What can we look at other than ALP?

Innovating Biomarkers for PSC Prognosis, Diagnosis, and Treatment Response

Mette Vesterhus

NoPSC group leader | National PI ScandPSC

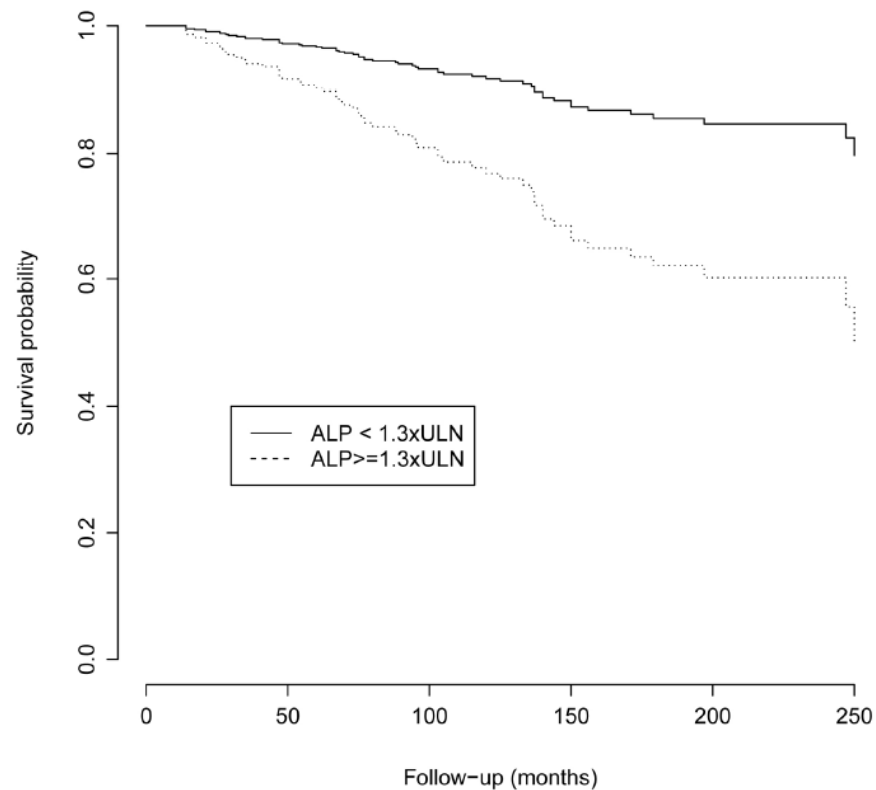Full Professor | University of Bergen
Senior Consult.| Haraldsplass Deaconess Hospital

Conflicts of interest

Received Speaker's fees from Siemens Healthineers, Intercept, Lilly, and GE

ALP IS ASSOCIATED WITH OUTCOME – BUT...

De Vries et al. Liver Int 2016

Amsterdam-Oxford Model

- PSC subtype, age at PSC diagnosis, **ALP**, **platelets, albumin**, AST, and **bilirubin**

de Vries et al., Gut 2018

PREsTO

- **Age**, PSC duration, **platelets**, **bilirubin**, **albumin**, **ALP** xULN, AST, hemoglobin, sodium
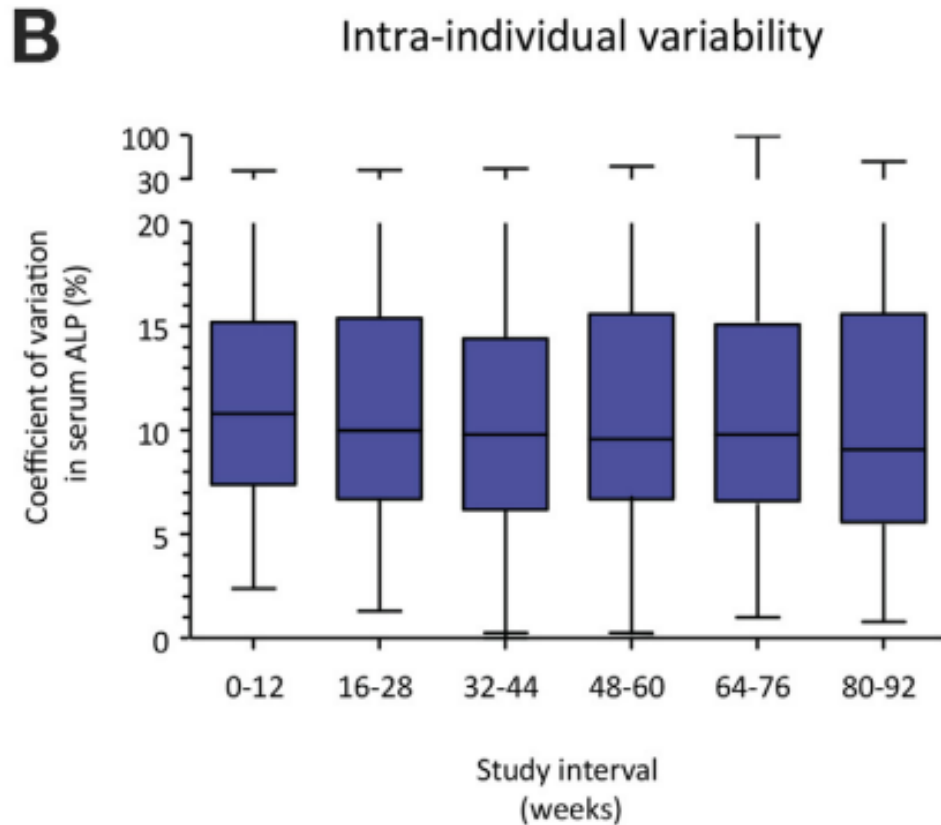
Eaton et al., Hepatology 2018

UK-PSC risk score

- Long-term risk score: **Age**, extrahepatic biliary disease; **Platelets**, **albumin**; **bilirubin**, **ALP** and variceal bleed
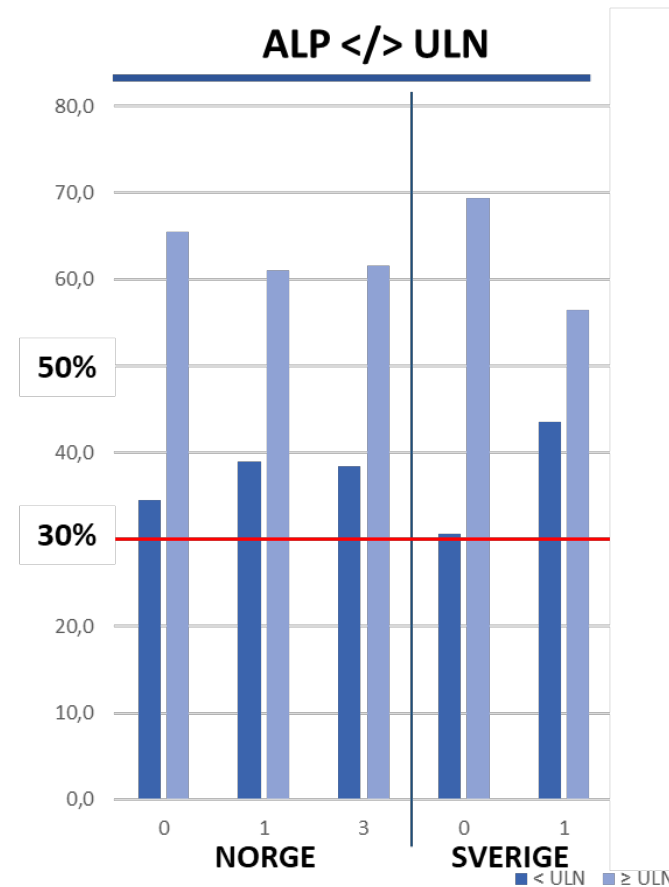
Goode et al., Hepatology 2019

WHAT IS THE PROBLEM WITH ALP?

WIDE WITHIN-PATIENT VARIATION IN ALP

ALP IS NORMAL IN 30%

"SPONTANEOUS" ALP REDUCTION
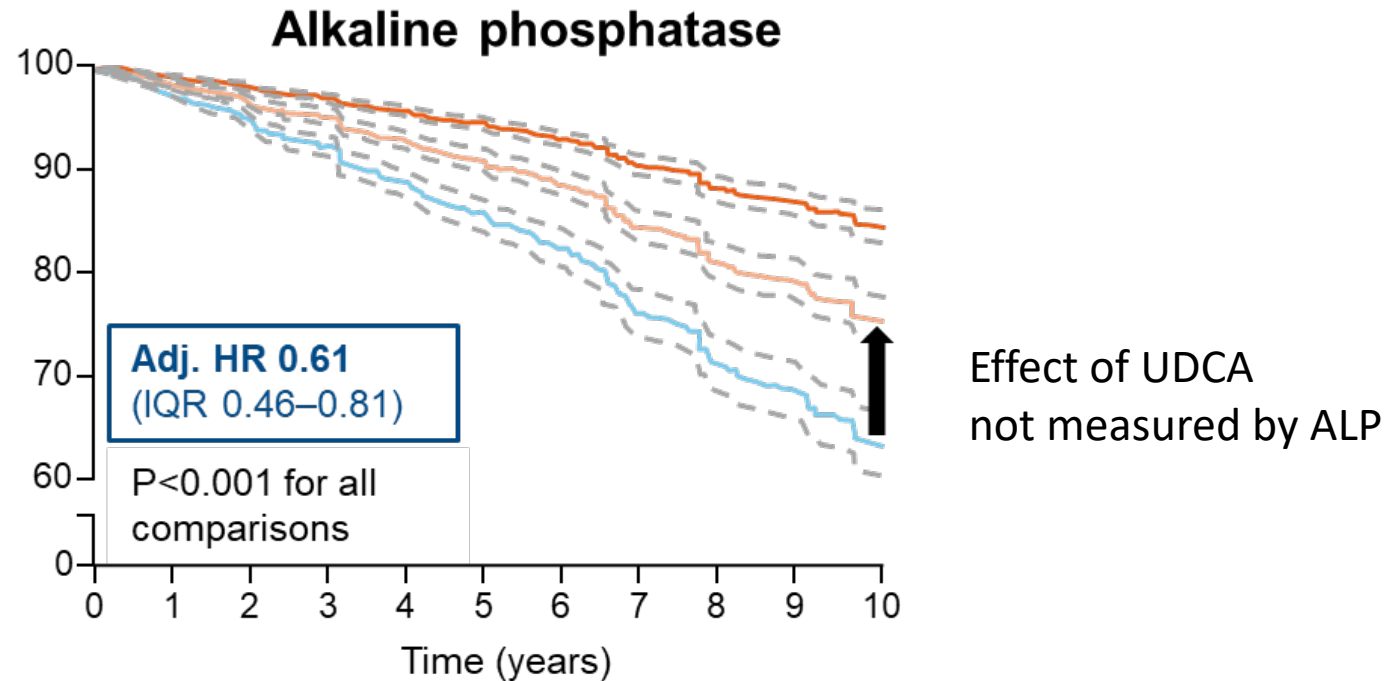
40% ALP reduction:

10-13% of patients with baseline ALP >1.3*ULN at 1-3 yrs
Fossdal

15% of patients with baseline ALP >2*ULN at 2 years
Trivedi

Trivedi et al., Clin Gas Hep 2021

Fossdal et al., JHEP rep 2021

WHAT IS THE PROBLEM WITH ALP?

Harms et al., EASL 2018
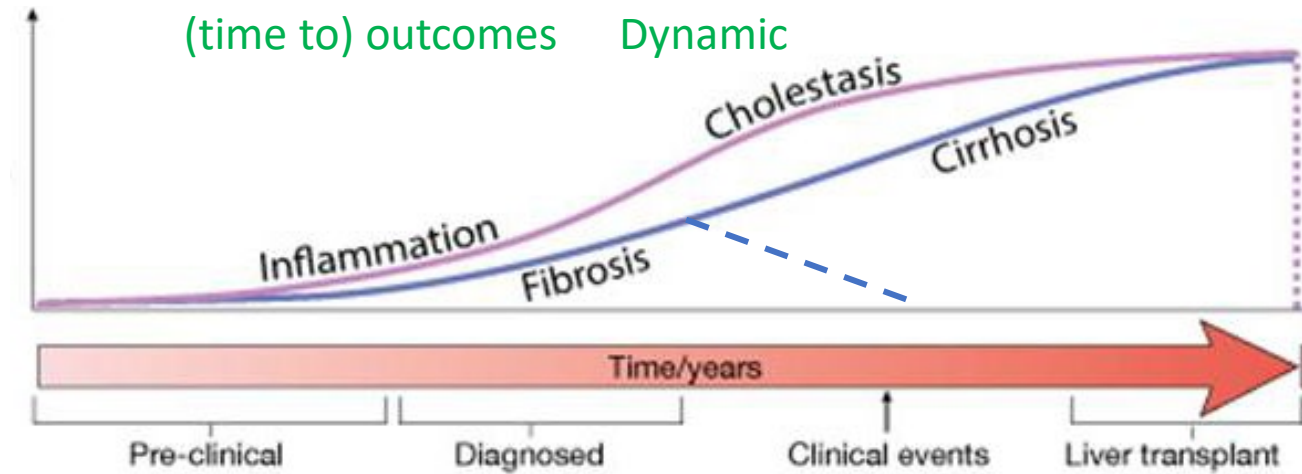(final paper in JHEP 2019)

THE IDEAL BIOMARKER

for different ends

RISK OF (FAST) PROGRESSION
Association with (time to) outcomes

REDUCTION OR LESS PROGRESSION
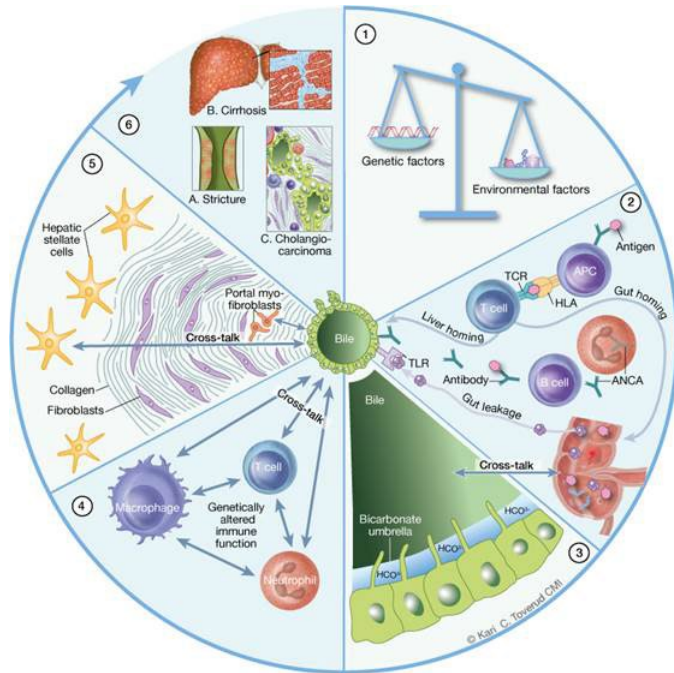Ass. with outcomes
Dynamic

Cholestasis

Cirrhosis

Inflammation

Fibrosis

Time/years

Pre-clinical | Diagnosed | Clinical events | Liver transplant

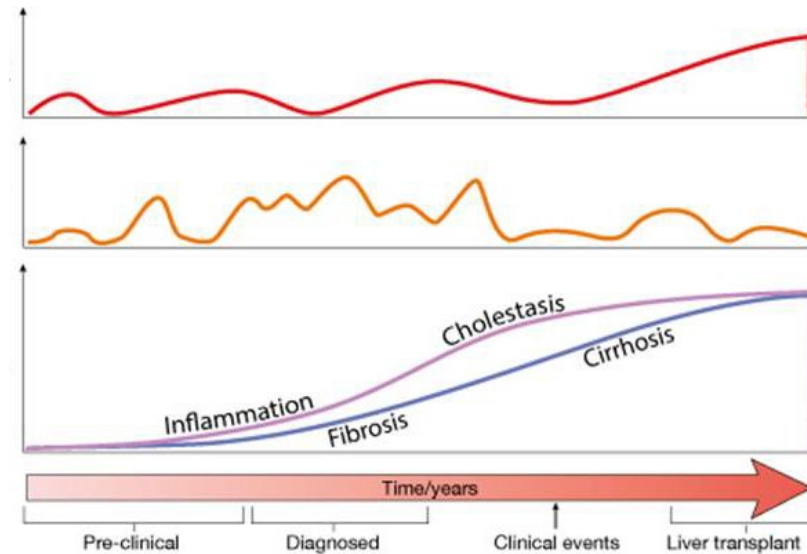**DIAGNOSTIC**   **PROGNOSTIC**   **TREATMENT RESPONSE**
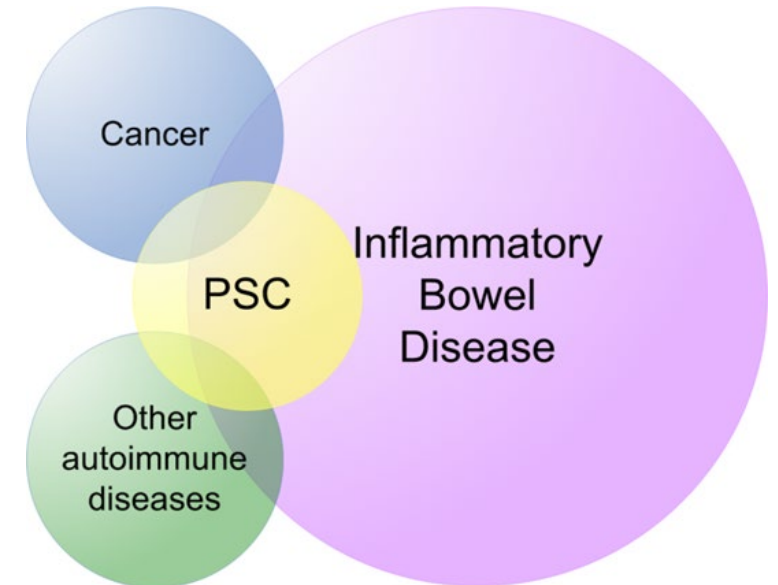Surrogate endpoint

WHY IS BIOMARKER DEVELOPMENT DIFFICULT IN PSC?

COMPLEX PATHOGENESIS

NATURAL FLUCTUATIONS

CO-MORBIDITIES

COMPLICATIONS

- Gallstones, bacterial cholangitis
- Relevant strictures - ERCP
- Clinical decompensation

Biomarkers of prognosis and treatment effect

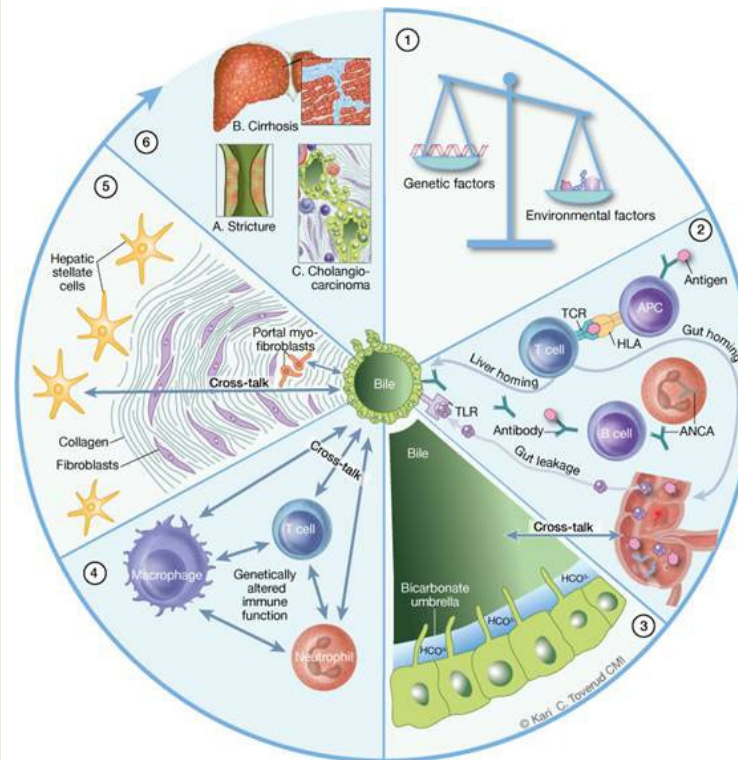**FIBROSIS**
ELF test
Pro-C3, C4M
CD163
CD14
Elastography

AUTOIMMUNITY
Anti-GP2
Autotaxin
IgG4

INFLAMMATION
IL-8
Calprotectin
Neopterin
KT-ratio
VAP-1

MICROBIOTA
Vit B6 metab.
TMAO

CHOLESTASIS
Bile acids
ALP

CLINICAL SCORES
UK PSC Score
PREsTo
Amsterdam-
Oxford
Model

PROMs

IMAGING
MRI
AI

Karlsen, Folseraas, Thorburn,
Vesterhus. JHEP 2017

Biomarkers of prognosis and treatment effect

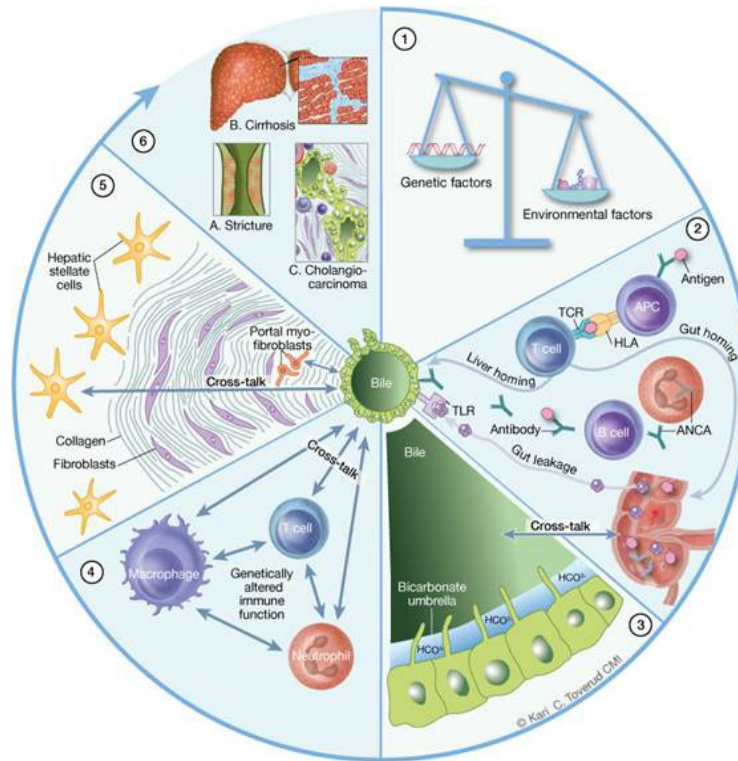**FIBROSIS**
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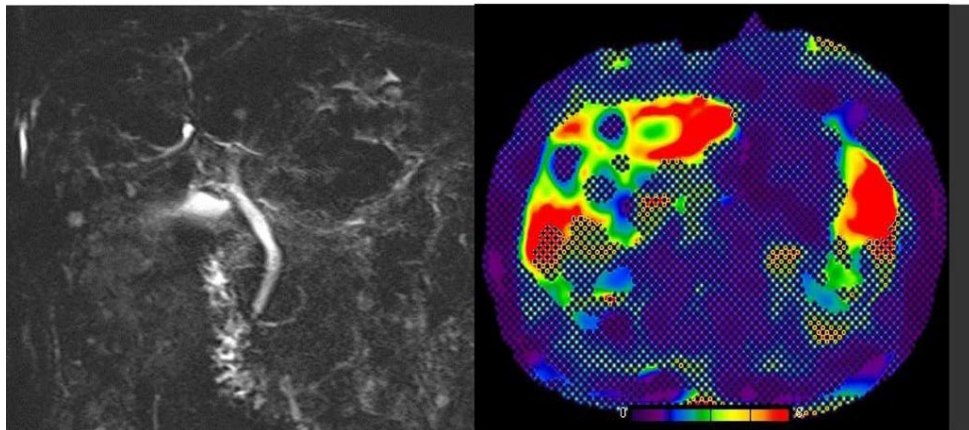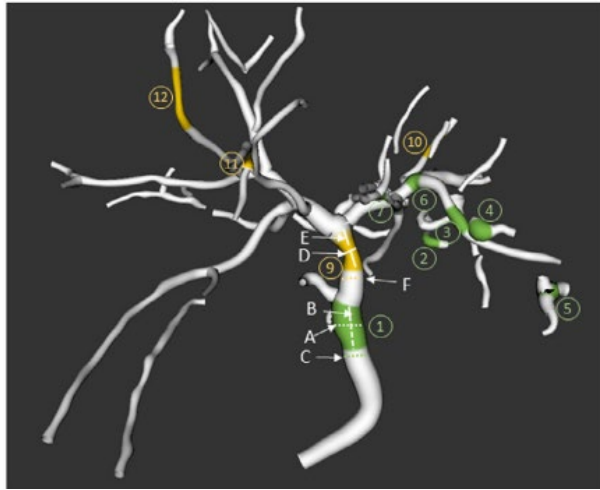Model

PROMs

IMAGING
MRI
AI

IDENTIFICATION ➡ VALIDATION ➡ PROSPECTIVE VALIDATION

Imaging as biomarkers

- Anali score

- DiStrict score

- qMRCP - MRCP+

- MRE

- AI & Machine learning

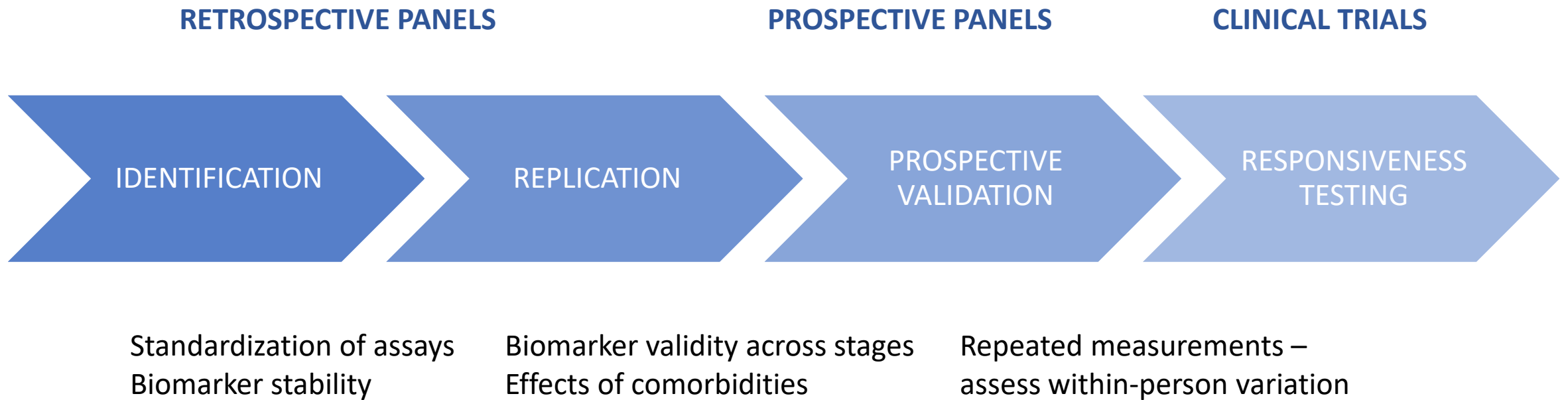*Eaton et al., J Gastro Hepatol 2016*
Lemoinne et al., CGH 2019
Grigoriadis et al., JHEP rep 2022
Cazzagon et al., JHEP rep 2022
Cristoferi et al., Dig Liv Dis 2023
Ismail, Eur Radiol 2022

Biomarker development program

RETROSPECTIVE PANELS   **PROSPECTIVE PANELS**   **CLINICAL TRIALS**

| IDENTIFICATION | REPLICATION | PROSPECTIVE VALIDATION | RESPONSIVENESS TESTING |

Standardization of assays
Biomarker stability

Biomarker validity across stages
Effects of comorbidities

Repeated measurements –
assess within-person variation
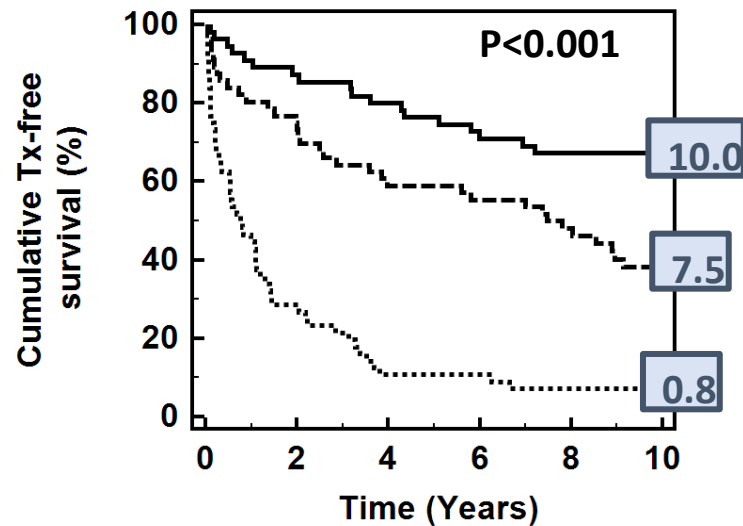
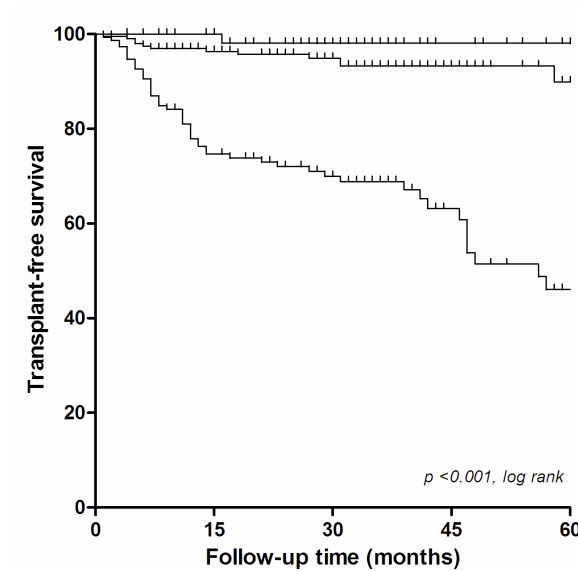# From identification to recommendation: ELF test

IDENTIFICATION
2 independent Norwegian panels

Vesterhus & Hov, Hepatology 2015
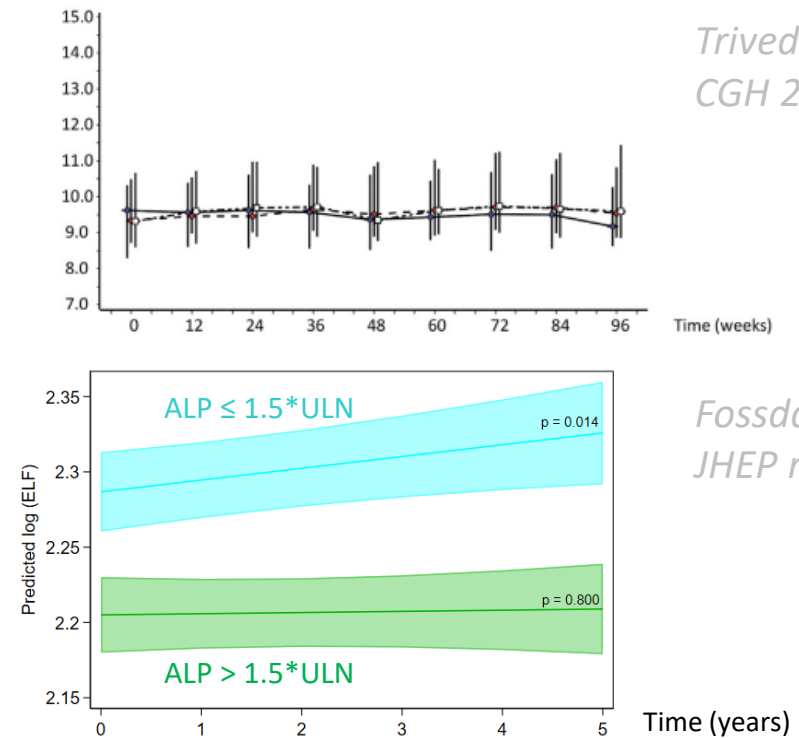
VALIDATION
Large, multicenter panel (n > 500)

De Vries, Liver Int 2017

VARIATION & RESPONSIVENESS
Large, multicenter panel (n > 500)

Trivedi, CGH 2021

Fossdal, JHEP rep 2021

Explorative biomarker in several trials

From identification to recommendation: ELF & LSM

PROGNOSTIC MARKER (CLINICAL)

- EASL CPG Noninvasive tests...2021 update: Recommends ELF and LSM at baseline and during FUP of PSC

- Clinical implementation - needs?
  - Prospective validation
  - Awareness
  - Availability: prize, platform

EFFECT / SURROGATE MARKER (TRIALS)

- Design and endpoints in clinical trials in PSC. *Ponsioen et al, Hepatology 2018*

- FDA & EMA approval - lacking

- Application needs?
  - Supply raw data
  - Data sets: large, repeated measurements, representative populations, endpoints association

Biomarkers of prognosis and treatment effect

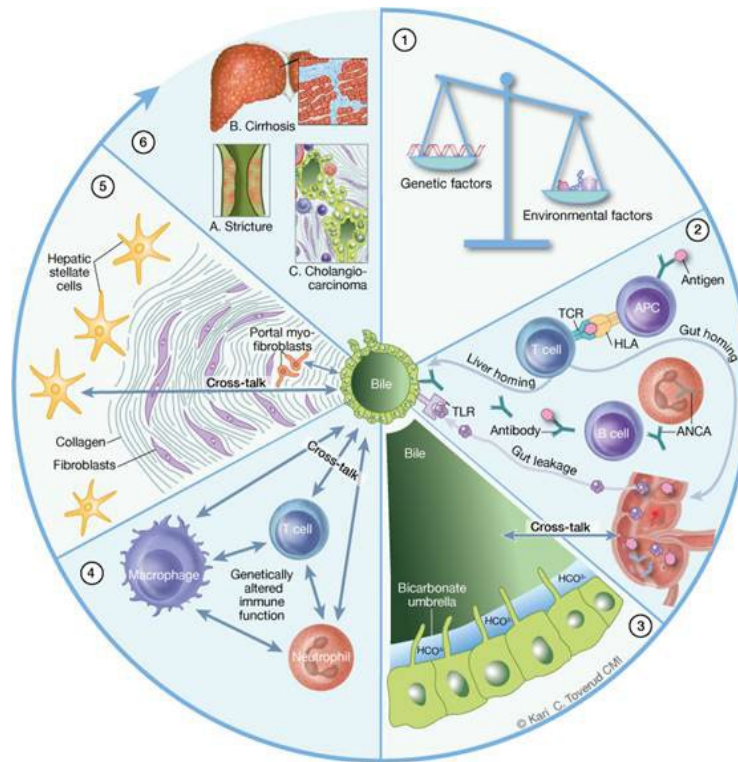**FIBROSIS**
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MORE VALIDATION NEEDED | MULTIPLE OR COMBINED MARKERS?

Biomarkers of prognosis and treatment effect

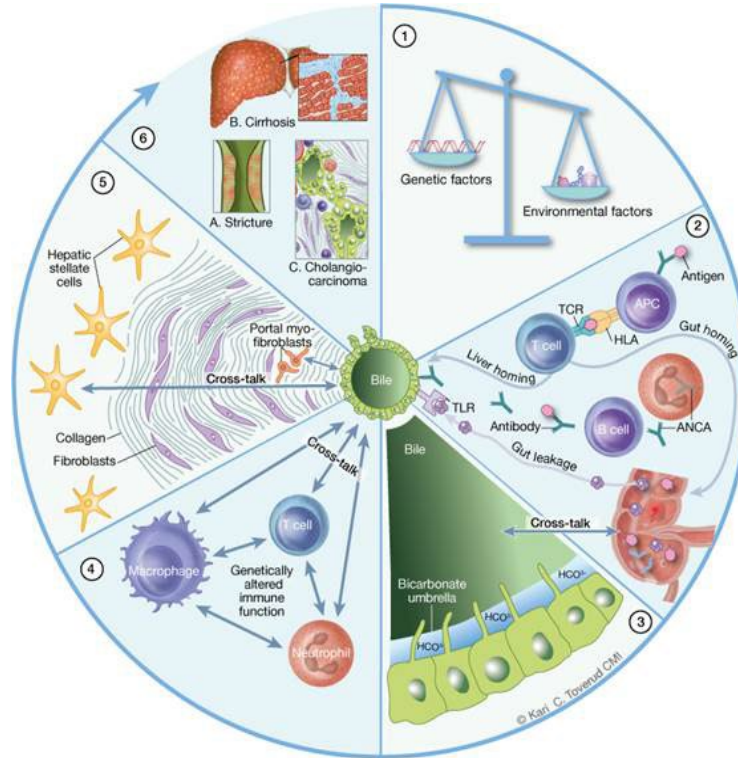**FIBROSIS**
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MORE VALIDATION NEEDED | MULTIPLE OR COMBINED MARKERS?

Kristin Harila & sherpa team
Dawa Ongju and Pasang Dawa

....If you want to go FAR, go TOGETHER