44 yo Male with Elevated ALP of 400 IU/L

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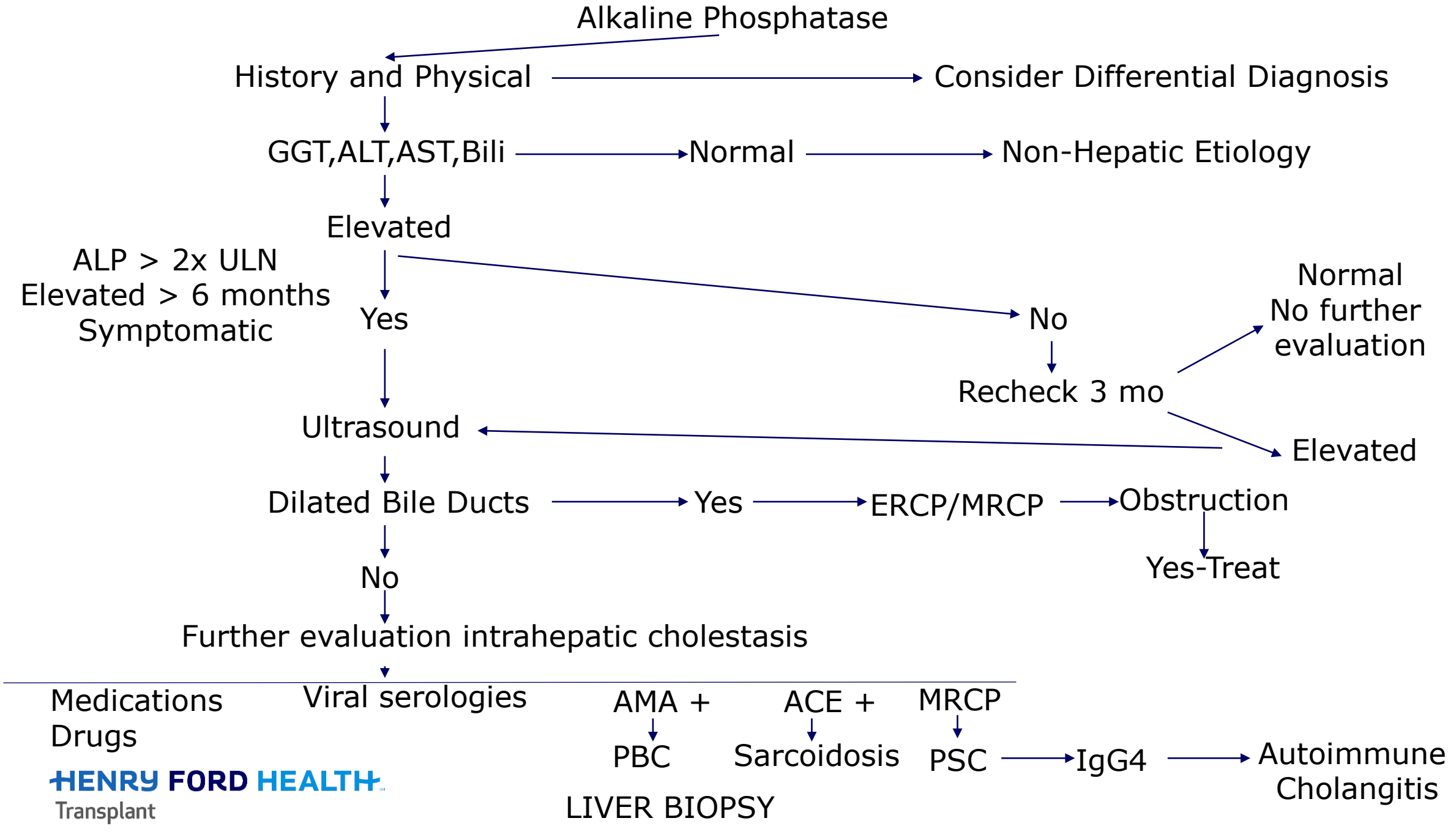
Elevated Alkaline Phosphatase: What do You do?

- This is a liver talk so we will obviously focus on the liver
- However, just to remind us all:
  - Differential diagnosis includes CHF, Hyperthyroidism, Renal Disease, Bone Disease, Malignancy
  - Multiple sources of ALP including bile duct, bone, intestine, placenta, kidney, granulocytes, mammary ducts
  - If isolated, 52% will normalize within 3-12 months
  - If >1.5x ULN, persistent elevation is more likely (68% vs 41%)

What is our approach?

Lieberman, P. J Clin Gastroenterol 1990;12(4):415-19

Siddique A, et al. Clin Liver Dis 2012 May;16(2):199-229



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Let’s Start with our Case

- 44 yo man is sent to you for elevated alkaline phosphatase found on yearly physical examination
- General health has been excellent
- PMH and PSH are non-contributory
- Family History is positive for mother with thyroid disease, cousin with “colitis”
- ROS is negative for diarrhea, IBS, pain, change in weight or appetite, fatigue, SOB, weakness, nausea, emesis
- He smokes 1ppd and uses alcohol approximately once per month
- He takes no medications and denies recent antibiotics, OTC medications, supplements
- PE vital signs normal, BMI normal, no evidence of wasting, no jaundice, chest and heart normal, no edema, abdomen soft without tenderness, liver edge palpable 2 cm below RCM, no spleen tip palpable

Siddique A, et al. Clin Liver Dis 2012 May;16(2):199-229

No weight loss (malignancy)
Not a woman (pregnancy/lactation)
Thyroid possible but asymptomatic
Asymptomatic from a cardiac standpoint
PE only finding slightly enlarged liver

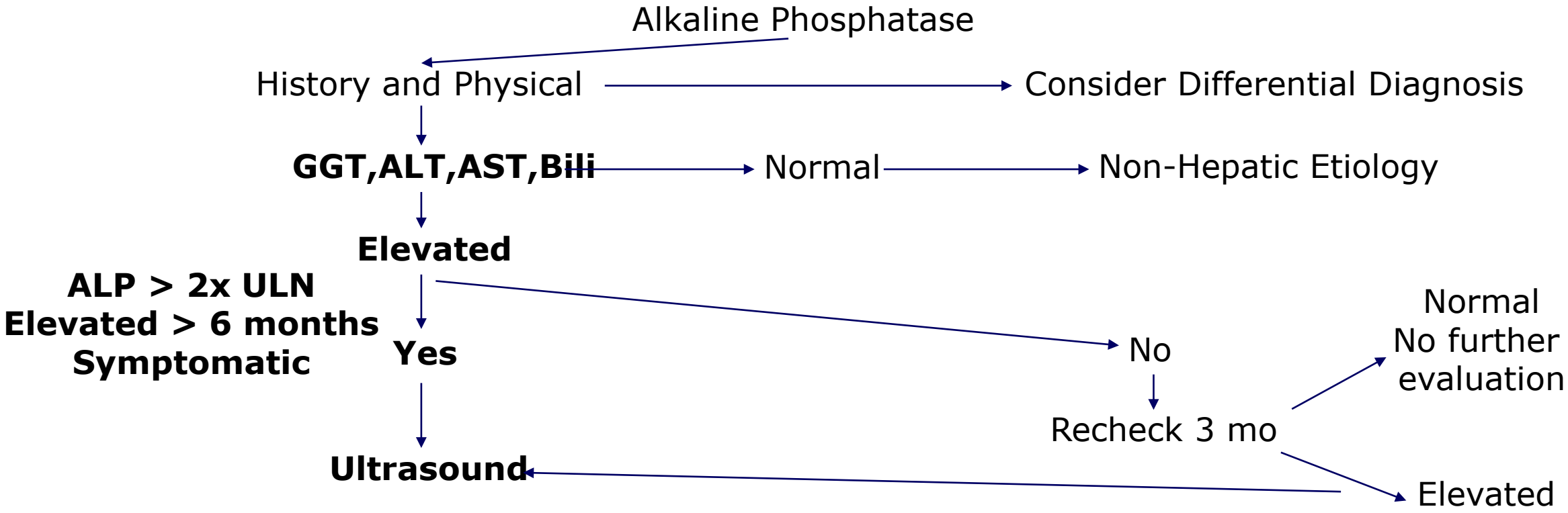
What is the next step?

Let’s Get Some Labs

- ALP 400 U/L
- ALT 85 U/L
- AST 54 U/L
- Total Bili 1.2
- CBC normal
- Lytes/BUN/Cr normal

Back to our Algorithm

Siddique A, et al. Clin Liver Dis 2012 May;16(2):199-229

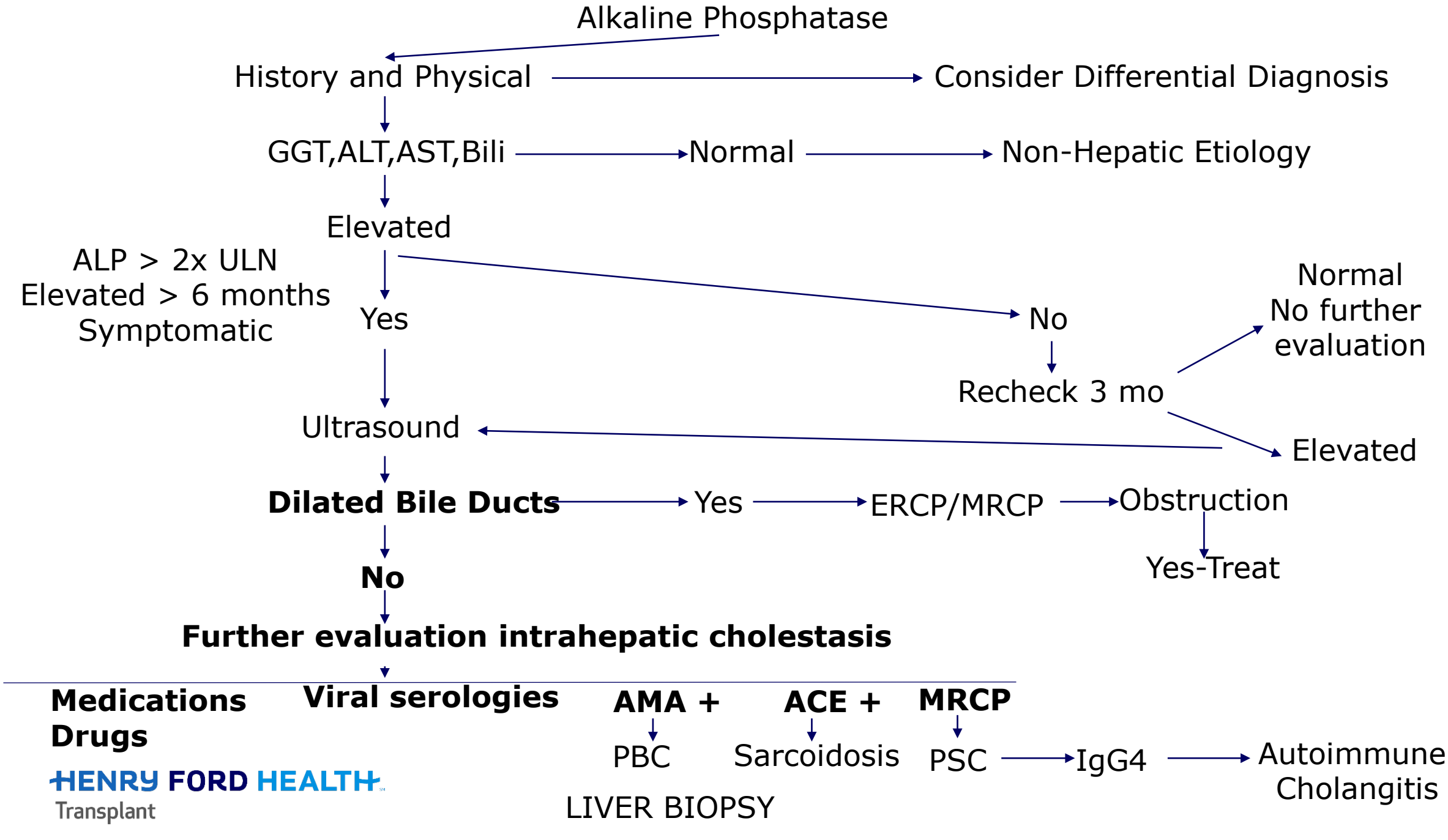


Ultrasound

- Concentric mural wall thickening of extrahepatic bile duct noted
- Echogenic portal triads
- Liver edge smooth
- No significant biliary dilation noted
- Gallbladder visualized, no stones present

- **Back to our Algorithm**

Siddique A, et al. Clin Liver Dis 2012 May;16(2):199-229



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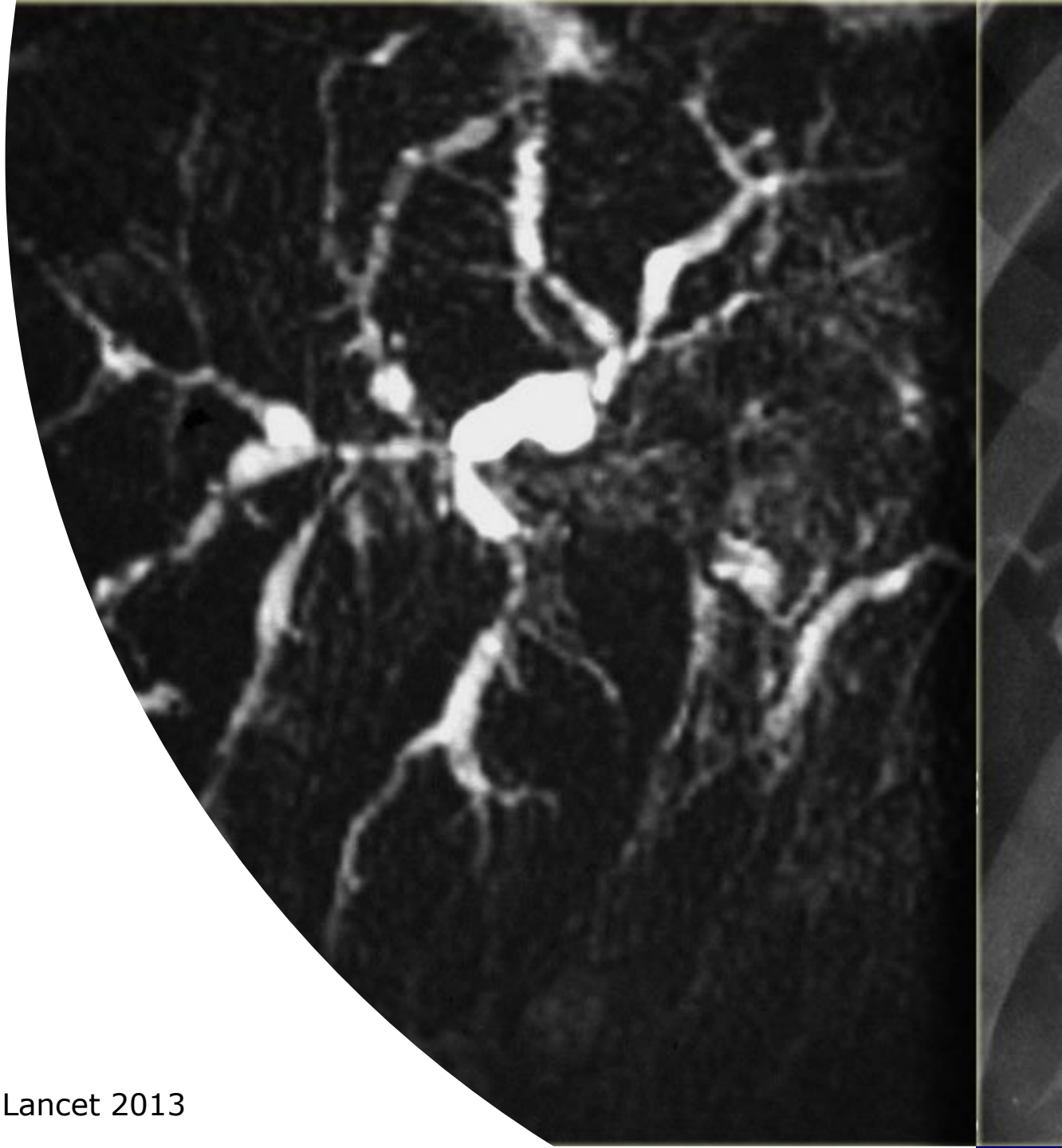
Further Work up

- Drug and Medication history reinforced and negative
- AMA negative
- ACE negative, CXR unremarkable
- Viral serologies (Hepatitis B and C) negative
- **MRCP**
  - Multiple intrahepatic and extrahepatic short segmental bile duct strictures with beading
  - No evidence of portal hypertension
  - No ascites present
  - No masses noted

Primary Sclerosing Cholangitis

- Male predominance
- Mean age at diagnosis: 35-40 years
- Variable clinical presentation & rate of progression
- 60-85% of PSC have IBD
- 2.4-5% of IBD have PSC



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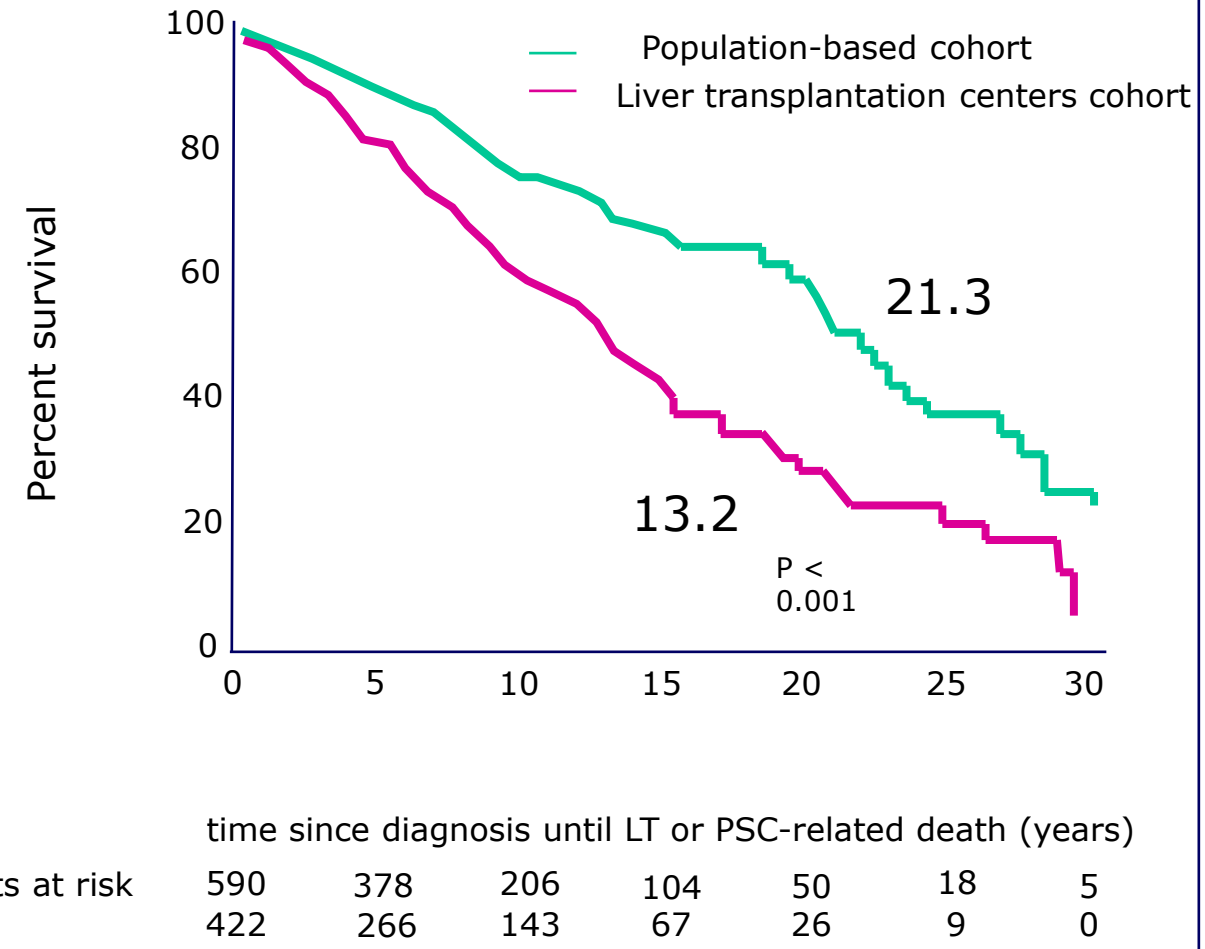
Hirschfield GM et al. Lancet 2013

Phenotypic Variants

Type of PSC	Cholangiographic appearance	Liver Histology
Classic PSC	Multifocal intra- and/or extrahepatic strictures and dilatations	Typical changes (i.e. non suppurative paucicellular cholangitis, periductal fibrosis, ductular reaction, ductopenia)
Small Duct PSC	Normal	Typical changes
Overlap PSC-AIH	Multifocal intra-and/or extrahepatic strictures and dilatations	Changes of PSC + moderate to severe interface hepatitis, lymphoplasmacytic infiltrates

Natural History: Survival Without Liver Transplant



Causes of death:

- CCA (32%)
- Liver failure (18%)
- LT-related complications (9%)
- CRC 8% (10 fold)
- CRC younger age 39 vs 59
- Surveillance improved outcomes

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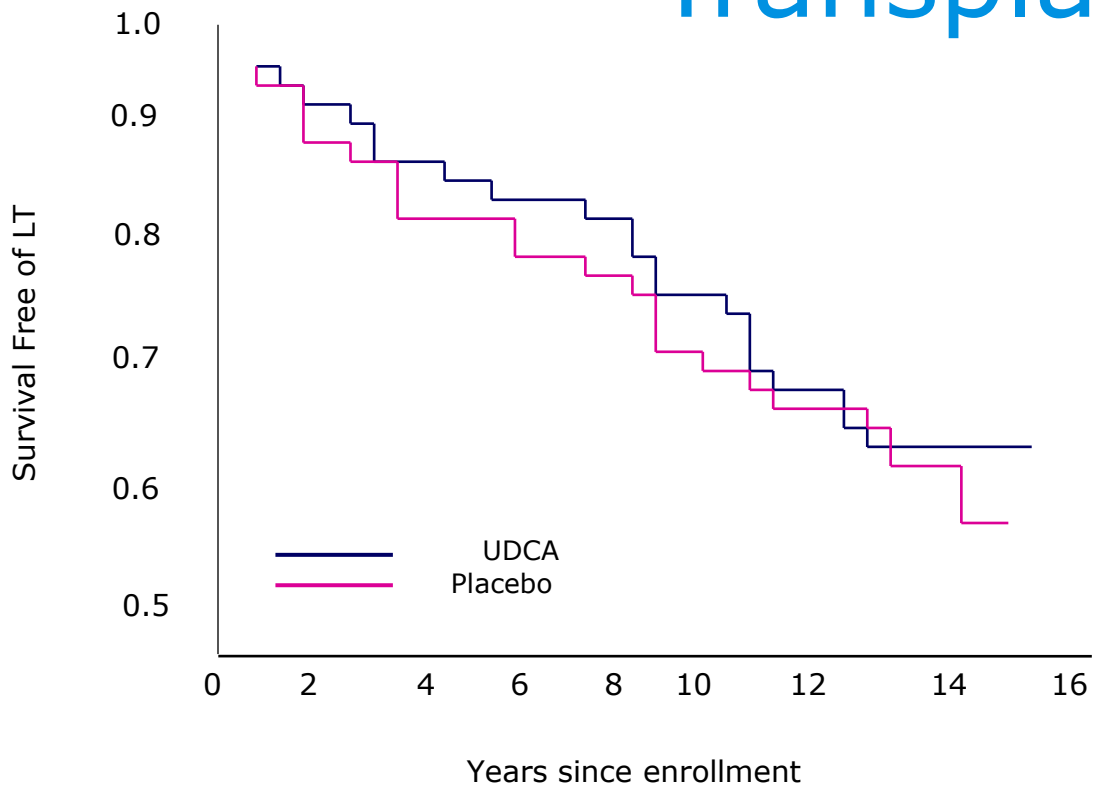
Boonstra et al. Hepatology 2013

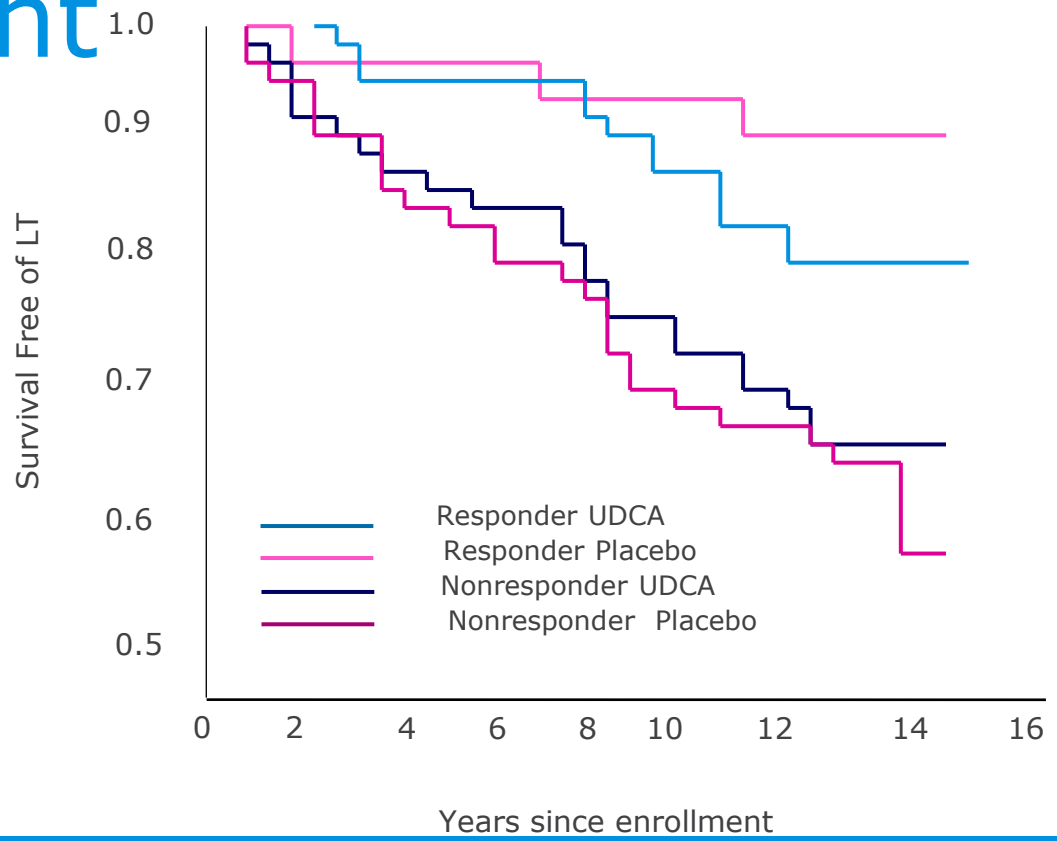
Prognostic Value of ALP in PSC

Author	Site	ALP measure	Outcome
Al Mamari	UK	ALP < 1.5x ULN	6% vs. 48% clinical decompensation or death
Lindstrom	Scandinavia	>40% drop	Improved survival
Stanich	USA	Normalization	14% vs. 33% reached clinical endpoint
Rupp	Germany	ALP < 1.5x ULN (+ all above)	Survival free of LT: 22.6 yrs vs. 16.2 yrs
De Vries	Netherlands	Normalization or reduction of ALP to < 1.5xULN	PSC related death Liver transplantation Cholangiocarcinoma

Al Mamari S, J Hep 2013;58(2):329-34, Lindstrom L, Clin Gastro Hep 2013; 11(17):841-6, Stanich P, Dig Liver Dis 2011;43(4):309-13, Rupp C, Aliment Pharm Ther 2014;40(11):1292-301, de Vries EM, Gut 2018;67(10):1864-69

UDCA: ALP and Risk of Death/Liver Transplant





No long term survival difference between patients given UDCA or Placebo for 5 years. However, those who have reduced or normal ALP have longer survival rates.

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Lindstrom L et al. Clin Gastroenterol Hepatol 2013; 11(17):841-46

There is no FDA-Approved Therapy

Role of UDCA in PSC: Controversial

- Used by 50% US pts and 57.8% International pts
- Improves liver biochemistries
- No demonstrable improvement in survival except for *trend* in Scandinavian study
- **High dose UDCA >28 mg/kg/day is detrimental**

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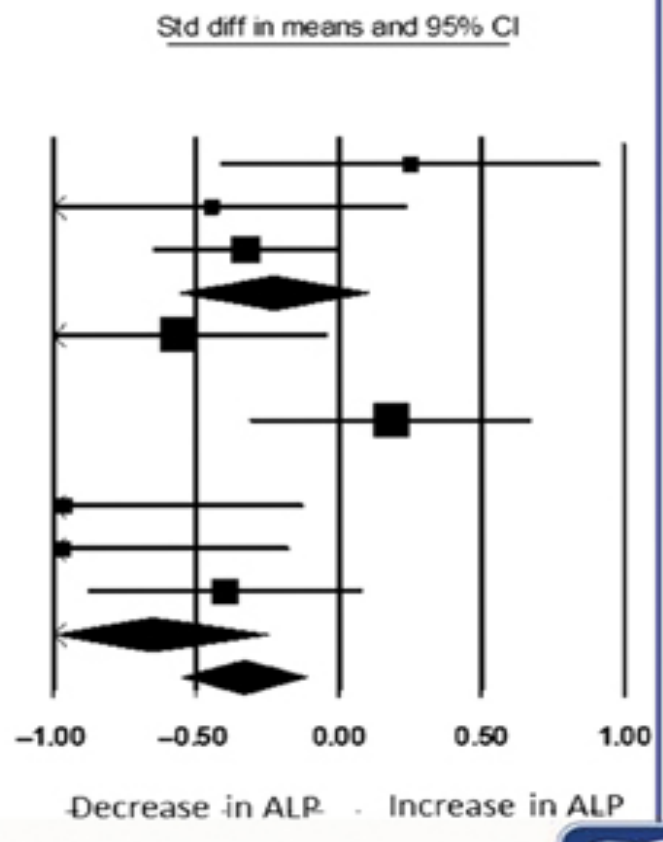
Kuo et al CGH 2018, Lindor et al Hepatology 2009

Meta-Analysis of Antibiotics in PSC

Effect of antibiotic treatment on ALP in PSC patients

Group by: Type of antibiotic	Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Metronidazole	Tabibian J et al Flagyl 125 mg	0.253	0.339	0.115	-0.411	0.916	0.747	0.455
Metronidazole	Tabibian J et al Flagyl 250 mg	-0.444	0.349	0.122	-1.128	0.241	-1.270	0.204
Metronidazole	Farkkila M et al Flagyl 800 mg	-0.324	0.164	0.027	-0.646	-0.002	-1.973	0.048
Metronidazole		-0.227	0.169	0.029	-0.558	0.105	-1.339	0.181
Minocycline	Silveira M et al Minocycline 100 mg	-0.562	0.269	0.072	-1.089	-0.035	-2.090	0.037
Rifaximin	Tabibian J et al Rifaximin 550 mg	0.185	0.252	0.064	-0.309	0.679	0.735	0.462
Vancomycin	Tabibian J et al Vanc 125 mg	-0.960	0.427	0.183	-1.797	-0.122	-2.246	0.025
Vancomycin	Tabibian J et al Vanc 250 mg	-0.965	0.404	0.163	-1.757	-0.174	-2.392	0.017
Vancomycin	Rahimpour S et al Vanc 125 mg	-0.397	0.245	0.060	-0.877	0.082	-1.623	0.105
Vancomycin		-0.656	0.210	0.044	-1.068	-0.243	-3.117	0.002
Overall		-0.332	0.112	0.013	-0.551	-0.113	-2.969	0.003



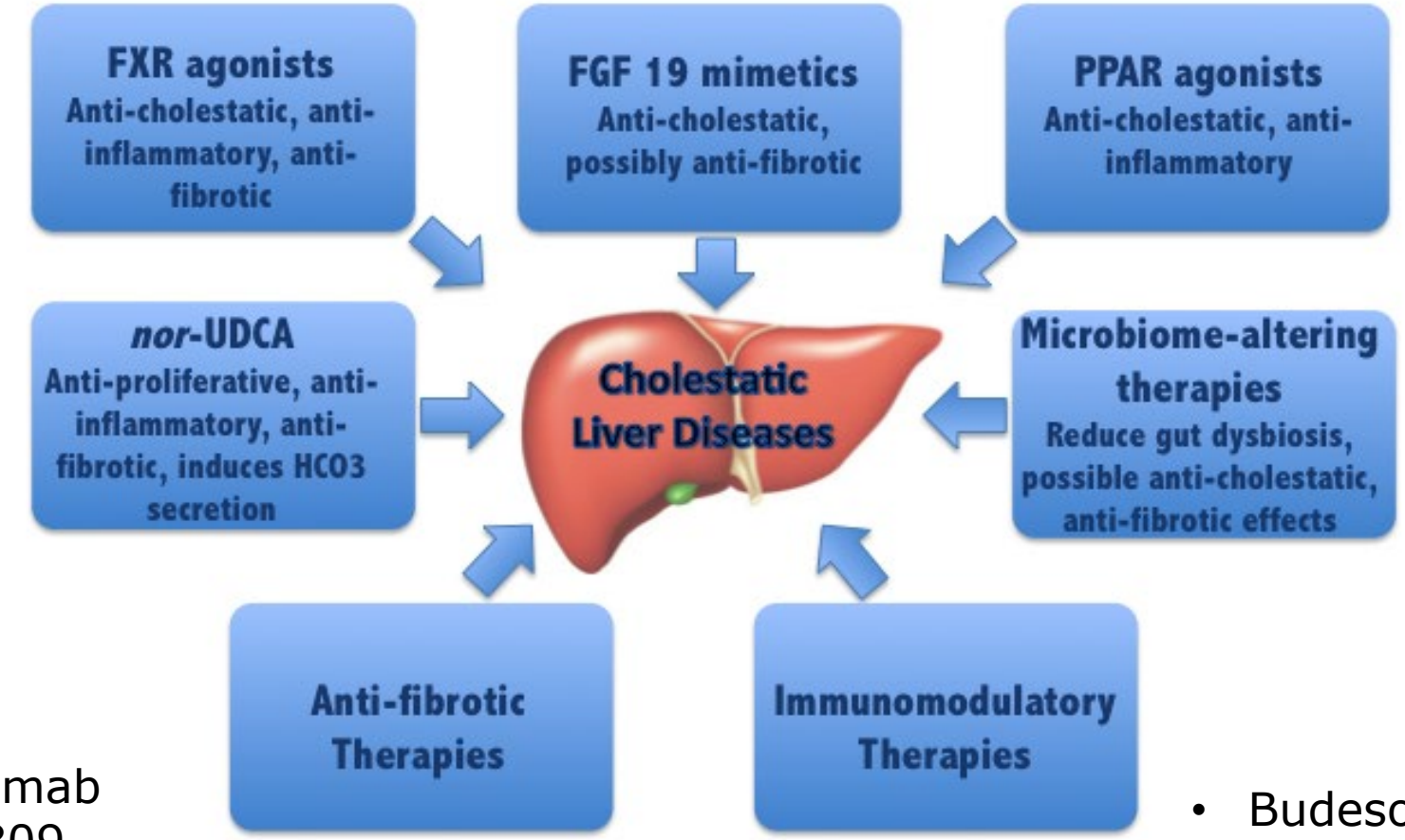
Significant reduction in ALP, Bili, Mayo Risk Score
8.9% AE leading to discontinuation

Shah et al, Semin Liver Dis 2019

Opportunities for Disease Modulation in PSC

- NGM 282

- Obeticholic acid
- Cilofexor
- ATRA (FXR/RXR)



- Fibrates
- ?seladelpar
- ?elafibranor

Adding BA modulation
- High dose udca
- DHA
- Maralixibat*

- FMT
- Antibiotics

- HighTide 1801
- Sulfasalazine

- Simtuzumab
- PLN-74809

- Budesonide
- BTT1023
- Cenicriviroc

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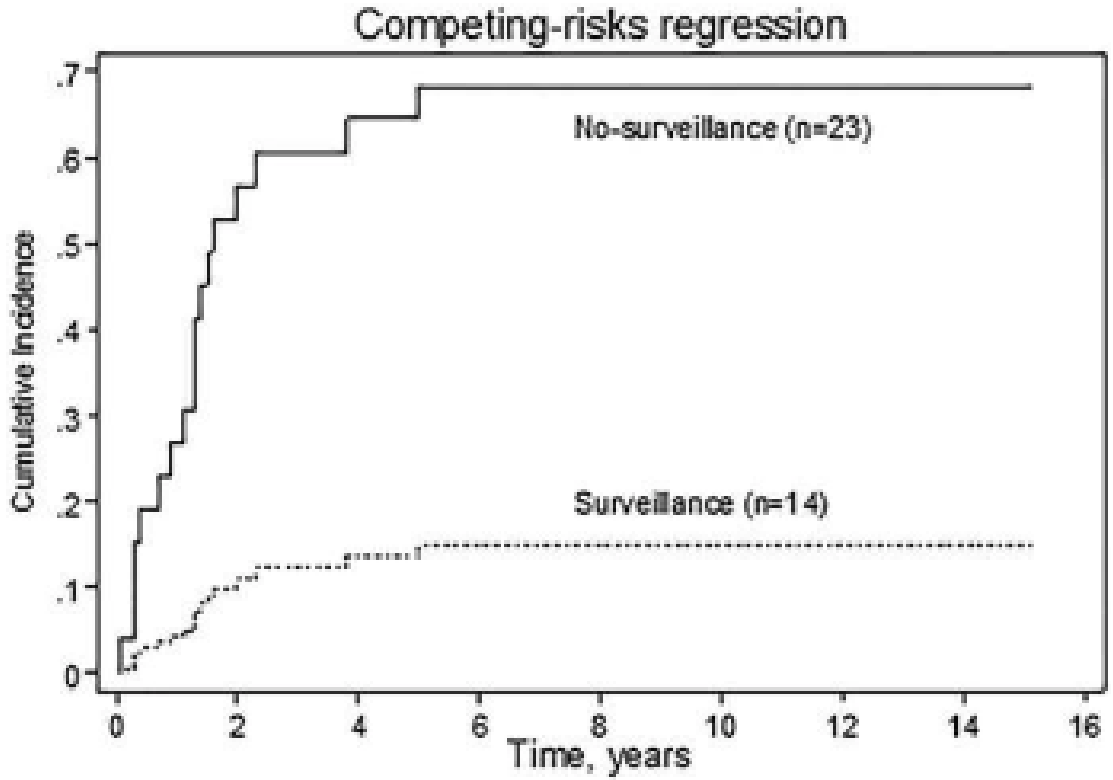
Santiago P et al. Therap Adv Gastroenterol 2018

PSC: Cancer Risk

- 15-20% lifetime risk of cholangiocarcinoma (400 X increase)
- 10 X increase in risk of gallbladder CA
- 5 X increase in risk of colorectal neoplasia in patients with PSC_IBD

Boonstra et al. Hepatology 2013

Surveillance for Malignancy is Associated with improved Outcomes in PSC



Patients who undergo surveillance have fewer cancer-related events (recurrence or cancer-related death).
All-cause mortality 5.5x higher in patients NOT undergoing surveillance.

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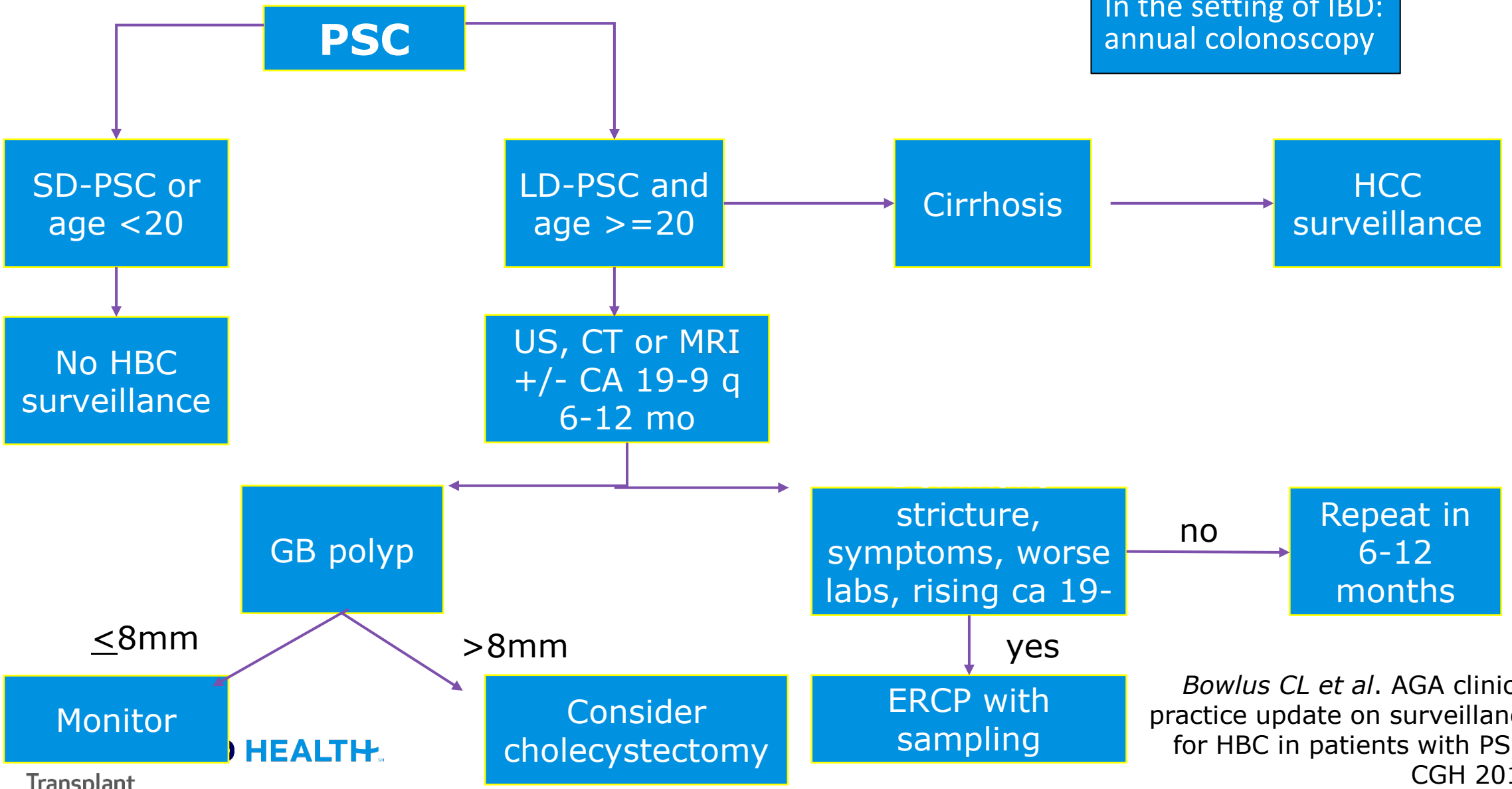
Ali, Tabibian, et al. Hepatology 67(6);2018

Surveillance Recommendations



Bowlus CL et al. AGA clinical practice update on surveillance for HBC in patients with PSC. CGH 2019

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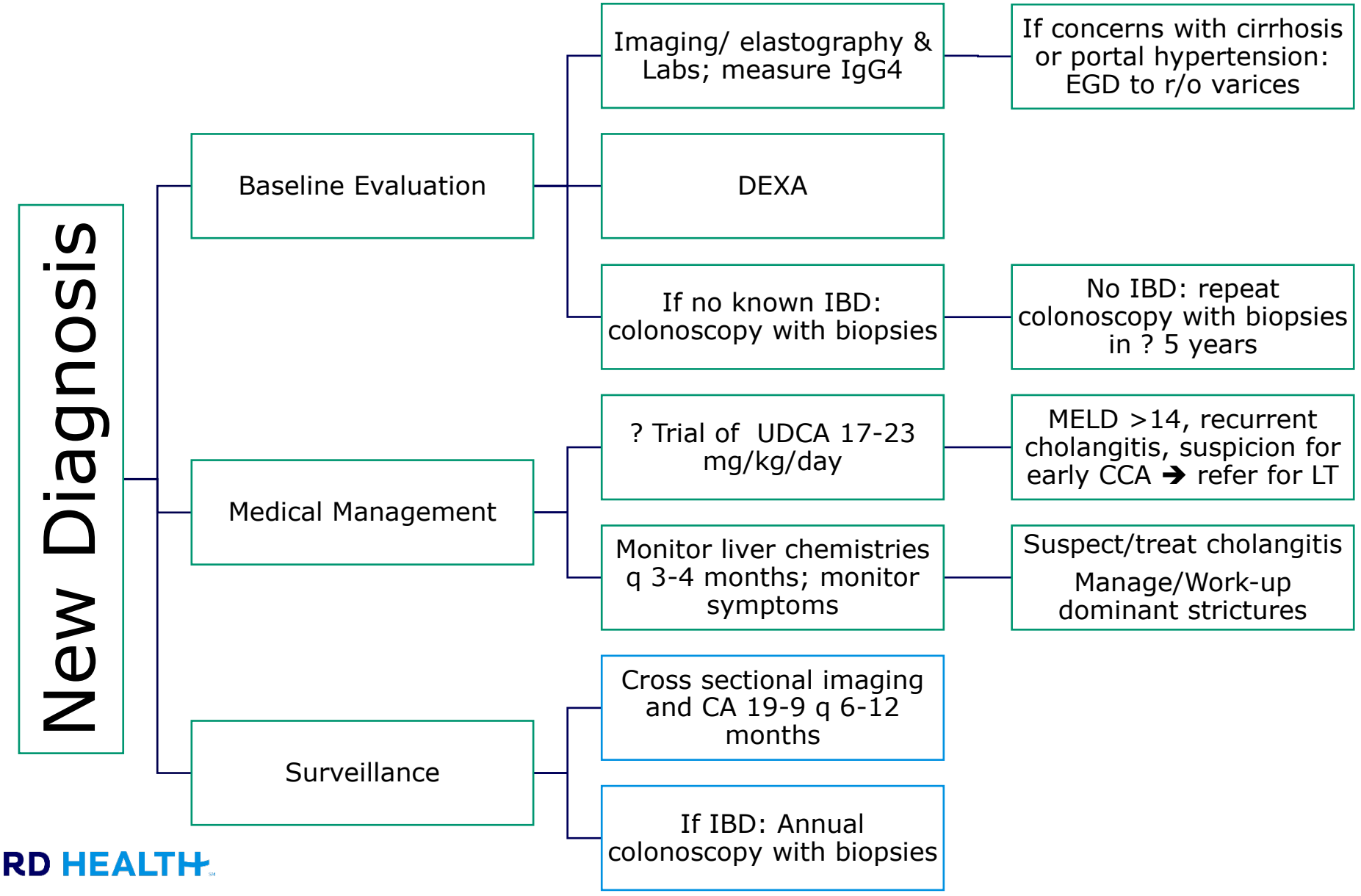
Liver Transplantation

- Definitive treatment for patients with decompensated liver disease
- Indications are similar to other causes of chronic liver disease (decompensated cirrhosis). Additional indications:
  - Recurrent cholangitis
  - Possibly early CCA with strict protocol
  - 5 yr survival 80-85% with 10 yr survival 70-80%
  - Recurrence 20% at 5 years (risk increased with presence of UC post transplant and young age)

Graziadei et al. Hepatology 1999; Fosby et al WJG 2012; Goldberg et al. Am J Transpl 2012; Campsen et al. Liver transplant 2008; Ravikumar et al. J Hepatol 2015

PSC Management Strategy

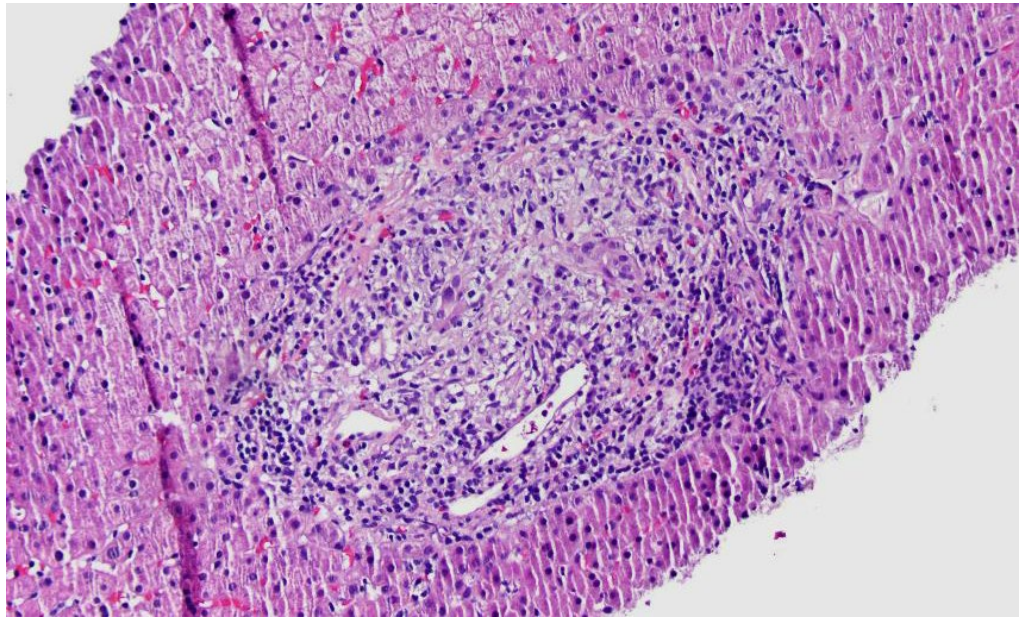


What if the Patient was a 40 yo Woman with an Alkaline Phosphatase Of 400 and a Positive AMA?

Primary Biliary Cholangitis (PBC)

PBC Diagnosis

- Unexplained Elevation of ALP ≥ 1.5x ULN
- Positive anti-mitochondrial antibody or PBC-specific ANA
- Non-suppurative destructive cholangitis on histology



Two out of these 3 criteria are required for the diagnosis of PBC

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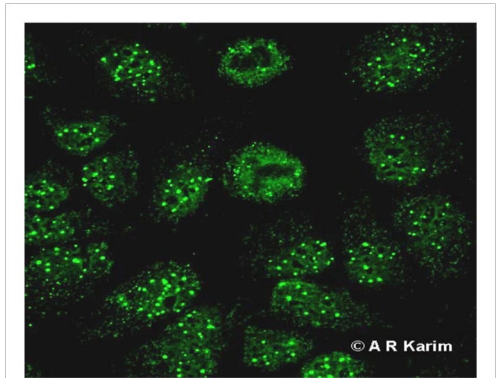
PBC – Specific Antinuclear Antibodies

- 90-95% PBC is AMA positive
- 40-50% PBC is ANA positive
- PBC-specific ANAs:
  - Anti-gp210 (nuclear rim pattern)
  - Anti-sp100 (multiple nuclear dots pattern)

Commercially Available In USA

Found in 20% of all PBC pts, and in 40-50% of AMA-neg PBC patients



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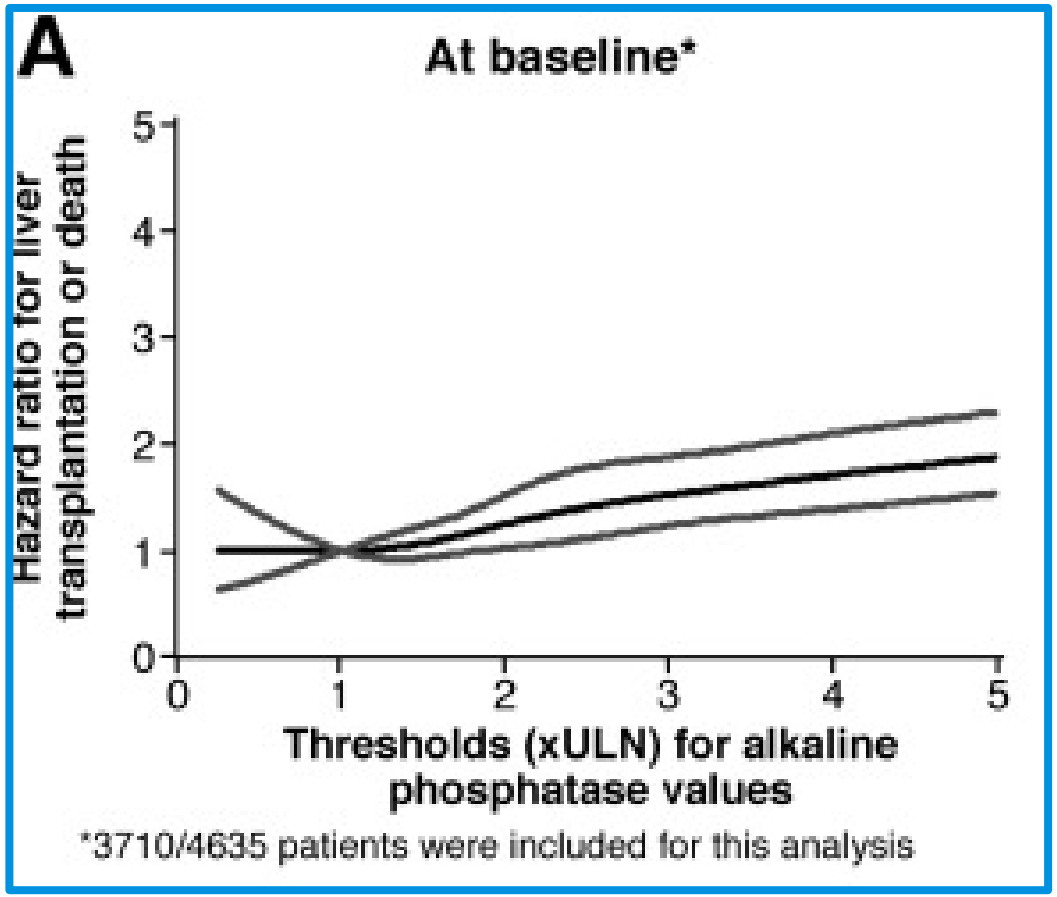
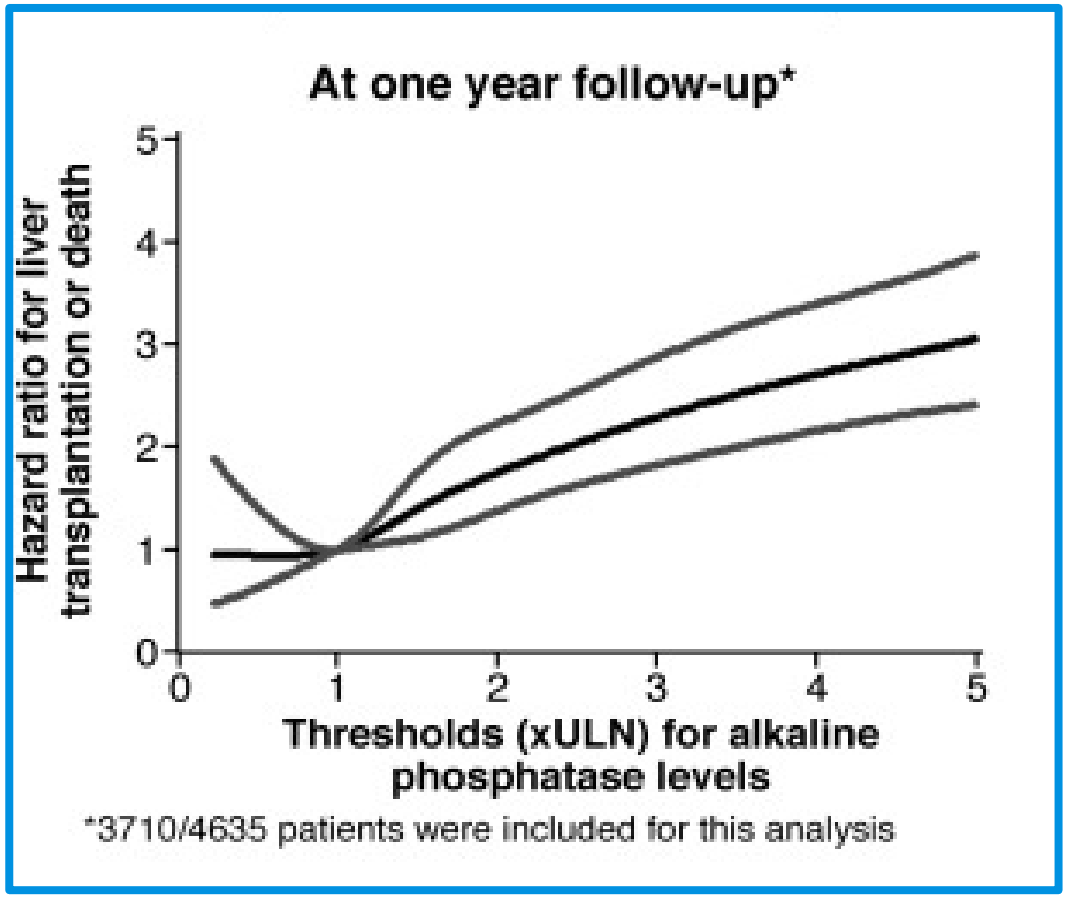
Levy C, Bowlus C, et al. *Am J Gastroenterology*. 2020.

Hazard of LT or death based on ALP levels at different time points





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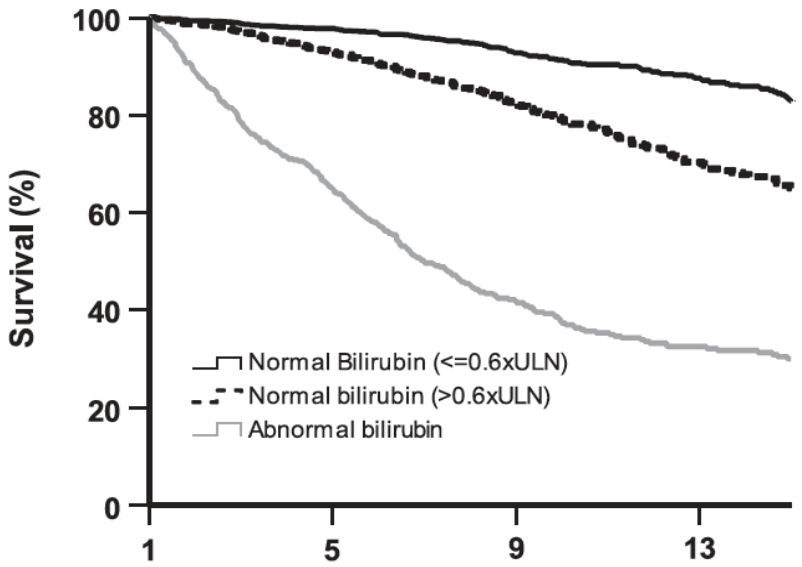
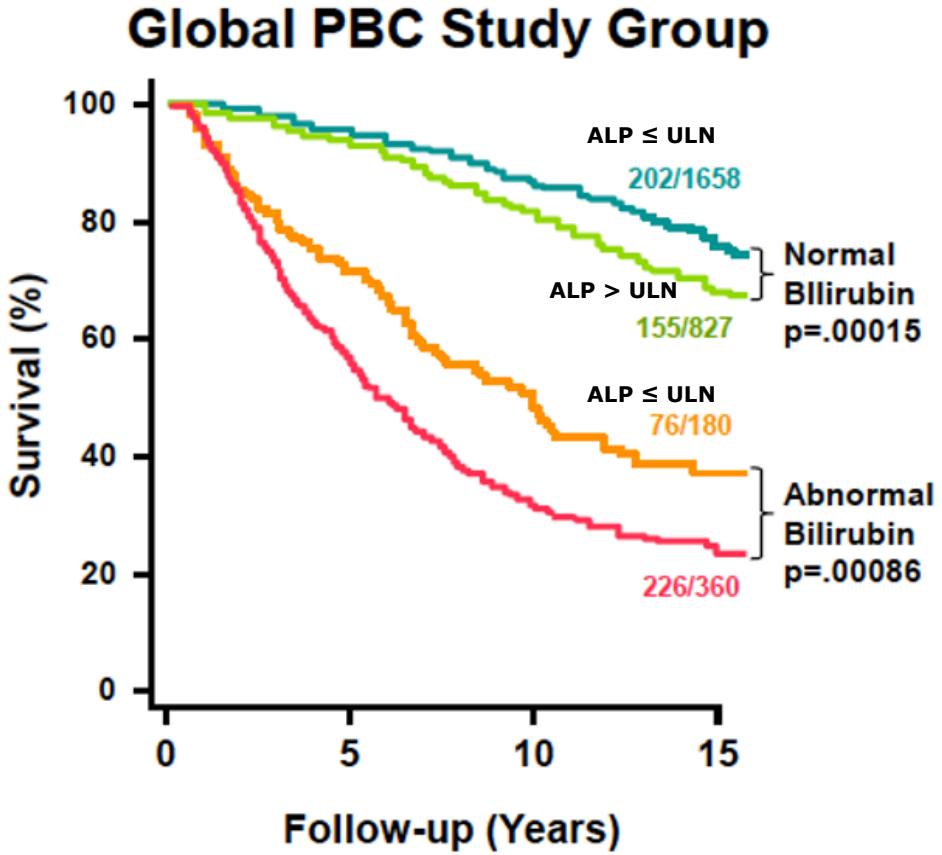
Lammers, et al. *Gastroenterology.* 2014; 147:1338-1349.

Biochemical Response to UDCA Predicts Survival



No. at risk

a	1718	1256	737	385
b	837	614	400	209
c	529	285	134	82



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Murillo Perez et al. Am J Gastro. 2020

Obeticholic Acid Is FDA-Approved:

- In combination with UDCA for patients with PBC who have been treated with UDCA for > 1 year and have incomplete response

- As monotherapy for patients with PBC who are intolerant to UDCA

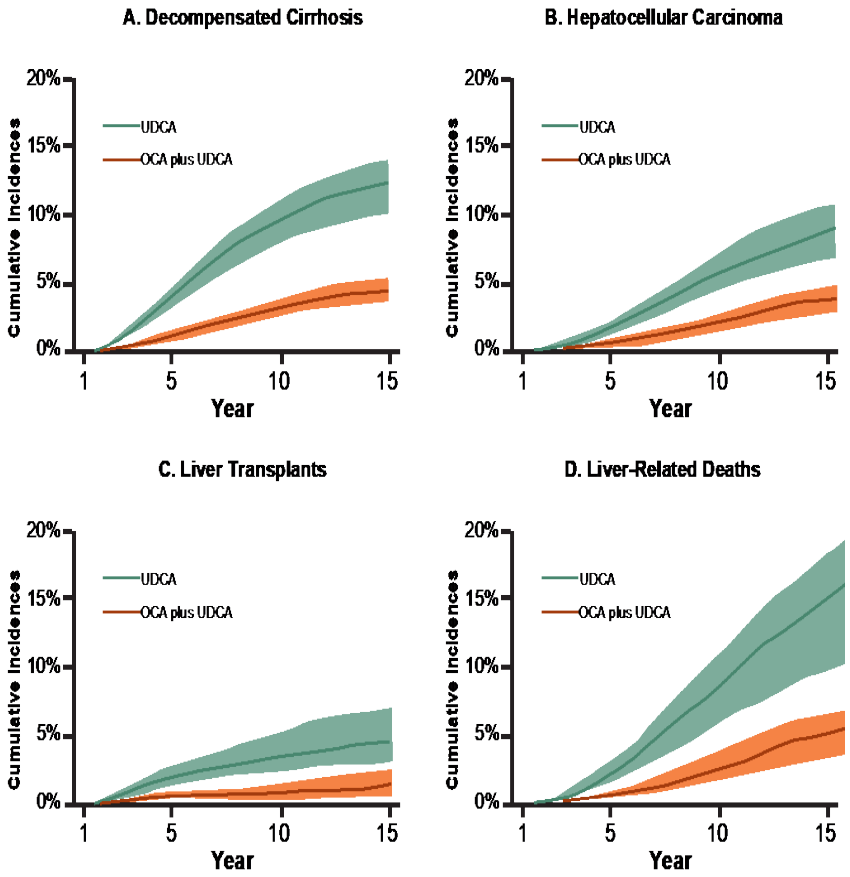
Phase 3 (POISE) TRIAL: RESULTS

210 patients randomized to placebo vs. 5-10 mg/day OCA vs.10 mg/day OCA

- 5x more patients on OCA met the primary endpoint compared to pts on placebo
- Significant drop in ALP, AST, ALT, GGT, TB
- Significant reduction in inflammatory markers
- Reduction in HDL-cholesterol (20% in 10mg/day, 9% in 5-10 mg/day)
- No change in liver stiffness scores (50% had LS measured)
- Itching was the most common side effect; mitigated by titration strategy

Nevens F et al. NEJM 2016

Cumulative Incidence of Complications of PBC



In patients with inadequate response to UDCA, **OCA decreased 15-yr cumulative incidences of**:

- Decompensated cirrhosis from 12.2% to 4.5%
- HCC from 9.1% to 4%
- OLT from 4.5% to 1.2%
- Liver-related deaths from 16.2% to 5.7%

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Samur S, et al. *Hepatology.* 2017.

Potential OCA Adverse Effects: Itch, Gallstones/Cholecystitis, Hepatotoxicity

- Pruritus: Common, dose related
- Gallstones/Cholecystitis
- Grade 3 Hepatoxicity:
  - 19 deaths and 11 cases of severe liver injury, most cirrhotic
- Black box warning and subsequent change in label to avoid in patients with cirrhosis and prior or current evidence of decompensation

Pruritus	Placebo	OCA 5->10mg	OCA 10 mg
Phase 3 trial	38%	56%	68%
4yr open label	n/a	77%	

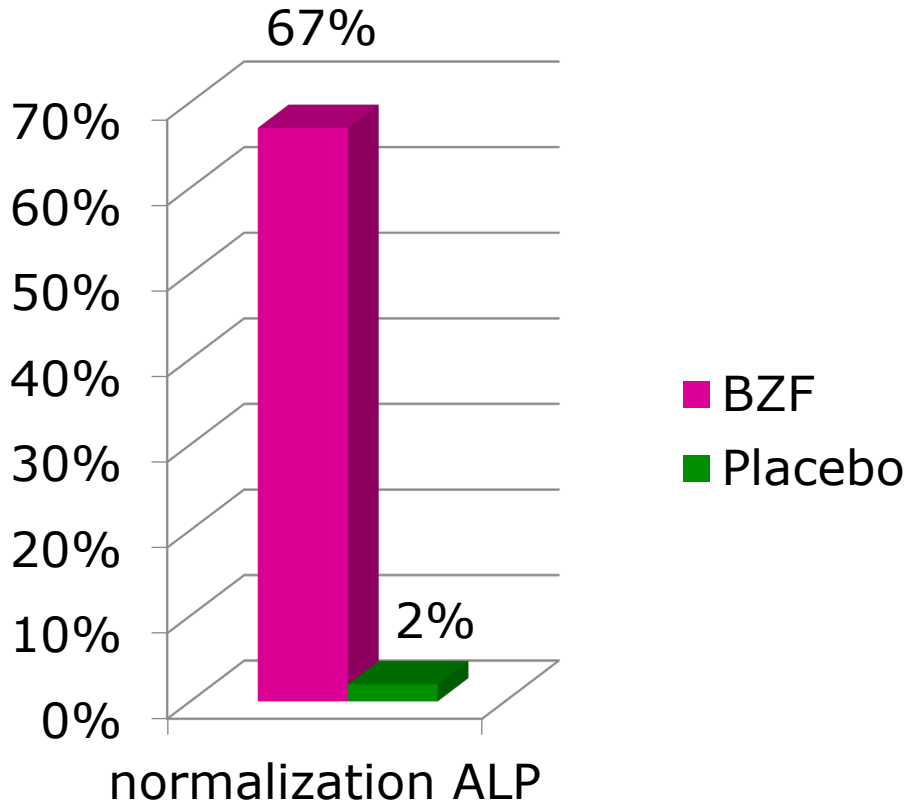
LiverTox.Nih.gov;
Nevens et al. *N Engl J Med*. 2016;
Kowdley et al. *AASLD*. 2019. Late Breaker;
Trauner et al. *Lancet Gastro & Hep*. 2019.

BEZURSO: Bezafibrate + UDCA vs. Placebo + UDCA

- ✓100 patients with incomplete response to UDCA
- ✓Randomized to BZF 400 mg/day or placebo, for 2 years
- ✓Primary endpoint* at 2 years:

  30% BZF vs. 0% Placebo

- ✓Itch score, LSM and ELF improved in BZF group



* Normal ALP, AST, ALT, GGT, T Bili, Albumin, INR

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Corpechot C et al. *N Engl J Med* 2018

Effect of Bezafibrate on Pruritus

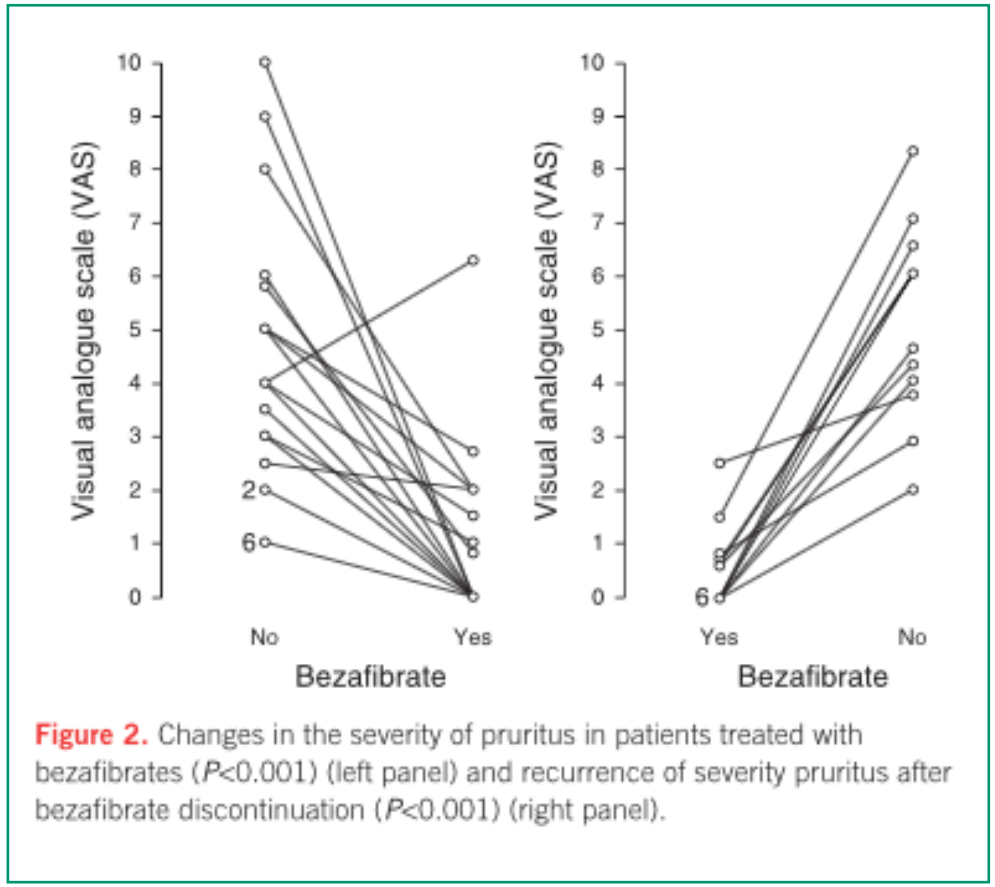

Figure 2. Changes in the severity of pruritus in patients treated with bezafibrates ($P<0.001$) (left panel) and recurrence of severity pruritus after bezafibrate discontinuation ($P<0.001$) (right panel).

- 48 patients treated with BZF for median 38 months
- ALP 2.4x ULN ➔ 1x ULN
- 26/48 had pruritus
- 16 resolved, 7 improved, 3 unchanged

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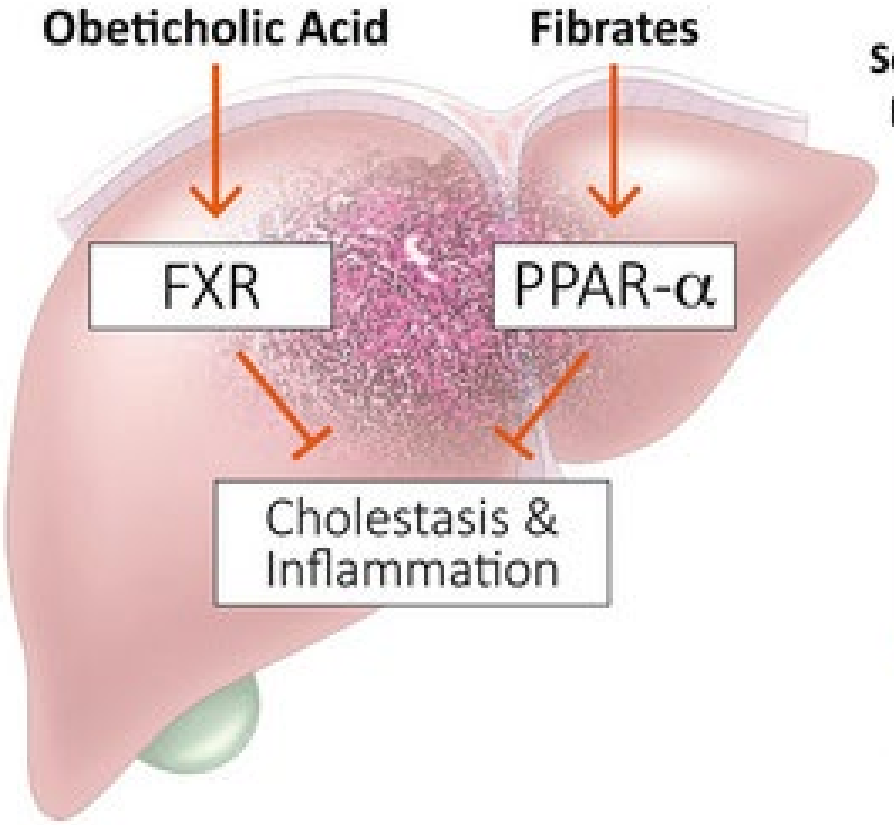
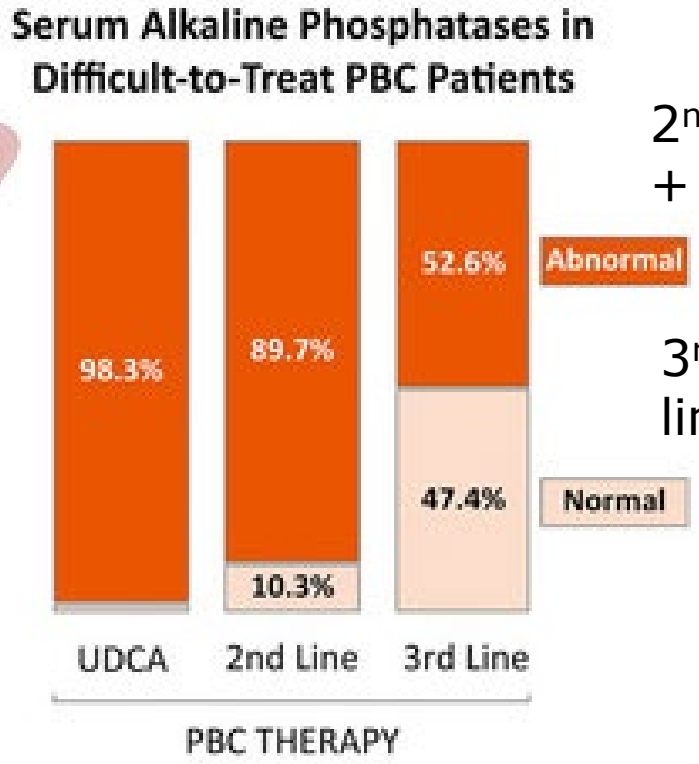
Reig et al. Am J Gastro 2017

UDCA+OCA+BZA X12 Wk

Phase 2 Trial Underway





2nd line group : OCA as 2nd line + Fibrate as 3rd line; N= 29

3rd line group : Fibrate as 2nd line + OCA as 3rd line; N= 29

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Soret et al. *Alim Pharmacology & Therapeutics*. 2021.

Summary

- PSC
  - UDCA has not shown benefit, high doses are dangerous
  - ALP improvement may correlate with improved outcomes
  - Mechanical treatment for dominant strictures
  - Surveillance for cholangiocarcinoma and CRC improves outcomes
  - Transplantation for decompensation, severe recurrent cholangitis
- PBC
  - New Treatment goal is Bili $\leq$ 0.6 X ULN and normal ALP
  - First line treatment is UDCA
  - Second line, add OCA
  - New Treatment goal is Bili $\leq$ 0.6 X ULN and normal ALP
  - ? Triple therapy: UDCA + FXR agonist + PPAR
  - Transplantation for decompensation