Wrap-Up Day 2

Norah Terrault, MD
Professor of Medicine
Chief, Gastrointestinal and Liver Diseases
University of Southern California

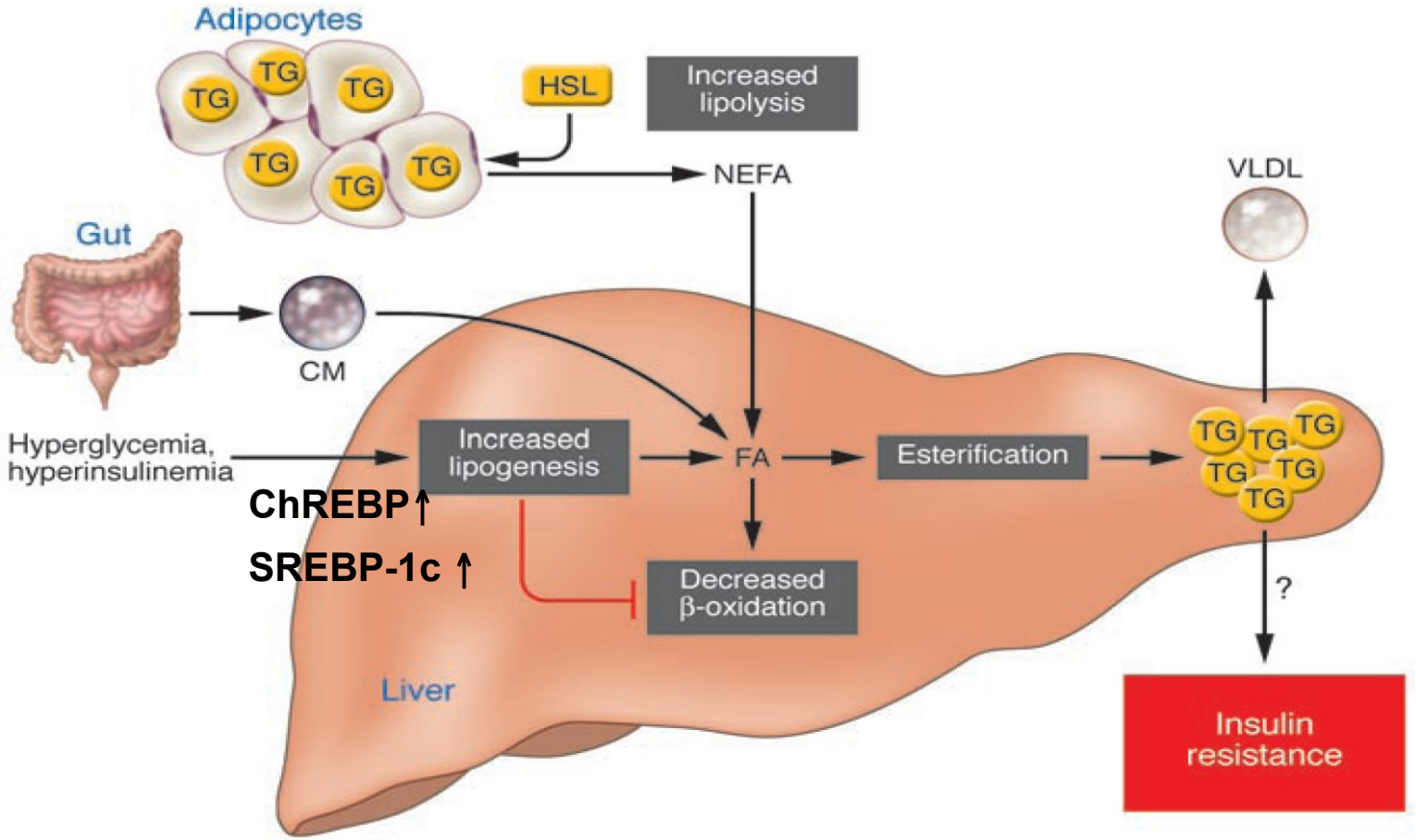
NASH
HCC
Cholestatic liver disease
Cirrhosis complications
Liver Imaging

Keck Medical Center of USC
Keck Medicine of USC

@norahterrault

Prof Massimo Pinzani: PATHOPHYSIOLOGY OF NAFLD AND NASH

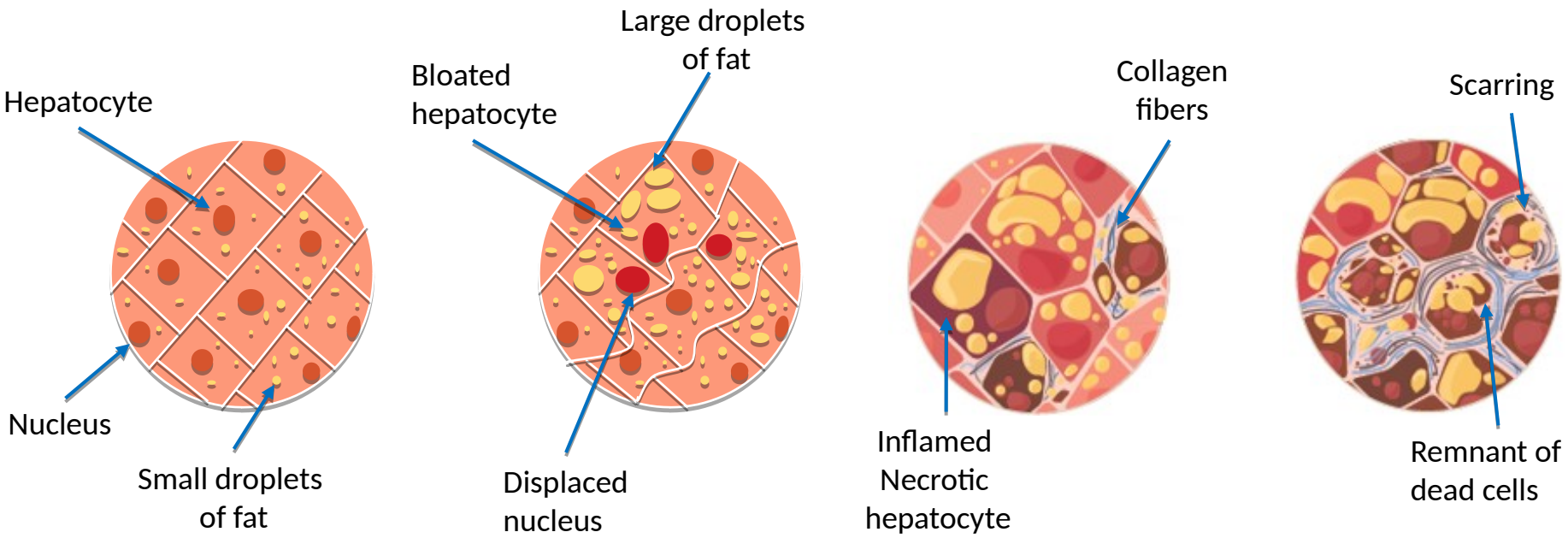
Metabolic Defects Leading to Steatosis



Postic and Girard, J

NASH Fibrosis: Stage-dependent Mechanisms

Adaptive phase



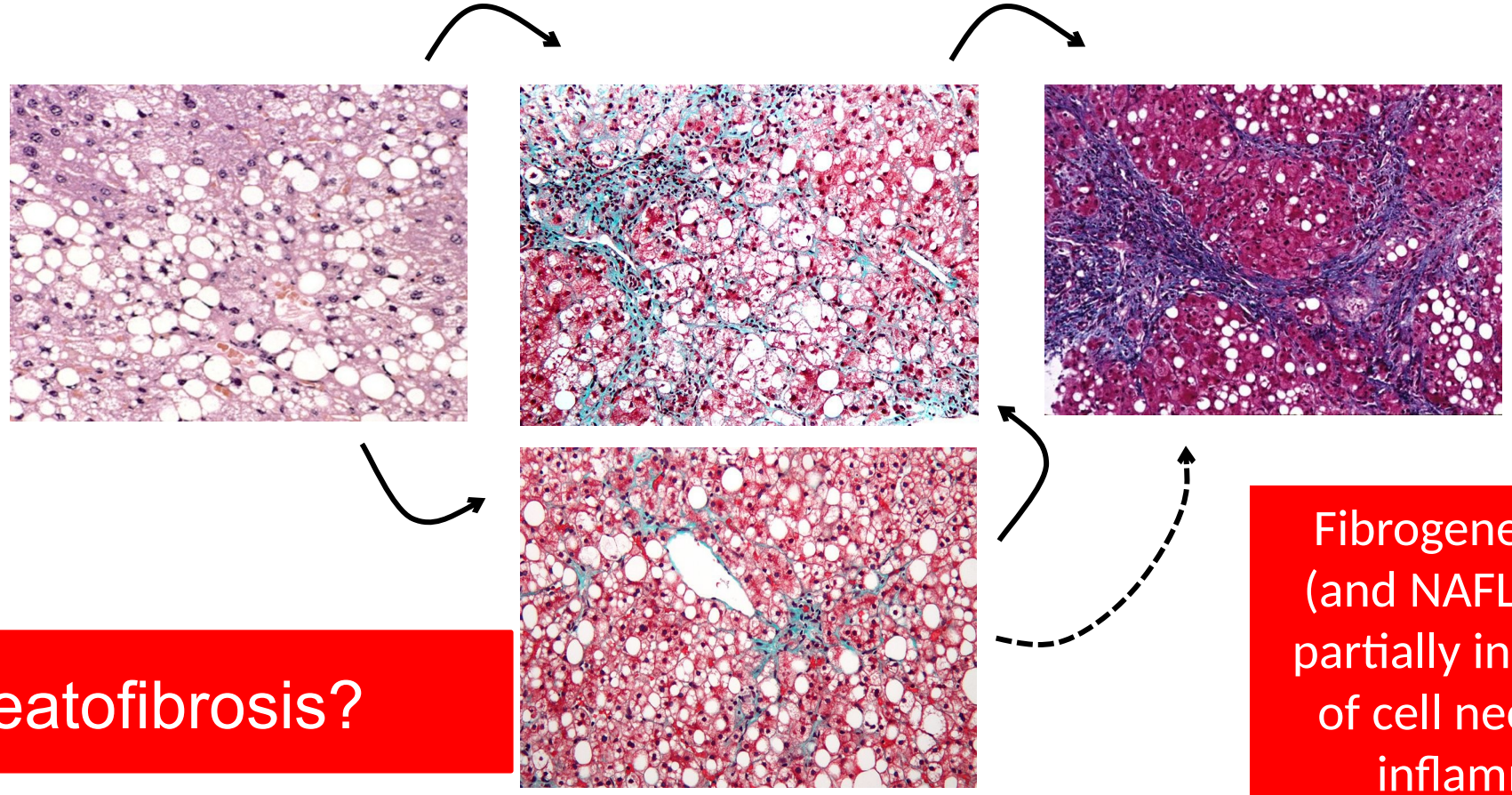
No evident necrosis

Defective Autophagy
LIPOTOXICITY
Oxidative Stress
Genetic factors

Evident necrosis

Chronic Wound Healing
Increase intestinal permeability
Complex inflammatory networks
Genetic factors

Fibrotic Evolution of NASH

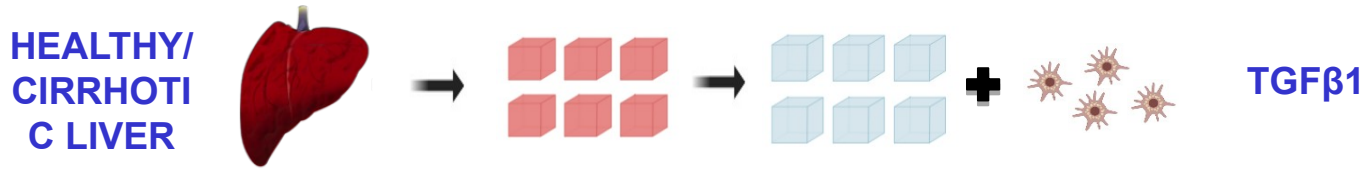


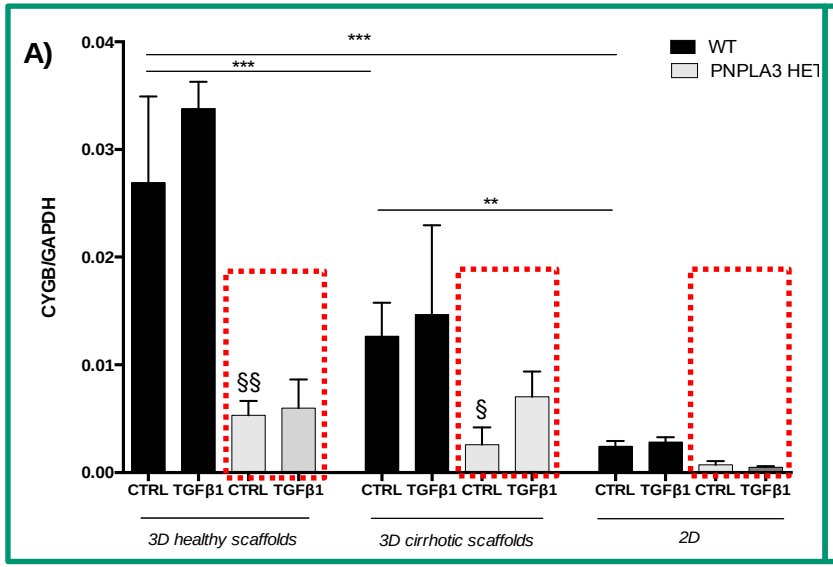
Steatofibrosis?

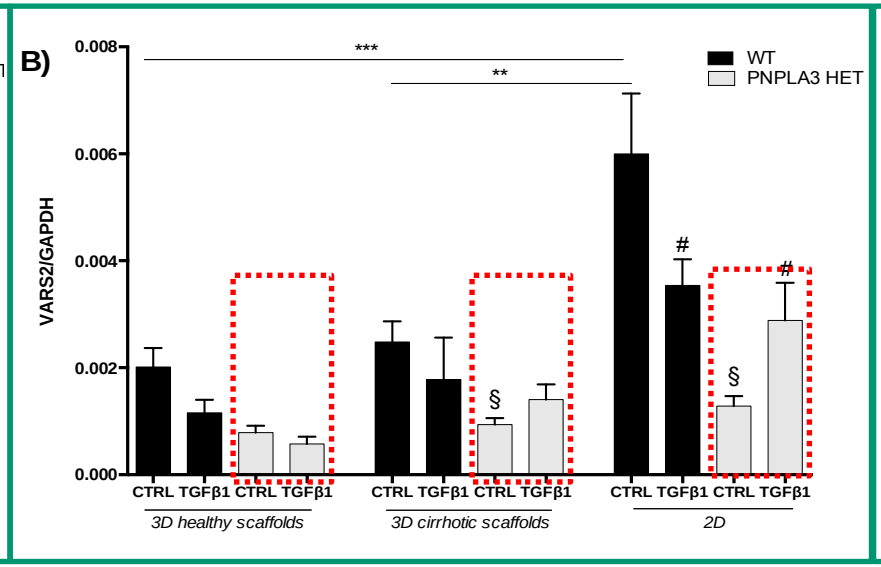
Fibrogenesis in ALD (and NAFLD) may be partially independent of cell necrosis and inflammation

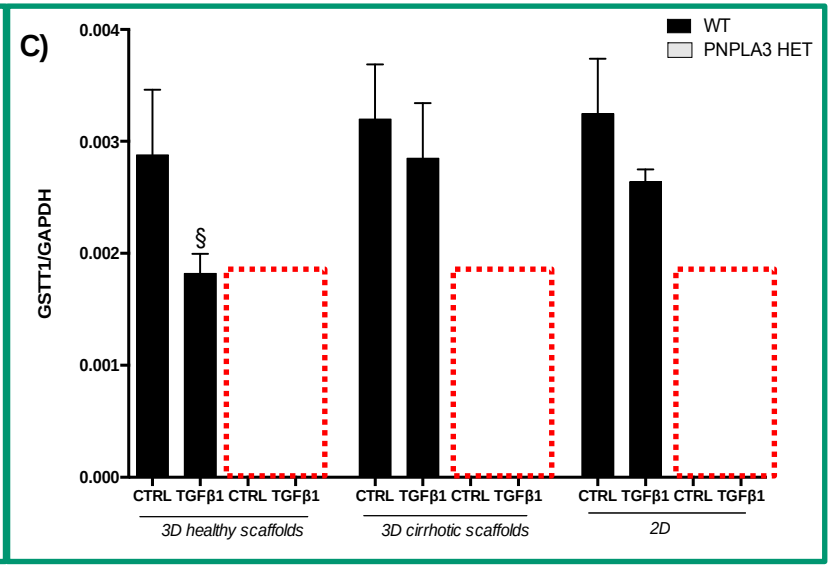
Oxidative stress → fibrosis (without inflammatory response)

PNPLA3 (148M) SNP promotes the activation of human HSC through a dysregulated oxidative stress response









Cytoglobin B: HSC quiescence marker

VARS2: a mitochondrial enzyme involved in fatty acid metabolism

GSTT1, a Glutathione-S-Transferase

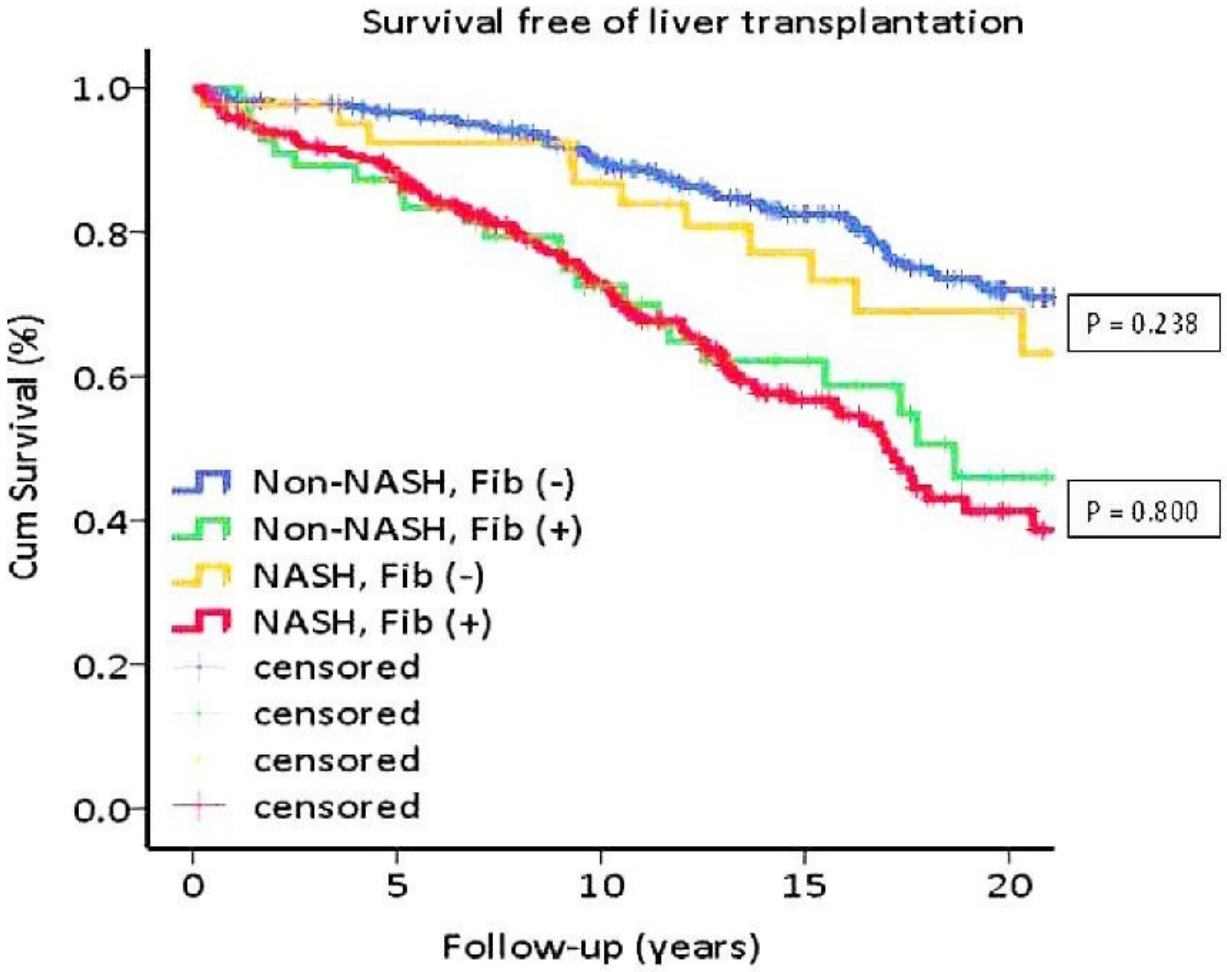
Caon E et al. 2020 unpublished

Prof Francesco Negro: Natural History of NASH and HCC

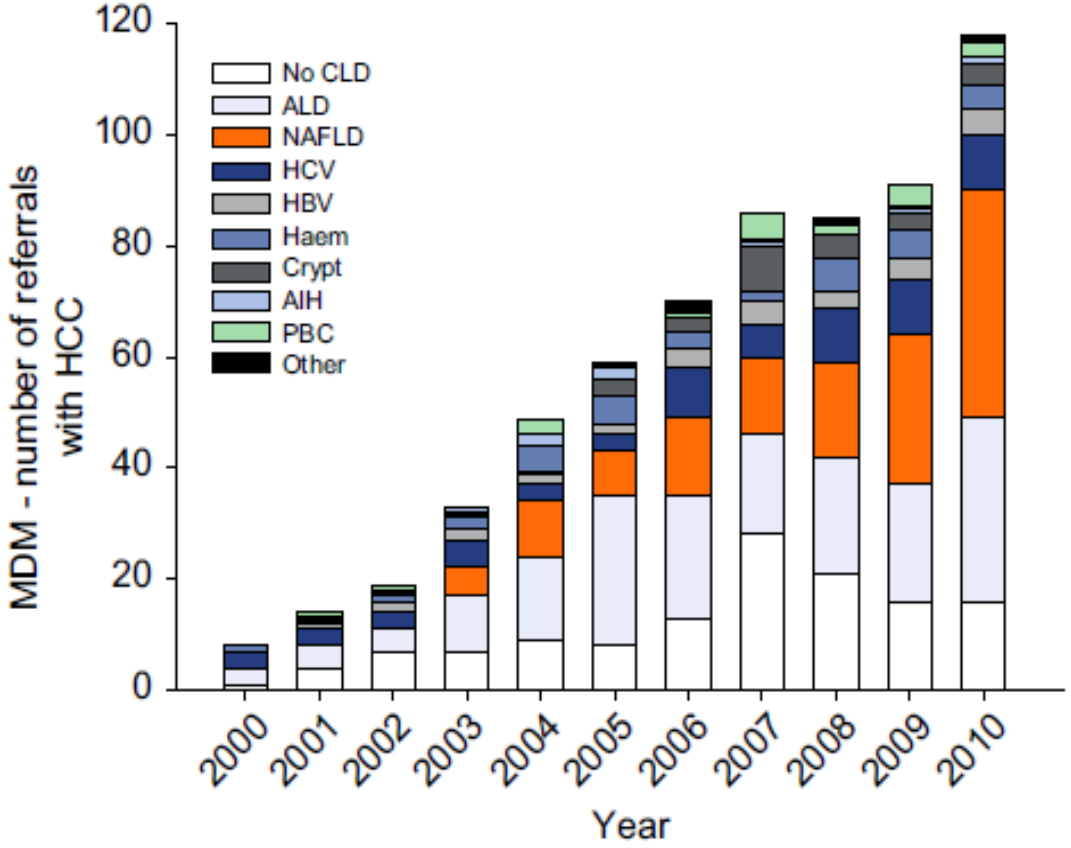
- NAFLD is the most prevalent chronic liver disorder worldwide: 25% of the global population
- Due to the increasing prevalence of metabolic syndrome and aging of the population, NAFLD prevalence and complications (including HCC) are projected to increase – 10-fold increase in past 10-15 years
- As many as 40 to 50% of HCC associated with NAFLD occur in non- cirrhotic livers

Fibrosis, not NASH, predicts survival

Retrospective study, n=619 NAFLD, 1975-2005, US + Europe + Thailand, FU 12.6 yrs



The proportion of HCC attributable to NAFLD: a tenfold increase compared to 2000



DYSON J, *et al.* J Hepatol 2014;60:110-

HCC in NAFLD/NASH

- Recognition of non-cirrhotic NAFLD-associated HCC
  - 53.8% of HCC occurred in the absence of cirrhosis
- The most important risk factors for HCC in NAFLD are metabolic
  - Obesity
  - Diabetes: 2-4 fold higher
  - Hypothyroidism
  - *PNPLA3* genotype: Carriage of each G allele → doubling of HCC risk
- Lifestyle modifications are currently the most effective measures to reduce the risk of HCC in NAFLD — exercise → 25% reduction in risk
- Chemoprevention? metformin, statins

Prof Laurent Castera: Non-Invasive Markers of NAFLD

- Availability, cost, applicability and context of use are critical issues when using non-invasive tests
- VCTE, FIB-4, and NAFLD fibrosis score are the most widely used and best validated tests
- The optimal way to identify F3-F4 NAFLD patients is the sequential use of FIB-4/NFS then VCTE to select those who should be considered for LB (versus combination)
- Effective pathways of referral from primary care and/or diabetes clinics to liver clinics needed given disease burden

Patients in Primary Health Care

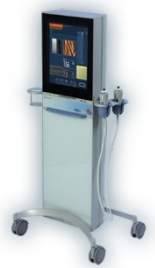
1st line: General practitioner

Rule-out advanced fibrosis

FIB-4

- **FIB-4 < 1.3** → **Low risk** → **Attempt lifestyle modifications and exercise** → **No further assessment. Repeat evaluation at 1 year?**
- **FIB-4 ≥ 1.3** → **Intermediate to high risk**

2nd line: Hepatologist

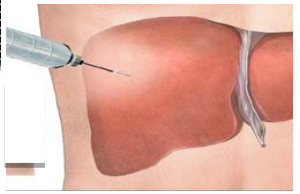


Rule-in advanced fibrosis

Transient Elastography

- **LSM < 8 kPa** → **Low risk** → **Attempt lifestyle modifications and exercise** → **Consider repeat evaluation (1 year)**
- **LSM ≥ 8 kPa** → **Intermediate to high risk** → **Consider Liver Biopsy** → **Attempt lifestyle modifications and exercise** → **Eligible for therapeutic trial?**

Failure (XL probe) 3.0- 6.7% → **Consider MRE, 2D SWE or ARFI according to local availability**



Patients with type 2 diabetes

1st line: diabetes clinics

Rule-in advanced fibrosis

Transient Elastography

LSM < 8 kPa

Low risk

Attempt lifestyle modifications and exercise

No further assessment

Repeat evaluation at 1 year?

LSM ≥ 8 kPa

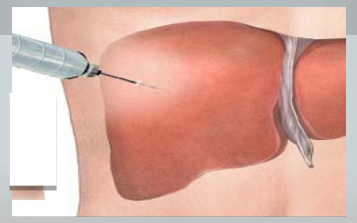
Intermediate to high risk

2nd line: Hepatologist

Failure (XL probe) 3.0- 6.7%

Consider MRE, 2D SWE or ARFI according to local availability

Consider Liver Biopsy



Attempt lifestyle modifications and exercise

Eligible for therapeutic trial?

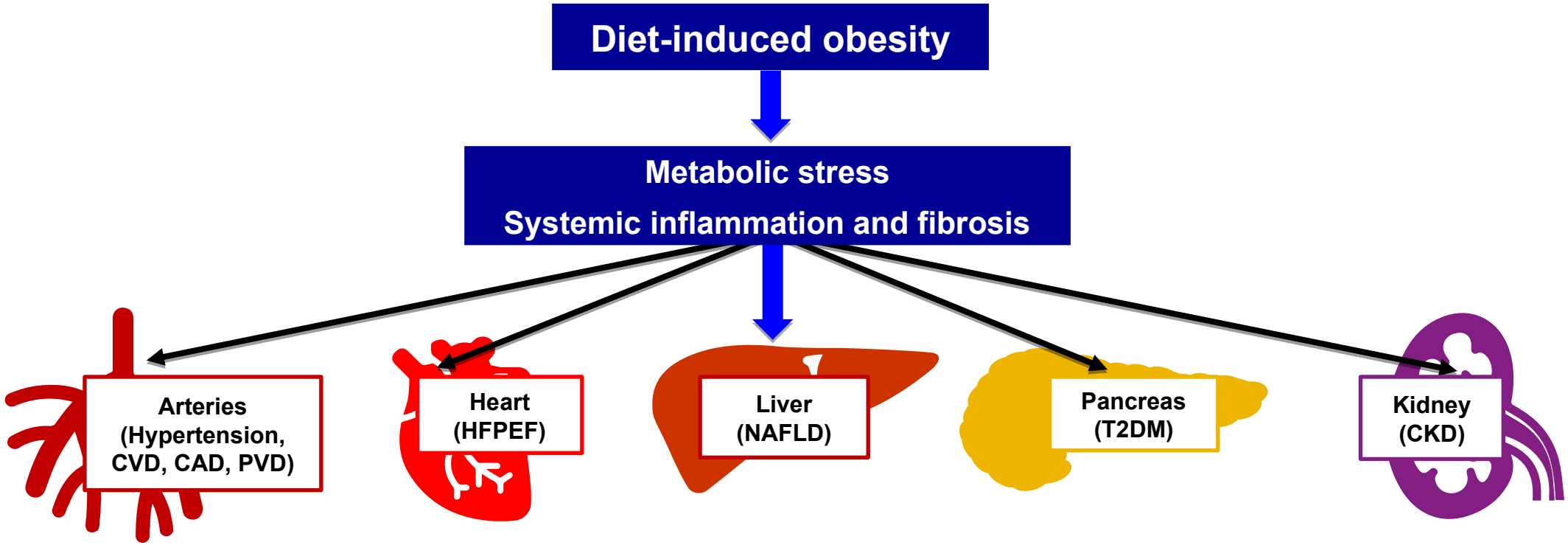
Prof Pierre Bedossa
Improving Histologic Score for NASH

- Liver biopsy is and will stay the gold standard for diagnosis of NASH for a while
- Classical definition of histogical NAFLD needs to evolve toward a more adaptative and linear classification (just like other chronic liver diseases)
  - Fibrosis score needs to be improved with more granularity in advanced stages
  - Activity score (NAS) is not prognosis and poorly reproducible : a need for a more efficient grading system, not including steatosis
- Any new scoring proposal should be validated regarding interobserver variability and clinical outcome

NASHCRN → EPOS	Comments
1a 1b 1c → 1	**Aggregate** because: - Poor reproducibility, Sampling error - No clinical relevance
2 → 2	**Changing definition** : - Introducing perisinusoidal fibrosis central or portal fibrosis + lobular fibrosis or portal + central fibrosis
→ 3 → 4	**Increase granularity**: - Few septa (no more than 2 /10mm length of biopsy) - Many septa (> 2….) without nodule
4 → 5 → 6	**Increase granularity**: - Many septa with few nodules - Annular fibrosis with complete nodulation

Prof Ana Carolina Cardoso: Current Management of NASH

NASH is part of a multi-system disorder



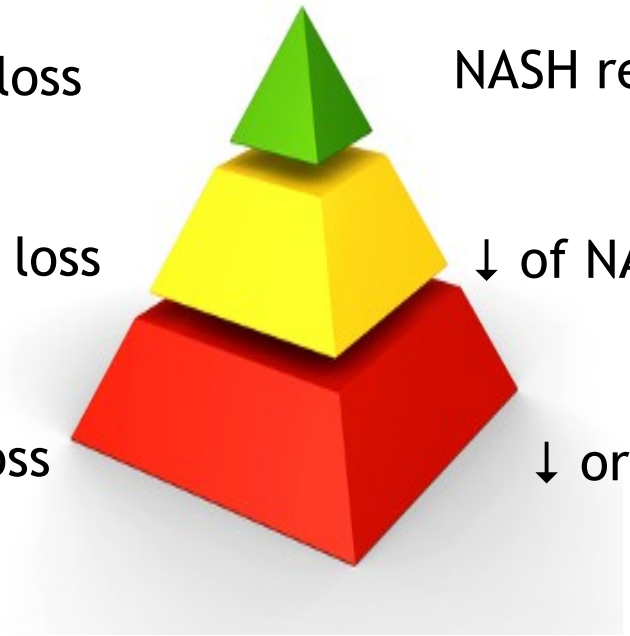
Weight loss results in improvement in liver and other affected organs

NASH Management
Weight loss is the cornerstone of the treatment

>10% weight loss — NASH remission (90%) and fibrosis (45%)[4]

7-10% weight loss — ↓ of NASH score parameters (72%)[1,3]

3-5% weight loss — ↓ or remission of steatosis (64%)[1,2]



Diet
Mediterranean?

Exercise (even in absence of weight loss)

Appetite suppressant therapy

Bariatric Surgery

Selectively

✓ Vitamin E

✓ Pioglitazone

Metformin
Liraglutide
Statins

Prof Sanyal: Current Pharmacological Treatments in Development for NASH

PPARs

FXR/FGF19

GLP-1 axis

FABAC, ACCi
FGF21

Thyβ receptor

Vitamin E

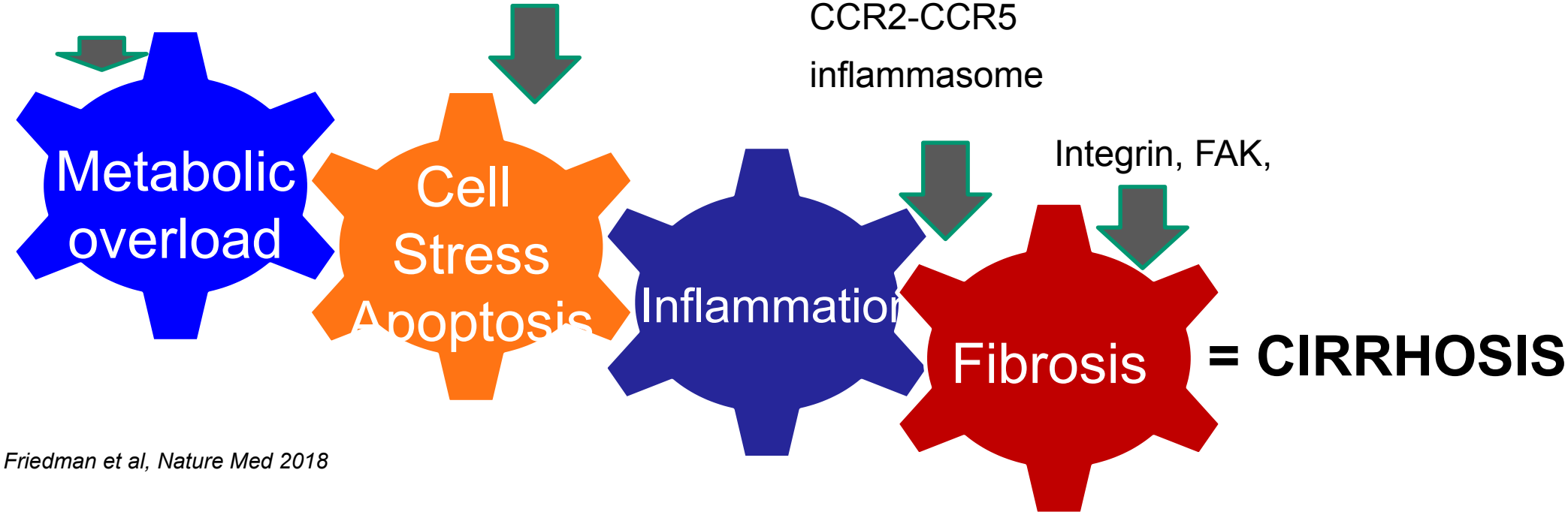
ASK1

Caspase inhibitors

CCR2-CCR5

inflammasome

Integrin, FAK,



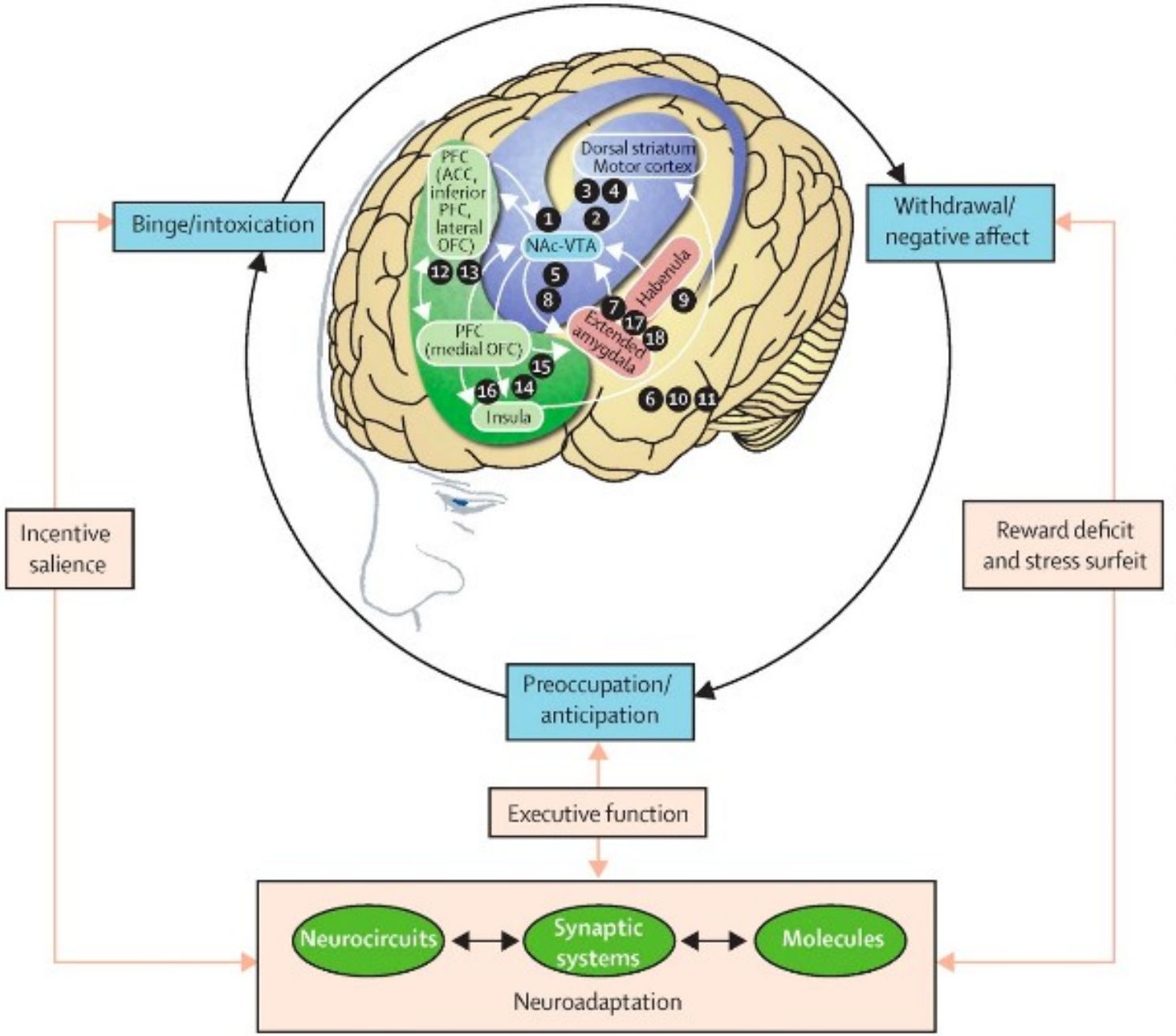
Adapted from Friedman et al, Nature Med 2018

Binge/Intoxication

↑ Dopamine
↑ Opioid peptides
↑ Serotonin
↑ GABA
↑ Acetylcholine

Preoccupation/ Anticipation

↑ Dopamine
↑ Glutamate
↑ Hypocretin
↑ Serotonin
↑ CRF



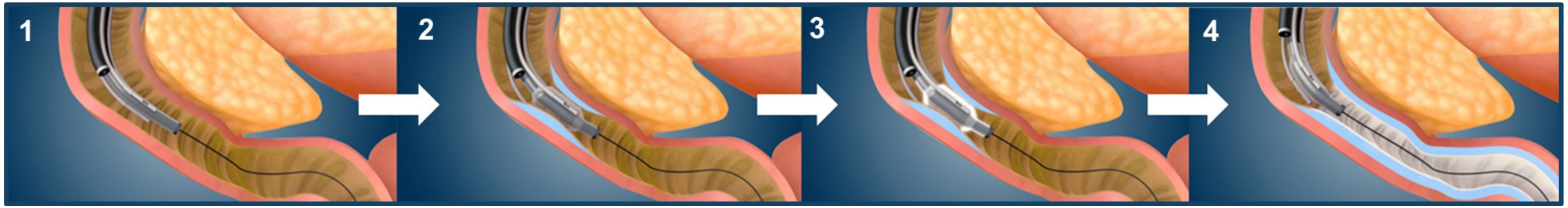
Withdrawal/ Negative Affect

↑ CRF
↑ Dynorphin
↑ Norepinephrine
↑ Hypocretin (Orexin)
↑ Substance P
↓ Dopamine
↓ Serotonin
↓ NPY
↓ Nociceptin
↓ Endocannabinoids
↓ Oxytocin

Koob, Volkow, 2017

Duodenal Mucosal Resurfacing

A novel, minimally invasive, outpatient, upper endoscopic procedure



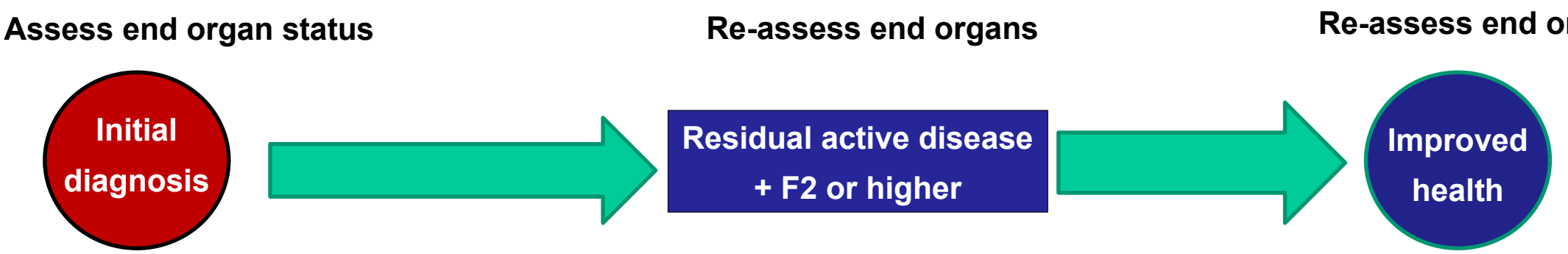
- **Revita® DMR catheter is designed to perform submucosal lift and hydrothermal ablation of hyperplastic duodenal mucosa, promote healthy epithelial regrowth within 12 weeks, and reduce insulin resistance and hyperinsulinemia[1,2]**
- ***Revita II: Phase 2A POC study showed 60% of subjects had 30% or more defatting of liver***
- ***A1C decreased by 0.8 vs 0.3 (DMR vs sham)***

1. Hadefi A et al., *Dig Dis*. 2018;36:322-324. 2. Rajagopalan H et al., *Diabetes Care*. 2016. 3. Cherrington A et al., *Gastrointest Endoscopy Clin N Am*. 2017;27:299-311. 4. Van Baar A et al. *Gut*. 2019. pii: gutjnl-2019-318349.
5. Haidry R et al., *GIE*. 2019; 673 - 681.e2. 6. van Baar ACG et al., DTM 2019 poster VAN 19122D. REVITA-2 NCT02879383

Sanyal et al, LB2, AASLD 2019

DMR = duodenal mucosal resurfacing; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; T2D = type 2 diabetes.

NASH management paradigm in next decade



Start:

- Weight loss regimen-drugs are second line
- Statins/fibrates vs Saroglitazar
- SGLT2i + GLP-1 agonist (as indicated)

Targeted therapy for:

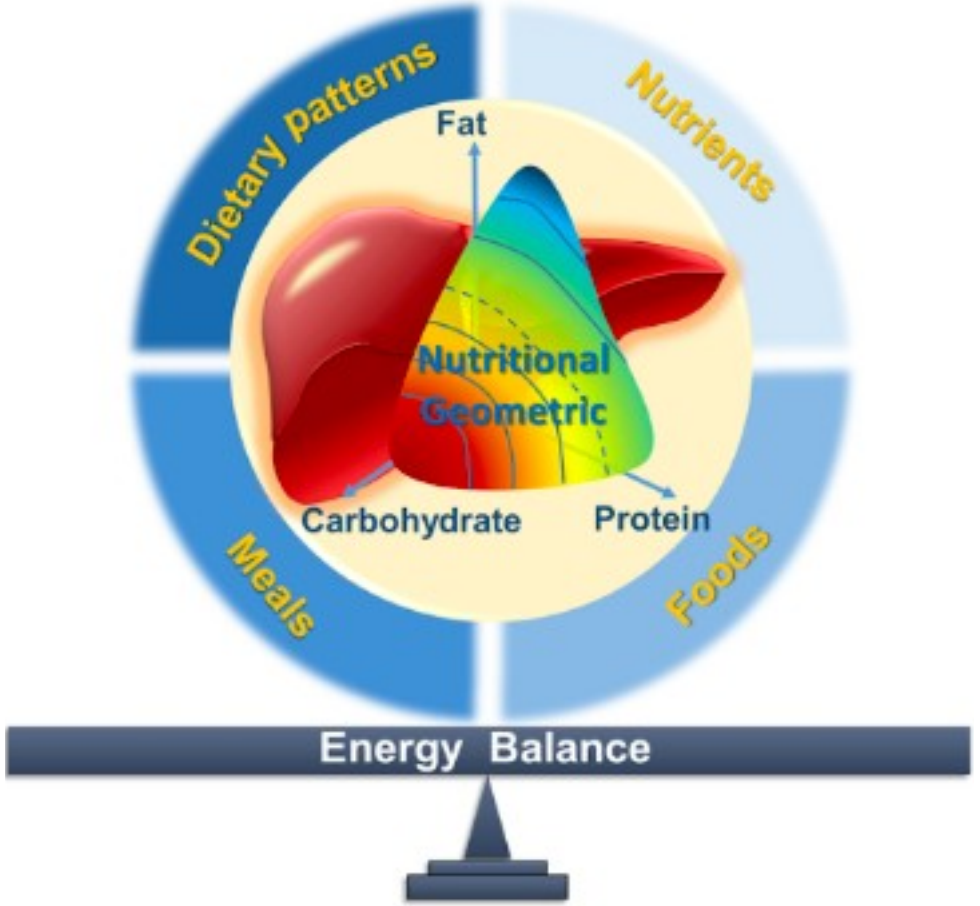
- Active NASH
- F3/F4
- Enhance healthy living/stop weight loss meds

Improved:

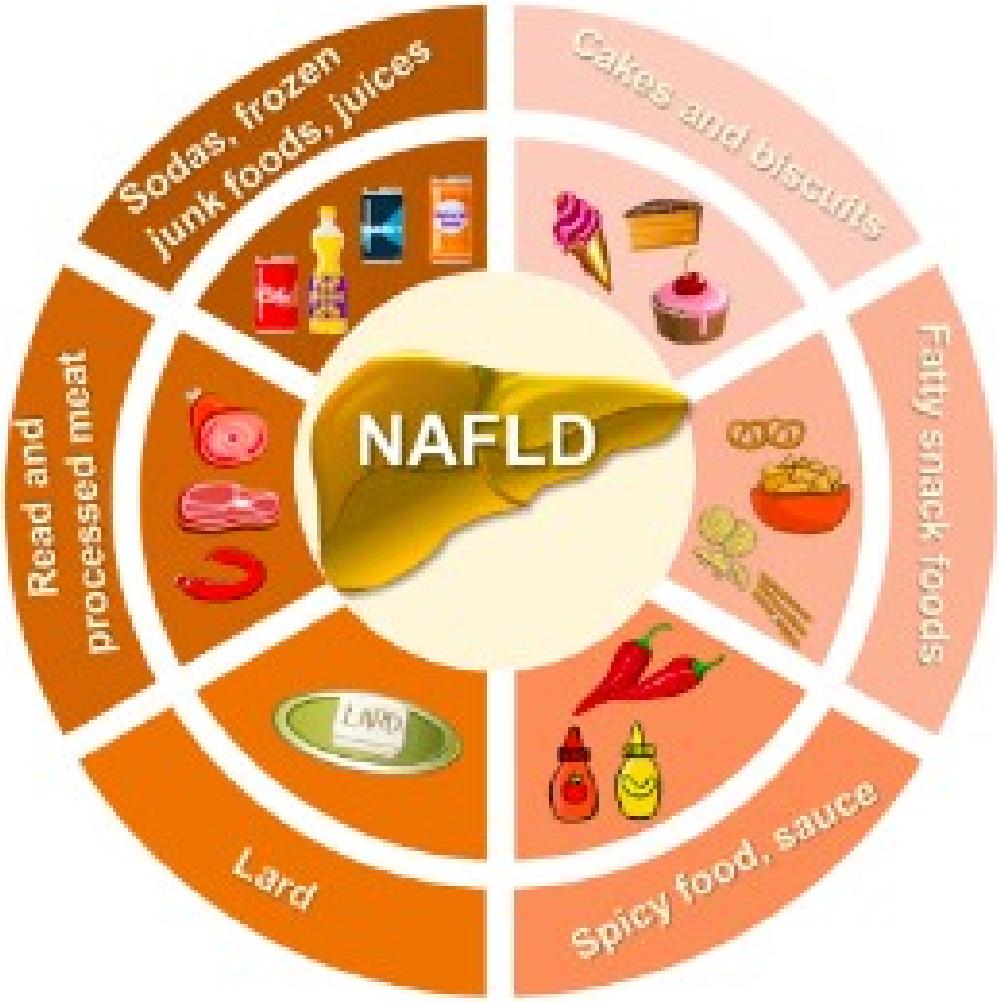
- mortality
- health care cost
- function
- QOL

Prof Manuel Romero-Gomez: Nutrition and NASH

- Dietary modifications are effective in NAFLD
- Nutritional geometry can be an excellent tool to study the relationships between the various aspects of diet and NAFLD pathophysiology
- Future algorithms developed by artificial intelligence for personalized nutritional counselling to prevent and treat NAFLD



Nutrition: The Good and the Bad



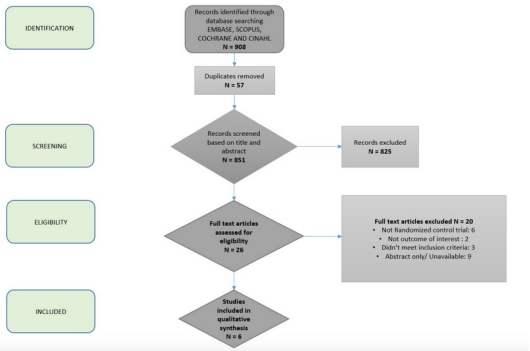
nutrients

MDPI

Review

Evaluation of Dietary Approaches for the Treatment of Non-Alcoholic Fatty Liver Disease: A Systematic Review

Naba Saeed [1], Brian Nadeau [1], Carol Shannon [2] and Monica Tincopa [1,*]



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Effects of Intermittent Fasting on Health, Aging, and Disease

Rafael de Cabo, Ph.D., and Mark P. Mattson, Ph.D.

- Diet
  - Metabolic
  - Hepatic
  - Weight loss

Mediterranean Diet (MD)

- *Extra virgin olive oil*
- *Vegetables and Fruits*
- *Cereals, legumes, nuts*
- *Moderate intakes of fish and other meat, dairy products and red wine*
- *Low intakes of eggs and sweets.*

↓SFA
↑**MUFA**
↑**PUFA**
↑protein vegetables
↓sugar fructose
↓cholesterol
↑**fiber**
↑**polyphenols,**
↑**carotenoids**

- Dietary pattern
  - MD — 3/5 WL — 3/5 HS imp — 2/4 HOMA — 2/5 Triglyc
  - LFD — 1/2 WL — 1/2 HS imp
  - IF — 1/2 IF — 1/2 HS imp
  - LCH — No WL — 1 HS imp

Saeed N et al. Nutrients 2019;11:3064

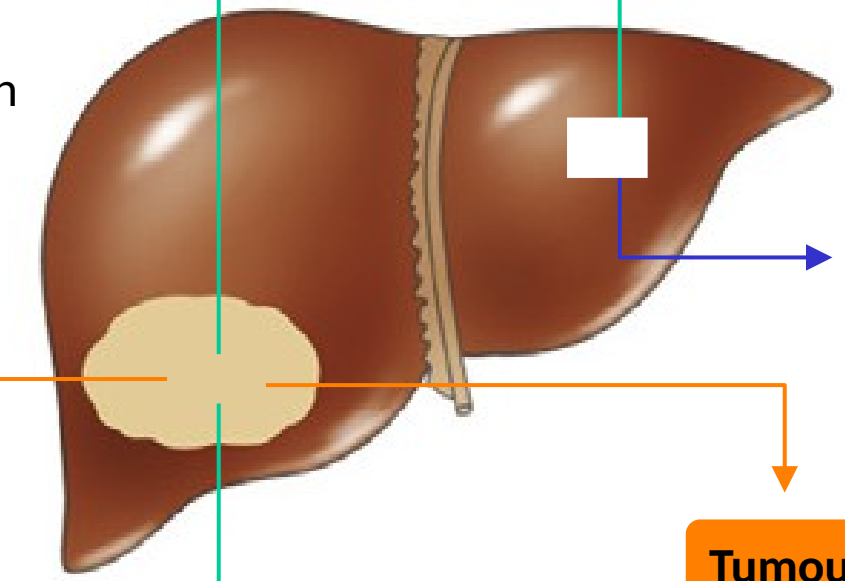
Prof Pierre Nahon: Optimal management of HCC today (and tomorrow)

Inclusion in « adjuvant » trials

- Neoadjuvant and/or adjuvant strategies (?)
- Sequential biopsy for identification of responders (?)

Liver disease management

- Treatment of the cause
- PHT monitoring and bleeding prevention



Underlying liver disase and patient

- Cirrhosis
- PHT/liver function
- Cause
- Age
- Male gender

Pathology-Molecular biology

- Differenciation
- Progenitor cells markers
- MVI
- Macro-trabecular subtype
- Molecular classification (?)

Tumour characteristics

- Number, size
- Infiltrating pattern
- AFP level

Quality of resection/ablation

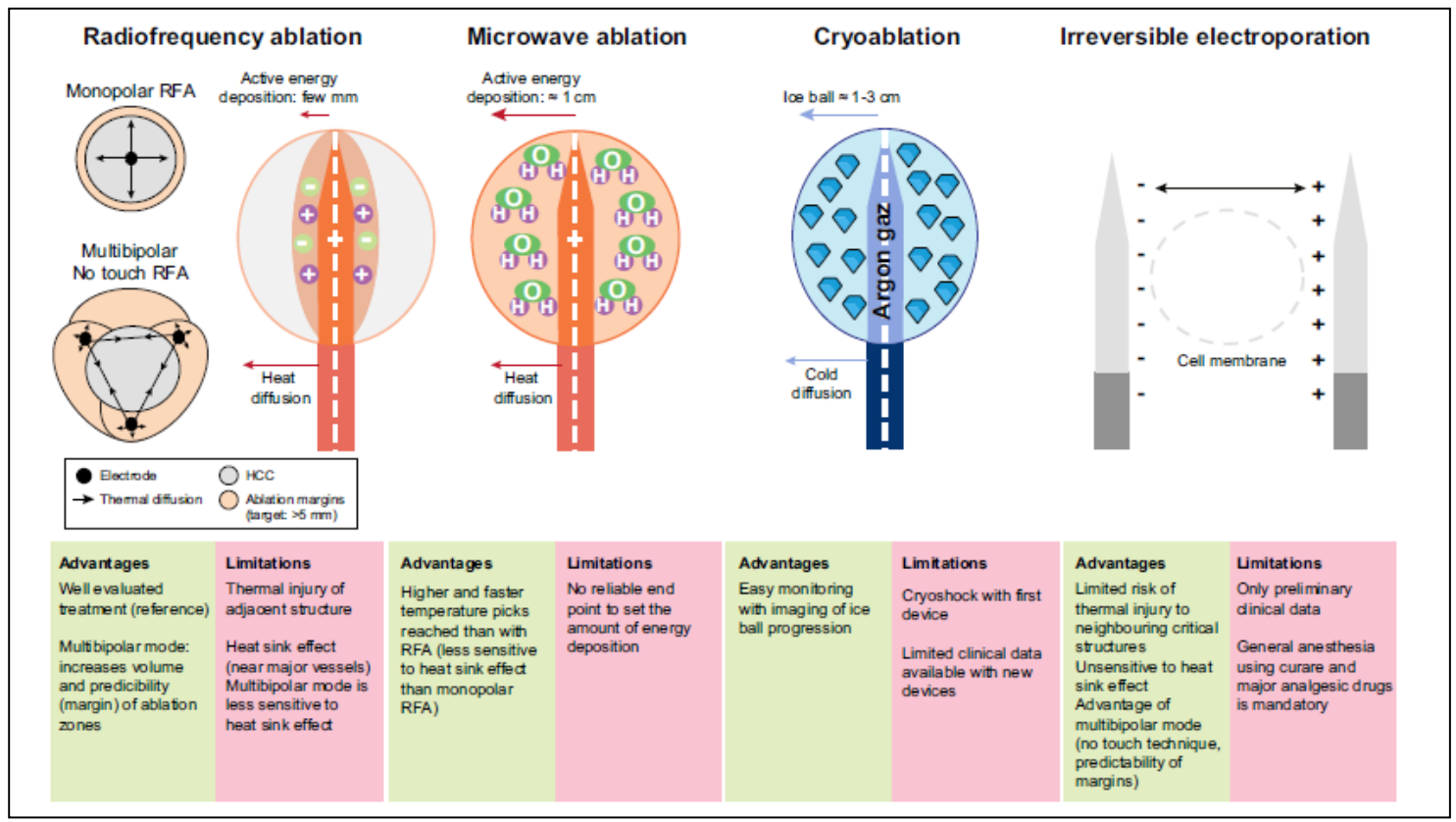
Nahon P, Liver Int 2020

Review

JOURNAL
OF HEPATOLOGY

Percutaneous treatment of hepatocellular carcinoma: State of the art and innovations

Jean-Charles Nault[1,2,3,*,†], Olivier Sutter[4], Pierre Nahon[1,2,3], Nathalie Ganne-Carrié[1,2,3], Olivier Séror[2,3,4,*]

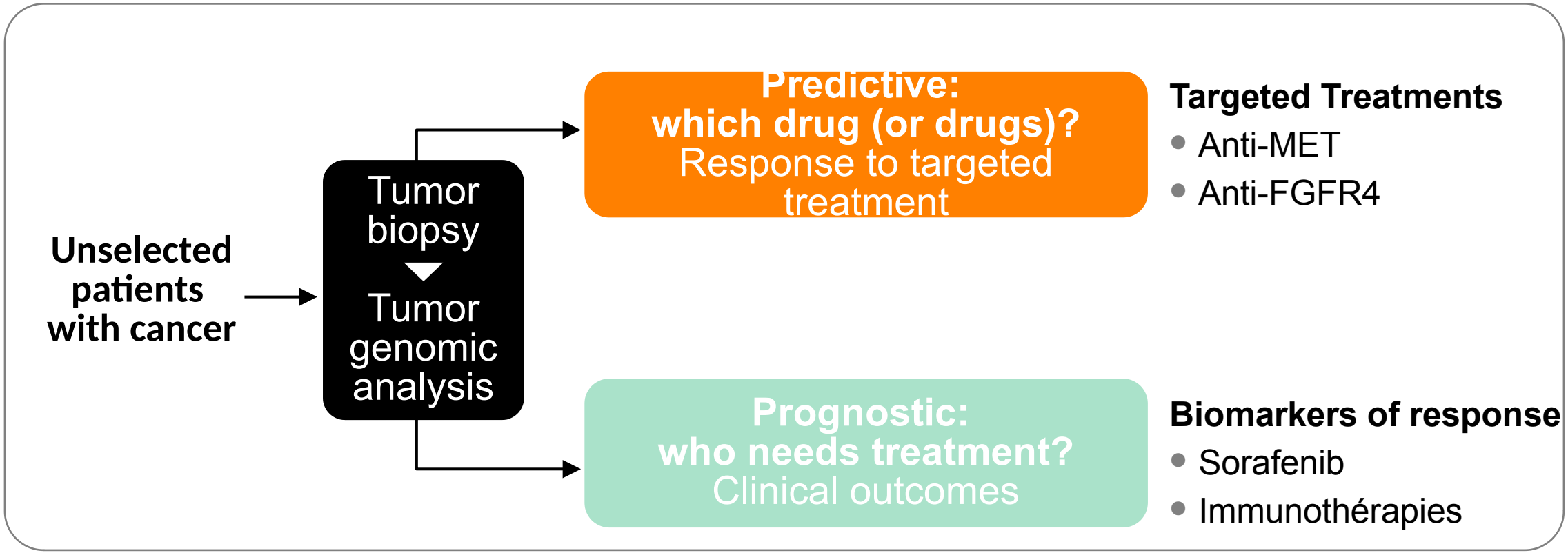


Advantages	Limitations	Advantages	Limitations	Advantages	Limitations	Advantages	Limitations
Well evaluated treatment (reference) Multibipolar mode: increases volume and predicibility (margin) of ablation zones	Thermal injury of adjacent structure Heat sink effect (near major vessels) Multibipolar mode is less sensitive to heat sink effect	Higher and faster temperature picks reached than with RFA (less sensitive to heat sink effect than monopolar RFA)	No reliable end point to set the amount of energy deposition	Easy monitoring with imaging of ice ball progression	Cryoshock with first device Limited clinical data available with new devices	Limited risk of thermal injury to neighbouring critical structures Unsensitive to heat sink effect Advantage of multibipolar mode (no touch technique, predictability of margins)	Only preliminary clinical data General anesthesia using curare and major analgesic drugs is mandatory

Several trials in adjuvant setting, with immune checkpoint inhibitors in patients high risk of recurrence after curative treatment of HCC

Phase III Trial	Experimental Arm	Control Arm	Primary endpoint	Secondary endpoints	Planned participant recruitment
ChekMate 9 DX (NCT03383458)	Nivolumab	Placebo	Recurrence-free survival	Overall survival Time to recurrence	530
KEYNOTE-937 (NCT03867084)	Pembrolizumab	Placebo	Recurrence-free survival overall survival	Adverse event QoL	950
EMRALD 2 (NCT03847428)	Durvalumab Bevacizumab	Placebo	Recurrence-free survival	Overall survival Time to recurrence	888
IMbrave050 (NCT04102098)	Atezolizumab Bevacizumab	Active surveillance	Recurrence-free survival	Overall survival Time to recurrence	662

Tumour Genomics Expected to Aid in Decision-making in the Future



Important role of biobanking to help in this effort

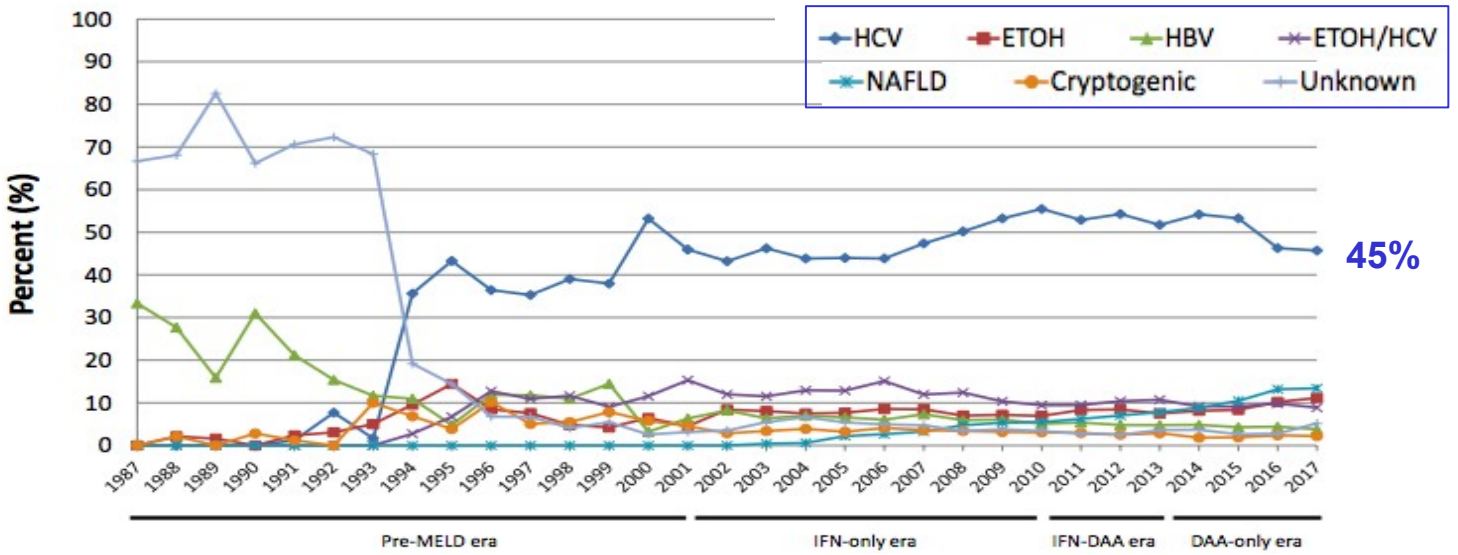
Simon R, Nature Reviews 2013

Prof Norah Terrault
Liver Transplantation for HCC

U.S.

UNOS

30% for HCC



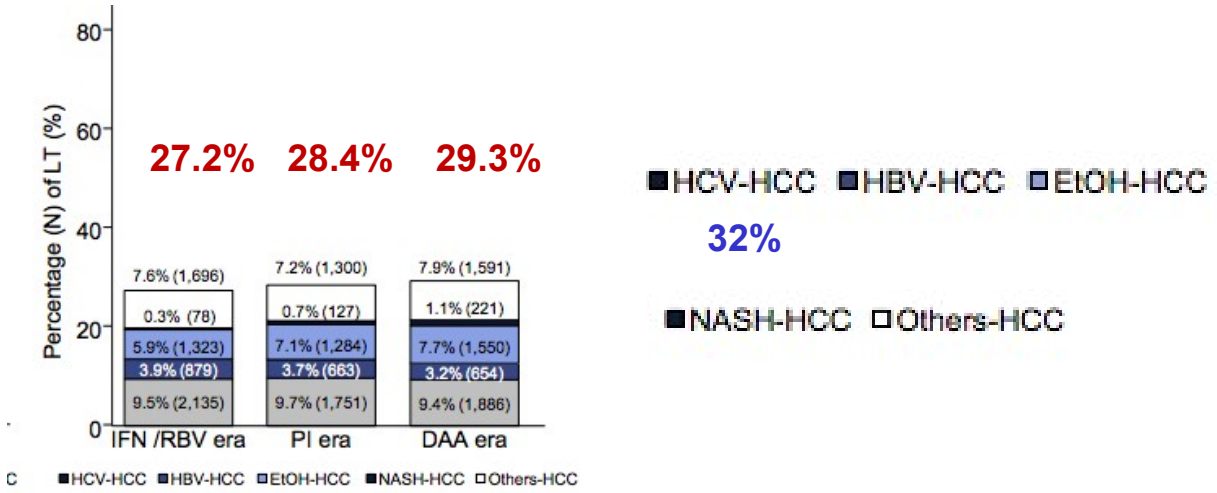
45%

HCV is most common underlying cause

NAFLD increasing

Europe

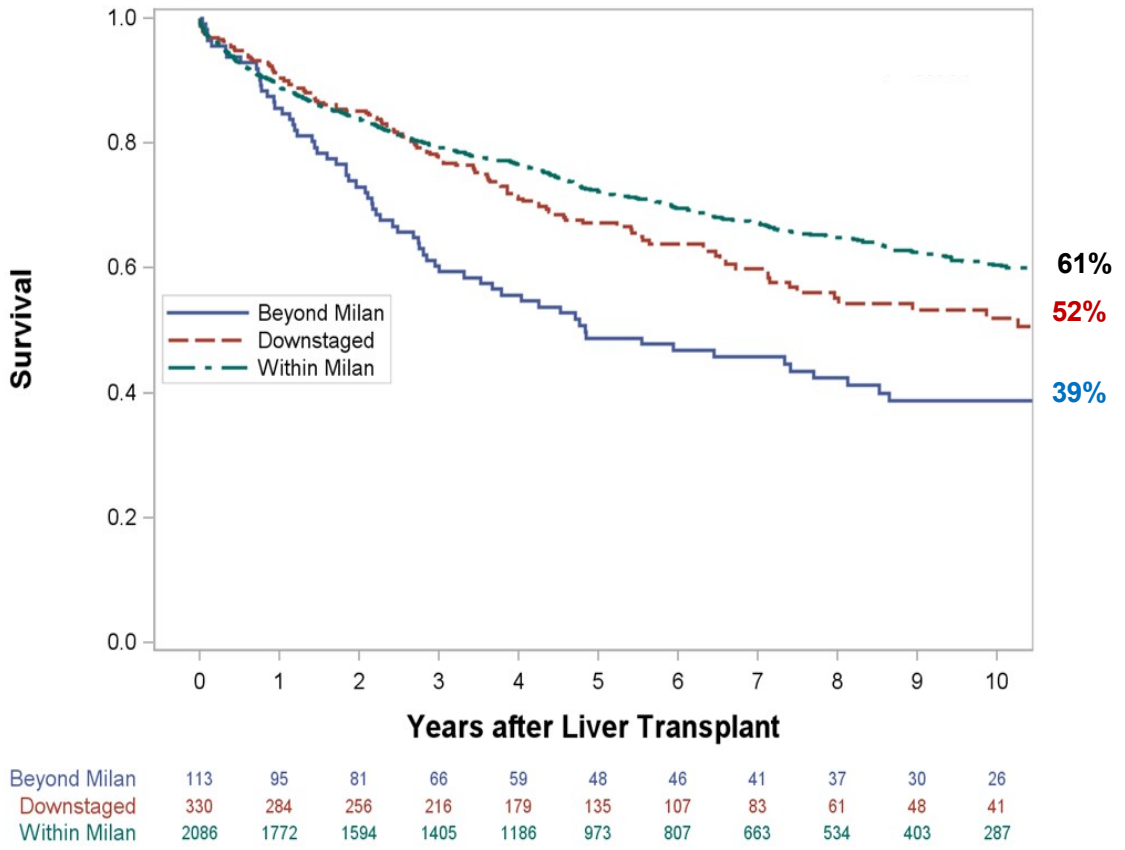
ELTR



Puigvehi M, Am J Transplant 2020;20:220-230
Belli L, J Hepatol 2018; 69(4):810-817

Milan to Beyond Milan Criteria

- Size and number define Milan criteria
- Additional benefit in adding:
  - AFP
  - Response to LRT
- Modest expansion of Milan criteria can achieve acceptable post-transplant outcomes
  - Downstaging to Milan criteria is goal
  - Drop-out on wait-list higher for those outside Mc



Tabrizian P, AASLD 201

Recurrent HCC in Liver Transplant Recipients

Recurrence in ~15-20%, mostly within first 2 years

Systematic review: 1021 recipients

Treatment	total # patients	Median survival (mos) ± SD (weighted)	# studies
Resection	27	42 ± 24.5	6
LRT (TACE)	40	11.2 ± 8.81	6
Sorafenib	76	12.1 ± 9.95	7
Sorafenib + mTOR	68	18.2 ± 6.53	5
Systemic chemotherapy	35	5.79 ± 2.7	2
Support care	54	3.3 ± 2.12	4

De'Angelis N, WJG 2015;21:11185-11198

Prof Bruno Sangro: Immunotherapy for HCC -When and How

- **Immunotherapy through ICPIs is emerging as a key therapy for patients with HCC → produces durable and clinically relevant responses with few side effects.**
- **Combination of Atezolizumab and Bevacizumab may become the standard of care for 1L therapy (and this will impact downstream options).**
- **Single agents and combinations of ICPIs with other ICPIs, VEGF inhibitors or multi-TKIs are being tested in across tumor stages.**
- **Combinations of ICPIs with VEGF inhibitors or multi-TKIs carry significant toxicities in cirrhotic patients that demand a specific work-up for diagnosis and management.**

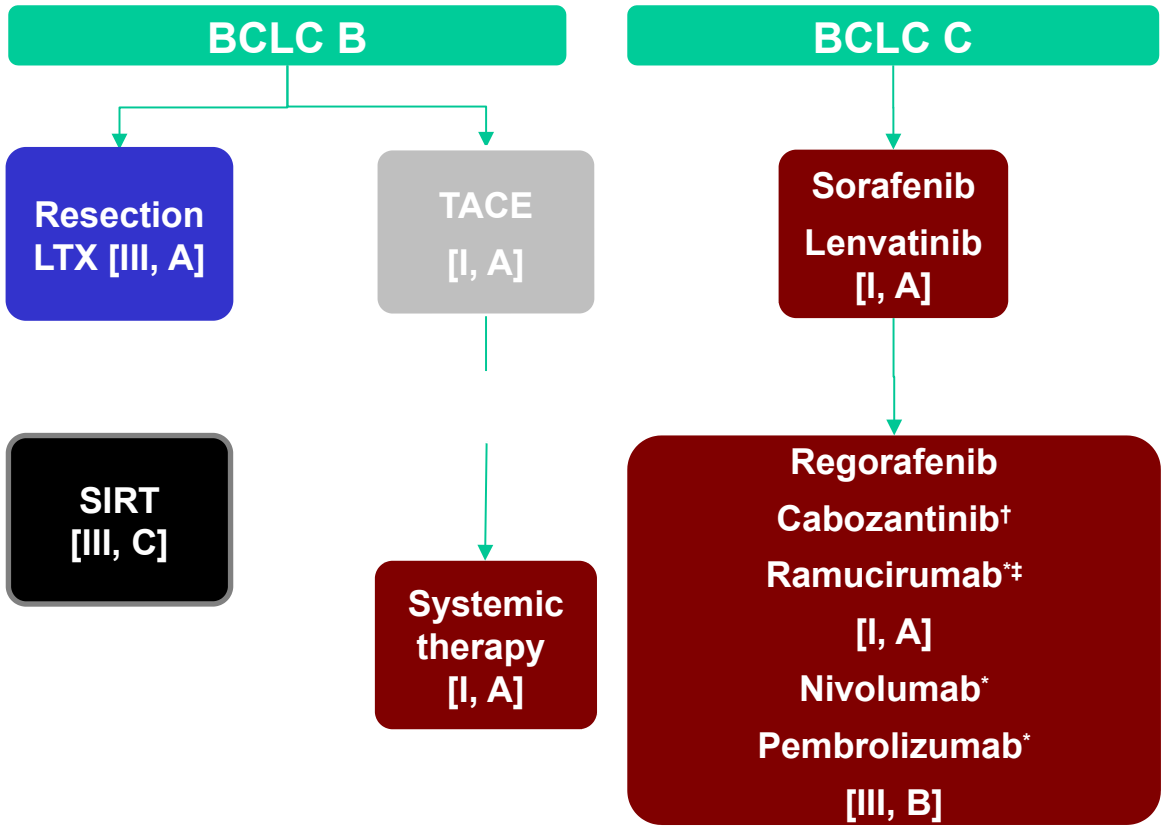
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29 (Supplement 4): iv238–iv255, 2018
doi:10.1093/annonc/mdy308

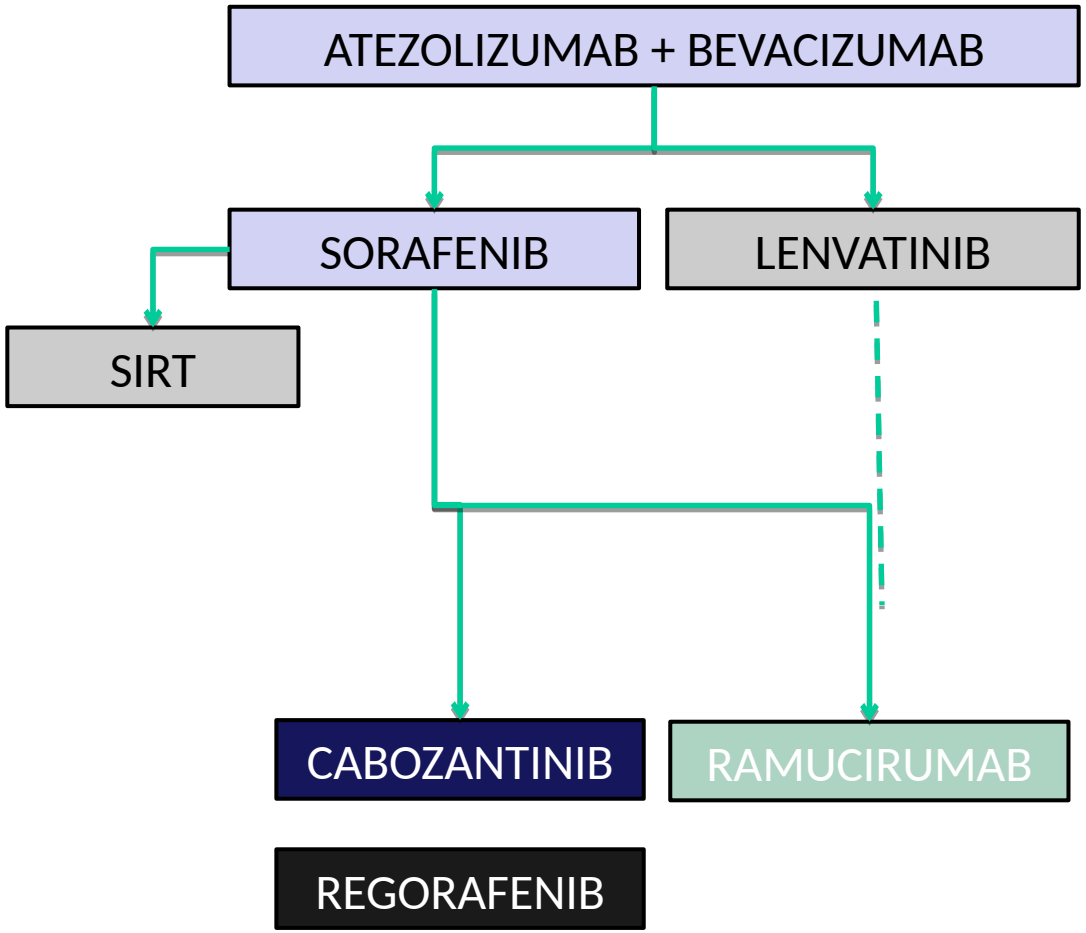
CLINICAL PRACTICE GUIDELINES

Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

A. Vogel[1], A. Cervantes[2], I. Chau[3], B. Daniele[4], J. M. Llovet[5,6,7], T. Meyer[8,9], J.-C. Nault[10], U. Neumann[11], J. Ricke[12], B. Sangro[13], P. Schirmacher[14], C. Verslype[15], C. J. Zech[16], D. Arnold[17] & E. Martinelli[18], on behalf of the ESMO Guidelines Committee*



Systemic Therapy of HCC



Prof. Ulrich Beuers: Cholestatic Liver Diseases and Cholangiocarcinoma

Amsterdam UMC
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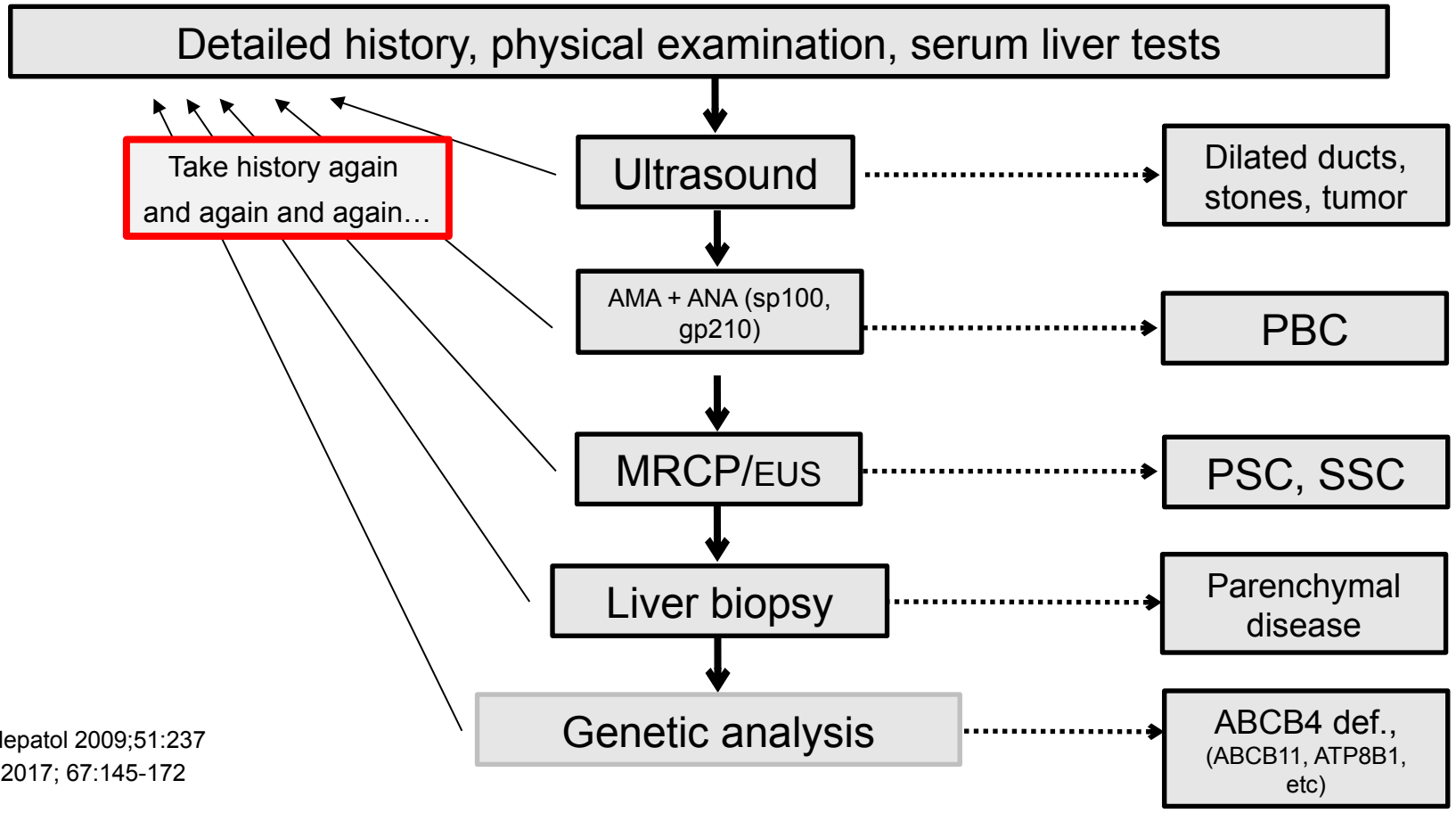
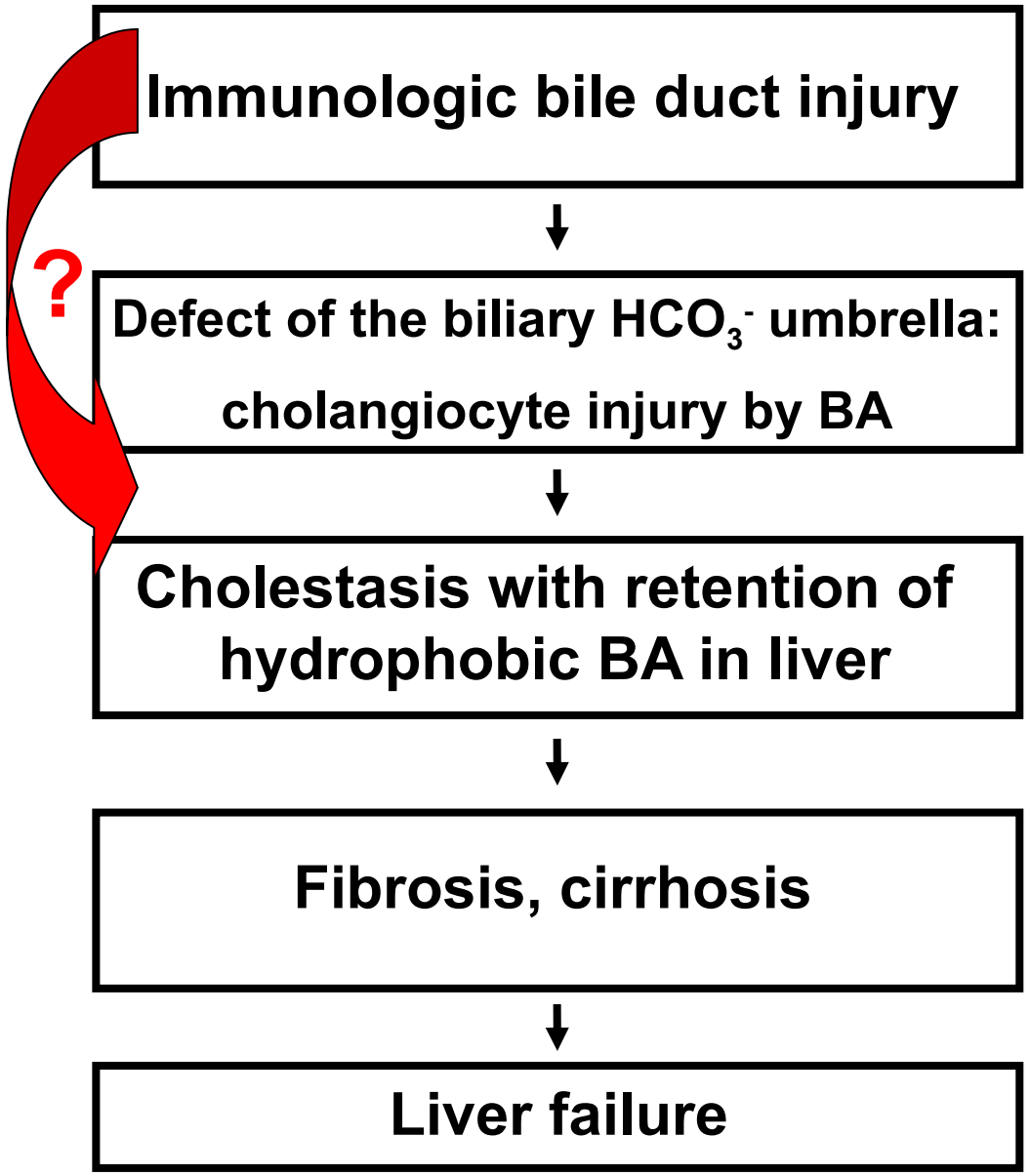
Management of Cholestatic Liver Diseases 2020



EASL CP Guidelines Cholestasis, J Hepatol 2009;51:237
EASL CP Guidelines PBC. J Hepatol 2017; 67:145-172

Primary biliary cholangitis: *Potentially new* Therapy

Potential pathogenetic mechanisms



FXR agonist: **Obeticholic acid**
Nevens et al., New Engl J Med 2016; 375: 631

PPAR agonist: **Bezafibrate**
Corpechot et al., New Engl J Med 2018;378:2171

GR/PXR-Agonists: e.g., Budesonide?
Hirschfield et al, in preparation

Ursodeoxycholic acid
(13-15 mg/kg/d)

Liver transplantation

EASL CP Guidelines PBC. J Hepatol 2017; 67:145

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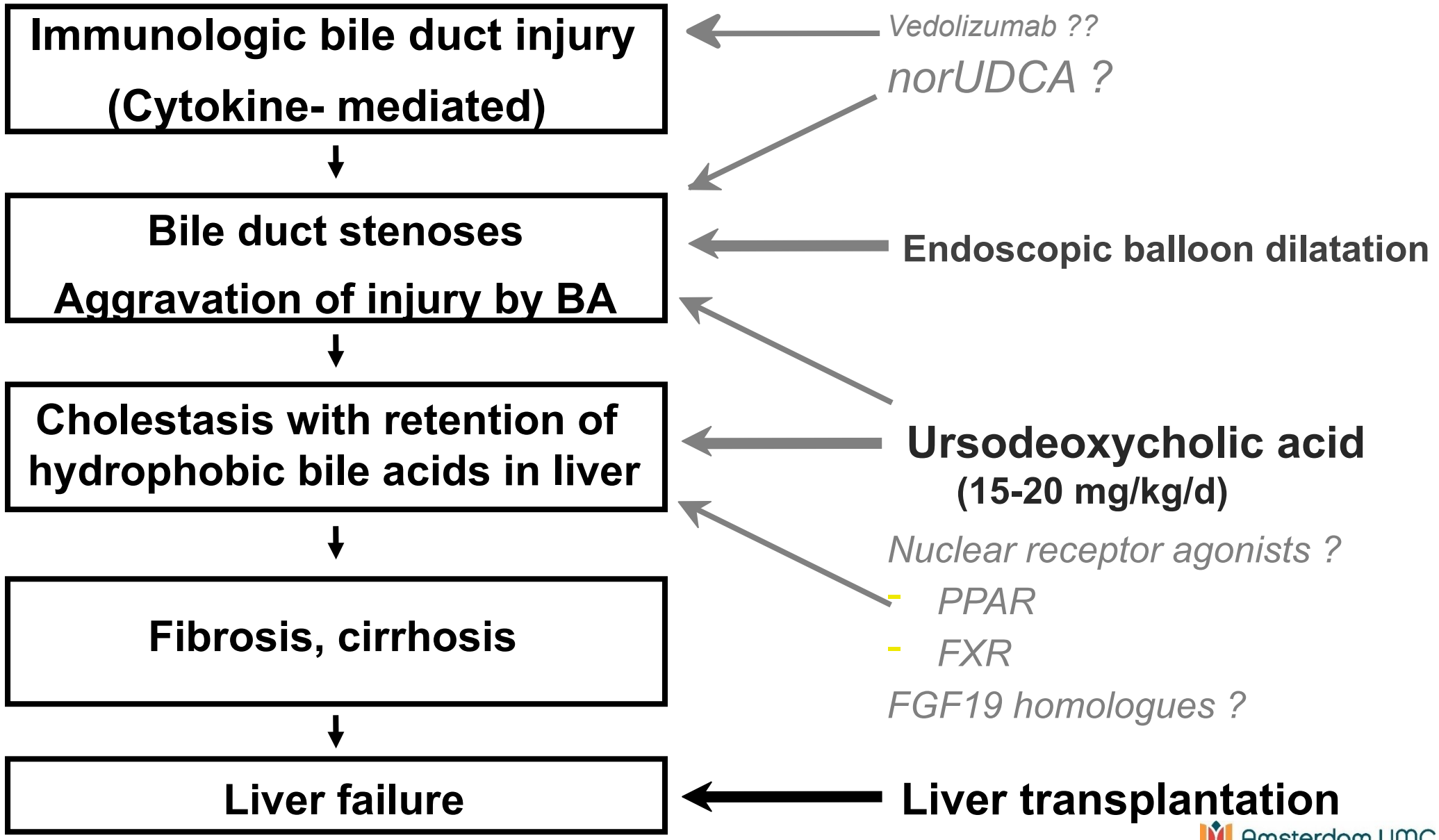
PSC Therapy *under evaluation*

Pathogenetic model



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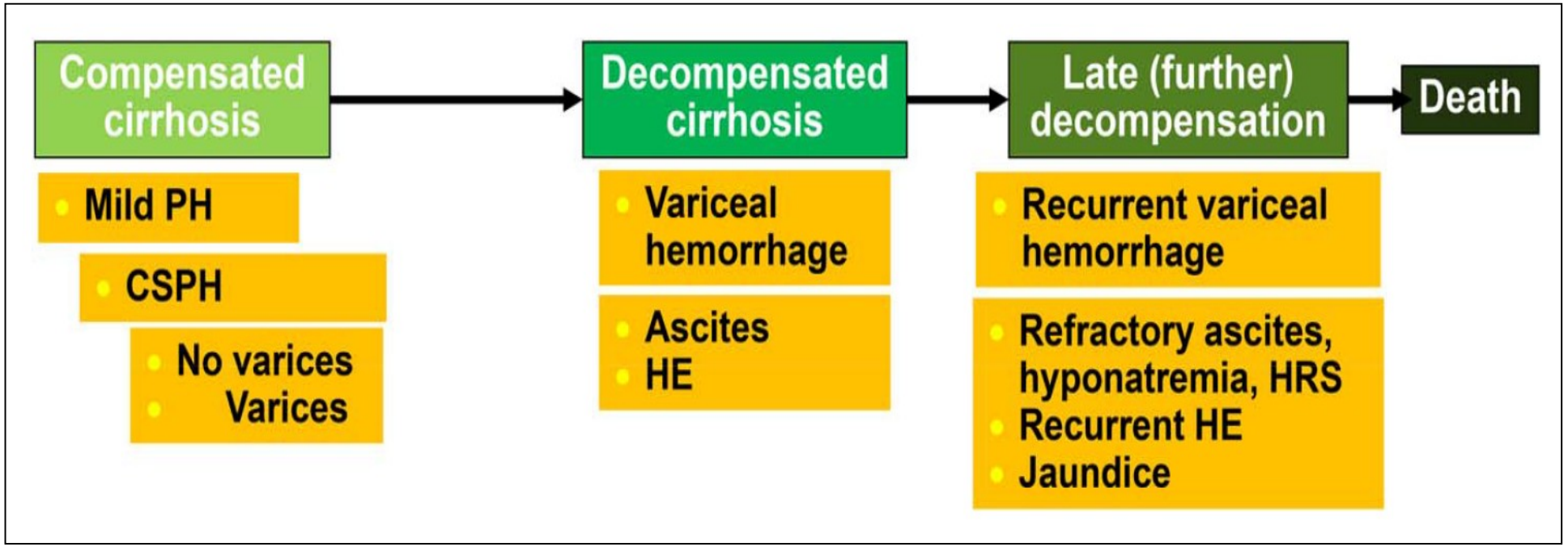
Prof Adrian Gadano: What is New in Portal Hypertension?



- **Cirrhosis should be managed in two distinct clinical stages, compensated and decompensated, defined by the presence or absence of overt clinical complications (ascites, VH, and HE).**
- **The identification of patients with cirrhosis and clinically significant portal hypertension (CSPH) is extremely important. Non invasive tests will probably be of great help as diagnostic tools**

What's New in the Diagnosis of Portal Hypertension ?

Liver Stiffness Measurement (LSM) by Transient Elastography:

LSM ≥ 21 kPa **rules in CSPH**

- Ability to identify the presence of CSPH

LSM < 20 kPa and a platelet count > 150.000/mm^3 **very unlikely to have high risk varices** → 21 % EGDs could be avoided…

- Ability to rule out the presence of high-risk varices

de Franchis R and Baveno VI Faculty. J Hepatol 2015

What's New in the Management of Portal Hypertension ?

- After an episode of acute variceal bleeding in patients at high risk of failure or rebleeding, an "early" (pre-emptive) TIPS within 72 hours from EGD/EBL may benefit selected patients → Refined selection criteria: CP 10-13?
- Anticoagulation may improve intrahepatic microcirculation from a theoretical point of view but its clinical impact still needs to be demonstrated → not ready for prime time (Rivaroxaban trial results expected this year)
- Statins have shown to lower the incidence of decompensation and mortality in different populations of patients with cirrhosis → not enough data yet?

Early Therapy with NSBB in Patients with Compensated Cirrhosis with CSPH

The PREDESCI Study

- Cooperative, multicenter, placebo-controlled, randomized clinical trial
- Population studied: compensated cirrhotics with HVPG ≥ 10 mmHg (CSPH), **without high risk varices or previous decompensation** (n=201)

Acute HVPG response to iv Propranolol*:

acute responders ➔ **Propranolol vs placebo**

non-responders ➔ **Carvedilol vs placebo**

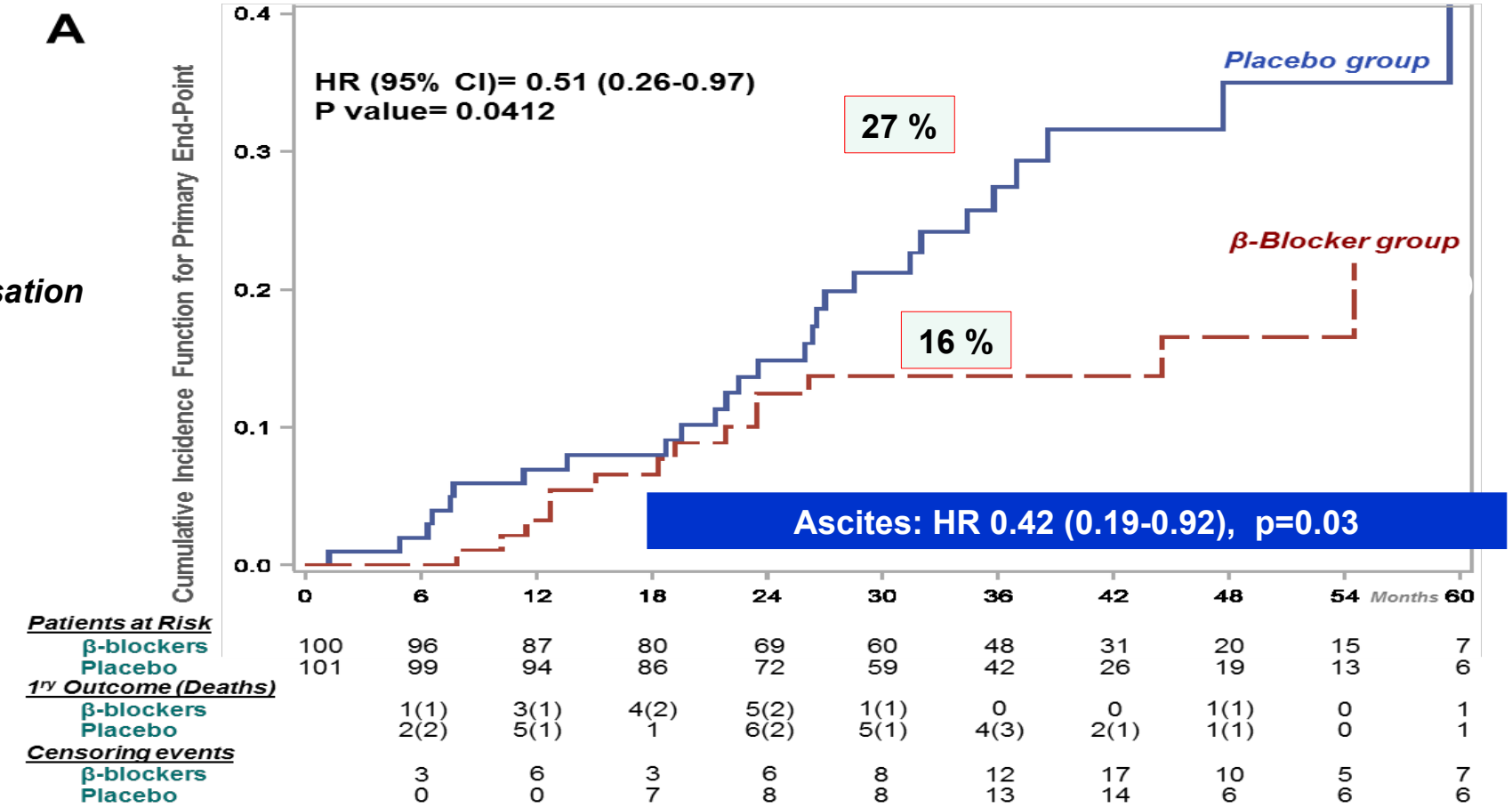
- Primary endpoint: Decompensation (ascites, bleeding or encephalopathy) or death.

0.15 mg/Kg IV; Acute Responders: ↓ HVPG ≥ 10% of baseline

Villanueva et al, Lancet 2019

Propranolol/Carvedilol Prevents Decompensation of Cirrhosis
The PREDESCI Study

First clinical decompensation



New recommendation may be anticipated....

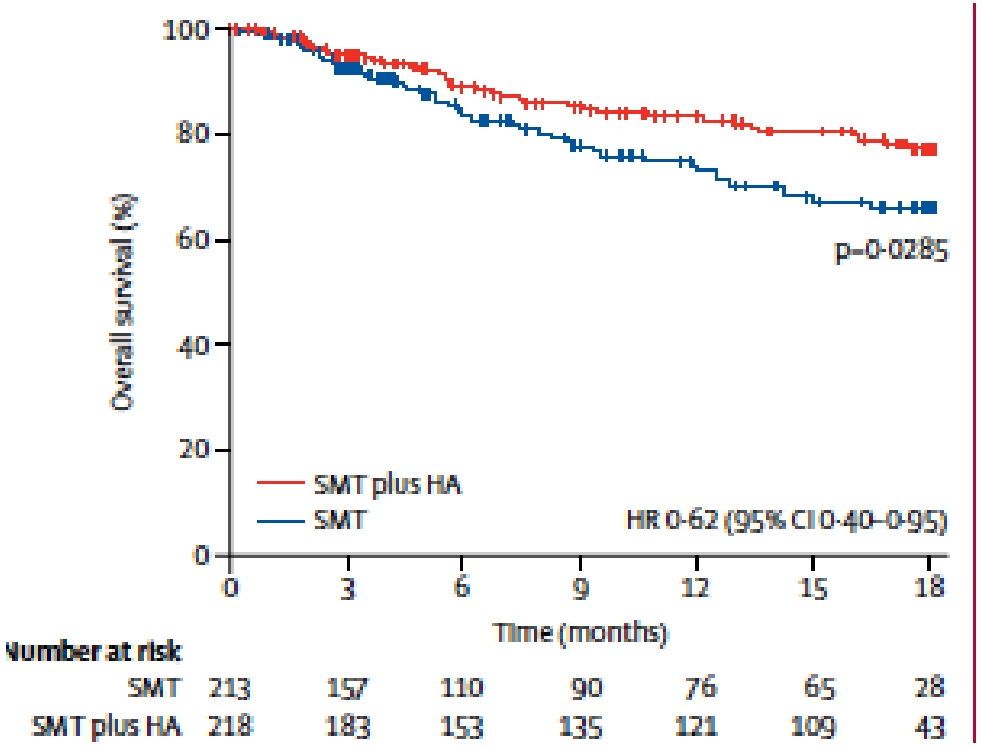
Villanueva et al, Lancet 2019

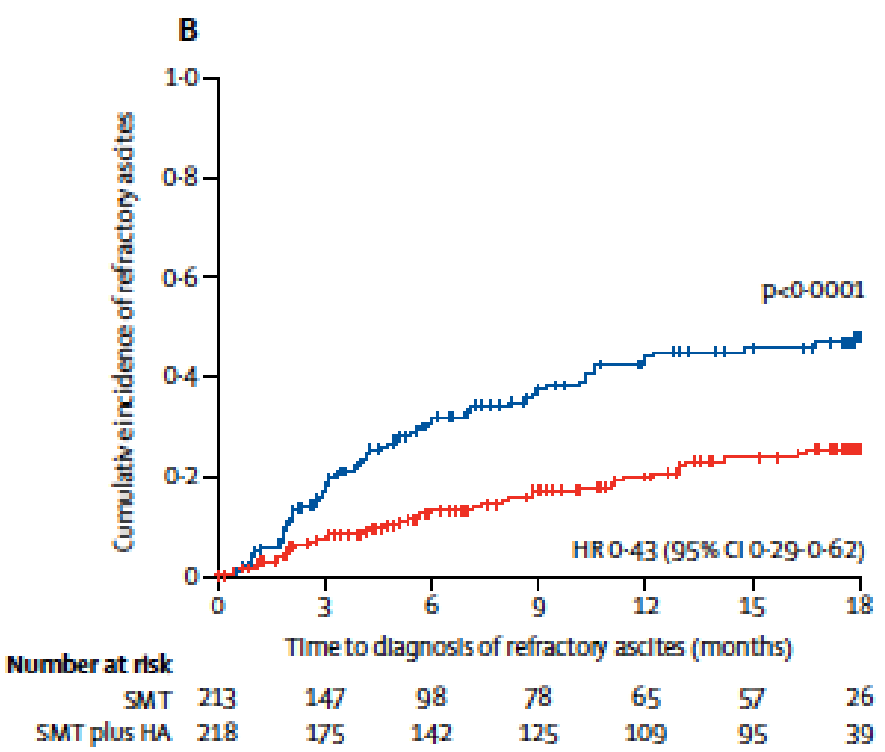
Prof Marika Rudler: Optimal Management of Ascites

- Ascites: poor prognosis
  - TIPS should be discussed « early » in the course of ascites
  - Discussion TIPS/LT at the same time
- Non-refractory ascites
  - Albumin infusions for non-refractory ascites offers benefit
  - TIPS (covered stents) – consider earlier (non-refractory)
- Refractory ascites – careful selection (and LT backup)

Non-Refractory Ascites Albumin Infusions: ANSWER study

40g twice a week for two weeks and then 40g weekly in patients treated with diuretics





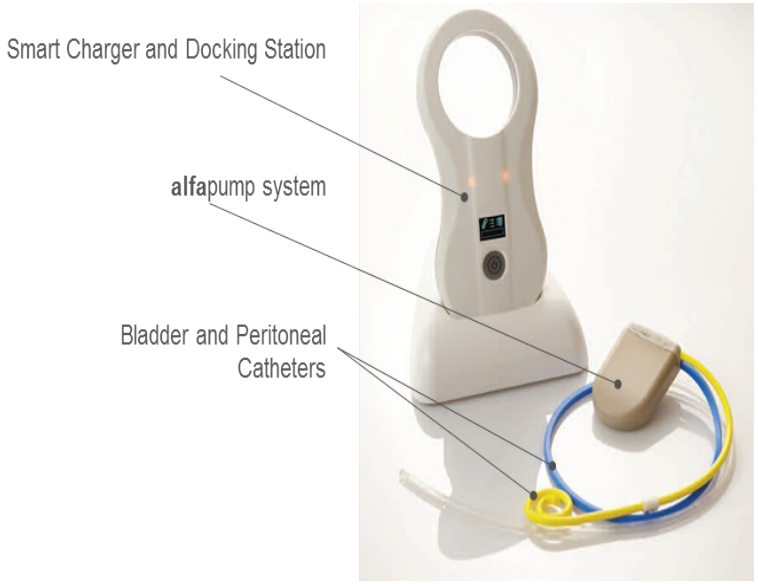
Caraceni et al.
The Lancet 2018

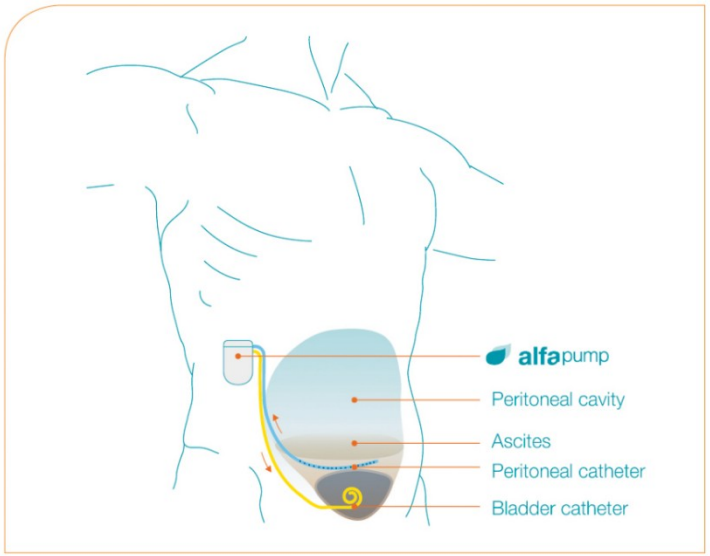
TIPS for Refractory Ascites: how to select the patients

- Reasonable option in carefully selected patients
- Concurrent consideration of LT
  - ✓BiliT < 50 µmol/L
  - ✓Plt > 75G/L
  - ✓Child-Pugh score <13, MELD score<19
  - ✓No chronic HE, < 2 previous episodes of HE
  - ✓No infection (delay)
  - ✓BNP< 40 Nt-pro BNP<125 and normal echocardiography
  - ✓No pulmonary hypertension

Good liver function

Refractory ascites: Alfapump®





- **Decreased frequency of LVP**
- **Improved HRQOL and nutritional status**

Caveats:

- **Learning curve**
- **Costs**

Prof Francois Durand: Acute on Chronic Liver Failure

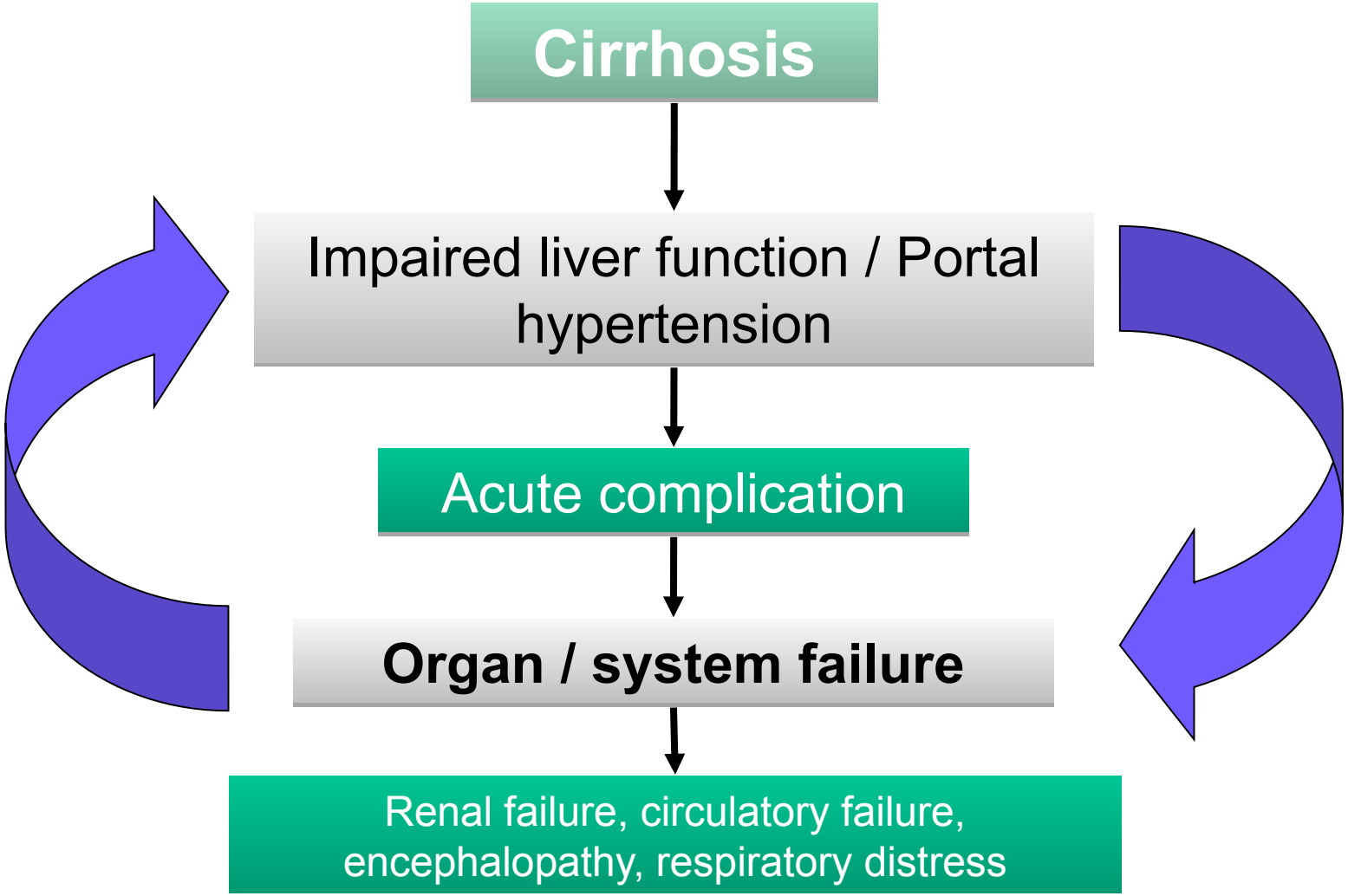
- ACLF is defined as:
  - Underlying cirrhosis
  - Occurrence of organ / system failure
- Precipitants: infection, drug toxicity, surgery

Organs failure:

- Liver failure: bilirubin ≥ 200 µmol/L
- Kidney failure: creatinine ≥ 180 µmol/L
- Coagulation failure: INR ≥ 2.5 and/or platelets ≤ $20*10^9$/L
- Circulatory failure: use of vasopressors
- Cerebral failure: grade III or IV encephalopathy
- Respiratory failure: PaO2/FiO2 ≤ 200

High mortality rate: 28-day mortality > 15%

Exiting the Vicious Circle of ACLF



GCSF

MARS

Transplantation

Limits to be defined to avoid futility

Prof Valerie Vilgrain: Advances in Imagery for Liver Tumors

- Liver imaging is improving in many ways: diagnosis and characterization
- New questions emerging on screening imaging of liver malignancies
- Quantitative imaging benefits from mathematics and artificial intelligence