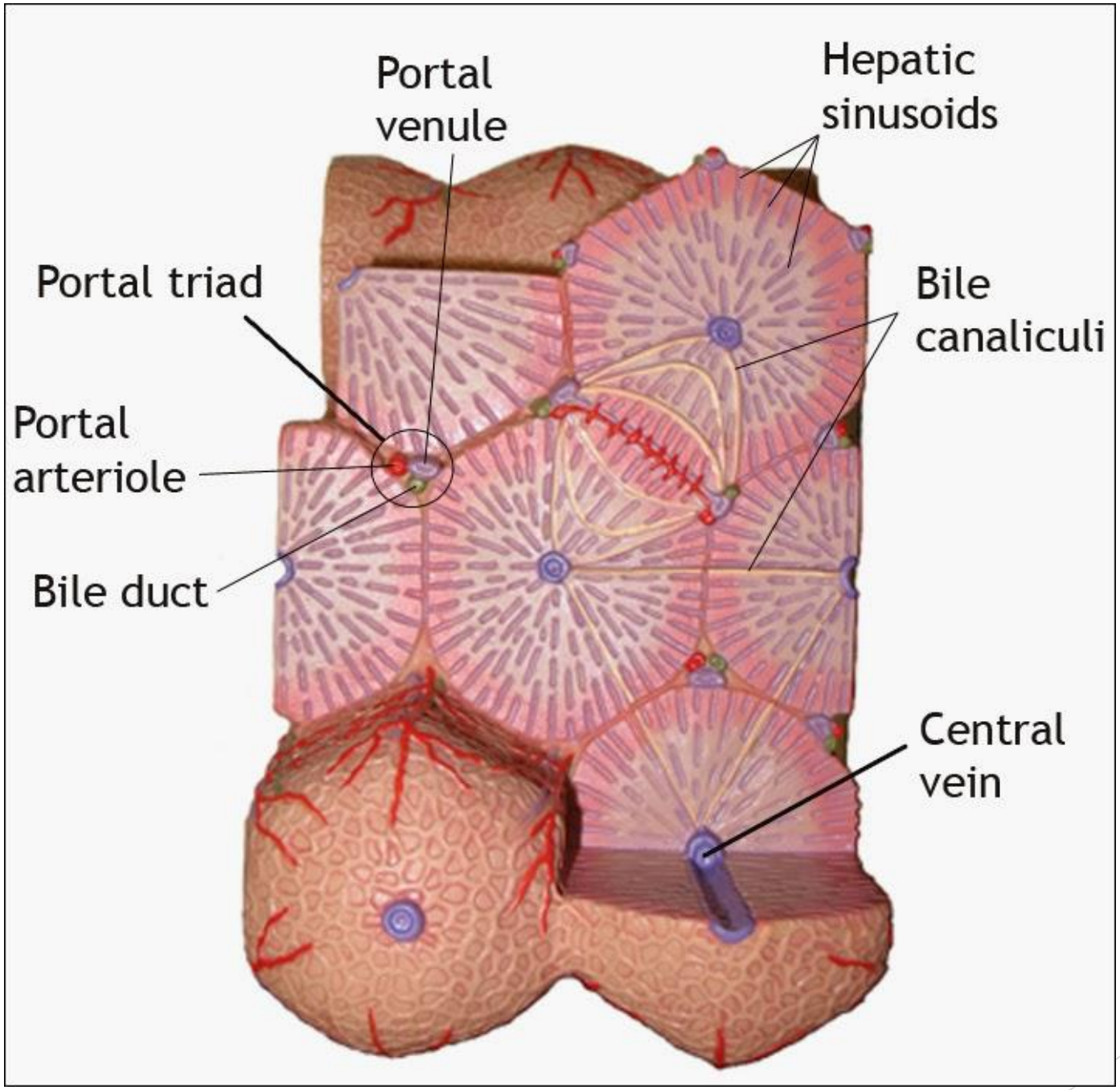


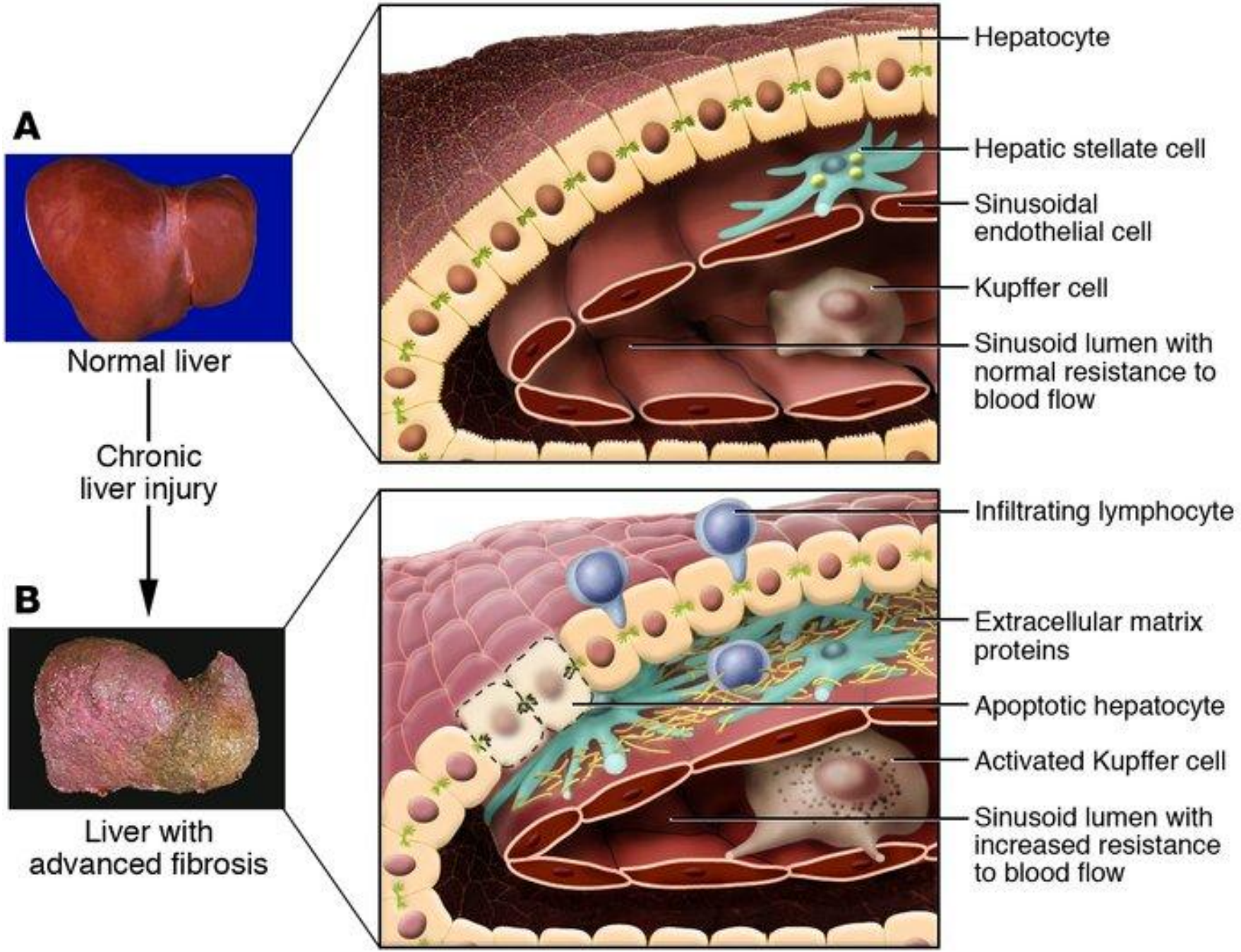
Magnetic Resonance Elastography

- When would you need this?
- Advantages
  - Good correlation with pathology results
  - Covers more areas of liver than VCTE
  - Can be used in conjunction with contrast enhanced MRI to provide more information about the liver, cirrhosis, and hepatomas

Magnetic Resonance Elastography

- Disadvantages
  - Limited availability
  - Cost


Portal venule
Hepatic sinusoids
Portal triad
Bile canaliculi
Portal arteriole
Bile duct
Central vein


A
Normal liver
Chronic liver injury
B
Liver with advanced fibrosis
Hepatocyte
Hepatic stellate cell
Sinusoidal endothelial cell
Kupffer cell
Sinusoid lumen with normal resistance to blood flow
Infiltrating lymphocyte
Extracellular matrix proteins
Apoptotic hepatocyte
Activated Kupffer cell
Sinusoid lumen with increased resistance to blood flow

Dynamics of liver fibrosis

Pro fibrotics

- aHSC
- Bone marrow-derived cells
- Adipokines (from adipose tissue)
- Bacterial lipopolysaccharide

Anti fibrotics

- NK cells
- Bone marrow derived macrophages

Treatments of fibrosis

- Coffee
- Ursodeoxycholic acid
- INF-alpha and gamma
- FXR receptor activation
- Antioxidants like vitamin E
- ACE inhibitors
- Sorafenib
- Atorvastatin