Primary Biliary Cholangitis:
Advances and Opportunities

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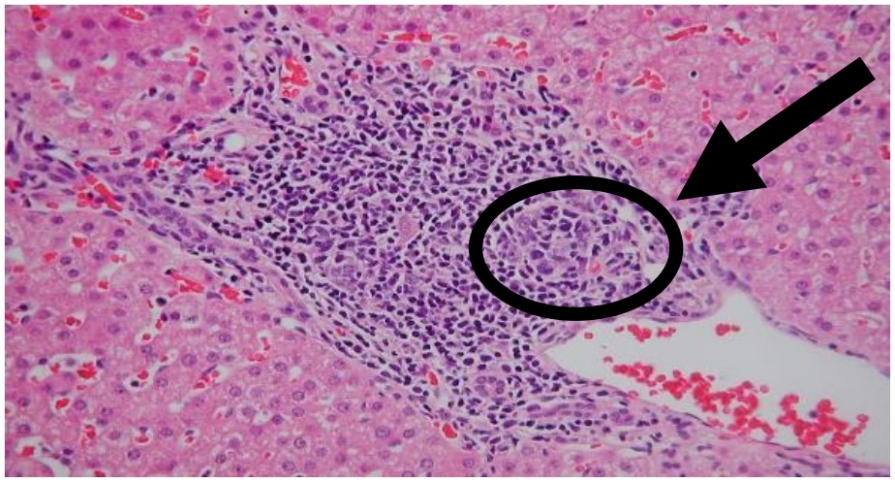
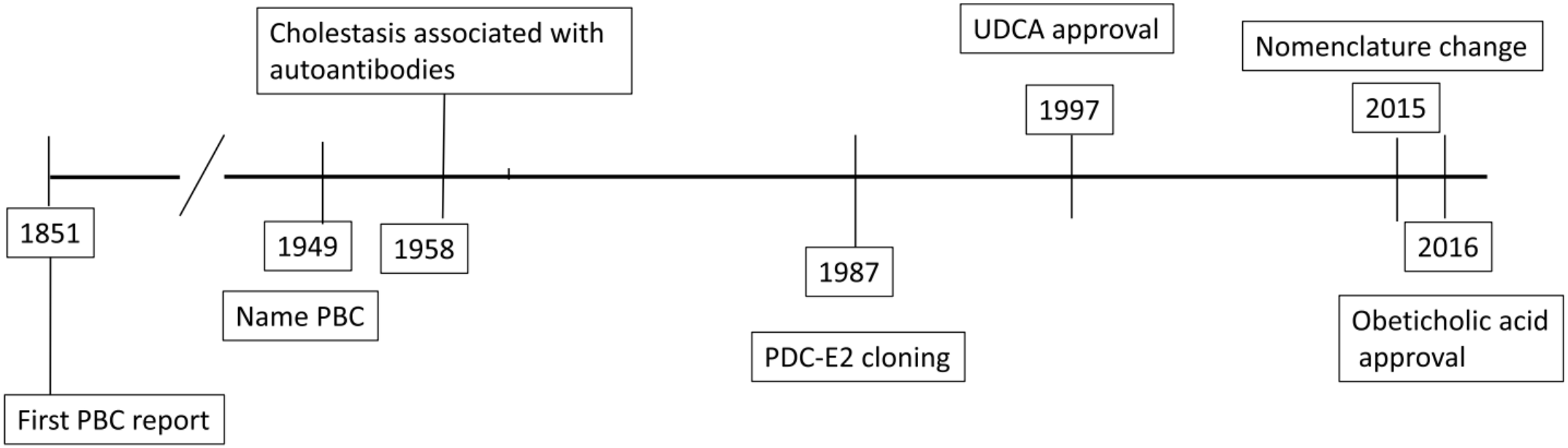
Primary Biliary Cholangitis (PBC): What is it?

- A **rare, chronic, cholestatic disease** characterized by the anti-mitochondrial autoantibody (**AMA**) and **strong female** preponderance
- **Previously known** as Primary Biliary Cirrhosis, but **name changed** in 2015 to reflect that most patients are now diagnosed in a pre-cirrhotic stage



The florid duct lesion – The pathognomonic lesion of PBC, characterized by granulomatous destruction of a bile duct.

A brief history of PBC



Beretta-Piccoli et al, J Autoimm 2019; 105: 102328.

Pathophysiology of PBC: Many Hypotheses

- Genetics: Association with HLA-DQ1, IL-12, IL-12R, and STAT4.
- Autoantibodies: AMA recognizes the E2 subunit of the 2-oxo-acid dehydrogenase complexes, usually pyruvate dehydrogenase, which is expressed on the surface of cholangiocytes.
- Molecular Mimicry: These pyruvate dehydrogenase complexes are highly preserved among species.
- Xenobiotics: There is increased prevalence of PBC in survivors of the Nagasaki atomic bomb and in persons who live near toxic waste sites in New York City.
- Bicarbonate Umbrella Hypothesis: Polymorphisms of the bicarbonate anion exchange protein 2 (AE2) are associated with PBC.

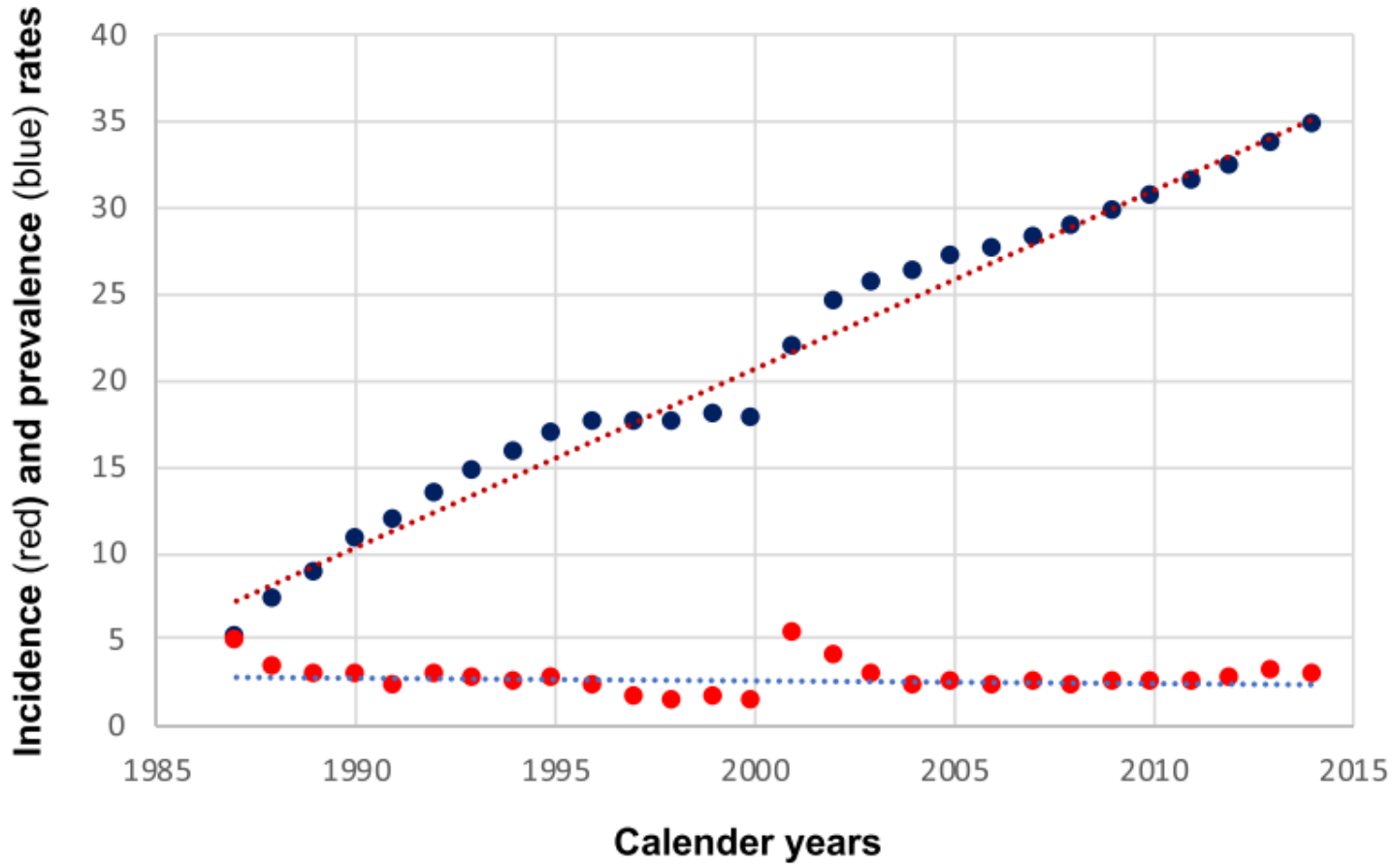
Lleo et al. Semin Liver Dis 2020; 40:34-48.

Many systemic symptoms and complications

	Fatigue	Pruritus (Itchiness)	Osteoporosis	Hyperlipidemia
Prevalence	60-80%	20-66%	9-93%	Nearly all as disease progresses
Severity	Can start early in disease and persist beyond transplant	Interferes with sleep in three-quarters; Severe in one-quarter	Osteoporosis by DEXA in about one third of PBC patients	The clinical implications of hyperlipidemia is unknown
Pathogenesis	**Unknown**			

Epidemiology

Global prevalence of PBC is rising.



Marschall et al. Sci Rep 2019; 9: 11525

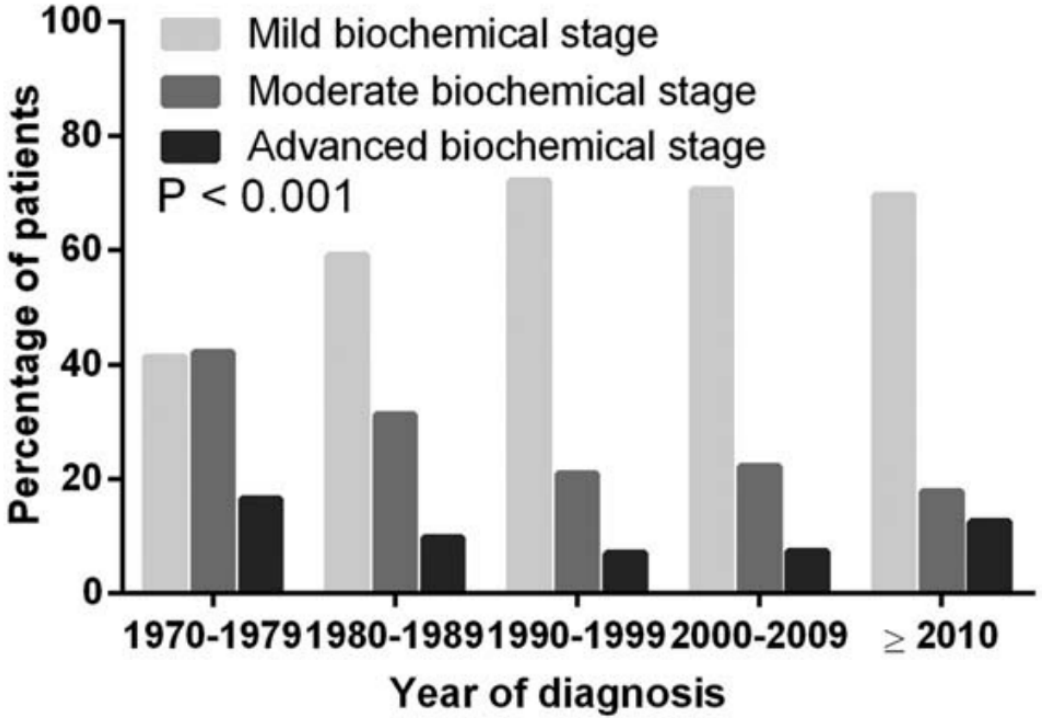
Prevalence depends on patient demographic features.

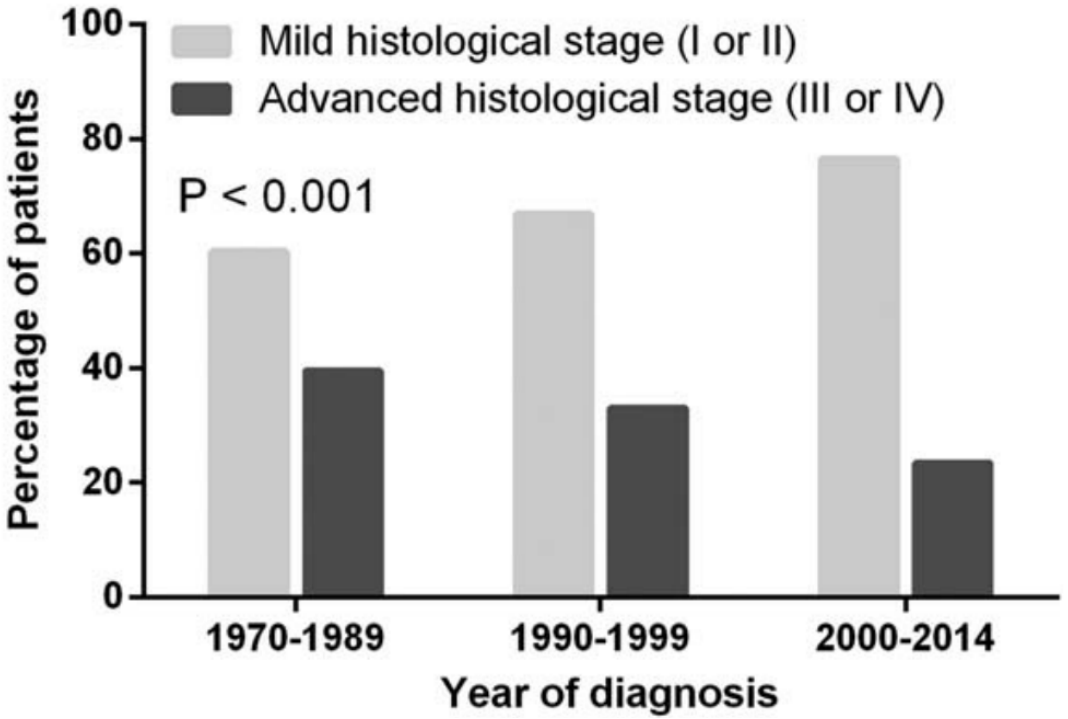
Table 3. Unadjusted and Adjusted PBC Prevalence by Geographic Region, Gender, Age Category, and Race

Description	PBC (n)	Prevalence[a]	95% CI[b]	Adjusted prevalence[a]	Adjusted 95% CI[b]
Overall					
	4241	29.3	28.4–30.2		
Region					
Northeast	882	30.5	27.5–33.6	18.1	16.1–20.3
Midwest	382	33.1	31.0–35.3	20.1	18.5–21.9
South	438	33.3	30.2–36.4	27.8	25.1–30.8
West	2539	27.5	26.4–28.6	20.7	19.5–21.9
Gender					
Women	3493	45.2	43.7–46.7	42.8	40.5–45.2
Men	748	11.1	10.3–11.9	10.7	9.8–11.7
Age category					
≤40	352	5.5	4.9–6.1	4.1	3.7–4.7
41–50	720	28.5	26.4–30.7	20.9	19.1–22.8
51–60	1307	55.3	52.3–58.3	39.1	36.4–42.1
61–70	1108	65.3	61.5–69.2	44.7	41.4–48.3
>70	754	46.1	42.9–49.3	29.7	27.2–32.4
Race					
ASINPI	306	26.0	23.1–28.9	21.9	19.4–24.8
Black/AA	327	26.2	23.4–29.1	19.7	17.6–22.1
White	2766	39.7	38.2–41.2	29.6	28.0–31.2

Lu et al. Clin Gastro Hep 2018; 1:1333-1341.

Overall, patients diagnosed at earlier stage…





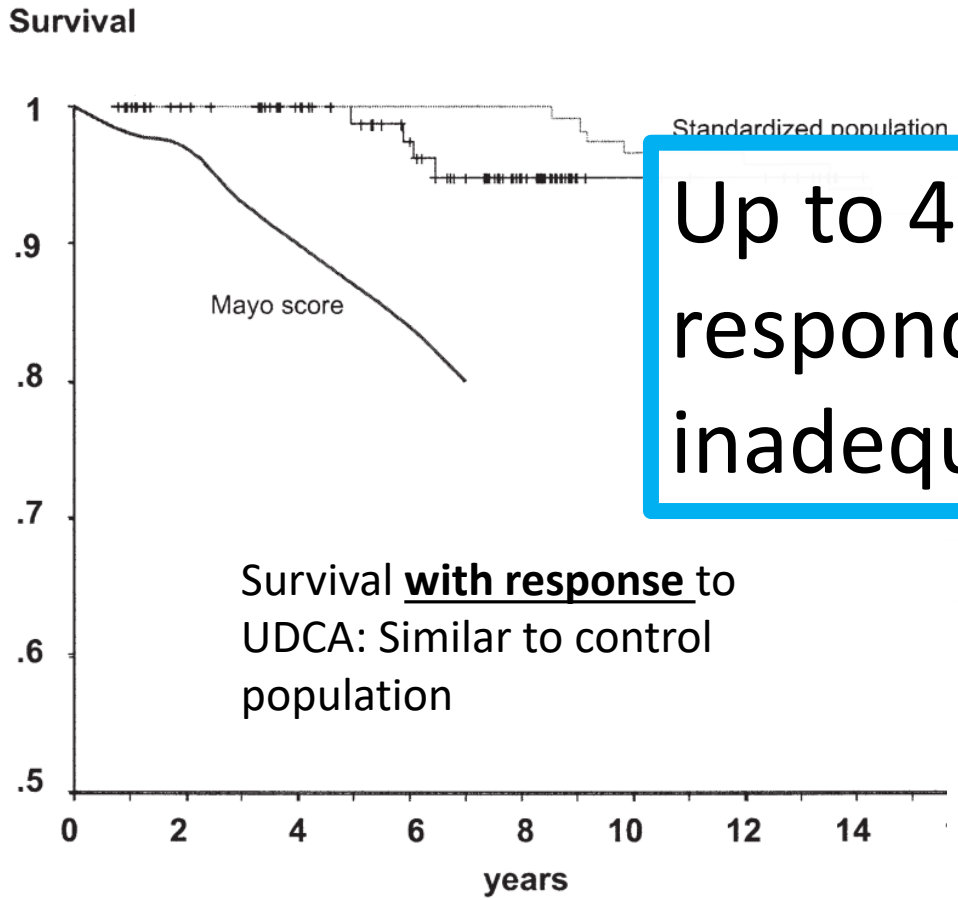
Murillo Perez et al. Hepatology 2018; 67: 1920-30.

But not for all patients.

	Caucasian	Non-Caucasian	*P*
n	462	73	
Activity level			0.00001*
Normal	208	13	
Regular activity but not well	188	36	
Limited activity	47	19	
Bed-bound	0	1	
History of pruritus			0.0001*
None	225	15	
No treatment	129	22	
Medication relieved	45	20	
Medication partly relieved	34	9	
Medication unrelieved	10	3	
History (%)			
Ascites	3.4	9.7	<0.06
Hepatic encephalopathy	1.3	5.6	<0.09
Variceal bleeding	3.4	9.9	<0.07
Severe disease†	4.7	16.7	<0.009

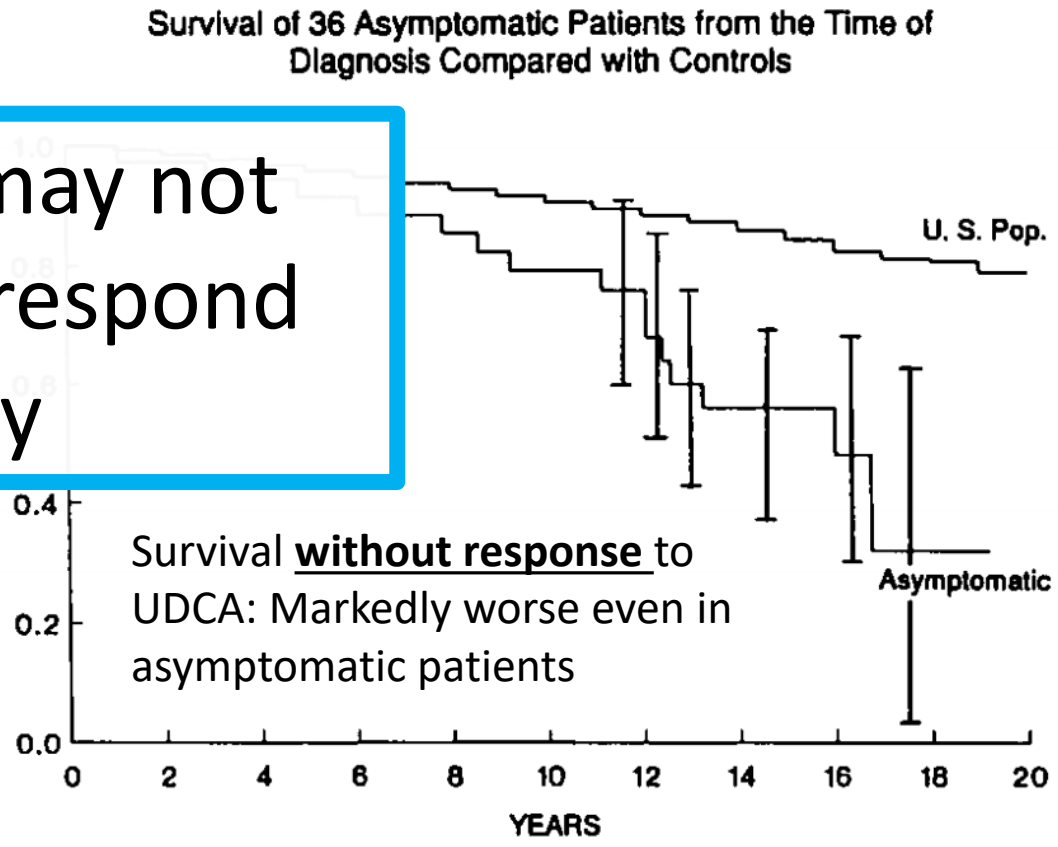
Peters et al. Hepatology 2007; 46: 769-75.

Survival depends on response to UDCA



Survival **with response** to UDCA: Similar to control population

Up to 40% may not respond or respond inadequately

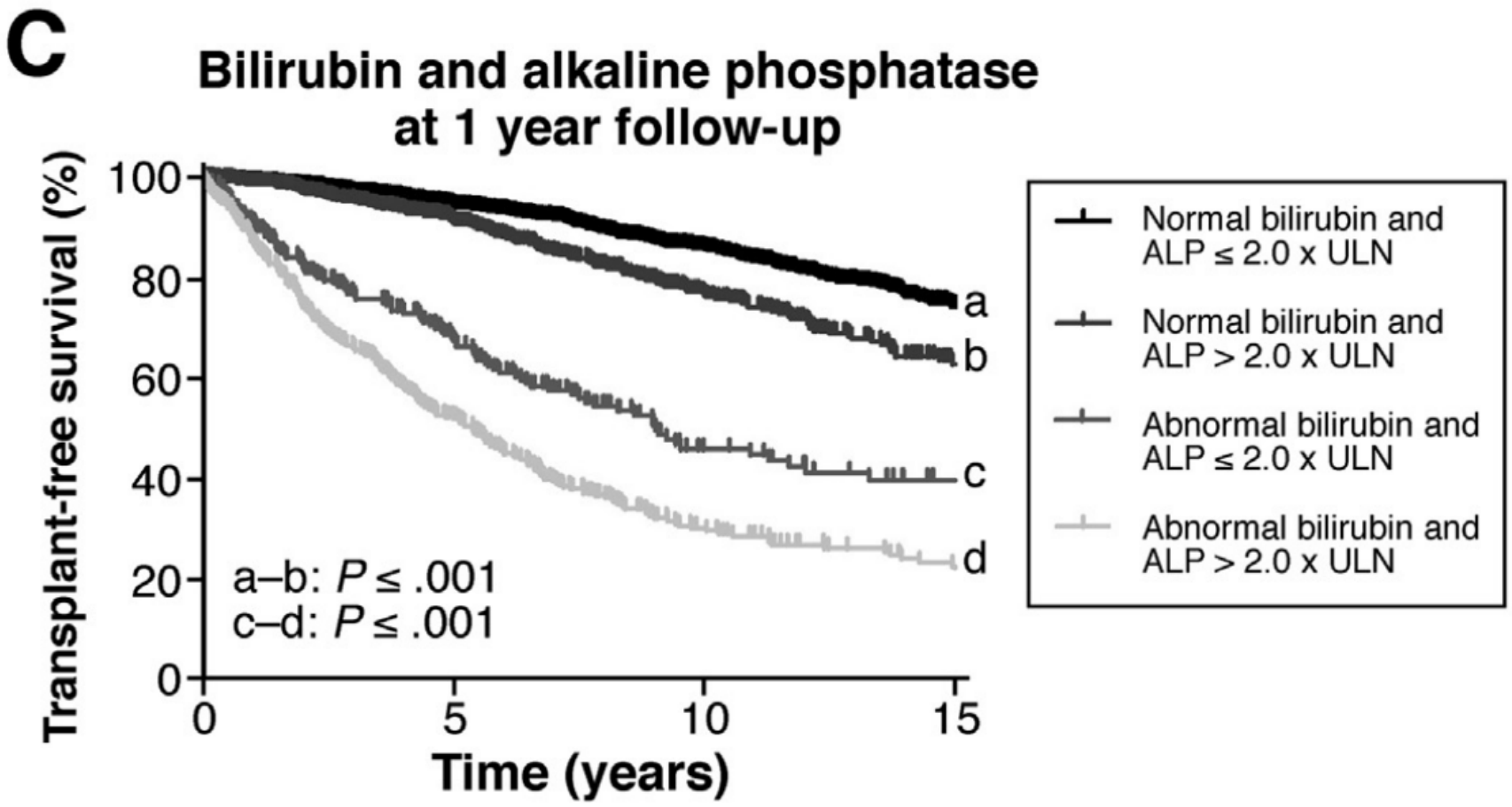


Survival **without response** to UDCA: Markedly worse even in asymptomatic patients

Pares et al. Gastroenterology 2006; 130: 715-20.
Mahl et al. J Hepatol 1994; 20: 707-713.

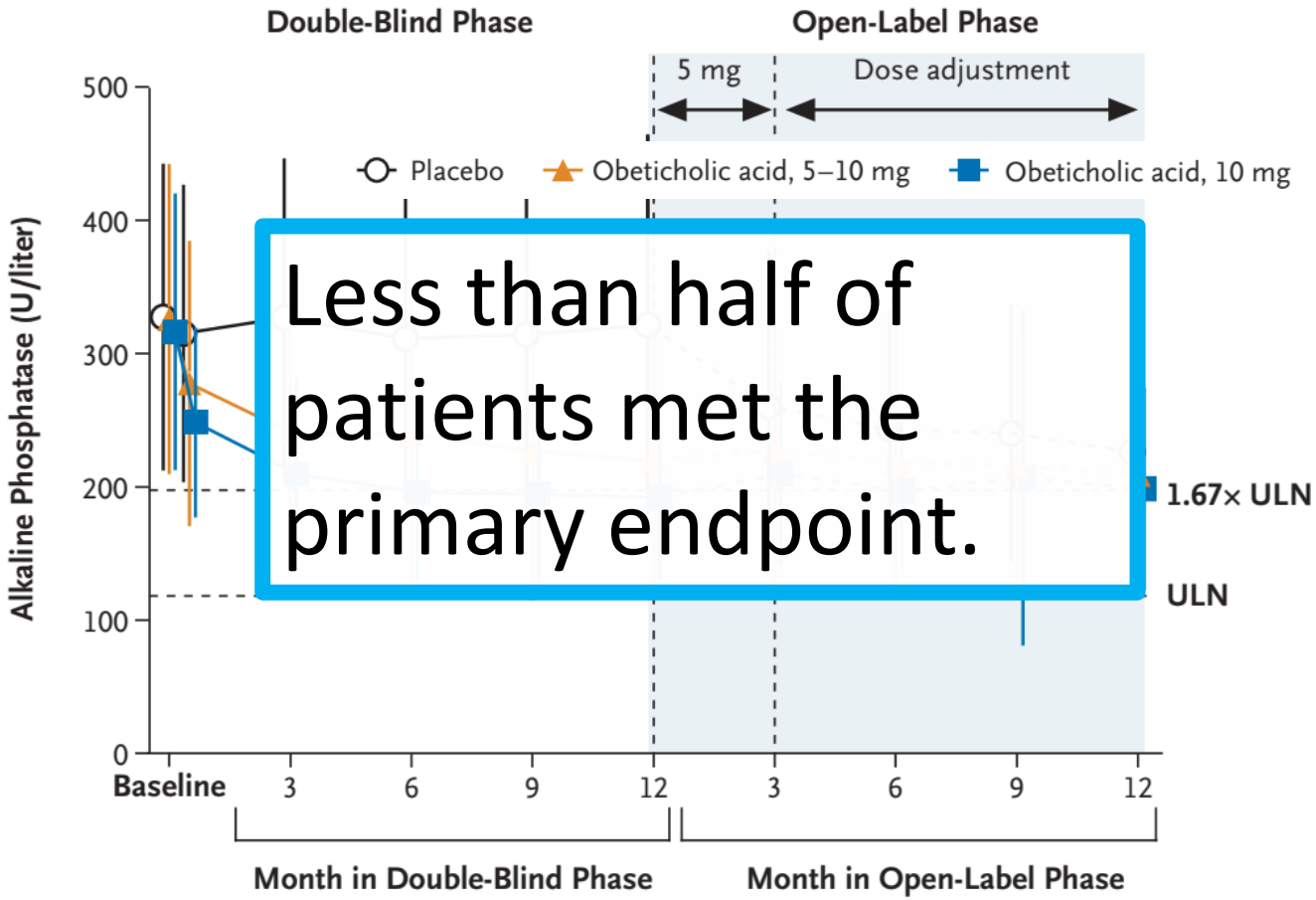
Advances and Needs for Cholestatic Liver Disease

A surrogate endpoint



Lammers et al. Gastroenterology 2014; 147: 1338-49.

Since 2016, one more treatment option: Obeticholic acid

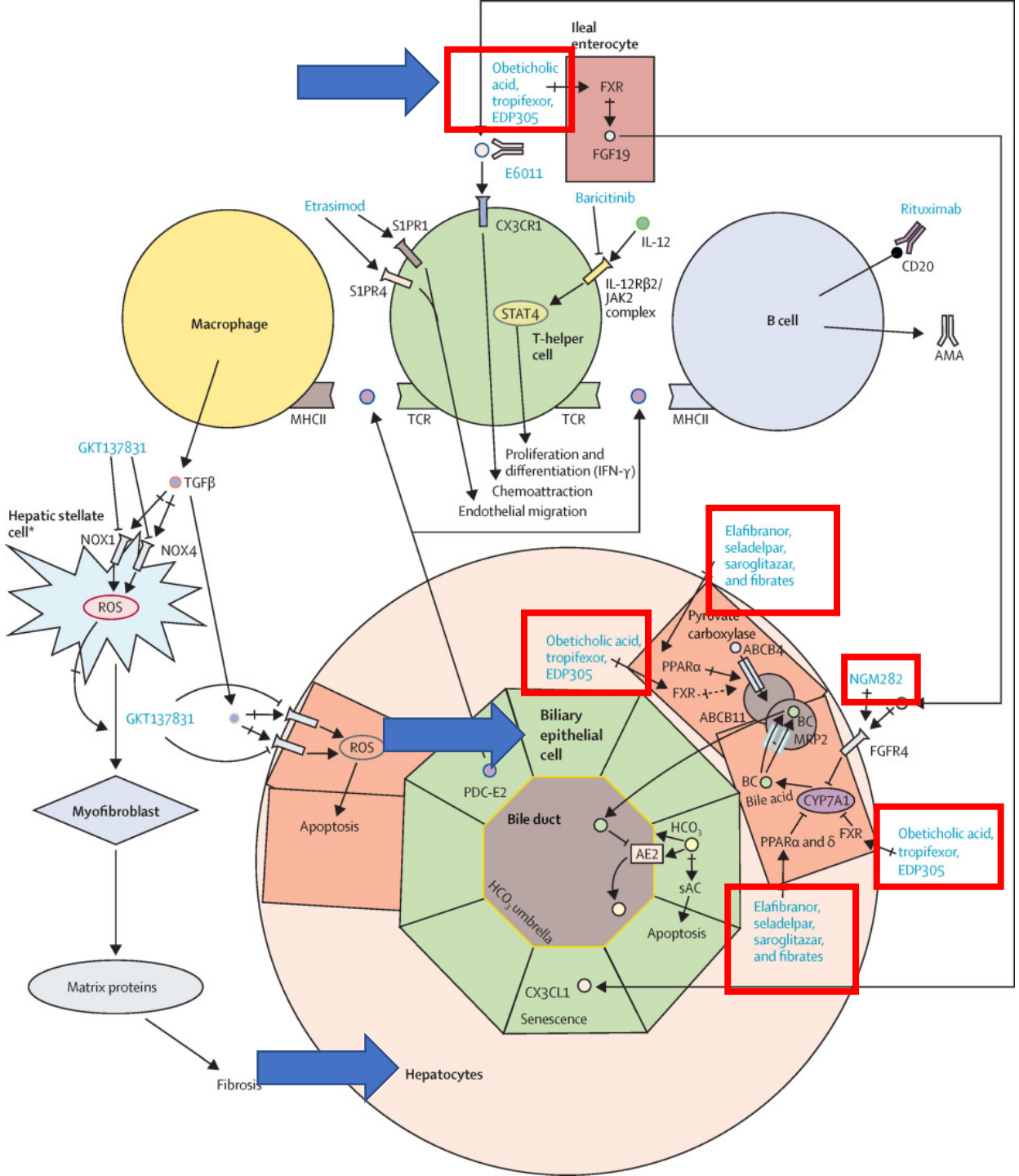


Less than half of patients met the primary endpoint.

Nevens et al. N Engl J Med 2016; 375: 631-43.

The nuclear hormone revolution

- PPAR-agonists (Seladelpar, Fibrates) – Increases expression of ABCB4, inhibits CYP7A1
- FXR-agonists (Obeticholic acid, Tropifexor, Cilofexor) – Inhibits CYP7A1 and increases expression of FGF19 in ileal enterocytes
- FGF-19-analogue (NGM282) – Acts through FGFR4 to inhibit CYP7A1.



Future of treatments for PBC:

Mechanism	Drug	Stage	Preliminary Outcomes
FXR Agonist	Obeticholic acid	Phase 3	Post FDA approval, double-blind, randomized, placebo-controlled study for long term outcomes
	Tropifexor LJN452	Phase 2 Completed	Final phase 2 results are pending, but 4 week interim analysis shows a 72% improvement in GGT Phase 3 trial planned
	Cilofexor GS9674	Phase 2 Ongoing	Preliminary results show 20.5% improvement in alkaline phosphatase with 30.3% reduction in GGT SE: Pruritus
	EDP305	Phase 2 Ongoing	Preliminary results show 45-45% improvement in aslkaline phosphatase at 12 weeks SE: Pruritus, GI symptoms
FGF-19 Analogue	NGM282	Phase 2	Alkaline phosphatase improved by 15% in 45-50% of treatment group at 28 days SE: GI side effects
PPAR agonist	Seladelpar (MBX8025) PPAR-α	Terminated	Phase 2 study terminated early due to 3 cases of elevations in serum transaminases Up to 65% improvement in alkaline phosphatase at 12 weeks Phase 3 study (ENHANCE) terminated early due to unexpected autoimmune hepatitis on biopsy
	Elafibrinor PPAR-α/δ	Phase 3 Planned	Significant decreases in alkaline phosphatase (41-48%) and GGT levels, serum lipids at 12 weeks Phase 3 trial planned
	Bezafibrate pan-PPAR	Phase 3 Ongoing	67% of patients showed normalization of alkaline phosphatase at 24 months; Also improves pruritus SE: Myalgias, increased creatinine. Phase 3 trials ongoing
NOX-1/4	Setanaxib GKT831	Phase 2	Preliminary results show an improvement in alkaline phosphatase and GGT over 24 weeks
S1PR Agonist	Etrasimod	Phase 2	Phase 2 proof of concept study is ongoing
JAK-1/2	Baricitninib	Phase 2	Phase 2 proof of concept study is ongoing
	Probiotics	Phase 2	Phase 2 proof of concept study is planned

Advances and Needs for Patient Reported Outcomes

Pruritus

- Etiology: Unknown. May be related to bile acids, lysophophatidic acid, endogenous opioids. Not related to histamine.
- A few trials are underway

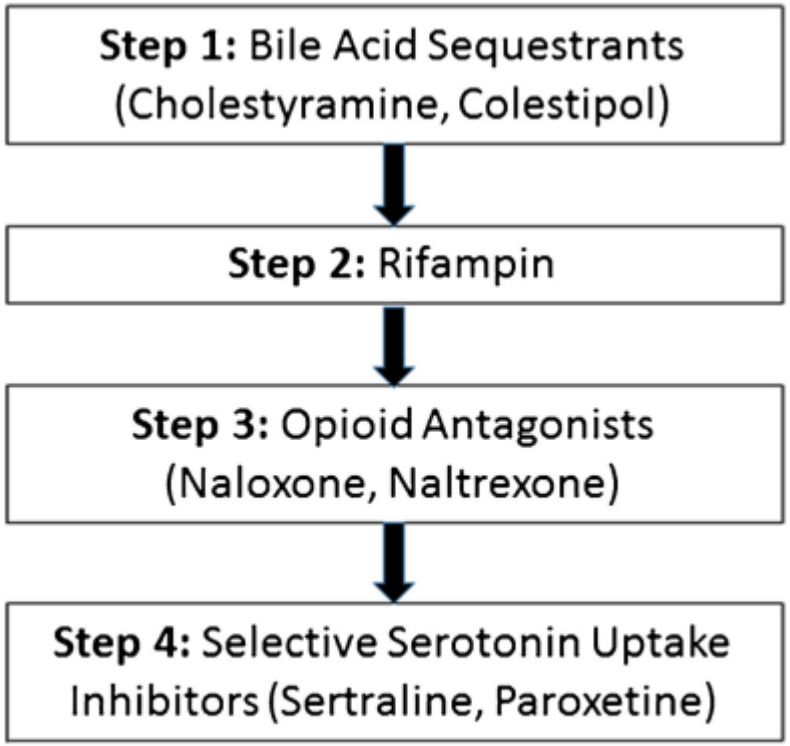


Fig. 1 Suggested treatment algorithm per guidelines from the American Association for the Study of Liver Disease and the European Association for the Study of the Liver

Pedersen et al. Curr Hep Rep 2018; 17: 143-151

The future of cholestatic pruritus:

Mechanism	Drug	State	Preliminary Outcomes
Ileal Apical Bile Acid Transporter Inhibitor	Linerixibat	Phase 3	Phase 2b study recently completed, with significant improvement in pruritus, seen with patients with moderate to severe pruritus Phase 3 study planning is underway
	Maralixibat	Terminated	Failed to show a difference between treated and placebo-controlled patients
Kappa Opioid Receptor Agonist	Difelikefalin CR845	Phase 2 Ongoing	After conditional acceptance by the FDA for treatment of uremic pruritus

Hyperlipidemia

- Commonly thought to be related to Lipoprotein-X, which is anti-atherosclerotic, but it is not always just Lipoprotein-X.

TABLE 1. Characteristics and antioxidation index in six patients with primary biliary cirrhosis

Patient No.	Age	Sex	Scheuer Stage	Total Cholesterol	LDL Cholesterol	Lipoprotein-X Content of LDL	Plasma Bilirubin	Antioxidation Index
	years			*mmol/l*	*mmol/l*	%	*μmol/l*	
1	47	Female	III	34.1	31.7	90	222.3	5+
2	41	Female	III	31.7	28.4	88	201.8	5+
3	34	Female	II	29.3	27.1	65	78.7	4+
4	54	Female	II	10.1	7.5	ND	17.1	1+
5	41	Male	I	13.2	12.0	Trace	59.9	2+
6	43	Male	II	10.8	7.6	ND	20.5	1+

ND, not detectable. The antioxidation index was arbitrarily determined by the ability of a patient's LDL to inhibit the mobility of control LDL on agarose gel electrophoresis after 4 h of copper exposure (5+ = 100% inhibition).

Chang et al. J Lipid Res 2004; 45: 2116-22.

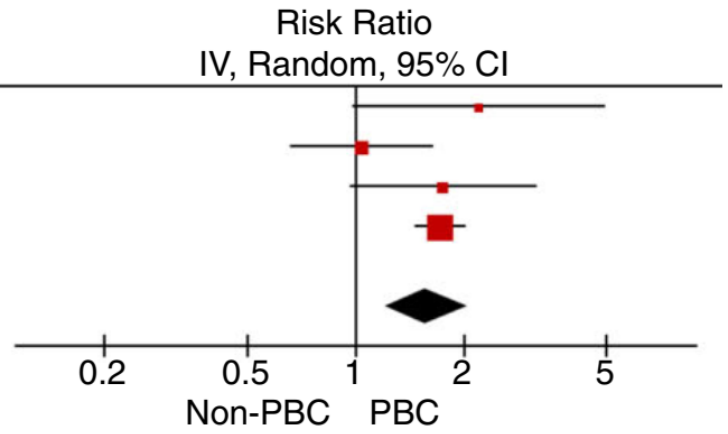
Cardiovascular risk

- Initial studies showed minimal cardiovascular risk, but this was in patients with high rates of decompensation (40%+) and already **advanced liver disease**.
- Implication of this for patients with early disease is unknown.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
Longo et al.	0.78845736	0.41	9.4%	2.20 [0.98, 4.91]	2002
Solaymani-Dodaran et al.	0.03922071	0.23	22.7%	1.04 [0.66, 1.63]	2008
Doycheva et al.	0.55961579	0.3	15.6%	1.75 [0.97, 3.15]	2011
Zoller et al.	0.54232429	0.08	52.3%	1.72 [1.47, 2.01]	2012
Total (95% CI)			100.0%	1.57 [1.21, 2.06]	

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 4.83$, df = 3 (P = 0.18); $I^2 = 38\%$

Test for overall effect: Z = 3.33 (P = 0.0009)



Ungprasert et al. Hepatol Res 2015; 45: 1055-61.

Fatigue

- Treatment: Modafinil, ondansetron, and fluoxetine have been studied with negative RCTs.
- One intervention trial underway: Mindfulness

Jones et al. Gut 2006 55: 536-41.
Stanca et al. AM J Gastroenterol 2005; 100: 1104-1109.
Talwalker et al. Dig Dis Sci 2006; 51: 1985-91.
Silveira et al. Am J Ther 2017; 24: e167-e176.
Theal et al. Hepatology 2005; 41: 1305-12.

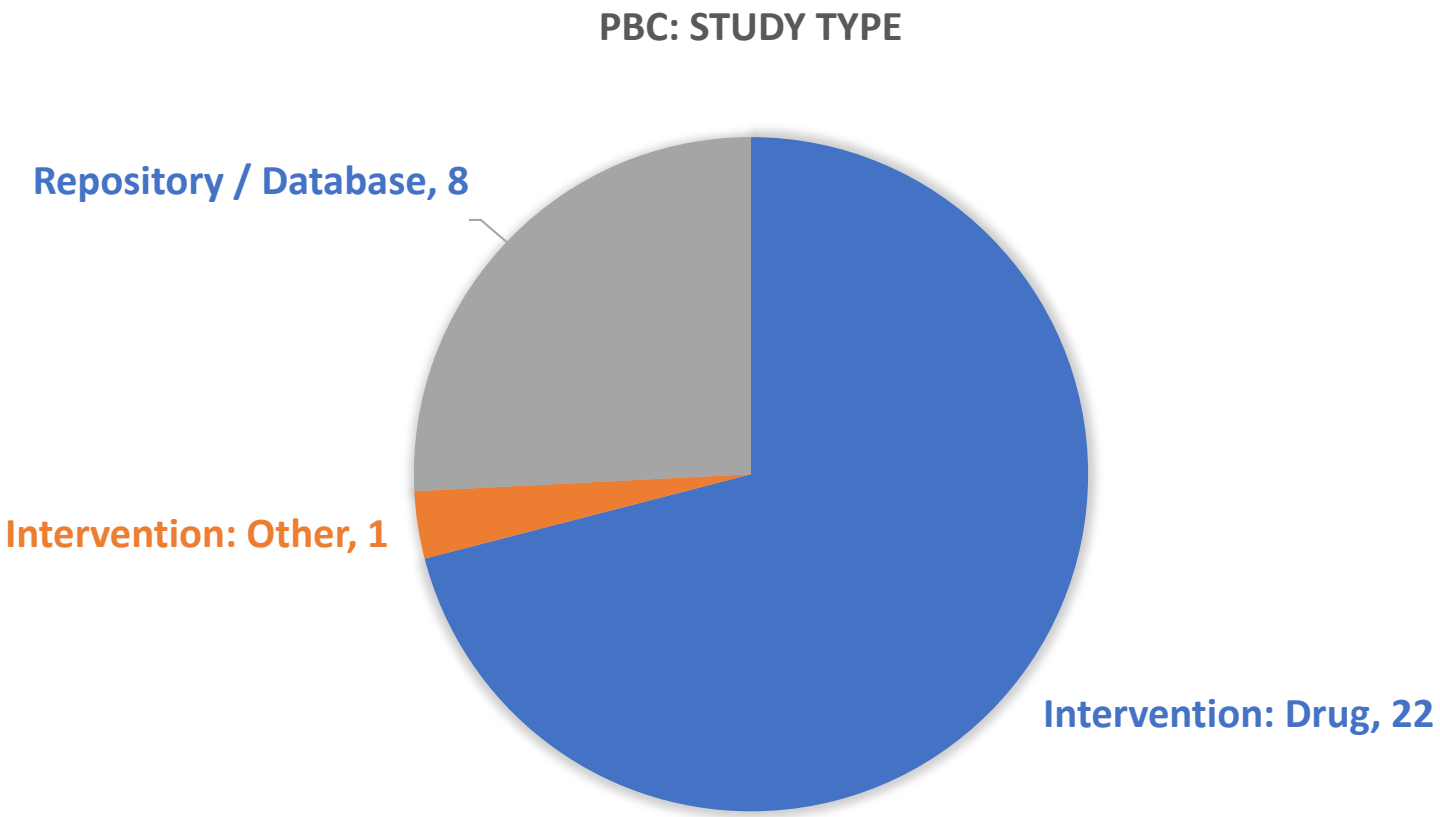
Metabolic Bone Disease

- Can progress even with repletion of vitamin D.
- Treatment: The same as a patient without PBC.
  - Replete vitamin D
  - Bisphosphonates
- Trials: None

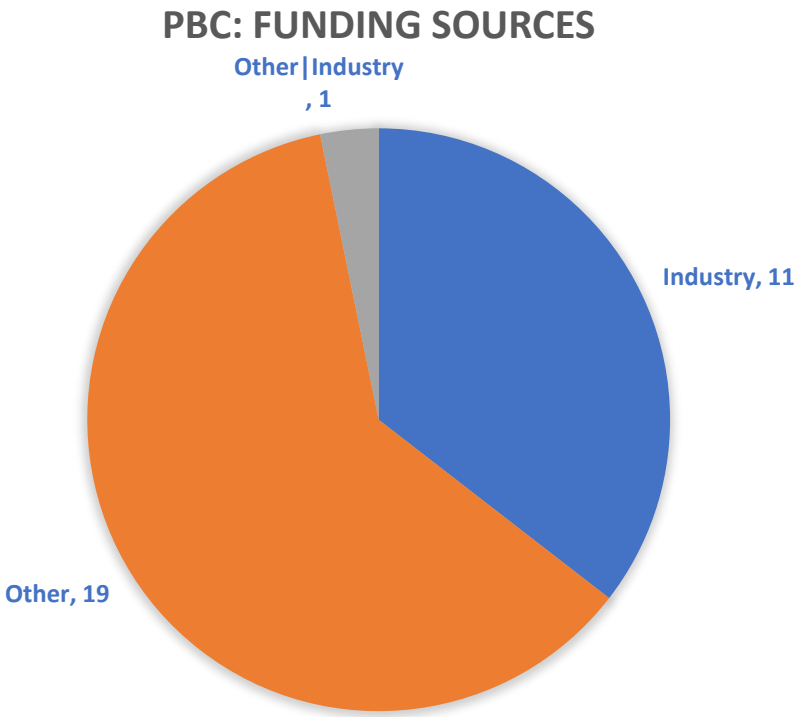
Menon et al. J Hepatol 2001; 35: 316-23.
Guanabens et al. Hepatology 2013; 58: 2070-8.

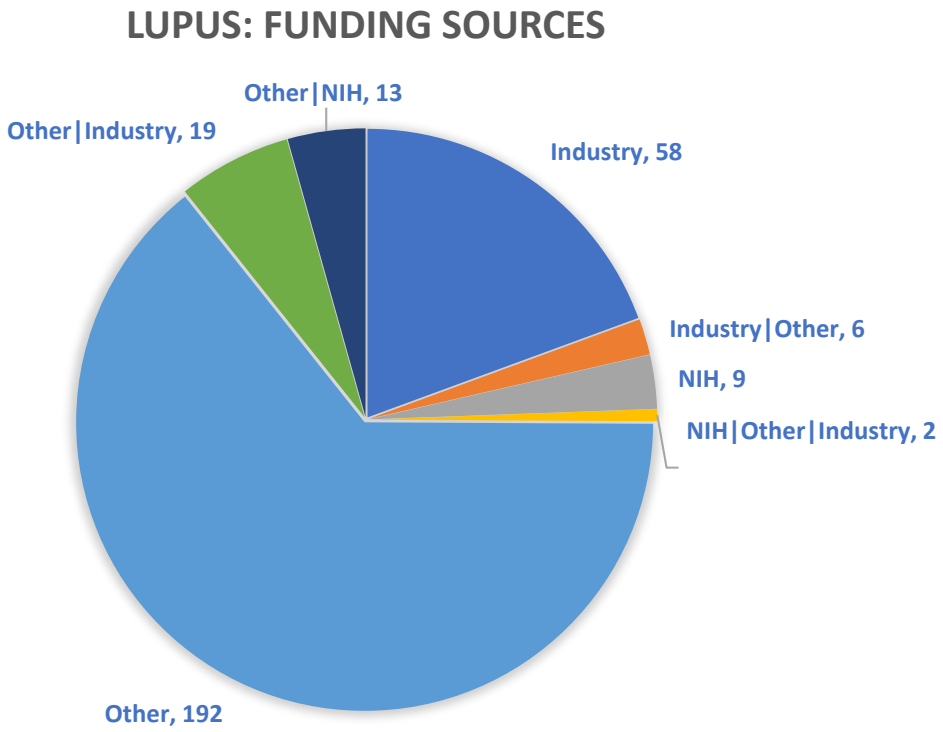
Future Directions

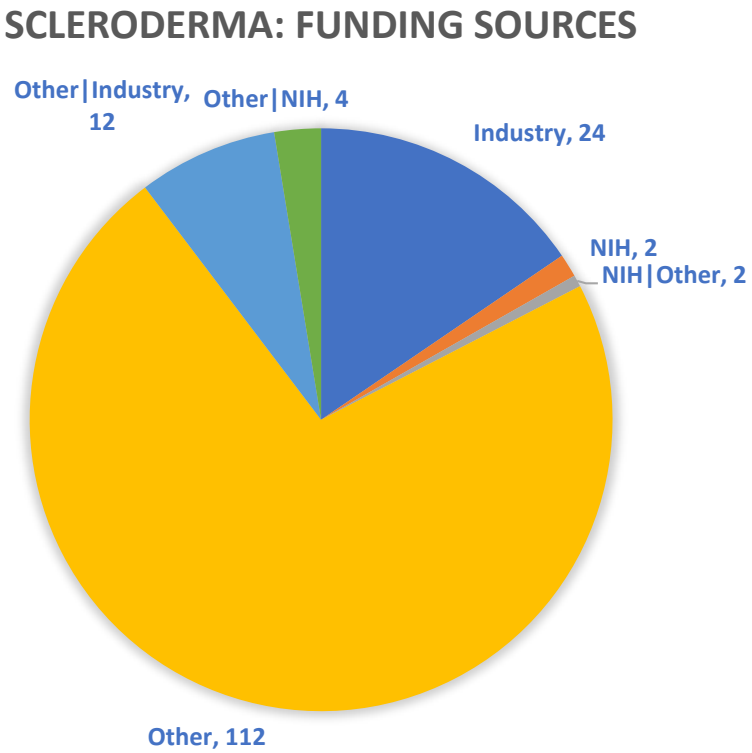
Current studies in PBC (clinicaltrials.gov)



Clinical Trial Funding: Where are we?







Prevalence: 29 per 100,000
NIH Studies: 0

Clinicaltrials.gov

Basic Sciences Research: Where are we?

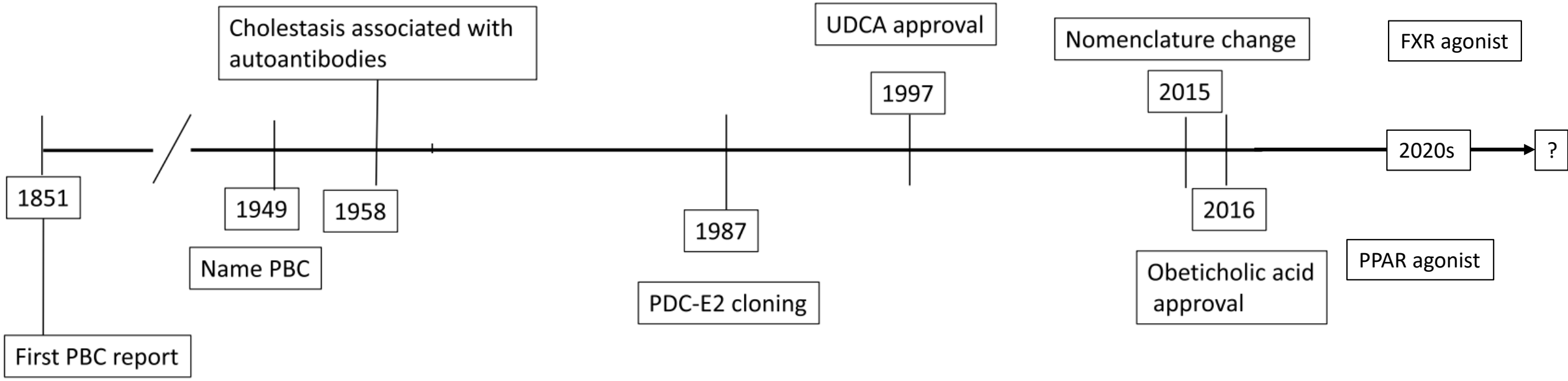
Area of Study	Title	Focus
Bile Acid Metabolism and Mechanisms of Cholestasis	Molecular Mechanisms of Cholestatic Fibrogenesis	EXH2
	Molecular Biology of Bile Acid Synthesis	FXR, Tgr5
	Ileal Bile Acid Transporter Metabolism and Regulation	ASBT and OST
	Cholestasis and the Unfolded Protein Response	FXR/SHP
	Ca2+ waves in hepatocytes: Mechanisms and effects	InsP3R-2
	Molecular regulation of cholestasis in cholangiocytes	InsP3R-2
	Role and regulation of beta-catenin in cholestatic liver disease	FXR and Beta-catenin
	Forkhead Box A3 and Bile Acid Metabolism	FOXA3
	Bile Acid and Sphingosine-1-phosphate Receptor-mediated Signaling in Cholestasis	S1PR2, SphK2, CBA
	LncRNA H19 in Cholestatic Liver Diseases	lncRNA H19
Cholangiocyte Regeneration and Fibrogenesis	Regulation of biliary growth and fibrosis by melatonin	Melatonin
	The Paracrine Regulation of Mast Cells During Biliary/Cholangiocyte Repair and Damage	HR and HDC
	Neuroendocrine Regulation of Biliary Growth and Fibrosis	Fibrosis
	Building a functional biliary system from hepatocytes	NOTCH and TGFbeta
	Pathophysiology of Biliary Disease	EST1
	Elucidating the Critical Functions of Yap1 in the Embryonic Development and Regeneration of the Biliary System	Yap1
	Beta-catenin-driven hepatobiliary reprogramming as a therapeutic modality for cholangiopathies	Beta-catenein
Microbiome	Coordination of gut-liver bile acid signaling by FXR	Src and FXR
	Cholestatic Liver Injury	MerTK
Immunopathogenesis	Mechanistically based therapeutic strategies in murine primary biliary cholangitis	IFN and JAK/STAT
	Pathogenesis of Primary Biliary Cholangitis	Multi-omics

NIDDK Funded Grants

What needs to be done?

- Determining the pathogenesis of PBC
- Determining the pathogenesis of the systemic manifestations of PBC
- Finding new targets for therapies
- Turning targets into treatments

To the future



Beretta-Piccoli et al, J Autoimm 2019; 105: 102328.

End