NASH Globally- *Pathways to combination therapies, biomarkers and outcomes*

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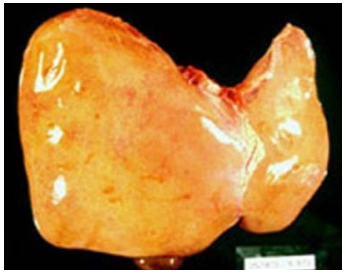
Conflicts of Interest

- President, Sanyal Biotechnologies
- Stock options: Genfit, Akarna, Tiziana, Indalo, Durect, Exhalenz, Hemoshear
- Advisor with compensation: Lilly, Pfizer, Novartis, Ardelyx, Salix, Hemoshear
- Advisor without compensation: Galectin, Intercept, Merck, Bristol Myers, Immuron, Gilead, Chemomab, Affimmune, Protalix, Nitto Denko, Novo Nordisk, Cirius, Boehringer Ingelhiem
- Grants to institution: Gilead, Tobira, Allergan, Merck, Bristol Myers, Astra Zeneca, Immuron, Intercept, Novo Nordisk, Shire, Boehringer Ingelhiem, Cirius

NAFLD: a silent killer in our midst

HEART DISEASE

NONALCOHOLIC FATTY LIVER DISEASE

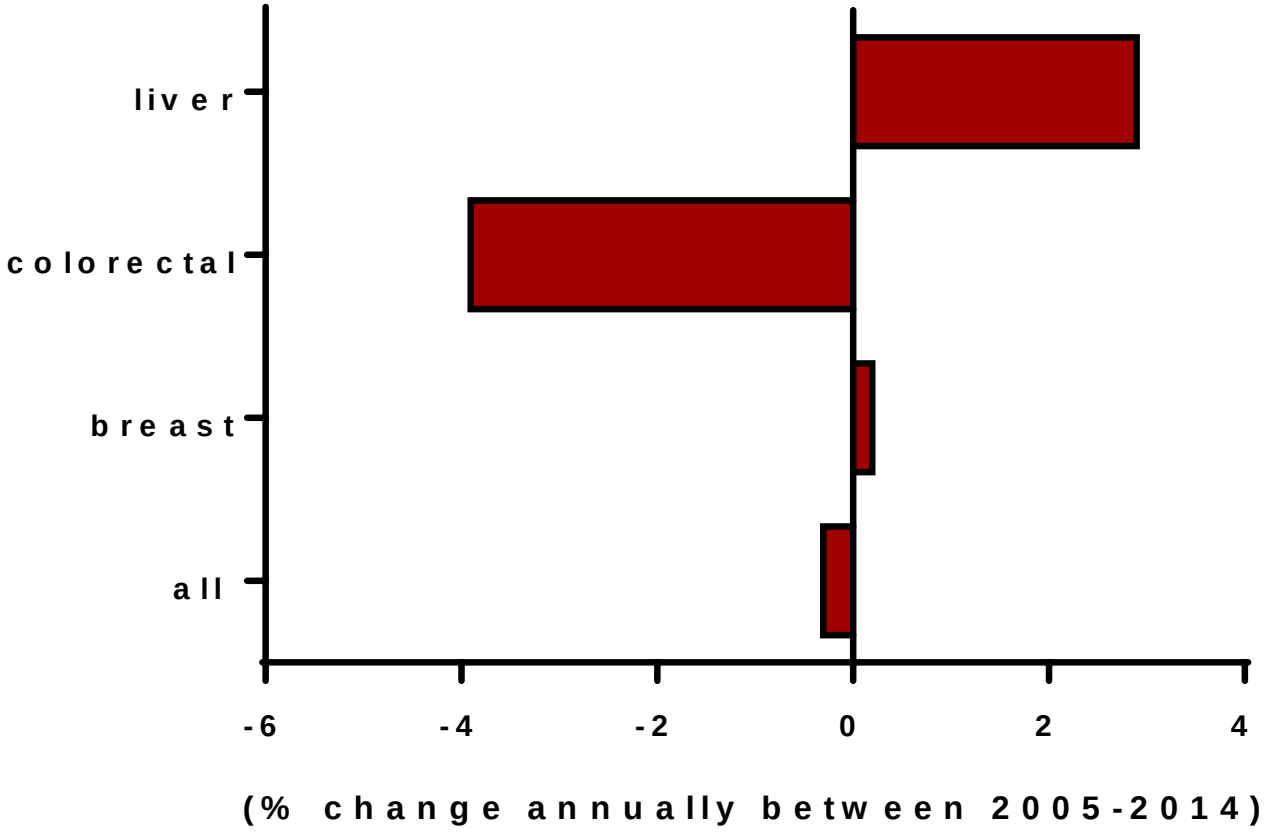


fatty liver or steatohepatitis

TYPE 2 DIABETES

NAFLD is driving the national increase in liver cancer

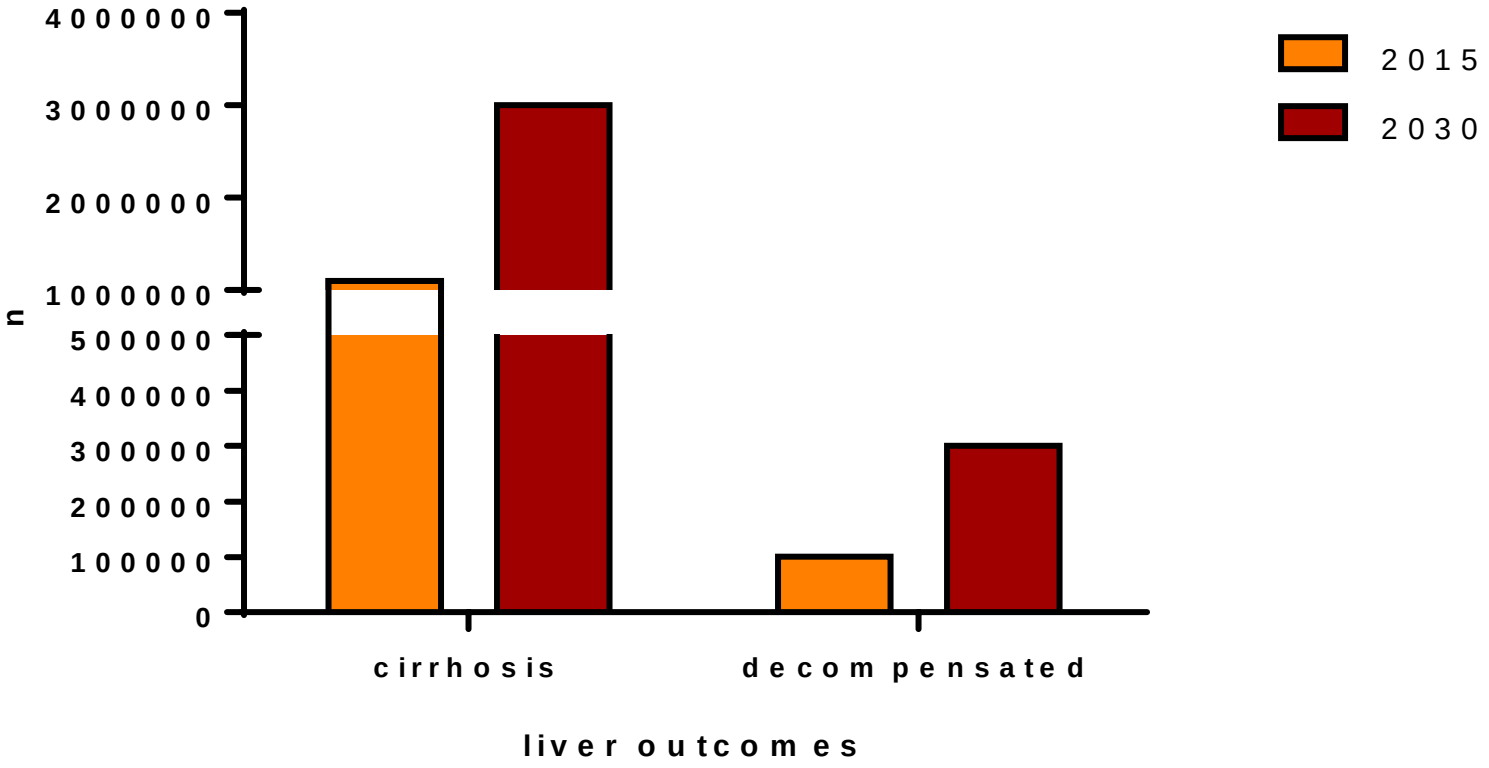
liver cancer rate related to obesity is increasing at 3% annually



Steele et al, MMWR, October 2017

The consequences of inaction will be serious:

- *number of those with cirrhosis will triple*
- *over 300,000 people will have end-stage liver disease*
- *many of these will be "todays" children*

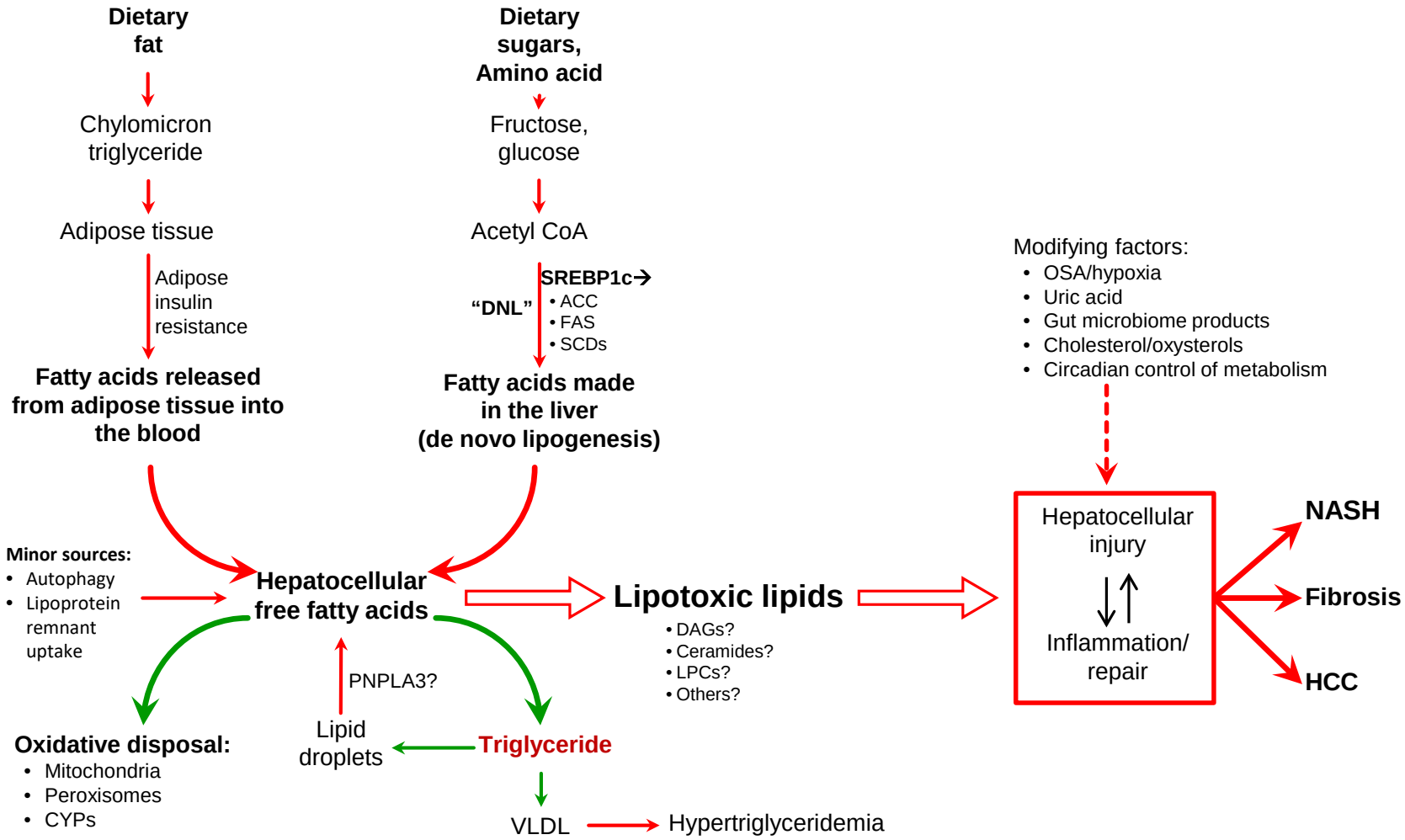


Estes et al, Epub Hepatology, 2017

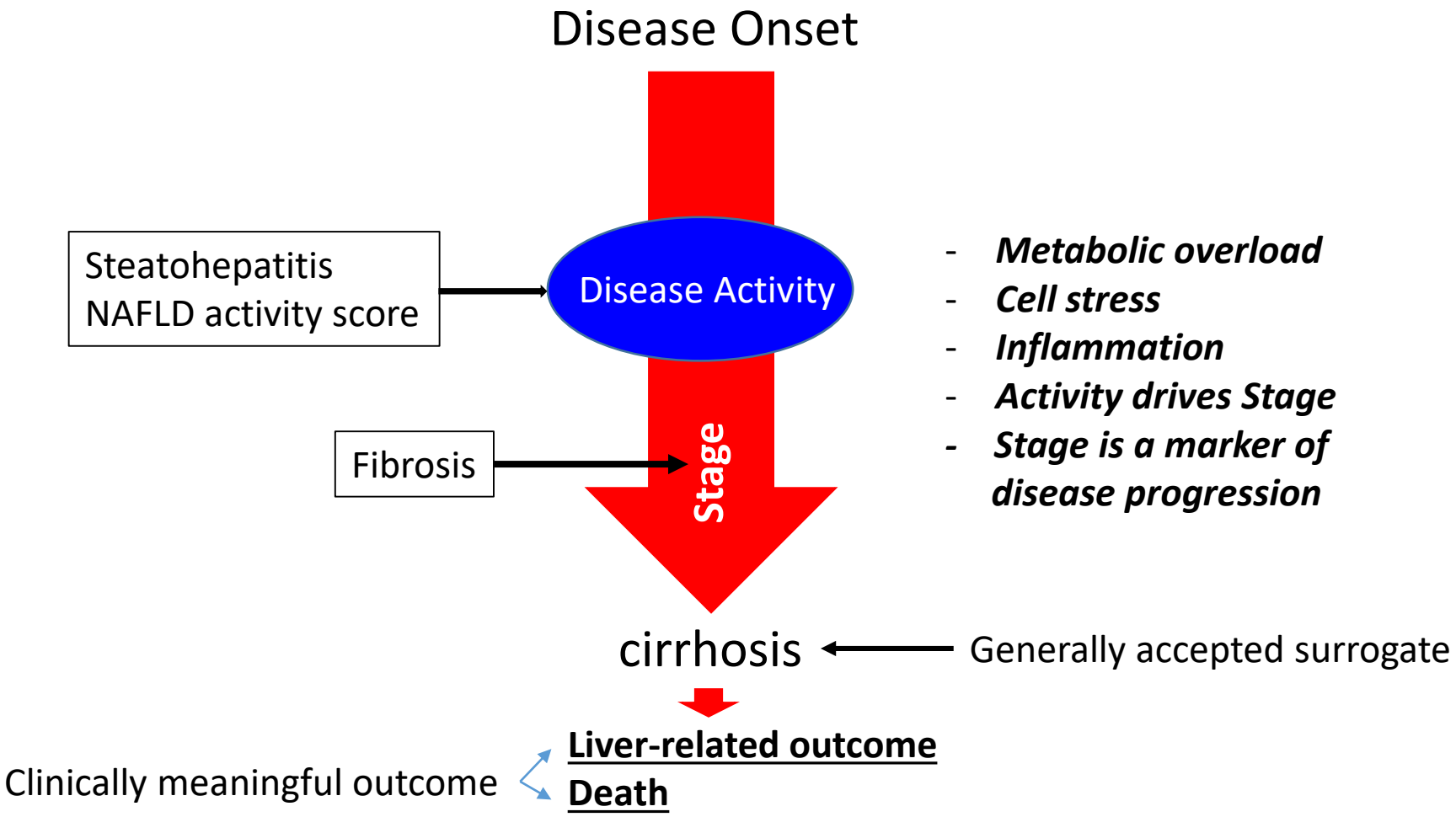
Making the case for combination therapies

NASH is a disease of metabolic substrate poisoning

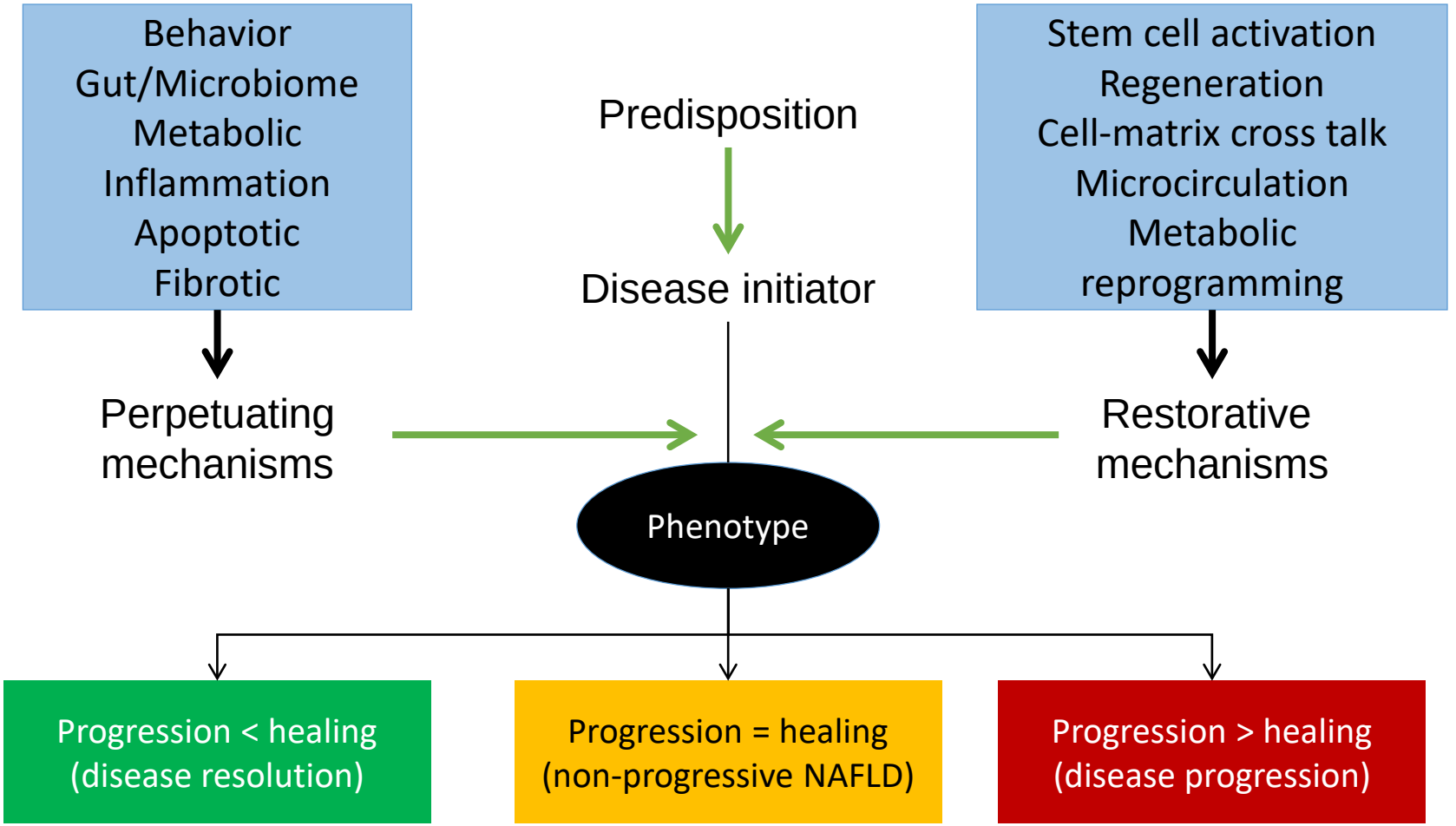
Pathogenesis of NASH and targets of therapy



Disease activity versus disease stage

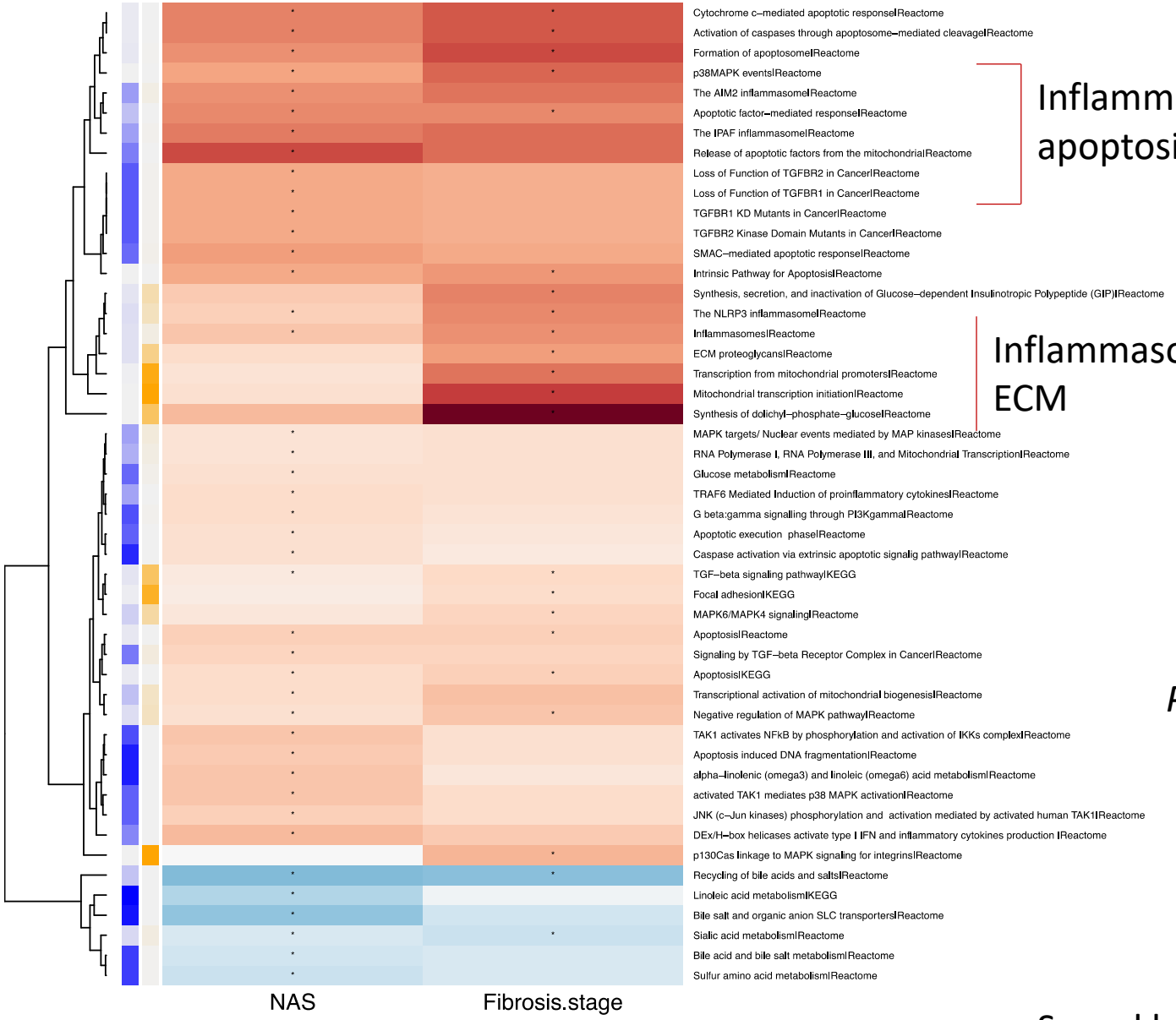


The progression of NASH is affected by many pathways



Ratziu V, Goodman Z, Sanyal A. *Journal of Hepatology* 2015;62;S65–S75.

NAS vs Fibrosis Exclusivity in NASH Pathways

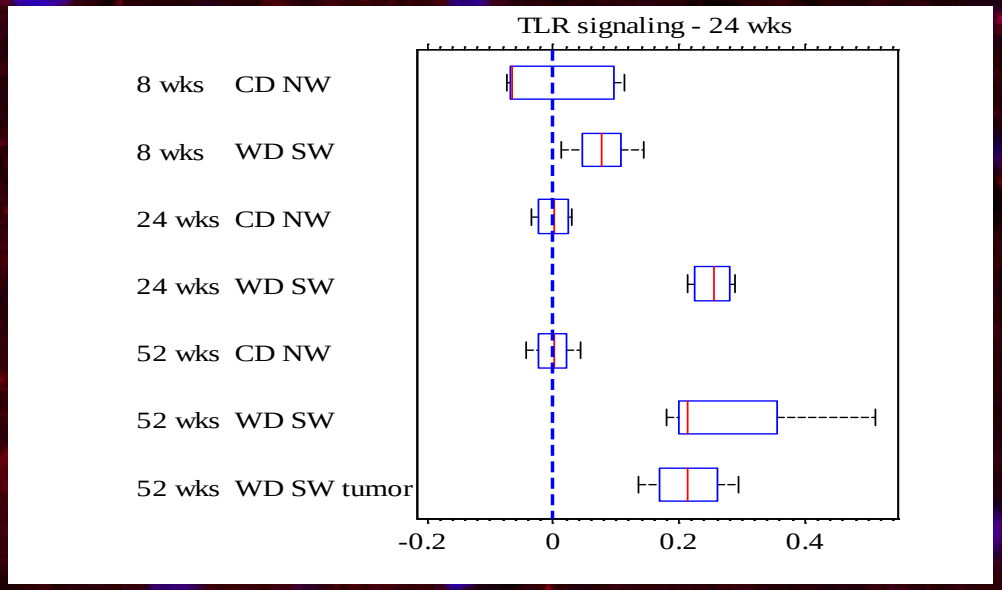


The exclusivity probability is the probability that the pathway is significant in one contrast and not in the other

$$P_{EA} = P_A * (1 - P_B)$$

Sanyal lab, unpublished data

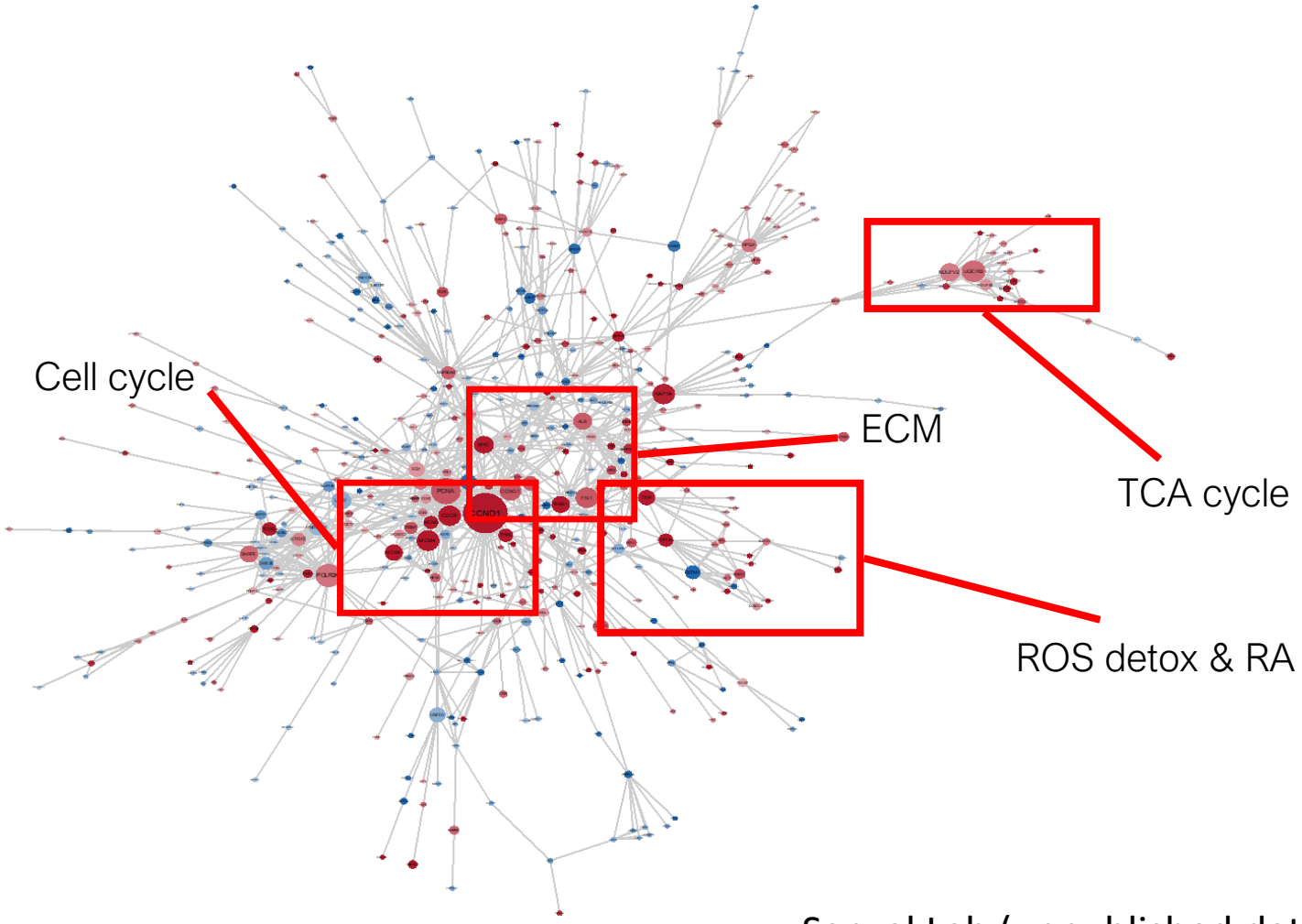
K. Human NASH (NAS 5)



Cazanave et al, Scientific Reports, Epub Dec 2017

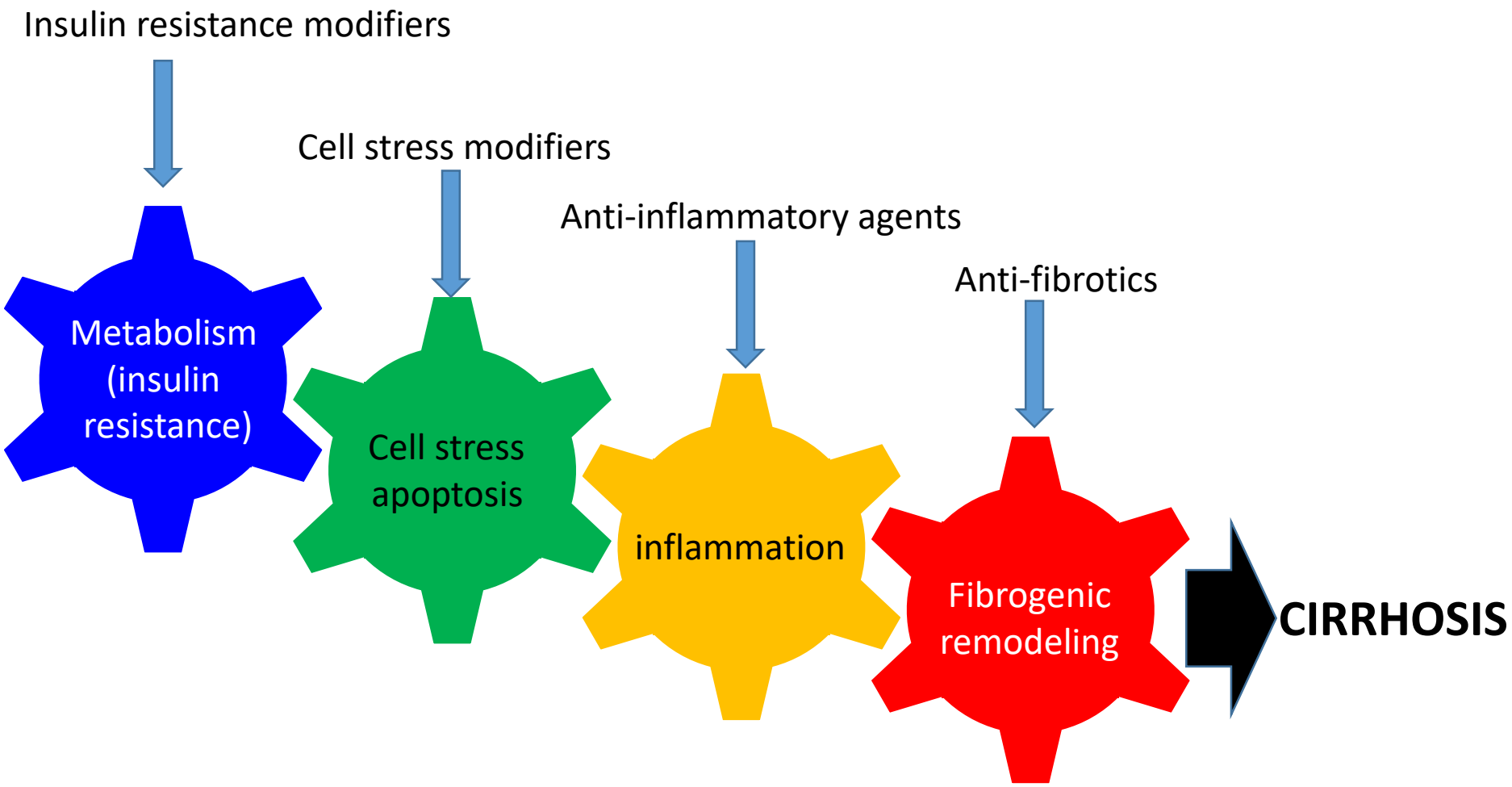
50um

Pathways with super-additive effects on disease activity and fibrosis stage

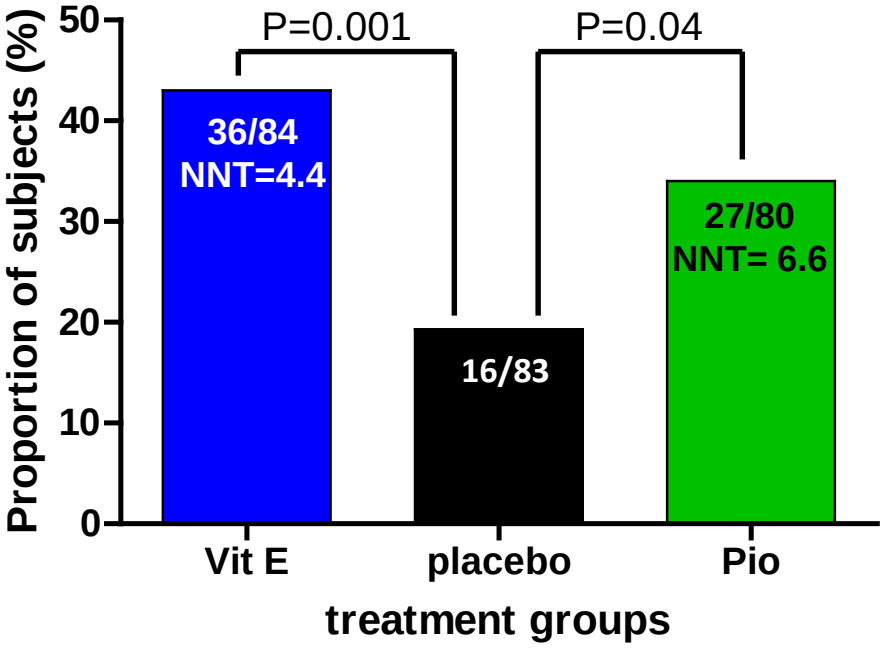


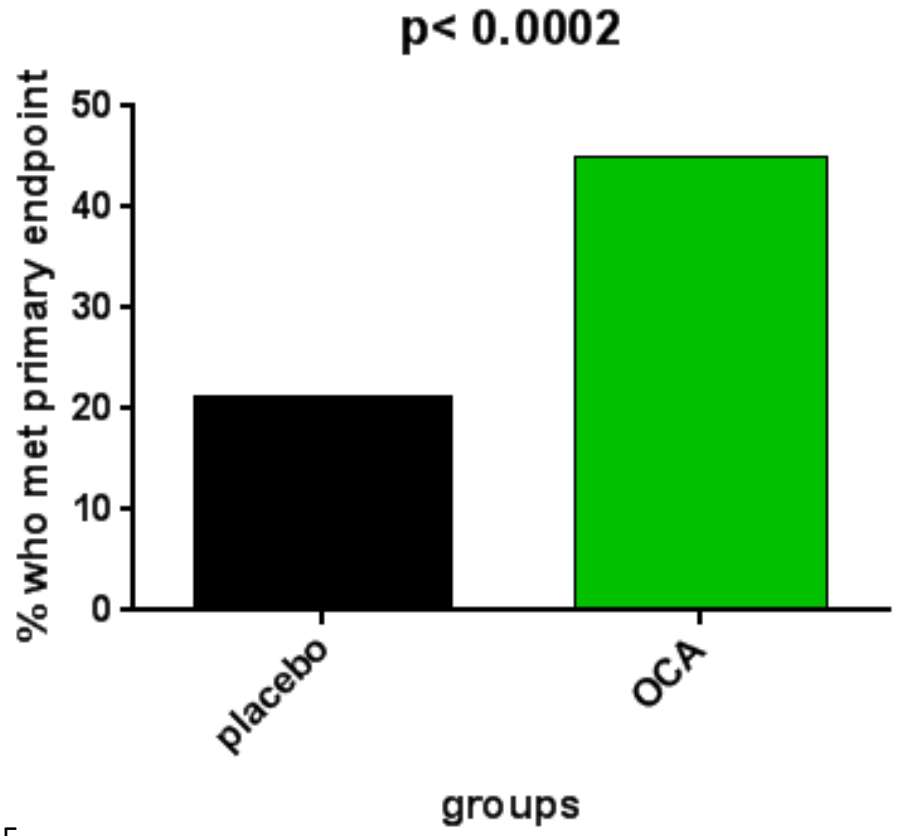
Sanyal Lab (unpublished data)

DISEASE BIOLOGY PROVIDES TARGETS FOR THERAPEUTICS



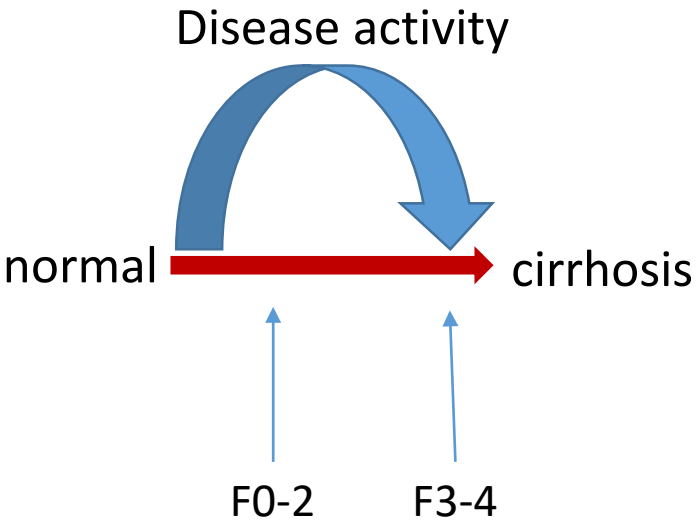
If everyone took the drug, why did only some individuals improve?

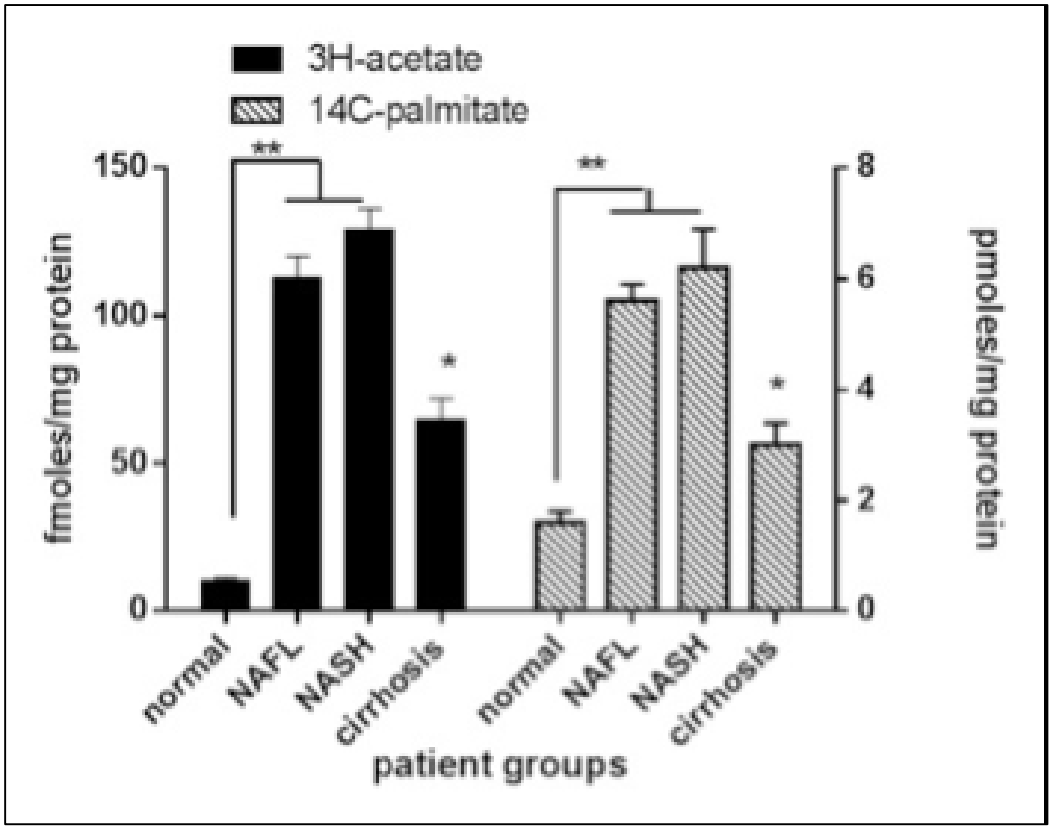




Sanyal et al, NEJM 2010, Neuschwander-Tetri, Lancet 2015

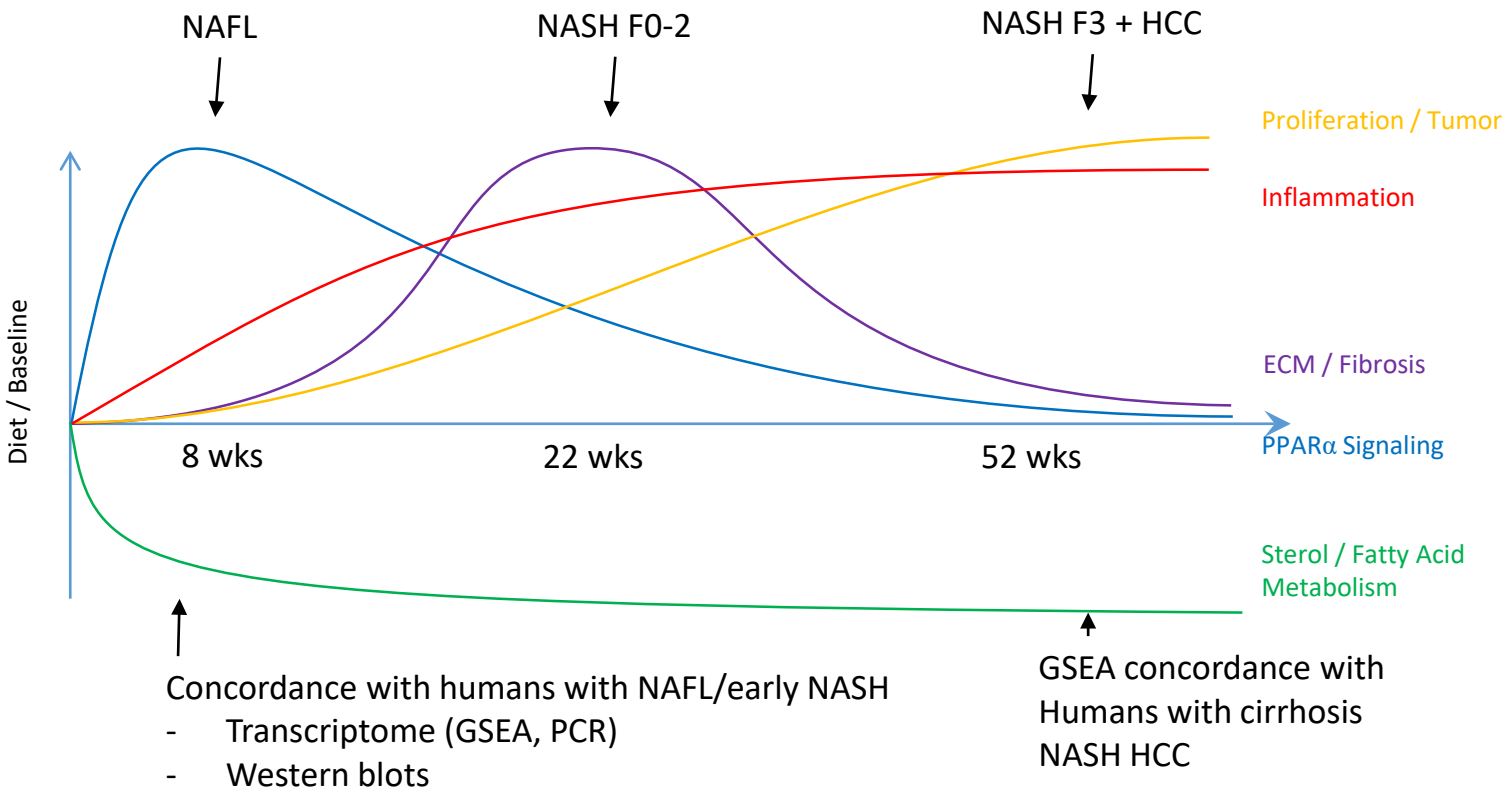
Disease activity burns out with progression in to cirrhosis





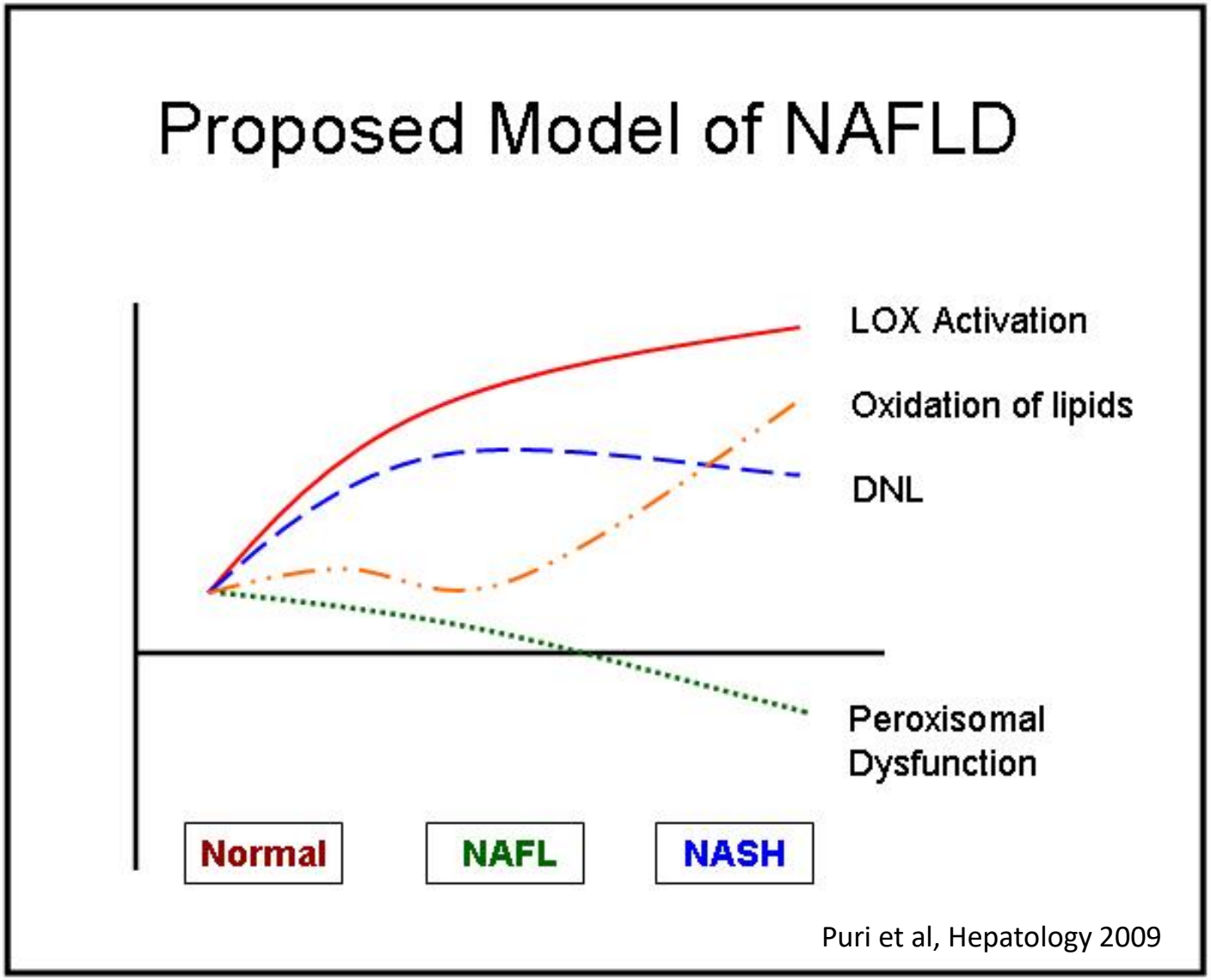
Siddiqui et al, Clin Gastro Hep 2015

Tracking the molecular evolution of NASH provides a comprehensive list of potential targets for therapy



Cazanave et al, Scientific Reports, Dec 2017

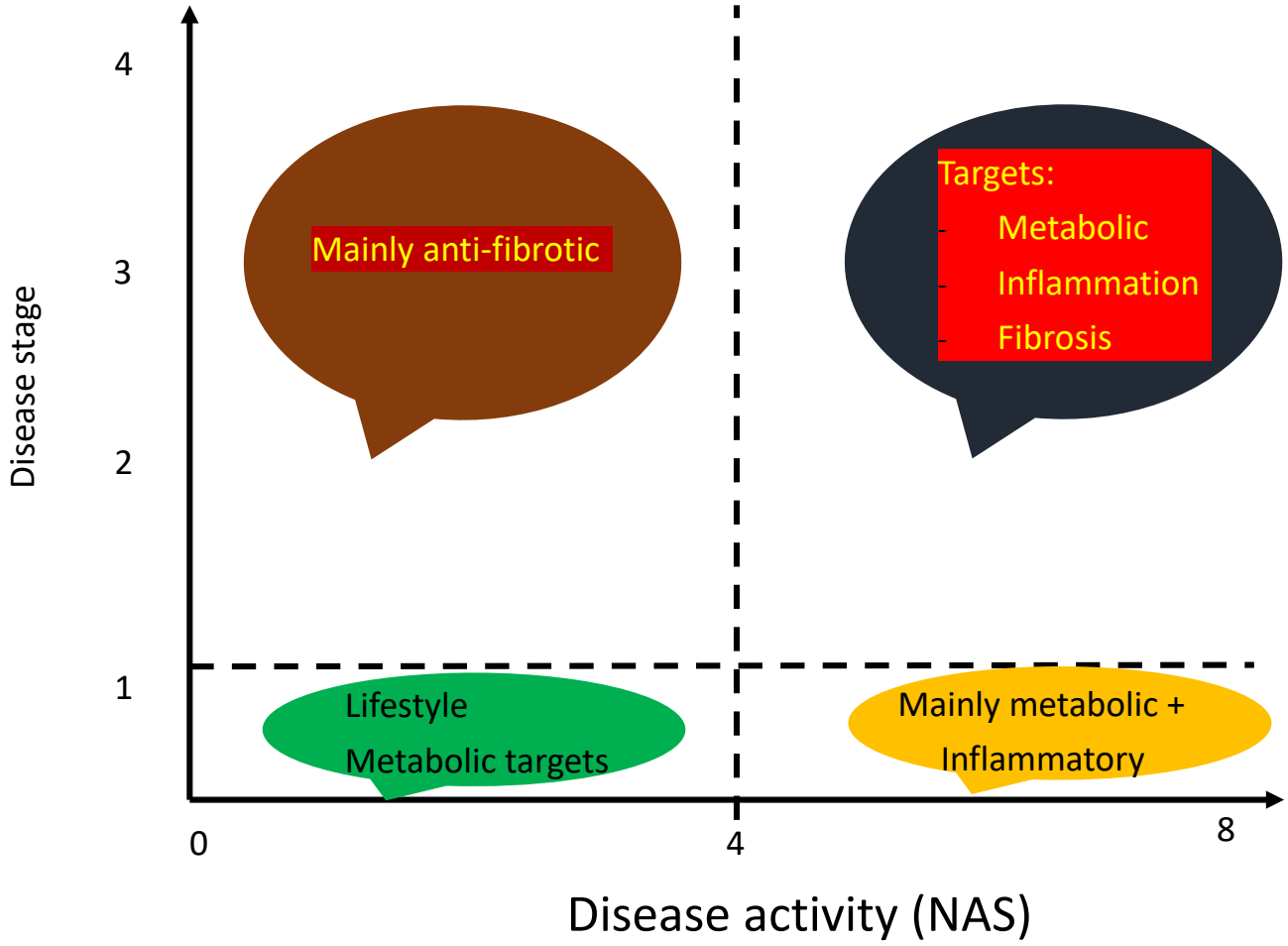
Lipidomic signature of NASH



Puri et al, Hepatology 2009

Matching the right patient to the right drug/s

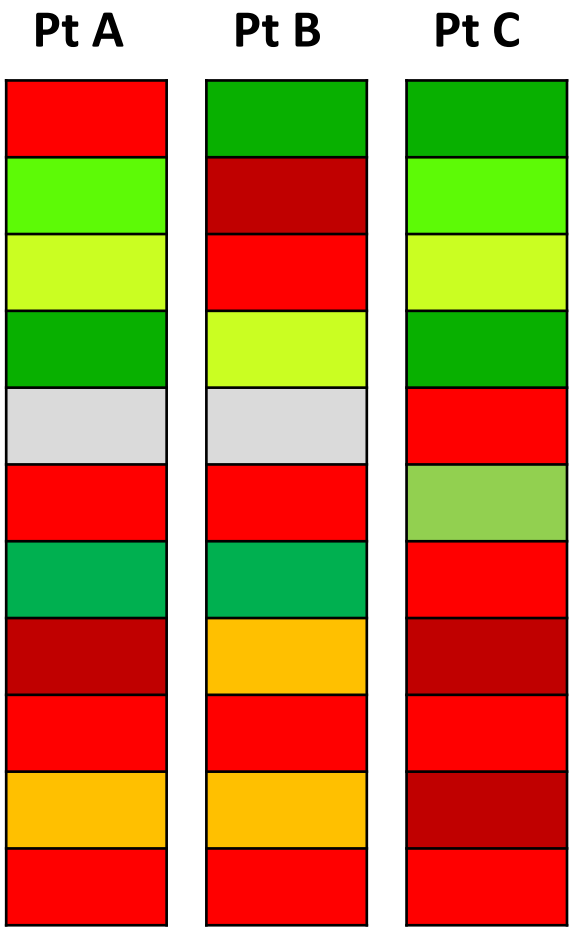
Rational approach to therapeutics for NASH



Hypothetical patient stratification

Pathway category:

- Impaired satiety mechanisms
- Impaired thermogenesis
- Periph adipogenesis/lipolysis
- Adipose inflammation
- Augmented DNL
- Impaired TG formation
- PNPLA3?→ Inappropriate TG lipolysis
- Active lipotoxic lipid synthesis
- Liver inflammatory pathways
- Impaired wound response
- Augmented fibrogenesis



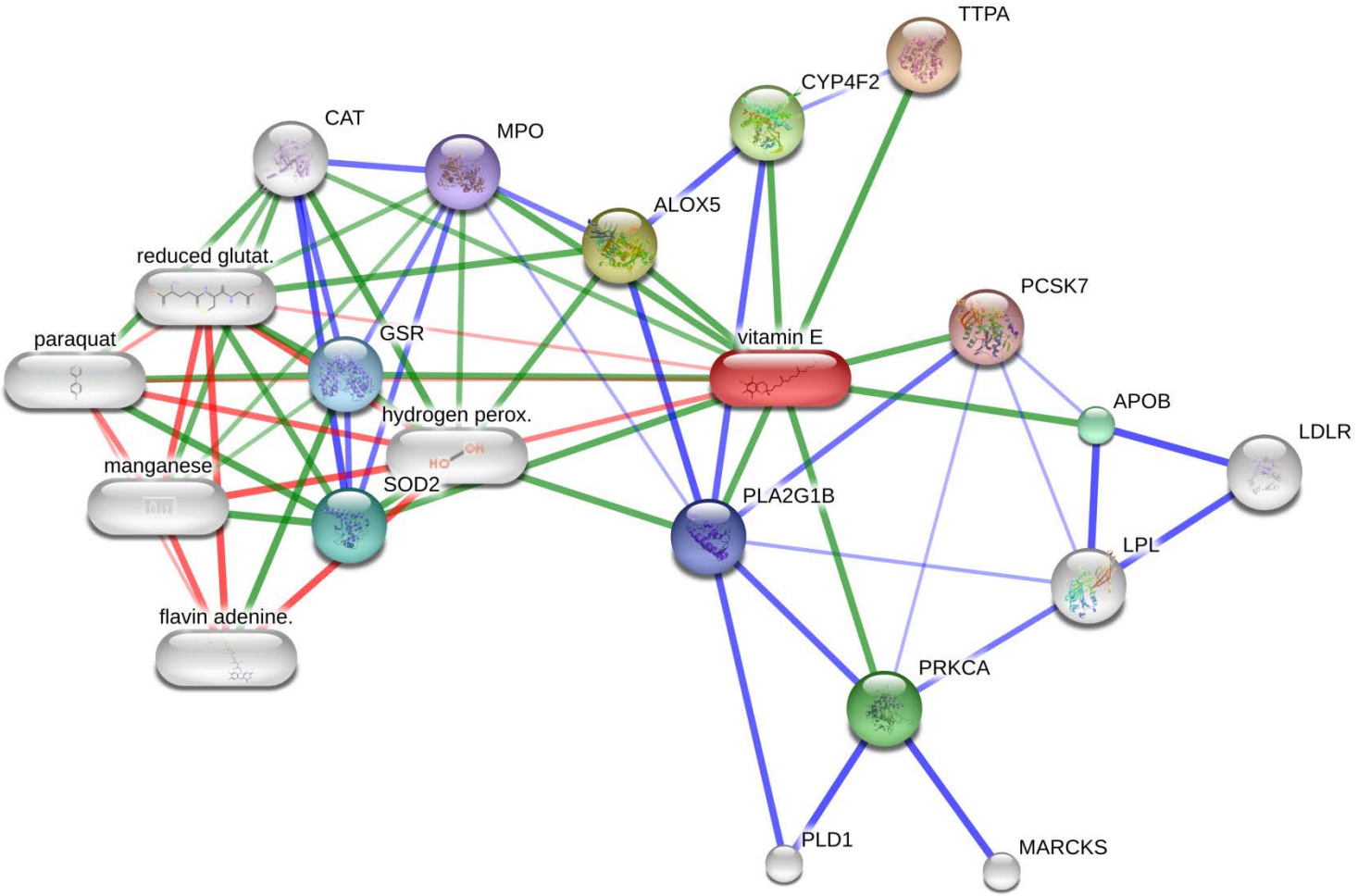
Likelihood of contributing to NASH phenotype

Low

High

"lean NASH"

Network analysis reveal vitamin E specific pathways that are relevant for its effects on NASH



Sookoian and Pirola, Clin Liv Dis, 2012

Baseline metabolites predict response to future treatment with vitamin E

Metabolites	OR	95% CI
gamma-CEHC	0.11	0.01-0.995
2-palmitoylglycerophosphoethanolamine	0.08	0.01 - 0.56
myristoleate (14:1n5)	0.04	0.002-0.64
3-phenylpropionate	29.4	1.23-707.0
Asparagines	20.2	1.2-338.6
indolepropionate	16.2	1.45-180.7

Only those that were significant are listed

Cheng et al, PlosONE, 2012

Stratification → targeted treatment

"Personalized medicine"

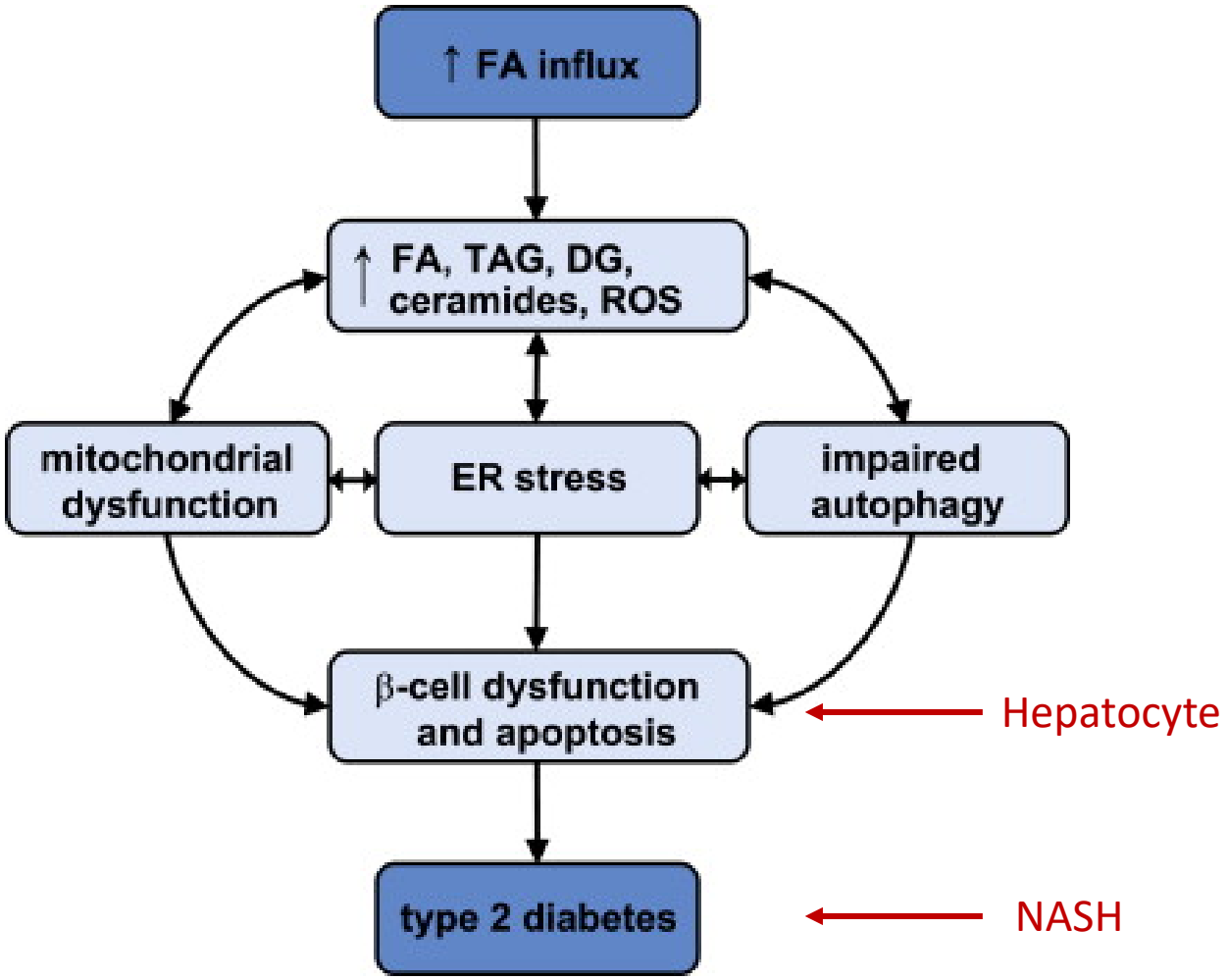
Pathway category:

	Pt A	Pt B	Pt C	
Impaired satiety mechanisms				Central modulation
Impaired thermogenesis				PGC1α activators
Periph adipogenesis/lipolysis				PPARγ ligands
Adipose inflammation				JNK inhib?
Augmented DNL				ACC1, SCD inhib.
Impaired TG formation				?
PNPLA3?→ Inappropriate TG lipolysis				DGAT2 activators
Active lipotoxic lipid synthesis				CYP4 inhibitors
Liver inflammatory pathways				$iPLA_2$ inhibitors
Impaired wound response				Hedgehog inhib
Augmented fibrogenesis				Galectin inhib?

"lean NASH"

Combination therapy: targeting multiple organs simultaneously

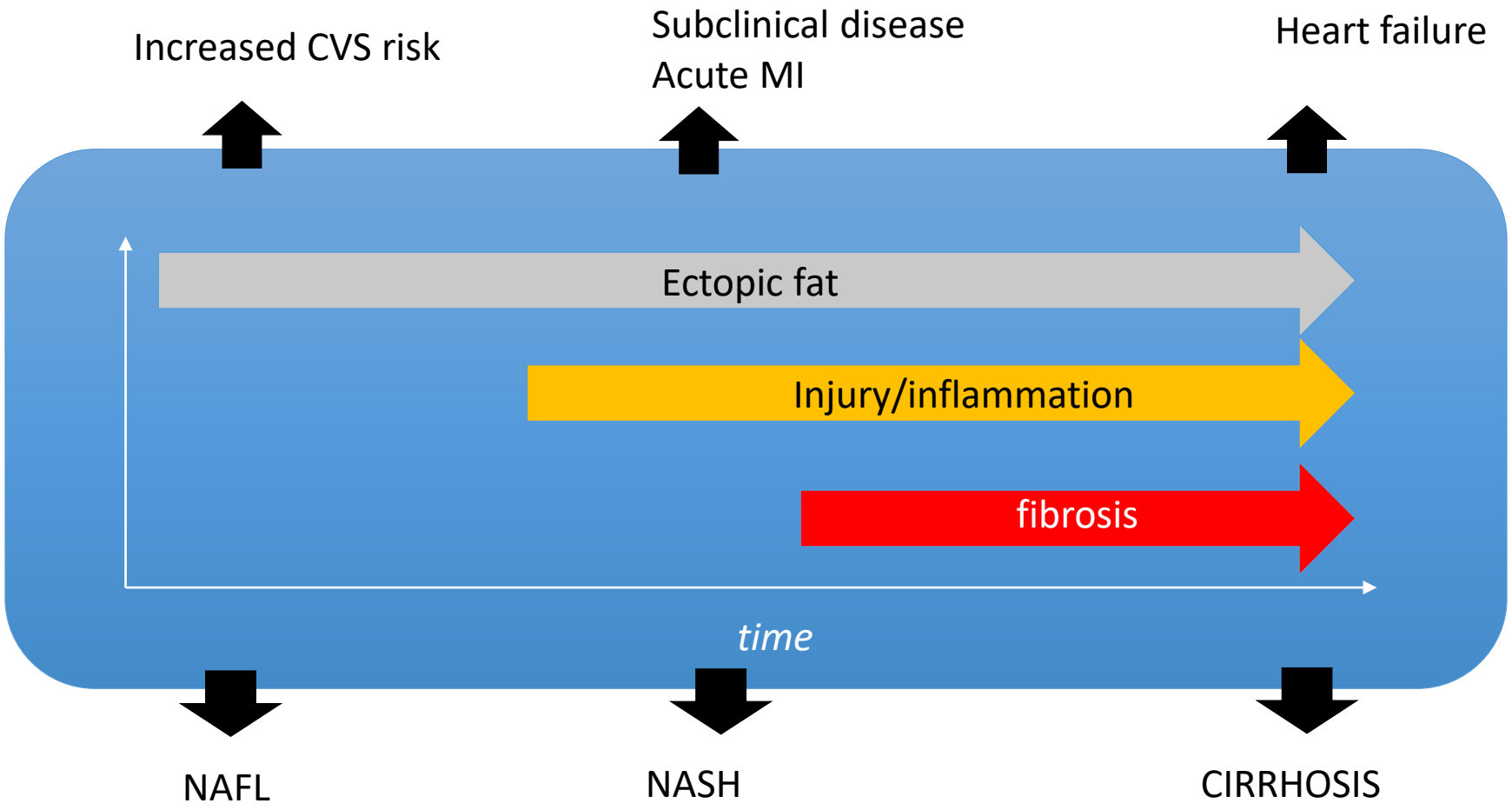
Pathogenesis of beta cell failure in type 2 diabetes



Janikiewicz, et al; Biochemical and Biophysical Research Communications, Volume 460, Issue 3, 2015, 491–496

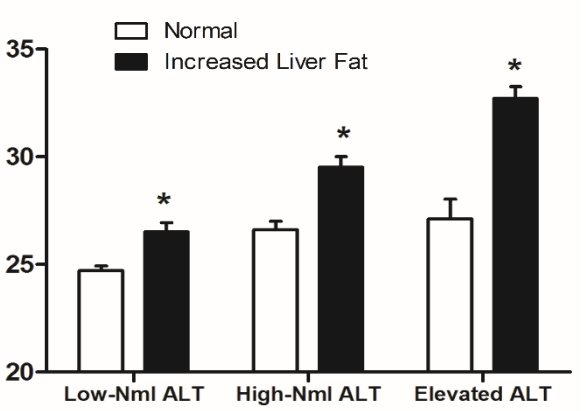
http://dx.doi.org/10.1016/j.bbrc.2015.03.153

The Liver-Heart connection



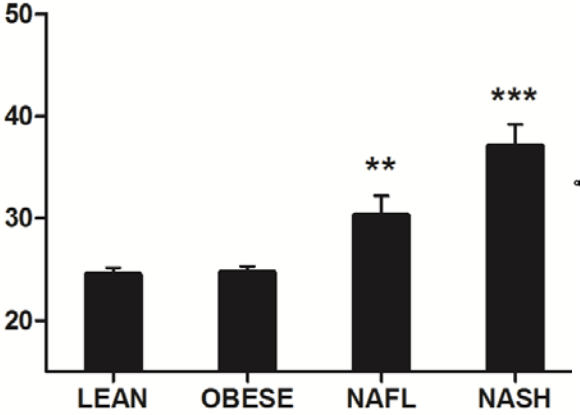
Disease Severity in NAFLD Drives Atherogenic Dyslipidemia

Small Dense LDL-Cholesterol



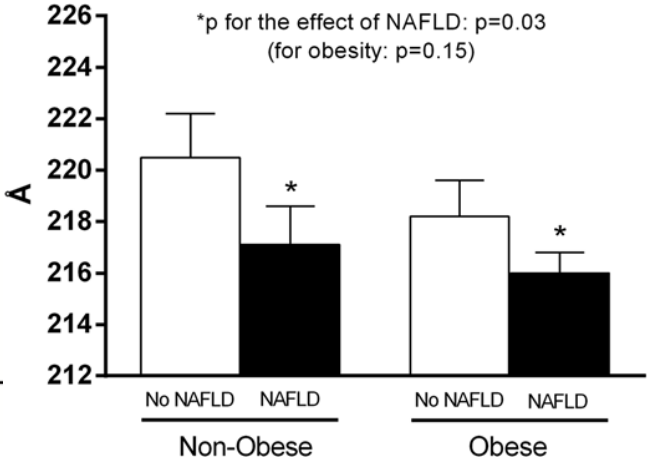
Siddiqui et al. Gastroenterology. 2013

Small Dense LDL-Cholesterol



Siddiqui et al. Clin Gastro & Hep 2014

LDL-Particle Size



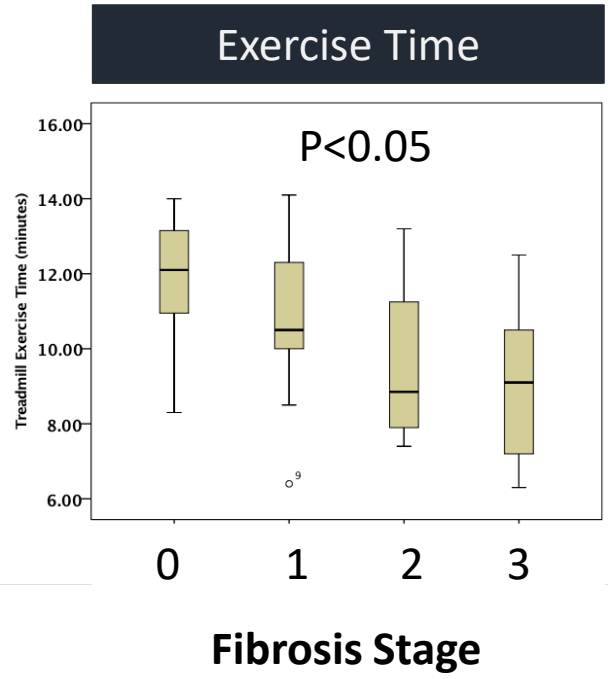
Bril et al. J Clin Endo Metabol 2016

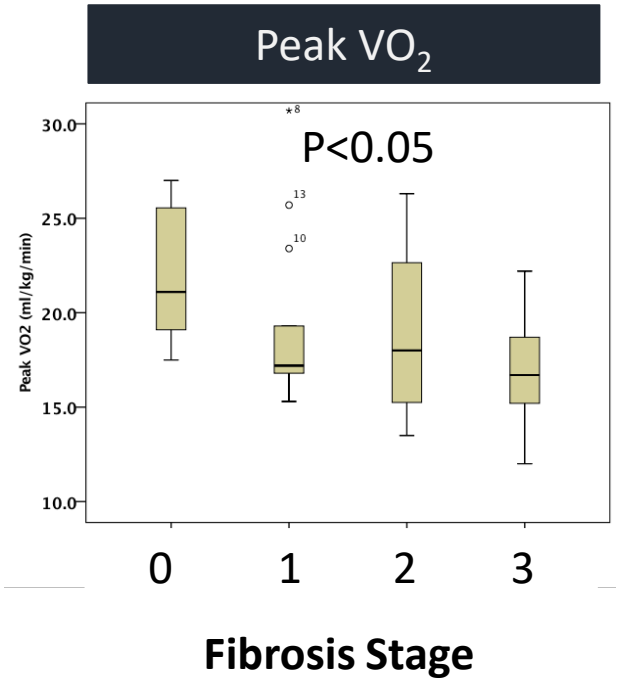
The more advanced the NASH, the greater the risk of cardiac events

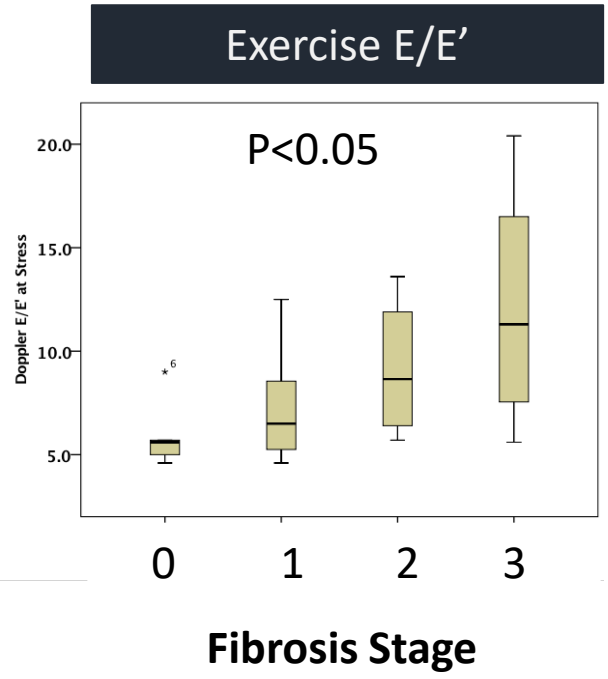
		Age, Sex-adjusted	Multivariable-adjusted
	n	Hazard ratio (95% CI)	Hazard ratio (95% CI)
All cause	778		
Minimal	251	1	1
Intermediate	404	1.50 (1.20-1.88)	1.40 (1.09-1.81)
Advanced	123	2.26 (1.59-3.21)	1.80 (1.23-2.64)
Cardiovascular disease	296		
Minimal	81	1	1
Intermediate	167	2.43 (1.69-3.50)	2.49 (1.71-3.64)
Advanced	48	**3.34 (2.00-5.60)**	**3.22 (1.92-5.42**)

Kim et al, Hepatology, 2013

Fibrosis Stage is Linked To Diastolic Dysfunction and Exercise Capacity



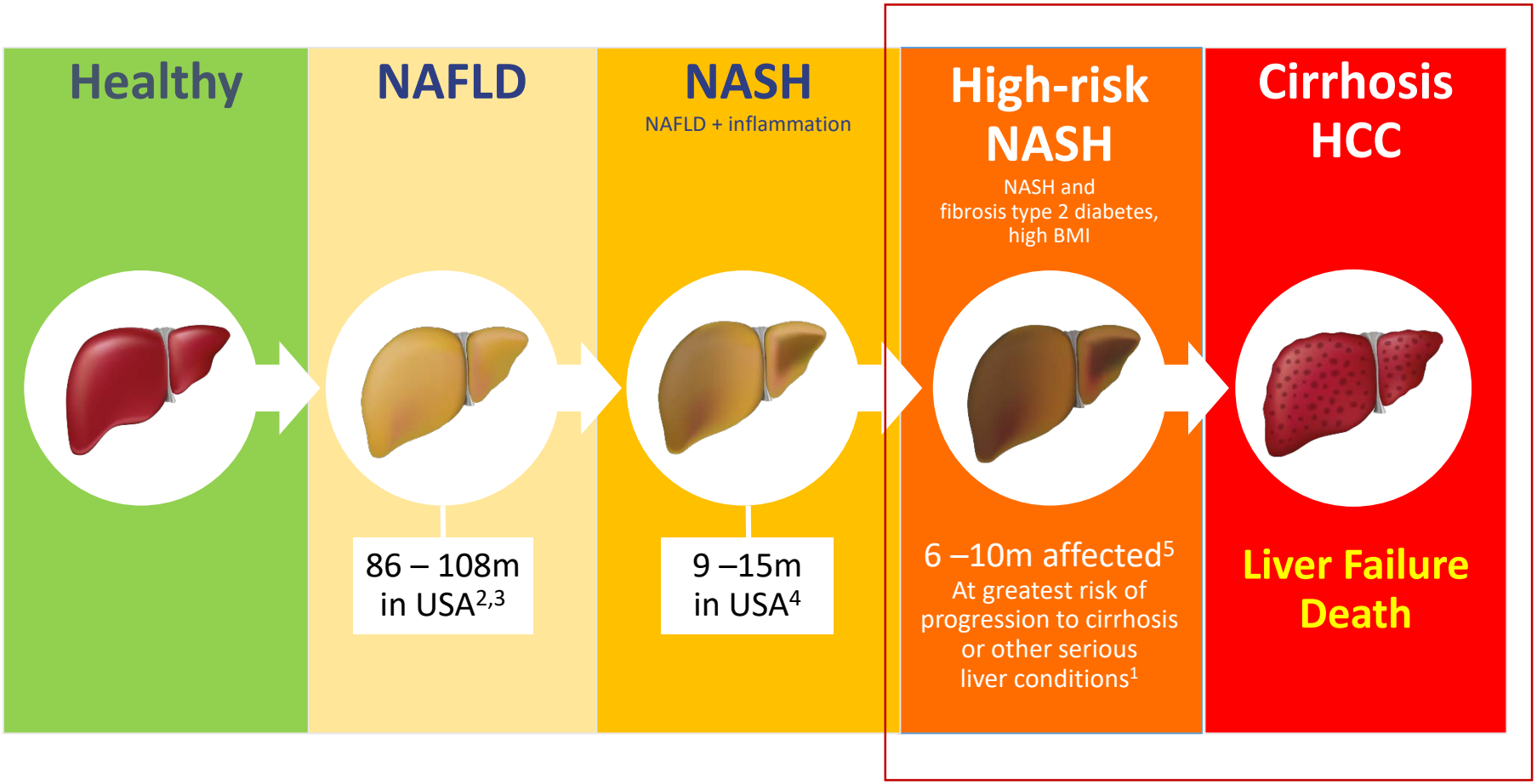




Siddiqui et al. AASLD 2017

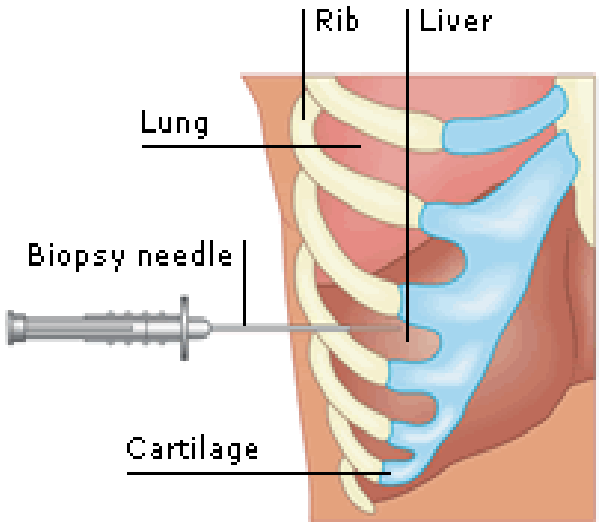
Finding the patients- *an urgent need to develop noninvasive methods for assessment*

Targeting the population at risk



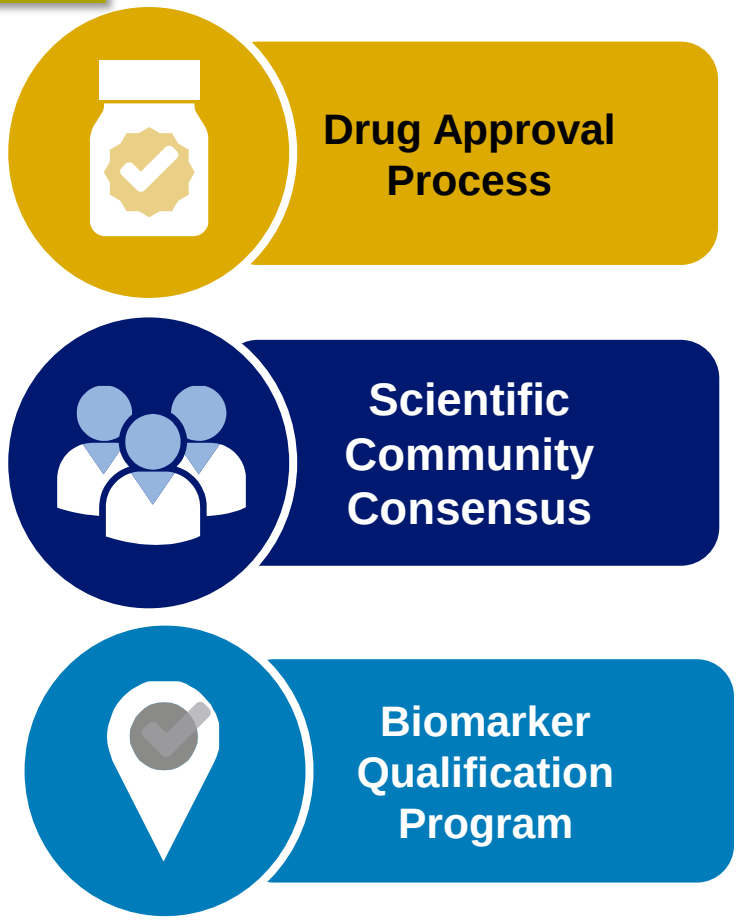
Liver biopsy is an inadequate tool for routine assessment

- Invasive, painful
- Risks- morbidity and mortality
- Sampling variability
- Observer variability
- Limited workforce capacity



With a mortality risk of 1:1000 and population at risk of 60 million, the total number of Diagnostics-associated mortality would be 60000

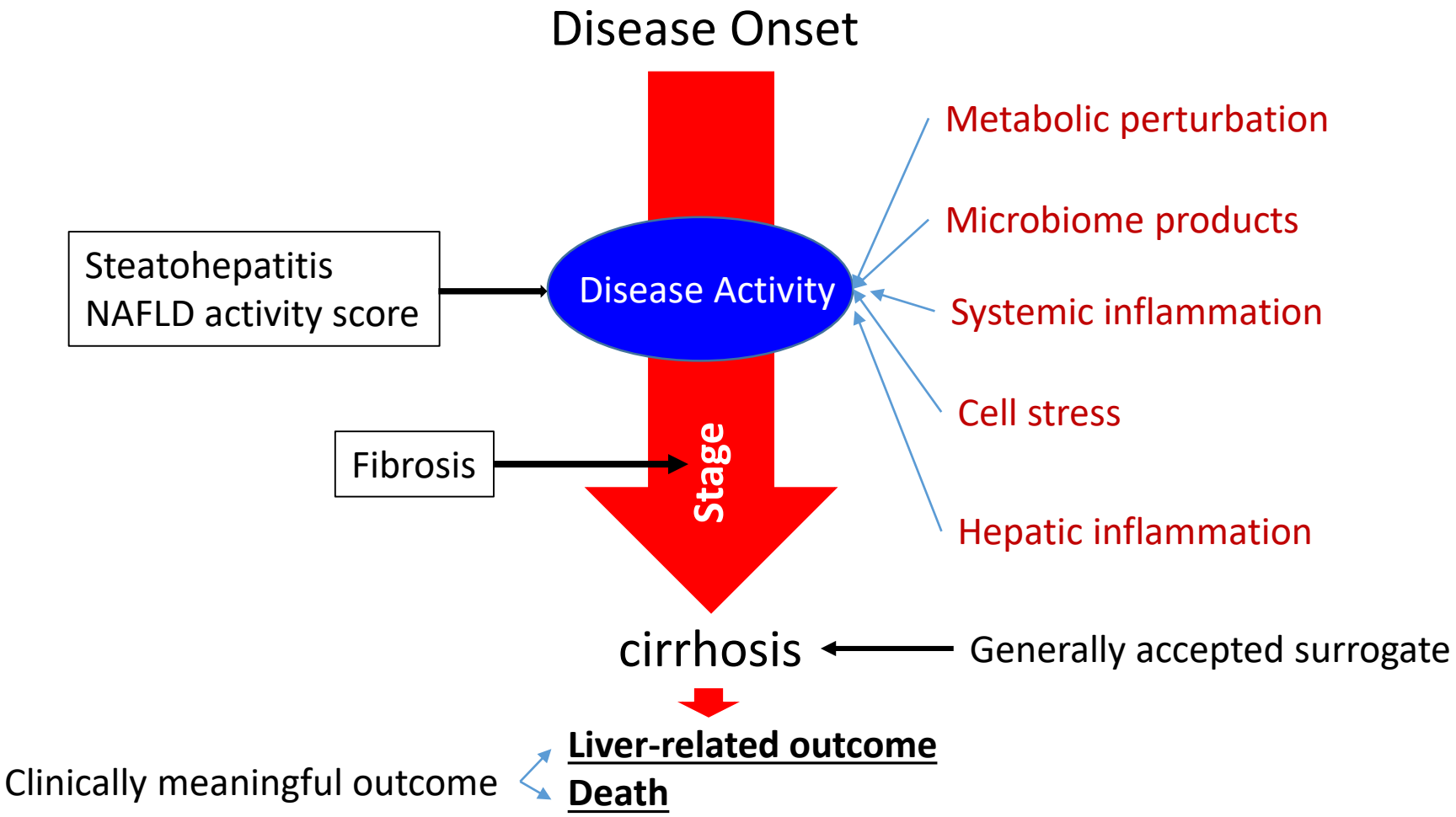
Biomarker development process



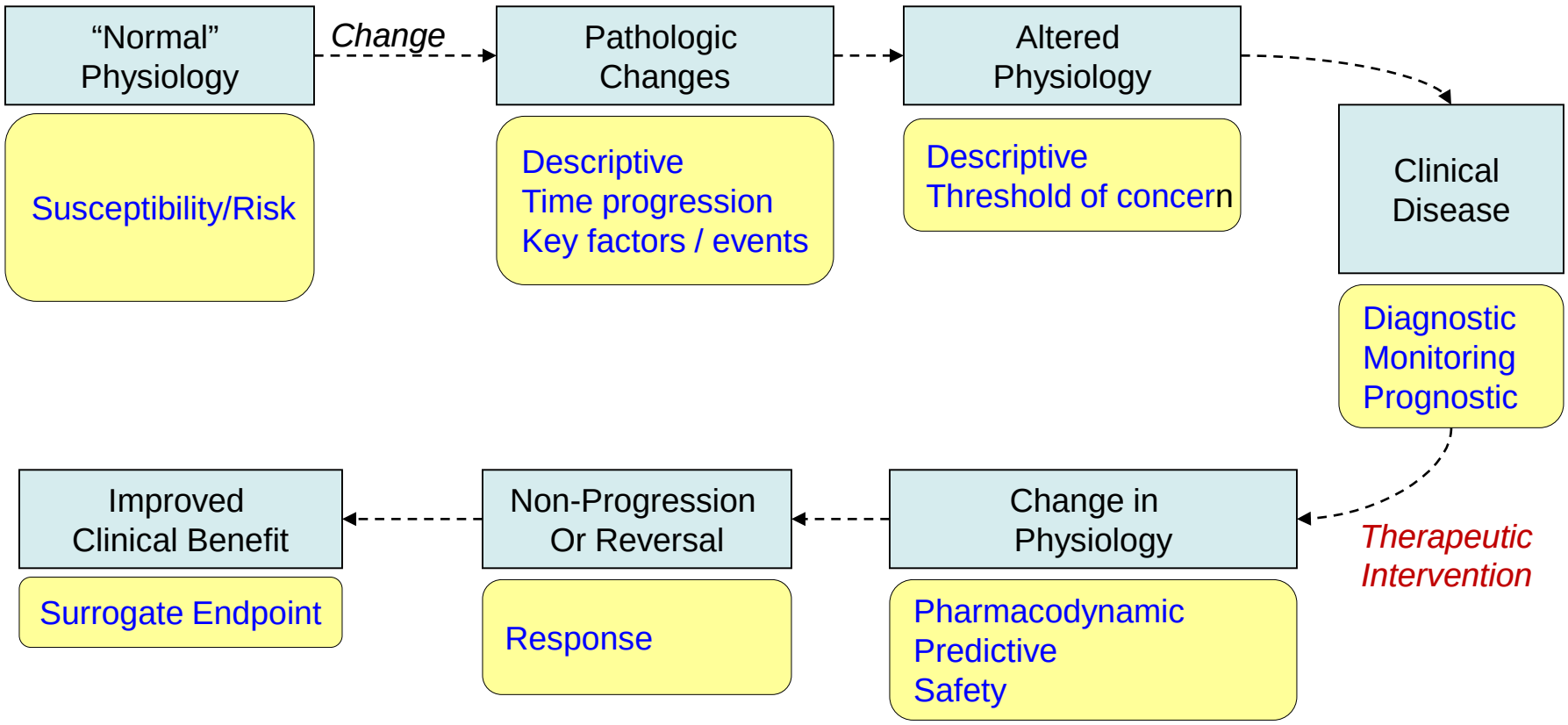
- Data Driven
- Subject to regulatory scrutiny
- More than one process can go on
- Liver Forum integrates biomarker development process across FDA and EMA

Facilitating Biomarker Development: Strategies for Scientific Communication, Pathway Prioritization, Data-Sharing, and Stakeholder Collaboration; Published June 2016, Duke-Margolis Center for Health Policy

Disease activity versus disease stage



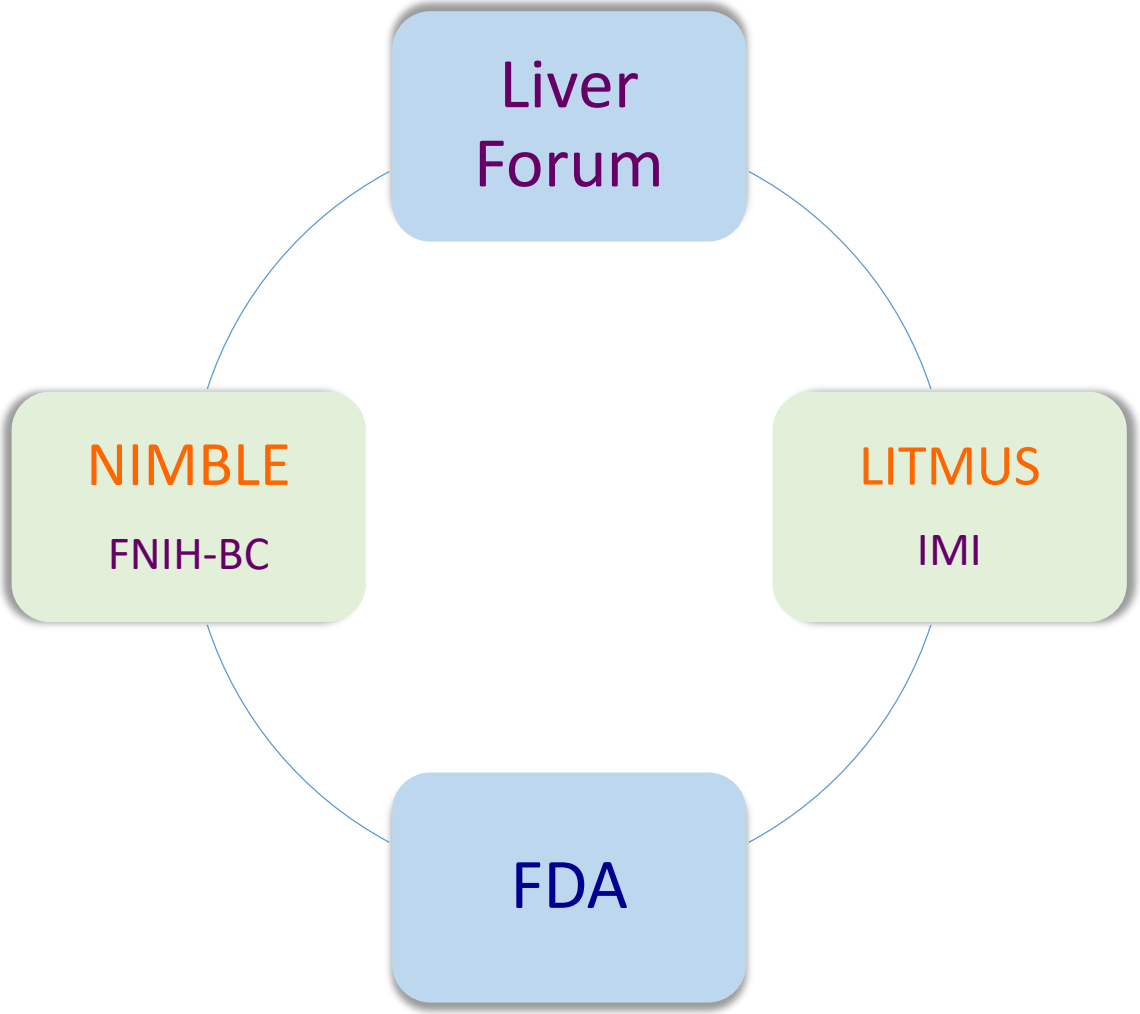
“Fit for Purpose” biomarkers



Companion vs Complementary diagnostic

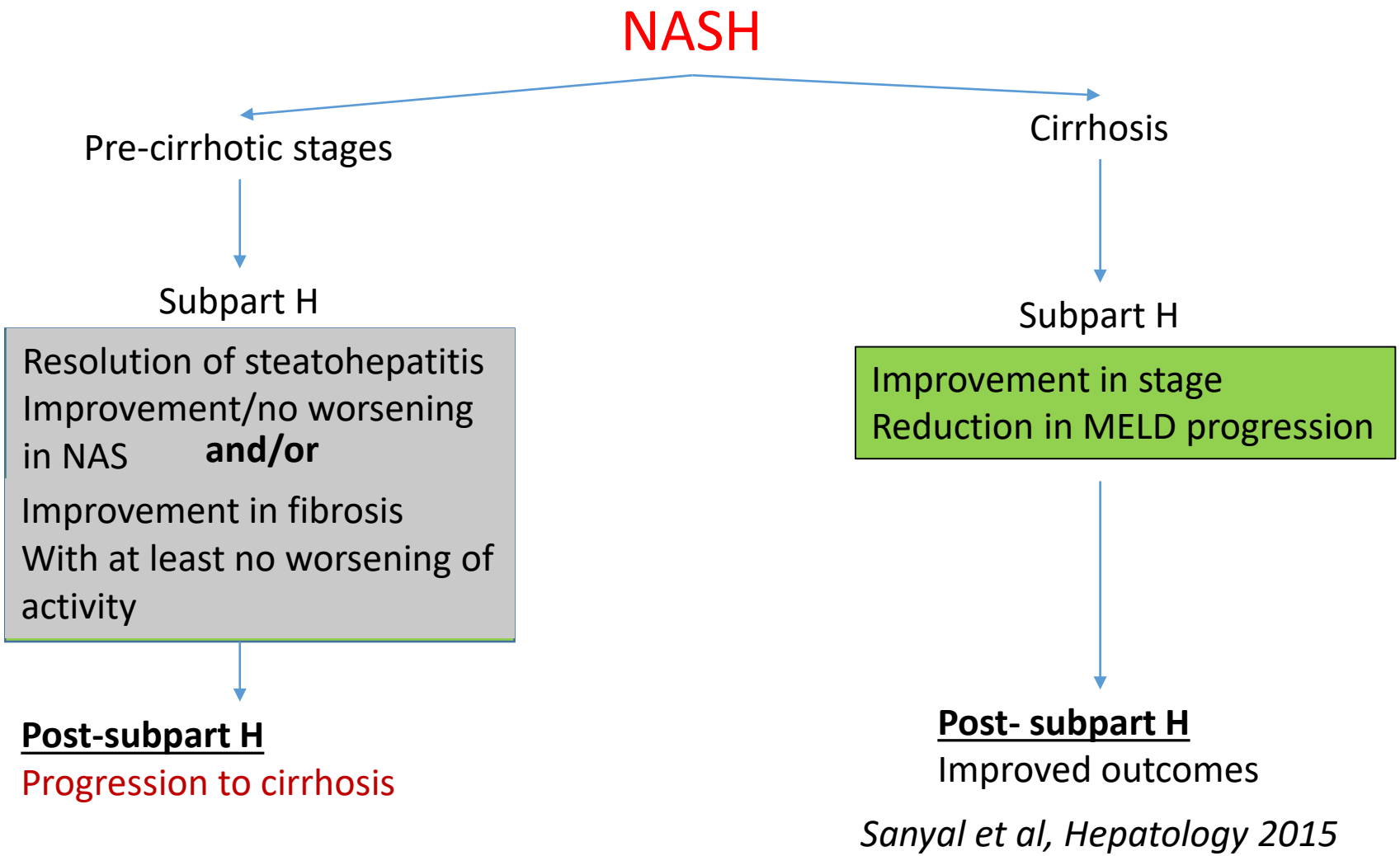
Adapted from Chris Leptak…Liver Forum Biomarker Workshop 2017

Trans-atlantic initiatives for NASH biomarker development

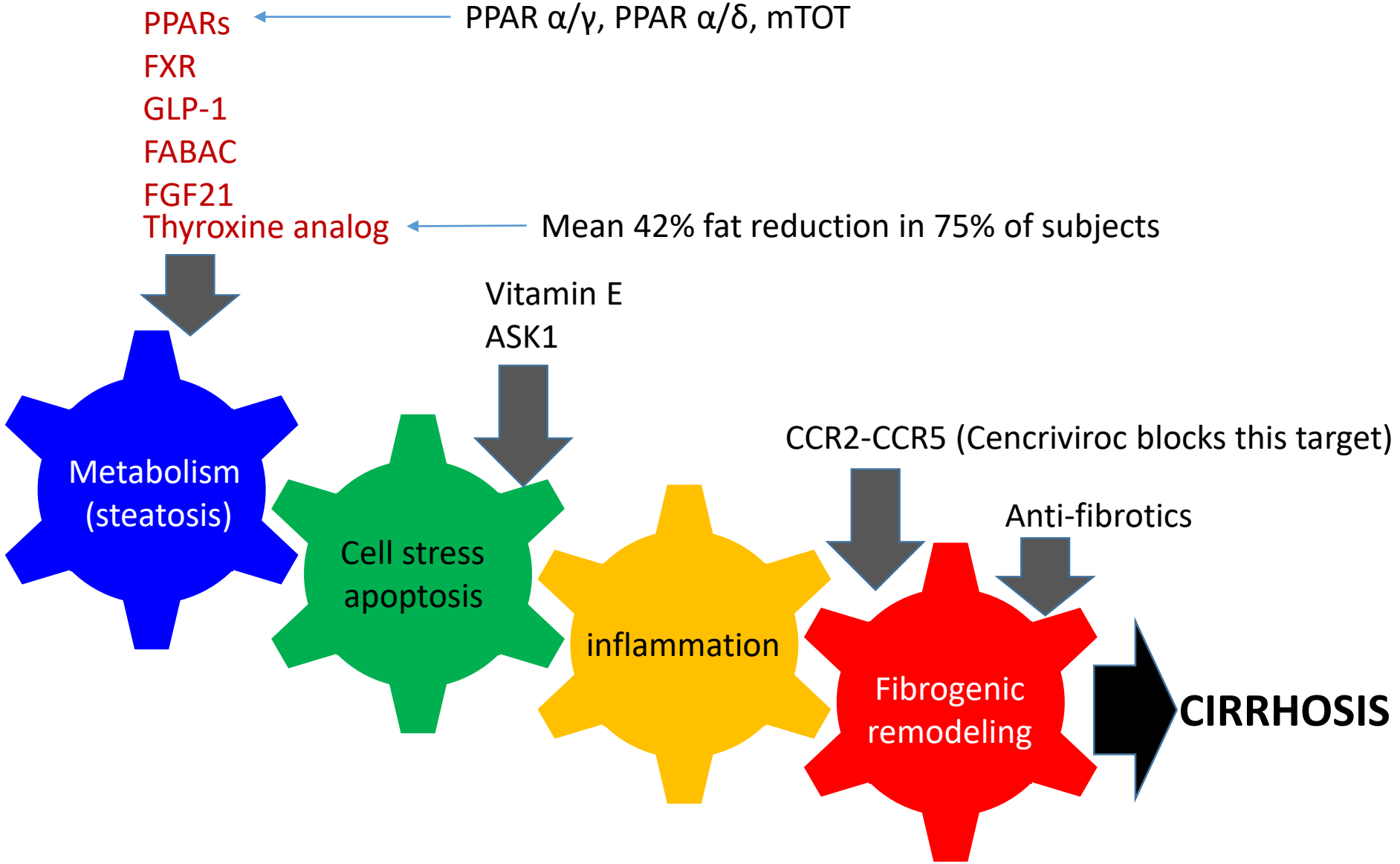


The path to approval

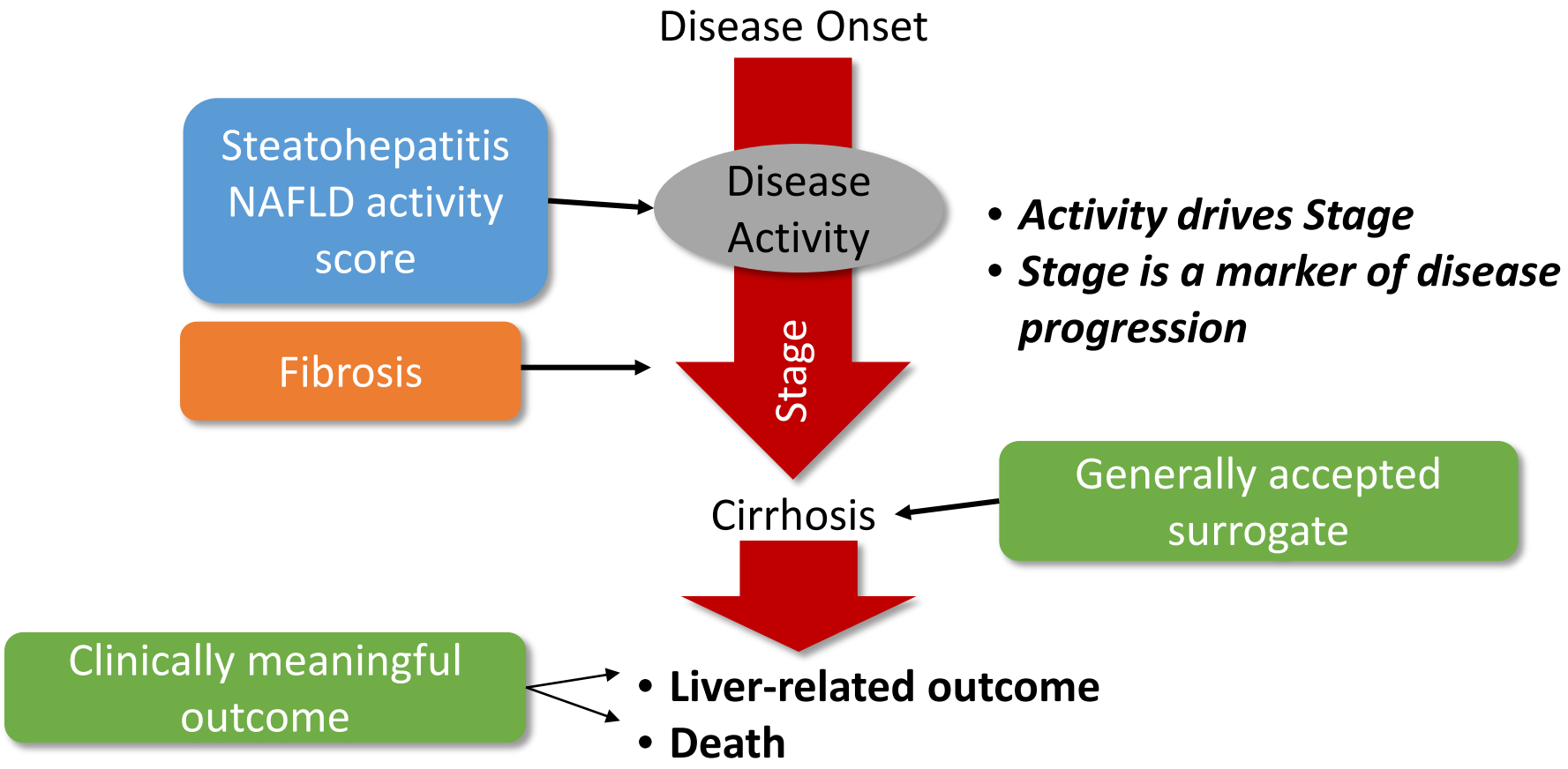
Evidence burden to have therapy approved for NASH



Sanyal et al, Hepatology 2015

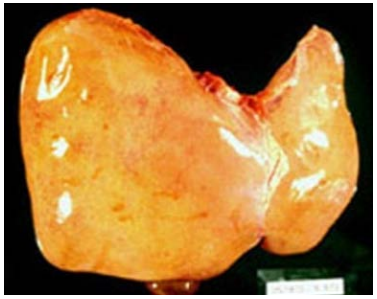

PPARs
PPAR α/γ, PPAR α/δ, mTOT
FXR
GLP-1
FABAC
FGF21
Thyroxine analog
Mean 42% fat reduction in 75% of subjects
Vitamin E
ASK1
CCR2-CCR5 (Cencriviroc blocks this target)
Anti-fibrotics
Metabolism (steatosis)
Cell stress apoptosis
inflammation
Fibrogenic remodeling
CIRRHOSIS

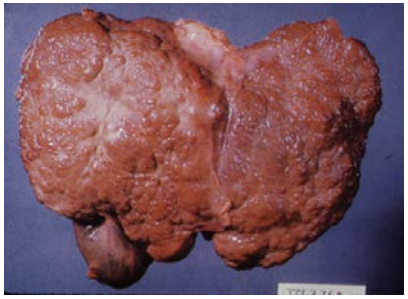
Endpoints: disease activity vs stage



In pre-cirrhotic stages, fibrosis is relevant mainly as a marker of *disease progression* towards cirrhosis

Progression to cirrhosis is a generally accepted surrogate endpoint for approval



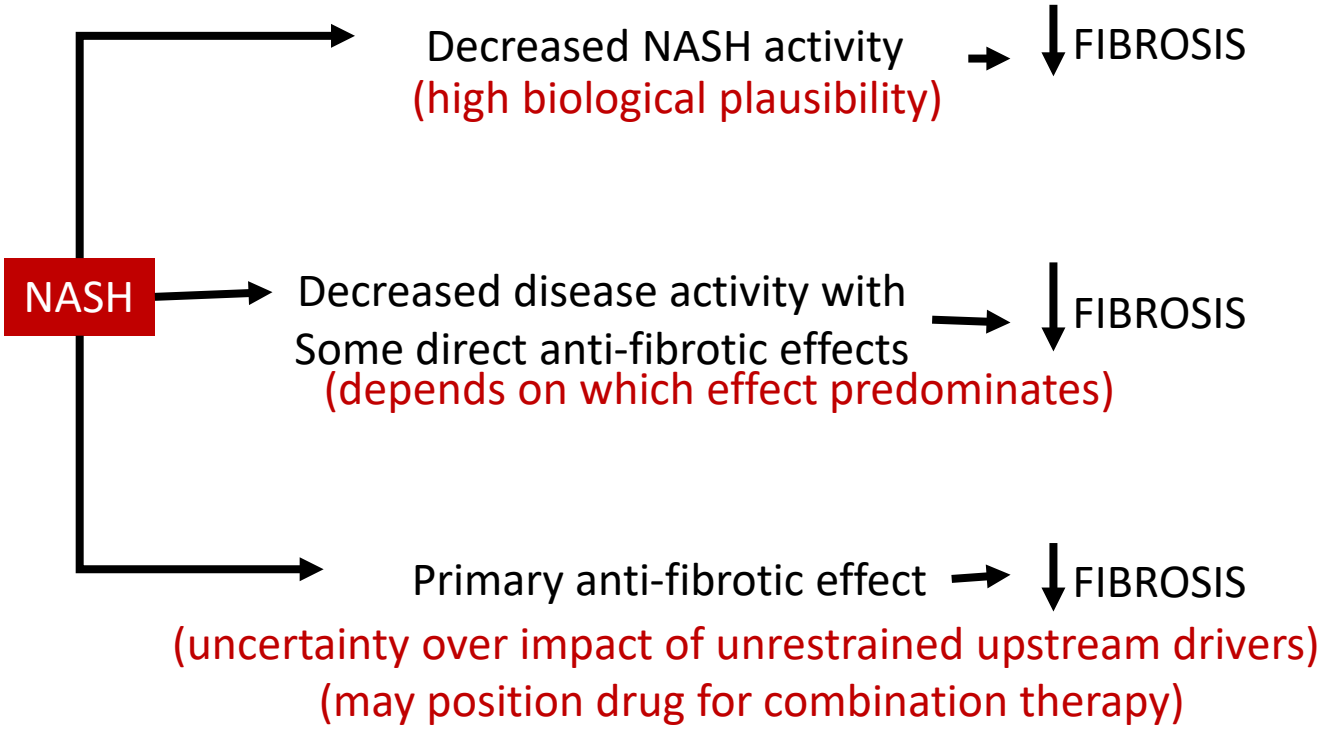


PREDICTABLE WORSENING OF OUTCOMES

Disease progression includes metabolic reprogramming, cell death, stem cell recruitment, regenerative activity, cell differentiation, changes in microcirculation, matrix, bile flow.

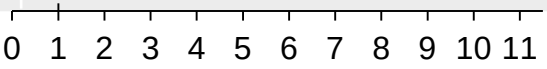
Fibrosis is an easily visible and quantifiable surrogate for this process.

Implications of decreased fibrosis in pre-cirrhotic stages of NASH is linked to drug mechanism of action



Impact of Fibrosis on Clinical Events

	Hazard Ratio *	95% CI	p-value
Ishak stage 5 vs 6 (baseline)	**1.25**	0.68, 2.29	0.48
No improvement vs improvement	**9.63**	1.33, 69.81	0.025
Hepatic collagen (baseline), per 5%	**1.39**	1.15, 1.69	<0.001
Change from baseline, per 5%	**1.20**	1.03, 1.39	0.017
ELF (baseline)	**2.37**	1.69, 3.31	<0.001
Change from baseline	**1.54**	1.10, 2.15	0.002

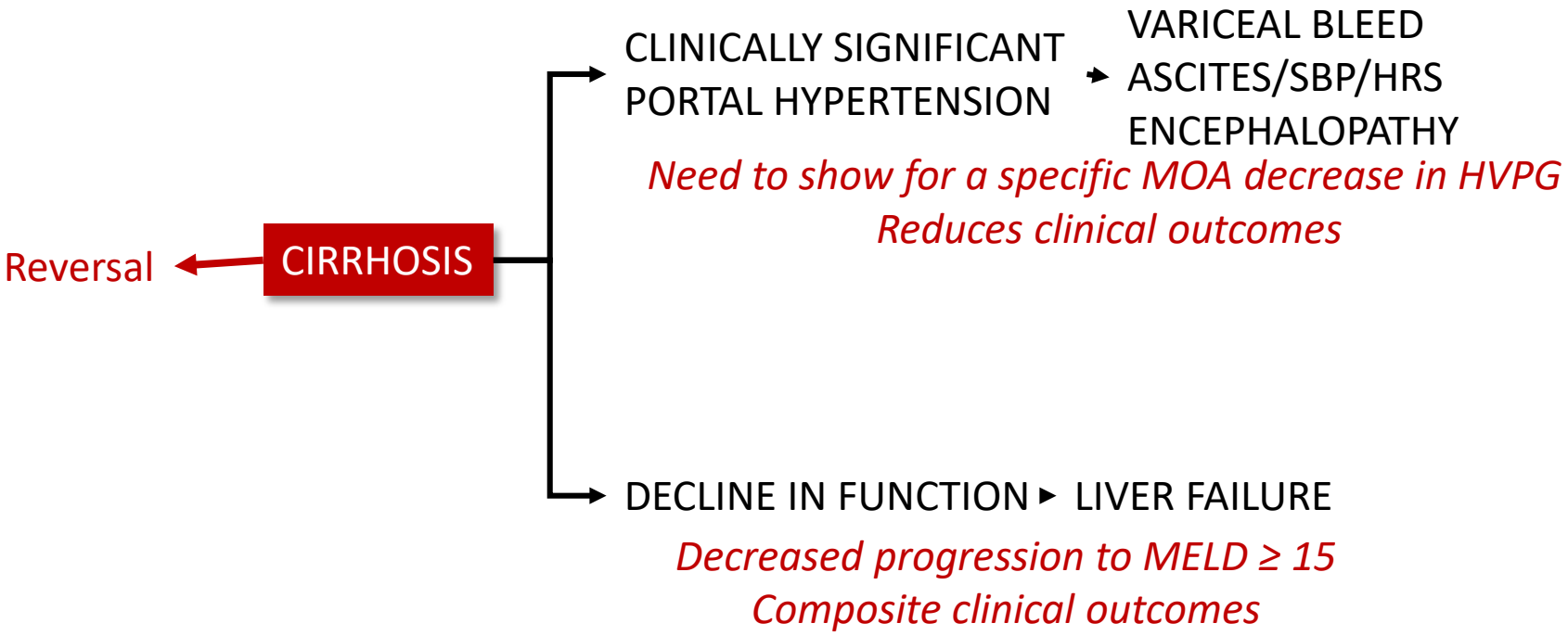


- Increased risk of clinical events with:
  - Higher baseline hepatic collagen content and ELF
  - Worsening of fibrosis (by Ishak stage, collagen content, ELF)

Sanyal et al, EASL 2017

* Separate multivariate models run with baseline and change from baseline for each variable.

How cirrhosis leads to clinically meaningful outcomes



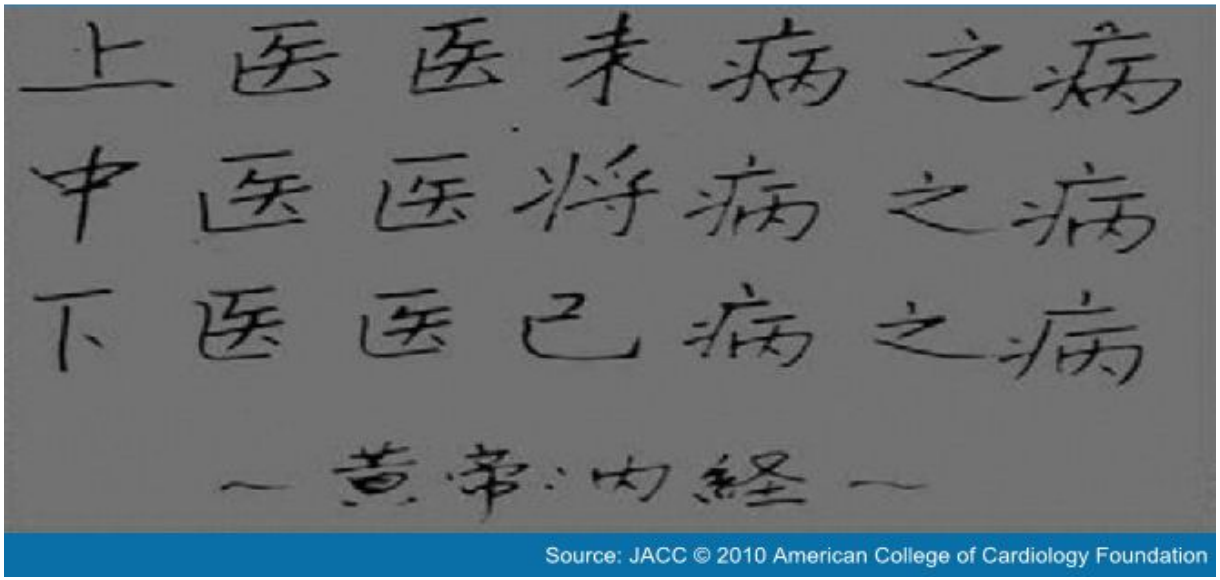
MELD as an endpoint

Pros	Cons
• Relates to mortality • Well known to clinicians • Widely available • Easy to measure • Threshold value of 10 or 14 identifies a important stage in clinical course	• Inter-lab variability • Related to 3 month mortality • Rate of progression of MELD score not linear • Most patients with compensated cirrhosis have a MELD < 10

Increase in MELD to ≥ 15 represents a point in course of disease where Transplant should be considered

Take home messages

- NASH is a clinical syndrome driven my metabolic substrate overload to the liver.
- The biology of NASH has significant collinearity with the biology of HFPEF and type 2 diabetes
- Integrated approaches to noninvasive assessments that provide a read out of disease activity and stage in key end organs is needed.
- Therapeutics should go after nodal targets that are key for disease development and progression. Combinations should be rational and based on proper step wise clinical development.
- Trial design innovations are under way to allow accelerated assessment of combination therapies to improve clinical outcomes



Source: JACC © 2010 American College of Cardiology Foundation

Huang Dee: Nai-Ching (2600 BC, First Medical Text)

Translation:

Superior doctors prevent the disease

Mediocre doctors treat the disease before evident

Inferior doctors treat the full-blown disease

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