Robert Engelmore Memorial Lecture

Cancer: A Computational Disease That AI Can Cure

Jay M. Tenenbaum
CEO and Chief Scientist
CollabRx

KSL Legacy in AI and Biomedicine

Russ Altman
Bruce Buchanan
Ed Feigenbaum
Peter Friedland
Peggy Karp
Josh Lederberg
Mark Musen
Tom Rindfleisch
Ted Shortliffe
Mark Stefik

Molgen
Mycin
Oncocin
PharmGKB
Protege

Blackboard systems
Rule-based systems
Probabilistic methods

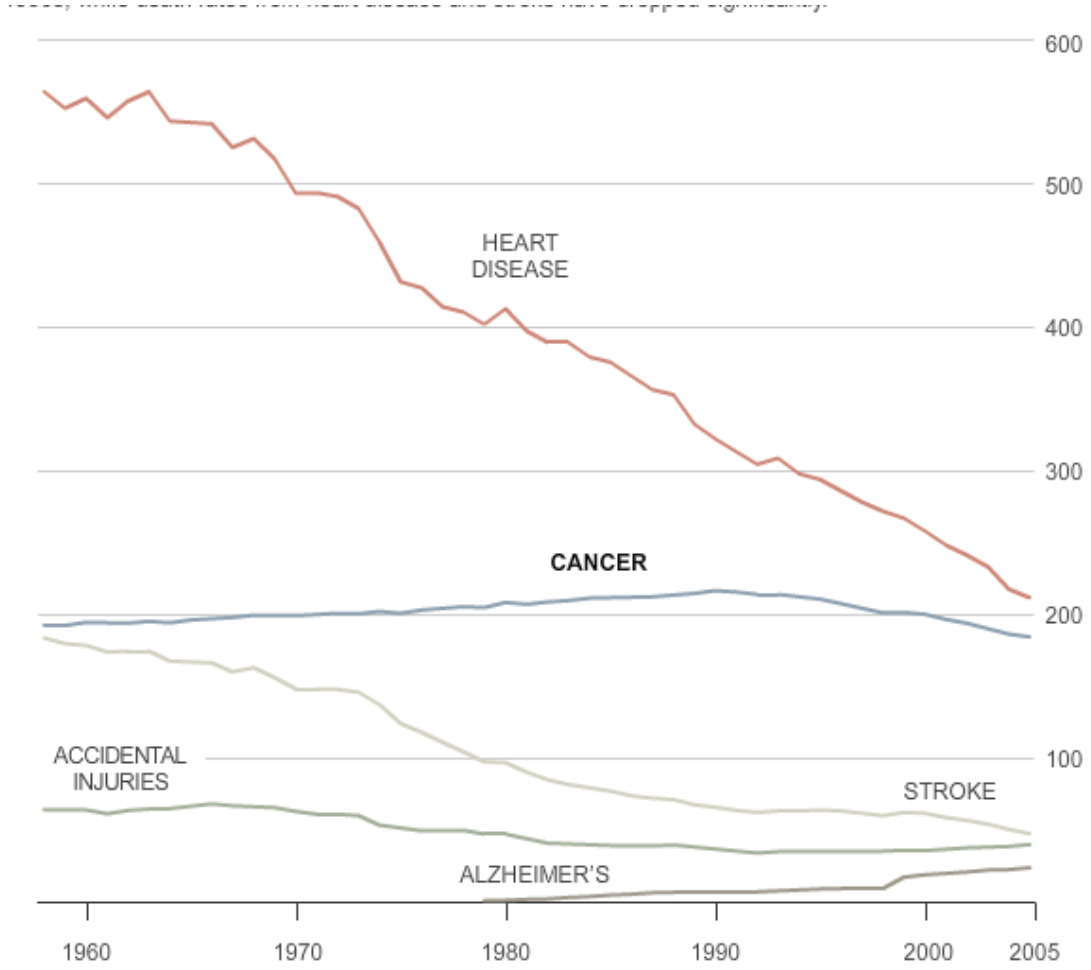
Stanford Medical Informatics Lab

Center for Biomedical Informatics Research

Outline

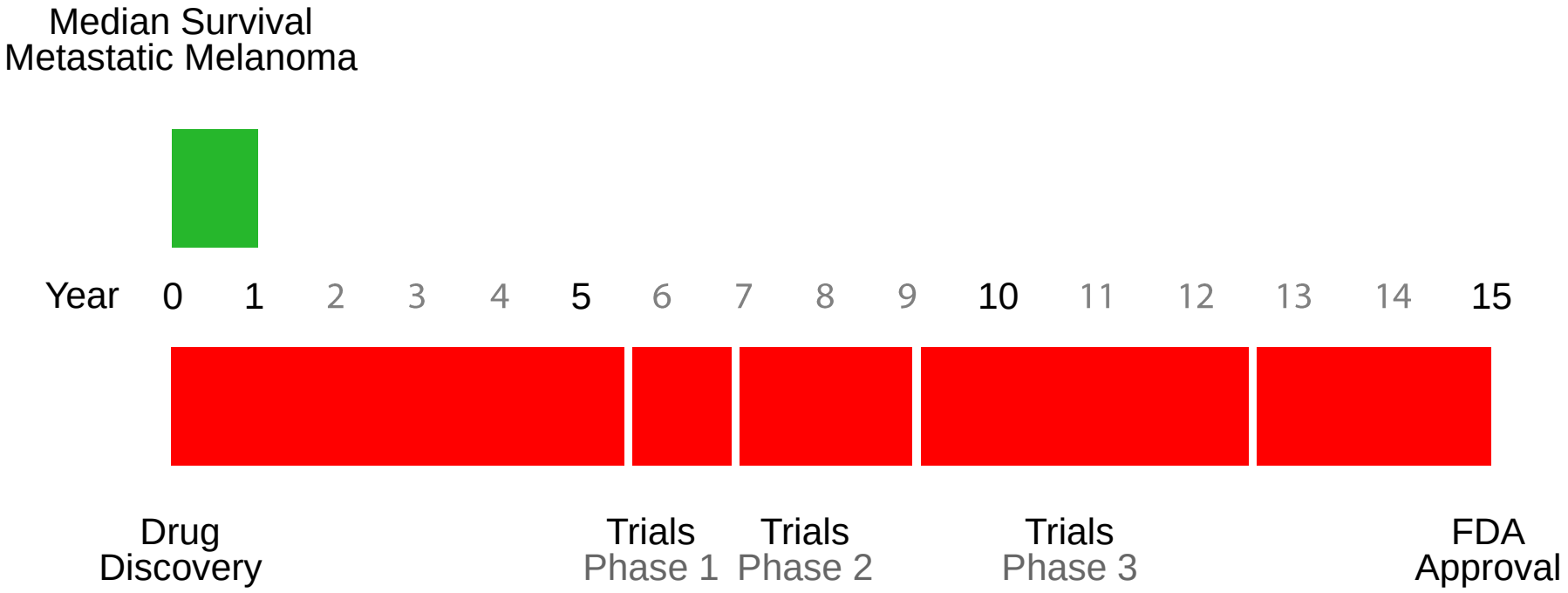
- Cancer – The Forty Years' War
- A new "N-of-1" paradigm
  - CollabRx ONE
  - Cancer Commons
- AI opportunities and challenges

The Forty Years' War



Age-adjusted death rates per 100,000 standard population **Source: NY Times**

Time's Up


Median Survival
Metastatic Melanoma
Year
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
Drug
Discovery
Trials
Phase 1
Trials
Phase 2
Trials
Phase 3
FDA
Approval

The McGraw-Hill Companies

BusinessWeek

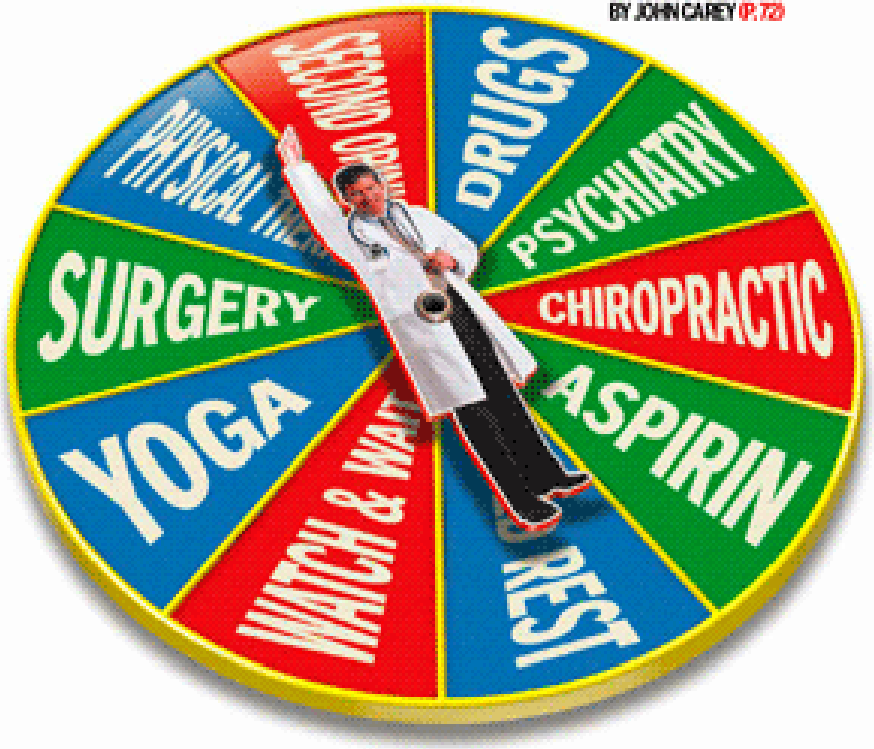
MAY 24, 2004

www.businessweek.com

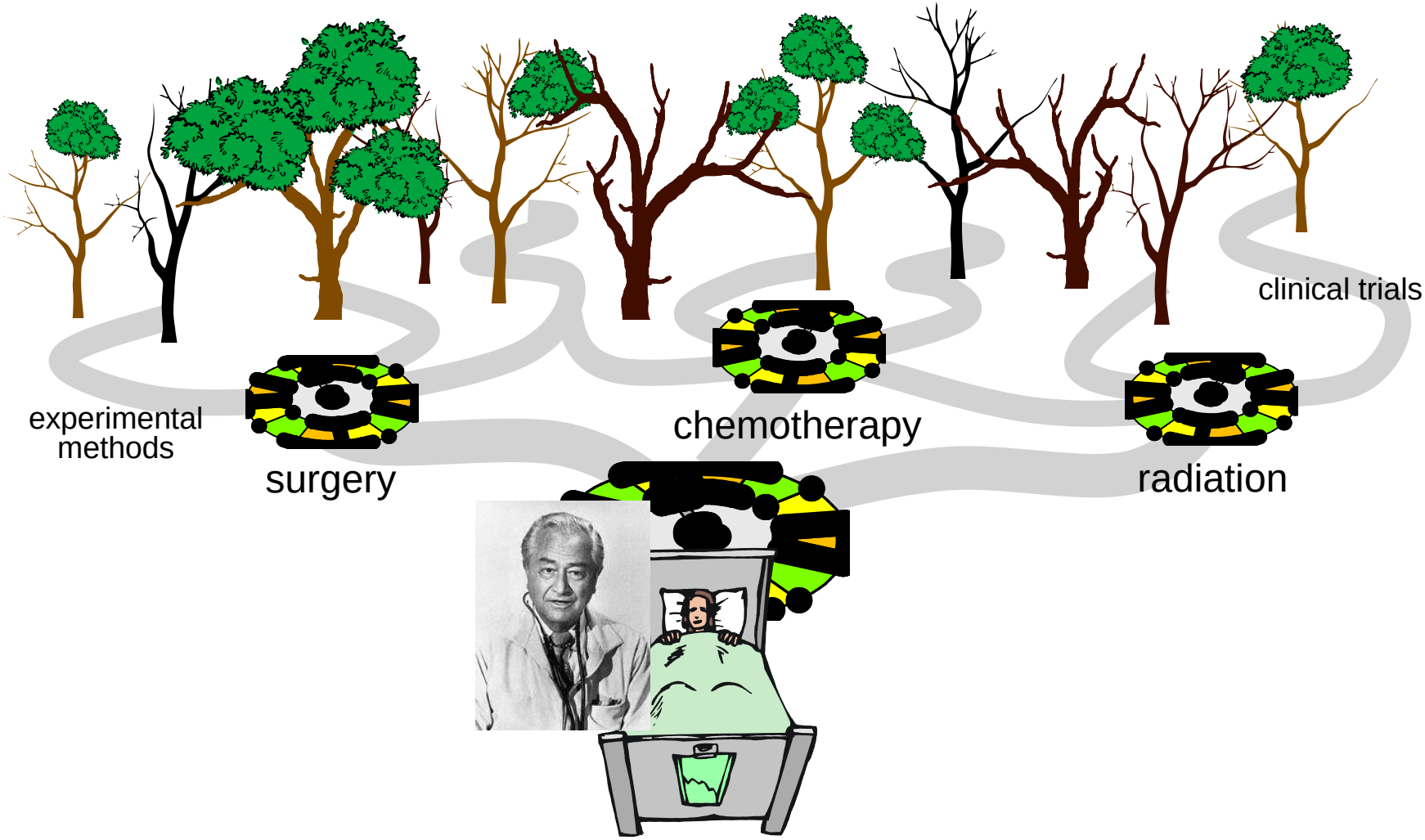
Medical Guesswork

From heart surgery to prostate care, the medical industry knows little about which treatments really work

BY JOHN CAREY (P. 72)



The Problem


clinical trials
experimental methods
surgery
chemotherapy
radiation

The New York Times

Cancer 'Vaccine' Is Set Back as Treatment Fails in Trial

By ANDREW POLLACK and TOM WRIGHT

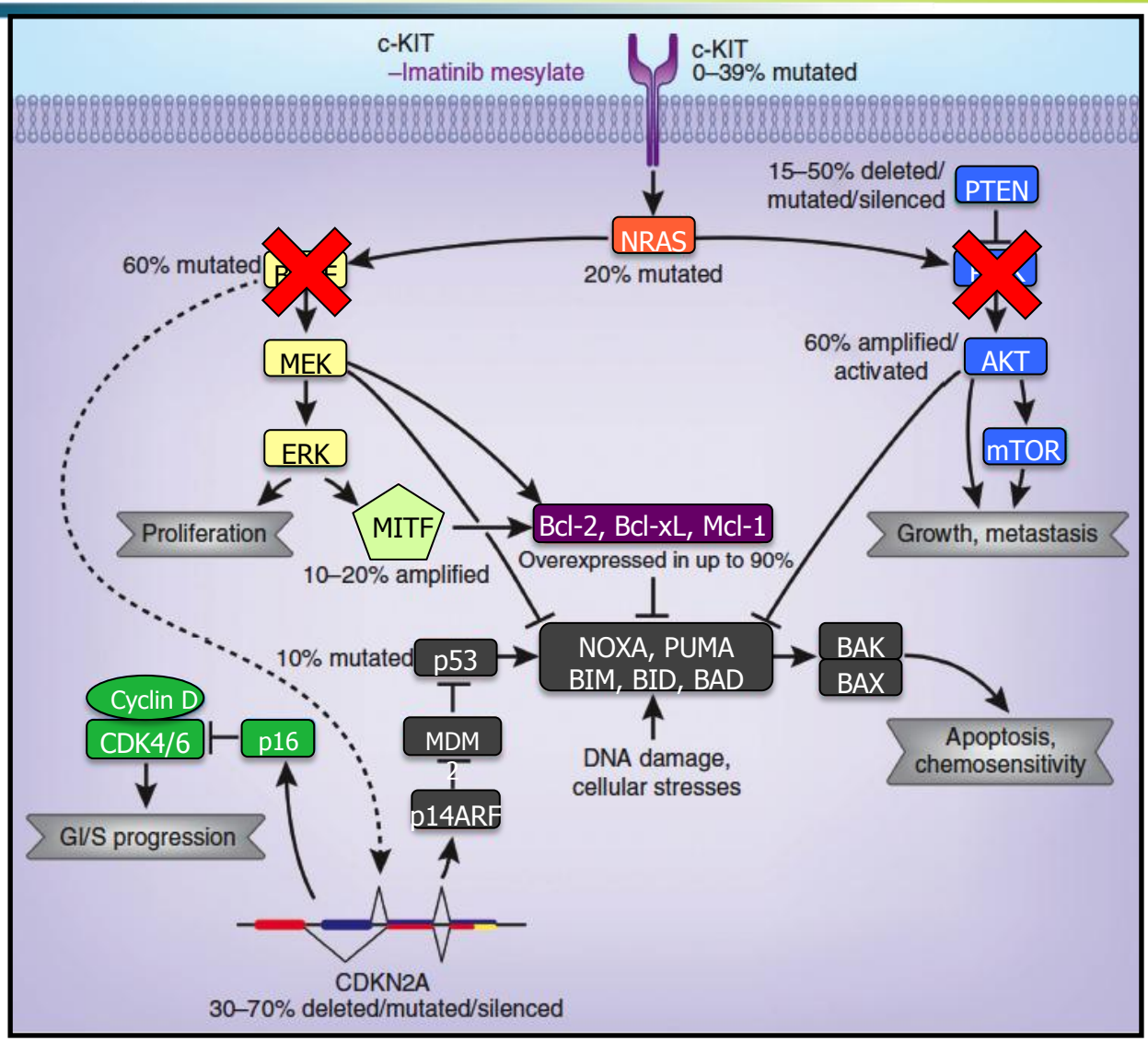
Published: April 7, 2005

LOS ANGELES, April 6 - A cancer treatment that has been under development for more than 40 years failed in the first clinical trial in which it was compared with a placebo. The failure, announced Wednesday, was a blow to the field of so-called cancer vaccines and to the two companies developing the treatment, Serono and CancerVax.

The Trouble With Trials

- Based on population statistics vs. individual response
- Results may not apply to a given individual
- Accepts marginal drugs and rejects good ones
- Goal of testing a drug raises ethical issues and minimizes learning

Cancer In The Genomics Age



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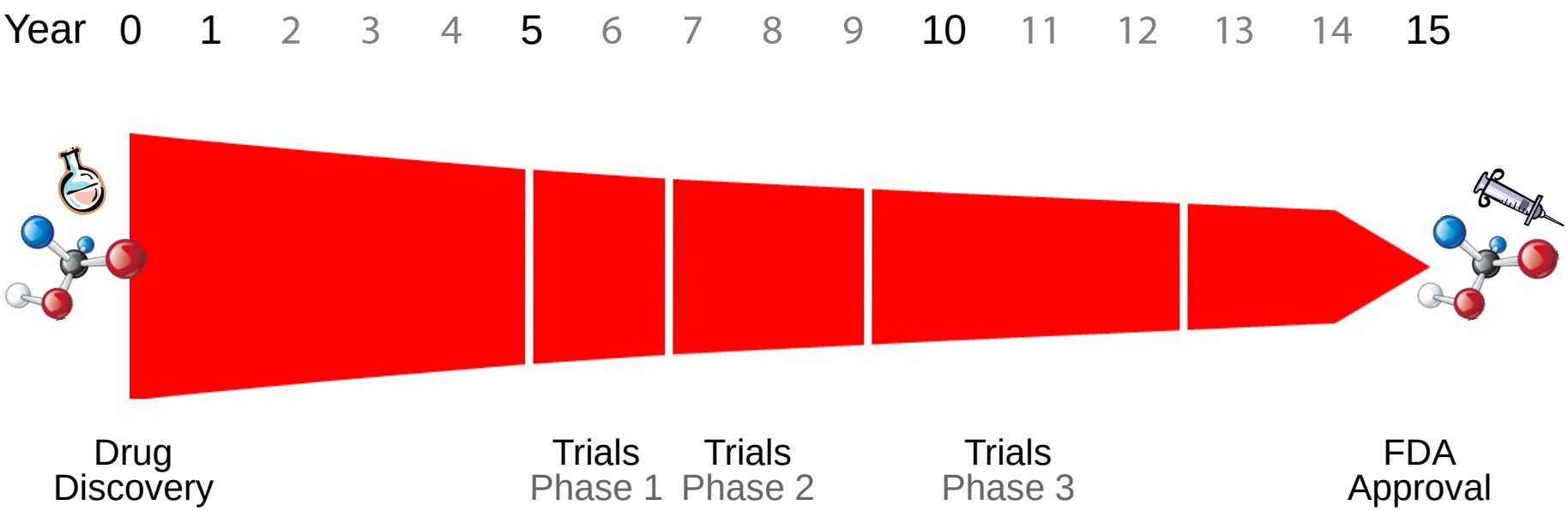
  - CollabRx ONE
  - Cancer Commons
- AI opportunities and challenges

The Opportunity

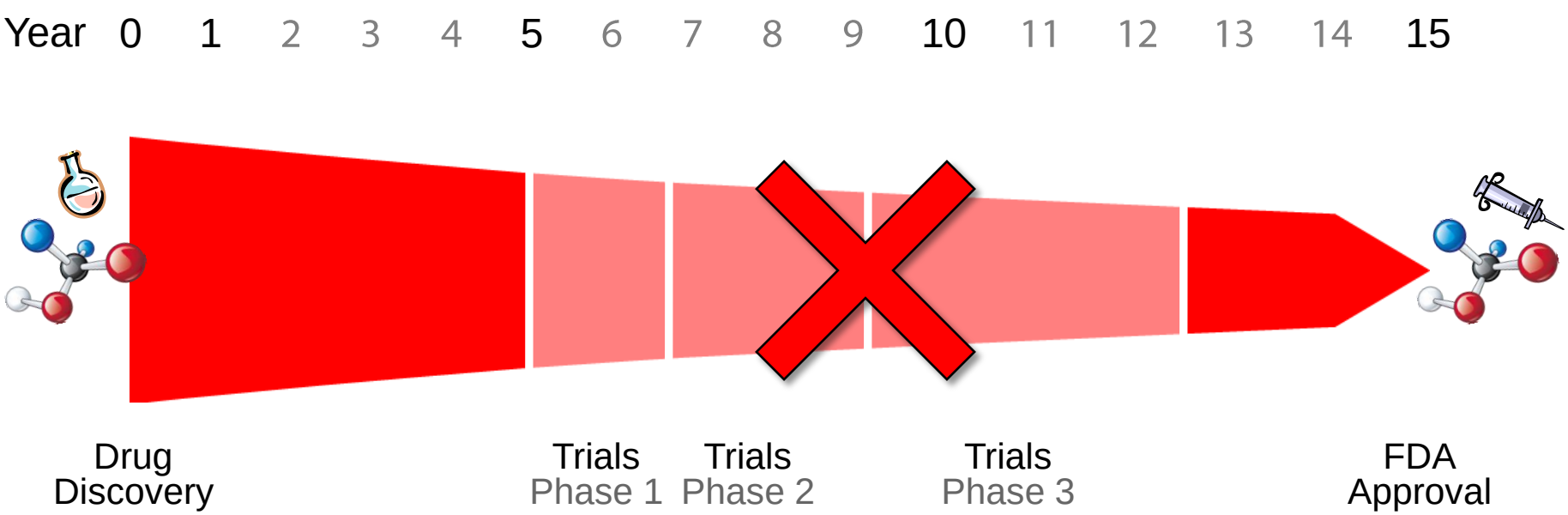
Use genomics, computational / systems biology and the Internet to:

- **Integrate** the worlds of cancer care and research
- **Personalize treatments** based on the most up to date data and knowledge
- **Aggregate the learnings** to rapidly improve the standard of care

15 Years To 3 Months

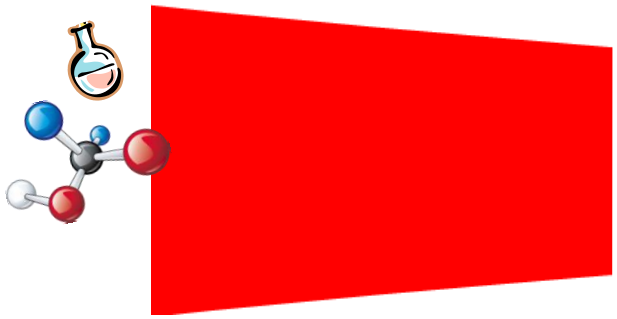


Replace Large Trials With…

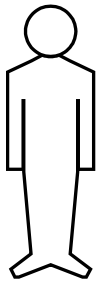


An N-of-1 Trial

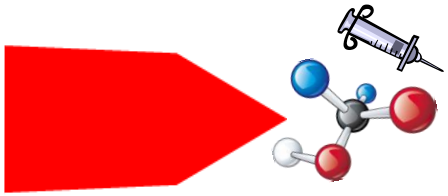
Year 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15



Drug Discovery



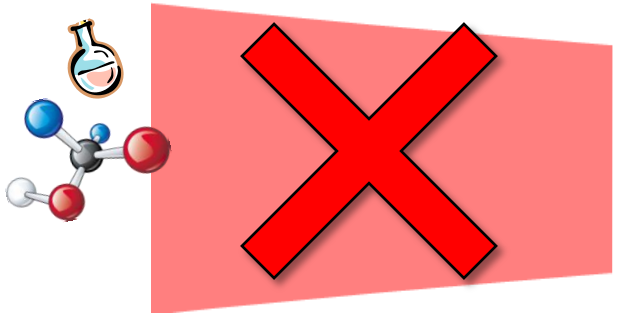
Causal Modeling



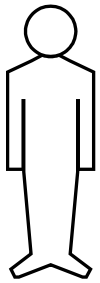
FDA Approval

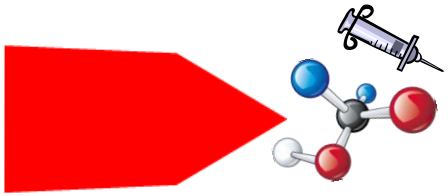
Replace Discovery With…

Year 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15



Drug Discovery

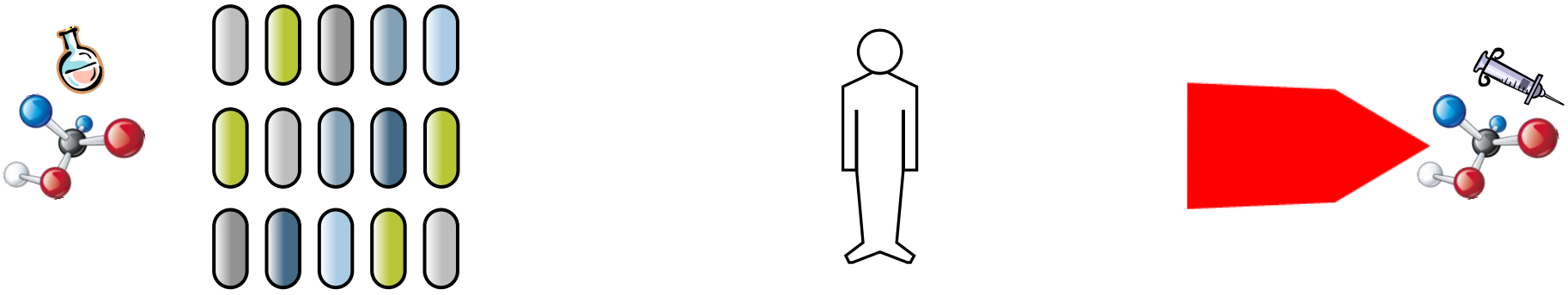




FDA Approval

All Approved + Investigational Drugs

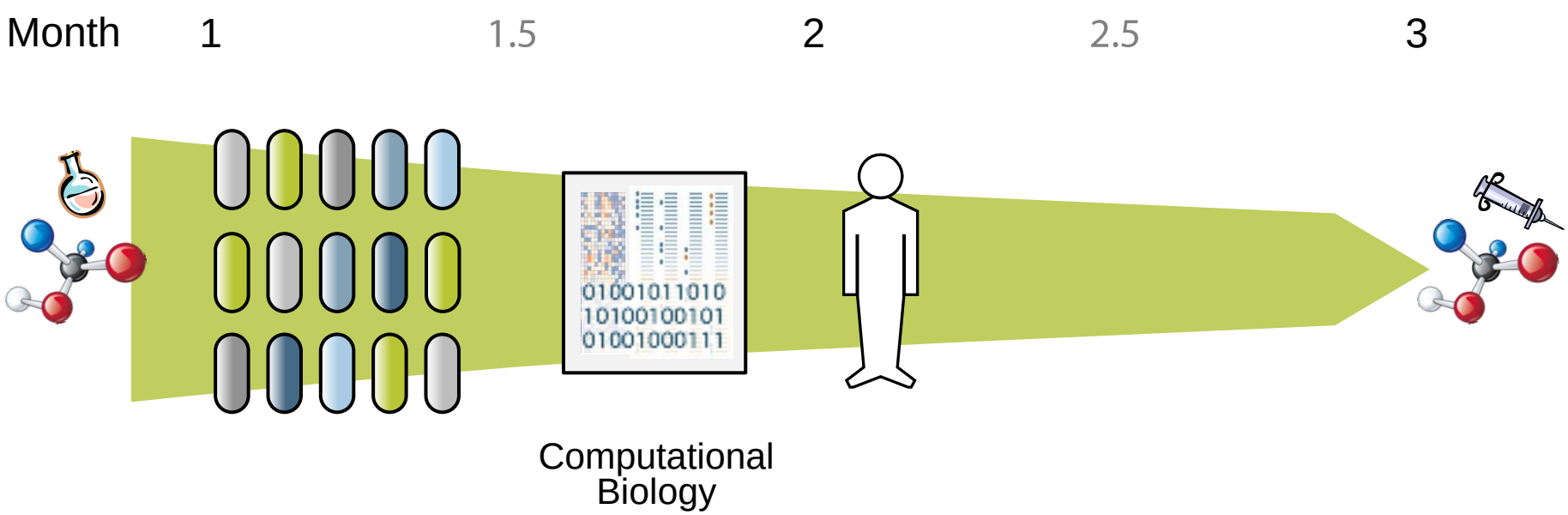
Year 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15



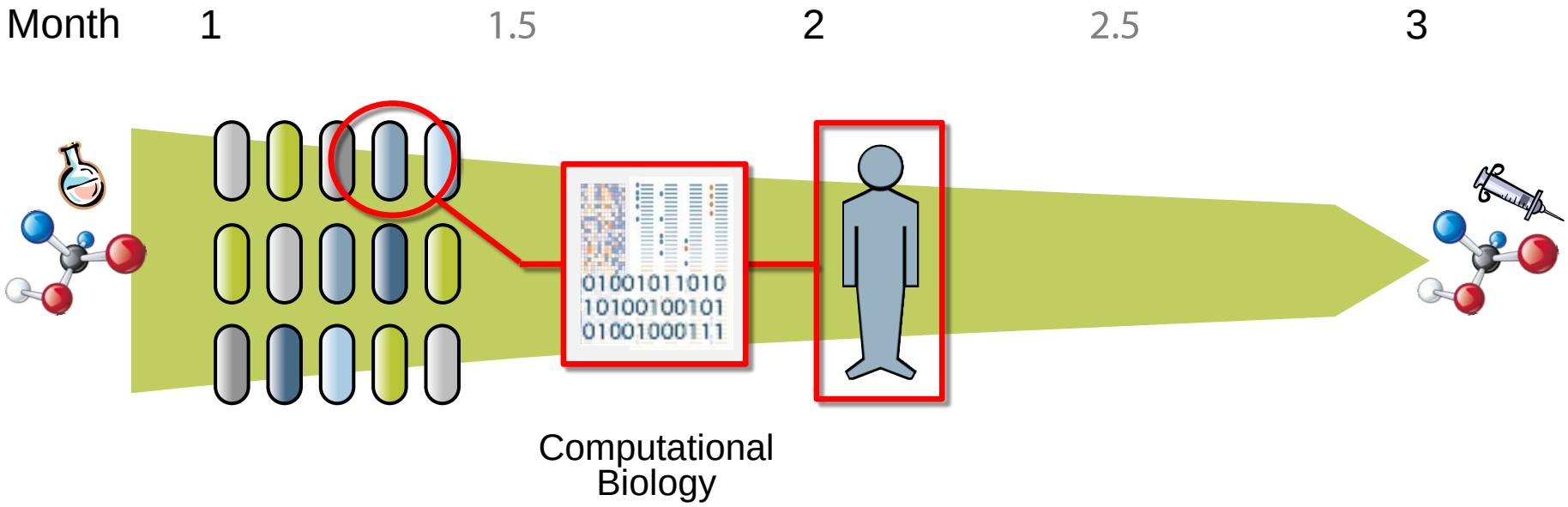
Drug Discovery

FDA Approval

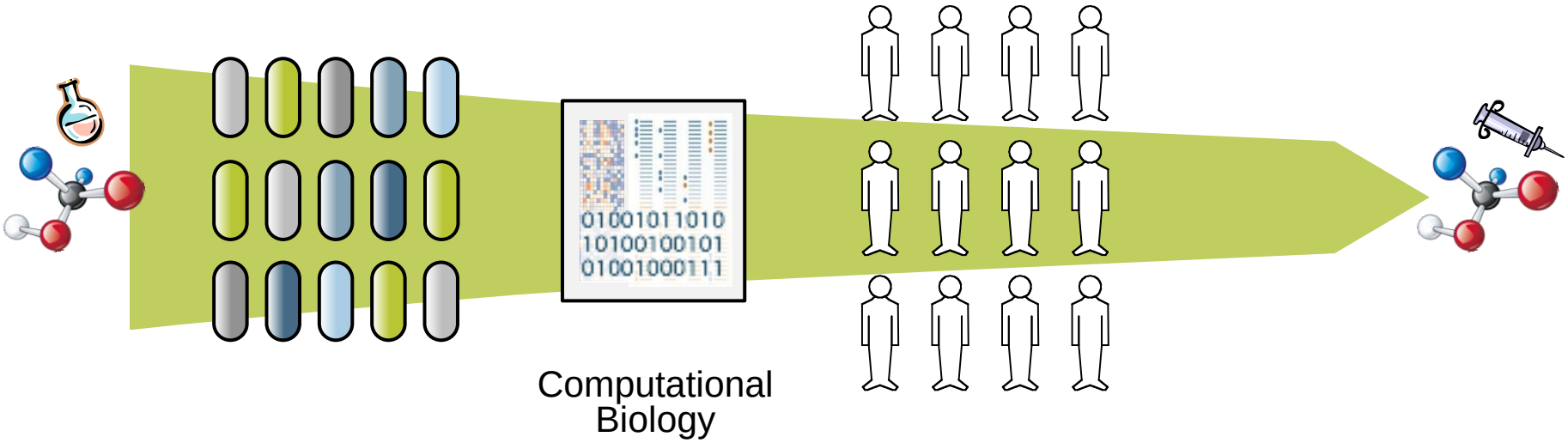
Years To Months



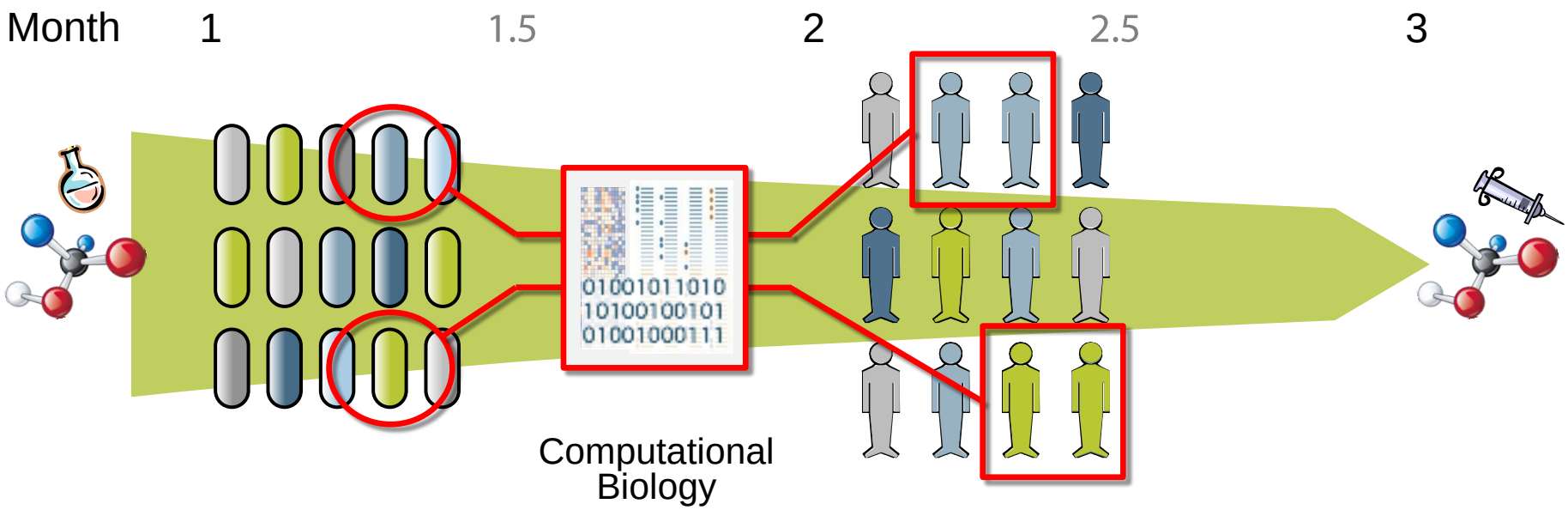
Years To Months



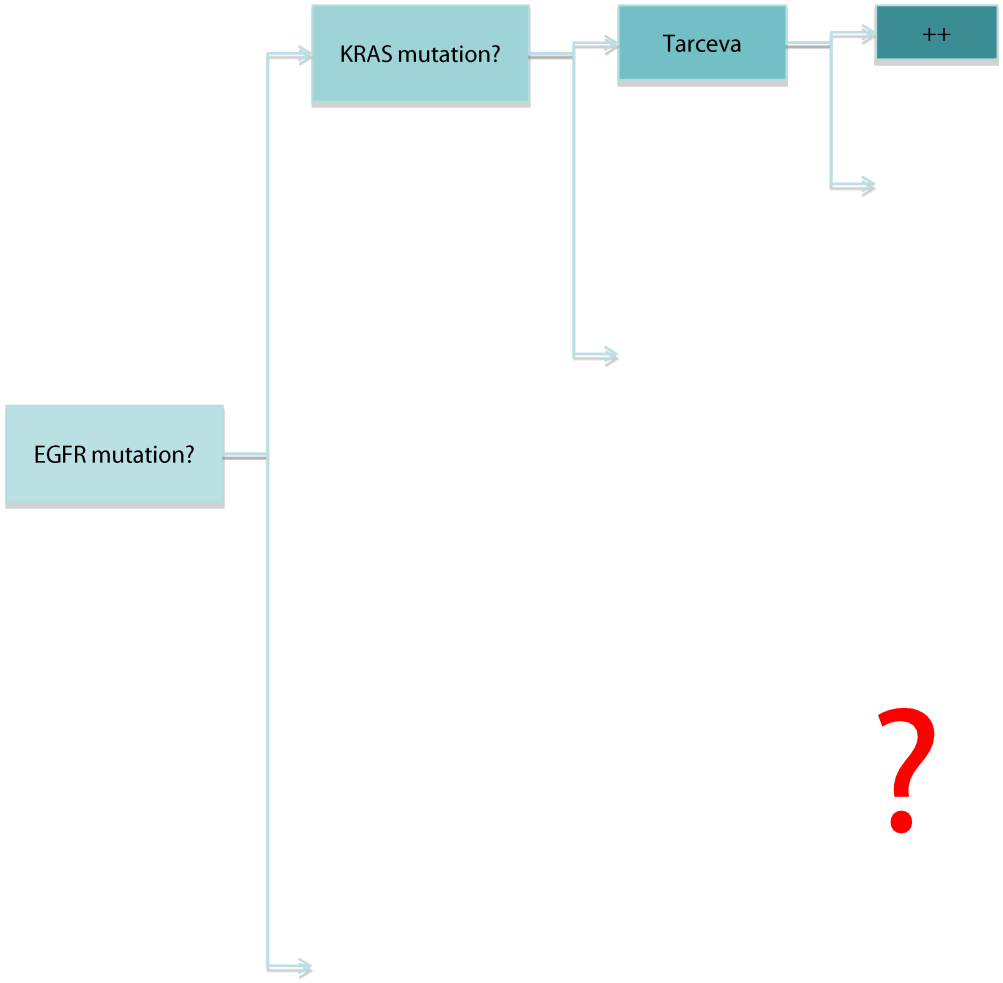
Drive Discovery By Aggregation



Therapies For Sub-Types



Emerging Model Of Therapy Identification (lung)



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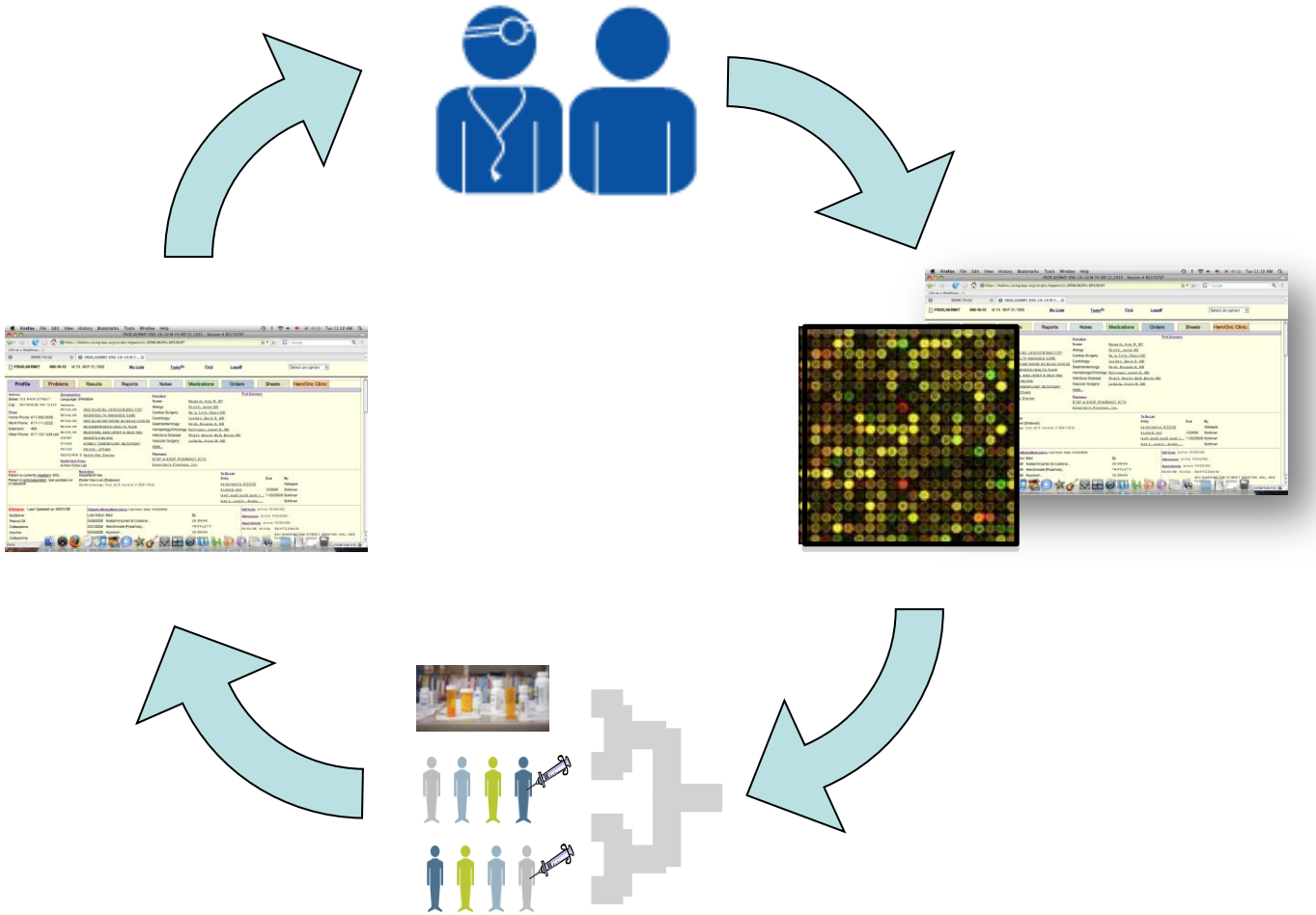
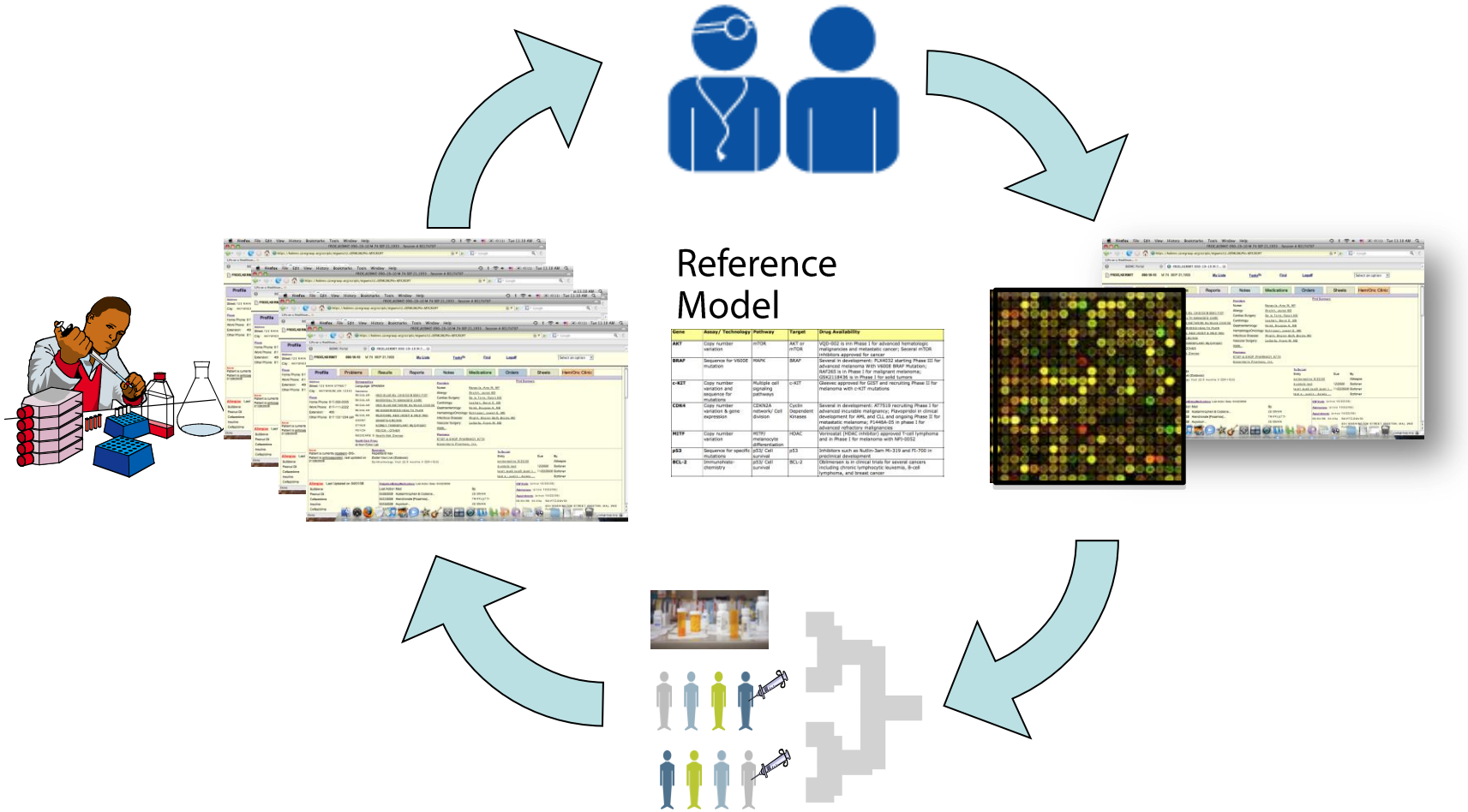
CollabRx ONE



CollabRx ONE



Melanoma Reference Model

1	MAPK
2	NRAS
3	MITF
4	PI3K
5	CDK
6	c-KIT
7	Bcl-2
8 8	MAPK/ PI3K
9 9	MAPK/ CDK
10 10 10	NRAS/ MAPK/ PI3K

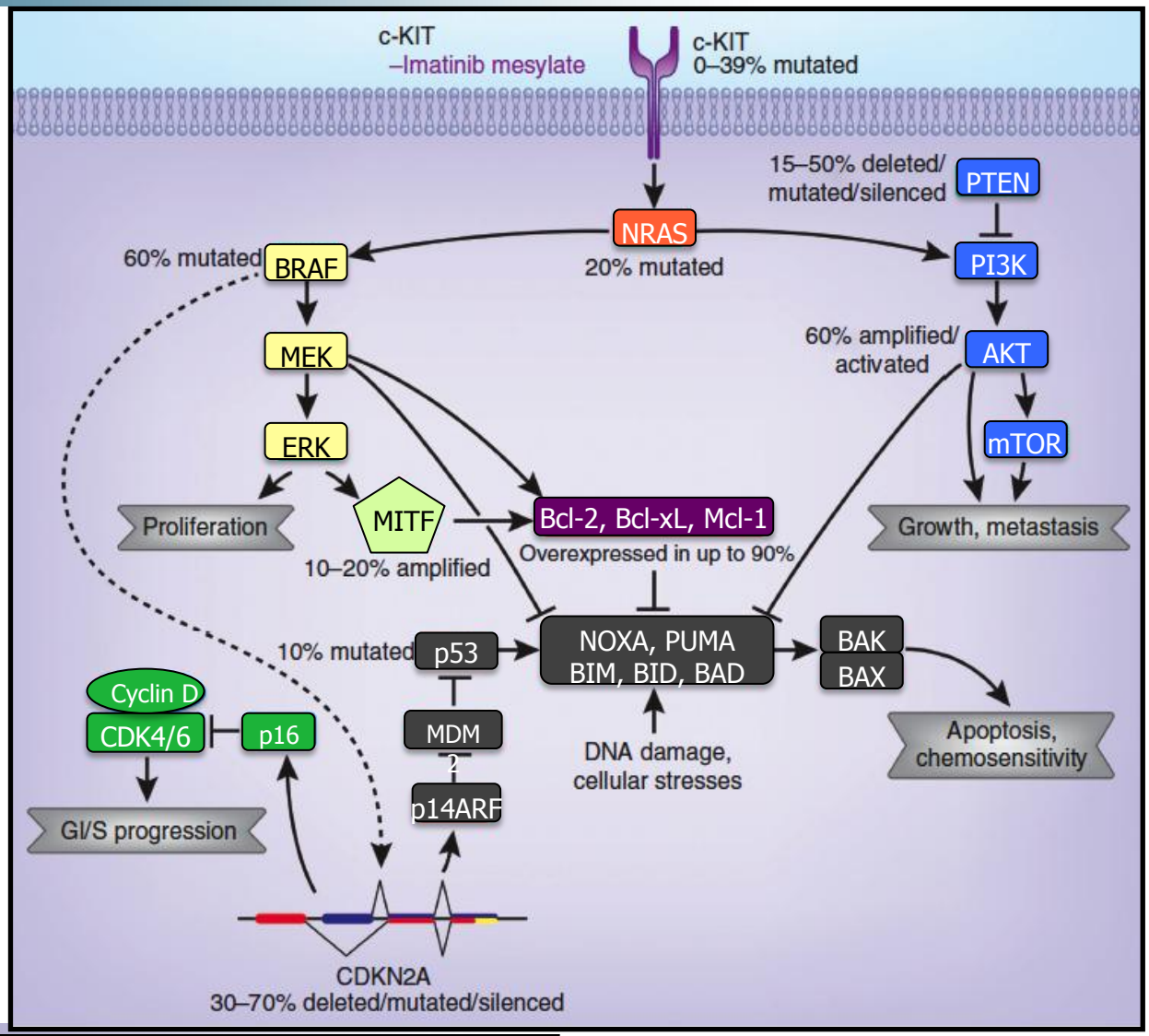


Figure FROM: J Invest Dermatol. 2008 Nov;128(11):2575-95.
Melanoma genetics and therapeutic approaches in the 21st century: moving from the benchside to the bedside.
Hocker TL, Singh MK, Tsao H.

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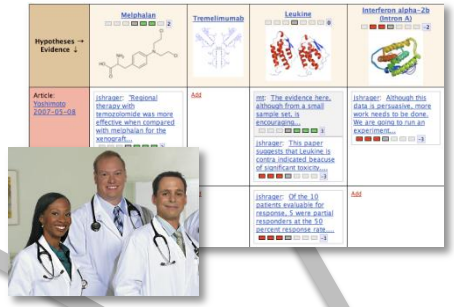
Cancer Commons: Rapid Learning Community

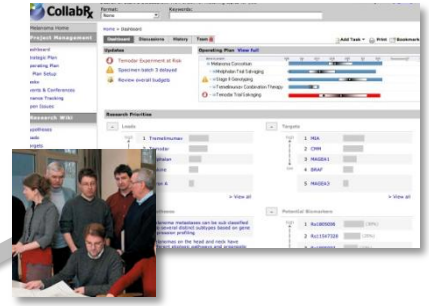
Biologists

Clinical Researchers

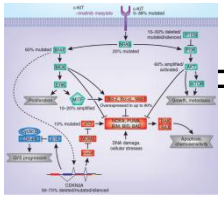
Physicians

Patients





CollabRx Platform

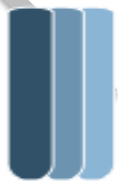


Reference Models

Specimens

Genomics

in silico

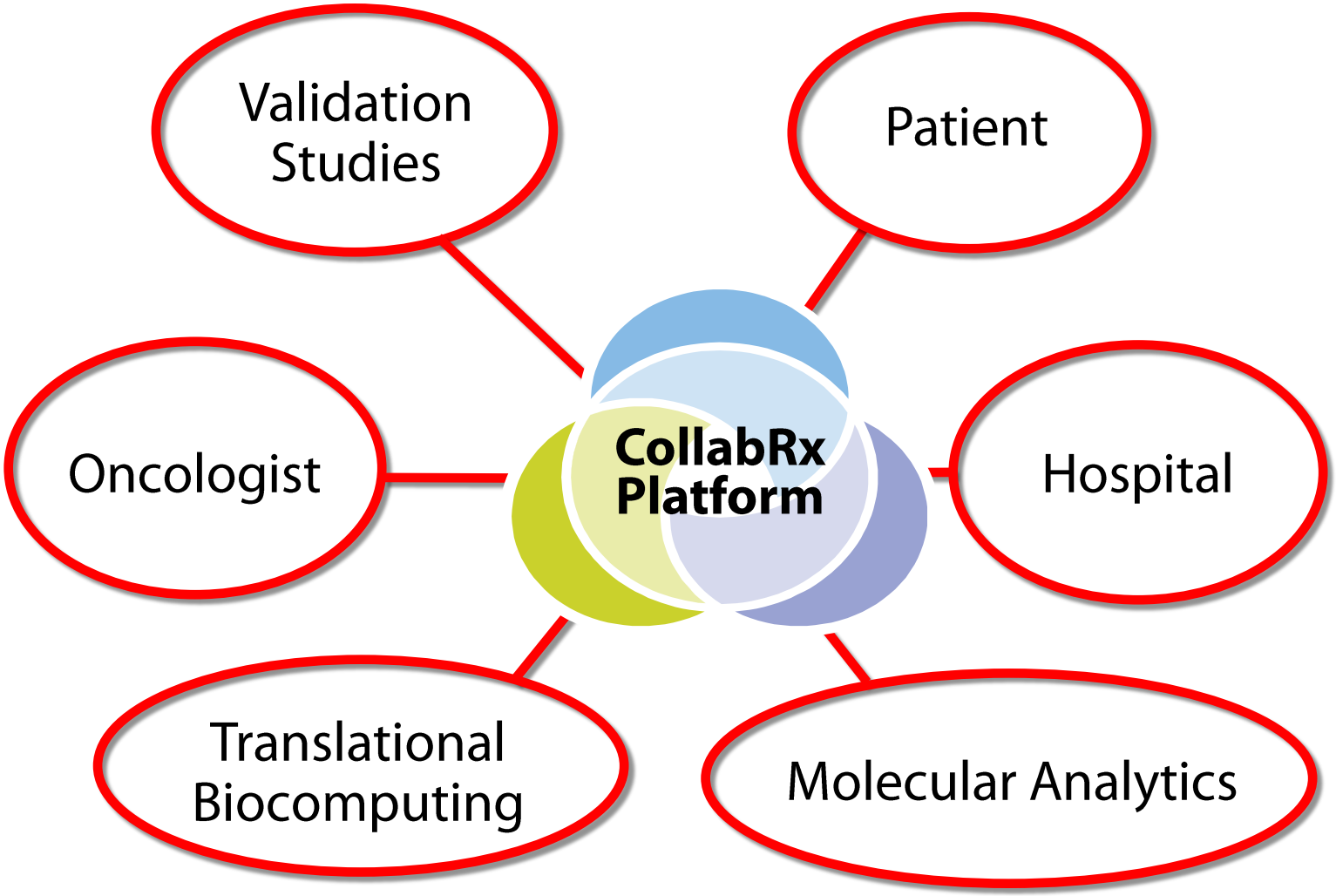


in vitro

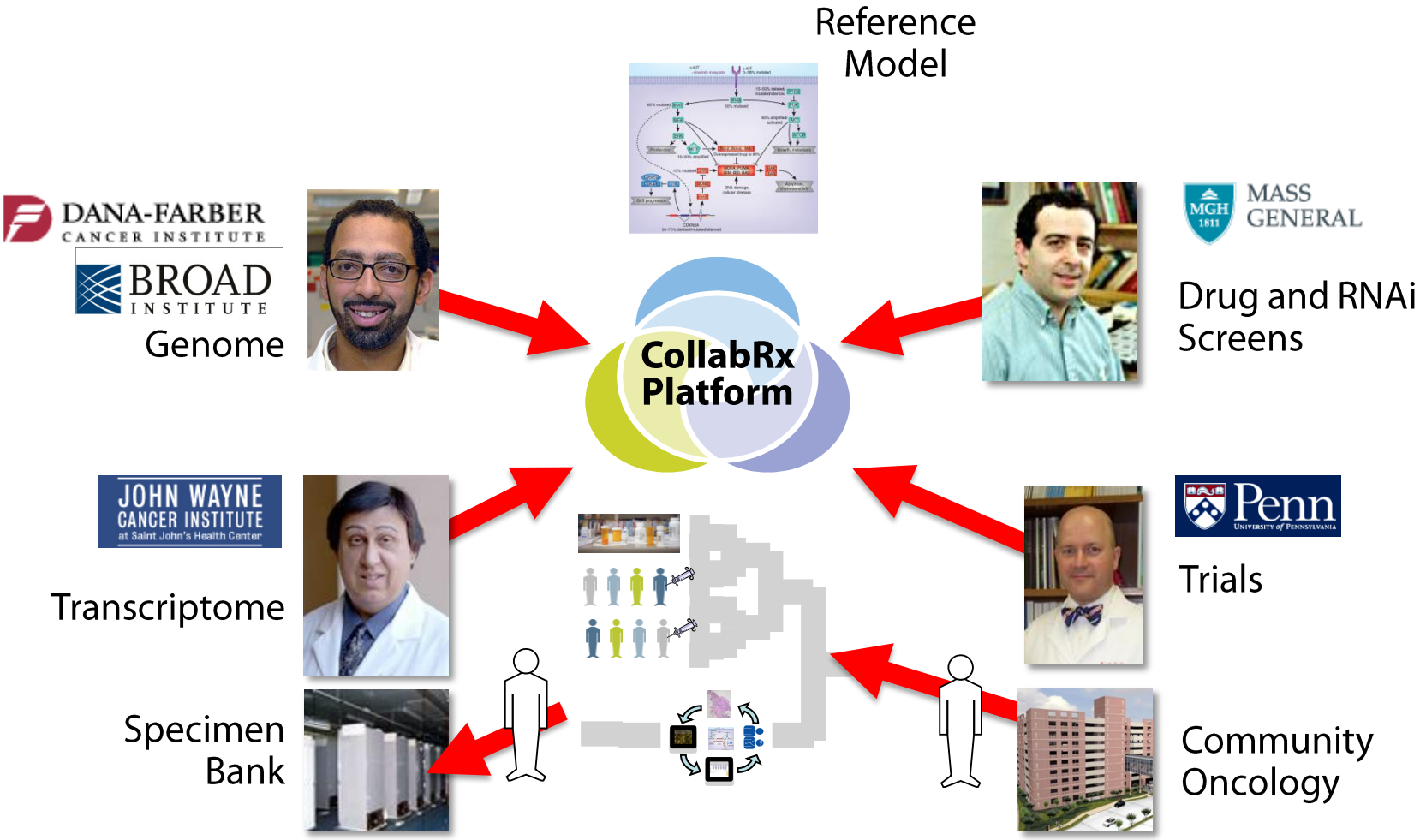
in vivo

in patient

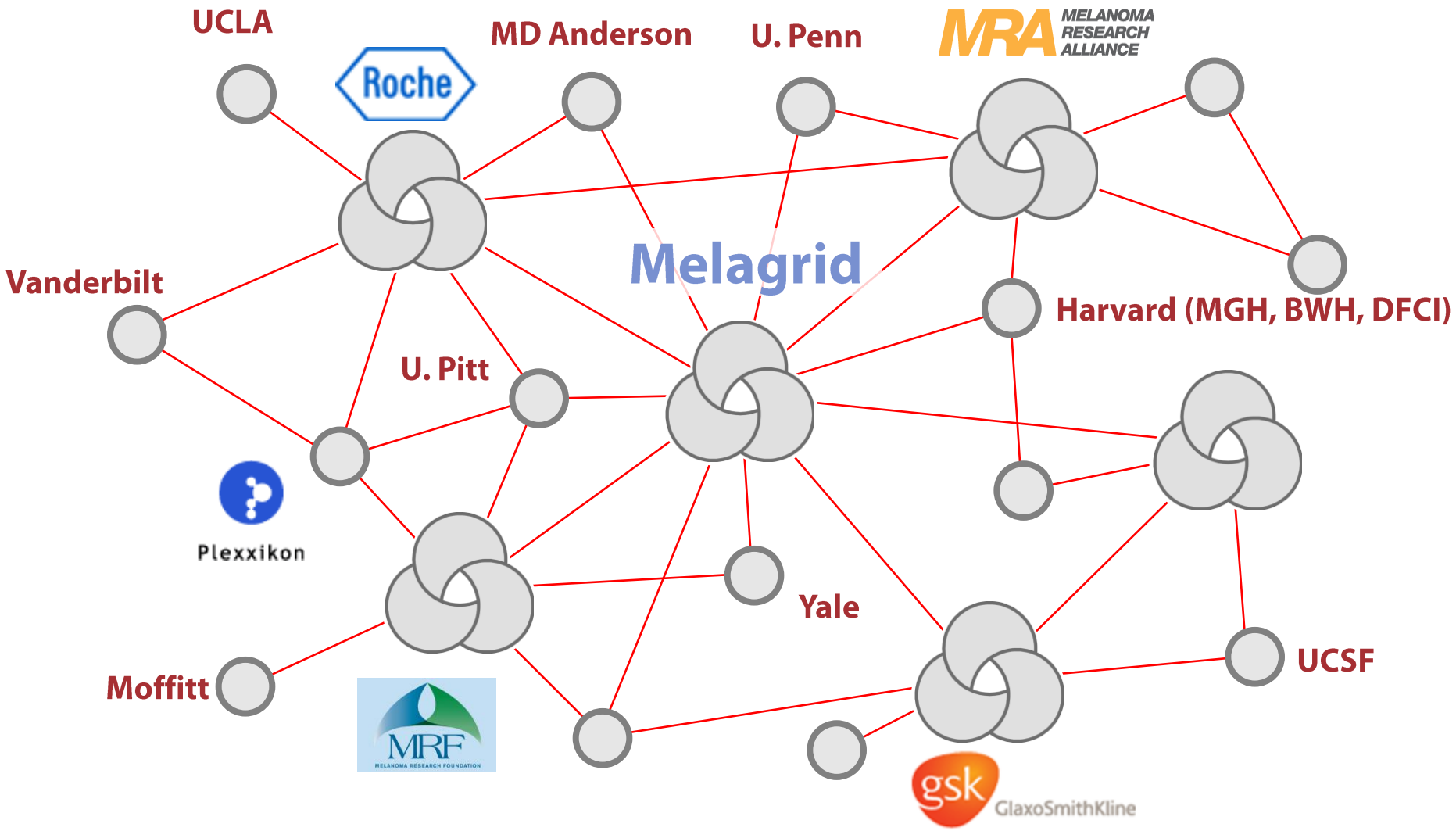
CollabRx ONE Application



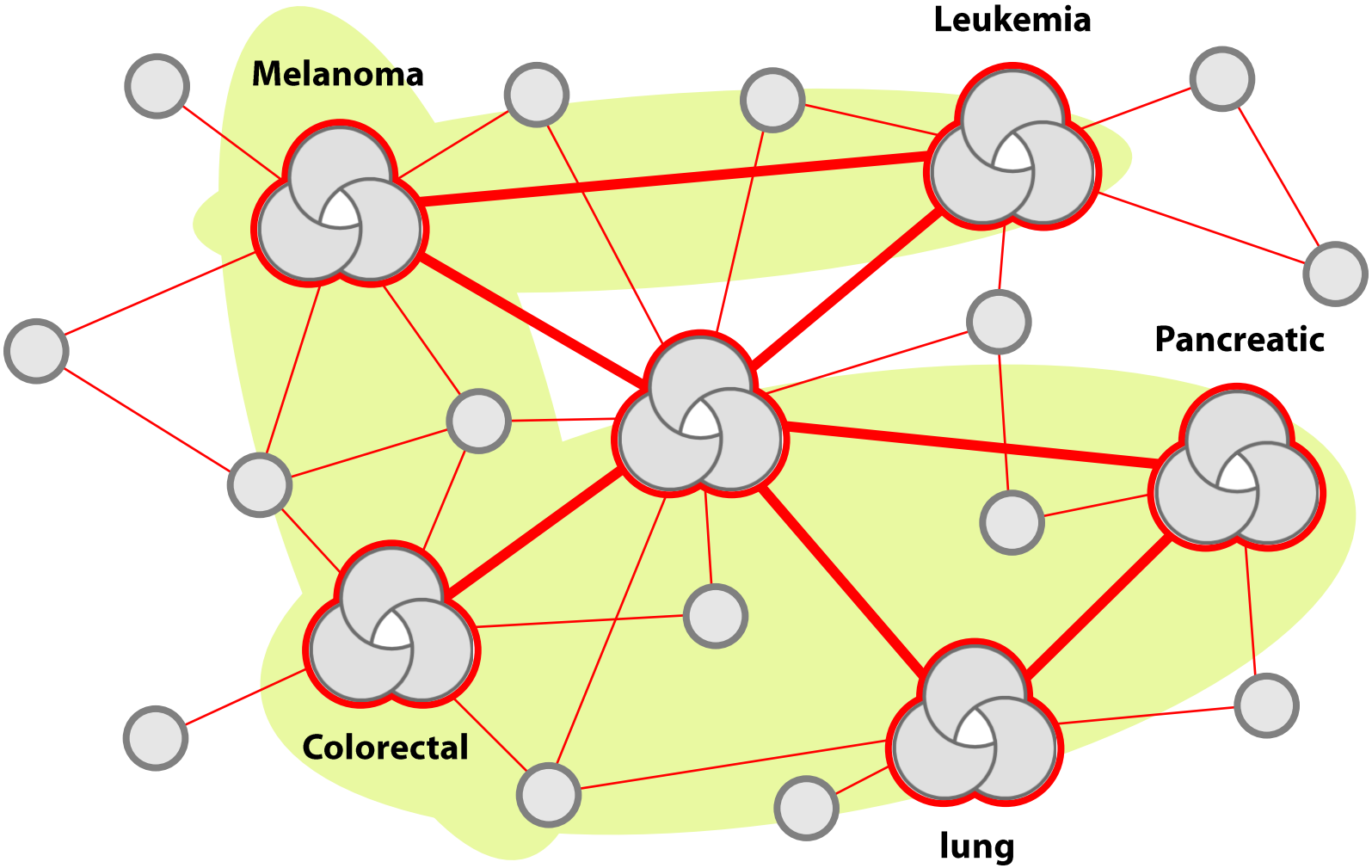
Melanoma Research Alliance



Melanoma Commons



Cancer Commons



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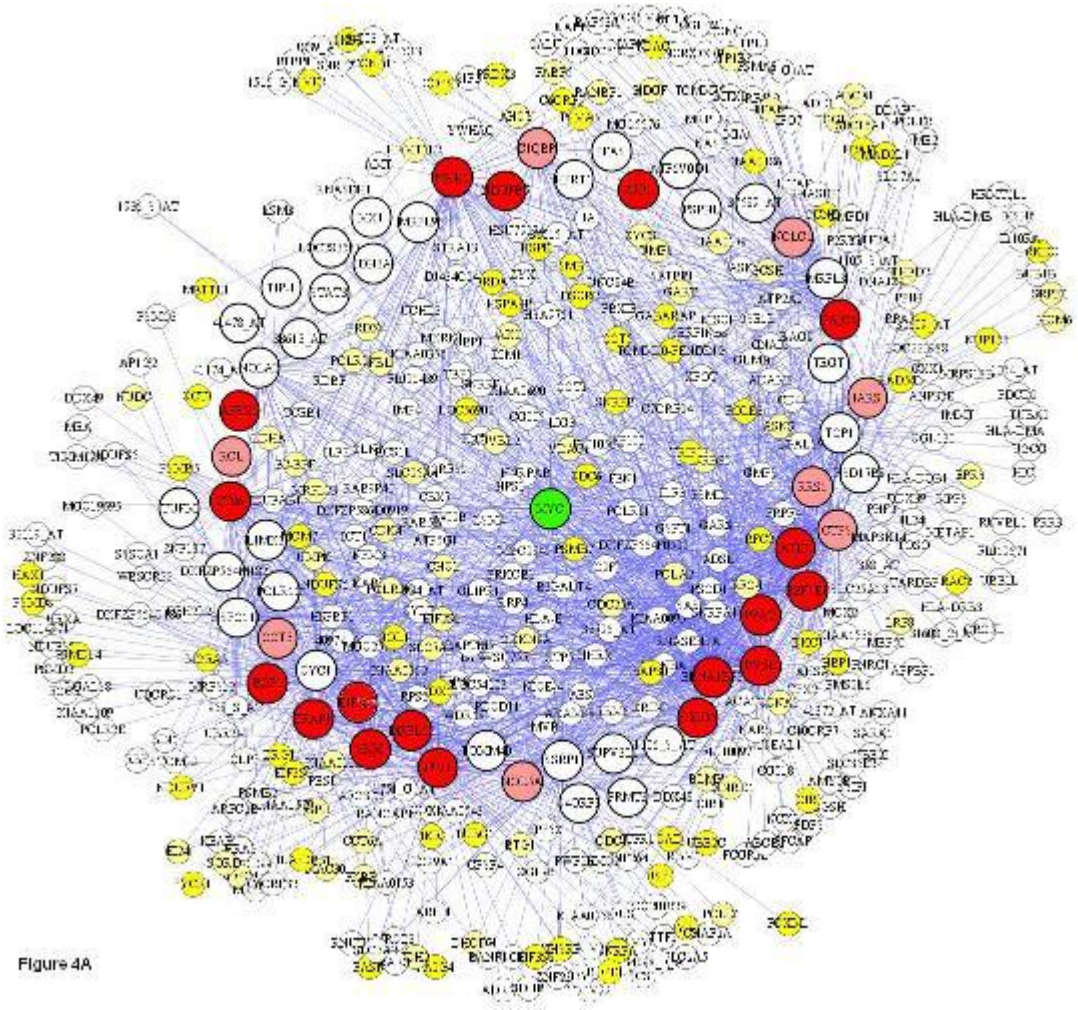
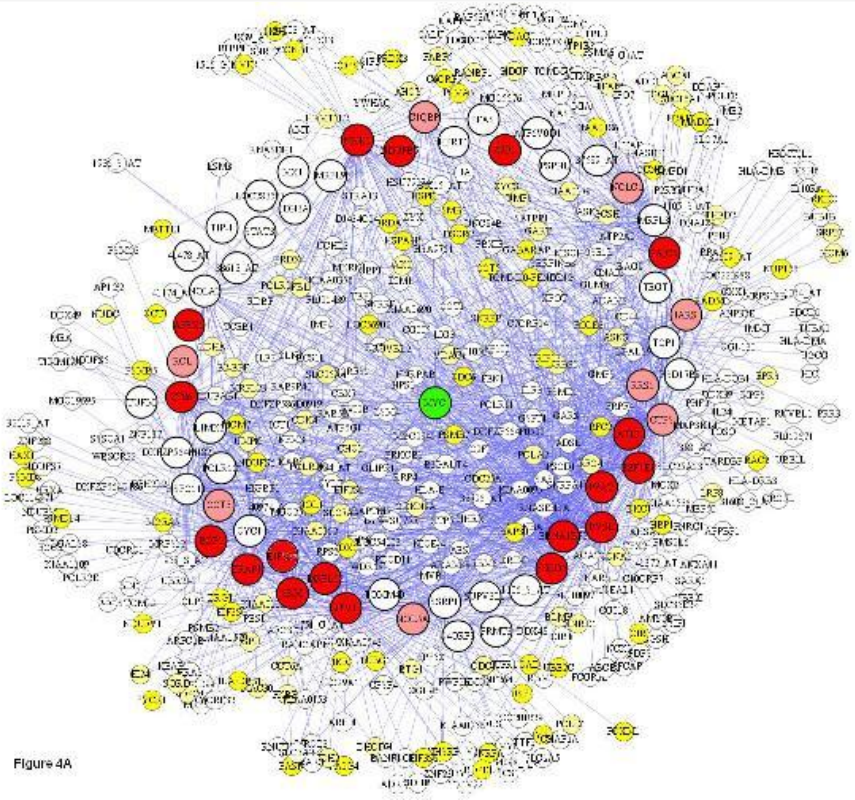
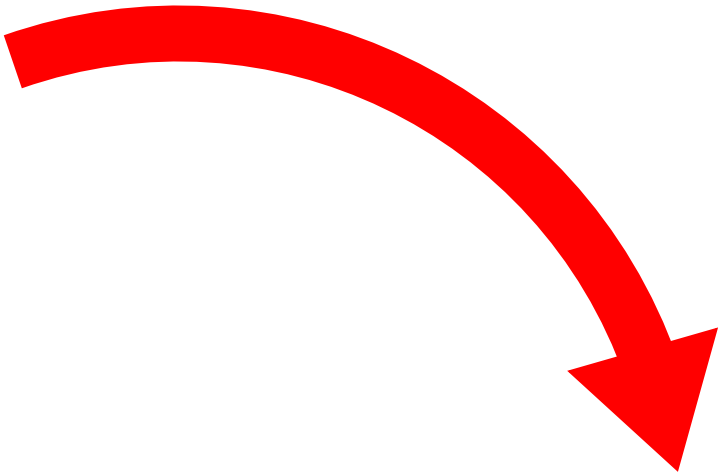
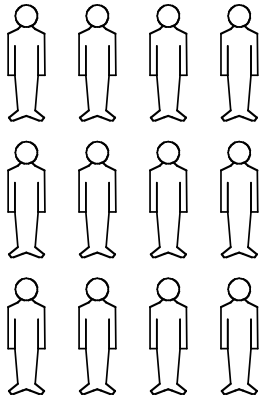
Search



Planning

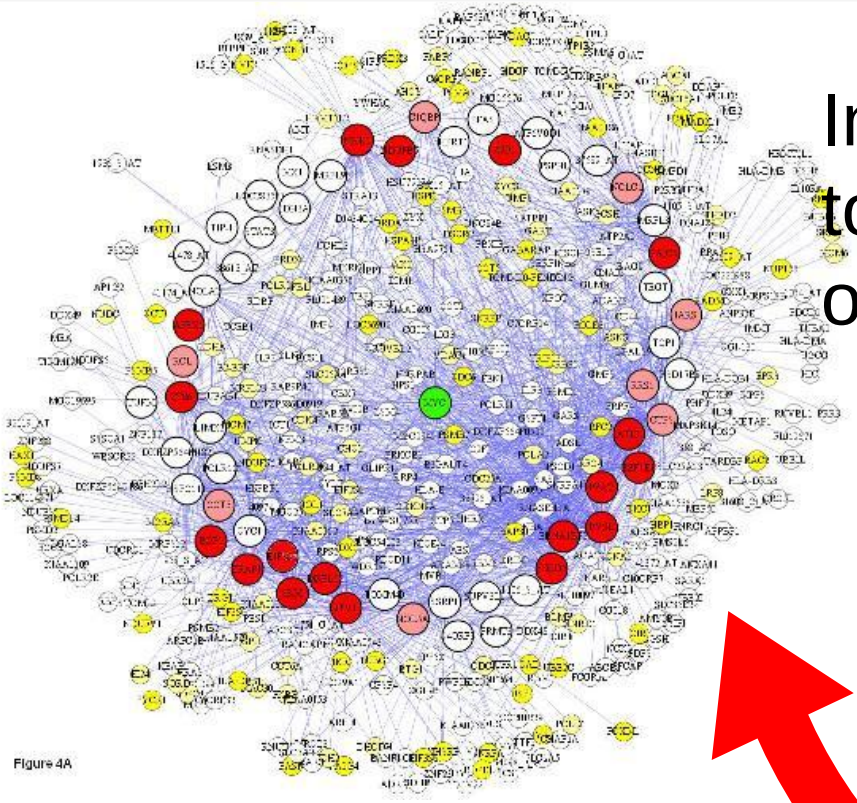




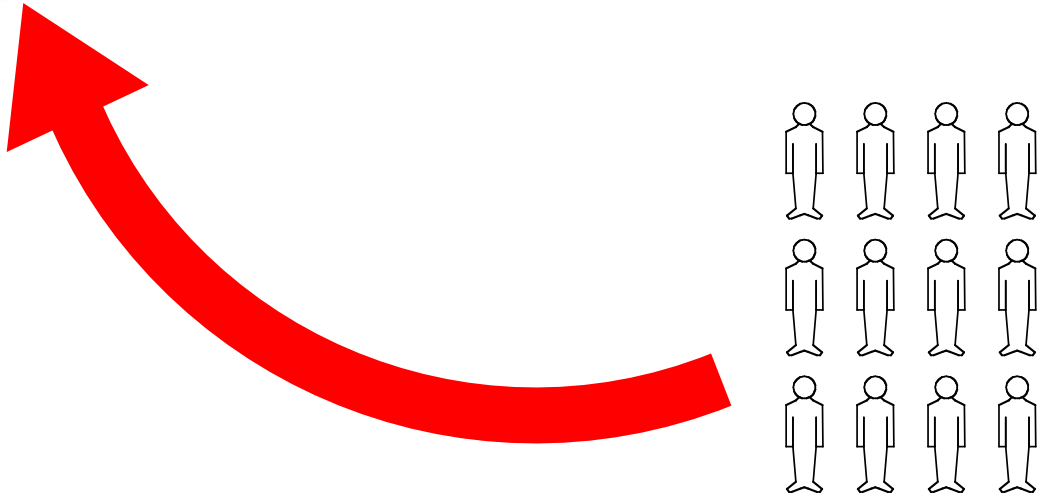


Thousands of adaptively-planned individual treatment experiments

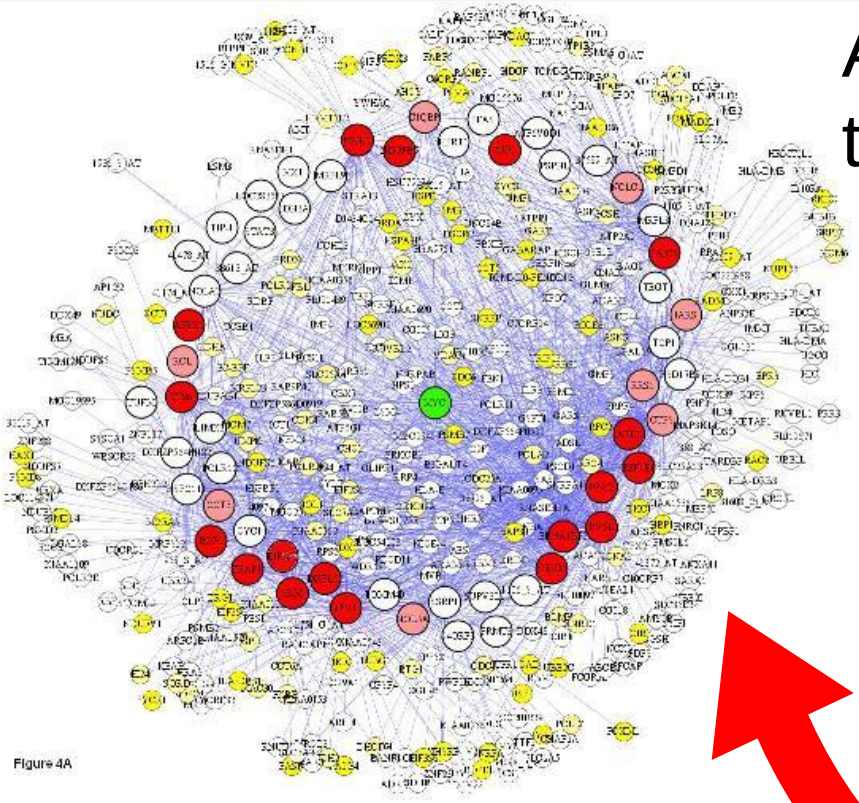
•Learning



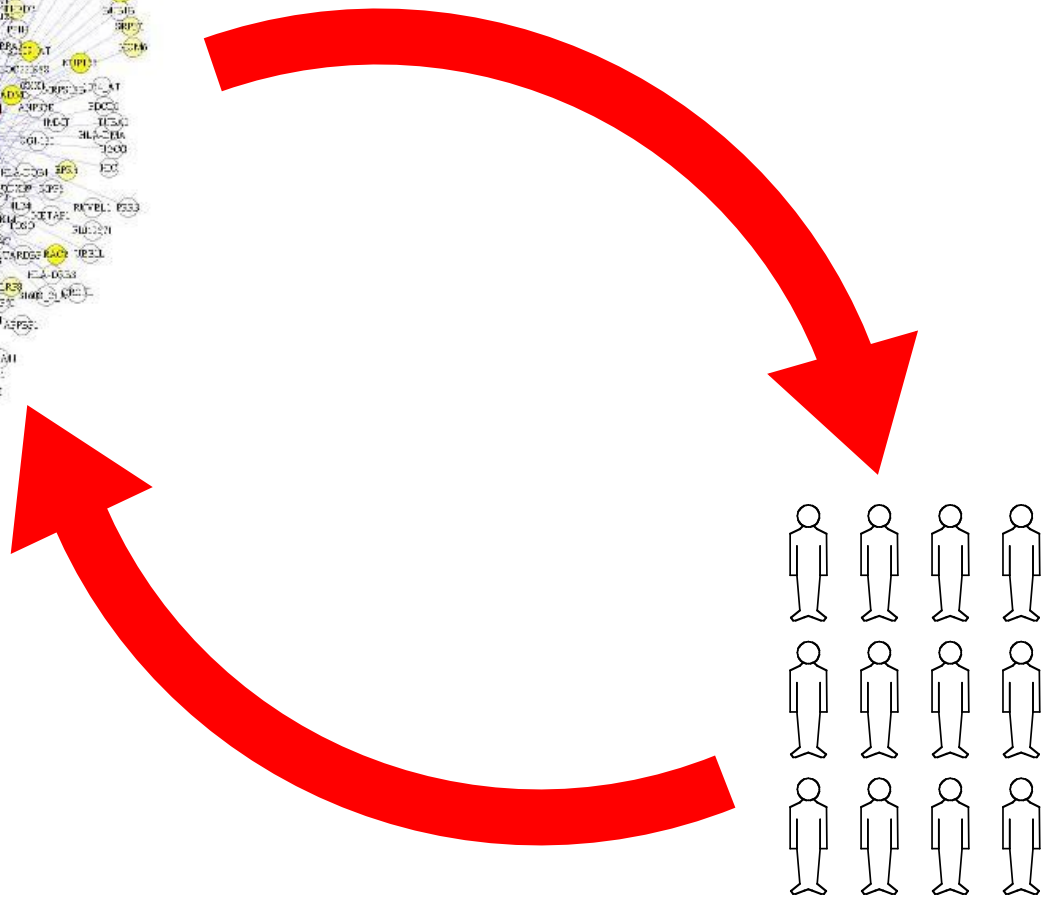
Integrate the resulting evidence to infer the causal mechanisms of tumors and drugs



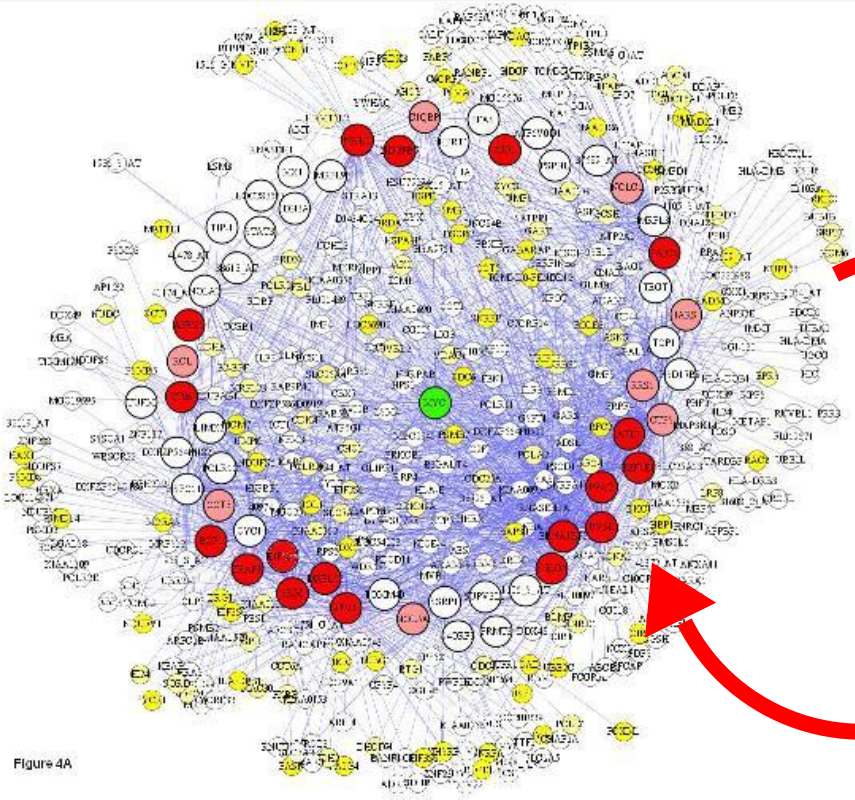
Generalization



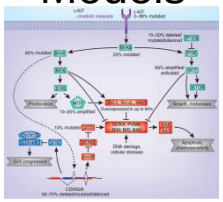
Apply the resulting knowledge to new cases

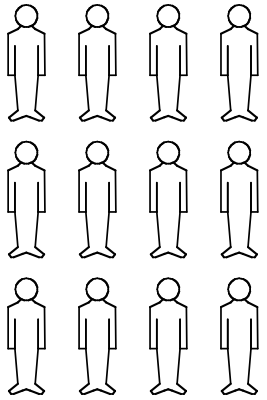


Search



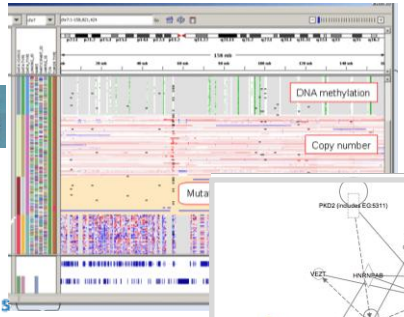
Reference Models





CollabRx ONE Knowledge Levels

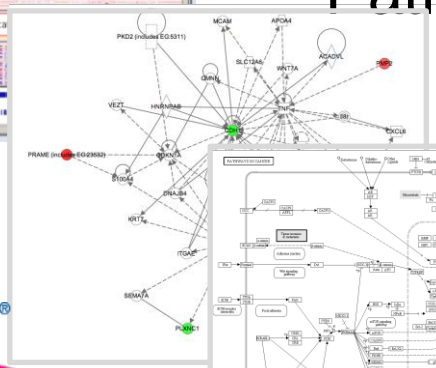
The Cancer Genome Atlas



Omics

GEO Gene Expression Omnibus

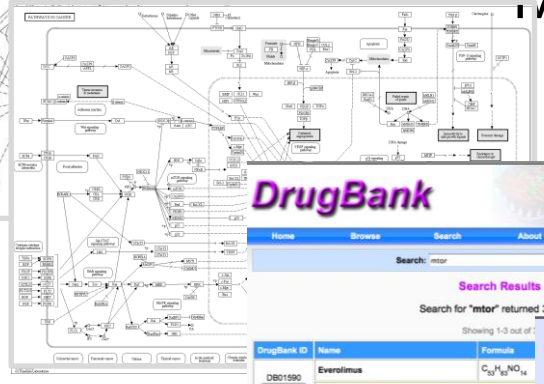
Pathway Analysis



Pathway Commons

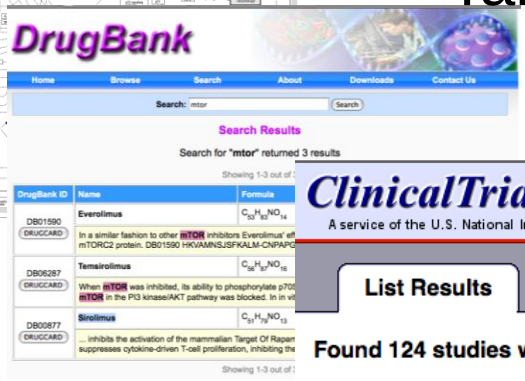
INGENUITY®

Mechanism Analysis

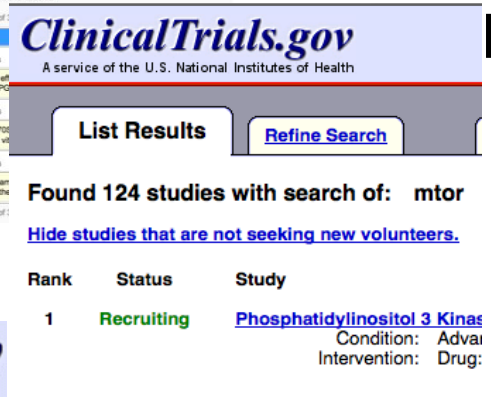


KEGG Kyoto Encyclopedia of Genes and Genomes

Target Identification



Treatment Planning

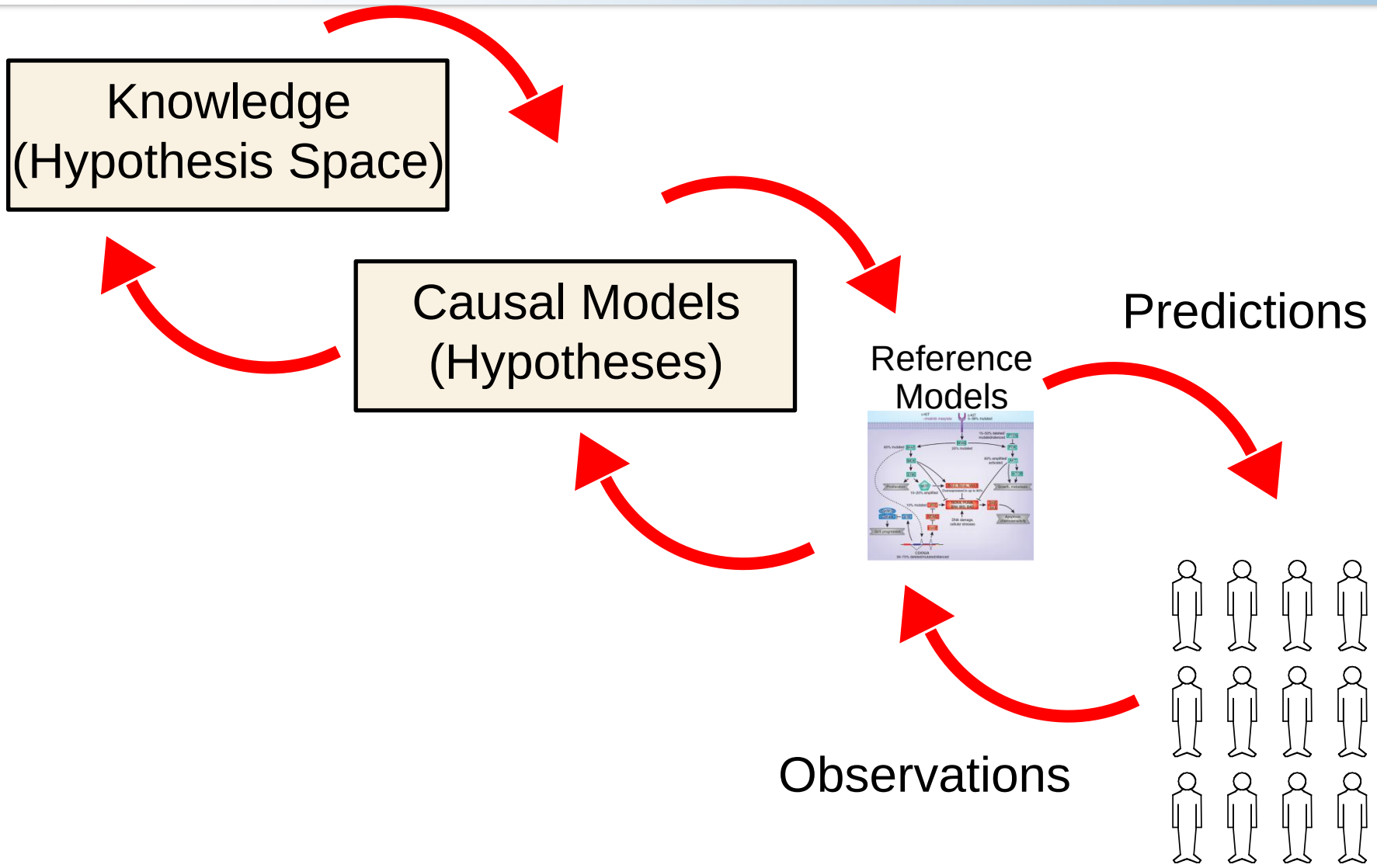


PubMed.gov

DrugBank

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Hierarchical Bayesian Learning



AI Opportunities

- Knowledge management
- Hierarchical planning
- Learning and generalization

Cancer Internet

ASCO


ASCO
EXHIBITS
GENERAL POSTERS
FOOD COURT 2
ASCO
2007
ASCO
SESSION HALL B1
CONCIERGE SERVICES
INTERNET KIOSK 1
MESSAGE CENTER

Connecting the Dots

1: Cancer Metastasis Rev. 1991 Jun;10(2):129-40.

Growth factors and tyrosine protein kinases in normal and malignant melanocytes.

1: Blood. 2000 Aug 1;96(3):925-32.

Inhibition of c-kit receptor tyrosine kinase activity by STI 571, a selective tyrosine kinase inhibitor

Heinrich MC, Griffith DJ, Druker BJ, Wait CL, Ott KA, Zigler AJ.

Division of Hematology and Medical Oncology, Department of Medicine, Oregon Health Sciences Un
Center, USA. heinrich@ohsu.edu

STI 571 (formerly k
(PDGFR) tyrosine ki
We sought to exten
structurally similar
stimulation with Ste
kinase, and activati
50% inhibition for these effects was approximately 100 nmol/L. STI 571 also significant
M-07e cells in a dose-dependent manner and blocked the antiapoptotic activity of SLF. I
MAP kinase activation or cellular proliferation in response to granulocyte-macrophage co
activity of STI 571 in a human mast cell leukemia cell line (HMC-1), which has an activa
more potent inhibitory effect on the kinase activity of this mutant receptor than it did or
wild-type rece
of target prot
increased c-ki

PMID: 10910906

"These findings show that STI 5
inhibits c-kit..." (2000)

"We determined c-kit expression. We decided to treat these patients with palliative imatinib mesylate, a tyrosine kinase inhibitor of KIT and PDGF-R." (2003)

Potential use of imatinib mesylate in ocular melanoma and liposarcoma expressing immunohistochemical c-KIT (CD117)

KIT is a transmembrane tyrosine kinase receptor in which the extracellular portion binds a ligand known as stem-cell factor and the intracellular portion contains the kinase enzymatic domain. KIT is similar in structure to several other receptor tyrosine kinases with oncogenic capabilities, including platelet-derived growth factor receptors (PDGF-R) A and B [1]. KIT activation normally occurs when two adjacent receptors are brought together through binding to ligand dimers; this process, known as homodimerization, is accompanied by structural changes in the

stromal tumor (GIST), while PDGF-R is expressed in most other sarcomas [5]. We determined c-KIT expression and concentration with Dako CD117 (DK-2600 Glostrup, Denmark) antibody in three cases of ocular melanoma (OM) and two of retroperitoneal liposarcoma (RL). We found positive immunoreactivity for CD117 in all three OM patients and one RL. We decided to treat these patients with palliative imatinib mesylate (IM), a tyrosine kinase inhibitor of KIT and PDGF-R.

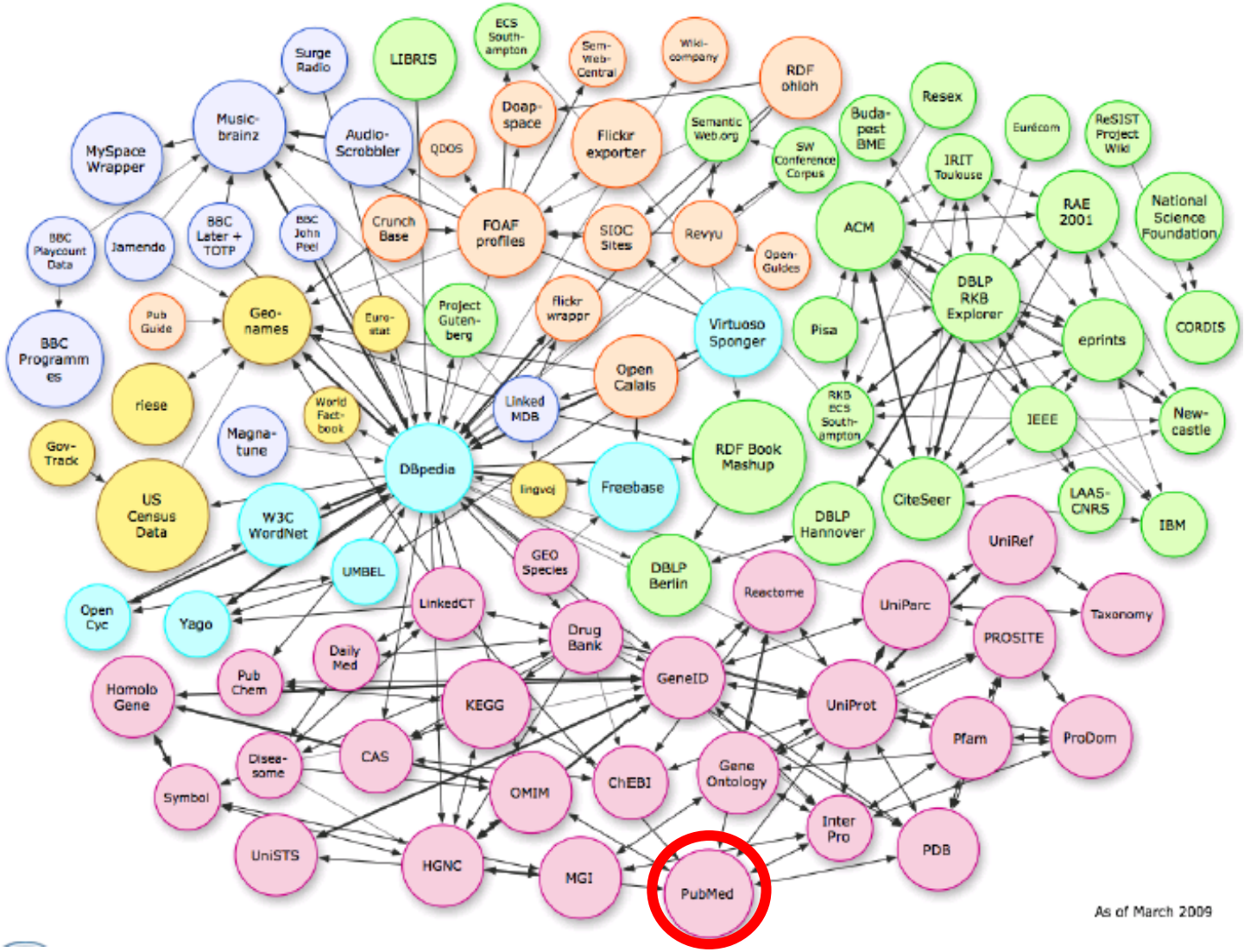
Connecting The Dots

1991: The uncontrolled growth of melanomas is due, in part, to constitutive activation of receptors with tyrosine kinase activity, esp. c-kit.

2000: Gleevec selectively inhibits c-kit.

2003: We determined c-kit expression and so decided to treat with palliative Gleevec, a tyrosine kinase inhibitor of KIT.

Datapedia: Semantic Web of Data



AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Smart Search and Analysis of ASCO Abstracts: The 2003 ASCO Pilot Breast Cancer Information Exchange (BCIE) project

A.T. Rappaport, D.R. Adamson, L. Shih, R. G. Smith, M. Tenenbaum, B. Khoo, S. Cho, A.C. Wolff, R.W. Carlson, and D. Whippen; Medstory, Inc., Burlingame, CA; ASCO, Alexandria, VA; Stanford University, Palo Alto, CA; Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

Providing powerful, targeted and precise access to ASCO information

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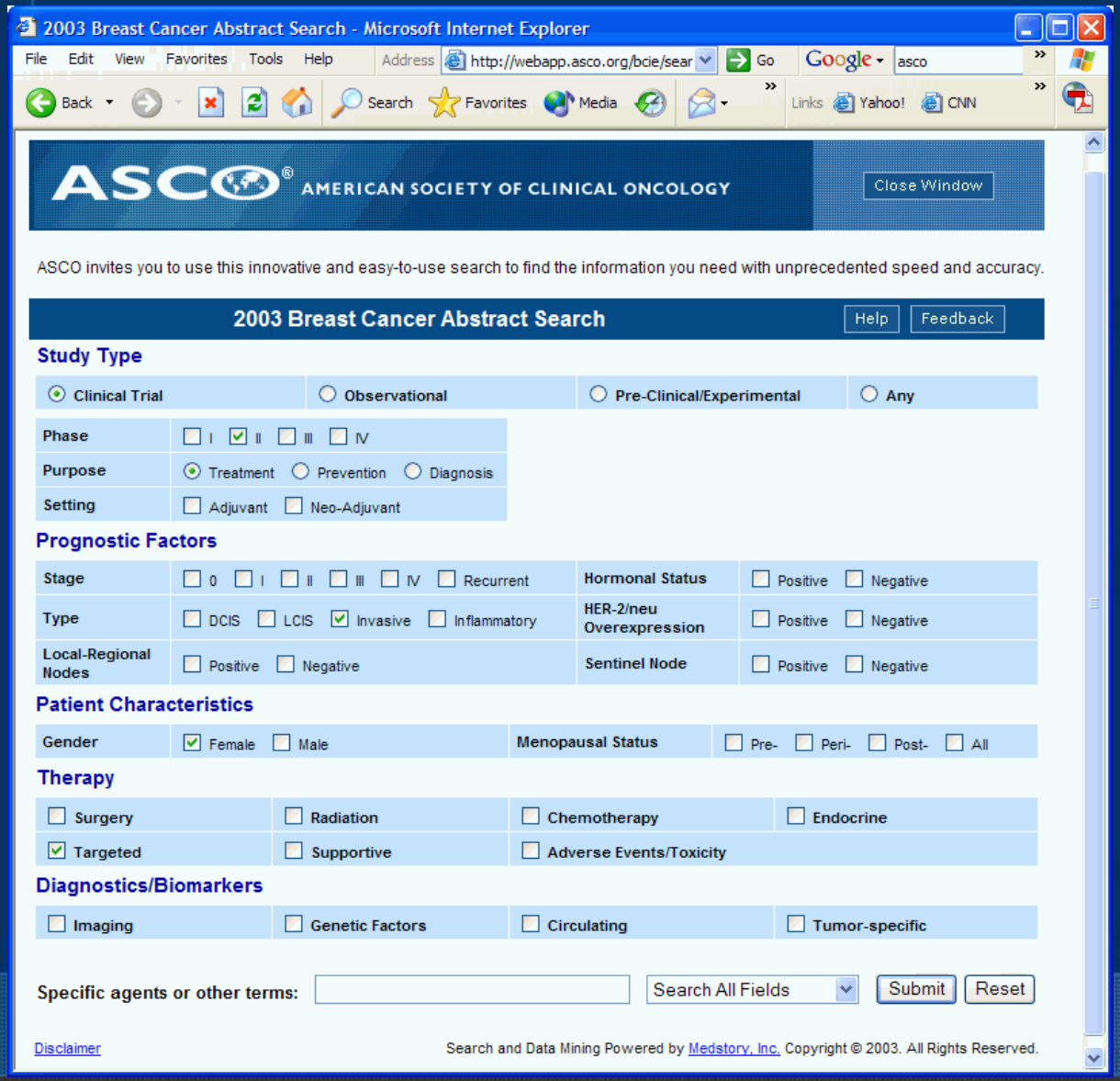

Results

- 95% of authors voluntarily populated the reference model
- >70% of users retrieved abstracts via the model

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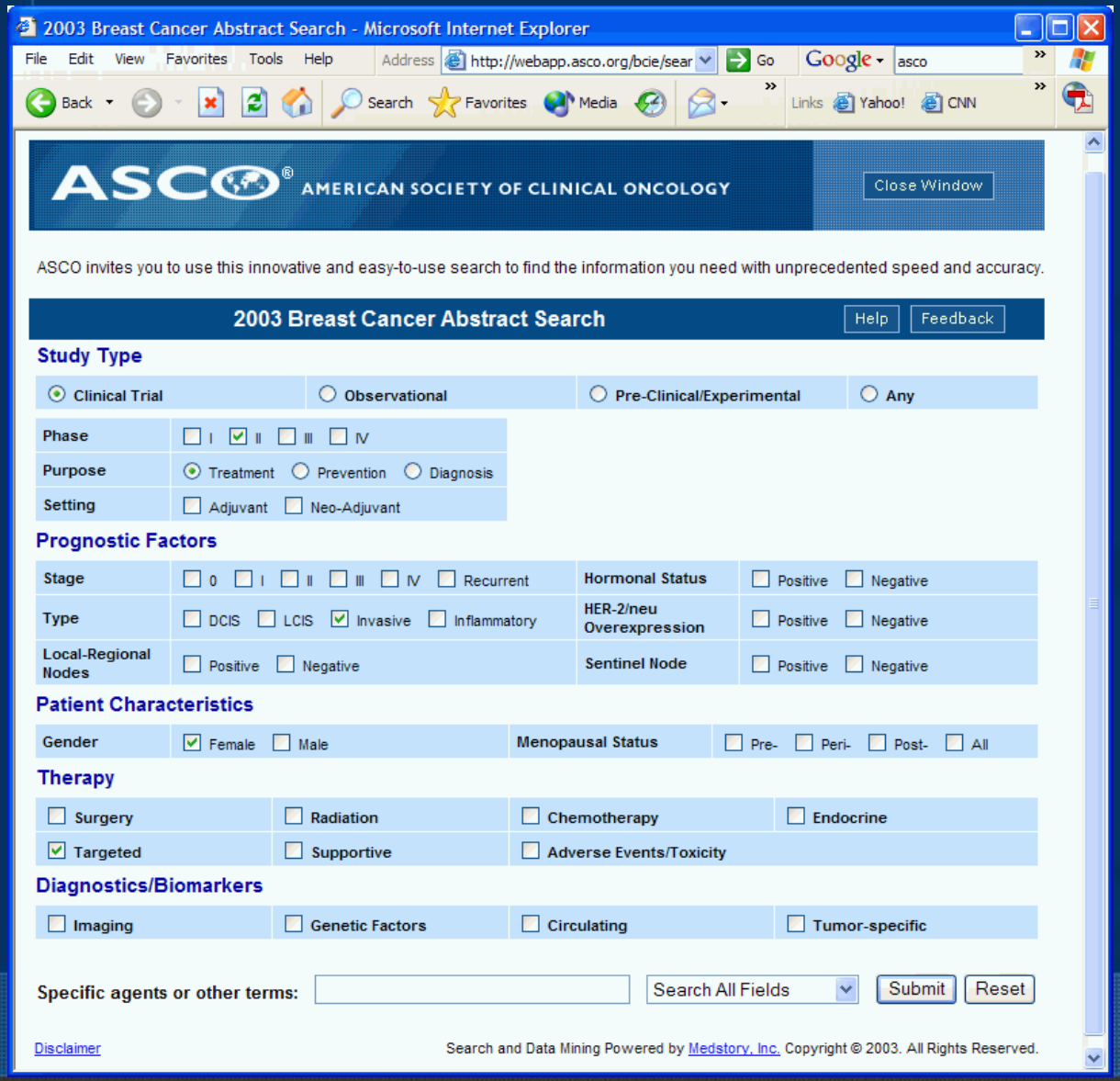

- Trials
- Treatments
- Guidelines
- Tests
- Literature
- Cases
- Experts

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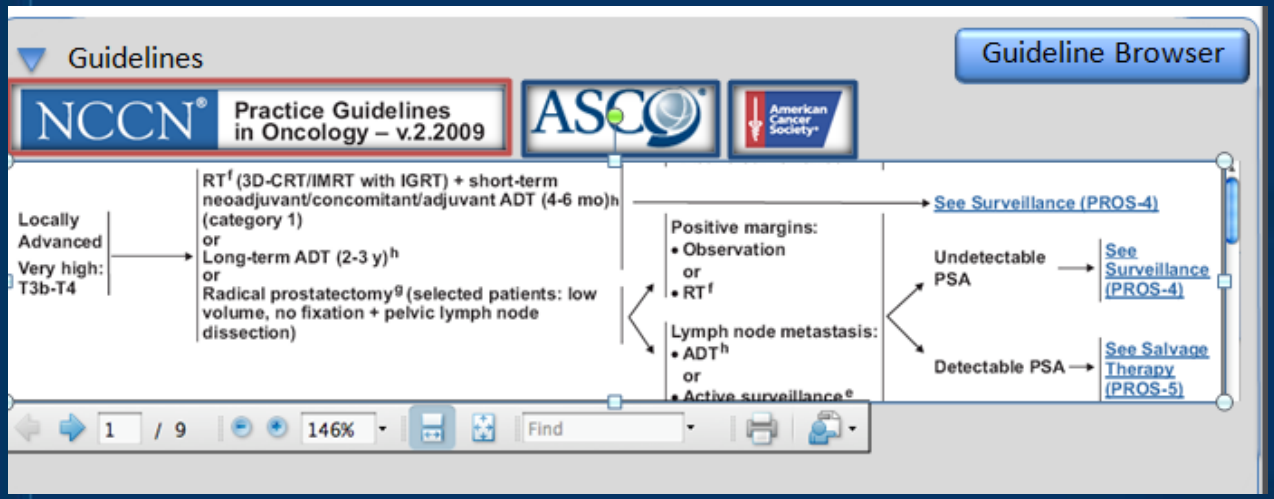

- Trials
- Treatments
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- Literature
- Cases
- Experts

ASCO® AMERICAN SOCIETY OF CLINICAL ONCOLOGY

- Trials
- Treatments
- Guidelines
- Tests
- Literature
- Cases
- Experts

Matching Trials

Patient		Physician
Name:	John Doe	**Dr. Smith** 123-456-7890
Date of Birth:	4/4/44	

Trial Status / Relevancy	Trial Details
Recruiting	**Chemotherapy Followed by Infusion of DMF6 Cells to Treat Metastatic Melanoma** **Conditions:** Melanoma; Malignant Melanoma; Melanoma, Experimental **Interventions:** Drug: DMF5 Melanoma Reactive TIL; Drug: Cyclophospamide; Drug Fludarabine
Recruiting	**Chemotherapy Followed by Infusion of DMF6 Cells to Treat Metastatic Melanoma** **Conditions:** Melanoma; Malignant Melanoma; Melanoma, Experimental **Interventions:** Drug: DMF5 Melanoma Reactive TIL; Drug: Cyclophospamide; Drug Fludarabine
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Tests that may reduce your uncertainty:

Gene Test	Status	Recommended?
BRAF	unknown	!
c-KIT	unknown	!
PTEN	unknown	?
NRAS	unknown	?
AKT	unknown	?
MITF	unknown	?
PI3K	unknown	?
CDKN2A	unknown	⦸
GNAQ	unknown	⦸
Bcl-2	unknown	⦸
CDK4	unknown	⦸
p53	unknown	⦸
Cyclin D	unknown	⦸

Cases

- Add cases
- View related cases
- Confidentially discuss this case with a professional trial counselor

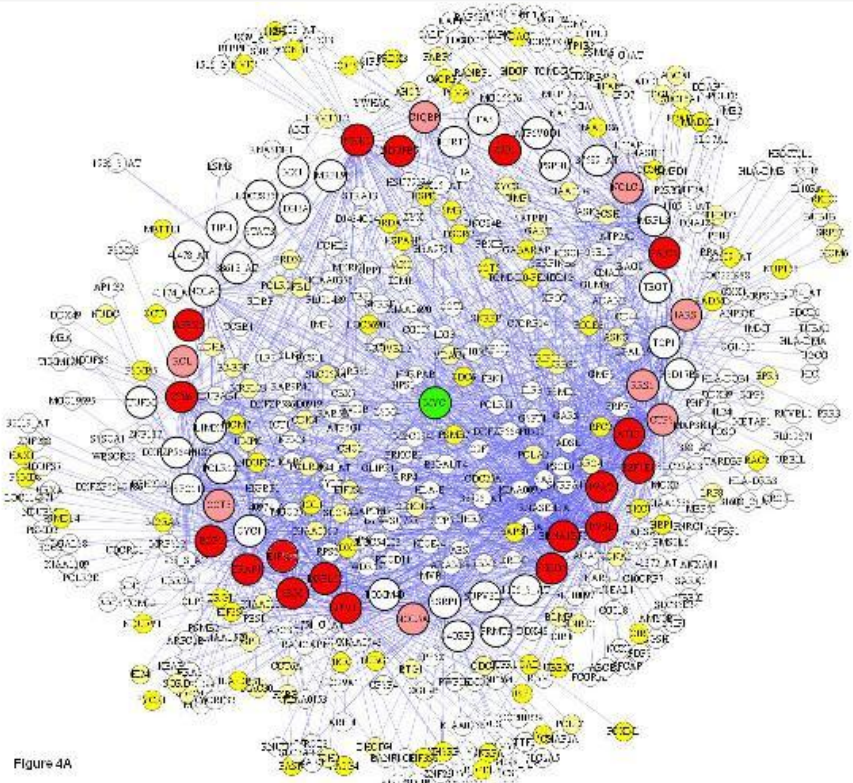
Knowledge Challenge

To organize the world's knowledge of cancer biology and therapeutics

and

Make it *actionable* for researchers and clinicians

Planning



ng

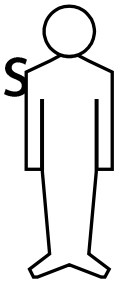
on therapies

ecimens, $, drug access

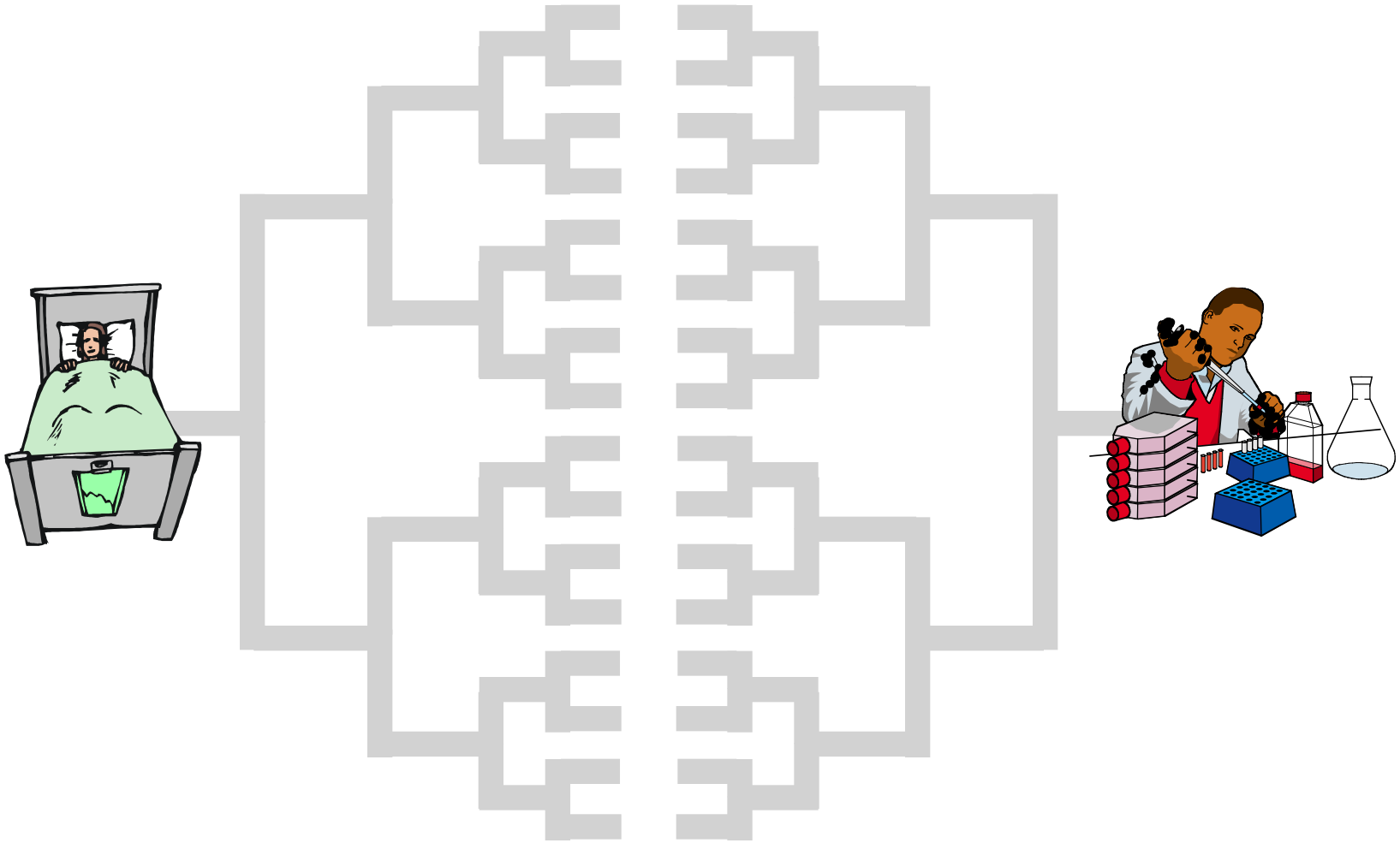
g

heses and patients

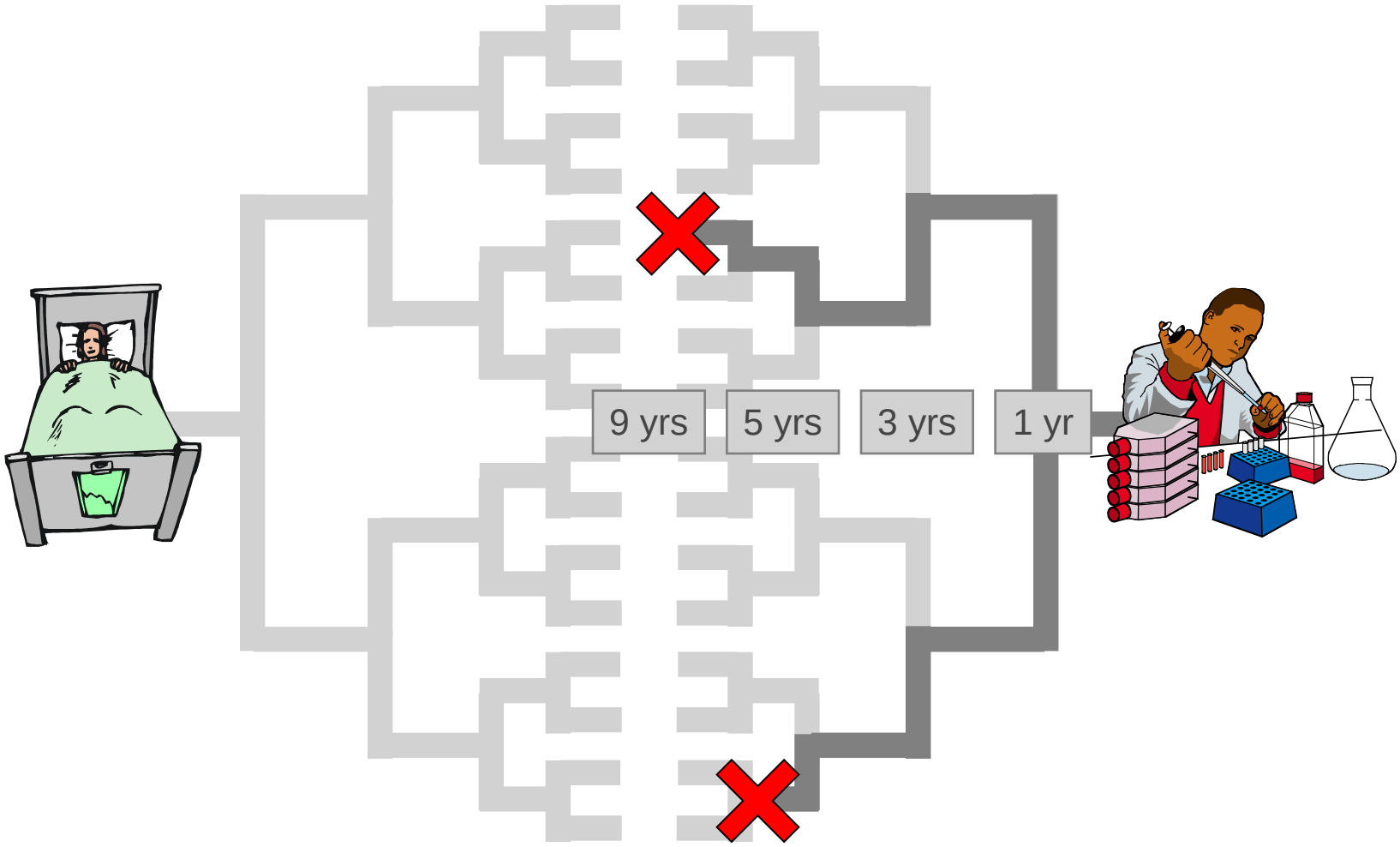
–Constraints: Ethics, alignment of incentives



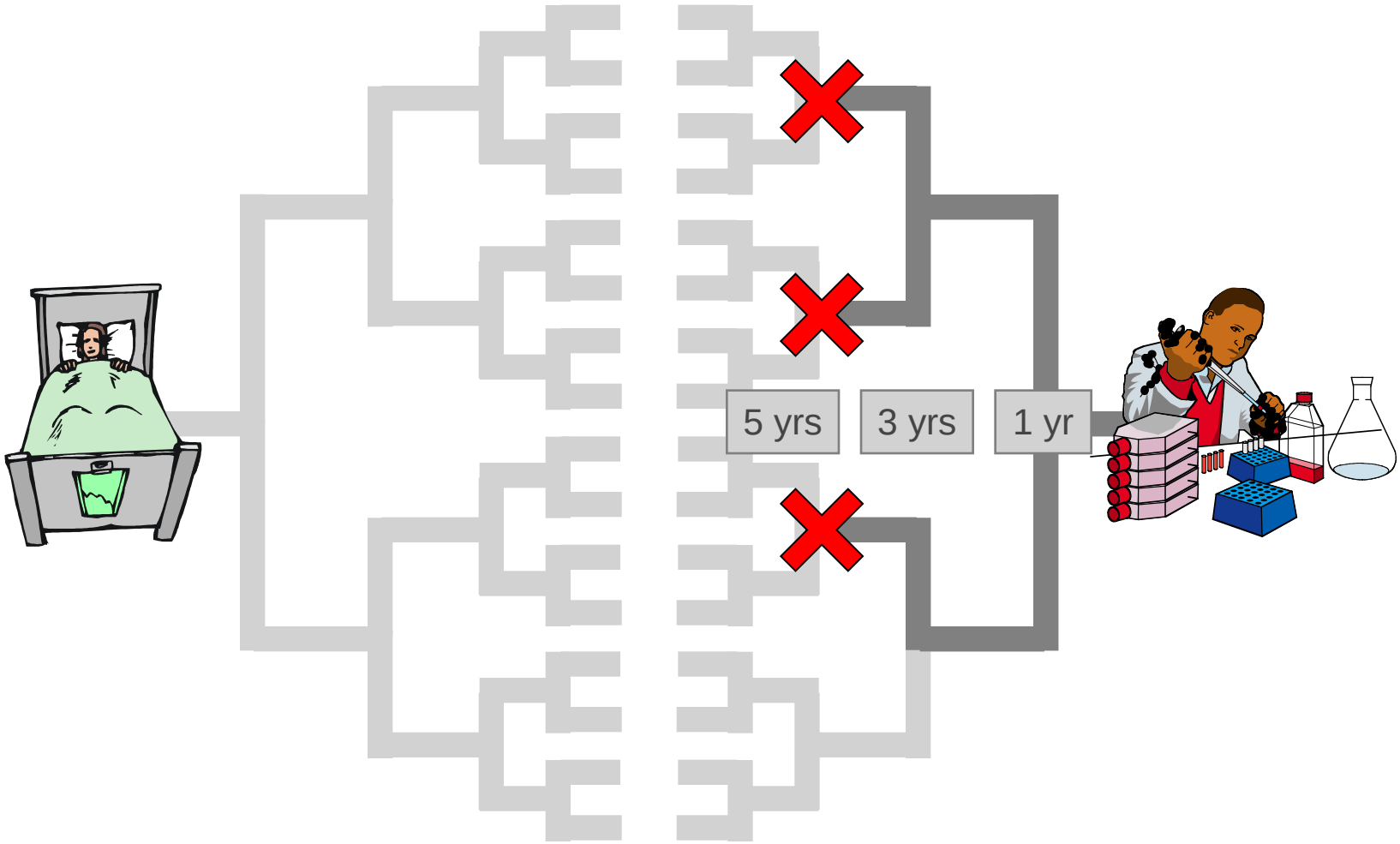
The Search For Cures



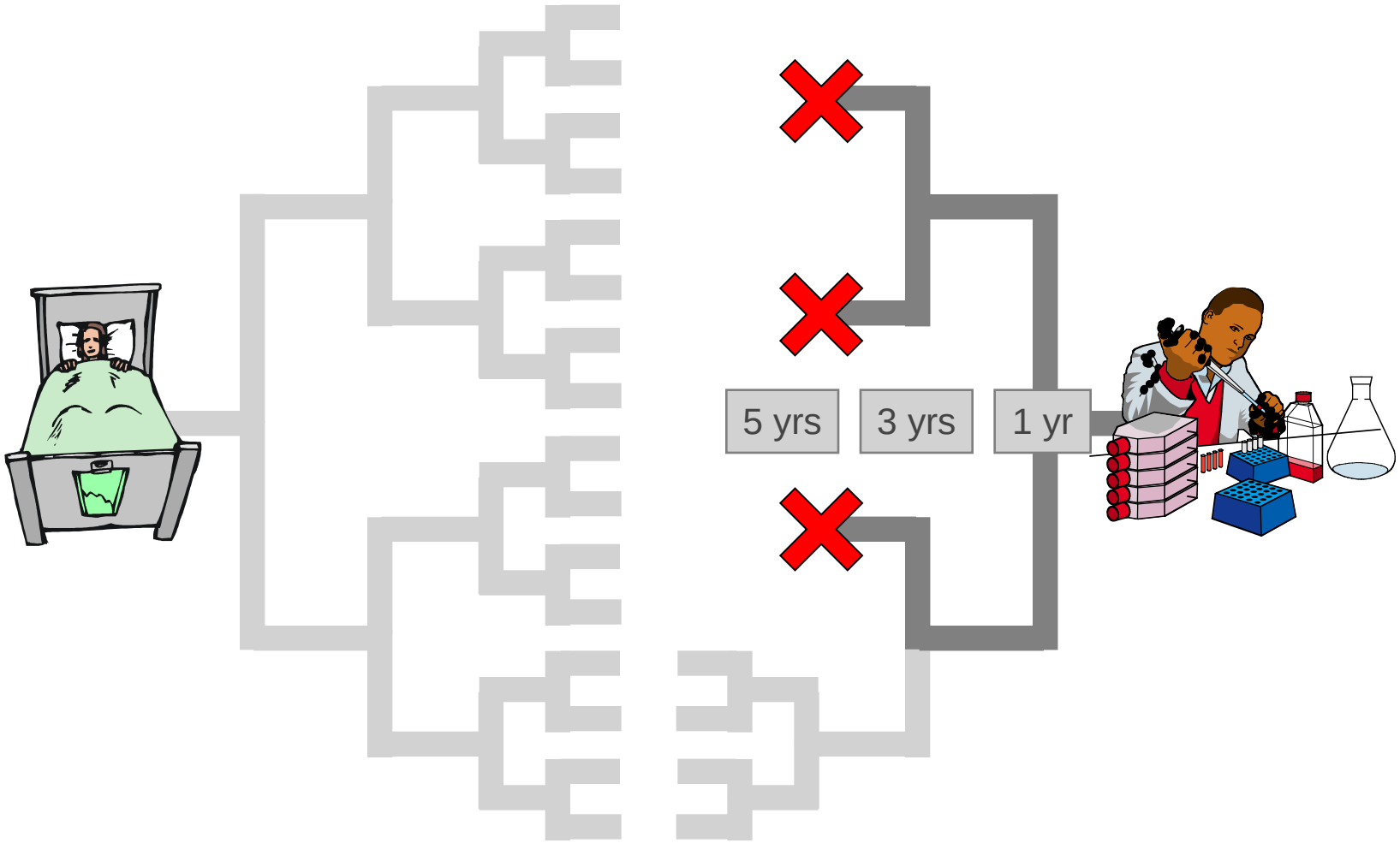
Succeed Slowly



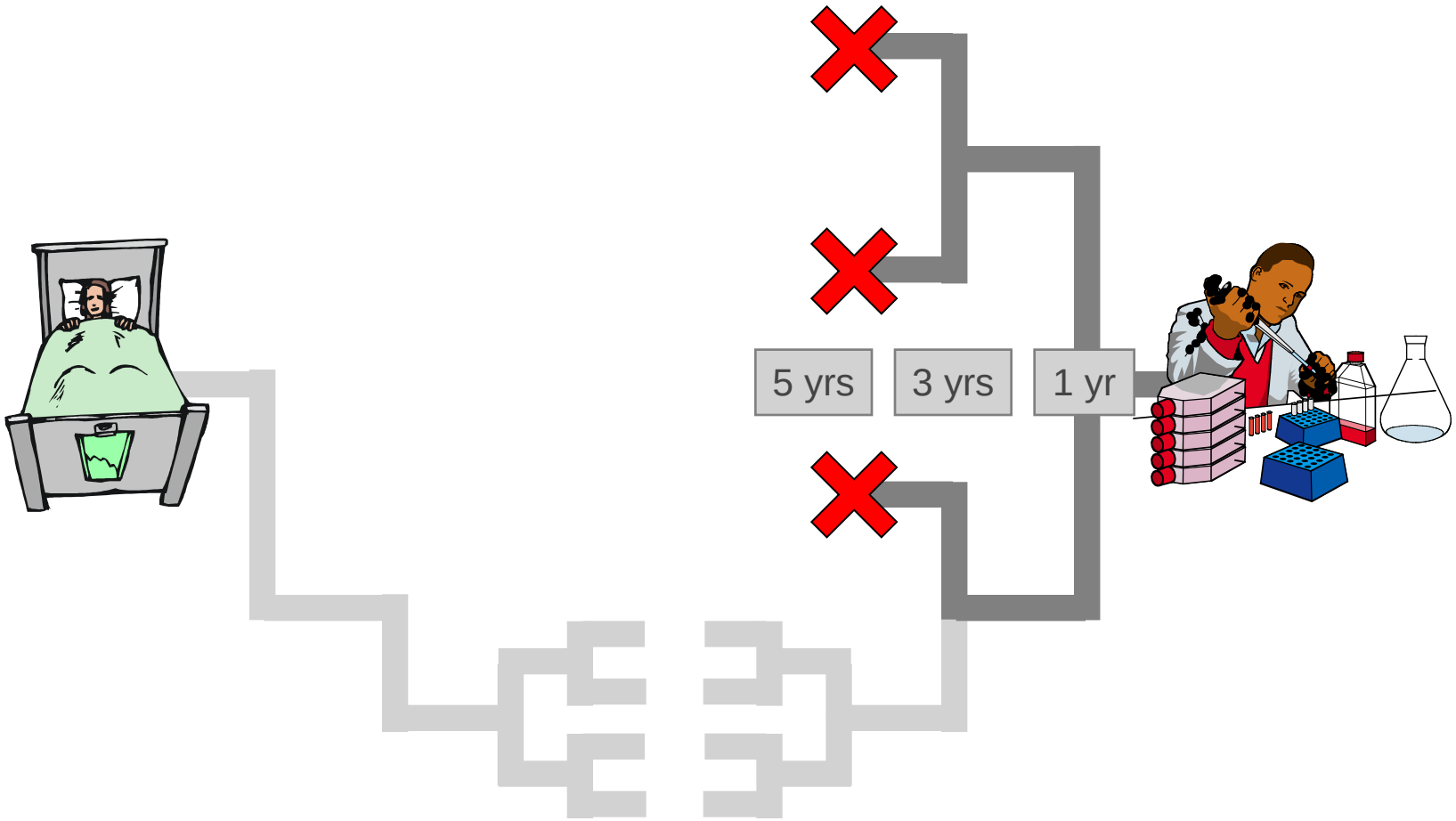
Fail Fast



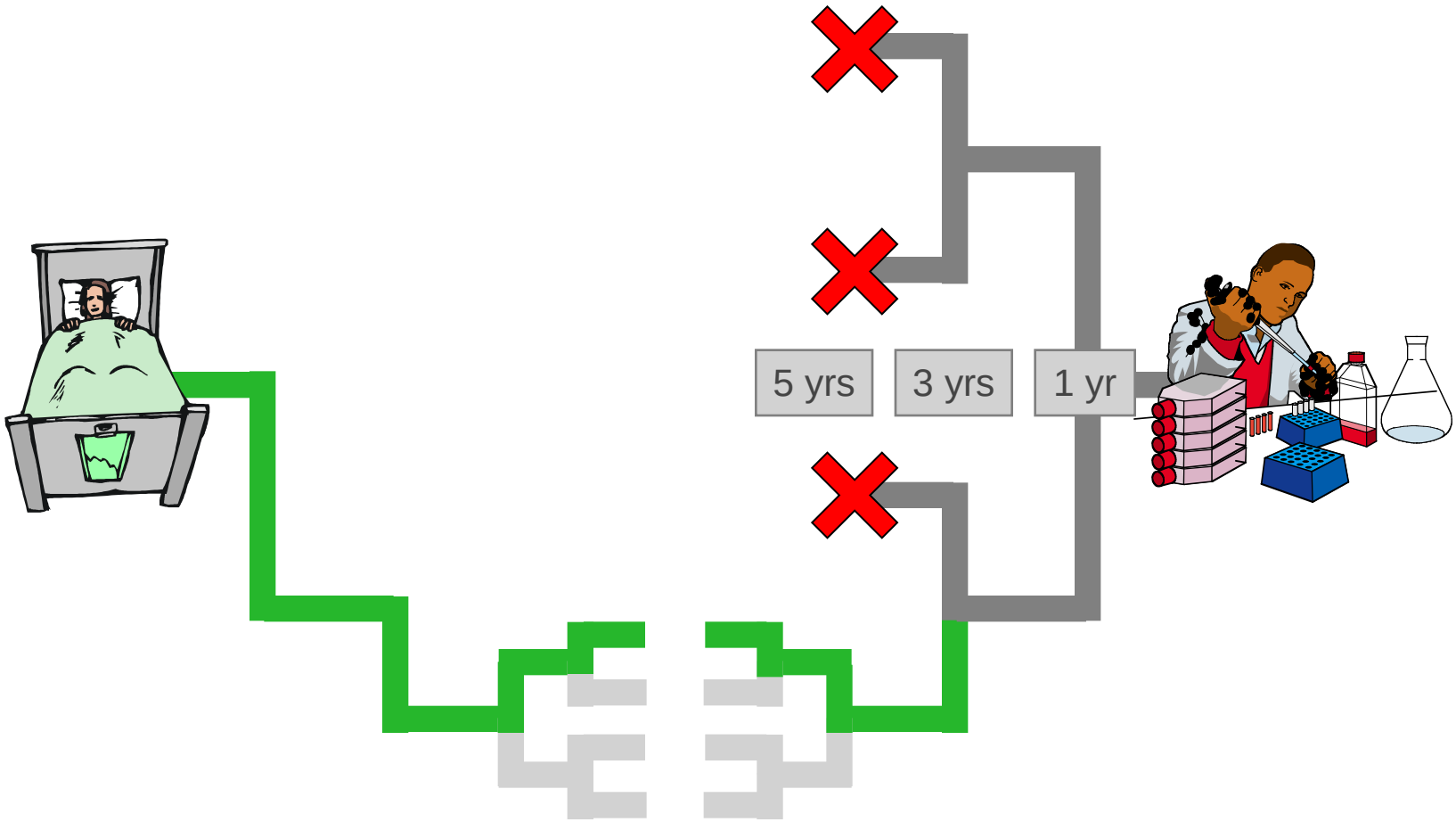
Fail Fast



Bed to Bench



Bed to Bench



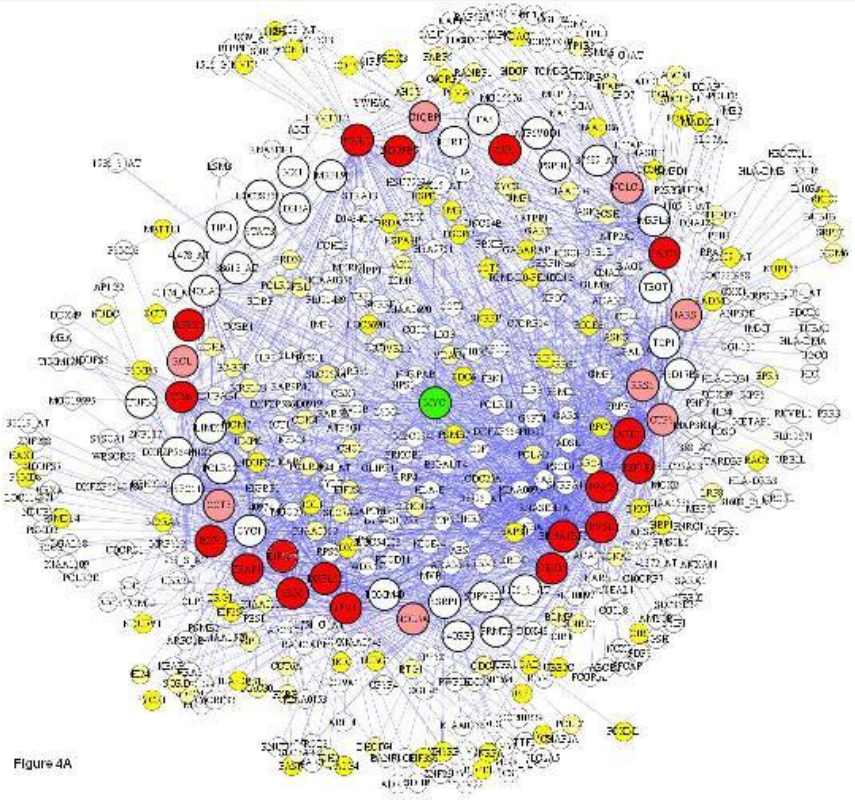
Planning Challenge

Adaptively plan individual treatment protocols to achieve optimal outcomes

while

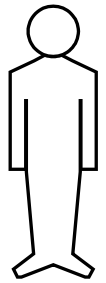
Maximizing the learnings for other patients and cancer research

Learning



for matching
and trials

tumors and drugs



Learning

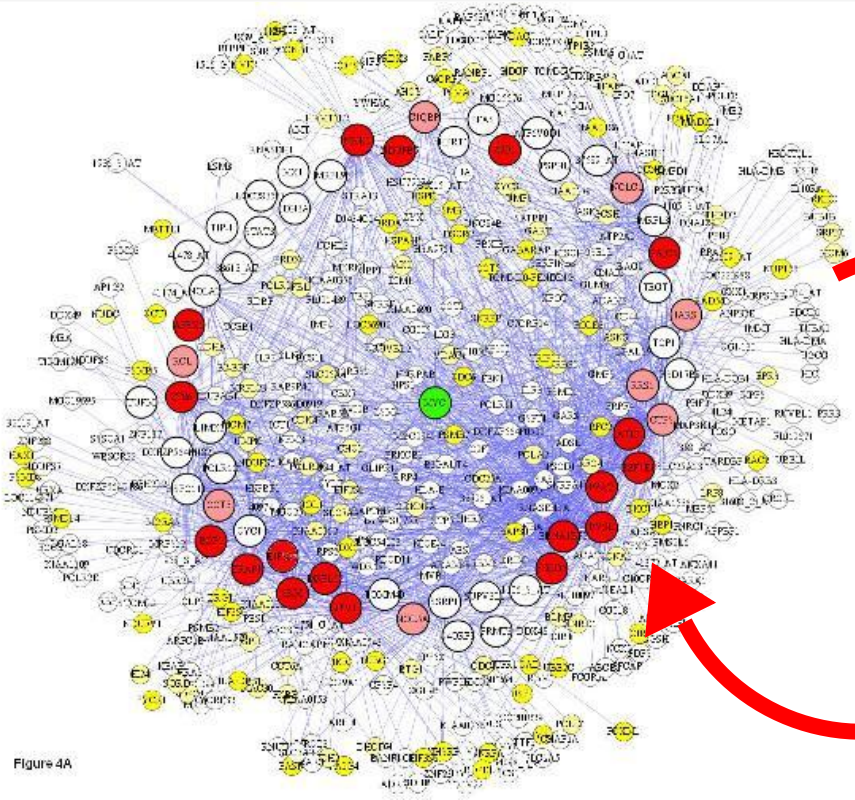
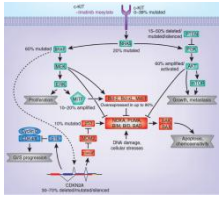
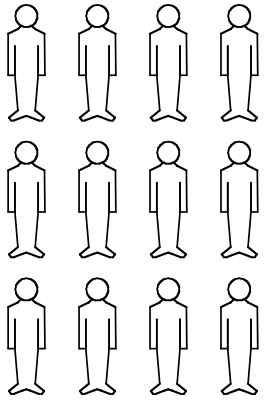


Figure 4A

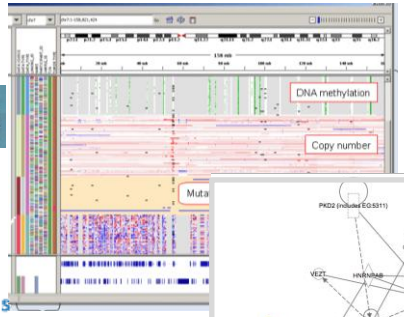
Reference Models





CollabRx ONE Knowledge Levels

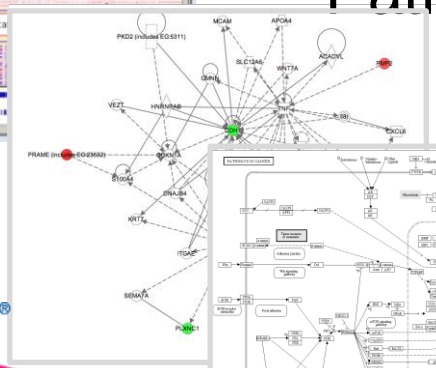
The Cancer Genome Atlas



Omics

GEO Gene Expression Omnibus

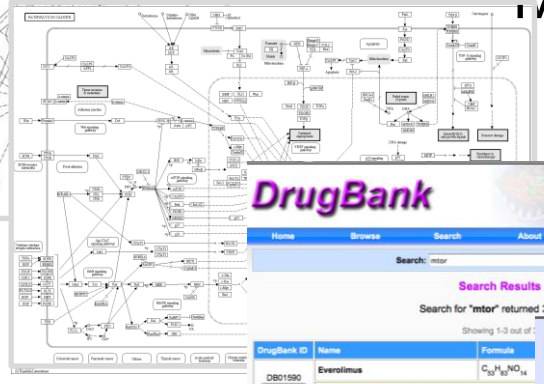
Pathway Analysis



Pathway Commons

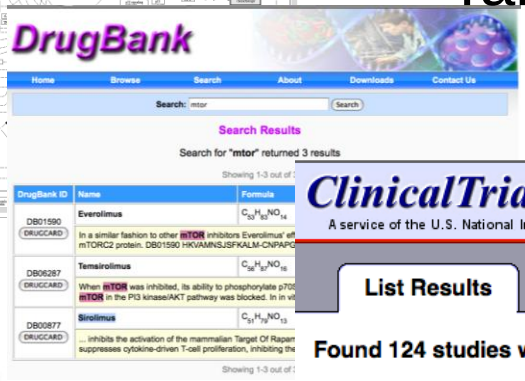
INGENUITY®

Mechanism Analysis

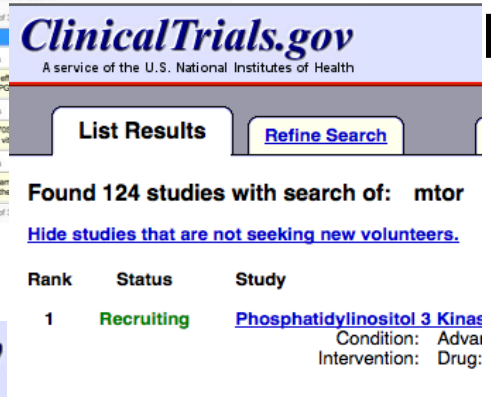


KEGG Kyoto Encyclopedia of Genes and Genomes

Target Identification



Treatment Planning



PubMed.gov

DrugBank

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Learning Challenge

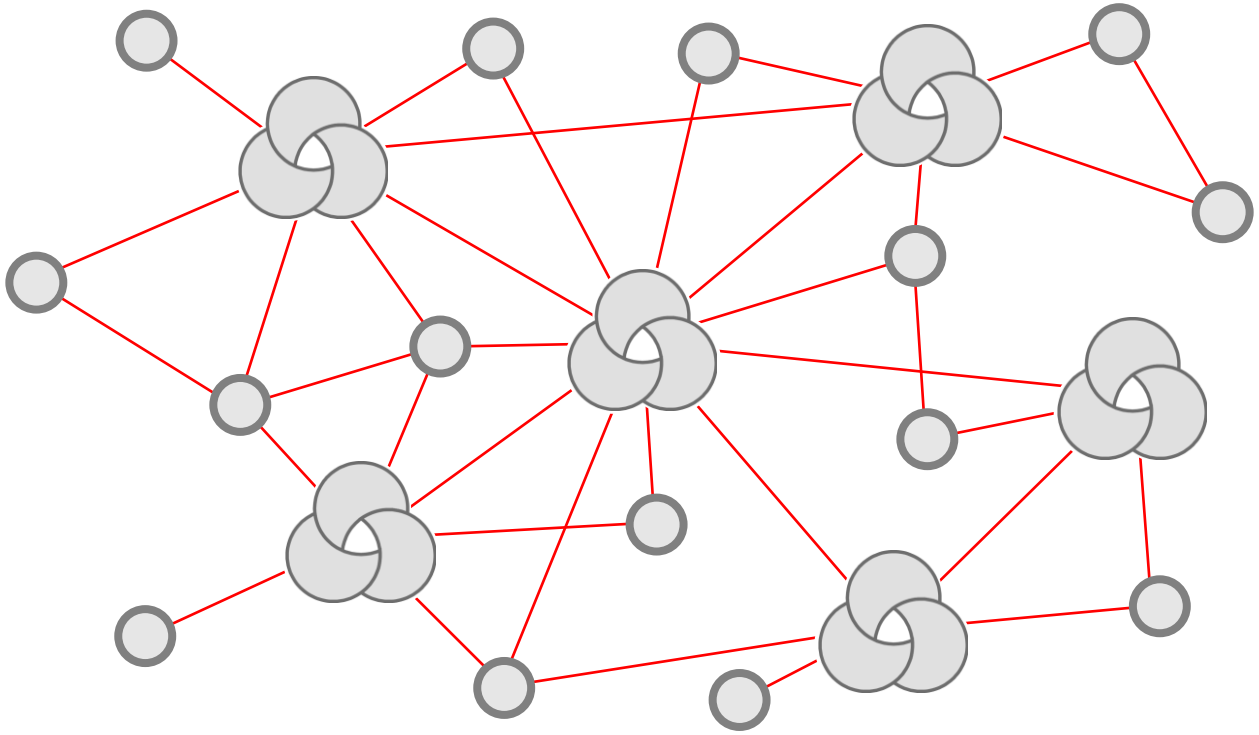
- Integrate the genomic and response data from individual treatment experiments
- Infer the true causal mechanisms of tumors and drugs
- Generalize the resulting knowledge so that it can be applied to new cases.

Summary

- Cancer – The Forty Years' War
- A new "N-of-1" paradigm
  - CollabRx ONE
  - Cancer Commons
- AI opportunities and challenges

Grand Challenge: Beat Cancer

- Organize the world's knowledge of cancer biology and therapeutics
- Adaptively plan thousands of ethical treatment "experiments"
- Integrate the resulting data to infer the true causal mechanisms of tumors and drugs
- Generalize the resulting knowledge so that it can be applied to new cases.



Thank You

jmt@collabrx.com