An American System for Evidence Generation

Robert M Califf MD

Melvin S Cutler Lecture

U Mass

April 27th, 2017

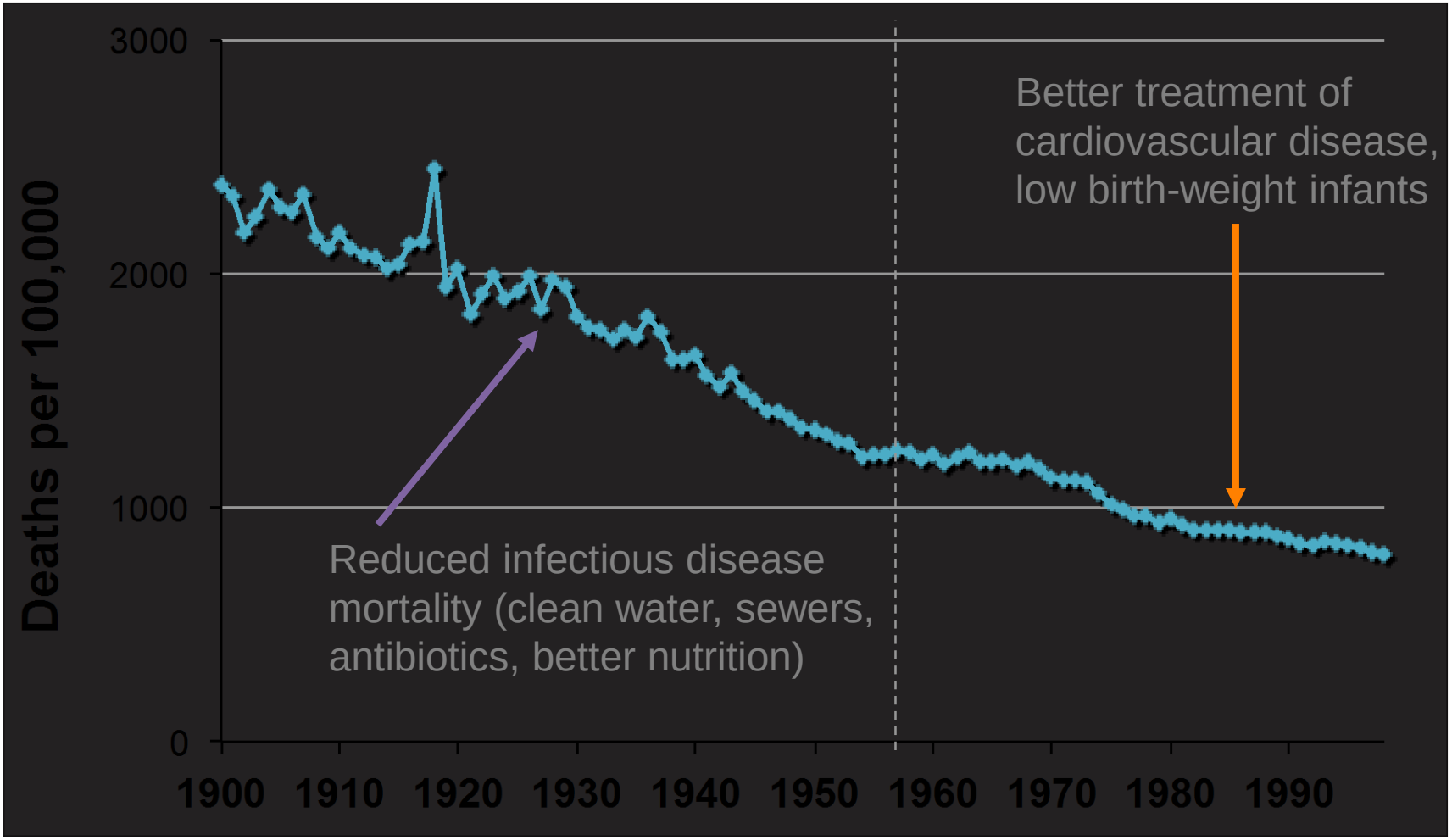
Personal Perspective

- I have witnessed a revolution in healthcare
- During my professional career
  - Insights into public health measures like blood pressure and fundamentals of diet have advanced dramatically
  - Amazing drugs and devices have been developed and deployed
  - We have taken on the menace of tobacco and we're winning the battle
  - Age specific mortality has been reduced by over 50% with resulting increases in American and global longevity and functional status

The Next Revolution

- **Will result from the transformation of information**
- In order to apply this fundamental revolution to improve health and quality of life, we must:
  - Learn how to share and create business models that work to improve sharing
  - Invest heavily in curating information
  - Work together to develop social and ethical constructs to deal with privacy, confidentiality and security
  - Create a workforce that can both create new methods and integrate information into practice
  - Give the workforce time to invest in knowledge generation as a routine part of practice
  - Work with the public to gain support and understanding

Mortality in the 20th Century



OPEN ACCESS Freely available online PLoS MEDICINE

Eight Americas: Investigating Mortality Disparities across Races, Counties, and Race-Counties in the United States

Christopher J. L. Murray[1,2,3], Sandeep C. Kulkarni[2,4], Catherine Michaud[2,3], Niels Tomijima[3], Maria T. Bulzacchelli[3], Terrell J. Iandiorio[3], Majid Ezzati[1,2*]

1 Harvard School of Public Health, Boston, Massachusetts, United States of America, 2 Harvard University Initiative for Global Health, Cambridge, Massachusetts, United States of America, 3 Center for Population and Development Studies, Harvard University, Cambridge, Massachusetts, United States of America, 4 University of California San Francisco, San Francisco, California, United States of America

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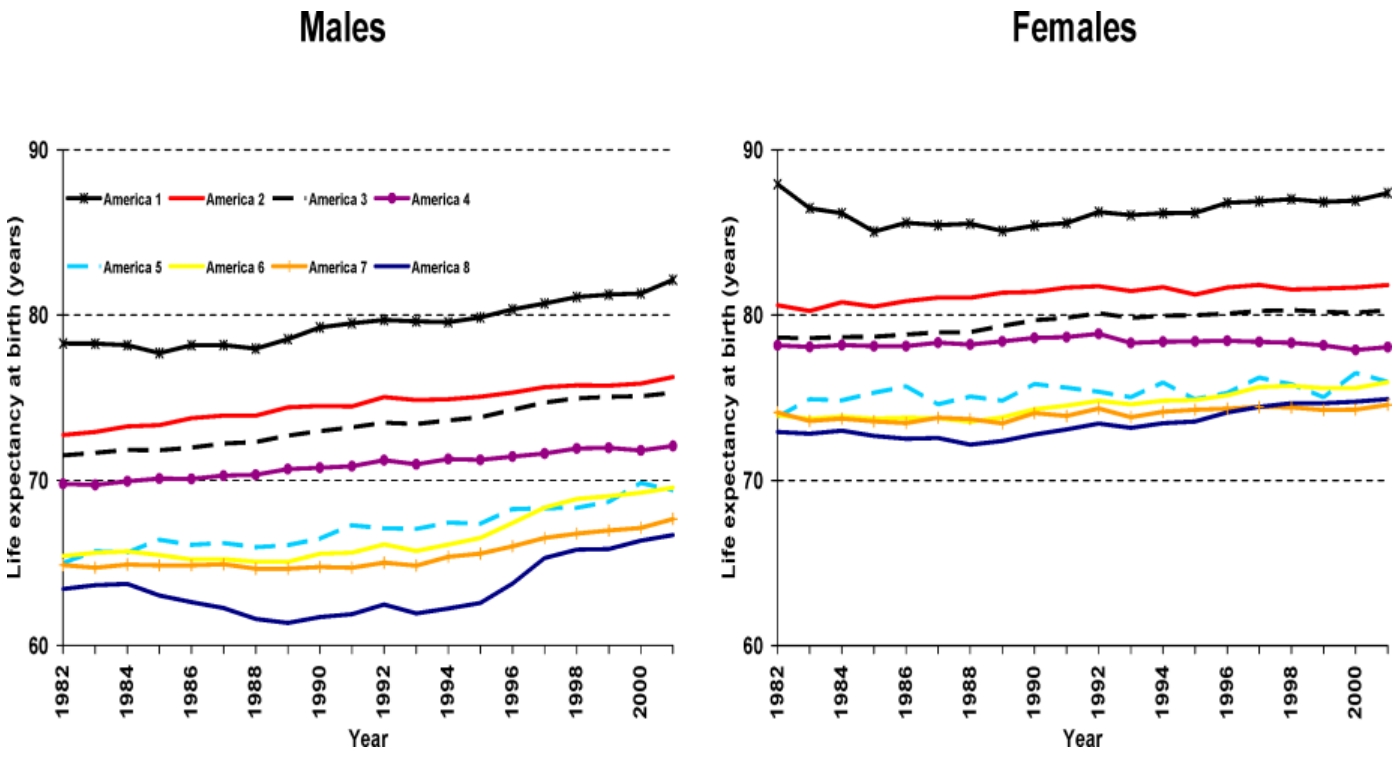
ABSTRACT

Background

The gap between the highest and lowest life expectancies for race-county combinations in the United States is over 35 y. We divided the race-county combinations of the US population into eight distinct groups, referred to as the "eight Americas," to explore the causes of the disparities that can inform specific public health intervention policies and programs.

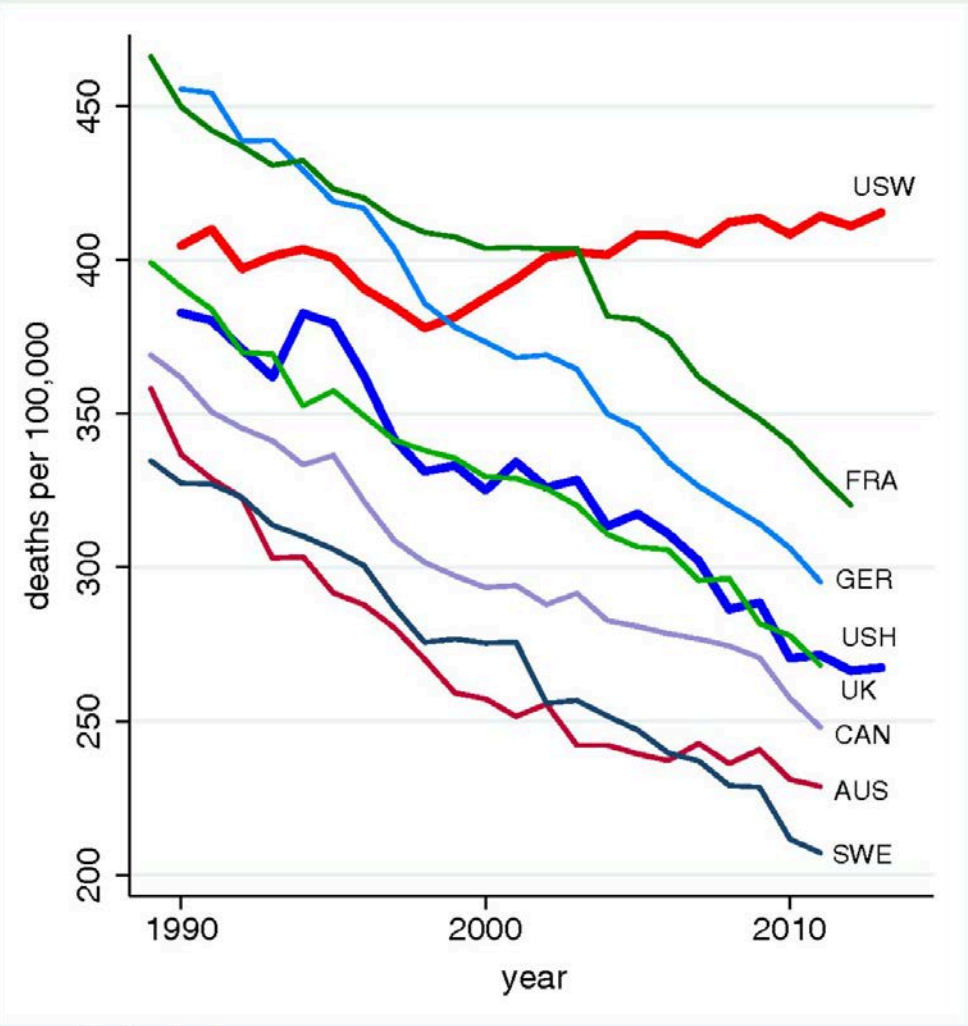
Murray et al. PLoS Med 2006; 3:1513-1524

Mortality Experiences of the 8 Americas

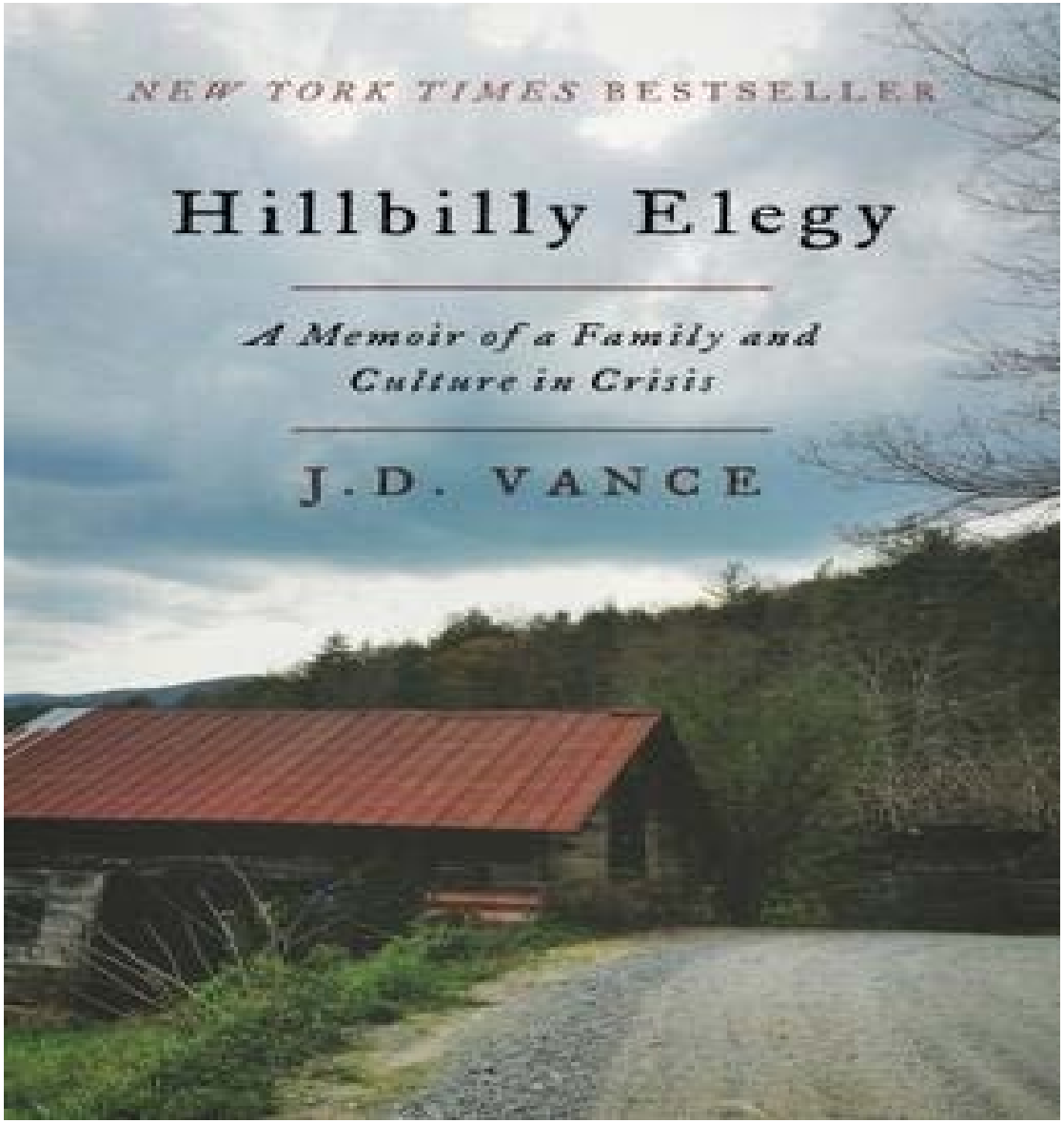


Murray et al. PLoS Med 2006; 3:1513-1524

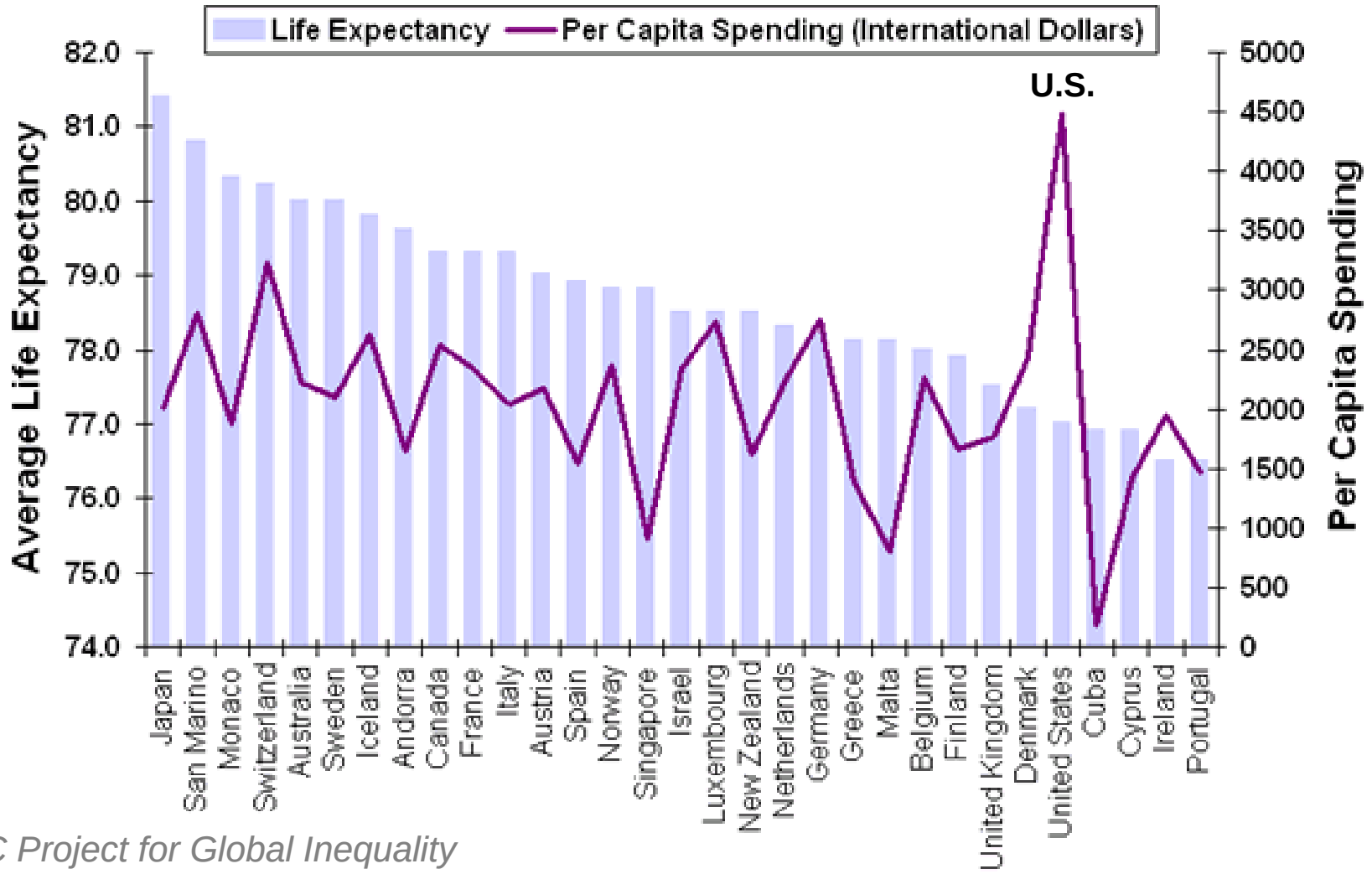
All-cause mortality, ages 45–54 for US White non-Hispanics (USW), US Hispanics (USH), and six comparison countries: France (FRA), Germany (GER), the United Kingdom (UK), Canada (CAN), Australia (AUS), and Sweden (SWE).



Anne Case, and Angus Deaton PNAS 2015;112:15078-15083


NEW YORK TIMES BESTSELLER
Hillbilly Elegy
A Memoir of a Family and Culture in Crisis
J.D. VANCE

Cost of a Long Life



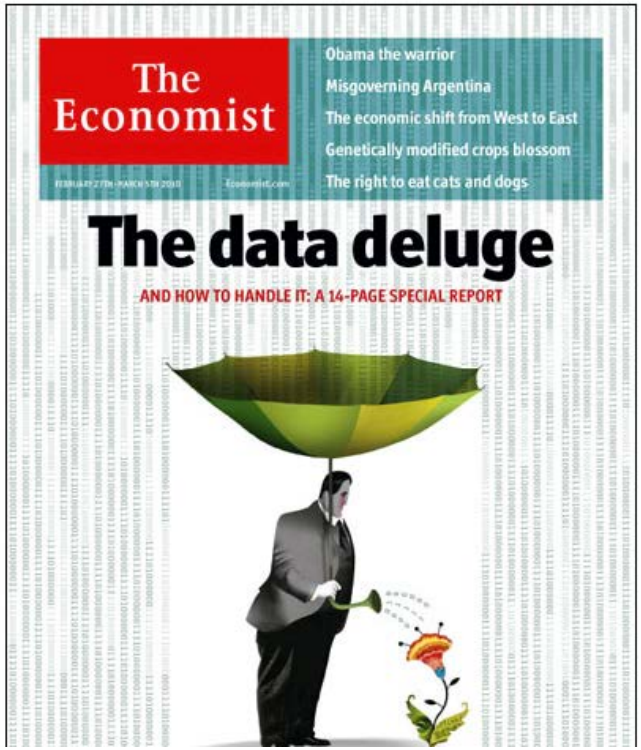
UC Project for Global Inequality

Economist.com

Print Edition

The Economist - North America Edition

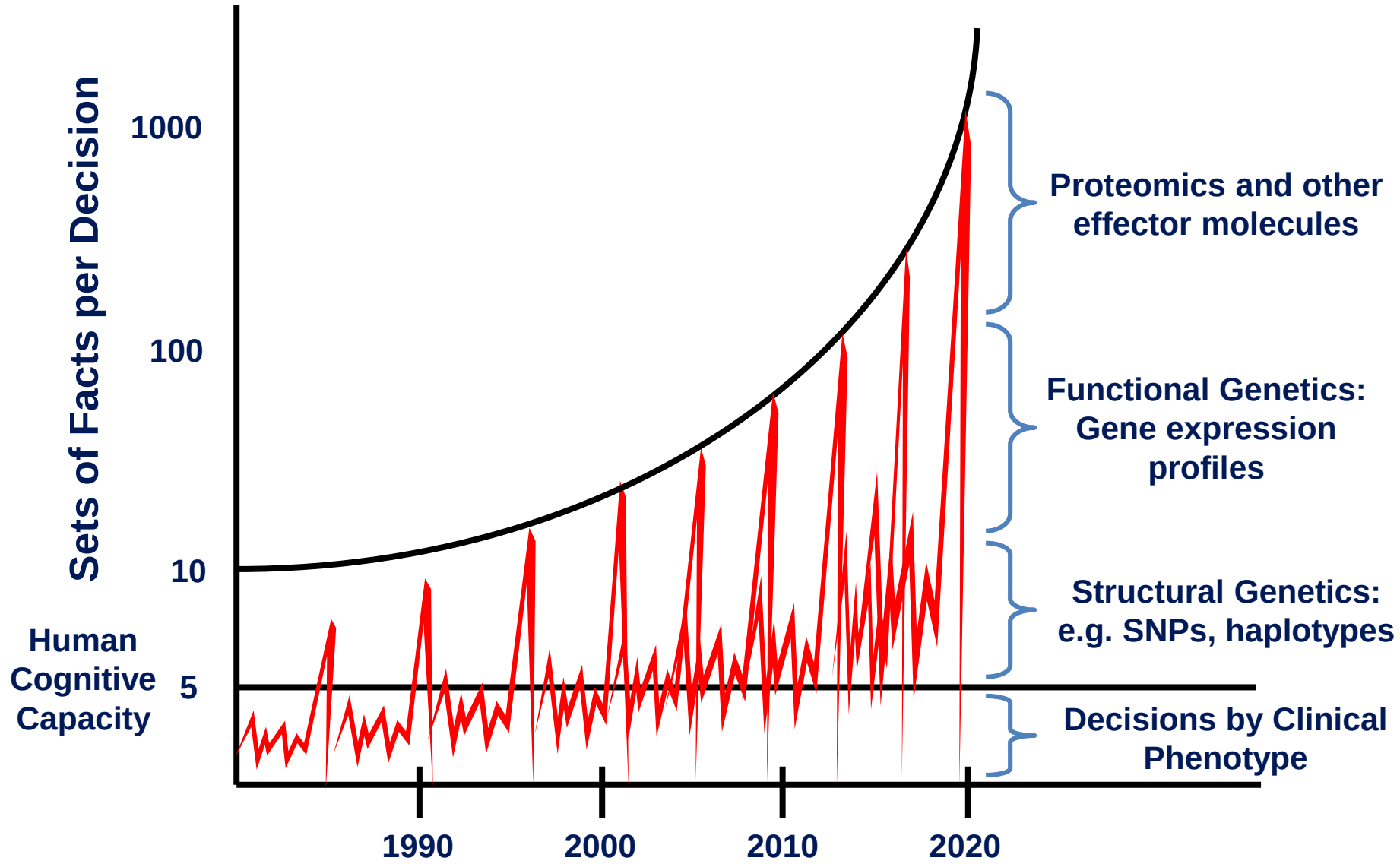
Feb 27th 2010



Truth and Expertise

- We are seeing an erosion in public confidence in:
  - Veracity of traditional sources of information
  - The value of credentialed expertise
  - Science itself
- The deluge of information is a key factor

Burning Platform: Overwhelming Complexity



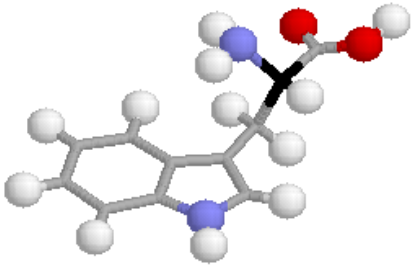
Stead WW. Beyond expert-based practice. IOM (Institute of Medicine). Evidence-based medicine and the changing nature of health care: 2007 IOM annual meeting summary,(Introduction and Overview, p. 19). Washington, DC: The National Academies Press 2008.

Precision Medicine Initiative: Modernizing FDA Regulation of Genomic Laboratory Tests

Traditional testing

Next generation sequencing

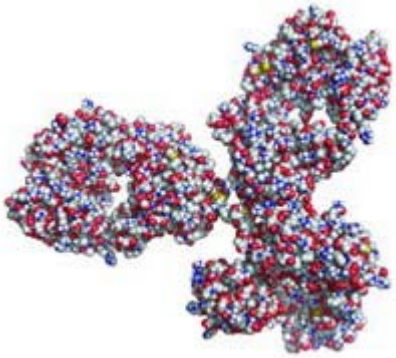
Relative Complexity of Therapies



One subunit of a protein

10^2 Atoms

L-tryptophan
Small Molecule Drug



Protein composed of about 1100 subunits

10^5 Atoms

IgG antibody molecule
Protein Biologic

Cell composed of about 3.6×10^6 proteins

10^{14} Atoms

Mesenchymal stem cell
Cellular Biologic

CRISPR/Cas9 Gene Editing

- Cas9 nuclease can be directed to cut at specific locations designated by guide RNAs
- Though there is some concern for off-target effects, CRISPR/Cas9 is a powerful technique for altering genes

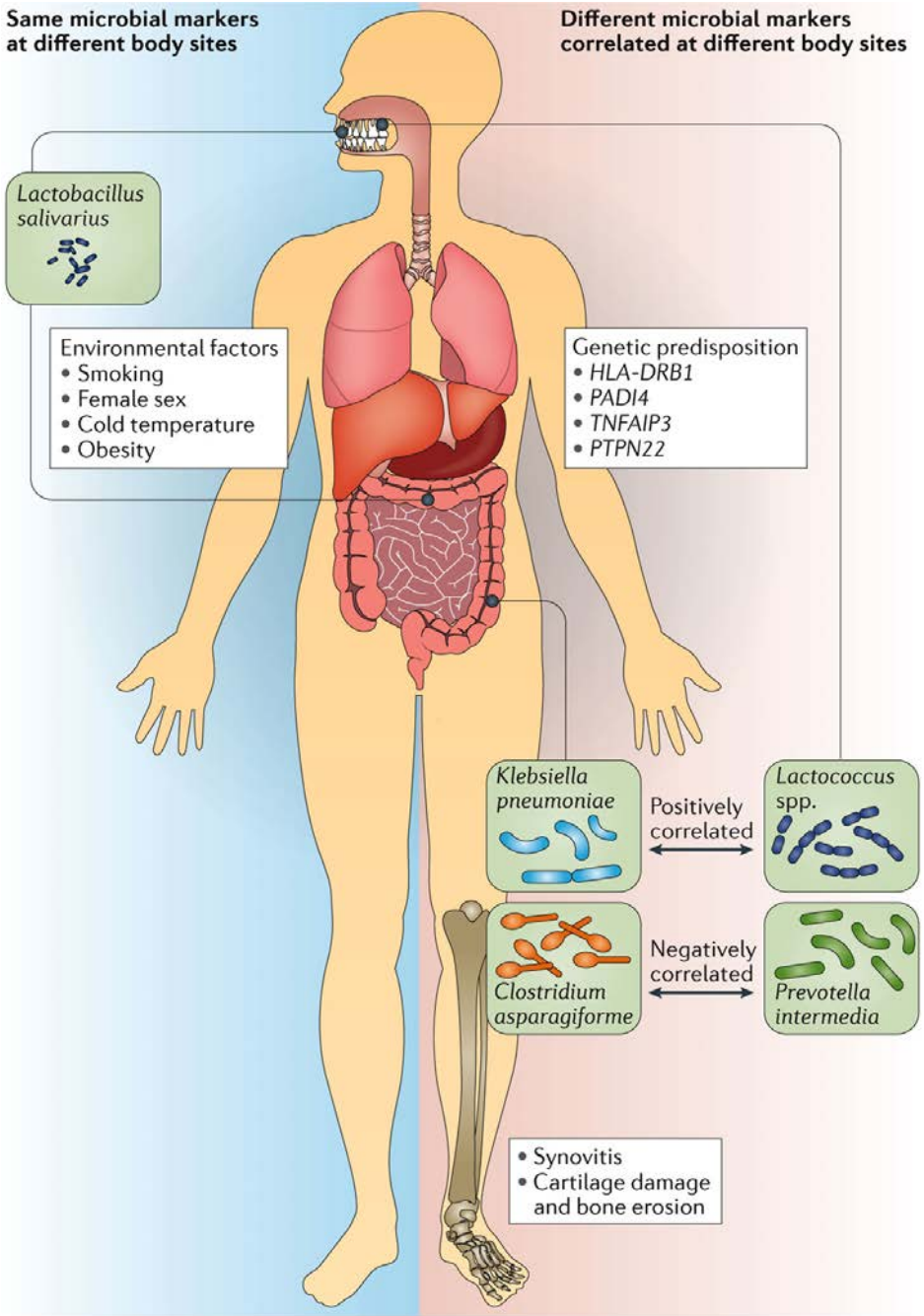
Short Introduction to Genome Editing

Three major forms of genome editing:

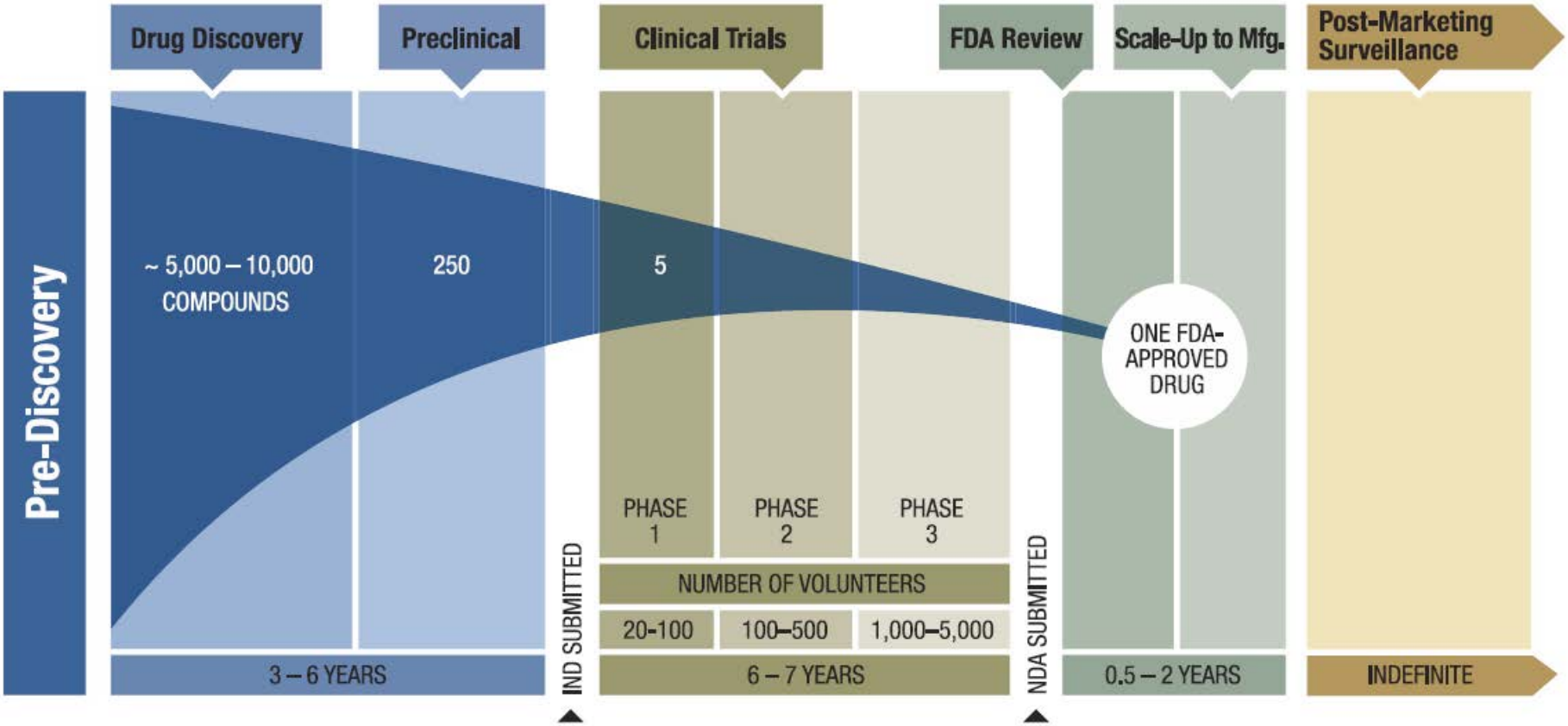
- Zinc Finger Nucleases (mid-2000s)
- TALENs (Transcription activator-like effector nucleases) (late 2000s)
- **CRISPR (clustered regularly interspersed short palindromic repeats and associated enzymatic activities (e.g., Cas9) (2011-2012 depending on whom you ask)**

Until these three forms of editing, alteration of genomic DNA could control the *nature* of the change (i.e., sequence-specific alterations), but except for the technically very difficult homologous recombination, neither:

- the specific location (i.e., site-specific alterations), nor
- the exact nature of the change
  - Deletion of specific nucleotides
  - Substitution of nucleotide/s
  - Addition of sequences by insertion at a specific site


Same microbial markers at different body sites
Different microbial markers correlated at different body sites
Lactobacillus salivarius
Environmental factors
• Smoking
• Female sex
• Cold temperature
• Obesity
Genetic predisposition
• HLA-DRB1
• PADI4
• TNFAIP3
• PTPN22
Klebsiella pneumoniae
Positively correlated
Lactococcus spp.
Clostridium asparagiforme
Negatively correlated
Prevotella intermedia
• Synovitis
• Cartilage damage and bone erosion

Drug Discovery and Development Timeline



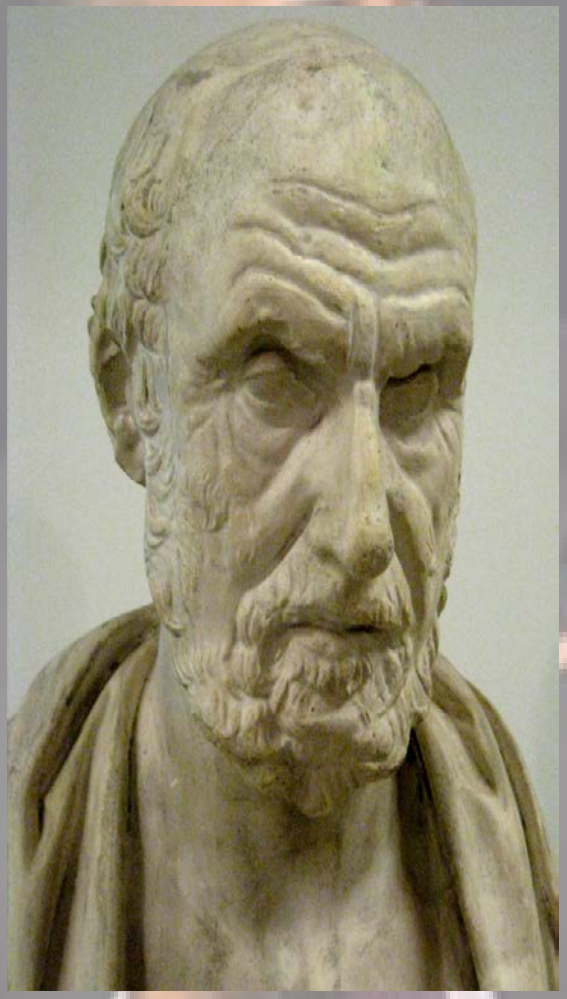
The Opportunity

- Information technology and “data science” have reached a phase of rapid acceleration
- We can sense, measure, compute, analyze and transmit in a manner that was imaginable only to a few a decade ago
- The translation of this capacity across the translational spectrum is “wide open”
- Technology advances rapidly, people change slowly
- I’ve never seen a better time to be in translational medicine
- **“Luck is what happens when preparation meets opportunity.”**

The Engine

- Data—abundant and overwhelming
- Information—a lot going into the computer, not much coming out
- Knowledge--< 15% of major clinical decisions informed by high quality information
- Wisdom—how often are we “the emperor with no clothes” given the paucity of evidence
- **The time is right to shift the action to the right on this continuum**

Precision medicine for the population, and the patient



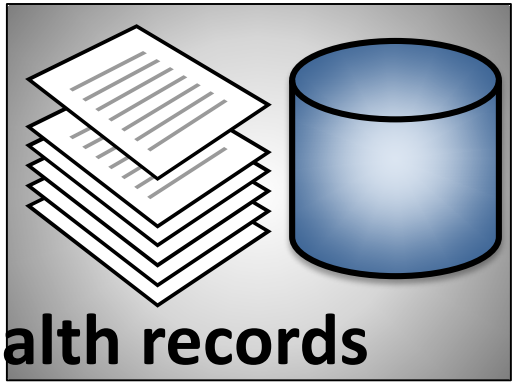
It is more important to know what sort of person has a disease than to know what sort of disease a person has.

Hippocrates

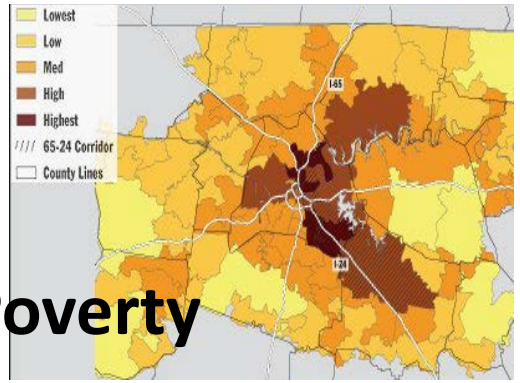
A Critical Conceptual Issue in Precision Medicine

- Personalized medicine was sold in many quarters as an approach in which deep study of a few people could be generalized to entire populations
- Deep dives into individuals and small groups will remain important, but…
- Precision medicine is evolving with the realization that due to the multidimensional heterogeneity of the problem, in order to devise effective therapies we need deep study of the entire population to find predictive (probabalistic) relationships that can be applied to individuals based on what they have in common with others (“patients like us”)

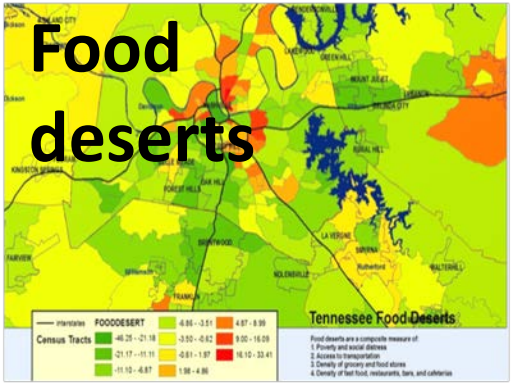
Many tools to dissect individualized health

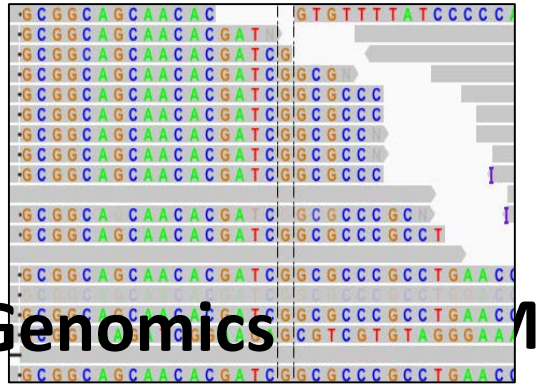


Health records

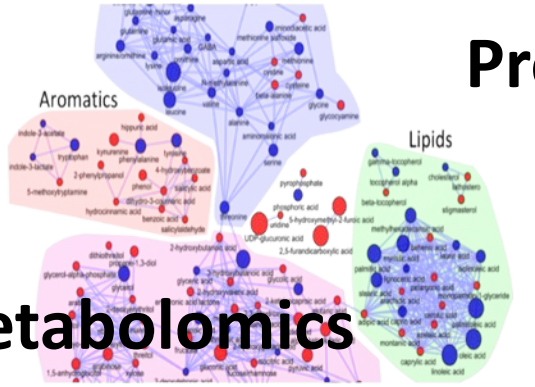


Poverty

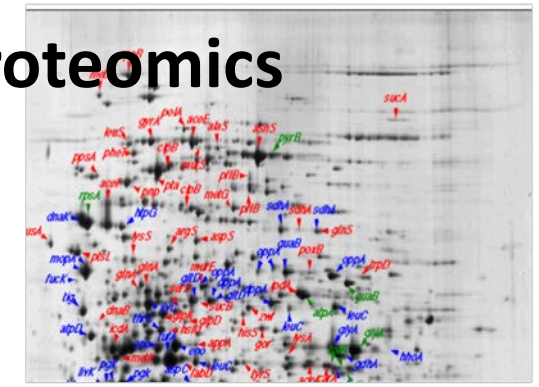




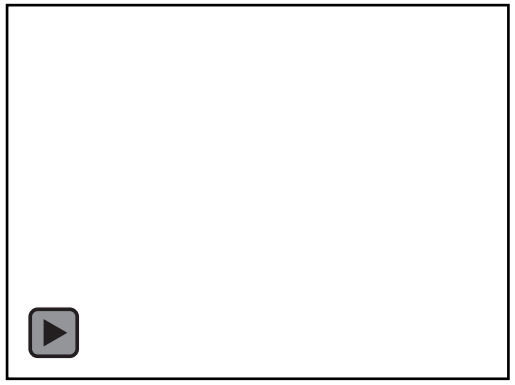
Genomics

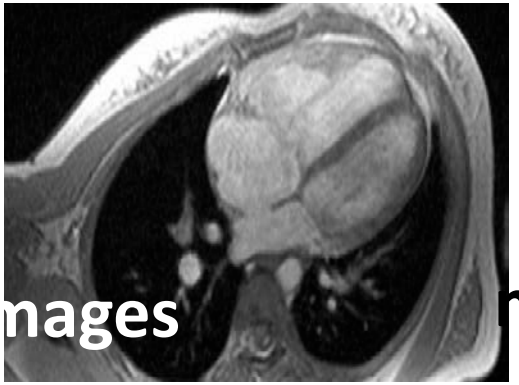


Metabolomics



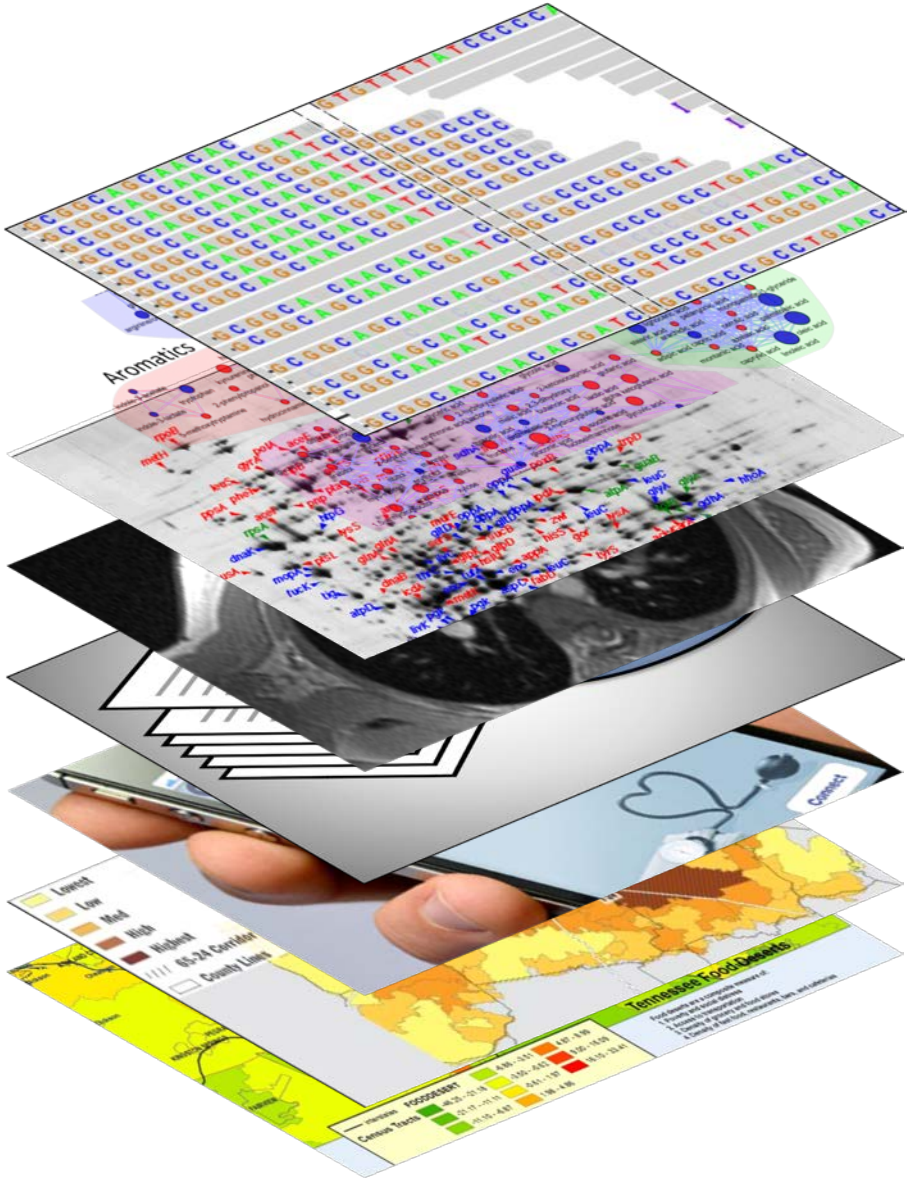
Proteomics





mages

mHealth



The challenge: integrating multiple datasets for discovery and implementation

Big Challenges in Biomedicine

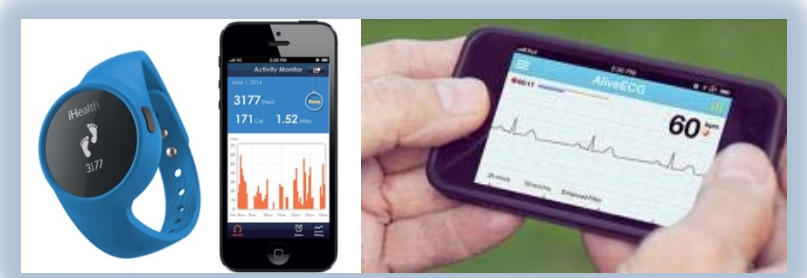
- Lack of significant information over the time dimension — Measurements made to assess biology and human health are made periodically in visits to healthcare or research
- Missing systems biology — When developing concepts of human biology or drug development we make limited measurements focused on specific mechanisms—we're looking "under the lamppost"
- Missing the ability to measure the interactions of biology, sociology, environment and decision-making that could enable optimization of individualized and population health — Although we know that health and disease are the product of the interactions of genes, multiple derivative biological systems, environment, social context and personal decisions, we tend to look at one part of the time

THE PRECISION MEDICINE INITIATIVE® COHORT PROGRAM

- One million or more volunteers, reflecting the broad diversity of the U.S.
- Opportunities for volunteers to provide data on an ongoing basis
- Data shared freely and fast to inform a broad variety of research studies

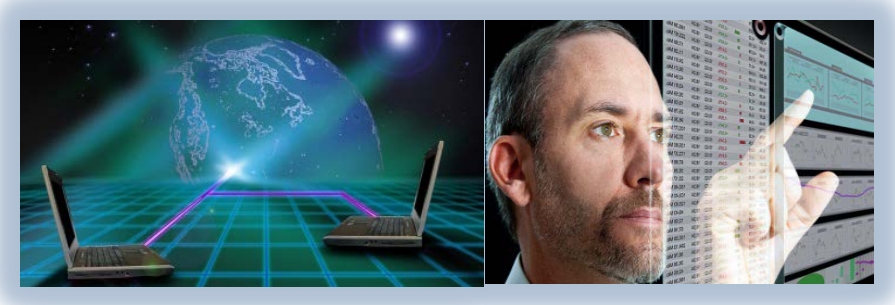
Patient Partnerships

EHRs



Technologies

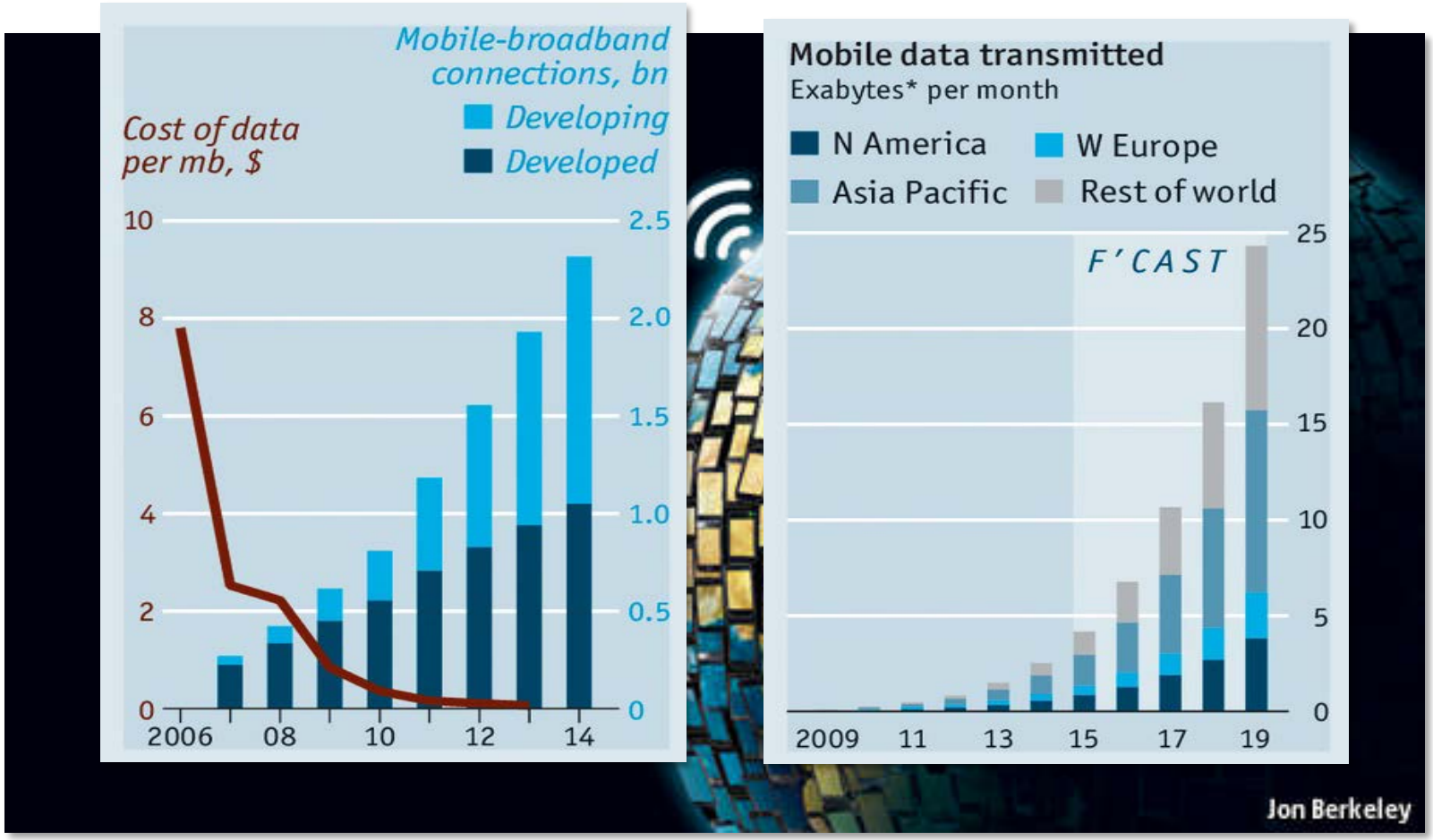
Genomics



Data Science

The Economist

Planet of the Phones



The Economist. Feb 2015

By Marie Lynn Miranda, Jeffrey Ferranti, Benjamin Strauss, Brian Neelon, and Robert M. Califf

DOI: 10.1377/hlthaff.2012.1199
HEALTH AFFAIRS 32,
NO. 9 (2013): 1608–1615

Geographic Health Information Systems: A Platform To Support The 'Triple Aim'

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Jeffrey Ferranti is the chief medical information officer and vice president for clinical informatics, and an assistant professor in newborn critical care, at Duke University Medical Center, in Durham, North Carolina.

Benjamin Strauss is an associate in research at the Nicholas School of the Environment, Duke University.

Brian Neelon is a statistician at the Nicholas School of the Environment, Duke University.

Robert M. Califf is vice chancellor for clinical and translational research and a professor of medicine in the Division of Cardiology, Duke University Medical Center.

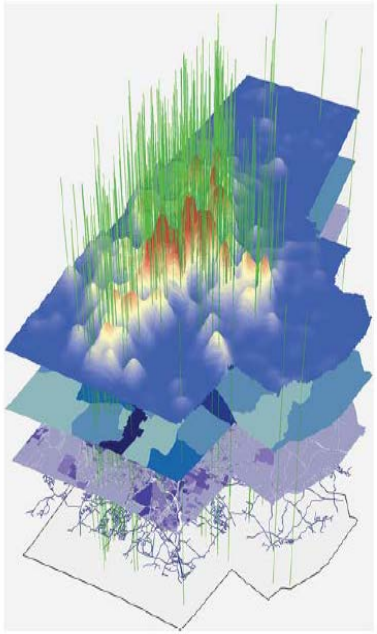
ABSTRACT **Despite the rapid growth of electronic health data, most data systems do not connect individual patient records to data sets from outside the health care delivery system. These isolated data systems cannot support efforts to recognize or address how the physical and environmental context of each patient influences health choices and health outcomes. In this article we describe how a geographic health information system in Durham, North Carolina, links health system and social and environmental data via shared geography to provide a multidimensional understanding of individual and community health status and vulnerabilities. Geographic health information systems can be useful in supporting the Institute for Healthcare Improvement's Triple Aim Initiative to improve the experience of care, improve the health of populations, and reduce per capita costs of health care. A geographic health information system can also provide a comprehensive information base for community health assessment and intervention for accountable care that includes the entire population of a geographic area.**

Donald Berwick and colleagues' influential 2008 *Health Affairs* article, "The Triple Aim: Care, Health, and Cost," describes a conceptual framework developed by the Institute for Healthcare Improvement for improving the US health care system.[1] In the Triple Aim, the institute has identified three aims that must be simultaneously pursued: improve the experience of care, improve the health of populations, and reduce per capita costs of health care. In this article we introduce and describe information technology designed to support health systems and communities in achieving the Triple Aim. We demonstrate how this technology can be used to assess the health of hood lead exposure; a health services application to better manage patient flow to emergency departments (EDs); and a clinical population health application designed to care for people with diabetes at the individual, neighborhood, and county levels.

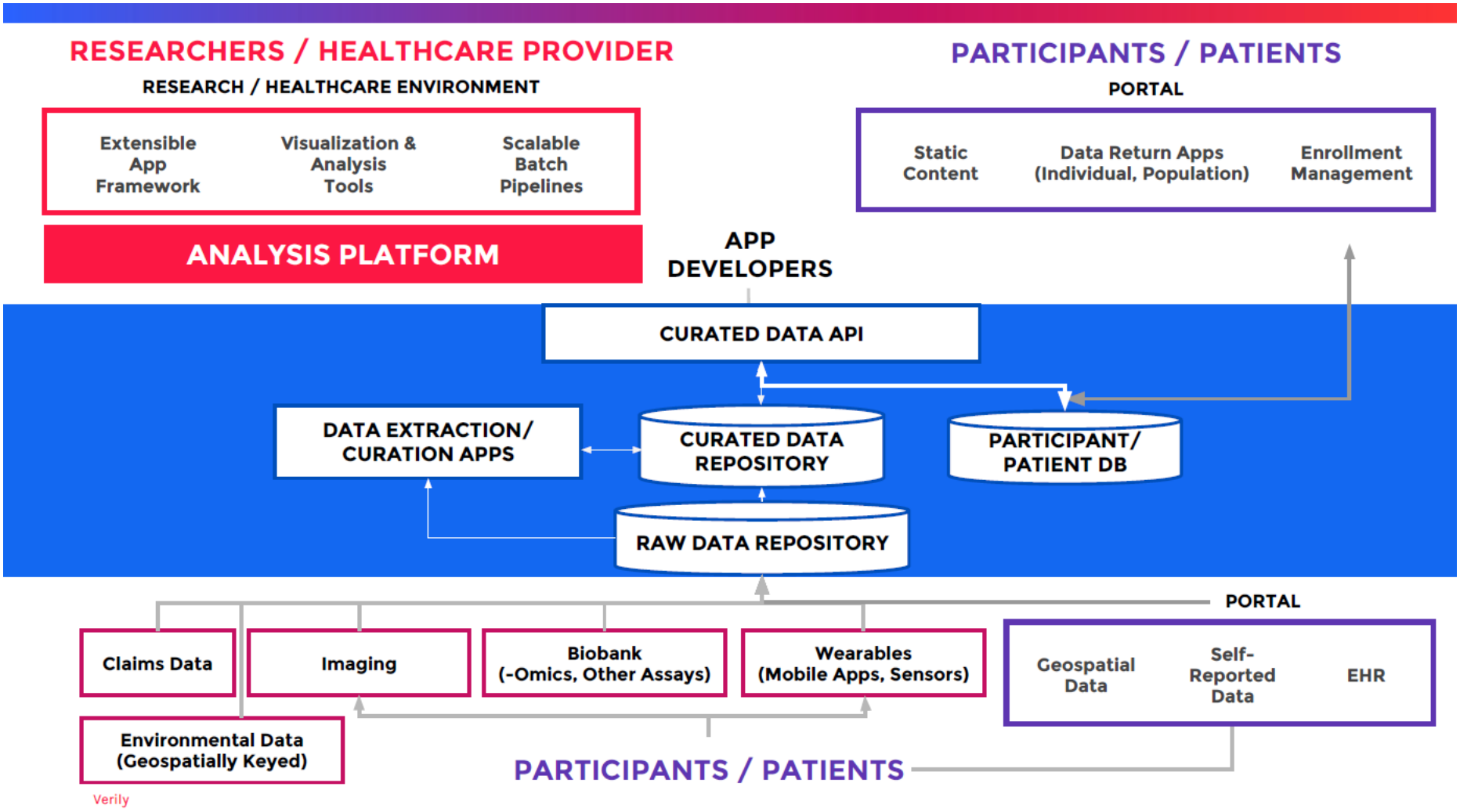
The Triple Aim has been used by a number of health systems as a conceptual framework for designing health system improvement programs.[2–4] The abundant electronic health data that are accumulating are highly relevant to managing population health and developing new insights.[5] Until recently, however, these data have been dispersed across many locations, with little integration.[6,7] As integrated health systems are becoming more widespread, these data are being

EXHIBIT 1

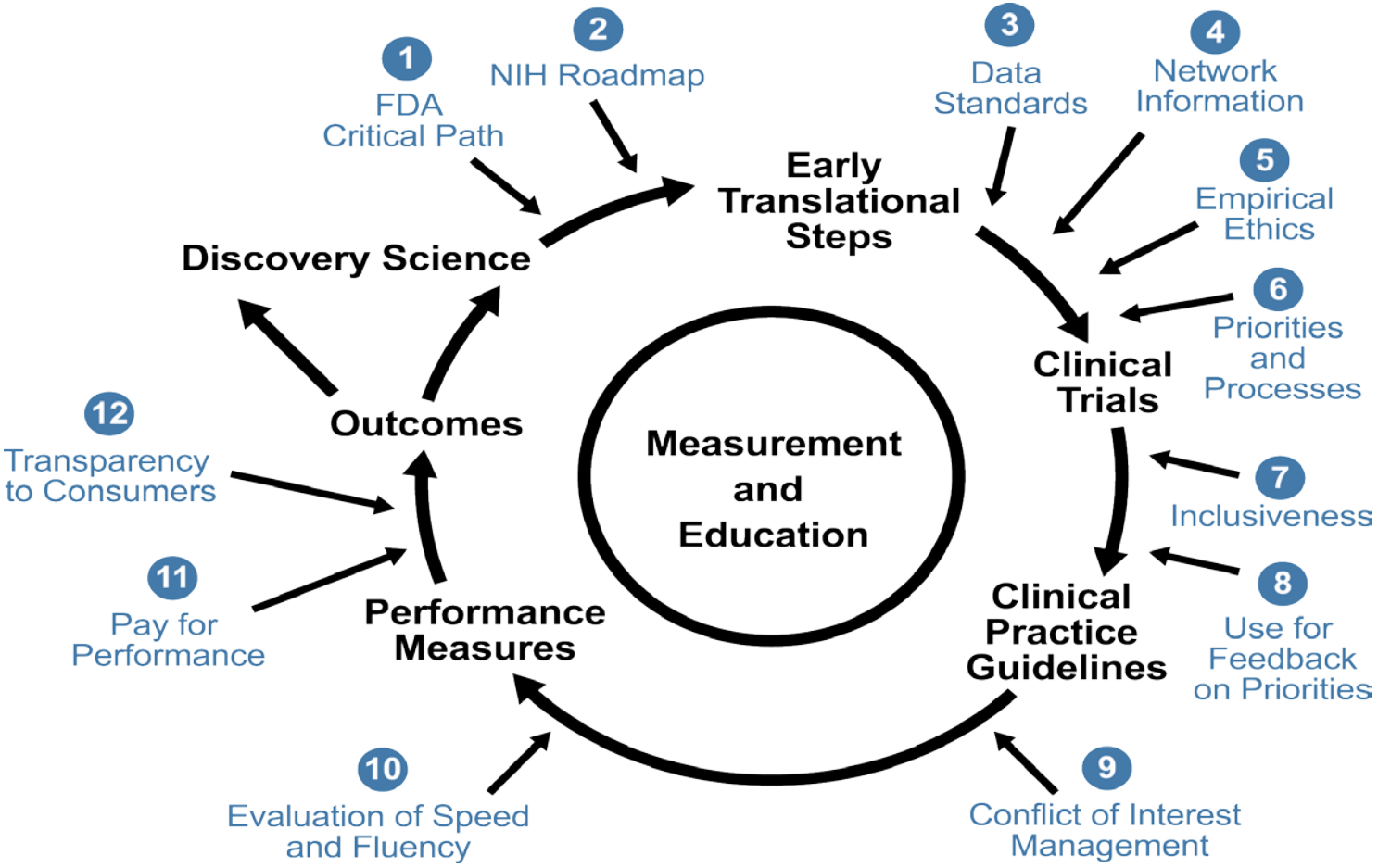
Example Of Geographic Health Information Systems (GHIS) For Mapping The Terrain Of Diabetes In Durham County, North Carolina



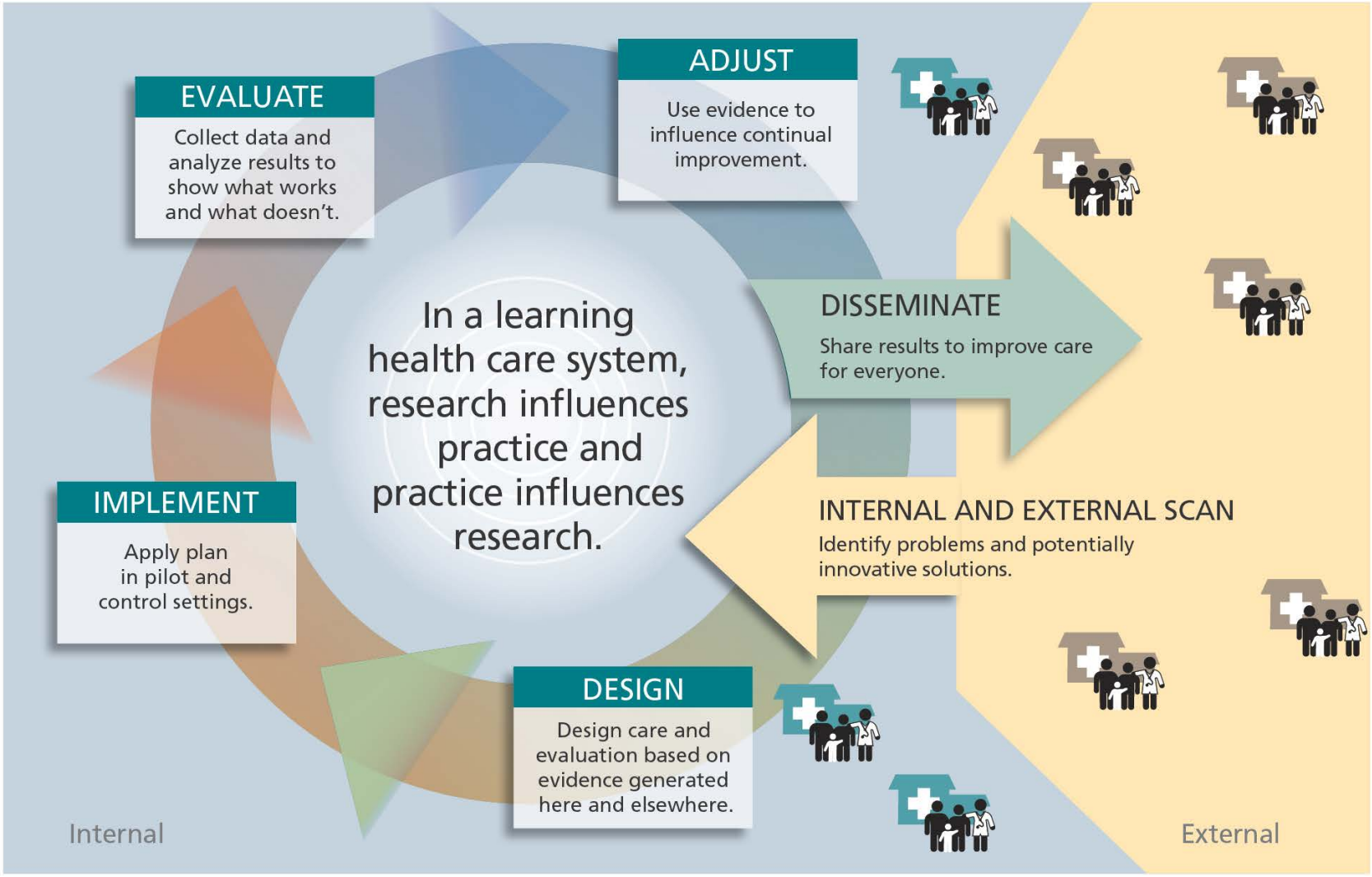
SOURCE Duke Health Technology Solutions Decision Support Repository (DSR), using information on boundaries and streets layers from the US Census Bureau Geography Division, census 2010; and tax-parcel data from the Durham County Tax Assessor. **NOTE** The elements of this GHIS map are ex-


RESEARCHERS / HEALTHCARE PROVIDER
RESEARCH / HEALTHCARE ENVIRONMENT
Extensible App Framework
Visualization & Analysis Tools
Scalable Batch Pipelines
ANALYSIS PLATFORM
PARTICIPANTS / PATIENTS
PORTAL
Static Content
Data Return Apps (Individual, Population)
Enrollment Management
APP DEVELOPERS
CURATED DATA API
DATA EXTRACTION/ CURATION APPS
CURATED DATA REPOSITORY
PARTICIPANT/ PATIENT DB
RAW DATA REPOSITORY
PORTAL
Claims Data
Imaging
Biobank (-Omics, Other Assays)
Wearables (Mobile Apps, Sensors)
Geospatial Data
Self-Reported Data
EHR
Environmental Data (Geospatially Keyed)
PARTICIPANTS / PATIENTS
Verily

Generating Evidence to Inform Decisions

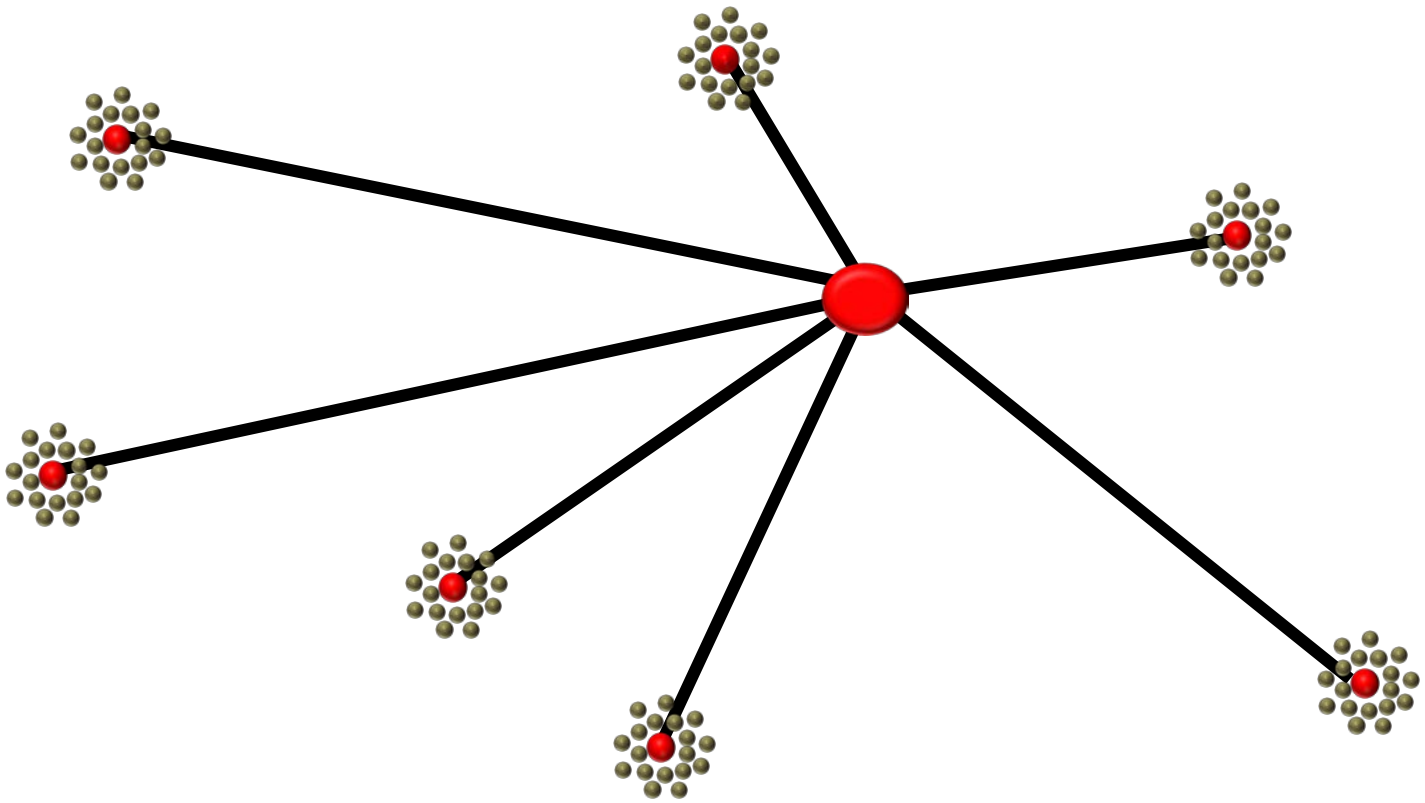


Learning health care systems

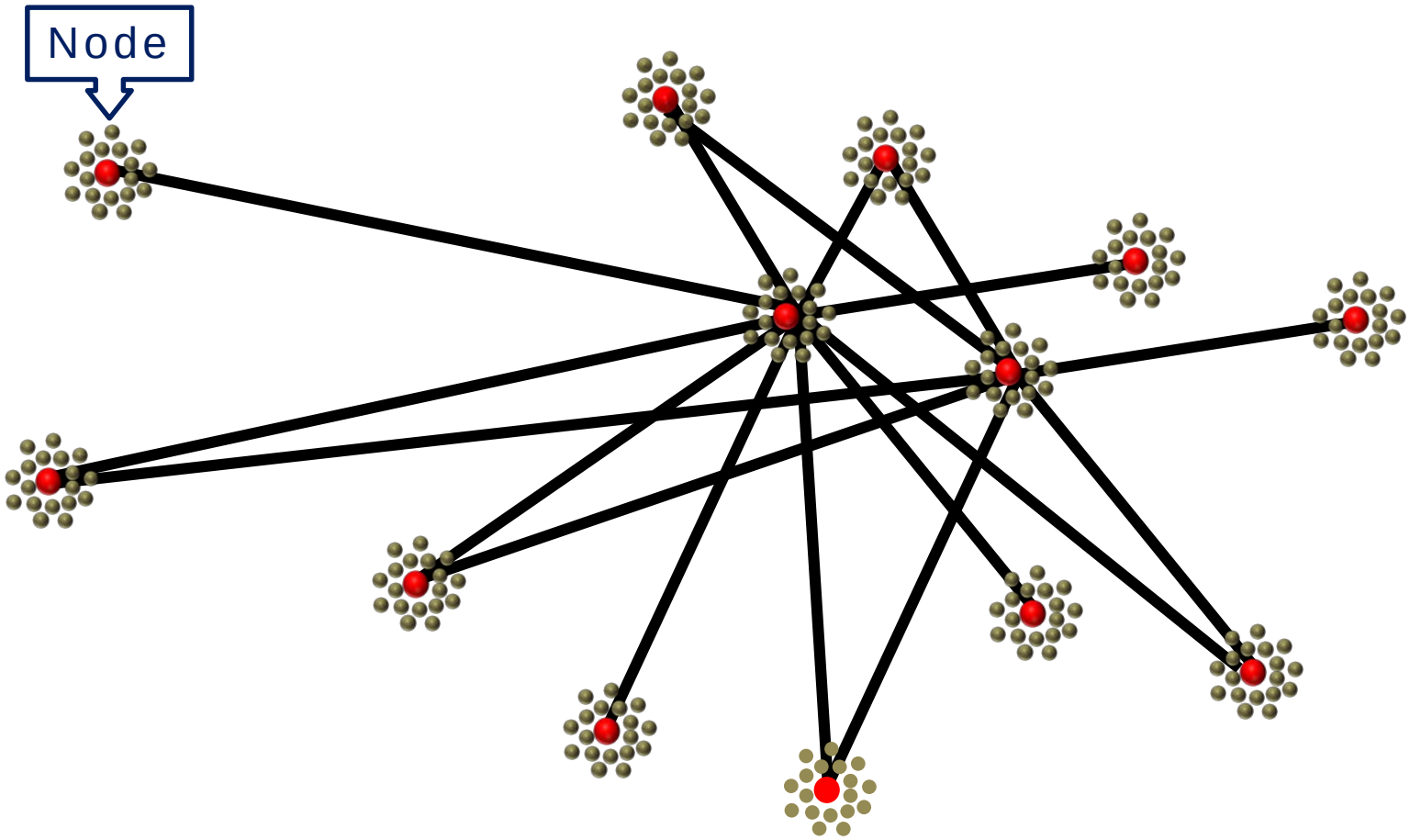


Historical model of clinical research: Many recruitment sites and a coordinating center

- Hub & spoke model
- Top-down decision-making
- Sites operated independently



Modified Model
Data Shared, Sites owned by Health Systems



Academic medical centers in the US have become academic health and science systems (AHASs!)—they are no longer ivory towers– they are major economic engines and social forces in our society

The “Biomedical Academic System”

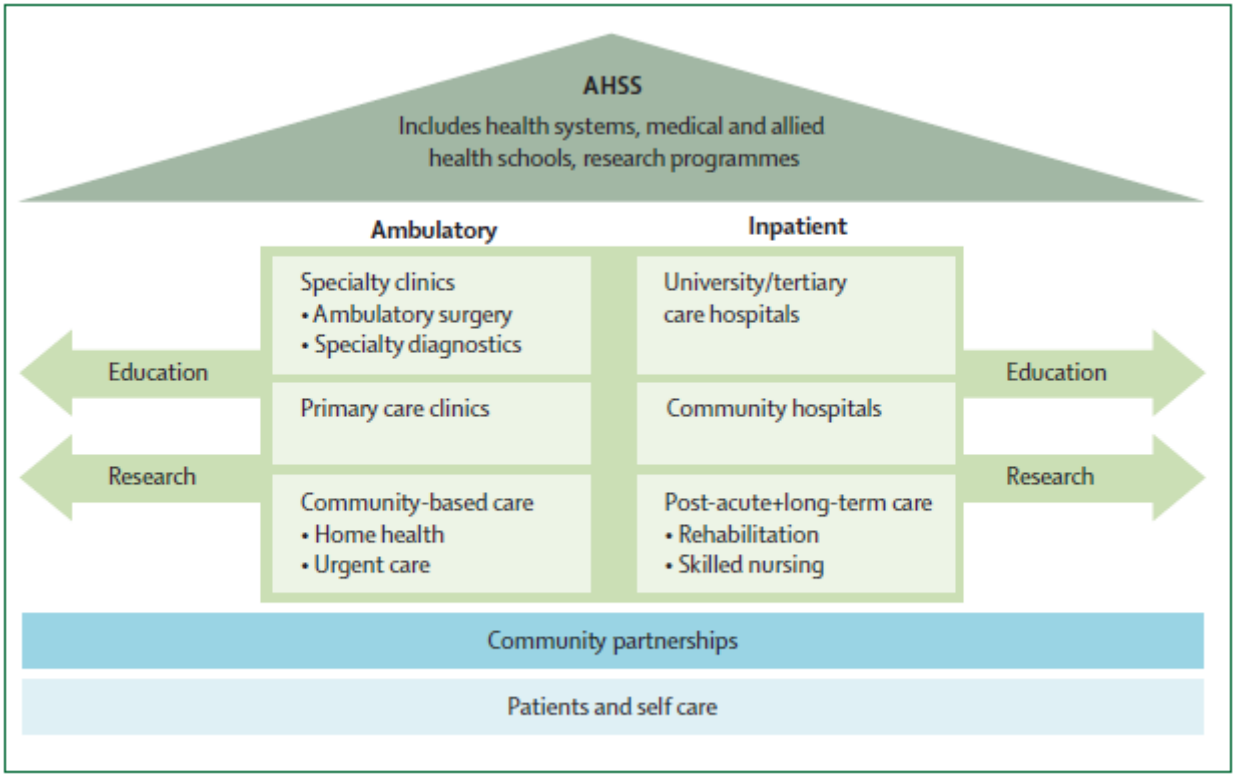
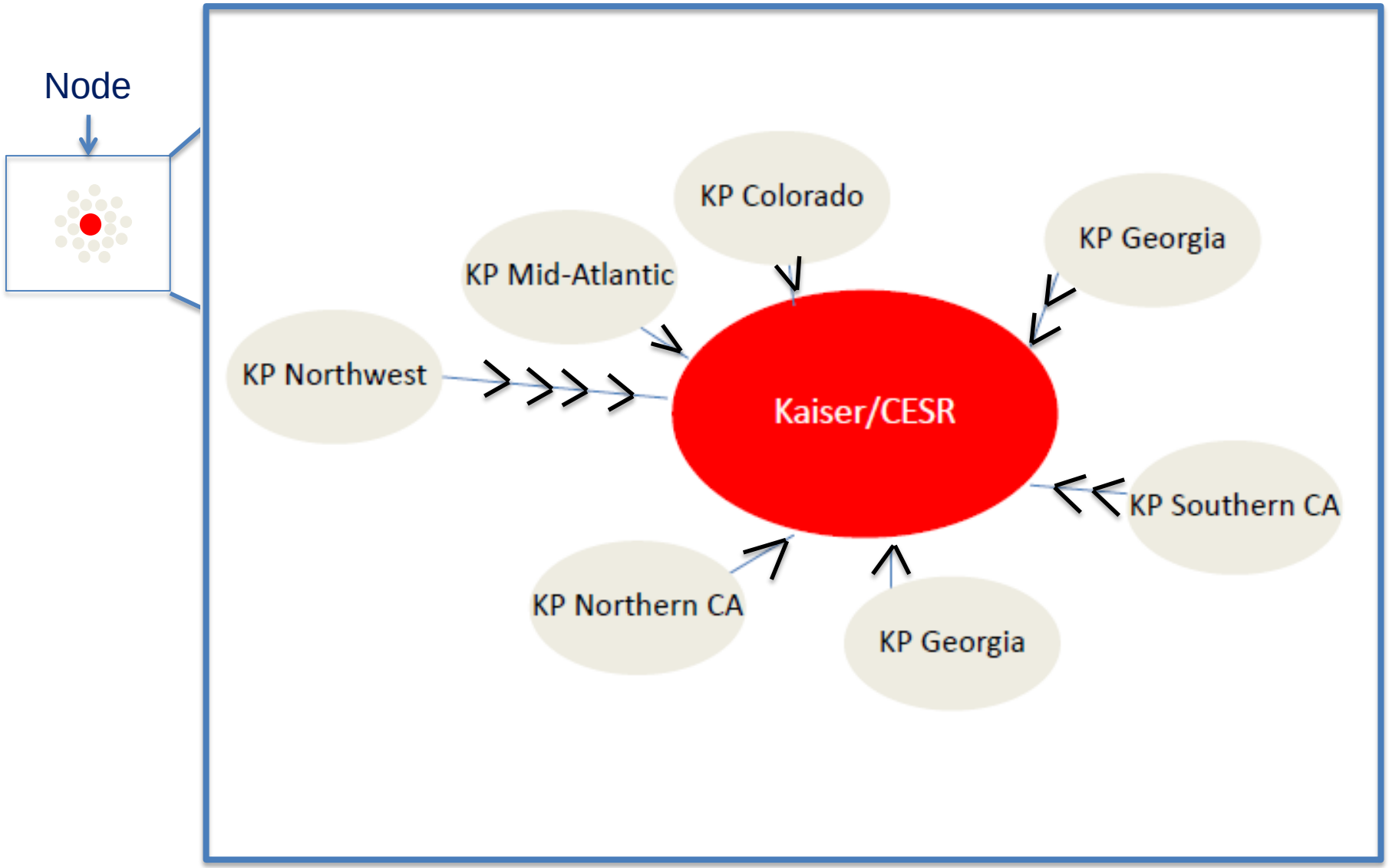


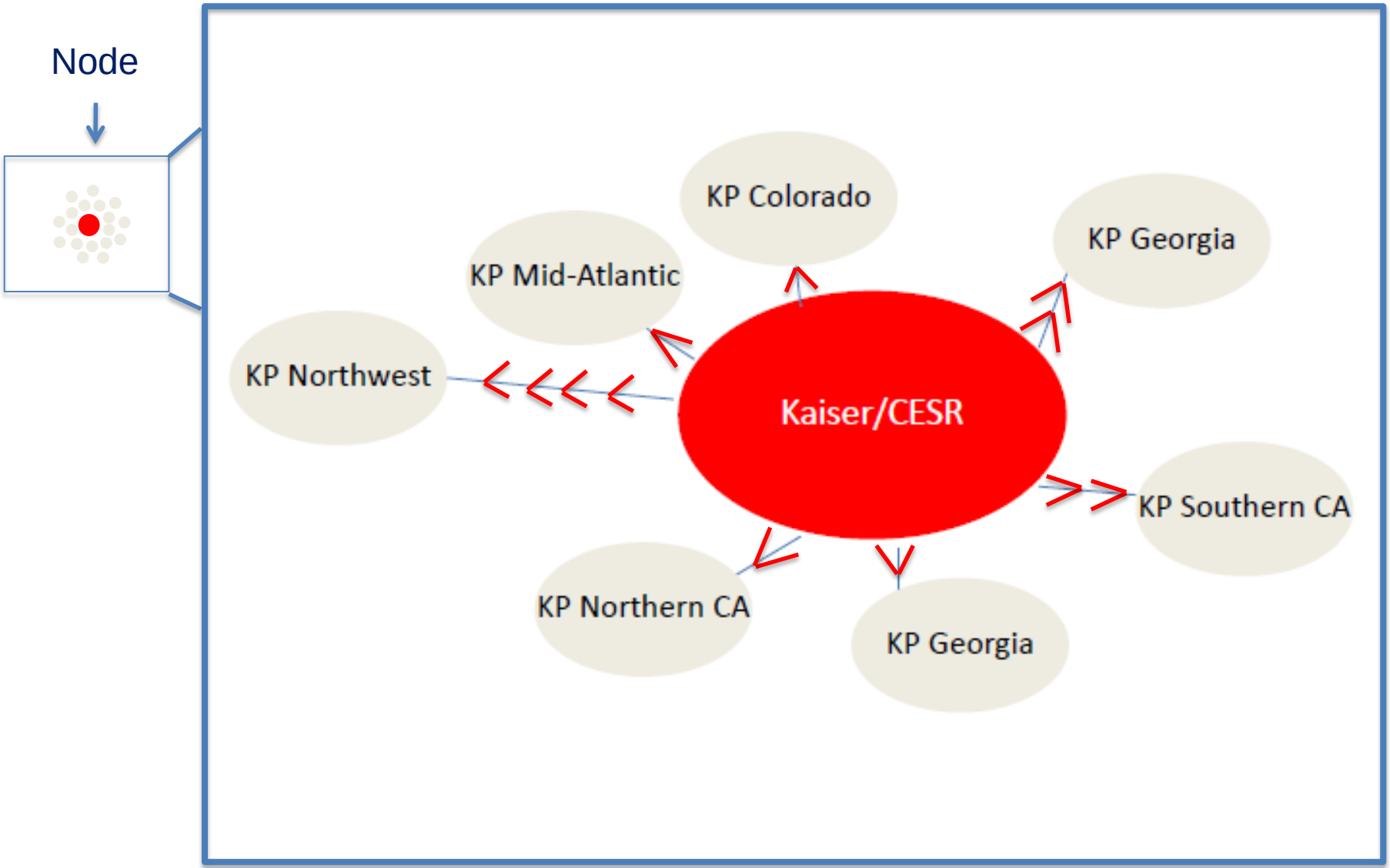
Figure 2: **Academic health sciences system (AHSS) as a vertically integrated care-delivery system**

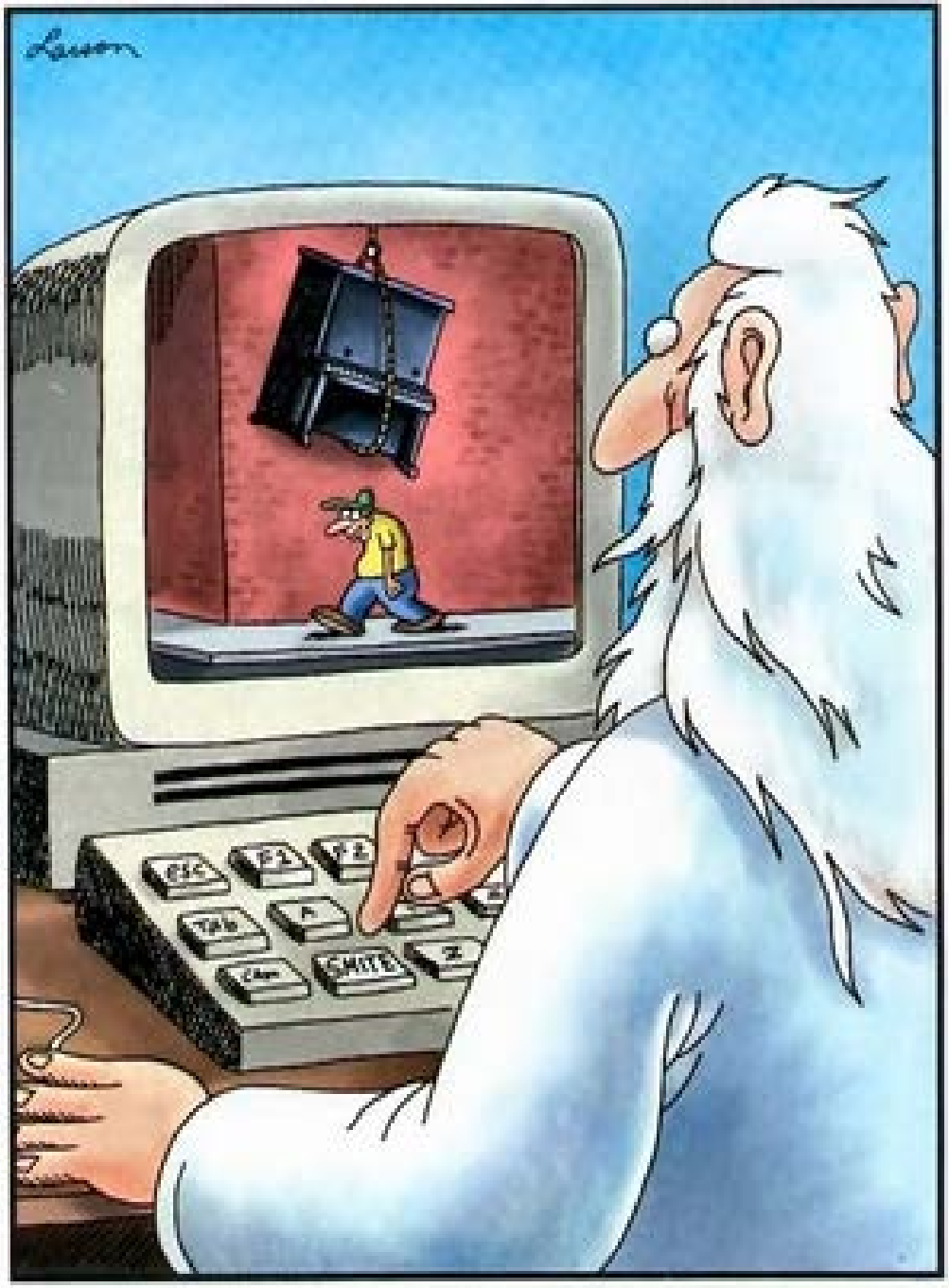
Dzau et al., “The Role of Academic Health Science Systems in the Transformation of Medicine,” *The Lancet* 375 (March 13, 2010): 951.

Previously Independent Sites now part of large integrated health systems
increasingly sophisticated data warehouses



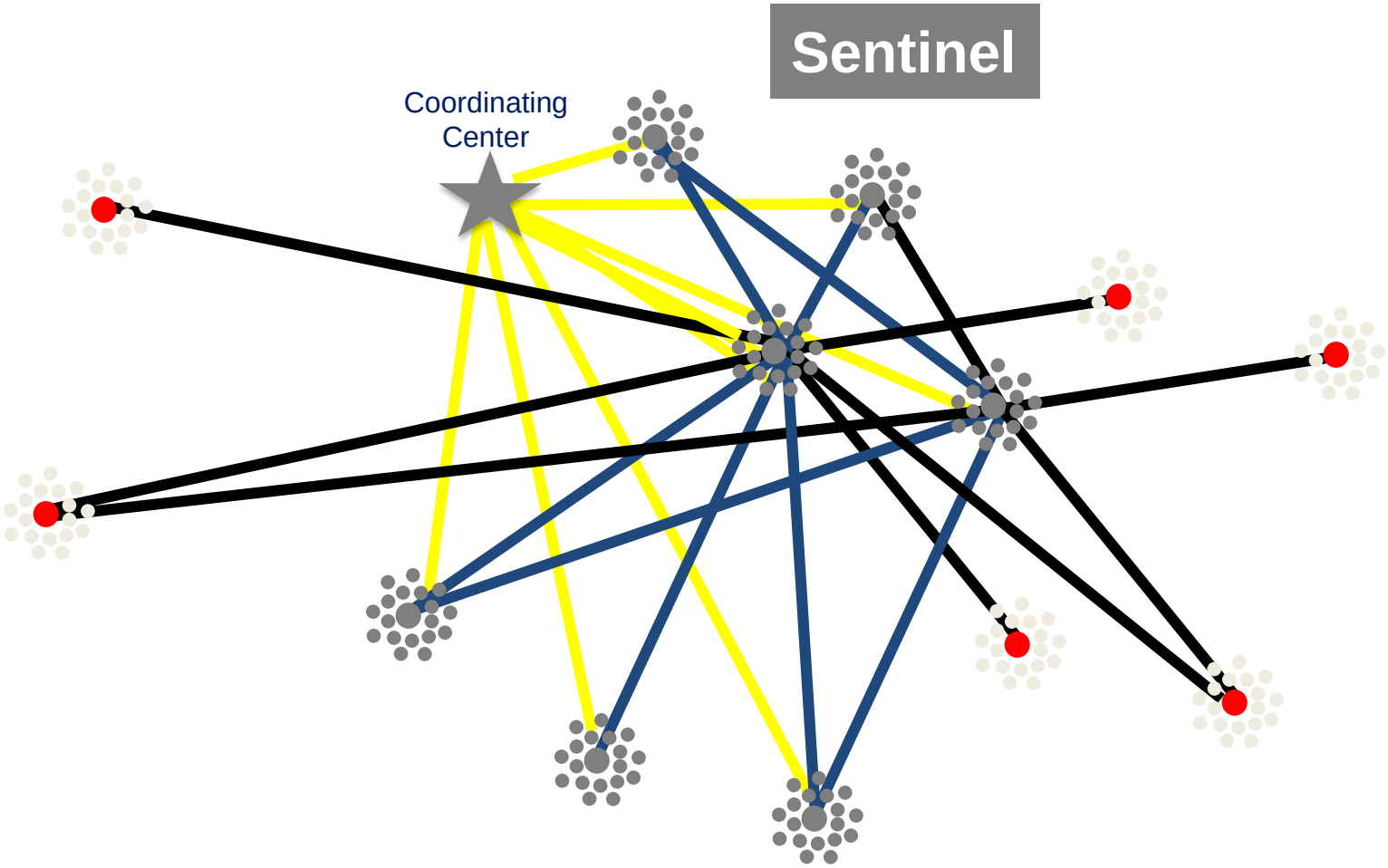
Nodes are Operational Clusters Using Common Data



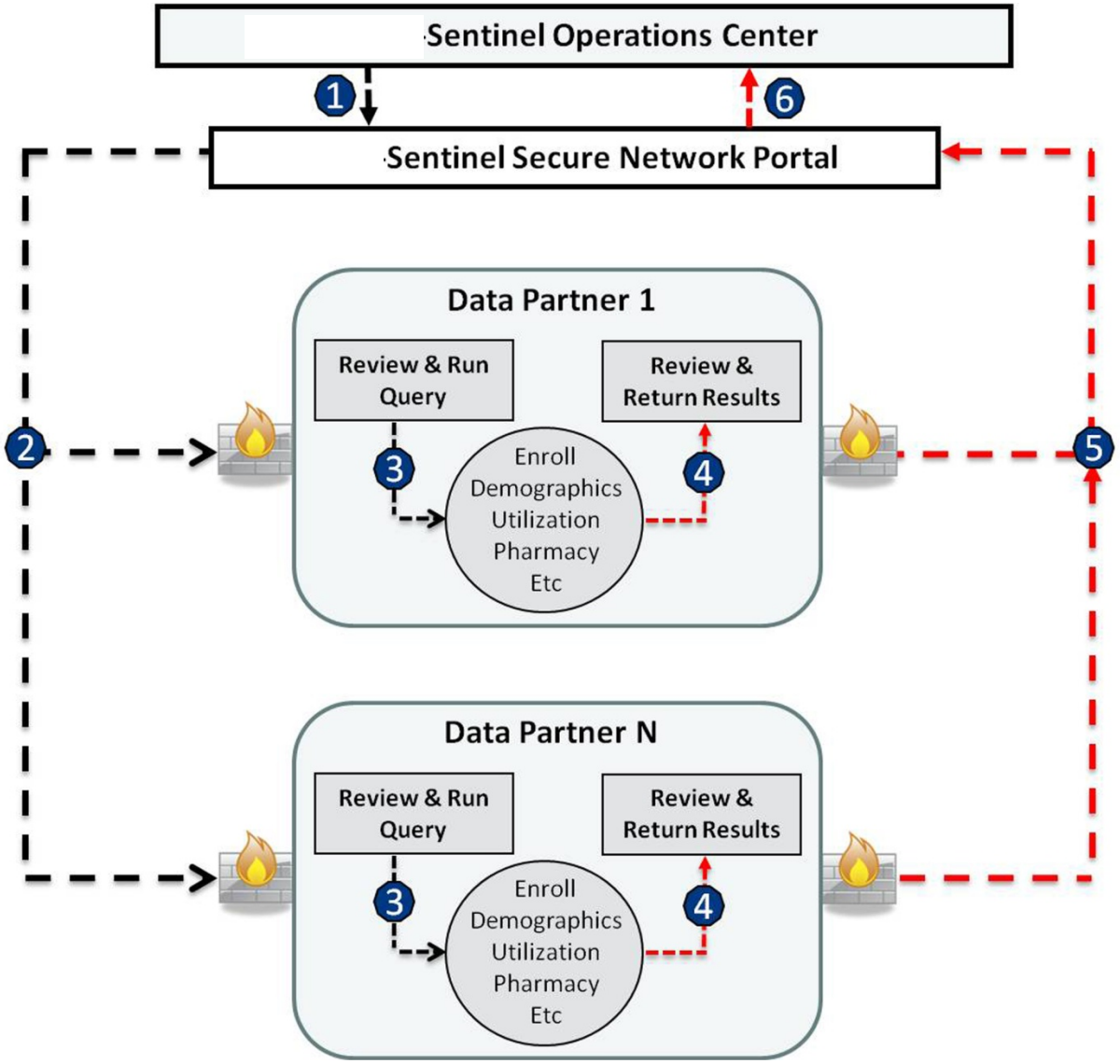


God at His computer

Drug Surveillance and Trials



Sentinel Distributed Analysis



1- User creates and submits query (a computer program)

2- Data partners retrieve query

3- Data partners review and run query against their local data

4- Data partners review results

5- Data partners return results via secure network

6 Results are aggregated

Sentinel Distributed Database*

- Populations with well-defined person-time for which most medically-attended events are known

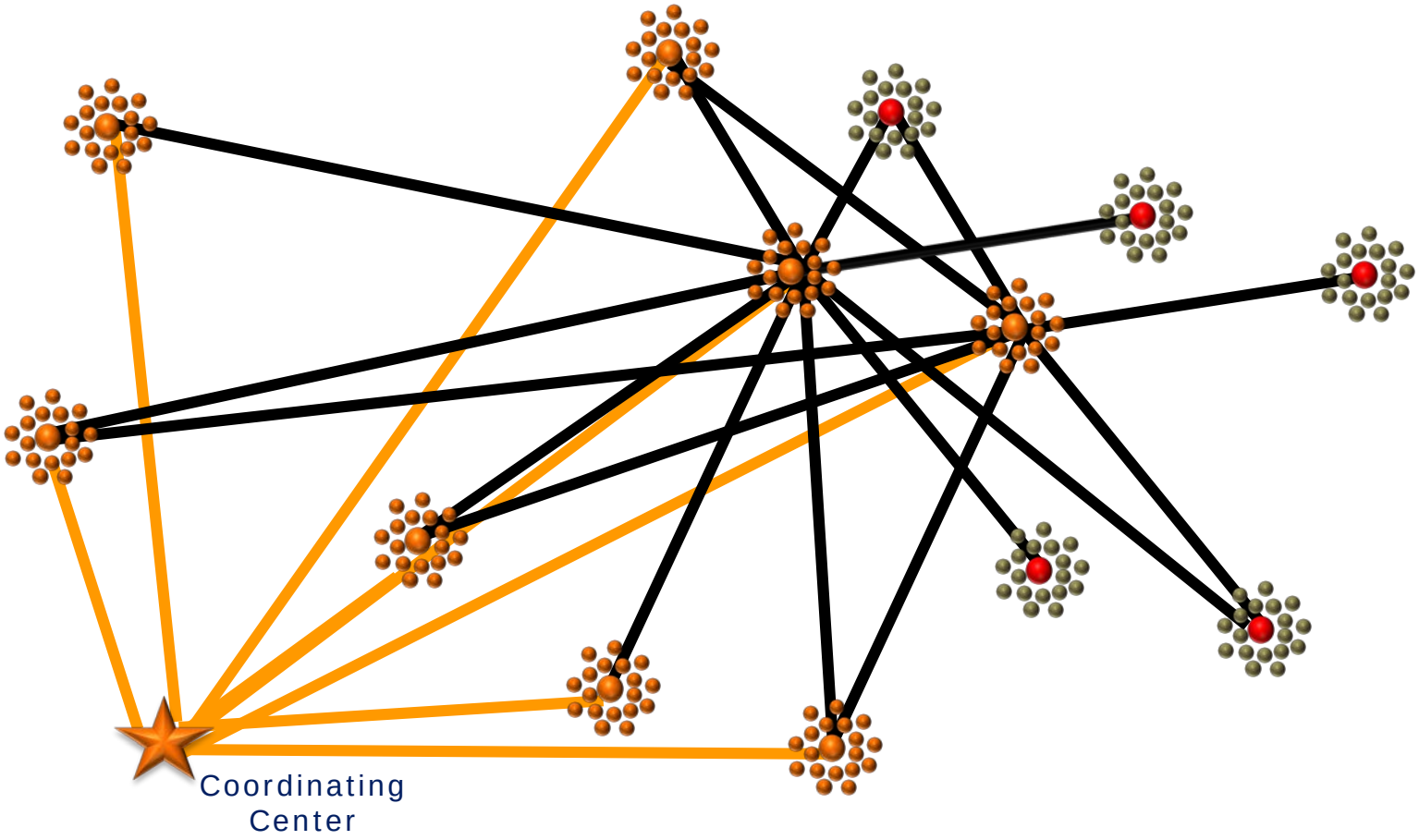
- 193 million members**
- 351 million person-years of observation time
- 39 million people currently accruing new data
- 4.8 billion dispensings
- 5.5 billion unique encounters
  - 51 million acute inpatient stays
- 33 million people with ≥1 laboratory test result

* As of August 2015, excludes HCA and BCBS of Massachusetts

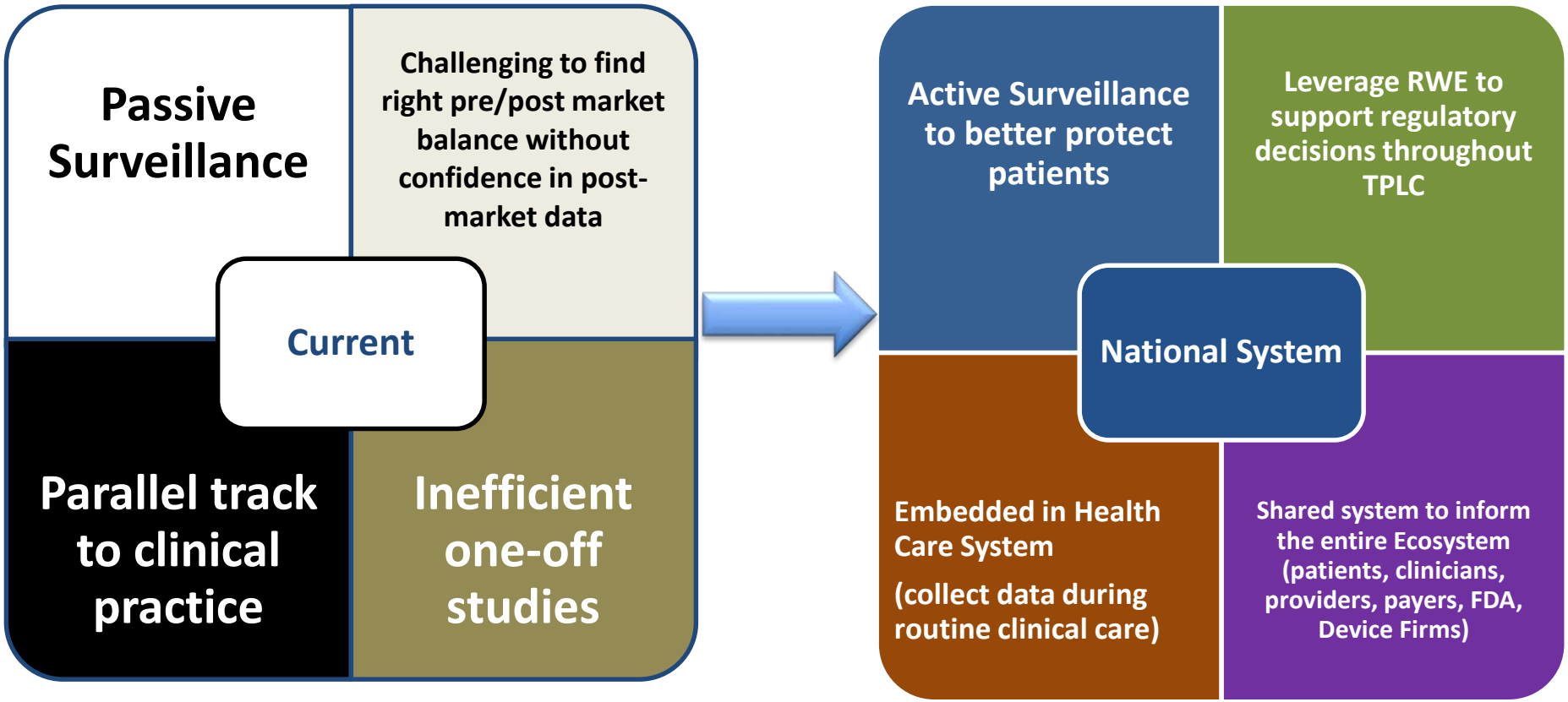
** Double counting exists for individuals who change health plans

Device Surveillance and Trials

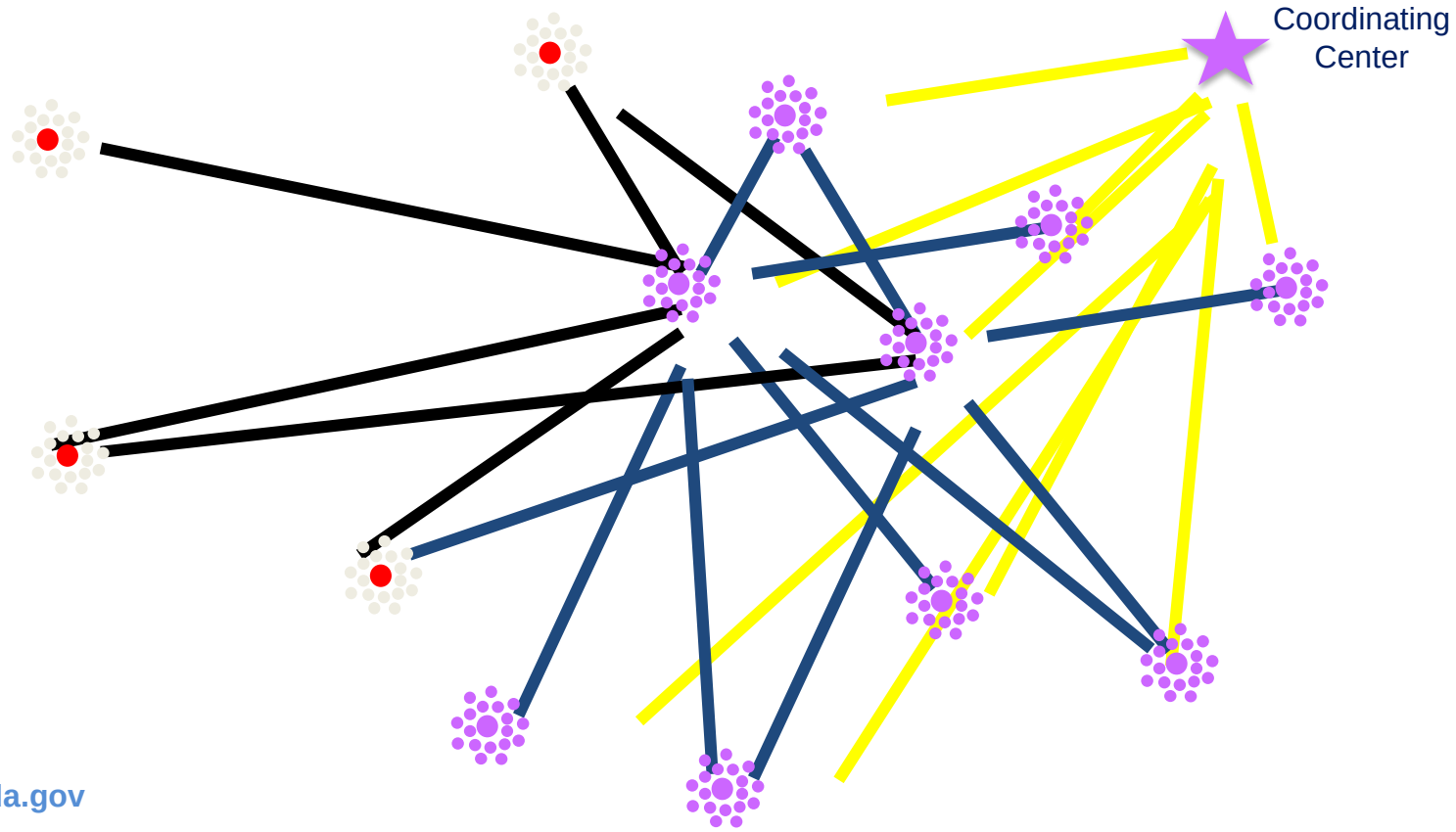
NEST



National System Paradigm Shift



Post Market Studies, including comparative effectiveness



Demonstration Project Overview-NIH Healthcare Systems Research Collaboratory

10 Demonstration Projects spanning 12 NIH institutes and centers

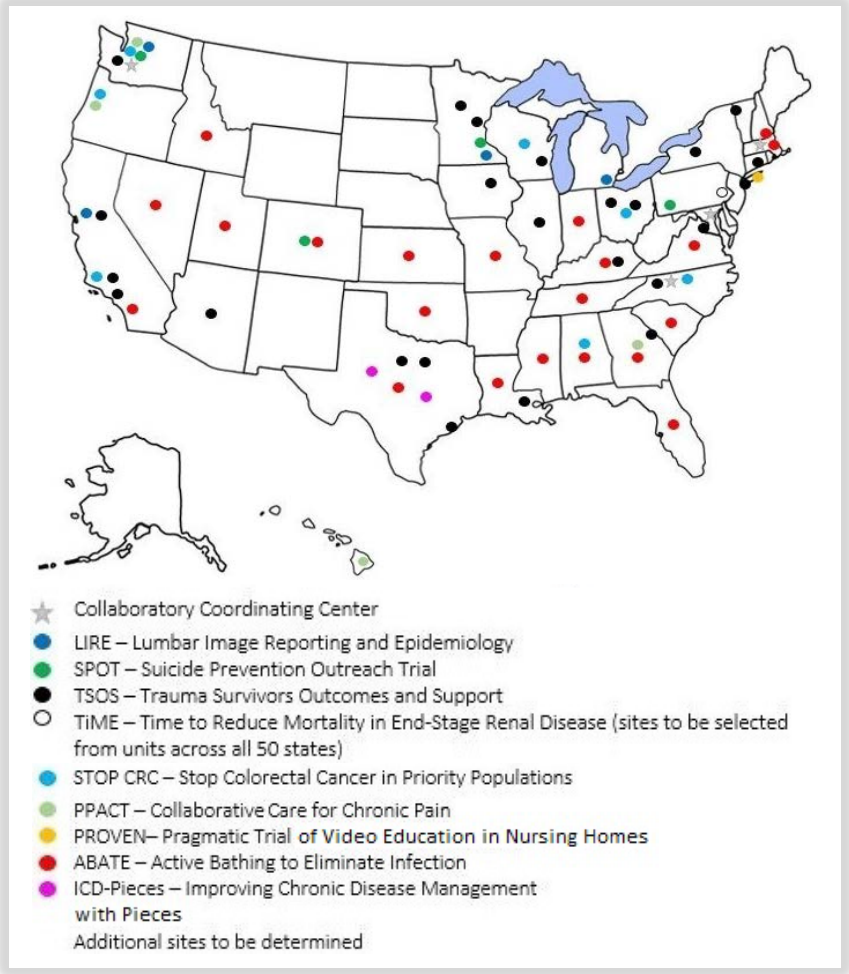
Major clinical outcome trials

1-year planning phase (UH2)

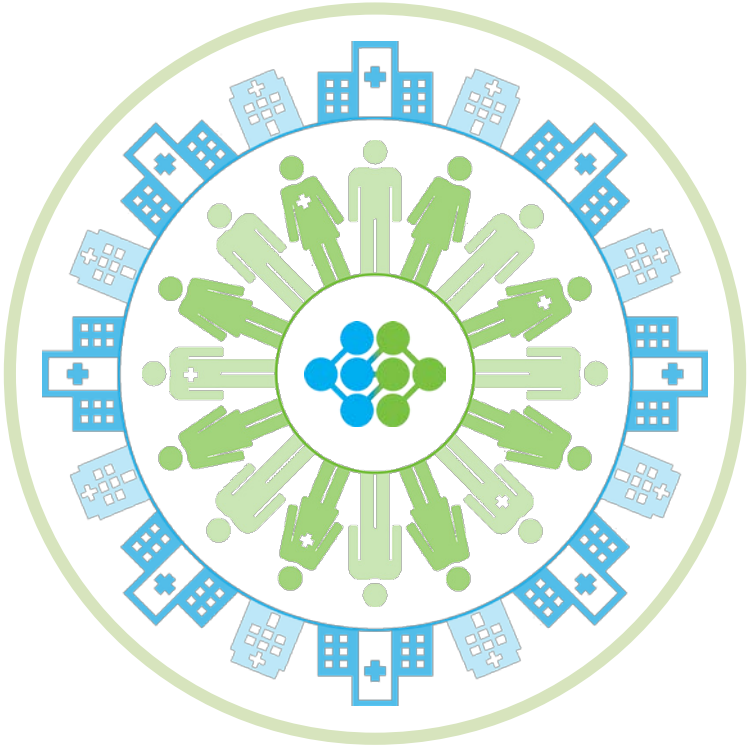
Implementation phase (UH3)

Using EHRs and minimal additional data collection

Log order reduction in cost



PCORnet embodies a “community of research”
by uniting people, clinicians & systems



20
Patient-Powered Research Networks (**PPRNs**)

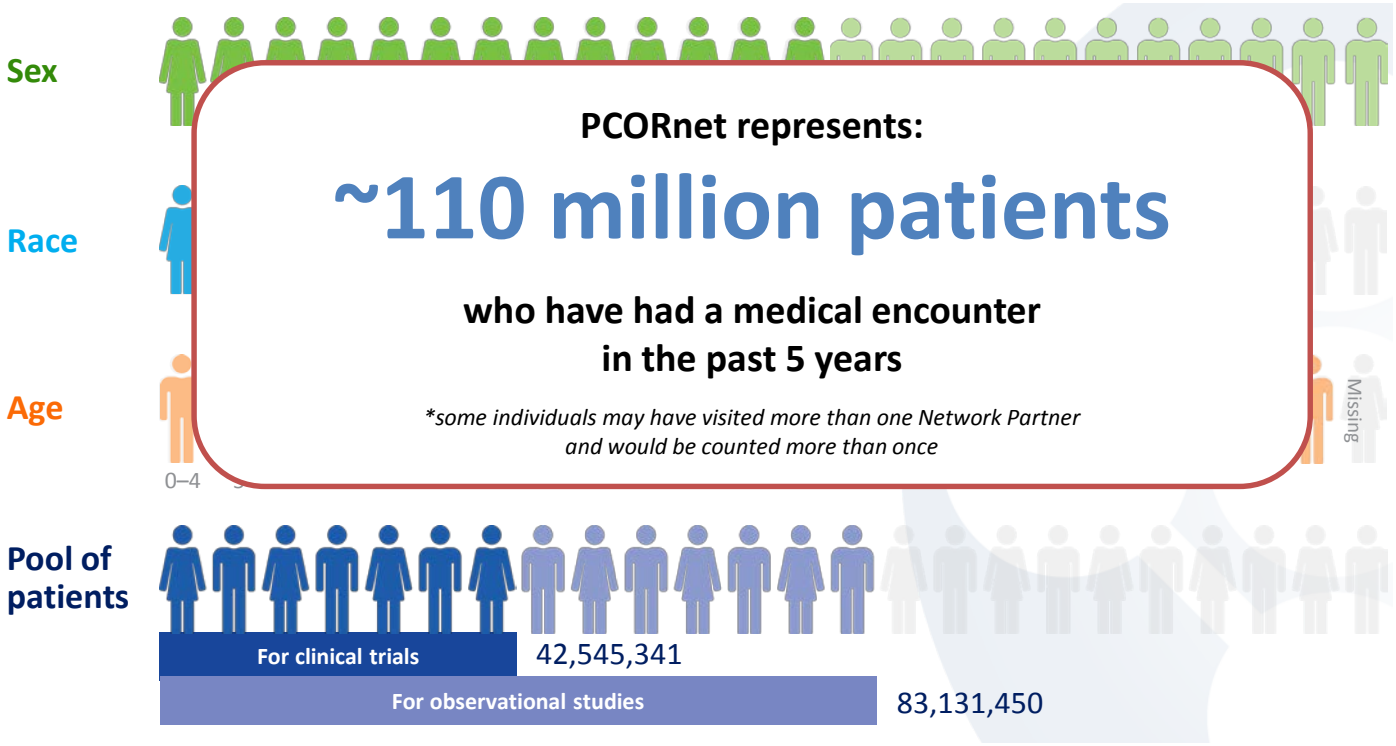
+

13
Clinical Data Research Networks (**CDRNs**)

=

PCORnet
A national infrastructure for people-centered clinical research

Resulting in a national evidence system with research readiness



Policy efforts underpinning RWE push

Cures provisions (Sec. 3022)

- Requires FDA to establish a program to evaluate the potential use of real world evidence to:
  - Help support the approval of new indications for an approved drug
  - Help support or satisfy post approval study requirements

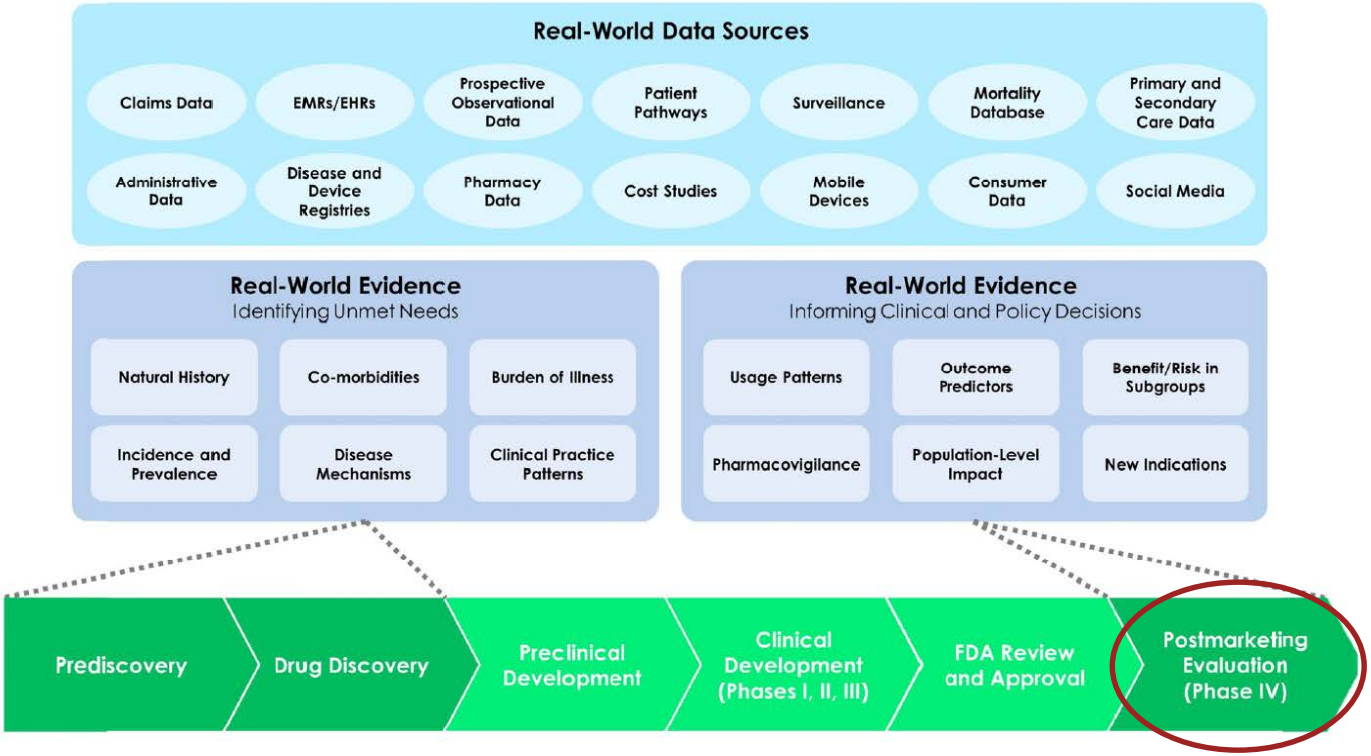
PDUFA RWE provisions

- Tracks with Cures Act
- Requires FDA to establish a program to evaluate the potential use of real world evidence to:
  - Help support the approval of new indications for an approved drug
  - Help support or satisfy post approval study requirements

Reinforcing of a Learning Health Care System:

- Doesn't change approval standards, rather it better supports and enables use of data and evidence on outcomes that are hard to get from traditional RCTs (e.g., outcomes that are too costly, too small populations with particular clinical features, too long follow-up needed, diff impact in diff clinical settings, etc.)
- Learning from real-world patient experiences can support better informed health care decision-making by a range of stakeholders

Real World Data vs Evidence



National Academies of Sciences, Engineering, and Medicine. 2017. *Realworld evidence generation and evaluation of therapeutics: Proceedings of a workshop*. Washington, DC: The National Academies Press. doi: 10.17226/24685

Real World Data and Efficacy

SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

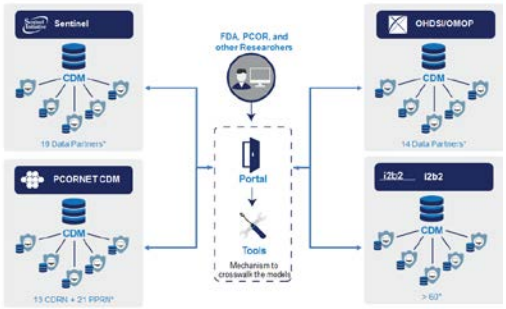
- Real-world evidence can be used across a wide spectrum of research, ranging from observational studies to studies that incorporate planned interventions, whether with or without randomization at the point of care.
- Incorrect to contrast the term “real-world evidence” with the use of randomization in a manner that implies that they are disparate or even incompatible concepts.
- Must consider the components of such trials that are critical to obtaining valid results and minimizing bias.

Laying the Foundation

FDA

Data Standards

Stakeholder Engagement



Duke | MARGOLIS CENTER for Health Policy

CLINICAL TRIALS TRANSFORMATION INITIATIVE

Guidances

Draft

Use of Electronic Health Record Data in Clinical Investigations

Electronic Source Data in Clinical Investigations

Use of Electronic Informed Consent

Demonstratio

Call to Action

- **Organize operational systems that bring together research networks embedded in practice**
  - to enable patients, consumers, clinicians, industry, government, and health care systems to participate in prospective trials and observational studies
  - Develop operational/regulatory approaches to facilitate practice-based systems for therapeutic research, safety surveillance, public health, and quality improvement.
  - Support adequate time commitment for clinicians to engage with patients to ensure mutual understanding and appropriate consent
  - Efficient systems for contracting and liability
  - Clinical care and research closely aligned in “learning health system” supported by education and training
  - **How can delivery systems with their evolving power create a system that encourages participation in an efficient system?**

Call to Action

- **Establish a robust framework for privacy, confidentiality, and security**
  - endorsed by patients and consumers to ensure the trust a learning health system will require,
  - Robust procedures that ensure data security and protect confidentiality
  - Efficient and thorough digital system of education and research permissions for patients
  - Balance of individual autonomy and public health needs
  - Great start: Precision Medicine Initiative: Privacy and Trust Principles
  - **How can delivery systems take on a more constructive role to move the system to a participatory learning system?**

Call to Action

- **Adopt a common approach to configuring, storing, and re-using digital health care data to enable use in care, research, safety surveillance, and public health**
  - As called for in the Nationwide Interoperability Roadmap published by the Office of the National Coordinator for Health Information Technology.
  - Common standards and terminology for prospective data collection
  - Continuous effort to curate data to produce high quality data sets for analysis using common data models
  - Leverage existing digital health/healthcare data to create efficiencies (registries, claims data, EHR data, personal devices)
  - **Can delivery systems figure out how to share data at the scale needed now that we understand the needed sample sizes?**

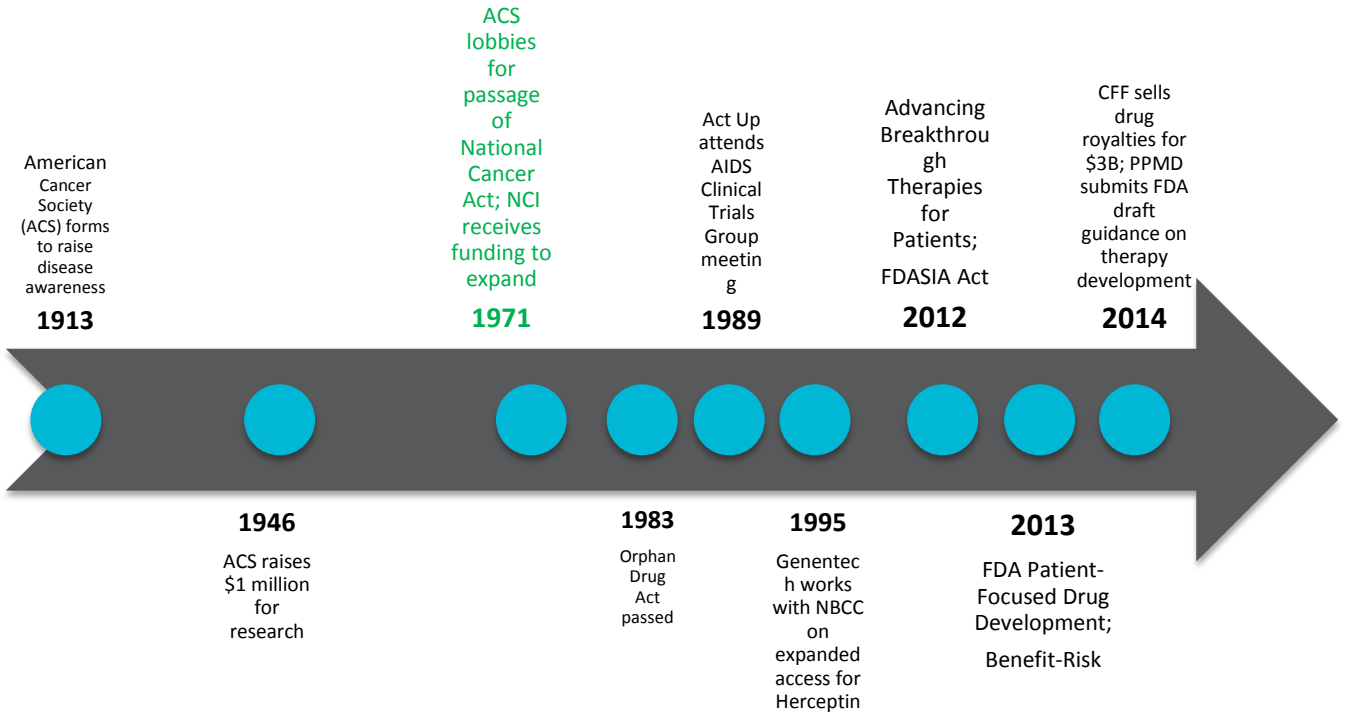
Call to Action

- **Develop and test new methods to reliably answer research questions**
  - more efficient RCTs,
  - Novel designs such as cluster-randomized trials, basket trials
  - And more reliable observational studies aimed at assessment of interventions
  - “Meta-knowledge” on which methods are best for which types of questions
  - By leveraging data already collected by health information technology and other electronic sources to answer research questions or facilitate the conduct of new trials.
  - **Will delivery systems value clinical science enough to create the needed work force and reward scholarly activity in this arena?**

Call to Action

- **Ensure the development of novel approaches focusing on streamlining and harmonizing processes in ways that eliminate barriers that promote unnecessary complexity, while ensuring safeguards that are truly needed.**
  - Streamlined and harmonized processes eliminate barriers to efficient research while ensuring needed safeguards
  - Systems for high quality and efficient ethics review and contracting
  - Development of approaches to assuring quality systems through better use of analytics
  - **Can delivery systems regard efficiency in research with the same seriousness as they have addressed efficiency in clinical care?**

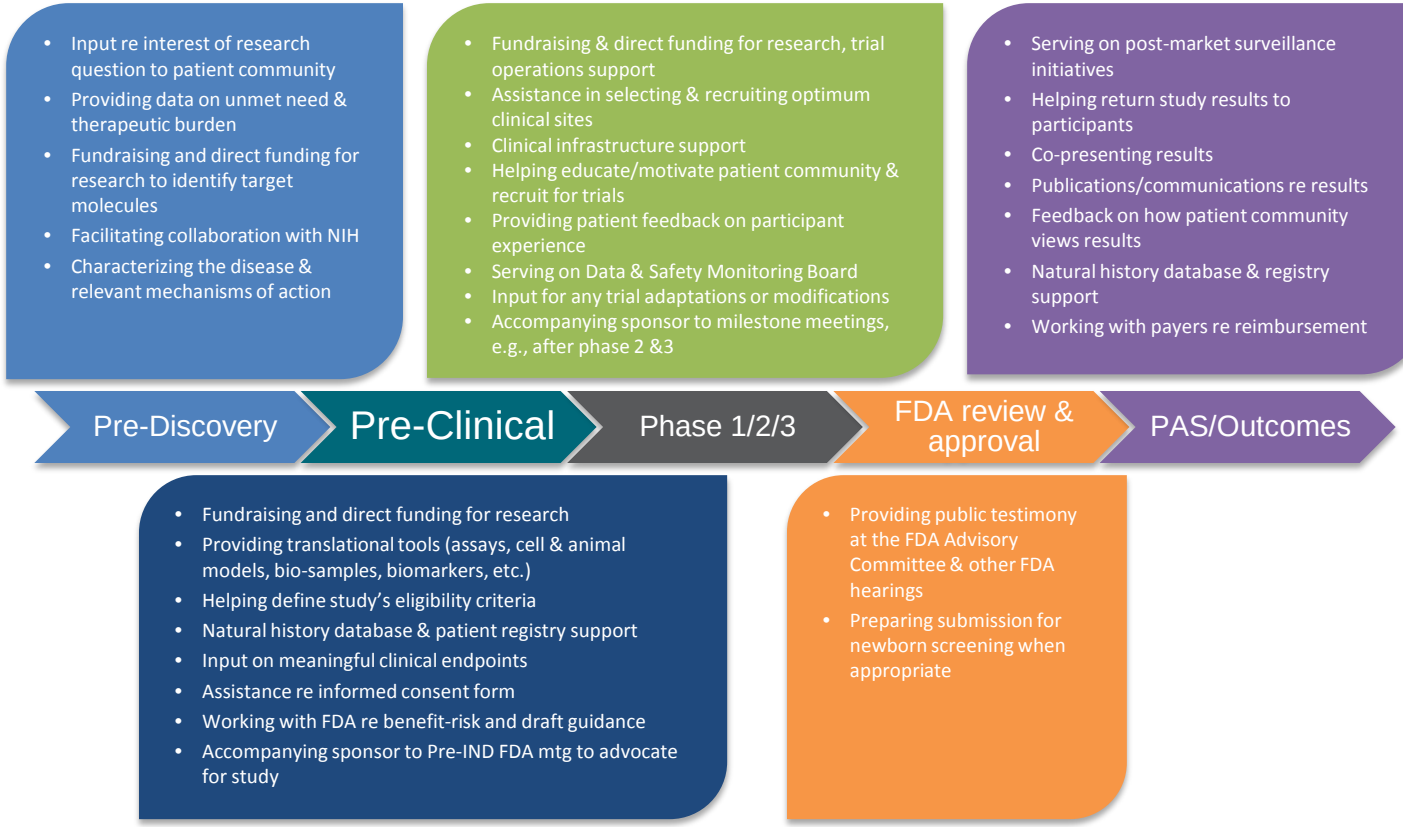
Background



Many of today's patient groups serve as active partners in the clinical trial enterprise and invest private funding in milestone driven research with focus on leveraging their assets to de-risk research and increase return on investment.

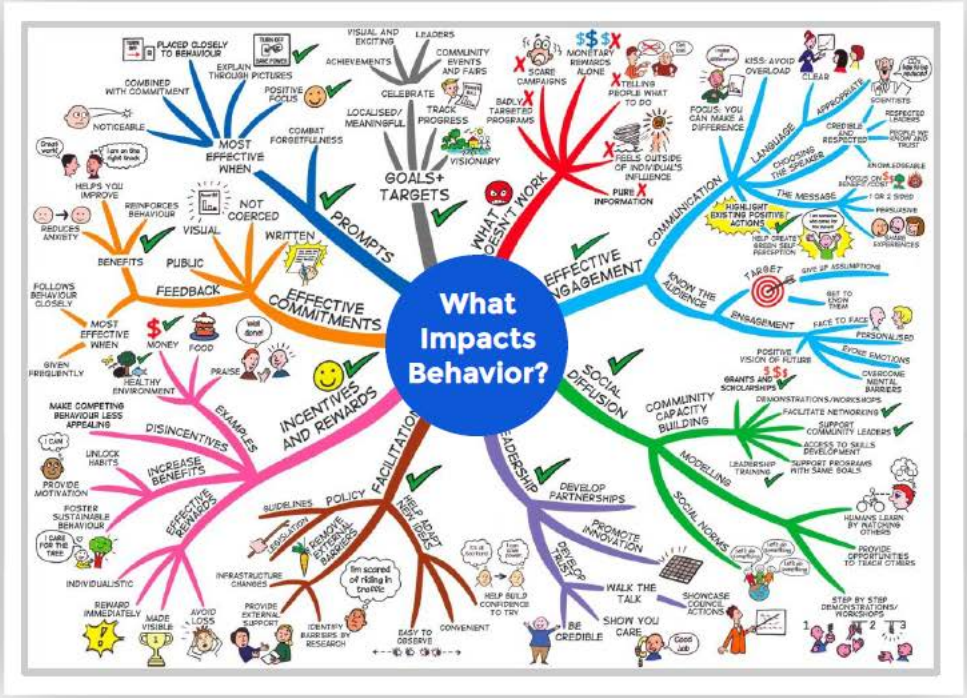
PG Engagement Across the Research & Development Continuum

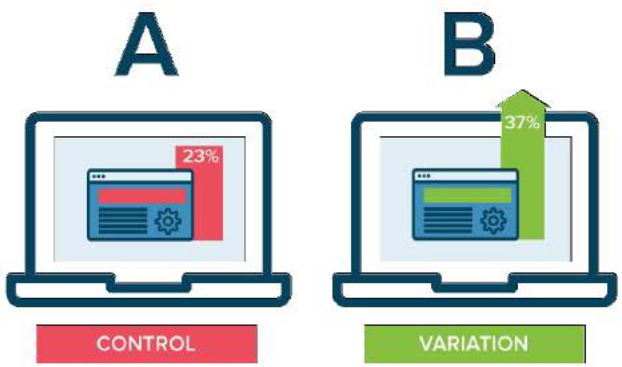
- From Bench to Bedside and Back



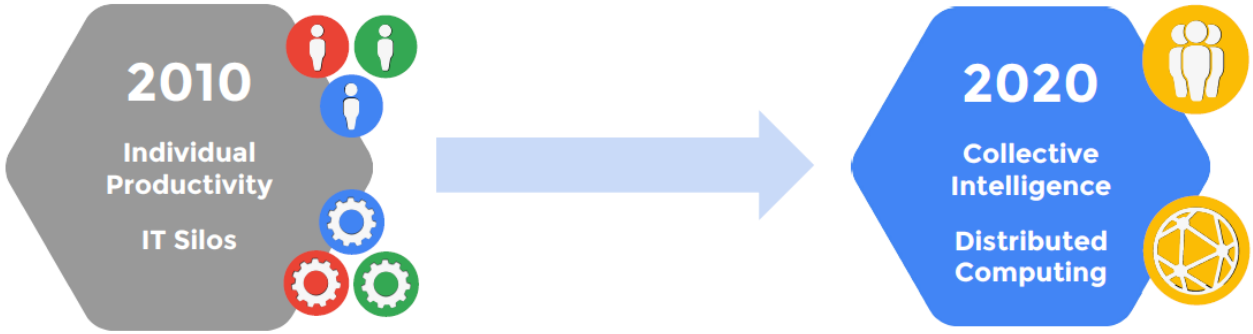
**Adapted from Parkinson's Disease Foundation materials for CTTI's Patient Groups & Clinical Trials Project*

Data Activation and Testing Outcomes





Digital Transformation



- Data on premise, hard to access, analyze and use
- Productivity tools built for individual, local usage
- IT focusing on **where** it computes

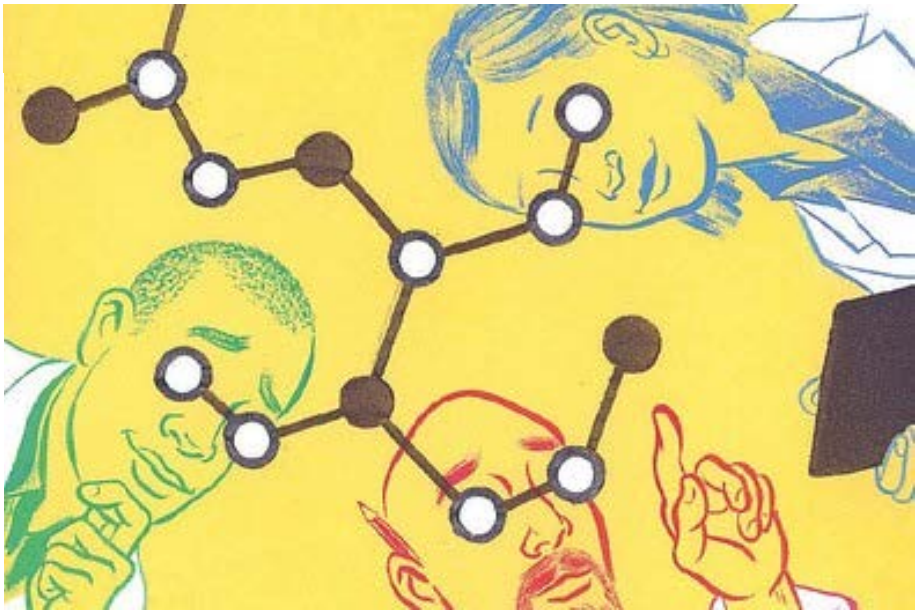
- Data stored in cloud, simple to query
- Collaborative, cloud based productivity applications
- Machine learning drives deep, actionable insights
- IT changing **how** it computes

The New Einsteins Will Be Scientists Who Share

From cancer to cosmology, researchers could race ahead by working together—online and in the open

By MICHAEL NIELSEN

In January 2009, a mathematician at Cambridge University named Tim Gowers decided to use his blog to run an unusual social experiment. He picked out a difficult mathematical problem and tried to solve it completely in the open, using his blog to post ideas and partial progress. He issued an open invitation for others to contribute their own ideas, hoping that many minds would be more powerful than one. He dubbed the experiment the Polymath Project.



Several hours after Mr. Gowers opened up his blog for discussion, a Canadian-Hungarian mathematician posted a comment. Fifteen minutes later, an Arizona high-school math teacher chimed in. Three minutes after that, the UCLA mathematician Terence Tao commented. The discussion ignited, and in just six weeks, the mathematical problem had been solved.

THE WALL STREET JOURNAL.

Whole Genome Sequencing Program (WGS)

GenomeTrakr

- State and Federal laboratory network collecting and sharing genomic data from foodborne pathogens
- Distributed sequencing based network
- Partner with NIH NCBI
- Open-access genomic reference database
  - http://www.ncbi.nlm.nih.gov/bioproject/183844
- Can be used to find the contamination sources of current and future outbreaks

http://www.fda.gov/Food/FoodScienceResearch/WholeGenomeSequencingProgramWGS/default.htm#trakr


Twitter's C.E.O., Dick Costolo, Is Set to Exit, Feeling Heat of Criticism


ROBOTICA EPISODE 5
Sex Dolls That Talk Back


STATE OF THE ART
For Twitter, Future Means Here and Now


Sidewalk Labs, a Start-Up Created by Google, Has Bold Aims to Improve City Living


Am Bus Eur Reg

TECHNOLOGY

For Big-Data Scientists, 'Janitor Work' Is Key Hurdle to Insights

By STEVE LOHR AUG. 17, 2014

PATIENT LEAVES HOSPITAL ALIVE

by **Dr James Leftonatrolley**

THERE was wide-spread shock today at the news that a patient had left a hospital today without having been killed by a medical error.

A spokesman for the hospital said, "This is a very rare occurrence and there is no cause for alarm. We will be launching a full enquiry at once into what went right. We can only apologise to the undertakers."

We Want you to be Creative Using Big Data and to be Responsible to Create High Quality Evidence to Support Intervention