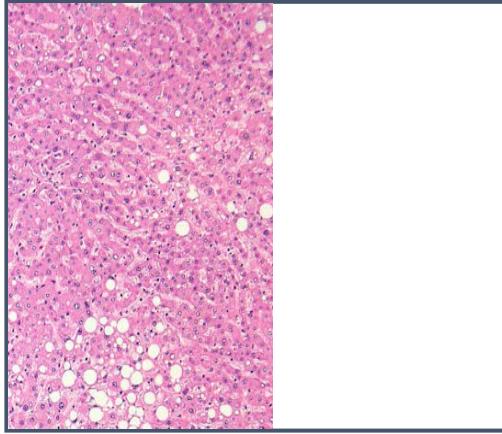
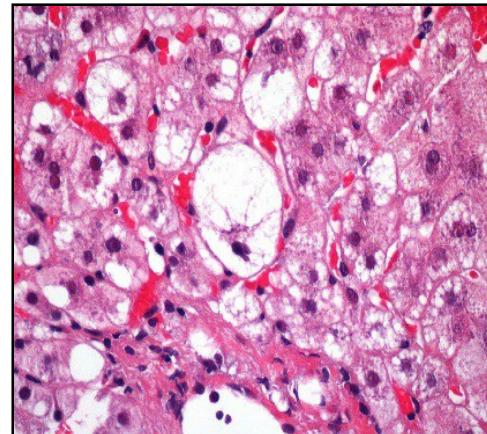


NASH- THERAPEUTIC ADVANCES

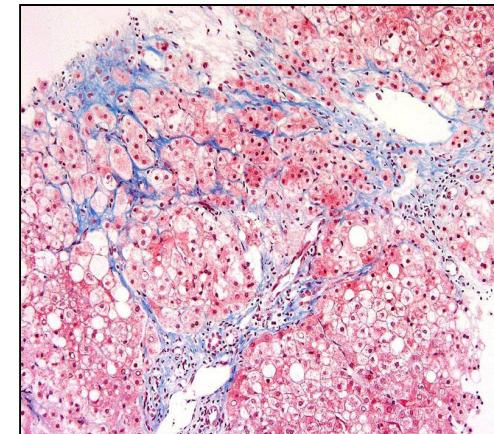
NAFL



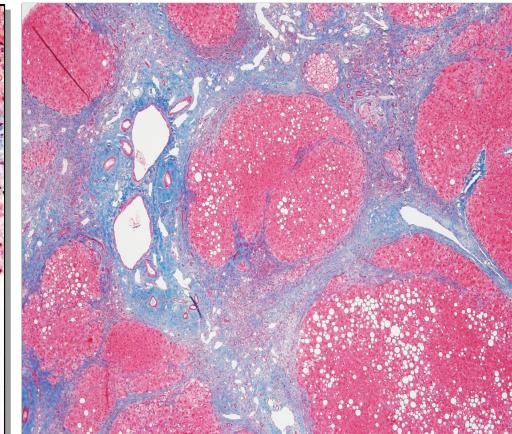
NASH



NASH with fibrosis



NASH Cirrhosis



Arun J. Sanyal M.D.

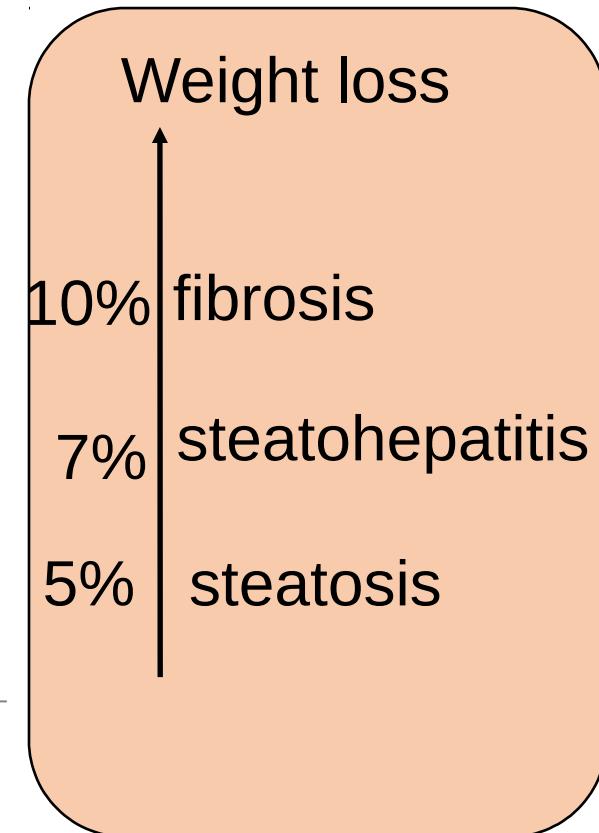
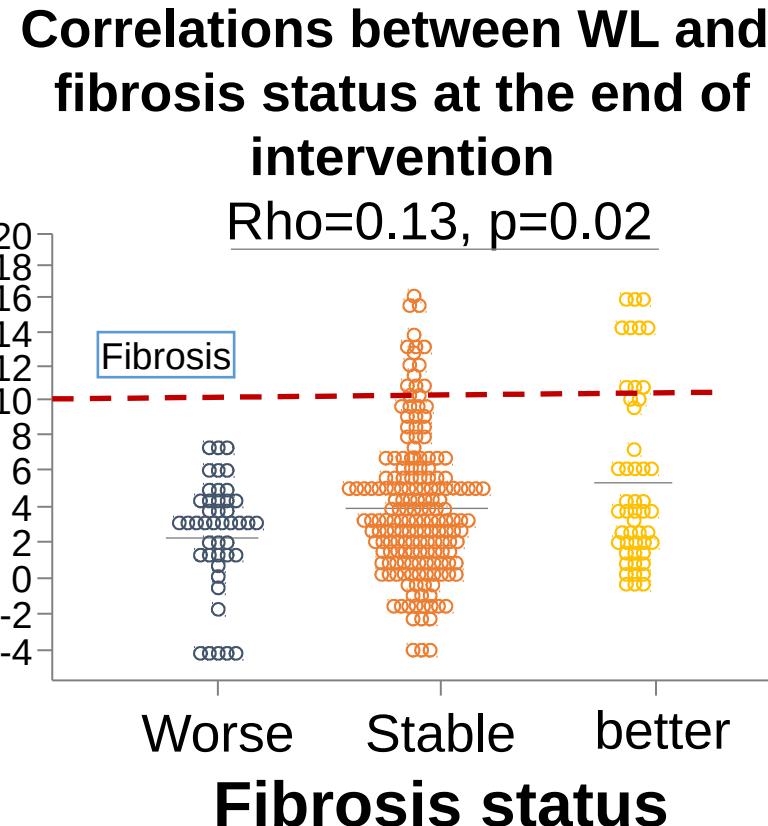
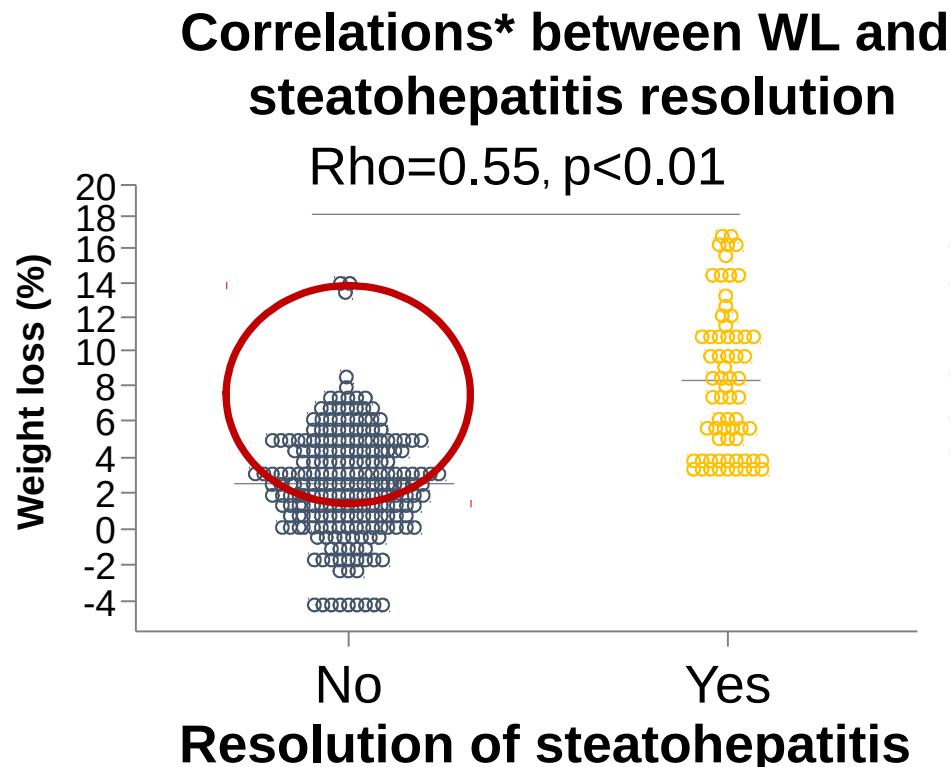
Z Reno Vlahcevic Professor of Medicine, Physiology and Molecular Pathology

Virginia Commonwealth University School of Medicine

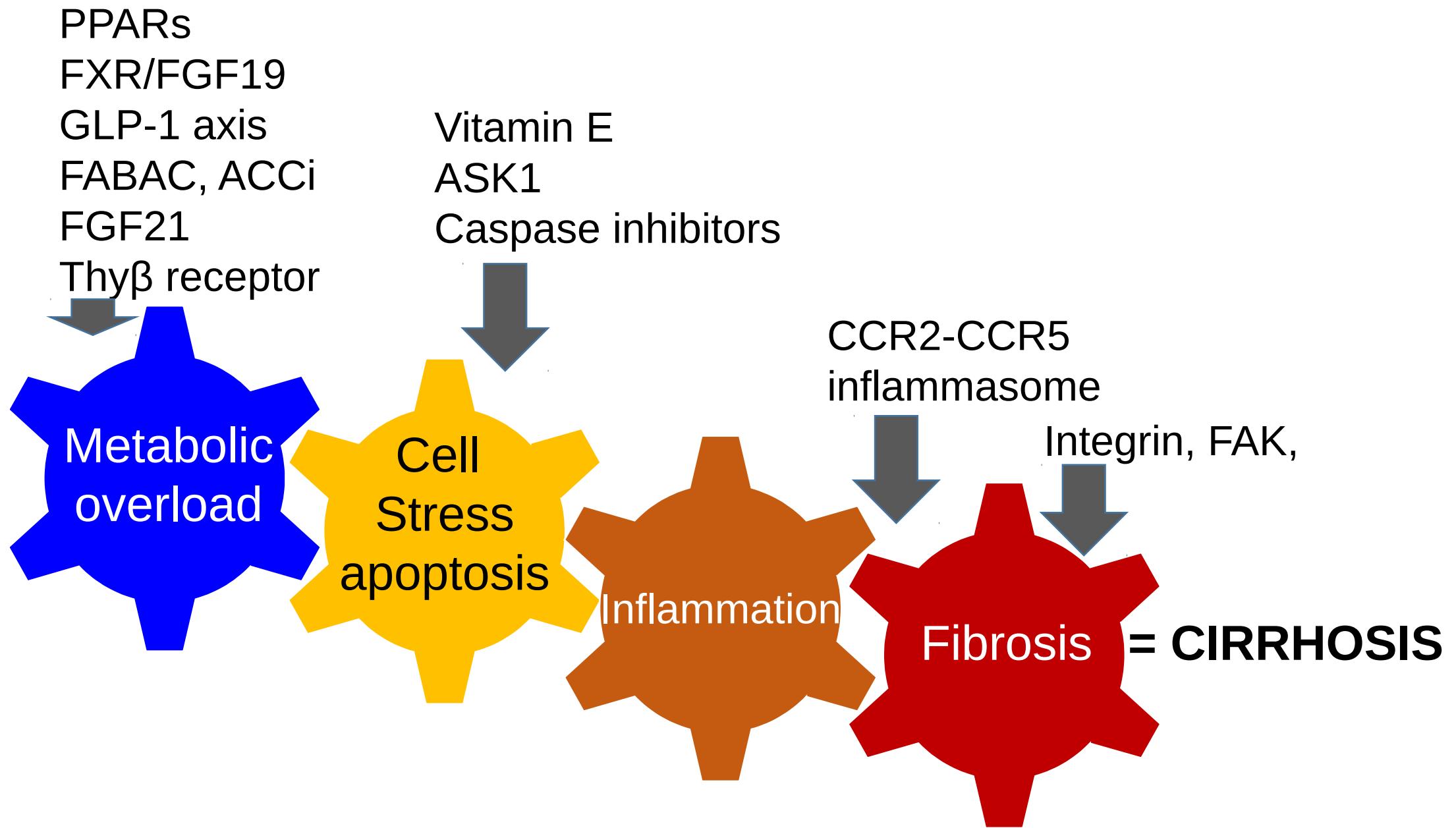
Conflicts of Interest

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

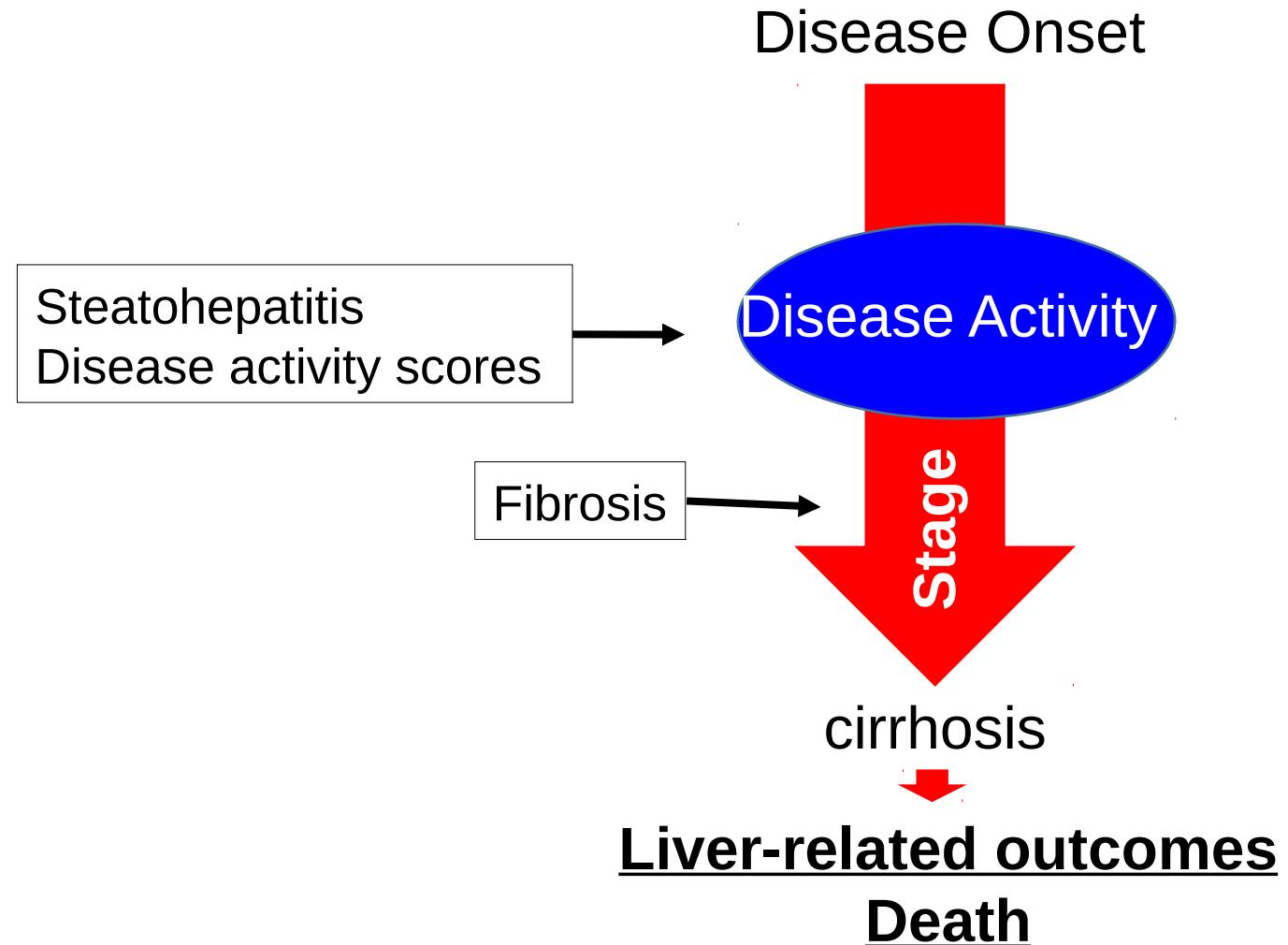
Weight loss (WL) can improve histology



- Weight loss does not guarantee NASH resolution
- Fibrosis improvement can occur with less than 10% weight loss



Key concepts in approach to treatment of NASH



**In the short term: improve disease activity
And/or fibrosis (surrogate outcome)**

**In the long term: reduce progression to
Cirrhosis and clinical outcomes**

Sanyal et al, Hepatology, 2015; 61: 1392-1405

Current status of drug treatment- impact on NASH resolution



- Populations different
- Endpoint evolution
- Methods of assessment
- Duration of treatment

Sanyal et al, NEJM 2010, Cusi et al, Ann Intern Med 2016

Tetri et al, Lancet 2015, Ratziu et al, Gastro 2016, Armstrong et al, Lancet 2016

AASLD late breakers LB 5, LB22,

Fibrosis improvement with current agents



Sanyal et al, NEJM 2010, Cusi et al, Ann Intern Med 2016

Tetri et al, Lancet 2015, Ratziu et al, Gastro 2016, Armstrong et al, Lancet 2016

AASLD late breakers LB 5, LB22,

Bariatrics can improve liver histology



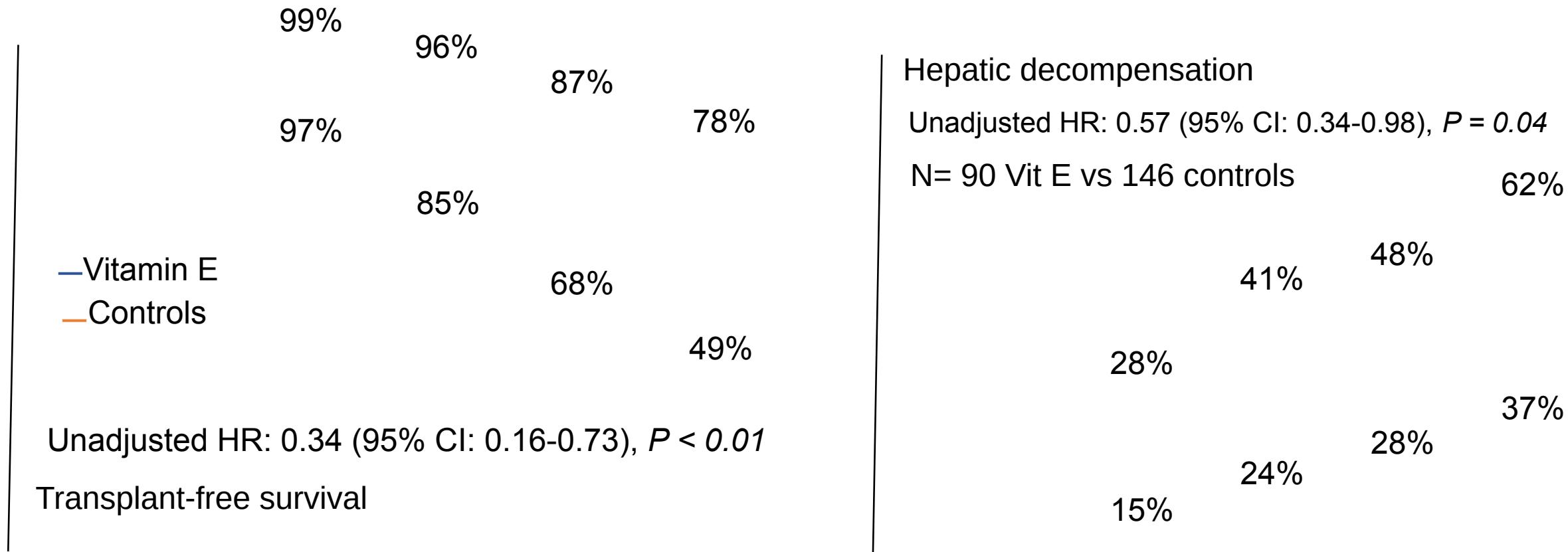
Histological resolution:

- Steatosis resolution: 66%
- Lob Inflammation: 50%
- Ballooning: 76%
- Fibrosis: 40%
- 12% had worsening fibrosis
- Overall GRADE quality low

Fisher et al, JAMA. 2018;320(15):1570-1582

Lee et al, [Clin Gastroenterol Hepatol](#). 2018 Oct S1542-3565

Vitamin E improves transplant free survival and decompensation rates in NASH with stage 3 or 4 fibrosis



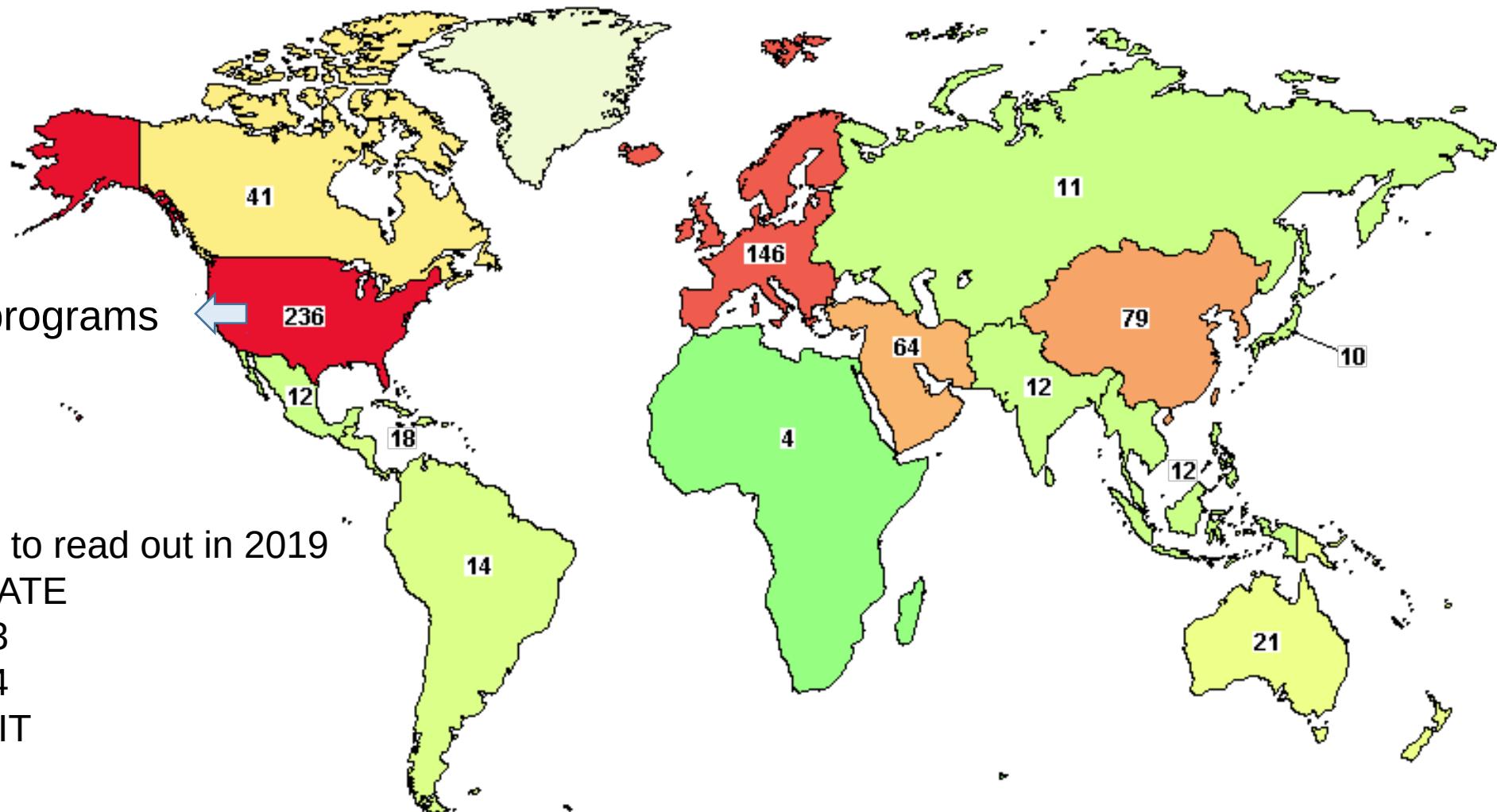
Intense clinical trial activity for NASH

4 phase 3 programs



Pivotal trials to read out in 2019

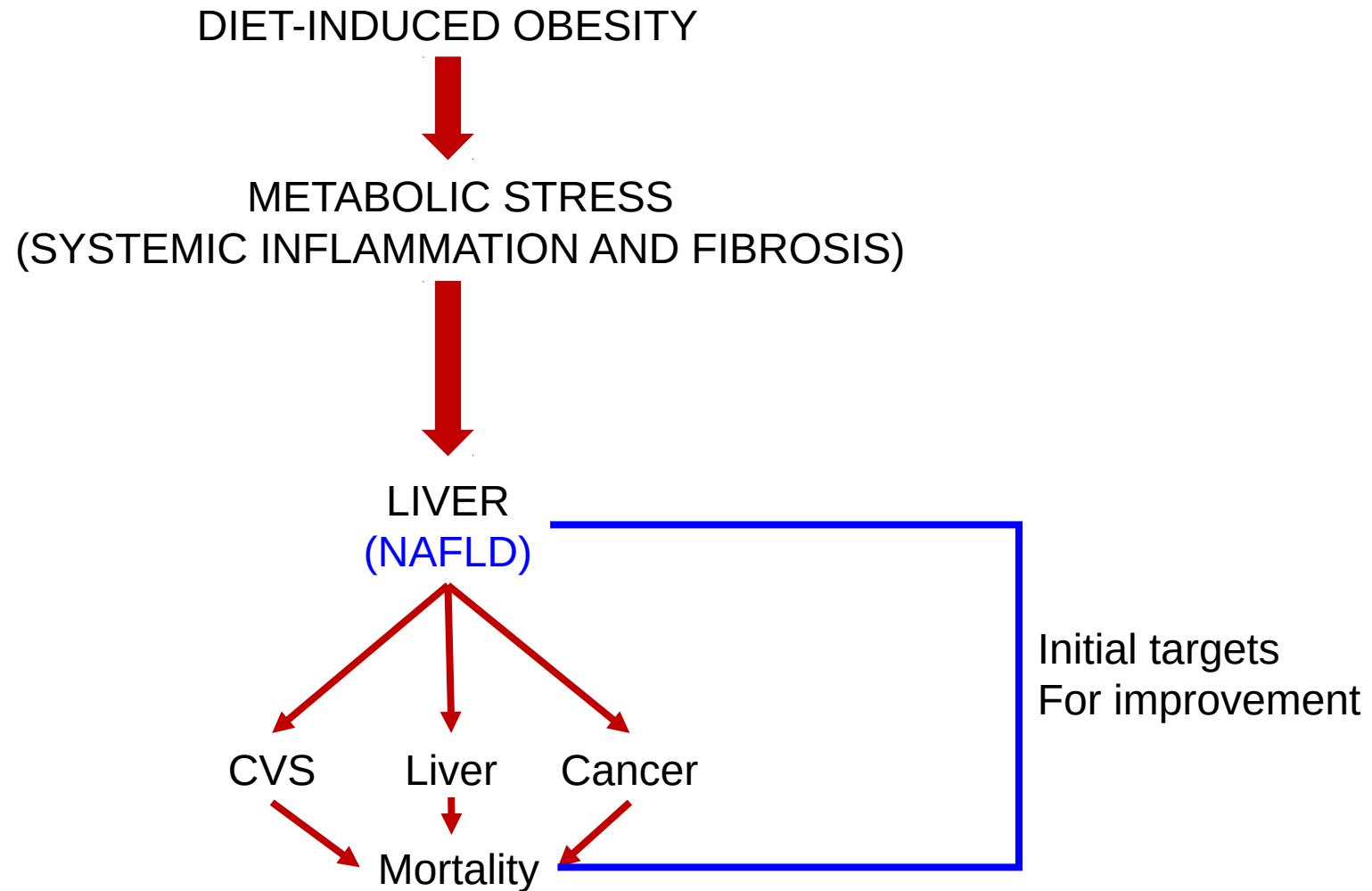
- REGENERATE
- STELLAR 3
- STELLAR 4
- RESOLVE-IT



**Sustainable therapeutics
have to be anchored on
treatment of the root cause
of NASH**

What does cure look like?

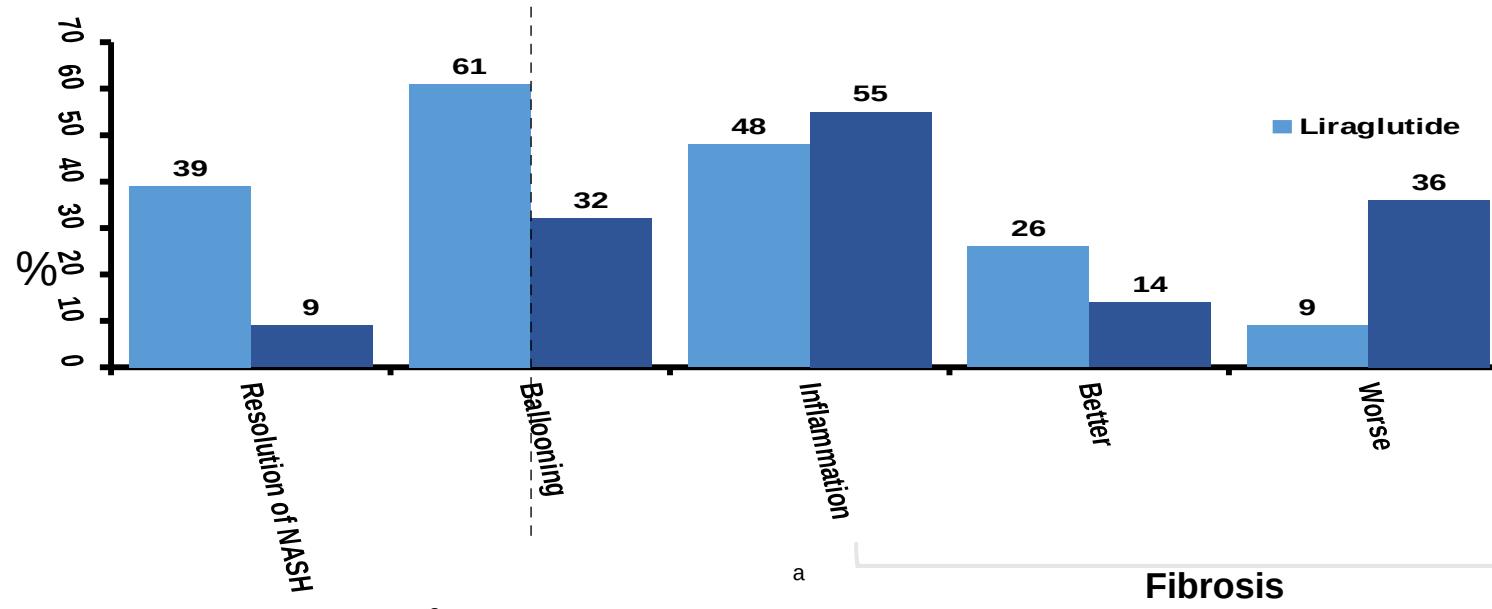
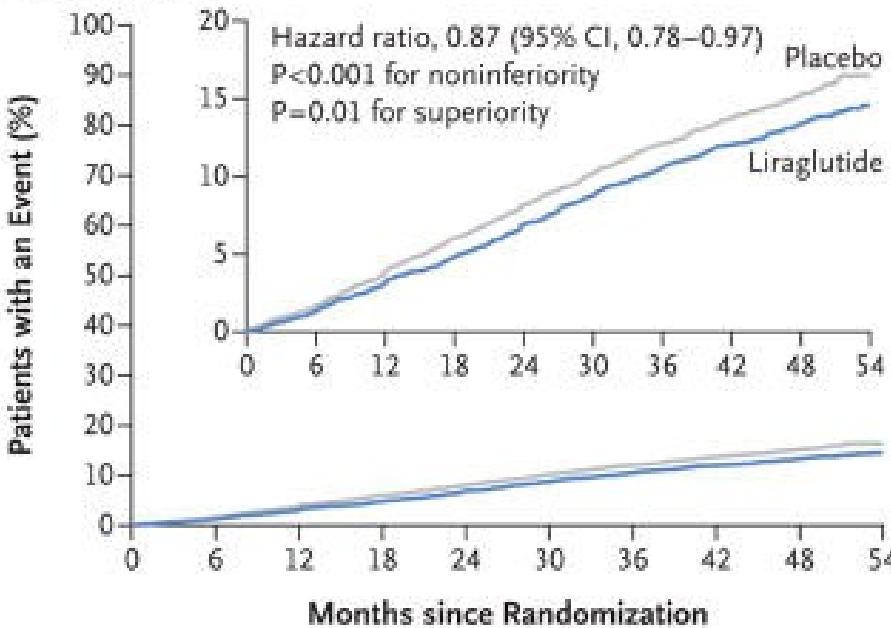
restoration of health, soundness and normality (Websters dictionary)



Adapted from Sanyal AJ, Nature Reviews Gastro Hep 2019 in press

GLP-1 receptor agonists have the potential for cardio-metabolic as well as liver-benefits

Primary Outcome



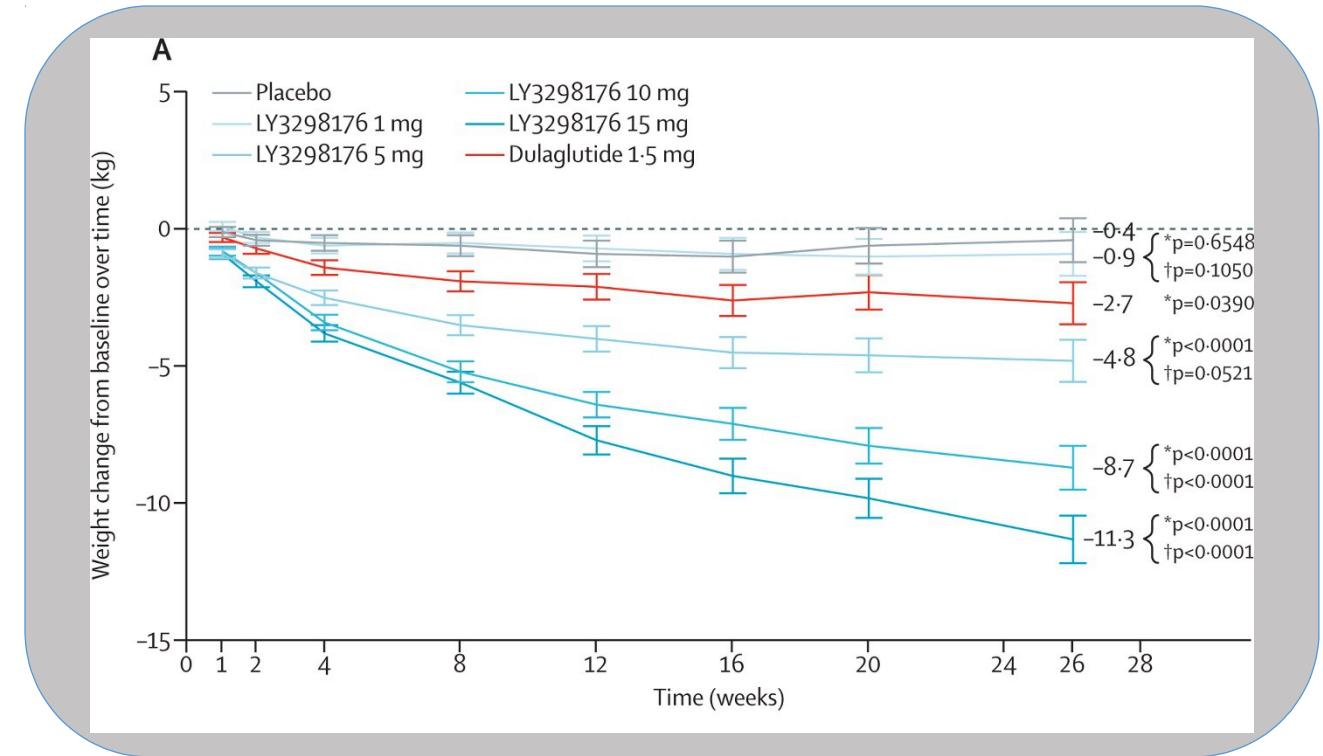
Marso et al, *N Engl J Med*. 2016 Jul 28;375(4):311-22

Armstrong MJ, et al. *Lancet* 2016;387(10019):679-690.

Pharmacological-bariatric therapy is improving

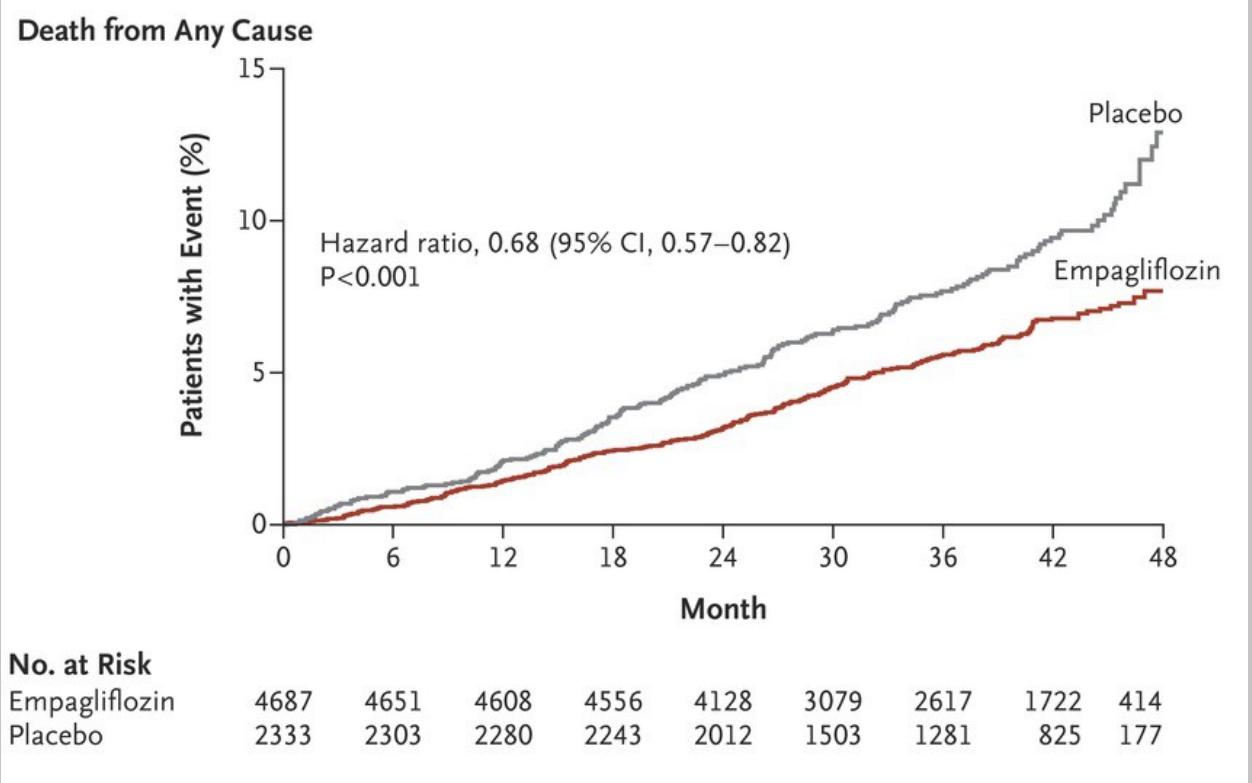
P< 0.005 after multiple comparison for all Semaglutide groups

N=957

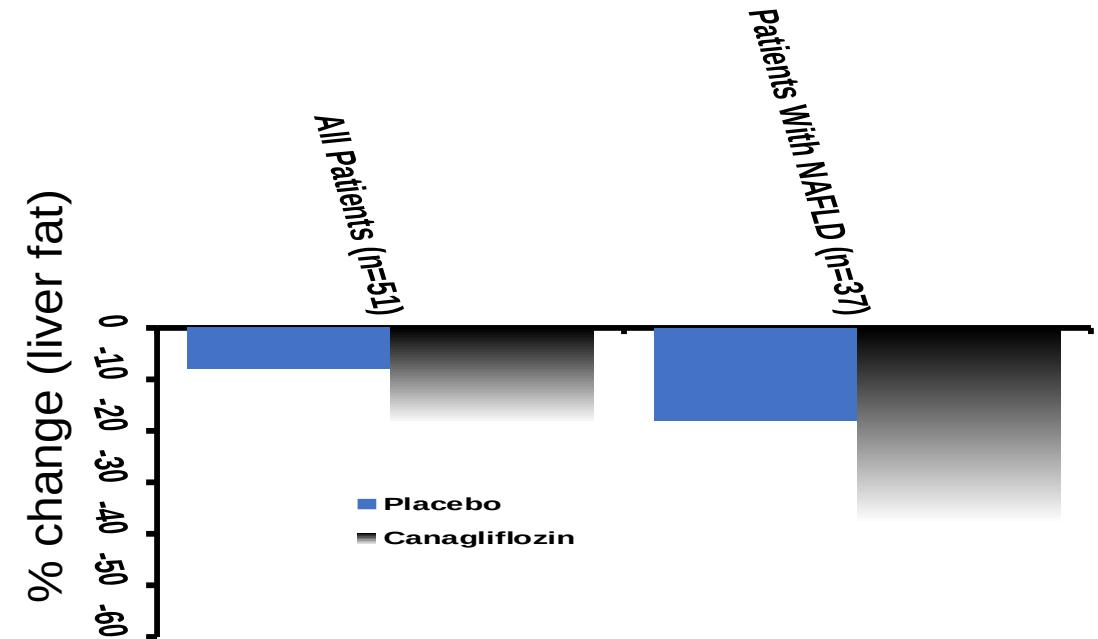


GLP-1/GIP agonist (terzepatide)

SGLT2 inhibitors also have the potential for improved cardiac-metabolic-renal-liver outcome improvement



Zinman et al, *N Engl J Med.* 2015 Nov 26;373(22):2117-28

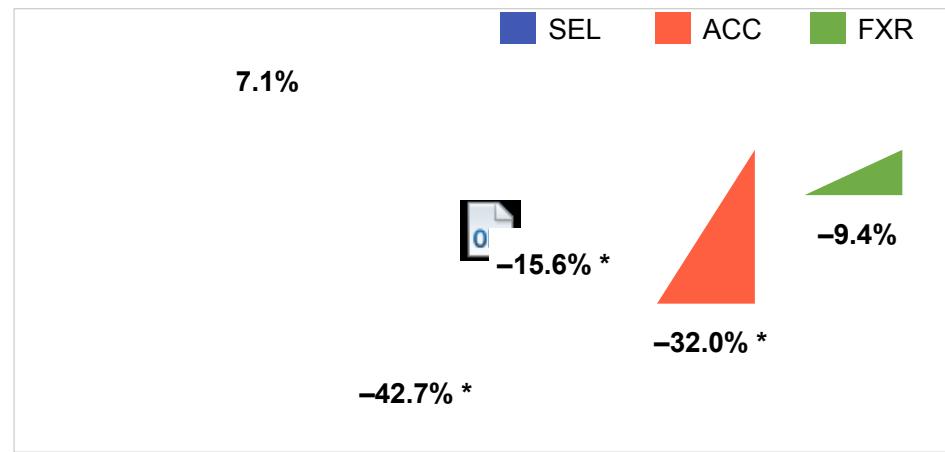


Cusi K, et al. Endocrine Society. 2018; Abstract OR05-3

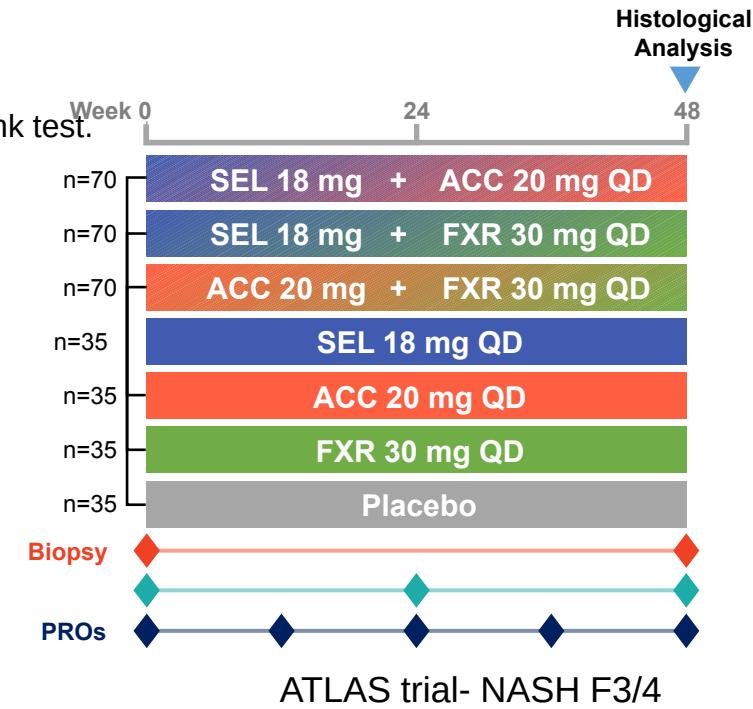
Combination therapy: the next frontier

Leveraging varying mechanisms to build synergy

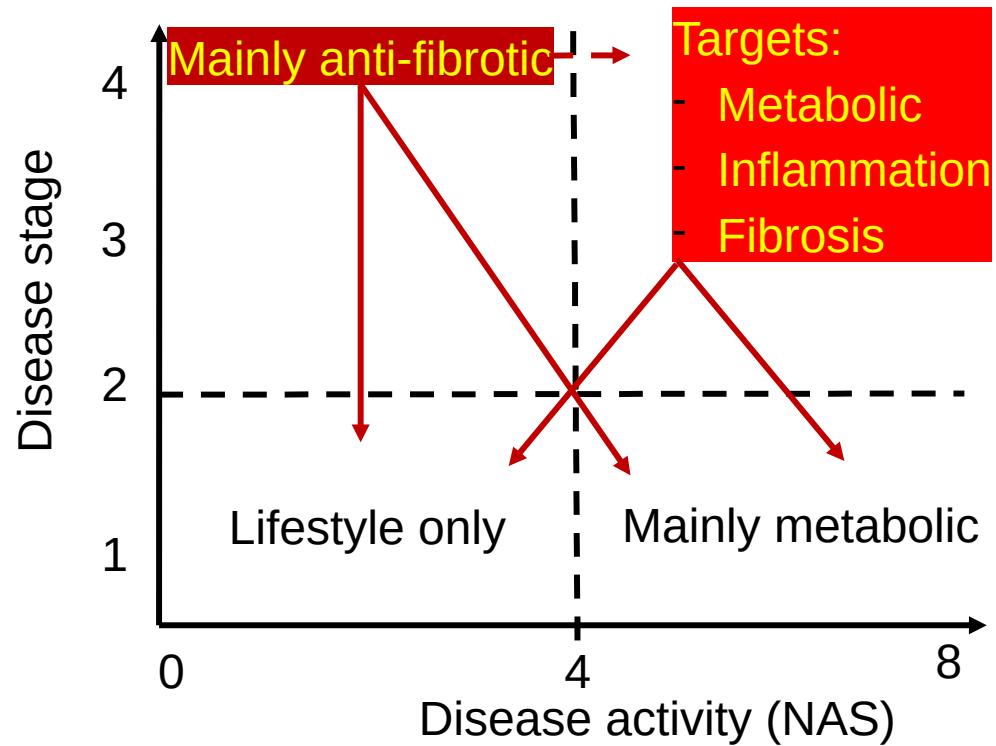
* p<0.05 for comparison of week 12 vs. baseline by Wilcoxon signed-rank test.



Lawitz et al, EASL 2018, courtesy Rob Myers

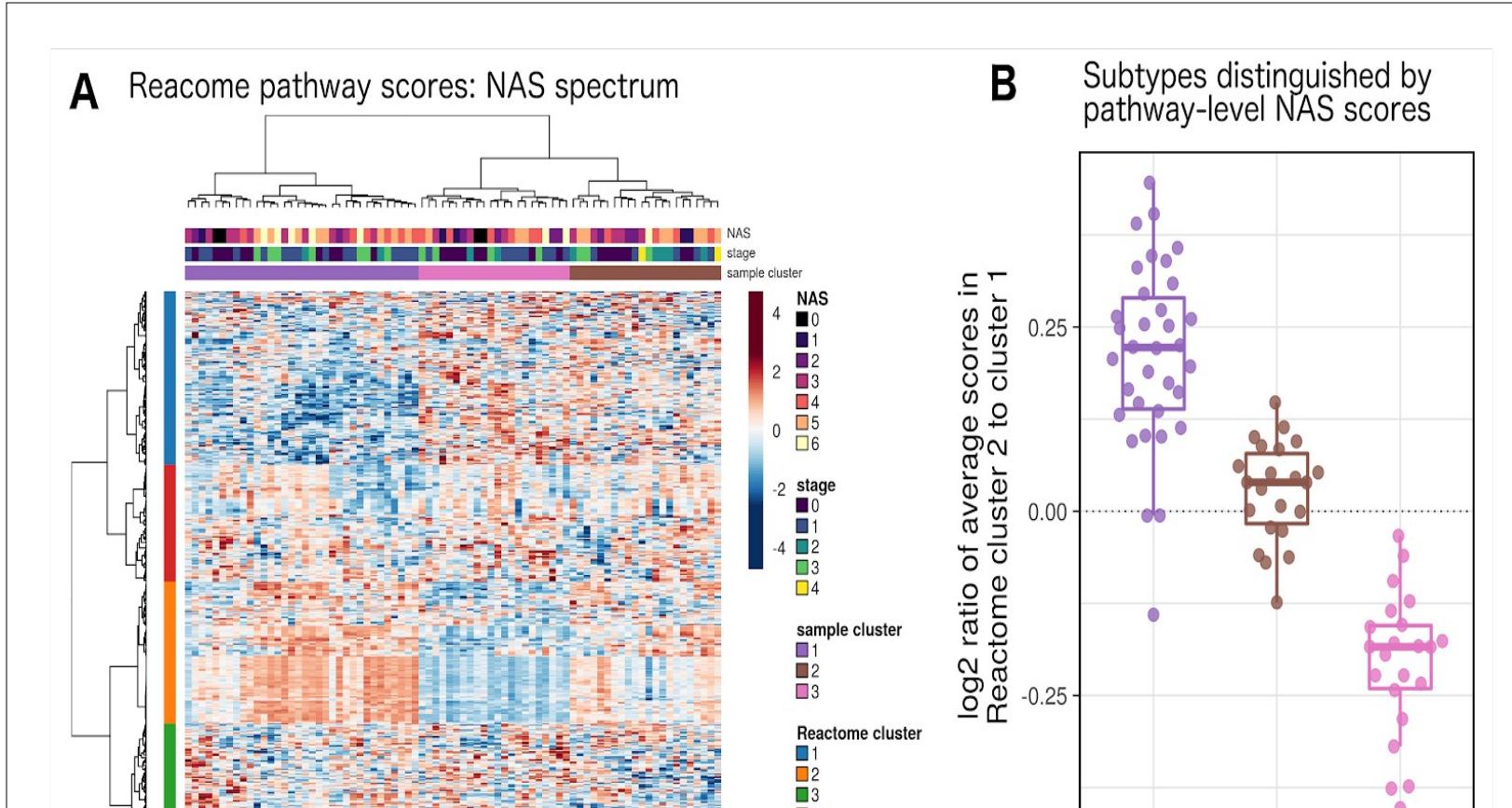


Combination approaches must be tailored to need



- Population
- Relevant targets
- Relevant endpoints
- Booster strategies
- Induction vs maintenance
- Development path

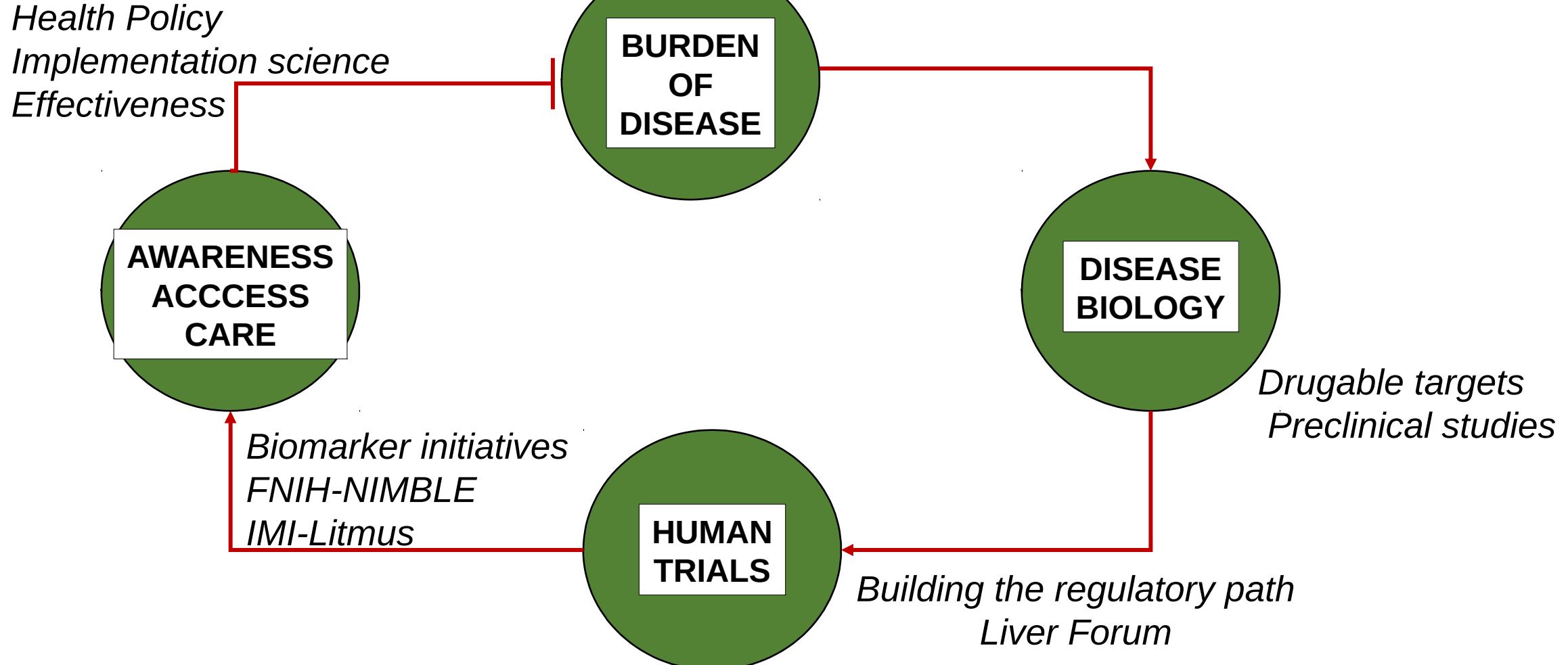
Molecular subtypes with distinct reactome clusters not distinguishable by histological NAS



Cluster 1: immune regulation, cluster 2: cell proliferation, cluster 3: ECM

Hoang et al, AASLD 2018

And miles to go before we sleep- Robert Frost



The Surgeon General's
Call To Action
To Prevent and Decrease
Overweight and Obesity
2001



U.S. Department of Health and Human Services

While progress is being made to control liver outcomes and tackle greatest unmet need in those with advanced fibrosis, this is only a band aid.
We face a moral, ethical and medical imperative to tackle the root cause of diabetes, cardiovascular disease and NASH i.e. diet-induced obesity

