



**THE FORUM**  
For Collaborative Research<sup>SM</sup>

# What can we look at other than ALP? Innovating Biomarkers for PSC Prognosis, Diagnosis, and Treatment Response

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Nordic Bioscience, Herlev, Denmark

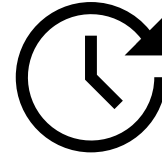


# Disclosures

- I am a full-time employee of Nordic Bioscience, a company involved in developing serological markers for the extracellular matrix

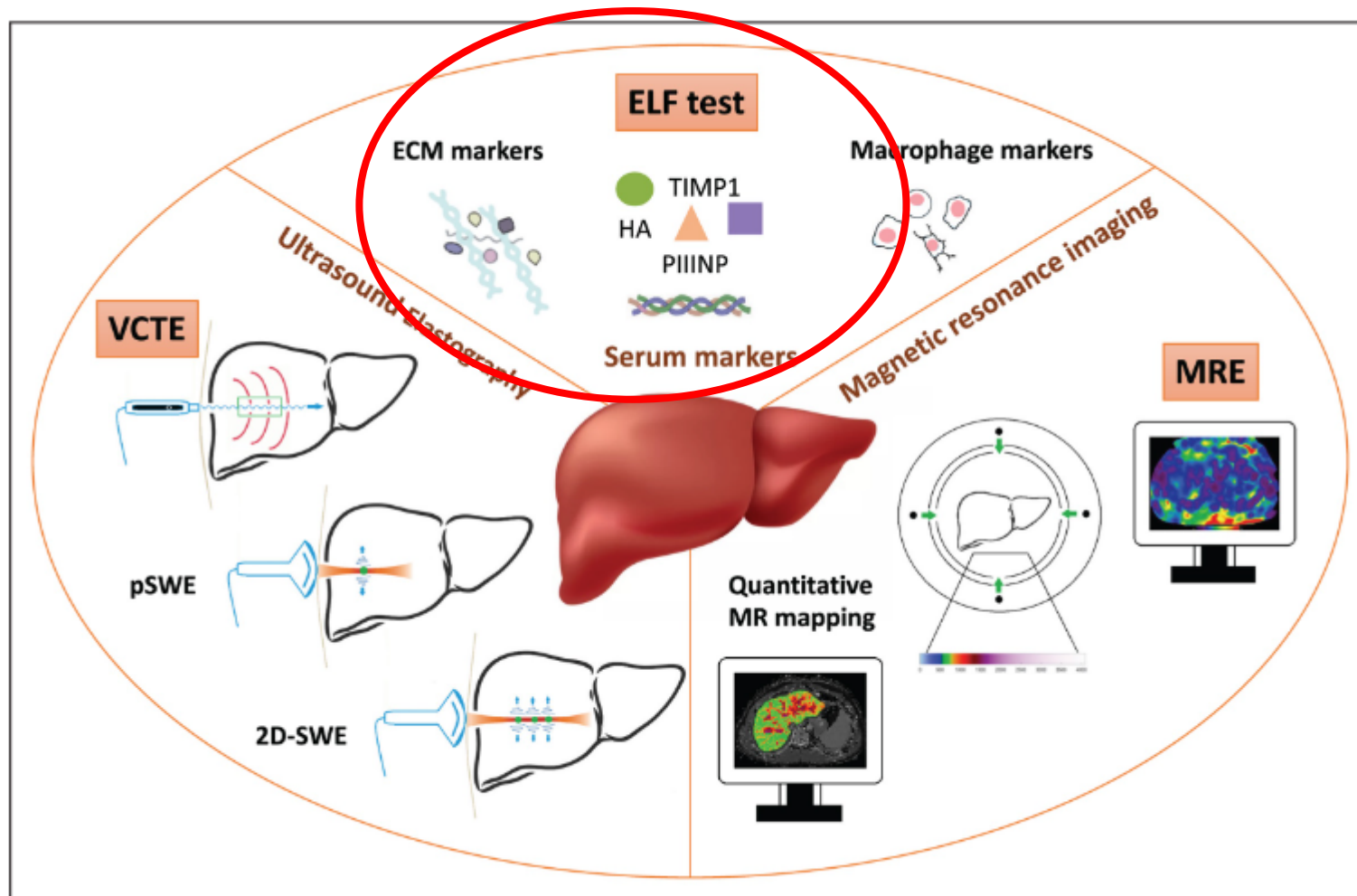
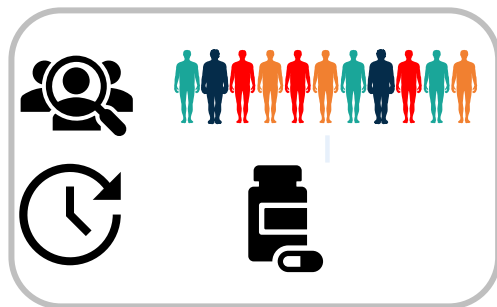
# There is a medical need for non-invasive serological tests (**NITs**) for fibrosis remodeling in biliary disease

- **Diagnosis & Staging**
- **Prognostic for events**
- **Endotyping of patients**
- **Prediction of Tx effect**



# There is a medical need for non-invasive serological tests (NITs) for fibrosis remodeling in biliary disease

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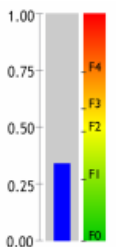


# State of the art Non-Invasive Tests (NITs) for disease status

## Indirect markers

**FibroTest**  
assesses the scarring of the liver (fibrosis)

Age, Gender, A2M, Haptoglobin, ApoA1 Bili, GGT



**FibroTest** is the test that assesses liver fibrosis:

- ▶ F0 : no fibrosis
- ▶ F1 : minimal fibrosis
- ▶ F2 : moderate fibrosis
- ▶ F3 : advanced fibrosis
- ▶ F4 : severe fibrosis

Fibrosis: lesion caused by the liver's reaction to hepatitis virus attack, fat or alcohol. Liver fibrosis is usually compared to a scar which spreads in the liver.

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}}$$

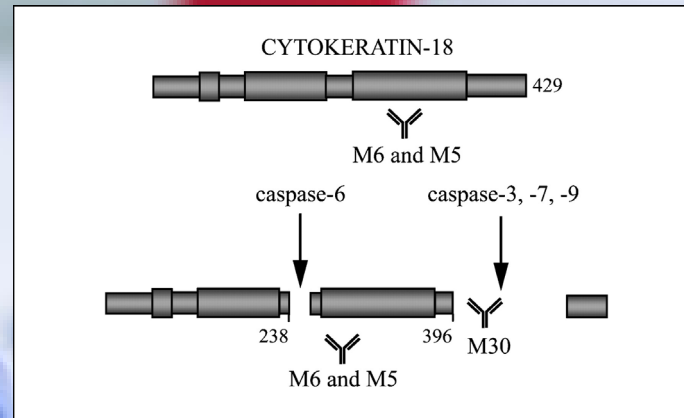
$$\text{APRI} = \frac{\text{AST Level (AST (Upper Limit of Normal))}}{\text{Platelet Count (10}^9\text{/L)}} \times 100$$

**AST / ALT**

Elevations above the upper limit of normal

<b>&lt;5x</b>	<b>5-10x</b>	<b>&gt;10x</b>
NAFLD	EtOH	Viral Hepatitis
Drug Induced EtOH	Drug Induced Biliary Disease	Acetaminophen
		Shocked Liver
		HELLP
		Autoimmune

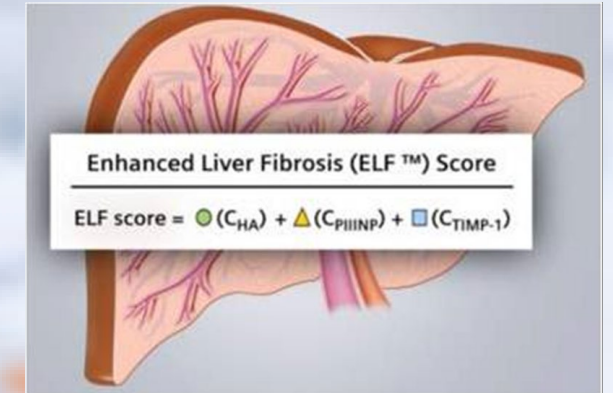
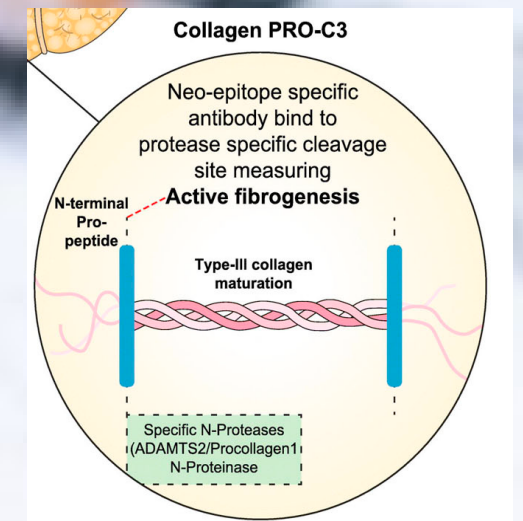
## Apoptosis markers



## Direct fibrosis markers

**Enhanced Liver Fibrosis (ELF™) Score**

ELF score =  $(C_{HA}) + (C_{PIIINP}) + (C_{TIMP-1})$

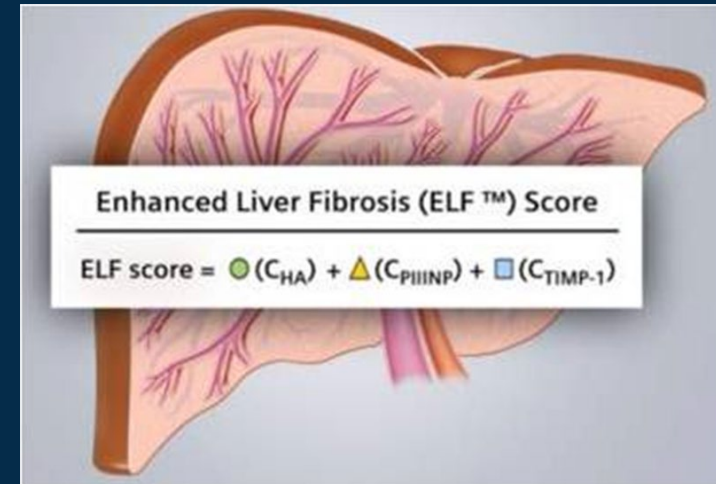



## Neopeptide technology

# Current use of NITs for fibrosis in biliary disease

## KEY POINTS

- Large studies confirm that in PBC, LSM by VCTE identifies at-risk patients and should be used in addition to biochemical response criteria and prognostic scores.
- ELF test and LSM are recommended for fibrosis and prognosis evaluation at diagnosis and during follow-up in PSC.
- ELF test may be more reliable than LSM in PSC.
- MRE accurately detects fibrosis and cirrhosis in PSC, but more studies are warranted to finally conclude regarding cutoff levels and comparisons to VCTE and ELF test.



ELF= Enhanced Liver Fibrosis  
Part of EASL guideline 2022 for PSC  
as a prognostic NIT

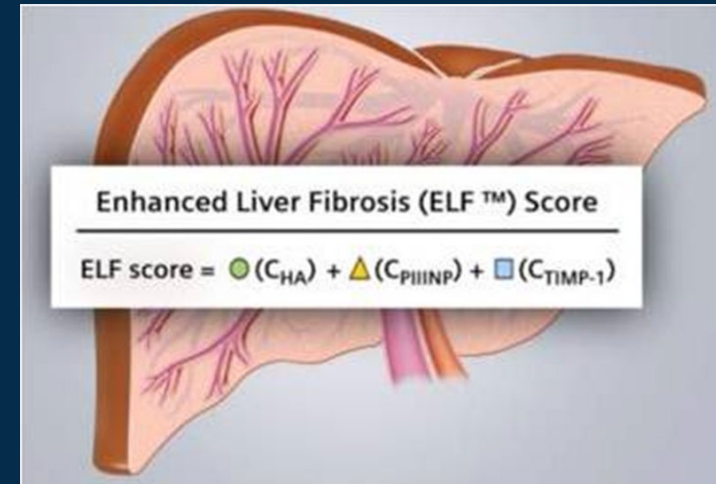
*Helgadottir & Vesterhus  
Curr Opin Gastroenter 2023*

# Current use of NITs for fibrosis in biliary disease

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Helgadottir & Vesterhus  
Curr Opin Gastroenter 2023



Markers of ECM  
remodelling –  
May they aid?



# The **Extracellular matrix** is important

## - Collagens are the supporting pillars of all biological structures

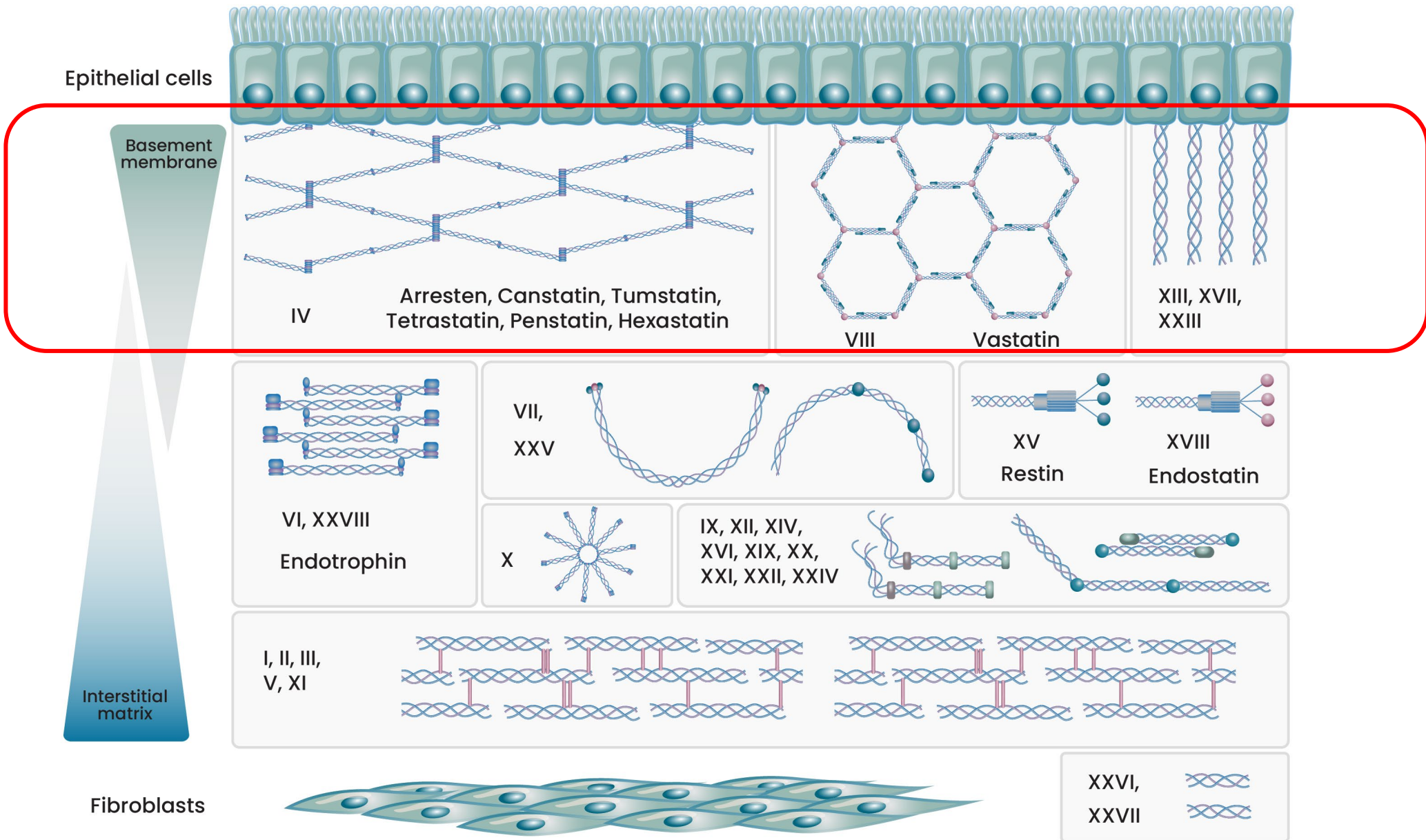
- ✓ Collagens constitute 30% of all tissues
- ✓ Collagens are the backbone of all tissues
- ✓ Type I collagen is the most abundant protein in the body
- ✓ Eight collagens on the top 20 list of the most abundant proteins
- ✓ There is more ECM than cells in many tissues – are we looking at the right thing?





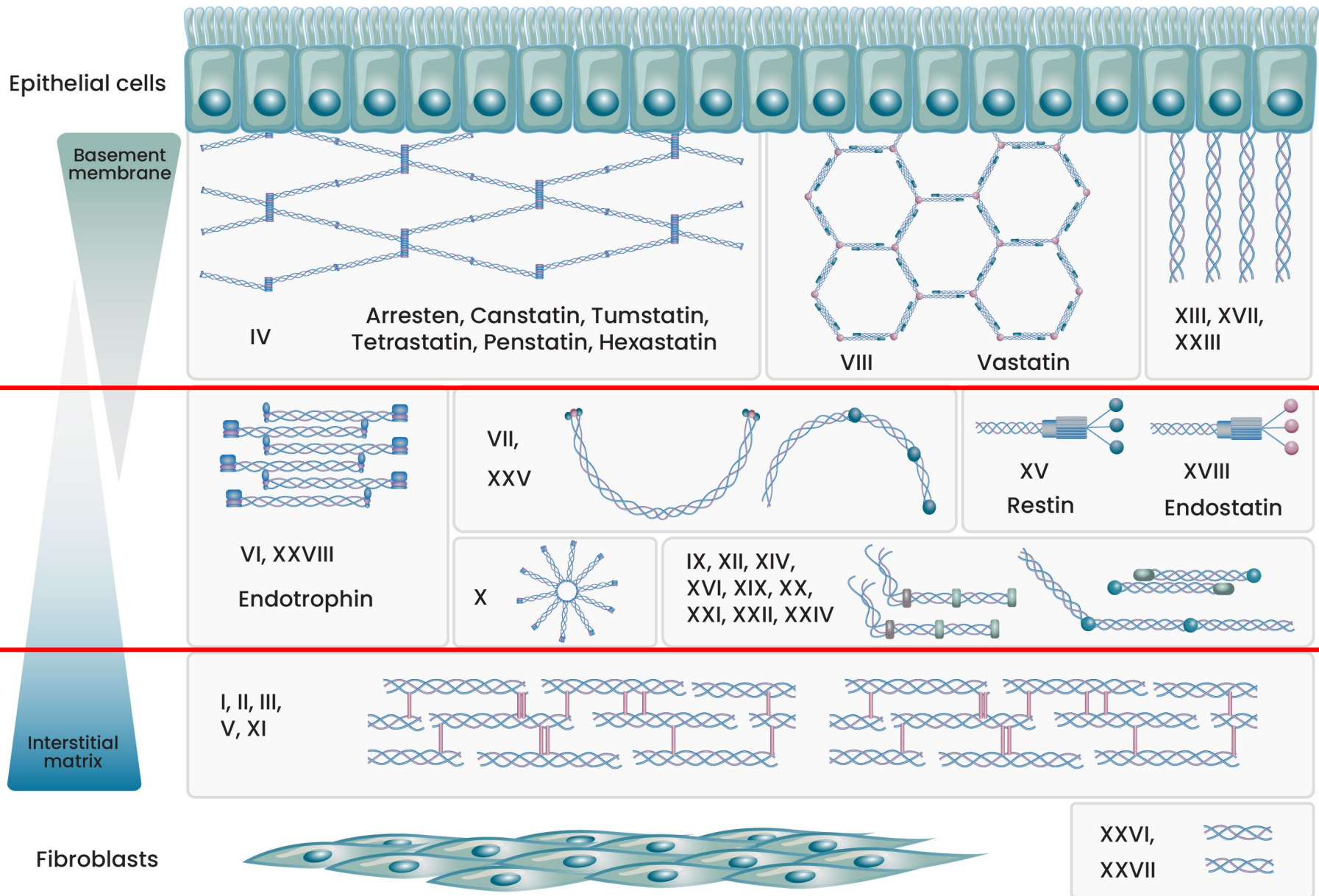
# Get to know the ECM

## The 28 Collagens - Potential biomarkers



# Get to know the ECM

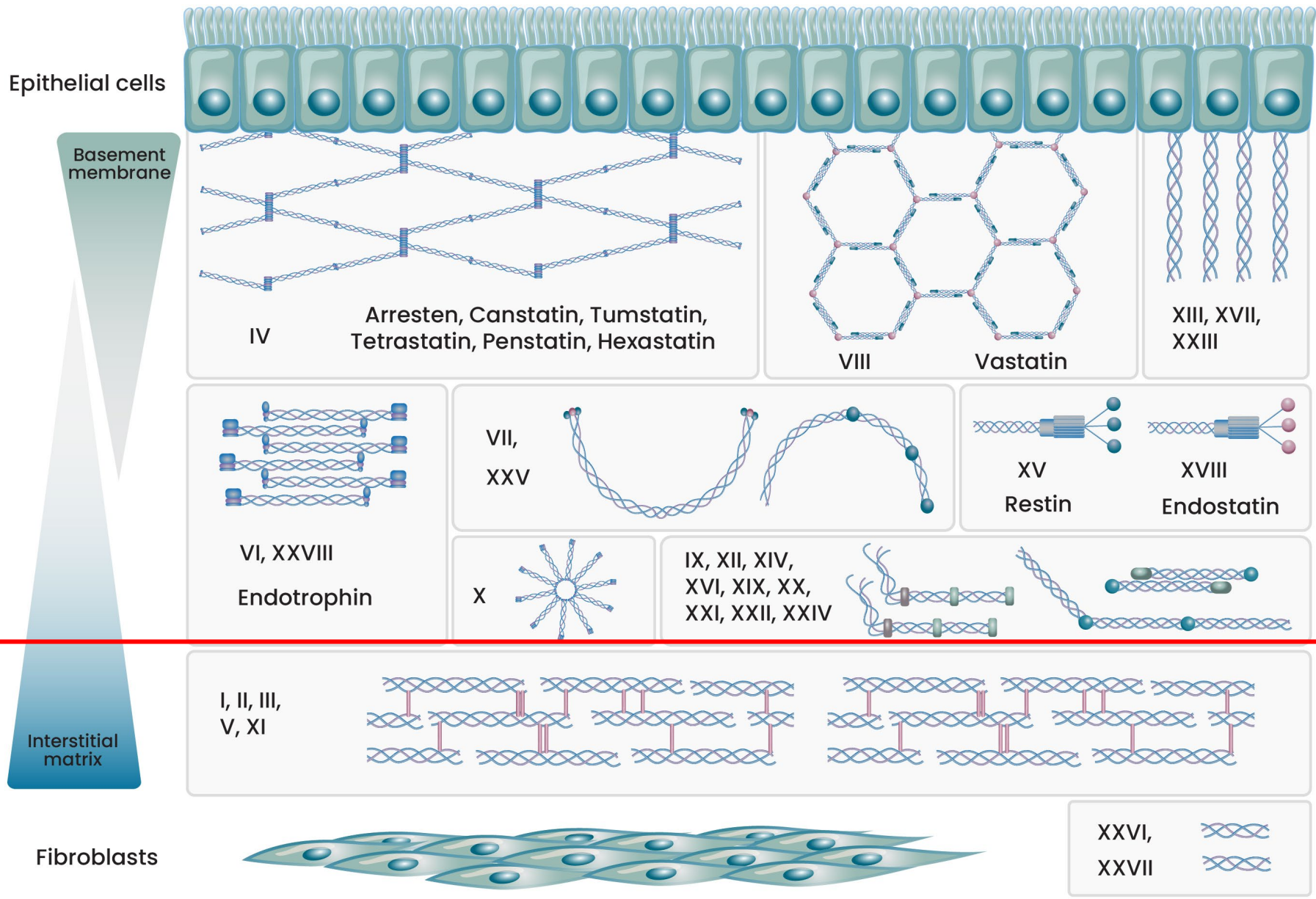
## The 28 Collagens - Potential biomarkers





# Get to know the ECM

## The 28 Collagens - Potential biomarkers



# Demolition & Repair 24-7

## You continue to remodel



Patients may develop fibrosis because of two very different endotypes – more tissue formation, or less tissue degradation

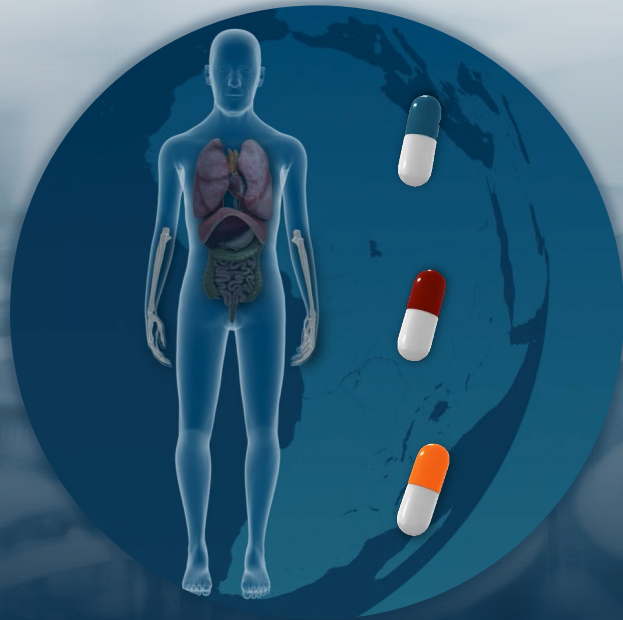
-Do you know which one your patients have?



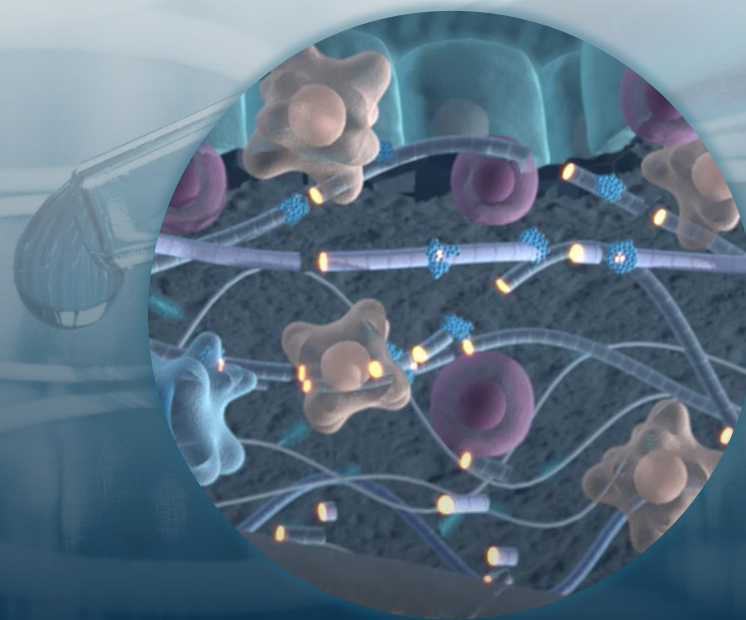


# Nordic Bioscience

## Neopeptide technology



We develop biomarkers that aid **preclinical and clinical** drug development



Our specialty are **extracellular matrix** based biomarkers



Our assays measure **pathologically relevant** ECM fragments in the bloodstream



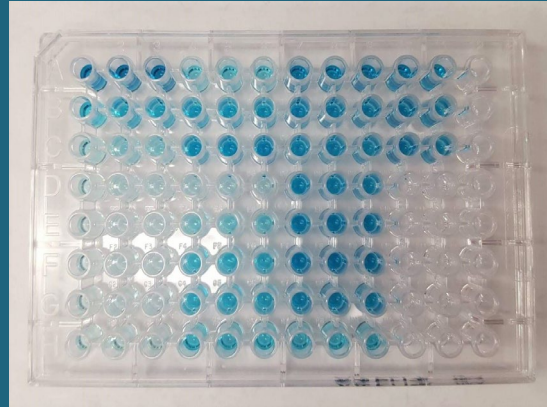
# Filling the biomarker gap for the future - High Precision!

Discovery



10.000 Ideas

Refinement



200 Assays

Robustness



50 Assays

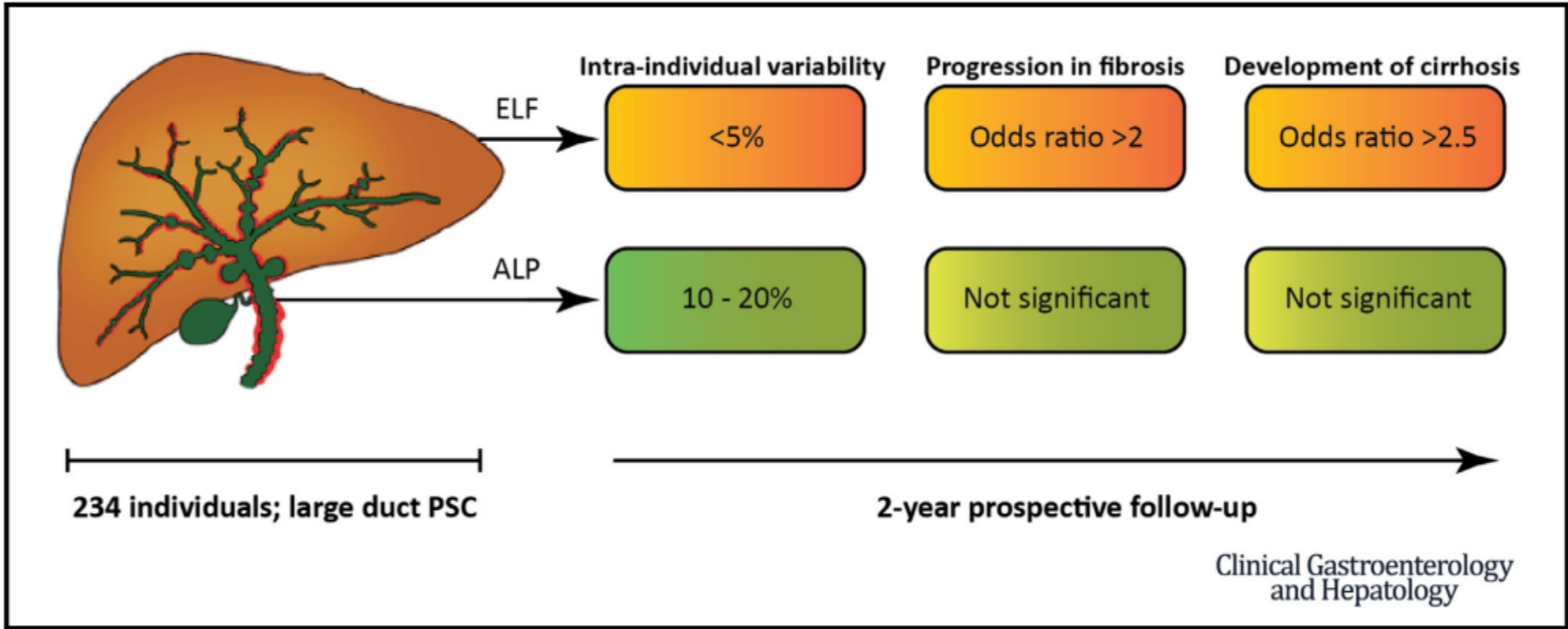
World Wide



15 Assays

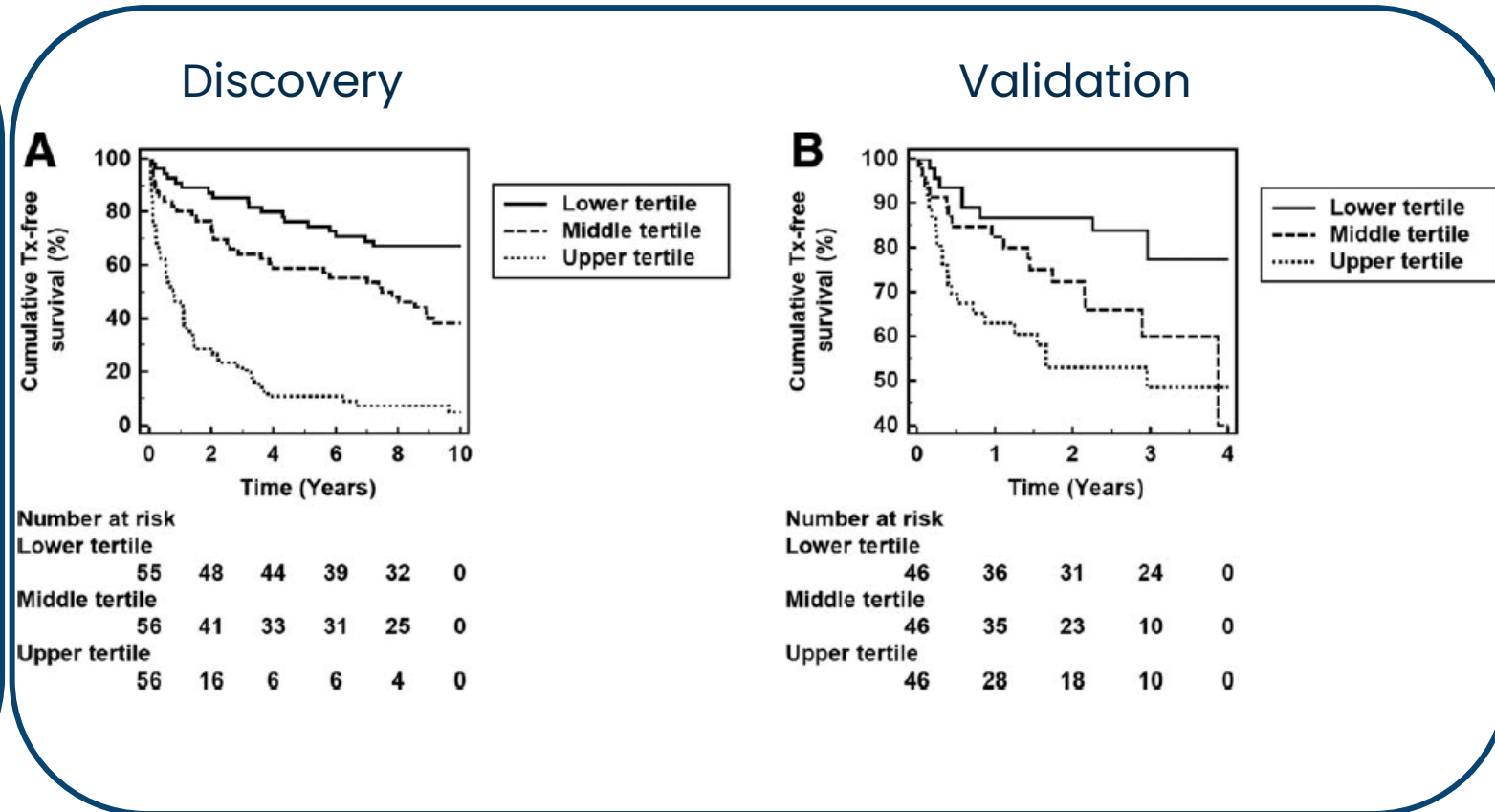
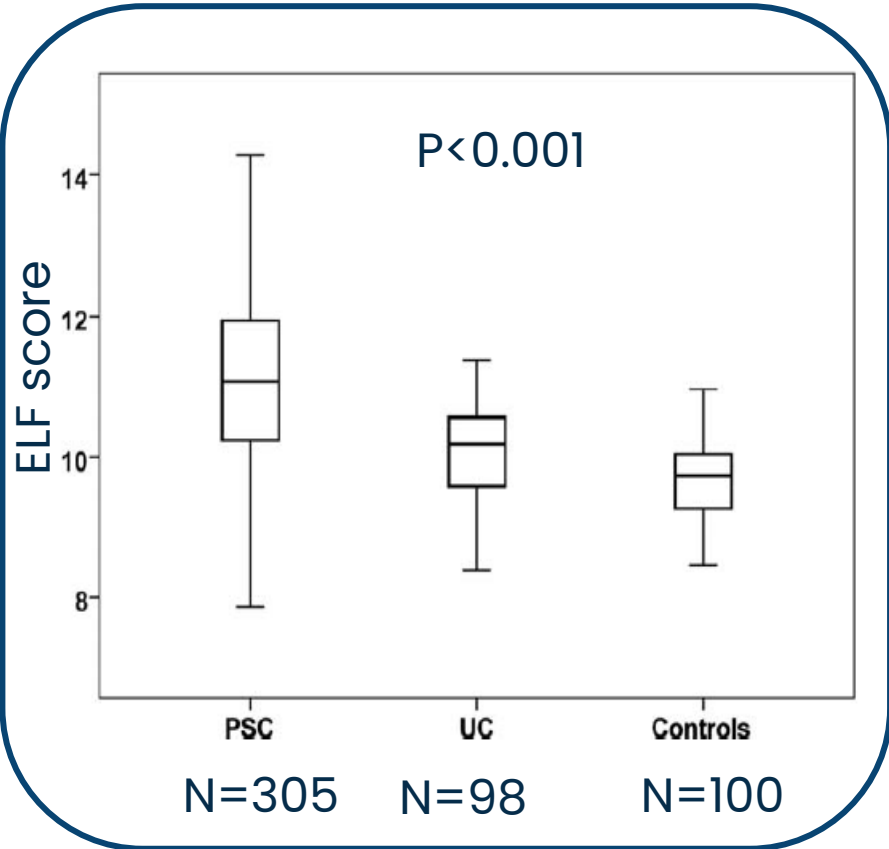
PRO-C3; PRO-C6

# Large variability is seen in ALP versus ELF in PSC



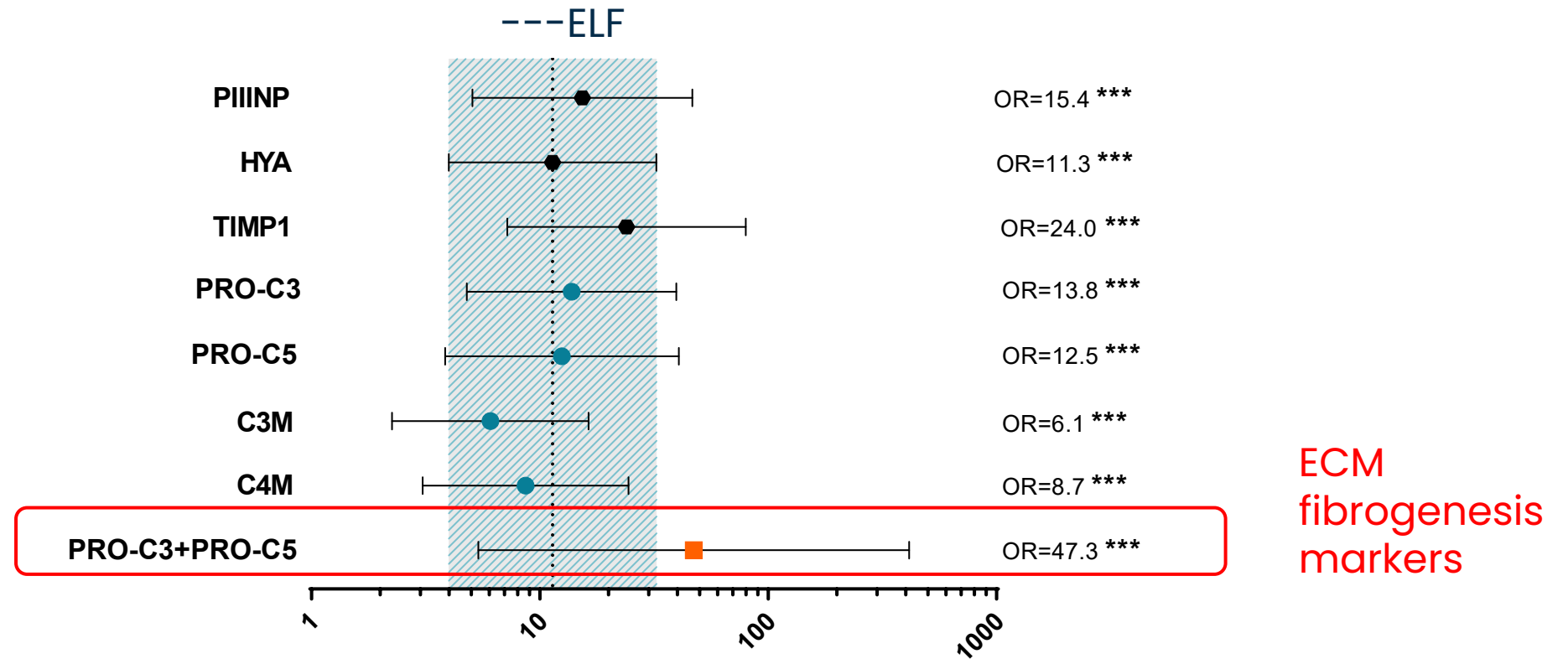
Trivedi PJ et al, Clinical Gastroenterology and Hepatology, 2021

# Direct Fibrosis markers for **Diagnosis & Prognosis**



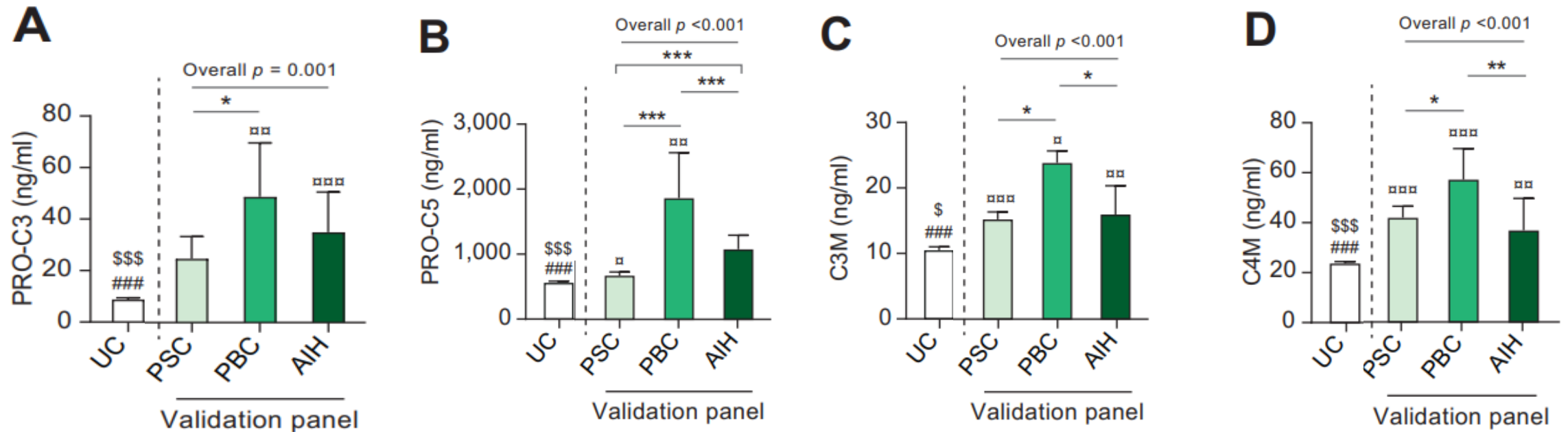


# Odds ratio for predicting transplant free survival in PSC patients – Prognosis



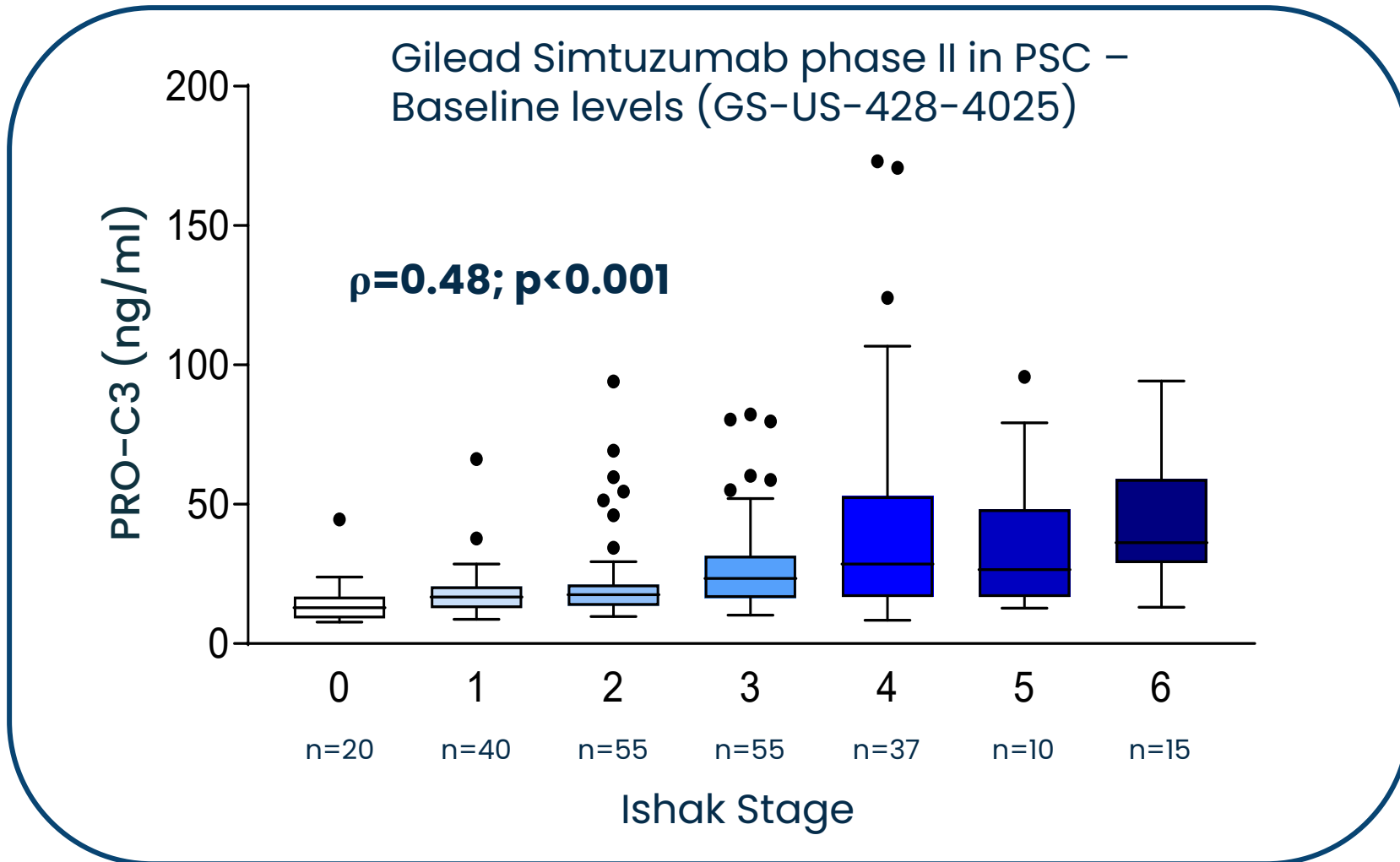
N=138 PSC patients. Baseline highest tertile serum compared to patients with lowest baseline tertile serum level of ELF test. Data shown as median with 95% CI. Dotted line and scattered area represents ELF test OR with 95% CI. \*\*\*=P<0.001

# ECM remodeling neoepitope markers are high in biliary diseases- **Diagnosis**

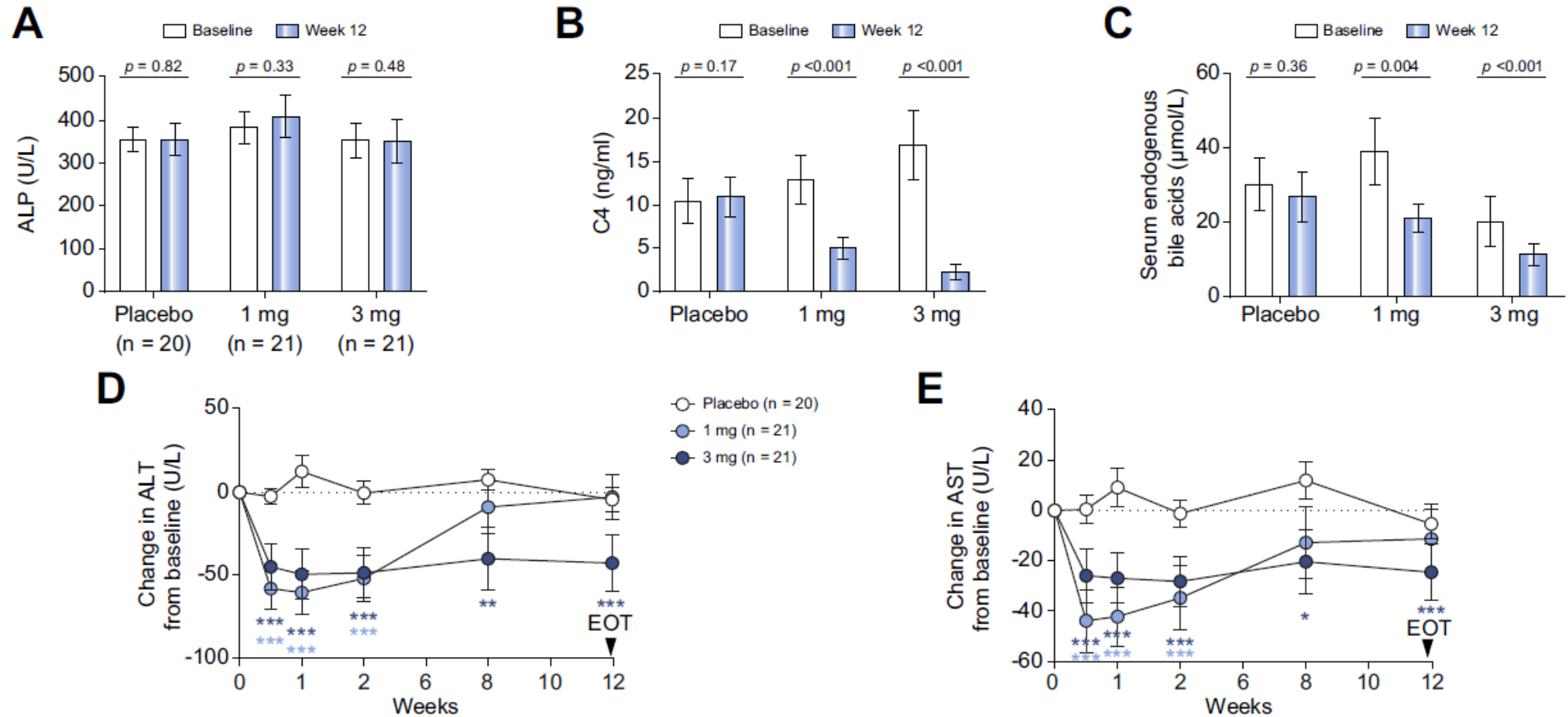


Validation panel: PSC n=138; PBC n=28; AIH n=27  
Controls (Ulcerative Colitis) n=194

# PRO-C3 is associated with Ishak stage in PSC patients – Diagnosis



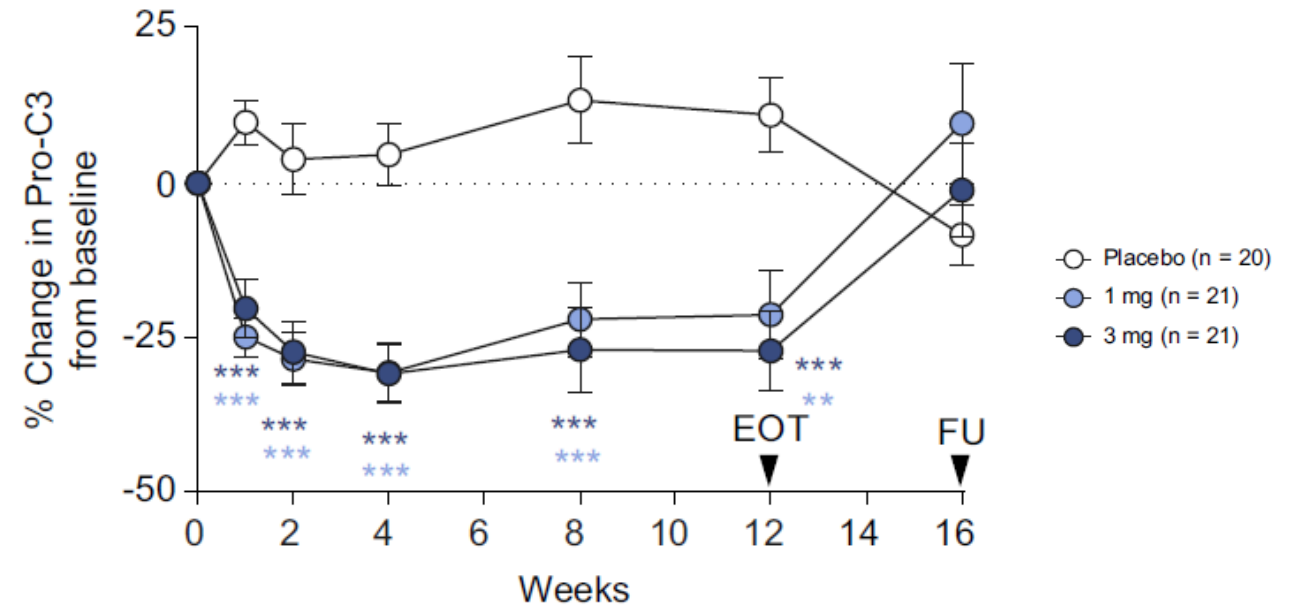
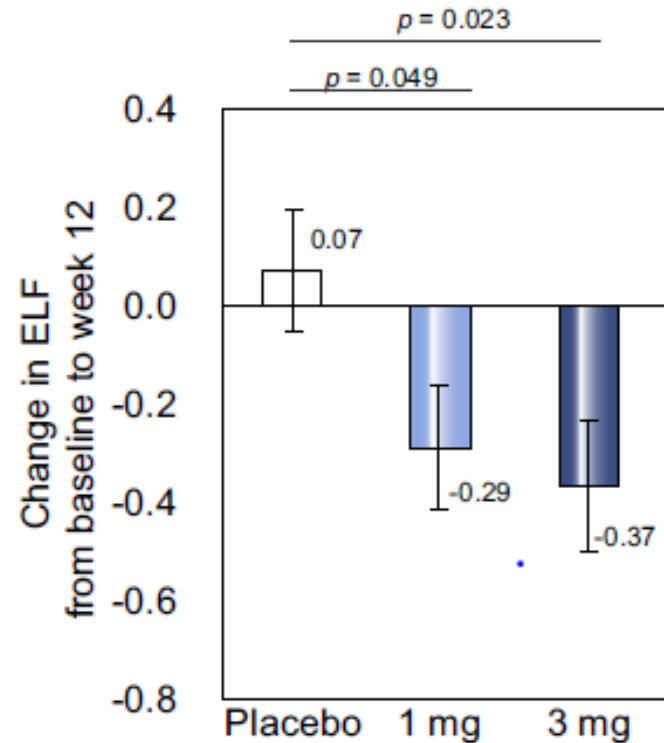
# ALP was not modulated by Aldafermin (FGF19) in PSC phase II - Pharmacodynamic



PL n=20; 1mg: n=21; 2mg n=21



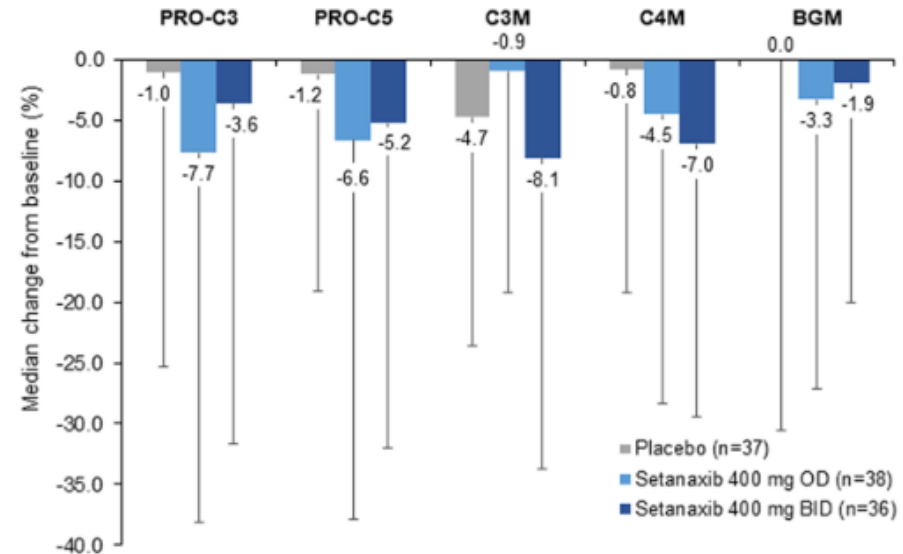
# ELF & PRO-C3 are dynamically modulated by Aldafermin – Pharmacodynamic



PL n=20; 1mg: n=21; 2mg n=21

# Markers of ECM remodelling are overall reduced in PBC by Setanaxib at week 24 - Pharmacodynamic

FIGURE 4 Median percentage change from baseline in collagen fragment serum levels after 24 weeks of treatment. Intention-to-treat population. PRO-C3 and PRO-C5 are biomarkers that indicate the formation of type III and type V collagen, respectively. Error bars indicate IQR. C3M, C4M and BGM indicate collagen III and IV and biglycan degradation. BGM, biglycan degradation; BID, twice daily; C3M: collagen III degradation; C4M, collagen IV degradation; IQR, interquartile range; OD, once daily; PRO-C3/C5, pro-peptide of type III/V collagen.

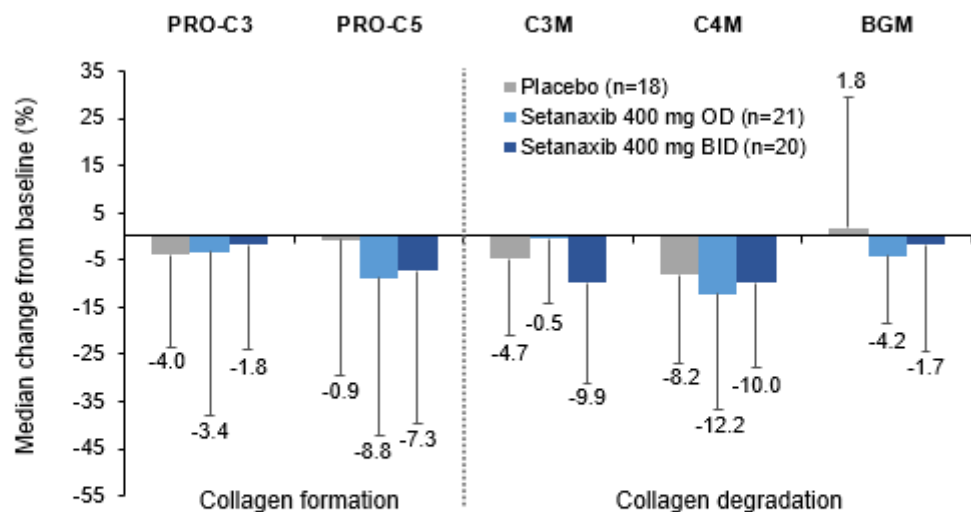


Median baseline collagen fragment serum levels (ng/ml)

Treatment	PRO-C3	PRO-C5	C3M	C4M	BGM
Placebo	15.1	970.8	15.5	51.4	15.3
Setanaxib 400 mg OD	20.8	1246.7	16.7	57.7	18.3
Setanaxib 400 mg BID	19.0	1076.7	15.1	49.0	17.3

# Interstitial matrix markers are substantially modulated in patients with high LSM at baseline ( $\geq 9.6$ kPa) - Pharmacodynamic

A) Baseline liver stiffness <9.6 kPa

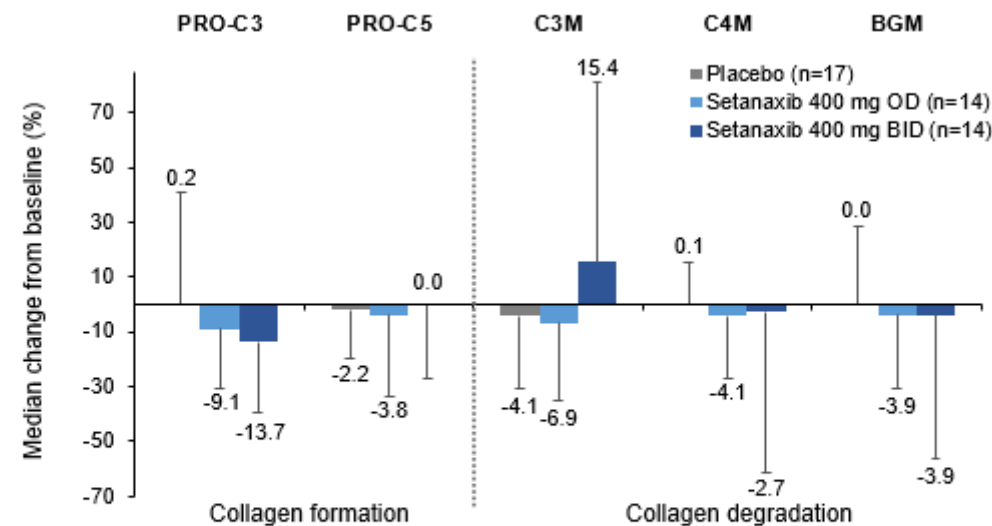


Median baseline collagen fragment serum levels (ng/ml)

	PRO-C3	PRO-C5	C3M	C4M	BGM
Placebo	12.4	970.8	14.6	51.8	15.9
Setanaxib 400 mg OD	17.5	1270.8	16.6	57.5	18.8
Setanaxib 400 mg BID	13.7	1025.3	13.7	44.9	14.4

The basement membrane marker C4M is mostly decrease in low LSM (<9.6 kPa)

B) Baseline liver stiffness  $\geq 9.6$  kPa

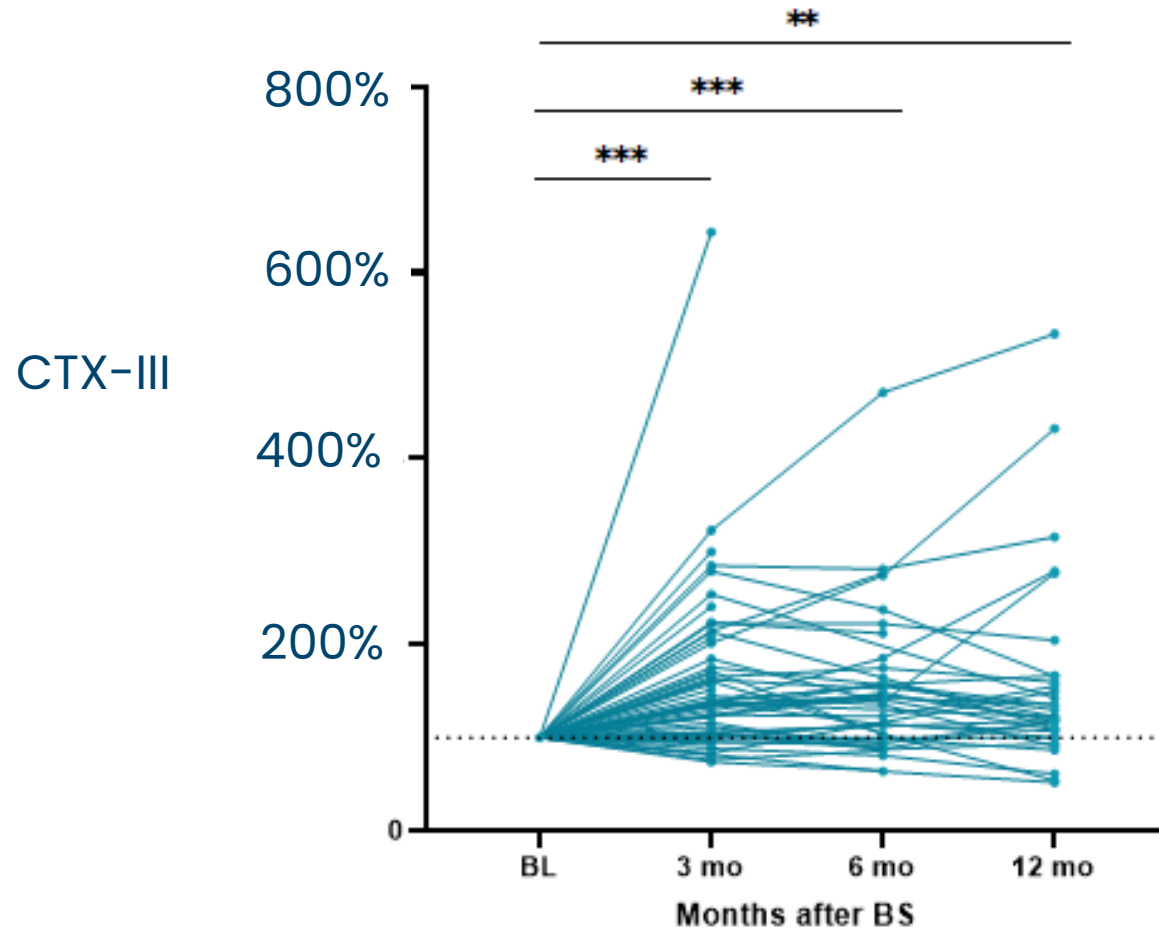


Median baseline collagen fragment serum levels (ng/ml)

	PRO-C3	PRO-C5	C3M	C4M	BGM
Placebo	20.1	819.4	17.2	47.8	14.2
Setanaxib 400 mg OD	23.7	1144.5	18.6	58.5	17.5
Setanaxib 400 mg BID	21.1	1252.2	15.8	54.0	19.6

# Induction of fibrolysis in bariatric surgery patients

## Weight loss induced fibrosis resolution in NAFLD

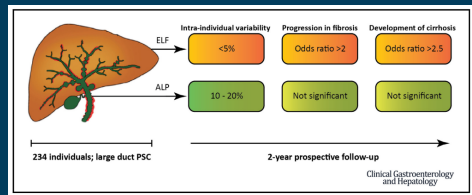


POSTER ID SAT-507 EASL 2023  
*Lønsmann I et al*

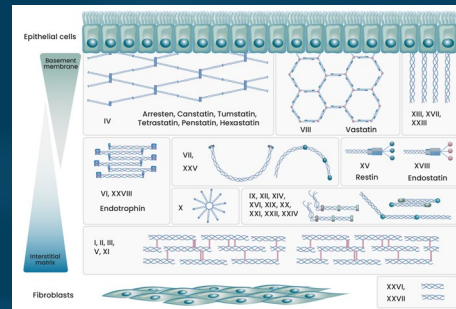


# Key Take Home Messages

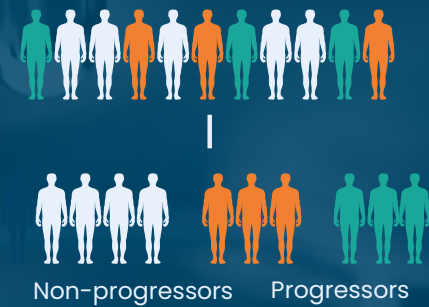
- ❖ ALP is not optimal as a marker in biliary disease due to variation



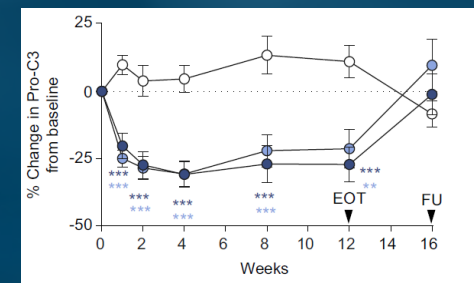
- ❖ ECM remodelling is important to understand in PSC



- ❖ Direct fibrosis NITs may be important for patient staging, and prognosis



- ❖ Markers of the ECM are modulated by potential anti-fibrotic therapies



## Nordic Bioscience:

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Maja Strangeways  
Andressa Zawadzki  
**Alejandro Mayorca**  
Kathrine Engelbrekt

**Morten Karsdal**  
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- Rohit Loomba, Cyrielle Caussy, UCSD, UK
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- **Mette Vesterhus, Tom Karlsen, Johannes Hov, University of Oslo, Norway**



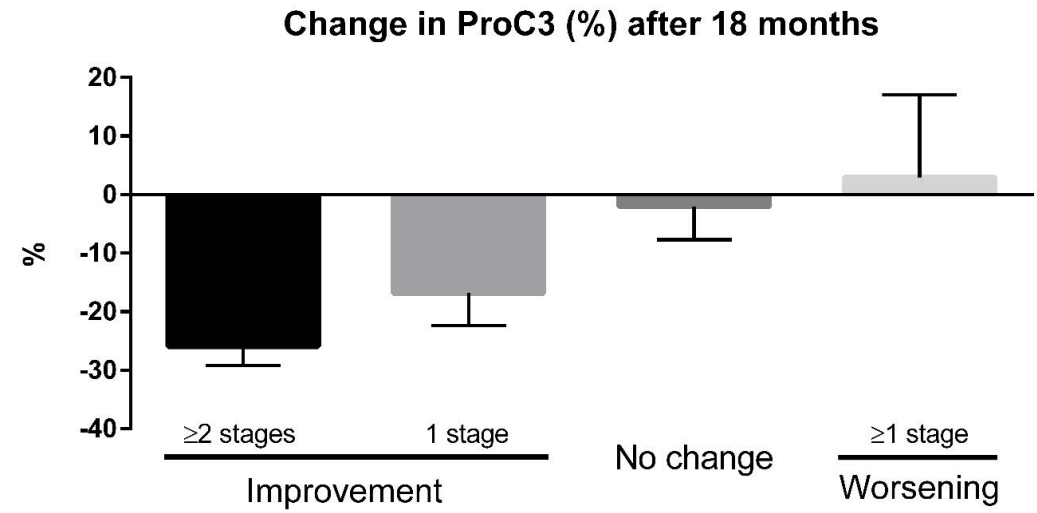
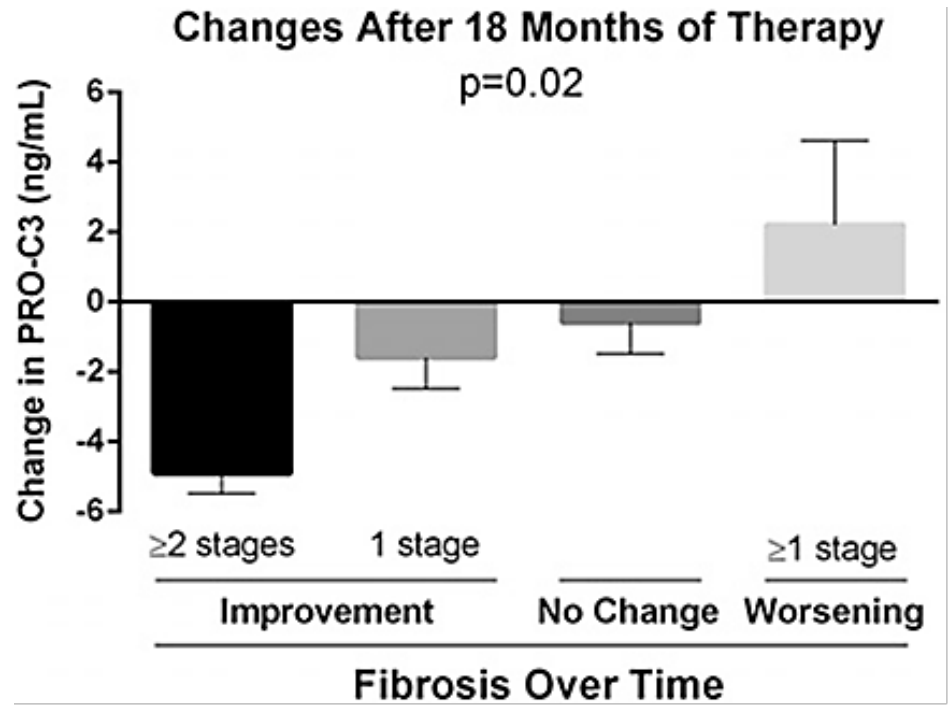
**Thank you**

- Back up slides





# Change in PRO-C3 was related to change in histological liver fibrosis stage



All patients were pooled regardless of therapy (pioglitazone and/or Vitamin E)

Bril & Cusi et al Diabetes Care 2019