Berkeley Public Health

THE FORUM For Collaborative Research℠

PSC Forum 5

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Session I:

Implementing Recent Treatment Guidelines for PSC Clinical Trial Enrollment

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Faculty Disclosure

Advisor

Abbvie, Albireo, BiomX, Boehringer Ingelheim, Cymabay, Falk, Gilead, Genfit, Hightide, Intercept, Jannsen, MSD, Novartis, Phenex, Pliant, Regulus, Siemens, Shire

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PRACTICE GUIDANCE

AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma

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Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines on sclerosing cholangitis☆

European Association for the Study of the Liver*

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PRACTICE GUIDANCE

AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma

WHAT'S NEW SINCE THE 2010 GUIDELINES?

- Introduction of the term *relevant stricture*, defined as any biliary stricture of the common hepatic duct or hepatic ducts associated with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis (Table 1).
- In patients with equivocal MRI with cholangiopancreatography (MRI/MRCP) findings, a repeated high-quality MRI/MRCP should be performed for diagnostic purposes. Endoscopic retrograde cholangiopancreatography (ERCP) should be avoided for the diagnosis of PSC
- New clinical risk tools for PSC are available for risk stratification, but probabilities of events in individual patients should be interpreted with caution (Figure 4 and Table 3).
- All patients with PSC should be considered for participation in clinical trials; however, ursodeoxycholic acid (13–23 mg/kg/day) can be considered and continued if well tolerated with a meaningful improvement in alkaline phosphatase (γ-glutamyl transferase in children) and/or symptoms with 12 months of treatment.

What's New in these CPG ? (vs 2009 EASL guidelines)

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines on sclerosing cholangitis☆

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- **Scope: first EASL CPG specifically dedicated to sclerosing cholangitis,**

  not only PSC but also secondary sclerosing cholangitis including IgG4 related cholangitis (IRC), sclerosing cholangitis of the critically ill patients (SC-CIP) and those with ABCB4 deficiency

- **Increased attention to:**
  - **Pediatric issues**
  - **Quality of life, patient perspectives and delivery of care**
  - **Specificities of liver transplantation for PSC**
  - **Management of IBD associated with PSC**
  - **Participation in clinical studies**

Slide courtesy Olivier CHAZOUILLERES, ILC 2022

What's New in these CPG ? (vs 2009 EASL guidelines)

- **Emerging role of non-invasive tests for staging and prognosis**
- **Detailed recommendations on the diagnosis and treatment of hepatobiliary malignancy**
- **Definition of biliary strictures (in collaboration with AASLD and iPSCsg) and strong recommendations on endoscopic intervention**
- **Recognized role of bezafibrate in the treatment of cholestatic pruritus**

Slide courtesy Olivier CHAZOUILLERES, ILC 2022

What has NOT markedly changed ? (vs 2009 EASL guidelines)

- **Diagnosis:**

« In adult patients presenting with elevated serum markers of cholestasis, a diagnosis of large duct PSC should be made in the presence of typical findings of sclerosing cholangitis on high-quality cholangiography and after exclusion of secondary causes. The preferred diagnostic test is MRCP."

- **Still unclear role for UDCA:**

« UDCA at doses of 15-20 mg/kg/d can be given since it may improve serum liver tests and surrogate markers of prognosis. Available data does not allow for a firmer recommendation " (weak recommendation)

Slide courtesy Olivier CHAZOUILLERES, ILC 2022

Use of UDCA possible

Guidance statements

11. All patients with PSC should be considered for participation in clinical trials.
12. In patients not eligible or interested in clinical trials with persistently elevated ALP or GGT, UDCA 13–23 mg/kg/day can be considered for treatment and continued if there is a meaningful reduction or normalization in ALP (GGT in children) and/or symptoms improve with 12 months of treatment.

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Should people with PSC be treated with ursodeoxycholic acid?

Recommendations

- UDCA at doses of 15-20 mg/kg/d can be given since it may improve serum liver tests and surrogate markers of prognosis. Available data does not allow for a firmer recommendation **(LoE 1, weak recommendation, 76% consensus).**
- UDCA at doses of 28-30 mg/kg/d should not be given **(LoE 1, strong recommendation, 100% consensus).**

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- UDCA (up to 20mg/kg) usually allowed in clinical studies (60-80%) – stratification
- Depending on ALP inclusion citeria – selection for UDCA non-responder

No role for liver biopsy in clinical routine

Guidance statements
In patients with suspected PSC and a normal, high-quality MRI/MRCP, liver biopsy should be considered to rule out small-duct PSC.
A liver biopsy should not be performed in patients with typical cholangiographic findings on MRI/MRCP, except when there is concern for AIH overlap.

What is the role of liver biopsy in adults suspected of having PSC?

Recommendations

- A liver biopsy should be performed in adults suspected of having PSC whose high-quality MRCP is normal, to confirm or exclude small duct PSC (**LoE 4, strong recommendation, 88% consensus**).
- A liver biopsy should be considered in people with PSC and co-existing features of AIH including markedly elevated transaminases, high IgG levels, and positive autoantibodies compatible with AIH (**LoE 4, strong recommendation, 92% consensus**).

- Discrepancy to current clinical studies with biopsy-driven endpoints
- Most studies allow historical biopsies (up to 6 months)

Management of pruritus

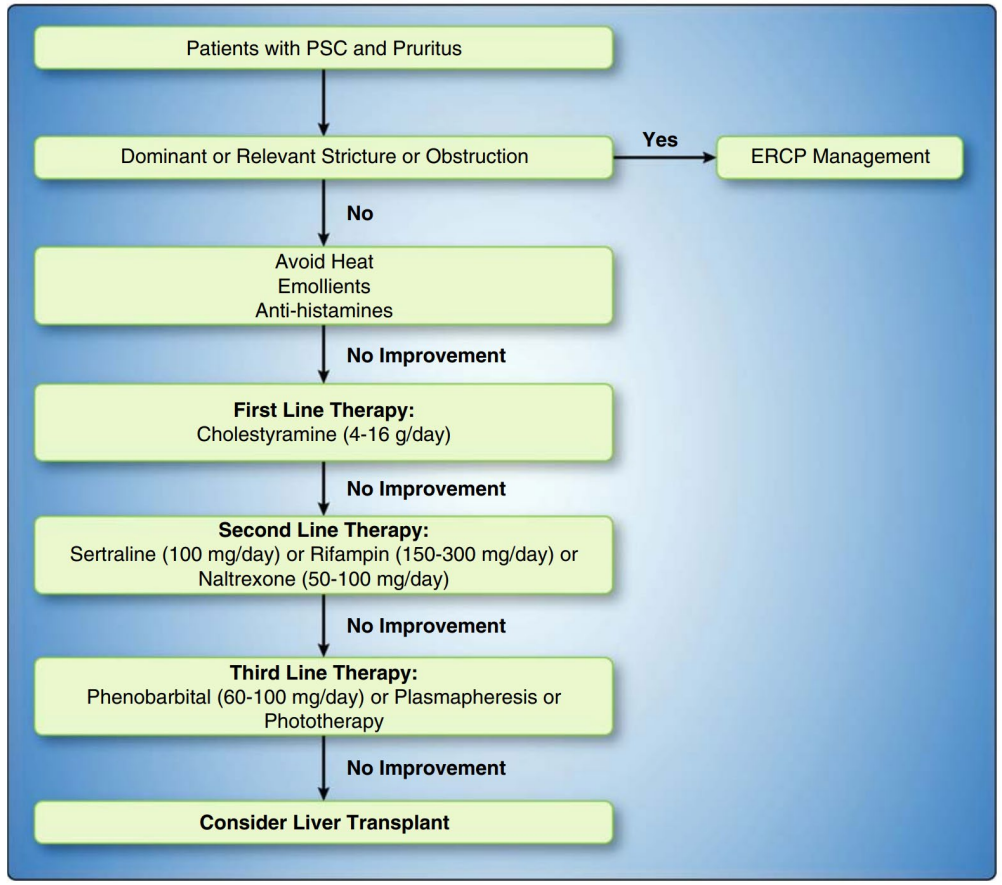

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Table 6. Medical treatment of pruritus in sclerosing cholangitis.

Evidence	Drug
1st line	Bezafibrate (400 mg daily)
2nd line	Rifampicin (150-300 mg/d)
3rd line	Naltrexone (12.5-50 mg/d)
No evidence for PSC	Anion exchange resins (cholestyramine [4 g once to four times daily], colesevelam [1,250-1,875 mg twice daily]; 4 hours separate from other medication)
No evidence for PSC	Sertraline (50-75 mg/d)
Experimental	ASBT inhibitors
Experimental	Selective PPARα and PPARδ agonists

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- Most studies allow stable fibrate dose
- Implications for IBAT inhibitor studies?

Definition of strictures & cholangitis

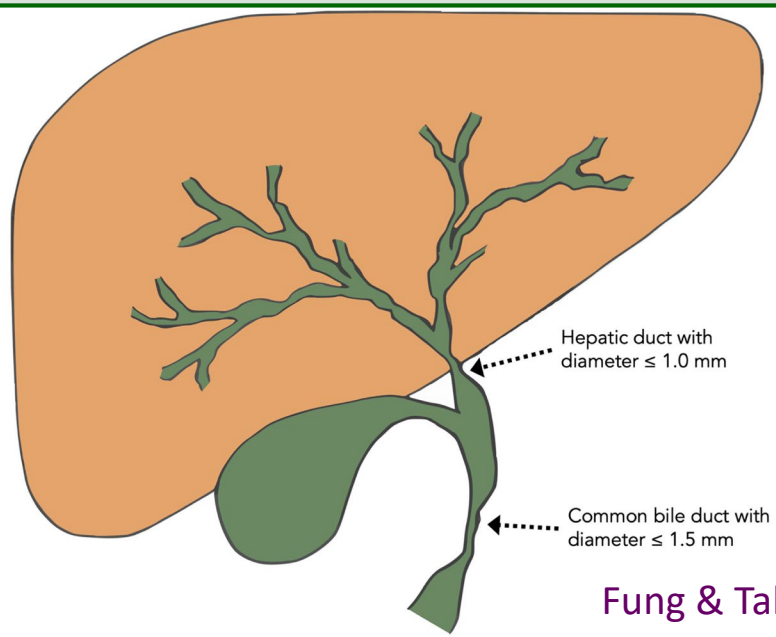
- **Relevant / high grade** (dominant) stricture ~ 45% of people with PSC

Table 7. Definition and nomenclature of strictures in primary sclerosing cholangitis. EASL CPG, *J Hepatol* 2022

Type	Definition
Relevant stricture	A high-grade biliary stricture on imaging in the common bile duct or hepatic ducts with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis.
High-grade stricture	A biliary stricture on MRI/MRCP with >75% reduction of duct diameter in the common bile duct or hepatic ducts.

High-grade stricture	A biliary stricture on MRI with cholangiopancreatography with >75% reduction in the common bile duct or hepatic ducts
Relevant stricture	Any biliary stricture of the common bile duct or hepatic ducts associated with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis

AASLD PG, *Hepatology* 2023



Dominant stricture (ERCP):

right/left hepatic main duct ≤ 1 mm

CBD ≤ 1.5 mm,

Fung & Tabibian, *Liver Res* 2019

Definition of strictures & cholangitis

- **Relevant / high grade** (dominant) stricture ~ 45% of people with PSC
  - Historically dominant stenosis were often an exclusion criterium
  - Strictures anticipated to require endoscopic treatment usually excluded

- **Bacterial cholangitis** – broad range, poorly defined, no universal consensus
  - Current / recent cholangitis episode an exclusion criterium
  - 40% of people with PSC experience this complication during the disease course
  - 6% at diagnosis of PSC
  - Most common PSC-related clinical event in recent SIM trial observed in 13% of patients over a median follow-up of 23 months

EASL CPG, *J Hepatol* 2022
AASLD PG, *Hepatology* 2023

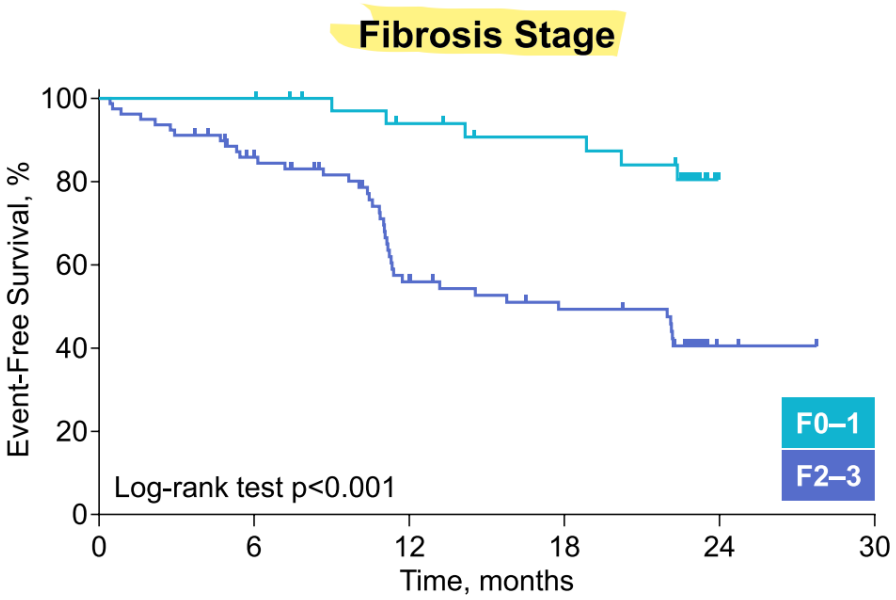
IBD

- Most studies still do not yet clearly define PSC-IBD
- IBD a safety but not an efficacy issue
  - Restriction to mild and well controlled IBD
- Potential for one stop shopping for some group of drugs?

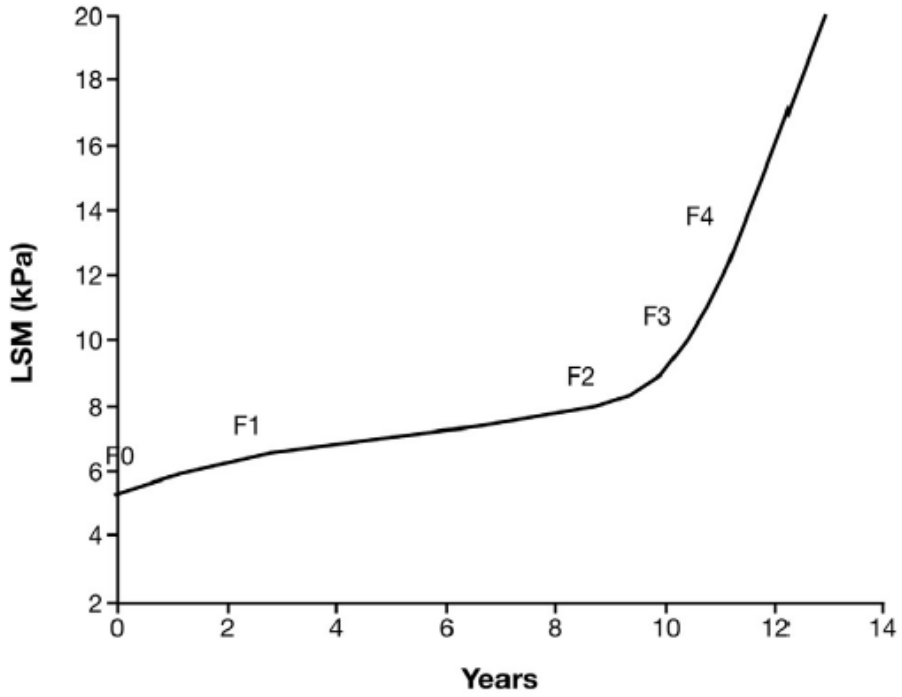
- Management of IBD in patients with PSC is similar to that in those without PSC
  - Stable biologics etc usually allowed

Enrichement of study populations

- Use of NITs
- Enrichement for more advanced patients reaching clinically relevant endpoints?



Trauner et al., *BMC Gastro* 2023



Corpechot et al., *Gastroenterology* 2014

Follow-up and risk stratification

Box 3. Suggested algorithm for follow-up of primary sclerosing cholangitis.

A) Routine surveillance (reappraisal of disease progression and risk)

- Every 12 months (for all, every 6 months in patients with significant risk):
  - Clinical evaluation (including quality of life)
  - Serum liver-related tests including bilirubin, ALP, AST, platelets, and PT
- Every 12 months (even for patients at low risk):
  - MRI/MRCP and/or US (with a special attention for gallbladder wall abnormalities)* §
  - Colonoscopy**
  - Elastography and/or ELF test
- Every 2 to 4 years (for all): DEXA for bone mineral density assessment (and serum vitamin D measurement)

B) Additional work-up when clinically indicated (new symptoms or evolving abnormalities in routine investigations (ALP/bilirubin rising) or ΔLSM >1.5 kPa/year or ductal progression):

- Suspected cholangiocarcinoma: serum CA 19.9 and MRCP/MRI liver with contrast and ERCP with cytologic or histologic sampling
- Suspected features of auto-immune hepatitis or drug toxicity: serum IgG and autoantibodies of AIH, consider liver biopsy
- Suspected clinically relevant portal hypertension (Baveno VII criteria[114]): EGD, consider non-selective beta blockers

In UDCA treated patients, consider non-compliance

Box 2. Potential approaches to simple risk stratification of PSC at initial work-up using non-invasive tools (adapted from[106,108]).

"Low risk" of events:

- Small duct PSC and no evidence of cirrhosis

OR

- Classical PSC and (all to be present): asymptomatic with normal bilirubin, albumin, platelets, and PT, ALP <1.5 ULN, LSM (VCTE) <6.5 kPa (or ELF test <7.7), limited biliary changes on MRI/MRCP.

"Significant risk" of events if any present:

- Symptomatic, ALP >1.5 ULN, abnormal bilirubin, albumin, platelets or PT, LSM (VCTE) >9.9 kPa (or ELF test >10.6), extensive biliary changes (especially intra-hepatic biliary dilatation) on MRI/MRCP.

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How should surrogate markers of PSC or prognostic scoring systems be applied in clinical practice?

Recommendation

- Risk assessment at the time of diagnosis and sequentially is recommended, based on phenotypic factors and non-invasive tests including: (1) standard biochemistry (including serum bilirubin, albumin, ALP, ALT, platelets, prothrombin time), (2) MRI of the liver with MRCP, and (3) liver elastography or serum fibrosis tests **(LoE 2, strong recommendation, 96% consensus).**

Table 5. Rational approaches to non-invasive risk stratification in PSC.

Level of applicability	Prognostic tools
High (High applicability, robust validation)	◦ Baseline (early *vs.* advanced) disease stage as defined by biochemical (bilirubin, albumin, platelets, prothrombin time) and imaging analyses ◦ Small duct PSC *vs.* classical PSC
Moderate (High applicability, further validation pending)	◦ ALP ◦ LSM by VCTE ◦ ELF test ◦ MRI/MRCP
Indeterminate (Insufficient applicability and/or validation)	◦ Age, gender and type of IBD ◦ AIH features ◦ IgG4 serum levels ◦ PSC-specific prognostic scores* (except for Mayo Risk Score in advanced PSC)

How should people with PSC be monitored for disease progression?

Recommendations

- Non-invasive routine liver surveillance is suggested, based on:
  - Clinical review and standard serum liver tests including bilirubin, albumin, ALP, aspartate aminotransferase, platelets and prothrombin time, every 6 or 12 months depending on risk stratification, are recommended **(LoE 2, strong recommendation, 96% consensus).**
  - Liver elastography and/or serum fibrosis tests at least every 2 to 3 years are recommended **(LoE 3, strong recommendation, 96% consensus).**
  - Liver ultrasound and/or abdominal MRI/MRCP every year are suggested **(LoE 3, weak recommendation, 96% consensus).**

TABLE 3 Validated clinical prognostic models of PSC

	Models Amsterdam-Oxford 2017[230]	UK-PSC 2019[231]	PREsTO 2020[232]	SCOPE 2020[162]
Variables	Age Bilirubin Albumin AST ALP Platelets PSC subtype (large-duct or small-duct)	Age Bilirubin Albumin ALP Platelets Presence of extrahepatic biliary disease History of variceal hemorrhage	Age Bilirubin Albumin AST ALP Platelets Hemoglobin Sodium Years since PSC diagnosis	Bilirubin Albumin Platelets GGT Cholangiography (large-duct or small-duct involvement)
Endpoint	LT or liver-related death by 15 years	Short term: death or LT by 2 years Long term: death or LT by 10 years	Hepatic decompensation (ascites, variceal hemorrhage, encephalopathy) by 5 years	Portal hypertensive complications, biliary complications, CCA, listing for LT, or death from liver disease by 5 years
Risk thresholds[a]	Lower risk: < 1.58 Higher risk: ≥ 1.58	Lower risk: < 1.46 Higher risk: ≥ 1.46	Lower risk: $< 20\%$ Higher risk: $\geq 20\%$	Lower risk: 0–5 Higher risk: 6–11
Website	https://sorted.co/psc-calculator/	http://www.uk-psc.com/resources/the-uk-psc-risk-scores/	rtools.mayo.edu/PRESTO_calculator/	Scopeindex.net

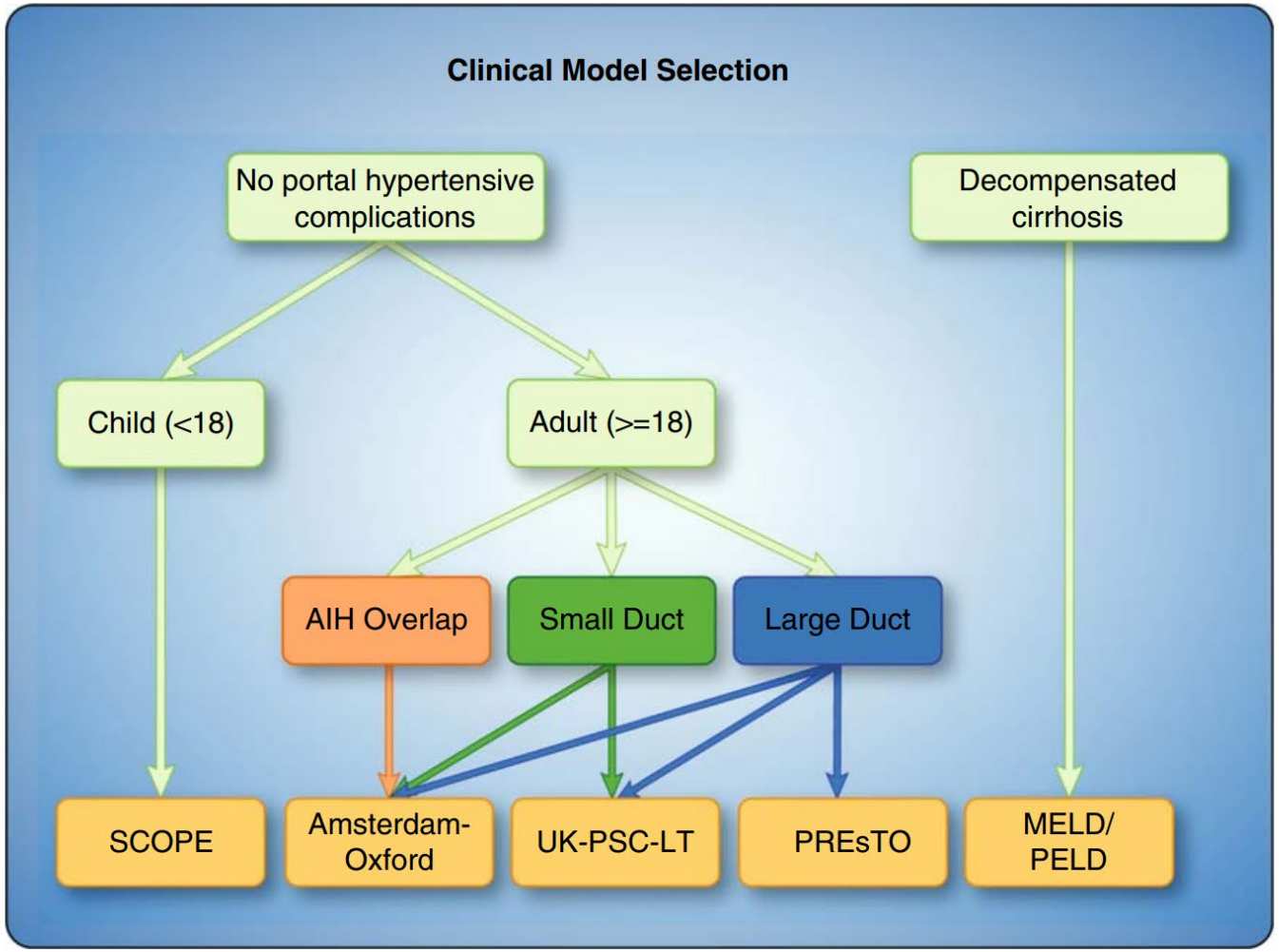

FIGURE 4 Current prognostic models in PSC. Clinical prognostic model selection for patients with PSC should take into account the age of the patient and the presence of small-duct PSC and/or overlap with AIH. Abbreviation: PELD, Pediatric End-Stage Liver Disease score.

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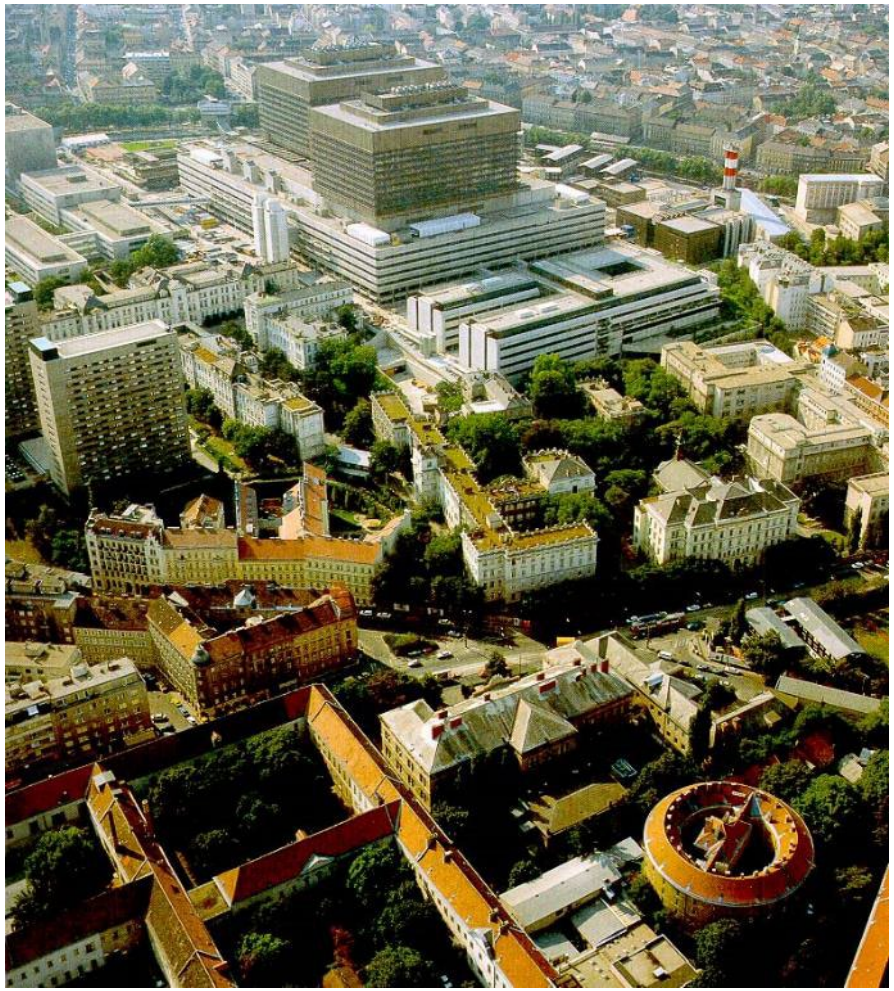
Implementing Recent Treatment Guidelines for PSC Clinical Trial Enrollment – Take Home

- Participation in clinical trials explicitly encouraged
- More liberal use of UDCA may impact on study populations (in North America, also in Europe?)
- Baseline liver biopsy remains a hurdle to pass
- Better implementation of NITs for risk stratification in clinical practice may further facilitate enrichement of study populations



Thank you for your attention!

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