Noninvasive Assessment of Fibrosis in Hepatitis B

Richard K. Sterling, MD, MSc, FACP, FACG, AGAF, FAASLD

VCU Professor of Hepatology

Chief of Hepatology

Program Director, Transplant Hepatology

Associate Program Director, IM Resident Scholarship

Medical Director, Viral Hepatitis and HIV Liver Clinics

Assistant Chair for Research, Department of Medicine

Virginia Commonwealth University

Richmond, Virginia

Conflicts of Interest in the last 12 months

- Advisory Board (DSMB)
  - AskBio/Baxter, Pfizer
- Research support
  - Roche/Genentech, AbbVie, Gilead, Abbott
- Speaker
  - None
- Stock/Financial interest
  - None

Outline

- What non-invasive assessments are available ?
- Which one(s) should I use ?
- When should I use them ?
- How do I approach to the patient and when to biopsy ?

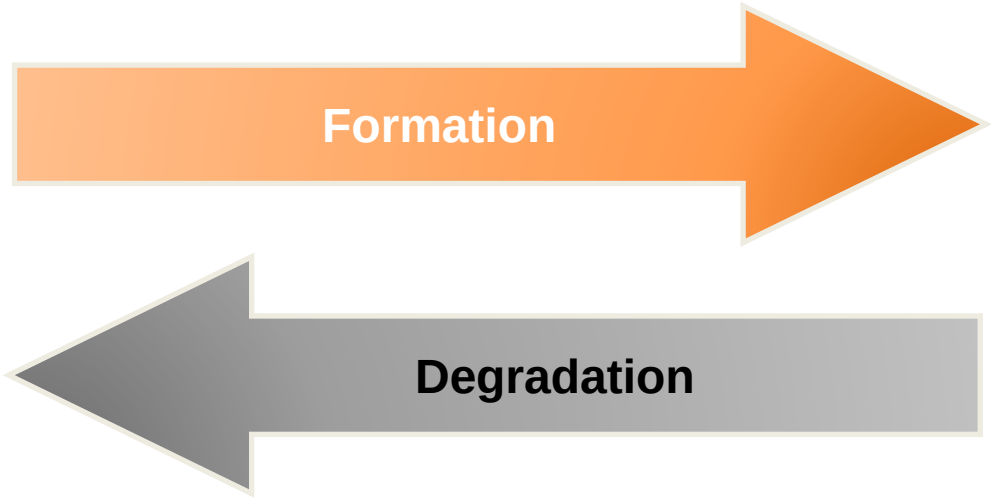
Liver Biopsy

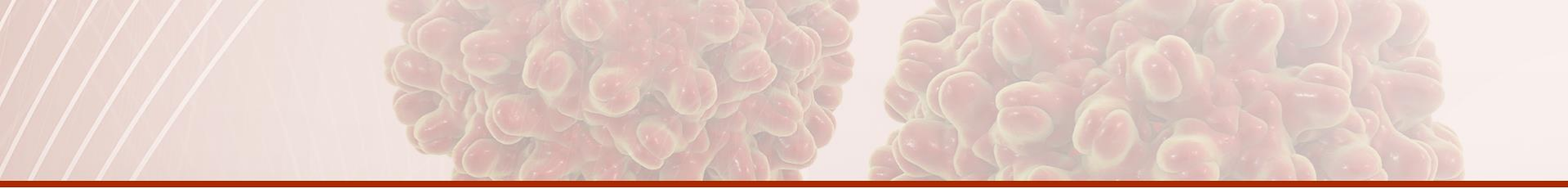
- Gold standard for grading and staging disease
- Invasive, expensive
  - Bleeding <1%
  - Pain 25%
  - Puncture wrong organ (lung, GB, colon)
- Needle liver biopsy samples < 1/50,000th of the liver
- Incorrect staging of 1 stage in up to 25% of cases
  - Dependent upon:
    - Length of biopsy - 20mm optimal (16%)
    - Number of biopsies performed
    - Type of biopsy needle used
    - Etiology of liver disease

Rocky et al. Hepatology 2009;49:1017-1044.

Fibrosis is a Dynamic Process not Reflected in Static Biopsy Sample

Fibrosis Staging is Non Linear





The only things worse than doing a liver biopsy is teaching someone else how to do it or having one done on your self

Richard K Sterling, MD, MSc

Non-Invasive Assessment of Liver Fibrosis

Model	Components
APRI	AST, PLT
FIB-4	AST, ALT, Age, PLT
BAAT	ALT, BMI, age, TG
BARD	AST/ALT>.8, BMI>28, DM
NAFLD score	AST, ALT, Age, PLT, BMI, Albumin
European Liver Fibrosis	Age, TIMP1, PIIINP, HA
Fibrosure	A2macroglobulin, apolipoprotein A1, haptoglobin, bilirubin, GGT
Fibroscan (M and XL probe)	Liver stiffness
Shear Wave Elastography	Liver stiffness
Magnetic Resonance Elastography	Liver stiffness

Interpreting tests

Need to ask 2 questions

NPV ?

PPV ?

Serum Markers of Fibrosis

Indirect

- AST
- ALT
- Bilirubin
- Albumin
- Platelet

Direct

- Hyaluronic acid
- Type III collagen
- Matrix Metalloproteinase-1
- Tissue inhibitor of metalloproteinases
- Fibronectin
- Laminin
- YKL-40
- N-terminal propeptide

How do serum tests perform to differentiate F0-2 vs F3-4

Test	Disease	Cut off	Sensitivity	Specificity
APRI	HCV	*0.5 / 1.5*	0.83 / 0.55	0.58 / 0.86
	HBV	*0.5 / 1.5*	0.73 / 0.22	0.66 / 0.90
	NASH	*0.5 / 1.5*	0.73 / 0.25	0.69 / 0.96
FIB-4	HCV	*1.45 / 3.25*	0.86 / 0.55	0.72 / 0.91
	HBV	*1.45 / 3.25*	0.69 / 0.23	0.70 / 0.97
	NASH	*1.45 / 3.25*	0.79 / 0.38	0.77 / 0.97
		2.67	0.41	0.94
Fibrosure	HCV	*0.32 / 0.58*	0.84 / 0.75	0.26 / 0.74
	HBV	*0.52*	0.86	0.90
	NASH	*0.47*	0.61	0.90

Unpublished data from AASLD Guidelines 2021

How do serum tests perform to differentiate F0-3 vs F4

Test	Disease	Cut off	Sensitivity	Specificity
APRI	HCV	*1.5/2.0*	0.75 / 0.41	0.81 / 0.94
	HBV	*0.5 / 1.5*	0.83 / 0.19	0.57/ 0.75
	NASH	*0.5 / 1.5*	0.77 / 0.60	0.71 / 0.90
FIB-4	HCV	*3.25*	0.72	0.81
	HBV	*1.45 / 3.25*	0.78 / 0.22	0.71 / 0.3
	NASH	*1.9*	0.73	0.89
Fibrosure	HCV	*0.75*	0.61	0.86
	HBV	*0.68*	0.80	0.84
	NASH	*0.57*	0.75	0.95

Unpublished data from AASLD Guidelines 2021

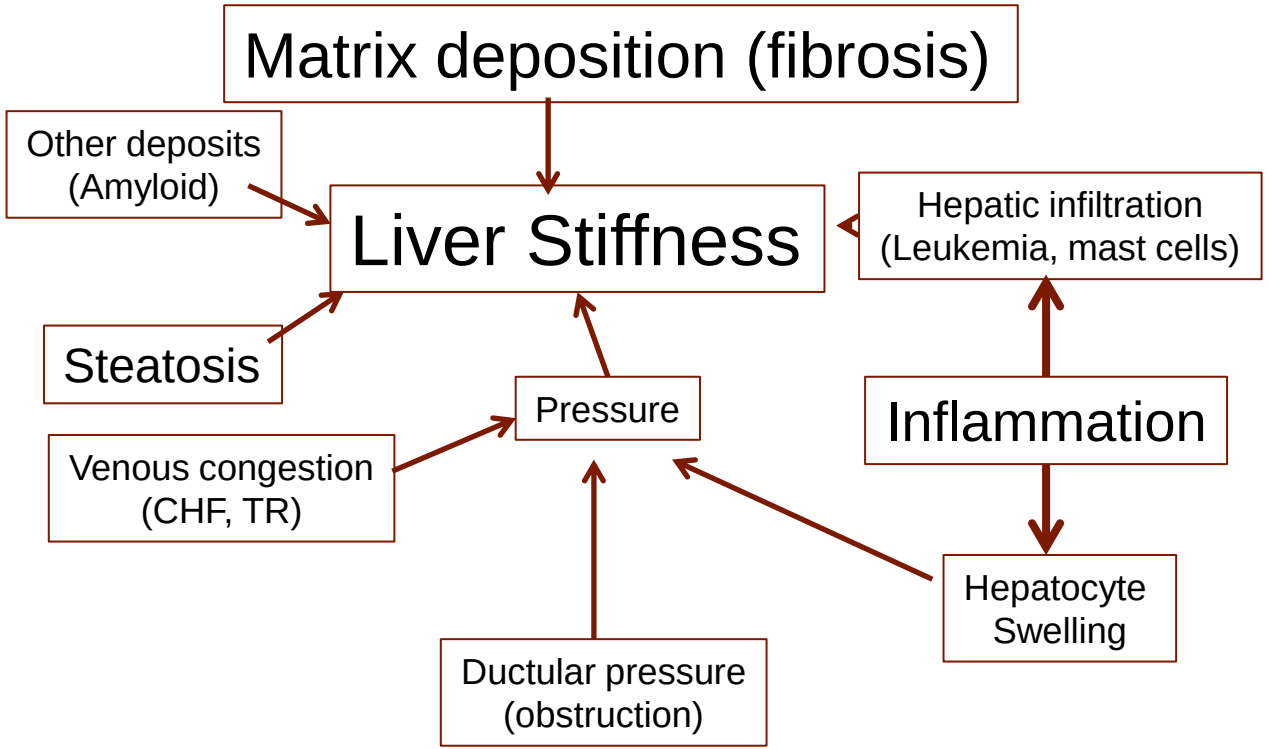
Summary of serum-based tests

- Good specificity and negative predictive value
  - Good at ruling out advanced fibrosis (F3-4) at low score
- Moderate sensitivity and positive predictive value
  - Not so good at ruling in advanced fibrosis (F3-4) at high score
- APRI and FIB-4 work as well as proprietary tests and are free
- Good for initial assessment

Comparison of Elastography Methods

Method	Availability	Cost	Evidence	Sampling area	Sampling placement	Reported parameter	Main reasons for failure or unreliable results
TE	Widespread	Low	Excellent validation	Small	Restricted, no guidance	Young modulus (kPa)	High BMI (M probe), ascites
ARFI/SWE	Moderate	Low	Moderate validation	Small (pSWE); Medium (SWE)	Flexible with US guidance	Young modulus (kPa) or wave speed (m/sec)	High BMI
MRE	Limited	High	Limited validation	Large	Large organ coverage	Complex shear modulus (kPa)	Liver iron deposition, large ascites, BMI*, 3T (for 2D GRE)

Factors that affect liver stiffness



Bonder and Afdhal. Curr Gastro Rep 2014;16:372

How do imaging tests perform to differentiate F0-2 vs F3-4

Test	Disease	Cut off (kPa)	Sensitivity	Specificity
SWE	HCV	*8.7*	0.97	0.85
	HBV	*8.3*	0.90	0.77
	NASH	*1.64*	1.0	0.80
VCTE	HCV	*8*	0.89	0.90
	HBV	*9*	0.82	0.83
	NASH	*9*	0.80	0.78
MRE	HCV	-	-	-
	HBV	*5.45*	1.0	1.0
	NASH	*3.7*	0.90	0.94

Unpublished data from AASLD Guidelines 2021

How do imaging tests perform to differentiate F0-3 vs F4

Test	Disease	Cut off (kPa)	Sensitivity	Specificity
SWE	HCV	*10.3*	0.88	0.96
	HBV	*8.3*	0.90	0.77
	NASH	-	-	-
VCTE	HCV	*11*	0.93	0.80
	HBV	*13*	0.97	0.92
	NASH	*11*	0.90	0.88
MRE	HCV	-	-	-
	HBV	*6.87*	1.0	0.99
	NASH	*4.67*	0.80	0.94

Unpublished data from AASLD Guidelines 2021

Performance of non invasive imaging methods for diagnosis of liver fibrosis

Disease	Fibrosis stage	TE cutoff (kPa)	pSWE/2D-SWE cutoff*	DOR (95% CI)
HCV	F0-1 vs F2-4	6.5-6.7	1.2 (pSWE)	1.5 (0.57 to 3.96)
	F0-2 vs F3-4	9.6	1.61 (pSWE)	1.41 (0.18 to 10.91)
	F0-3 vs F4	12.2-13.1	1.8-2 (pSWE)	1.4 (0.36 to 5.47)
HBV	F0-1 vs F2-4	6.9-7.3	7.1 (2D-SWE)	0.68 (0.34 to 1.39)
	F0-3 vs F4	10.6-11.2	11.3 (2D-SWE)	0.53 (0.12 to 6.38)
			1.75 (pSWE)	0.86 (0.25 to 3)
NAFLD	F0-3 vs F4	16.1	2 (pSWE)	1.45 (0.53 to 3.98)

DOR: Diagnostic odds ratio; kPa, Kilopascals; * m/s for pSWE, kPa for 2D-SWE

Unpublished data from AASLD Guidelines 2021

What about combining serum and imaging tests

Tests	Disease	AUROC (95% CI)	Author (year)
VCTE APRI VCTE + APRI	HCV	0.88 (0.80-0.94) 0.89 (0.81-0.94) 0.84 (0.75-0.90)	Ferraioli (2012)
VCTE FIB-4 VCTE + FIB-4	NAFLD	0.86 (0.79-0.92) 0.79 (0.70-0.87) 0.88 (0.84-0.94)	Petta (2015)
VCTE FIB-4 APRI VCTE + FIB-4 VCTE + APRI	HBV	0.85 (0.73-0.91) 0.82 (0.72-0.91) 0.78 (0.68-0.89) 0.91 (0.85-0.98) 0.91 (0.83-0.98)	Zhang (2016)
APRI FIB-4 APRI + FIB-4	HBV	0.745 (0.66-0.82) 0.74 (0.65-0.82) 0.74 (0.66-0.82)	Yang (2017)

Unpublished data from AASLD Guidelines 2021

Outline

- What non-invasive assessments are available?
  - Serum and imaging used alone or in combination (cutoff varies by disease).
- Which one(s) should I use?
  - I start with FIB-4 (and APRI), then use VCTE (Fibroscan®).
- When should I use them?
  - Definitely at initial evaluation. Use in follow-up controversial.
- How to approach to the patient and when to biopsy?

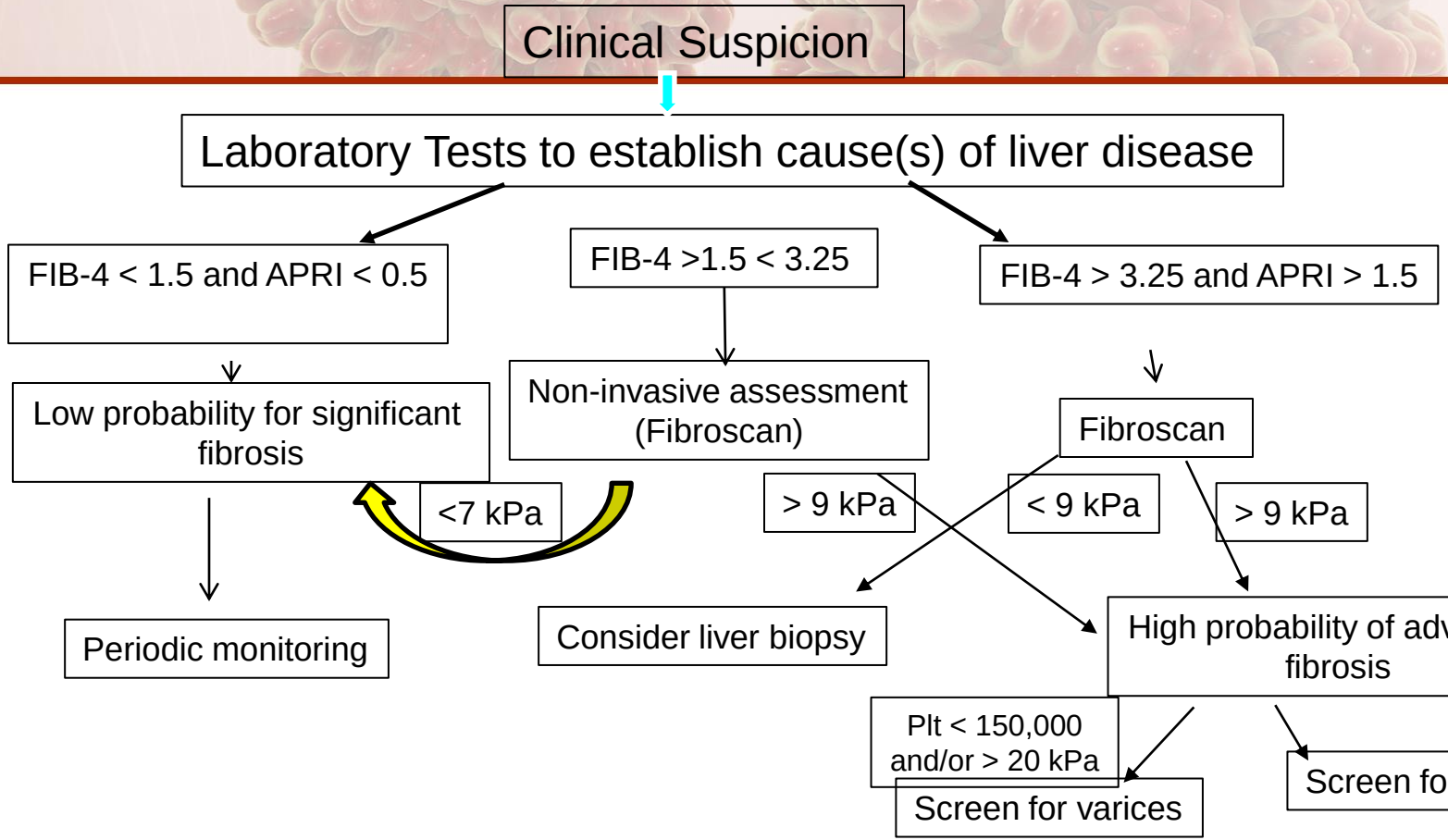
Ways to Practice Medicine

Evidence based

- PubMed
- Meta-analysis
- Systematic reviews
- Society Guidelines

Eminence based

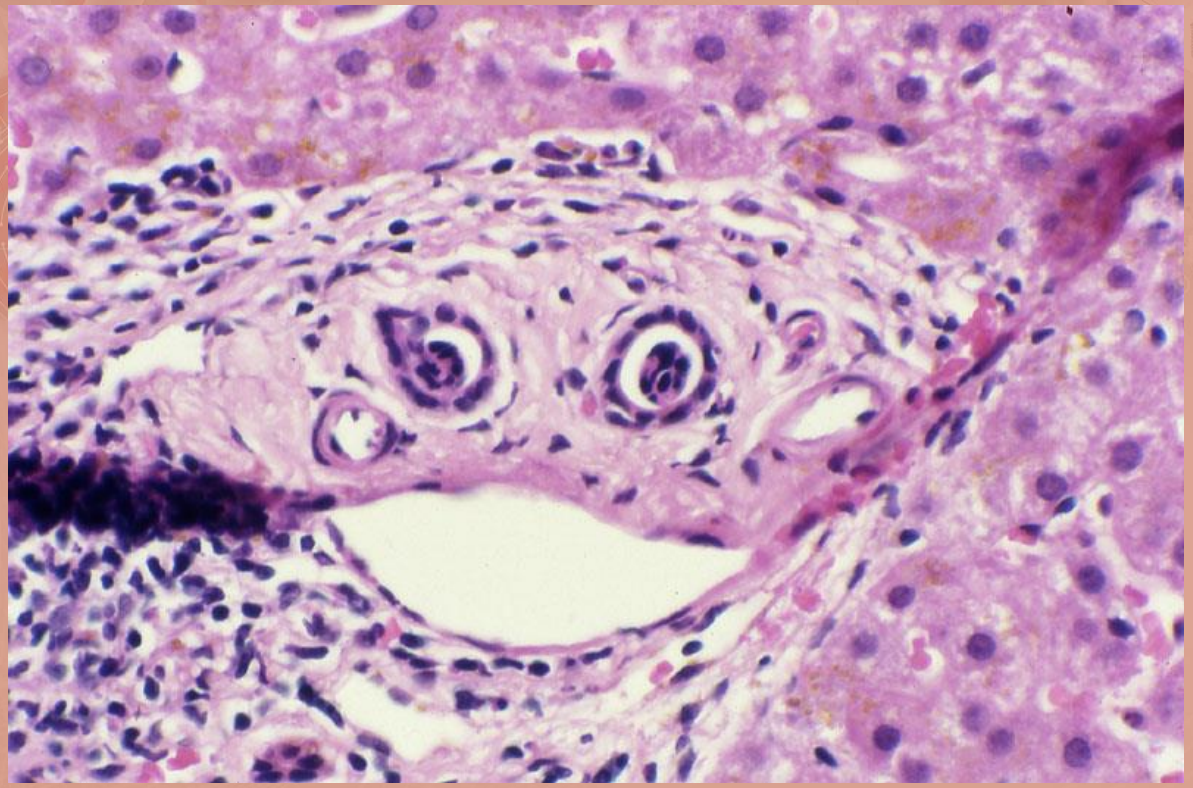
Proposed Diagnostic Algorithm for Clinical Practice



Conclusions

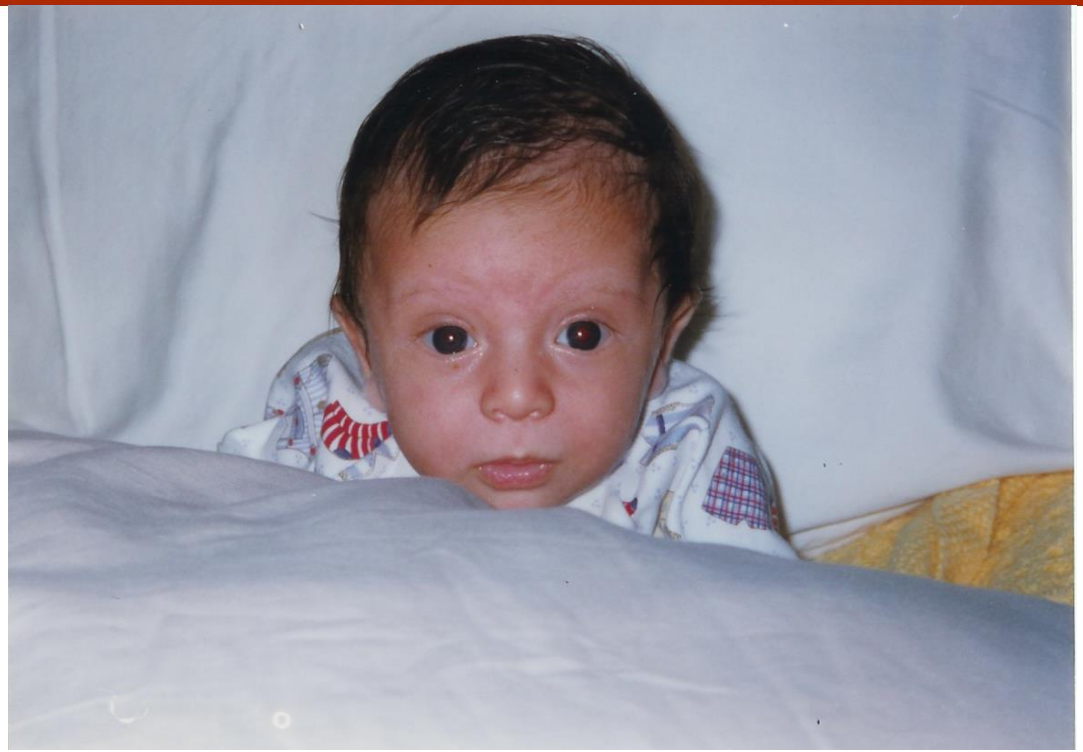
- Knowledge is power
  - Fibrosis related to liver-related outcomes
- Start with non-invasive assessments
  - FIB-4 and APRI (simple, free)
  - Fibroscan® with CAP (office based if available, SWE/ARFI if not)
  - MRI/MRE may be new gold standard, but not widely available
- Consider liver biopsy if:
  - Indeterminate or high risk
  - When you need to differentiate from other conditions (NASH)
  - When in doubt

The End



Courtesy- Dr. David Kleiner

Discovery Comes to the Prepared Mind



Thank you for your attention

804-828-9034
Richard.Sterling@vcuhealth.org
Twitter: @RichSterlingMD