Mystery Case Presentation

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Ms. Jan Dice

- 45-year-old woman comes to your clinic complaining of pruritus and fatigue for several months.
- No significant medical history.
- Family history
  - Mother has Hashimoto's disease, dyslipidemia.
  - Father has hypertension, T2DM.
  - Sister has plaque psoriasis.
- Physical exam unremarkable except for xanthomas and skin excoriations on extremities.
- You order labs and schedule follow up visit in 1 week.

Initial Workup

CMP	
Na	140
K	3.7
Chl	102
HCO	31
BUN	10
Cr	0.89
AP	467
Alb	3.6
TP	7.8
AST	112
ALT	146
TB	5.4
GGT	135
Lipase	144

HIV
Negative

CBC	
WBC	6.0
HGB	13.7
HCT	42.9
MCV	91.6
PLTS	222

ESR	8
CRP	2.0

TSH	1.2
T-4	6.0

INR
1.0

Hepatitis serologies	
HAV IgM	Non-reactive
HBsAg	Non-reactive
HBcAB	Non-reactive
HBcIgM	Non-reactive
HCV Ab	Non-reactive

What Could This Be?

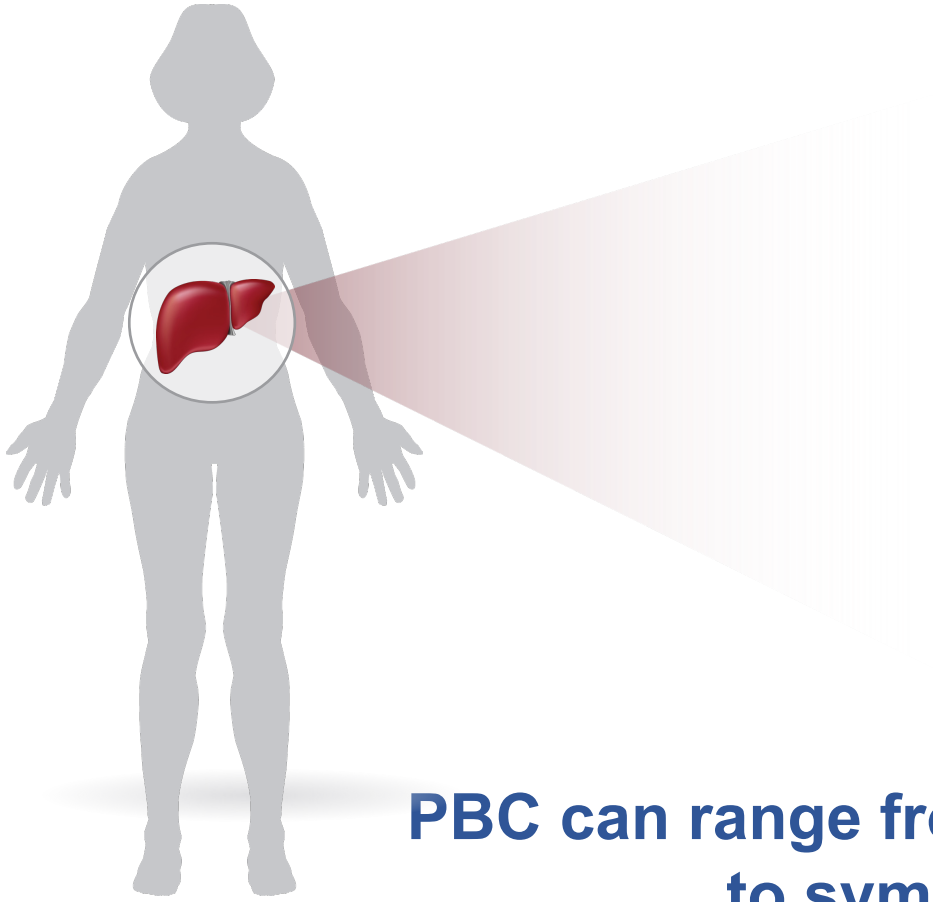
Differential Diagnosis

- Cholestatic liver disease (symptoms, elevated ALP/GGT/TB)
    - Primary biliary cholangitis (PBC)
    - Primary sclerosing cholangitis (PSC)
- What would you order next?
    - Labs
    - Imaging

Primary Biliary Cholangitis (PBC)

What is the typical presentation?

Clinical Features Vary Greatly Between Patients



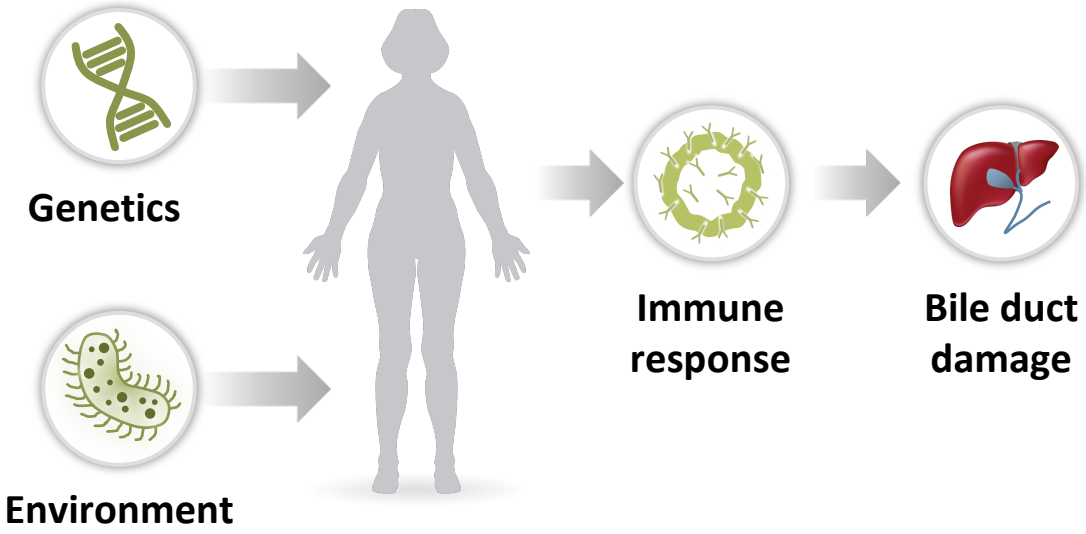
- Fatigue[1,2]
- Pruritus[1,2]
- Concurrent autoimmune diseases[1,2]
- Reduced bone density[1,2]
- Hypercholesterolemia[1,2]
- Xanthoma and Xanthelasma[2,3]

PBC can range from asymptomatic and slowly progressive to symptomatic and rapidly evolving.[1]

1. Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609; 2. Carey EJ, et al. *Lancet*. 2015;386(10003):1565-1575;
3. Lindor KD, et al. *Hepatology*. 2009;50(1):291-308.

PBC is a Chronic, Progressive Autoimmune Disease

- Factors possibly associated with onset and perpetuation of bile-duct injury in PBC



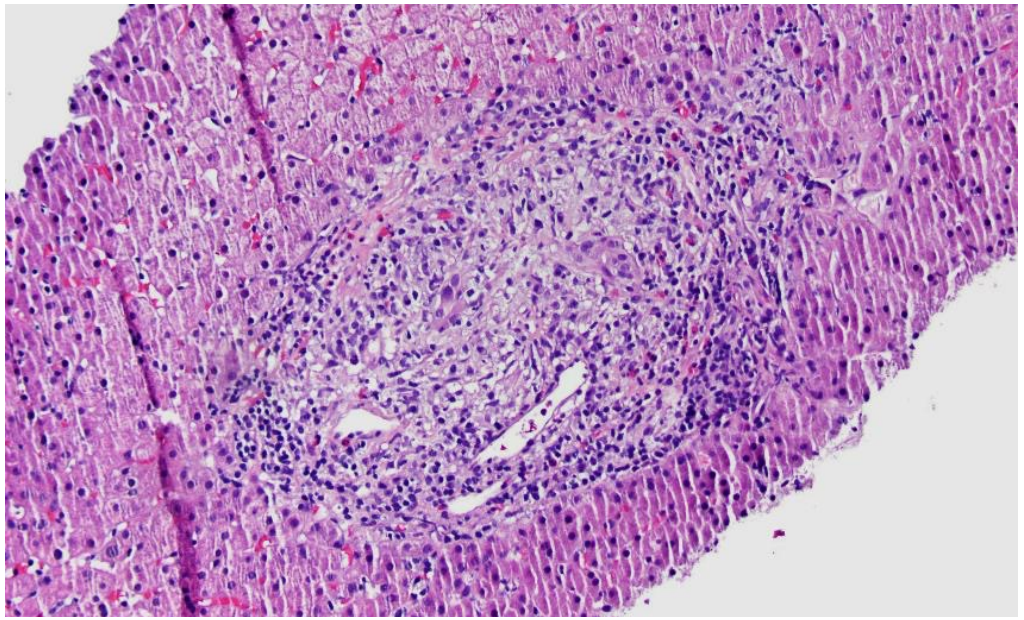
PBC is characterized by destruction of the interlobular and septal bile ducts that may lead to cirrhosis

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.

PBC Diagnostic Criteria

PBC Diagnosis

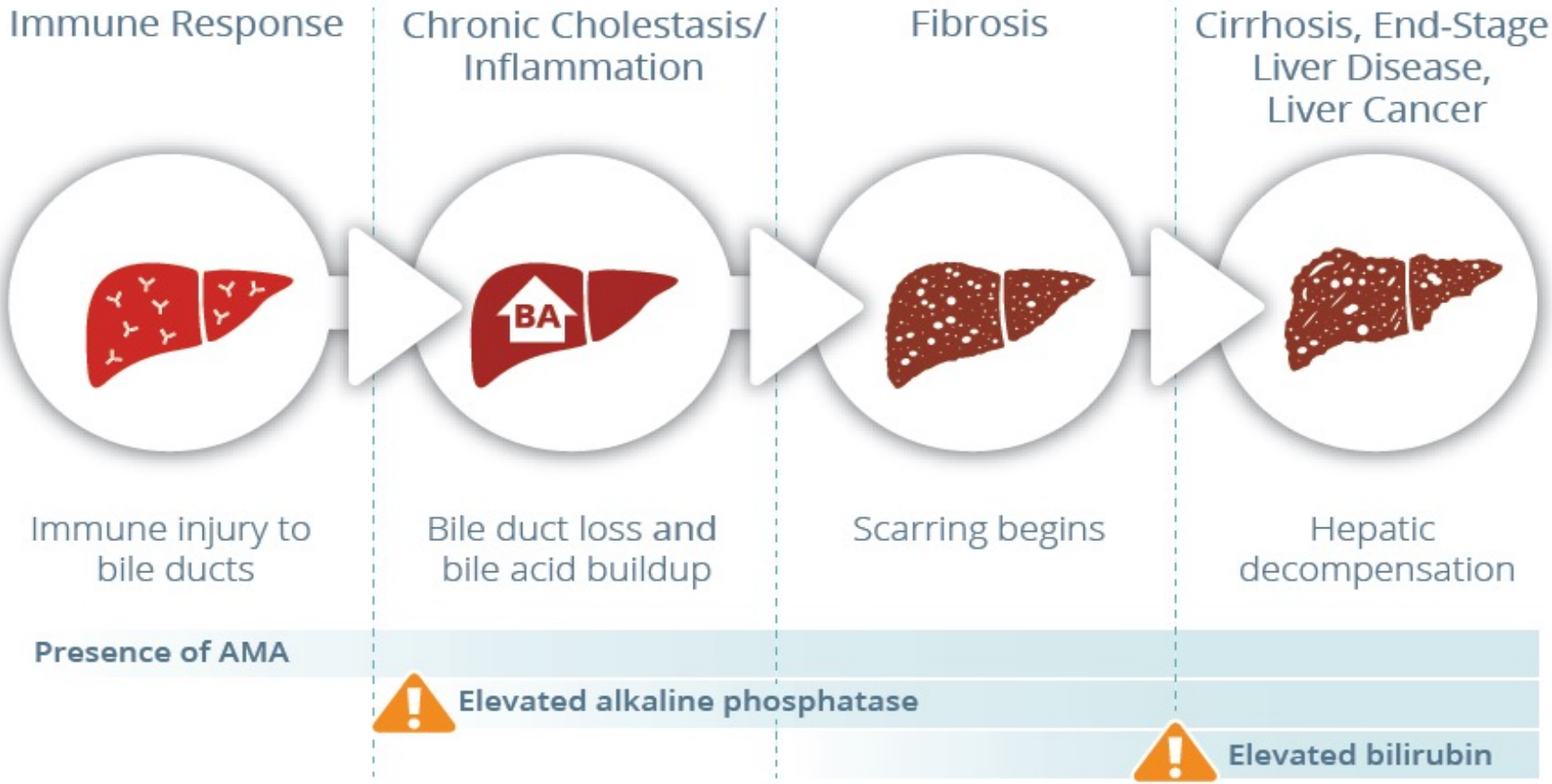
- Unexplained Elevation of ALP ≥ 1.5x ULN
- Positive anti-mitochondrial antibody (AMA)
- Non-suppurative destructive cholangitis on histology



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

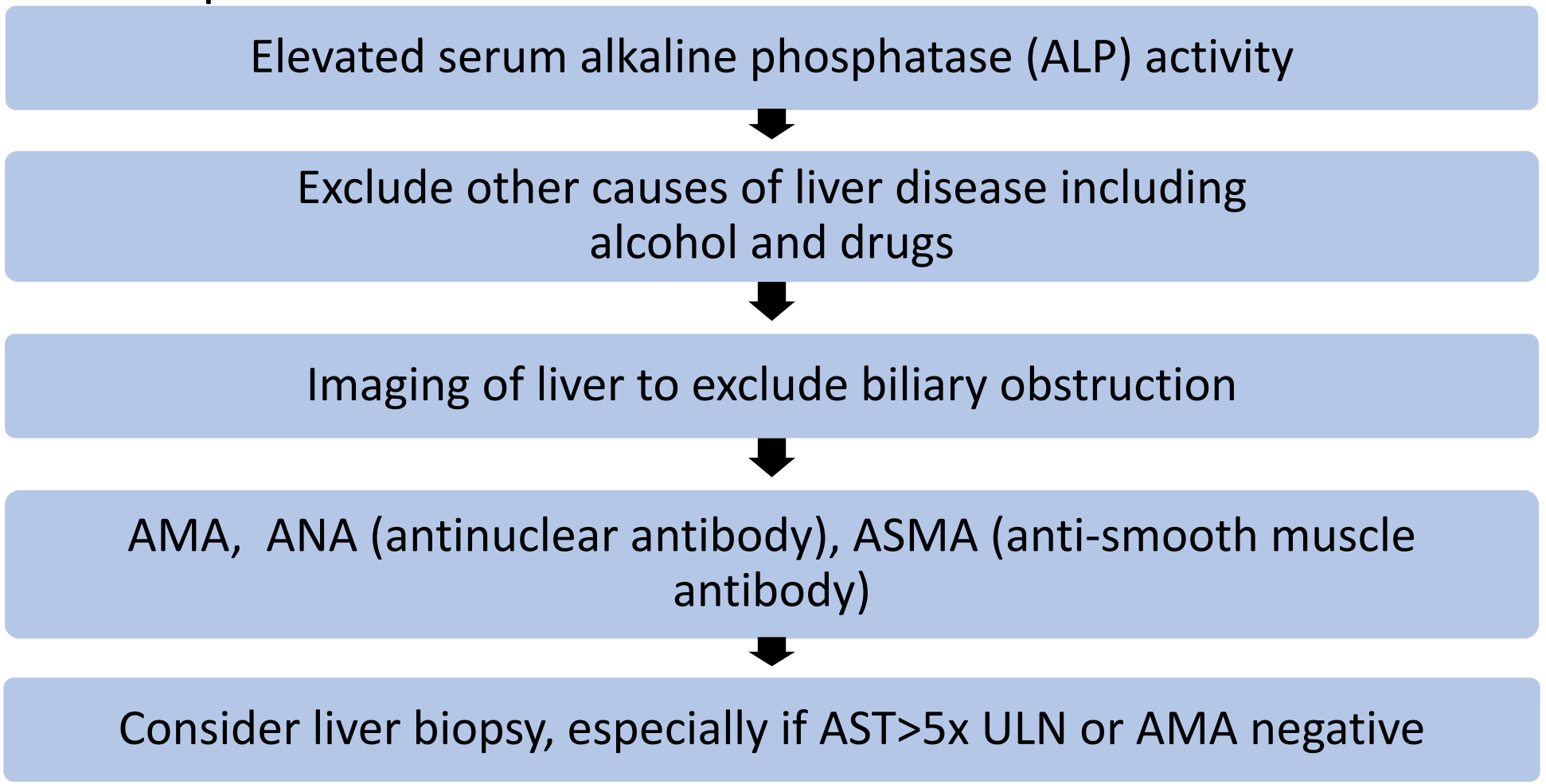
If Left Inadequately Treated, PBC May Result in Liver Failure, Transplant, or Death

Persistent, toxic exposure to bile acid buildup ultimately leads to end-stage disease



1. Poupon R. *J Hepatol.* 2010;52(5):745-758. 2. Dyson JK, et al. *Nat Rev Gastroenterol Hepatol.* 2015;12(3):147-158. 3. Lammers WJ, et al. *Gastroenterology*. 2014;147(6):1338-1349. 4. Selmi C, et al. *Lancet.* 2011;377(9777):1600-1609.

AASLD Suggested Diagnostic Algorithm for Patients with Suspected PBC



Fatigue Is the Most Common Symptom in PBC

- Fatigue is present in up to 85% of patients with PBC
  - >40% report moderate to severe
- The mechanism of fatigue in PBC is not well understood
- Fatigue in PBC is unrelated to disease activity or stage, and tends to wax and wane throughout the course of illness
- Fatigue in PBC typically is characterized as daytime somnolence, potentially impairing QoL[1]

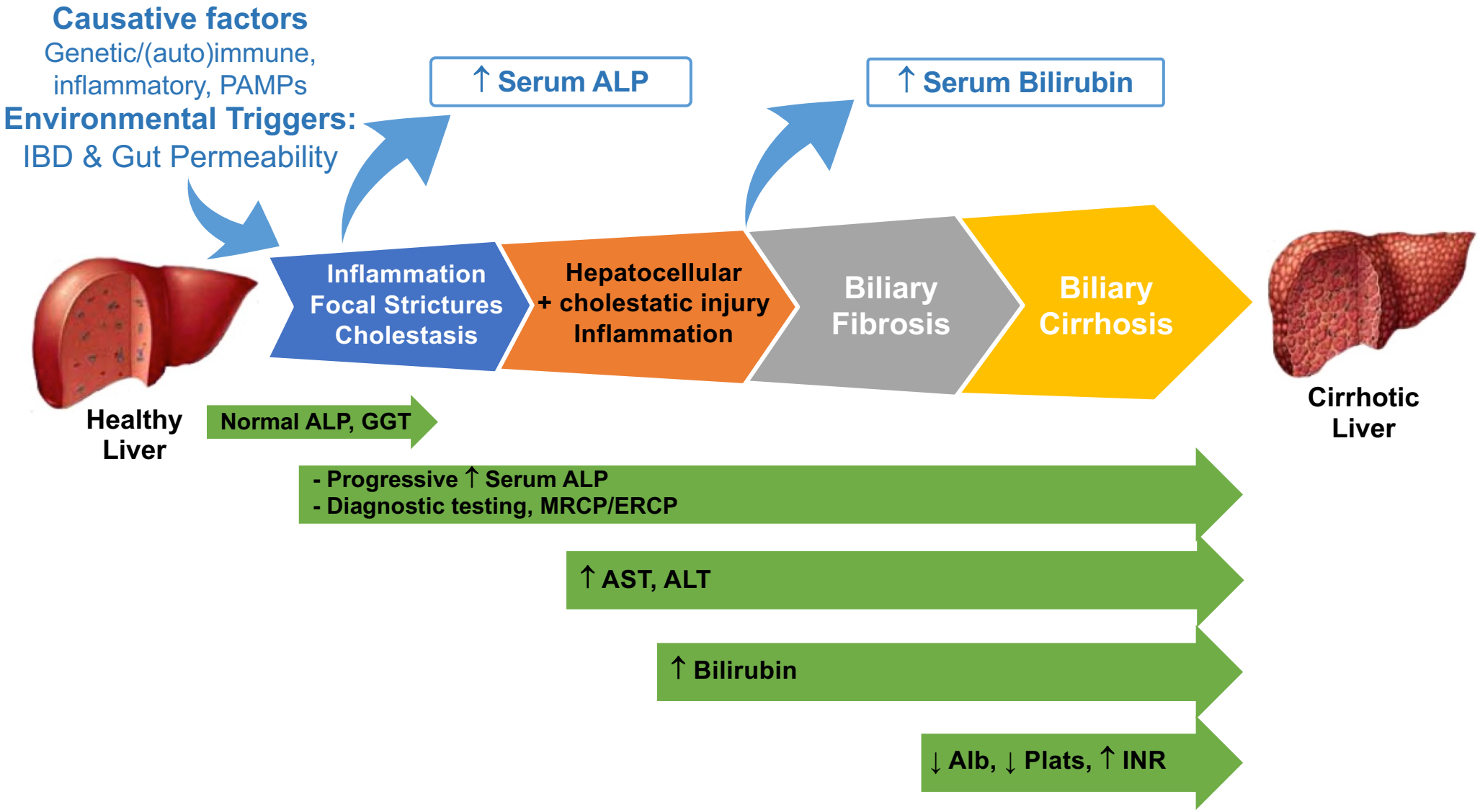
Despite sparse correlation between fatigue and severity of liver disease, fatigue can be associated with decreased overall survival[1]

1. Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609. 2. Carey EJ, et al. *Lancet*. 2015;386(10003):1565-1575. 3. Huet PM, et al. *Am J Gastroenterol.* 2000;95(3):760-767.

Primary Sclerosing Cholangitis (PSC)

What is the typical presentation?

Primary Sclerosing Cholangitis (PSC): Autoimmune Disease



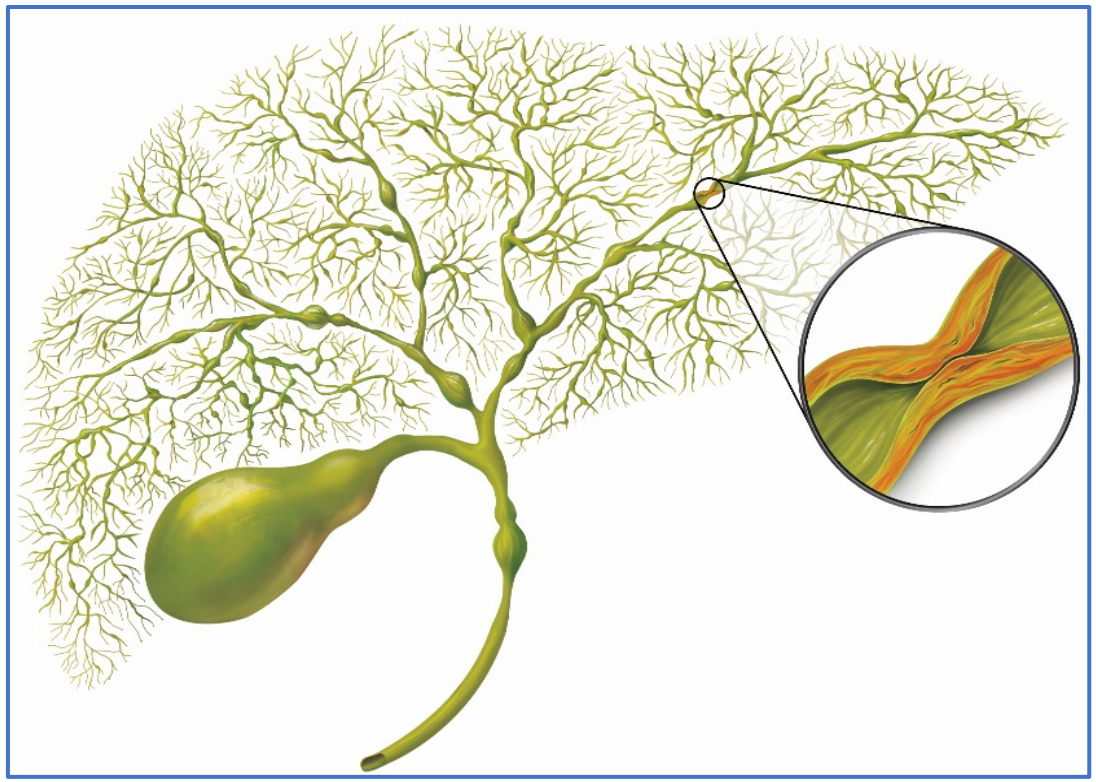
Primary Sclerosing Cholangitis (PSC)

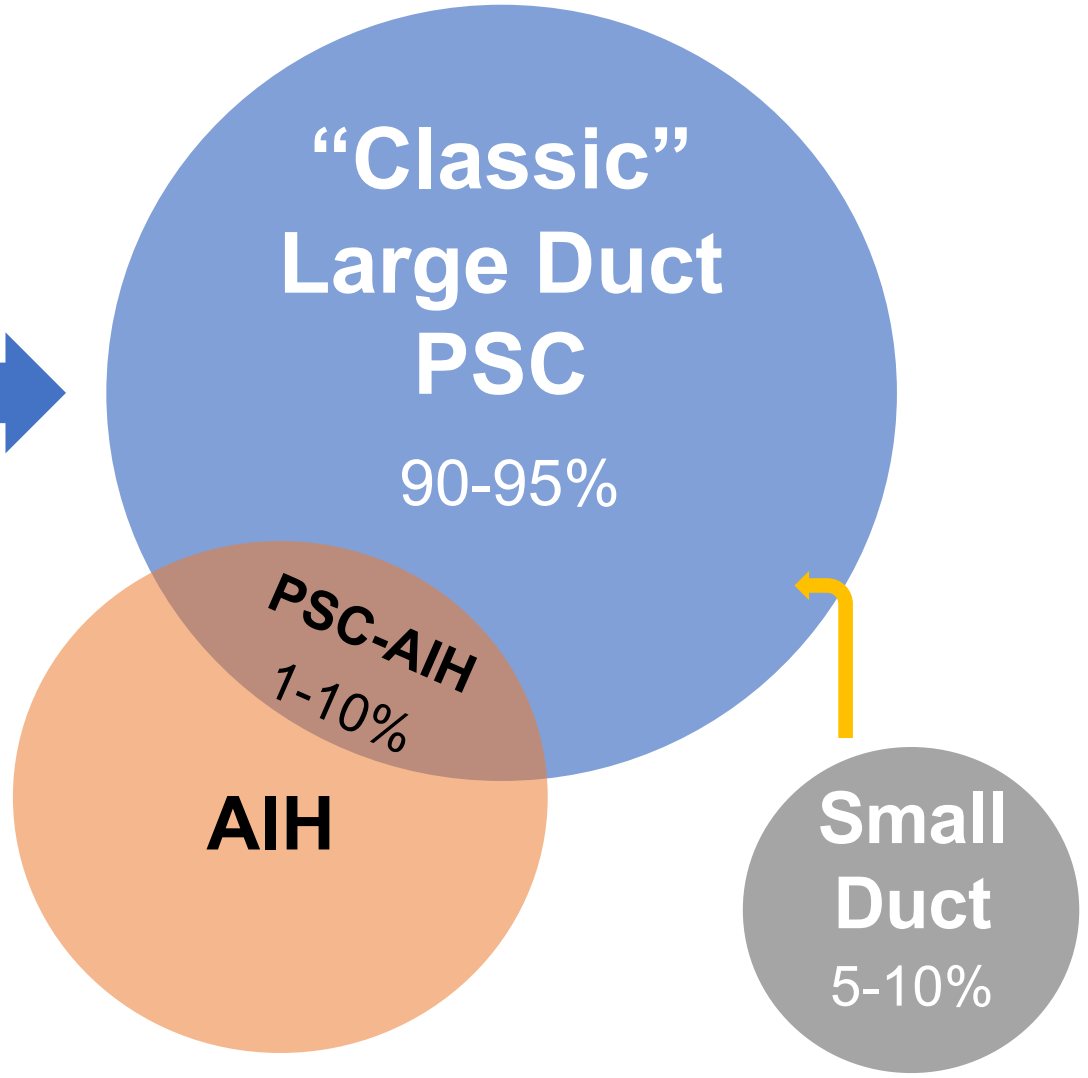
Demographics and Epidemiology

- Afflicts all ages and races
- Prevalence ~ 40 per million with familial predisposition
  - 0.7% among 1st degree relatives (100-fold ↑)
  - 1.5% among siblings
- Male: Female Ratio: 1.5:1 (60% males)
- Diagnosis <45 years of age in 67%

Primary Sclerosing Cholangitis (PSC)

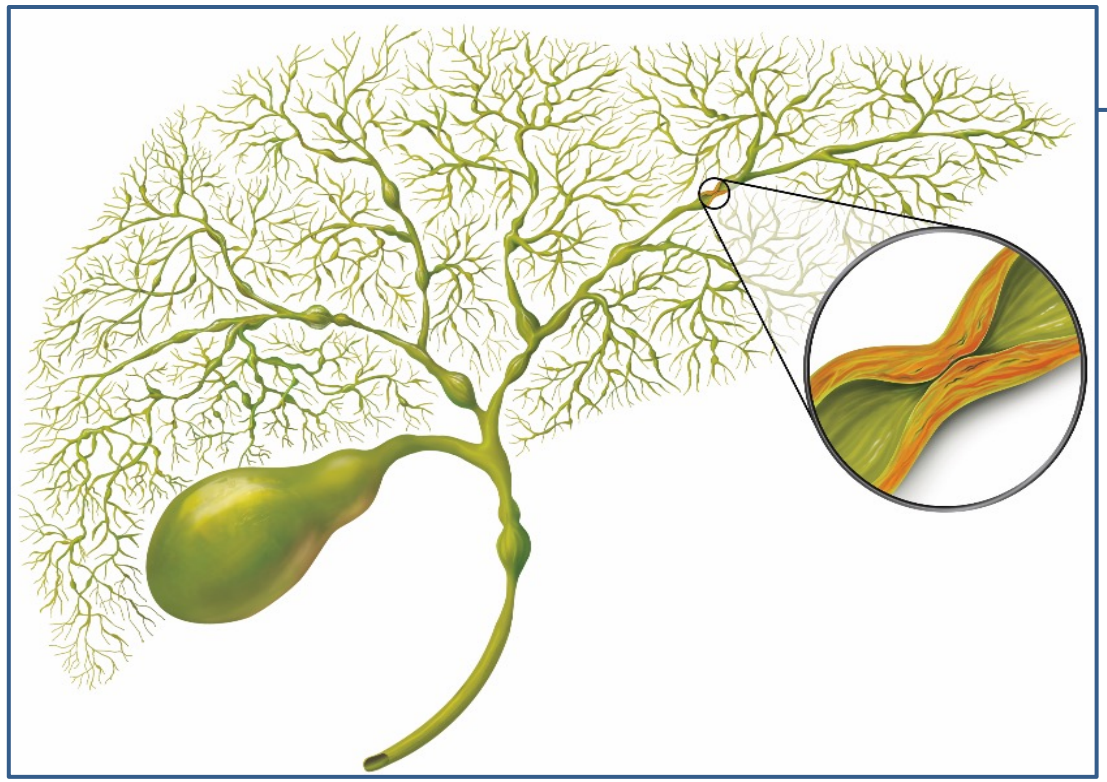
Three Distinct Clinicopathological Entities

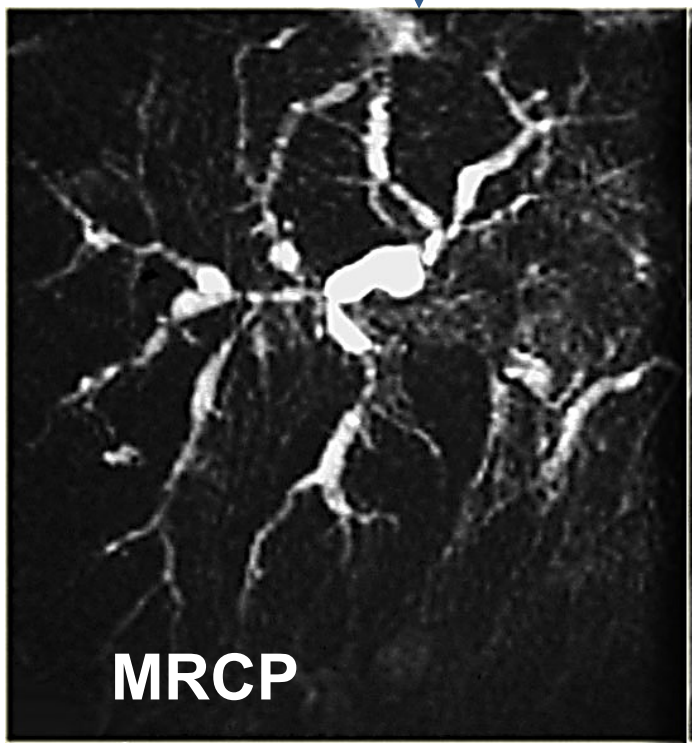


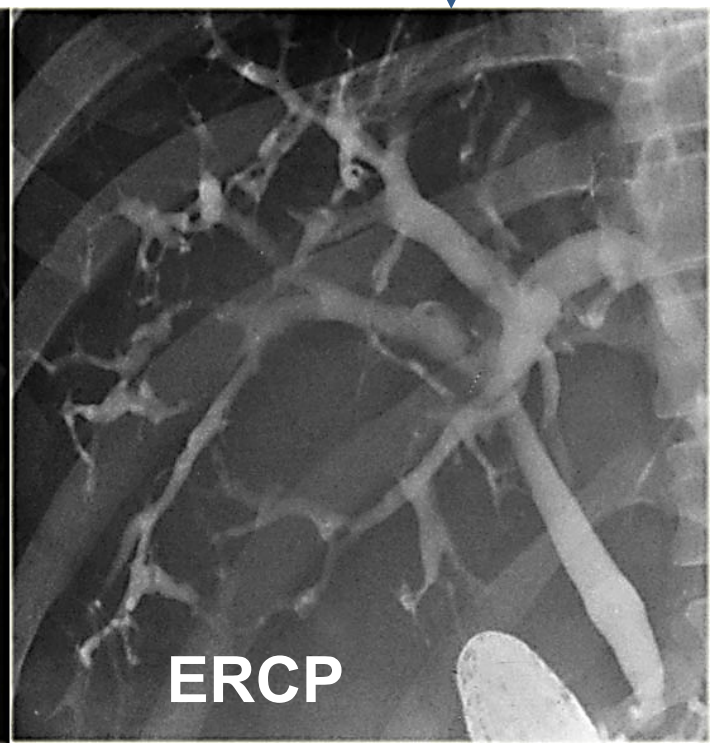


Primary Sclerosing Cholangitis (PSC)

Cholangiography for Detection of Large Duct Disease







Vierling JM. PSC. *Schiff's Liver Diseases.* 12th Ed. 2017.

Primary Sclerosing Cholangitis (PSC)

Strong Association with Inflammatory Bowel Disease (IBD)

Association with colitis:

- Ulcerative colitis: 70-98%, often with a rarer UC phenotype
  - Rectal sparing (52% vs 6%)
  - Backwash ileitis 51% vs 7%)
- Crohn's colitis or ileocolitis: 3-13%

Prevalence of IBD Colitis:

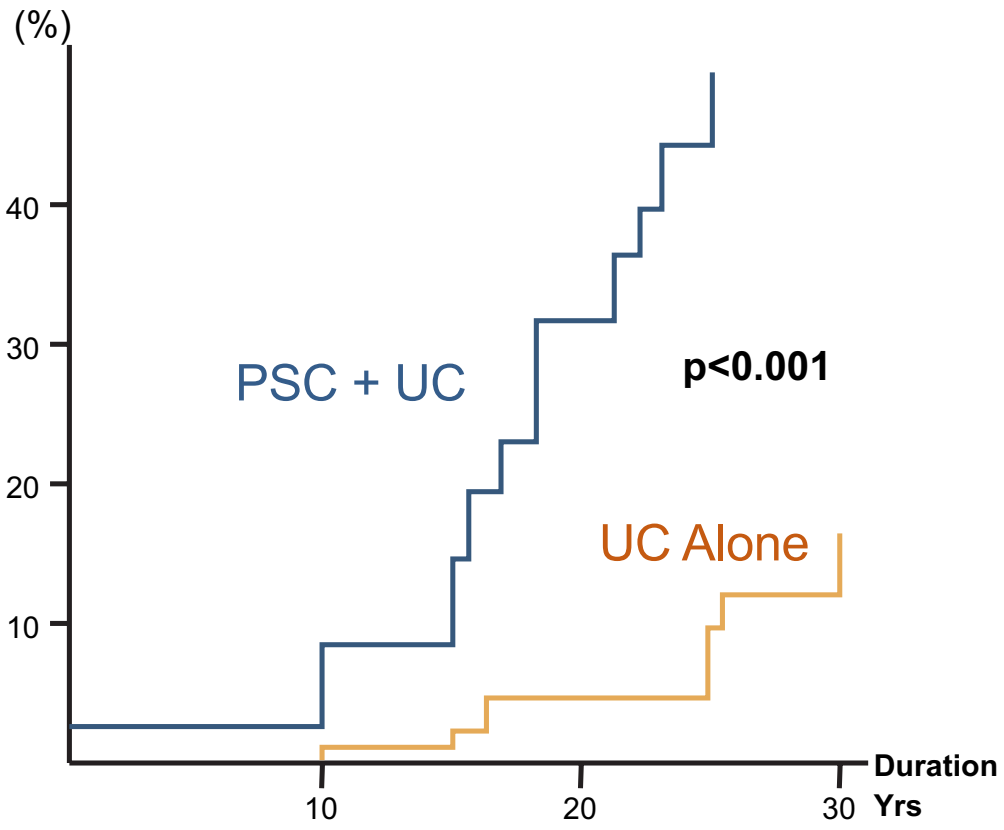
- 50% at time of PSC diagnosis
- Increases to ≥80% with time
- Prevalence of PSC in IBD Centers
  - USA using ERCP for elevated ALP:
    - 2.3-4.6% in UC
    - 1.2-3.6% in CD
- Systematic MRCP screening: PSC in 8.1% (65% had liver tests WNL)

Vierling JM. PSC. *Schiff's Liver Diseases.* 12th Ed. 2017.

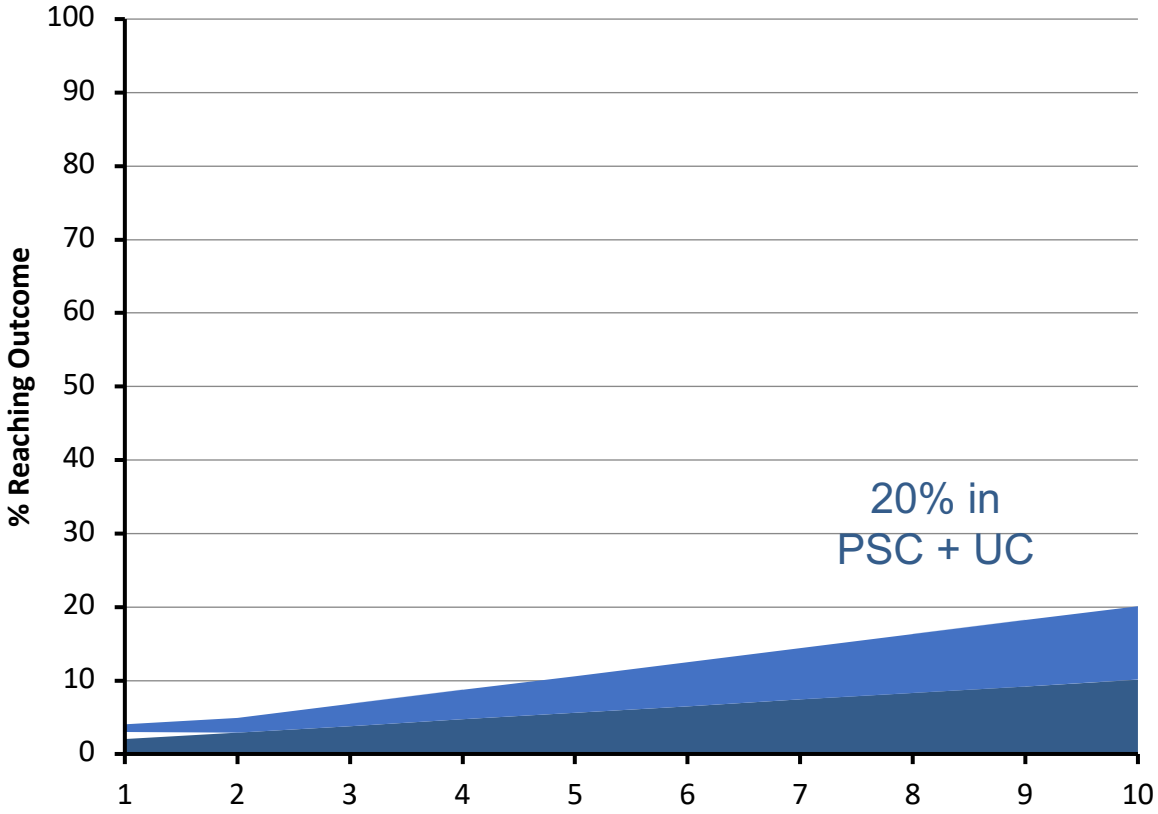
Primary Sclerosing Cholangitis (PSC)

Independent Risk Factor for Colorectal Carcinoma

Historic Cumulative Rate



Current Cumulative Rate



Broome U, et al. *Hepatology*. 1995; 22: 1404-8;
Vierling JM. PSC. *Schiff's Liver Diseases.* 12th Ed. 2017.

Primary Sclerosing Cholangitis (PSC)

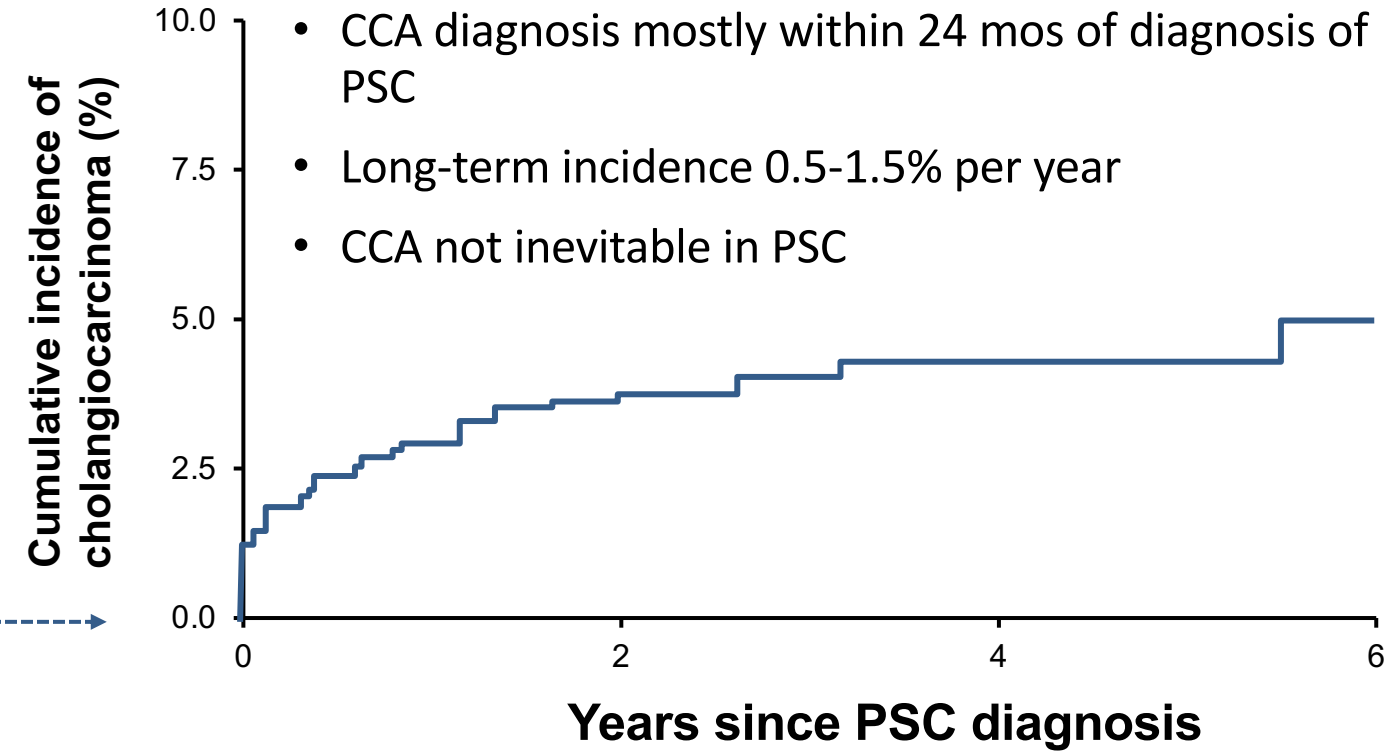
Risk Factor for Cholangiocarcinoma

Cholangiocarcinoma:

- Relative Risk = 160 to 1560
- Prevalence = 4.8% to 36.4%
- Annual incidence = 0.6% to 1.5%
- 38% to 50% of cases diagnosed within 1-year
- 2.5% incidence in first year

Important Conclusions:

- CCA diagnosis mostly within 24 mos of diagnosis of PSC
- Long-term incidence 0.5-1.5% per year
- CCA not inevitable in PSC



Am J Gastroenterol. 2004;99:523-526; *J Hepatol.* 2002;36:321-327; *Am J Surg Pathol.* 2007;31:907-13; *J Hepatol.* 2010;53:313-7; Burak et al. *Am J Gastroenterol*. 2004;99:523.

Primary Sclerosing Cholangitis (PSC)

Risk Factor for Gallbladder Adenocarcinoma

Gallbladder Adenocarcinoma:

- Prevalence = 0.9% to 14%
- High rate of dysplastic polyps
- Cholecystectomy appropriate:
  - Any growing polyp (regardless of size)
  - Any polyp ≥1 cm

Am J Gastroenterol. 2004;99:523-526; *J Hepatol.* 2002;36:321-327; *Am J Surg Pathol.* 2007;31:907-13; *J Hepatol.* 2010;53:313-7.

Primary Sclerosing Cholangitis (PSC)

Surveillance for Cancers

Cancer	Imaging and/or Endoscopy	Laboratory Testing	Comments
Colorectal carcinoma	Annual Colonoscopy	CEA	4 quadrant biopsies every 10 cm cecum to anus to assess for both aneuploidy & dysplasia
Cholangiocarcinoma	Annual MRCP ERC & cholangioscopic biopsies of suspicious strictures	CA-19-9 semiannually (only ABO Lewis Ag+) CEA?	FISH aneuploidy analysis required CA-19-9: false+ elevations with cholangitis or non-malignant obstruction
Gallbladder carcinoma	Annual US or cross-sectional imaging	No defined or exploratory biomarkers	High suspicion for any polyp, especially if enlarging. Inappropriate to observe until 1 cm dia

Vierling JM. PSC. *Schiff's Liver Diseases.* 12th Ed. 2017.

Next Steps for Ms. Dice

- Order additional labs
  - Rule out metabolic/genetic and infectious causes
  - Differentiate between PBC and PSC
- Imaging
  - FibroScan for disease severity
  - DEXA for bone density
  - MRCP if PSC is disease suspected

Further Workup

Autoimmune	
ASMA	Non-detected
AMA	1:640
Anti-LKM	2.0
Serine protease 3-Ab	Non-detected
ANA	<1:40
IgM	500
IgA	202
IgG	1412

U/S: Hepatomegaly with increased echogenicity; no splenomegaly

Infectious	
HBV PCR	Non-detected
HEV IgM	Negative
HEV IgG	Negative
HCV Ab	Non-reactive
HCV RNA PCR	Non-detected
HSV IgG/IgM	0.34/0.59
CMV PCR Quant	<137
EBV plasma	Non-detected

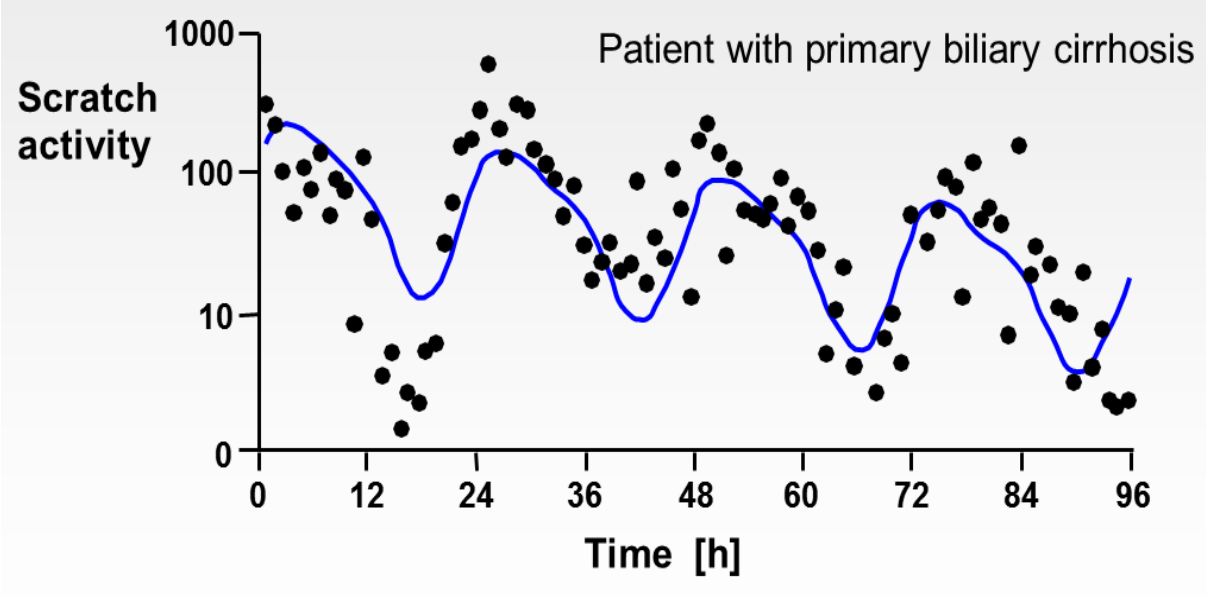
Metabolic/Genetic	
A1AT	132
Ceruloplasmin	22
Copper urine 24 hour	24
Ferritin	123
HFE mutations	Negative
Iron	231
LDH	250
B12	9102

**Positive AMA and elevated ALP = PBC

First Let’s Manage Pruritus

Cholestatic Pruritus – PBC

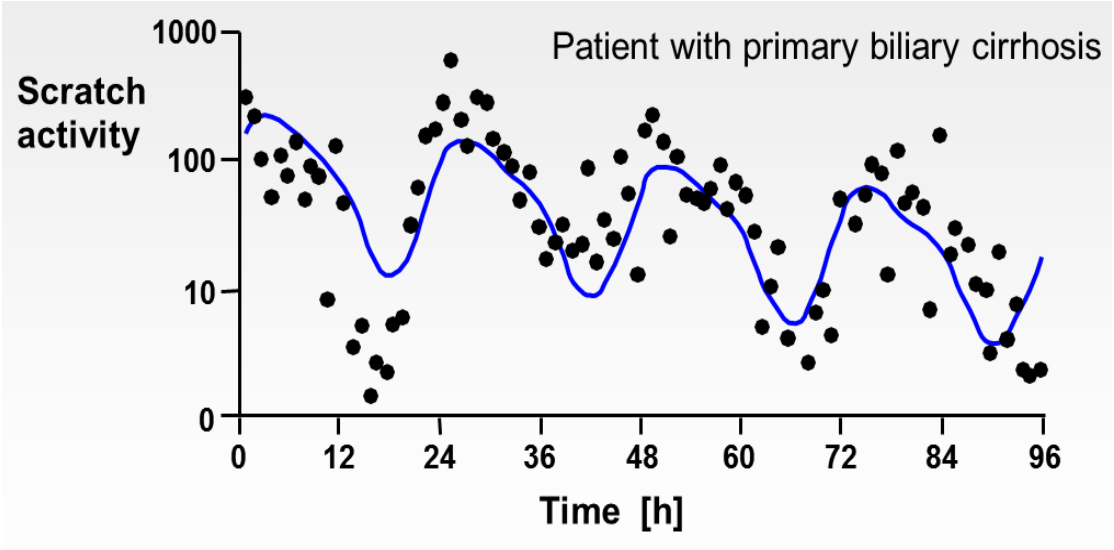
- Unpleasant sensation of the skin that triggers need to scratch
- Intermittent; seasonal variation; worse in the heat
- Diurnal variation, worse at night
- Among those reporting pruritus: 64.5% mild, 31.3% moderate and 4.2% severe



Talwalkar et al. *Clin Gastroenterol and Hepatol*. 2003; Carbone et al. *Gastro*. 2013.

Pruritus in Cholestatic Disease

- Occurs in 20%-70% of patients with PBC
  - In most patients, pruritus is mild to moderate
- Pruritus severity is variable and not correlated to disease severity or prognosis
- Characteristics
  - Diurnal variation: most intense in late evening
  - Typically localized to limbs, soles of feet, and palms of hands
  - Often exacerbated by contact with wool or other fabrics, heat, or pregnancy
- Impact of pruritus should not be underestimated – represents a significant burden for patients living with PBC
- Intractable pruritus can lead to liver transplant



1. Carey EJ, et al. *Lancet*. 2015;386(10003):1565-1575. 2. Imam MH, et al. *J Gastroenterol Hepatol*. 2012;27(7):1150-1158.

Stepwise Approach to Pruritus

General advice

First-line agent:
Cholestyramine

Second-line agents:
Rifampin
Naltrexone
Sertraline

Other treatments:
Fibrates
IBATs
Nasobiliary drainage
MARS
Phototherapy
Plasmapheresis
**Active area of clinical research

Liver Transplantation
Patients without significant hepatic dysfunction will need exemption points

**Prescribed cholestyramine (4g/day and will titrate up to 16g/day, if needed)

De Vries et al. *Gastroenterology*. 2021; Golpanian, Yosipovitch and Levy. *Dig Dis Sci*. 2021; Lindor et al. *Hepatology*. 2019.

Staging Liver Disease

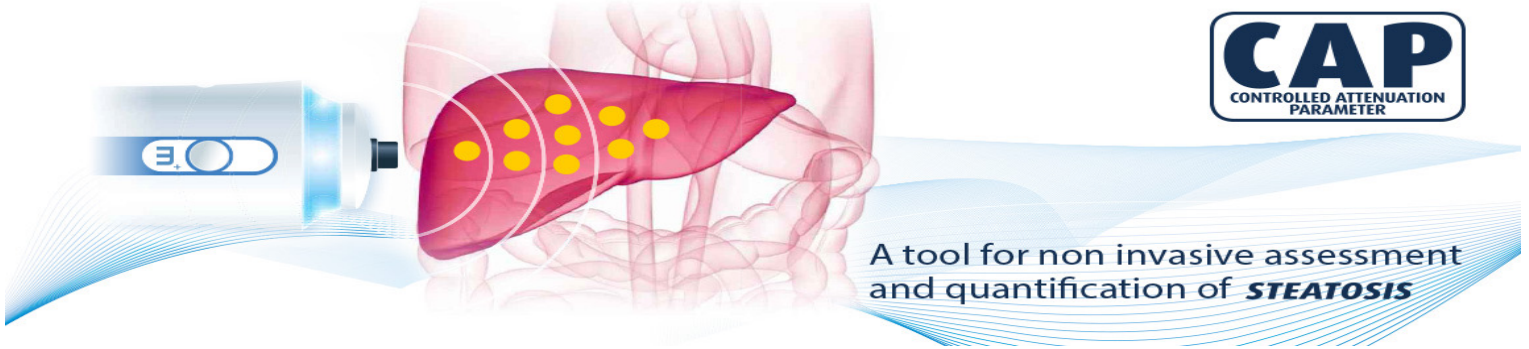
Laboratory Tests For Liver Fibrosis

- Simple
  - Fibrosis-4 (FIB-4)
  - NAFLD fibrosis score (NFS)
  - AST/platelet ratio index (APRI)
- Proprietary
  - Enhanced Liver Fibrosis Test (ELF)
  - ADAPT/Pro-C3
  - FibroSure
  - Hepascore

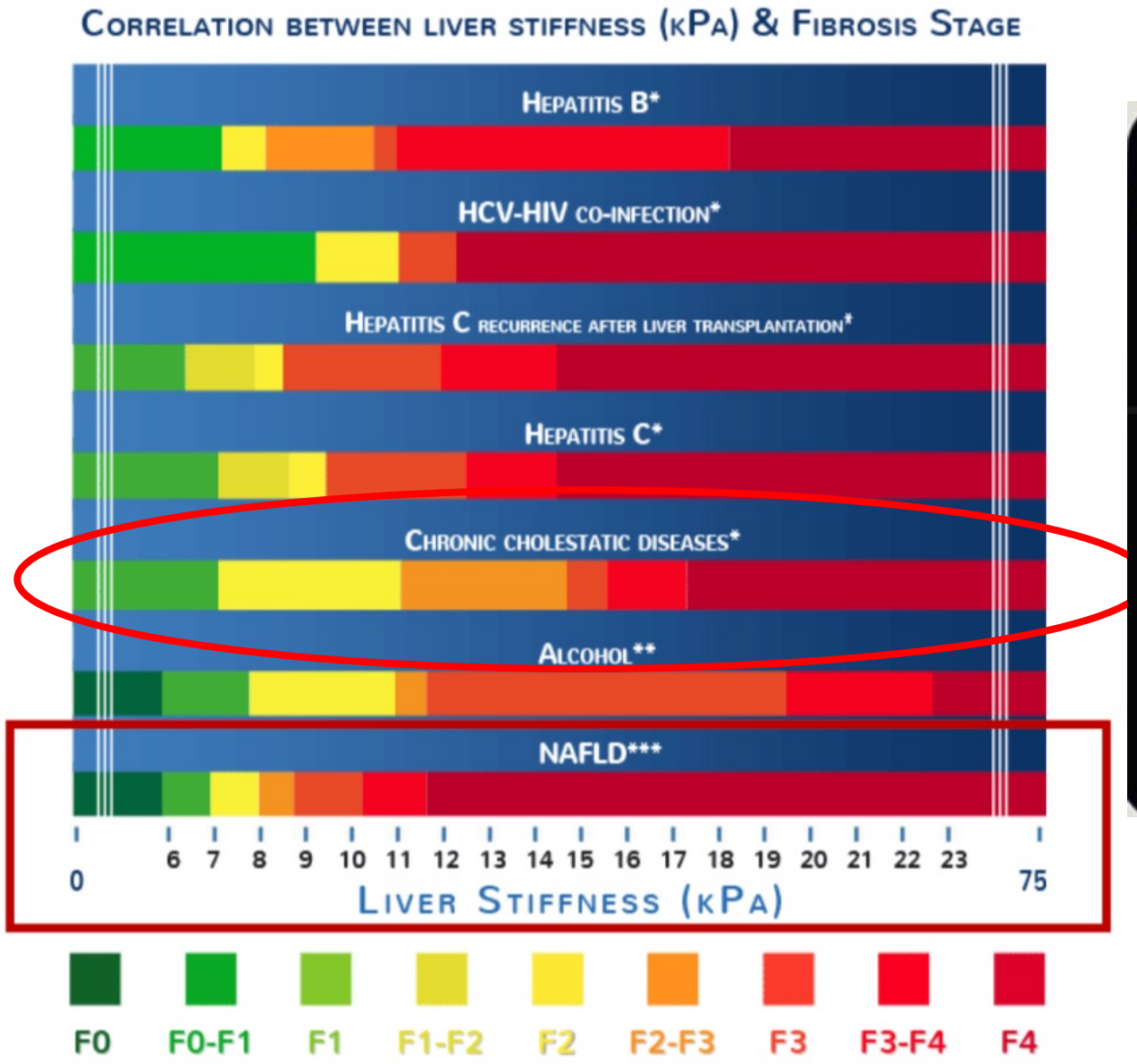
Imaging For Liver Fibrosis

- Measure liver stiffness, which is an indirect measure of hepatic fibrosis
- Types
  - Vibration controlled transient elastography (VCTE) (e.g., FibroScan)
    - Most reliable in ruling out advanced hepatic fibrosis (great NPV)
    - Can be point of care
  - 2D shear wave elastography
    - May require radiology referral
    - Can be point of care with minimal training
  - Magnetic resonance elastography (MRE) or corrected T1 (cT1) (Liver MultiScan)
    - Requires radiology referral

FibroScan (VCTE technology)



VCTE: Fibrosis



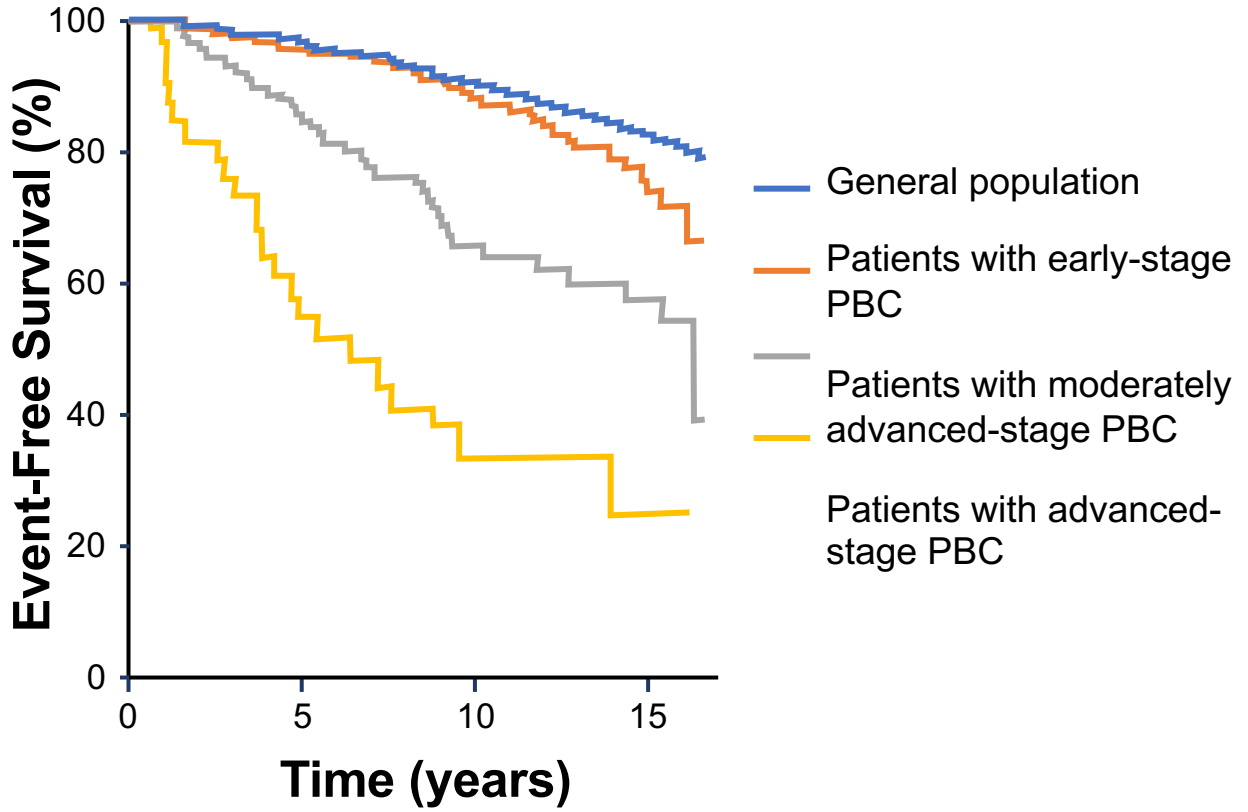
Our patient has minimal fibrosis/ early-stage disease.

Treating PBC

Treatment of PBC: First Line Therapy

First line therapy: Ursodeoxycholic acid/Ursodiol (UDCA)

- Dose: 13-15 mg/kg/day
- Improvement in liver tests may be seen within a few weeks and 90% of the improvement usually occurs within 6-9 months



- 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)

Lindor K, et al. *Hepatology.* 2009;50:291-308.

Treatment of PBC: Second Line Therapy

- Obeticholic acid (OCA)
  - Can be added to UDCA in cases of inadequate response or replace UDCA in cases of UDCA intolerance.
  - Dose: Start at 5 mg once a day. If adequate response is not achieved with 5 mg/day and OCA is well tolerated, increase to 10 mg/day after 3 months
  - **New Contraindication**: Cirrhosis Child-Pugh Class B or C. PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension
- Fibrates in late-stage development for PBC

Ms. Dice: Case Continued

- Continue UDCA (13-15 mg/kg/day)
- Cholestyramine (4g/day up to 16g/day) for pruritus
- DEXA for bone density
- Repeat labs in 3 months
- If no improvement in ALP and TB, add OCA to UDCA

Summary

- PBC associated with female sex and autoimmune genetics
- PSC associated with male sex, IBD (UC>>CD), autoimmune genetics and malignancies (CRC in IBD, CCA, gallbladder adenoca)
- Diagnosis:
  - PBC: cholestatic liver tests, AMA (+) or if AMA (-), compatible liver biopsy
  - PSC: cholestatic liver tests, pANNA (68%) + MRCP or ERCP showing strictures/ectasias
  - Fibrosis staging with non-invasive methods (e.g., FibroScan)
- Risk of HCC in cirrhotics merits surveillance imaging + AFP
- PBC Therapy: UDCA (13-15 mg/kg/d) first line; OCA second line for non-response or intolerance in patients without decompensated cirrhosis
- Clinical trials enrolling for both PBC and PSC