All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.
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ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.

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If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.
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Joseph C. Anderson, MD, MHCDS, FACG
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---

**Disclosures:**

**Speaker:**
Mark W. Russo, MD, MPH, FACG
Dr. Russo, faculty for this activity, has no relevant financial relationship(s) with ineligible companies to disclose.

**Moderator:**
Stevan A. Gonzalez, MD, MS
Dr. Gonzalez, moderator for this activity, has no relevant financial relationship(s) with ineligible companies to disclose.
Primary Sclerosing Cholangitis: Non-invasive Prognostic Scores and Evolving Therapies

Mark W. Russo, MD, MPH, FACG
Clinical Professor of Medicine
Chief, Hepatology, Medical Director Liver Transplantation
Atrium Health Wake Forest Baptist

PSC

- Epidemiology and natural history
- Alkaline phosphatase, revised Mayo Risk Score
- PREsTo, UK-PSC, Amsterdam-Oxford, ELF
- Elastography, MRI-MRCP
- Integration of prognostic models into evaluating evolving therapies
**PSC Incidence Rate, by Age and Gender**

![Graph showing incidence rate per 100,000/yr by age and gender.](image)

Adapted from Boonstra, EpiPSCPBC study group et al. Hepatology 2013;58:2045-2055.

---

**Natural History of PSC**

![Graph showing transplant-free survival and cumulative risk of CCA.](image)

Median transplant free survival 20.6 years
Cumulative risk of CCA @ 20 years was 14%

Adapted from Boonstra, EpiPSCPBC study group et al. Hepatology 2013;58:2045-2055.
# PSC, IBD, and Gender

N=7,121, 37 centers, 1980-2020

<table>
<thead>
<tr>
<th></th>
<th>Liver transplant or death</th>
<th>HPB malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s disease vs UC</td>
<td>HR=0.64, p&lt;0.001</td>
<td>HR=0.69, p=0.01</td>
</tr>
<tr>
<td>Female</td>
<td>HR=0.84, p=0.022</td>
<td>HR=0.68, p=0.001</td>
</tr>
<tr>
<td>Small vs Classical PSC</td>
<td>HR=0.30, p&lt;0.001</td>
<td>HR=0.15, p&lt;0.001</td>
</tr>
</tbody>
</table>


## Selected studies of alkaline phosphatase (ALP) and outcomes in PSC

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Primary Outcome in ALP decline or normalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanich, et al N=87 Retrospective</td>
<td>CCA, liver transplant or death</td>
<td>ALP normalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14% vs 33%</td>
</tr>
<tr>
<td>Hilscher, et al N=86 Retrospective study</td>
<td>CCA, HCC, gallbladder cancer, liver transplant or liver death</td>
<td>ALP persistent normalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6% vs 40%, p=0.0075</td>
</tr>
<tr>
<td>Lindstrom, et al N=198 Retrospective study</td>
<td>Liver transplantation, death, CCA</td>
<td>ALP normalization with UDCA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15% vs 53% at 12 years p=0.001</td>
</tr>
<tr>
<td>Al Mamari, et al N=139 Retrospective study</td>
<td>Liver related deaths</td>
<td>ALP&lt;1.5 X ULN, 3 values 6 months apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0% vs 23%, p&lt;0.0001</td>
</tr>
<tr>
<td>Rupp, et al N=215 Prospective study</td>
<td>Liver transplantation or death</td>
<td>ALP&gt;50% reduction from baseline, &lt;1.5xULN or normal ALP within 12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.7% vs 49.3%, p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median followup 10 years</td>
</tr>
<tr>
<td>Goode, et al N=1,453 Retrospective study Derivation, validation</td>
<td>Liver transplantation</td>
<td>ALP&lt; 2.4 XULN 1yr from diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Median transplant free survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>108 months vs 63 months, p&lt;0.0001</td>
</tr>
</tbody>
</table>

American College of Gastroenterology
Normalization of ALP

Persistently abnormal ALP

Survival in patients with PSC with and without alkaline phosphatase normalization

Survival in patients with PSC with and without persistent improvement in serum alkaline phosphatase


**Inclusion**
- Cholestatic liver disease > 6 mos
- Alk phos > 1.5 xULN
- Cholangiogram with PSC
- Liver biopsy

**Exclusion**
- Treated with urso, other meds
- Age < 18, > 70 y/o
- Coexisting liver disease
- Anticipated liver transplant
- Hx stones, biliary operations, hospitalization

**Variables**
- Age
- T Bili
- AST
- Variceal bleed
- Albumin

**Primary Outcome**
- Up to 4 yr survival


American College of Gastroenterology
**UK-PSC score**

**INCLUSION**
- >18 y/o
- PSC on MRCP, ERC, histology
- Liver transplant recipients

**EXCLUSION**
- Congenital biliary disease
- Biliary surgery 2nd SC
- HIV
- CCA
- AMA+
- DILI
- Hepatic sarcoidosis

**VARIABLES**
- Hgb
- T bilir
- ALB
- Plt
- Age
- ALP
- Disease type
- Variceal bleed

**PRIMARY OUTCOME**
- Liver transplantation
- Or death
- (transplant free survival)

Long term Transplant free survival by UK-PSC score, by quartile

AUC 10 yr outcome
UK-PSC 0.85
MRS 0.69
MELD 0.70

Primary sclerosing cholangitis risk estimate tool

INCLUSION
PSC on MRC, ERC

VARIABLES
Age
ALP
AST
T BILI
ALB
Sodium
Hemoglobin
PLT
PSC duration (yrs)

EXCLUSION
Small duct PSC
Other liver disease, PSC-AIH
MELD>14
Prior LT
Portal HTN: ascites, HE varices, plt<150, splenomegaly CCA

PRIMARY OUTCOME
Hepatic decompensation


Performance of PREsTo score, other prognostic markers for hepatic decompensation

<table>
<thead>
<tr>
<th>Markers</th>
<th>C-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREsTo</td>
<td>0.90</td>
</tr>
<tr>
<td>MRS</td>
<td>0.85</td>
</tr>
<tr>
<td>MELD</td>
<td>0.72</td>
</tr>
<tr>
<td>ALP&lt;1.5x ULN</td>
<td>0.65</td>
</tr>
</tbody>
</table>

5-year risk of decompensation

Relative influence of each variable in PREsTo

<table>
<thead>
<tr>
<th>Variable</th>
<th>Influence</th>
</tr>
</thead>
<tbody>
<tr>
<td>T bili</td>
<td>20</td>
</tr>
<tr>
<td>ALB</td>
<td>15</td>
</tr>
<tr>
<td>ALP</td>
<td>12</td>
</tr>
<tr>
<td>PLT</td>
<td>10</td>
</tr>
<tr>
<td>AST</td>
<td>8</td>
</tr>
<tr>
<td>Age</td>
<td>7</td>
</tr>
<tr>
<td>Duration</td>
<td>5</td>
</tr>
<tr>
<td>Hgb</td>
<td>4</td>
</tr>
<tr>
<td>Sodium</td>
<td>2</td>
</tr>
</tbody>
</table>

Median followup derivation cohort 4 years
Median PREsTo score 5.1%

Amsterdam-Oxford Model

>40 centers in UK, Netherlands
Derivation N=692
Validation N=264

INCLUSION
Small and large duct PSC
PSC-AIH overlap

VARIABLES
PSC subtype
AST
ALP
T bili
ALB
PLT
AGE at dx

PRIMAR Y OUTCOME
Transplant free survival

https://sorted.co/psc-calculator/
Amsterdam-Oxford Model
Transplant free survival at 5, 10, 15 yrs

C-statistic = 0.68

Enhanced Liver Fibrosis Score

INCLUSION
PSC on MRC, ERC
PSC-AIH
Also included UC patients and healthy controls

VARIABLES
TIMP-1,
PIINP
Hyaluronic acid

EXCLUSION
2ndary sclerosing cholangitis
Small duct PSC

PRIMARY OUTCOME
Transplant free survival

Enhanced Liver Fibrosis Score


Performance of prognostic scores for PSC

<table>
<thead>
<tr>
<th>Model</th>
<th>Endpoint</th>
<th>C-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREsTo</td>
<td>Hepatic decompensation</td>
<td>0.90</td>
</tr>
<tr>
<td>UK-PSC</td>
<td>Transplant free survival</td>
<td>0.81-0.85</td>
</tr>
<tr>
<td>ELF</td>
<td>Transplant free survival</td>
<td>0.81</td>
</tr>
<tr>
<td>rMRS</td>
<td>Overall survival transplant free survival</td>
<td>0.69-0.85</td>
</tr>
<tr>
<td>Amsterdam-Oxford</td>
<td>Transplant free survival</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Prospective
N=73
liver biopsy
VCTE

INCLUSION
PSC on cholangiogram
Small duct PSC
PSC-AIH
UDCA
>2 VCTEs

VARIABLES
Change in LSM

EXCLUSION
Liver transplant
2ndary sclerosing cholangitis, IgG4
Untreated DS
Decompensation
HCC, CCA

PRIMARY OUTCOME
Severe liver fibrosis
Death, liver transplant,
decompensation,
HCC, CCA

Retrospective 2 cohorts
Internal N=119
External N=119

INCLUSION
>18 y/o
Large duct PSC
1 baseline MR image

EXCLUSION
Poor quality MRI
Small duct PSC
PSC-AIH overlap
Previous LT, hepatico-J
Other liver conditions
 Decompensation
HCC, CCA

VARIABLES
Intrahepatic biliary dilatation
Dysmophy
Portal HTN
Parenchymal enhancement heterogeneity

PRIMARY OUTCOME
Liver transplant, death, decompensation


Anali score for noncontrast and contrast MRI-MRCP

Anali without gadolinium = (1 x dilatation of intrahepatic bile duct) + (2 x dysmophy) + (1 x portal HTN)
(range of possible score: 0-5)

Anali with gadolinium = (1 x dysmophy) + (1 x parenchymal enhancement heterogeneity)
(range of possible score: 0-2)

Dysmophy was defined by significant atrophy of either the right or left hepatic lobe and/or marked lobulations of liver surface and/or increase of the caudate/right lobe ratio >0.9

Portal HTN- portosystemic shunts +/- splenomegaly

Anali score on MRI without gadolinium

Intrahepatic dilatation  Dysmorphism  Portal HTN/ Splenomegaly

Anali score = \(1 \times \text{dilatation of intrahepatic bile duct} + 2 \times \text{dysmorphism} + 1 \times \text{portal HTN}\)

Anali score = 5


Outcomes for patients with PSC based on Anali score without gadolinium

Retrospective
3 Centers
N=162

INCLUSION
Age>18
Large duct PSC
1- 3D MRC,
VCTE with 6 mos

VARIABLES
MR (Anali score)
- Intrahepatic
dilatation (0-2)
- Dysmorphism (0-1)
- Portal HTN (0-1) &
VCTE

EXCLUSION
Small duct PSC
PSC-AIH variant
Previous LT
Other liver disease

PRIMARY OUTCOME
Liver related death,
Transplant free survival,
Decompensation

Dysmorphology was defined by an increase in the modified caudate/right lobe volume ratio 0.90
Portal HTN- portosystemic shunts +/- splenomegaly


Outcomes in patients with PSC stratified by Anali score and liver stiffness score

Group 1 AS<2 LS<10.5 kPa
Group 2 AS>2 or LS>10.5 kPa
Group 3 AS>2 & LS >10.5 kPa

Figure 3b. Elastogram images acquired during a liver MR elastography examination. (a) Gray-scale elastogram with the 95% confidence map superimposed shows a freehand ROI measurement of an area (outlined) with a mean liver stiffness of 7.4 kPa. (b) Color elastogram with a 0–8-kPa scale shows the stiffness distribution in organs for qualitative evaluation. Orange or red regions have higher stiffness values, and blue and purple regions have lower stiffness values. (c) Color elastogram with a 0–20-kPa scale. Although color elastograms with this scale are not commonly used clinically, they are helpful for evaluating liver heterogeneity, especially in livers with advanced fibrosis or cirrhosis.

Guglielmo FF. Published Online: October 18, 2019
https://doi.org/10.1148/rg.2019190034

Magnetic Resonance Elastography (MRE)

Retrospective
N=204
Median followup 4 yrs
Median time btwn MREs 1.1 yrs

INCLUSION
PSC on cholangiogram
2 or more MREs

VARIABLES
Change in liver stiffness

EXCLUSION
Hx hepatic decompensation
Liver transplant before 2nd MRE

PRIMARY OUTCOME
Hepatic decompensation
(ascites, variceal bleed, HE)

Responder = normalization or >40% reduction in ALP after 1 year in trial urso 17-23 mg/kg/d


High dose UDCA associated with higher rate of serious adverse events

<table>
<thead>
<tr>
<th></th>
<th>UDCA (28-30 mg/kg/d)</th>
<th>Placebo N=74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Liver Transplant</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Develop cirrhosis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Varices</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Death, transplant, minimal listing</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>30</td>
<td>19</td>
</tr>
</tbody>
</table>

Primary outcome= death, transplantation, meeting minimal listing criteria, development of varices, cholangiocarcinoma, or progression to cirrhosis

Randomised clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis - a pilot study

- Low dose vanco: 125 mg QID x 12 weeks, N=8, P=0.03
- High dose vanco: 250 mg QID X 12 weeks, N=9, P=0.02

A randomized, placebo-controlled, phase II study of obeticholic acid for primary sclerosing cholangitis

- Placebo: N=25
- 1.5-3.0 mg OCA: N=25
- 5 mg-10 mg OCA: N=26

Simtuzumab for Primary Sclerosing Cholangitis

- Simtuzumab is a monoclonal antibody directed against lysl oxidase like-2 function in matrix remodeling
- Randomized placebo controlled trial over 96 weeks
- No difference between treatment and placebo in primary outcome=change in hepatic collagen content
- Secondary outcomes= PSC related progression (SBP, variceal bleed, HE, cholangitis, CCA, HCC, liver transplant, death)
- Alkaline phosphatase was not associated with disease progression

Enhanced Liver Fibrosis score

PSC event=SBP, variceal bleed, HE, cholangitis, CCA, HCC, LT, death

**Take Home Points: PSC Prognostic Models**

C-statistics for PSC Models and Clinical Outcomes

<table>
<thead>
<tr>
<th>Model</th>
<th>Large duct PSC</th>
<th>Small Duct PSC*</th>
<th>PSC-AIH*</th>
<th>Liver Transplant Recipients</th>
<th>Outcome</th>
<th>C-statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRS</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Transplant free, Survival</td>
<td>0.69-0.85</td>
</tr>
<tr>
<td>UK-PSC</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Transplant free survival</td>
<td>0.81</td>
</tr>
<tr>
<td>Amsterdam-Oxford</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>Transplant free survival</td>
<td>0.68</td>
</tr>
<tr>
<td>PREsTo</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Hepatic Decompensation</td>
<td>0.90</td>
</tr>
<tr>
<td>ELF</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
<td>Transplant free survival</td>
<td>0.81</td>
</tr>
<tr>
<td>VCTE</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>Composite</td>
<td>---</td>
</tr>
<tr>
<td>MRI MRCP w gad</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Composite</td>
<td>0.89</td>
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<tr>
<td>MRI+VCTE</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Composite</td>
<td>---</td>
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<tr>
<td>MRE</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>Hepatic Decompensation</td>
<td>---</td>
</tr>
</tbody>
</table>

*these studies include few patients with PSC-AIH or small duct PSC

Questions?

Speaker:
Mark W. Russo, MD, MPH, FACG

Moderator:
Stevan A. Gonzalez, MD, MS

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