THE FORUM FOR COLLABORATIVE RESEARCH

PSC Forum 9

Meeting Summary

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THE FORUM
For Collaborative Research℠
Berkeley's Hub for Regulatory Science

UC Berkeley Public Health

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SESSION I: ACUTE CHOLANGITIS: CLINICAL AND PATIENT PERSPECTIVES

Clinical Definition of Acute Cholangitis

Acute cholangitis remains underreported in PSC trials, highlighting the need for a standardized, clinically grounded definition. Current work centers on objective infection indicators, such as visible pus, positive bile cultures, or bacteremia with jaundice, supported by symptom, inflammatory, and cholestasis features. A proposed tiered model classifies episodes as probable (1 symptom + 1 inflammation + 1 cholestasis feature) or definite (adds an infection criterion), with visible pus qualifying on its own. Antibiotic or drainage response may be used to fulfill the infection criterion during adjudication. Ongoing refinement with industry and adjudication experts will ensure that clinical judgment remains central to final diagnosis.

Panel Discussion

Symptom Dynamics and Diagnostic Practicality

Fatigue and liver pain show the greatest fluctuation during cholangitis, making changes in symptom severity more informative than presence alone. Routine care rarely yields timely cultures, ERCP findings, or other microbiologic tests. Therefore, trial definitions rely on clinically observable features, using antibiotic response only as supportive evidence when objective data are unavailable. Patient experience can help differentiate baseline symptoms from cholangitis attacks, especially in recurrent disease. Regulatory endpoints require objective and reproducible criteria, and guidance on operationalizing patient voice in adjudication is limited.

Operational Constraints and Clinical Relevance

Many cholangitis episodes occur outside study sites, limiting data capture and requiring criteria that depend on information consistently available across healthcare settings. Cholangitis does not follow fibrosis trajectories but remains a clinically meaningful early endpoint, with many individuals failing to return to baseline after an episode. Laboratory thresholds based on percentage increases from baseline are difficult to standardize due to high variability and limited historical data. Participants emphasized the need to focus on parameters that are realistically collectible, reproducible across geographies, and compatible with site coordinator capacities.

Overall Need

A practical, clinically grounded definition is needed to reliably identify meaningful events while remaining feasible for global trials and acceptable for regulators. The Definition of Acute Cholangitis Working Group has advanced this effort, with a manuscript nearing completion.

SESSION II: INNOVATIVE PSC TESTING MODALITIES

Advancements in Functional MRI and Molecular Imaging

Antaros Medical's gadoxetate-enhanced MRI and PDGFR-β PET imaging provide functional assessments not captured by MRCP or conventional staging. Gadoxetate MRI identifies changes in hepatocellular uptake and biliary excretion that distinguish placebo progression from treatment stability, while PDGFR-β PET offers a sensitive measure of fibrogenesis with clear signal separation and strong repeatability. Together, these modalities may enable earlier and more precise monitoring of PSC disease activity.

Noninvasive Cholate Challenge Test in PSC

The HepQuant cholate challenge test provides a noninvasive functional measure of hepatic extraction, shunting, and reserve that aligns closely with PSC disease activity. It reliably predicts varices and clinical outcomes, stratifies patients into distinct functional progressor groups, and identifies early portal hypertension through elevated shunting. A ≥2-point change in DSI is associated with meaningful deterioration, supporting the test's potential as a reproducible functional biomarker and trial endpoint.

MRCP+ and the Biomarker Qualification Program

Perspectum's MRCP+ provides quantitative ductal measures, particularly stricture count, that overcome limitations of conventional MRCP and track with PSC disease progression. The FDA has accepted stricture count into the Biomarker Qualification Program, and the ongoing CHAMP study is evaluating whether longitudinal MRCP+ changes predict major clinical outcomes. Early CHAMP data show measurable interval ductal changes across serial scans. Final results will inform whether MRCP+ can serve as a qualified biomarker for monitoring progression and treatment response in PSC.

Developments in Contrast-Enhanced MRI: Clinical Perspectives

Advanced MRI techniques can differentiate anatomical from functionally significant strictures, with gadoxetate excretion helping identify lesions likely to benefit from intervention. Scoring systems such as ANALI and a functional stricture score show prognostic value and good reproducibility, and multi-parametric MRI integrating MRCP, MRE, and excretory imaging can better guide ERCP decisions. Imaging-histology correlation suggests MRI abnormalities may precede cholangiographic changes, indicating a potential role in detecting early PSC. Emerging tools, such as FAPI-PET, offer future potential for distinguishing inflammatory from fibrotic strictures.

Open Discussion

Biomarker Performance
Panelists noted that ALP may not reliably track disease progression in PSC, citing baseline differences and the limited ability of changes over time to predict clinical outcomes. Functional measures such as the Disease Severity Index demonstrate stronger predictive performance and better reflect clinically meaningful change.

Gadoxetate-Enhanced MRI
Gadoxetate-enhanced MRI provides functional information beyond standard MRCP but is not yet widely scalable due to cost, infusion sensitivity, and workflow requirements. Current applications remain mainly exploratory, and pediatric data are limited.

MRCP+ Reproducibility
MRCP+ produces many correlated metrics and has shown variable reproducibility across retrospective cohorts. About 30% of scans do not meet quality criteria, usually because of acquisition parameters or de-identification issues; scanner field strength does not appear to influence processability.

Interpretation Challenges
Fibrosis and cholestasis reduce uptake and excretion of gadoxetate, which complicates the interpretation of changes in contrast behavior and limits the ability to attribute improvements solely to ductal flow.

Future Imaging Direction
Conventional MRCP has variable image quality, while gadoxetate-enhanced imaging provides clearer ductal visualization. Integrating gadoxetate-based imaging with MRCP+ and temporal data may offer a more reliable imaging framework. Continued development of scalable, reproducible imaging and functional biomarkers is essential for defining meaningful endpoints in PSC.

SESSION III: GENERAL PSC FORUM MEMBER UPDATES

Updates on WIND and Other PSC Partners Research Programs

WIND-PSC enrollment is steadily increasing, with strong retention and growing longitudinal data that will support biomarker-outcome analyses. The international cohort reflects typical PSC characteristics, with routine symptom assessments showing fatigue, difficulty sleeping, and anxiety as major burdens. High completion rates emphasize patient commitment to symptom documentation. Clear definitions and approaches to how these symptoms are addressed are relevant to clinical trial design. The recent progress includes protocol simplification, standardized event documentation, abstract preparation, and development of a biospecimen repository.

The investigator grants program continues to support a range of PSC studies, with current recipients covering multiple research areas. Audience members were encouraged to review available funding opportunities offered through the program. Grant and research opportunities are available for review on the PSC Partners Seeking a Cure website for those interested in conducting clinical or basic research in PSC or a closely related disease.

IPSCSG Updates

The International PSC Study Group (IPSCSG) supports active working groups in imaging, malignancy and cholangiocarcinoma, and liver transplantation. IPSCSG led the international FICUS transient elastography validation, informing subsequent ELF score evaluation. Priorities include advancing imaging efforts, malignancy- and cholangiocarcinoma-focused studies, with several emerging diagnostic and surveillance tools now undergoing international validation. Transplant-related research is also expanding in response to high recurrence rates and growing activity at major clinical centers. IPSCSG emphasizes the development of early-career investigators, supported through multiple annual workshops designed to strengthen the future PSC research workforce.

IMPLICATIONS FOR PSC DRUG DEVELOPMENT

PSC Forum 9 reflected a sense of momentum among our audience of patient advocates, industry professionals, clinical experts, and regulatory leaders. The manuscript from our acute cholangitis working group is nearing completion, aiming to present a consensus on a clinically meaningful PSC endpoint. Acute cholangitis is strongly linked to disease progression, with 30% of patients failing to return to baseline after an episode. This manuscript will address a gap in clinical trial research, seeking to capture events earlier in patients' disease progression.

The field continues to make progress in disease monitoring and biomarker modalities, moving from biopsies and ALP toward enhanced imaging techniques and new technologies. Functional imaging tools such as gadoxetate-enhanced MRI, PDGFR-β PET, MRCP+, and the HepQuant cholate test offer early detection of disease activity. MRCP+ has already achieved FDA Biomarker Qualification Program acceptance for stricture count, and CHAMP results will be an important signal for the field. The growing WIND-PSC registry and IPSCSG working groups are building data infrastructure to support future biomarker-outcome analyses. The Forum for Collaborative Research's MASH data-harmonization project and the PSC Partners patient registry are expanding high-quality real-world datasets. These will strengthen biomarker development, natural history modeling, and future PSC trial design.

PSC Forum priorities include disseminating the acute cholangitis manuscript, facilitating sponsor alignment on adjudication criteria, and tracking CHAMP results as they become available.

ACKNOWLEDGEMENT

Kris Kowdley has served as co-chair of the PSC Forum for several years, and Michael Trauner will now step in as the new co-chair. We appreciate the leadership of our current co-chair Pam Vig, Kris Kowdley for his years of support, and Michael Trauner for his commitment to the new role with the Forum.