Biliary Cirrhosis in PBC is Irreversible:
Mandate for Early Stage Detection and Treatment

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Disclosures

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Research Grants: CymaBay, Escient, Genfit, Genkyotex, Gilead, Intercept, NGM Biopharmaceuticals, Lilly, Novartis, Roche-Genentech, Taiwan J, Zydus

Scientific Advisor-Consultant: Amgen, Arbormed, Arena, Blade, Gilead, GlaxoSmithKline, Horizon, Intercept, Ipsen, Kezar, Kowa, Lilly, Moderna, Novartis, Orphalon, Perspectum, Roche Genentech, Taiwan J, Umecrine, IQ-DILI, DI-AIH

Speaker: Gilead

DSMBs: NIH NIDDK DILIN; Fractyl

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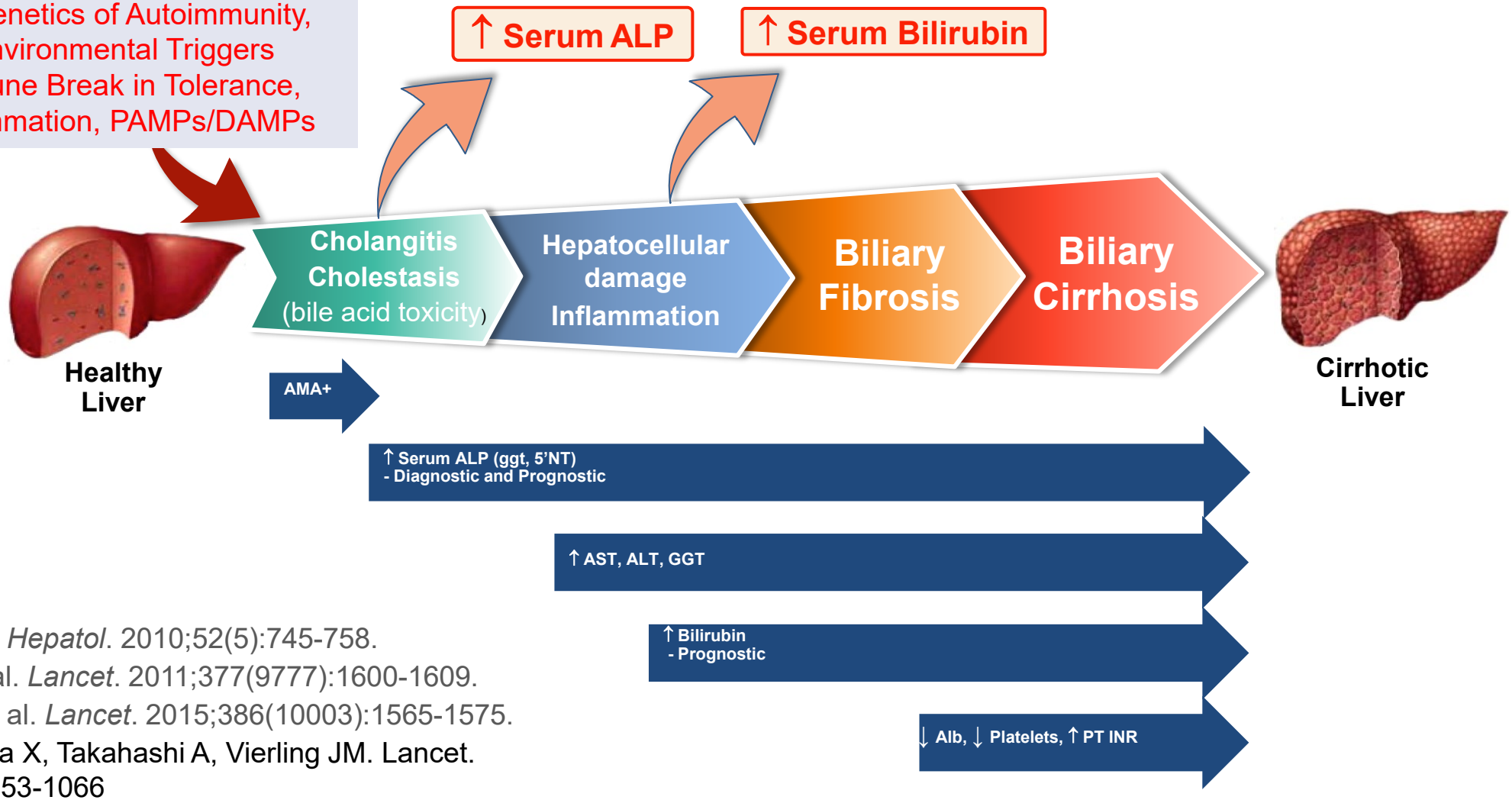
Primary Biliary Cholangitis
Natural History of Untreated or Partially Treated Patients

Causative factors
- Genetics of Autoimmunity,
- Environmental Triggers

Immune Break in Tolerance, Inflammation, PAMPs/DAMPs



Poupon R. *J Hepatol*. 2010;52(5):745-758.
Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609.
Carey EJ, et al. *Lancet*. 2015;386(10003):1565-1575.
Tanaka A, Ma X, Takahashi A, Vierling JM. Lancet. 2024;404:1053-1066

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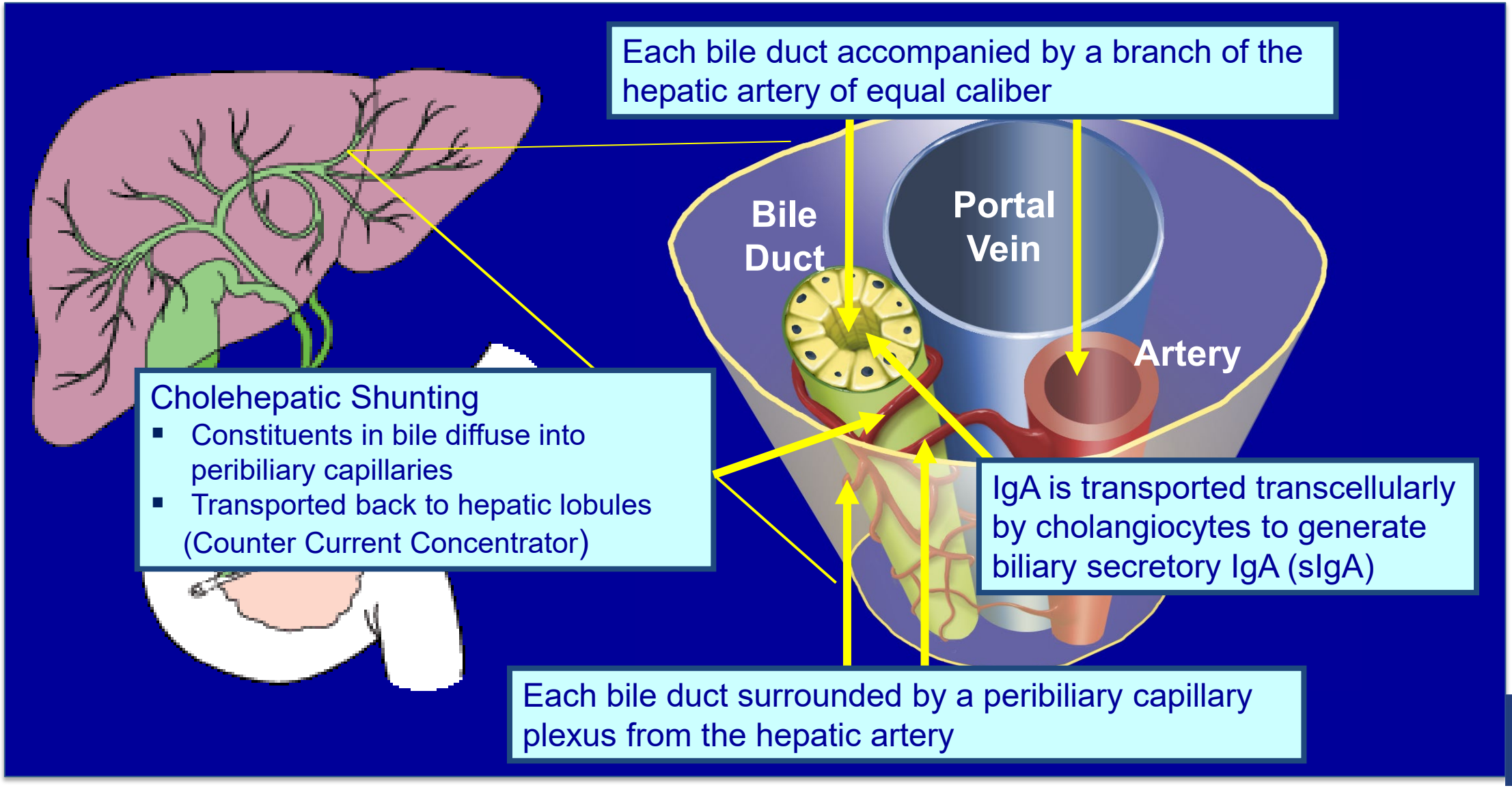
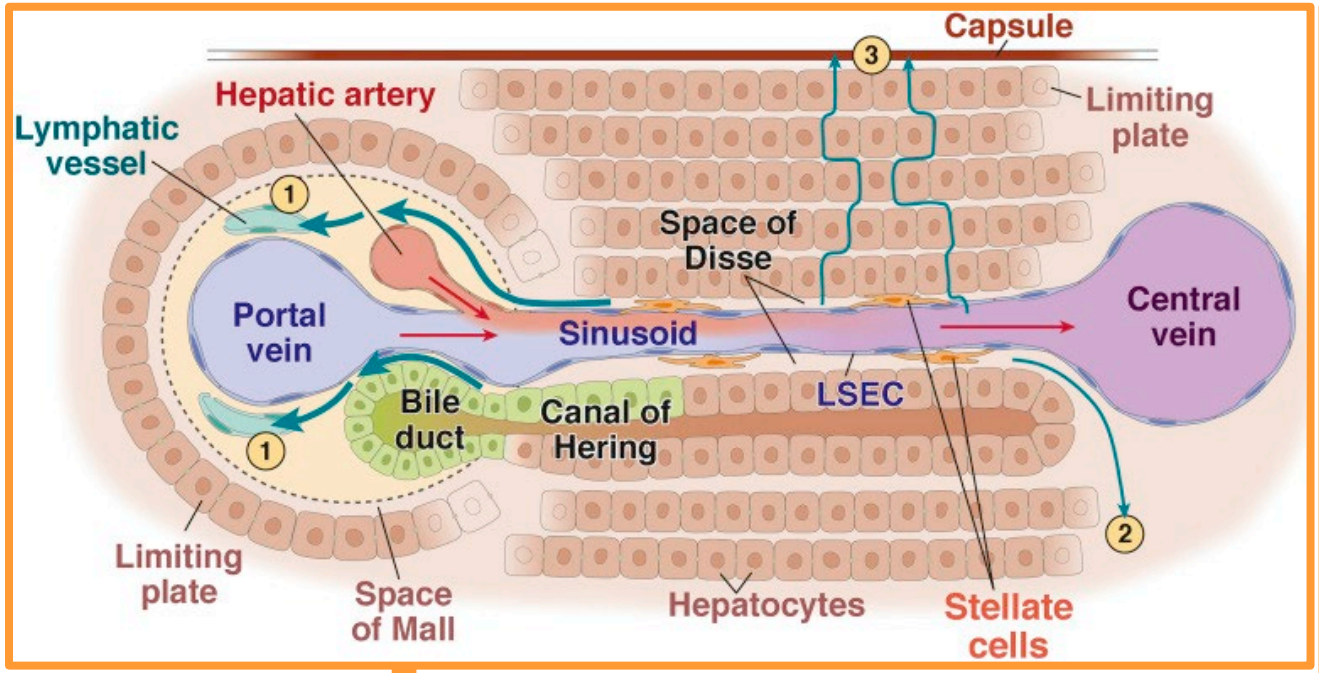
Primary Biliary Cholangitis

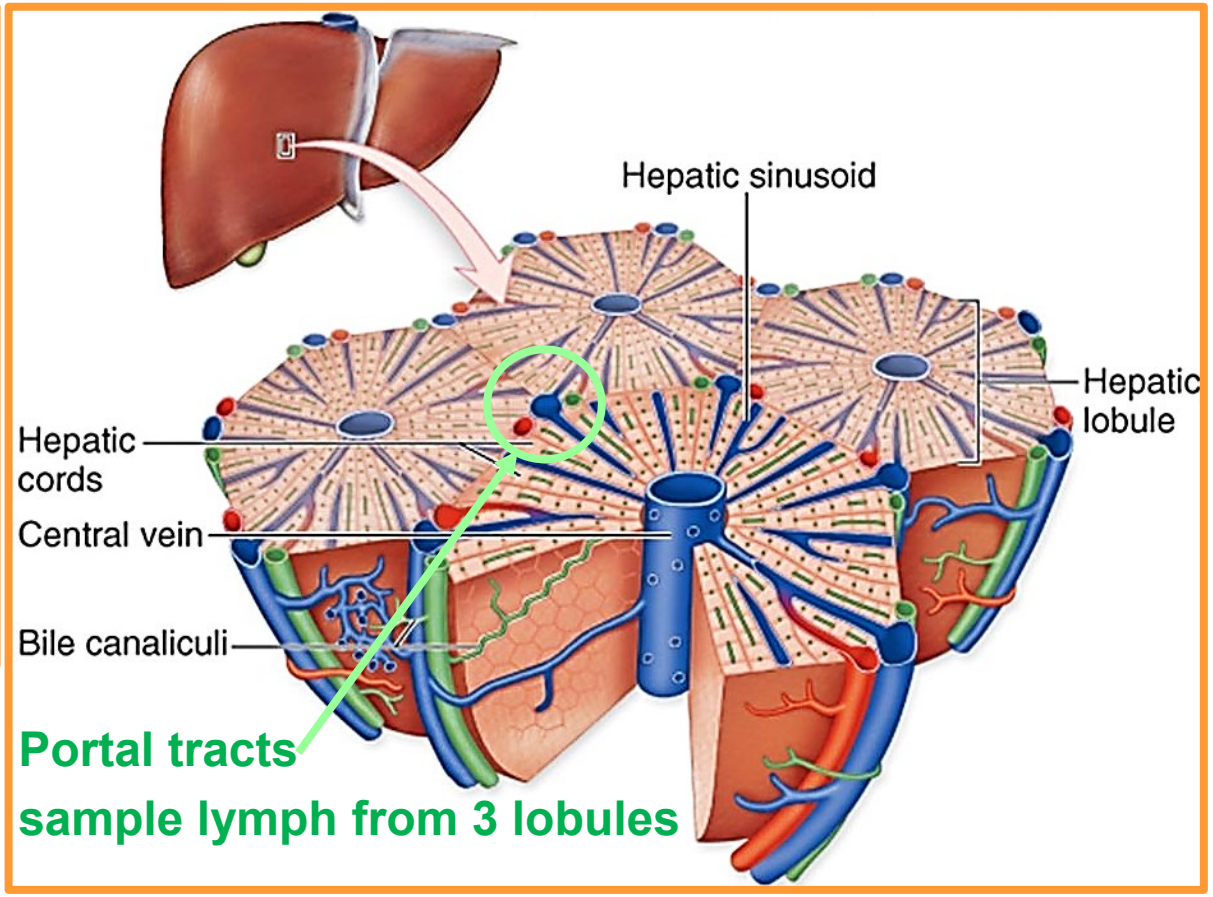
Important Anatomic Factors in Progression



Primary Biliary Cholangitis

Important Anatomic Factors: Lymphatics and Portal Tracts





Tanaka M and Iwakirir Y Cell Molec Gastro Hepatol 2016; 2: 733-49;

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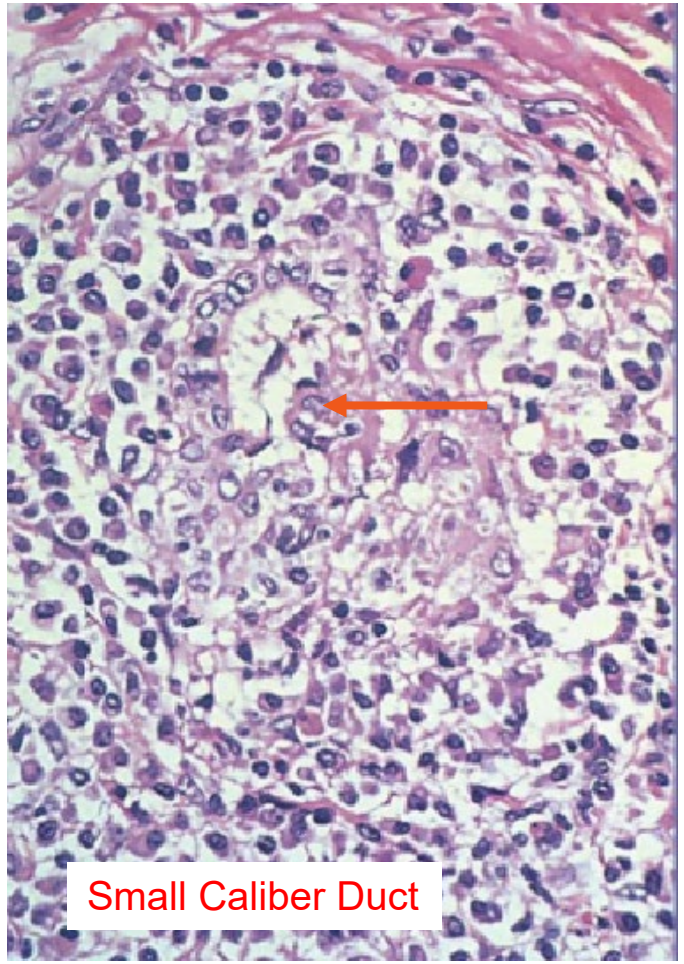
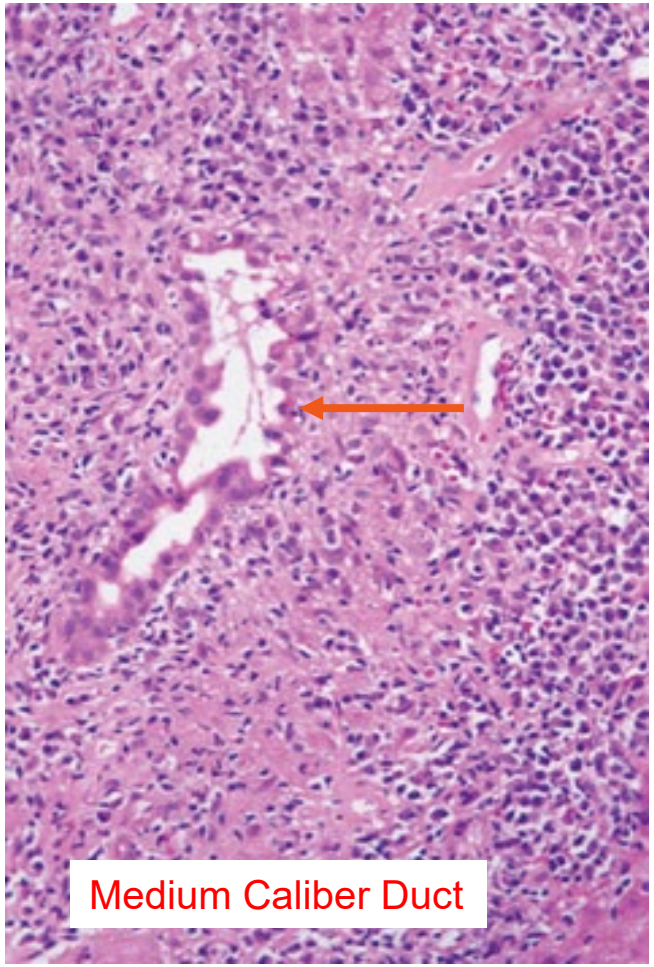
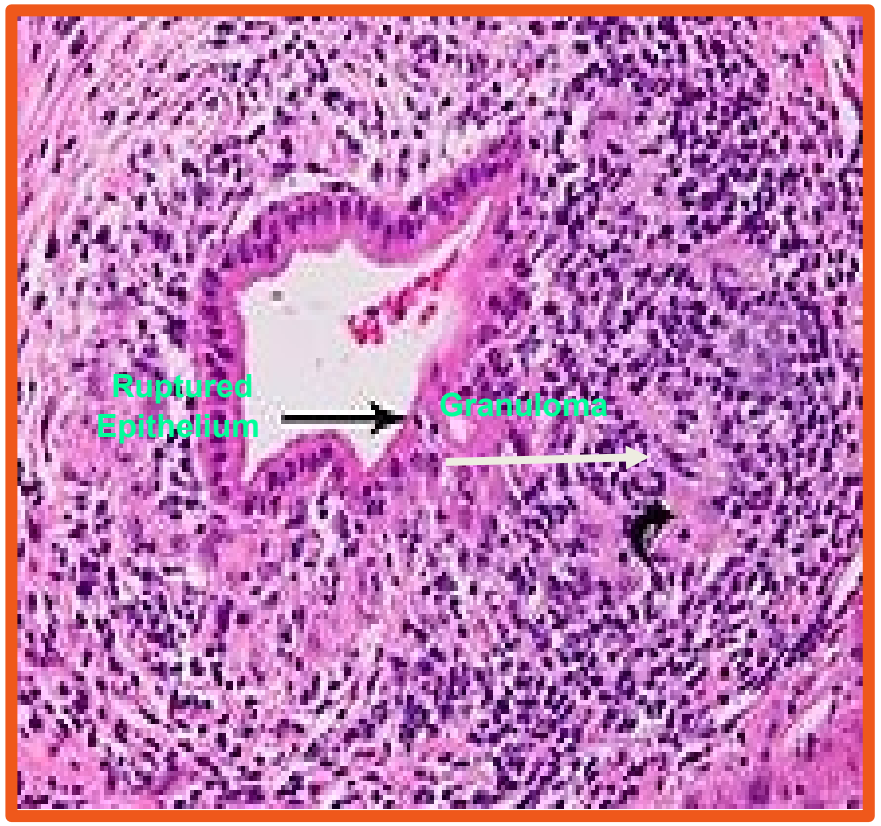
Primary Biliary Cholangitis
Lymphocytic Cholangitis* and Florid Duct Lesion







Florid Duct Lesion= Pathognomonic

*aka, Non-Suppurative Destructive Cholangitis (NSDC)

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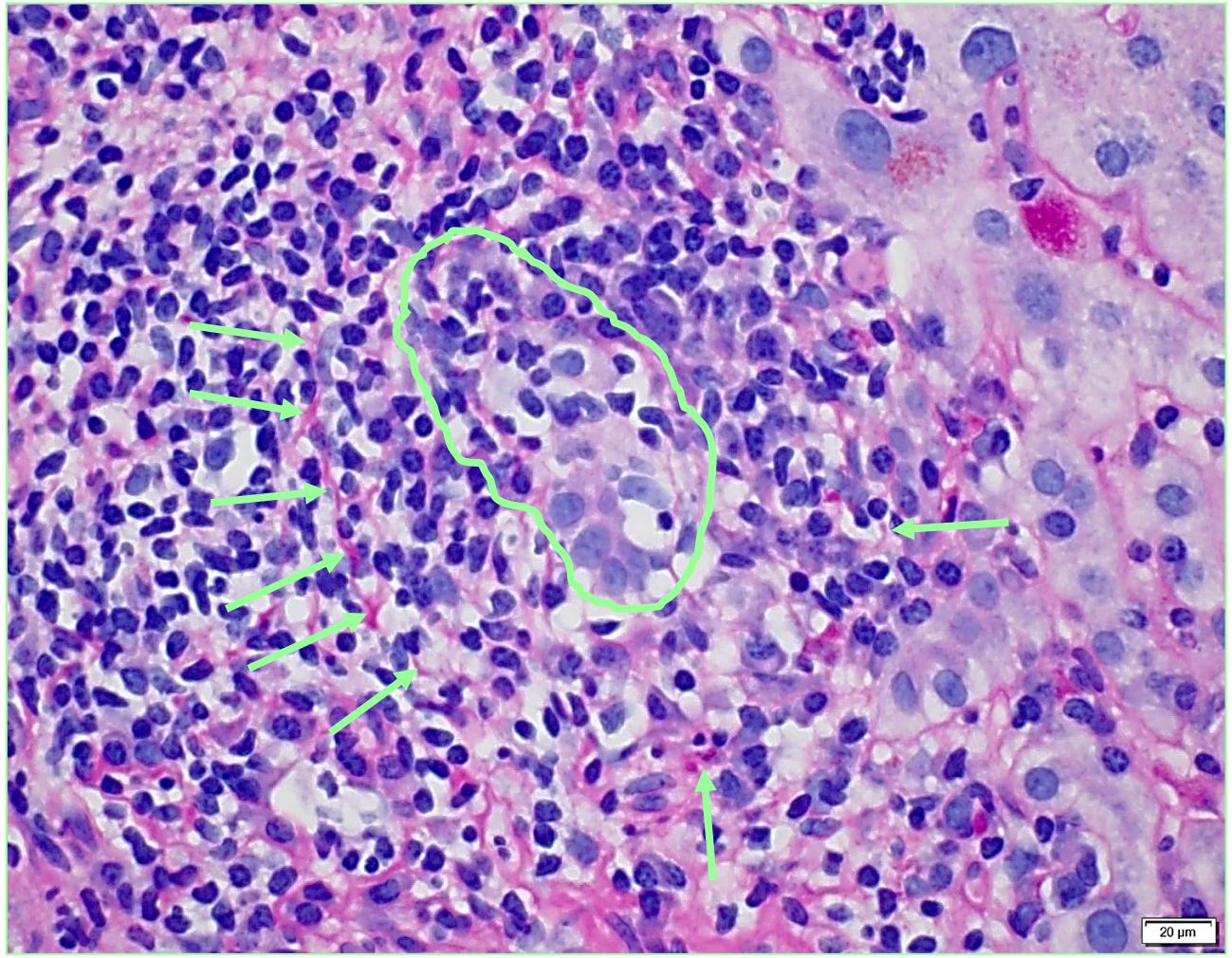
Primary Biliary Cholangitis
Displacement and Fragmentation of Basement Membranes



Photomicrograph Courtesy of S Dhringra, MD, Baylor College of Medicine, Dept of Pathology

Destructive Lymphocytic Cholangitis*:

- Bile Duct Basement Membrane (arrows):
  - Displacement by inflammatory cells
  - Fragmentation and destruction
- Consequences:
  - Loss of protective bicarbonate umbrella
  - Altered cholangiocytes transport of sIgA
  - Loss of mucosal barrier to bile leakage

*aka, Non-Suppurative Destructive Cholangitis (NSDC)

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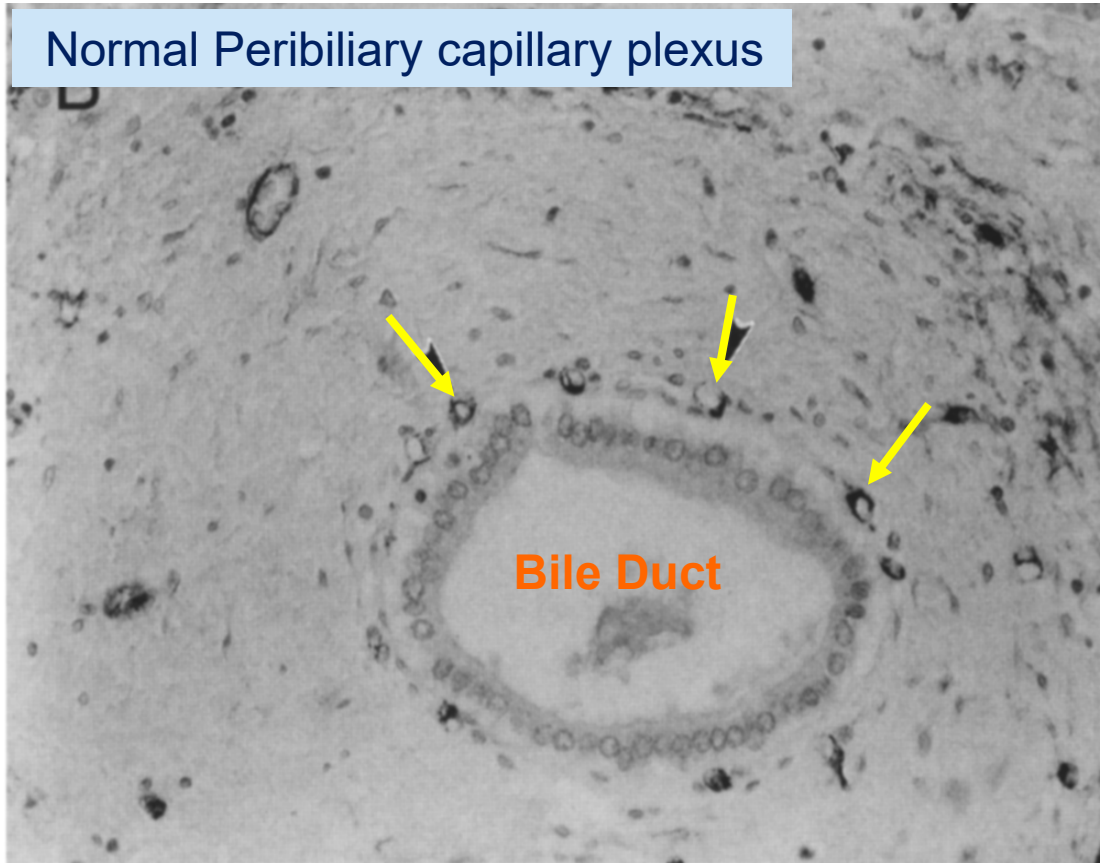
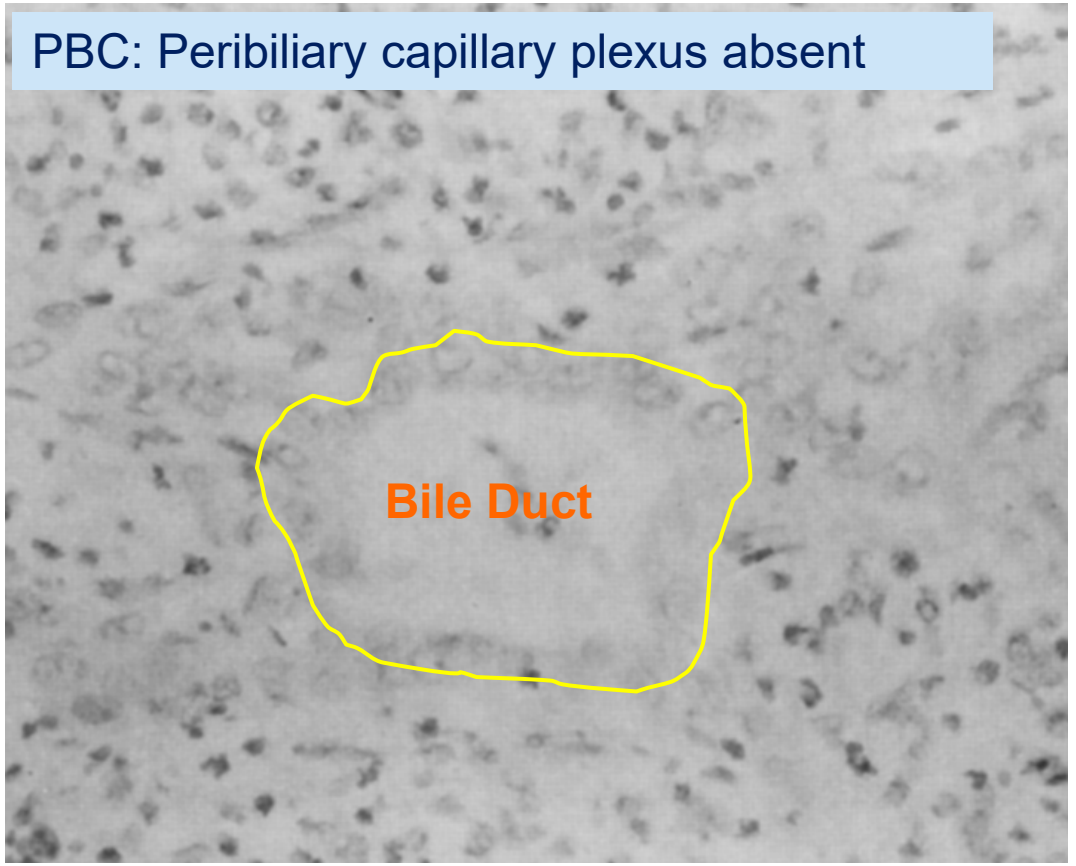
Primary Biliary Cholangitis

Ischemia and Absence of Cholehepatic Shunting with Loss of Peribiliary Capillary Plexi





Washington K, et al. Hum Pathol 1997; 28: 791-5

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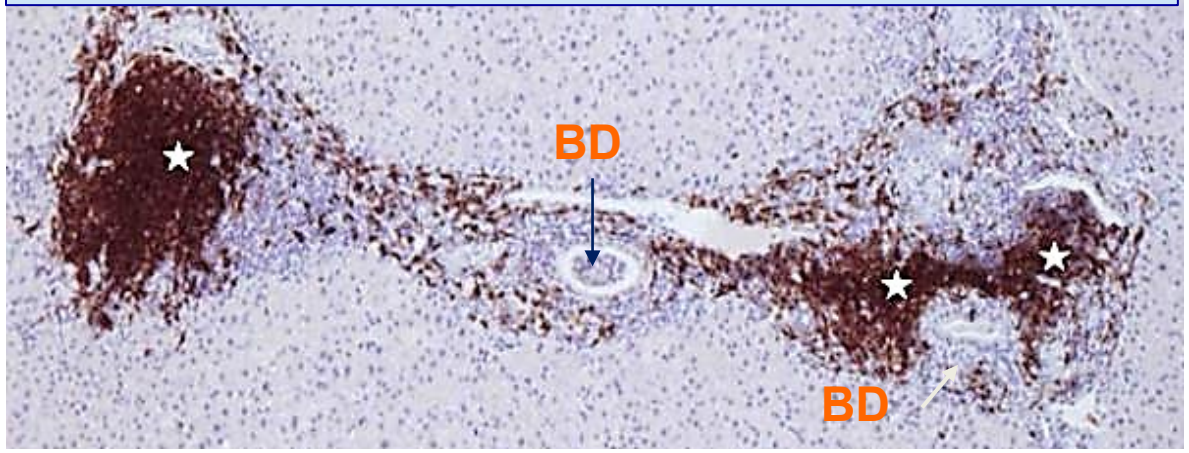
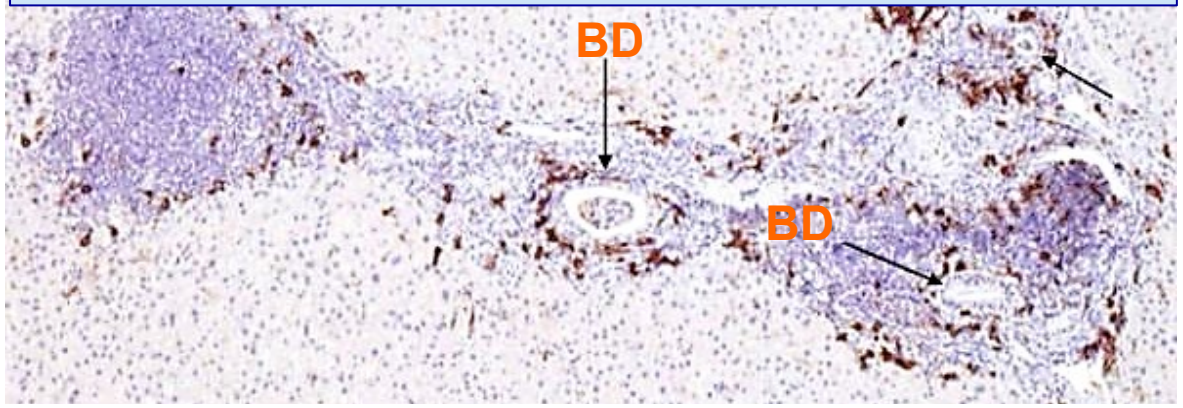
Primary Biliary Cholangitis

Portal Inflammatory Infiltrates with B Cells and Plasma Cells

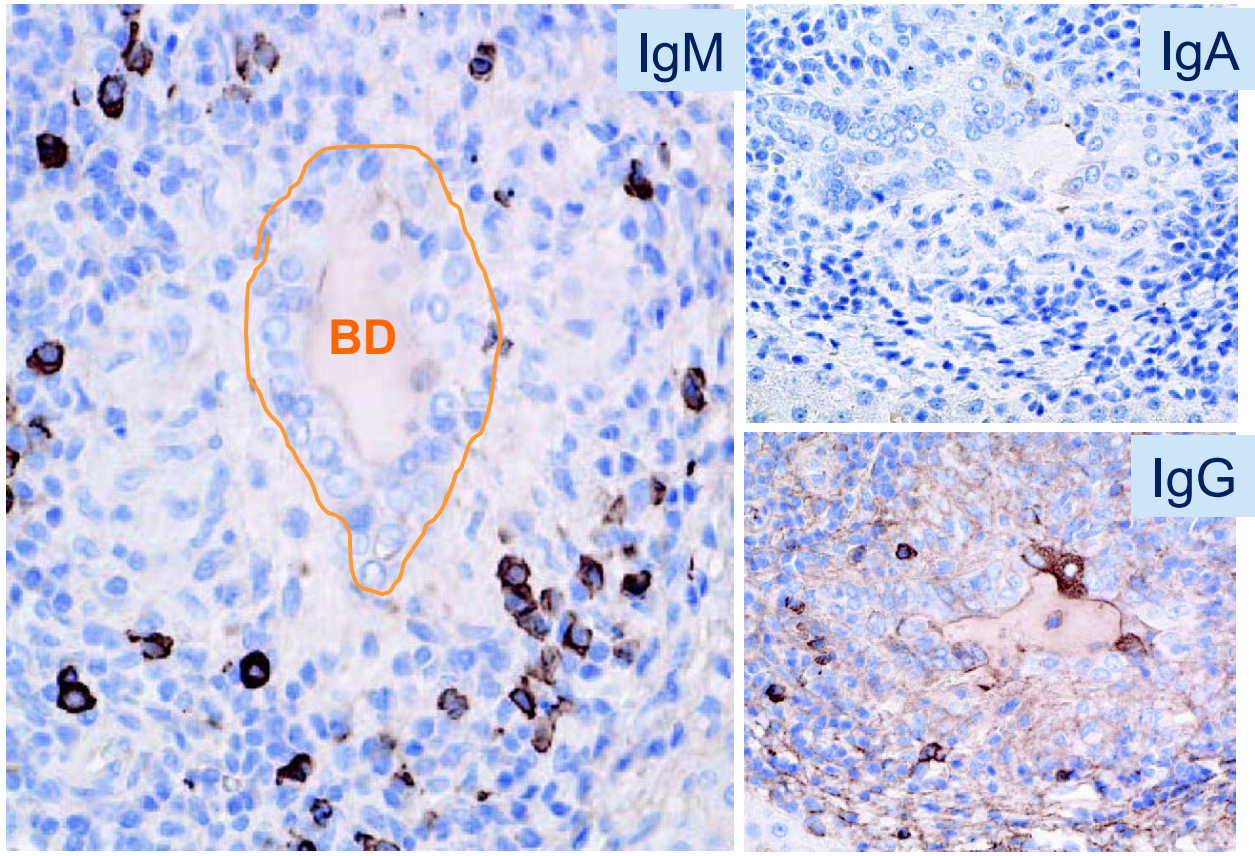
CD20+ B Cell Infiltrates
Forming Lymphoid Aggregates



CD38+ Plasma Cell Infiltrates
Periductal Coronal Distribution



Takahashi T, et al. Hepatology 2012; 55: 846-55



Daniels JA, et al. Am J Clin Path 2009; 131: 243-9

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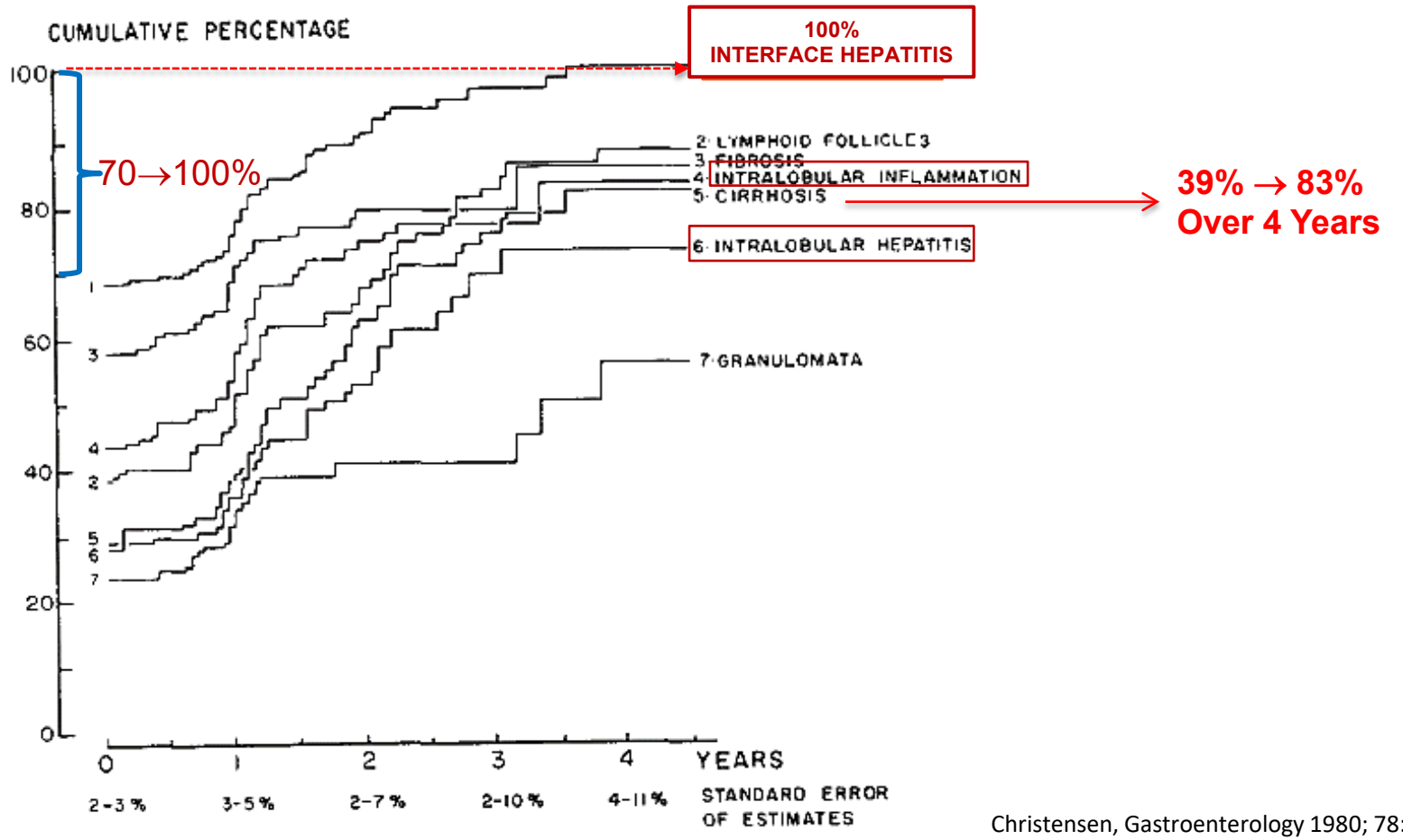
Progressive Primary Biliary Cholangitis
Universal Interface Hepatitis + Plasma Cells

Interface Hepatitis Universal in Progression of Untreated PBC (n= 231)



Christensen, Gastroenterology 1980; 78: 236-246

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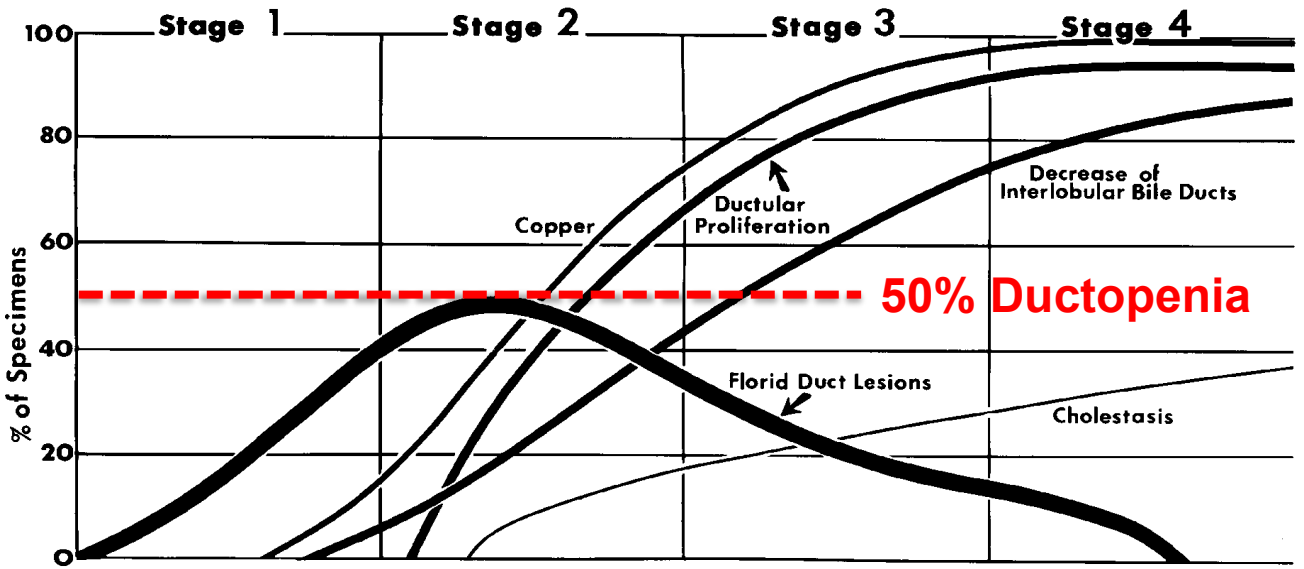
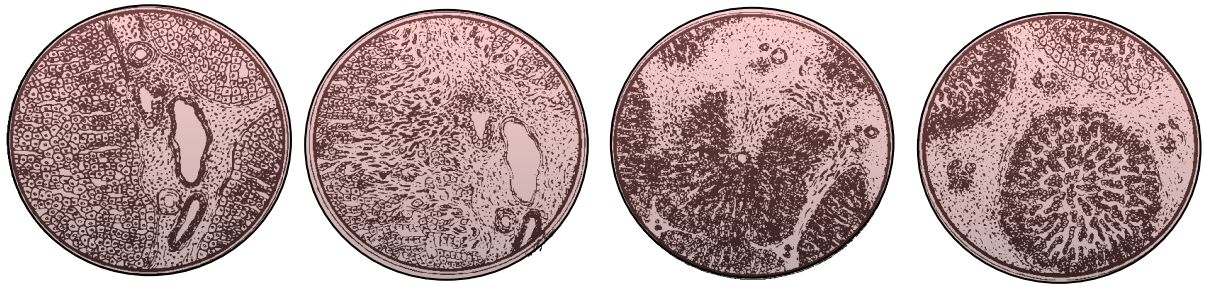
Primary Biliary Cholangitis
Clinicopathological Progression to Biliary Cirrhosis

Asymptomatic →

Symptomatic →

Preclinical	**Clinical**	**Compensated**
- AMA +	- AMA (+) or AMA (-)	↘
- ALP, ggt WNL	- ↑ ALP, ALT/AST with later ↑ Bilirubin	**Decompensated**





Adapted from Dickson R. Prog Liver D

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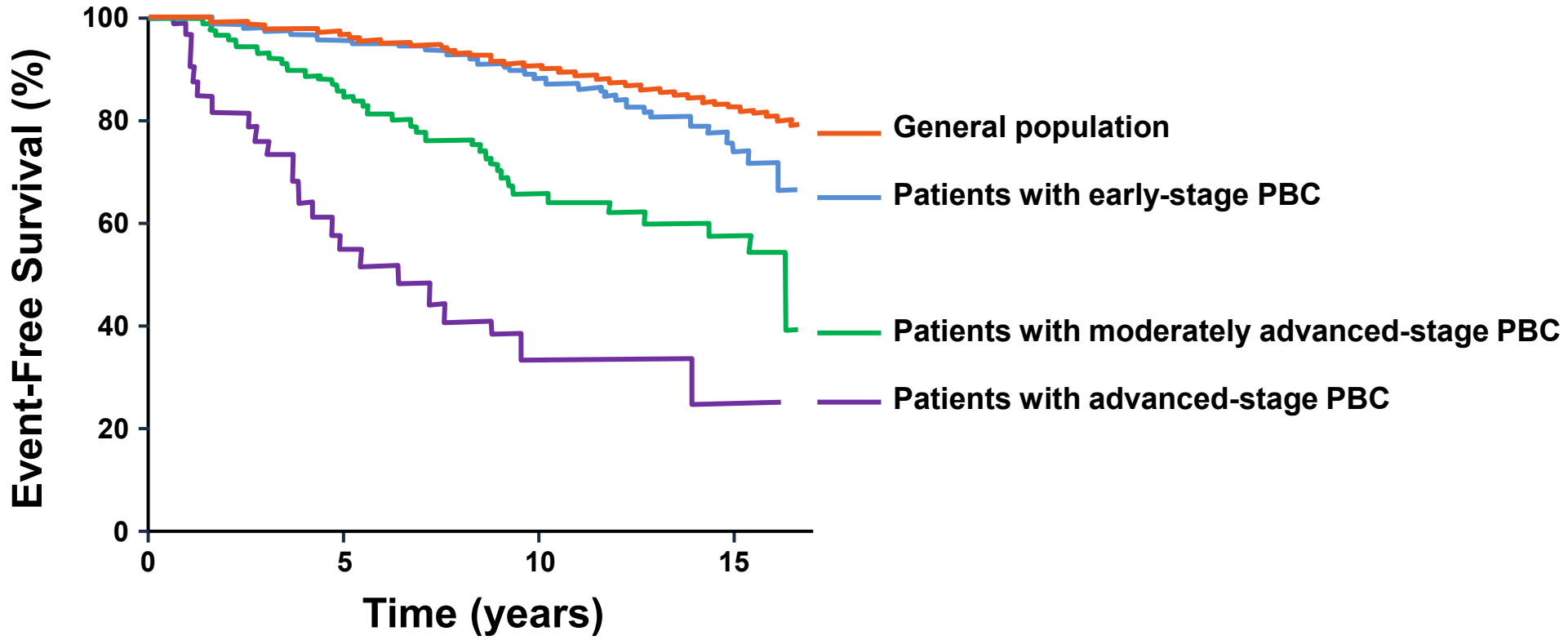
UDCA Treatment of PBC
Event-Free Survival Optimal in Earlier Stages



Survival on UDCA is inversely related to stage of PBC when treatment initiated:

- Survival of patients with early-stage PBC comparable to survival of the general population (p=.254)
- Survival in advanced-stage PBC significantly worse (p<0.001)

Kuiper EMM, et al. Gastroenterology. 2009;136(4):1281-1287.

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Cirrhosis

Varies by Etiology, Pathogenesis, and Reversibility

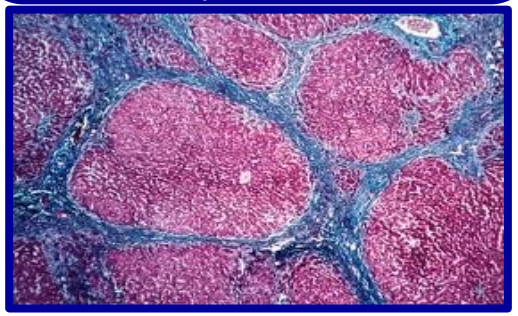
Cirrhosis

Fibrosis + Regenerative Nodules

Post Necrotic

(macronodular)

Viral, AIH, NASH, DILI, Genetic

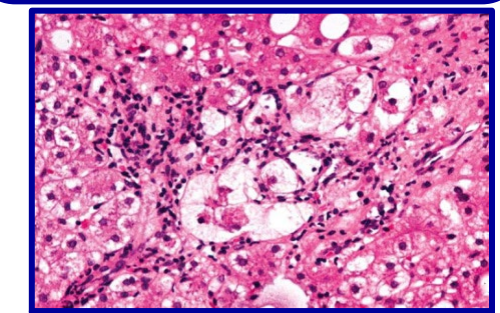


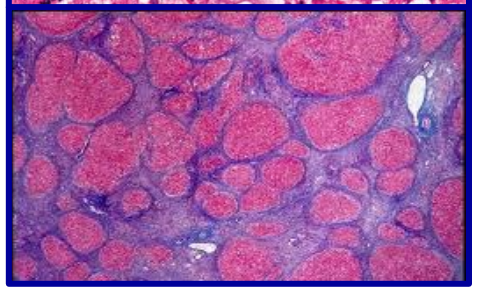
Alcohol-Related

(micronodular)

↓

(micro/macro)

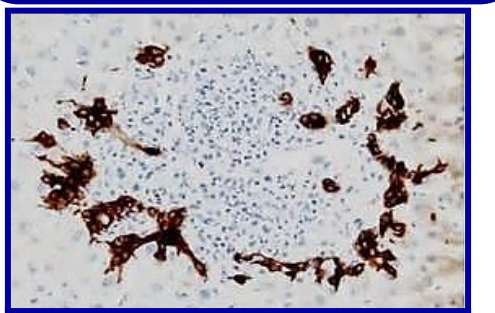


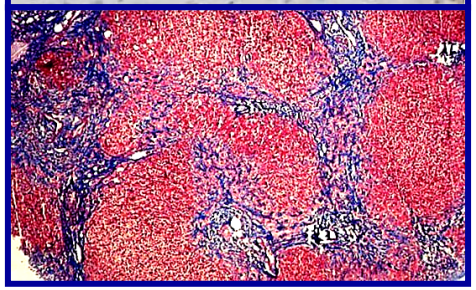


Biliary

EHBO, PBC, PSC

(unique nodularity)





Reversible

Less Reversible

Irreversible

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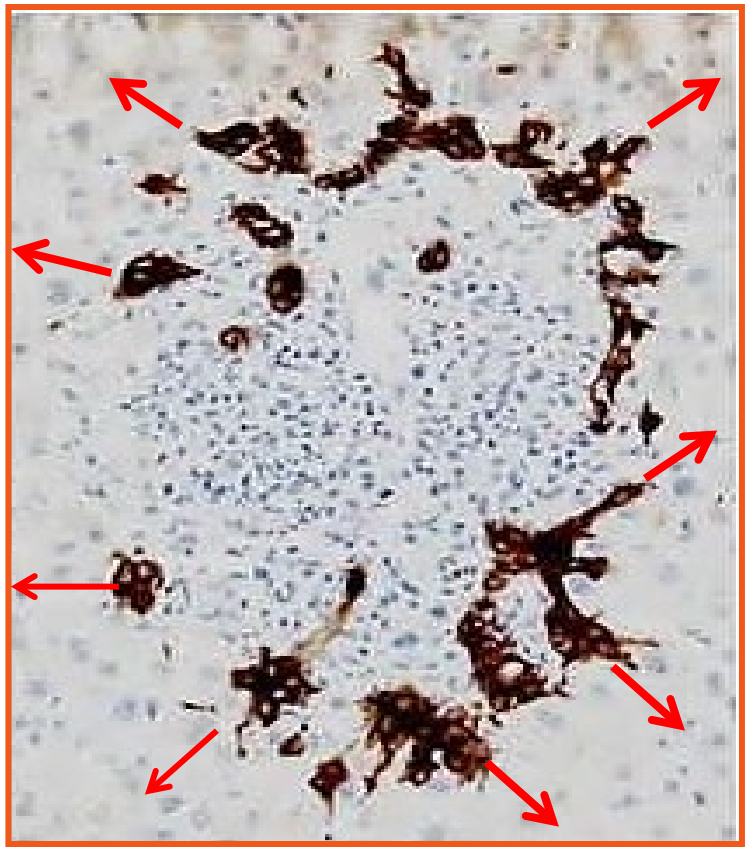
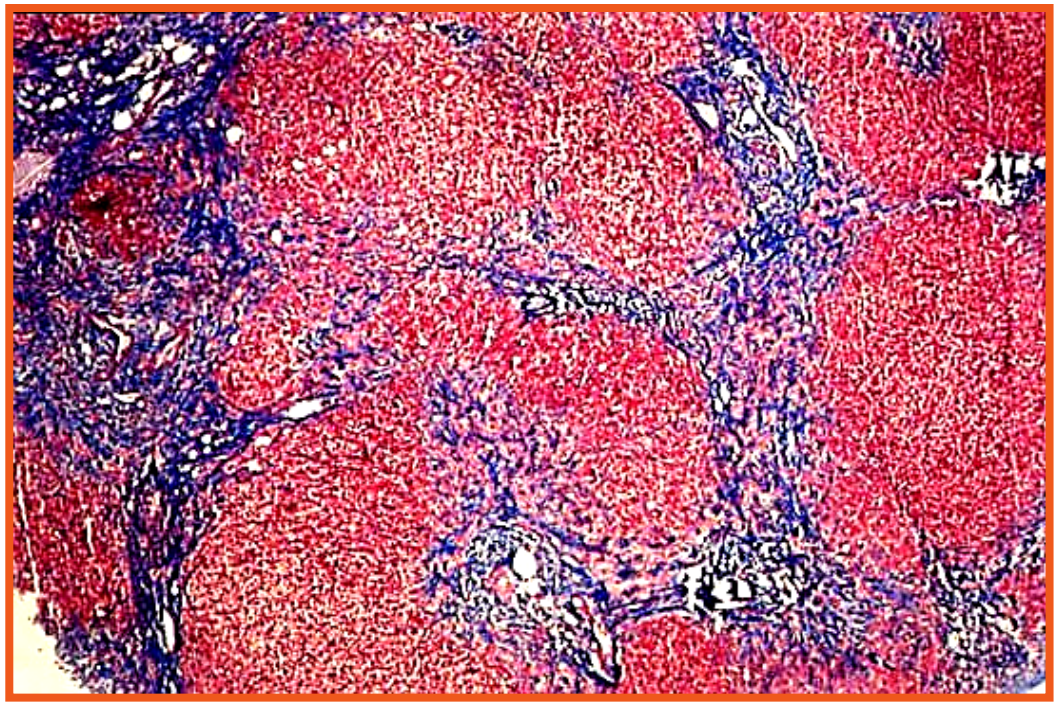
Primary Biliary Cholangitis
Ductular Reaction and Generation of Biliary Cirrhosis



Bile Ductular Reaction (CK-7+)



Biliary Cirrhosis (Jig Saw Puzzle)

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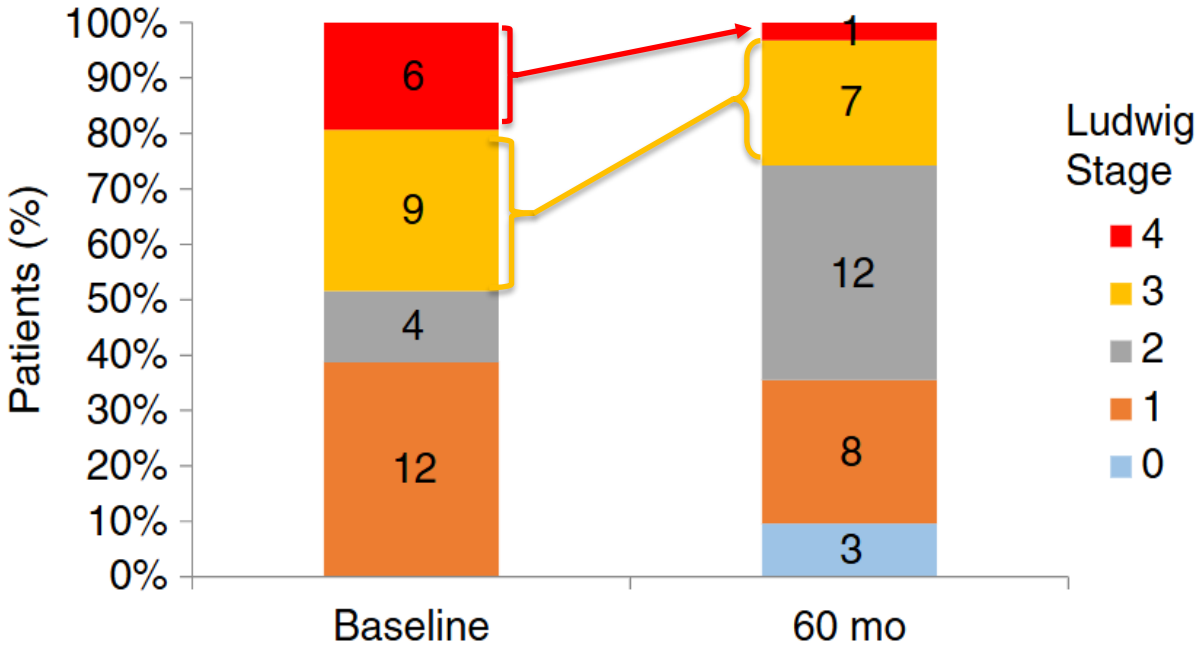
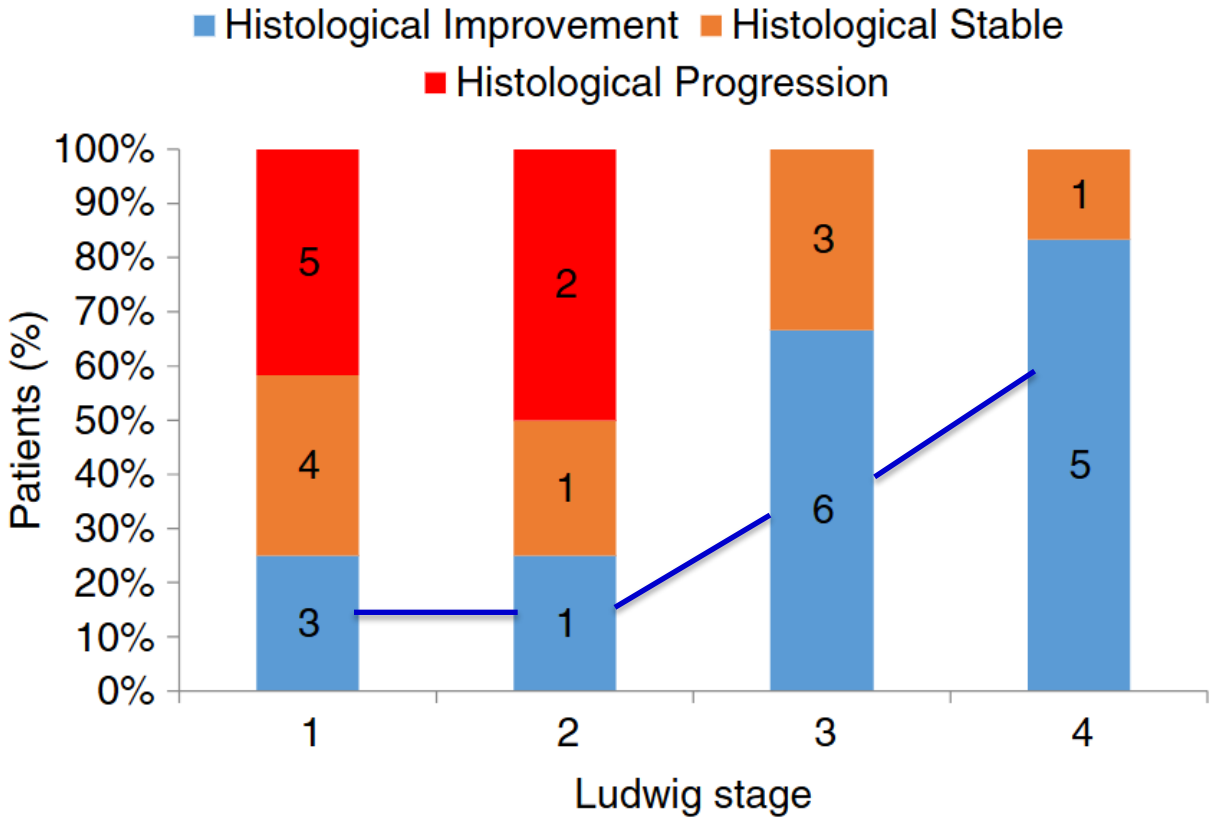
Primary Biliary Cholangitis
Reversibility of Partial/Incomplete Biliary Fibrosis

5-Year Data: Improvement in Fibrosis and Inflammation on Bezafibrate + UDCA

N= 49; 31 had paired liver biopsies





Sorda JA, et al. Aliment Pharmacol Ther. 2021 Nov;54(9):1202-1212.

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Key Points

1. Early diagnosis of patients with precirrhotic stages of fibrosis is required for optimal patient outcomes with either first or second-line therapies

2. Progressive ductopenia intensifies hepatocyte cholestasis, triggers the bile ductular reaction and drives biliary fibrosis

3. Partial/Incomplete biliary cirrhosis MAY BE reversible with multiple years of treatment

4. Ductopenia sufficient to generate **Complete Biliary Cirrhosis** creates a positive feedback loop producing additional fibrosis and preventing reversal of cirrhosis

Conclusion:

Effective treatment of early stage PBC (ductopenia <50%) crucial to prevent cirrhosis, complications of portal hypertension, liver failure, HCC, and need for OLT

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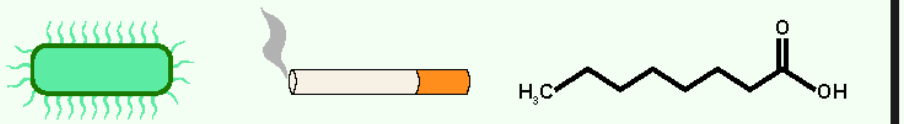
Thank You

Primary Biliary Cholangitis
Genetic Susceptibility and Environmental Triggers

Genetic factors

HLA genes:
HLA-DRB6, HLA-DQA2, HLA-DRB1, etc.

non-HLA genes:
IL-12A, IL-12B, IL-12RB2, CCL20, TNFSF15, POU2AF1, PRKCB, IL-21, IL-21R, STAT4, CD28/CTLA4/ICOS, CD58, ARID3A, IL16, etc.



Microbiome **Smoking** **Xenobiotics**

Environmental Triggers

Canada and N. America	Europe	Japan	China
IL-12A, IL-12RB2	CCL20, IL-12B ID2, TMEM163, PRDM1, CCR6, ETS1, FAM177A1	TNFSF15, POU2AF1, PRKCB	IL-21. IL-21R, STAT4, CD28-CTLA4-ICOS, CD58, ARID3A, IL-16 ID2, TMEM163, PRDM1, CCR6, ETS1, FAM177A1

Gut Dysbiosis (Abnormal Microbiota)	Smoking and Xenobiotics
Decreased diversity with ↑ levels of Enterobacteriaceae, Pseudomonas, Veillonella, Clostridium ↓ levels of beneficial Oscillospira, Sutterella ↓ conversion of primary to secondary bile acids	Cigarettes UTIs with antimicrobial treatment, Nail polish, Hair dyes, Poor hygiene in older patients

Tanaka A, Ma X, Takahashi A, Vierling JM. Lancet. 2024;404:1053-1066.

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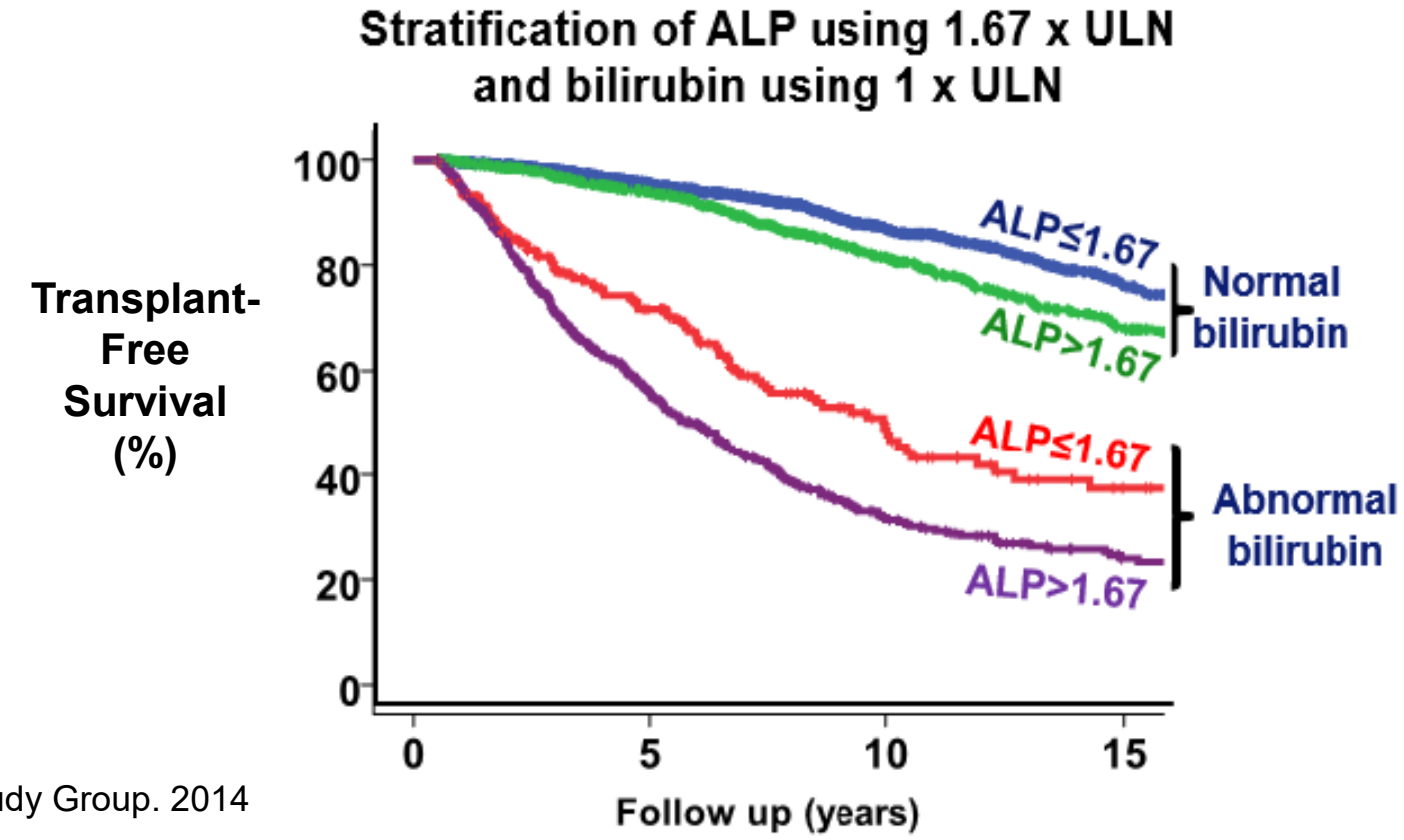
Surrogate Biochemical Endpoints for Therapeutic Trials in PBC
Biomarkers of Transplant-Free Survival

Composite Primary Endpoint for Clinical Trials:

- ALP <1.67xULN with ≥15% decline from baseline + Normal Total Bilirubin
- Accepted as primary endpoint for Regulatory Approvals of Second Line Therapies



Lammers WJ, et al. Global PBC Study Group. 2014

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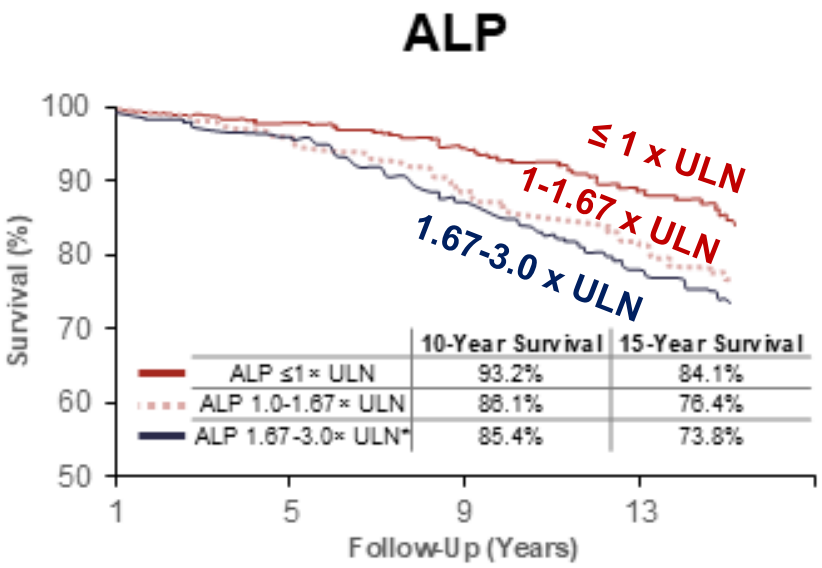
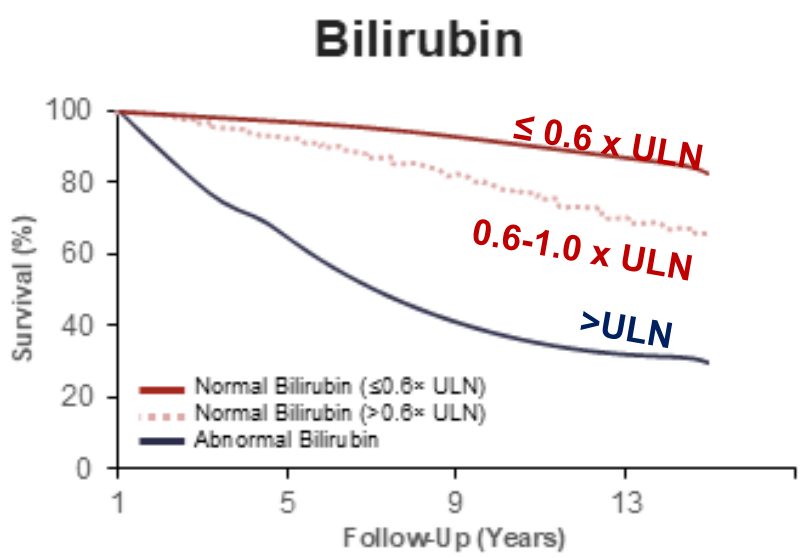
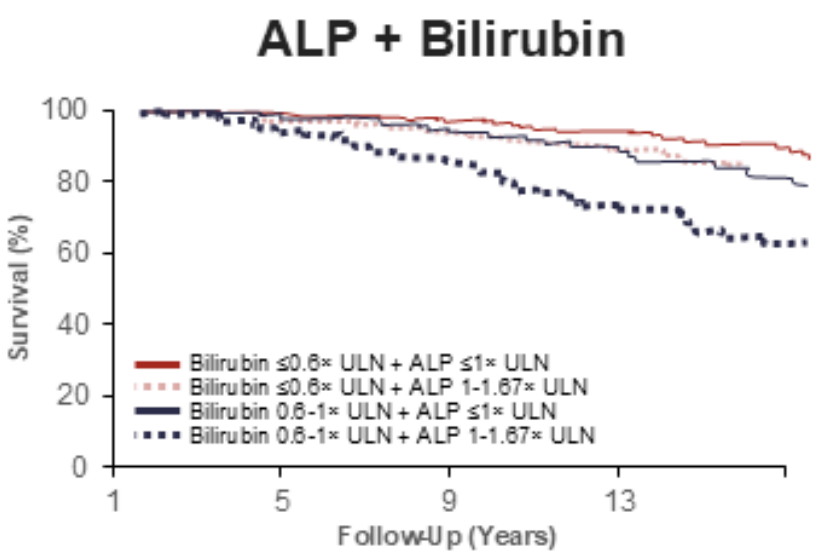
New PBC Biochemical Biomarkers of OLT-Free Survival
Normal ALP (≤ 1 x ULN) + Total Bilirubin <0.6 x ULN







Corpechot C, Hepatology. 2024 Jan 1;79(1):39-48; Murillo Perez CF, Am J Gastroenterol. 2020 Jul;115(7):1066-1074.

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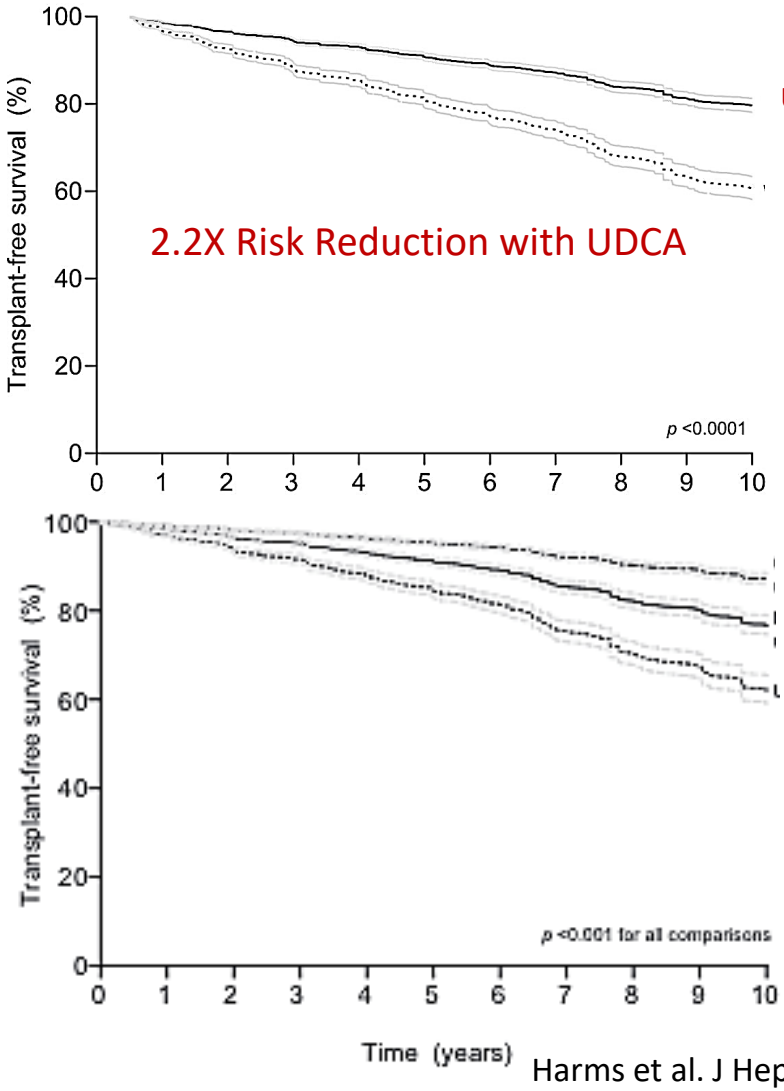
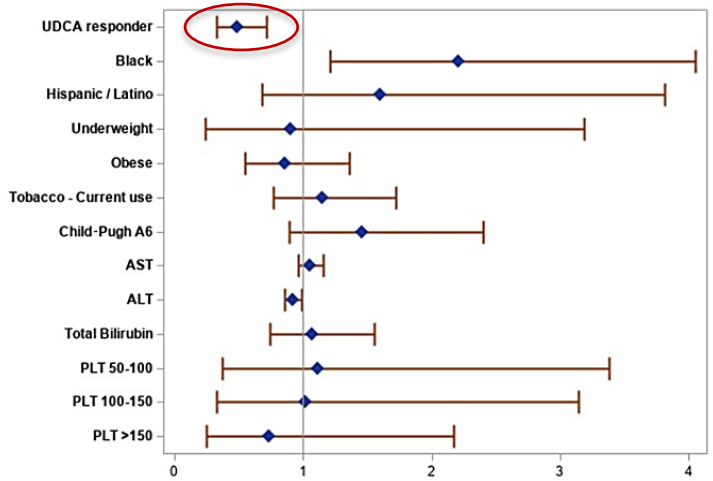
Primary Biliary Cholangitis: Positive Outcomes from UDCA Treatment

UDCA Impact on Transplant-Free Survival

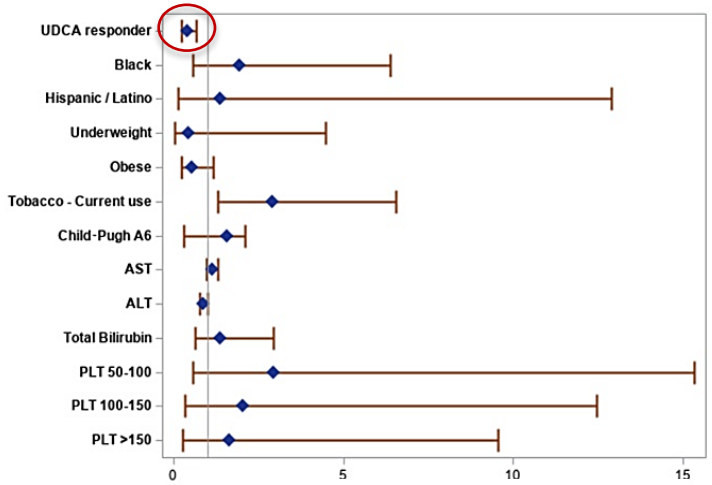


Harms et al. J Hepatol, 2019

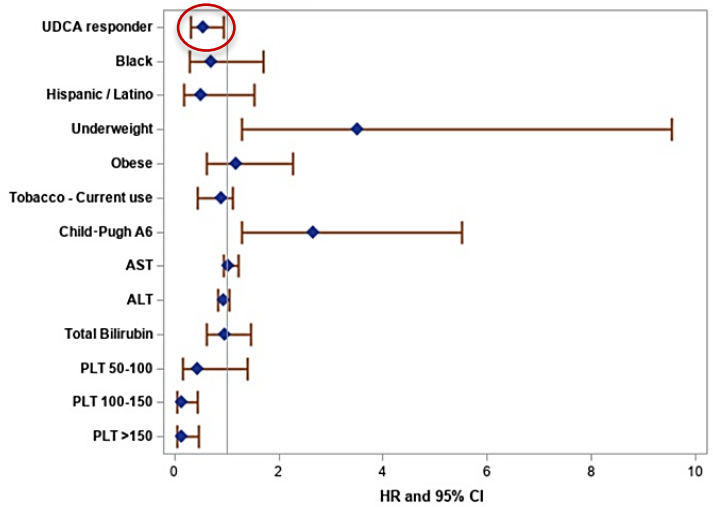
Death or Transplantation



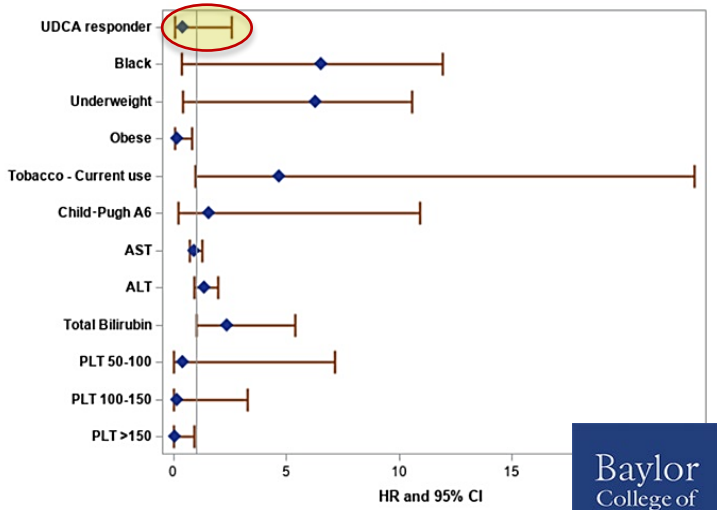
Liver Death or Transplantation



Decompensation



Hepatocellular Carcinoma



John B et al. Am J Gastroenterol, 2021

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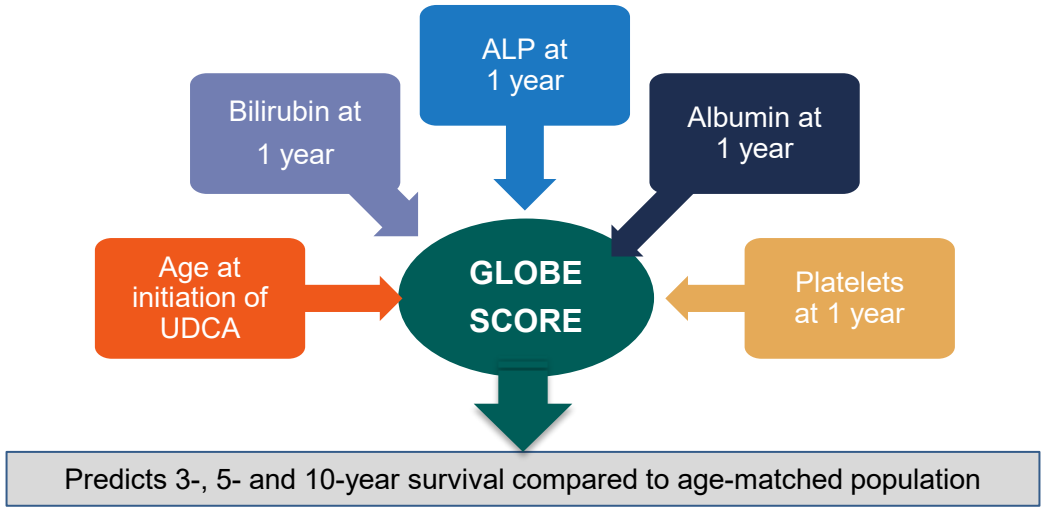
Primary Biliary Cholangitis:
GLOBE Score: Survival Benefit of UDCA Treatment

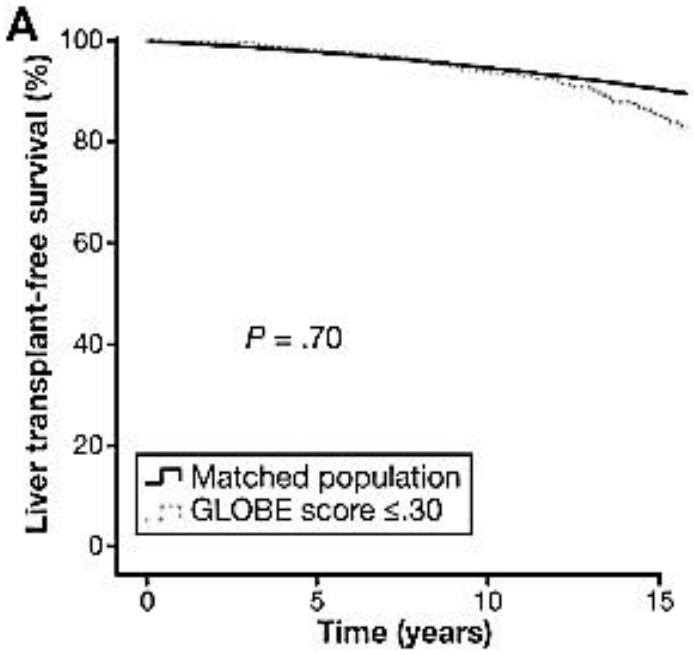


www.globalpbc.com

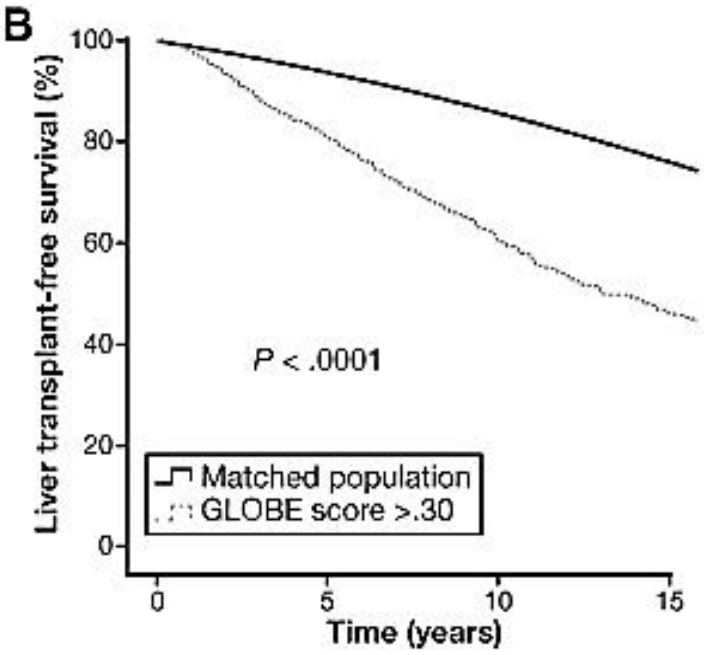
GLOBE Score Equation:

0.44378 X age at *start of UDCA*
+
0.93982 X Ln(Bili X ULN at 1 yr F/U)
+
0.335648 X Ln(ALP X ULN at 1 yr F/U)
–
2.266708 Alb X LLN at 1 yr F/U
–
0.002581 X Plts/10^9/L at 1 yr F/U

GLOBE Score ≤ 0.30



GLOBE Score > 0.30



Lammers WJ, et al. Gastroenterology. 2015; 149: 1804-12
AASLD Guideline. Lindor KD, et al. Hepatology. 2019;69(1):394-419

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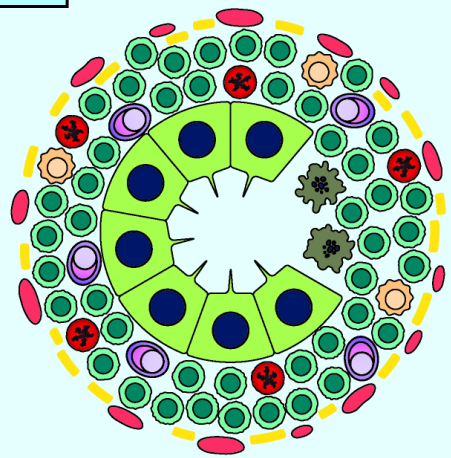
Primary Biliary Cholangitis
Summary of Progression

Initiation	Pre-Clinical	Early Clinical	Advanced Clinical
PBC 	**Histopathology:** ▪ Lymphoplasmacytic Portal Infiltrates ▪ Lymphocytic Cholangitis ± Florid Duct Lesions ▪ Displaced BM and PCP ▪ ± Granulomas **Autoantibodies:** ▪ AMA, ANA (Non-specific or Specific gp210, sp100), SMA	**Laboratory Tests:** ▪ Elevated ALP and ggt ▪ Variable elevation ALT, AST ▪ Elevated IgM **Signs or Symptoms:** ▪ Asymptomatic or Fatigue ▪ Cholestatic Pruritus ▪ Other AI Diseases **SOC Therapy:** ▪ UDCA ▪ FXR and PPARα/δ Agonists	**Intolerance or Inadequate Response to UDCA:** ▪ Progressive Ductopenia ↓ ▪ Progressive Ductular Reaction ↓ ▪ Biliary Fibrosis ↓ ▪ Biliary Cirrhosis

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