Masterclass 2023

The gut-liver axis in alcohol related liver disease

Mads Israelsen, MD, PhD

Twitter @IsraelsenMads

FLASH • LIVER RESEARCH CENTRE • ODENSE

OUH Odense University Hospital

GALAXY

MICROBLIVER

SDU University of Southern Denmark

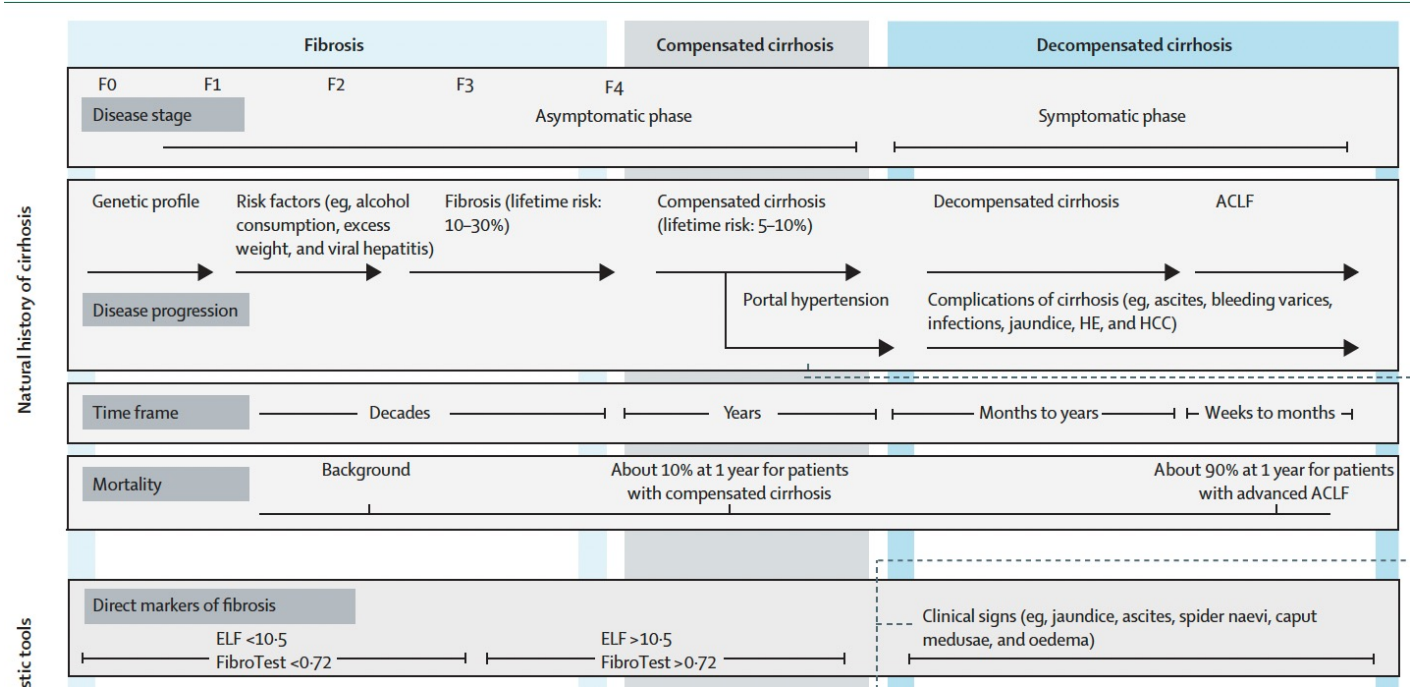
Denmark

Odense Liver Research Centre

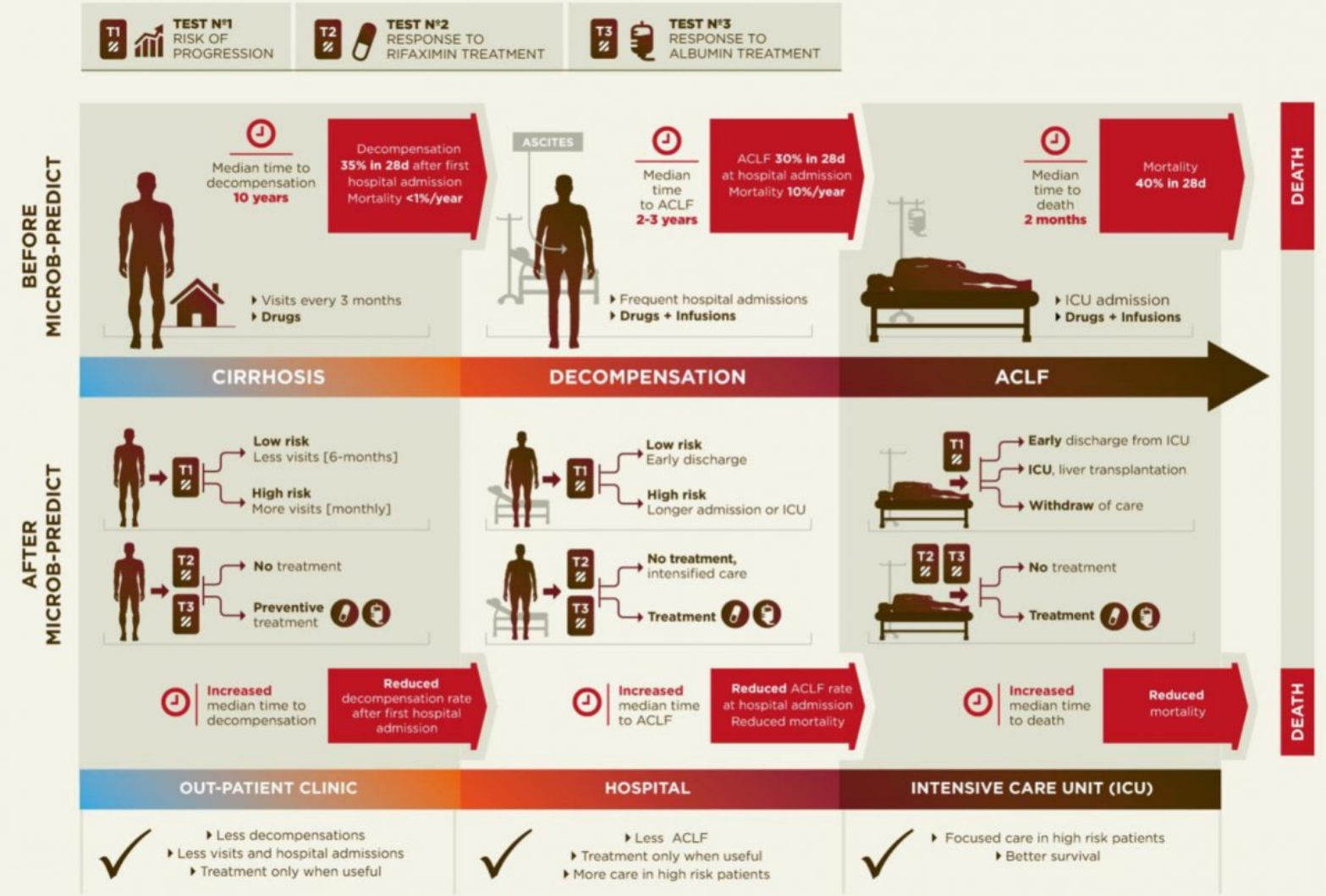
Agenda

- *Chronic liver disease and alcohol-related liver disease*
- *Gut-liver axis hypothesis*
- *Results from three intervention studies from GALAXY/MICROBLIVER*
- *Discussion*

White board

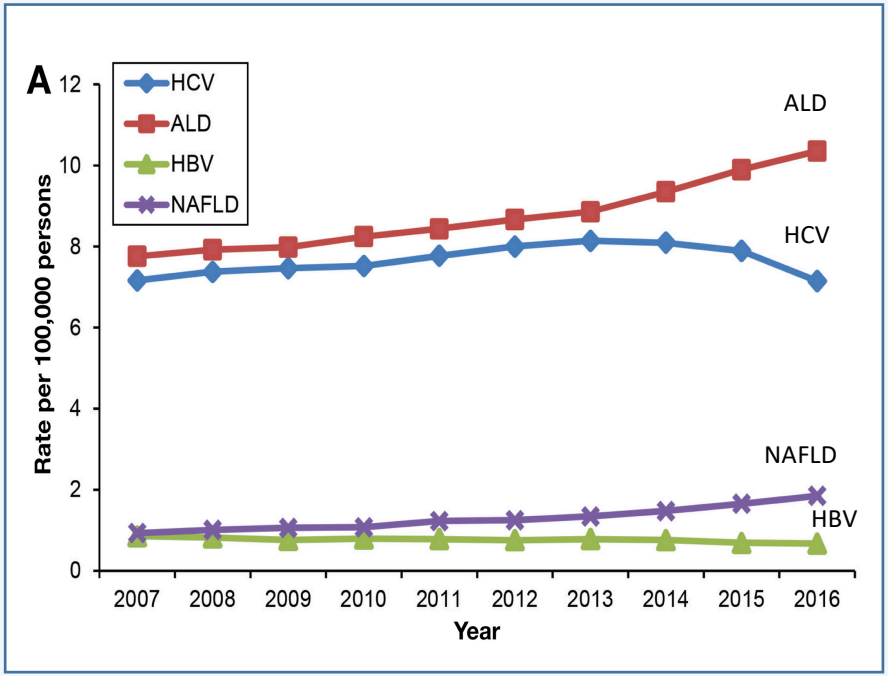


Gines 2021, Lancet


T1 TEST Nº1 RISK OF PROGRESSION
T2 TEST Nº2 RESPONSE TO RIFAXIMIN TREATMENT
T3 TEST Nº3 RESPONSE TO ALBUMIN TREATMENT
BEFORE MICROB-PREDICT
Median time to decompensation 10 years
Decompensation 35% in 28d after first hospital admission Mortality <1%/year
ASCITES
Median time to ACLF 2-3 years
ACLF 30% in 28d at hospital admission Mortality 10%/year
Median time to death 2 months
Mortality 40% in 28d
DEATH
Visits every 3 months
Drugs
Frequent hospital admissions
Drugs + Infusions
ICU admission
Drugs + Infusions
CIRRHOSIS
DECOMPENSATION
ACLF
AFTER MICROB-PREDICT
Low risk Less visits [6-months]
High risk More visits [monthly]
Low risk Early discharge
High risk Longer admission or ICU
Early discharge from ICU
ICU, liver transplantation
Withdraw of care
No treatment
Preventive treatment
No treatment, intensified care
Treatment
No treatment
Treatment
Increased median time to decompensation
Reduced decompensation rate after first hospital admission
Increased median time to ACLF
Reduced ACLF rate at hospital admission Reduced mortality
Increased median time to death
Reduced mortality
DEATH
OUT-PATIENT CLINIC
HOSPITAL
INTENSIVE CARE UNIT (ICU)
Less decompensations
Less visits and hospital admissions
Treatment only when useful
Less ACLF
Treatment only when useful
More care in high risk patients
Focused care in high risk patients
Better survival

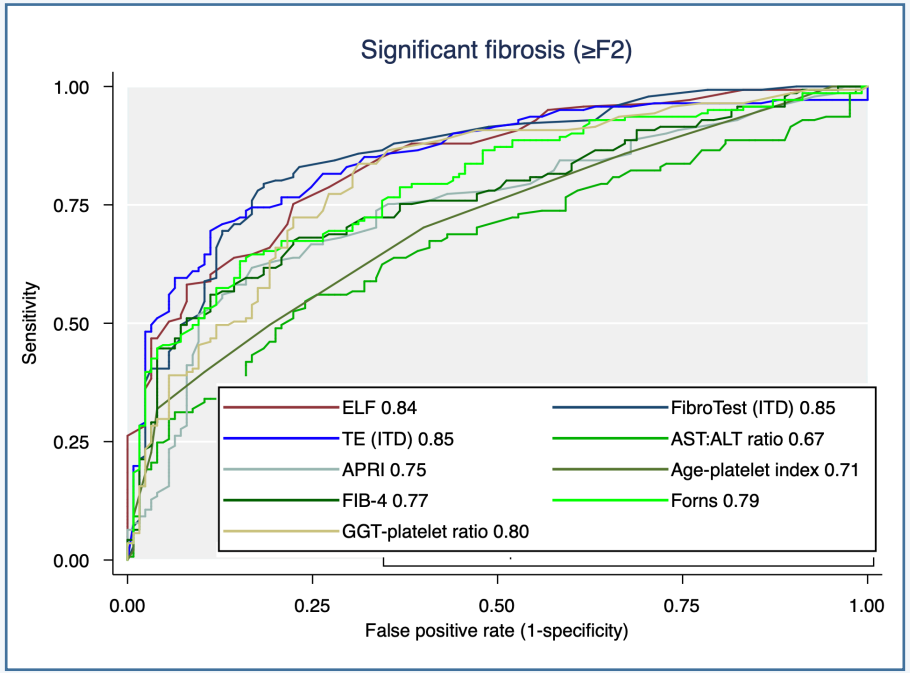
Alcohol-related liver disease (ALD)

Alcohol is a leading cause of liver-related **death** and **hepatic decompensation**



Kim 2018, Gastroenterology

Non-invasive tests have enabled **early detection** of liver **fibrosis**



Thiele 2018, Gastroenterology

nature medicine

ARTICLES

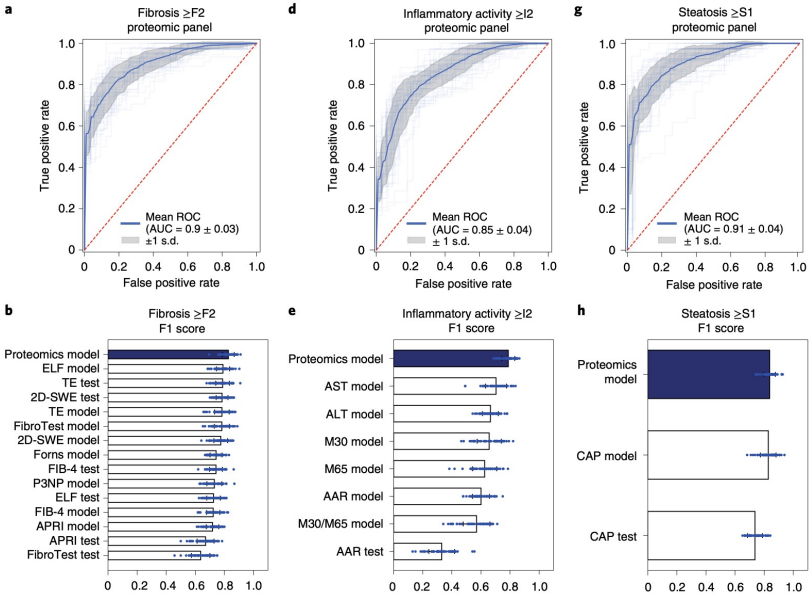
https://doi.org/10.1038/s41591-022-01850-y

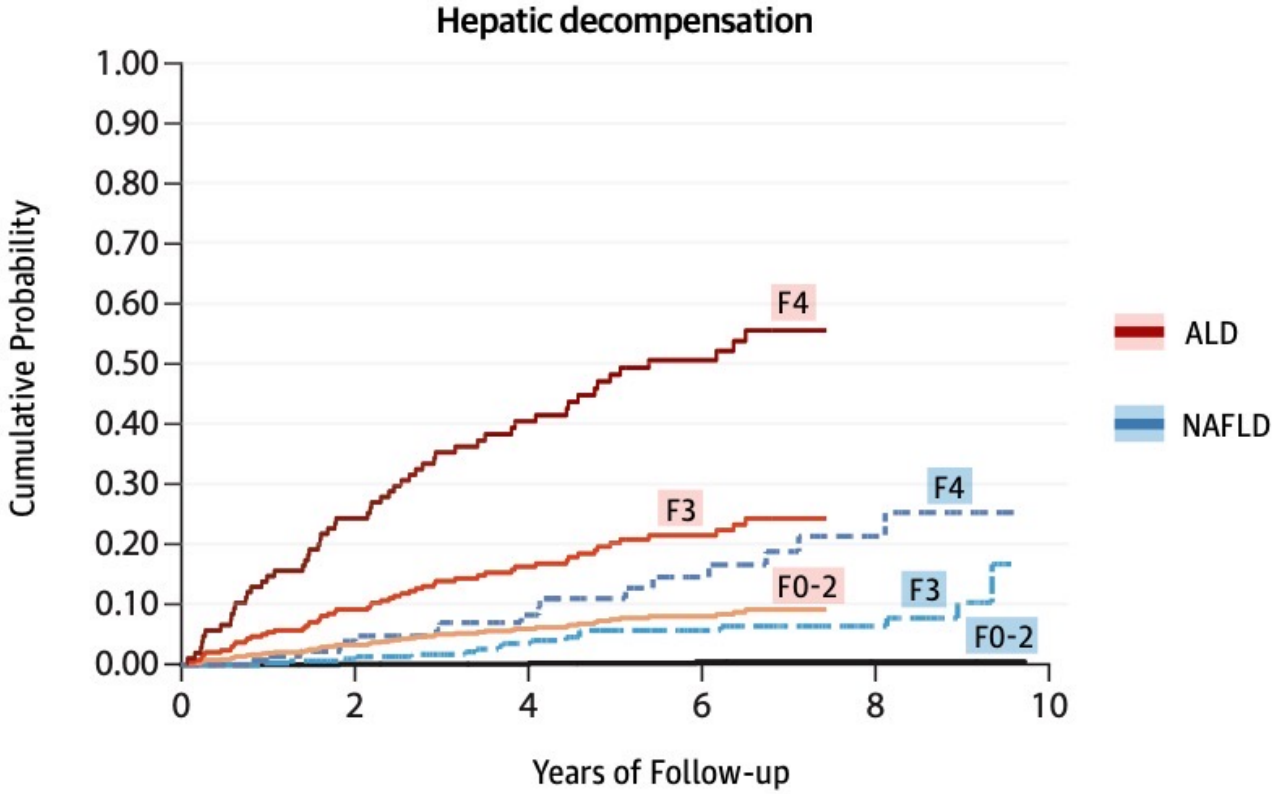
Check for updates

OPEN

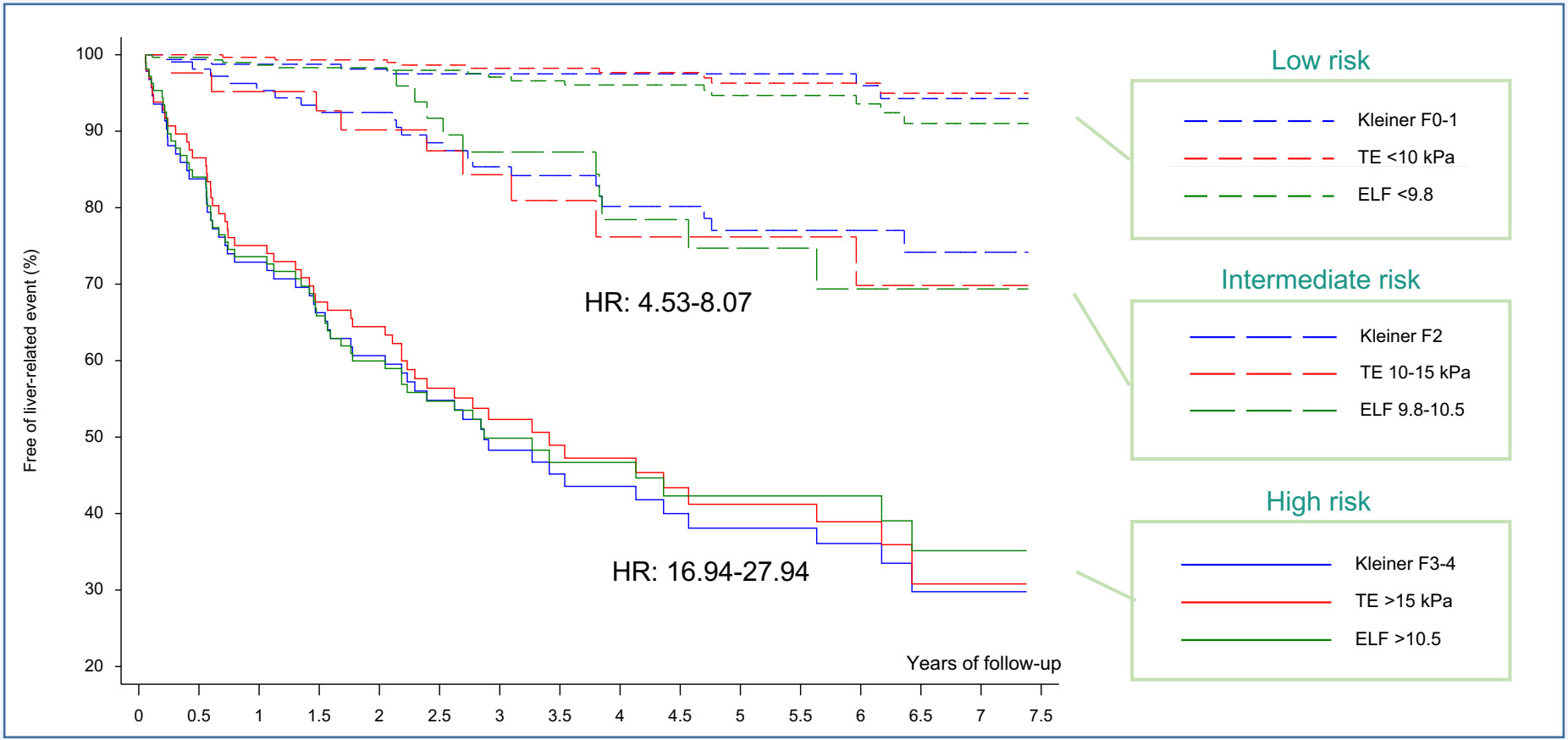
Noninvasive proteomic biomarkers for alcohol-related liver disease

Lili Niu[1,2], Maja Thiele[3,4], Philipp E. Geyer[2,5], Ditlev Nytoft Rasmussen[3], Henry Emanuel Webel[1], Alberto Santos[1,8], Rajat Gupta[1,9], Florian Meier[2,6], Maximilian Strauss[1,2], Maria Kjaergaard[3], Katrine Lindvig[3], Suganya Jacobsen[3], Simon Rasmussen[1], Torben Hansen[7], Aleksander Krag[3] and Matthias Mann[1,2] ✉



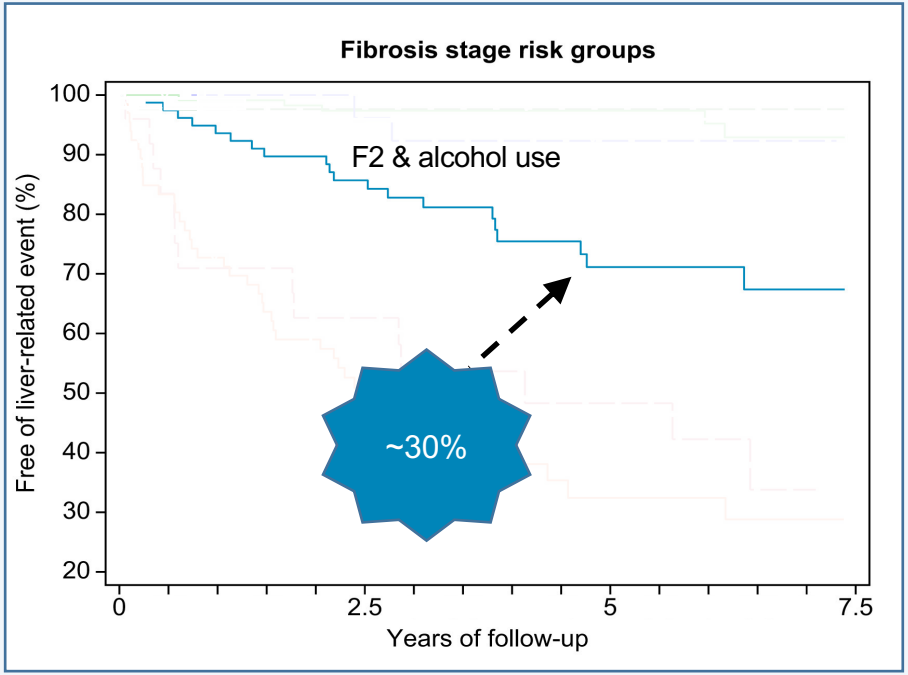


Combined data from Sanyal 2021, NEJM & Rasmussen 2021, J Hep



Rasmussen 2021, J Hep

High risk of hepatic decompensation in **moderate fibrosis (F2)**



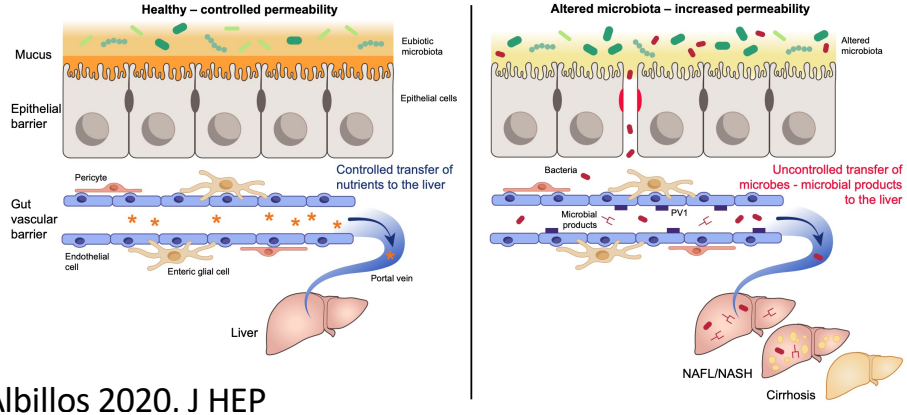
Rasmussen 2021, J Hep

Alcohol **abstinence** is **hard to achieve** and **relapse** is common*

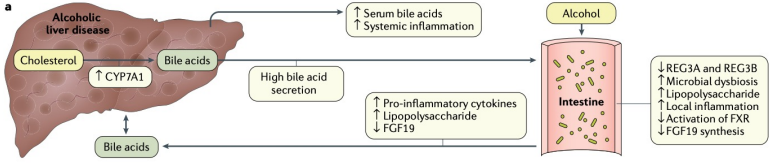
**Moos 2006, Addiction*

The gut-liver axis

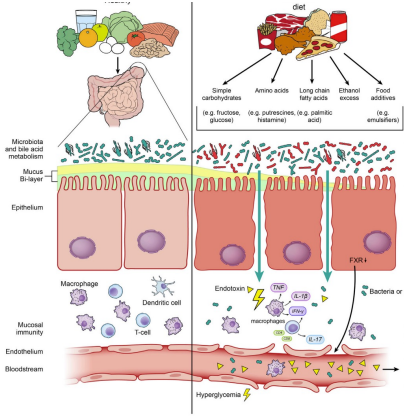
- a target for therapy?



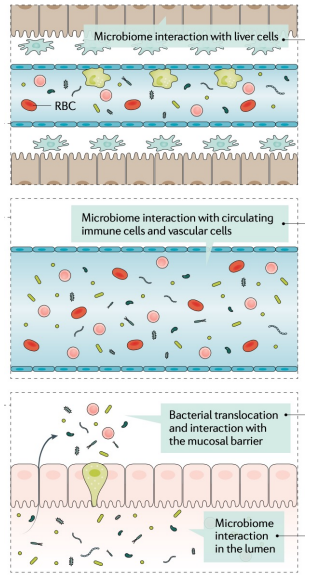
Albillos 2020. J HEP



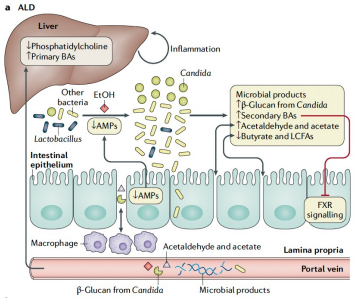
Bajaj 2019, Nature Rev



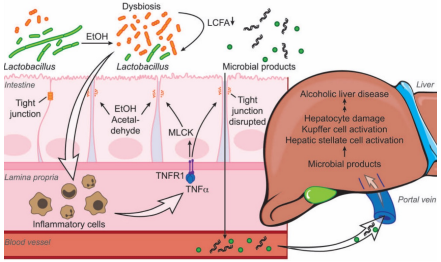
TIlg 2022, Cell Metab



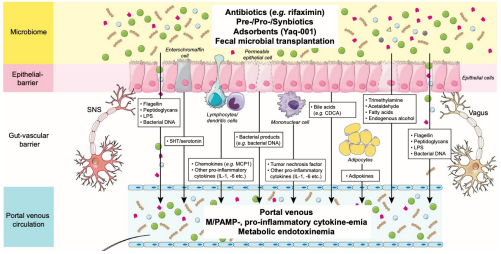
Trebicka 2021, Nature Rev



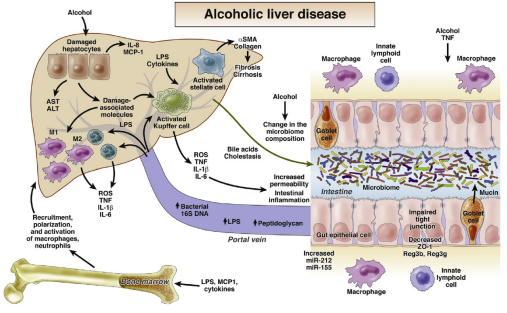
Tripathi 2018, Nature Rev



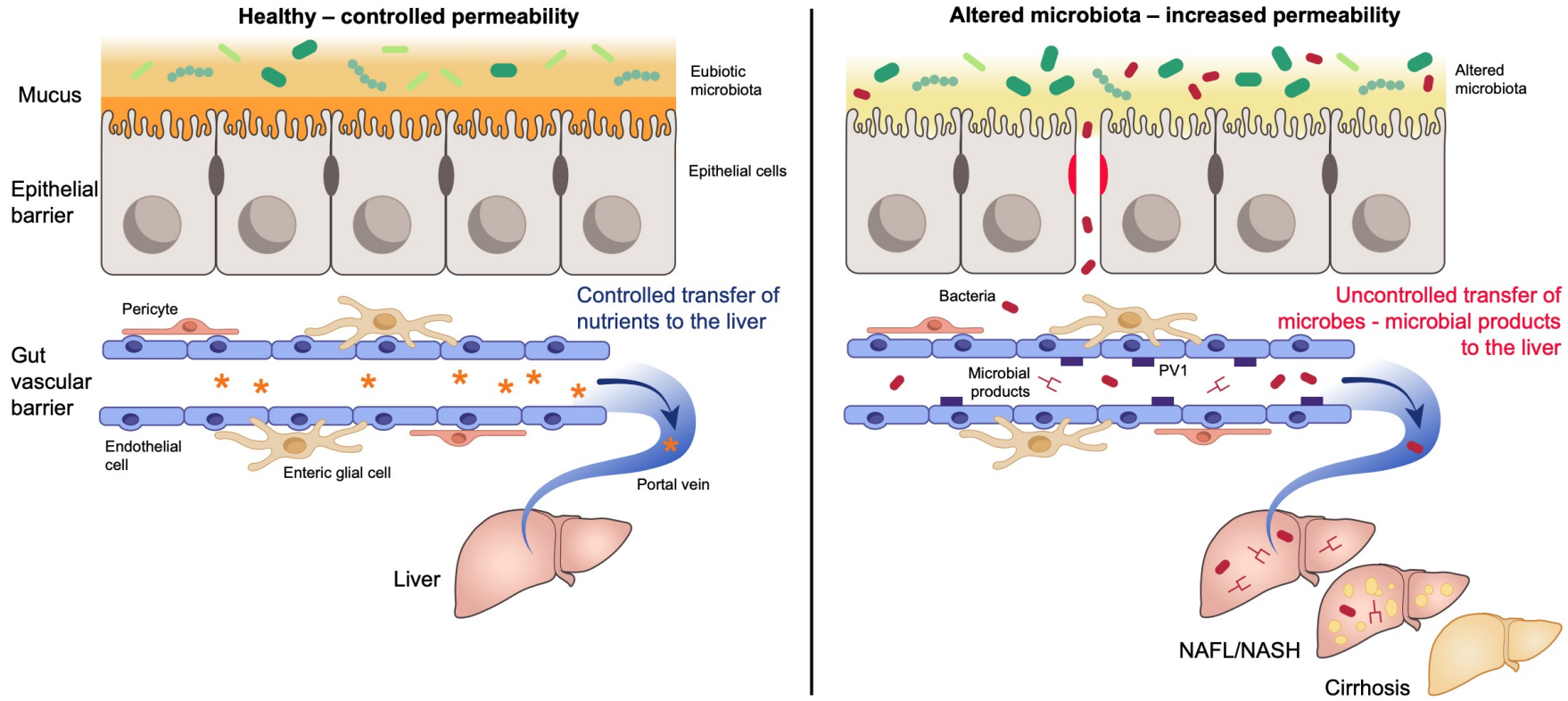
Hartmann 2016, ACER



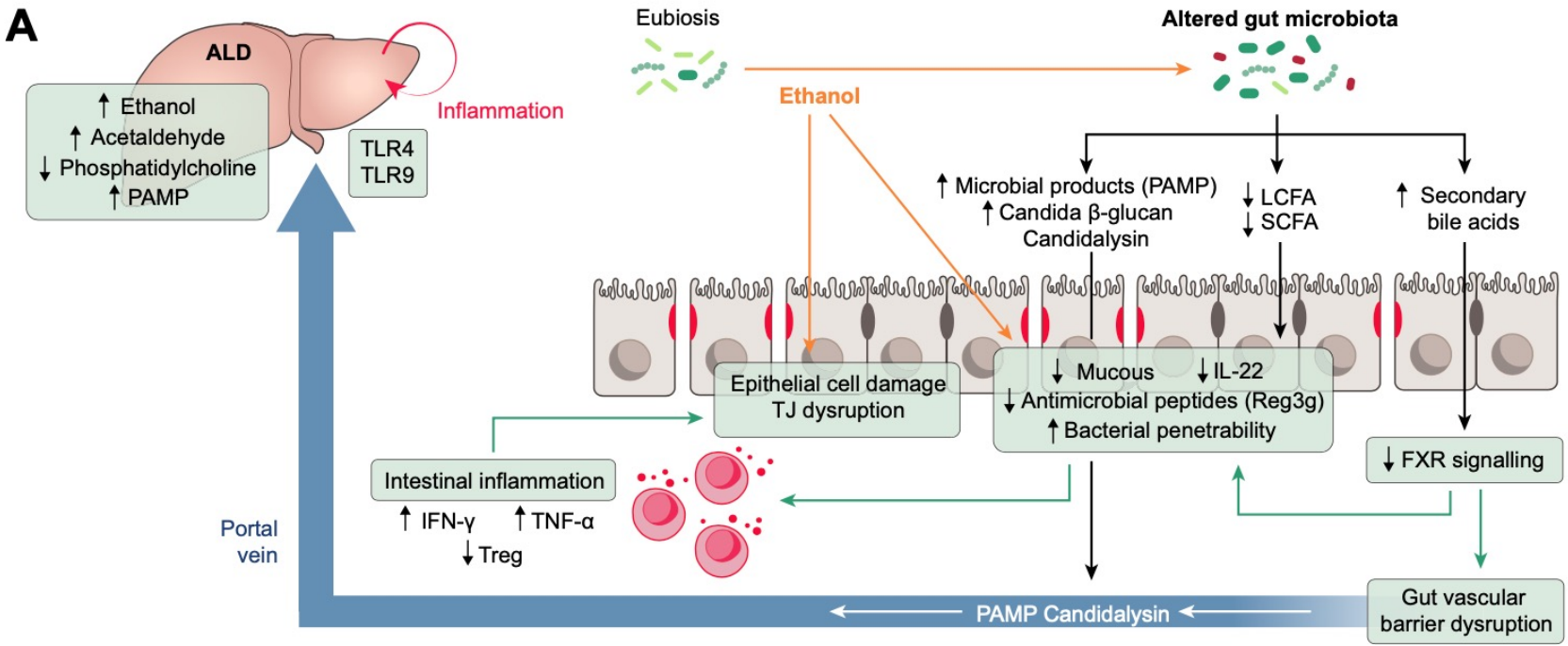
Wiest 2017, J HEP



Szabo 2015, Gastro

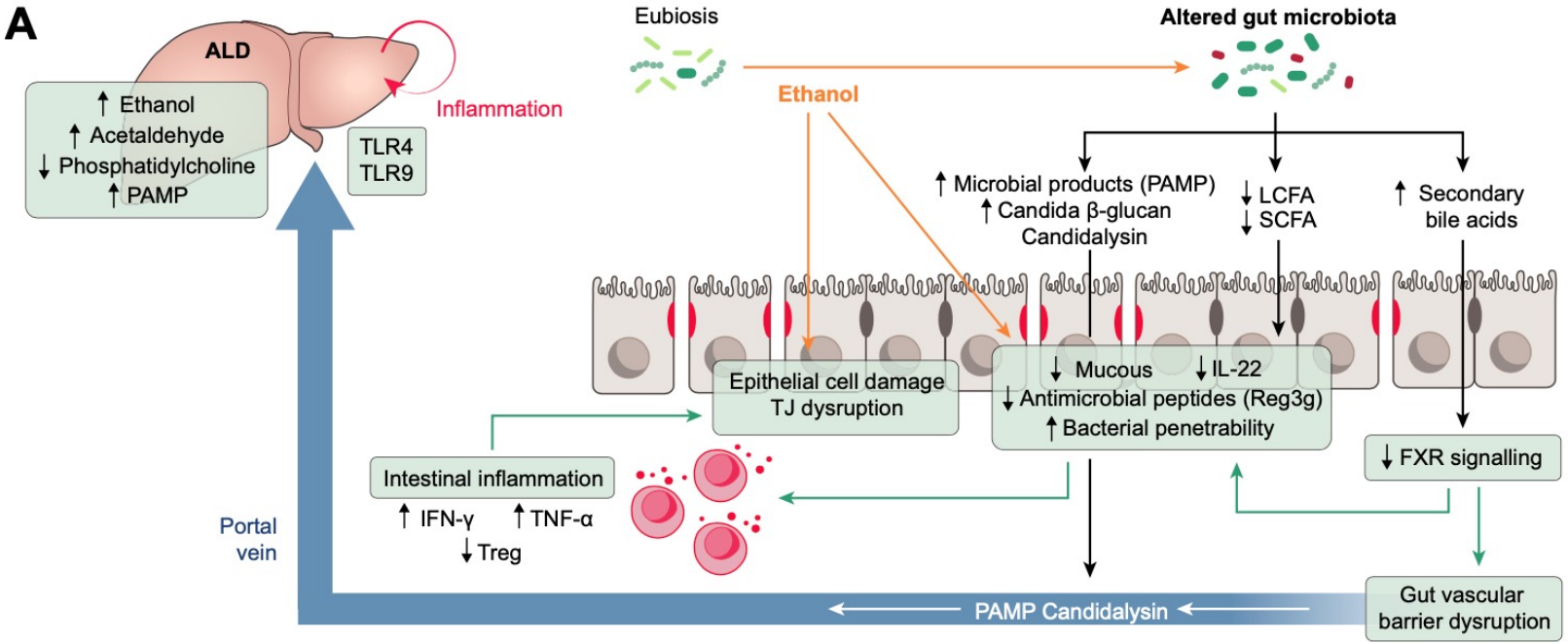


Albillos 2020, J Hep



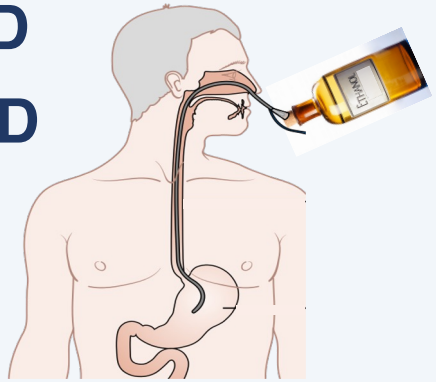
Albillos 2020, J Hep

AlcoChallenge - Ethanol	GALA-RIF - Rifaximin	Referm® study - Postbiotic



AlcoChallenge

IMPACT OF BINGE DRINKING ON GUT AND CIRCULATING MICROBIOME IN EARLY ALD



Mads Israelsen, Camila Alvarez Silva, Bjørn Stæhr Madsen, Stine Johansen, Camilla Dalby Hansen, Nikolaj Christian Torp, Johanne Kragh Hansen, Helene Bæk Juel, Thorsten Brach, Katrine Lindvig, Jean-Louis Insonere, Virginie Riviere, Benjamin Lelouvier, Lars Juhl Jensen, Torben Hansen, Manimozhiyan Arumugam, Aleksander Krag, on behalf of the MicrobLiver consortium

Novo Nordisk Foundation CENTER FOR BASIC METABOLIC RESEARCH

UNIVERSITY OF COPENHAGEN

FLASH • LIVER RESEARCH CENTRE • ODENSE

MicrobLiver

VAIOMER PIONEER IN TISSUE MICROBIOMES

Gut permeability in the spectrum of ALD

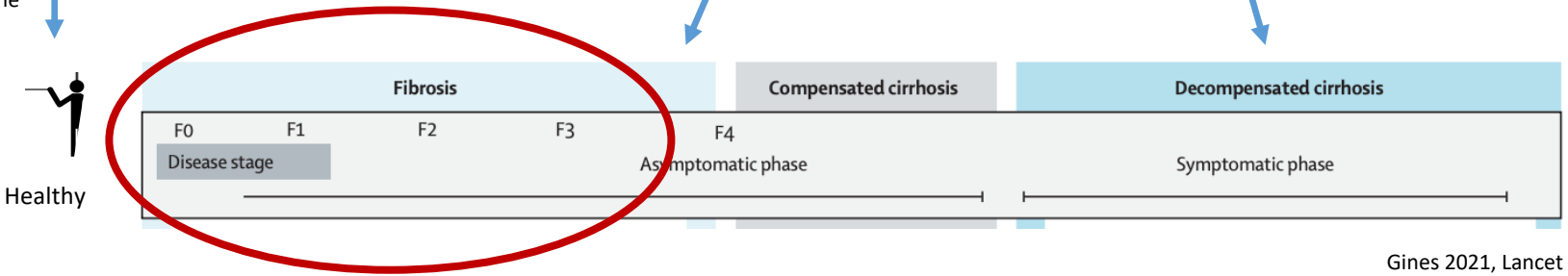
Controlled gut permeability
Minimal effect of alcohol

De Jong 2015, Alcohol
Lanng 2020, Alcohol
Bala 2014 Plos One

Increased uncontrolled gut permeability

Parlesak 2001 J Hep

Keshavarzian 1999 AJG
Bajaj 2014 HEP



Gines 2021, Lancet

We aimed to study the effect of **acute alcohol** consumption on **gut leakiness** in **early stages** of **alcohol-related liver disease**

Design

Type:

Pathophysiological intervention study

Groups: 3

Group A (ALD)
N = 14

Group B (NAFLD)
N = 14

Group C (Healthy)
N = 8

Inclusion criteria

General inclusion criteria

- Age 30-75
- Informed consent

General exclusion criteria

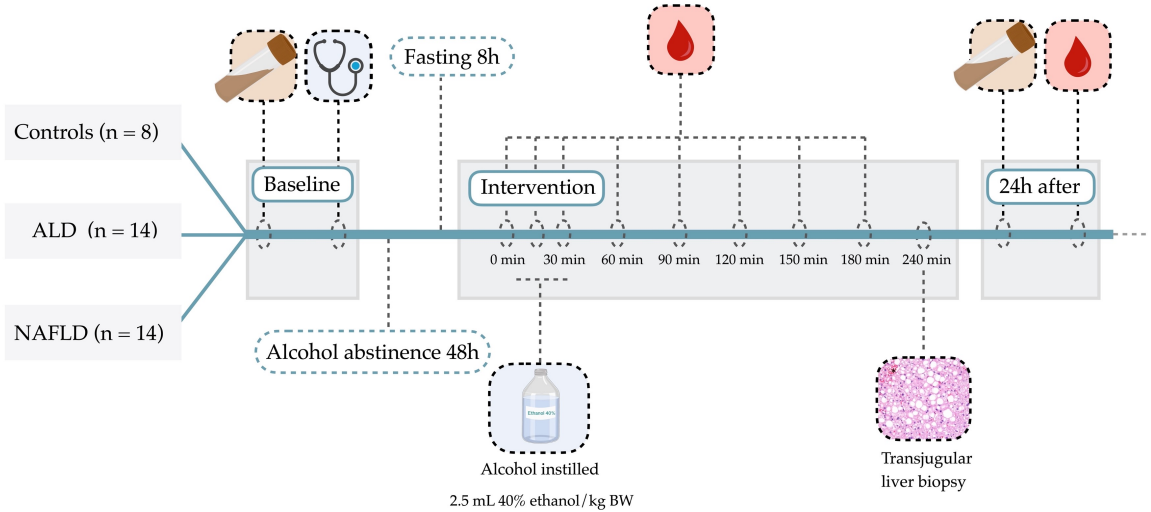
- Abstinence/desire of abstinence

- Biopsy verified ALD (F1-F3)
- Biopsy verified NAFLD (F1-F3)
- Daily alcohol intake < 24 g
- BMI < 30, No diabetes
- Liver stiffness < 6 kPa

Participant characteristics

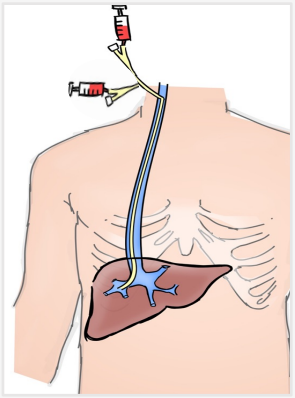
	 **ALD (F1-F3) N = 14**	 **NAFLD (F1-F3) N = 14**	 **Healthy (F0) N = 8**
Age, years	54.7 (±2.7)	52.9 (±3.1)	53.4 (±3.2)
Gender, Male/Female	12/2	7/7	4/4
Daily use of alcohol, g	60 (24-120)	0 (0-0)	6 (0-6)
BMI, kg/m^2	28.6 (±6.3)	35.3 (±7.0)	24.9 (±3.0)
Liver Stiffness by TE, kPa	9 (5.9-11)	10.4 (9.5-11.4)	4.55 (3.9-5)

Study design

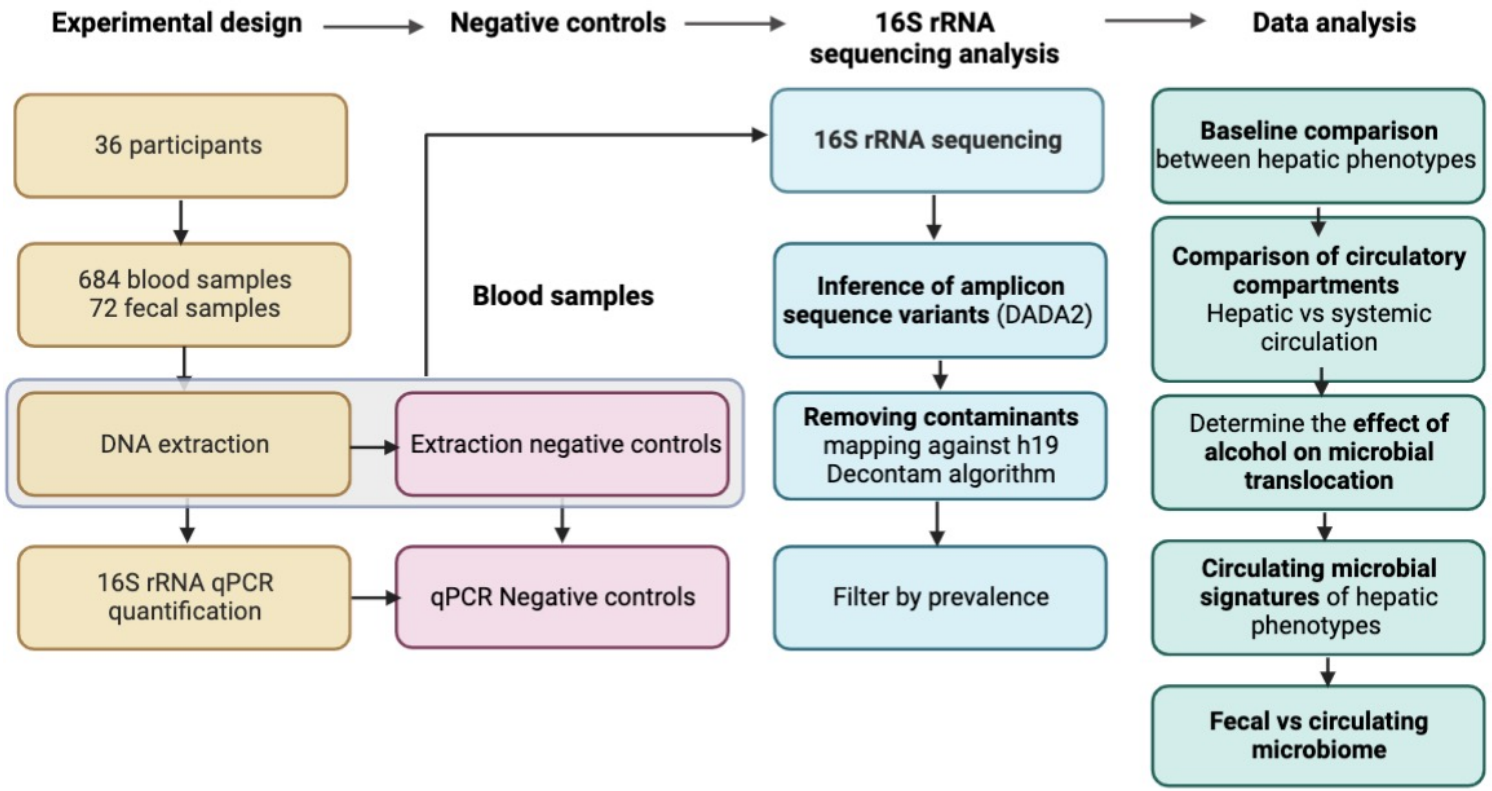


Simultaneously blood sampling from:

- Central vein catheter
- Hepatic vein catheter

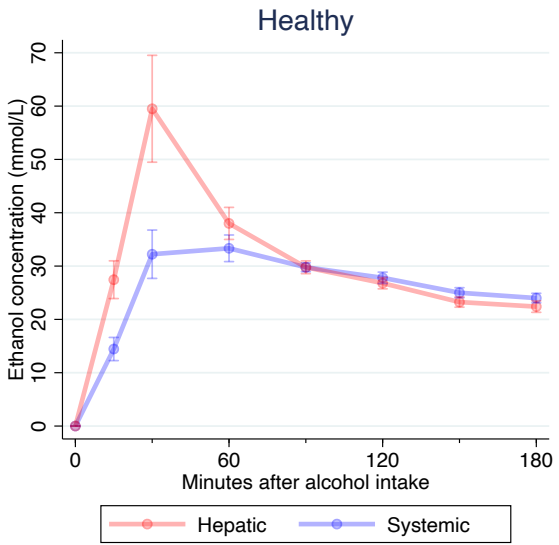


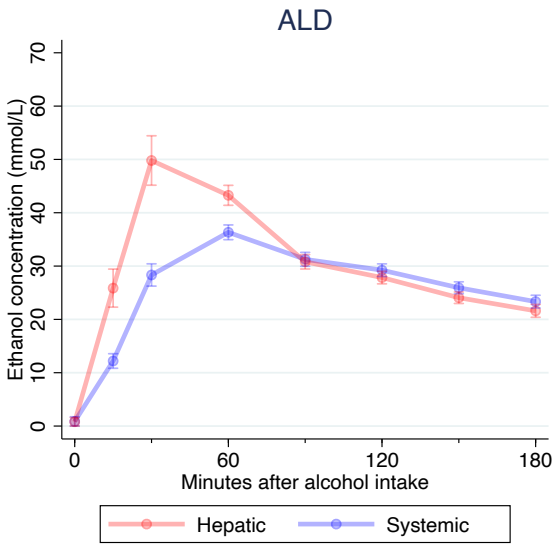
All samples were prepared according to SOPs for 16S sequencing

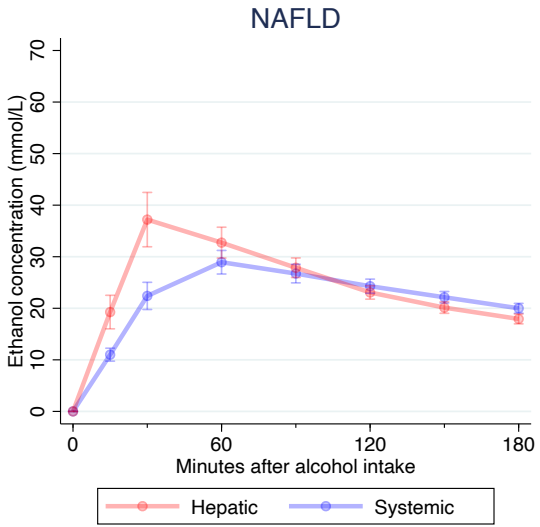

Experimental design
Negative controls
16S rRNA sequencing analysis
Data analysis
36 participants
684 blood samples
72 fecal samples
Blood samples
DNA extraction
Extraction negative controls
16S rRNA qPCR quantification
qPCR Negative controls
16S rRNA sequencing
Inference of amplicon sequence variants (DADA2)
Removing contaminants mapping against h19 Decontam algorithm
Filter by prevalence
Baseline comparison between hepatic phenotypes
Comparison of circulatory compartments Hepatic vs systemic circulation
Determine the effect of alcohol on microbial translocation
Circulating microbial signatures of hepatic phenotypes
Fecal vs circulating microbiome

Results

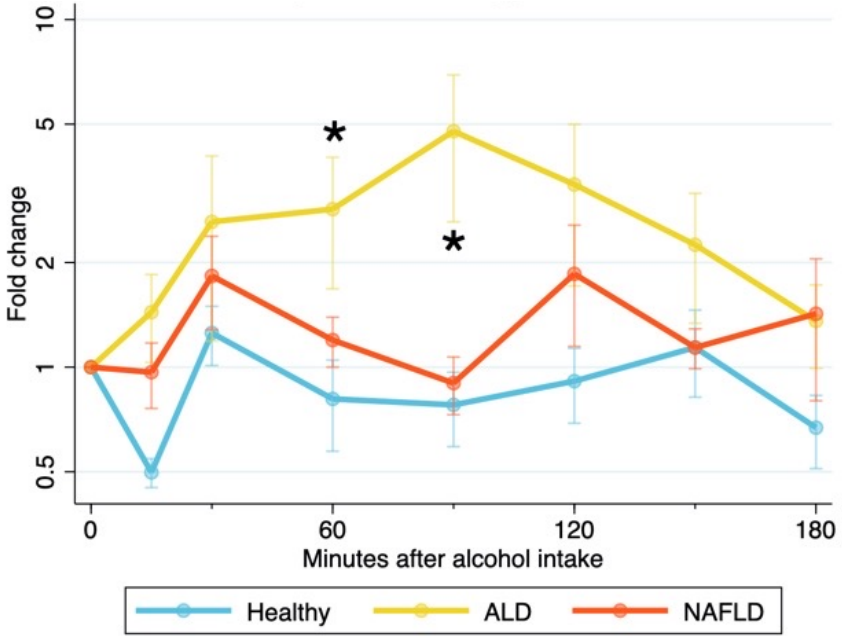
Alcohol concentration over time



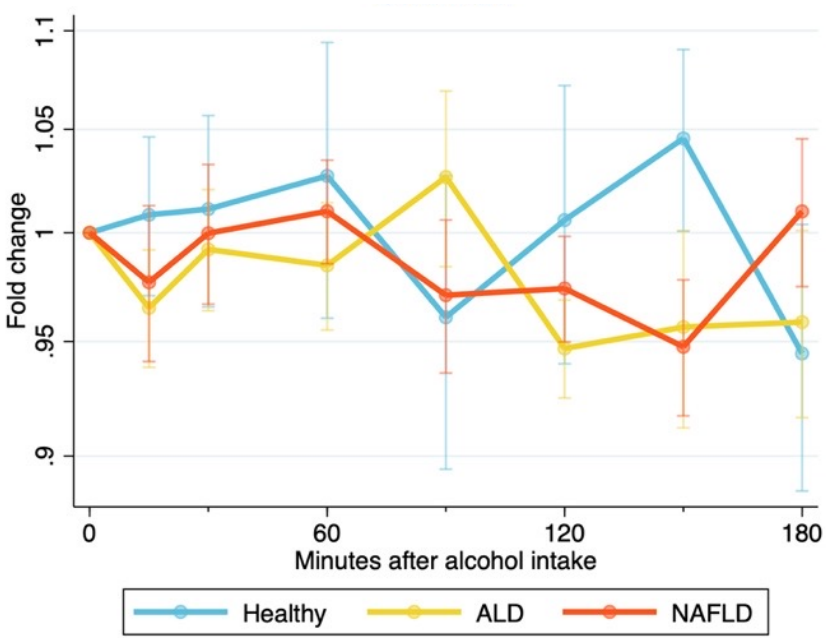




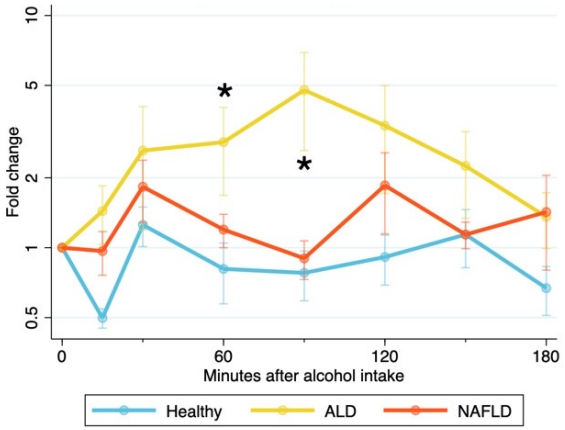
Circulating microbial DNA quantity (16S qPCR)



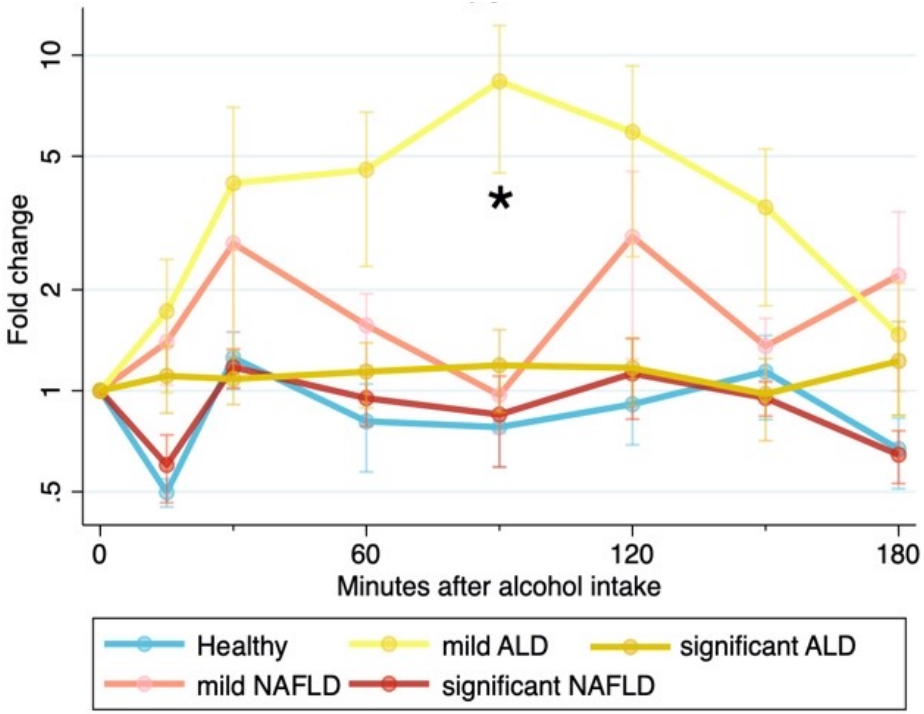
Diversity (Shannon)



Circulating microbial DNA quantity (16S qPCR)



Mild = F0-F1
Significant = F2-F4



Research in context

Limitations

- Small sample size
- Two days abstinence

Normal gut permeability
Minimal effect of alcohol

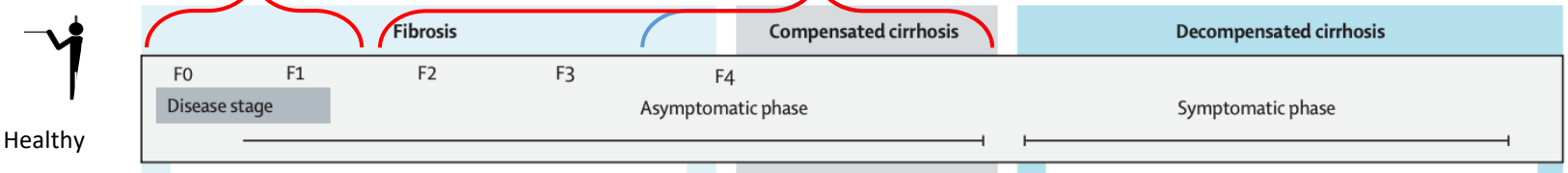
Alcohol induces increased gut permeability

Gut permeability permanently increased

De Jong 2015, Alcohol
Lanng 2020, Alcohol
Bala 2014 Plos One

Parlesak 2001 J Hep

Keshavarzian 1999 AJG
Bajaj 2014 HEP



Gines 2021, Lancet

The GALA-RIF study

A randomised double-blind, placebo-controlled trial of rifaximin-α in alcohol-related liver disease

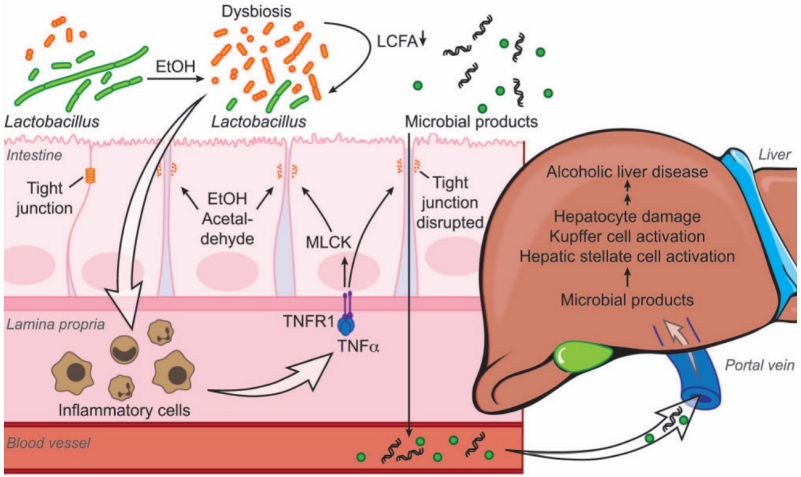
Mads Israelsen, MD, PhD
Twitter @IsraelsenMads

Mads Israelsen, Bjørn Stæhr Madsen, Nikolaj Torp, Stine Johansen, Camilla Dalby Hansen, Sönke Detlefsen, Peter Andersen, Johanne Kragh Hansen, Katrine Prier Lindvig, Ditlev Nytoft Rasmussen, Katrine Thorhauge, Maria Kjærgaard, Torben Hansen, Manimozhiyan Arumugam, Jonel Trebicka, Maja Thiele, Aleksander Krag
The GALAXY and MicrobLiver consortia

Gut dysbiosis and **impaired barrier function** are driving **progression** of ALD

Rifaximin-α prevents **HE**

The gut-liver axis



Hartman 2016, Alcohol Clin Exp Res
Szabo 2015, Gastroenterology

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 25, 2010 VOL. 362 NO. 12

Rifaximin Treatment in Hepatic Encephalopathy

ABSTRACT

BACKGROUND

Hepatic encephalopathy is a chronically debilitating complication of hepatic cirrhosis. The efficacy of rifaximin, a minimally absorbed antibiotic, is well documented in the treatment of acute hepatic encephalopathy, but its efficacy for prevention of the disease has not been established.

METHODS

In this randomized, double-blind, placebo-controlled trial, we randomly assigned 299 patients who were in remission from recurrent hepatic encephalopathy resulting from chronic liver disease to receive either rifaximin, at a dose of 550 mg twice daily (140 patients), or placebo (159 patients) for 6 months. The primary efficacy end point was the time to the first breakthrough episode of hepatic encephalopathy. The key secondary end point was the time to the first hospitalization involving hepatic encephalopathy.

RESULTS

Rifaximin significantly reduced the risk of an episode of hepatic encephalopathy, as compared with placebo, over a 6-month period (hazard ratio with rifaximin, 0.42; 95% confidence interval [CI], 0.28 to 0.64; P<0.001). A breakthrough episode of hepatic encephalopathy occurred in 22.1% of patients in the rifaximin groups, as compared with 45.9% of patients in the placebo group. A total of 15.0% of the patients in the rifaximin group had a hospitalization involving hepatic encephalopathy, as compared with 22.6% of patients in the placebo group, for a hazard ratio of 0.50 (95% CI, 0.29 to 0.87; P=0.01). More than 90% of patients received concomitant lactulose therapy. The incidence of adverse events reported during the study was similar in the two groups, as was the incidence of serious adverse events.

CONCLUSIONS

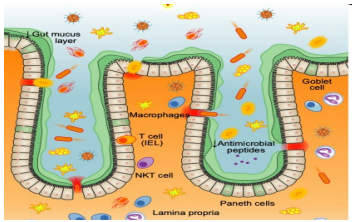
Over a 6-month period, treatment with rifaximin maintained remission from hepatic encephalopathy more effectively than did placebo. Rifaximin treatment also significantly reduced the risk of hospitalization involving hepatic encephalopathy. (ClinicalTrials.gov number, NCT00298038.)

N ENGL J MED 362;12 NEJM.ORG MARCH 25, 2010 1071

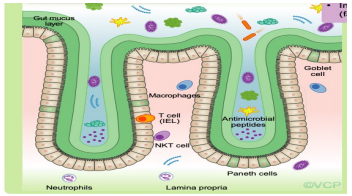
The New England Journal of Medicine
Downloaded from nejm.org on June 20, 2022. For personal use only. No other uses without permission.
Copyright © 2010 Massachusetts Medical Society. All rights reserved.

Bass 2010, NEJM

Before Rifaximin-α



After Rifaximin-α



Patel 2021, J Hep

We aimed to investigate the **efficacy** and **safety** of **rifaximin-α** on liver **fibrosis** in patients with **biopsy-confirmed ALD**

Methods

Design

Type
- Investigator-initiated
- Randomised (1:1)
- Double-blind
- Placebo-controlled

Stratification
- Fibrosis stage
- Abstinence

Patients

Inclusion criteria
- 18-75 years
- Biopsy-confirmed ALD

Main exclusion criteria
- Decompensated cirrhosis
- Coexistent liver disease
- Recent use of antibiotics (<4 weeks)

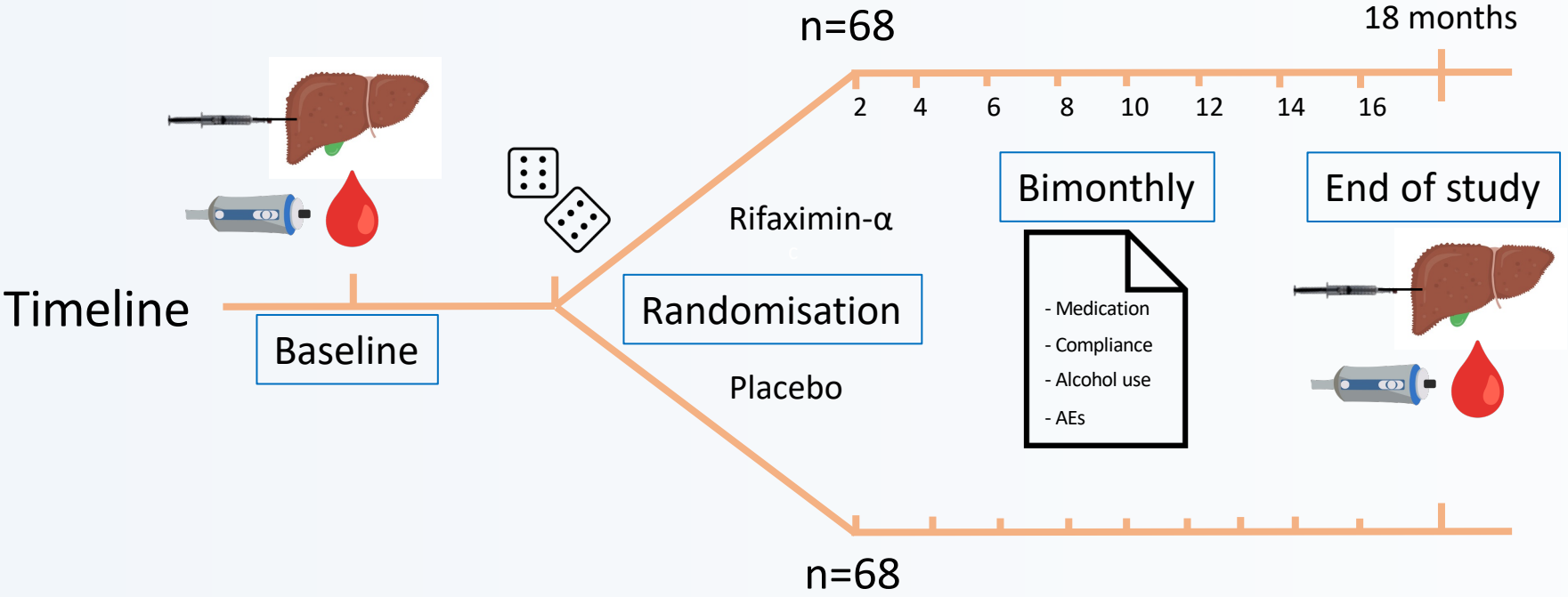
Intervention

18 months:

- Tablet rifaximin-α 550 mg twice daily

OR

- Tablet placebo twice daily


n=68
18 months
2
4
6
8
10
12
14
16
Timeline
Baseline
Randomisation
Rifaximin-α
Placebo
Bimonthly
- Medication
- Compliance
- Alcohol use
- AEs
End of study
n=68

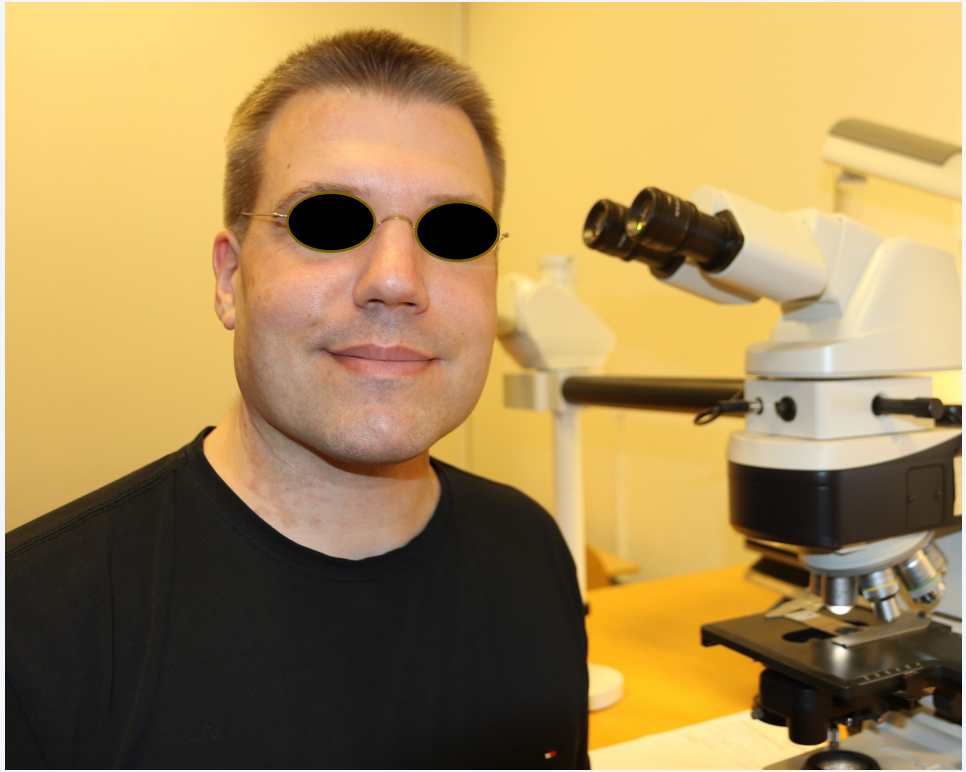
Outcome

Primary outcome

- Regression of fibrosis
  (decrease ≥1 fibrosis stage)

Secondary outcomes

- Progression of fibrosis
  (increase ≥1 fibrosis stage)
- Non-invasive tests
- Adverse events



Professor Sönke Detlefsen

Results

Study flow

March 2015 - November 2021

Drop-out rate = 21 %

Baseline characteristics

60 years (median)

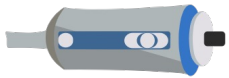
17%

83%

Abstinent at inclusion

Daily alcohol consumption of 51 g

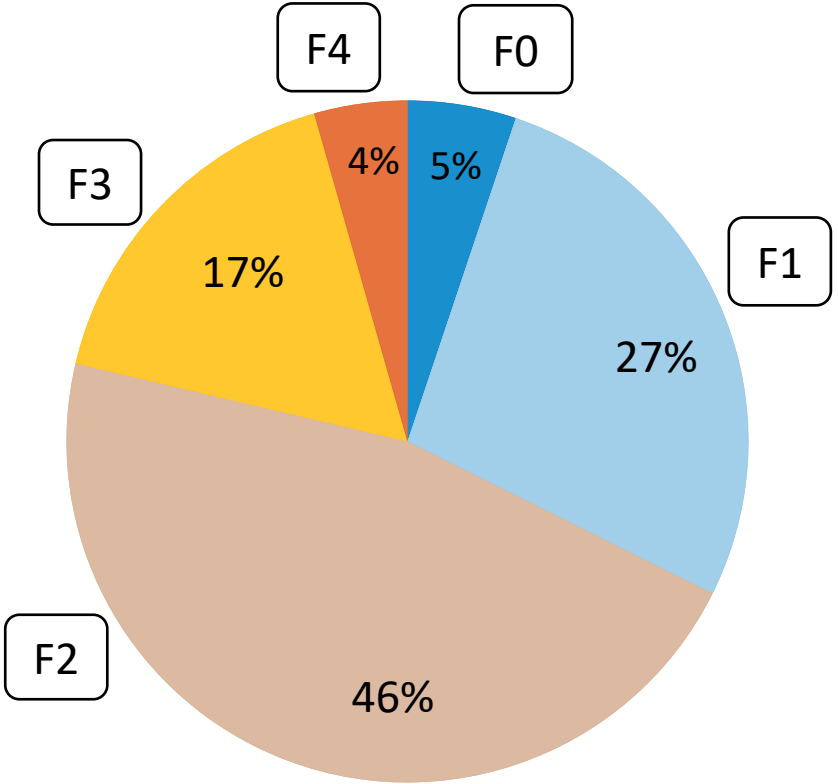
Fib-4 index = 1.7



Liver stiffness = 8.6 kPa

Routine liver tests	
GGT (U/L)	93 (41-237)
ALT (U/L)	38 (25-55)
Alkaline phosphatase (U/L)	79 (69-99)
Bilirubin (umol/L)	10 (7-14)
Platelet count (10^9/L)	224 (179-263)
INR	1 (0.9-1.2)
Albumin (g/L)	43 (41-45)
All summary data are medians (25%-75% percentile)	

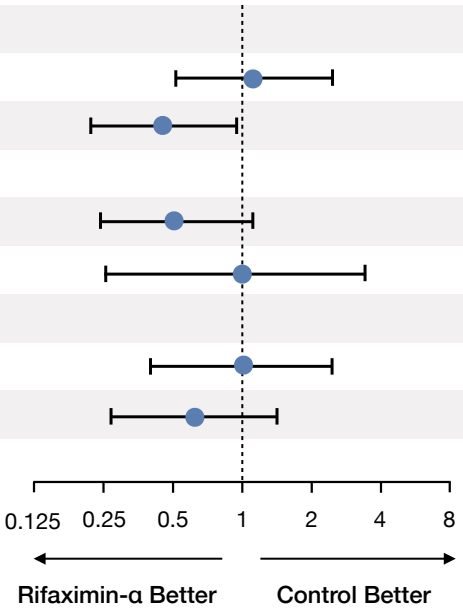
Baseline: Distribution of liver fibrosis



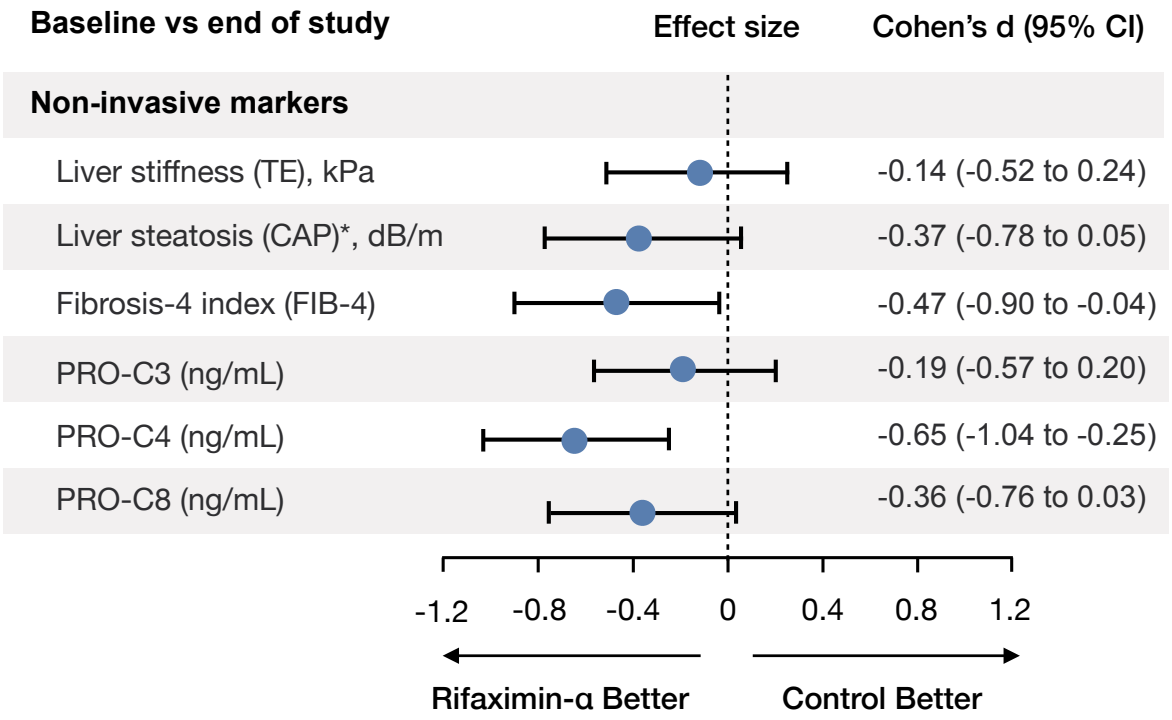
Efficacy of intervention

Histology

Endpoint	Rifaximin group	Control group	Odds Ratio (95% CI)
	no. of events/total no. (%)		
Fibrosis			
Regression vs no regression	14/54 (26)	15/54 (28)	1.10 (0.45-2.68)
Progression vs no progression	13/54 (24)	23/54 (43)	0.42 (0.18-0.98)
Inflammation			
Regression vs no regression	27/54 (50)	18/54 (33)	0.50 (0.22-1.11)
Progression vs no progression	5/54 (9)	5/54 (9)	1.00 (0.27-3.69)
Steatosis			
Regression vs no regression	11/54 (20)	11/54 (20)	1.02 (0.39-2.70)
Progression vs no progression	14/54 (26)	19/54 (35)	0.64 (0.28-1.47)



Non-invasive markers



Adverse events

	Rifaximin-α	Placebo
Adverse events	48 (71%)	53 (78%)
- Most common adverse event, GI-symptoms	26 (38%)	32 (47%)
Serious adverse events	15 (21%)	14 (21%)

No cases of infection with C. difficile or MDR bacteria

Limitations

- Single centre
- Unequal sex distribution

Strengths

- 18 months intervention
- NITs support the histological findings
- High compliance

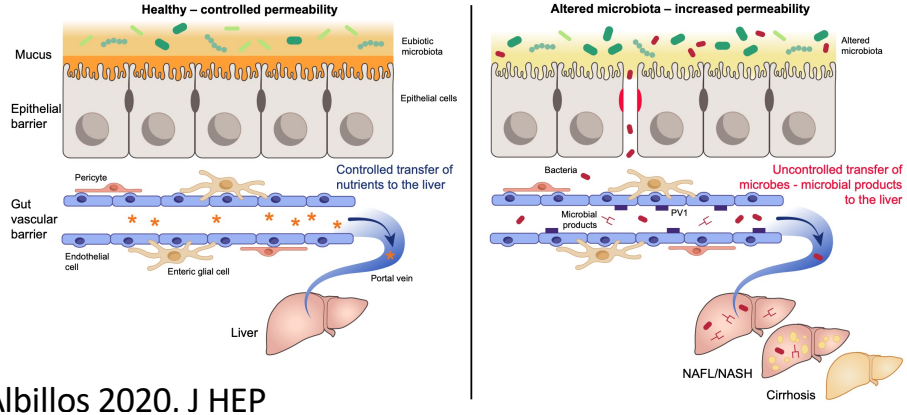
Conclusion

Rifaximin-α does not promote regression of liver fibrosis - but it seems to prevent progression of liver fibrosis

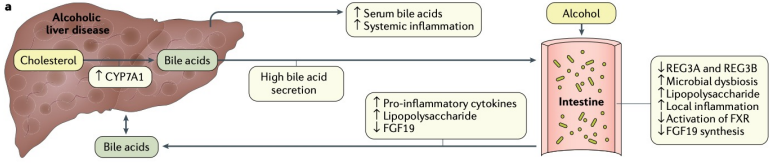
Rifaximin-α may be beneficial for patients with alcohol-related liver disease who cannot achieve alcohol abstinence

The gut-liver axis appears to be a modifiable target in early alcohol-related liver disease

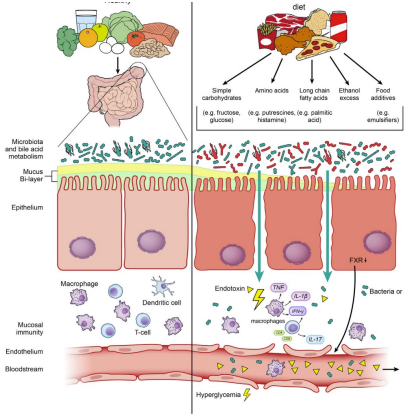
- Are therapies targeting the gut-liver axis the future treatment for ALD?



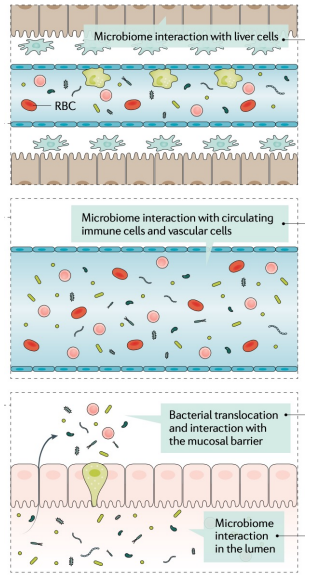
Albillos 2020. J HEP



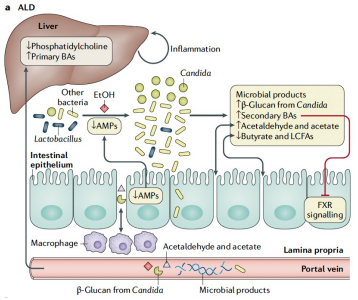
Bajaj 2019, Nature Rev



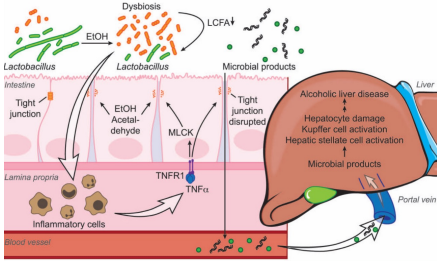
TIlg 2022, Cell Metab



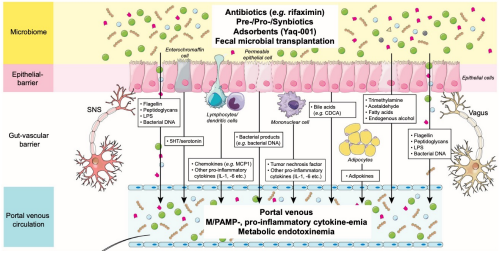
Trebicka 2021, Nature Rev



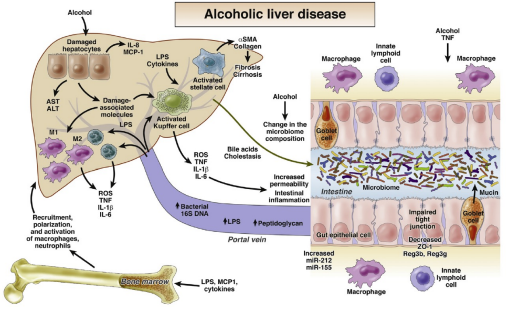
Tripathi 2018, Nature Rev



Hartmann 2016, ACER



Wiest 2017, J HEP



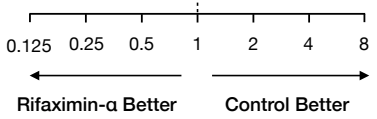
Szabo 2015, Gastro

Pros

- **Promising results**

Cons

Endpoint	Rifaximin group	Control group	Odds Ratio (95% CI)
	no. of events/total no. (%)		
Fibrosis			
Regression vs no regression	14/54 (26)	15/54 (28)	1.10 (0.45-2.68)
Progression vs no progression	13/54 (24)	23/54 (43)	0.42 (0.18-0.98)
Inflammation			
Regression vs no regression	27/54 (50)	18/54 (33)	0.50 (0.22-1.11)
Progression vs no progression	5/54 (9)	5/54 (9)	1.00 (0.27-3.69)
Steatosis			
Regression vs no regression	11/54 (20)	11/54 (20)	1.02 (0.39-2.70)
Progression vs no progression	14/54 (26)	19/54 (35)	0.64 (0.28-1.47)



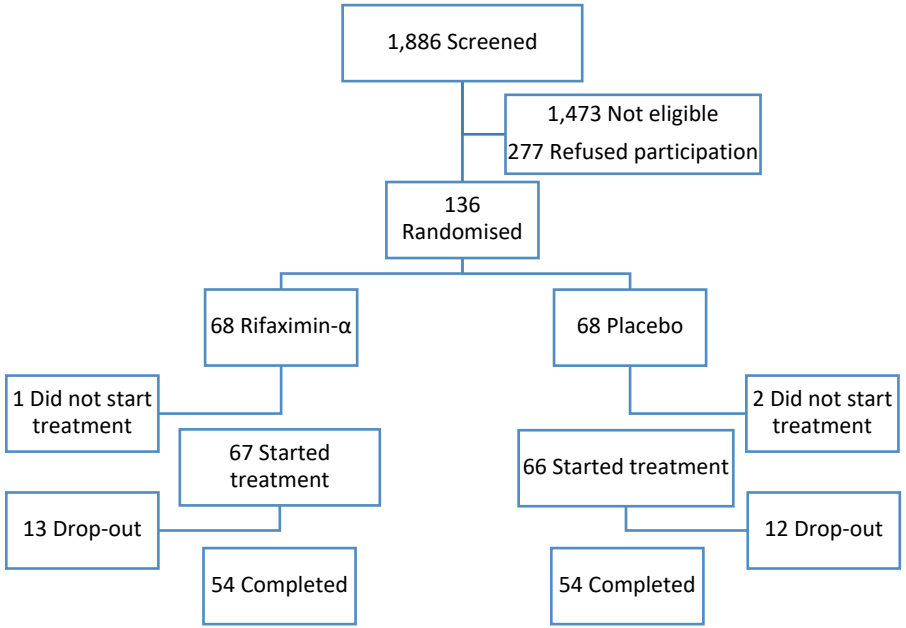
Pros

- Promising results
- **RCTs in ALD are feasible**

Cons

GALA-RIF study flow

March 2015 - November 2021

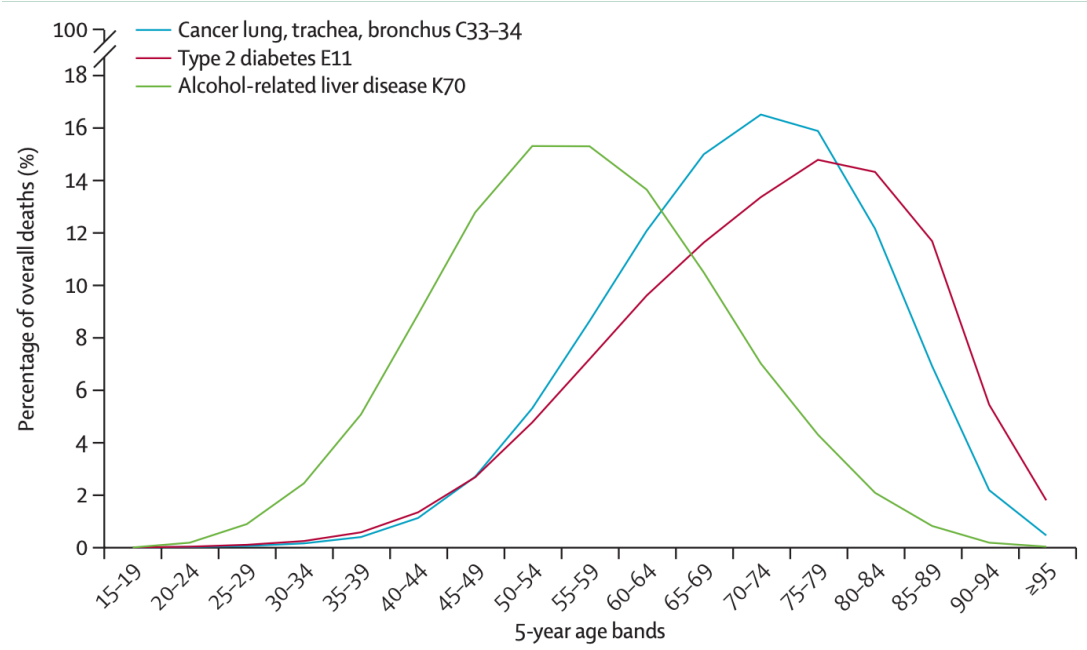


Drop-out rate = 21 %

Pros

- Promising results
- RCTs in ALD are feasible
- **Large disease burden**

Cons



Karlsen 2022, The Lancet

Pros

- Promising results
- RCTs in ALD are feasible
- Large disease burden
- **Blue ocean**

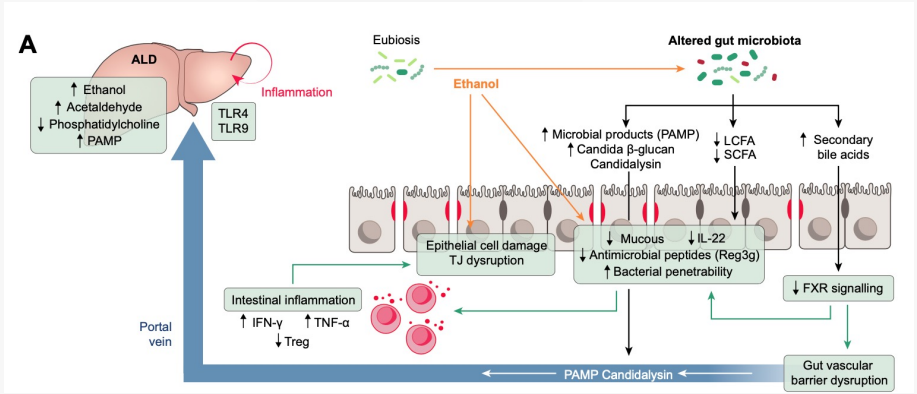
Cons

Pros

- Promising results
- RCTs in ALD are feasible
- Large disease burden
- Blue ocean

Cons

- **Unclear mode of action**

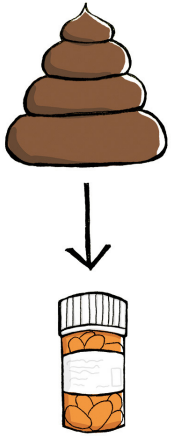


Pros

- Promising results
- RCTs in ALD are feasible
- Large disease burden
- Blue ocean

Cons

- Unclear mode of action
- **Several interventions**

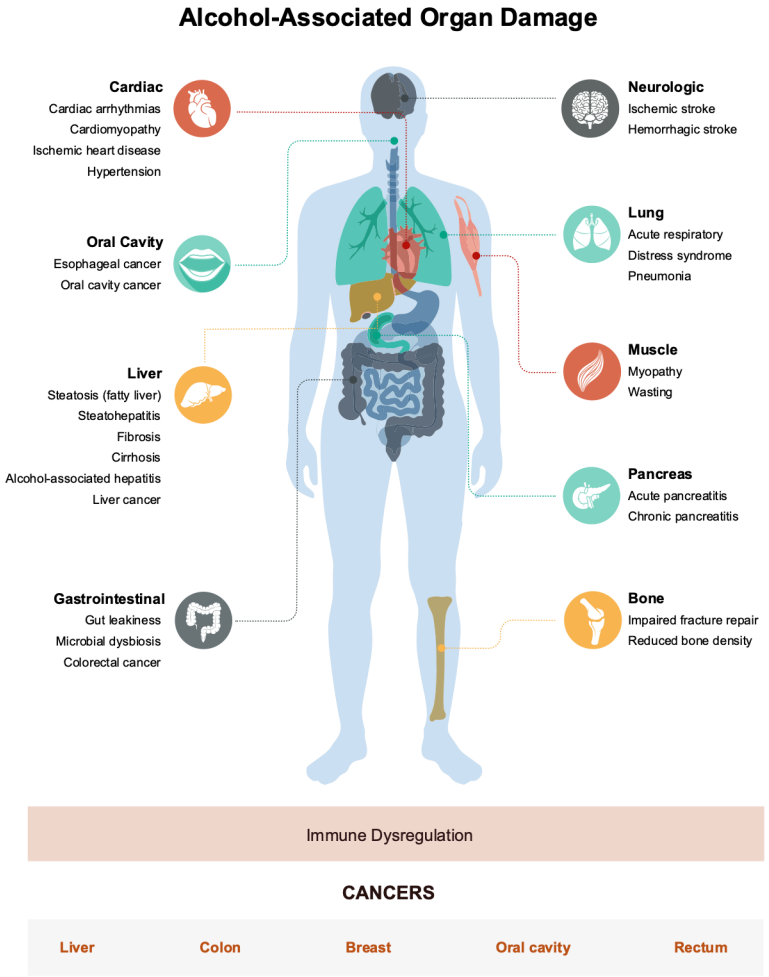


Pros

- Promising results
- RCTs in ALD are feasible
- Large disease burden
- Blue ocean

Cons

- Unclear mode of action
- Several interventions
- **Underlying cause**



National Institutes of Health (NIH)

Acknowledgements

University of Copenhagen
Evelina Stankevic
Tobias Wistisen
Camila Alvarez Silv
Lise Ryborg
Helene Bæk Juel
Manimozhiyan Arumugam
Torben Hansen

Department of Biochemistry, OUH
Lea Grip
Mette Møller Andreasen
Anette Tyrsted Mikkelsen

Münster University Hospital
Jonel Trebicka
Robert Schierwagen

Nordic Bioscience
Mette Juul Nielsen
Diana Leeming
Morten Karsdal

Odense University Hospital Pharmacy
Lene Sehested

GCP monitor
Tanja Busk Bidstrup

Odense Liver Research Centre

Bjørn Madsen
Camilla Dalby Hansen
Nikolaj Torp
Stine Johansen
Charlotte Wernberg
Mette Munk Lauridsen
Ditlev Rasmussen
Ida Villesen
Jane Møller Jensen
Maria Kjærgaard
Trine Møller
Charlotte Damby Jensen
Minna Ingham
Line Jensen
Maria Fogt
Helle Lindholm Schnefeld
Peter Andersen
Julie Hansen
Katrine Thorhauge
Johanne Kragh
Katrine Lindvig
Louise Just
Maja Thiele
Aleksander Krag

Supported by European Union's Horizon 2020 Research and Innovation Program,668031
Novo Nordisk Foundation Challenge Grant "MicrobLiver", NNF15OC0016692

@IsraelsenMads

Funding

This study has obtained financial support from Horizon 2020, the European Union's Program for Science and Innovation (fund number 668031), the Novo Nordisk Foundation Challenge Program, Odense University Hospital, the University of Southern Denmark, Region of Southern Denmark, the Knud and Edith Eriksens Memorial Foundation, the Beckett Foundation, and the Foundation of 17–12-1981.

Norgine was partner in the EU Horizon 2020 consortium "Galaxy". Trial medication was sponsored **unconditionally and free of charge** by **Norgine Denmark A/S**