MICROB-PREDICT and DECISION – Symposium ‘Management of acute-on-chronic liver failure’

Wim Laleman, MD, PhD
Department of Liver and Biliopancreatic disorders
University Hospitals Gasthuisberg, Leuven, BELGIUM

co-chairs:
Minneke Coenraad MD PhD (LUMC, Leiden, The Netherlands)
Pierre-Emmanuel Rautou MD PhD (Hôpital Beaujon, Inserm UMR, France)

2nd September 2021, ONLINE
at the occasion of the EASL School of Hepatology

This project hast received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 825694.

Welcome on behalf of the MICROB-PREDICT FAMILY

Prof. Dr. med. Jonel Trebicka

Scientific coordinator/inspirer/supreme leader/PI
European Foundation for the study of Chronic Liver Failure (EF-CLIF)
Goethe-University Frankfurt (GUF)


MICROB-PREDICT

Programme:

Chairs: M. Coenraad, W. Laleman, PE Rautou

12:30-13:00	**ACLF and microbiome – introduction of the MICROB-PREDICT project** (Wim Laleman, Katholieke Universiteit Leuven, Belgium)
13:00-13:30	**ACLF and combinatorial therapies – introduction of the DECISION project** (Pierre-Emmanuel Rautou, Hôpital Beaujon, Inserm UMR, France)
13:30-14:00	**Microbiome: recent insights and future challenges** (Suguru Nishijima - European Molecular Biology Laboratory, Germany)
14:00-14:30	**Proteome and liver disease: how deep is deep enough** (Matthias Mann - Max Planck Institute of Biochemistry, Germany)
14:30-15:00	Break
15:00-15:30	**Metabolomics and its way into the hepatology** (Christophe Junot, Commissariat a l'energie atomique et aux energies alternatives, France)
15:30-16:00	**Mechanisms of action of albumin in cirrhosis** (Joan Claria, Hospital Clinic -EFClif, Spain)
16:00-16:30	**Role of albumin in treatment of cirrhosis** (Minneke Coenraad, Leiden University Medical Center, The Netherlands)

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MICROB-PREDICT and DECISION – Symposium
'Management of acute-on-chronic liver failure'

ACLF & Microbiome
Introduction of the MICROB-PREDICT project

Wim Laleman, MD, PhD
Department of Liver and Biliopancreatic disorders
University Hospitals Gasthuisberg, Leuven, BELGIUM
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ACLF & Microbiome
Introduction of the MICROB-PREDICT project

1. ACLF: setting the stage
2. Gut microbiome: a holistic view in relation to ACLF
3. Exploring ACLF & microbiome: MICROB-PREDICT-project

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ACLF (**A**cute-on-**C**hronic **L**iver **F**ailure): Setting the stage

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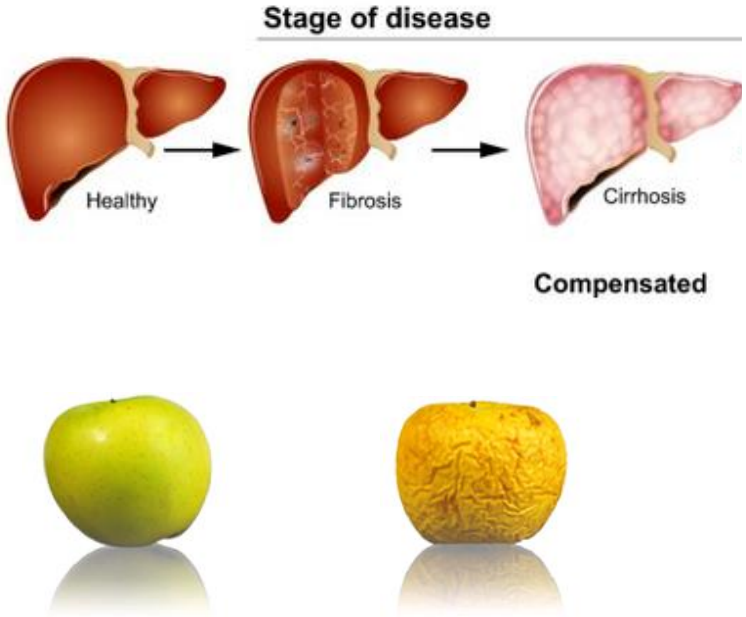
EVOLVING CIRRHOSIS

setting the stage for ACLF



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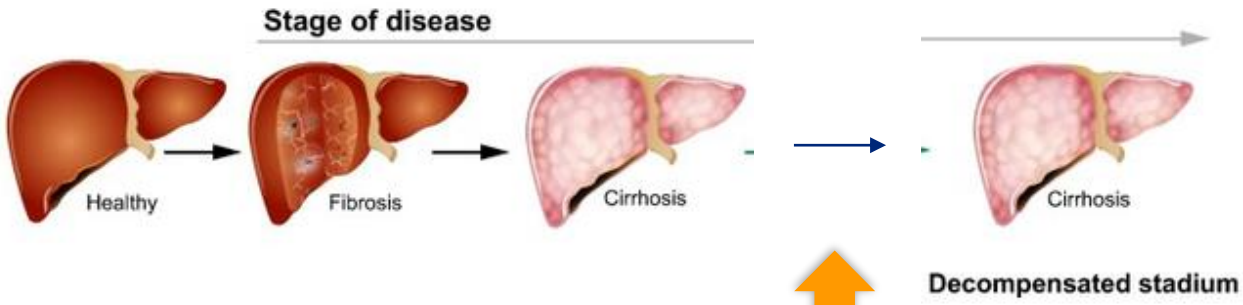
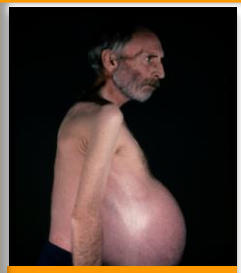
DECOMPENSATION OF CIRRHOSIS

a decisive time point both in terms of medical management and prognosis

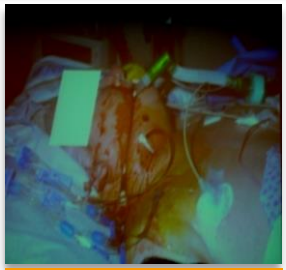


Death

Development of complications



Ascites



Gastro-oesofageal bleeding

Encephalopathy

Jaundice

Bacterial infections

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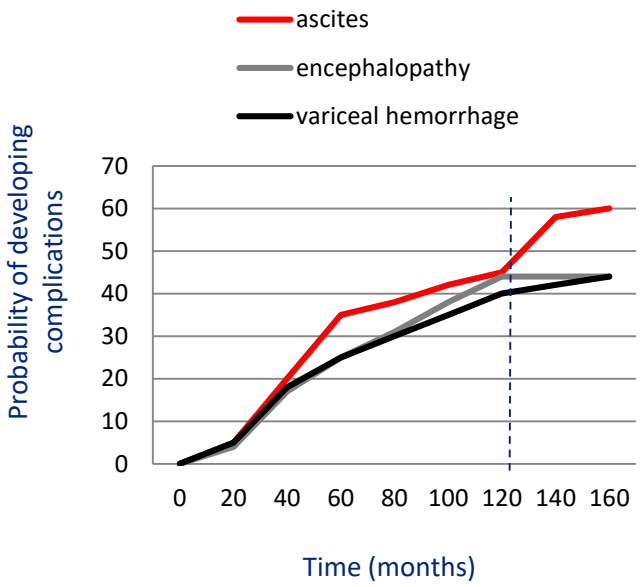
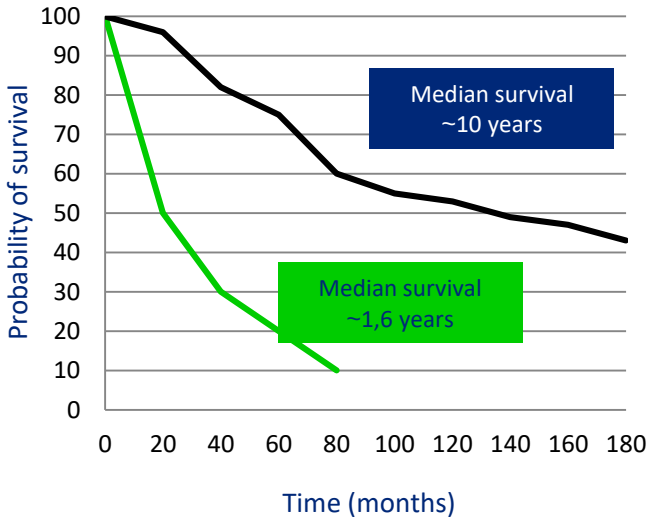
IMPACT OF DECOMPENSATION ON PROGNOSIS





Gines et al. Hepatology 1987

D'Amico J Hepatol 2006

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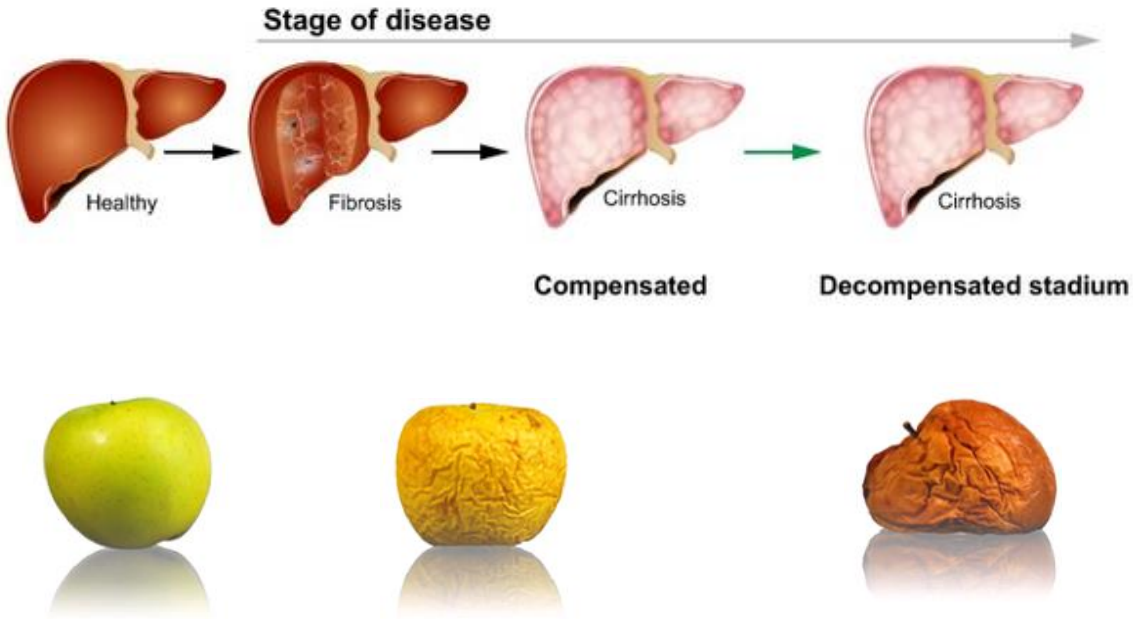
EVOLVING CIRRHOSIS

An ominous natural history…



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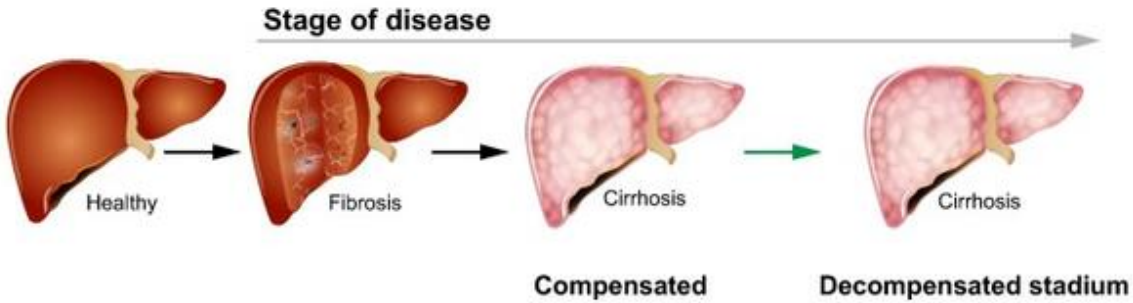
EVOLVING CIRRHOSIS

but it can get worse …



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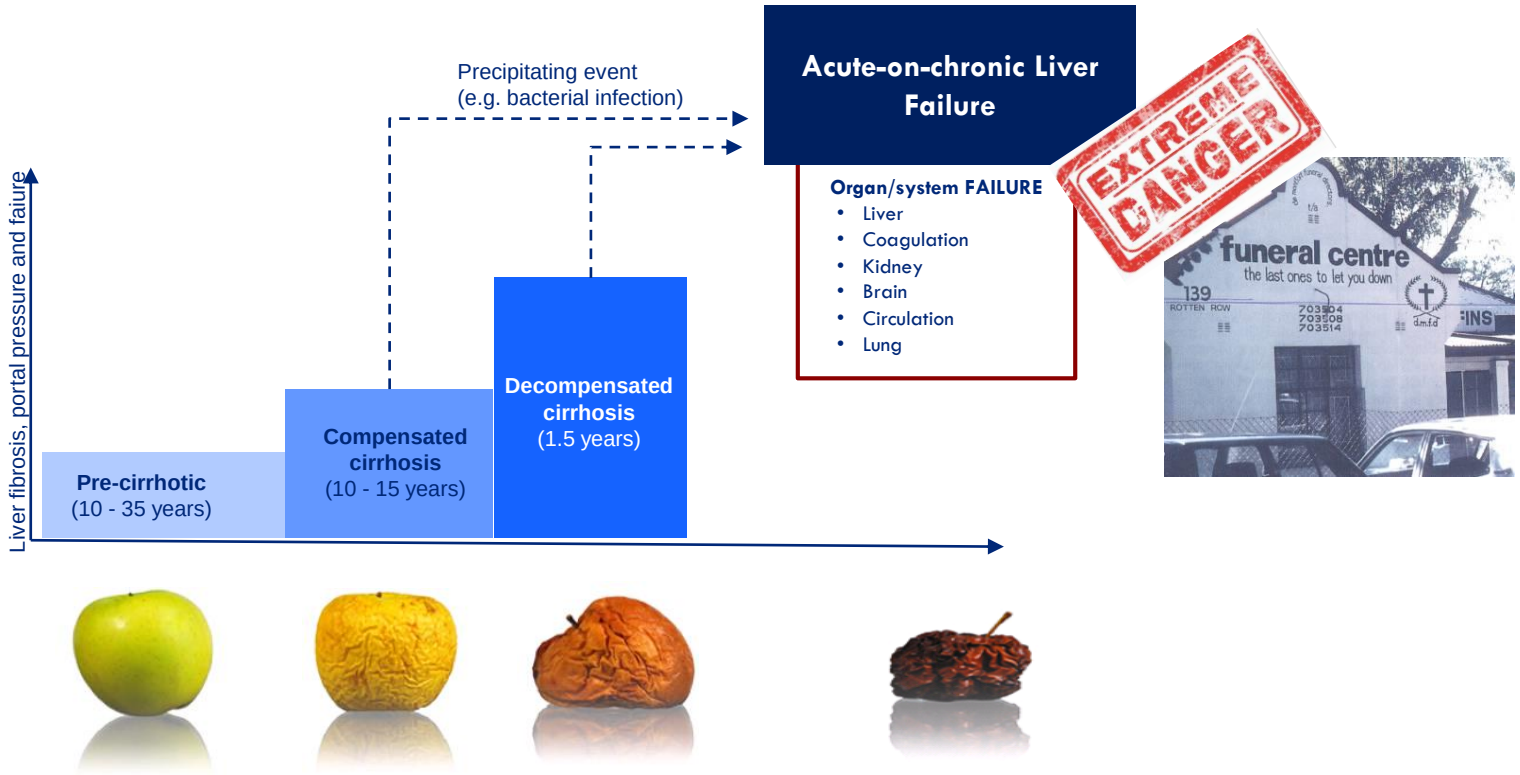
Acute on Chronic Liver Failure: a more distinct and aggressive form of acute decompensation



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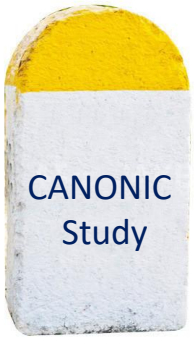

Acute-on-Chronic Liver Failure Is a Distinct Syndrome That Develops in Patients With Acute Decompensation of Cirrhosis

RICHARD MOREAU,[1] RAJIV JALAN,[2] PERE GINES,[3] MARCO PAVESI,[4] PAOLO ANGELI,[5] JUAN CORDOBA,[6] FRANCOIS DURAND,[1] THIERRY GUSTOT,[7] FAOUZI SALIBA,[8] MARCO DOMENICALI,[9] ALEXANDER GERBES,[10] JULIA WENDON,[11] CARLO ALESSANDRIA,[12] WIM LALEMAN,[13] STEFAN ZEUZEM,[14] JONEL TREBICKA,[15] MAURO BERNARDI,[9] and VICENTE ARROYO,[3] for the CANONIC Study Investigators of the EASL–CLIF Consortium

EF Clif
EUROPEAN FOUNDATION FOR THE STUDY OF CHRONIC LIVER FAILURE

1. **ACUTE DECOMPENSATION OF CIRRHOSIS (ASCITES,HEPATIC ENCEPHALOPATHY, GI BLEEDING AND/OR BACTERIAL INFECTIONS)**
2. **ORGAN/SYSTEM FAILURE**
3. **HIGH RISK of SHORT-TERM MORTALITY (28-day-mortality)**

Moreau R et al. CANONIC study Gastroenterology 2013

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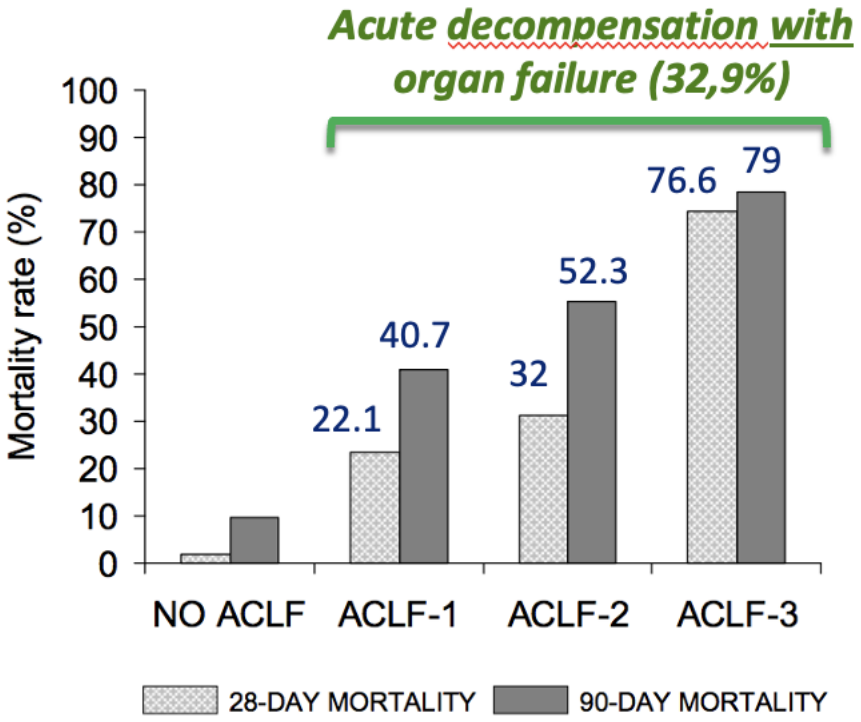
ACLF is relevant both in terms of prevalence as prognosis

	ACLF grades
No organ failure	→ No ACLF
Single nonrenal failure, creatinine < 1.5 mg/dL, no HE	
Single renal failure	→ ACLF-1
Single nonrenal failure, creatinine 1.5–1.9 mg/dL and/or HE	
2 organ failures	→ ACLF-2
3 organ failures	→ ACLF-3
4–6 organ failures	



Moreau R et al. CANONIC-trial. Gastroenterology 2013

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19th of January2017

Protocol of the **Predict**ing Acute-on-Chronic Liver Failure in Cirrhosis

(PREDICT) Study on behalf of the **EASL-CLIF Consortium**

Chairman of the EASL-CLIF Consortium and Director EF-CLIF:
Vicente Arroyo (Barcelona)

Principal Investigator (PI): Jonel Trebicka (Bonn, Germany)

Co-PIs: Wim Laleman (Leuven, Belgium), Joan Claria (Barcelona, Spain)

International-European, investigator-initiated, multicenter, prospective, observational study aiming to investigate

(1) the critical period prior to ACLF & find predictors of ACLF

(2) mechanisms and pathophysiology in ACLF development

(3) precipitating events of ACLF

(4) serve as a hub for numerous ancilliary mechanistic studies like f.e.

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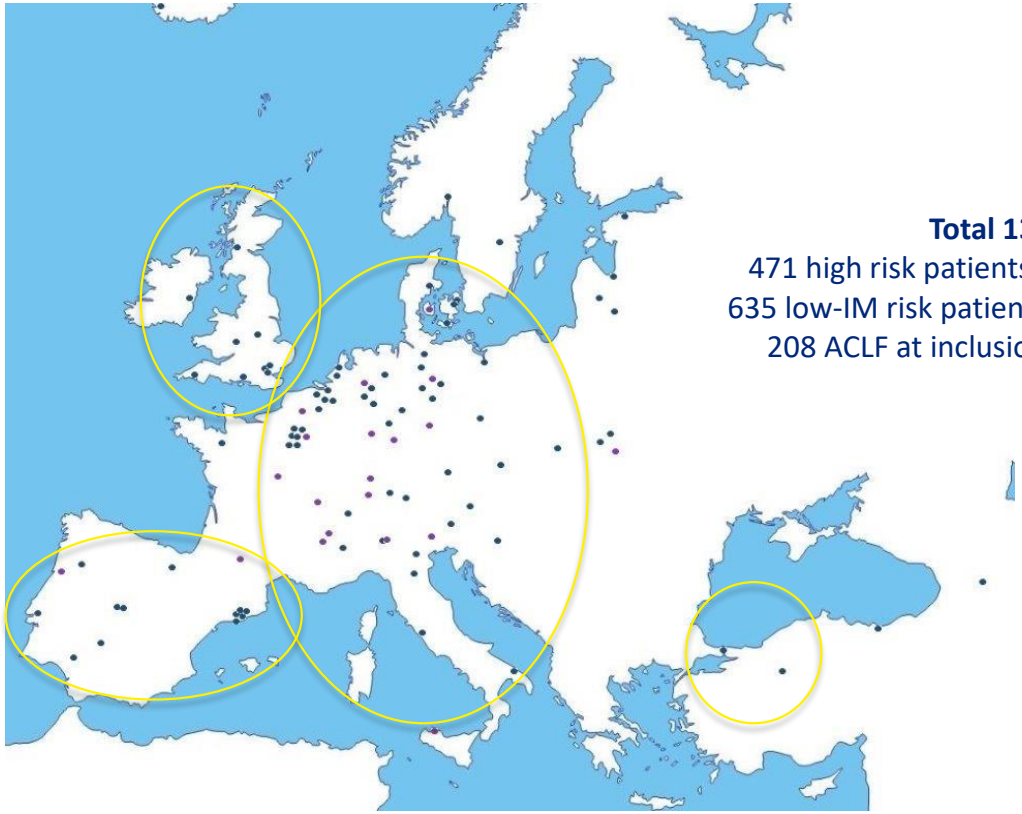
Centers (54 centers) – recruitment closed 31-7-2019



Total 1314 patients
471 high risk patients (33% ACLF)
635 low-IM risk patients (5% ACLF)
208 ACLF at inclusion (pos cont)

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Gut microbiome:
A holistical view* in relation to ACLF

*the theory that whole entities have an existence greater than as the mere sum of their parts

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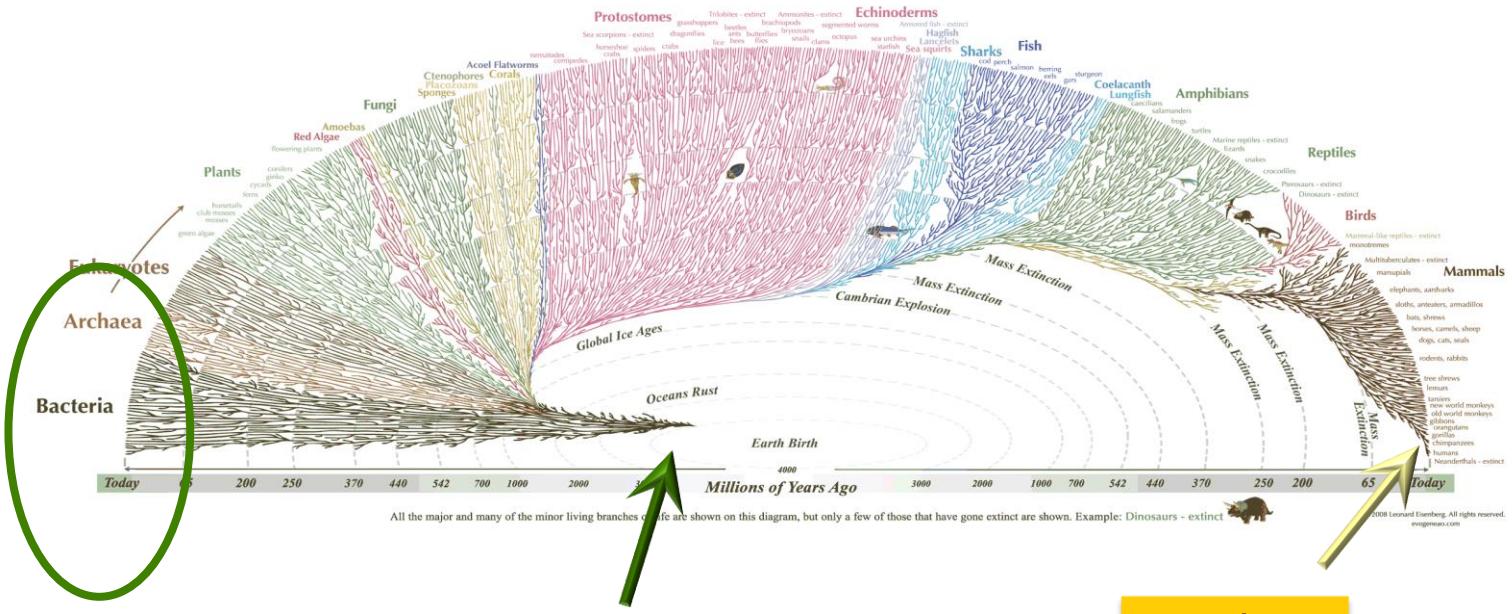
Evolutionary tree of life: Respect your elders



They were already there… 4 billion years ago

We are here…

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An extended view of ourselves…
we are more microbes than we are human

Cani and Delzenne *Pharmacology & Therapeutics* 2011

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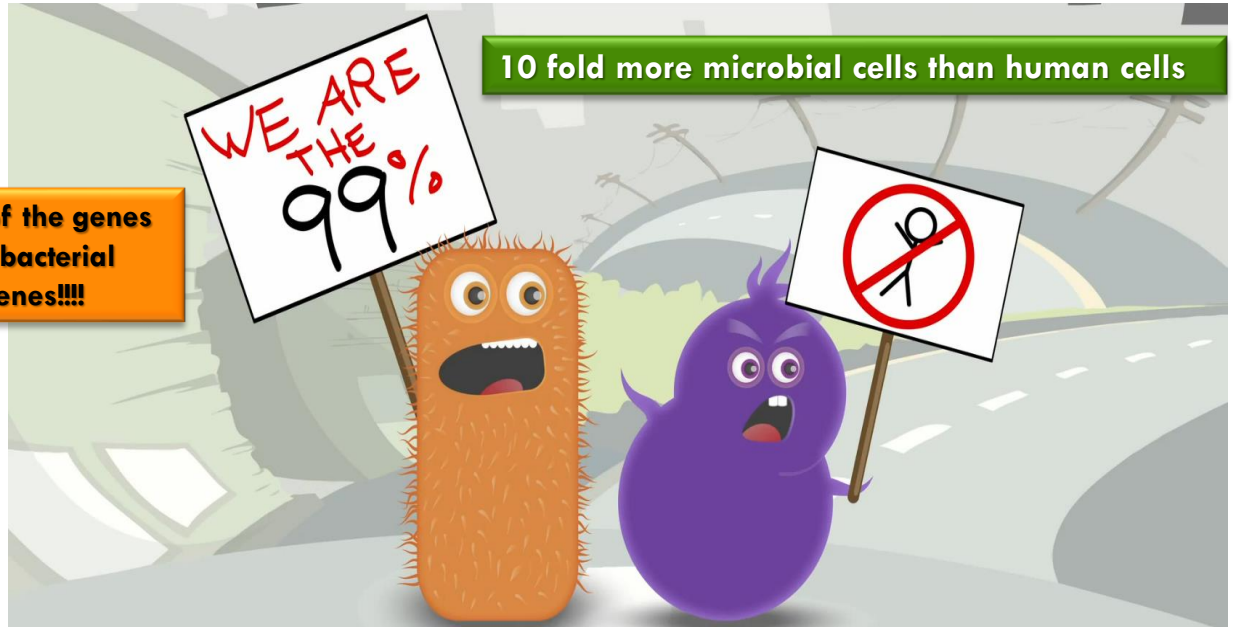
An extended view of ourselves…
We form a superorganism with our microbes



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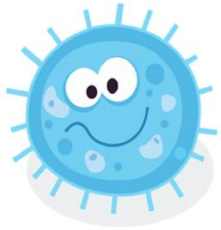
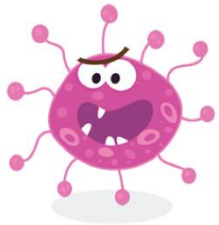
Tummy Buddy



Gut microbiota

Tummy Buddy vs Tummy Baddy

Tummy Baddy



Normal microbiota prohibitive for pathogen colonization by

- Direct interaction between commensals & pathogens
  - altering host environmental conditions (e.g. pH)
  - consumption of nutrients required by pathogens
  - production of specific metabolites which affect pathogen virulence (e.g. SCFA butyrate)
  - alter conditions required for virulence activity (e.g. ambient oxygen)

- Indirect control via activation of host immunity

Δ in composition
Δ modified metabolic activities
Δ local distribution of its members

→ DYSBIOSIS: Imbalanced intestinal microbial community

Changes in gut microbiota accompany cirrhosis and become more severe with decompensation

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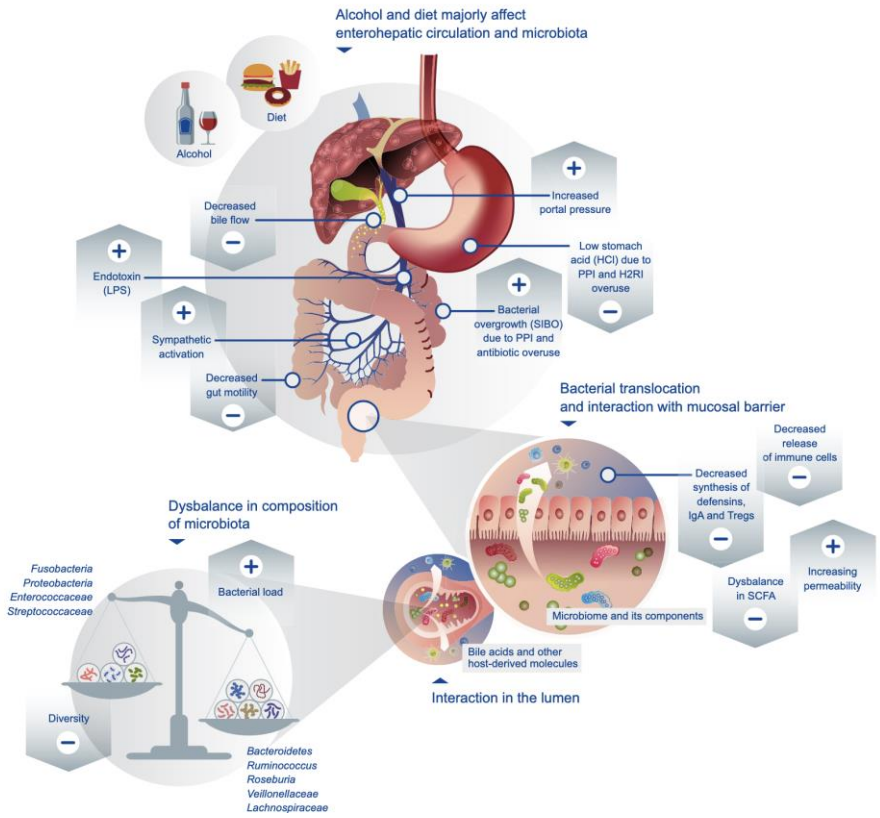
Microbiome and hepatic decompensation

Changes in the gut microbiome accompany cirrhosis and become more severe in the setting of decompensation



Trebicka J, Macnaughtan J, Schnabl B, Shawcross D, Bajaj J. J Hepatol 2021

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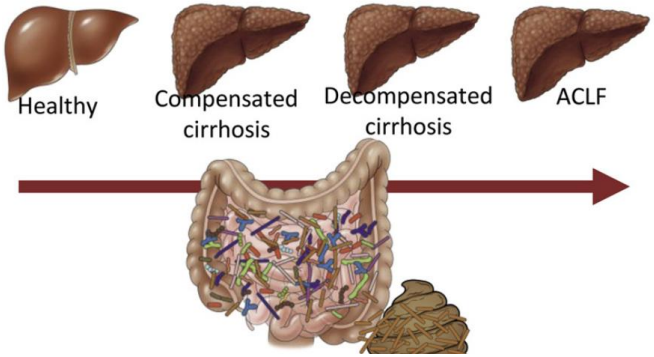
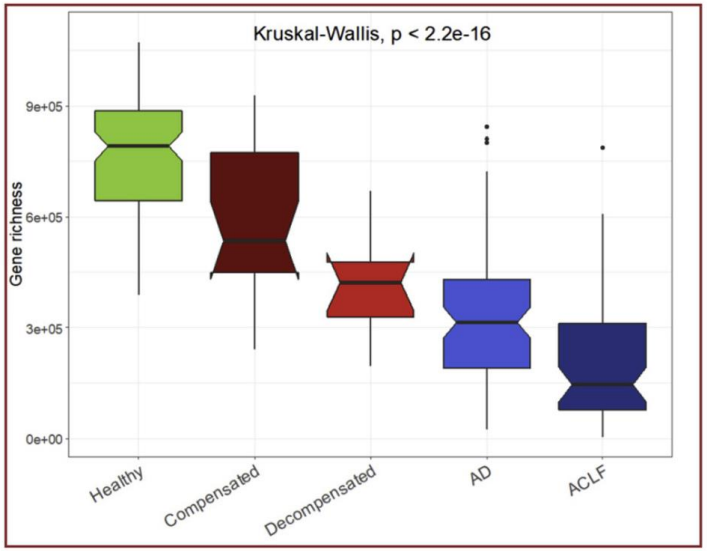
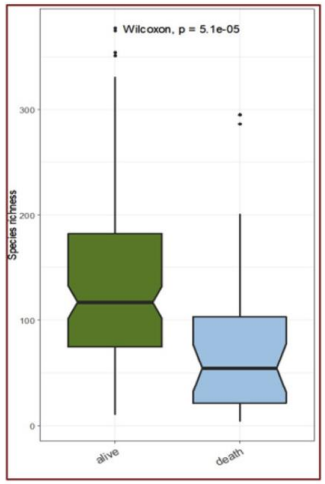
Changes in gut microbiota parallel evolving cirrhosis and become more severe with progressive decompensation

ALTERATIONS IN GUT MICROBIOME IN CIRRHOSIS AS ASSESSED BY QUANTITATIVE METAGENOMICS. RELATIONSHIP WITH ACUTE-ON-CHRONIC LIVER FAILURE AND PROGNOSIS

200 patients were studied using quantative metagenomics. Progression of cirrhosis, is associated with changes in gut-microbiome characterized by progressively reduced metagenomic species richness and increase in Peptostreptococous sp. Microbiome correlated with clinical outcomes, survival and functional changes.







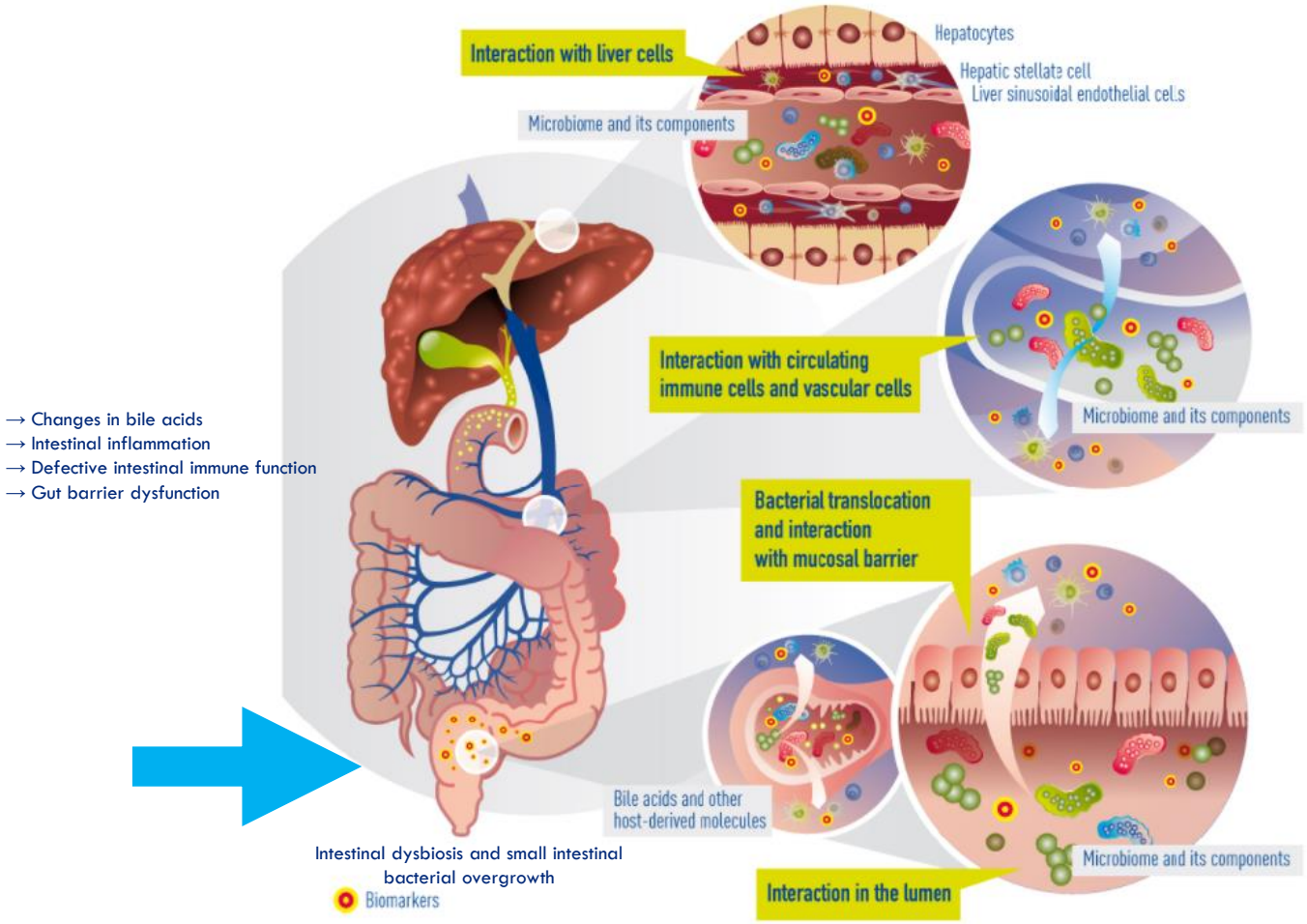
Gastroenterology

Decreased faecal microbial gene richness, microbial richness and species diversity

Sole et al Gastroenterology 2021

Bajaj Nature 2015
Qin Nature 2014
Bajaj et al Hepatology 2018

Linking the gut microbiome to hepatic decompensation



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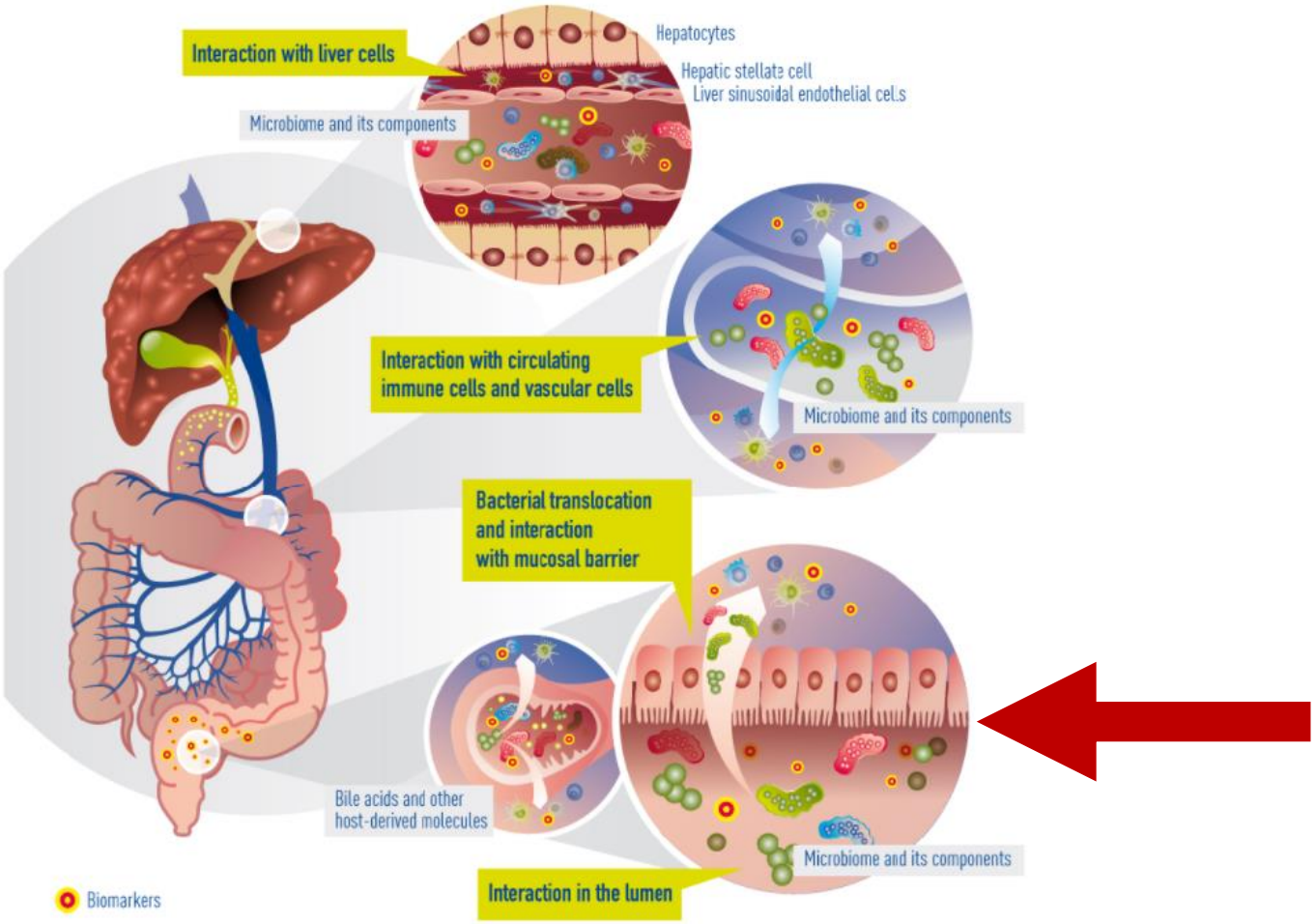
Linking the gut microbiome to hepatic decompensation



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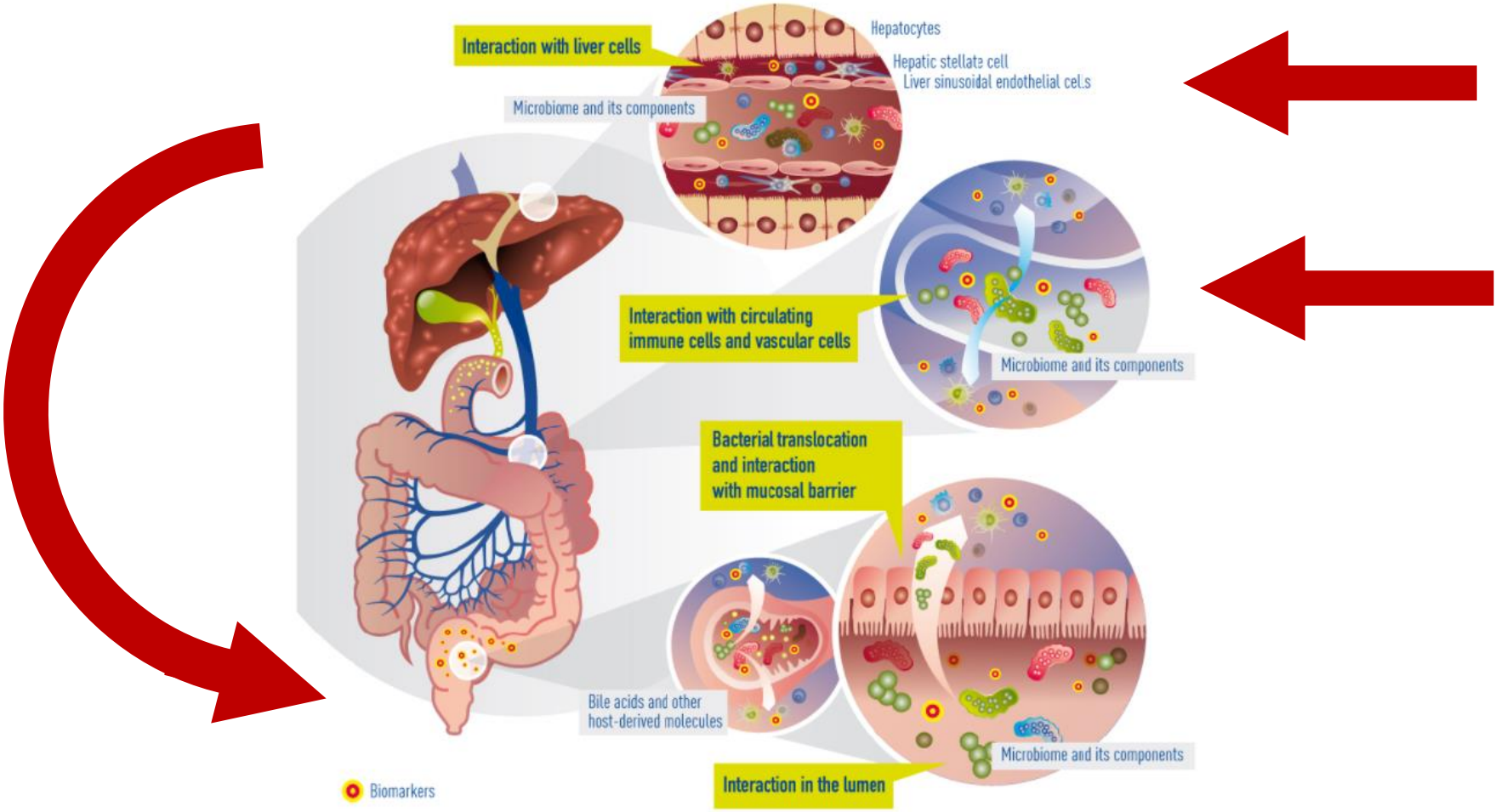

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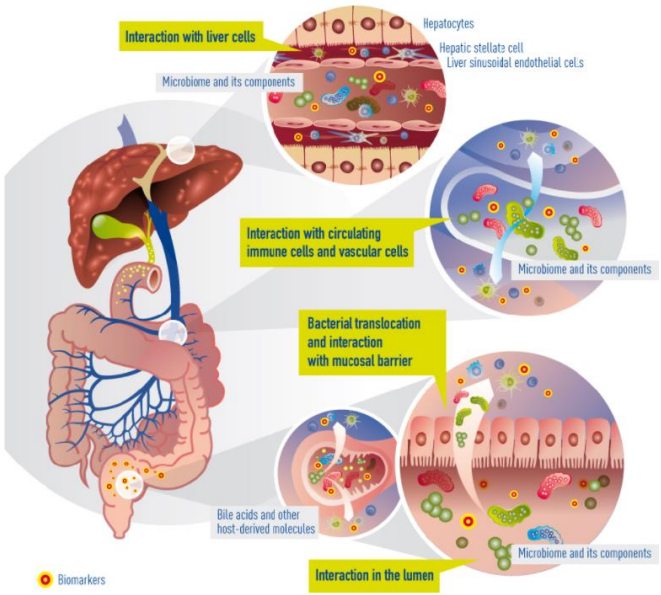

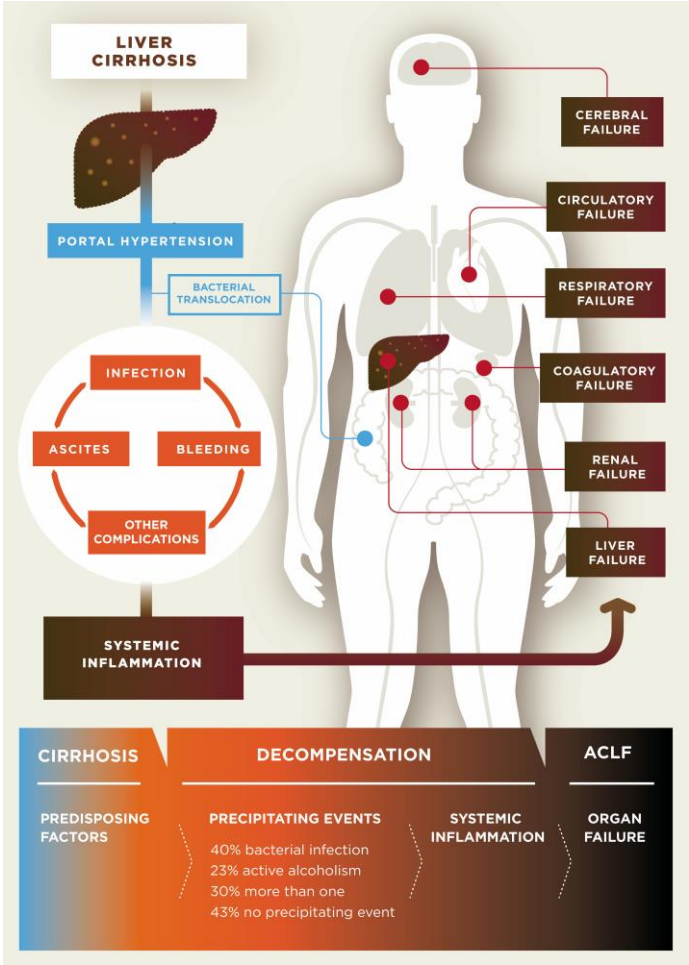

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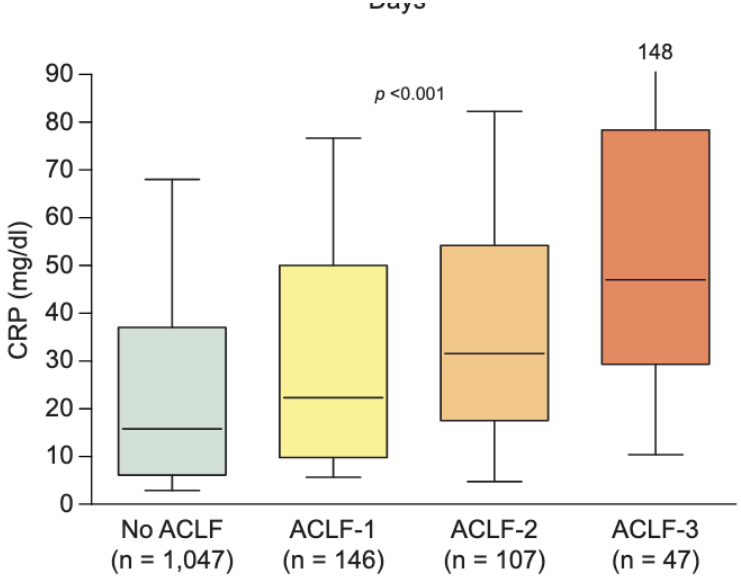
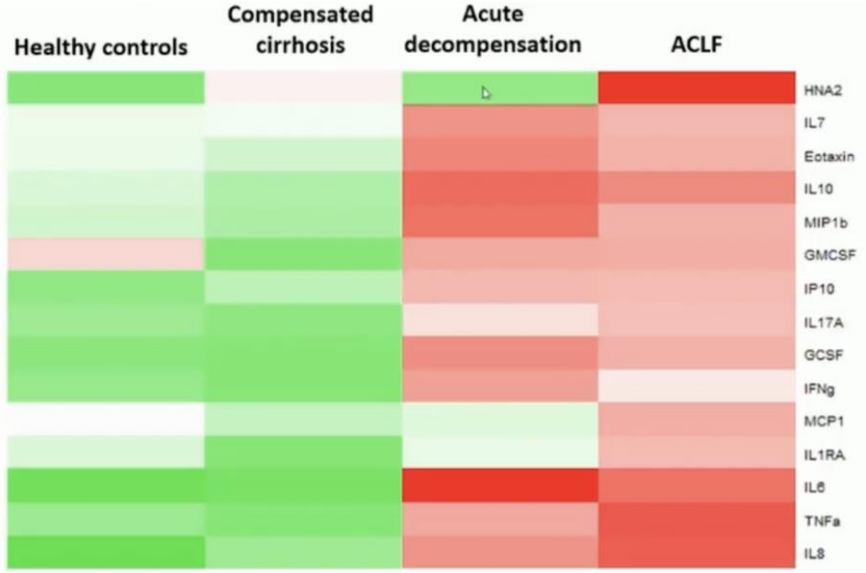
Extent of systemic inflammation in cirrhosis





Trebicka J et al. Front Immunol 2019
Moreau R et al. CANONIC. Gastroenterology 2013

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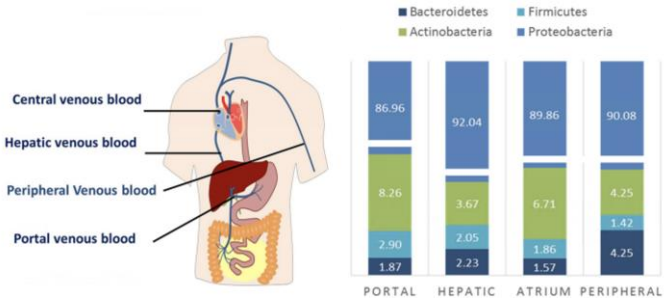
Circulating microbiome associated with systemic inflammation



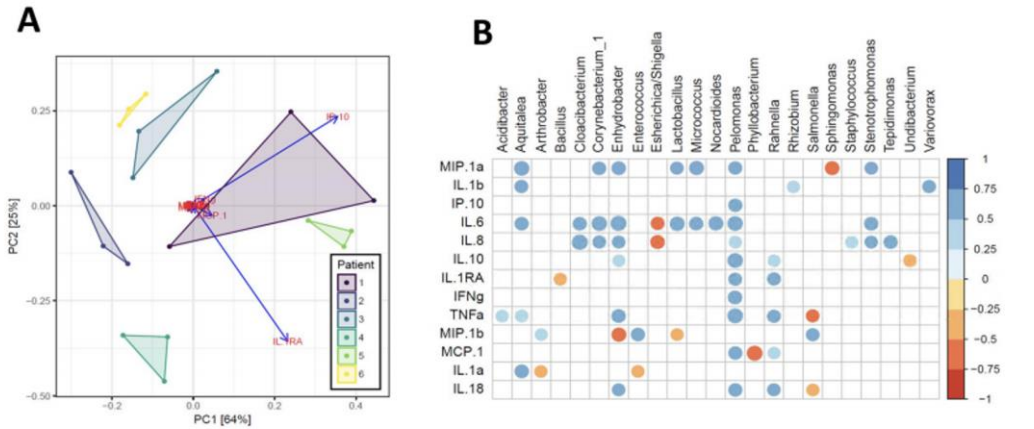


Figure 2 (A) Cytokine levels were patient specific, and the clustering was driven by interferon inducible protein 10 (IP-10) (CXCL-10) and interleukin 1 receptor antagonist (IL-1ra). Relative abundance of 65 identified genera in portal, hepatic and central venous, as well as peripheral blood. Heatmaps show relative abundance (scale showed on the right). Genera absent in a sample are marked by white boxes. (B) Spearman correlations between microbial genus abundance and inflammatory markers. Only statistically significant correlations (adjusted P<0.05) are shown.

Schierwagen et al. Gut 2018

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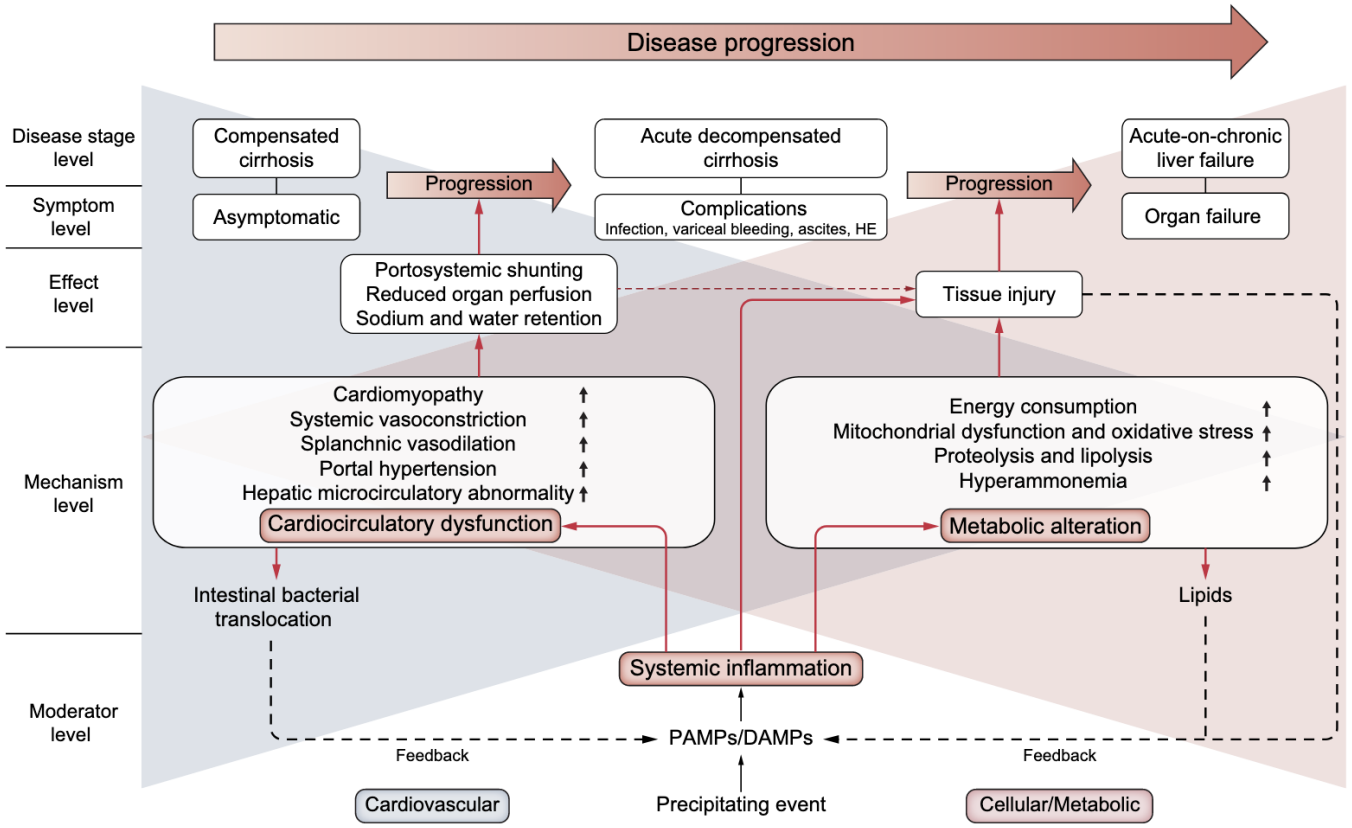
The current pathophysiological paradigm of decompensated cirrhosis integrates the microbiome & systemic inflammation as major disease modulators



Engelmann C et al. J Hepatol 2021

Trebicka J, Macnaughtan J, Schnabl B, Shawcross D, Bajaj J. J Hepatol 2021

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Exploring ACLF & microbiome: *MICROB-PREDICT-project*

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MICROB-PREDICT

MICROB-PREDICT

Focus on human microbiome to fight liver cirrhosis

22 European institutions join forces in MICROB-PREDICT to improve the prevention and treatment of chronic liver disease (cirrhosis). We aim to identify microbiome-based biomarkers and mechanisms that predict in advance when the body can no longer compensate for the dysfunctional liver (decompensated cirrhosis), when such decompensated cirrhosis will progress to acute-on-chronic liver failure (ACLF), and a patient's individual treatment response. Based on such biomarkers, we strive to develop novel diagnostic tools for earlier and better patient stratification and to establish personalised and effective treatment strategies.

Learn more

This project hast received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825694.

The MICROB-PREDICT community/family

This project hast received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825694.

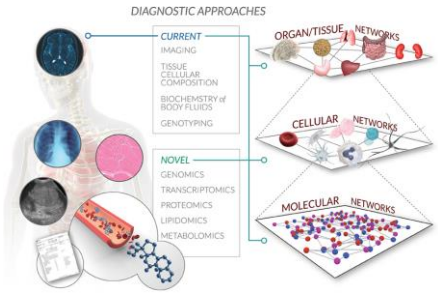
- Collaborative team of microbiome-, technology-, and clinical experts from 22 institutions spread over 10 European countries
- Support of leading European patient organisations (**ELPA**) and research associations (**EASL**, **EF-CLIF**).

This project hast received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825694.

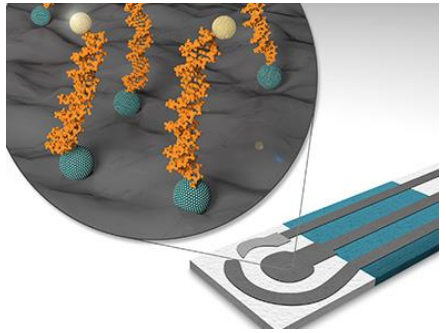
MICROB-PREDICT aims:

- To **identify major taxonomic and functional microbial traits** and their interaction with the host suffering from decompensated cirrhosis and (progression to) ACLF.

- To understand in depth and to better explain the **interaction of human microbiome with host , as well as their exact contribution to the development of acute decompensation and ACLF**, and thereby to provide important foundations for the **development of future prevention and treatment strategies modifying the microbiome and host co-factors**.



- To develop **prognostic tools, biomarkers and novel microbiome-based nano-biosensors** to allow better stratification tools of cirrhotic patients enabling microbiome-based intelligent and personalized allocation to treatment, and ultimately prevent ACLF and reduce mortality



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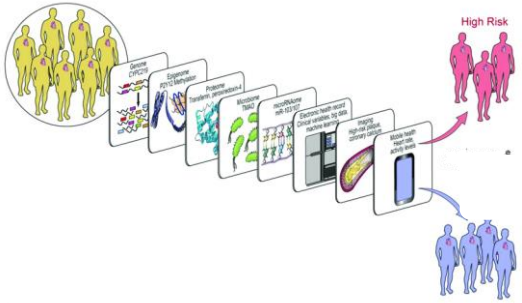
MICROB-PREDICT aims (2):



- To use these tools in the clinical trial of MICROB-PREDICT to **personalize treatments, improve the treatment response to approaches modifying the microbiome and host co-factors**

- To **decrease the individual, social and healthcare burden** caused by decompensated cirrhosis and ACLF.

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Our approach

Data and samples:

- **12 microbiome initiatives in the field of hepatology**
- **with altogether >10,000 patients and controls**
- **existing meta and -omics data from > 2,500 patients & > 7,000 controls**
- **multi-omics analysis of 1,050 patients**

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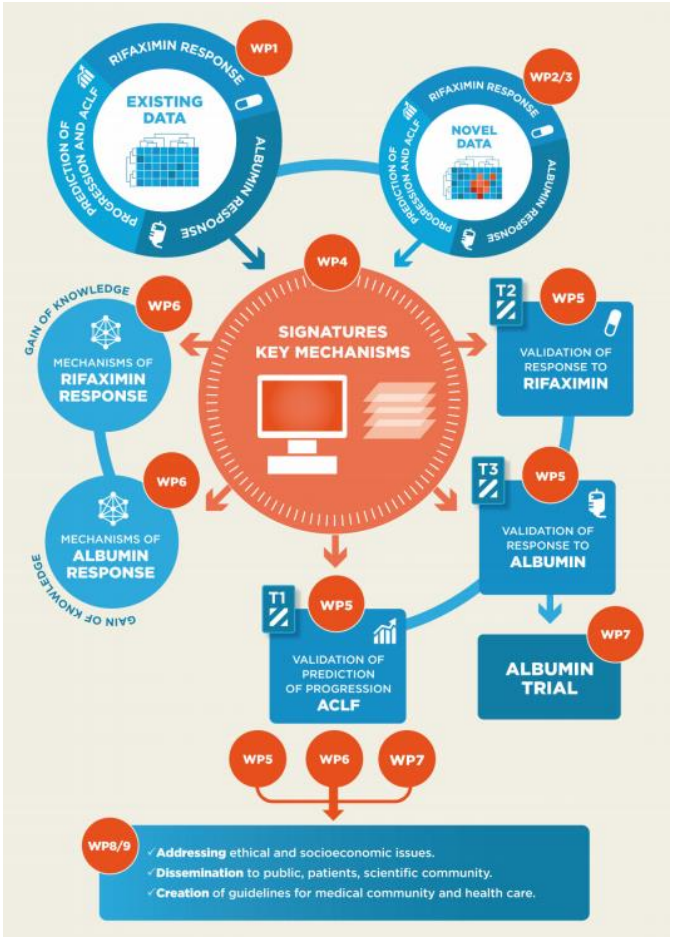
Work package leaders



WP1	Clinical, genetic, expositional and geographic characterization of existing data
WP2	Characterization of the microbiome
WP3	Proteomics and metabolomics of host and microbiome
WP4	Data management, integration and systems modelling
WP5	Validation of biomarker candidates and biosensor development
WP6	*In vitro* and *in vivo* experimental validation of targets
WP7	Clinical validation of signature guided interventions (ALB-TRIAL)
WP8	Ethics, health, and socio-economics
WP9	Dissemination, training, communication, exploitation and guideline development
WP11	Ethics requirements
WP10	Project management

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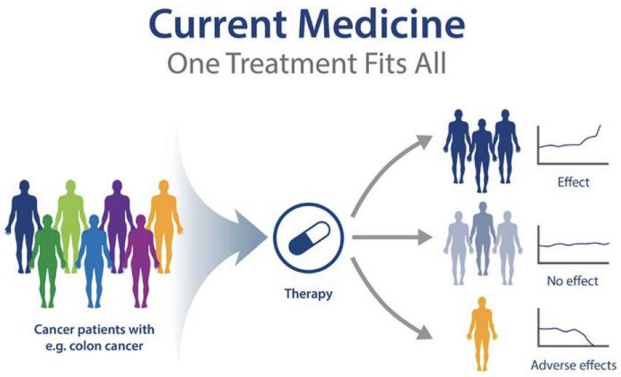

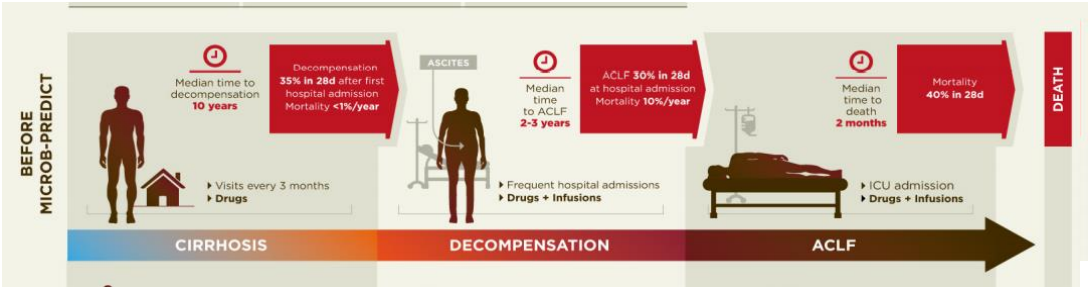

trial & error

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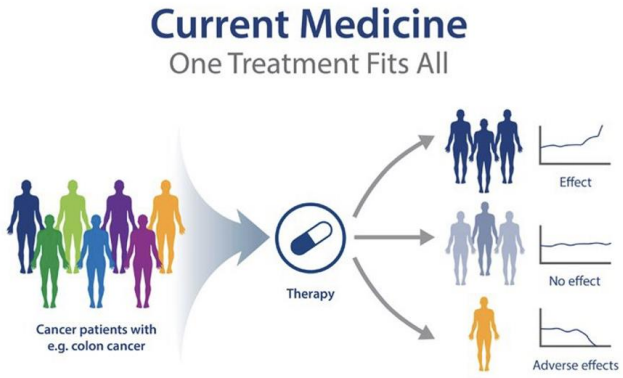

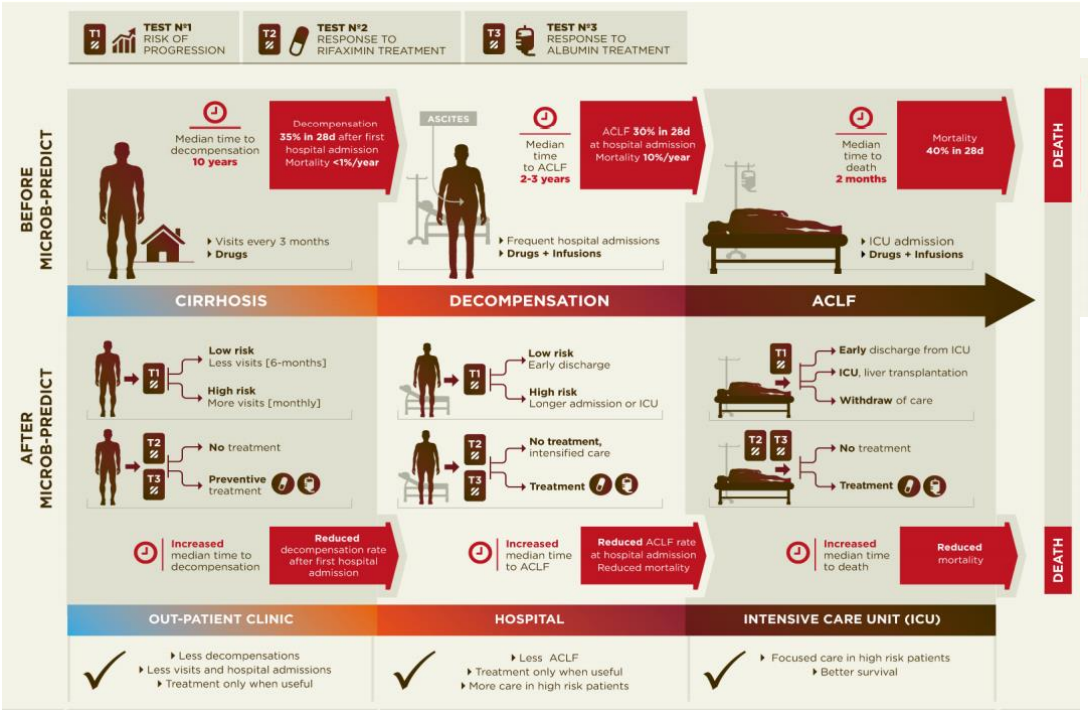

Stratification of cirrhotic patients driving microbiome-based intelligent treatment

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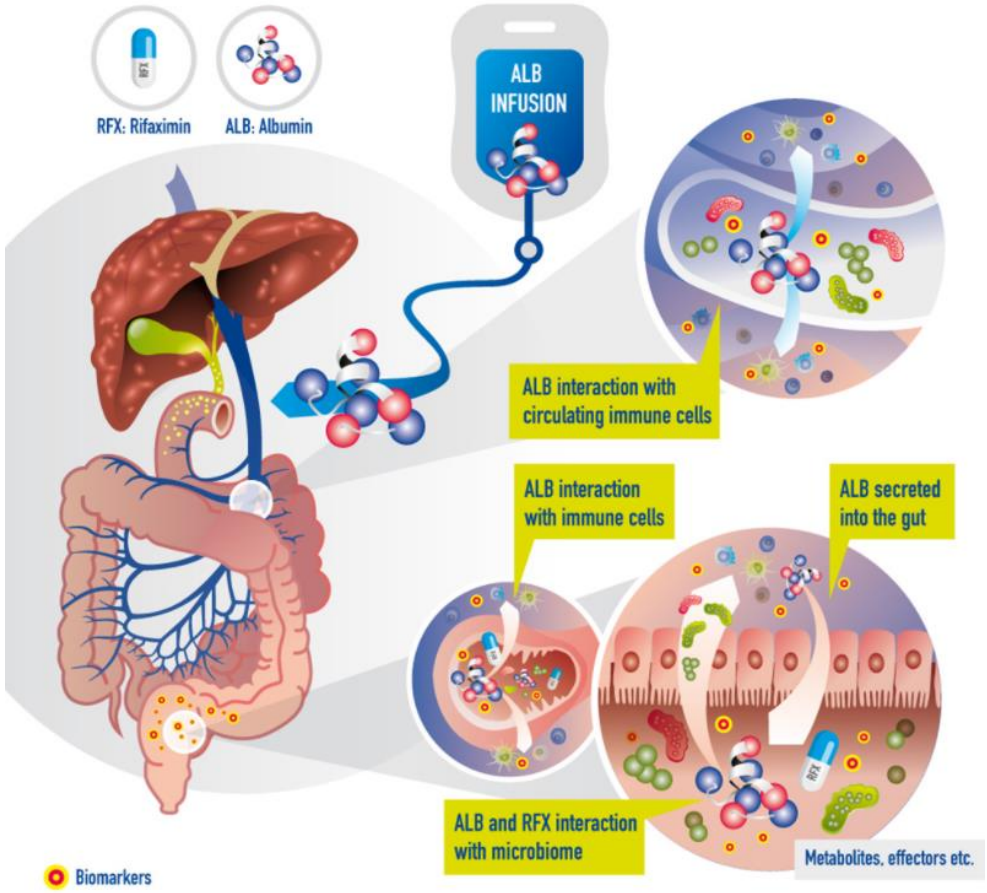
Biomarker-based stratification of cirrhotic patients enabling microbiome-based intelligent treatment



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Conclusions

ACLF represents the **most severe form of acute decompensation of cirrhosis** and is characterized by high-short-term mortality and organ failure

Evolving **gut microbiota fuel systemic inflammation in driving the liver towards acute decompensation and ACLF**

Individualizing and stratifiying care of cirrhotic patients **enabling microbiome-based intelligent treatment** are urgently needed ….

MICROB-PREDICT to the rescue !!!!!!

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“Doctors are men who prescribe medicine about which they know little, to cure diseases of which they know less, in human beings of whom they know nothing”

(Voltaire, 1694-1778)

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Programme:

Chairs: M. Coenraad, W. Laleman, PE Rautou

12:30-13:00	**ACLF and microbiome – introduction of the MICROB-PREDICT project** (Wim Laleman, Katholieke Universiteit Leuven, Belgium)
13:00-13:30	**ACLF and combinatorial therapies – introduction of the DECISION project** (Pierre-Emmanuel Rautou, Hôpital Beaujon, Inserm UMR, France)
13:30-14:00	**Microbiome: recent insights and future challenges** (Suguru Nishijima - European Molecular Biology Laboratory, Germany)
14:00-14:30	**Proteome and liver disease: how deep is deep enough** (Matthias Mann - Max Planck Institute of Biochemistry, Germany)
14:30-15:00	Break
15:00-15:30	**Metabolomics and its way into the hepatology** (Christophe Junot, Commissariat a l'energie atomique et aux energies alternatives, France)
15:30-16:00	**Mechanisms of action of albumin in cirrhosis** (Joan Claria, Hospital Clinic -EFClif, Spain)
16:00-16:30	**Role of albumin in treatment of cirrhosis** (Minneke Coenraad, Leiden University Medical Center, The Netherlands)

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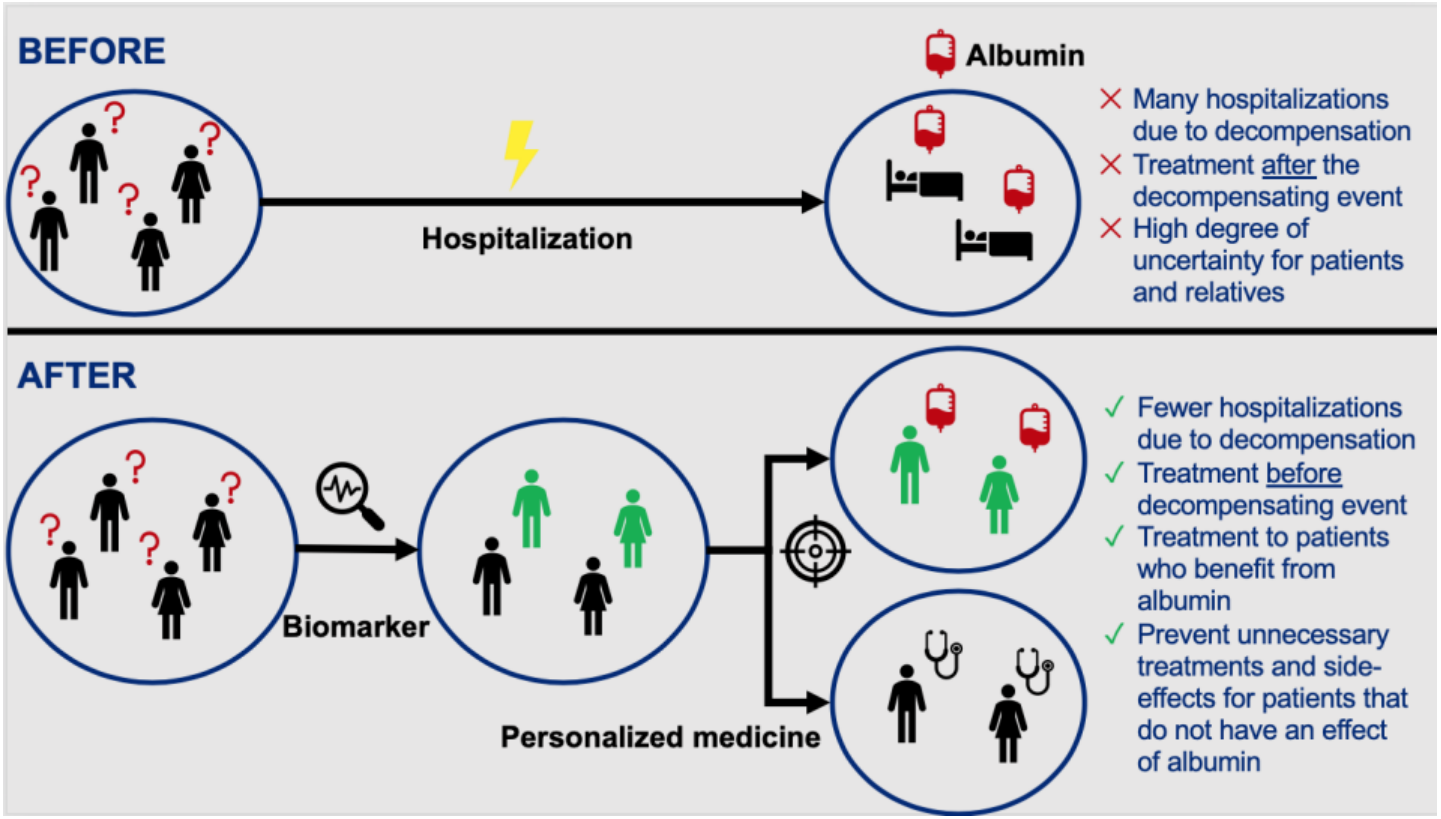
Biomarker-based stratification of cirrhotic patients enabling microbiome-based intelligent treatment: The ALB-trial



Biomarker-based stratification of cirrhotic patients enabling microbiome-based intelligent treatment: The ALB-trial

- Alb-Trial will **include 240 patients** from **8 hospitals** in **7 countries** in **Europe**
- The study will *commence* in **June 2022** and be *completed* in **September 2024**
- Patients are potentially **eligible** to **participate** regardless of the **cause of liver disease**
- **All participants** will in addition to their study treatment receive their **standard medical treatment** and **human albumin infusions** as recommended by **European guidelines** (previous slide)

Study site countries

- United Kingdom
- The Netherlands
- Belgium
- Spain
- Germany
- Hungary
- Denmark

- The study will be a **double-blinded placebo-controlled** trial to ensure results of the **highest scientific quality**.
- The study period for each participant will be **6 months**
- During the study period participants will have **intravenous infusions** of **human albumin** or **saline** performed by research nurses who also check for **participants well-being**.
- Infusions will happen every **10th day** (± 3 days) in **covered black bags** and **lines** to ensure that **no one can see** the **content** of the bags and lines.

Acute on Chronic Liver Failure (ACLF)

- 3 main used definitions -

"**acute hepatic insult** manifesting as jaundice [serum bilirubin ≥ 5mg%) and coagulopathy (INR ≥ 1.5) complicated within 4 wk by **clinical ascites and/or encephalopathy** in a patient with **previously diagnosed or undiagnosed chronic liver disease or cirrhosis and is associated with a high 28-day mortality** ""

APASL. Sarin SK et al. Hepatol Int 2009 + AARC 2019

" ....a syndrome that occurs in patients with **acute decompensation** (ascites,HE, GI bleeding and/or bacterial infections) of cirrhosis, often elicited by a *precipitating event*, characterized by rapid deterioration of the underlying liver disease associated with **organ failures** and a **high risk of short-term death** ..."

EASL-CLIF. Moreau R et al. Gastroenterology 2014

"Two or more **extrahepatic organ failures** in **cirrhotic patients** hospitalized with **infection**.
These organ failures are easy to assess and include cardiovascular (shock), brain (grade III/IV, hepatic encephalopathy), renal (need for dialysis), and respiratory (mechanical ventilation)"

NACSELD Bajaj J et al Hepatology 2014

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