Primary Biliary Colangitis (PBC): Screening and Treatment

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Case Presentation

- 55-year-old Caucasian female.
- Presents for evaluation of elevated ALK PHOS (413 U/L).
- What's your diagnosis?

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Primary Biliary Cholangitis (PBC)

- Chronic cholestatic liver disease
- Autoimmune in nature
- Inflammation and destruction of small interlobular bile ducts
- Affects predominantly middle-aged females
- Rising incidence and prevalence

Carey E, et al. *Lancet.* 2015.

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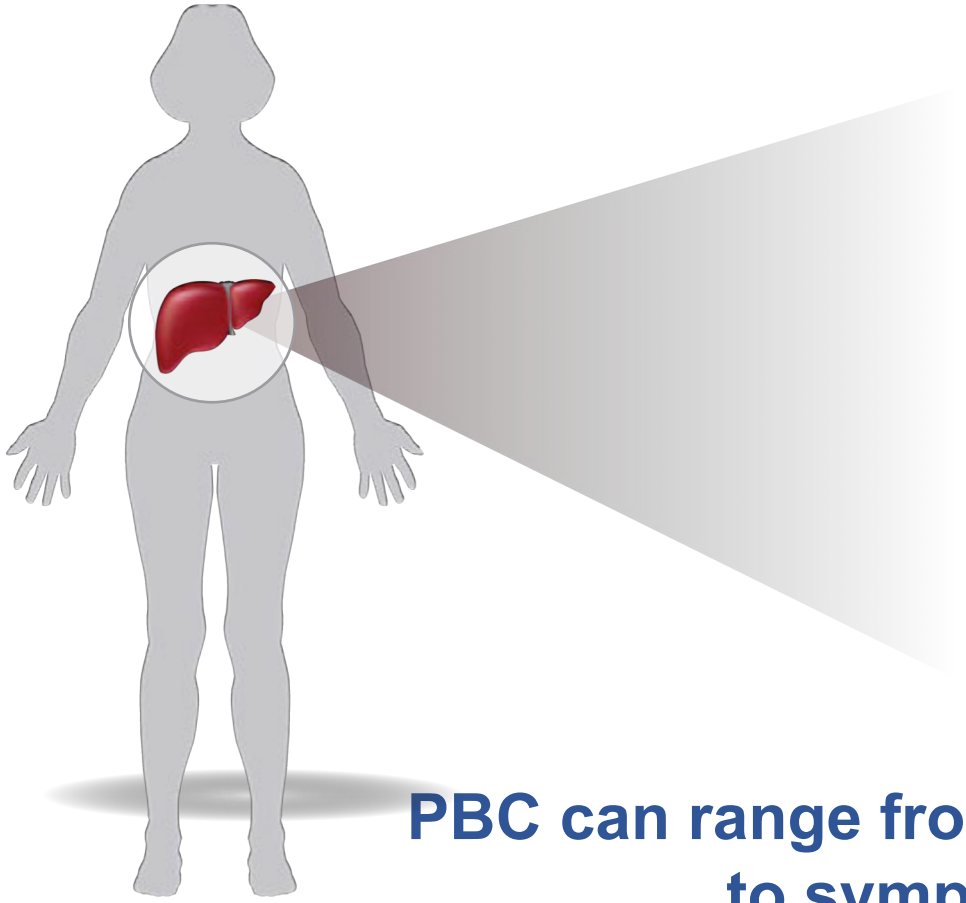
Clinical Features Vary Greatly Between Patients



- 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.

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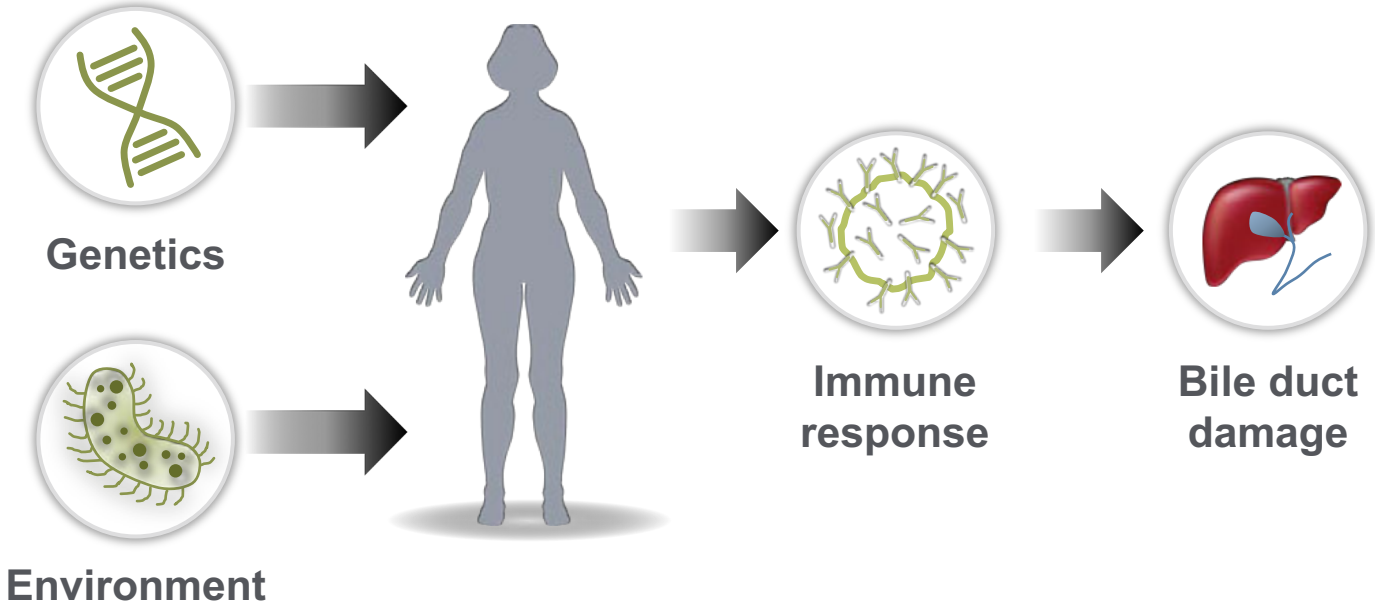
PBC Is a Chronic, Progressive Autoimmune Disease

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

1. Poupon R. *J Hepatol*. 2010;52(5):745-758. 2. Selmi C, et al. *Lancet.* 2011;377(9777):1600-1609. 3. Carey EJ, et al. *Lancet.* 2015;386:1565-1575.

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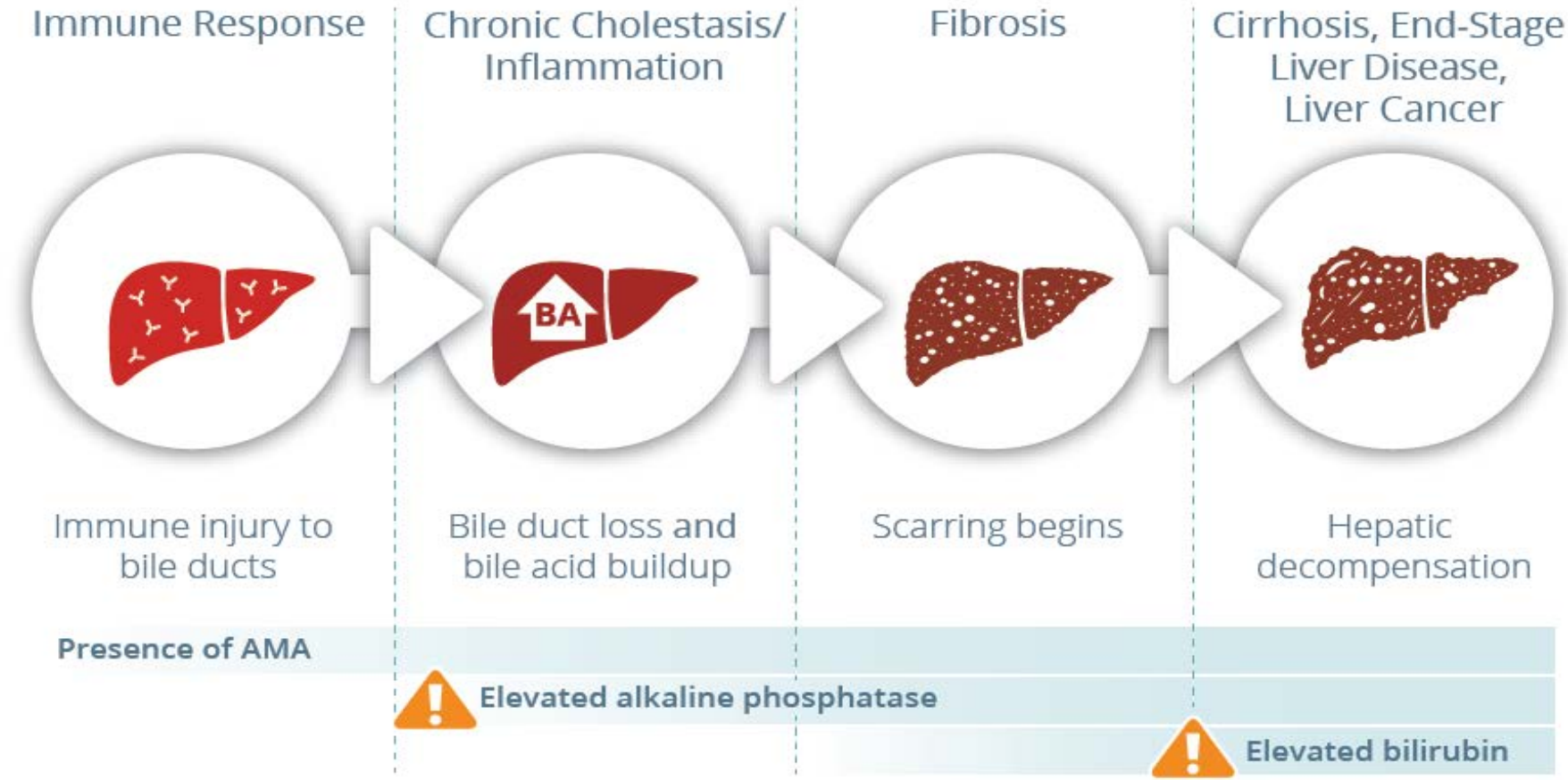
If Left Inadequately Treated, PBC May Result in Liver Failure, Transplant, or Death

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.

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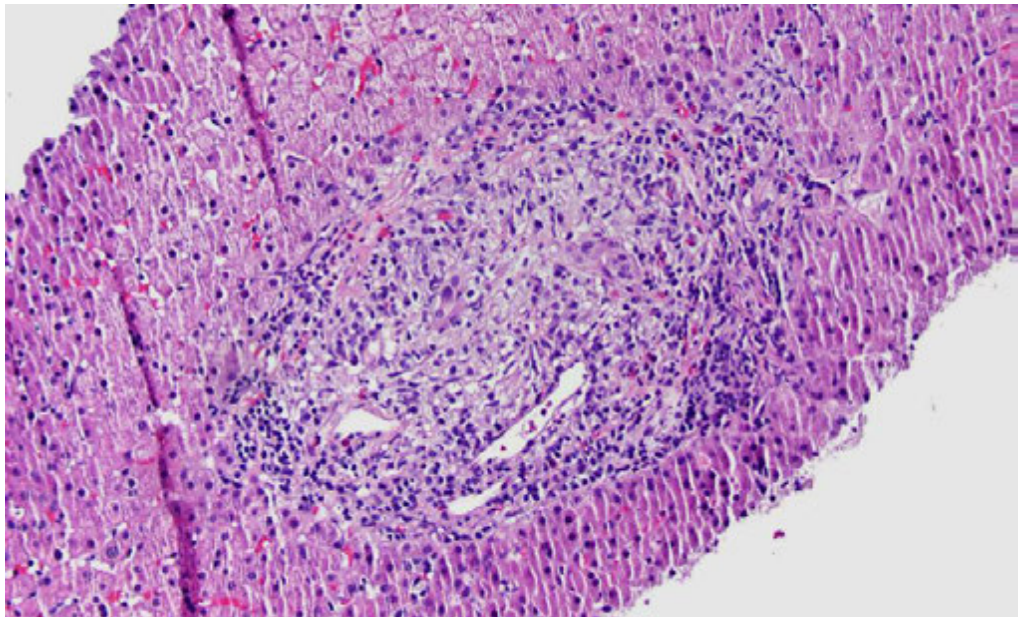
PBC Diagnostic Criteria

PBC Diagnosis

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



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

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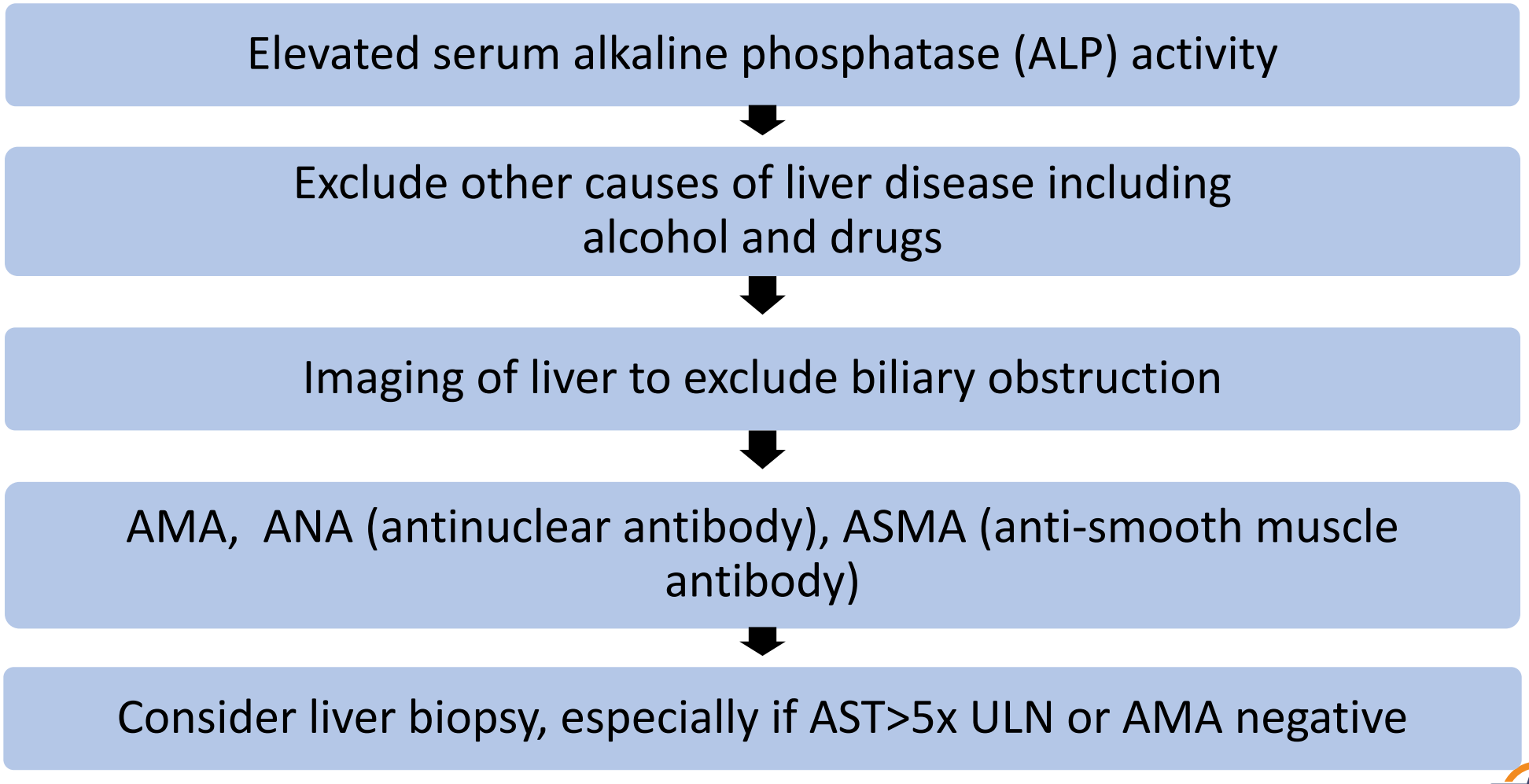
AASLD Suggested Diagnostic Algorithm for Patients with Suspected PBC



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Variant Syndromes

AMA-negative PBC

- 50% will have antinuclear antibodies (ANA)
  - PBC-specific ANA – anti gp210, anti sp100
  - Same clinical presentation

Overlap syndrome with autoimmune hepatitis

- Consider when ALP: transaminase ratio <1.5, IgG is elevated and smooth muscle antibodies are present with titer >1:80

Premature ductopenic variant

- 5-10%
- Very rapid onset of ductopenia, severe icteric cholestasis and fast progression towards cirrhosis

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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.

Associated and Alternate Causes of Fatigue Should Be Considered, and Coping Strategies Developed

As an initial step in fatigue management, associated and alternate causes of fatigue should be excluded and, if possible and appropriate, treated[1,2]

Associated Causes of Fatigue

- Anemia
- Depression
- Sleep disorder
- Hypothyroidism
- Type II diabetes
- Medications, including:
  - Anti-hypertensive therapy
  - Beta-blockers
- Pruritus at night
- Autonomic dysfunction
- Dehydration
- Restless legs syndrome

EASL Guideline Recommendations: Coping Strategies[1]

- EASL suggests advising patients with fatigue (which in some may be debilitating) on developing coping strategies, including the avoidance of social isolation, which can compound effects of fatigue

Neither UDCA nor OCA has been proven to improve fatigue in patients with PBC

1. EASL. *J Hepatol*. 2017;67(1):145-172. 2. Lindor KD, et al. *Hepatology*. 2009;50(1):291-308.

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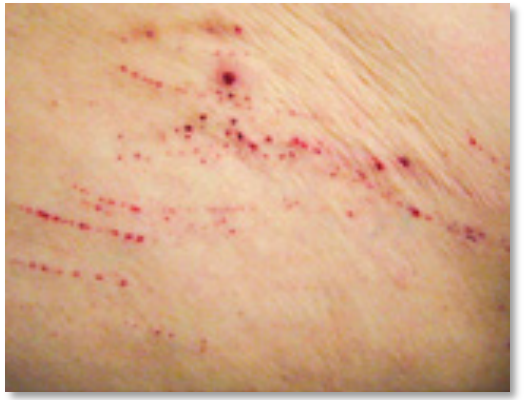
Pruritus Is Common Among Patients With PBC and Can Have Negative Effects on QoL

- Pruritus occurs in 20%-70% of patients with PBC
  - Pruritus can range in severity from mild to severe
  - In most patients, pruritus is mild to moderate
- Pruritus severity is variable and not correlated to disease severity or prognosis
- Characteristics of pruritus in PBC
  - Diurnal variation: most intense itch 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 even 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.

Current Guidelines Provide Non-Pharmacologic and Pharmacologic Pruritus Management Strategies

EASL Guideline-Recommended Non-Pharmacologic Strategies

- Use of emollients and oatmeal extract to improve dry and inflamed skin
- Use of cold water for baths or showers to provide some symptom relief of pruritus triggered or exacerbated by heat/warmth (at night)
- Psychologic intervention for addictive scratching/scratch dependence
- Searching for added allergens, especially in patients with associated hypereosinophilia or IgE-mediated allergy

AASLD and EASL Guideline-Recommended Pharmacologic Strategies

- Cholestyramine is considered first-line pharmacologic treatment for pruritus in PBC
  - 4 g per dose to a maximum of 16 g/day taken 2-4 hours before or after taking UDCA and at least 4 hours before or after taking OCALIVA
- AASLD and EASL practice guidelines provide recommendations on pharmacologic management in patients refractory to cholestyramine or first-line treatment with other bile acid sequestrants

Hyperlipidemia Is Common Among Patients With PBC

- As a result of cholestasis, hyperlipidemia is common in PBC, affecting 75%-95% of patients
- In early disease, elevated very low–density lipoprotein and LDL-C concentrations are reported, as well as significantly elevated HDL-C values
  - As disease progresses, HDL-C decreases while LDL-C may increase further
- Evidence suggests that there is no increased risk of cardiovascular disease in patients with PBC and hyperlipidemia

AASLD Guideline Recommendations[3]
• UDCA will lower LDL-C levels and is the initial step • When there is also a family history of lipid abnormalities or cardiovascular disease it may still be considered appropriate, depending on the lipid pattern, to treat with cholesterol-lowering drugs

EASL Guideline Recommendations[2]
• In the subgroup of patients with PBC and metabolic syndrome (with high cholesterol, low HDL-C and high LDL-C levels), EASL suggests considering a pharmacologic approach with cholesterol-lowering agents on a case-by-case basis; treatment is not contraindicated

1. Carey EJ, et al. *Lancet*. 2015;386(10003):1565-1575. 2. EASL. *J Hepatol*. 2017;67(1):145-172.

Cholestasis- and/or Cirrhosis-Associated Complications

	Patients Affected
Complications of chronic cholestasis	
Osteoporosis	20%-44%
Vitamin deficiency	8%-33%
Complications related to cirrhosis	
Varices associated with portal hypertension	6% (without cirrhosis) ~31% (with late-stage disease)
Hepatocellular carcinoma	4% with 10-year risk

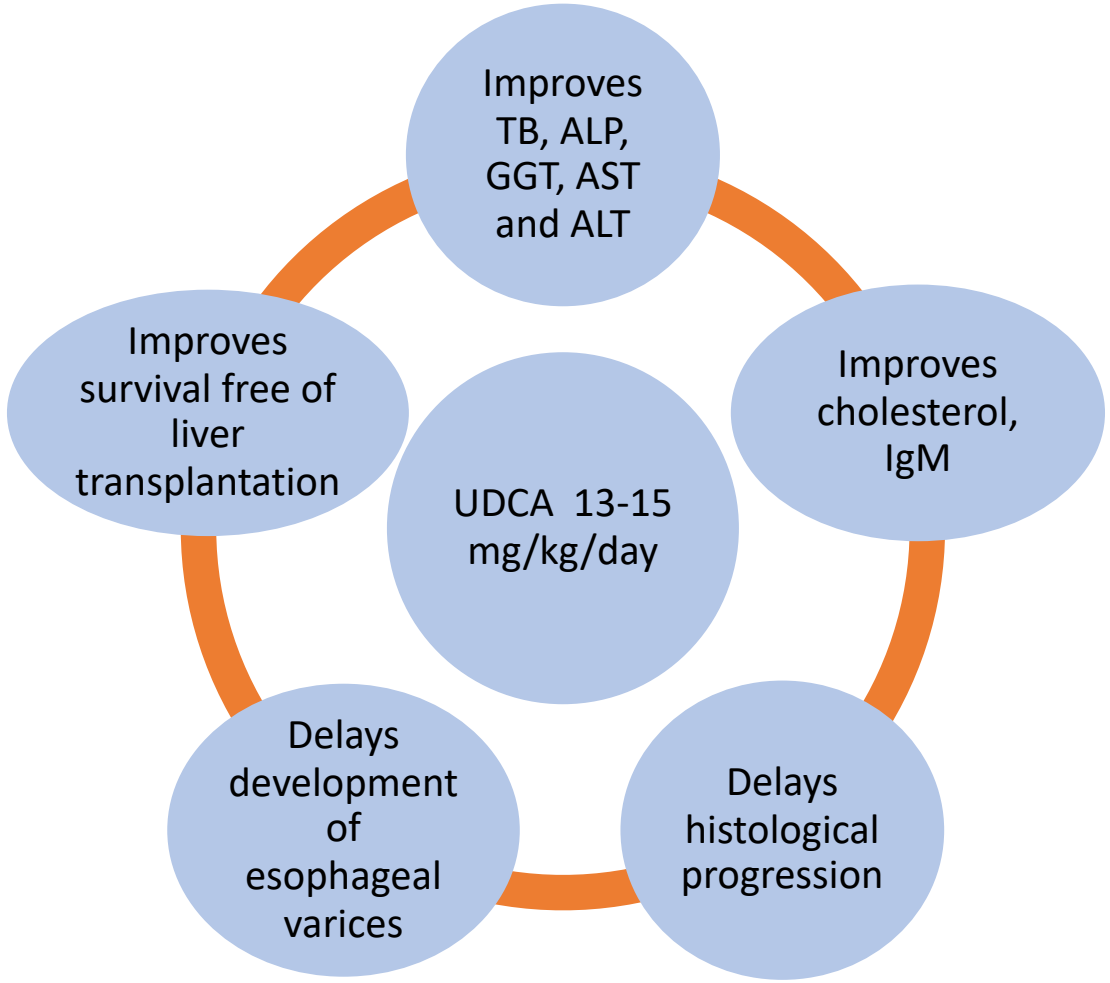
Current AASLD and EASL guidelines provide recommendations for the management of cholestasis- and/or cirrhosis-associated complications

First Line Therapy: Ursodeoxycholic Acid

- Orally administered, naturally occurring, hydrophilic secondary bile acid
- 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

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

Therapeutic Effects UDCA



Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IgM, immunoglobulin M; TB, total bilirubin; UDCA, ursodeoxycholic acid.

Levy C and Lindor KD. In: *Zakim and Boyer's Hepatology: A Textbook of Liver Disease.* Elsevier Inc;2011:738-753. Graphic courtesy of Dr. Cynthia Levy.

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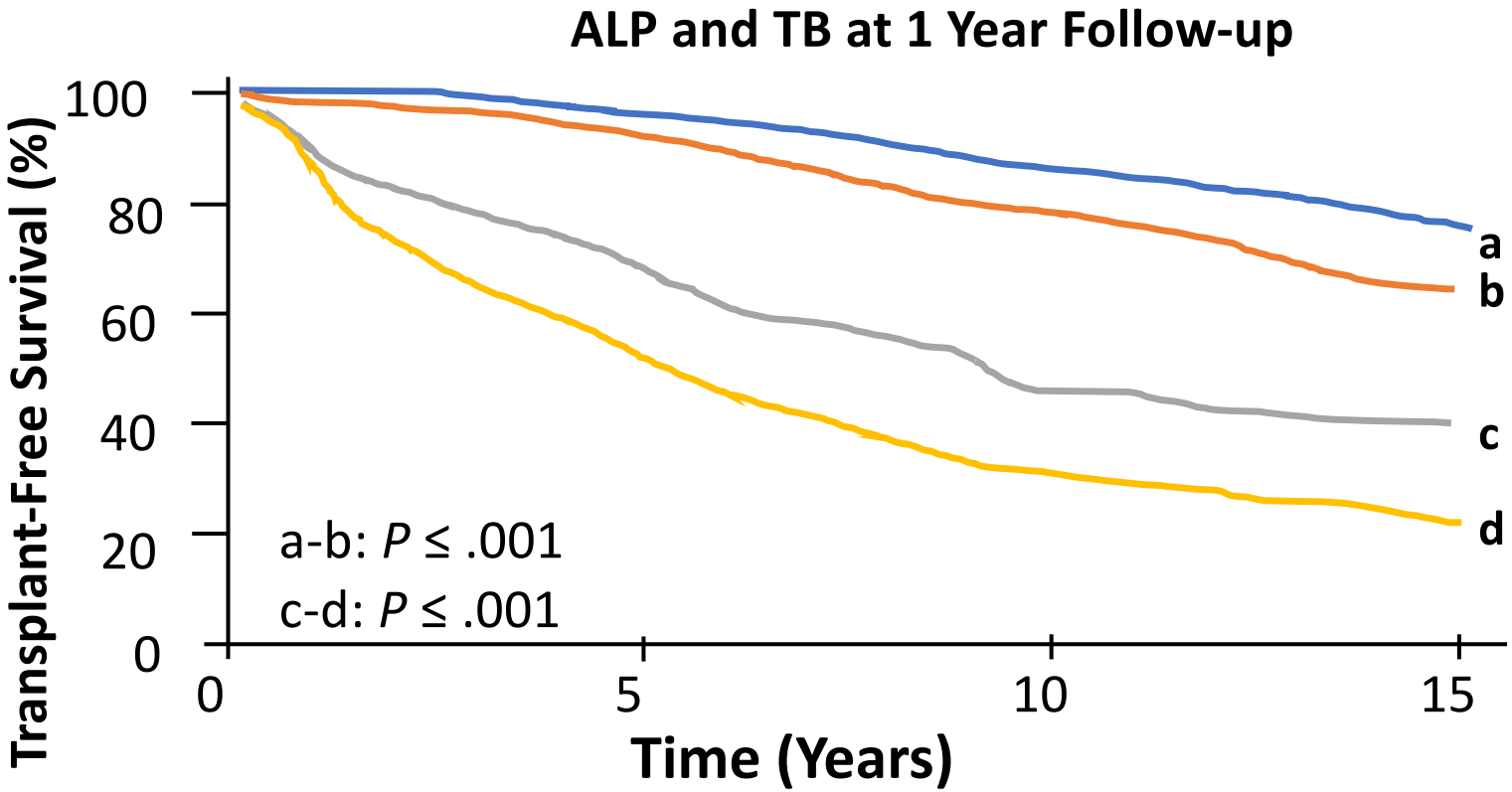
Combined Effect of TB and ALP on Transplant-Free Survival



a	2112	1482	887	504
b	681	489	337	228
c	271	193	153	137
d	400	345	302	283

- Normal bilirubin and ALP ≤ 2.0 x ULN
- Normal bilirubin and ALP > 2.0 x ULN
- Abnormal bilirubin and ALP ≤ 2.0 x ULN
- Abnormal bilirubin and ALP > 2.0 x ULN

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

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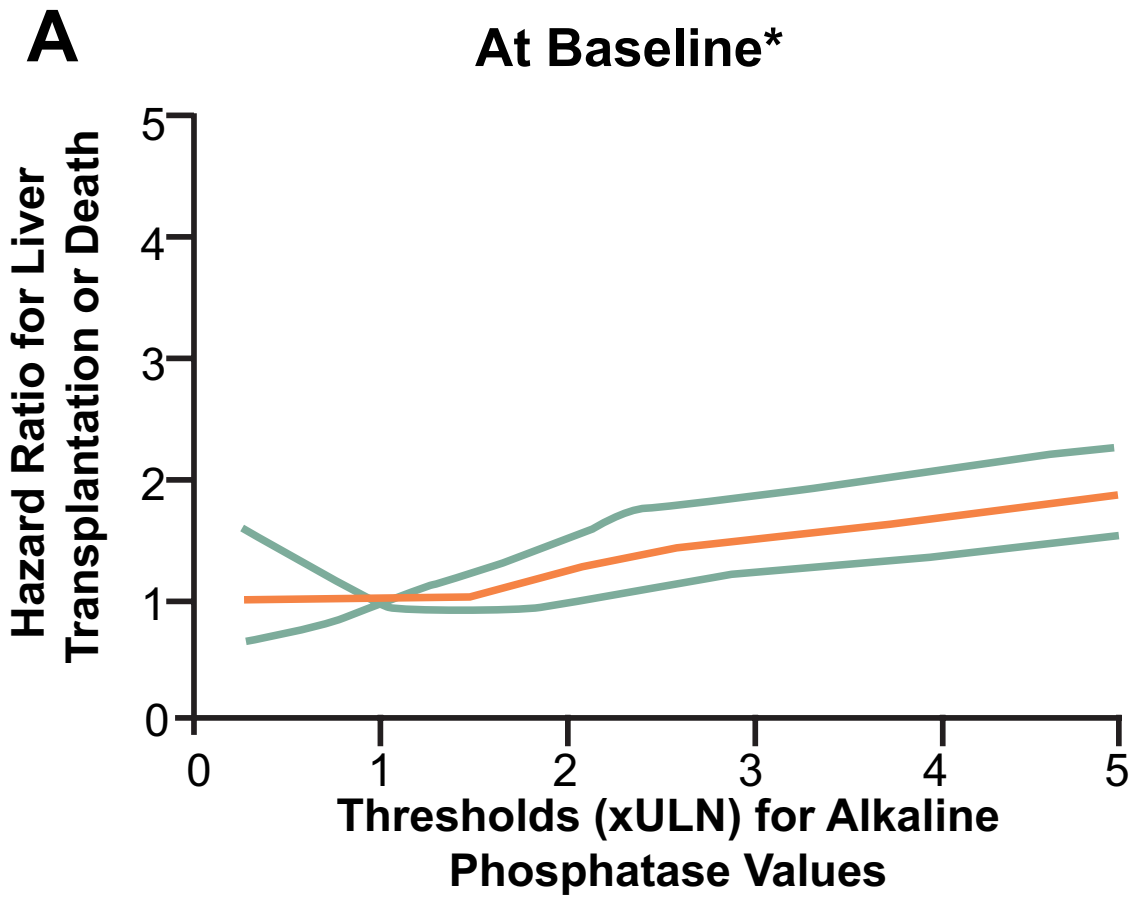
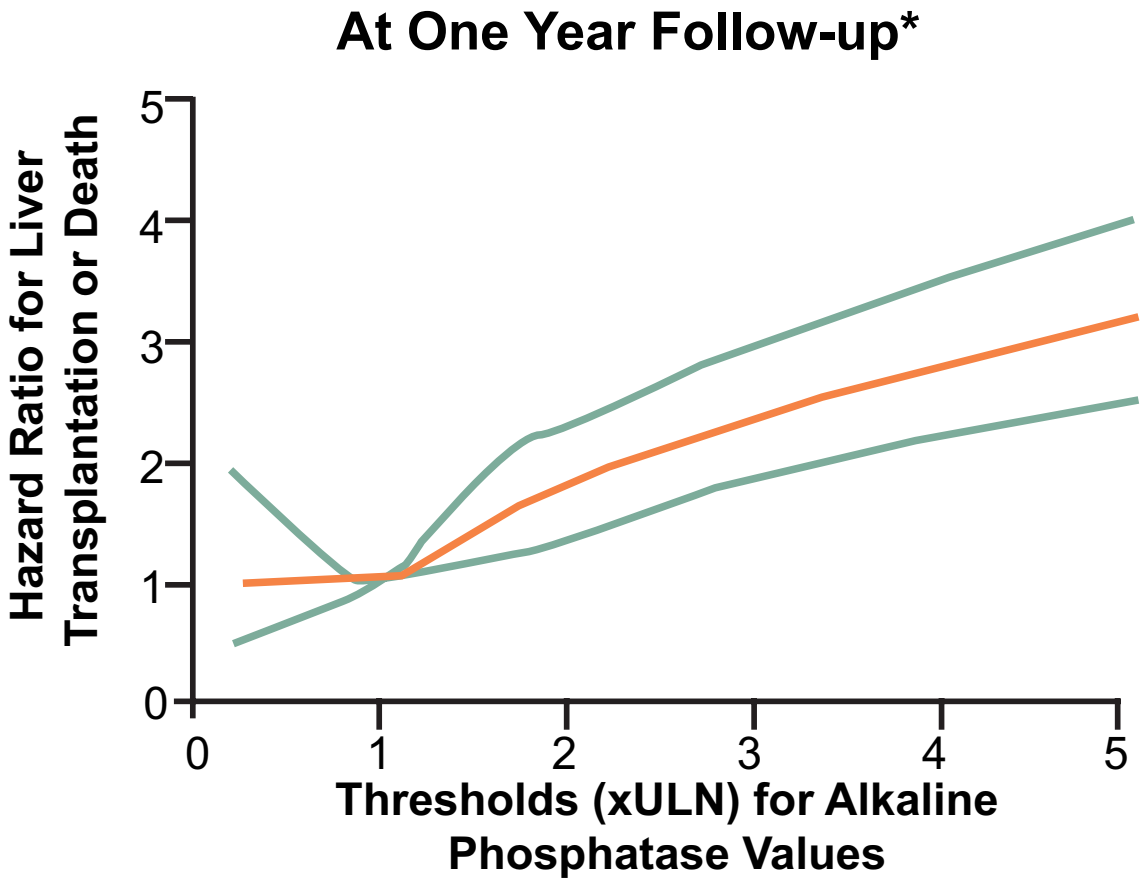
Hazard Ratio for LT/Death According to ALP





*3710/4635 patients were included for this analysis

Lammers, et al. *Gastro.* 2014.

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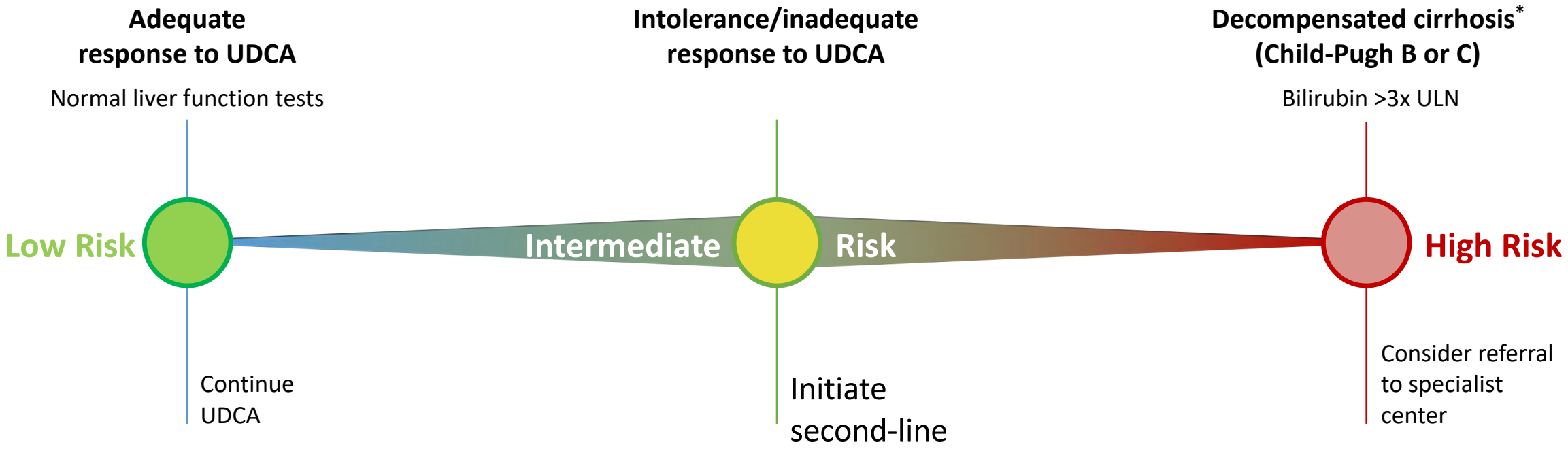
Risk for Disease Progression Should Be Assessed in All Patients on UDCA



"All patients should be evaluated for their risk of developing end-stage complications and, consequently, their potential need for additional treatments" – EASL

European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172.

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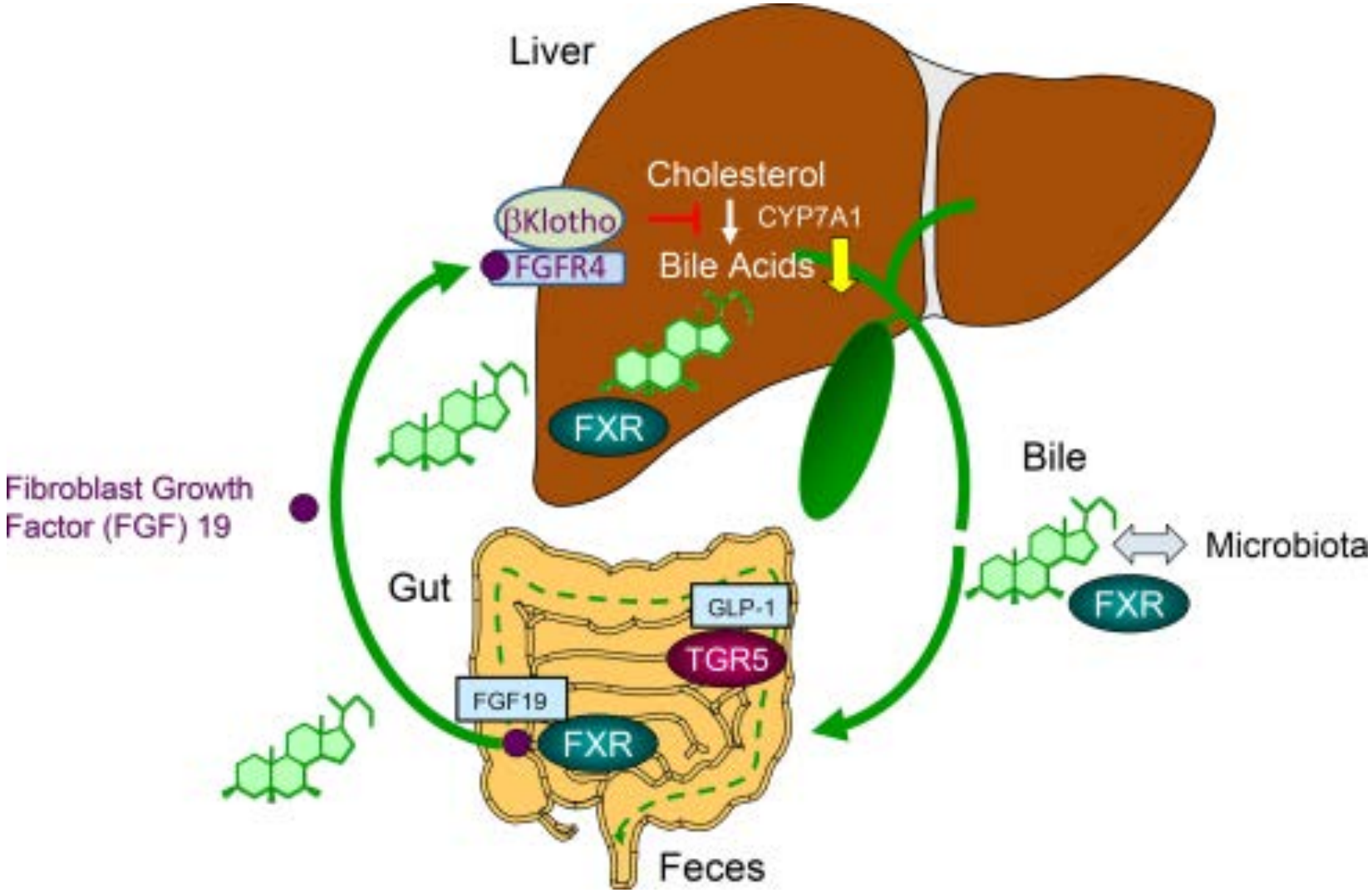
New Targets for Treatment of Cholestatic Diseases



Trauner M. *Hepatology.* 2017.

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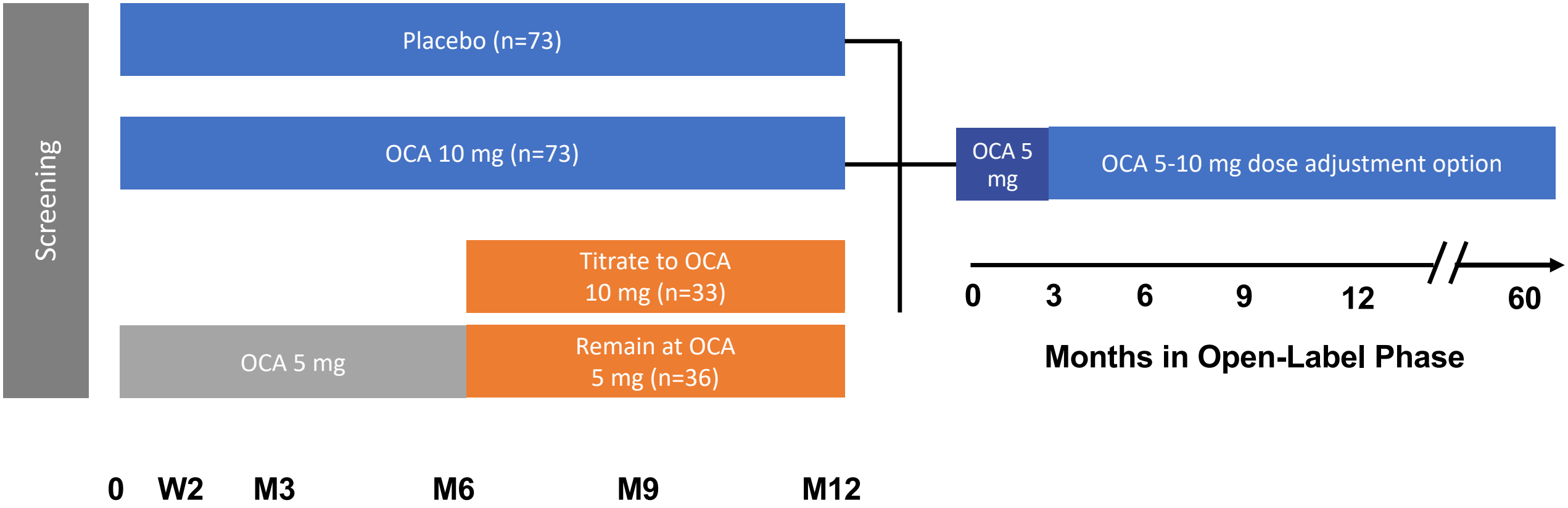
OCA in Patients with PBC: POISE Study Design



Modified from Nevens F, et al. *N Engl J Med.* 2016;375:631-643.

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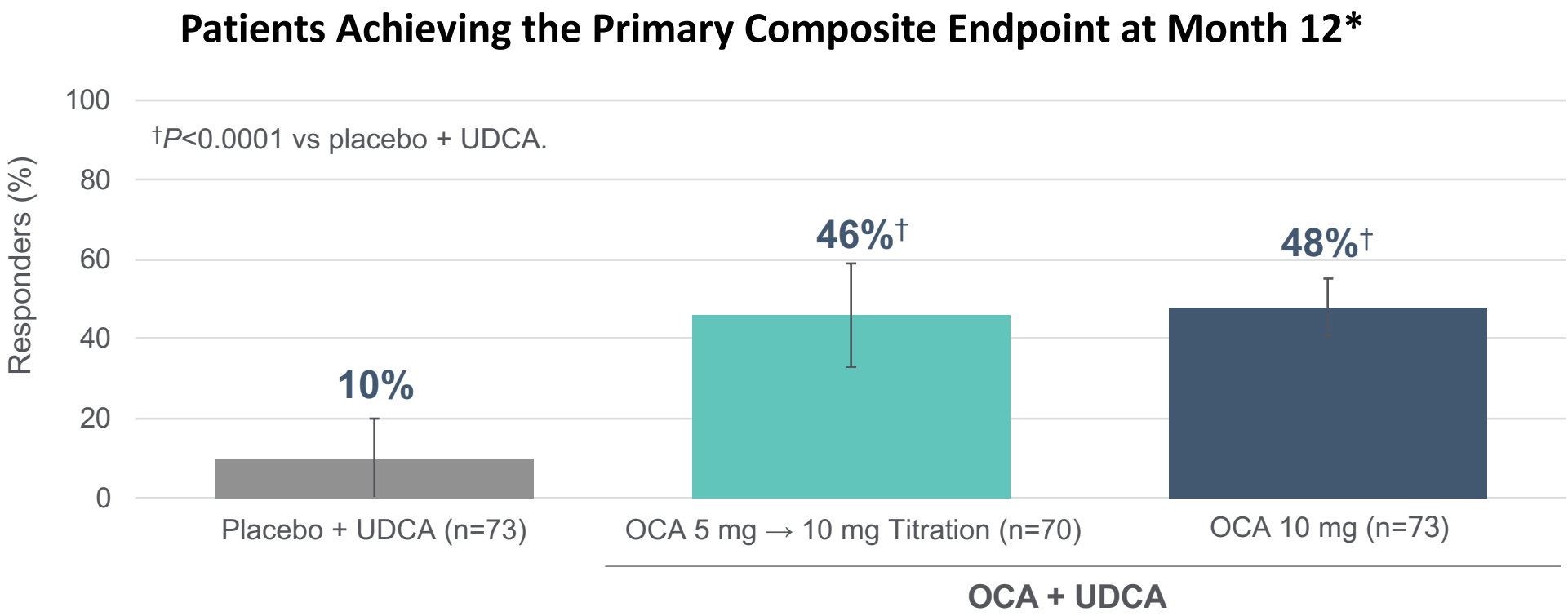
Primary Endpoint In the Phase 3 POISE Trial



- Patients taking OCA were 2.5x more likely to achieve a reduction in ALP ≥15%
- 16 patients (7%) who were intolerant did not receive concomitant UDCA.

Nevens F, et al. *N Engl J Med.* 2016;375:631-643.

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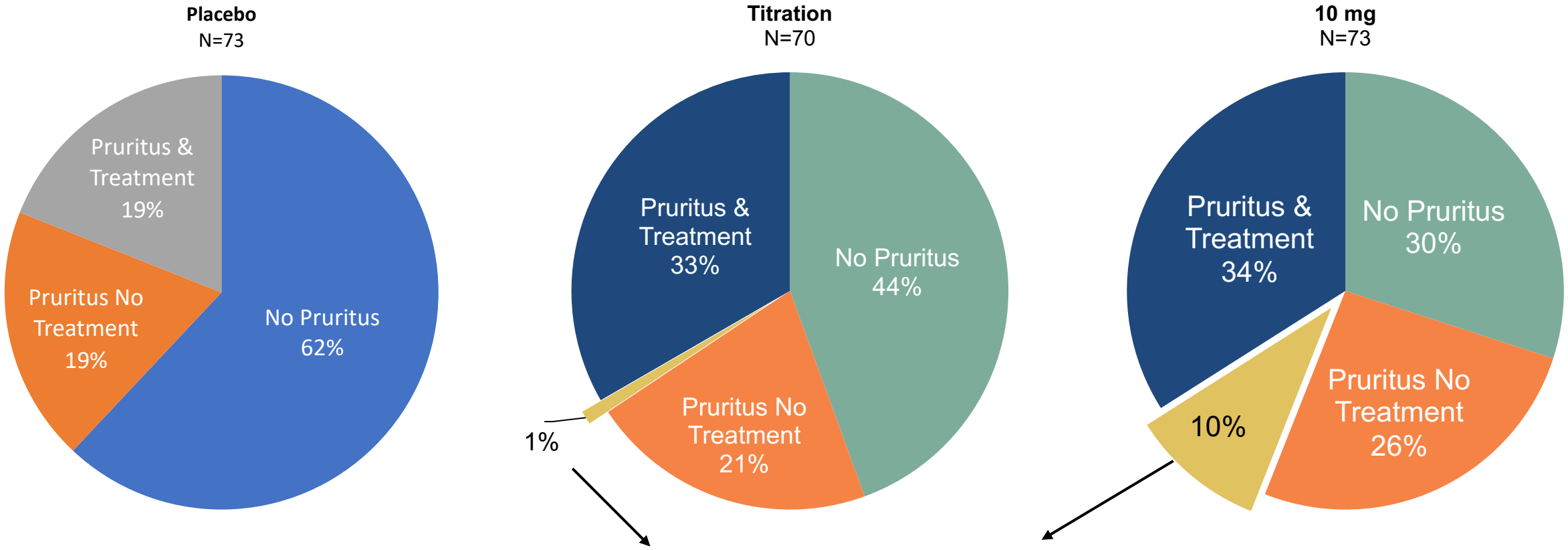
OCA POISE Trial–Titration Strategy Minimized Pruritus



Discontinued Due to Pruritus Regardless of Management Efforts

Abbreviation: OCA, obeticholic acid.

With permission from Mayo MJ, et al. Presented at: 2016 EASL; April 13-17, 2016; Barcelona, Spain. Poster SAT-357.

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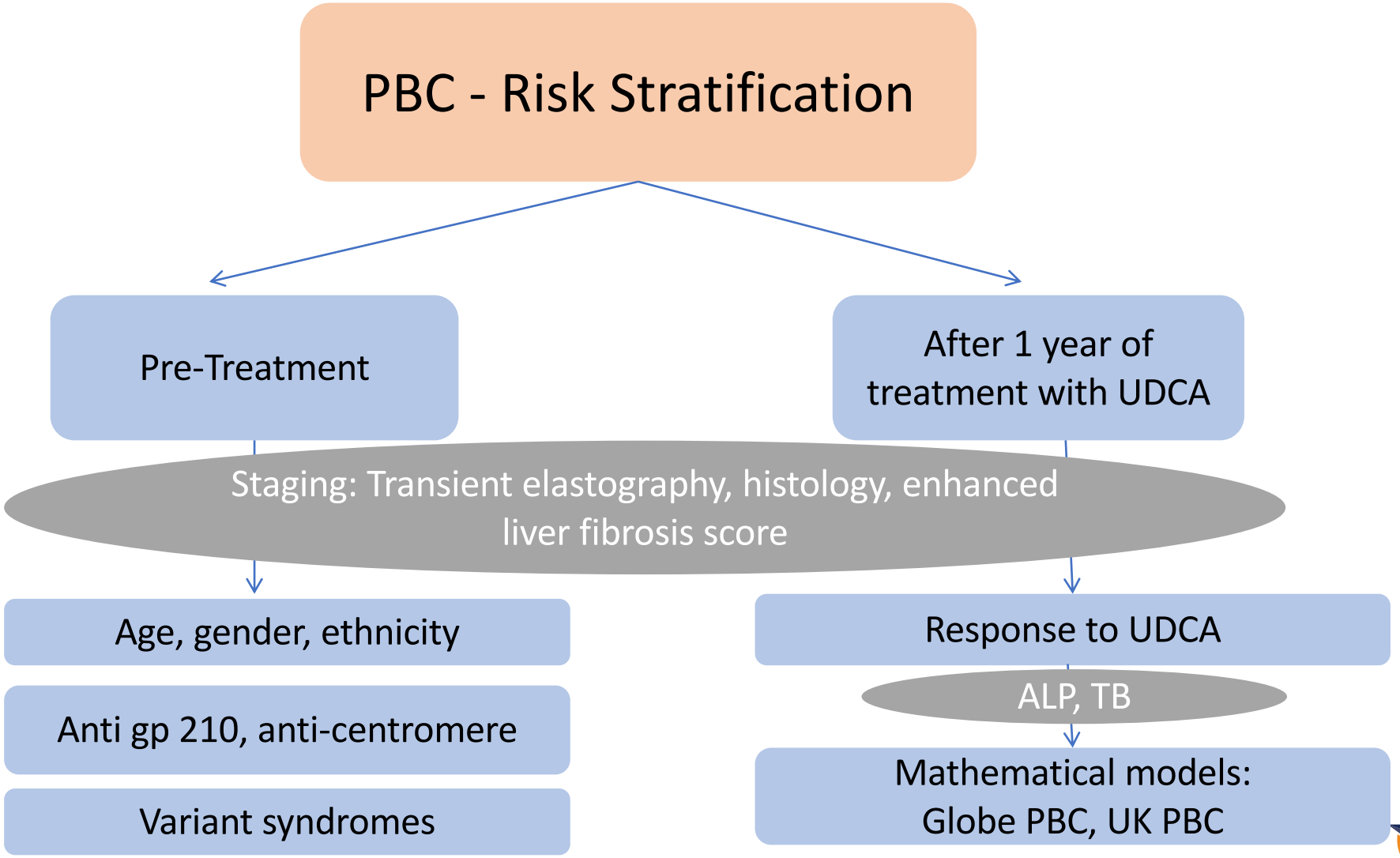
Obeticholic Acid Is Approved

- 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

Improvement in survival free of liver transplantation has not yet been demonstrated. Conditional approval granted.

Who is at Risk for Progression?



Levy C. *Hepatology.* 2017.

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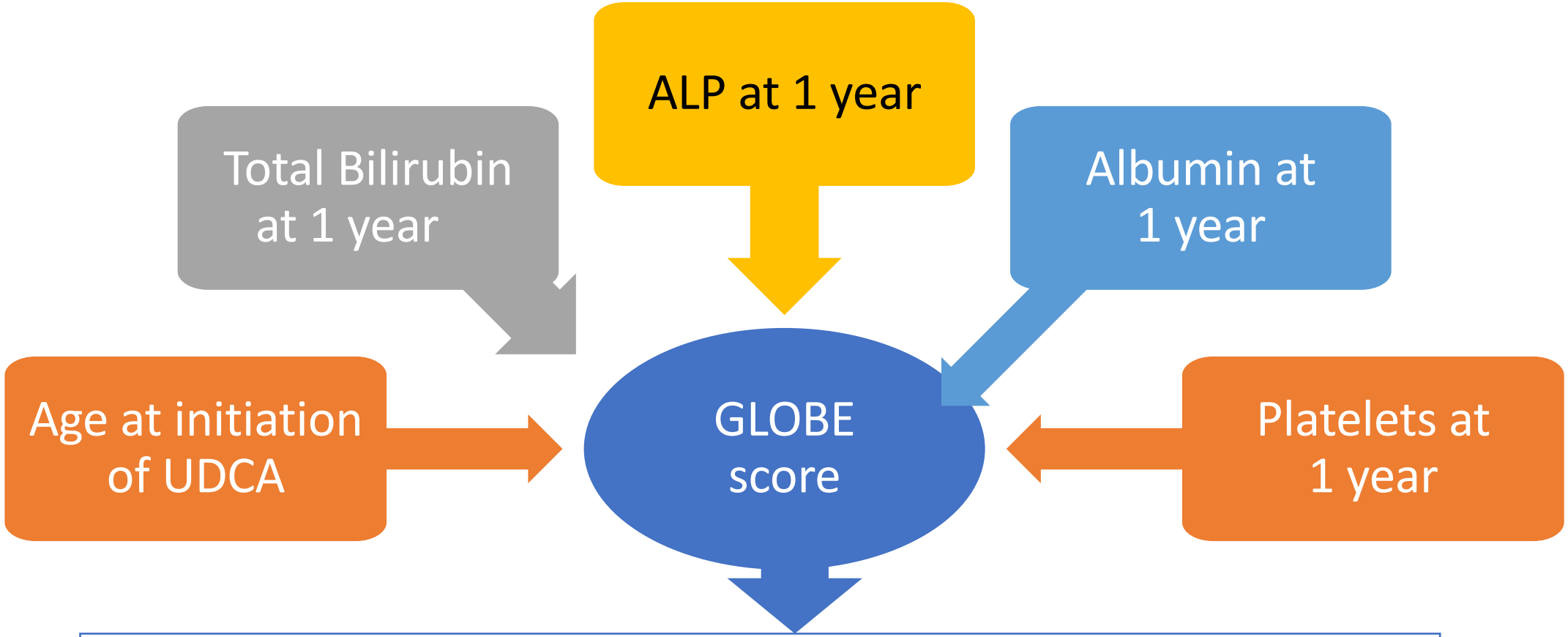
GLOBE Score: Online Calculation



Score > 0.30 indicates decreased survival without LT.
Predicts 3-, 5- and 10-year survival compared to age-matched population

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GLOBE Score: Online Calculation

The GLOBE score for patients with Primary Biliary Cholangitis (PBC)

The GLOBE score is an internationally relevant and validated risk assessment tool, able to stratify PBC patients to high and low risk.

Age, years *at initiation of UDCA therapy*	38		
Total bilirubin level, µmol/L or mg/dl *after one year of UDCA therapy*	1	Upper limit of normal:	1
Alkaline phosphatase level, U/L *after one year of UDCA therapy*	260	Upper limit of normal:	130
Albumin, g/L *after one year of UDCA therapy*	4	Lower limit of normal:	4
Platelets, x 10^9/L *after one year of UDCA therapy*	160		

GLOBE score: 0.46

Liver transplant-free survival

	GLOBE score	mean survival of healthy patients ≤45 years
3-year	**94.6%**	**99.5%**
5-year	**90.5%**	**99.2%**
10-year	**76.4%**	**98.0%**

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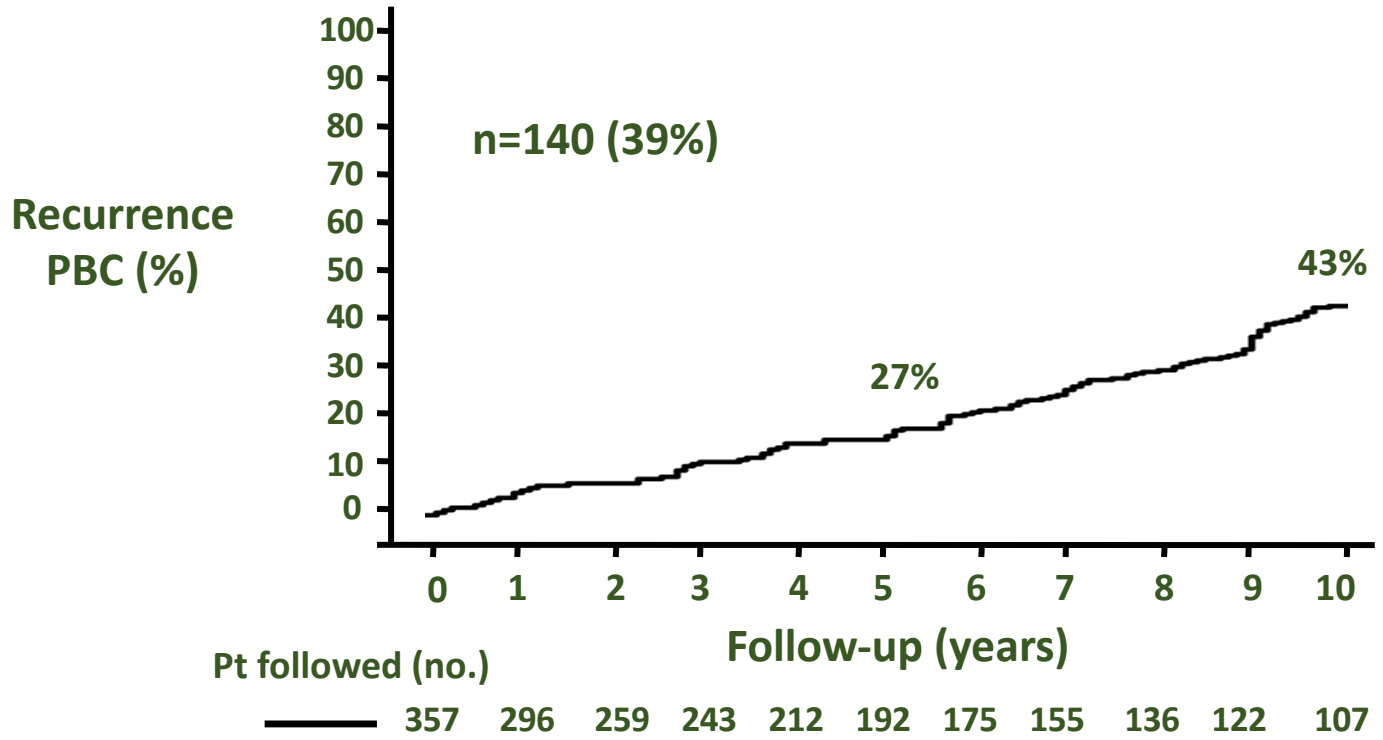
Recurrent PBC after LT



Montano-Loza AJ, et al on behalf of the Global PBC Study Group. EASL 2016

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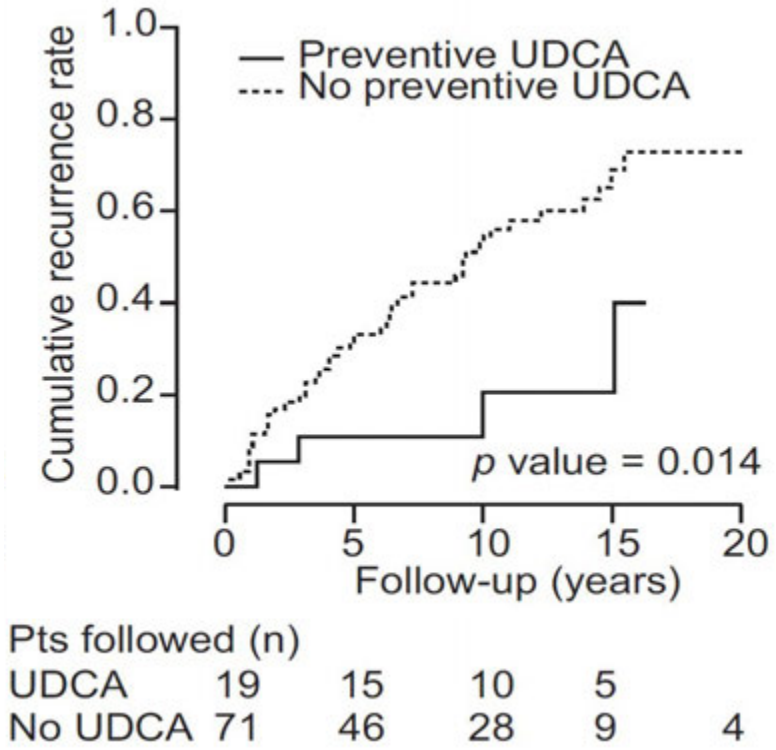
Recurrent PBC after LT: Preventive UDCA Therapy



Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Preventive UDCA				
No	1		1	
Yes	0.31 (0.11-0.85)	0.014	0.32 (0.11-0.91)	0.032

Bosch A, et al. *J Hepatol* 2015;63:1449

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Novel Therapies Under Evaluation for PBC

Compound	NCT	Mechanism of Action
Bezafibrate Fenofibrate	NCT01654731 NCT02823353	Pan PPAR agonist PPAR alpha agonist
Genfit		PPAR delta agonist
MBX-8025	NCT02955602	PPAR delta agonist
GS9674	NCT02943447	FXR agonist
LJN452	NCT02516605	FXR agonist
NGM 282	NCT02026401	FGF 19 analog
LUM001	NCT01904058	ASBT inhibitor
GSK 672	NCT02966834	IBAT inhibitor
FFP104	NCT02193360	CD40 Inhibitor
Abatacept	NCT02078882	Inhibits T cell activation

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