



Autoimmune Liver Disease Updates

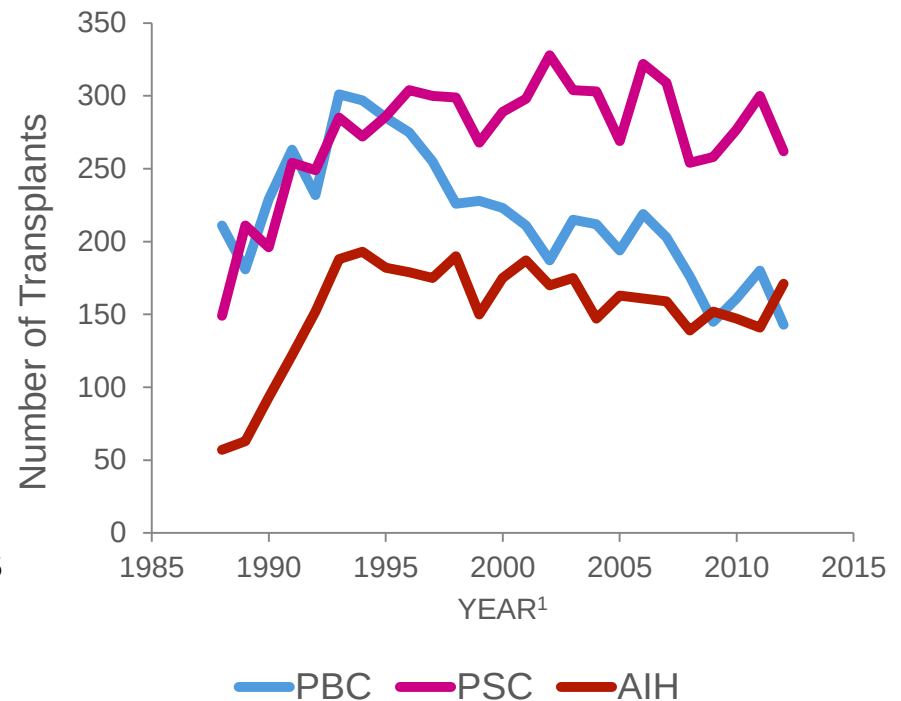
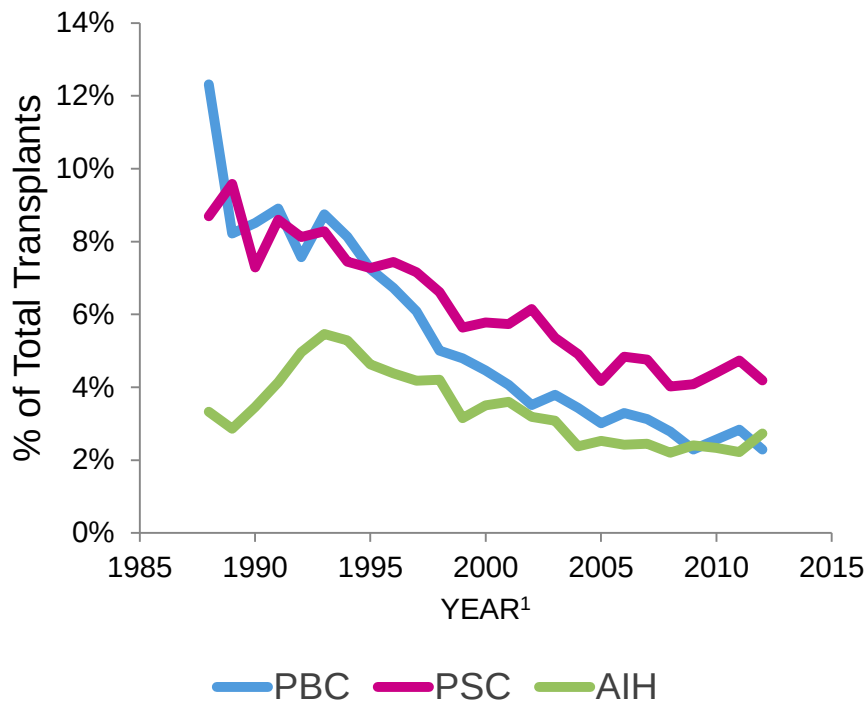
Christopher L. Bowlus, MD

Professor and Chief
University of California Davis
Davis, CA

Why you should care

- Autoimmune liver diseases account for ~10% of all liver transplantations
- New models to predict prognosis in PBC
- New treatments – approved and in trials
 - May have implications for more common liver diseases

Trends in Liver Transplants for Autoimmune Liver Diseases



1. Organ Procurement and Transplantation Network, U.S. Department of Health & Human Services

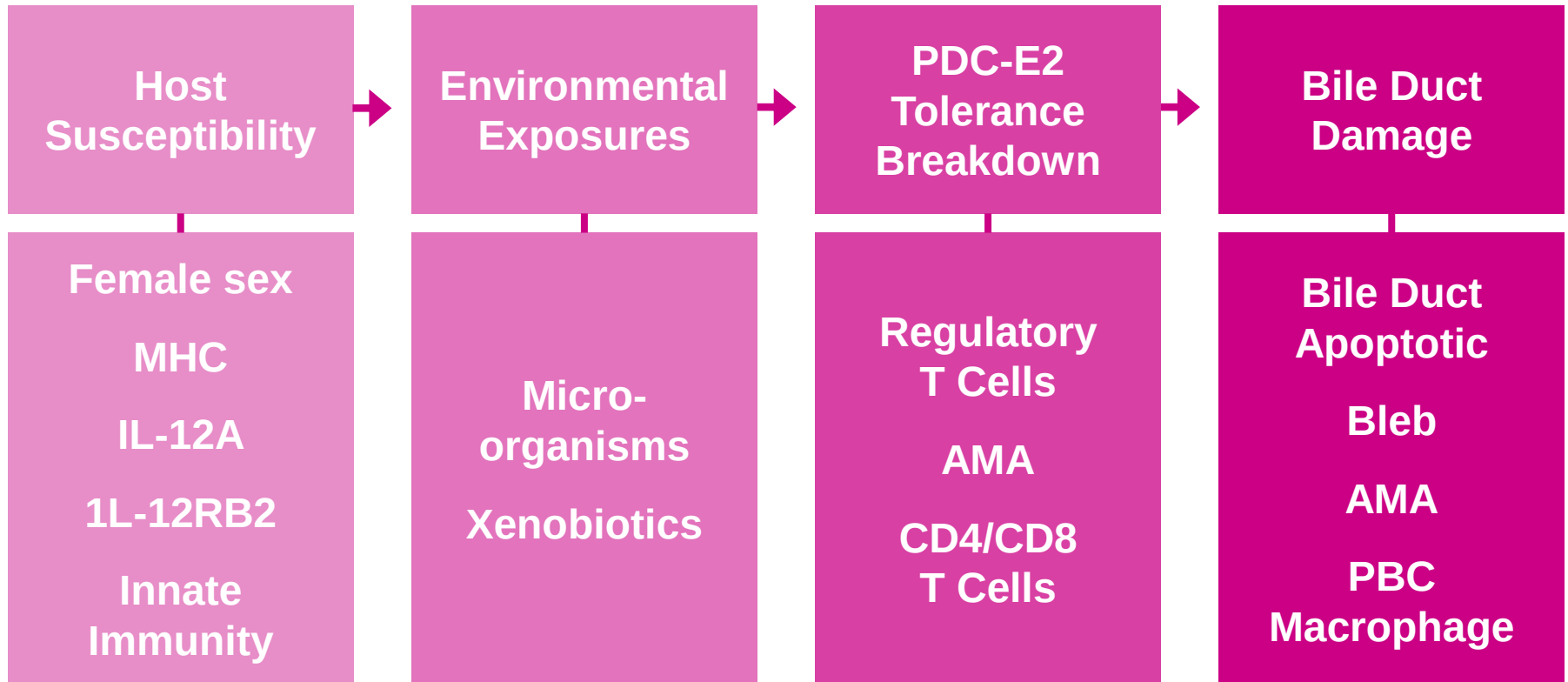
<http://optn.transplant.hrsa.gov/latestData/rptData.asp>. Accessed April 2, 2013.

2. 2014 U.S. Organ and Tissue Transplant Cost Estimates and Discussion, Milliman Research Report.

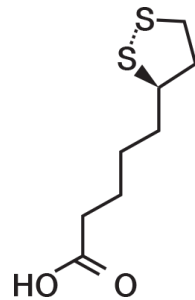
What's New?

- Primary Biliary Cholangitis
 - Name change
 - Pathogenesis
 - Prognostic models
 - Obeticholic Acid (FDA-approved)
 - Clinical trials
- Primary Sclerosing Cholangitis
 - Natural history
 - MR Elastography and Transient Elastography
 - Clinical trials
- Autoimmune Hepatitis
 - Not much

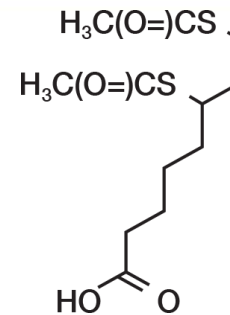
Pathogenic Model of PBC



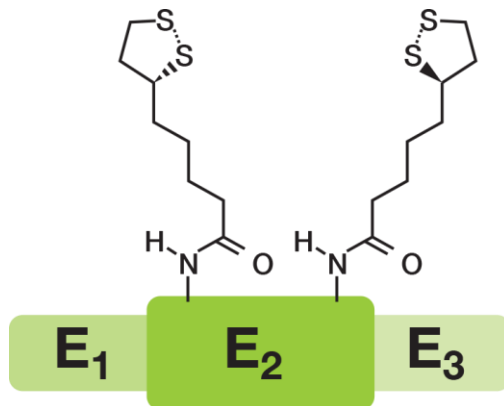
PDC-E2, Lipoic Acid, and Xenobiotics



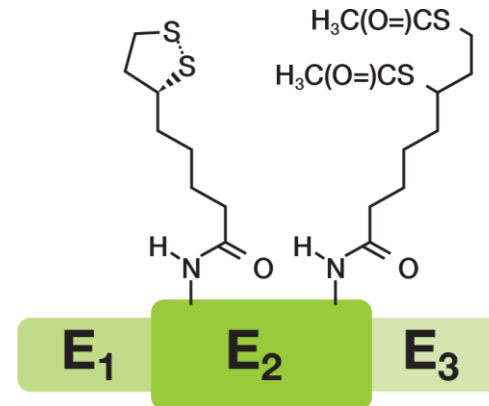
Lipoic acid



6,8-bis(acetylthiolate) of PDC-E2

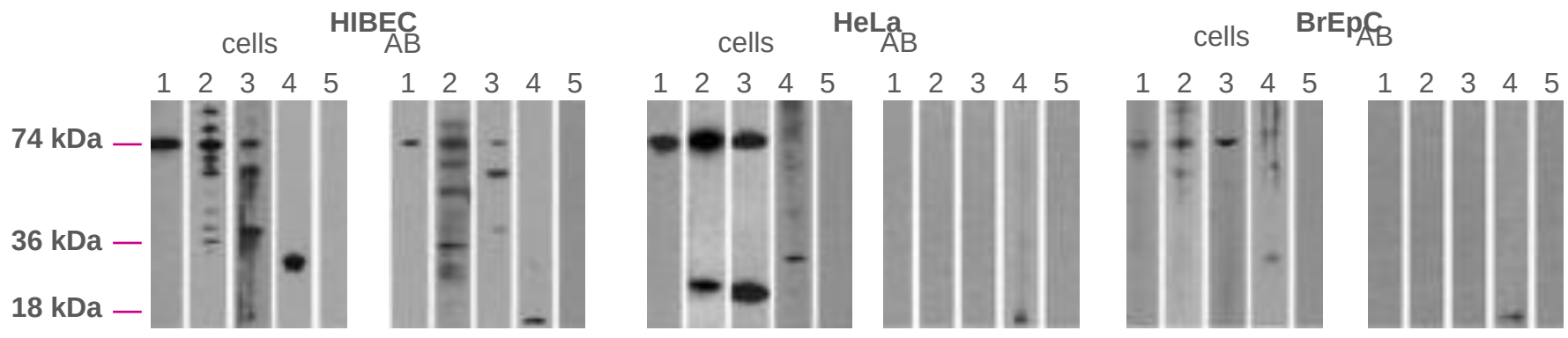
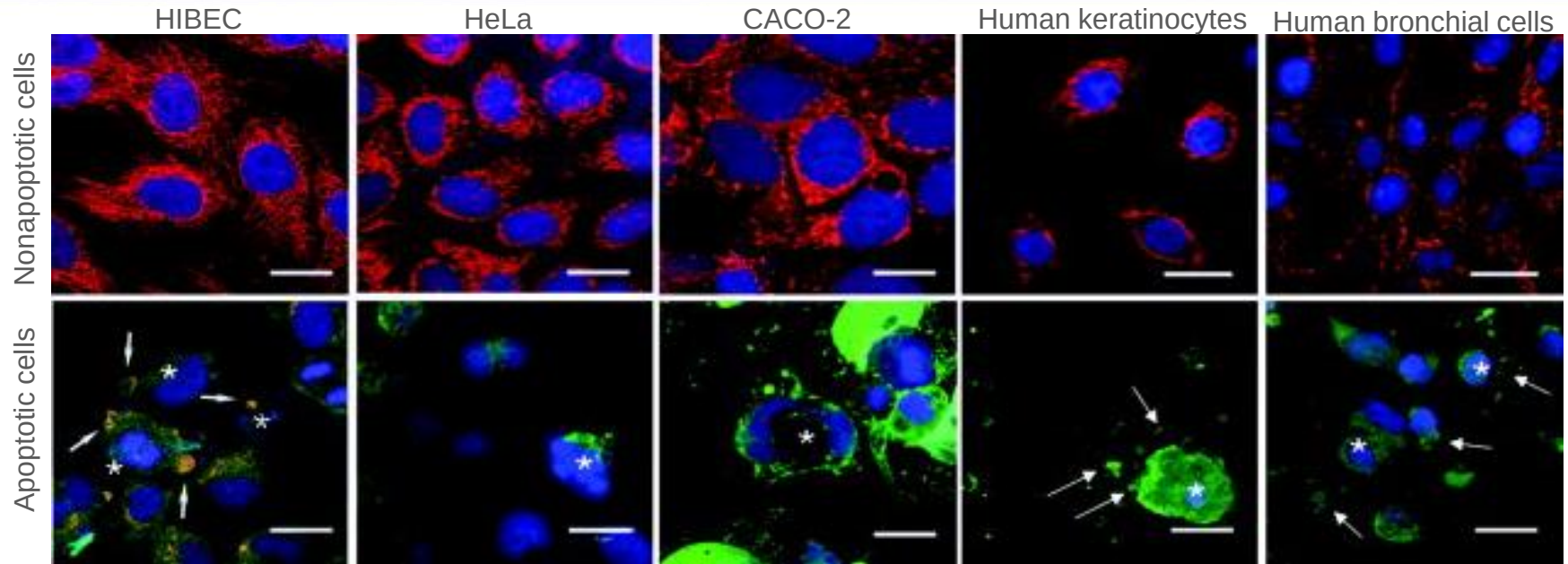


Lipoylated PDC-E2



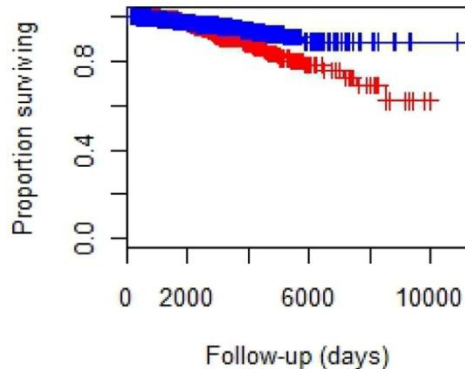
Hypothetical
6,8-bis(acetylthiolate) of PDC-E2

Specificity of the Biliary Apotope

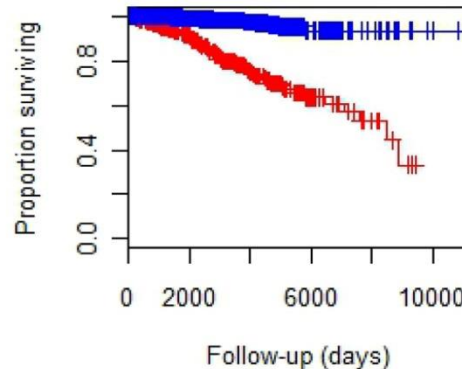


Defining Response to UDCA

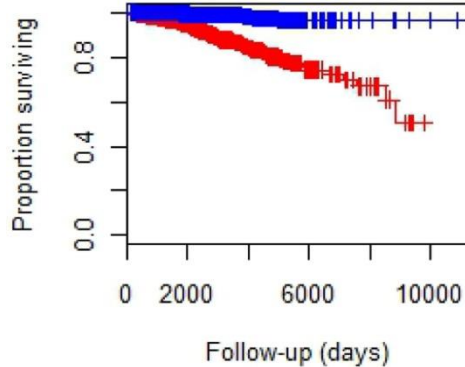
A. Barcelona criteria



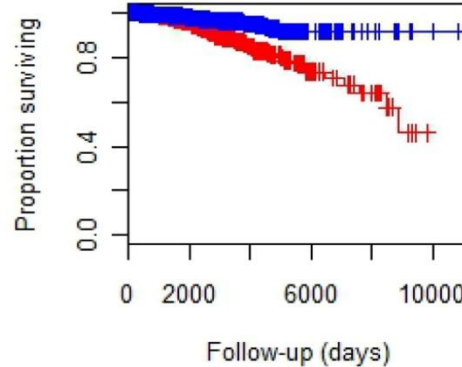
B. Paris I criteria



C. Paris II criteria



D. Toronto criterion



Barcelona

- Decrease in ALP level > 40% of baseline level or a normal level

Paris I (all criteria met)

- ALP level $\leq 3 \times \text{ULN}$
- AST level $\leq 2 \times \text{ULN}$
- Normal bilirubin level

Paris II (all criteria met)

- ALP level $\leq 1.5 \times \text{ULN}$
- AST level $\leq 1.5 \times \text{ULN}$
- Normal bilirubin level

Toronto

- ALP level $< 1.67 \times \text{ULN}$

PBC Subgroups

Younger age of onset

- Young women less likely to respond to UDCA
-

AMA-negative

- No difference in survival or response to UDCA
-

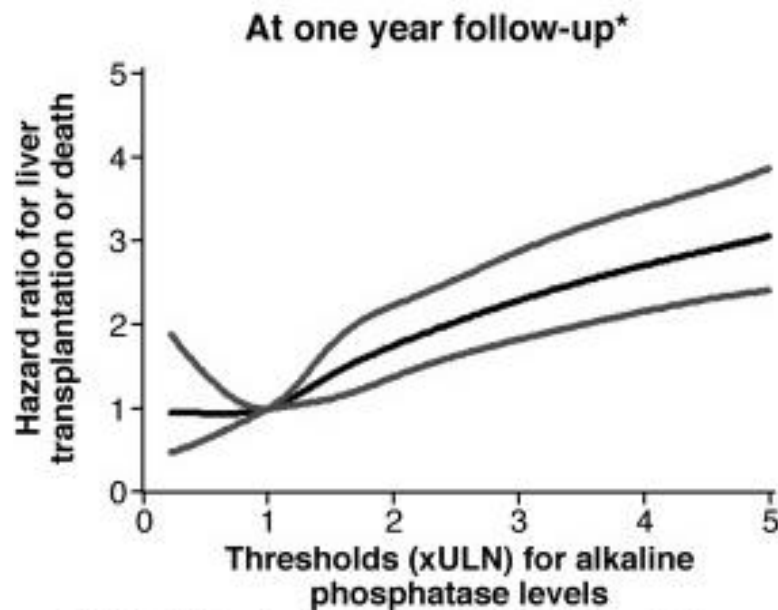
Male gender

- Less likely to respond to UDCA regardless of age

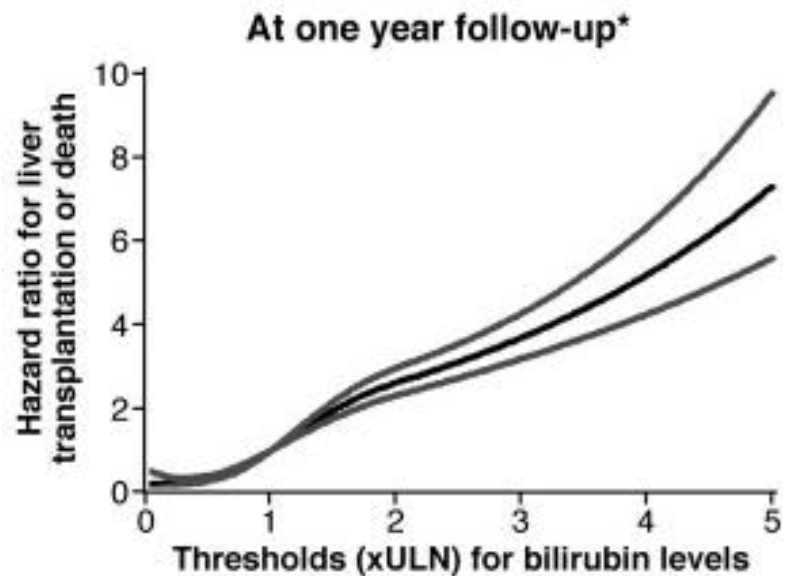
Disease stage (early versus late)

- Early stage more likely to respond to UDCA

PBC Surrogate Markers

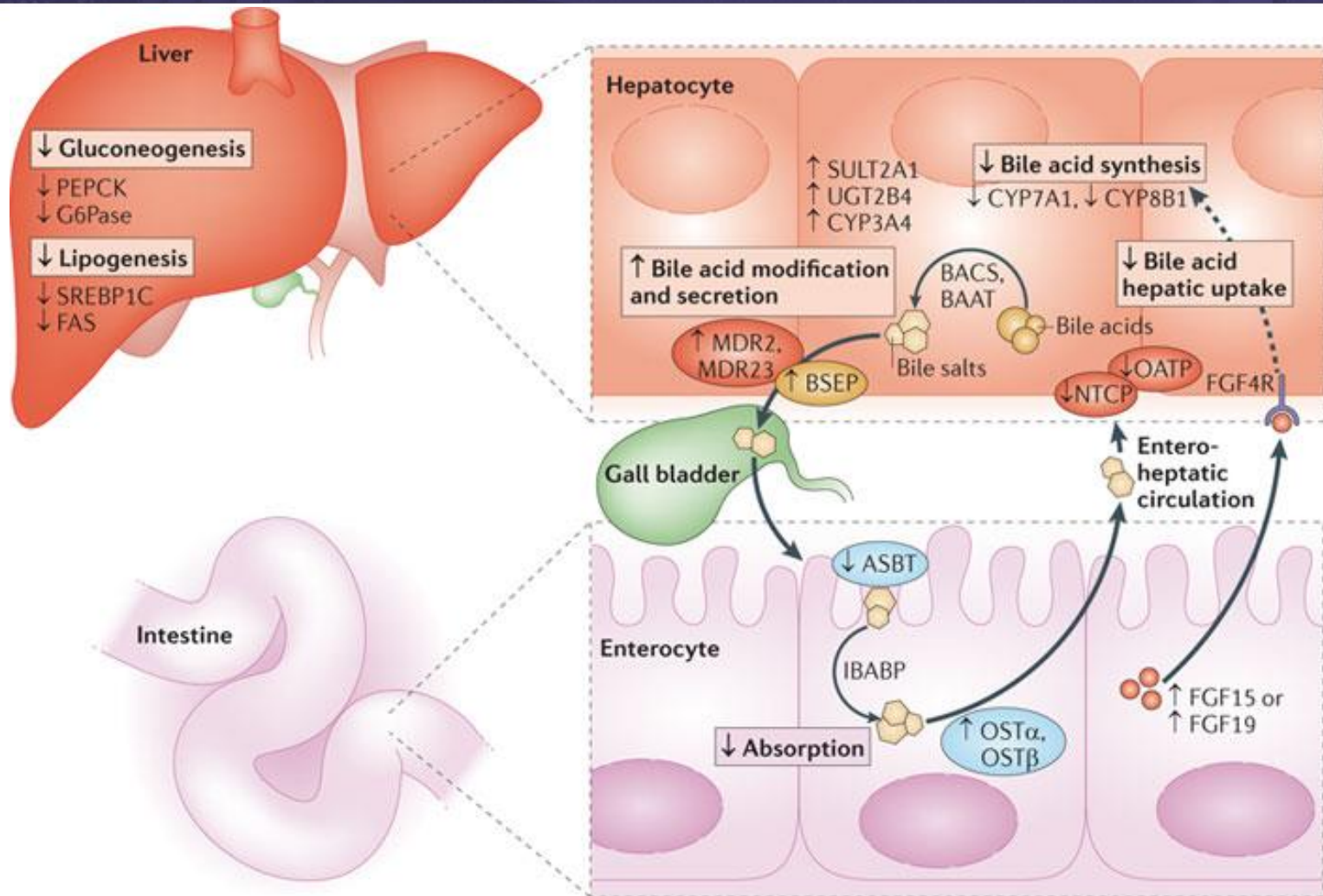


*3710/4635 patients were included for this analysis

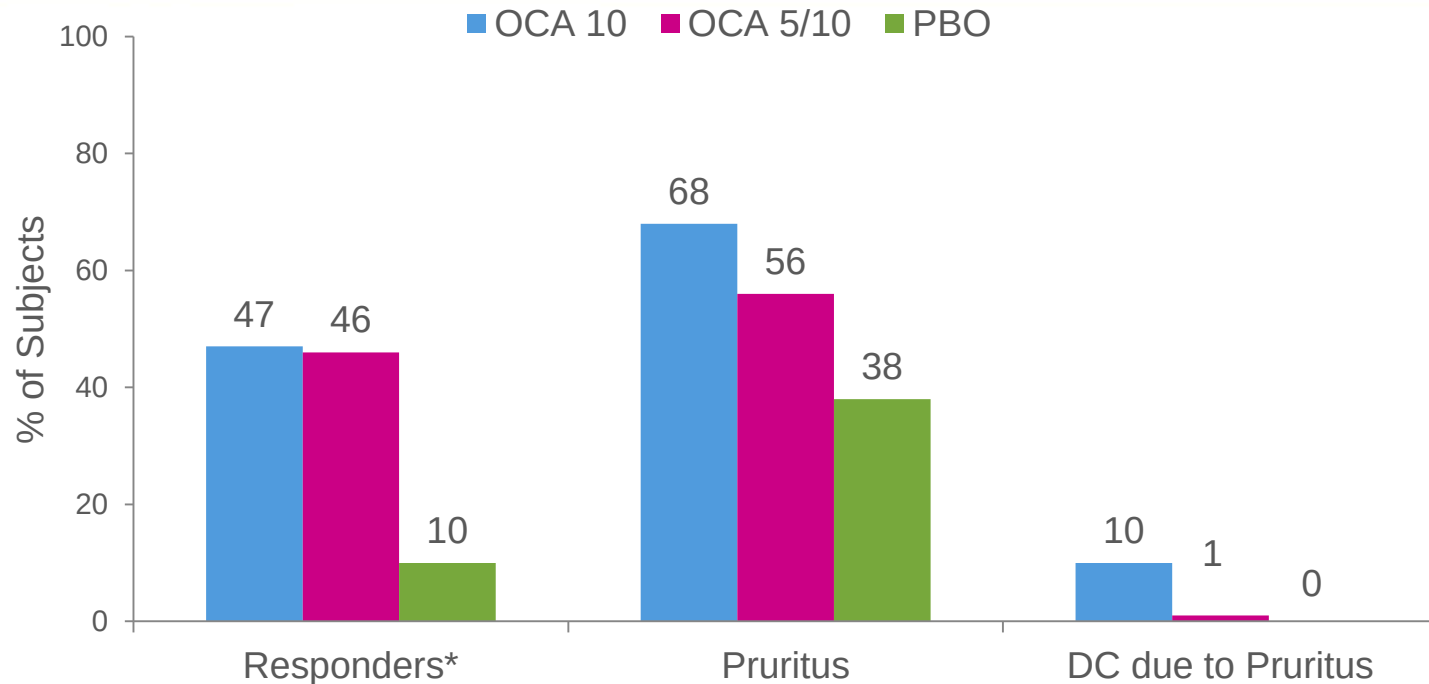


*3681/4635 patients were included for this analysis

Bile Acids – More than Just Detergents

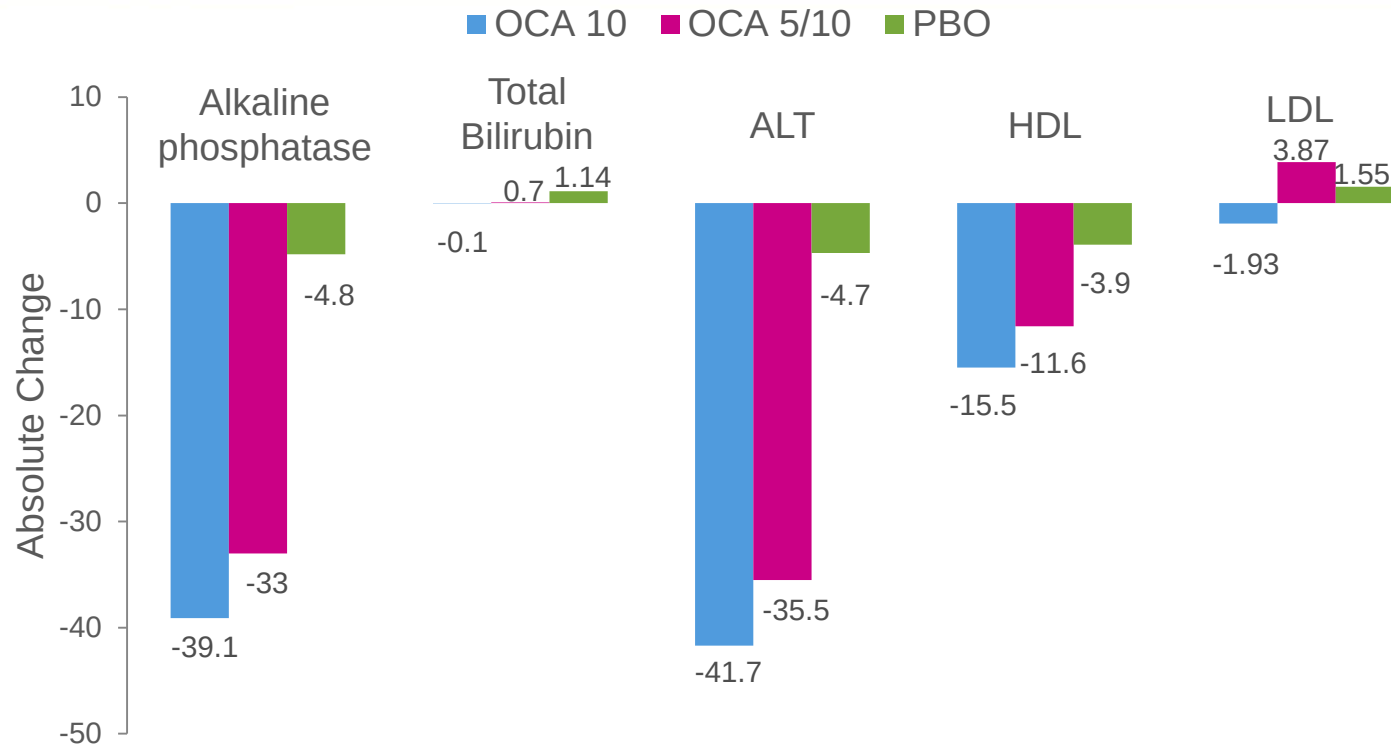


Obeticholic Acid in Primary Biliary Cirrhosis (POISE)



- **A Phase 3 International Trial of the FXR Agonist Obeticholic Acid in PBC Patients (POISE) Trial**
- Double-blind, placebo-controlled trial of PBC patients with an incomplete response to UDCA or intolerant of UDCA treated with OCA 10 mg daily; OCA 5 mg daily titrated to 10 mg daily at 6 months; or placebo for 12 months
- *Responders were defined as patients with ALP <1.67xULN, ≥15% ALP reduction and normal bilirubin

Obeticholic Acid in Primary Biliary Cirrhosis (POISE)

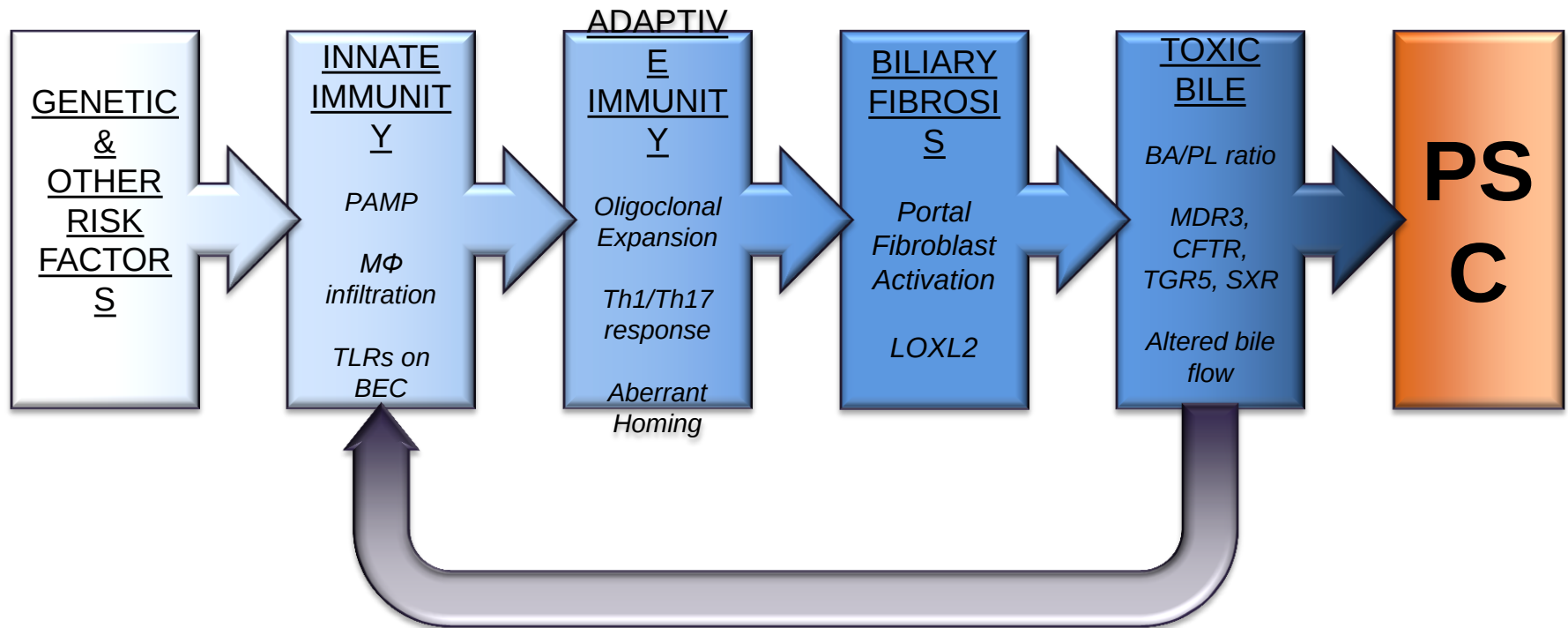


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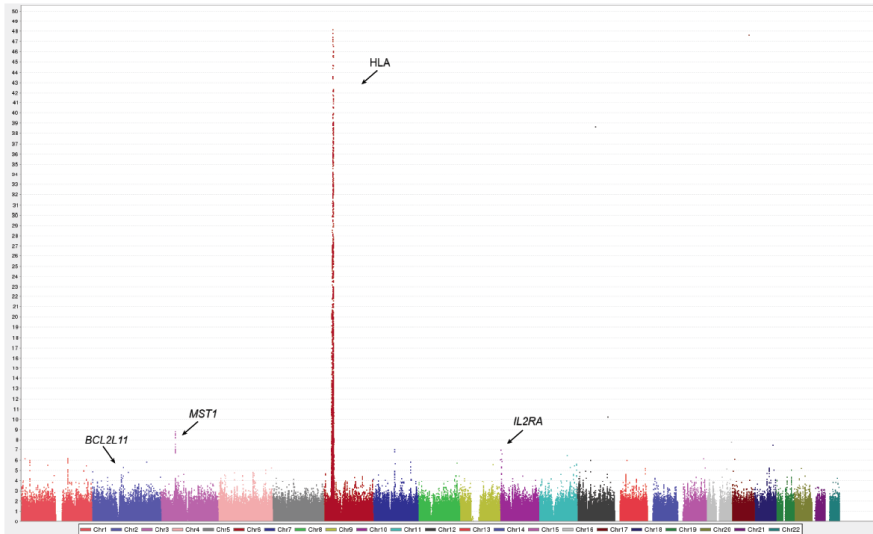
Drug Pipeline for PBC

	Phase of Clinical Development			
	1	2	3	4
FXR Agonists and related compounds				
OCA (Intercept)				
NGM282 (NGM Biopharmaceuticals)				
LJN 452 (Novartis Pharmaceuticals)				
MBX-8025				
Intestinal Apical Sodium Bile Acid Transport (iASBT) inhibitors				
LUM001 (Shire)				
GSK2330672 (GlaxoSmithKline)				
A4250 (Albireo Pharma)				
Immune-based Therapies				
Budesonide (Falk)				
Abatacept (BMS)				
FFP104 (FFPharma) (Anti-CD40)				
Ustekinumab (Janssen)				

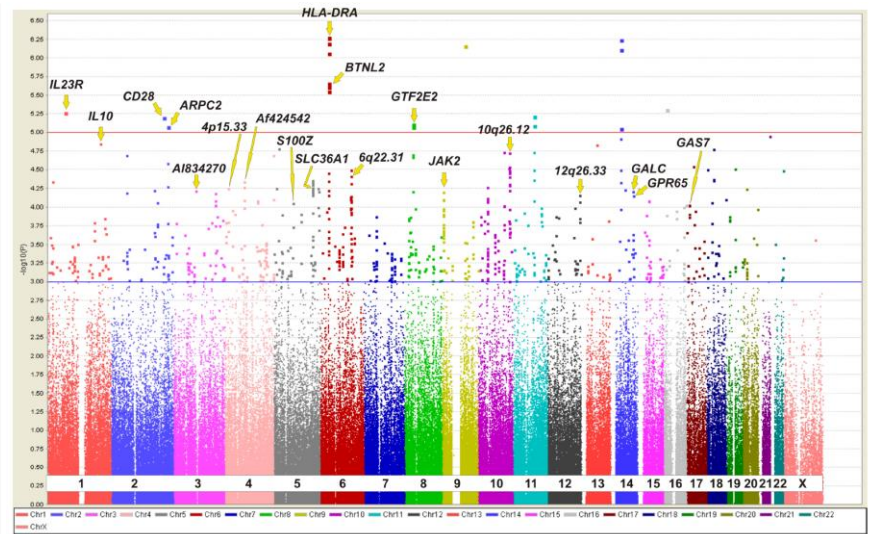
Proposed Model of PSC



GWAS in PSC versus UC

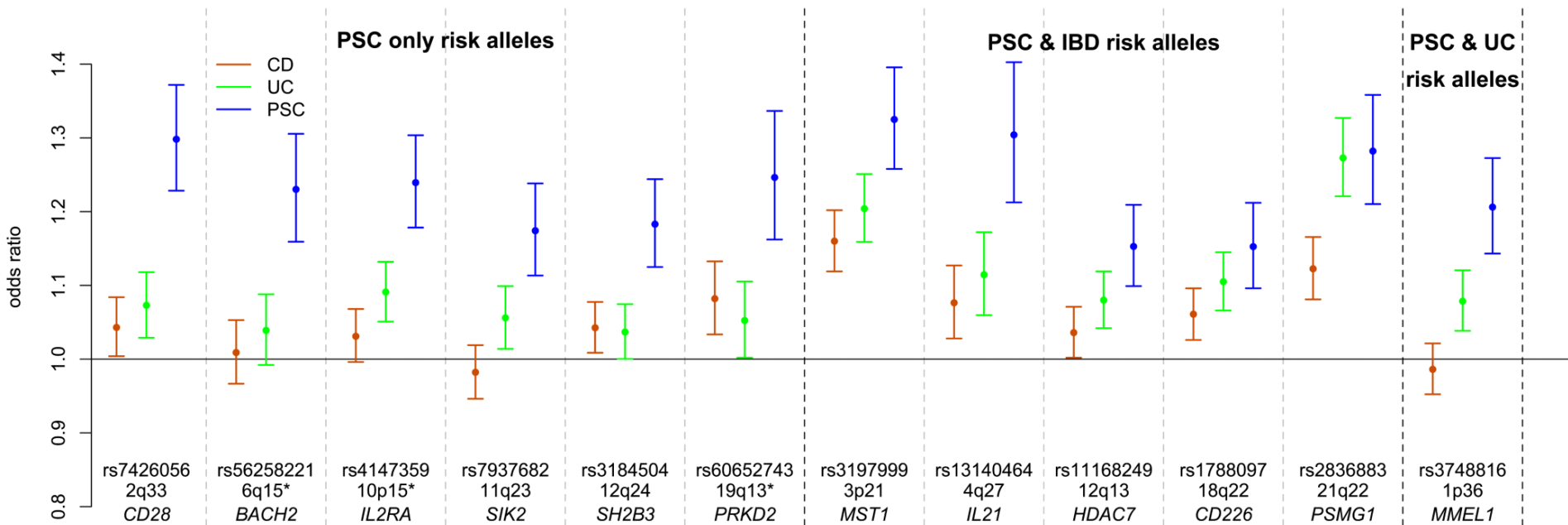


Melum E, et al. *Nature Genetics*. 2011;43:17-19.

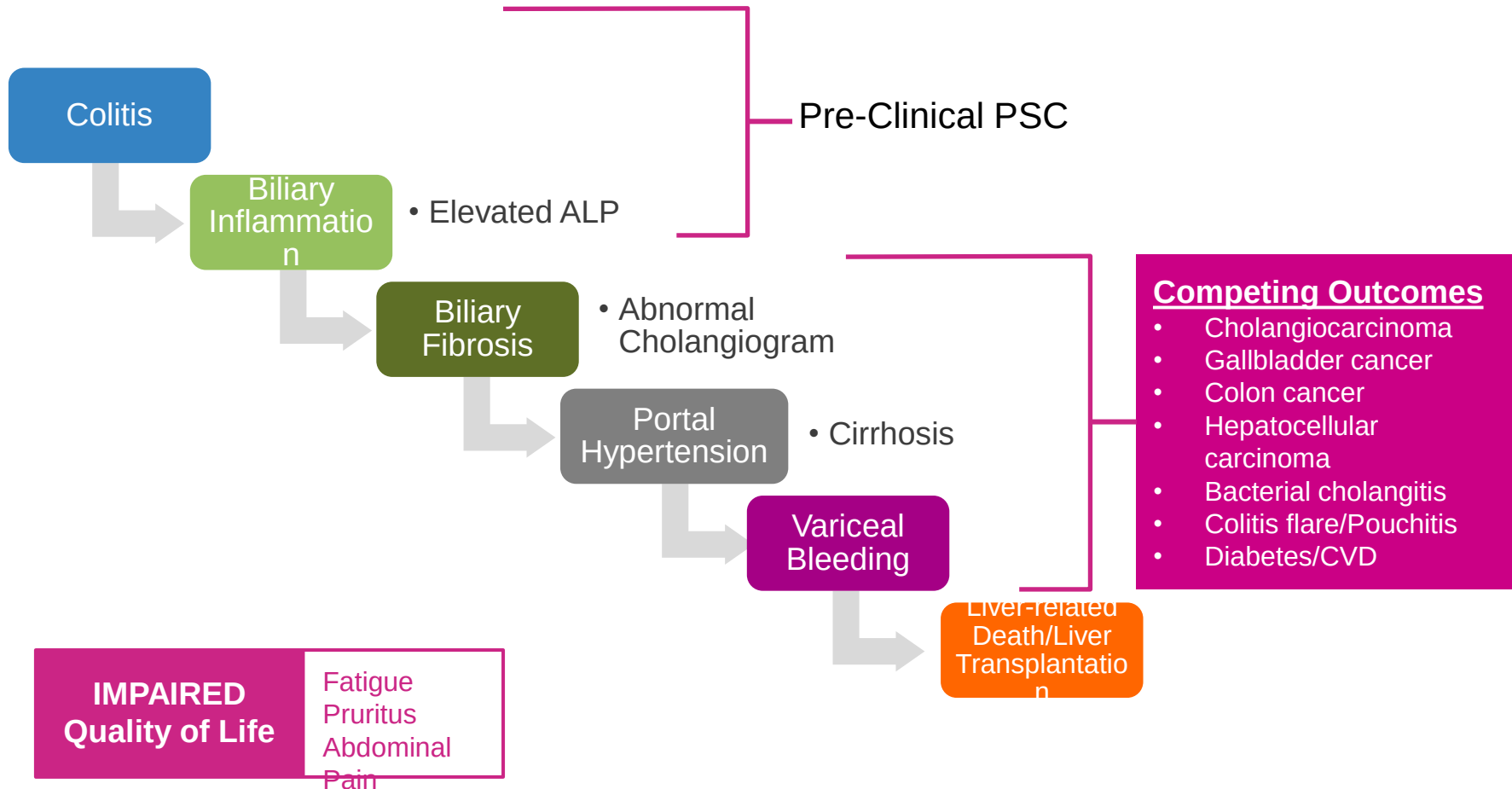


Silverberg MS, et al. *Nature Genetics*. 2009;41:216-220.

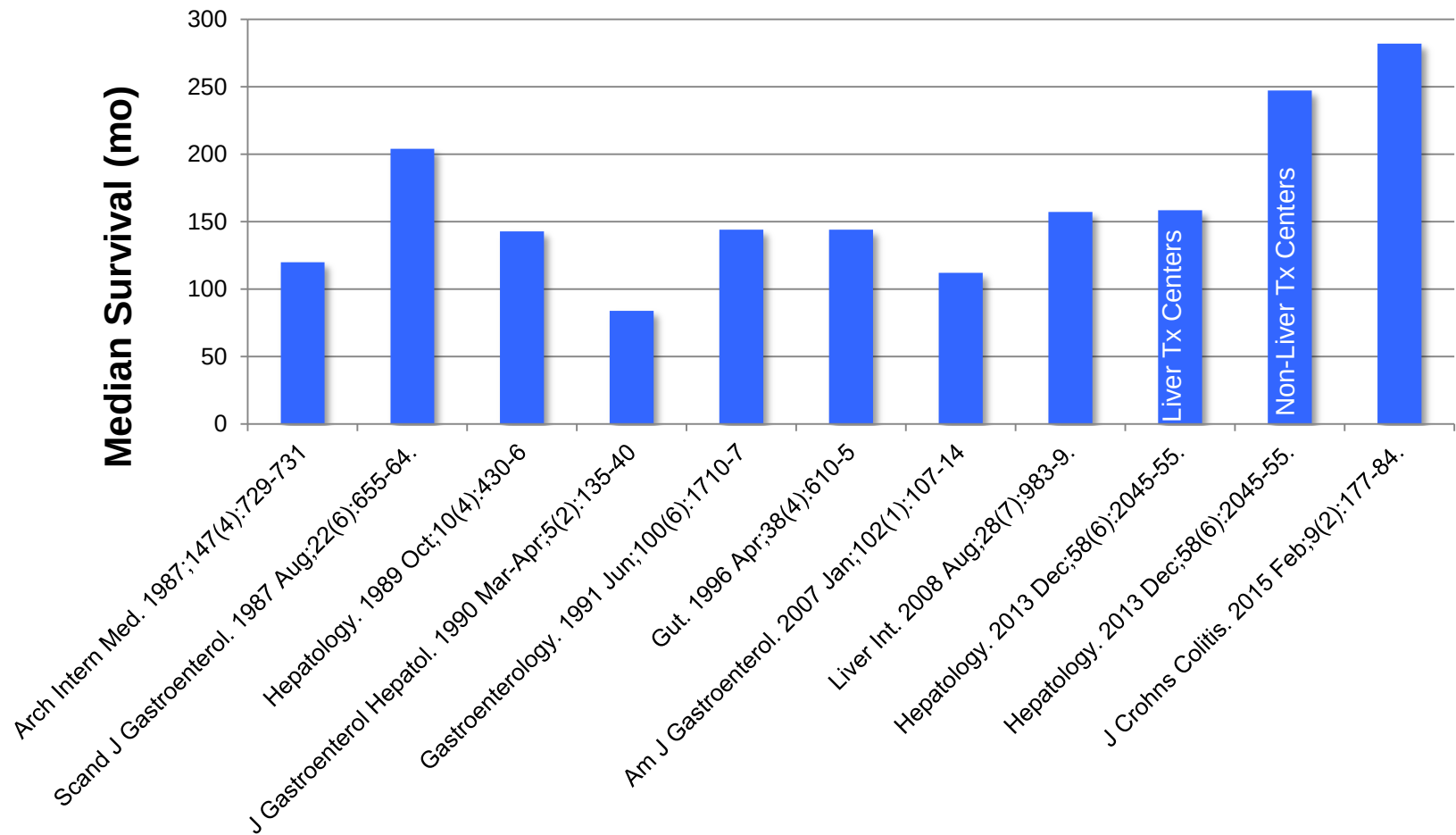
Shared Risk Variants – PSC and IBD



NATURAL HISTORY OF PSC



TRANSPLANT-FREE SURVIVAL IN PSC



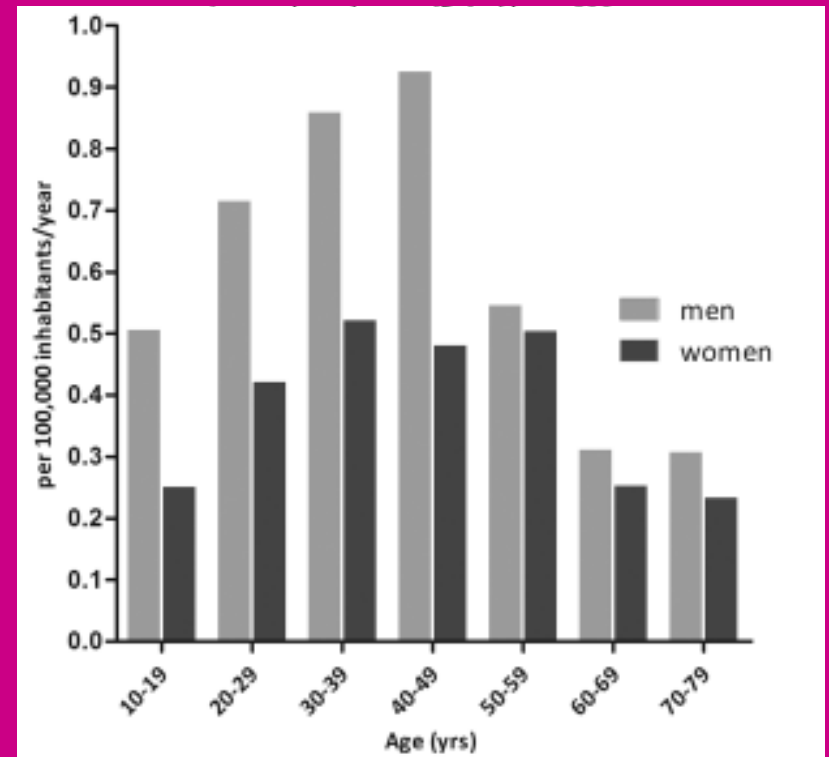
IBD and BILE DUCT PHENOTYPES

- IBD Phenotype
 - Unique PSC-IBD Phenotype
 - Crohn's disease associated with better prognosis
 - More small duct disease
 - Equal gender distribution
 - Lower risk of colon neoplasia
- Bile Duct Involvement
 - Small duct disease associated with better prognosis
 - Intrahepatic/Extrahepatic/Both
 - Dominant Stricture

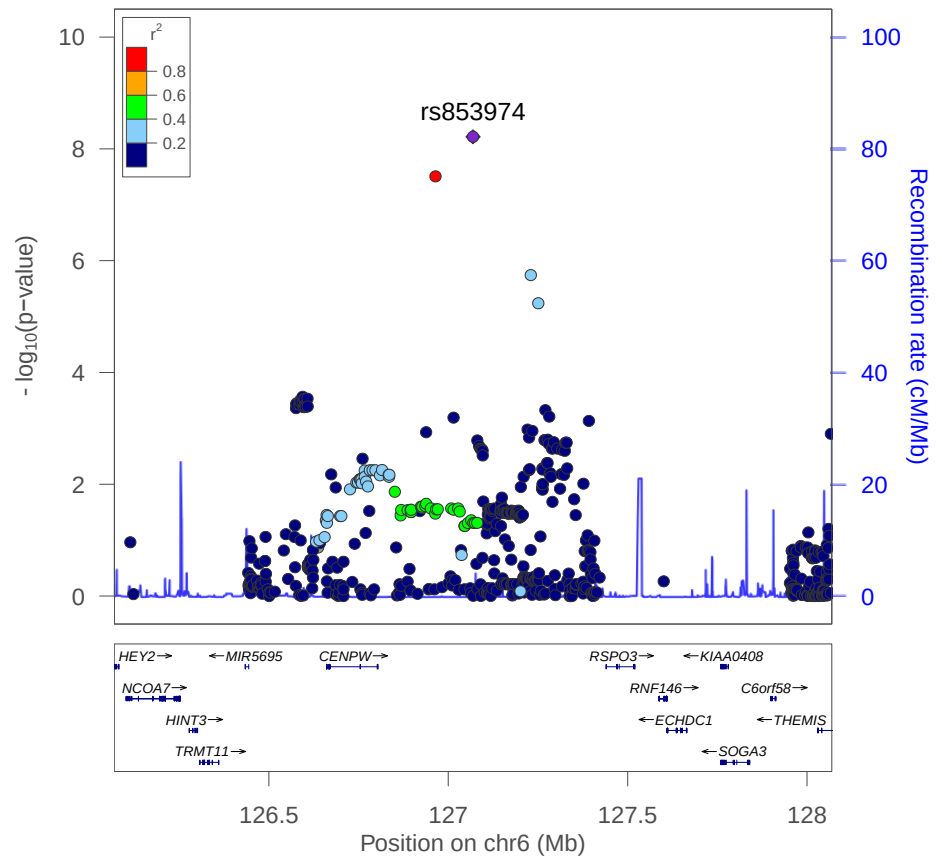
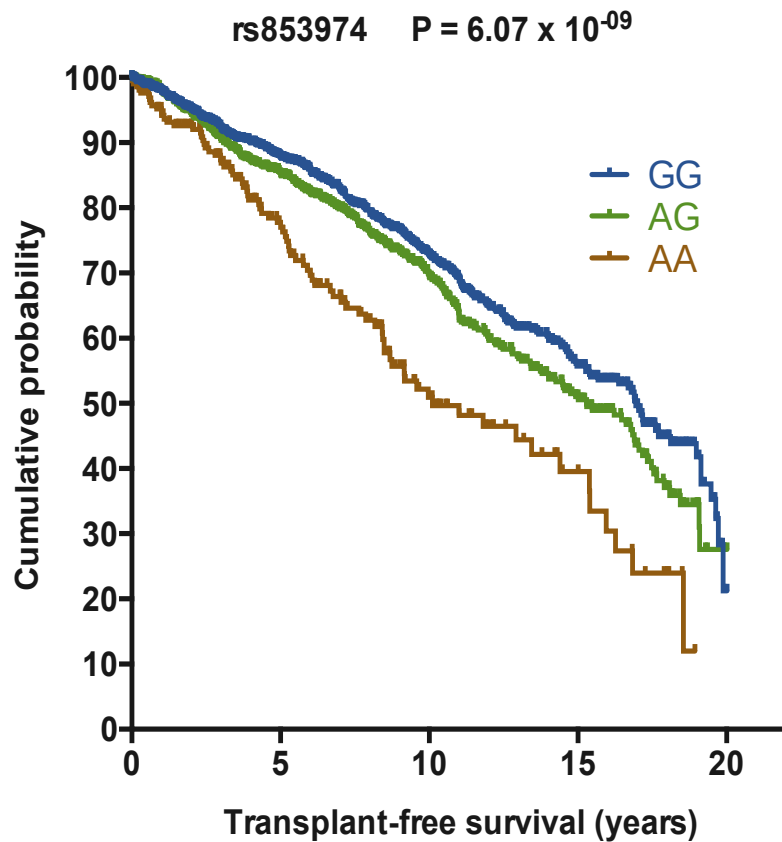
AGE & SEX

- Peak prevalence early in men
- IBD Frequency
 - Men (73.3%)
 - Women (51.5%)
- No difference in survival

Age and Sex Specific Incidence



RSPO3 AND SURVIVAL



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Welcome to the PSC Partners Patient Registry

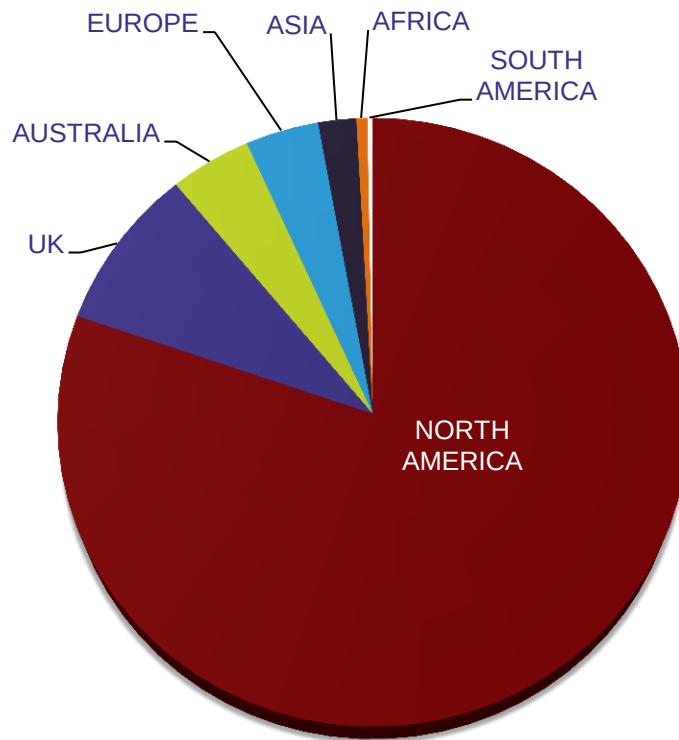
Help researchers worldwide unlock the mysteries of primary sclerosing cholangitis (PSC). Complete your profile and join PSC Partners Seeking a Cure in advancing PSC research towards a cure. Your participation is important!

The PSC Partners Patient Registry was established in collaboration with the National Institutes of Health (NIH) [The Office of Rare Diseases Research](#).

[Join the Registry!](#)[PSC Registry Instructions](#)

Residence of Participants

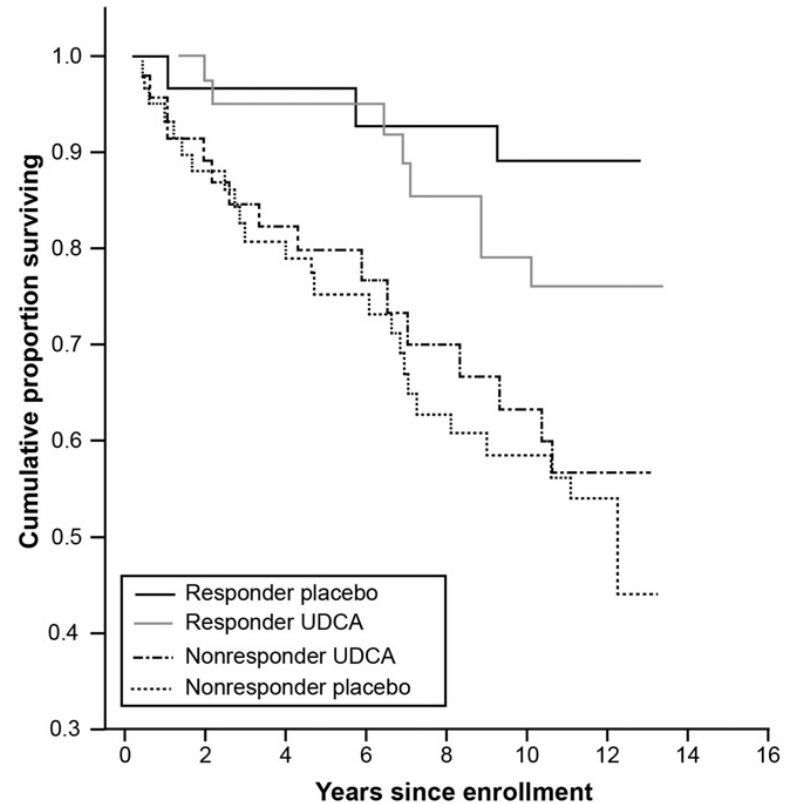
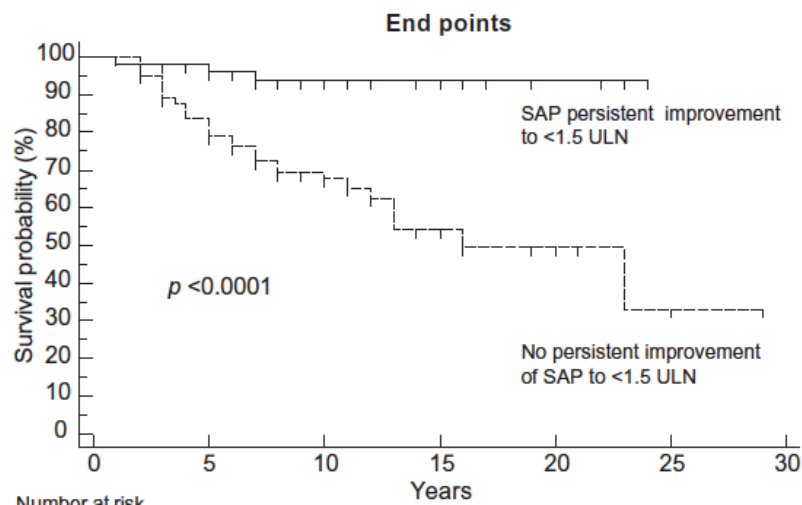
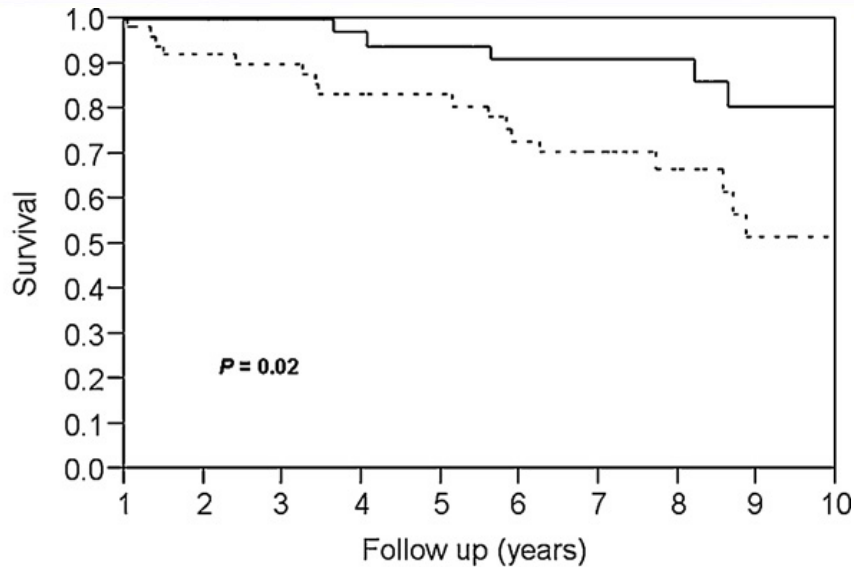
REGION OF RESIDENCE



Participant Characteristics

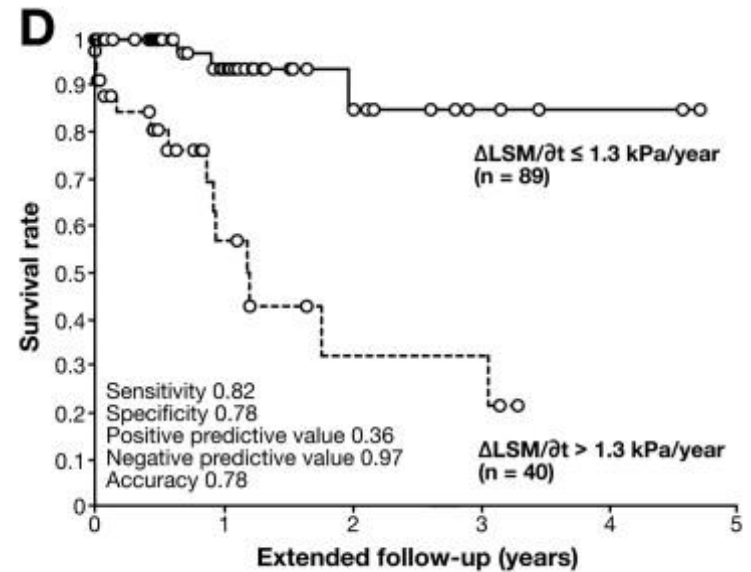
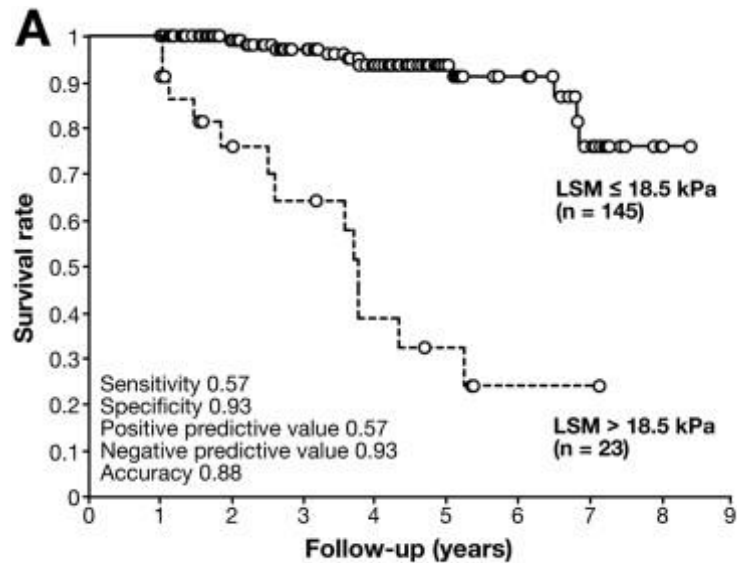
FEATURE	PSC PATIENTS (<i>n</i> = 699)
Age (<i>mean</i> $\pm$ <i>SD</i>)	40 $\pm$ 15.7 years
Male	48.2 %
IBD	74.7%
Ulcerative colitis	54.5%
Crohn's disease	15.6%
Indeterminate colitis	4.5%
Liver Transplantation	15.5%
Autoimmune Hepatitis	7.2%

Alkaline Phosphatase as a biomarker in PSC

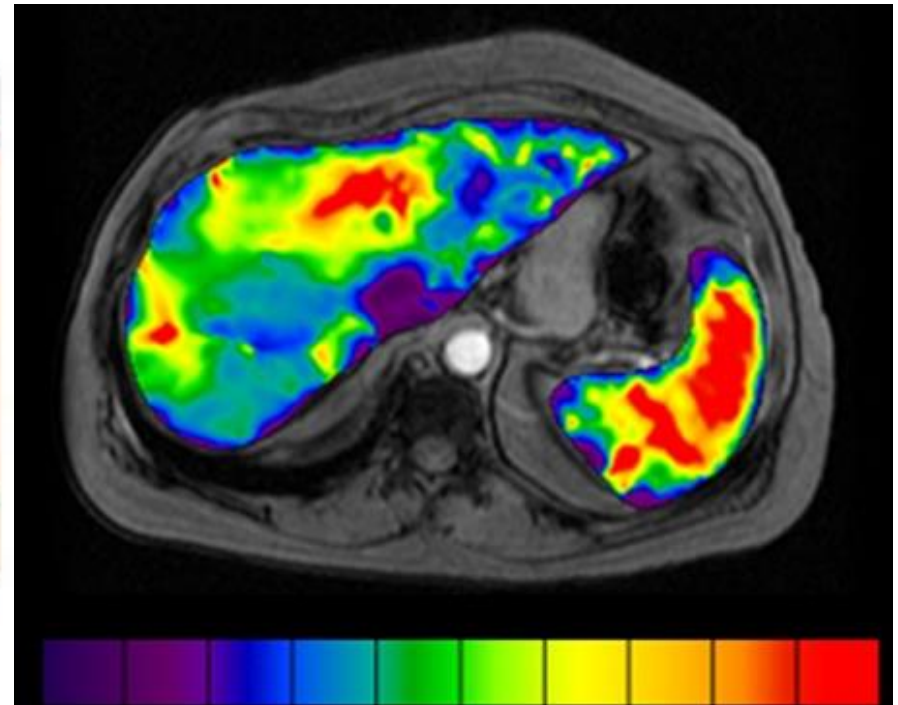
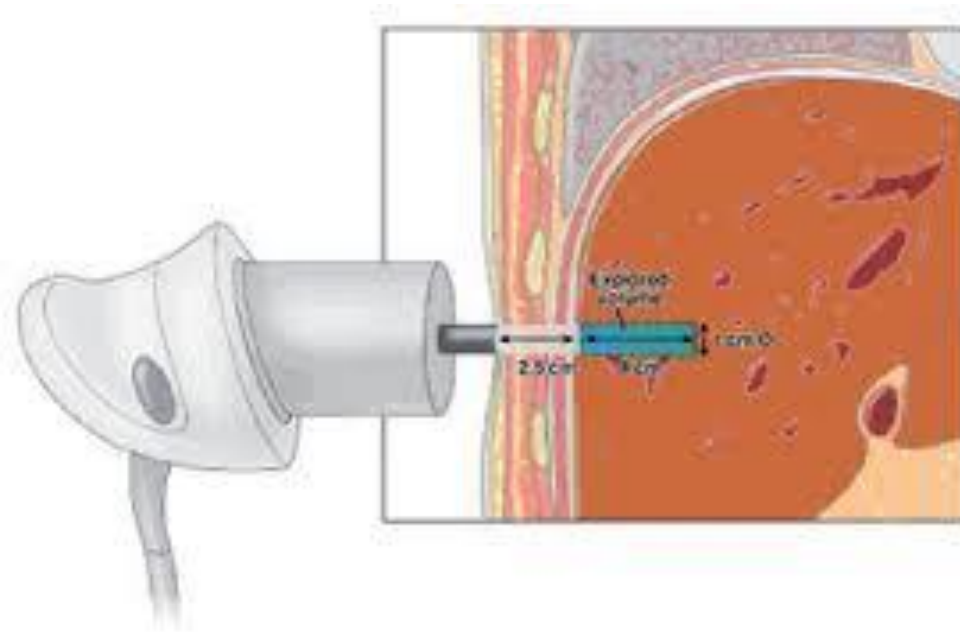


Stanich PP, et al. *Dig Liver Dis.* 2011. 43:309-13.
 Mamari A, et al. *J Hepatol.* 2013. 58:329-34.
 Lindstrom L, et al. *Clinic Gastroenterol Hepatol.* 2013.

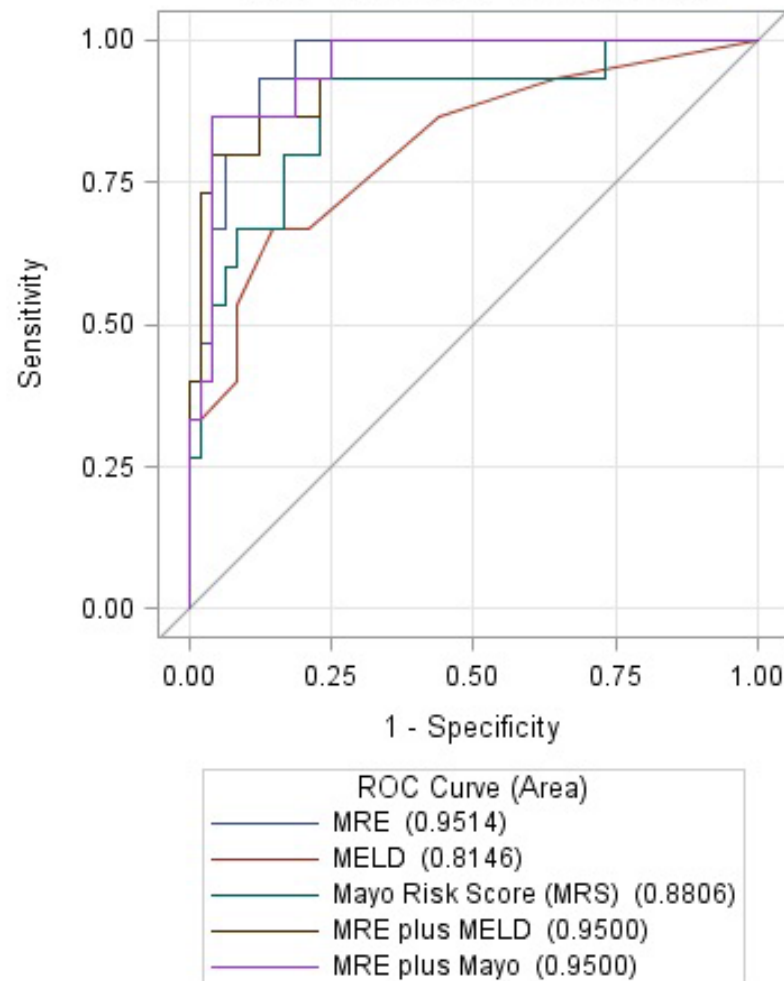
VCTE in PSC



Transient Elastography VS MR Elastography

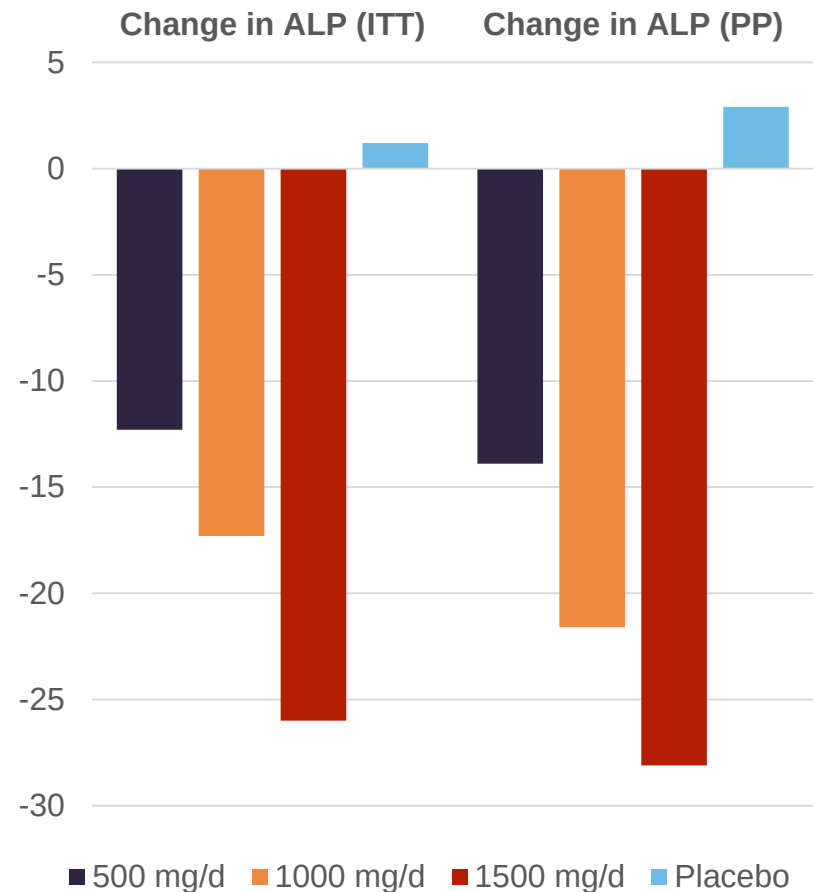


MR Elastography in PSC



NOR-URSO IMPROVES CHOLESTASIS IN PSC: PHASE II DOSE FINDING STUDY

- Double-blind, placebo-controlled trial
- 12 weeks treatment
- 222 pts. screened
 - 159 randomized
 - 126 PP analysis



Drug Pipeline for PBC

	Phase of Clinical Development			
	1	2	3	4
Bile Acid Based Therapies				
OCA (Intercept)				
NGM282 (NGM Biopharmaceuticals)				
Nor-UDCA (Falk)				
Intestinal Apical Sodium Bile Acid Transport (iASBT) inhibitors				
SHP625 (LUM001; Shire)				
Anti-Fibrotic				
Simtuzimab (Gilead)				
Immune-based Therapies				
Cenicriviroc (Tobira)				
Vedolizumab (Takeda)				
Microbiome Therapies				
Vancomycin (Stanford)				
FMT (Mass General)				

What Should I Do Now?

- PBC
 - Urso remains first-line treatment
 - Consider obeticholic acid in those with inadequate response to Urso
 - ALP > ~200 IU
 - Elevated bilirubin
 - Manage Symptoms
- PSC
 - Consider trial of Urso if ALP is elevated
 - MRE or TE for staging
 - Cancer Surveillance (Colon and Hepatobiliary)