# Managing Primary Biliary Cholangitis (PBC)

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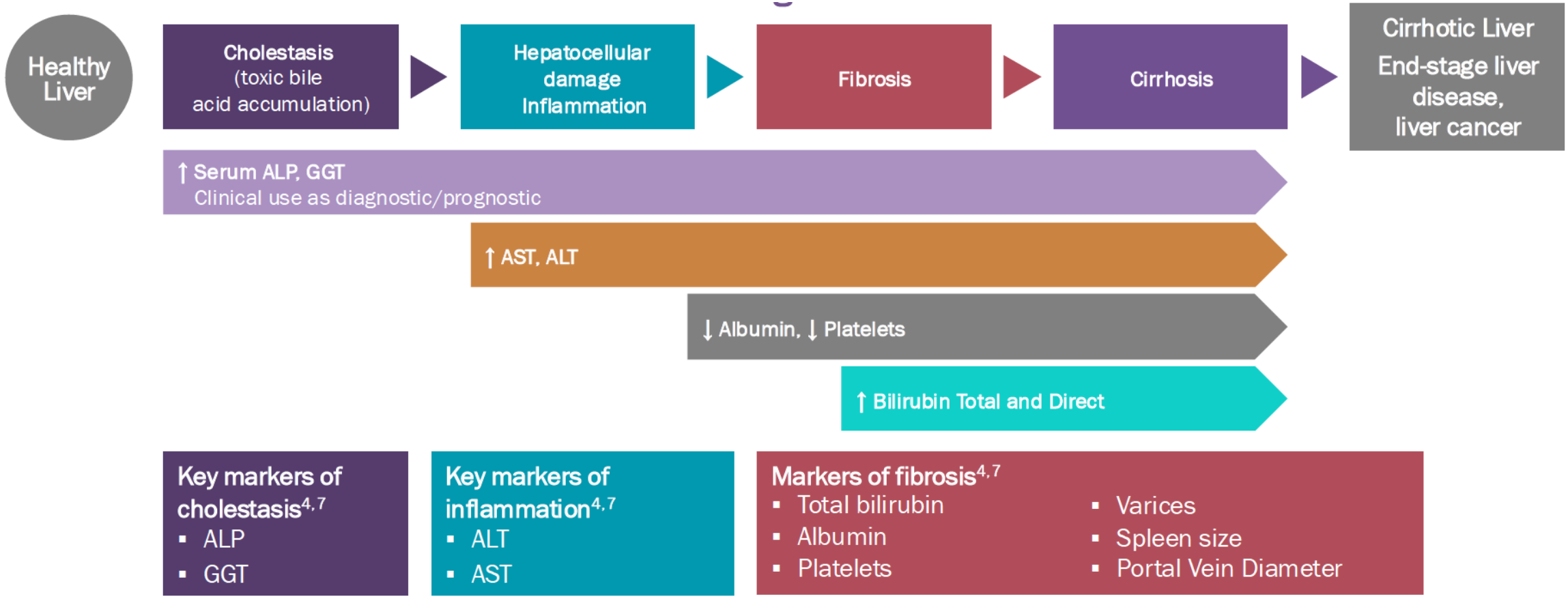
# Real-World Case: Primary Care Provider

- 39-year-old female with BMI of 24 $kg/m^2$ with h/o Vit D deficiency, Raynaud's syndrome and hypothyroidism
- Presents with incidental finding of echogenic liver and c/o significant pruritus.
- ALT 58 U/L (10-30 U/L)
- AST 38 U/L  (10-30 U/L)
- ALP 298 (IU/L)
- Albumin 4.4 g/dL (3.5-4.5 g/dL)
- Platelet count 325 k/uL (150-400 k/uL)

# 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.

# Clinical Features Vary Greatly Between Patients…

…but there are disease-associated symptoms, clinical manifestations, and co-existing autoimmune diseases that are recognized[1-3]

**Fatigue**[1,2]

**Pruritus**[1,2]

Most common symptoms of PBC[2]

**Xanthoma and xanthelasma**[2,3]

**Hyperlipidemia**[1,2]

**Osteoporosis**[1,2]

**Co-existing autoimmune diseases**[1,2]

The absence of symptoms at diagnosis may not predict prognosis (as many as ~60% of patients may be asymptomatic at diagnosis)[4]*

PBC, primary biliary cholangitis.

*Based on an examination of the natural history of a 770-patient cohort in Northeast England (incident cases, 1987-1994).[4]

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*. 2018. doi:10.1002/hep.30145; 4. Prince MI et al. *Gut*. 2004;53(6):865-870.

# Managing Fatigue and Pruritus

# Fatigue is the Most Common Symptom in PBC

- Present in up to 85% of patients with PBC[3]
  - >40% report moderate to severe[1]
- Mechanism not well understood[1,2]
- Unrelated to disease activity or stage
  - Tends to wax and wane throughout the course of illness[2]
- Typically characterized as daytime somnolence
  - Can impair QoL[1] → Associated fatigue, cognitive symptoms, social and emotional dysfunction, sleep disturbances, and depression.

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

QoL, quality of life.

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.

# Assessing and Managing Fatigue

- Though fatigue caused by PBC may not be reversible, associated causes of fatigue should be actively excluded—or identified and managed[1,2]

| Rule Out: |
| --- |
| **Associated causes of fatigue (disease or medication):**<br>• Anemia[2]<br>• Depression[2]<br>• Sleep disorder[2]<br>• **Hypothyroidism**[1-3]<br>• Medications that can cause or contribute to fatigue (eg, excessive antihypertensive medication)[1] |

| Consider Fatigue Management Strategies: |
| --- |
| **Fatigue may be improved by:**<br>• Maintaining regular physical activity[4,5]<br>• **Structured exercise program**<br>• The impact of mindfulness is under evaluation (NCT03684187, NCT05374200)<br>• Modafinil (100-200 mg)[6,7]<br>• Methotrexate for patients with severe fatigue[8] |

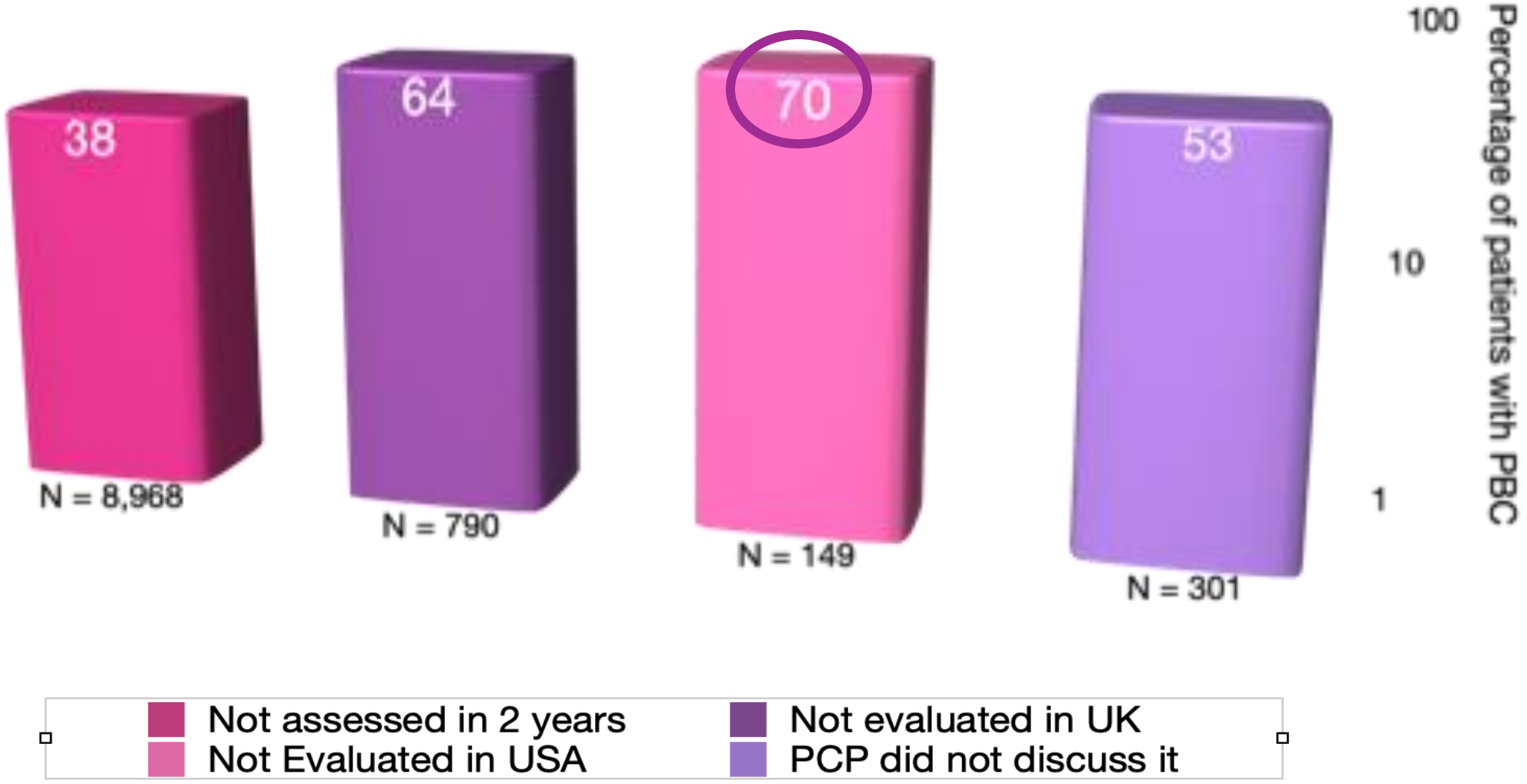
1. European Association for the Study of the Liver. *J Hepatol*. 2009;51(2):237-267; 2. Lindor KD et al. *Hepatology*. 2009;50(1):291-308; 3. Elta GH et al. *Dig Dis Sci*. 1983;28(11):971-975; 4. Cook NF et al. *Br J Nurs*. 1997;6(14):811-815; 5. Graydon JE et al. *Cancer Nurs*. 1995;18(1):23-28; 6. Jones DEJ et al. *Aliment Pharmacol Ther*. 2007;25(4):471-476; 7. Ian Gan S et al. *Dig Dis Sci*. 2009;54(10):2242-2246; 8. Babatin MA et al. *Aliment Pharmacol Ther*. 2006;24(5):813-820.

# Pruritus in Cholestatic Disease

- Occurs in 20%-70% of patients with PBC.  Could it be 80%?
  - Among those reporting pruritus: New study shows >50% mod-severe pruritus
  - ~~64.5% mild, 31.3% moderate and 4.2% severe.~~
- Pruritus severity is variable and not correlated to disease severity or prognosis
  - A study found that patients with significant cholestatic pruritus & higher alkaline phosphatase levels → cirrhosis
- Characteristics
  - Typically localized to limbs, soles of feet, and palms of hands
  - Often exacerbated by contact with wool or other fabrics, heat, or pregnancy.
  - Intermittent; seasonal variation, diurnal variation, worse at night.
  - Described as ‘deep’ and ‘relentless’, being ‘prickly’ or like ‘needles’, and feeling like ‘bugs crawling
- Intractable pruritus can lead to liver transplant

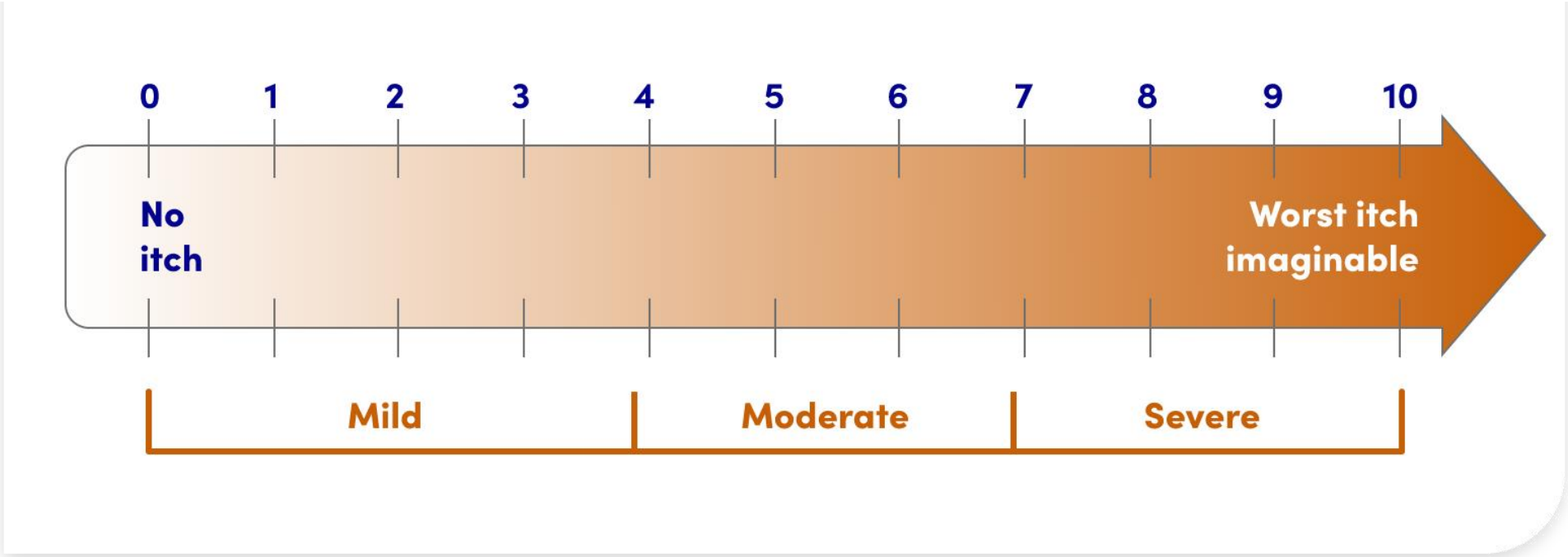
1. Carey EJ, et al. *Lancet*. 2015;386(10003):1565-1575.  2. Imam MH, et al. *J Gastroenterol Hepatol*. 2012;27(7):1150-1158.

# Underassessment of Pruritus in Patients With PBC




Rishe E et al. Itch. Acta Derm Venereol. 2008; Leighton, Frontline Gastro. 2020; Sivakumar, Frontline Gastro. 2021

# Worst Itching Intensity Numerical Rating Scale (WI-NRS) – 24 hrs



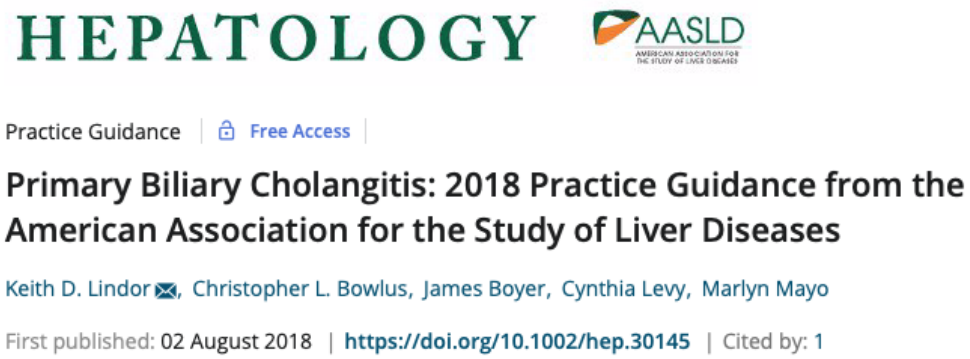

- WI-NRS is a validated scale that measures patient-reported itch intensity over a 24-hour period[1,]
- It is a numerical rating ranging from 0 (“no itch”) to 10 (“worst itch imaginable”)

1.Vernon M. J Am Acad Dermatol. 2021

# Stepwise Approach to Pruritus

**2023 systematic literature review 42 studies**[1]

- Evidence remains limited
- Small sample sizes (median n=18)
- Many poor quality with high risk of bias
- Inconsistent measures of pruritus
- Half conducted >20 years ago
- Only half were RCTs
- >50% followed patients ≤6 weeks




**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

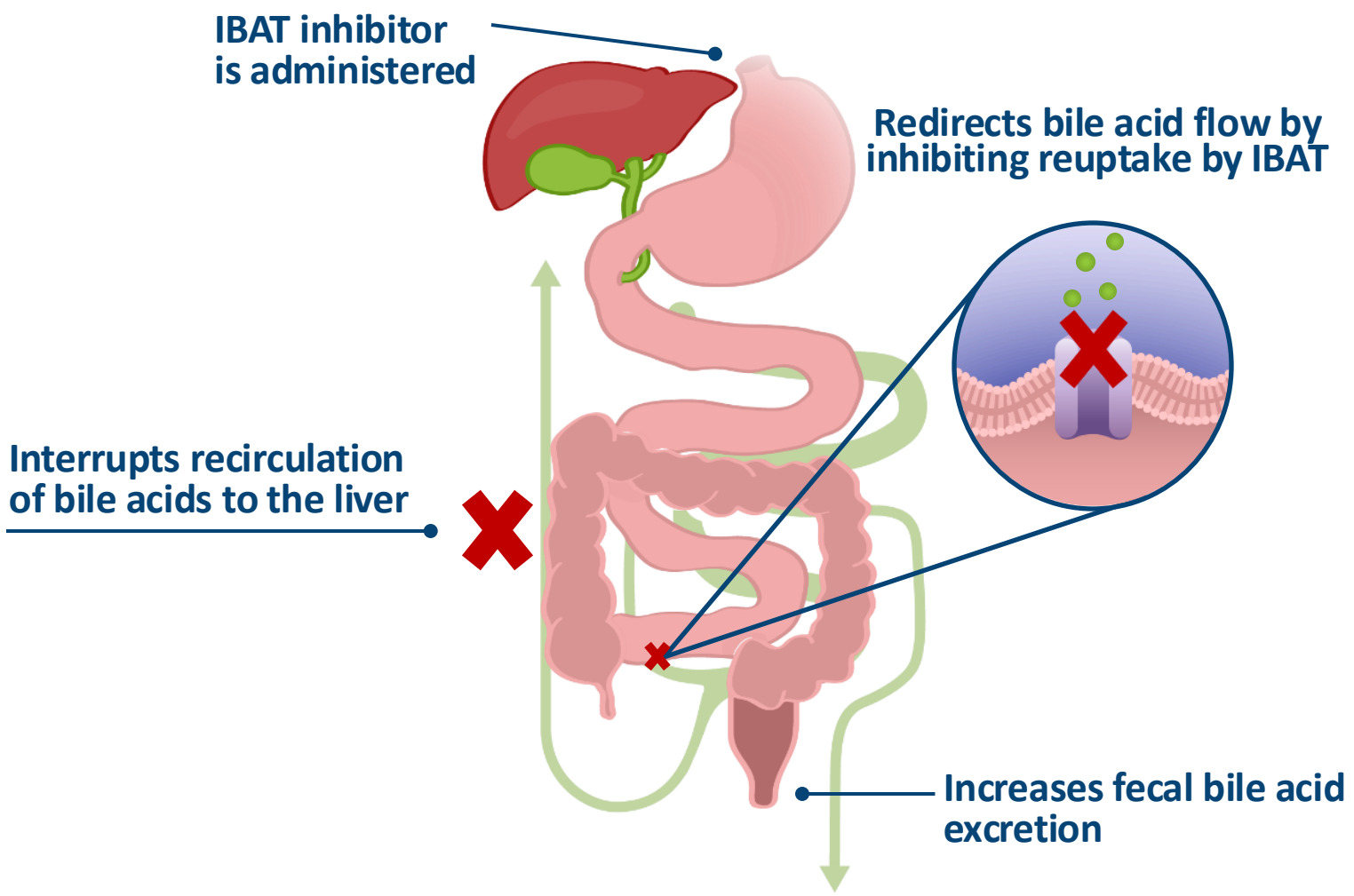
**Liver Transplantation**

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.

# IBAT Inhibitors: Pharmacologic Inhibition of Bile Acid Recirculation




## Clinical effects of IBATi in cholestasis:

- ✓ Improvements in pruritus (itch)
- ✓ Reductions in sBA
- ✓ Improved transplant-free survival

**FDA Approved IBAT Inhibitors**

- ✓ Maralixibat for Alagille Syndrome
- ✓ Odevixibat for PFIC

**Phase 2-3 trials for PBC**

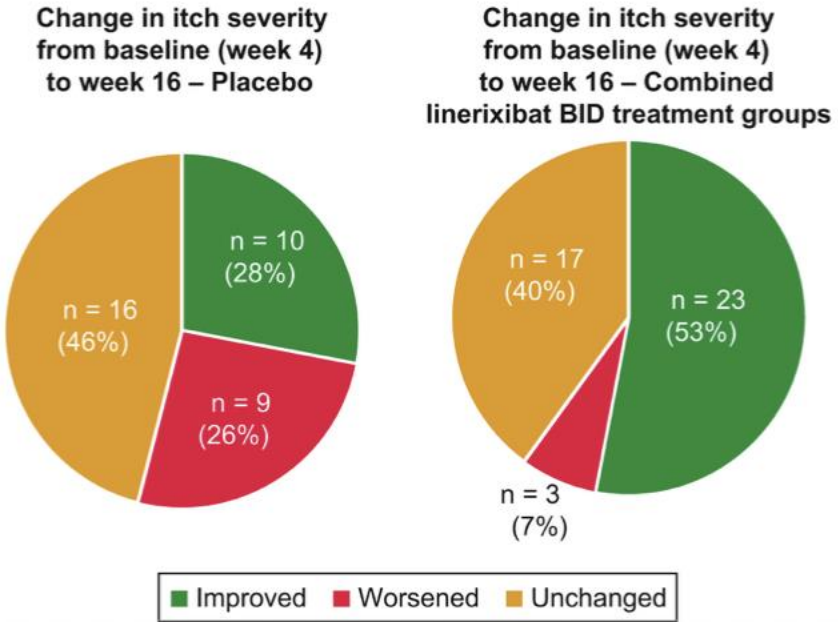
- ✓ Linerixibat
- ✓ Volixibat

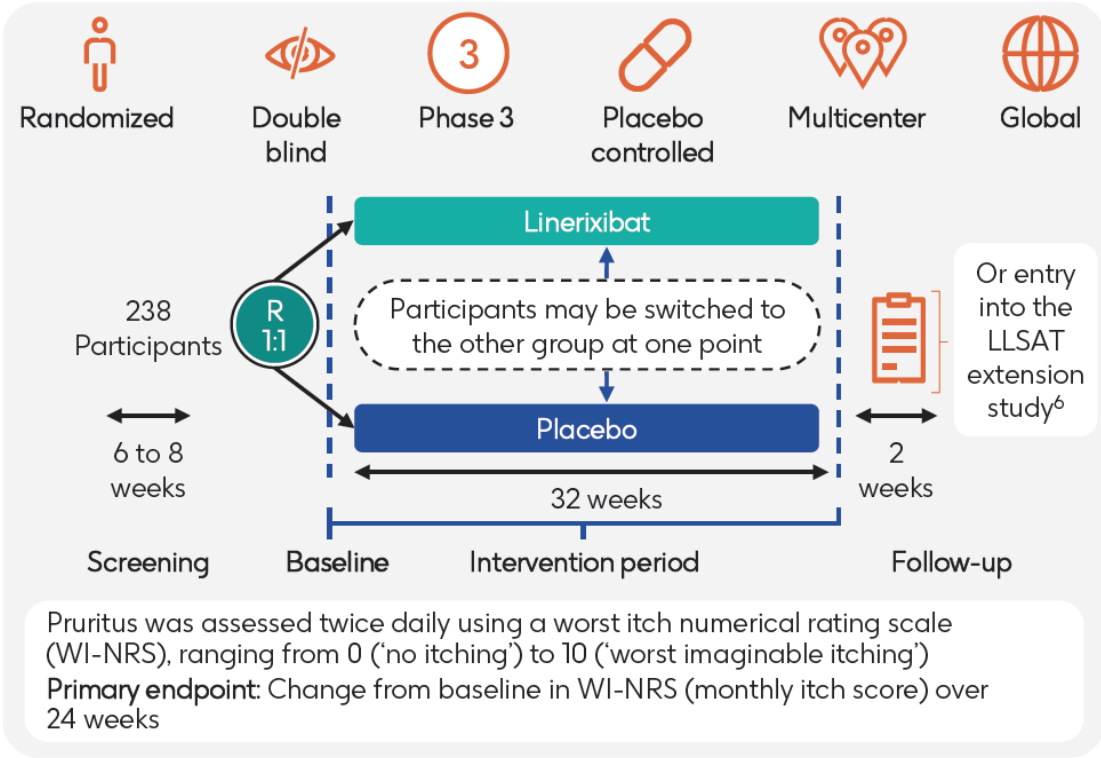
IBAT(i), ileal bile acid transporter (inhibitor); sBA, serum bile acid.

Gonzales E, *et al*. *Lancet* 2021; **398**:1581–1592; Tiessen RG *et al*. *BMC Gastroenterology* 2018; **18**:3. Figure adapted from: Slijepcevic D & van de Graaf SFJ. *Dig Dis* 2017;35:251–258.

# Linerixibat for PBC & Itch

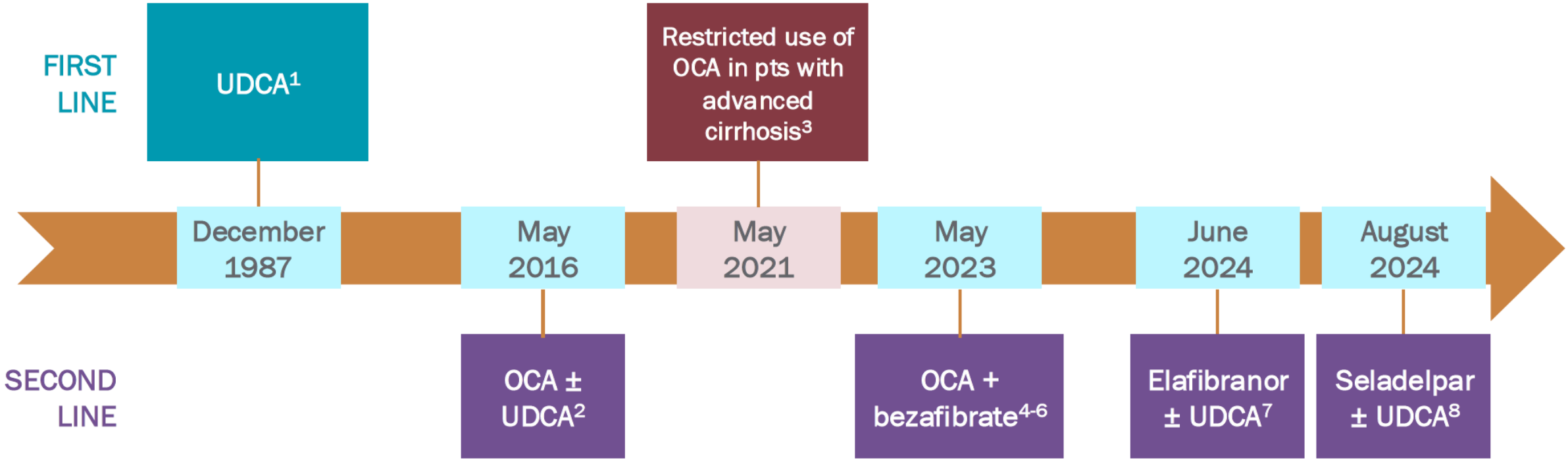
- Phase 2b randomized-controlled trial
- Patients with PBC and itching (NRS ≥ 3)
- Various doses of linerixibat vs placebo for 12 weeks
- 147 subjects with PBC
- Linerixibat was associated with a dose-dependent reduction in itching
- 40 mg bid dosing is undergoing Phase 3 trial




Levy et al. Clin Gastroenterol and Hepatol 2023

# PBC Therapeutic Options




1. Poupon R, et al. *Lancet*. 1987;329(8537):834-836.. 2. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-approves-ocaliva-rare-chronic-liver-disease. 3. Obeticholic acid. FDA Drug Safety Information. May 26, 2021. 4. ClinicalTrials.gov: NCT04594694. https://clinicaltrials.gov/study/NCT04594694 5. ClinicalTrials.gov: NCT05239468. https://clinicaltrials.gov/study/NCT05239468 6. Intercept Pharmaceuticals. Press release: May 16, 2023. https://ir.interceptpharma.com/news-releases/news-release-details/intercept-pharmaceuticals-receives-fda-orphan-drug-designation 7. Ipsen Press release: June 10, 2024https://www.ipsen.com/press-releases/ipsens-iqirvo-receives-u-s-fda-accelerated-approval-as-a-first-in-class-ppar-treatment-for-primary-biliary-cholangitis/. 8 Gilead Press release: August 14 2024.

# Evolving Paradigm in the Management of PBC

## Current Paradigm

- Start 1st Line: URSO 13-15 mg/kg/day
- Assess Response – 1 year- UK PBC, global score or Poise criteria
- 2nd Line agent

Wait to fail
40% are non-UDCA responders

## New Paradigm

- Evaluation of UDCA response as early as 6 months
- Lower ALP thresholds to assess UDCA response
- Earlier initiation of 2nd-line therapy
- Routine monitoring of liver tests every 3-6 months
- Fibrosis surveillance at all stages of PBC

# Personalized PBC Approach

**Comorbidities**

Osteoporosis

CKD

The need of statins

Use of anticoagulants

Interference with OCP

**Patient preference**

Cost

Easy to use

Potential side effects

**Evaluate pts risk**

No response to UDCA

LSM >10 kPA

> 65 y/o

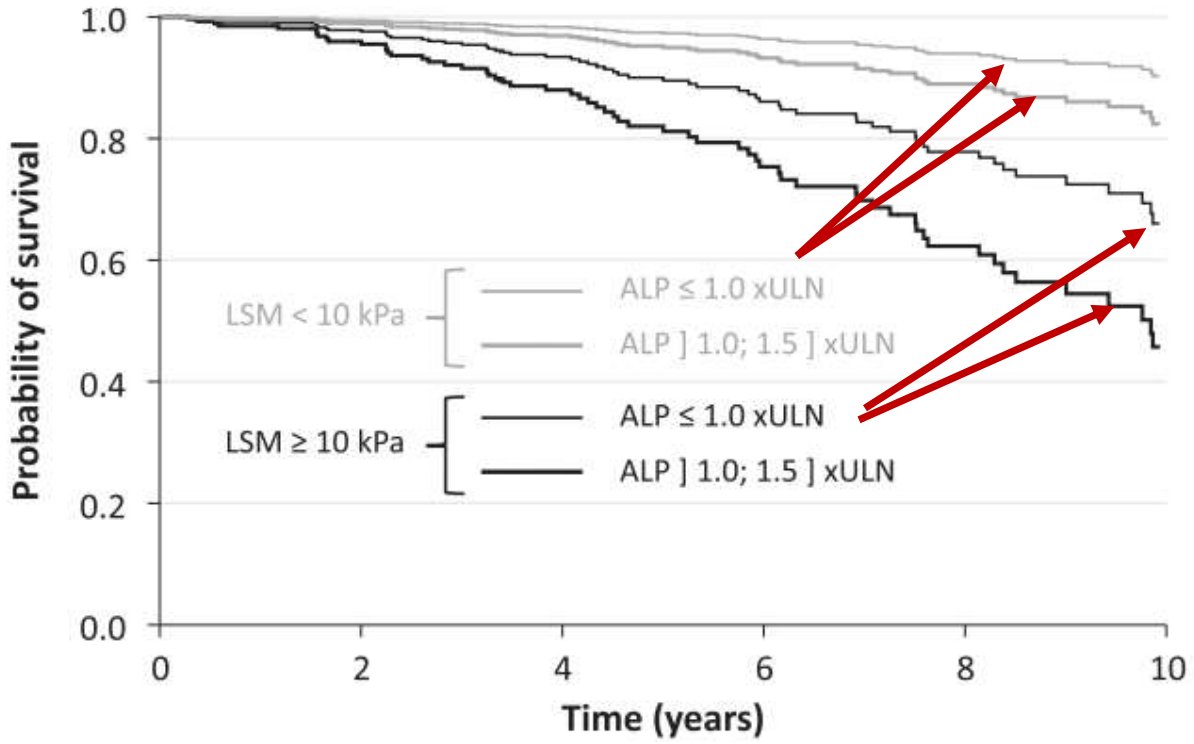
ELF >9.8

**Symptoms**

Sleep disturbances

Moderate to severe itchiness?

# Does Normalization of ALP Lead to Better Outcomes?




**Mean survival gain with ALP ≤ULN vs 1.1-1.5x ULN**

- Overall: 8 months (p=0.003)
- LSM ≥10 kPa: 19 months (p=0.002)
- LSM ≥10 kPa and ≤62 years: 53 months (p<0.001)

Corpechot et al Hepatology 2023

# FDA Approved Therapy for PBC

- First Line Treatment
  - Ursodeoxycholic acid (UDCA)
- Second Line Treatment
  - Obeticholic acid (OCA)
  - Elafibranor
  - Seladelpar

# 1st Line Therapy

**~40% of patients have inadequate response to UDCA**

- Query adherence (loose stools, hair loss; avoid TID dosing)
- Confirm UDCA dosage 13–15 mg/kg (no benefit with doubling dose)
- Check for comorbid liver disease (AST/ALT > 5x ULN…has overlap with AIH been ruled out?)
- Avoid coadministration of bile acid sequestrant

Evaluate UDCA Response at 6 Months

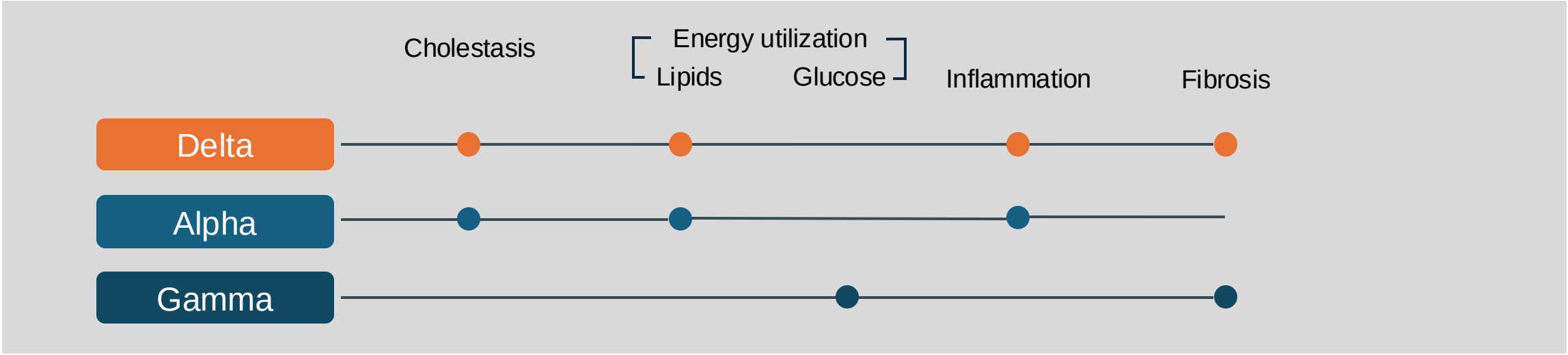
Lindor KD et al. *Hepatology*. 2019; 69(1):394-419. Kowdley et al. *Am J Gastroenterol*. 2023; 118:232-242.

# 2nd Line Indication

- All 3 approved for the following
  - Indication: Approved in combination with UDCA in adults who have not responded well to UDCA or used alone in patients unable to tolerate UDCA.
  - Should not be used in patients who have or develop decompensated cirrhosis.

# PPARs: A PBC Therapeutic Target

- Nuclear receptors
- PPAR isoforms modulate different biological processes, which include




Elafibranor: PPAR-α and PPAR-δ agonist

Seladelpar: PPAR-δ agonist

1. Haczeyni F et al. *Hepatol Commun*. 2017; 1(7):663-674; 2. Jones D et al. *Lancet Gastroenterol Hepatol*. 2017; 2(10):716-726; 3. Iwaisako K et al. *Proc Natl Acad Sci USA*. 2012; 109(21):E1369-E1376; 4. Dubrovsky AMK, Bowlus CL. *Gastroenterol Hepatol (NY)*. 2020; 16(1):31-38; 5. de Carvalho MV et al. *Int J Mol Sci*. 2021; 22(2):805; 6. Choi YJ et al. *Atherosclerosis*. 2012; 220(2):470-476.

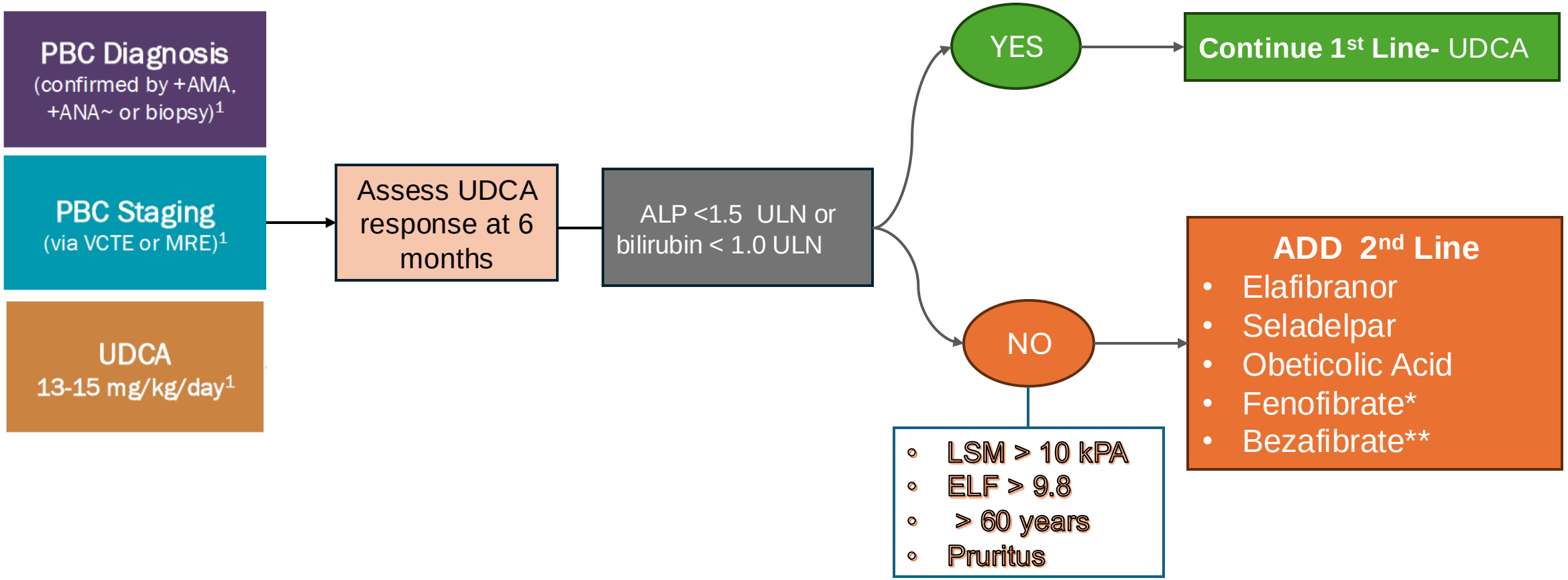
# Second Line Therapies

| Seladelpar | Elafibranor | OCA |
|---|---|---|
| • ↓ ALP from baseline 42%<br>• ALP normalization ≈ 25%<br>• 61% SEL vs 20%<br>• Improvement in Itch NRS<br><br>• **Side effects:** Headache and GI symptoms<br><br>• **Safety**<br>• Fracture rate 4%<br>• No decrease in GFR<br>• No increase in myalgias | • ↓ ALP from baseline 40%<br>• ALP normalization ≈ 15%<br>• 51% ELA vs 4%<br>• No change in NRS<br><br>• **Side effects:** Weight gain and GI symptoms<br><br>• **Safety**<br>• Fracture rate 6%<br>• No decrease in GFR<br>• Greater ↑ in CK | • ↓ ALP from baseline 39%<br>• ALP normalization ≈ 10%<br><br>• **Side effects:** Dose-dependent itching ≈ 40%<br><br>• **Safety**<br>• 🚫 Cirrhosis/portal hypertension |

**NO head-to-head comparisons with these medications!!!**

Obeticholic acid (OCA) Nevens et al., NEJM 2016; Bezafibrate, Corpechot et al., NEJM 2018; Elafibranor,Kowdley et al., NEJM 2024;Seladelpar,Hirschfield et al., NEJM 2024

# Liver Stiffness Measurement & Earlier UDCA Response Assessment




1. Kowdley KV, et al. *Am J Gastroenterol*. 2023;118(2):232-242. 2. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172. 3. Rodas, personalized therapies.

* OFF LABEL

** NOT available in the US

# Real-World Case: Primary Care Provider

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- Presents with incidental finding of echogenic liver and c/o significant pruritus.
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- ALP level : 298 (IU/L)
- Albumin 4.4 g/dL (3.5-4.5 g/dL)
- Platelet count 325 k/uL (150-400 k/uL)

**AMA, LSM, initiate UDCA → refer to Hepatology**

**Evaluate NRS itch, start cholestyramine, DEXA scan, evaluate in 3-6 months and consider 2nd line if no response to UDCA or cholestyramine**

# Summary

- Personalize care based on individual risk, symptoms and personal preferences.
- The addition of TE to evaluate LSM is relevant to further stratify for patients at risk of disease progression.
- Non responders to URSO at 6 months or those patients who are not candidates for OCA due to safety profile such as pruritus, consider initiation of 2$^{nd}$ line options.
- Goals of care in PBC include BOTH preventing the disease progression AND improving quality of life.