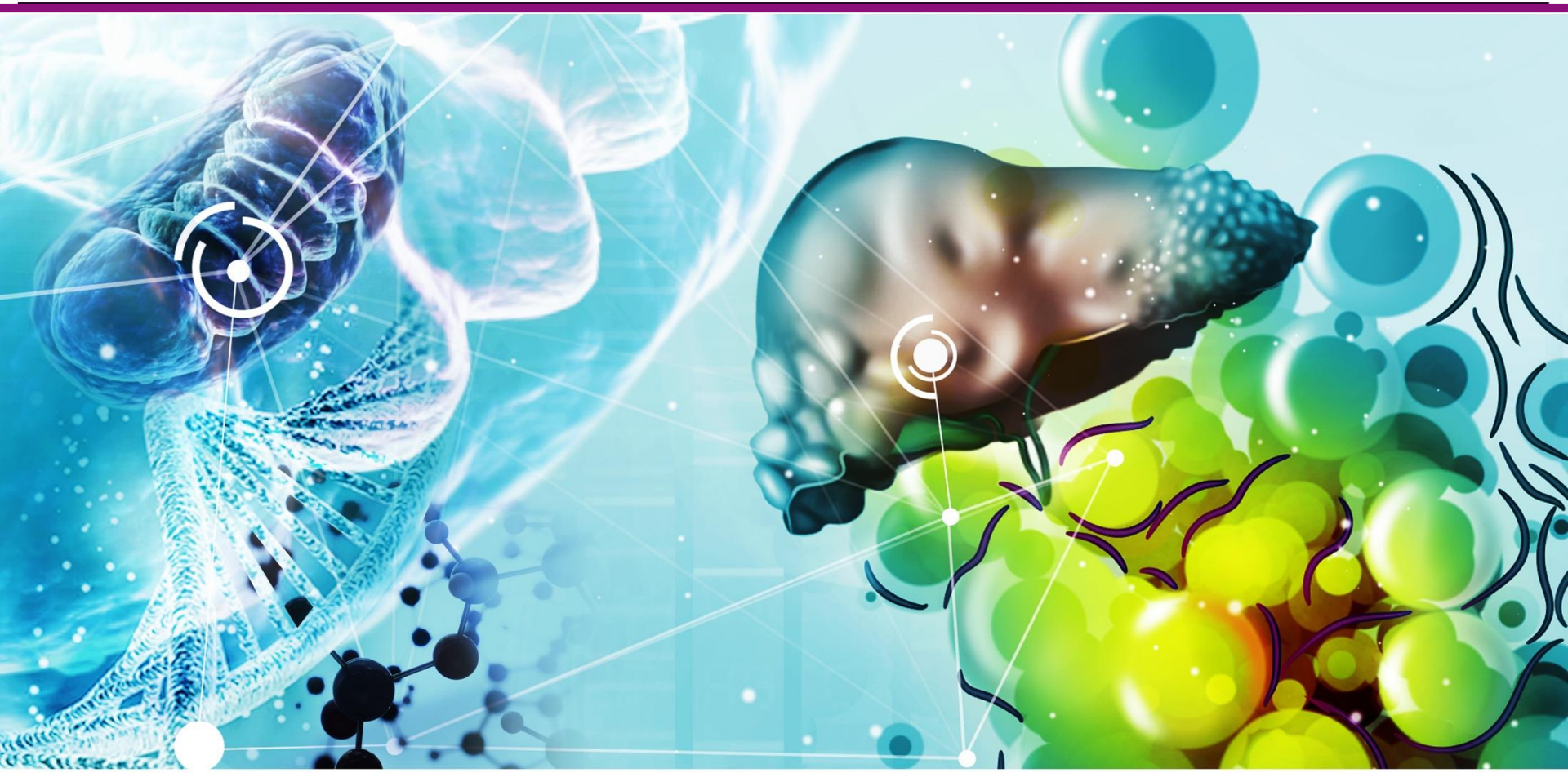
Molecular markers of disease progression in **NASH**



Professor Jean-François Dufour
Director University Clinic of Visceral Surgery and Medicine, Hepatology,
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Paris NASH Meeting
International Think Tank

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Disclosures

Advisory committees

Bayer HealthCare
Bristol-Myers Squibb
GENFIT
TOWARDS BETTER MEDICINE
GILEAD
Intercept
MERCK
NOVARTIS

Speaking and teaching

Bayer HealthCare
Intercept

Outline

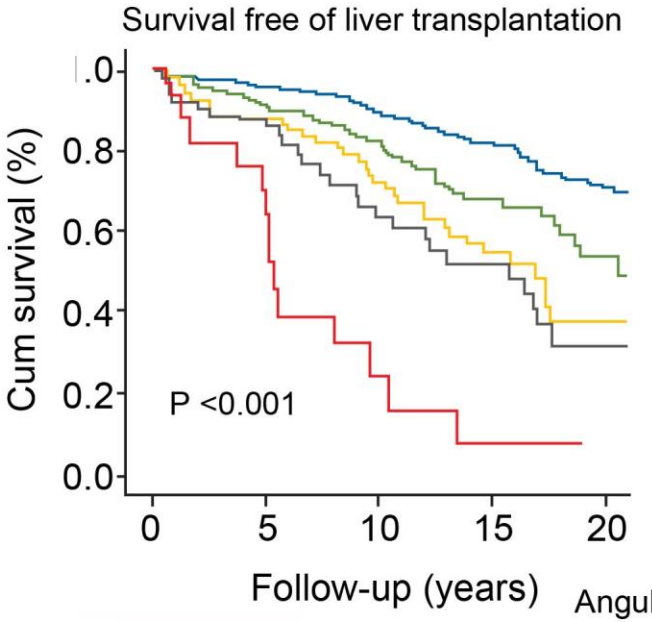
Progression of NASH

Molecular markers for insulin resistance

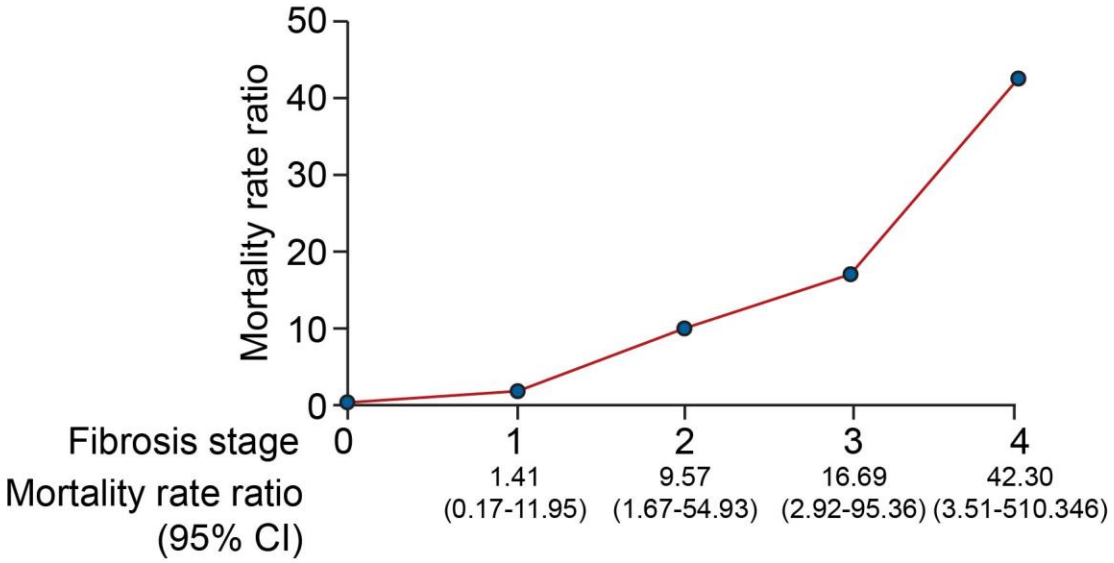
Molecular markers for fibrosis

Intervention on molecular markers

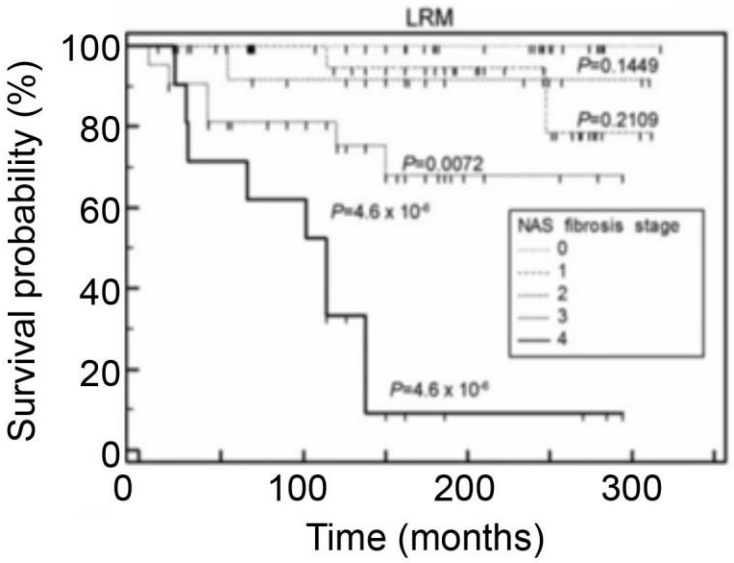
Fibrosis predicts all-cause & liver related mortality



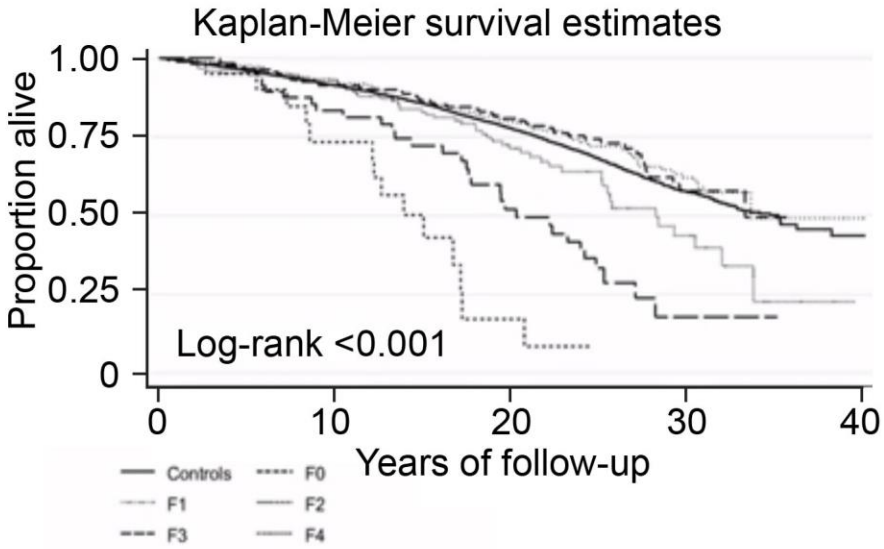
Angulo *et al.*, 2005



Dulai *et al.*, 2017



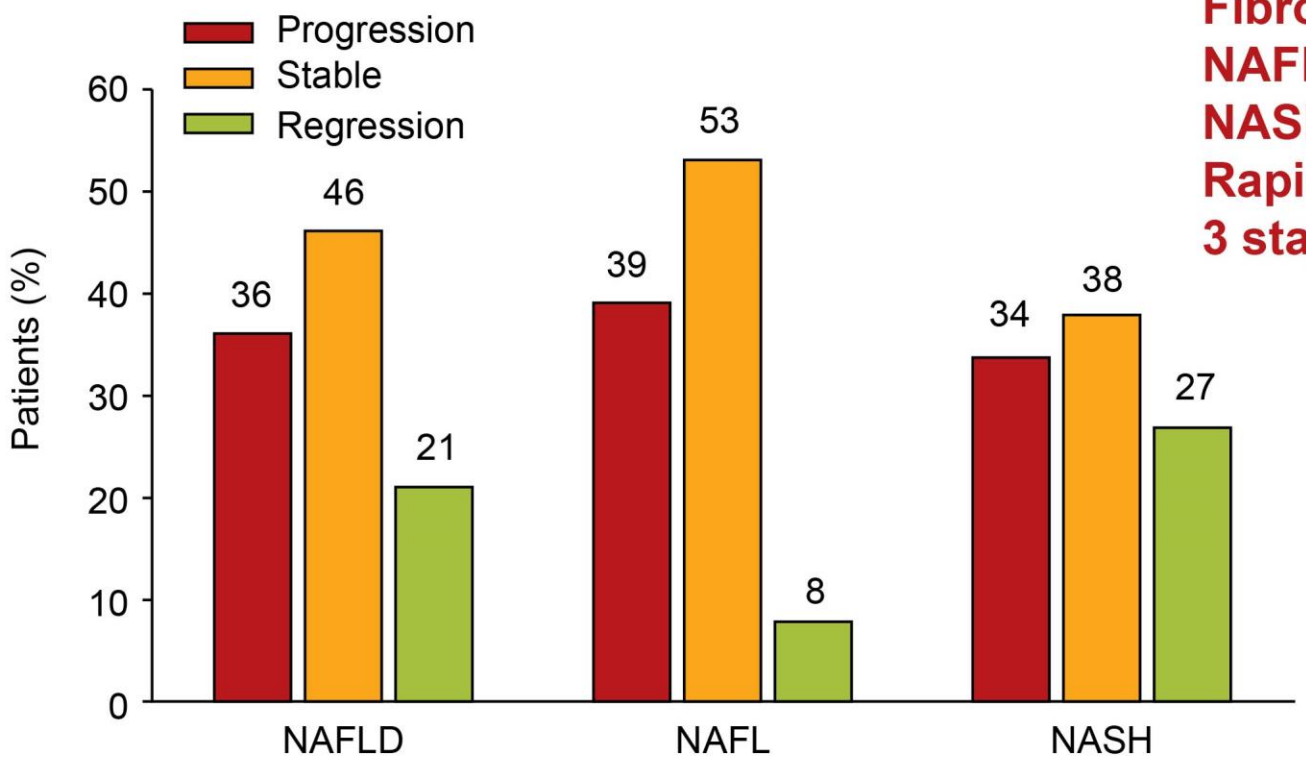
Younossi *et al.*, 2017



Hagström *et al.*, 2017

Fibrosis Progression - Regression

Meta-analysis of 11 studies with NAFLD paired biopsies
NASH, *n* = 116
NAFL, *n* = 133
Follow-up, 6 years



Fibrosis progression rate:
NAFL - 1 stage over 14 years
NASH - 1 stage over 7 years
Rapid progressors (21%) -
3 stages over 6 years

Singh *et al.*, Clin Gastroenterol Hepatol, 2015

Fibrosis Progression - Regression

Fibrosis Progressors:

More to gain > 5kg (55% vs. 24% p=0.02)

Greater increase in waist circumference

(+4.0 cm vs. -3.3 cm *P* = 0.001)

Higher HOMA-IR on follow-up (5.2. vs. 2.9 *P* = 0.04)

Diabetes more likely at follow-up (OR 6.2 95%CI 1.9-20)

Fibrosis Regressors

Greater reduction in HbA1c

(-1.9 vs. 0.3 *P* = 0.02)

McPherson et *al*. J Hepatol 2015

Hamaguchi et *al*. Diabetes Care 2010

Wong et *al.* Gut 2010

Ekstedt et *al.* Hepatology 2006

Outline

Progression of NASH

Molecular markers for insulin resistance

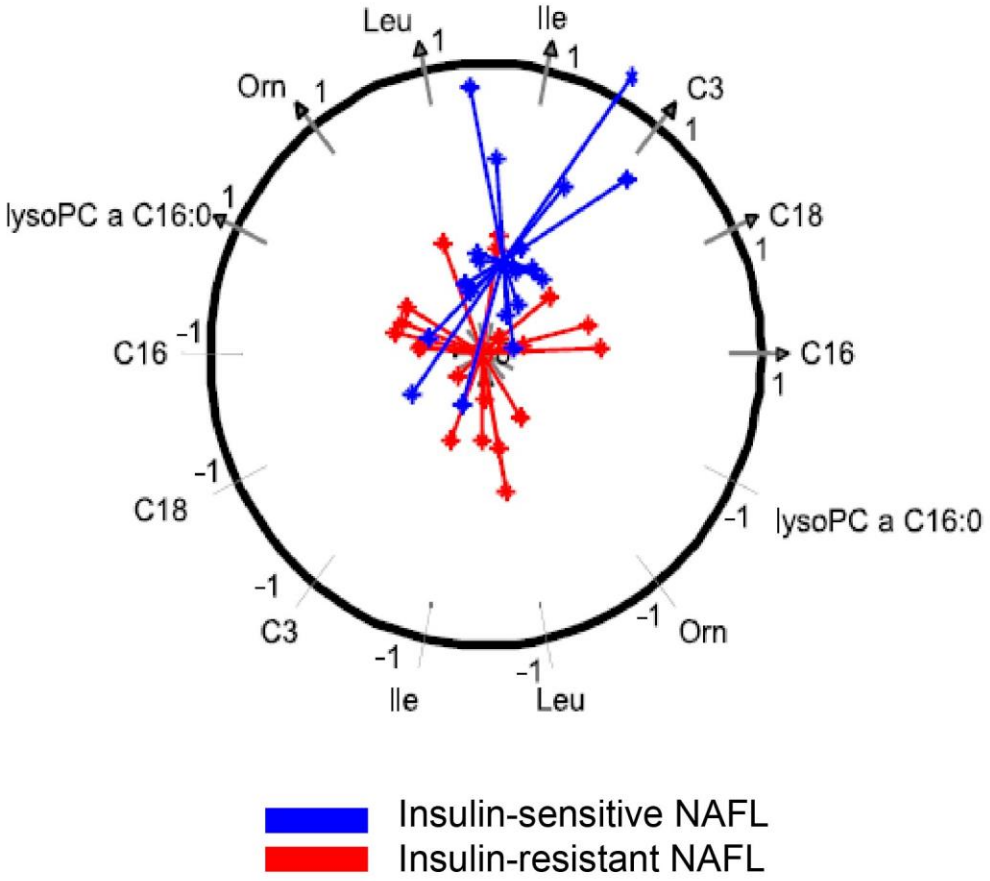
Molecular markers for fibrosis

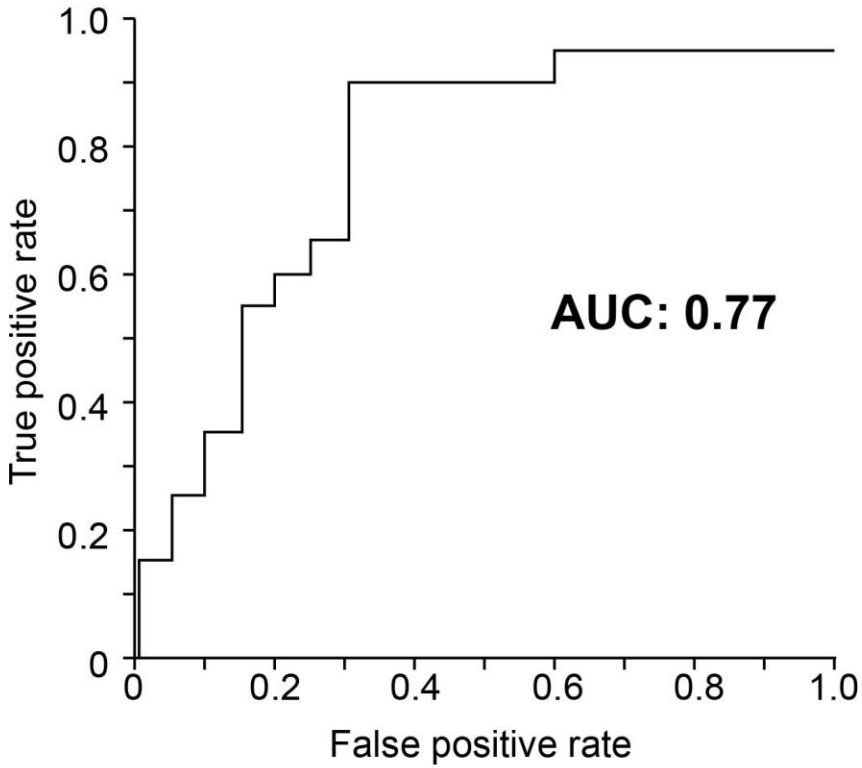
Intervention on molecular markers

Molecular markers for insulin resistance

265 plasma metabolites, 20 insulin-sensitive and 20 insulin-resistant subjects with NAFL

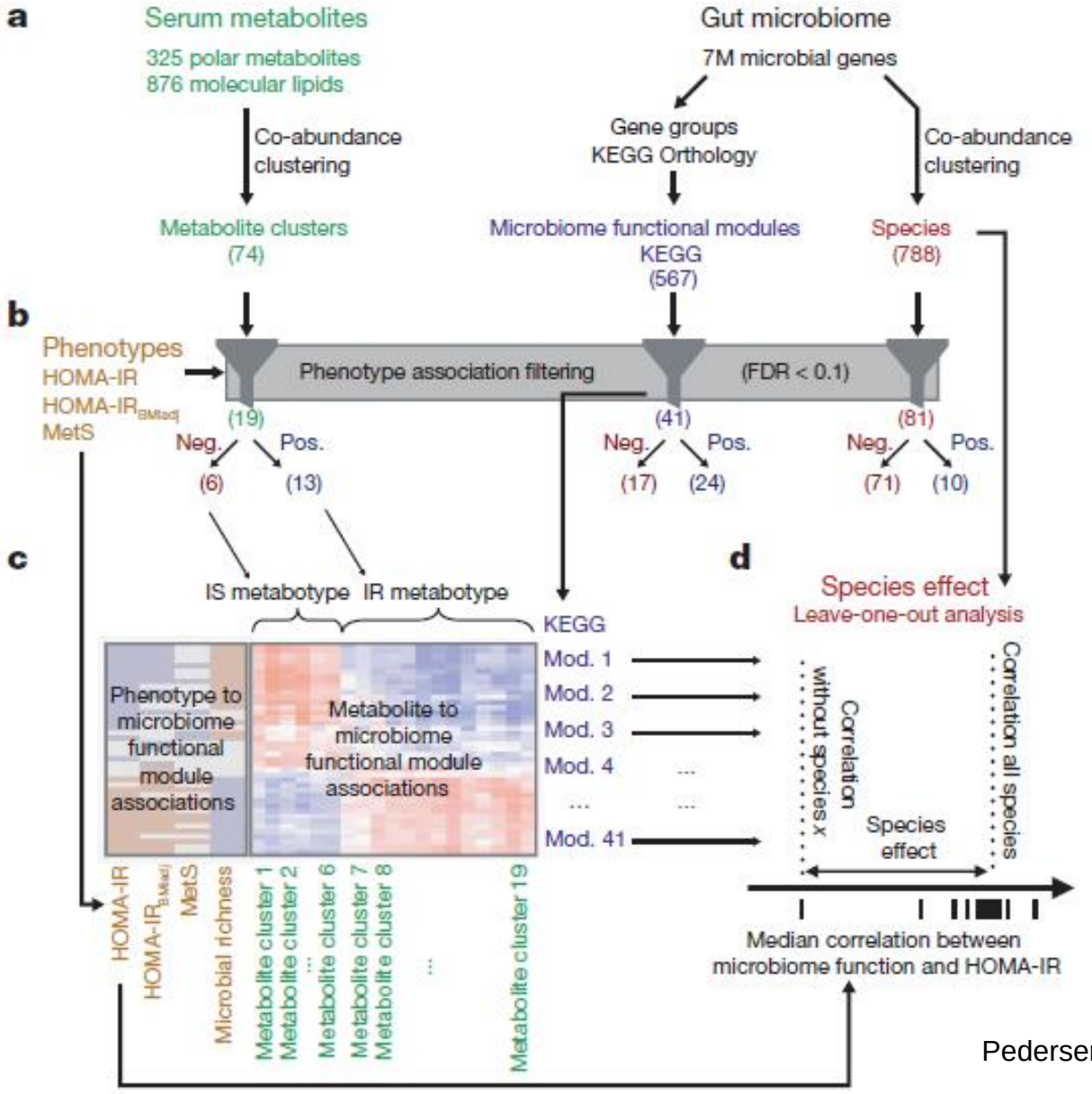
Pattern of 7 metabolites with a significant discriminating power





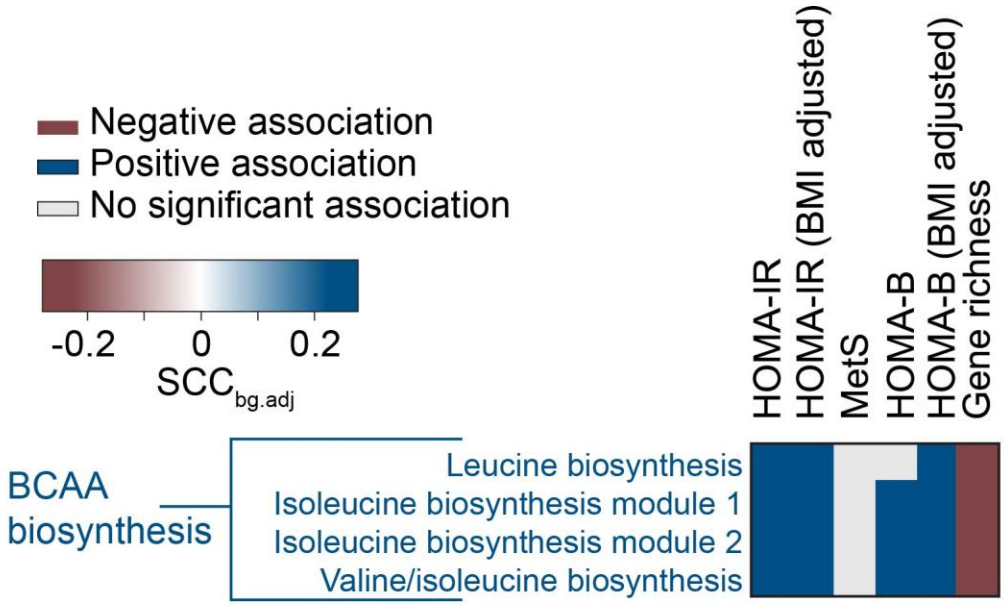
Lehmann *et al.* Diabetes Care 2013

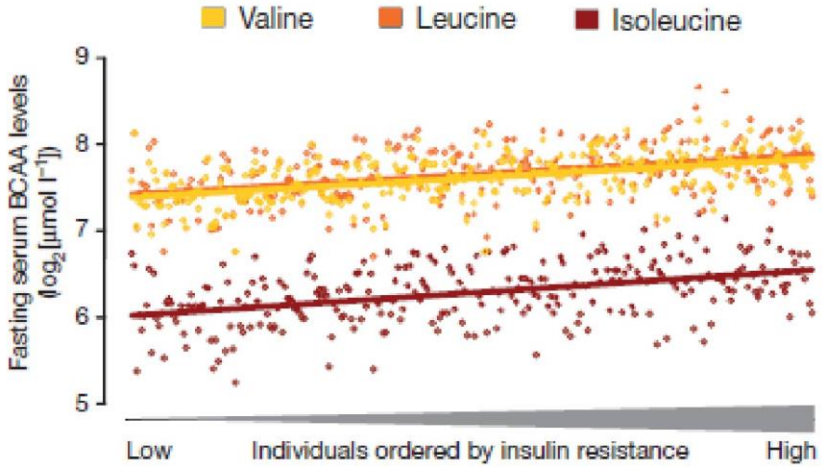
Molecular markers for insulin resistance



Pedersen *et al.* Nature 2016

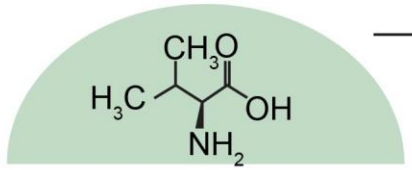
Molecular markers for insulin resistance

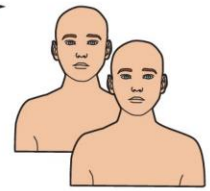


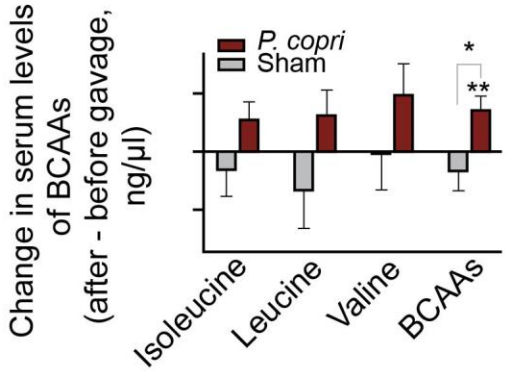


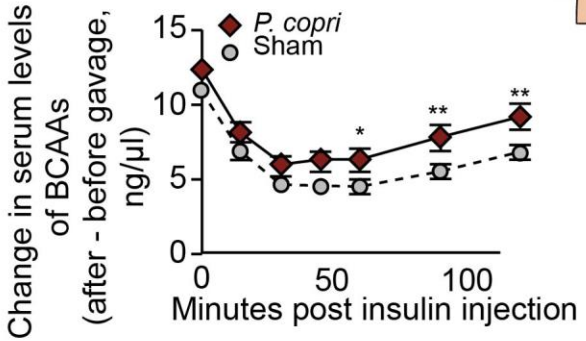
Gut microbes **Gut microbial functions** **Metabolite pool** **Insulin resistance**

Prevotella copri
Bacteroides vulgatus









Pedersen *et al.*
Nature 2016

Outline

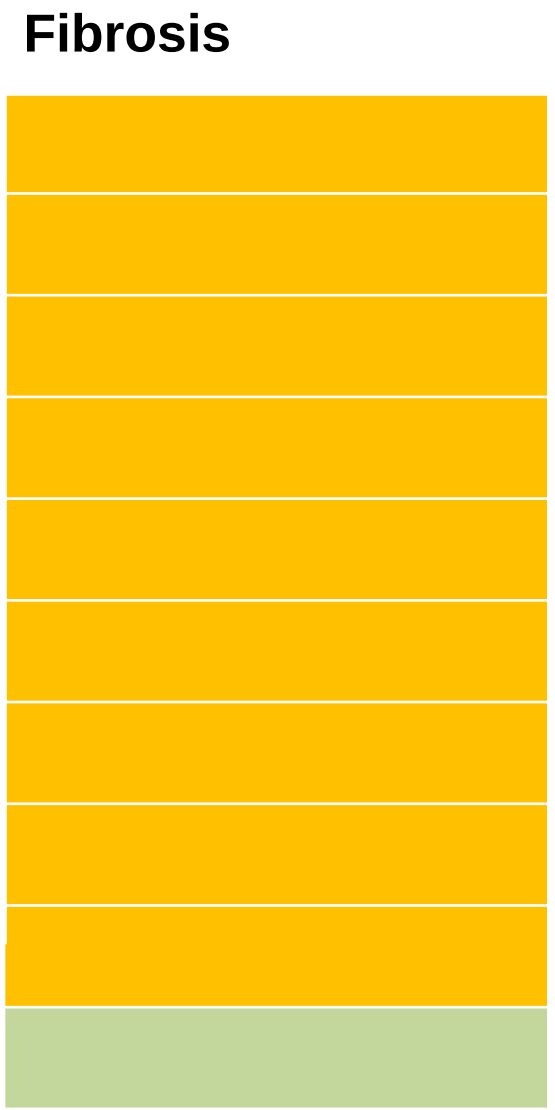
Progression of NASH

Molecular markers for insulin resistance

Molecular markers for fibrosis

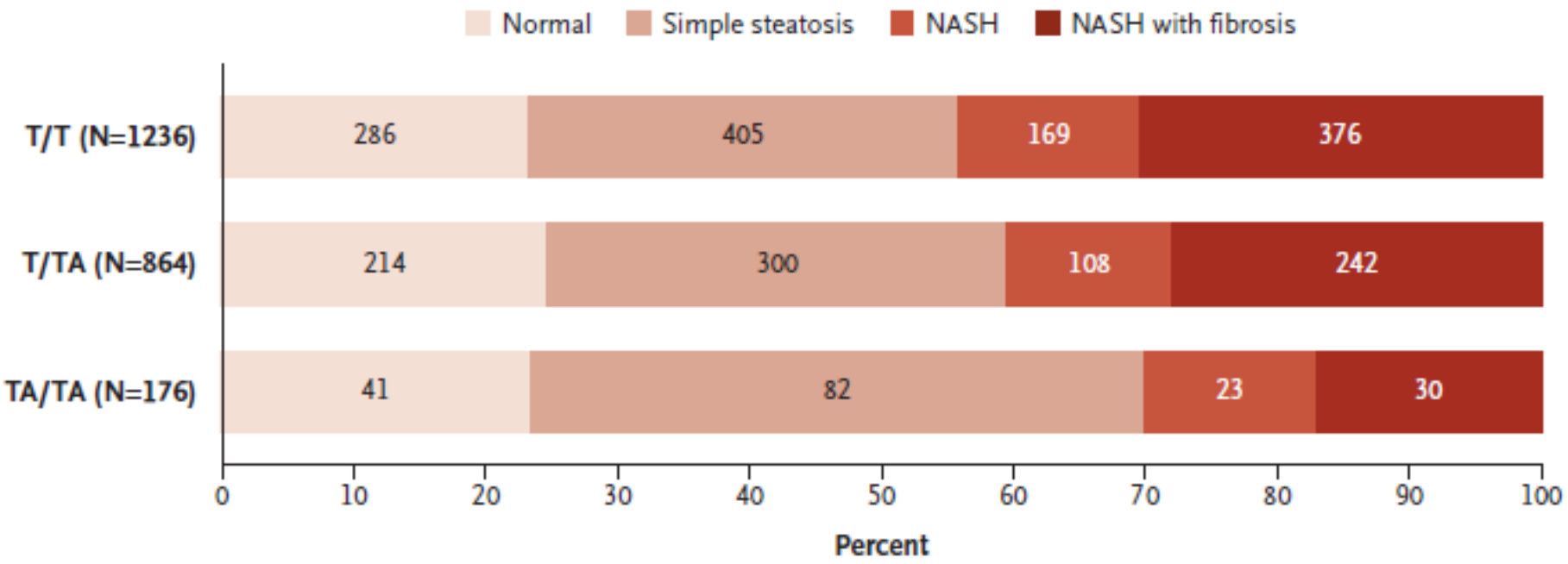
Intervention on molecular markers

Genetic Markers for fibrosis (not exhaustive)



Adapted from Anstee et al. Gastroenterology 2016 & Eslam et al. J Hepatol 2017

Truncated HSD17B13



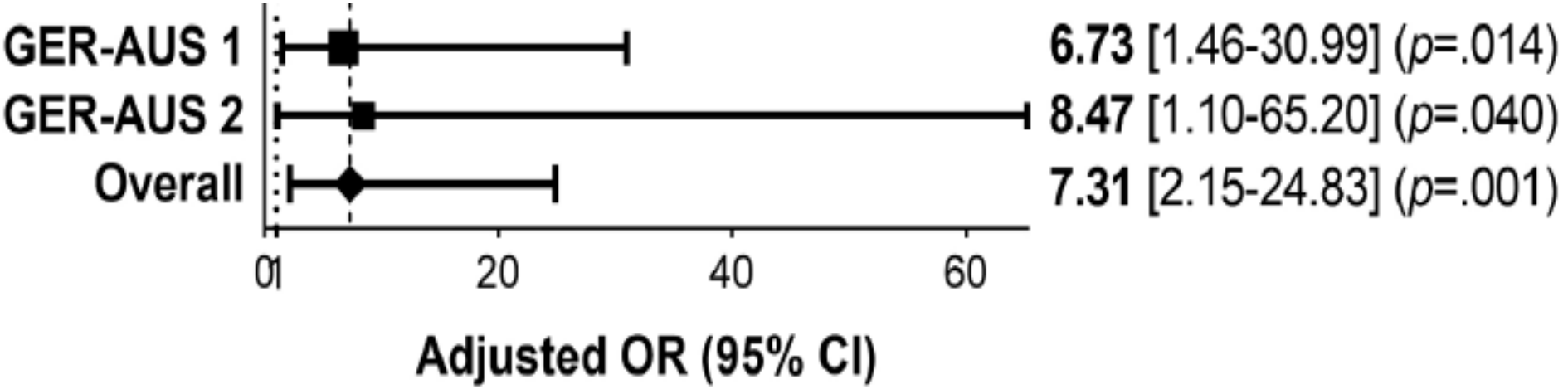
Abul-Husn *et al.* N Engl J Med 2018

Heterozygosity alpha1 antitrypsine Pi*Z

Risk of developing cirrhosis in 660 patients
with biopsy proven NAFLD

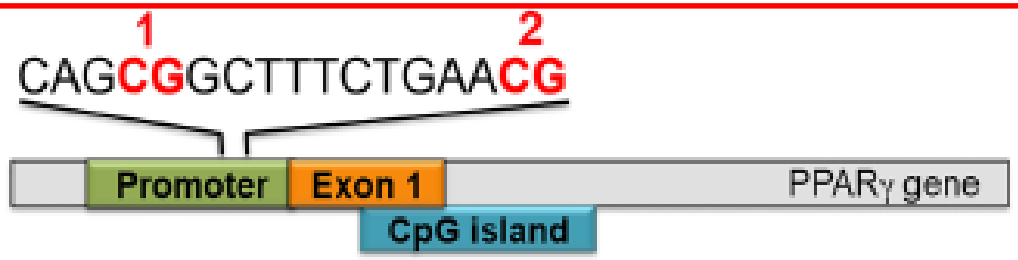
F4. vs. F0

Adjusted for gender, age, BMI and diabetes

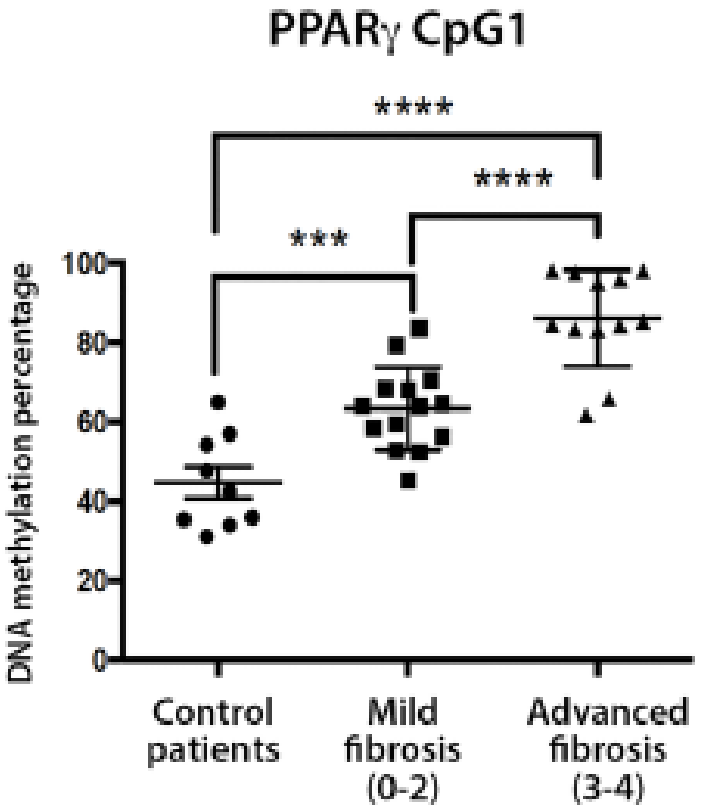


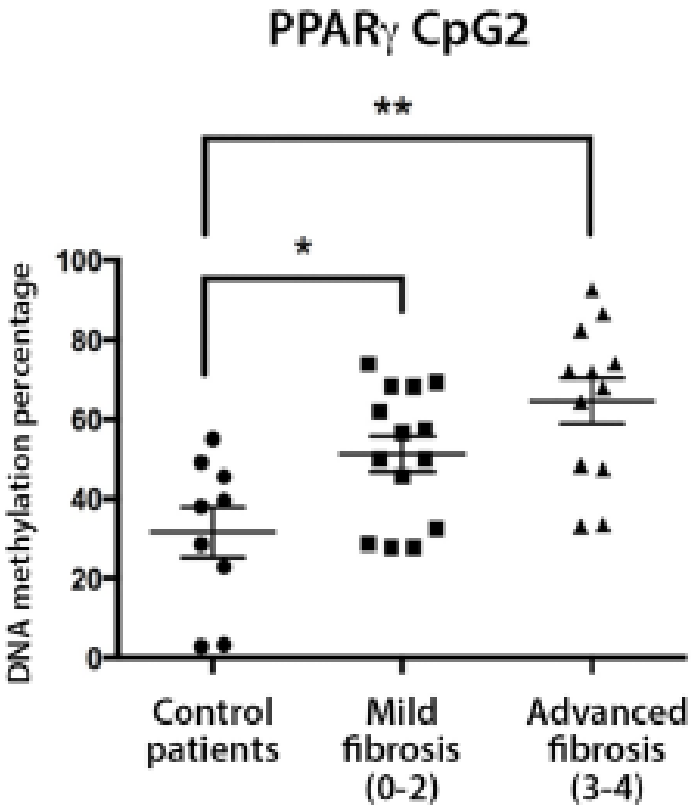
Strnad et al. GUT 2018

Epigenetic Markers for fibrosis



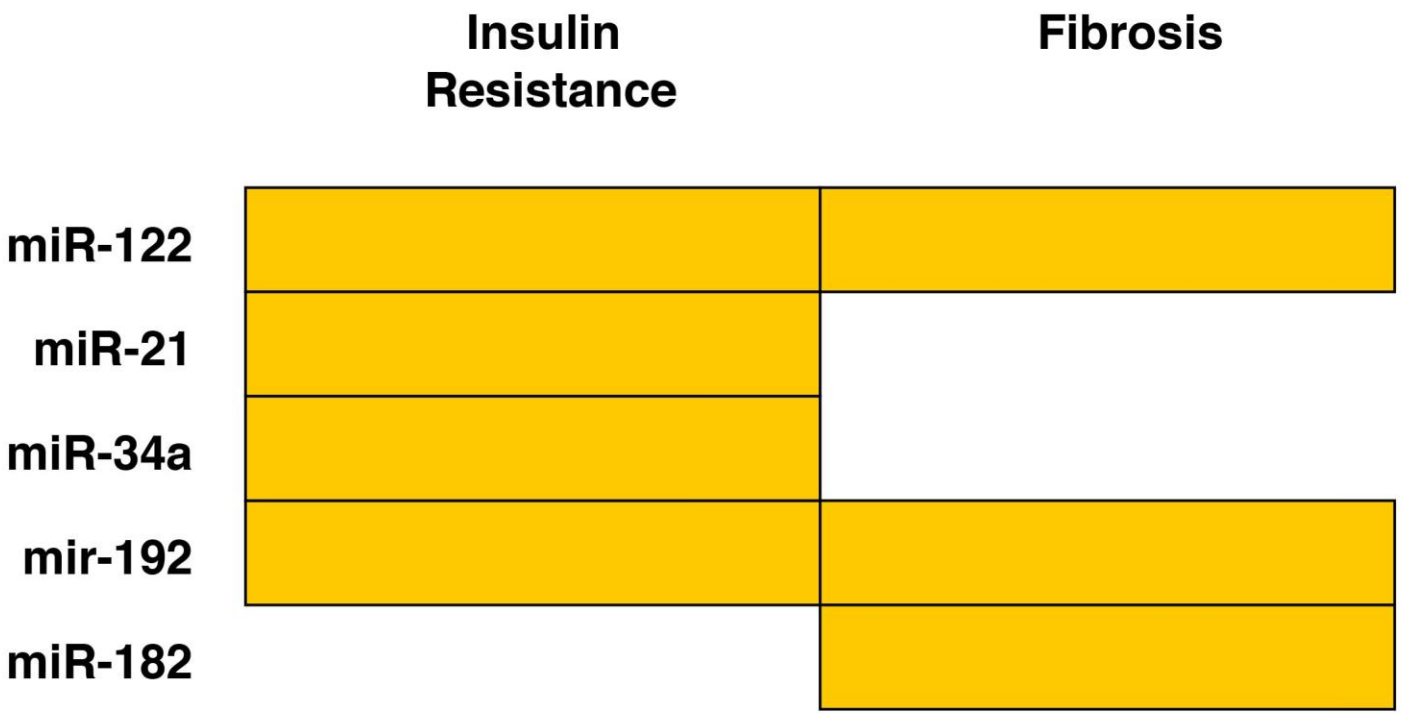
Plasma DNA





Hardy et al. GUT 2016

Increased circulating levels of miRNAs



Adapted from Eslam and Schuppan J Hepatol 2018

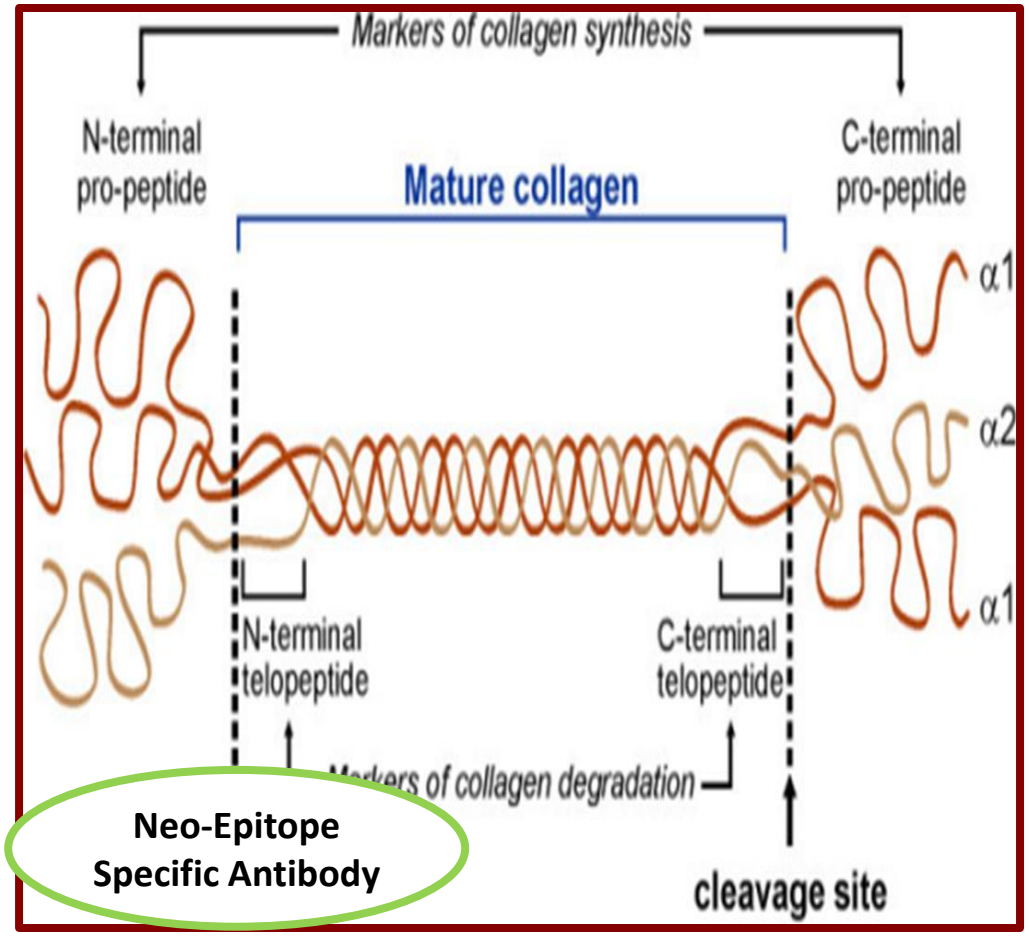
Molecular markers for fibrosis

	Cheap and reproducible	Sensitivity to exclude F≥3	Specificity to diagnose F≥3	Influenced by age	Allows predict clinical outcome
NAFLD fibrosis score	Yes	High	Modest	Yes	Yes
FIB-4	Yes	High	Modest	Yes	Yes
BARD score	Yes	High	Low	Unknown	Yes
APRI	Yes	High	Low	Unknow	Yes
Hepatoscore	Yes	High	Modest	Unknown	Yes

Adapted from Vilar-Gomez *et al.* J Hepatol 2018

Collagen Pro C3

- In fibrogenesis; Type III collagen synthesis is upregulated
- Pro-C3 is a neo-epitope marker reflecting true type III collagen formation
- It is released by ADAMTS2 during type III collagen maturation



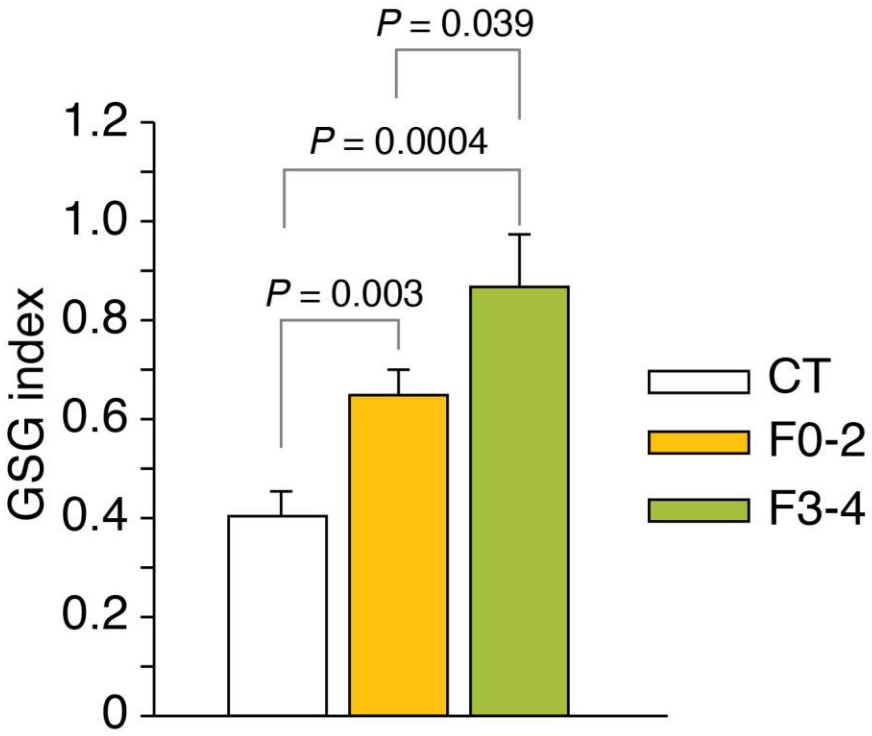
Specific N-Proteases (ADAMTS2/Procollagen 1 N-Proteinase

Courtesy Boyle

Molecular markers for fibrosis

AA profile of *n* = 44 subjects with NAFLD without diabetes and who had a liver biopsy

Glutamate–Serine–Glycine (GSG) index : glutamate/[serine + glycine]



Gaggini *et al.* Hepatology 2018

Outline

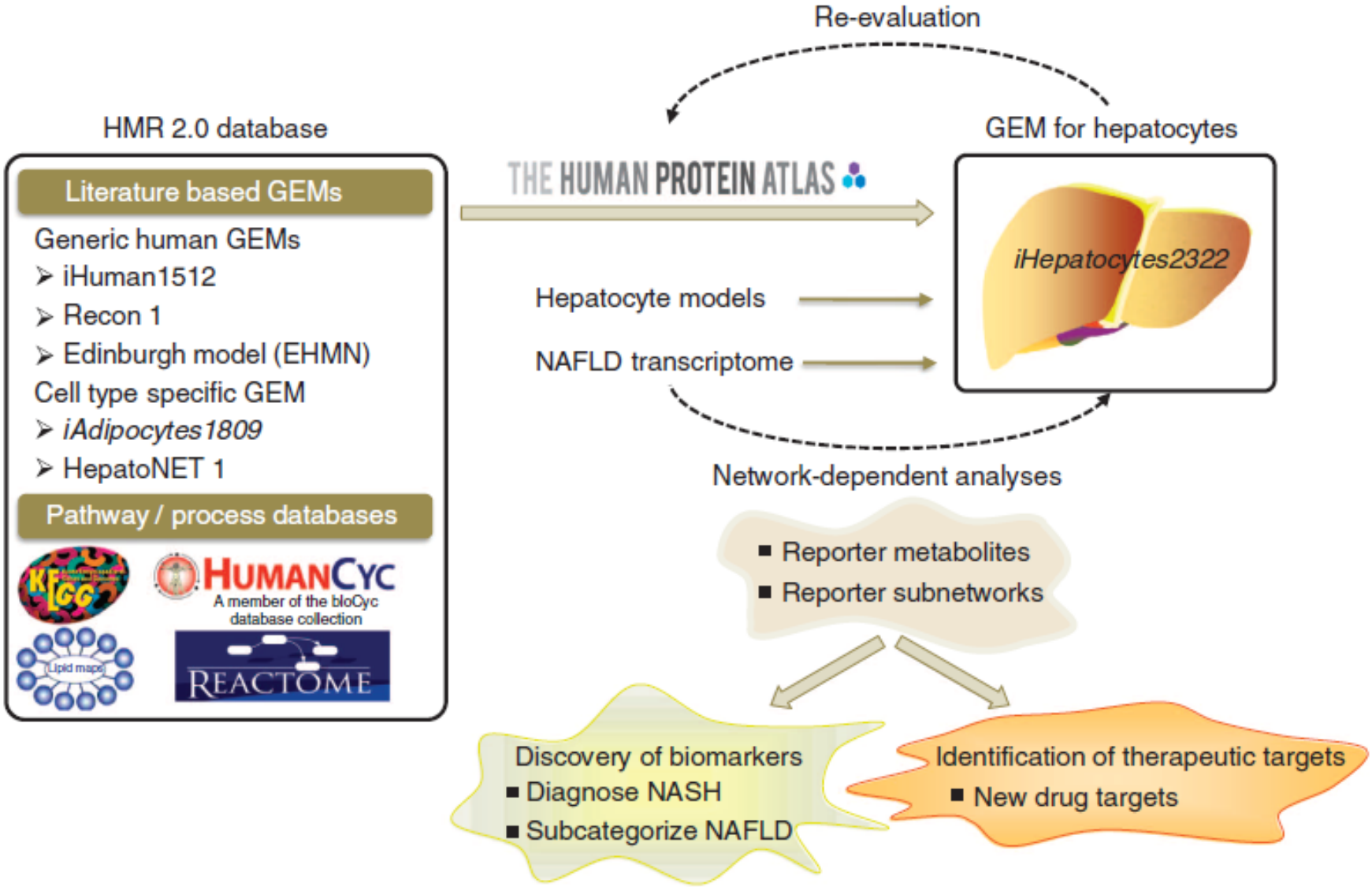
Progression of NASH

Molecular markers for insulin resistance

Molecular markers for fibrosis

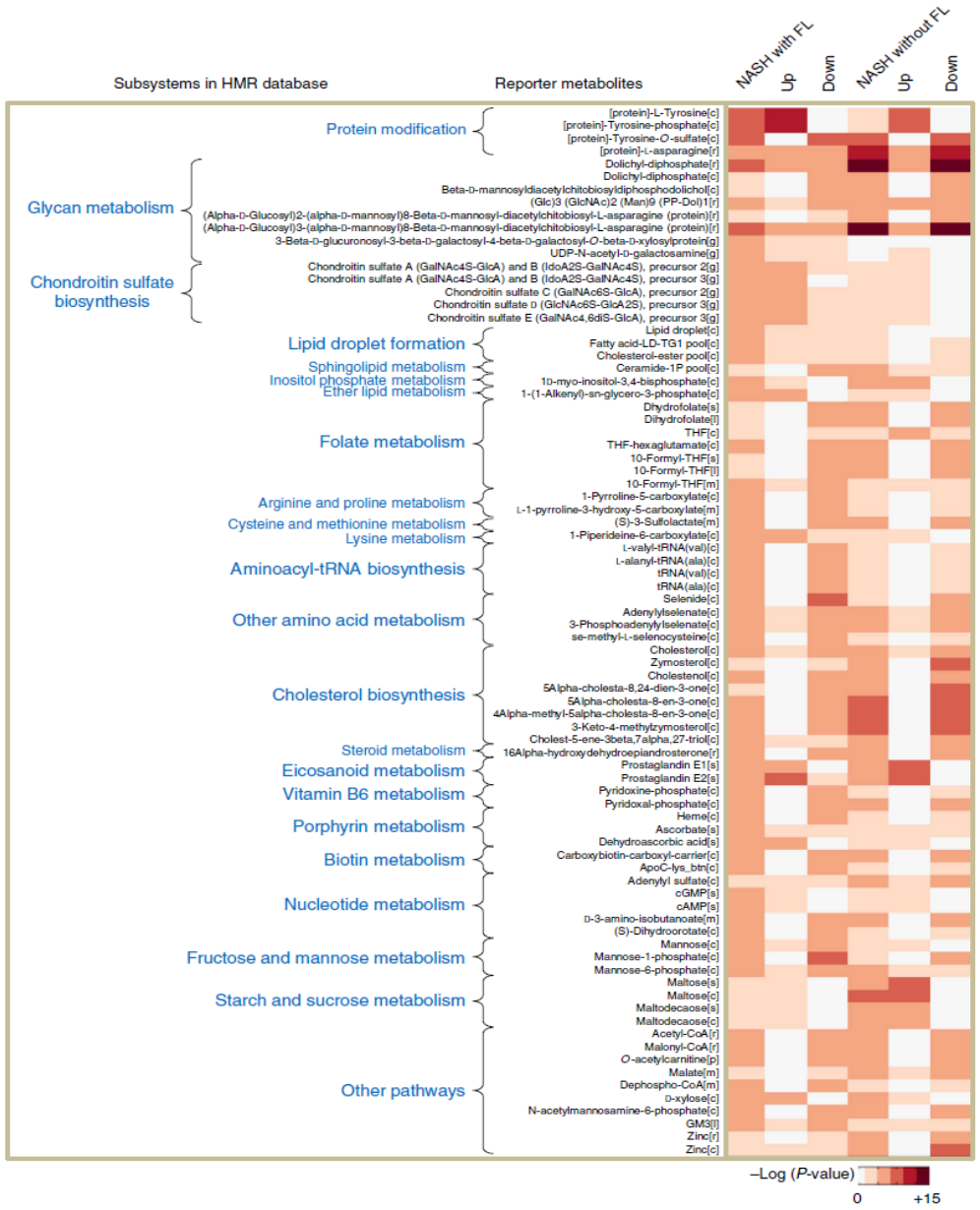
Molecular markers for intervention

Non-invasive diagnosis: Metabolomics



Mardinoglu et al. Nature Com 2014

Non-invasive diagnosis: Metabolomics



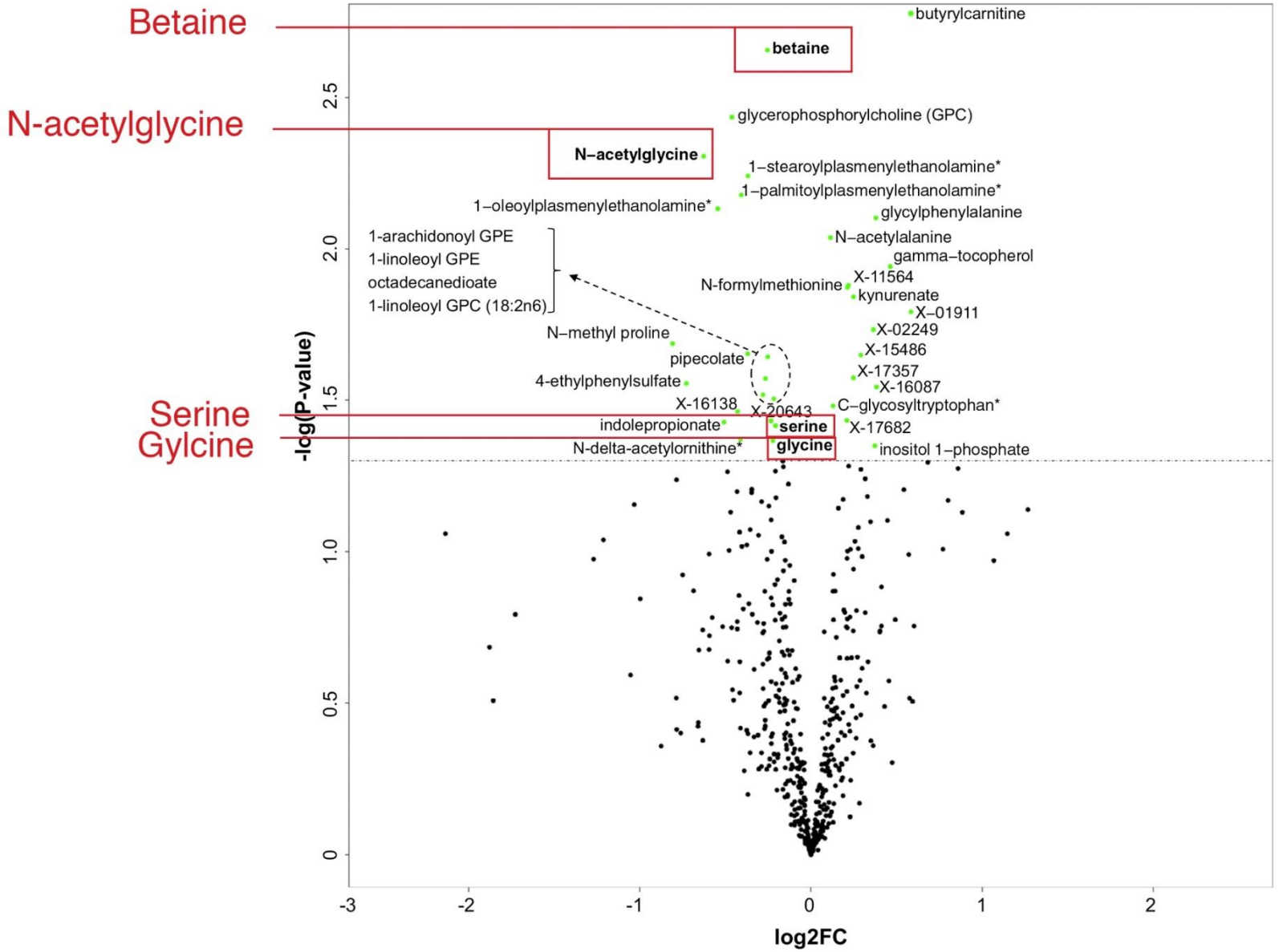
Predict that in case of NASH
Elevated blood levels of chondroitin and heparan sulphates

Serine deficiency

Identify
Phosphoserine phosphatase,
Serine hydroxymethyltransferase 1
Branched chain amino-acid transaminase 1
as potential therapeutic targets

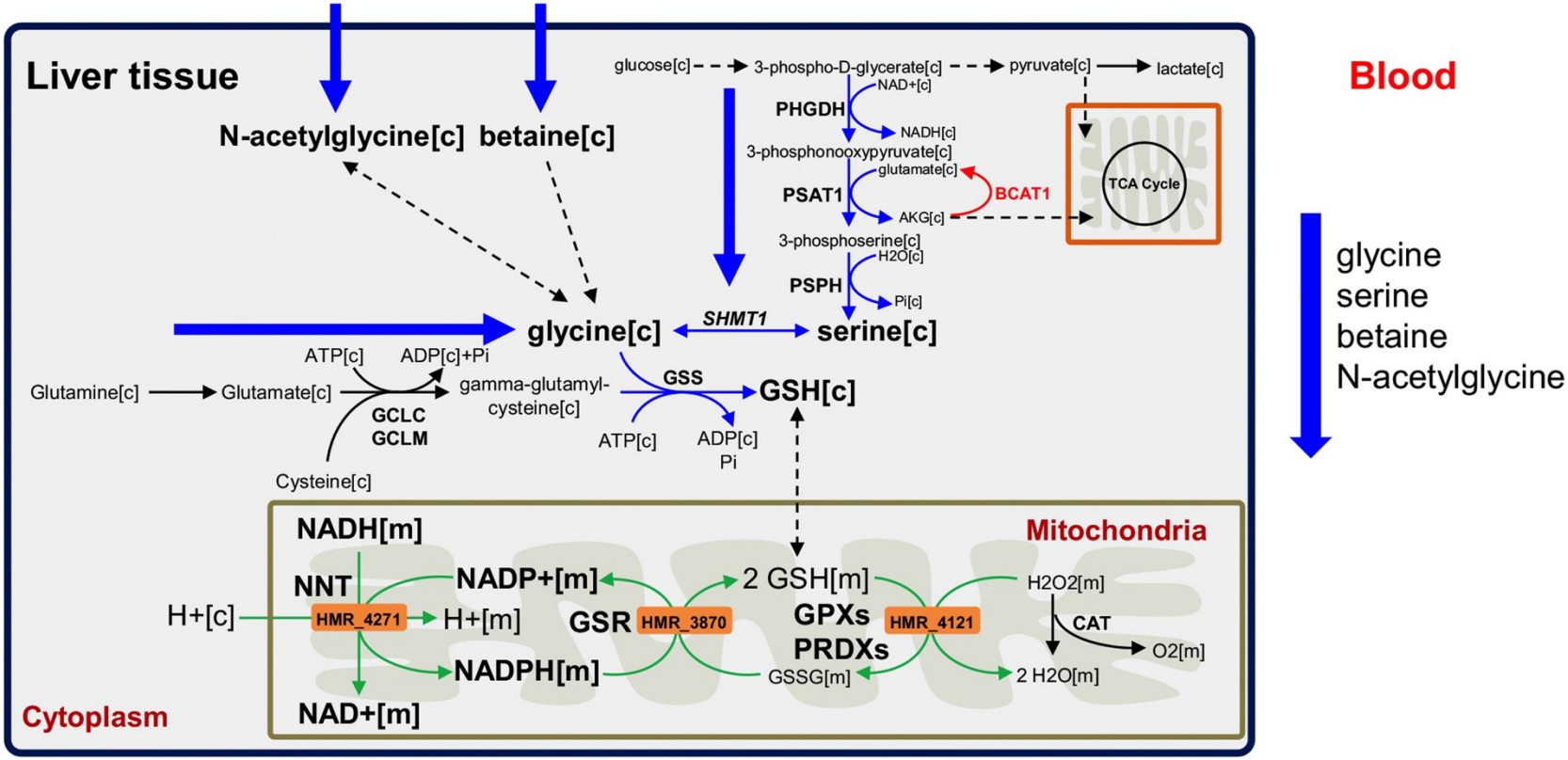
Mardinoglu et al. Nature Com 2014

Non-targeted Metabolomics Profiling



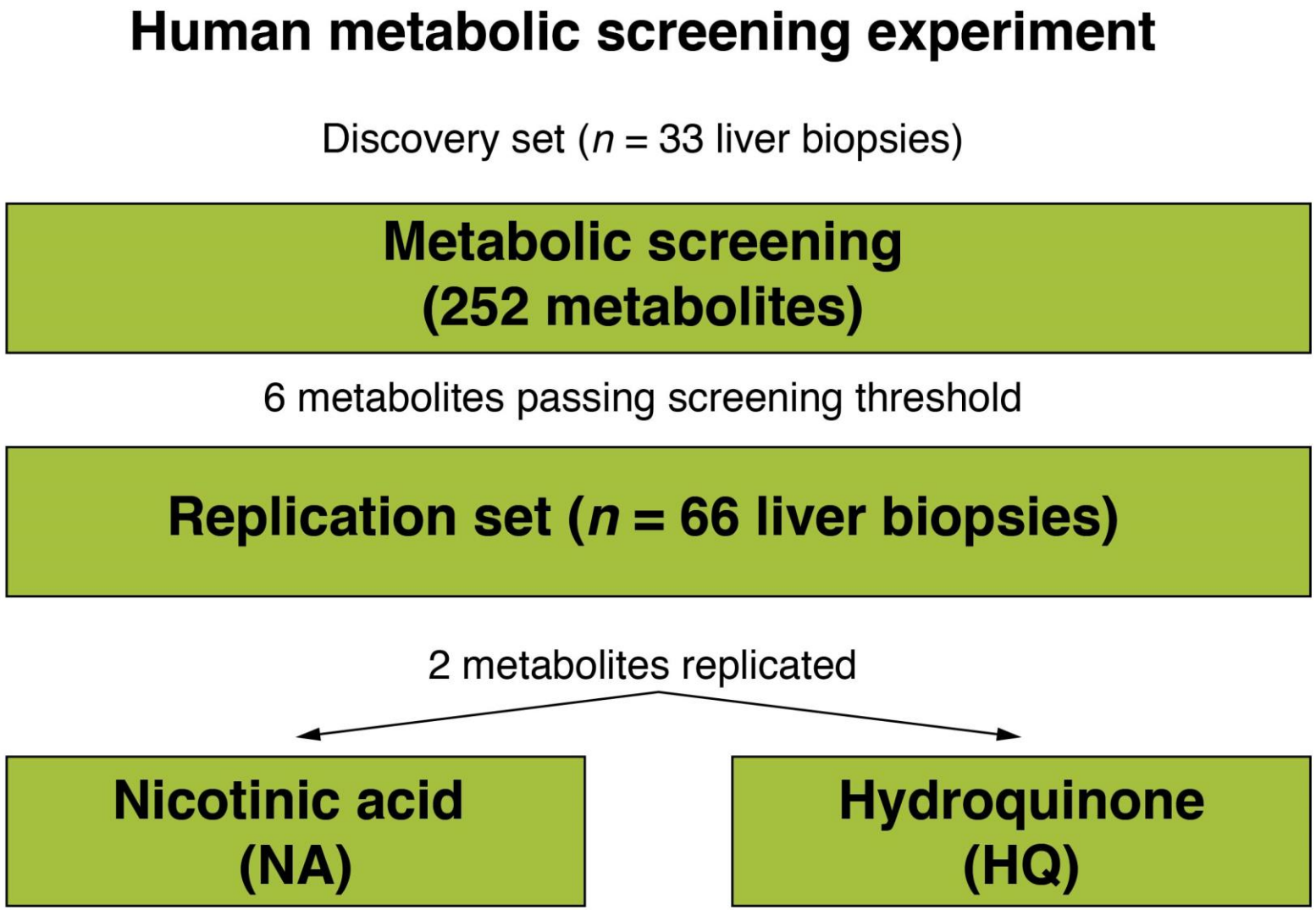
Mardinoglu *et al.* Molecular System Biology 2017

Metabolite intervention in NASH



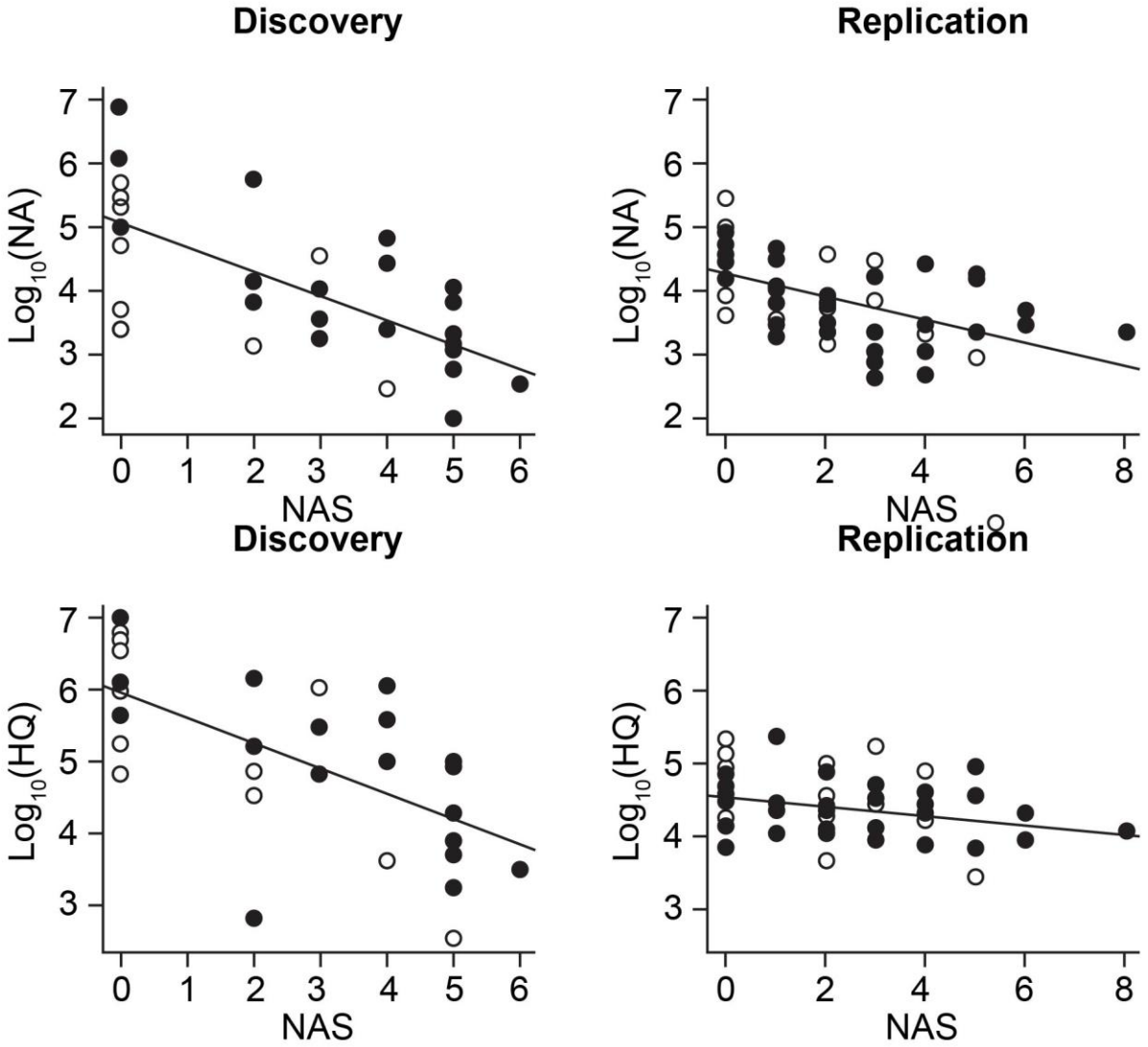
Mardinoglu *et al.* Molecular System Biology 2017

Protective metabolites in NAFLD



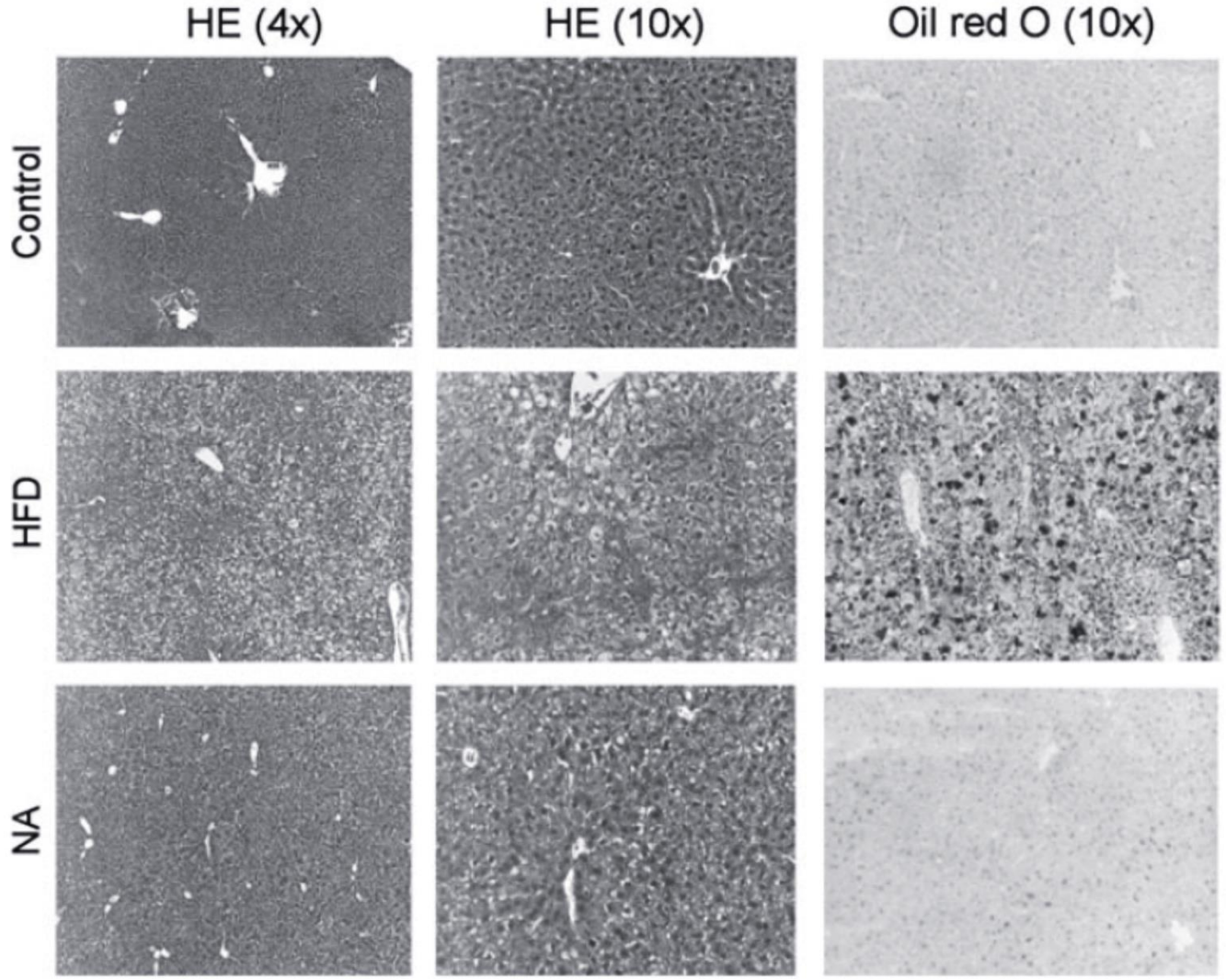
Von Schönfels *et al.* Liver Int 2014

Protective metabolites in NAFLD



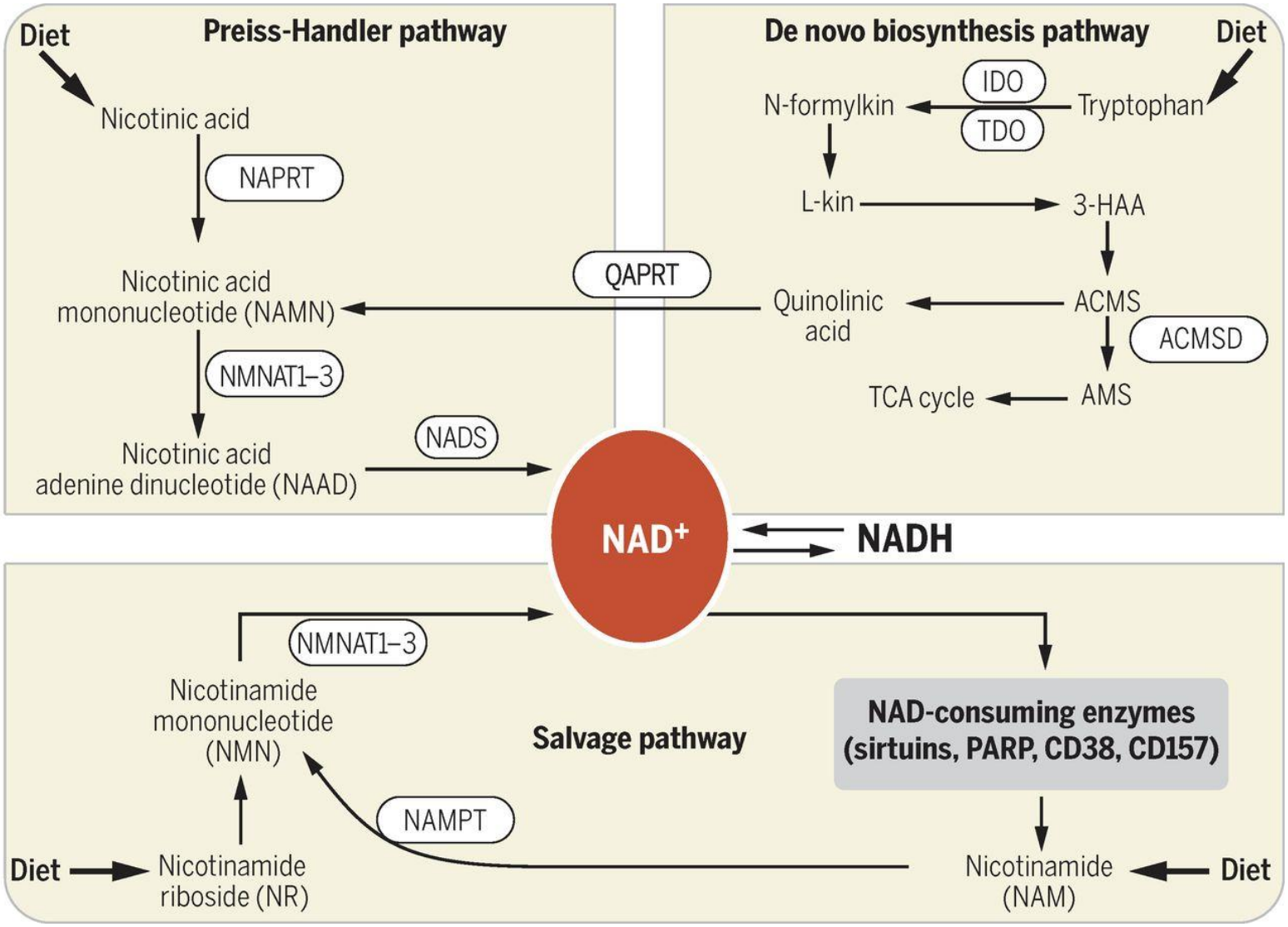
Von Schönfels *et al.* Liver Int 2014

Protective metabolites in NAFLD



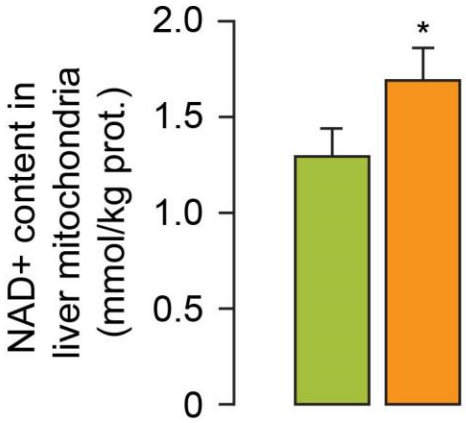
Von Schönfels *et al.* Liver Int 2014

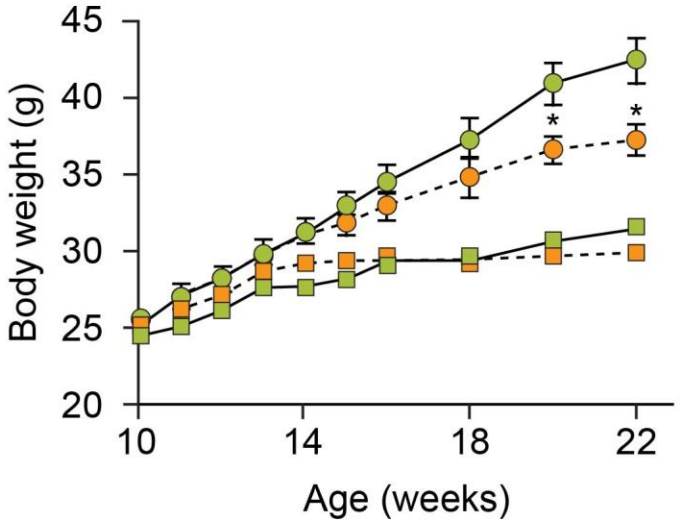
Protective metabolites in NAFLD

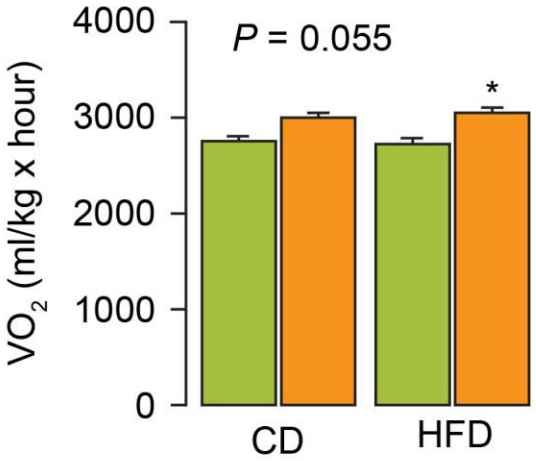


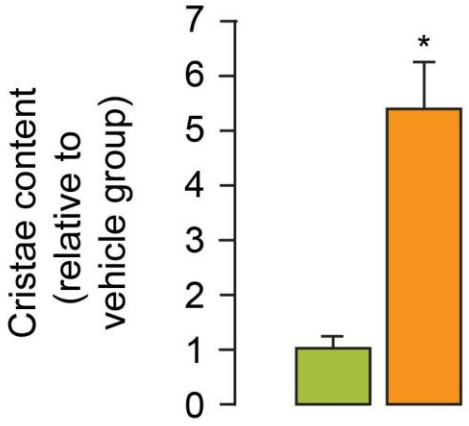
Verdin Science 2015

Nicotinamide riboside



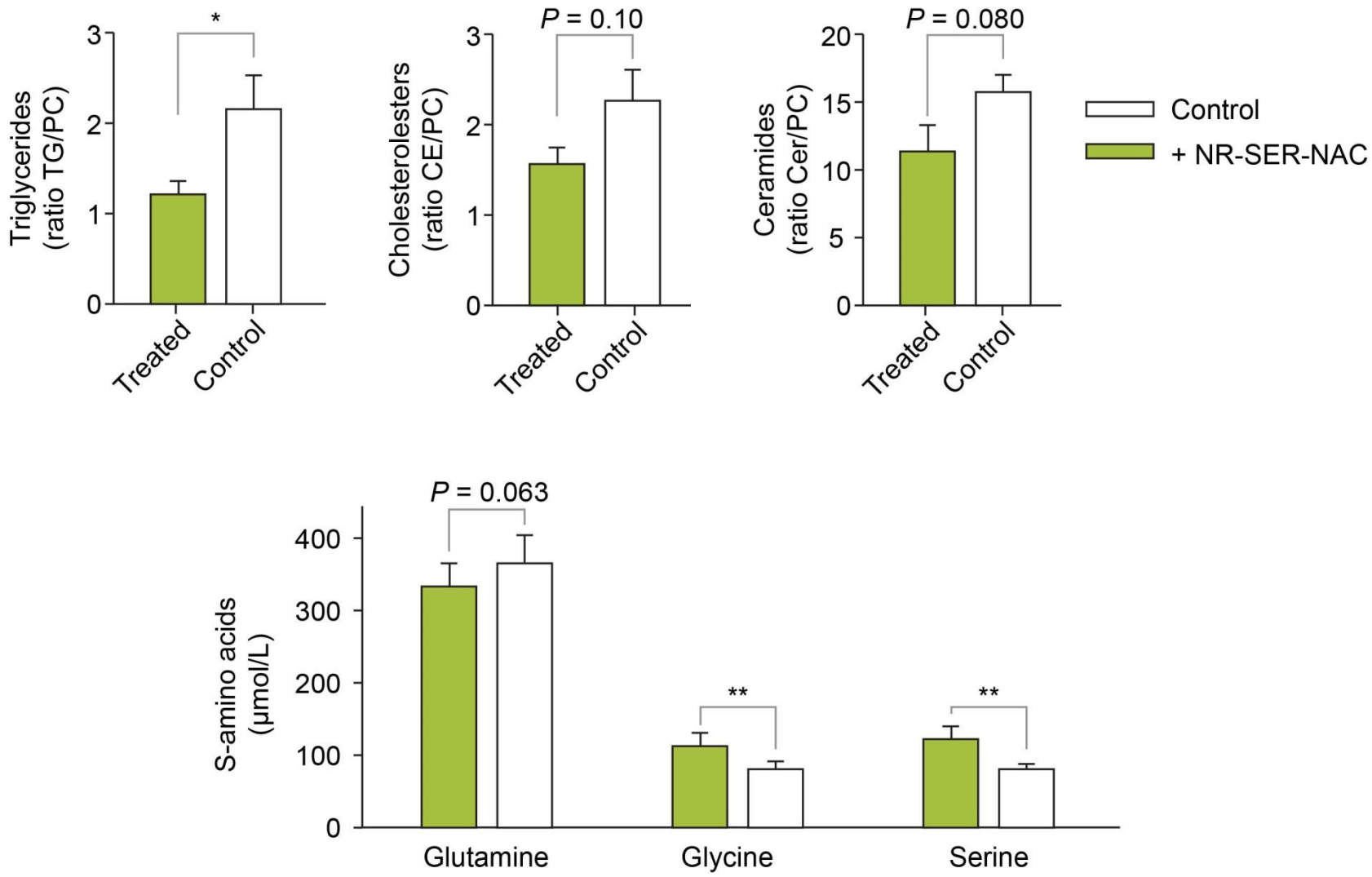






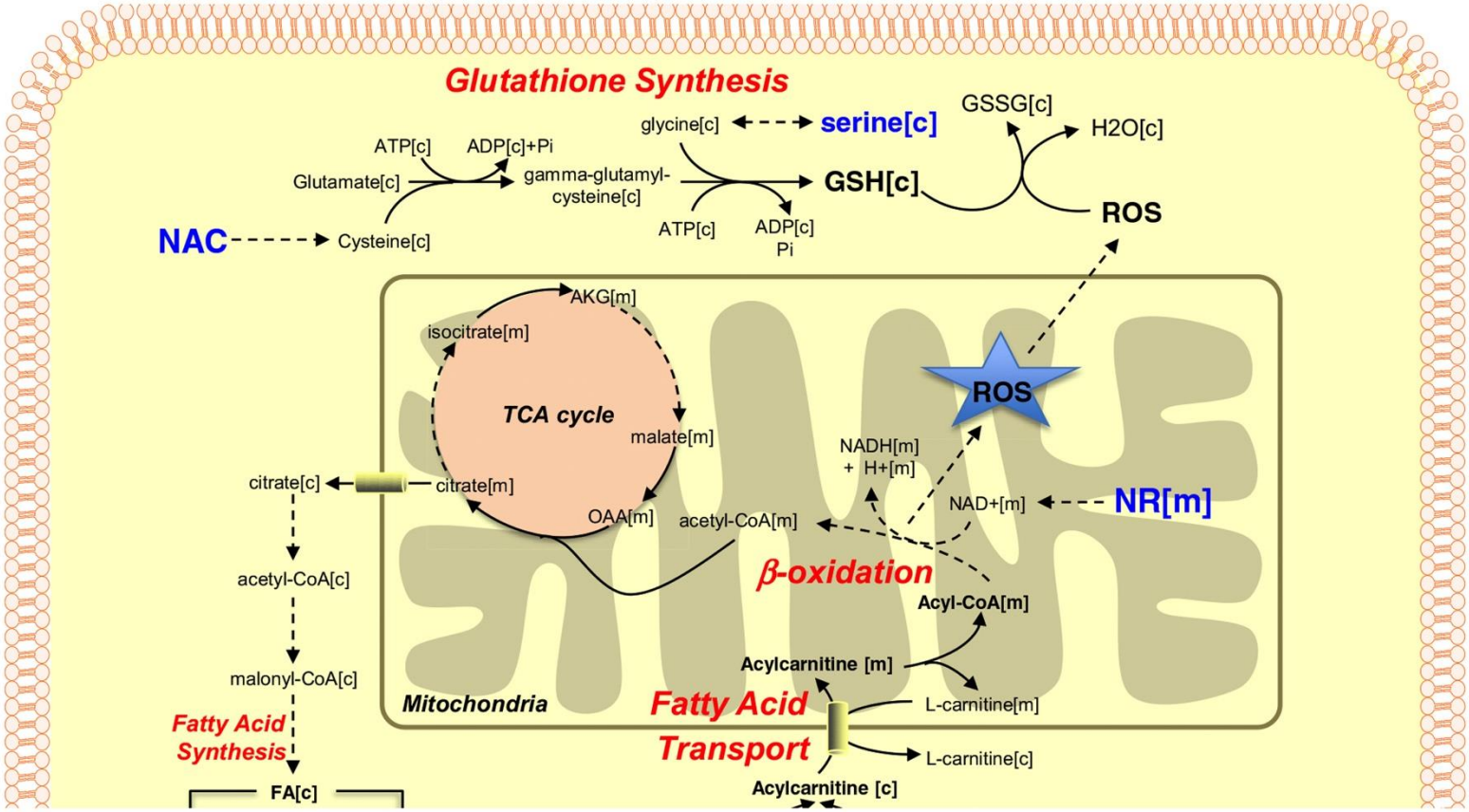
Canto *et al.* Cell Metabolism 2012

Supplementation with NR-SER-NAC



Mardinoglu *et al.* Molecular System Biology 2017

Metabolite intervention in NASH



Mardinoglu *et al.* Molecular System Biology 2017

Conclusions

- **Insulin resistance** is associated with **changes in circulating levels of AAs**
- Several **molecular markers** for **fibrosis**
- **Supplementation of specific metabolites** may have **therapeutic potential** in NASH

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