Regulatory Updates

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Forum for Collaborative Research

UC Berkeley SPH

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Disclosures

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Advisory: Sanofi

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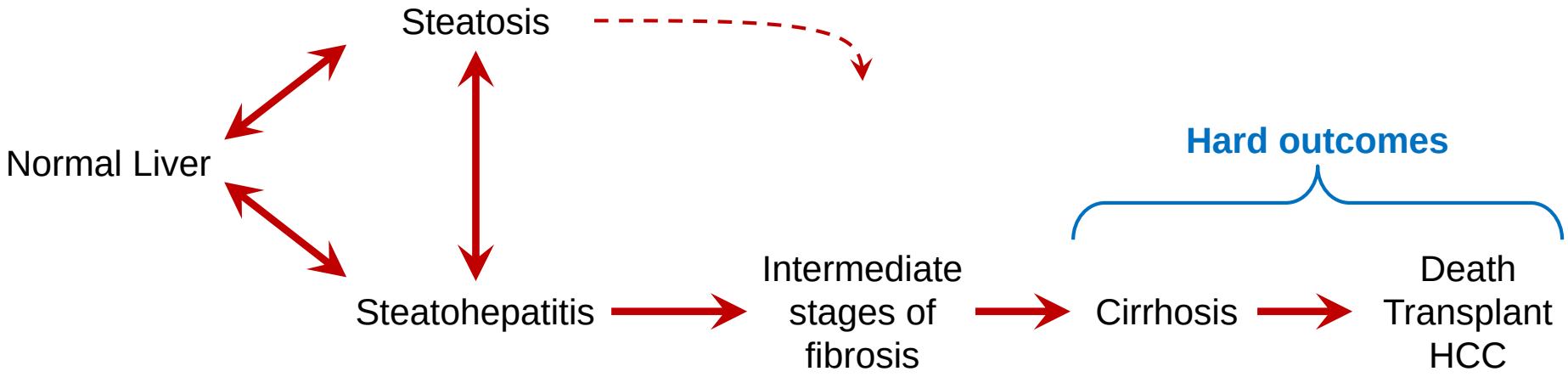
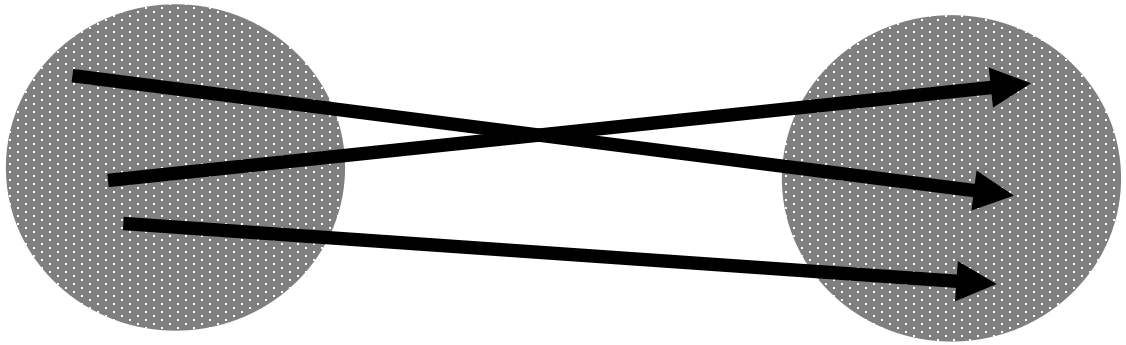
OUTLINE

- Challenges
- Progress
- Opportunities

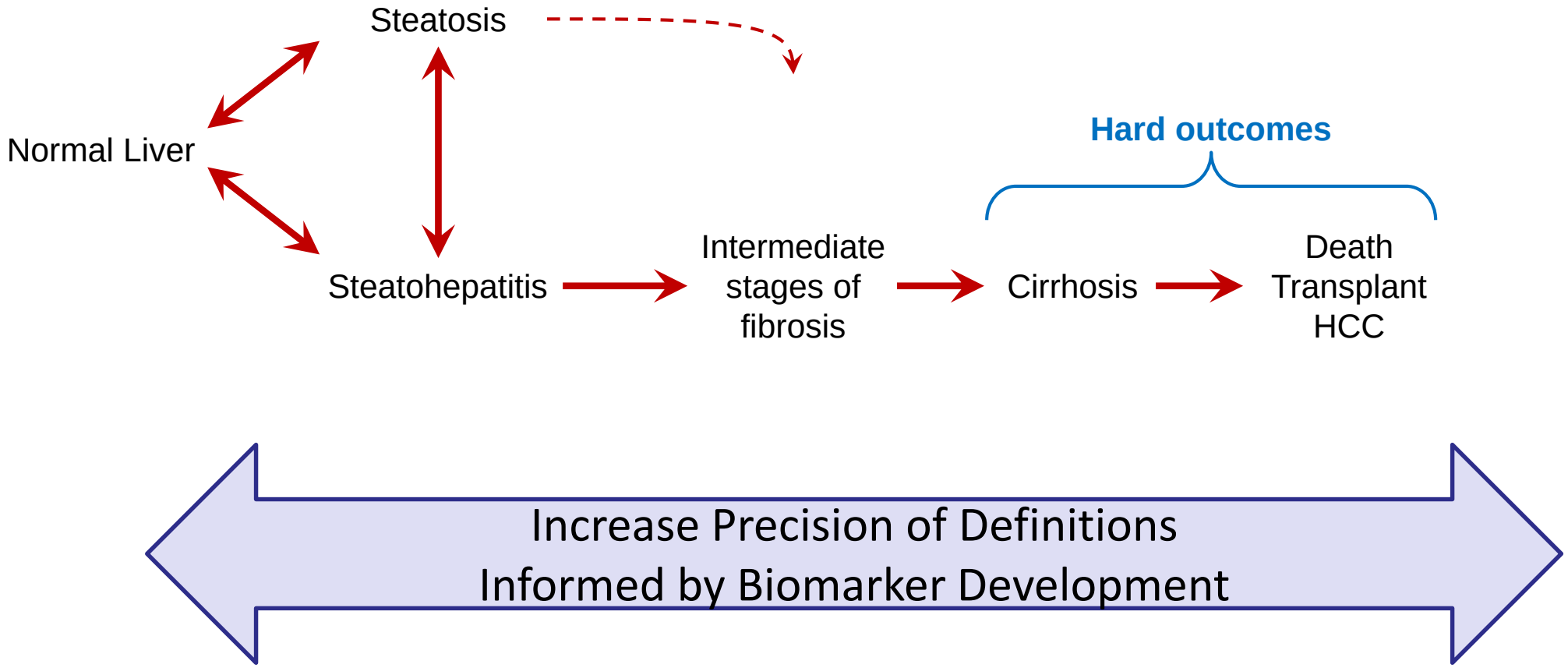
CHALLENGES:
NASH PROGRESSION (OR NOT?)

Progression of NAFLD—Need for Biomarkers





Progression of NAFLD—Need for Biomarkers



Targets for Therapy

- NASH
- Fibrosis
- Need for combination therapy

CHALLENGES: ENDPOINTS

Endpoints

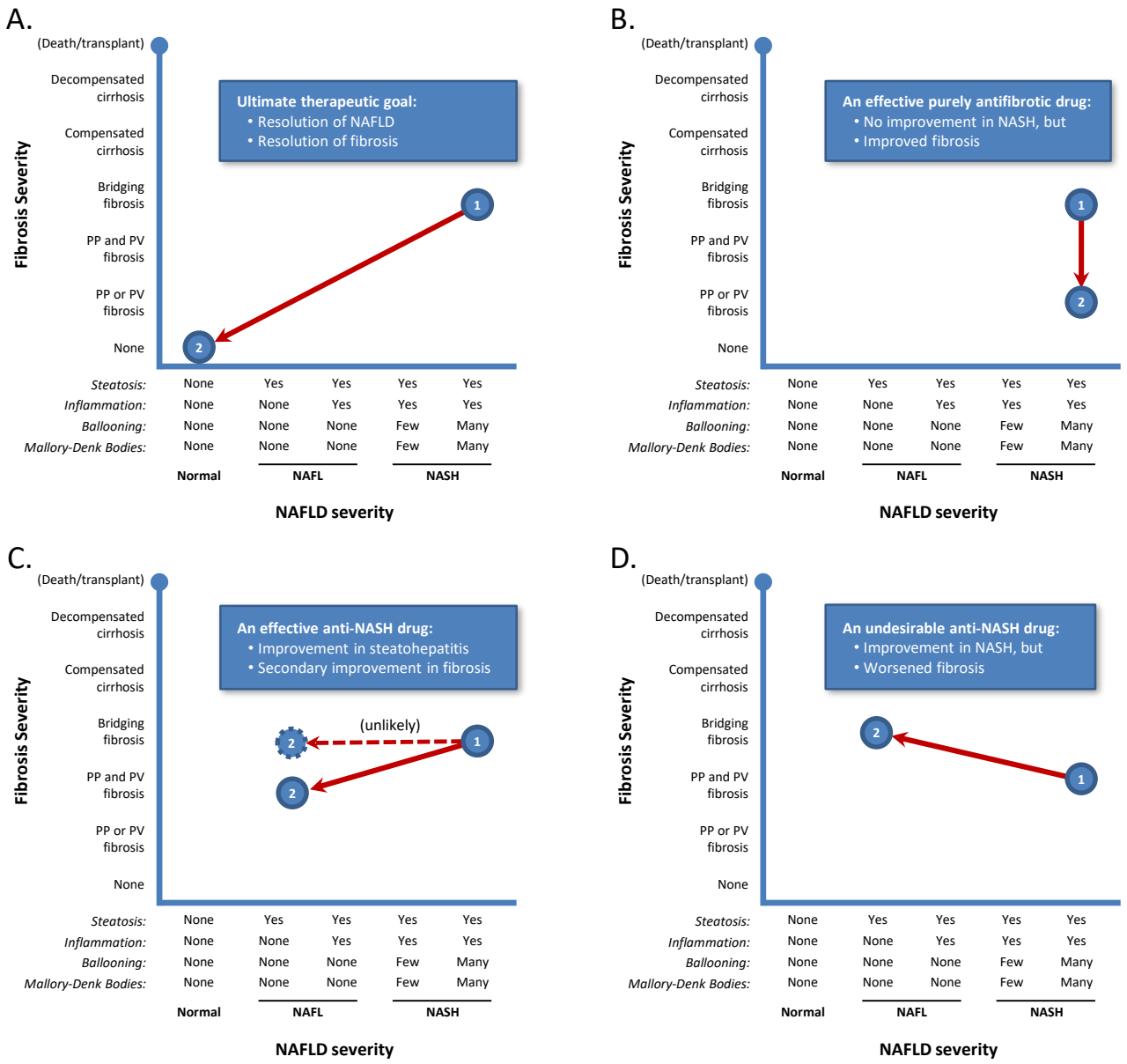
- Resolution of NASH without worsening of fibrosis
- Improvement of fibrosis without worsening of NASH
- Resolution of NASH + improvement of fibrosis

Endpoints

- Resolution of NASH without worsening of fibrosis
  - Disappearance of hepatocyte ballooning
  - Resolution (minimal) lobular inflammation
- Improvement of fibrosis without worsening of NASH
  - ≥ 1 stage (Brunt-Kleiner_
- Resolution of NASH + improvement of fibrosis

Surrogate Endpoints

Figure 1.



Cheung et al MS in preparation

Surrogate endpoints

- Accelerated Approval (US)
- Conditional Approval (EU)

Demonstrate clinical improvement

Hard Endpoints: How a patient feels, functions or survives

Surrogate Endpoints

Reasonably Likely to Predict

- Accelerated Approval
- Traditional Approval based on clinical endpoint

Accepted to Predict

- Traditional Approval

NASH

Today's Surrogate: Invasive (Histology)

Tomorrow's Surrogate: Non-Invasive

CHALLENGES BIOMARKERS

Why Biomarkers? What Biomarkers?

- Context of Use
  - Diagnostic
  - Prognostic
  - Predictive
  - PK/PD
  - Endpoint

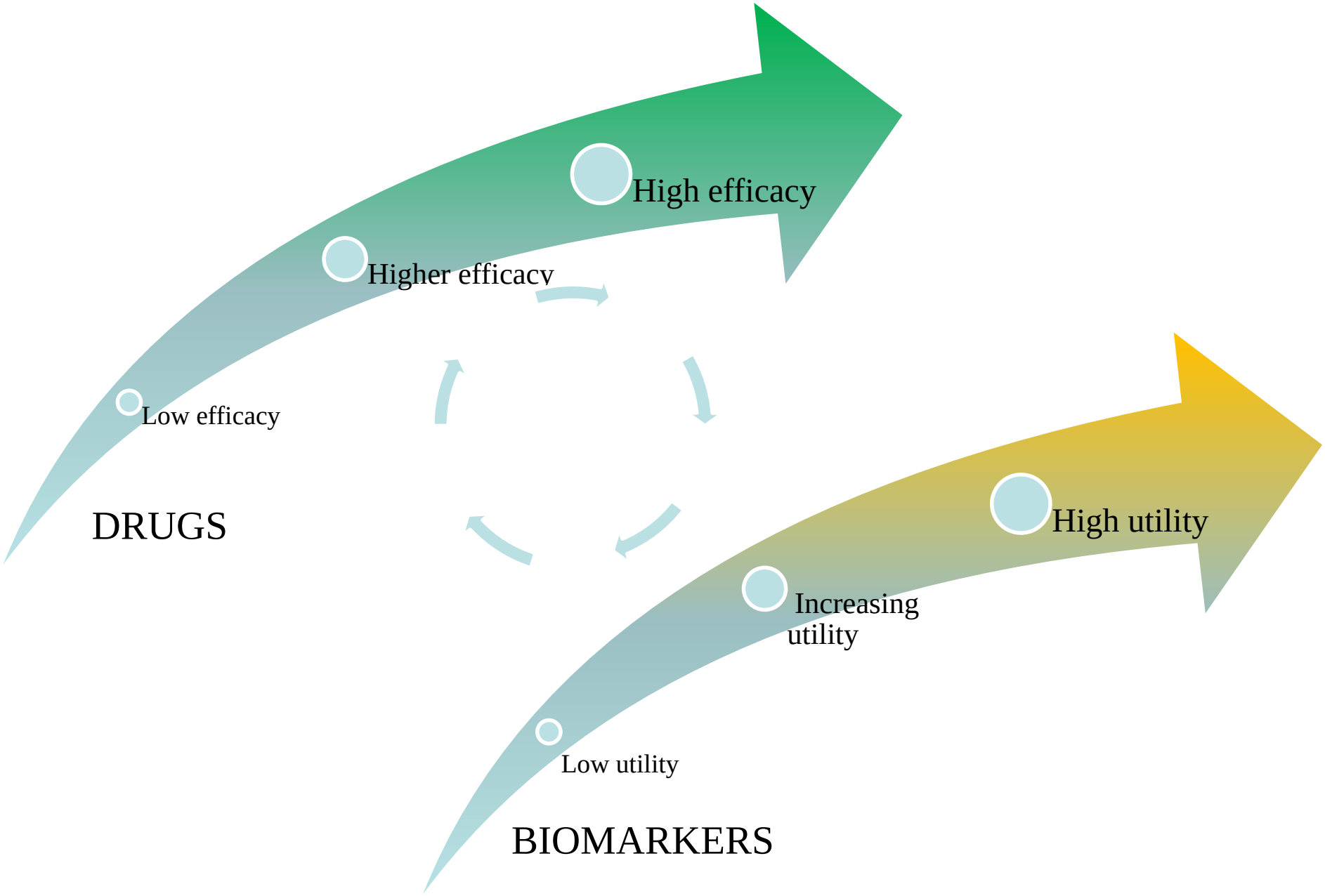
Opportunities for Improved Integration of Biomarker Development Activities within Drug Development

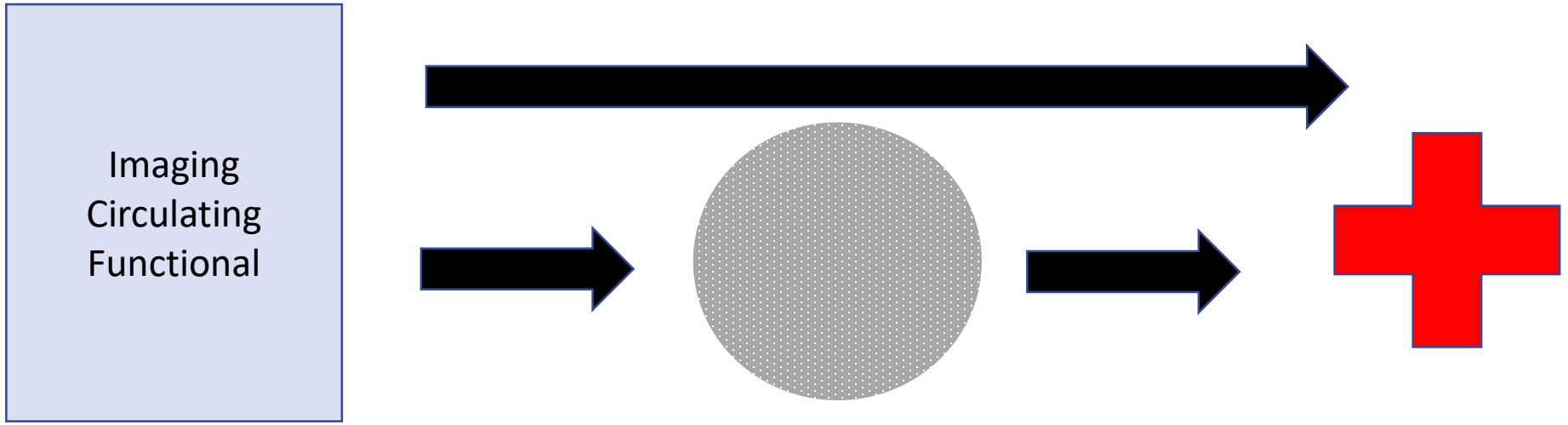
Note: These pathways do not exist in isolation and many times parallel efforts are underway within or between pathways. All share common core concepts, are data-driven, and involve regulatory assessment and outcomes based on the available data.

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

Challenges in biomarker development

- What is the best comparator?
  - Histology based surrogate endpoint
  - Clinical endpoint


High efficacy
Higher efficacy
Low efficacy
DRUGS
High utility
Increasing utility
Low utility
BIOMARKERS



Non-Invasive Biomarkers

Accepted Surrogate
Histology

Hard/Clinical Endpoint

CHALLENGES
GLOBAL CONTEXT

Gaps

- Natural history
- Regulatory capacity

PROGRESS

Increase precision of definitions

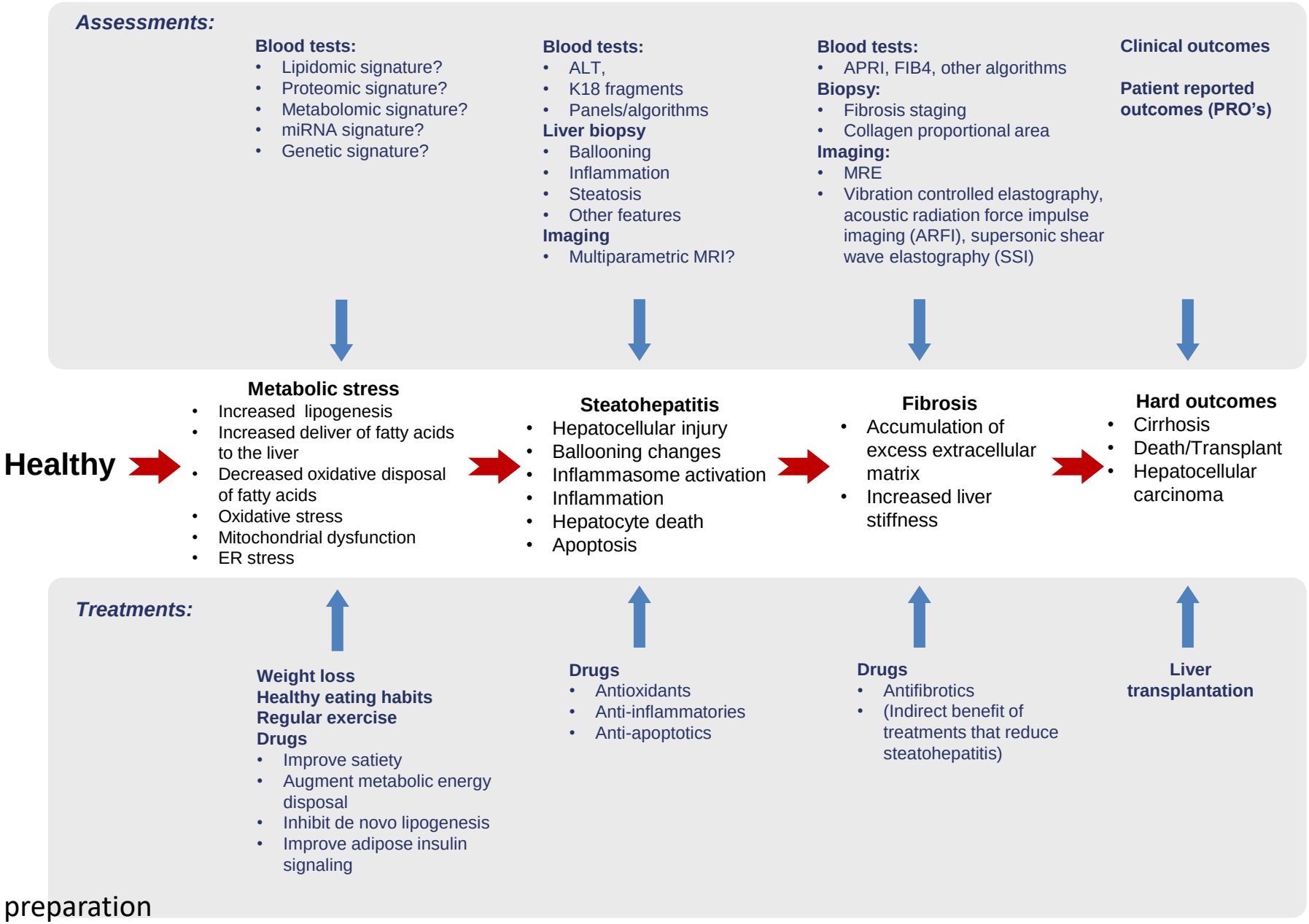
- Baseline
- NASH improvement
  - To be submitted
    - Cheung et al
- Cirrhosis
  - compensated+ decompensated
  - Working groups established

HEPATOLOGY
AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES
SPECIAL ARTICLE | HEPATOLOGY, VOL. 00, NO. 00, 2017

Case Definitions for Inclusion and Analysis of Endpoints in Clinical Trials for Nonalcoholic Steatohepatitis Through the Lens of Regulatory Science

Mohammad Shadab Siddiqui,[1*] Stephen A. Harrison,[2*] Manal F. Abdelmalek,[3] Quentin M. Anstee,[4] Pierre Bedossa,[5] Laurent Castera,[6] Lara Dimick-Santos,[7] Scott Friedman,[8] Katherine Greene,[14] David Kleiner,[9] Sophie Megnien,[10] Brent A. Neuschwander-Tetri,[11] Vlad Ratziu,[12] Elmer Schabel,[13] Veronica Miller,[14] and Arun J. Sanyal[1];
on behalf of the Liver Forum Case Definitions Working Group

Figure 2.



Cheung et al MS in preparation

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Increase cross-trial standardization

- Standardization of data collection (CDE)
  - Baseline
  - Lifestyle
    - Working Group
      - Manal Abdelmalek & Svenne Franque
  - Co-morbidities
    - Working Group
      - Vlad Radziu & Morten Hansen

Baseline Parameters in Clinical Trials for Nonalcoholic Steatohepatitis: Recommendations From the Liver Forum

Gastroenterology 2017;153:621–625

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OPPORTUNITIES

Current regulatory context

- 21st Century Cures Act

Title III: Development

Subtitles

A. Patient-Focused Drug Development

B. Advancing New Drug Therapies

C. Modern Trial Design and Evidence Development

D. Patient Access to Therapies and Information

E. Antimicrobial Innovation and Stewardship

F. Medical Device Innovations

G. Improving Scientific Expertise and Outreach at FDA

H. Medical Countermeasures Innovation

I. Vaccine Access, Certainty and Innovation

J. Technical Corrections

Highlights

- 21st Century Cures and PDUFA VI increasingly places FDA as an *active participant* in drug development, broadening our traditional regulatory role
- Requires expanded efforts to enhance drug development
  - *Patient-focused drug development*: collect / analyze patient experience, to use in designing drug development programs (endpoints), and in regulatory decision making (endpoints and risk/benefit considerations)
  - *Novel, innovative trial designs*: use of complex adaptive and other novel trial designs – and how such clinical trials can be used to satisfy the substantial evidence standard
  - *Real world evidence*: using data regarding use or potential benefits and risks of a drug derived from sources other than randomized clinical trials – in support of new indications and post-approval study requirements
  - ***Drug development tools: biomarkers and COAs***

Collaboration

- Biomarker development
  - LITMUS & NIMBLE
    - Address challenges for combination treatment
- Data use
  - Patient level placebo data collaboration
  - Explore innovative analytics
  - Potential to reduce placebo arm burden in future trials

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Global reach

- US-EU
  - Canada
- Other regions:
  - China
  - Latin America


非酒精性脂肪性肝炎
（NASH）临床试验研讨会
李宏霞
Hongxia Li
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Ying Chen

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