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Diagnostic and Therapeutic Advances in Primary Biliary Cholangitis: Maximizing Opportunities to Improve Patient Care and Outcomes

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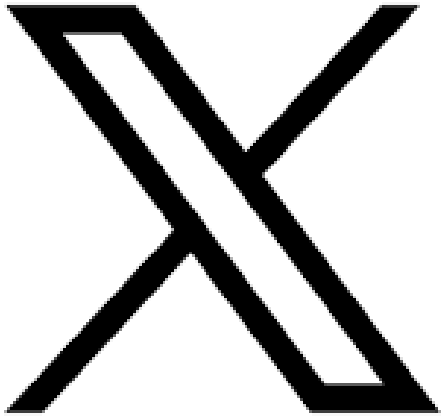

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Mayo Clinic College of Medicine and Science
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Maria Morais, RN - Patient with PBC
VP Patient Advocacy, Canadian PBC Society

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Learning Objectives

1. Assess the burden of PBC
2. Implement evidence-based strategies for early and accurate diagnosis of PBC
3. Incorporate contemporary clinical pathways for treating PBC that consider MOA, indications, efficacy, and safety

The Burden of PBC

Aliya Gulamhusein, MD, MPH, FRCPC

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Learning Objective 1

Assess the burden of PBC.

Audience Response

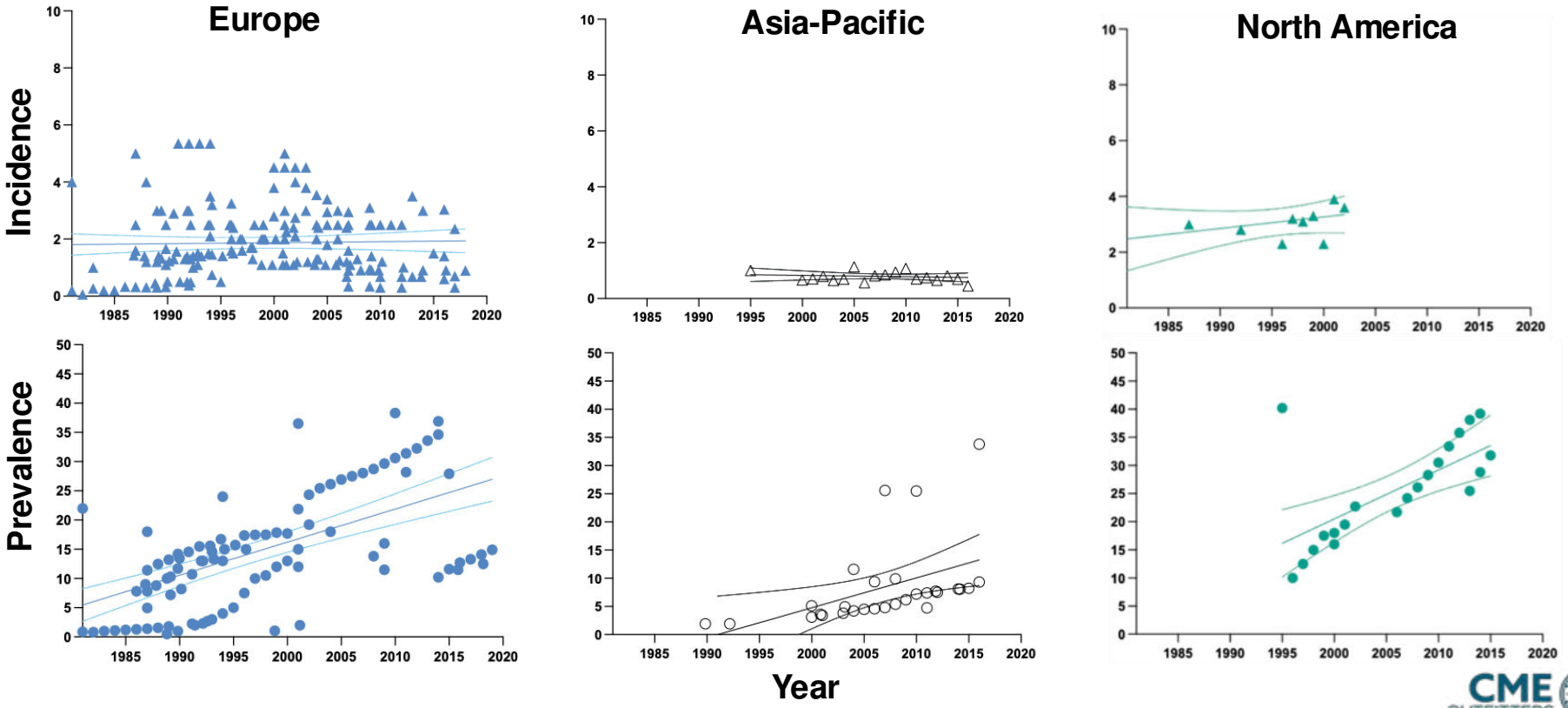
What percentage of patients with PBC are incomplete responders to ursodeoxycholic acid (UDCA)?

A. 10%
B. 20%
C. 30%
D. 40%
E. I don’t know

Patient Introduction: Maria Morais, RN

PBC Epidemiology: Incidence and Prevalence

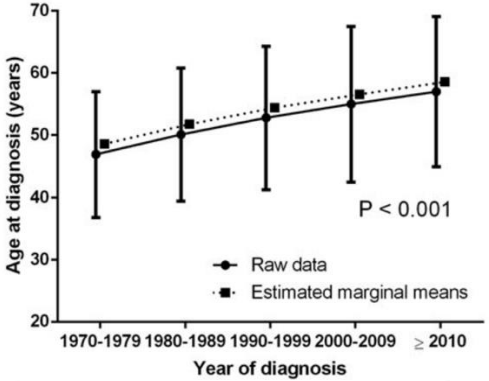
- Incidence rose until 2000, then plateaued (0.84 [Asia-Pacific] to 2.75 per 100,000)
- Prevalence rose (UDCA effect), currently ~14.6 per 100,000

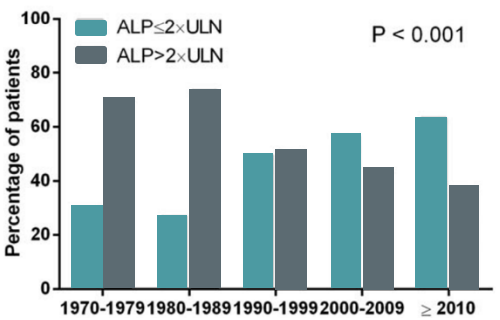


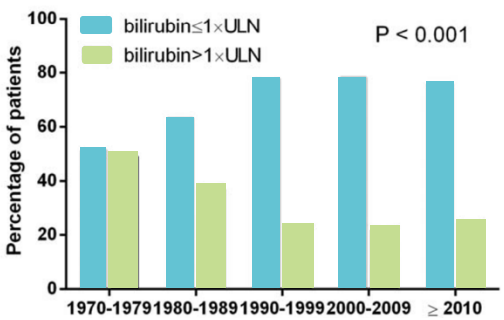
Trivedi PJ, Hirschfield GM. *Gut.* 2021;70(10):1989-2003.

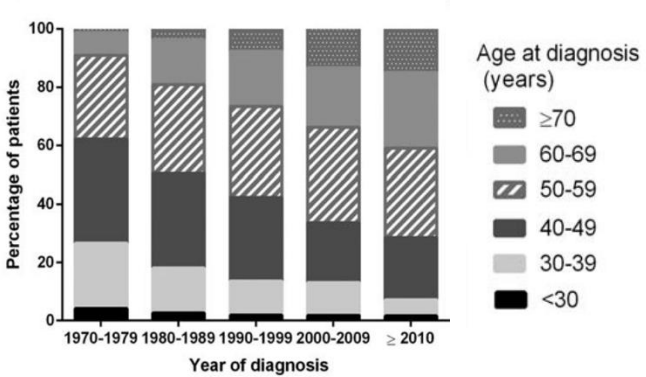
Temporal Trends: Age and Disease Stage

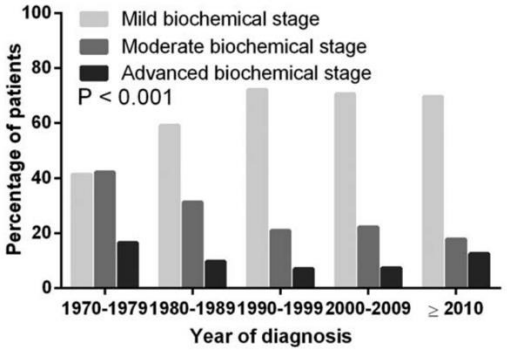
- Older age at diagnosis
- Milder disease stage (biochemically and histologically)

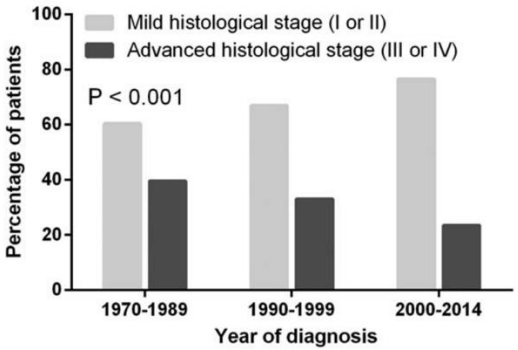












ALP = alkaline phosphatase; ULN = upper limit of normal.

Murillo Perez CF, et al. *Hepatology*. 2018;67(5):1920-1930.

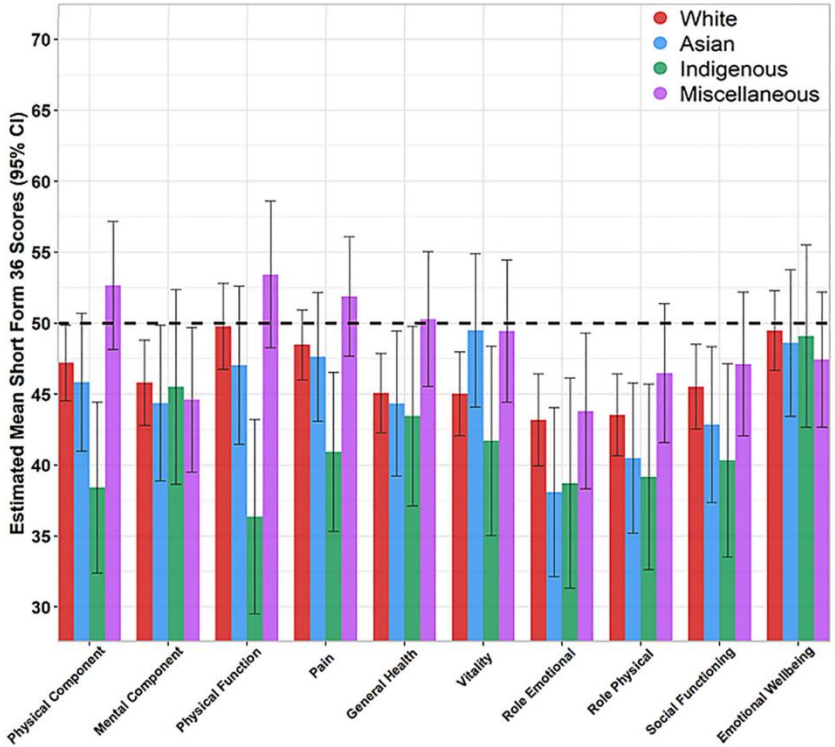
Poor Outcomes in Indigenous Patients, Male Patients, and No UDCA Use

	Liver transplantation or death, 290 events/1483 patients		Decompensation, HCC, liver transplantation, death, 358 events/1468 patients	
Independent variable	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
Ethnicity	–	–	–	–
Asian East	0.67 (0.35–1.26)	0.21	0.87 (0.53–1.42)	0.57
Asian South	1.24 (0.55–2.80)	0.6	1.47 (0.75–2.87)	0.26
Indigenous	3.66 (2.23–6.01)	<0.001	3.03 (1.88–4.88)	<0.001
Miscellaneous	0.86 (0.48–1.54)	0.62	0.95 (0.57–1.58)	0.84
Age at diagnosis	1.08 (0.97–1.20)	0.15	1.10 (1.00–1.21)	0.05
Male sex	2.36 (1.72–3.25)	<0.001	2.00 (1.48–2.71)	<0.001
No UDCA	5.50 (3.98–7.60)	<0.001	3.81 (2.79–5.20)	<0.001
Diagnosis year	0.92 (0.79–1.07)	0.28	0.97 (0.84–1.11)	0.64

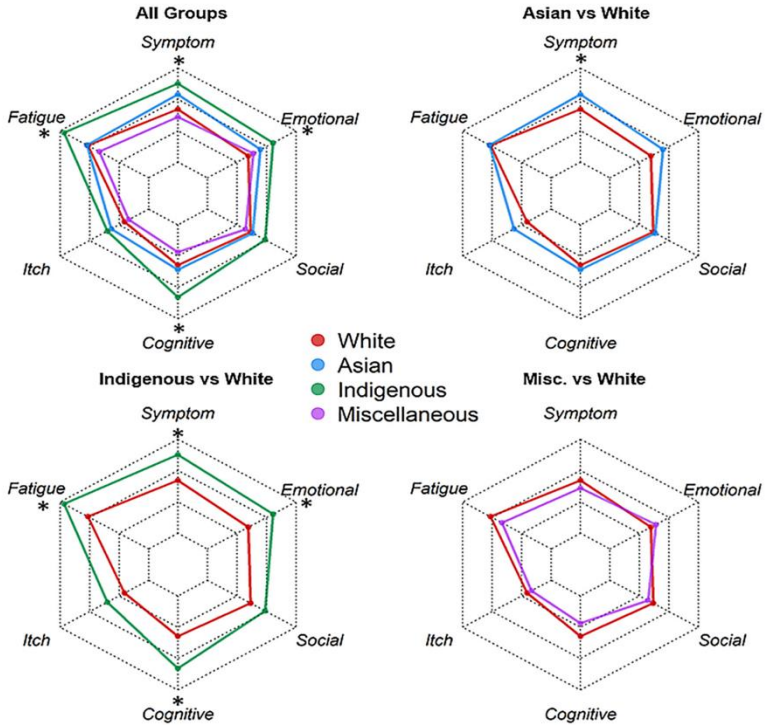
HCC = hepatocellular carcinoma.

Roberts SB, et al. *Hepatology*. 2022;76(2):303-316.

Symptoms/Quality of Life Vary With Race and Ethnicity



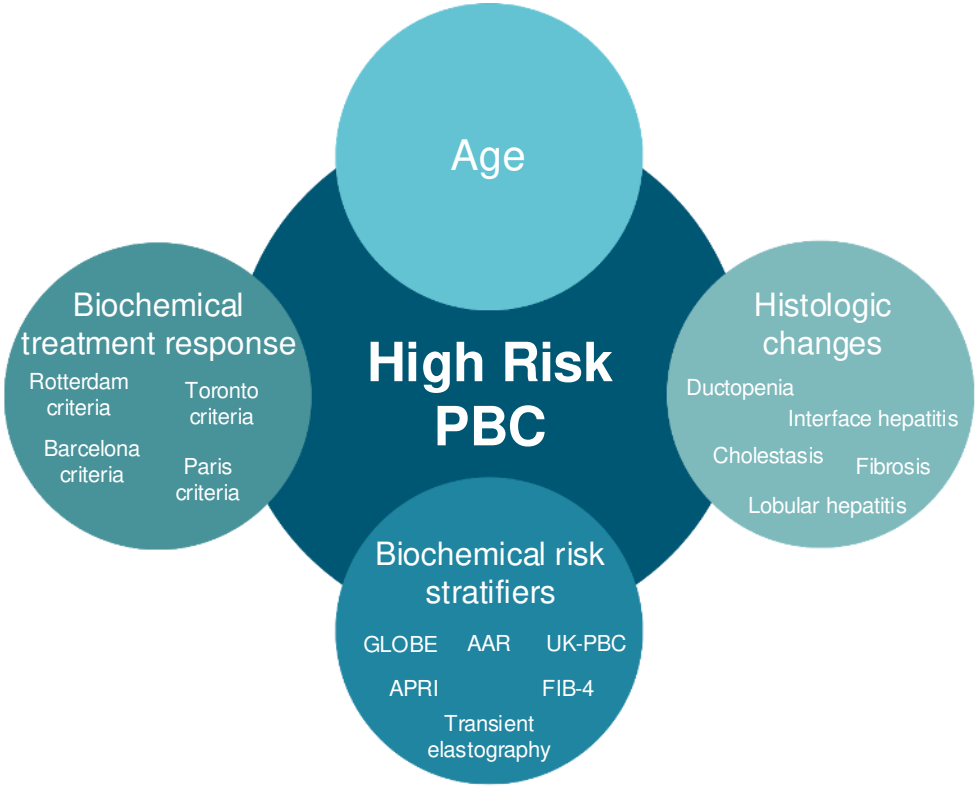
SF-36



PBC-40

Roberts SB, et al. *Hepatology*. 2022;76(2):303-316.

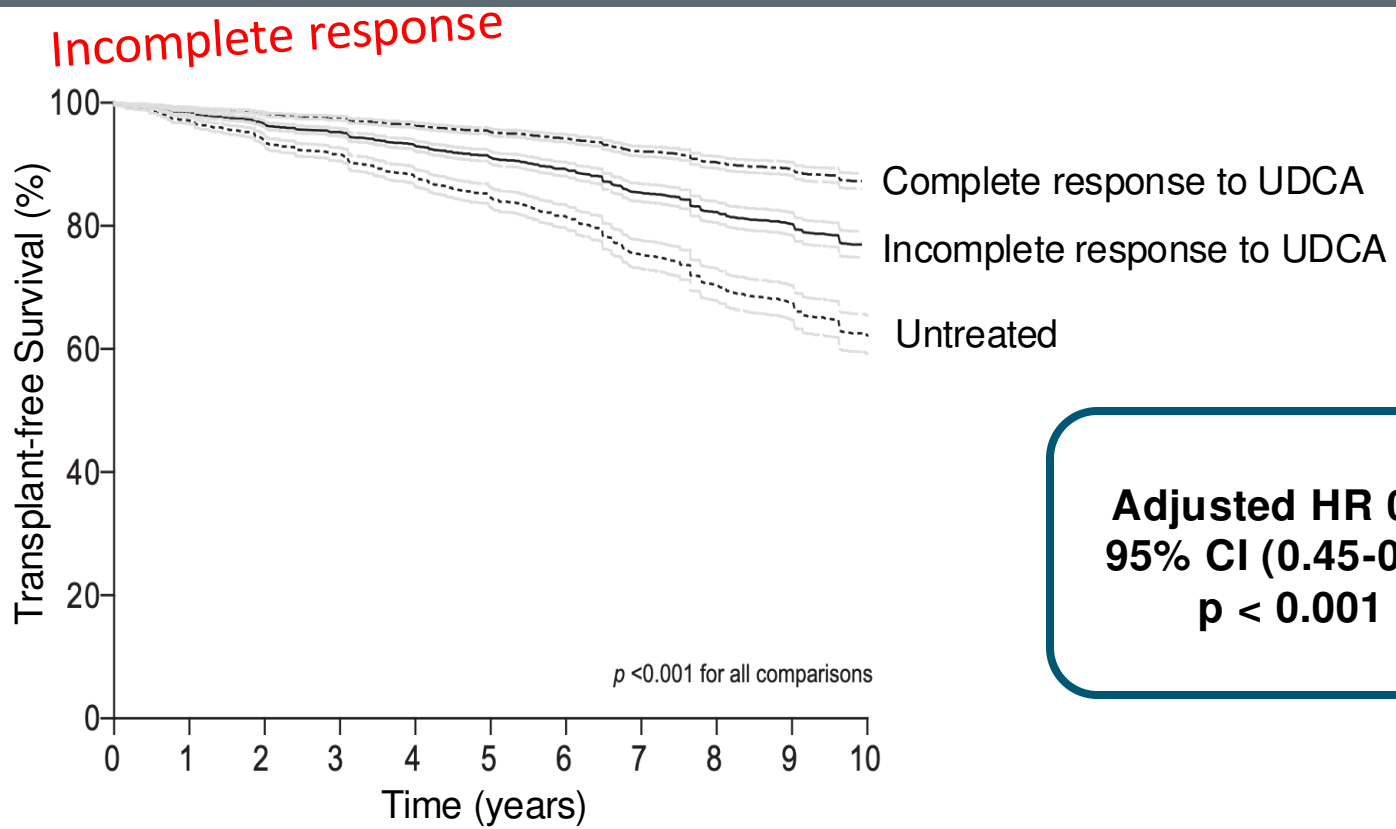
Characterization of Disease Risk



AAR = aspartate aminotransferase to alanine aminotransferase ratio; APRI = aspartate aminotransferase to platelet ratio index; FIB-4 = fibrosis-4 score; UK-PBC = United Kingdom Primary Biliary Cholangitis (risk scores).

Gulamhusein AF, et al. *Clin Gastroenterol Hepatol*. 2020;18(5):1033-1035.

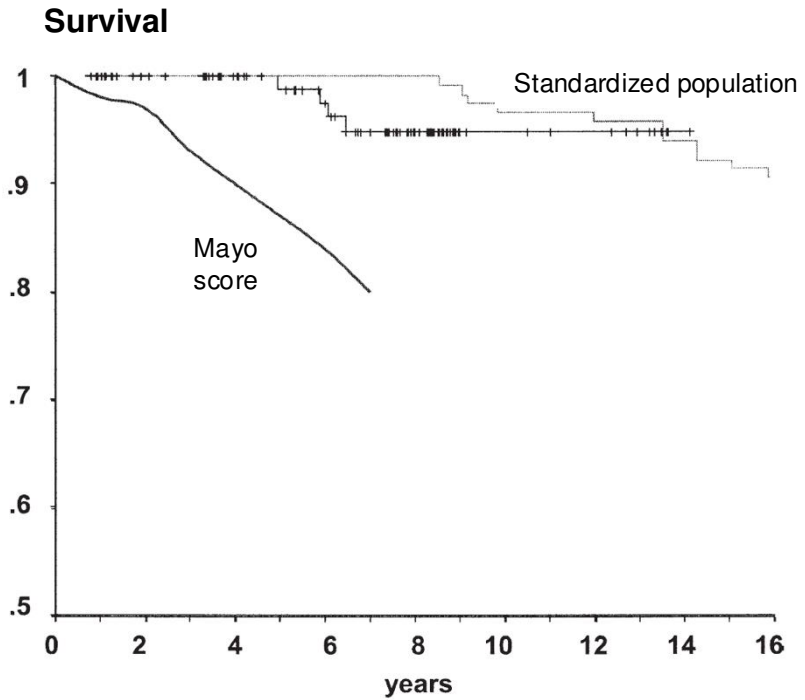
Prolonged Transplant-Free Survival in Case of "~~Non-~~Response" to UDCA



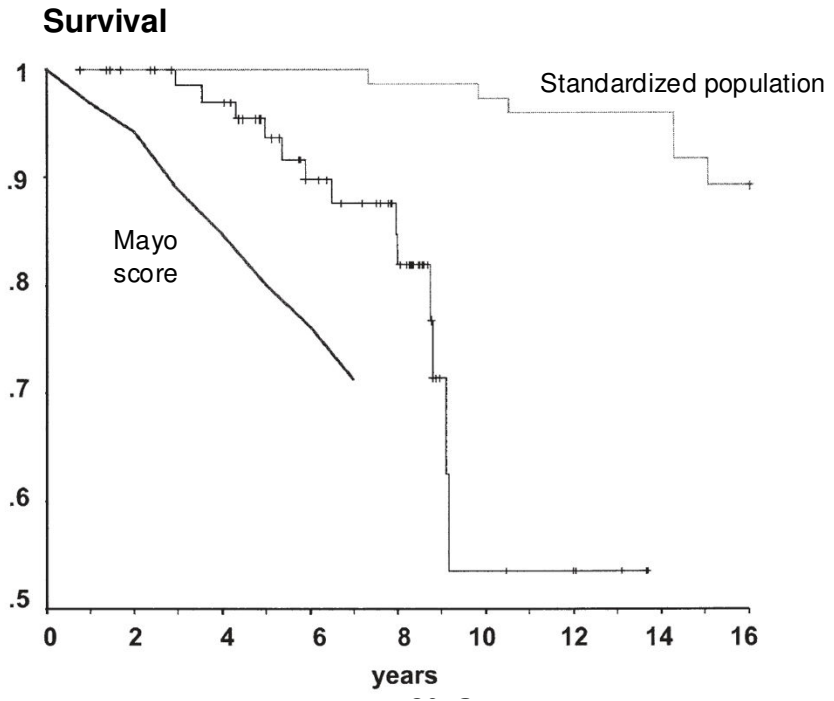
Adjusted HR 0.56
95% CI (0.45-0.69)
p < 0.001

Harms MH, et al. *J Hepatol*. 2019;71(2):357-365.

Up to 40% of Patients With PBC are Incomplete Responders to UDCA



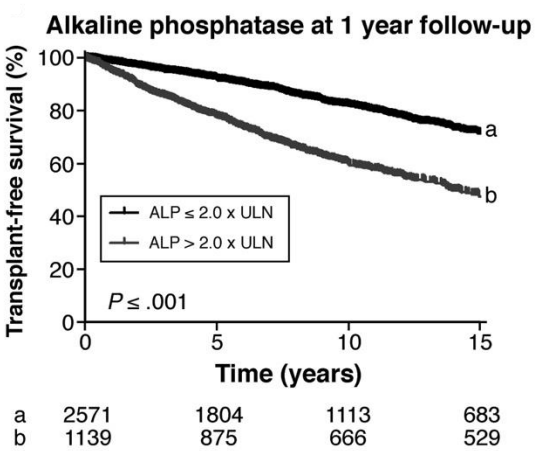
Responders

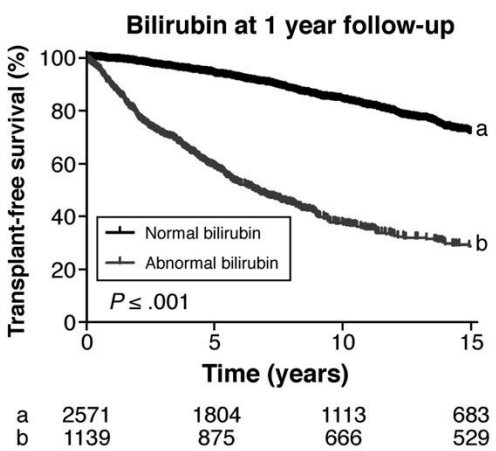


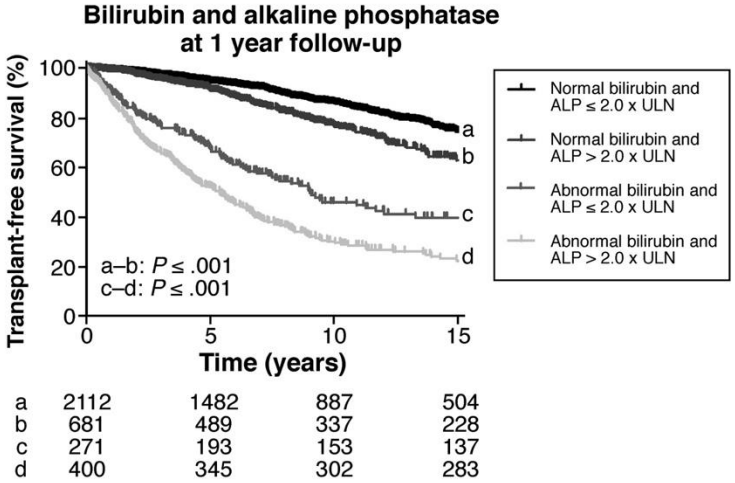
Non-Responders

Parés A, et al. *Gastroenterology*. 2006;130(3):715-720.

Predictors of Prognosis: Validated Surrogates





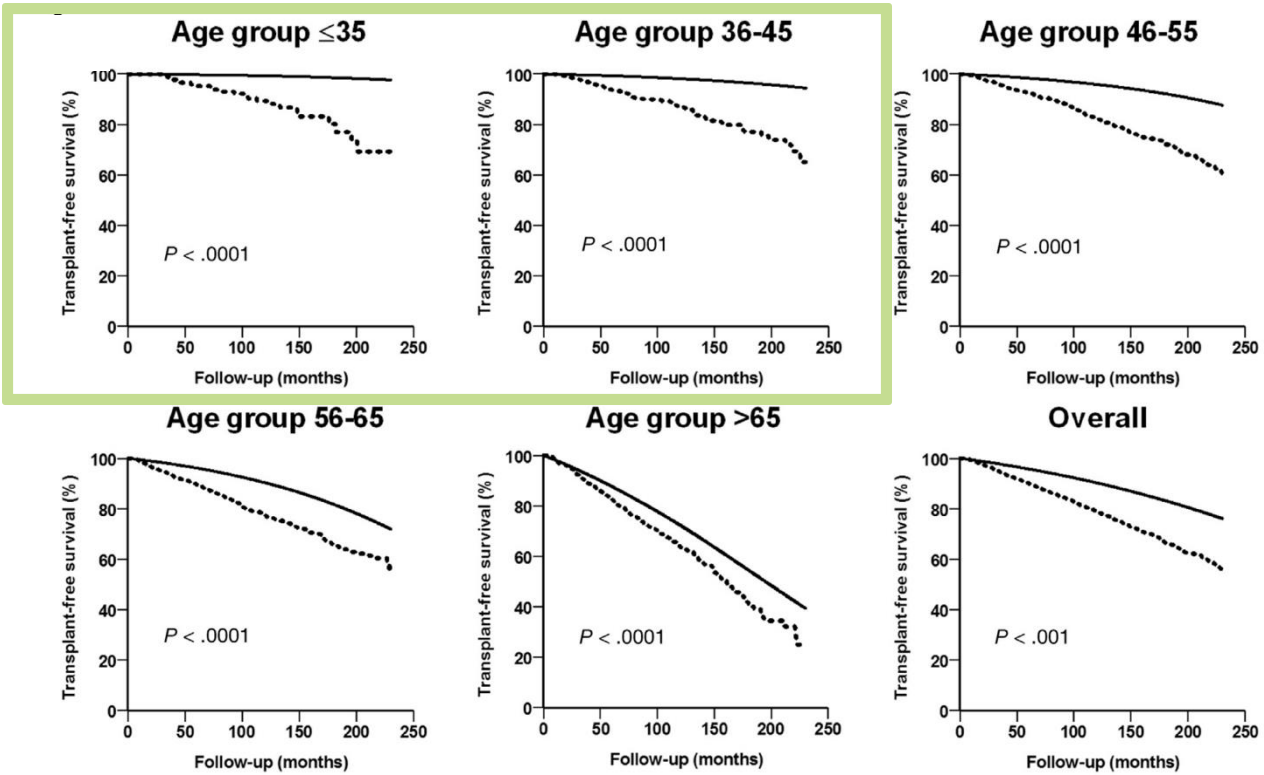


Lammers WJ, et al. *Gastroenterology*. 2014;147(6):1338-1349.

Effects of Age and Sex on Response to UDCA and Transplant-Free Survival in Patients With PBC

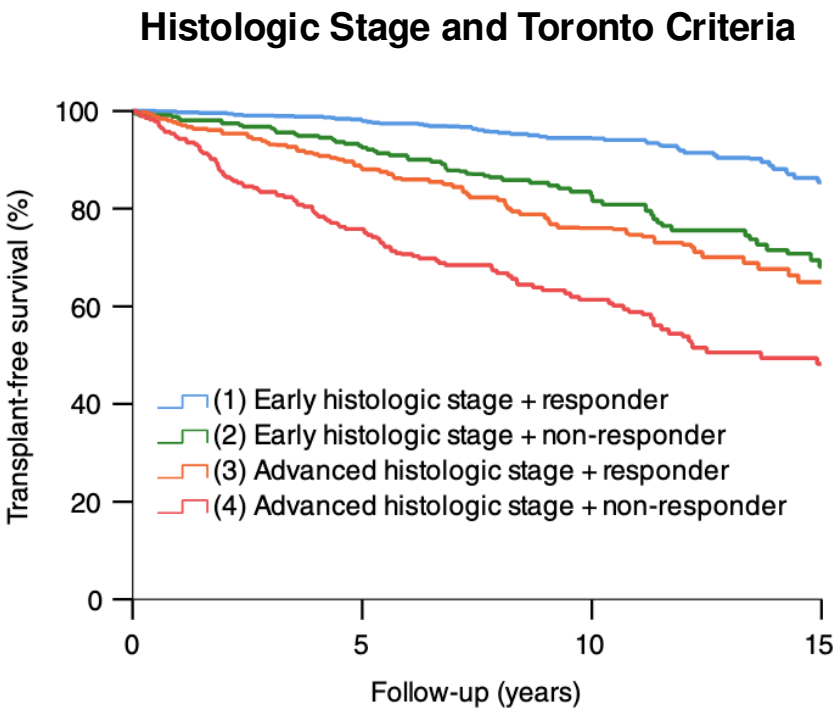
General Population ——

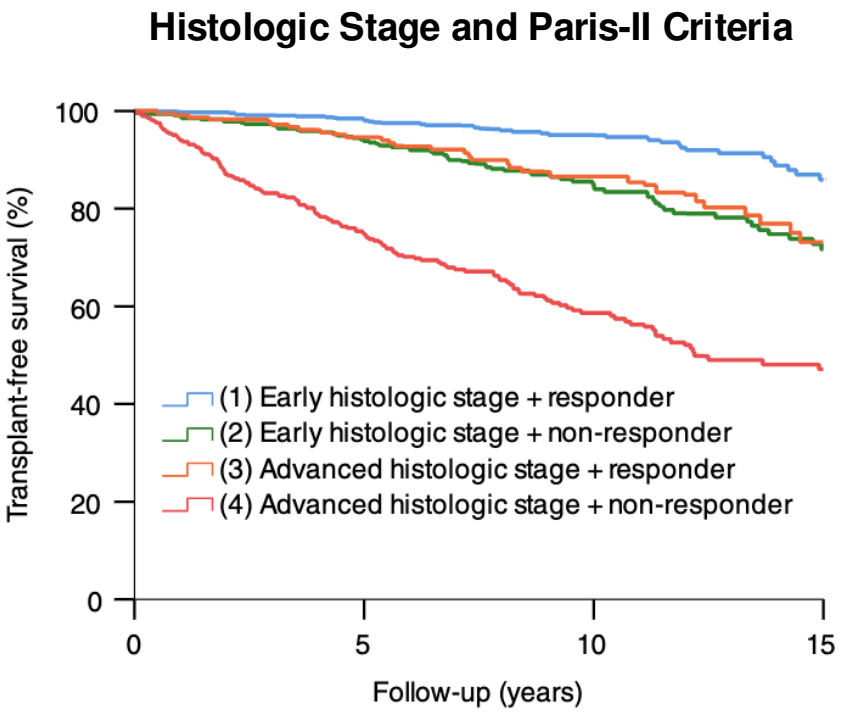
PBC Population - - - - -



Cheung AC, et al. *Clin Gastroenterol Hepatol*. 2019;17(10):2076-2084.

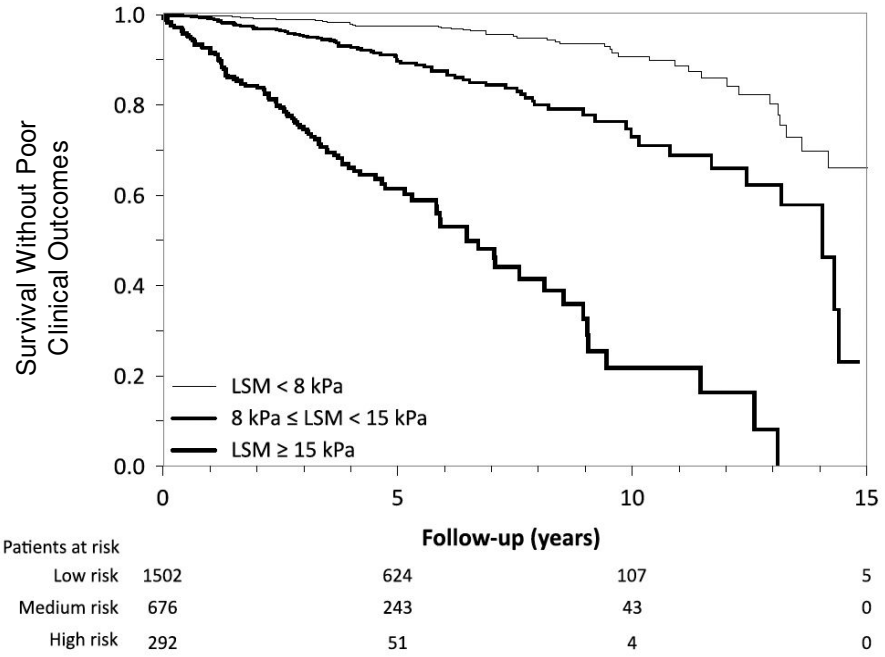
Histologic Fibrosis Stage Predicts Outcome Despite Biochemical Response



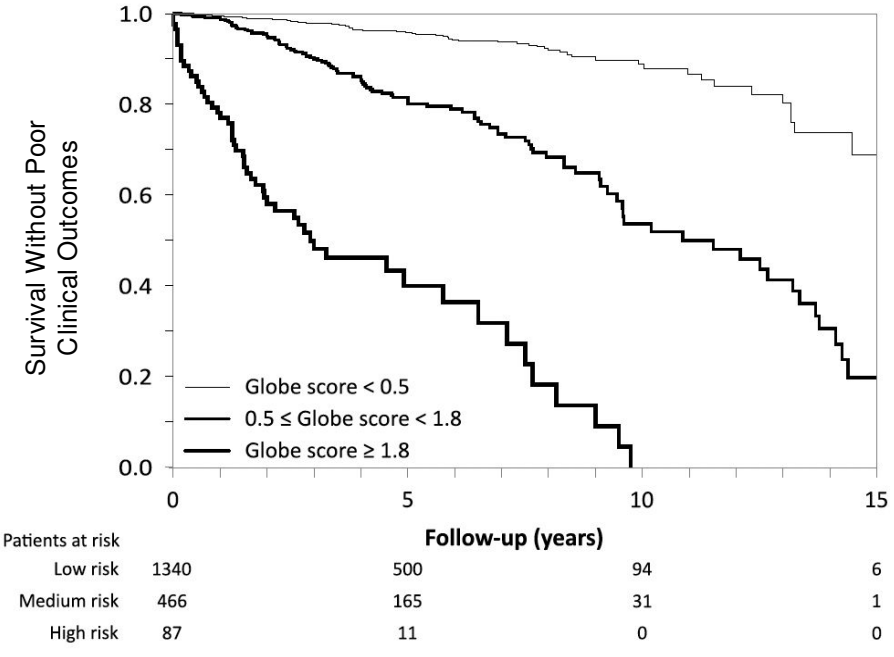


Murillo Perez CF, et al. *Aliment Pharmacol Ther*. 2019;50(10):1127-1136.

Liver Stiffness Measurements (LSMs) of < 8 kPa and ≥ 15 kPa are Thresholds of Risk



Patients at risk				
Low risk	1502	624	107	5
Medium risk	676	243	43	0
High risk	292	51	4	0



Patients at risk				
Low risk	1340	500	94	6
Medium risk	466	165	31	1
High risk	87	11	0	0

Corpechot C, et al. *J Hepatol.* 2022;77(6):1545-1553.

PBC Revealed: Deciphering the Clinical Clues

K. Tuesday Werner, DNP, AGACNP, FNP-BC, AF-AASLD

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Learning Objective 2

Implement evidence-based strategies for early and accurate diagnosis of PBC.

Audience Response

If you suspect a patient may have PBC, what should be checked as a first step in the diagnostic pathway?

A. Anti-nuclear antibody (ANA)
B. Antimitochondrial antibody (AMA)
C. Anti-glycoprotein 210 (gp210) or anti-speckled protein 100 (sp100)
D. Liver biopsy
E. I don’t know

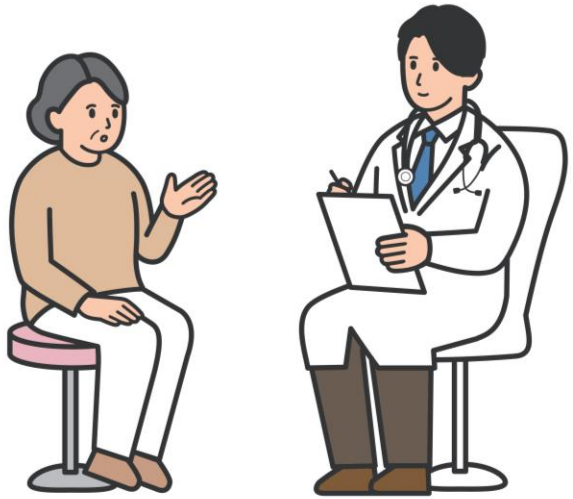
How PBC Presents in the Clinic

- **Chronic, cholestatic, autoimmune disease** with a variable progressive course that may extend over many decades
- Thought to be caused by a combination of **genetic** predisposition and **environmental** triggers (e.g., nail polish, hair dye, cigarette smoking, xenobiotics)
- "Common rare" disease: **most clinicians** will encounter PBC in practice
- Mostly seen in **women** in their **fifth or sixth decade** of life
- **~10% of cases in men**, often with advanced disease & worse prognosis

Younossi ZM, et al. *Am J Gastroenterol.* 2019;114:48-63.

How PBC Presents in the Clinic (continued)

- **Pruritus** is the most common symptom (20-70% of patients)
- Fatigue is a **frequent complaint** (suspect PBC when coupled with pruritus)
- Can be asymptomatic, but **abnormal liver tests** should raise suspicion
- Prompt diagnosis (and subsequent treatment) is **critical** to prevent liver-related sequelae
  - (e.g., cirrhosis, liver failure, need for transplantation, death)



Younossi ZM, et al. *Am J Gastroenterol.* 2019;114:48-63.

Diagnostic Delays

On average, it takes **women 12 months** to receive a PBC diagnosis and **men nearly 3 years.**

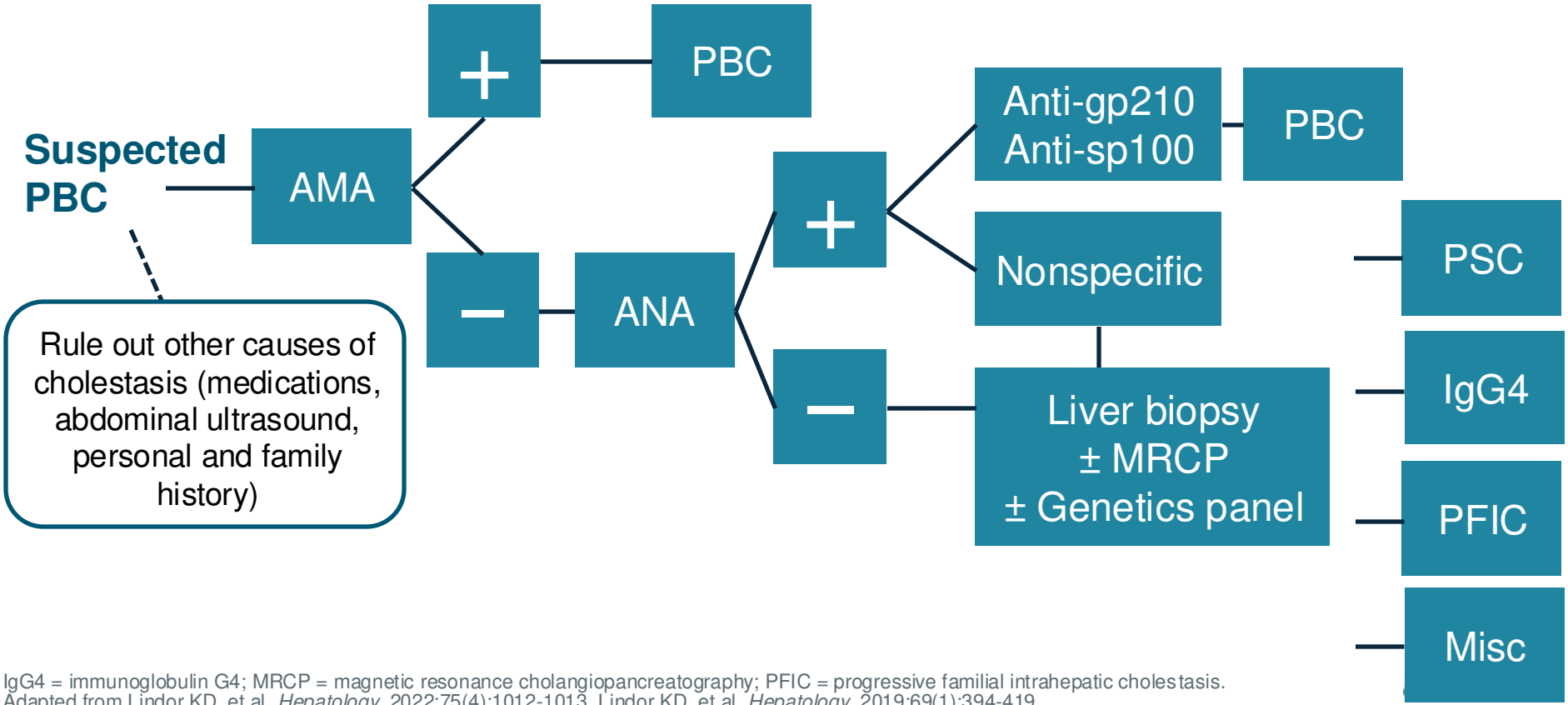
*"You know those symptoms that you think maybe are in your head? They're not. It's **real** and you need to make sure that you speak up for yourself. The symptoms of PBC may **not be immediately obvious** and may be dismissed by clinicians without experience caring for PBC patients."*

- Kris Kowdley, MD

Society for Women's Health Research. www.swhr.org. More Than PBC. https://www.morethanpbc.com/what-is-pbc.

Patient Perspective (Symptoms): Maria Morais, RN

Diagnostic Pathways: PBC



IgG4 = immunoglobulin G4; MRCP = magnetic resonance cholangiopancreatography; PFIC = progressive familial intrahepatic cholestasis.
Adapted from Lindor KD, et al. *Hepatology*. 2022;75(4):1012-1013. Lindor KD, et al. *Hepatology*. 2019;69(1):394-419.

Diagnosing PBC: AASLD Guidelines

PBC Diagnostic Criteria (2 of 3 must be met)

1. Biochemical evidence of cholestasis based on ALP elevation
2. Presence of AMAs or other PBC-specific autoantibodies, including sp100 or gp210, if AMA is negative
3. Histopathologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts (if biopsy is performed)

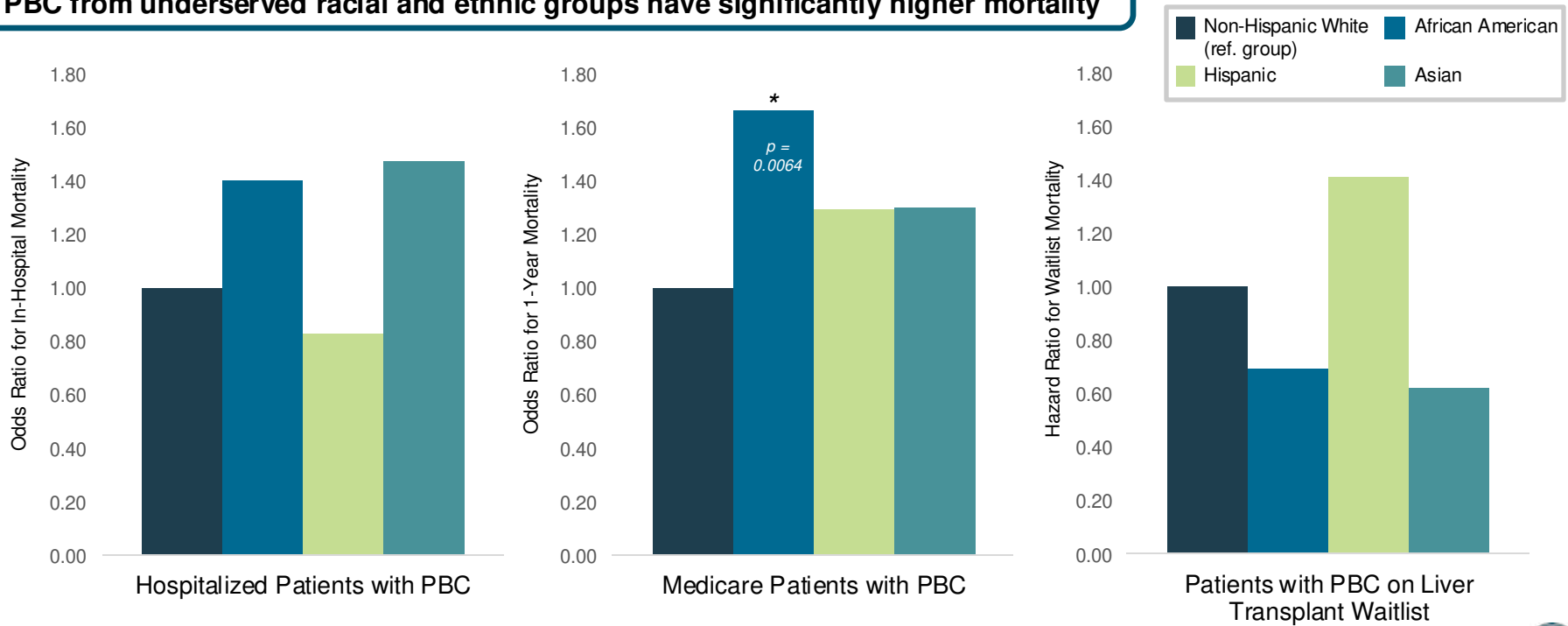
- The differential diagnosis includes a cholestatic drug reaction, biliary obstruction, sarcoidosis, AIH, and primary sclerosing cholangitis
- Transient elastography can be done to assess stage of disease
- Liver biopsy is often not required but may be helpful in disease prognosis/staging

AASLD = American Association for the Study of Liver Diseases.

Lindor KD, et al. *Hepatology*. 2022;75(4):1012-1013. Lindor KD, et al. *Hepatology*. 2019;69(1):394-419. Sivakumar M, et al. *Frontline Gastroenterol*. 2022;13(1):32-38.

Racial and Ethnic Disparities in PBC Outcomes

Compared to non-Hispanic White individuals, studies have found that patients with PBC from underserved racial and ethnic groups have significantly higher mortality



Galoosian A, et al. *Dig Dis Sci*. 2020;65(2):406-415. Sayiner M, et al. *Hepatology*. 2019;69(1):237-244. Cholankeril G, et al. *Clin Gastroenterol Hepatol*. 2018;16(6):965-973.

Social Drivers of Health (SDoH) in the Context of Managing PBC

Adapted from Essien UR, et al. *Nat Rev Cardiol*. 2021;18(11):763-773.

How Do I Ask Patients About SDoH?

- What challenges do you have getting to appointments?
- Do you have access to a pharmacy?
- Do you have access to care in your preferred language?
- Do you have insurance for visits and prescriptions?
- Do you have safe housing?
- Do you have a safe place to store/refrigerate medications?
- Can you afford and access healthy food?
- How do you prefer to learn about things?
- Are you experiencing discrimination that is negatively impacting your health?
- Do you ever need to use a cane, walker, or wheelchair for any physical limitations? Are there family members, friends, or neighbors who can help you?

Adapted from Cleveland Clinic. 2024. https://my.clevelandclinic.org/health/articles/social-determinants-of-health.

Evolving Therapeutic Approaches for Patients with PBC

Kris V. Kowdley, MD, FACP, FACG, AGAF, FAASLD

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Learning Objective 3

Incorporate contemporary clinical pathways for treating PBC that consider MOA, indications, efficacy, and safety.

Audience Response

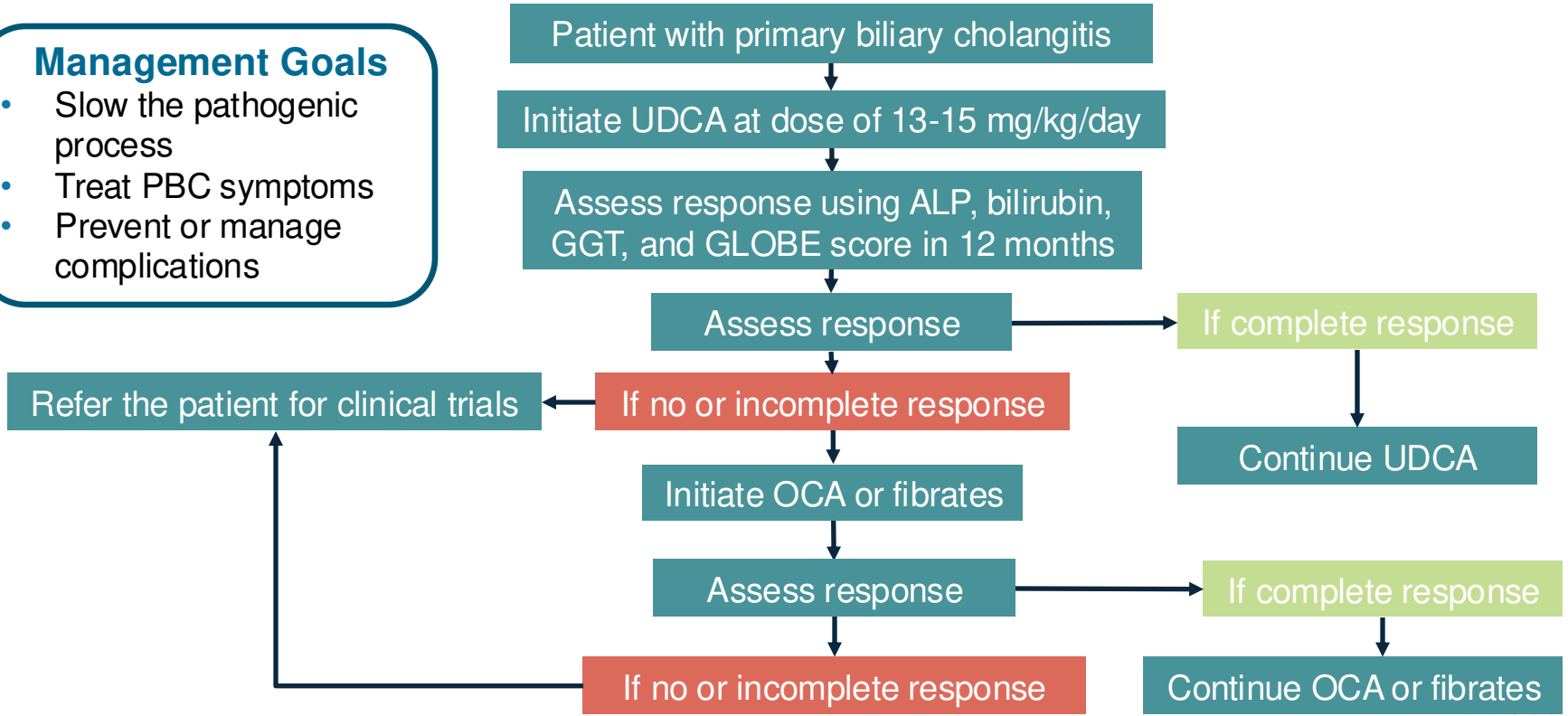
Which of the following was shown with seladelpar in the RESPONSE trial?

A. Durable biochemical response, increased ALP normalization, reduction in pruritus
B. Transient biochemical response, increased ALP normalization, improvement in “brain fog”
C. Sustained positive antimitochondrial antibody, reduction in pruritus, complete remission of PBC
D. 78% of patients receiving 5 mg of seladelpar met the composite study endpoint
E. I don’t know

Treatment Pathways with Conventional Therapies

Management Goals

- Slow the pathogenic process
- Treat PBC symptoms
- Prevent or manage complications



OCA = obeticholic acid.
Adapted from Sohal A, et al. *Hepat Med*. 2023;15:63-77.

New Treatments Are Needed Beyond UDCA and OCA

- UDCA (first-line therapy)
  - 25%-50% of patients do not have a biochemical response
  - Non-responders have a fivefold risk of progression to cirrhosis and a threefold increase in age-adjusted mortality
  - AEs can negatively impact patient QoL
- OCA (second-line therapy)
  - **May 2021**: Warning added for hepatic decompensation and failure in PBC with cirrhosis ➔ AASLD revised guidance on OCA
  - **Sept 2024**: FDA panel voted 13 to 1 that confirmatory trials did not verify clinical benefits of OCA in PBC; pointed to harm vs benefit
  - AEs (pruritus) led to significant discontinuation

AE = adverse event.

Kowdley KV, et al. *Am J Gastroenterol*. 2023;118:232-242. Younossi ZM, et al. *Am J Gastroenterol*. 2019;114:48-63. D'Amato D, et al. *JHEP Rep*. 2021;3:100248.

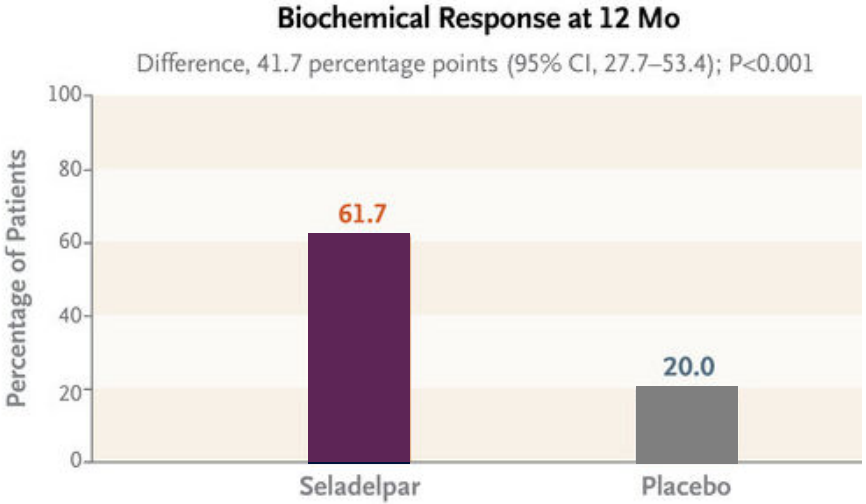
Patient Perspective (Treatment): Maria Morais, RN

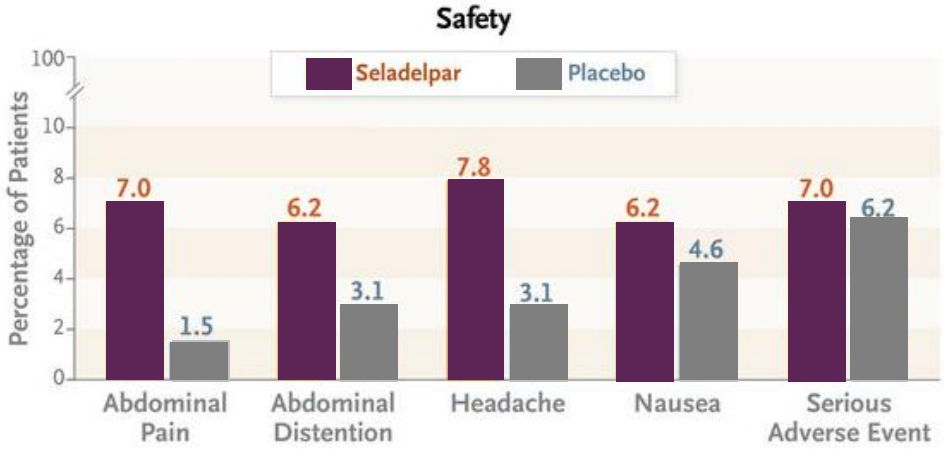
FDA-Approved Agents for PBC in 2024

Seladelpar (a selective peroxisome proliferator-activated receptor-**δ** (PPAR) agonist

Elafibranor (a dual peroxisome proliferator-activated receptor (PPAR) **α** and **δ** agonist

Seladelpar
RESPONSE: Phase III Results



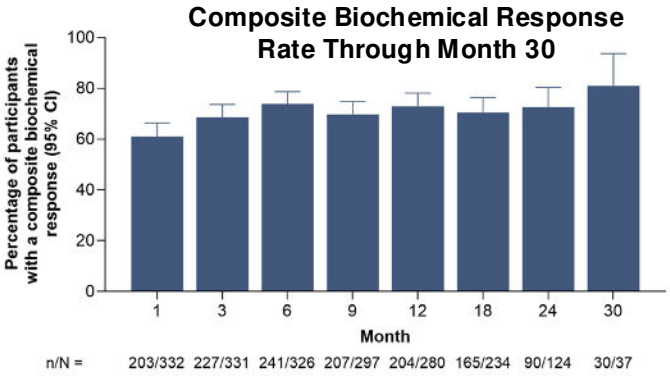


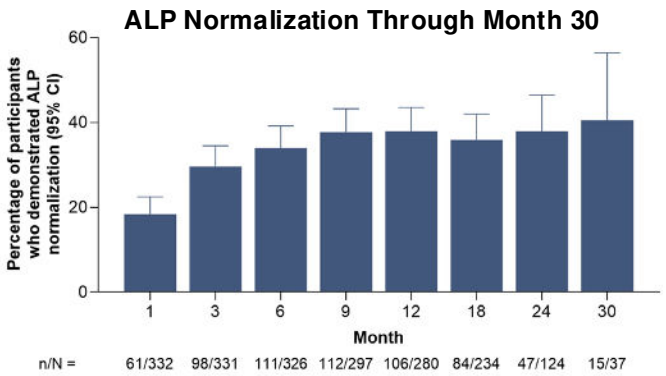
- Efficacy and safety of seladelpar in patients with PBC who had inadequate response to UDCA
- 193 patients assigned in 2:1 ratio to seladelpar 10 mg daily or placebo
- Primary endpoint: biochemical response (defined by ALP level < 1.67 times ULN range with a 15% decrease from baseline and a normal total bilirubin level)

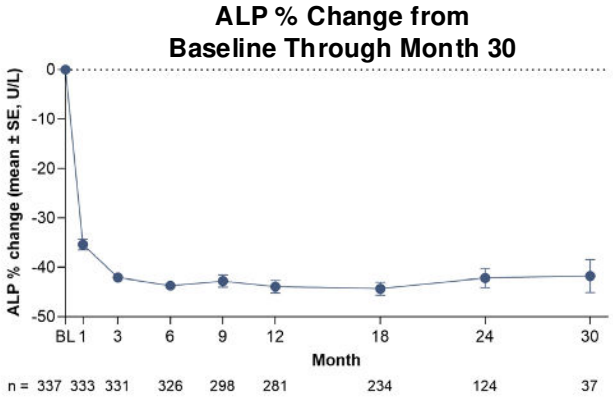
Hirschfield GM, et al. *N Engl J Med*. 2024;390:783-794.

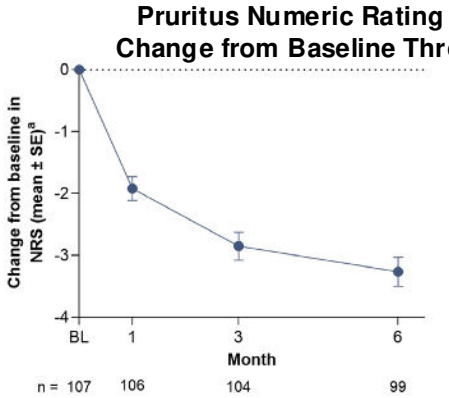
Seladelpar 3-Year Study Outcomes: AASLD 2024 Late Breaker

- Durable and sustained biochemical response to seladelpar in patients with PBC in ongoing phase III ASSURE Study
- No serious treatment-related AEs reported



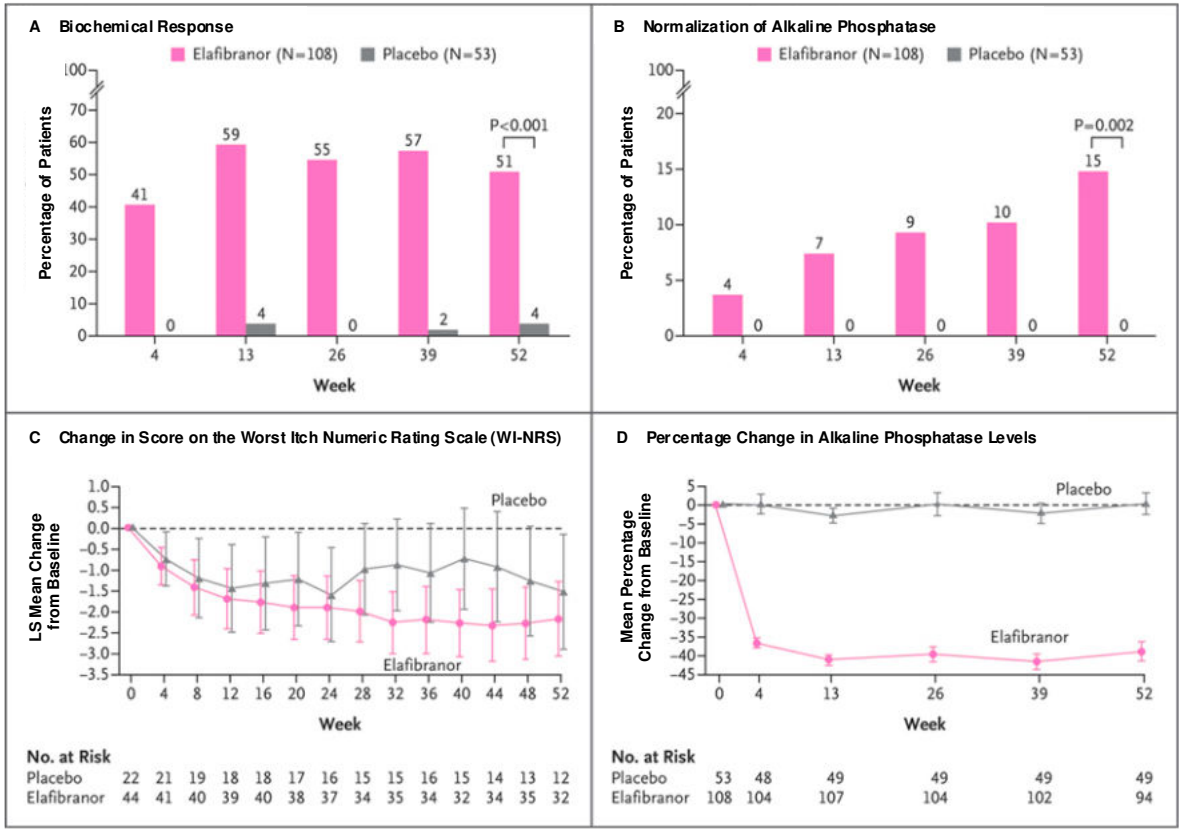


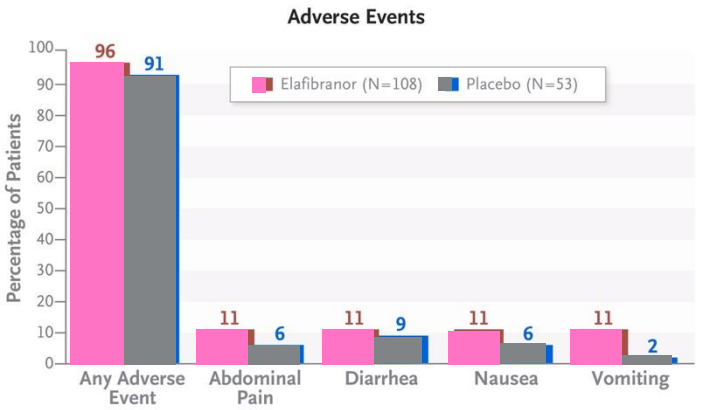




Lawitz E, et al. AASLD: The Liver Meeting; 2024. Abstract No. 5044. https://www.aasld.org/sites/default/files/2024-11/TLM2024LBA_20241115A.pdf.

Elafibranor
ELATIVE: Phase III Results





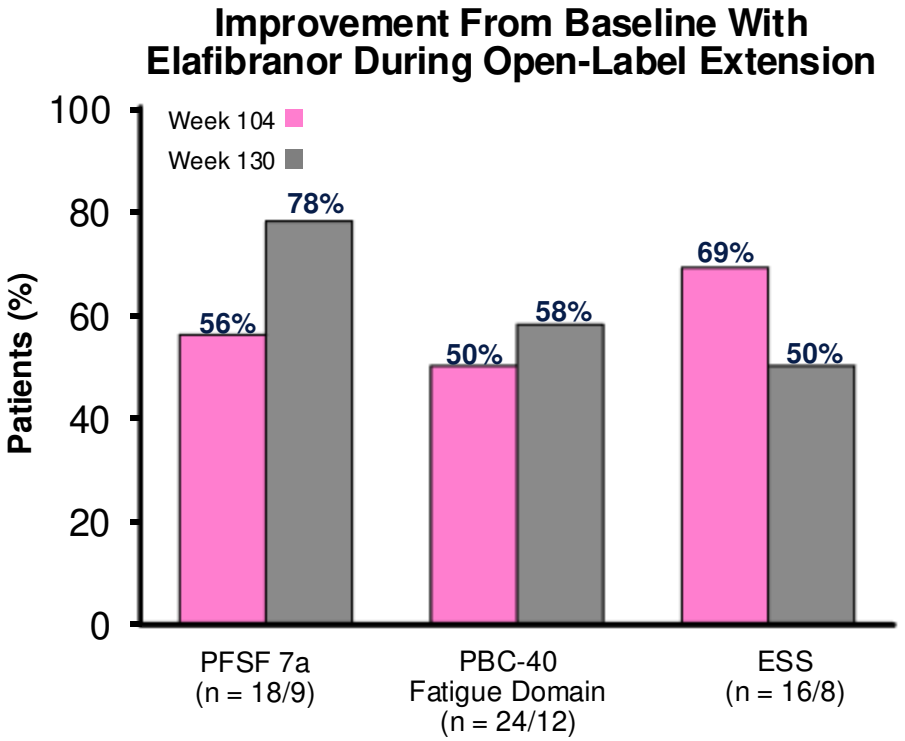
Conclusions:

In patients with PBC in whom UDCA was associated with inadequate response or unacceptable side effects, treatment with elafibranor led to greater improvements in relevant biochemical indicators of cholestasis than placebo.

Kowdley KV, et al. *N Engl J Med*. 2024;390(9):795-805.

ELATIVE: Impact of Elafibranor on Fatigue During the Open-Label Extension

- Patients randomized to elafibranor during double-blind phase included in open-label extension analysis measured fatigue and sleep domains*
- Clinically meaningful improvements shown with elafibranor treatment in patients with moderate-to-severe fatigue or excessive sleepiness at baseline



*PFSF 7a = Fatigue Short Form 7a; ESS = Epworth Sleepiness Scale.

Swain MG, et al. AASLD: The Liver Meeting; 2024. Abstract No. 5042. https://www.aasld.org/sites/default/files/2024-11/TLM2024LBA_20241115A.pdf.

Other Treatments in Development

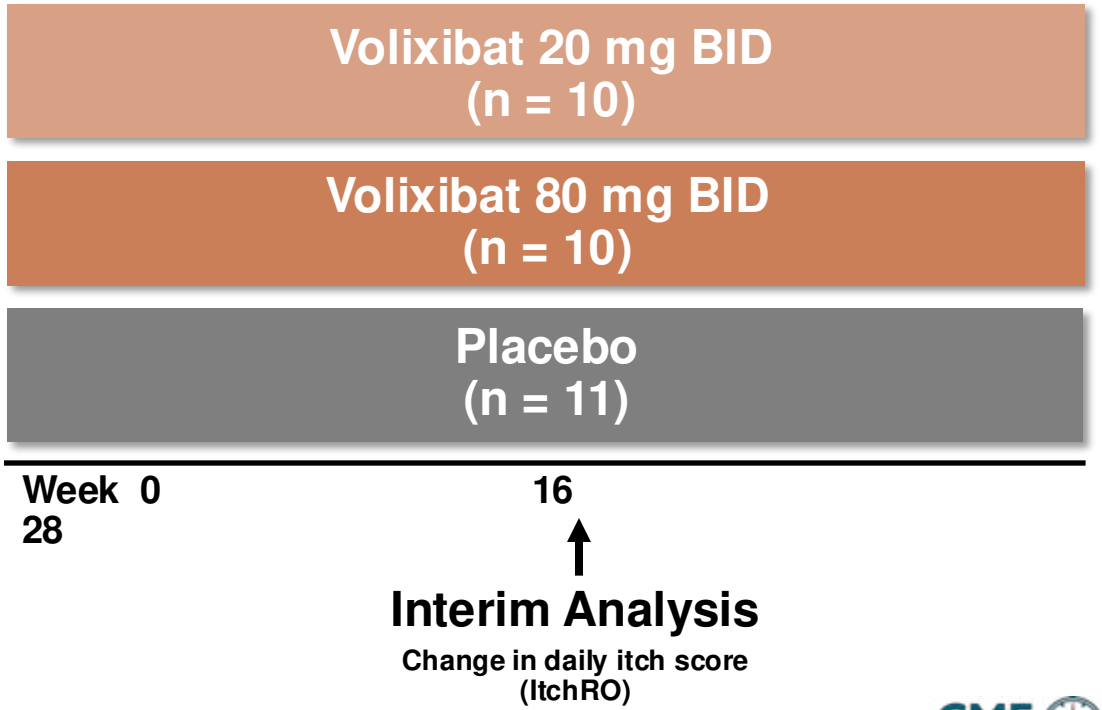
- Agents that target FGF-19 pathway: NGM292 (aldafermin)
- Fibric acid derivatives (bezafibrate, fenofibrate)
- Non-bile acid FXR agonists: EDP-305 (tropifexor)
- NOX inhibitors (setanaxib)
- IBAT inhibitors (volixabat, linerixibat)
- Antiretroviral combinations (LPR, TDF/FTC)
- Immunomodulatory therapy (rituximab, budesonide, NI-0701, ustekinumab, baricitinib, abatacept, FFP-104, MSC transplantation)
- Other PPAR agonists (saroglitazar)

FGF-19 = fibroblast growth factor; LPR = lopinavir-ritonavir; TDF/FTC = tenofovir-emtricitabine; MSC = mesenchymal stem/stromal cells; FXR = farsenoid X receptor; NOX = nicotinamide adenine dinucleotide phosphate oxidase; IBAT = ileal bile acid transporter.

VANTAGE: Impact of Volixibat, an Investigational Agent, on Cholestatic Pruritus in Patients with PBC

- Phase IIb adaptive randomized trial
- PBC (AASLD guidelines)
- ≥ 18 years of age
- Moderate-to-severe pruritus
- Primary outcome: change in daily itch at week 28
- Baseline characteristics:
  - Age: 56 years
  - Female: 87%
  - Serum bile acids: 42 µmol/L
  - ItchRO score: 6.4
  - ALP: 211
  - Total bilirubin: 0.9 mg/dL

Volixibat: ileal bile acid transporter inhibitor



BID = twice daily; ItchRO = Adult Itch-Reported Outcome questionnaire. Scale: 0 (no itch) to 10 (worst possible itch).

Kowdley KV, et al. AASLD: The Liver Meeting; 2024. Abstract No. 5038. https://www.aasld.org/sites/default/files/2024-11/TLM2024LBA_20241115A.pdf.

VANTAGE (Interim Analysis): Outcomes With Volixibat, an Investigational Agent, at Week 16

- Significant improvements in pruritus with volixibat 20 and 80 mg compared with baseline ($p < 0.0001$)
- Improvements in quality of life observed after treatment with volixibat
- Safety of volixibat
  - Diarrhea: 77% (pooled volixibat data; mild in severity, led to 1 discontinuation)
  - No clinically relevant changes in total bilirubin, ALT, AST, or ALP
- Volixibat 20 mg dose was selected for part 2 of VANTAGE study

Outcomes With Volixibat at Week 16

	20 mg (n = 10)	80 mg (n = 10)	Placebo (n = 11)
Change in serum bile acids (µmol/L)	-3.7*	-3.98*	-1.3
Serum bile acids responders (%)	80	60	36
Grade ≥ TEAEs related to study drug (%)	9	0	0
TEAEs leading to study drug discontinuation	9	0	0

*$p < 0.01$ versus placebo

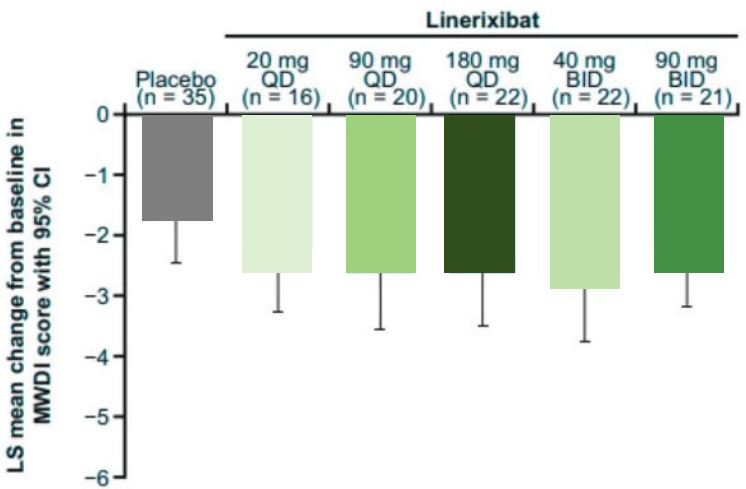
TEAEs = treatment-emergent adverse events.

Kowdley KV, et al. AASLD: The Liver Meeting; 2024. Abstract No. 5038. https://www.aasld.org/sites/default/files/2024-11/TLM2024LBA_20241115A.pdf.

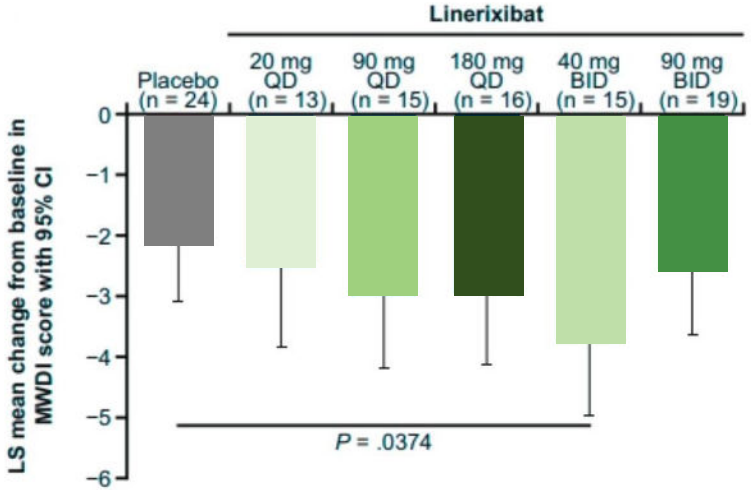
GLIMMER
Linerixibat: An Investigational Agent for PBC Pruritus

- Randomized, multicenter, parallel-group, placebo-controlled phase IIb trial in patients with PBC and moderate to severe pruritus (N = 1476). Most frequent AE: diarrhea and abdominal pain (identified linerixibat dose for phase III trials)

MWDI Score in ITT Population



Post Hoc Analysis of MWDI Score



UPDATE 11.19.24 – Ongoing **GLISTEN** phase III trial met primary endpoint ➔ linerixibat showed significant improvement in itch.

ITT = intention to treat; LS = least squares; MWDI = mean worst daily itch; PP = per protocol; QD = once daily.

Levy C. *Clin Gastroenterol Hepatol*. 2023;21:1902. GlaxoSmithKline. *Dose Response Study of GSK2330672 for the Treatment of Pruritus in Participants With Primary Biliary Cholangitis*. ClinicalTrials.gov Identifier: NCT02966834. First Received 2017. Thomas E. *ClinicalTrials Arena*. 2024. https://www.clinicaltrialsarena.com/news/positive-phase-iii-results-linerixibat-cholestatic-pruritus-pbc-patients/?cf-view.

Faculty Discussion

(including AASLD 2024 perspectives)

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Elevate PBC on your diagnostic radar: the changing epidemiology of PBC relates to improved awareness, enhanced diagnostics, and impact of therapy
- Listen to patients carefully: diagnostic delays are common due to pruritus, fatigue, and/or brain fog being attributed to other conditions. Keep social drivers of health in mind during counseling
- Become proficient at implementing noninvasive diagnostic pathways for PBC
- Implement contemporary treatment strategies for PBC, including the use of recently approved PPAR agonists
- Keep abreast of new drugs in development for symptomatic and disease management of PBC

To Ask a Question

To ask a question, select the *Ask Question* tab below the slide viewer. Please include the faculty member's name if the question is specifically for them.

Questions and Answers

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