New Targets, New Modalities, New Challenges – The *Inconvenient* Path of Human Genetics in Drug Discovery

Enabling Precision Medicine: The Role of Genetics in Clinical Drug Development – A Workshop

March 8, 2017

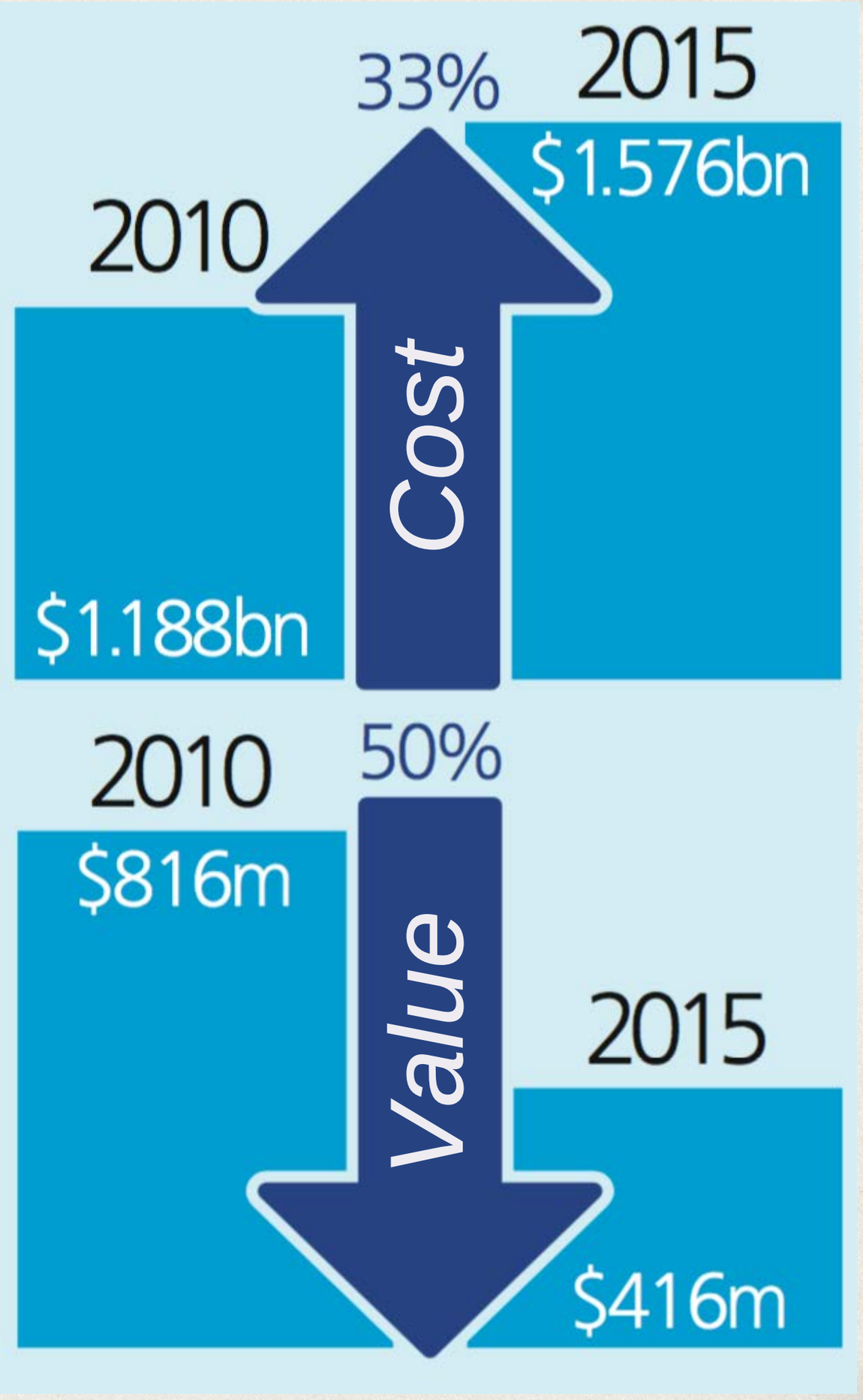
Overall message

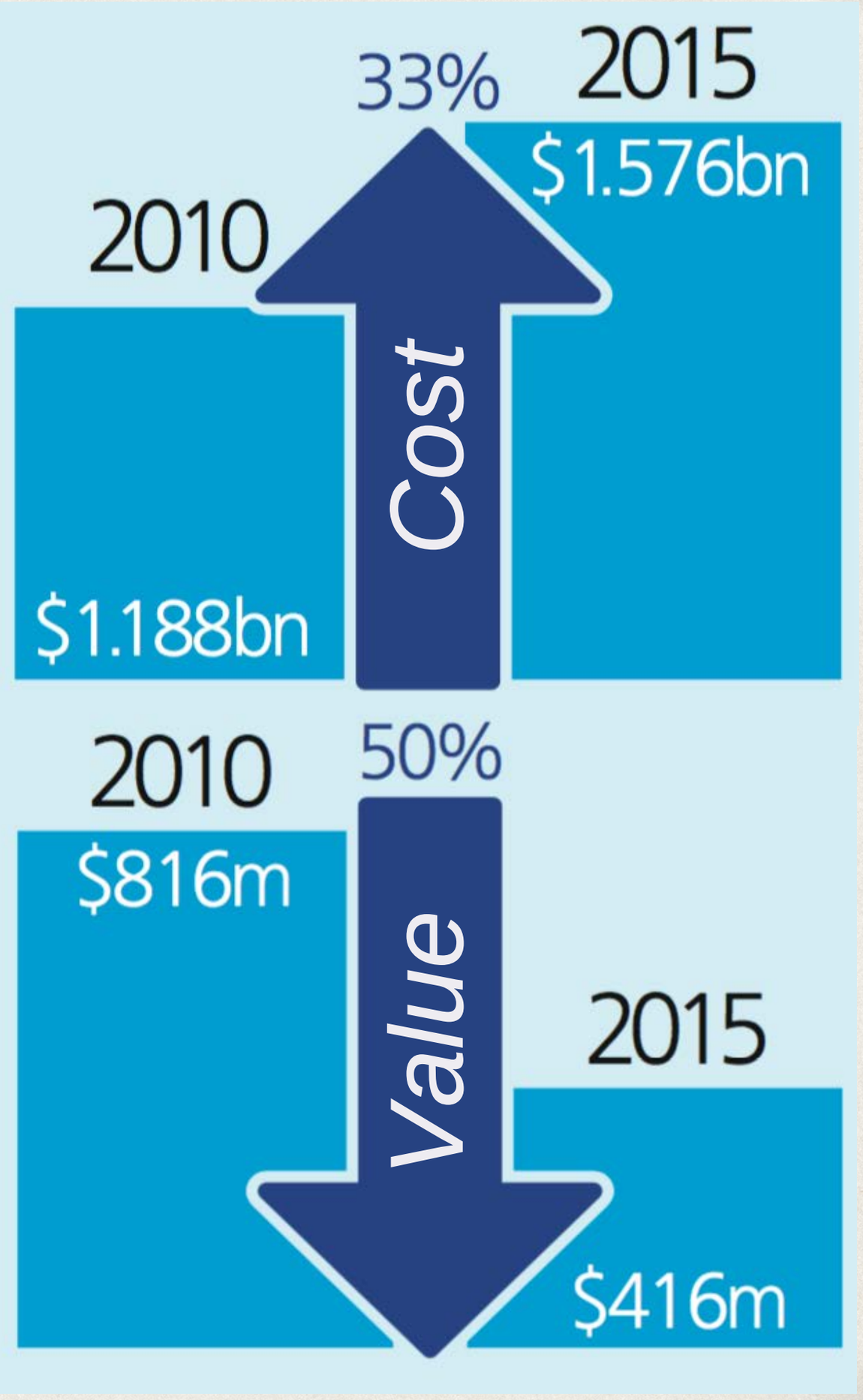
- precision medicine: *patient subsets for whom therapeutic intervention works better*

- few approved drugs will benefit from precision medicine

- greatest impact will be to guide new drug development, which will be tested and approved in patient subsets

- However, this path is *inconvenient*, and will require biological insight into targets, new therapeutic modalities, and a more creative approaches to clinical development


33%
2015
$1.576bn
2010
Cost
$1.188bn
2010
50%
$816m
Value
2015
$416m

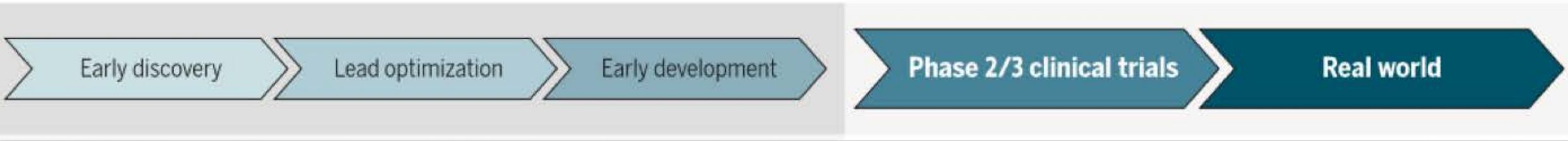

33%
2015
$1.576bn
2010
Cost
$1.188bn
2010
50%
$816m
Value
2015
$416m

PERSPECTIVE

LIMITING RISK

Disciplined approach to drug discovery and early development

Robert M. Plenge



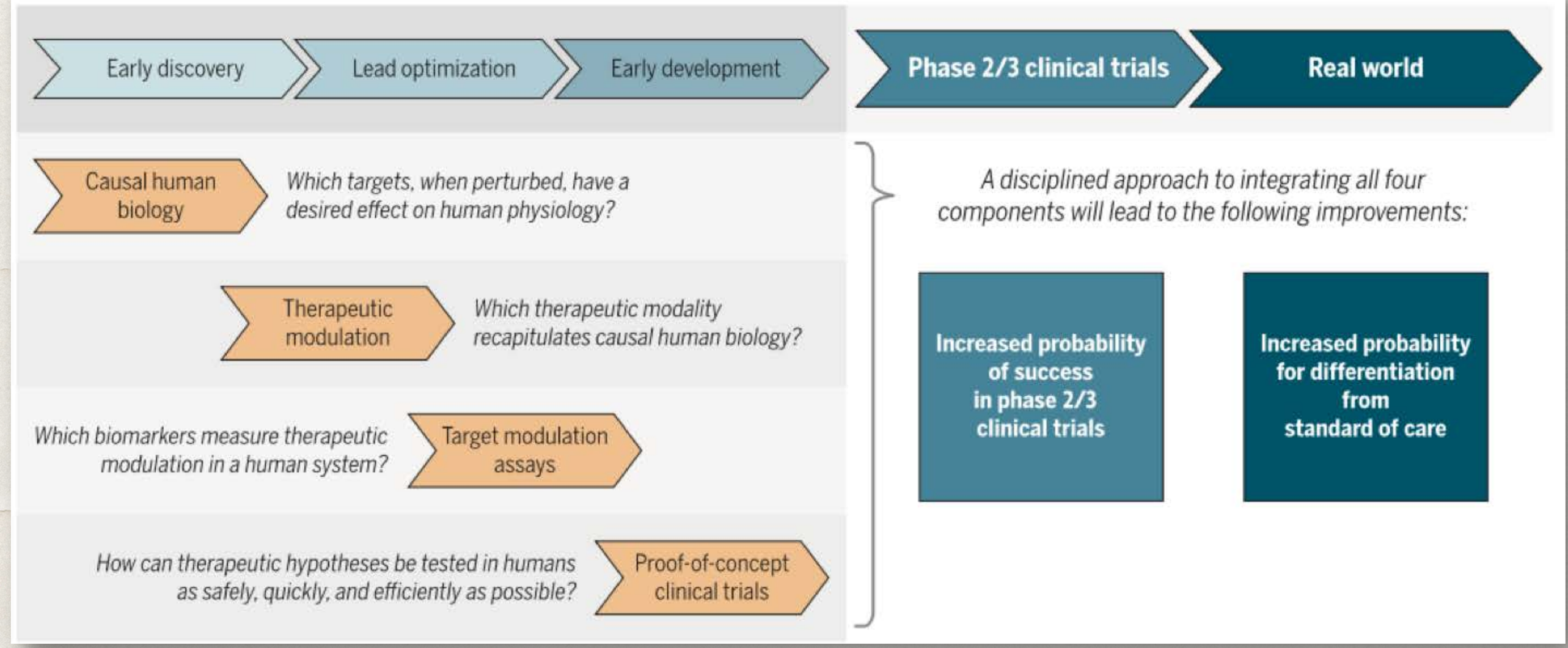
PERSPECTIVE

LIMITING RISK

Disciplined approach to drug discovery and early development

Robert M. Plenge

Why is cost increasing?



1. Too many Phase 2/3 studies fail
2. Time between discovery and PoC is too long

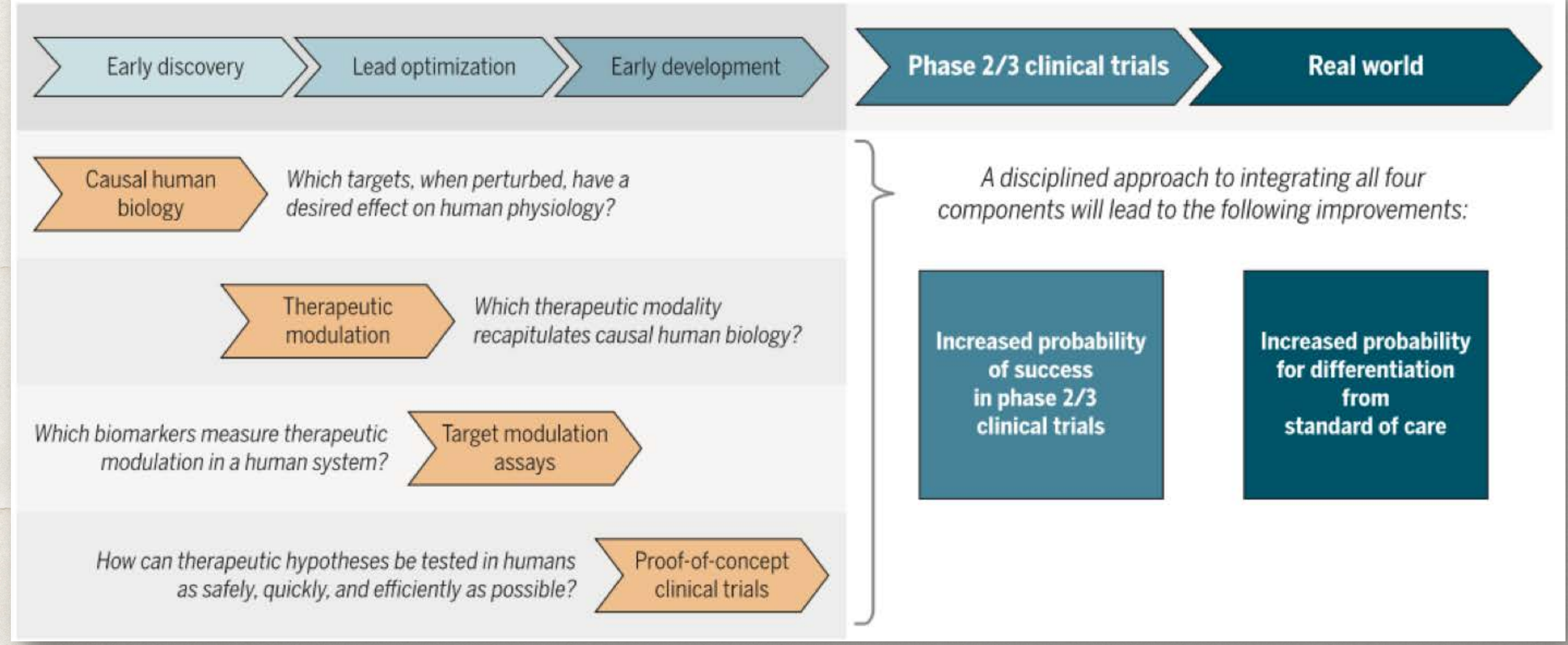
PERSPECTIVE

LIMITING RISK

Disciplined approach to drug discovery and early development

Robert M. Plenge

Why don't drugs differentiate?



1. Not enough sound therapeutic hypotheses!

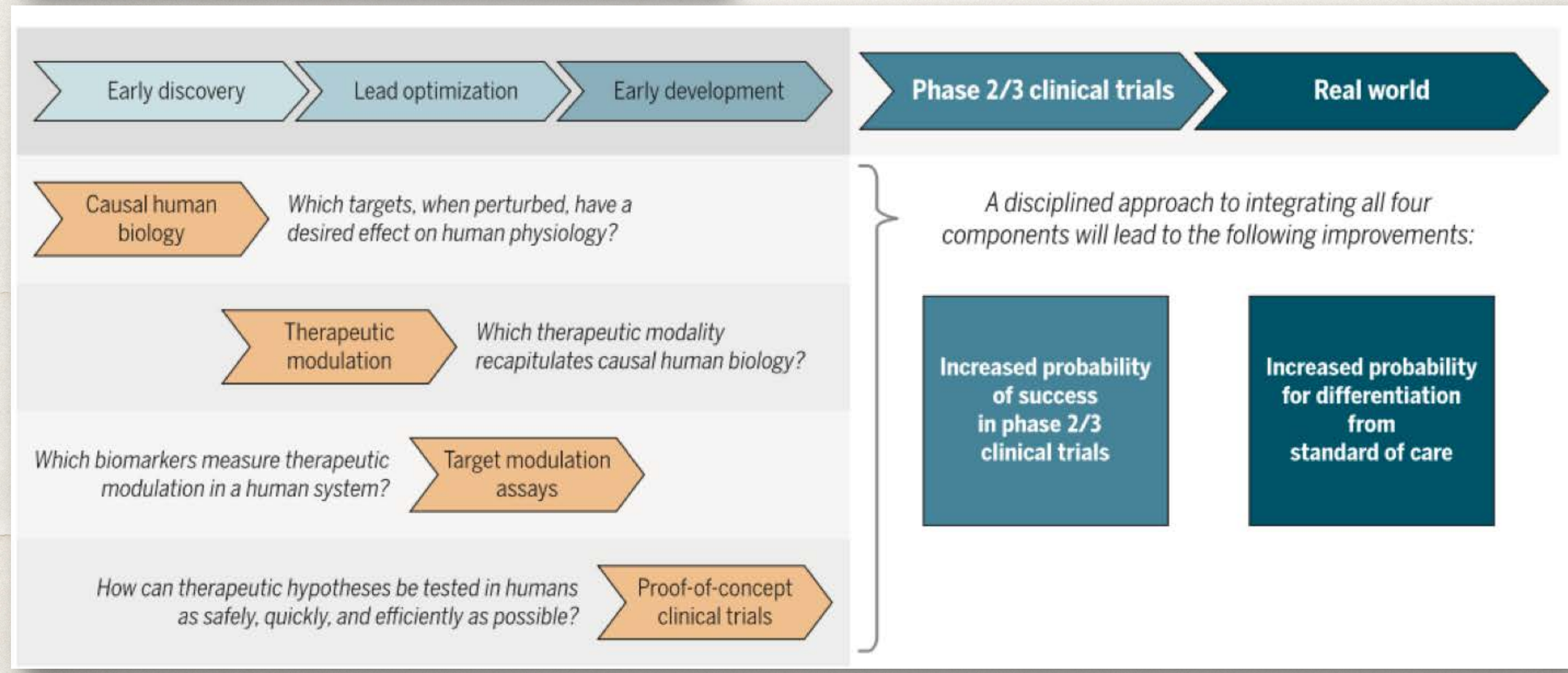
PERSPECTIVE

LIMITING RISK

Disciplined approach to drug discovery and early development

Robert M. Plenge

How will ***precision medicine*** *help?*



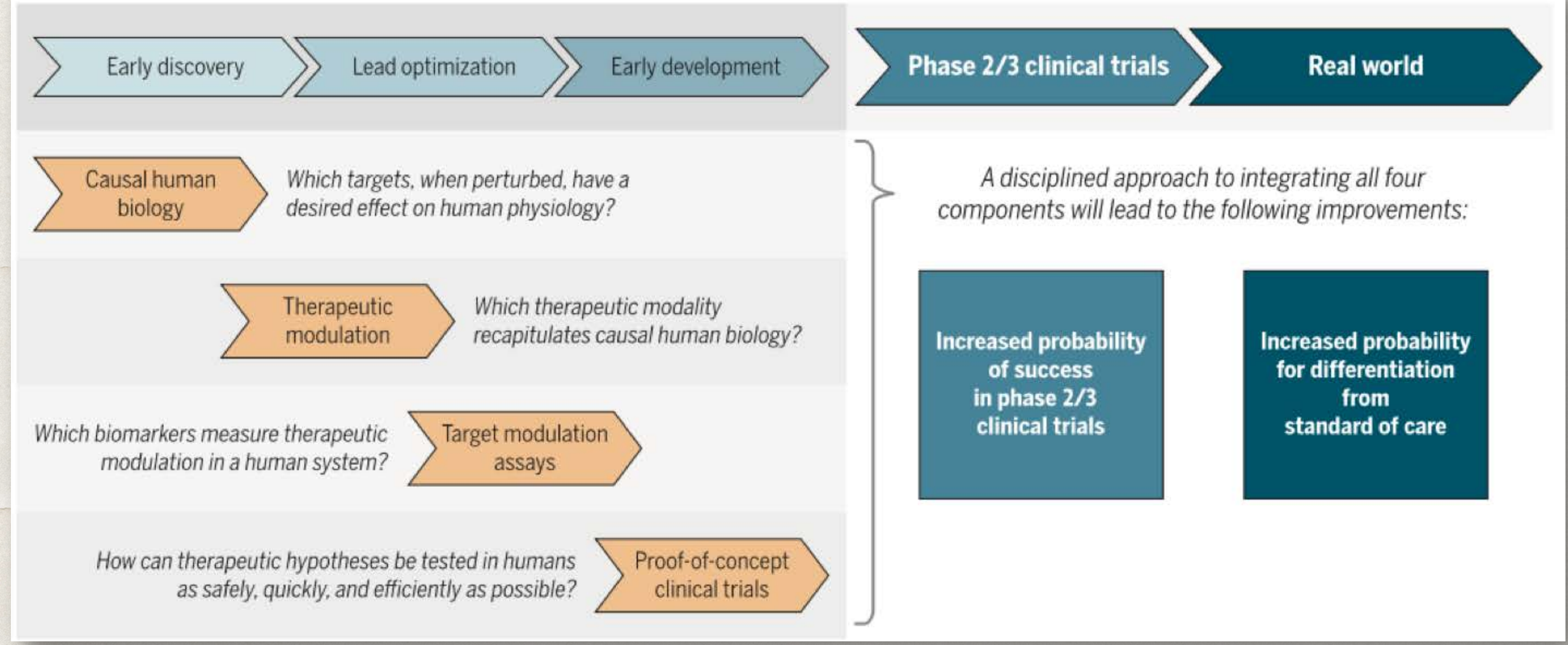
1. Improve cycle time from therapeutic hypothesis to clinical PoC…*efficiently and safely*

PERSPECTIVE

LIMITING RISK

Disciplined approach to drug discovery and early development

Robert M. Plenge



Today: *5-7 years*

PERSPECTIVE

LIMITING RISK

Disciplined approach to drug discovery and early development

Robert M. Plenge

Early discovery → Lead optimization → Early development → Phase 2/3 clinical trials → Real world

Causal human biology — *Which targets, when perturbed, have a desired effect on human physiology?*

Therapeutic modulation — *Which therapeutic modality recapitulates causal human biology?*

Which biomarkers measure therapeutic modulation in a human system? → Target modulation assays

How can therapeutic hypotheses be tested in humans as safely, quickly, and efficiently as possible? → Proof-of-concept clinical trials

A disciplined approach to integrating all four components will lead to the following improvements:

Increased probability of success in phase 2/3 clinical trials

Increased probability for differentiation from standard of care

<1 yr

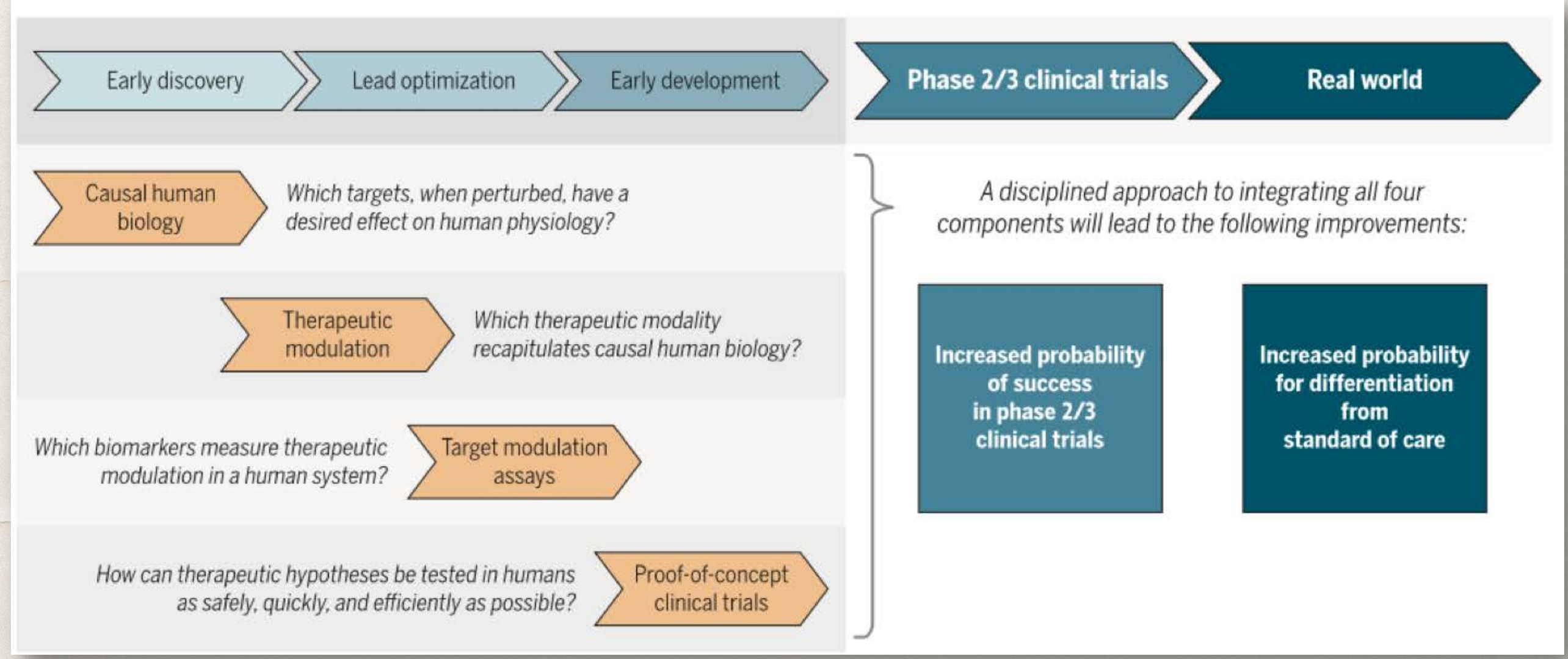
PERSPECTIVE

LIMITING RISK

Disciplined approach to drug discovery and early development

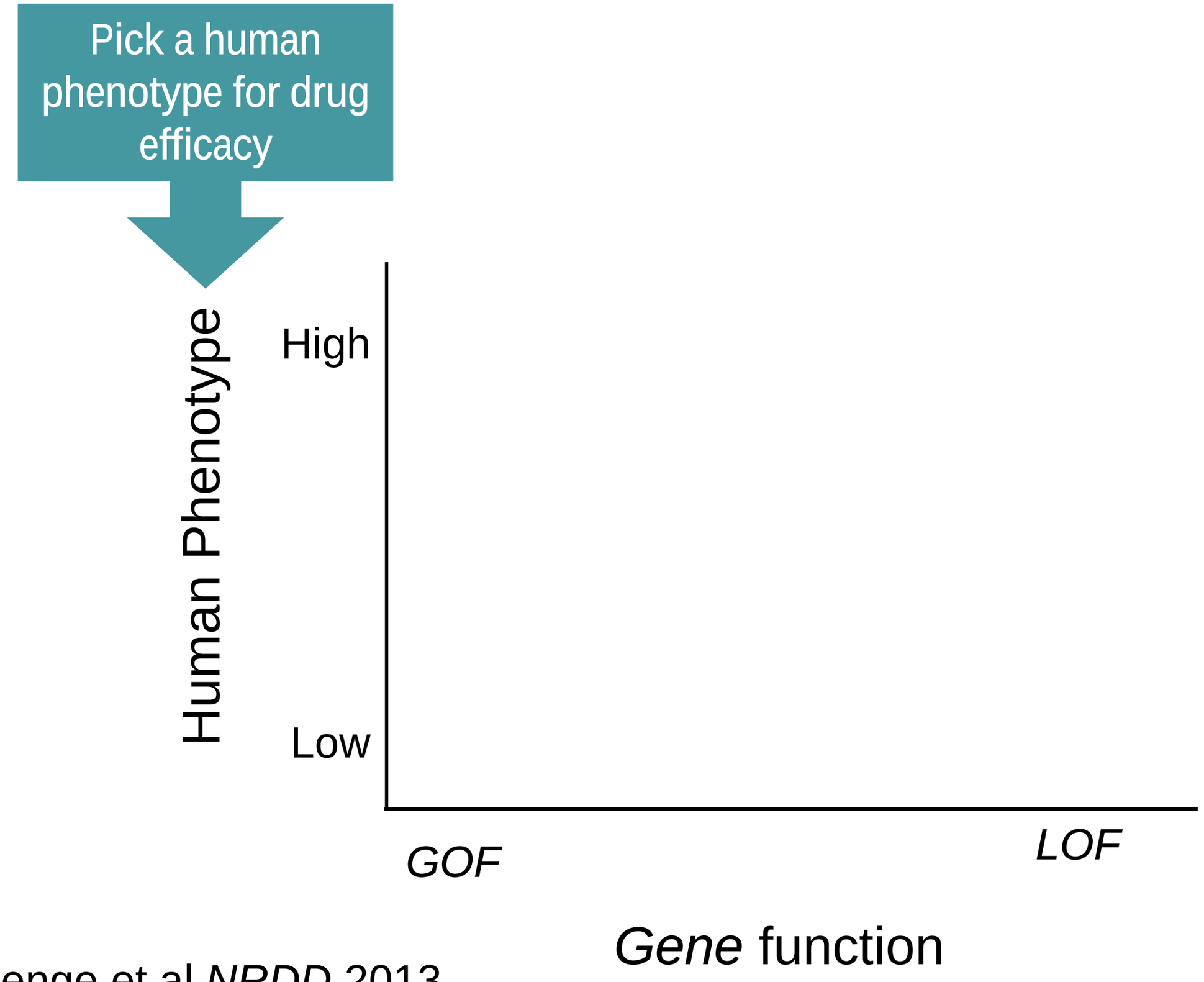
Robert M. Plenge

What are potential solutions?



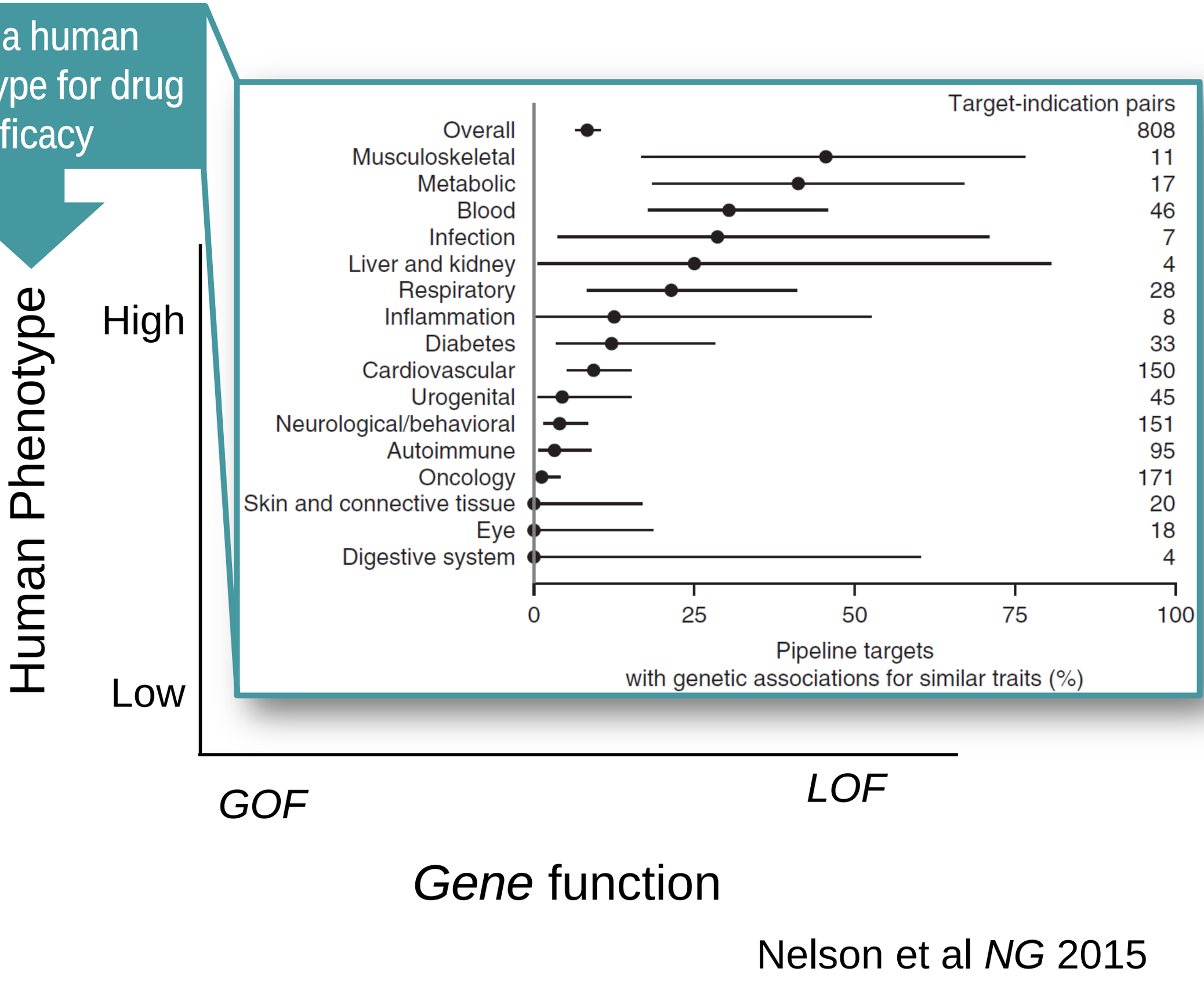
1. Pick targets based on human biology
2. Programmable therapeutics to test PoC

human genetics to pick targets



Plenge et al *NRDD* 2013

Pick a human phenotype for drug efficacy



Nelson et al *NG* 2015

Pick a human phenotype for drug efficacy

Human Phenotype

High

Low

X

X

X

X

X

Identify a series of alleles with range of effect sizes in humans (but of unknown function)

GOF

LOF

Gene function

Pick a human phenotype for drug efficacy

Human Phenotype

High

Low

GOF

LOF

Gene function

JAMA | Original Investigation

Association of Rare and Common Variation in the Lipoprotein Lipase Gene With Coronary Artery Disease

Amit V. Khera, MD; Hong-Hee Won, PhD; Gina M. Peloso, PhD; Colm O'Dushlaine, PhD; Dajiang Liu, PhD; Nathan O. Stitziel, MD, PhD; Pradeep Natarajan, MD; Akihiro Nomura, MD; Connor A. Emdin, DPhil; Namrata Gupta, PhD; Ingrid B. Borecki, PhD; Rosanna Asselta, PhD; Stefano Duga, PhD; Piera Angelica Merlini, MD; Adolfo Correa, MD; Thorsten Kessler, MD; James G. Wilson, MD; Matthew J. Bown, MD; Alistair S. Hall, MD; Peter S. Braund, PhD; David J. Carey, PhD; Michael F. Murray, MD; H. Lester Kirchner, PhD; Joseph B. Leader, BA; Daniel R. Lavage, BS; J. Neil Manus, BS; Dustin N. Hartzel, BS; Nilesh J. Samani, MD; Heribert Schunkert, MD; Jaume Marrugat, MD, PhD; Roberto Elosua, MD, PhD; Ruth McPherson, MD; Martin Farrall, FRCPath; Hugh Watkins, MD, PhD; Eric S. Lander, PhD; Daniel J. Rader, MD; John Danesh, FMedSci; Diego Ardissino, MD; Stacey Gabriel, PhD; Cristen Willer, PhD; Gonçalo R. Abecasis, PhD; Danish Saleheen, MD; Frederick E. Dewey, MD; Sekar Kathiresan, MD; for the Myocardial Infarction Genetics Consortium, DiscovEHR Study Group, CARDIoGRAM Exome Consortium, and Global Lipids Genetics Consortium

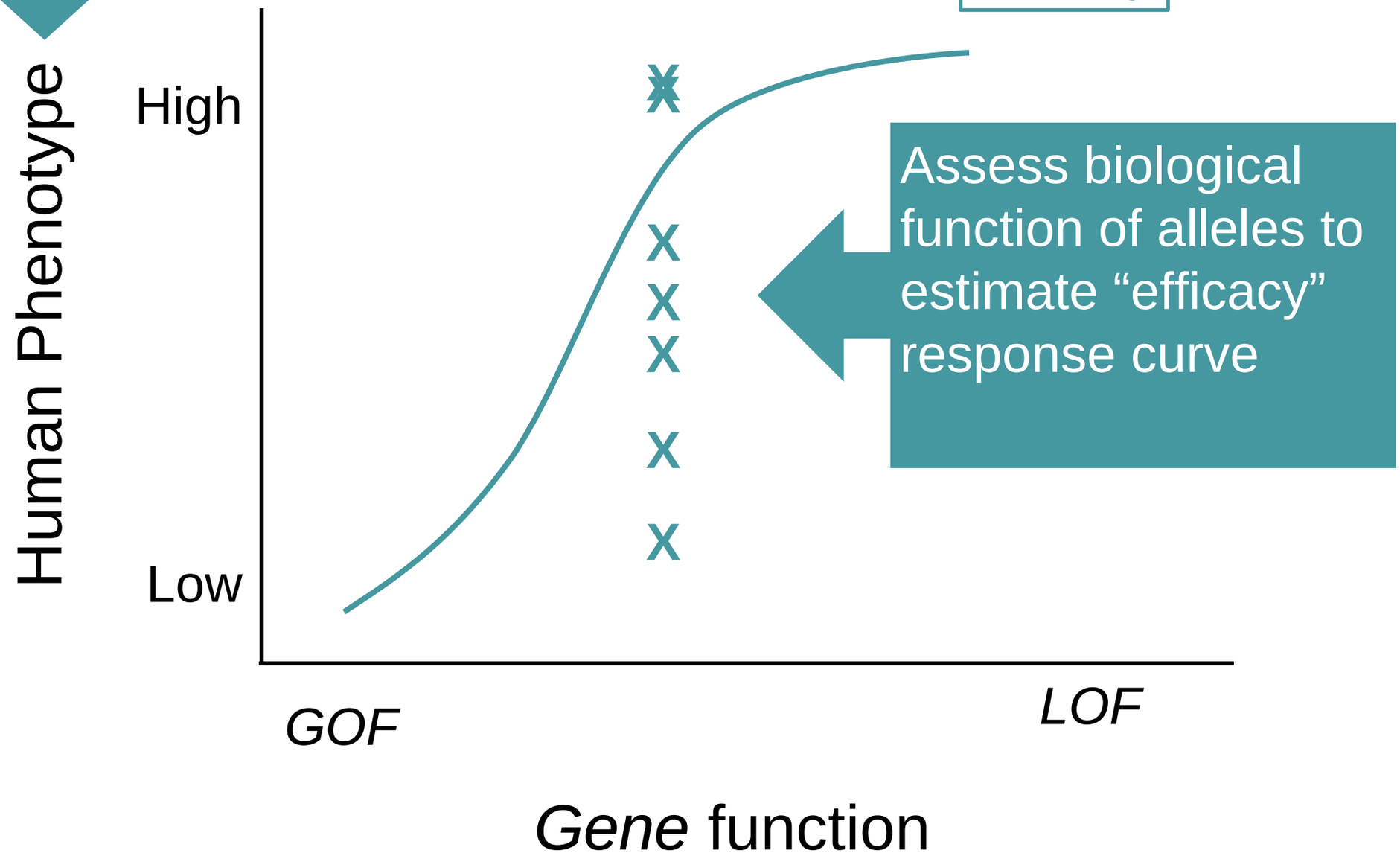
RESULTS Among 46 891 individuals with *LPL* gene sequencing data available, the mean (SD) age was 50 (12.6) years and 51% were female. A total of 188 participants (0.40%; 95% CI, 0.35%-0.46%) carried a damaging mutation in *LPL*, including 105 of 32 646 control participants (0.32%) and 83 of 14 245 participants with early-onset CAD (0.58%). Compared with 46 703 noncarriers, the 188 heterozygous carriers of an *LPL* damaging mutation displayed higher plasma triglyceride levels (19.6 mg/dL; 95% CI, 4.6-34.6 mg/dL) and higher odds of CAD (odds ratio = 1.84; 95% CI, 1.35-2.51; $P < .001$). An analysis of 6 common *LPL* variants resulted in an odds ratio for CAD of 1.51 (95% CI, 1.39-1.64; $P = 1.1 \times 10^{-22}$) per 1-SD increase in triglycerides.

>100 rare variants

6 common variants

Khera et al *JAMA* 2017

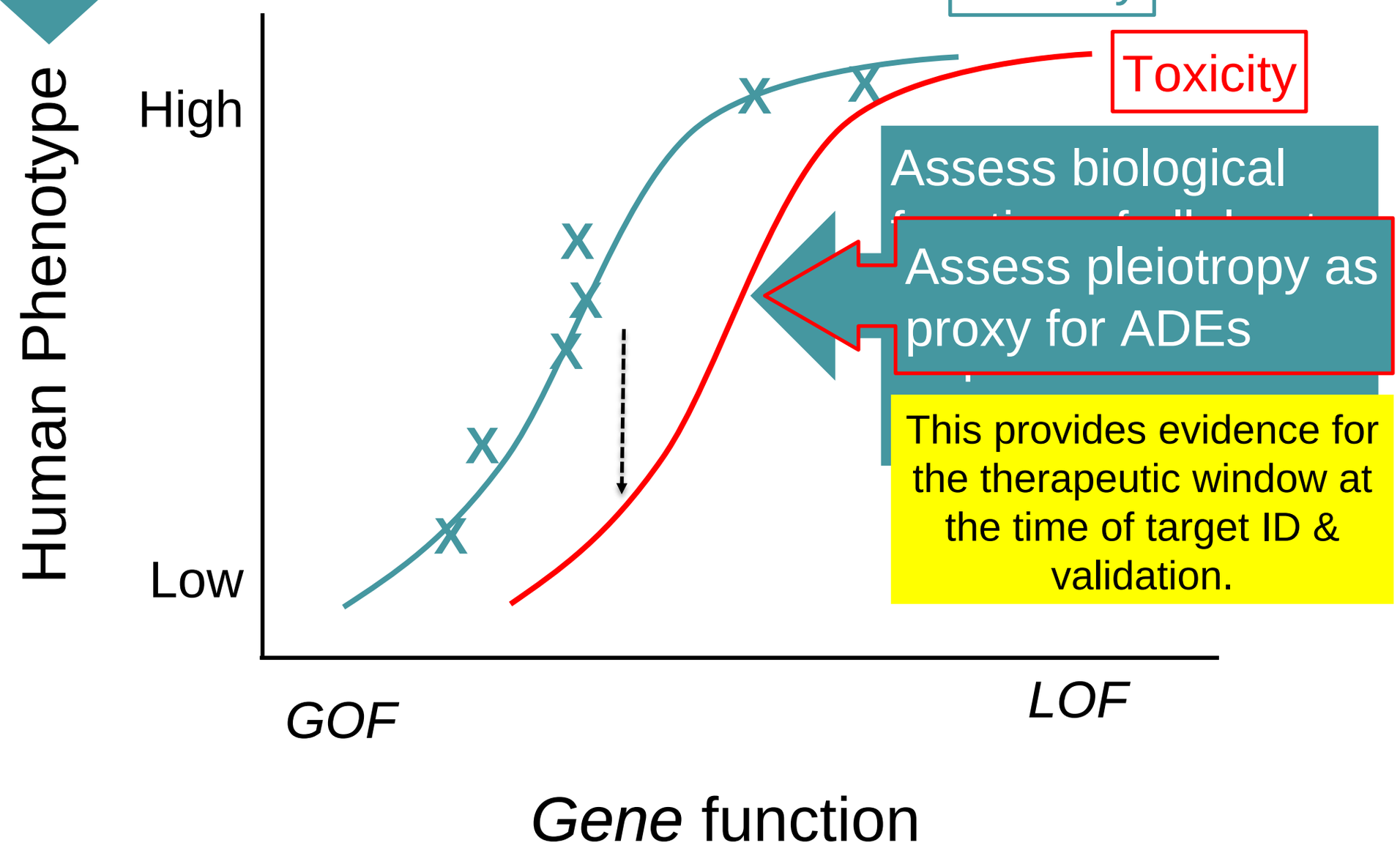
Pick a human phenotype for drug efficacy



Assess biological function of alleles to estimate “efficacy” response curve

New target for drug screen!

Pick a human phenotype for drug efficacy



Gene function

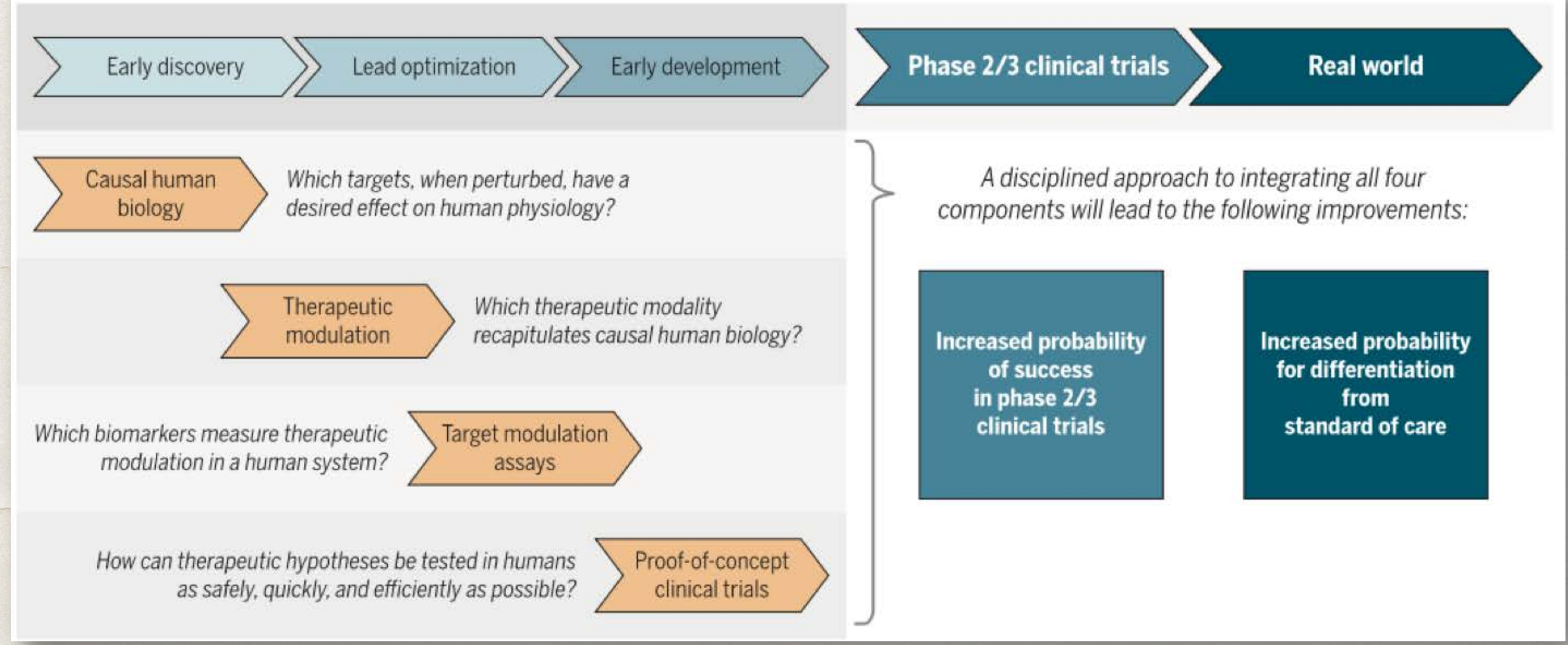
programmable therapeutics to test therapeutic hypotheses quickly

PERSPECTIVE

LIMITING RISK

Disciplined approach to drug discovery and early development

Robert M. Plenge



Today: *5-7 years*

PERSPECTIVE

LIMITING RISK

Disciplined approach to drug discovery and early development

Robert M. Plenge

Early discovery → Lead optimization → Early development → Phase 2/3 clinical trials → Real world

Causal human biology — *Which targets, when perturbed, have a desired effect on human physiology?*

Therapeutic modulation — *Which therapeutic modality recapitulates causal human biology?*

Which biomarkers measure therapeutic modulation in a human system? → Target modulation assays

How can therapeutic hypotheses be tested in humans as safely, quickly, and efficiently as possible? → Proof-of-concept clinical trials

A disciplined approach to integrating all four components will lead to the following improvements:

Increased probability of success in phase 2/3 clinical trials

Increased probability for differentiation from standard of care

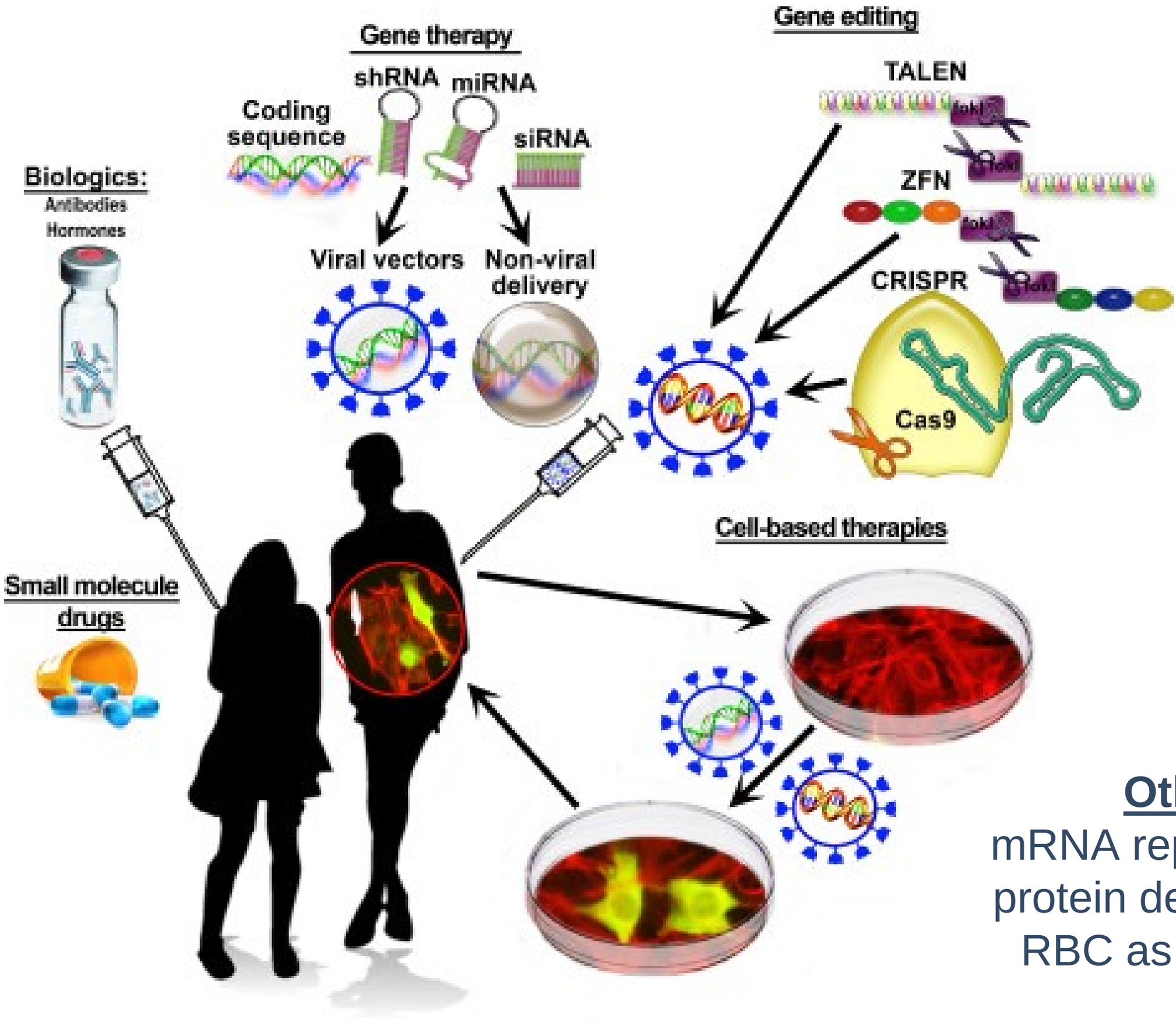
<1 yr

Limitations that we face today

- Biological function of associated variants, genes & pathways incompletely understood

- Conventional modalities (e.g., small molecules, monoclonal antibodies) modulate <20% of targets

- ***New modalities are desperately needed***, but today are limited by delivery and pharmacological properties



Other

mRNA replacement
protein degradation
RBC as vehicles

Burning platform for precision medicine

- understand molecular mechanism of disease-associated variants, genes and pathways

- recapitulate mechanism with a credible therapeutic molecule

- shorten cycle time to test therapeutic hypotheses in small PoC trials defined by specific molecular features

Conclusion

Overall message - inconvenient path to precision medicine

- precision medicine: *patient subsets for whom therapeutic intervention works better*

- few approved drugs will benefit from precision medicine

- greatest impact will be to guide new drug development, which will be tested and approved in patient subsets

- However, this path is *inconvenient*, and will require biological insight into targets, new therapeutic modalities, and a more creative approaches to clinical development