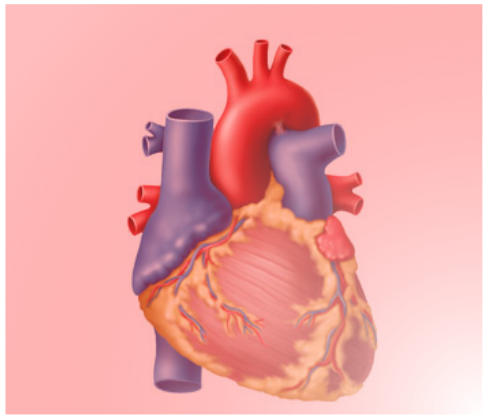
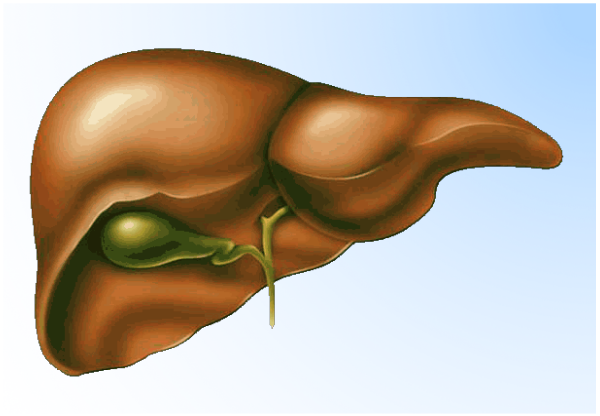
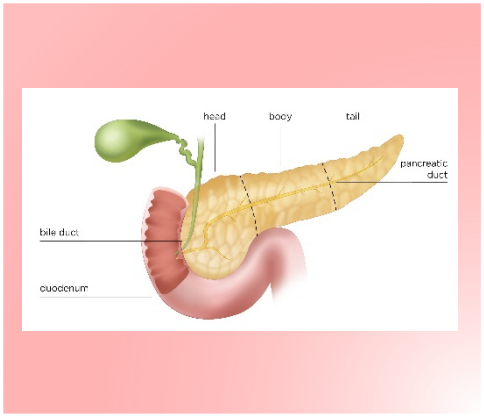
INNOVATIONS IN CLINICAL TRIAL DESIGN FOR NASH







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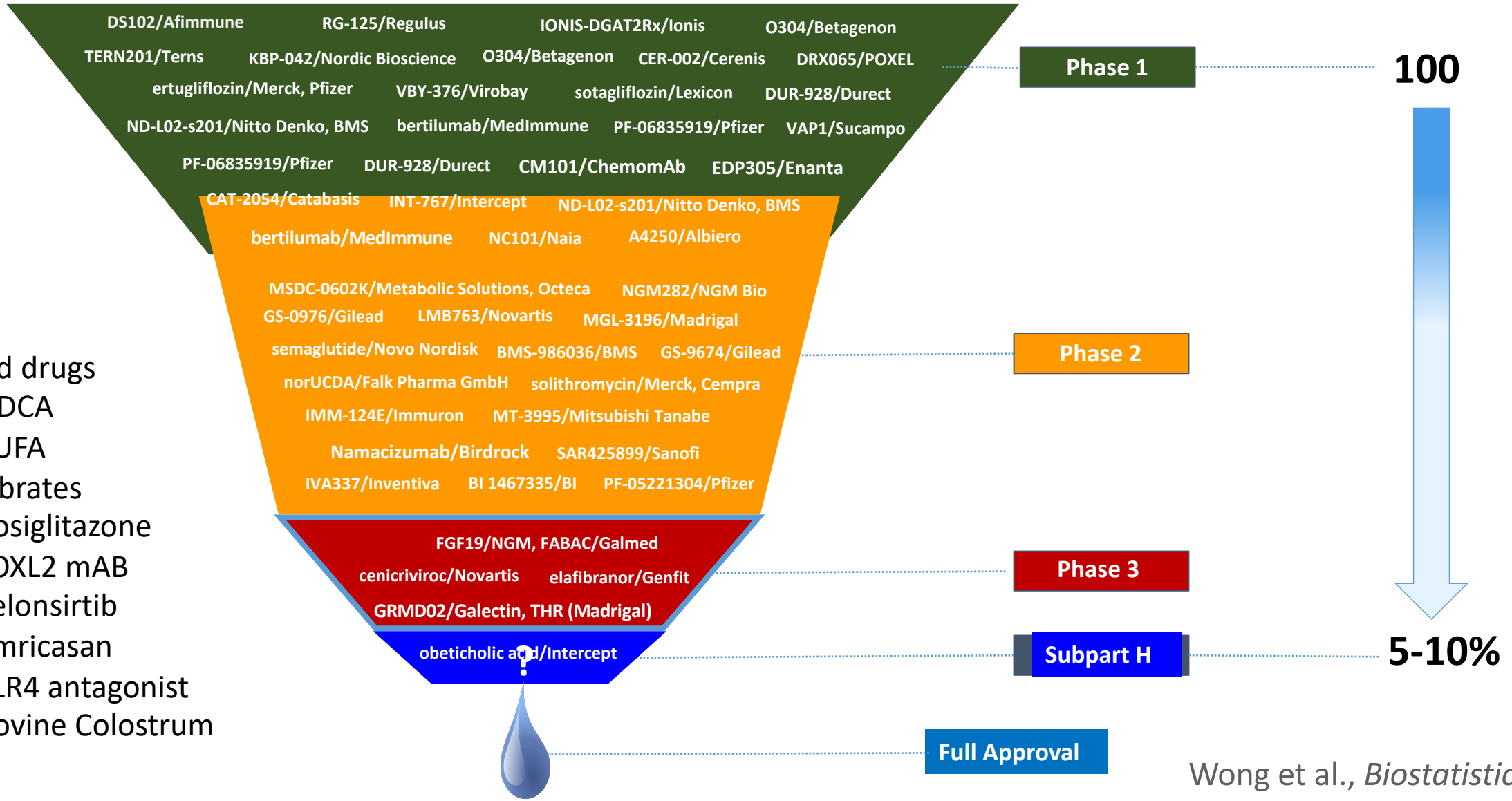
Conflicts of Interest

- Dr. Sanyal is President of Sanyal Biotechnologies
- Stock options for Genfit, Tiziana, Indalo, Durect, Exhalenz, Galmed
- Consultant- Gilead, Intercept*, Allergan*, Lilly, Novo Nordisk, Astra Zeneca-Medimmune*, Novartis, Pfizer, Genentech*, Merck, Bristol Myers*, Boehringer Ingelhiem*, Immuron*, Echosense, GE, OWL*, Birdrock, Tern, Sundise, RedX*, IFMO, Lipocine*, Innovate*, Zydus*, AMRA, Hemoshear,
- Grant support: Bristol Myers, Intercept, Gilead, Allergan, Merck, Echosense, Novartis, Boehringer Ingelhiem

* *no financial remuneration in last 24 months*

Global Pipeline for NASH



Failed drugs

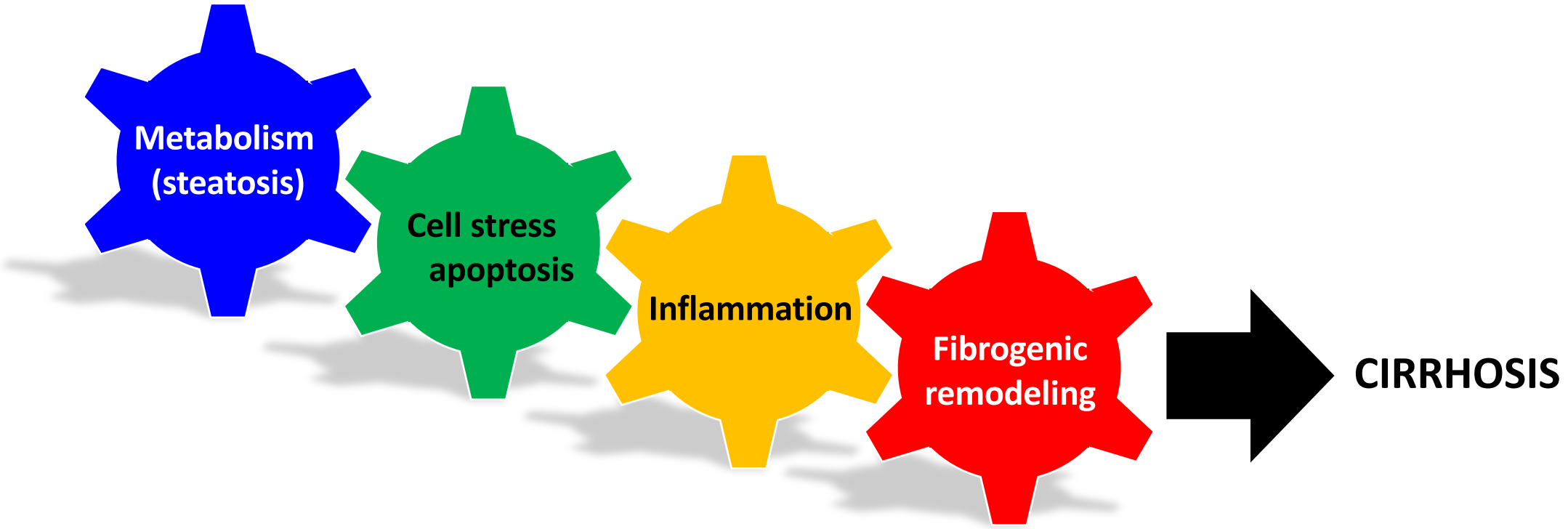
- UDCA
- PUFA
- Fibrates
- Rosiglitazone
- LOXL2 mAB
- Selonsirtib
- Emricasan
- TLR4 antagonist
- Bovine Colostrum

Wong et al., *Biostatistics* 2018

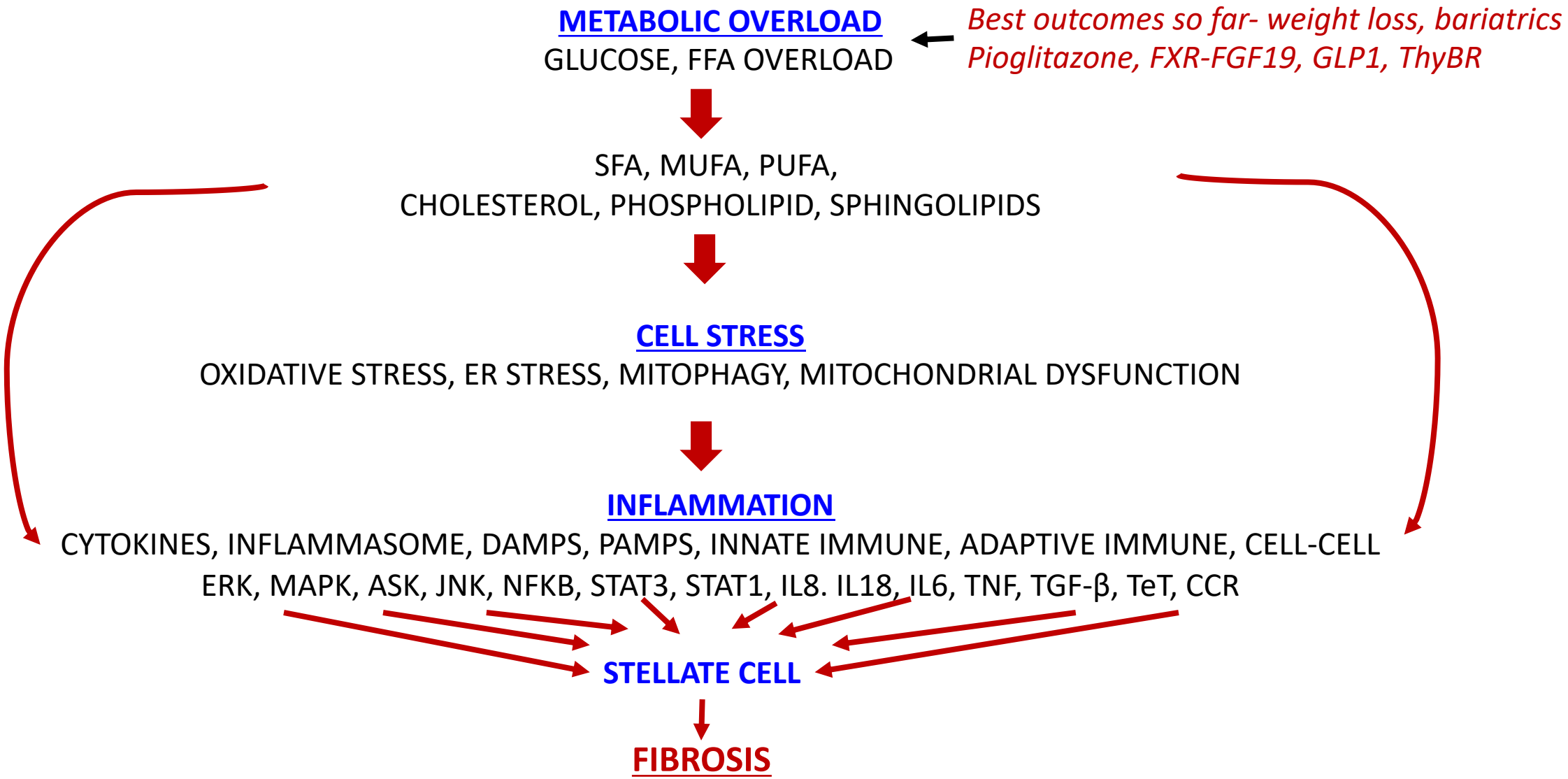
STRENGTHS	WEAKNESSES
• **Path to approval is clear** • **Target enriched disease**	• **Does not provide value proposition** • **No drug shown to prevent OR reverse cirrhosis** • **Ignores hierarchies of outcomes**
• Reconsider populations/endpoints • Design innovations: - Master protocols - E2E protocols	• New knowledge re systemic nature of disease process • Competing risks for outcomes • No reliable way to keep patients on placebo for long periods
OPPORTUNITIES	**THREATS**

Targeting a relevant target

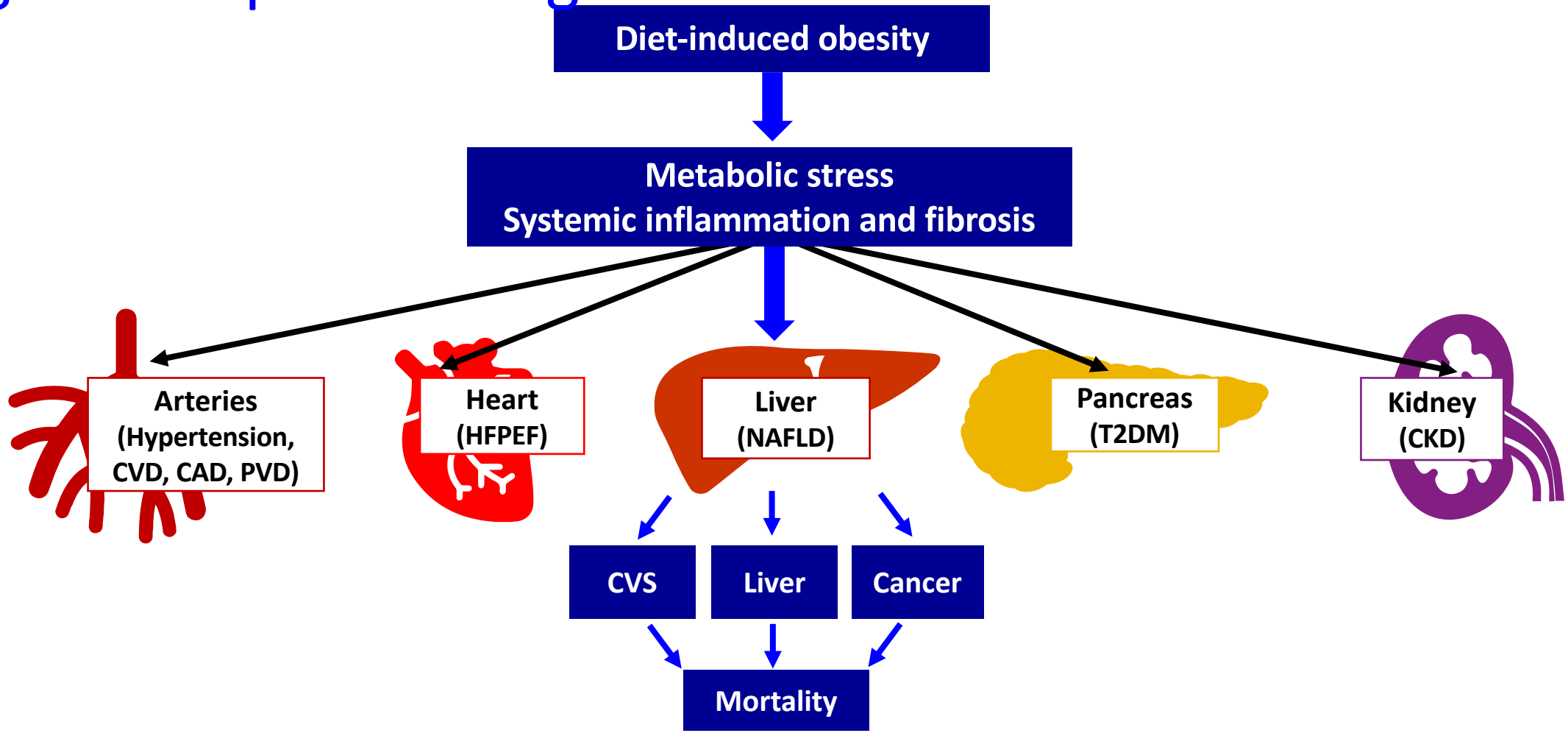
Therapeutic targets for NASH



Caveat # 1: Choice of target should take in to consideration the redundancies in pathogenic pathways



Caveat # 2: NAFLD is part of a multi-system disease with multiple competing risks to patient- need to target multiple end organs



CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; CVS, cardiovascular system; HFPEF, heart failure with preserved ejection fraction; PVD, peripheral vascular disease; T2DM, type 2 diabetes mellitus.

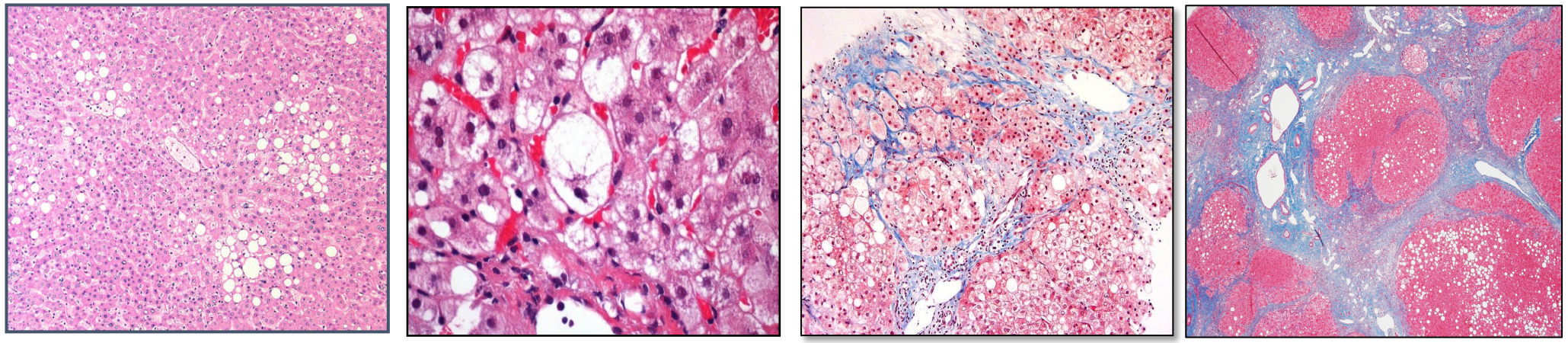
Targeting the right population and pairing with study design

Sources of excess clinical outcomes in NAFLD and where interventions will have greatest impact

Closest to cirrhosis
And most likely to benefit from prevention
Of progression

Closest to liver-related
Mortality

NAFL | NASH | NASH with fibrosis | NASH Cirrhosis



Cardiovascular, CKD and all-cause cancer outcomes

Liver decompensation

Challenges in NASH trials

- Background therapy will increasingly include GLP-1 agonists and SGLT2 inhibitors
- Increasing number of approved drugs for obesity
  - Lorcaserin- (Merck)
  - Hydrogels- (Gelesis)
- How to keep patients on placebo in post subpart-H?

The use of master-protocols may accelerate drug development

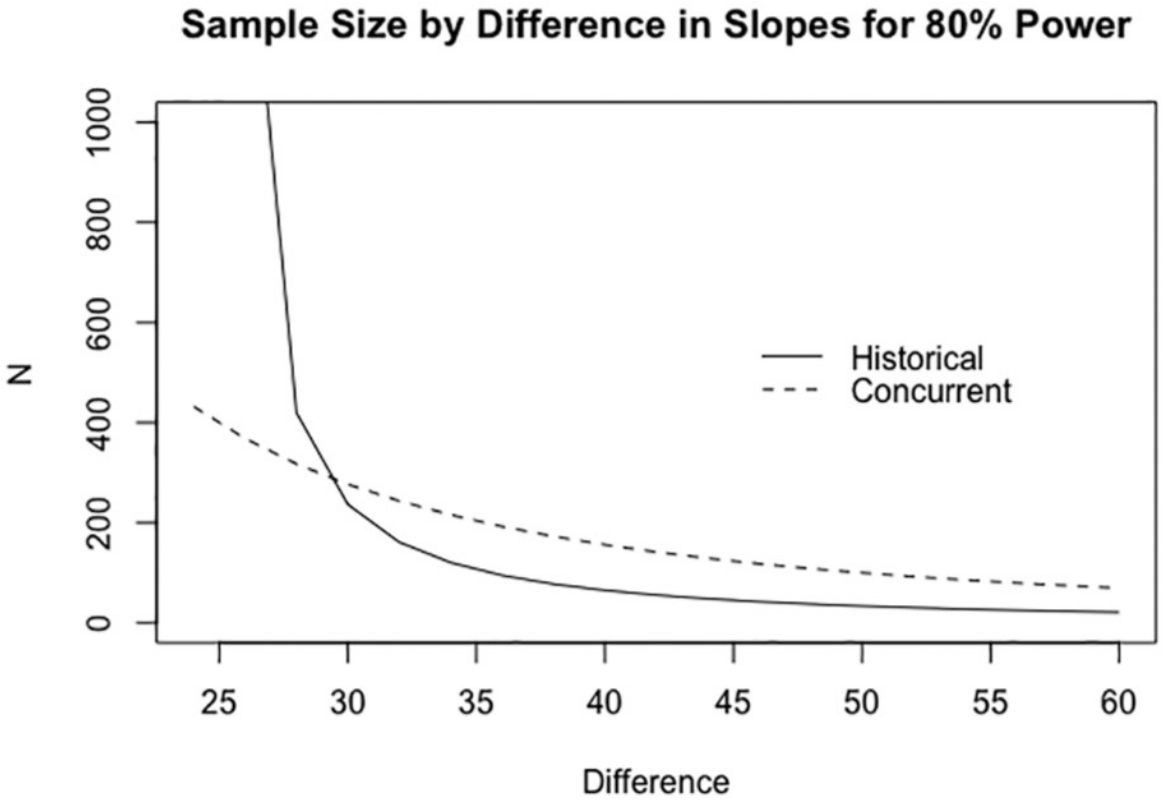
Types of master protocols	What they do
Umbrella	Test multiple drugs in the context of a homogeneous population with a single disease
Basket	Test single drug in multiple populations
Platform	To study multiple therapies for a single disease in a sequential perpetual manner

Woodcock and LaVange, NEJM 2017,;377:62-70.

Design and analysis of a clinical trial using previous trials as historical control

“ Bayesian hierarchical model, providing a sample from the posterior predictive distribution of the outcome estimand of a new trial, which, along with the standard error of the estimate, can be used to calculate the probability that the estimate exceeds a threshold. We then calculate criteria for statistical significance as a function of the standard error of the new trial and calculate sample size as a function of difference to be detected”

Schonfeld and Finkelstein, Clinical Trials, 2019



A prospective analysis of non-hepatic outcomes in NASH

	Cirrhosis (n=159)		No Cirrhosis (n=1539)		R.R.
	# events	Rate/1000 py	# events	Rate/1000 py	
Death	13	18.7	31	4.4	4.3 (< 0.0001)
CAD event	5	8.7	54	8.3	1 (n.s.)
CVD	6	9.1	24	3.5	2.7 (0.03)
eGFR < 60 ml/min	24	42.3	143	22.6	1.9 (0.04)

Sanyal et al, AASLD 2019

A prospective analysis of liver outcomes in NASH

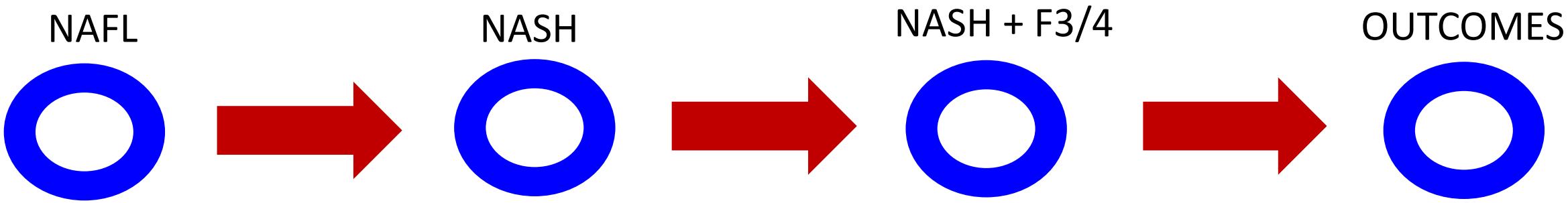
	Cirrhosis (n=159)		No Cirrhosis (n=1539)		R.R.
	# events	Rate/1000 py	# events	Rate/1000 py	
Death	13	18.7	31	4.4	4.3
HCC	2	2.9	8	1.1	2.7
Variceal bleed	5	7.5	1	0.1	54.4
Ascites	15	23.5	11	1.6	14.8
HE	16	23.5	11	1.6	16.1
MELD ≥ 15	2	3	7	2.9	2.9

Sanyal et al, AASLD 2019

Alternate drug development paradigm # 1- for MOA targeting root cause

STUDY A LARGE POPULATION WITH NAFLD
- Population defined non-invasively
- Composite outcome measure:
  - All cause mortality
  - Liver outcomes
  - Progression to cirrhosis
  - Progression to CKD
  - MACE

CHALLENGES
- What to do with heterogeneous response
- Label implications
- Applicable for drugs targeting root cause



Goals: reduced outcomes

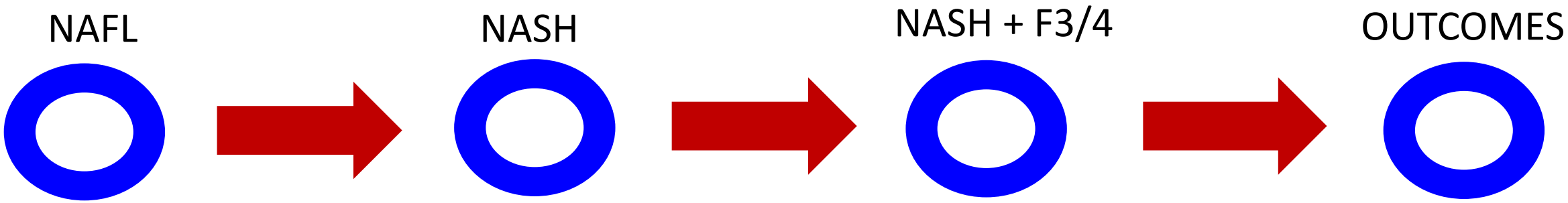
Alternate drug development paradigm # 2

LIVER TARGETED APPROACH

- NAFLD- f3/f4 COMPENSATED vs those with advanced liver stiffness
- Composite outcome
  - All cause mortality
  - Ascites
  - HE
  - Varices requiring treatment
  - MELD 15

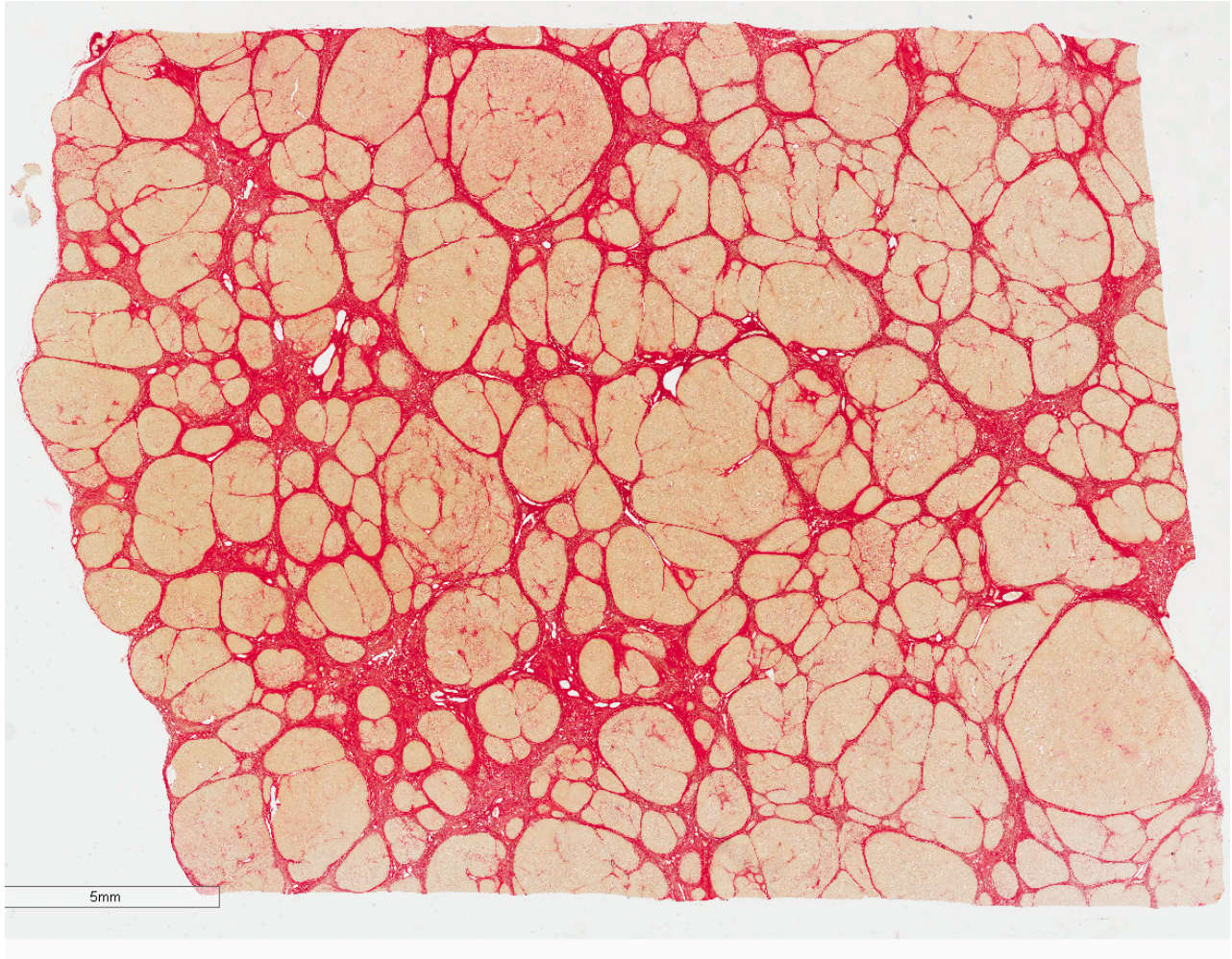
CHALLENGES

- What to do with heterogeneous response
- Long time to outcomes



Goals: reduced outcomes

Clinical trials for NASH-cirrhosis pose specific challenges



Many patients also have:

- Diastolic dysfunction
- Lower eGFR
- Prolonged QTc
- T2DM
- Peripheral neuropathy

Phase 2 paradigm for NASH F3/F4 trials for drugs with MOA targeting root cause

- Stratify by eGFR
- Stratify by LSM or histology
- Endpoints:
  - Primary (weight loss)
  - Secondary:
    - liver stiffness, histology, HVPG, varices, ascites, HE,
    - eGFR
    - Cardiac MRI based assessment of function
    - PRO
    - resource utilization

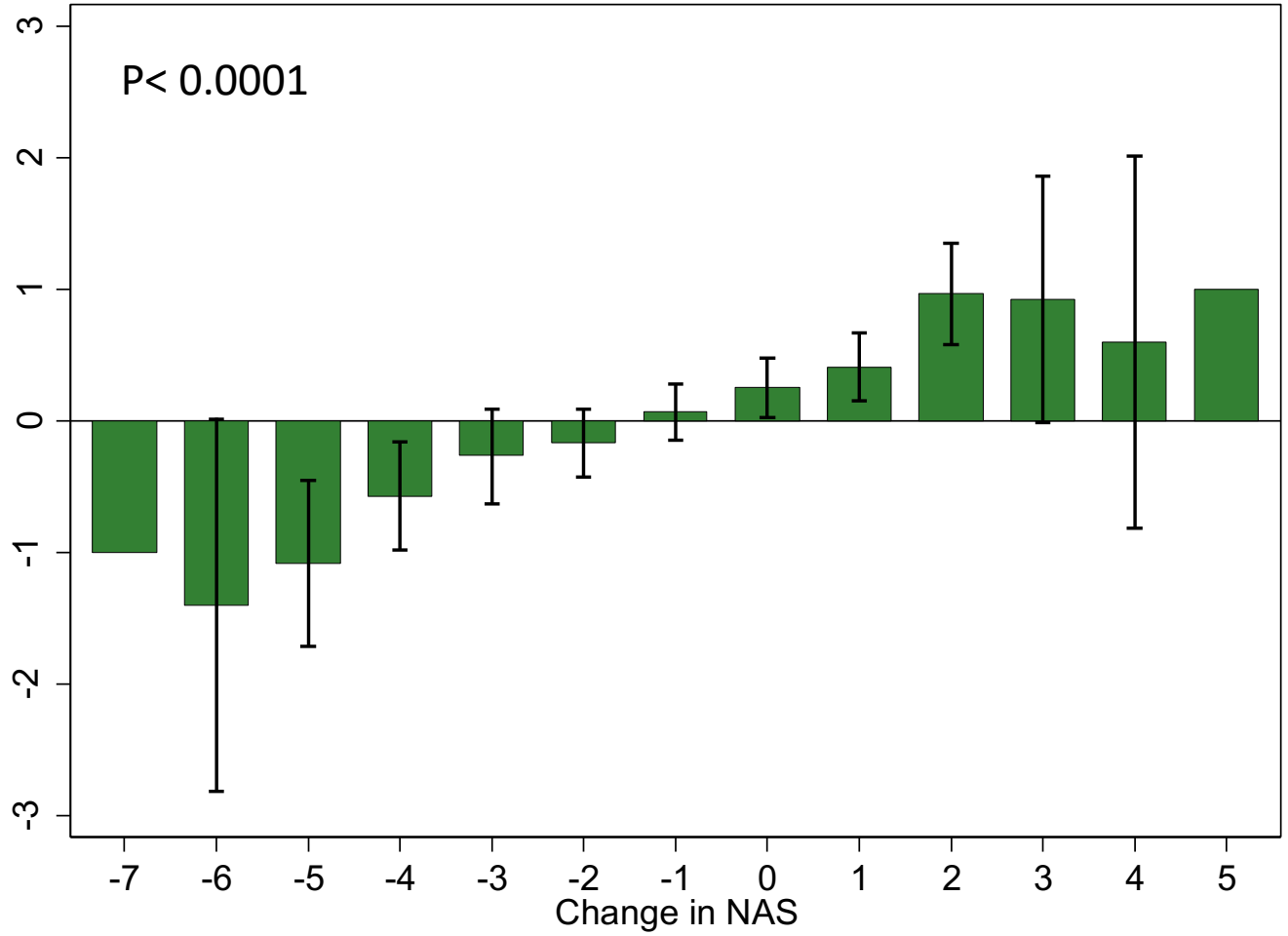
This approach will allow you to assess if your drug benefits any patients and how to design phase 3 trial

Phase 2 development paradigm for NASH F3/4 with anti-inflammatory, anti-fibrotic MOA

- Study populations F3/compensated F4
- Endpoints:
  - liver stiffness vs histology
  - Static biomarkers- ELF, PROC3
  - Proteolytic signatures (novel potentially important approach)
  - Secondary endpoints:
    - liver outcomes
    - stabilization of myocardial dysfunction
    - stabilization of eGFR

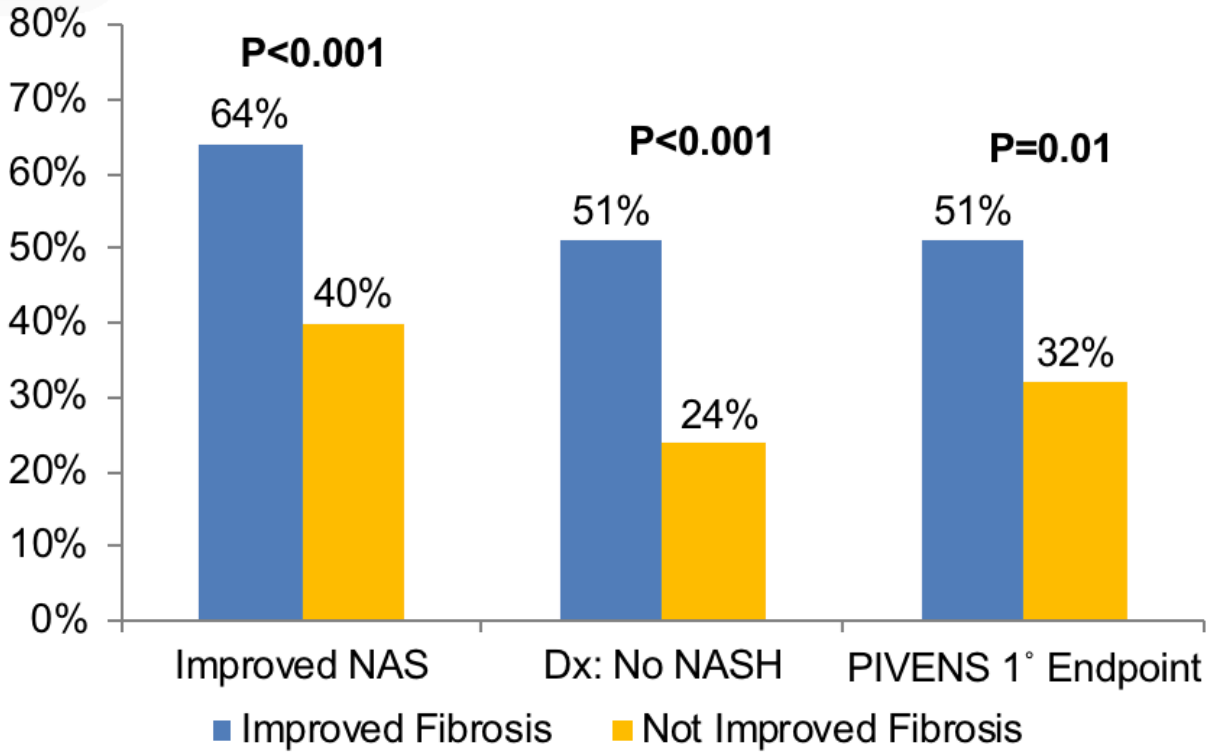
Endpoint assessment

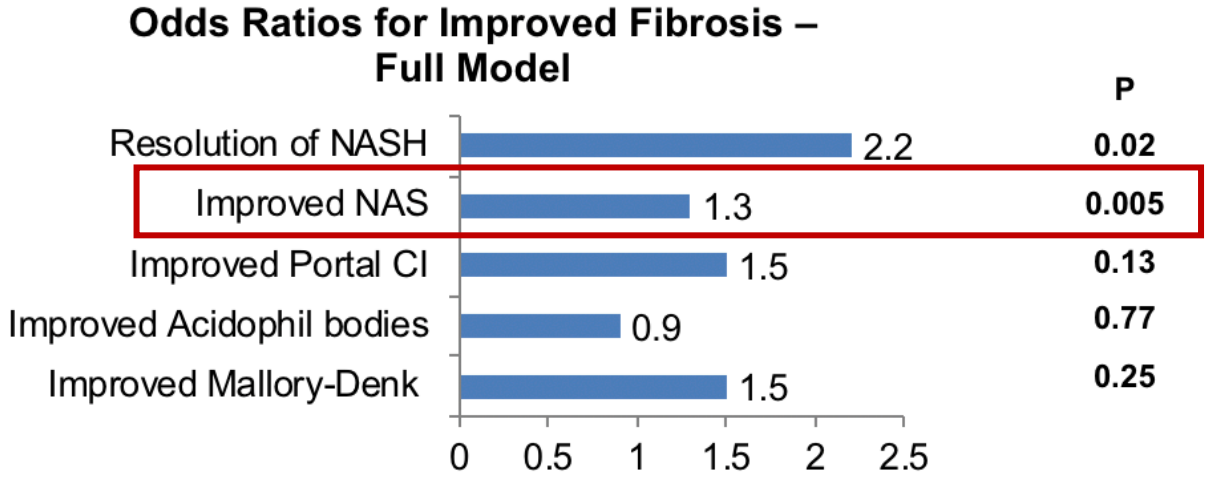
Changes in disease activity are closely linked to changes in disease stage



Kleiner Sanyal et al, In press 2019

Reduction in NAS is strongly linked to fibrosis regression

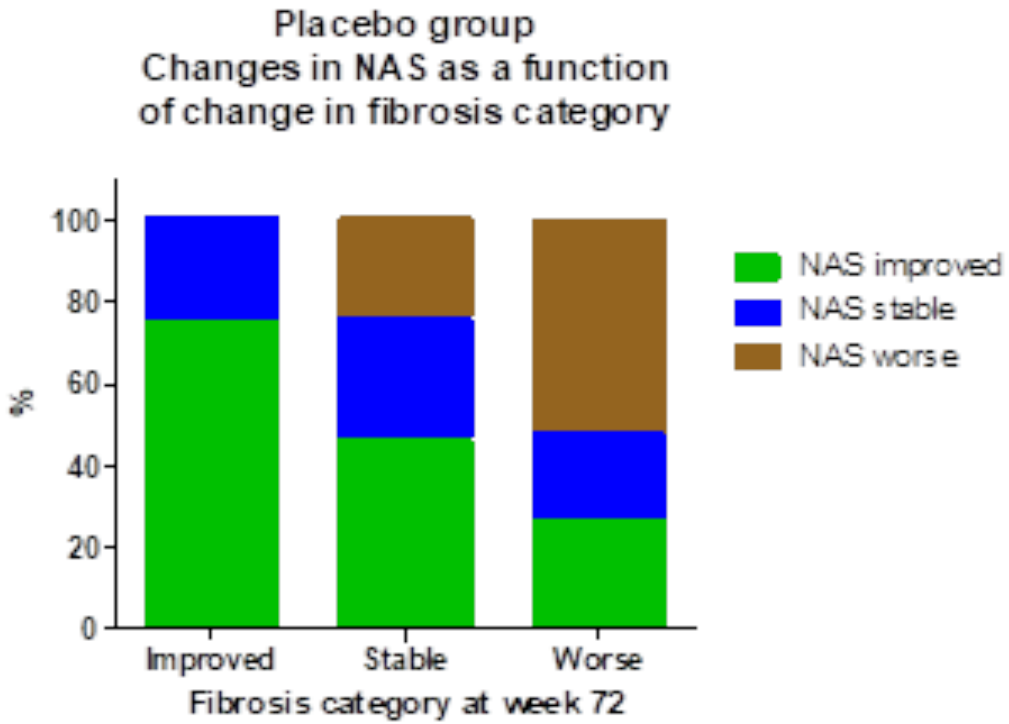


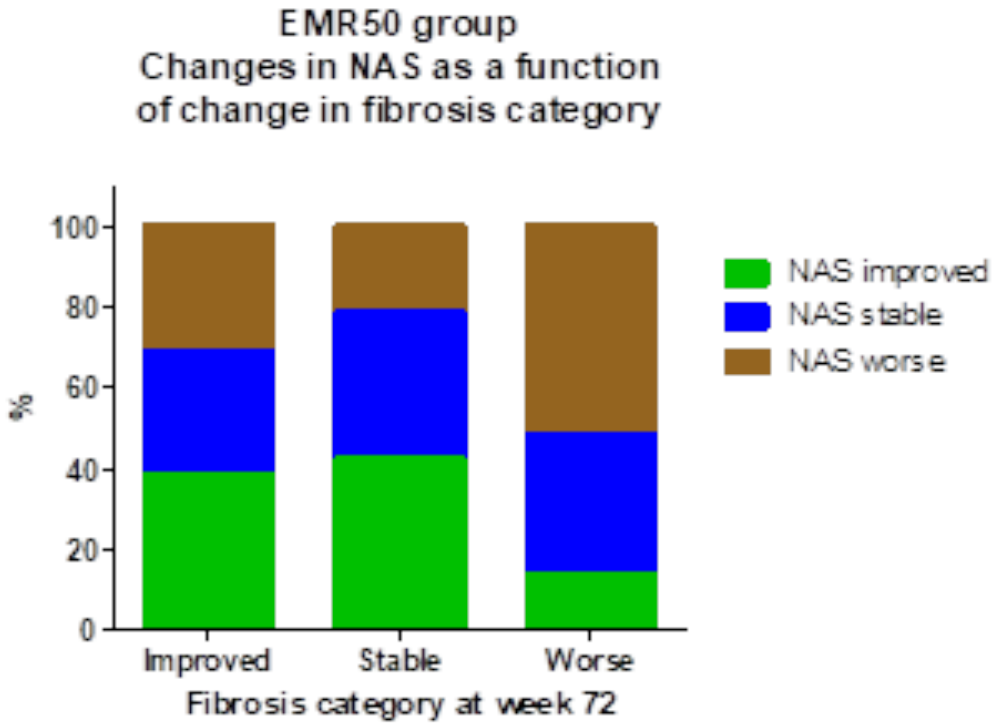


Sanyal et al, N Engl J Med. 2010 May 6;362(18):1675-85.

Brunt et al. Hepatology. 2018 Dec 14. doi: 10.1002/hep.30418. [Epub ahead of print]

NAS correlates with changes in fibrosis





Data from Conatus phase 2B trial

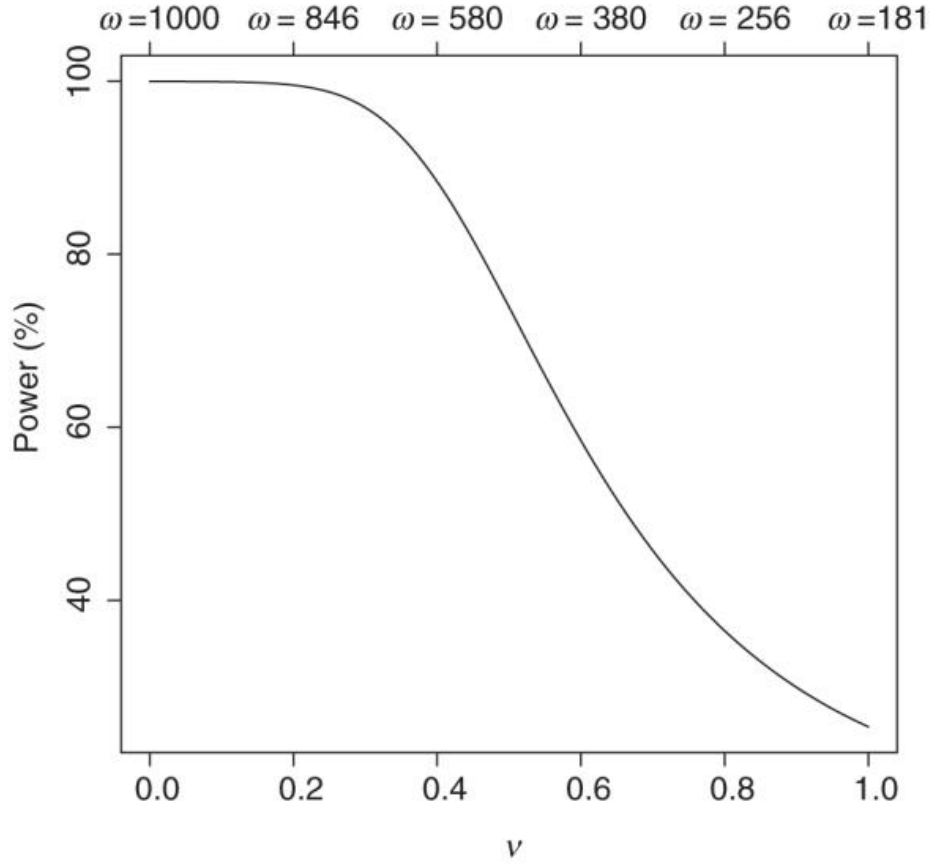
Additional points to consider

- Heirarchical care and outcomes- heriarchical mixed logistic regression. (see Munoz Venturelli et al…J Am Heart Assoc. 2019 Jul 2; 8(13): e0126400
- Estimands
- Finkelstein-Schonfeld approach of comparisons of all pairs of ordered outcomes.

The special case of children with NASH

Bayesian design using adult data to augment pediatric trials.

- a hierarchical model for which the efficacy parameter from the adult trial and that of the pediatric trail are considered to be draws from a normal distribution



Power of Bayes analysis for varying *v* and *ω* values

Schoenfeld et al, Clin Trials. 2009 Aug;6(4):297-304. doi: 10.1177/1740774509339238.

In summary, back to basics

- Right target(s)
- Right population
- Right endpoints
- Right design

THANK YOU FOR YOUR ATTENTION

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