Target Validation in Drug Discovery

Lon Cardon

GlaxoSmithKline

Translation and Genetics

21st century genetics clearly contributing to

- Understanding disease etiology
- Mechanistic hypotheses and (sometimes) direct insights
- Broad spectrum of trait-gene relevance
- Technology and unforeseen tools

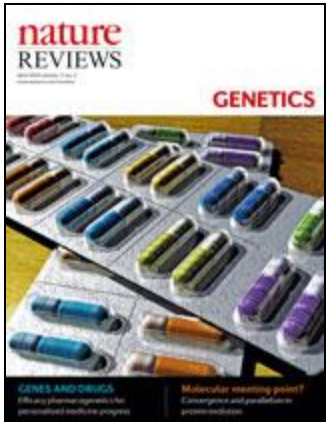
Translation?

- Diagnostics, prognostics, treatment?
- Pharmacogenetics?
- Novel targets?

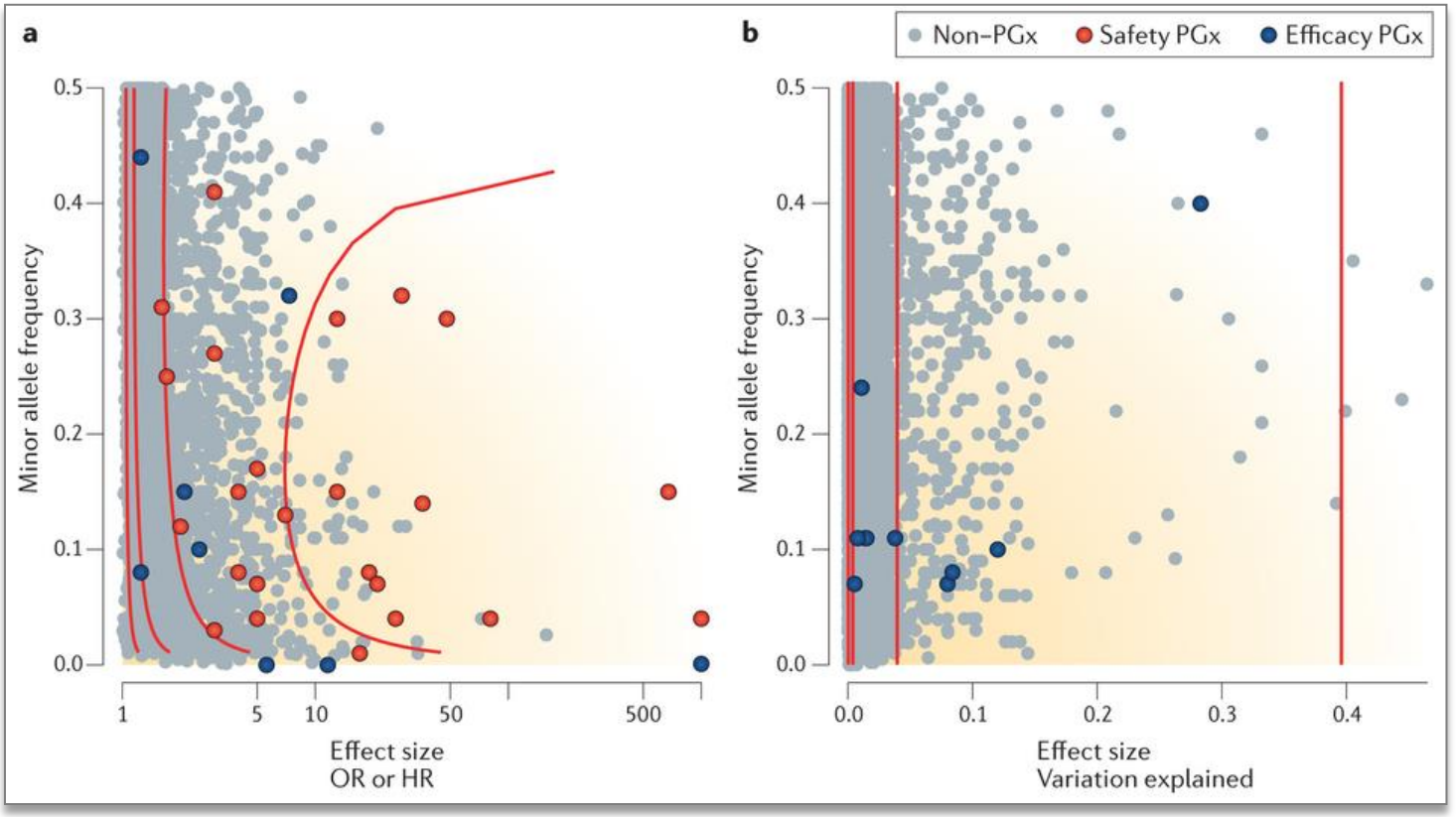
✓ **Oncology**, **rare diseases** and (ad hoc) **drug safety**
Otherwise, “Valley of Death” is as wide as ever

The genetics of drug efficacy: opportunities and challenges

Matthew R. Nelson[1], Toby Johnson[2]*, Liling Warren[3,4], Arlene R. Hughes[5], Stephanie L. Chissoe[6], Chun-Fang Xu[2] and Dawn M. Waterworth[1]*



APRIL 2016 VOL 17 NO 4

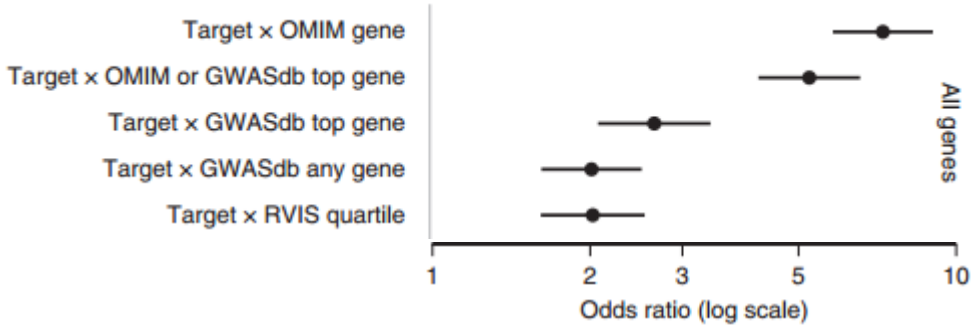


The support of human genetic evidence for approved drug indications

nature genetics

Matthew R Nelson[1], Hannah Tipney[2], Jeffery L Painter[1], Judong Shen[1], Paola Nicoletti[3], Yufeng Shen[3,4], Aris Floratos[3,4], Pak Chung Sham[5,6], Mulin Jun Li[6,7], Junwen Wang[6,7], Lon R Cardon[8], John C Whittaker[2] & Philippe Sanseau[2]

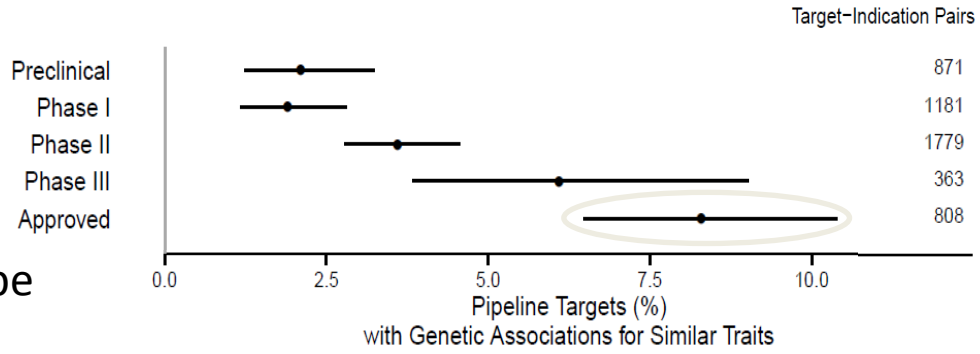
Drugs with human genetic information >2x more likely to be successful



Those that succeed are more likely to be genetically validated

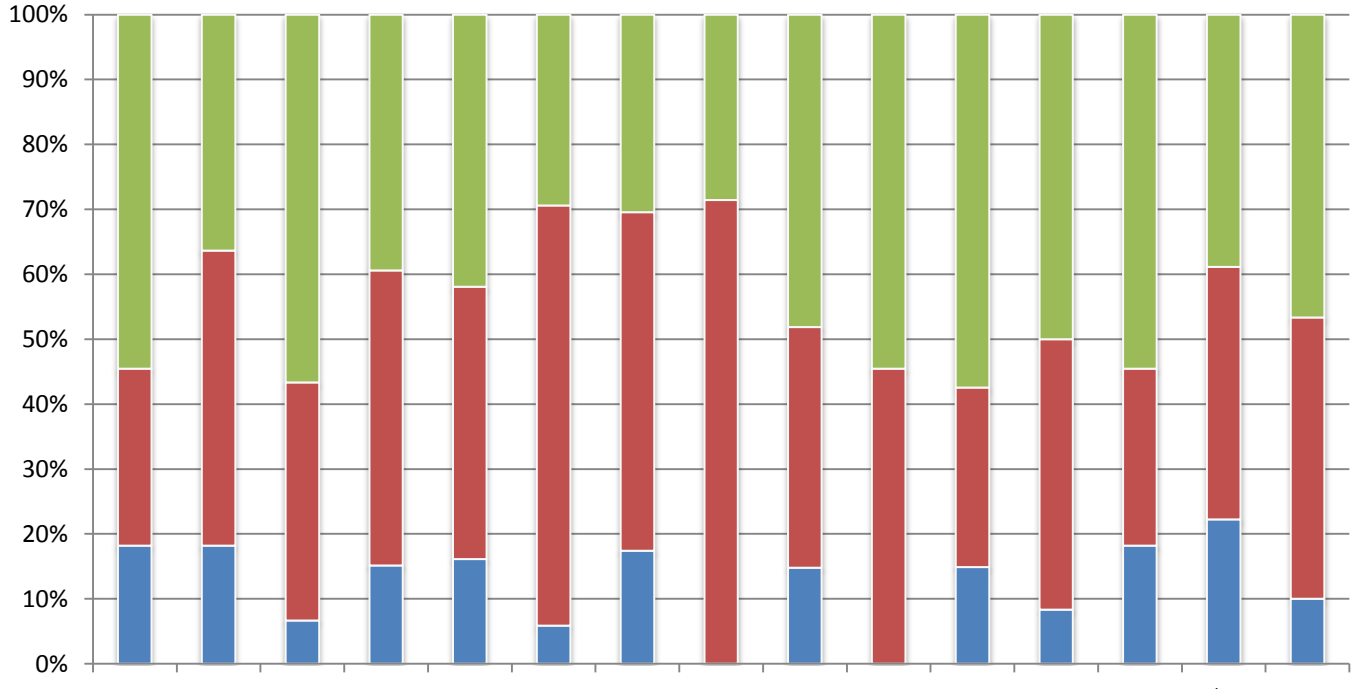
or

Failures at each stage are more likely to be those **without** genetic validation



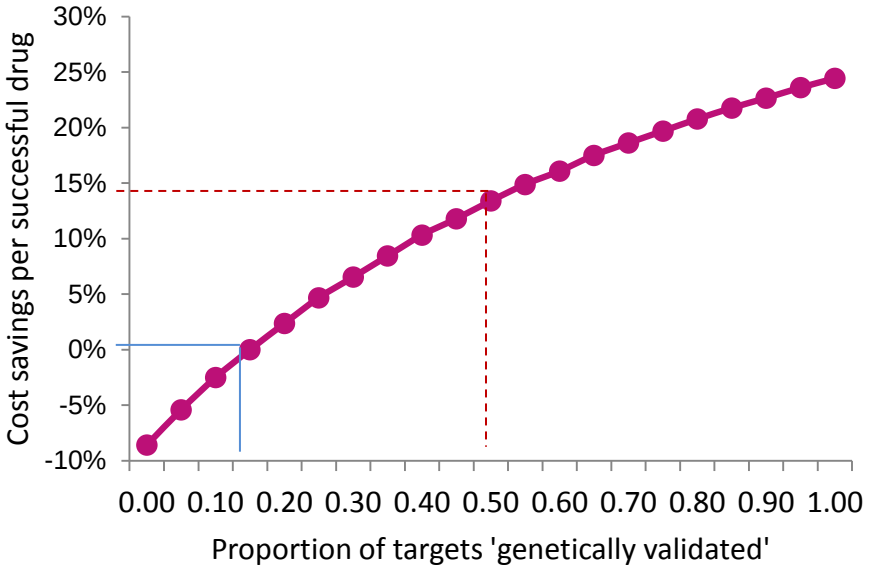
Genetics in clinical studies today

Proportion of new targets with genetic support for **ongoing** or **another** indication



CTTV
Centre for Therapeutic Target Validation

Target validation and cost reduction



10-15% targets have genetic data today

If increase to **50%**, expect **13-15%** cost reduction

If increase to **100%**, expect **25%** cost reduction

Tufts Center for the Study of Drug Development

November 18, 2014

Cost to Develop and Win Marketing Approval for a New Drug Is $2.6 Billion

BOSTON – Nov. 18, 2014 – Developing a new prescription medicine that gains marketing approval, a process often lasting longer than a decade, is estimated to cost $2,558 million, according to a new study by the Tufts Center for the Study of Drug Development.

The $2,558 million figure per approved compound is based on estimated:

- Average out-of-pocket cost of $1,395 million
- Time costs (expected returns that investors forego while a drug is in development) of $1,163 million

The $2.6 Billion Pill — Methodologic and Policy Considerations

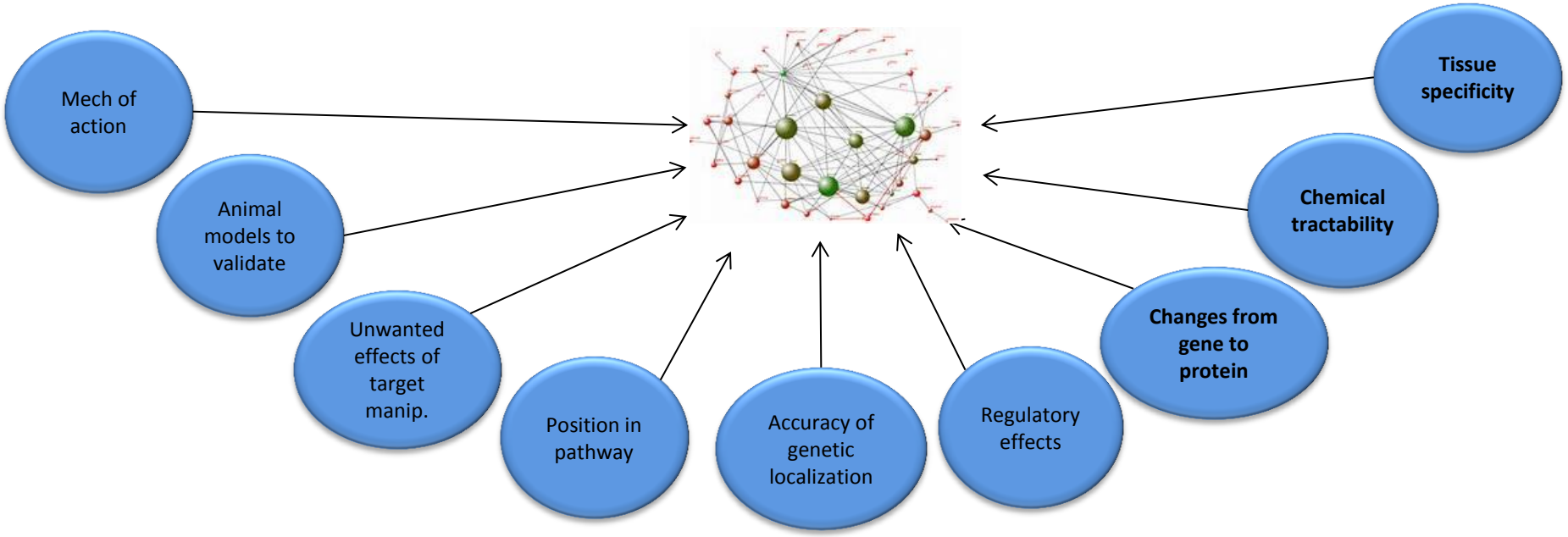
Jerry Avorn, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

Not all genes are targets

…GWAS catalogue is not enough. DNA sequencing is not enough

- Mechanism of action (GoF, LoF, Dom Neg, …)?
- Pleiotropy, generalized vs undesirable effects?
- Druggability? Chemical tractability?
- Predicting drug effect size from lifelong exposure (genetics)?
- Position in pathway?
- Tissue specificity, delivery?

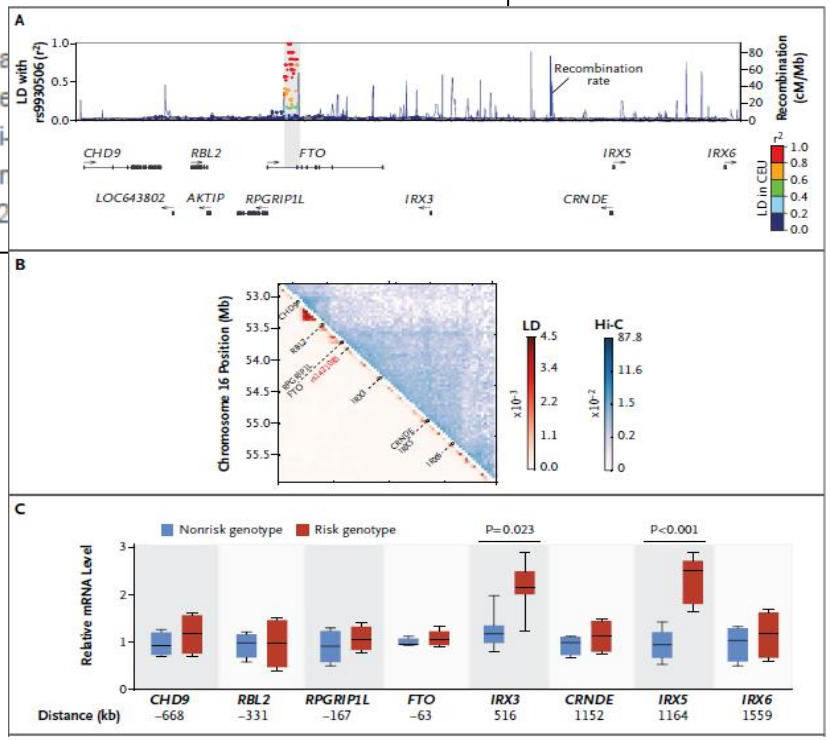


It is not going to be easy

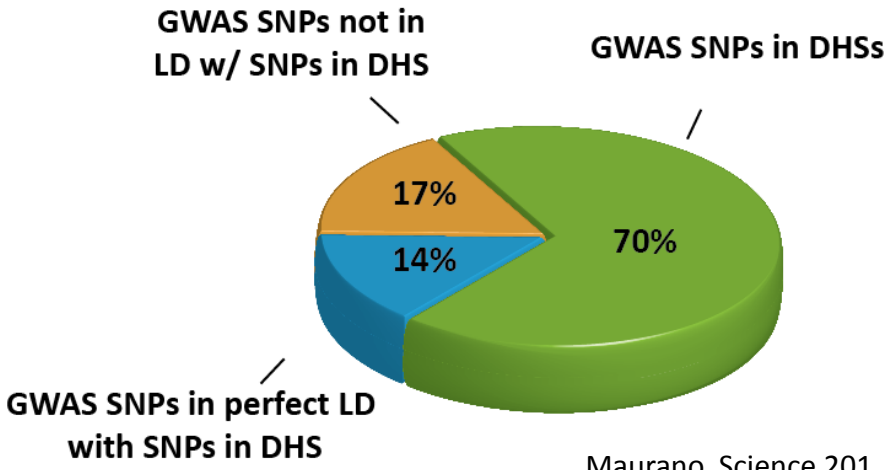
ORIGINAL ARTICLE

FTO Obesity Variant Circuitry and Adipocyte Browning in Humans

Melina Claussnitzer, Ph.D., Simon N. Dankel, Ph.D., Kyoung-Han Kim, Ph.D., Gera
Christine Haugen, M.Sc., Viktoria Glunk, M.Sc., Isabel S. Sousa, M.Sc., Jacqueline
B.Sc., Nezar A. Abdennur, M.Sc., Jannel Liu, B.Sc., Per-Arne Svensson, Ph.D., Yi-
M.D., Gunnar Mellgren, M.D., Ph.D., Chi-Chung Hui, Ph.D., Hans Hauner, M.D., ar
N Engl J Med 2015; 373:895-907 | September 3, 2015 | DOI: 10.1056/NEJMoa1502



…and this may not be the exception



Maurano, Science 201

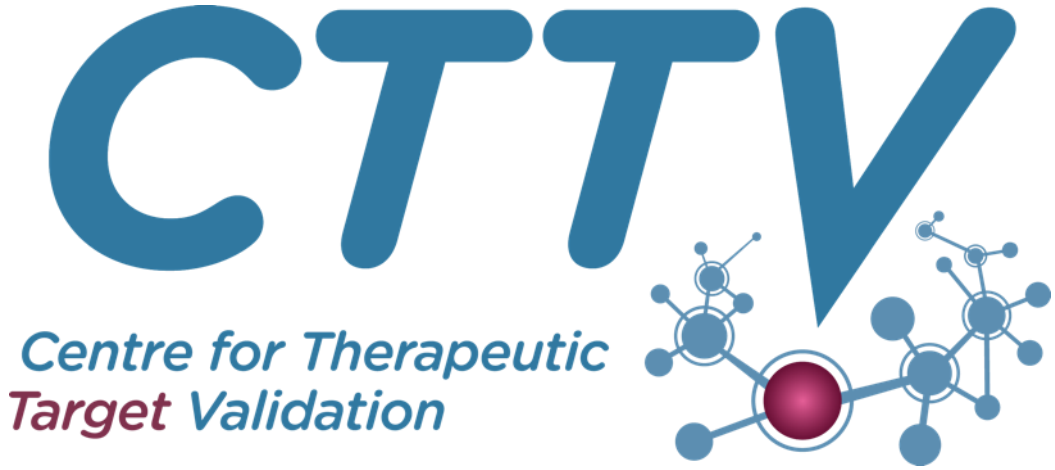
Early observations

Centre for Therapeutic Target Validation

1. **Genetics** yielding actionable findings for translation

2. **Complexity** is increasing, leading to more specialization
   - Biology & genetics becoming 'big data' problem.
   - Drug discovery evolving from previous comfort-zone of approaches
   - Separation of basic sciences and translation remains large, possibly *worsening* ("valley of death")

3. Targets themselves can be **Pre-Competitive**



Comprehensive, robust data integration
Responsive, dynamic human cellular experiments
A pioneering partnership

www.targetvalidation.org

CTTV
Centre for Therapeutic Target Validation

- **Premise**: no single entity, *public or private*, has all of the skills to fully exploit the information emerging
- Consortium of 3 founders, **computational, experimental, translational**

EMBL-EBI wellcome trust sanger institute gsk GlaxoSmithKline

- Formal agreement to **share findings openly**
- Pooling of expertise
  - Joint approach, joint expertise, pre-competitive
  - Enable a new generation of translational scientists

CTTV
Centre for Therapeutic Target Validation

- Key promi… …l of …lay
- …es

Biogen Joins Pioneering Target Validation Collaboration

The Centre for Therapeutic Target Validation Welcomes New Member Biogen, Expanding Its Efforts to Accelerate Drug Discovery Research

Category:
Autoimmune diseases, Collaborations, Corporate, Neurodegenerative diseases, Rare and Genetic diseases

Monday, February 8, 2016 7:00 am EST

GlaxoSmithKline

wellcome trust sanger institute

- State of art **experimental** and **computational** approaches previously not fully deployed for translation
- Formal agreement to **share findings openly**
- Pooling of expertise
  - Joint approach, joint expertise.
  - Train a new generation of translational scientists

Target Validation is one piece of puzzle.

Current paradigm:

(Im-)Precision Medicine Development

Variable target evidence
- 'Hunch'
- Mechanistic hypothesis
- …
- Previously drugged

Traditional translation to clinic
- Tenuous animal models
- Intermediate endpoints
- Limited tox understanding
- High attrition rate

Clinical trials
- Small number doses
- Ph III clinical endpoints don't match models or Ph I/II endpoints
- Little sample stratification

Missing the link from (new) phenotypes to (better) targets

A New Initiative on Precision Medicine

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

THE PRECISION MEDICINE INITIATIVE

State of the Union
Jan 2015

Feb 2016

To enable a new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized care.

PMI for Oncology
PMI Cohort Program

Key principles around privacy & trust:
Governance, transparency, participant empowerment, data access & sharing

Focus on the individual