NIH Health Care Systems Research Collaboratory

Taking Stock and Moving Forward

Robert M Califf MD

May 23rd, 2017

CONFLICTS

- I start working half-time at Verily Life Sciences (member of Alphabet family) starting June 1
- I also work half-time at an academic medical center/health system that is dealing with balancing learning and margin
- And an appointment at another AMC/system with hard choices to make about technology alignment

Five Years Ago

- Idea of learning health system gaining intellectual traction
- EMR's being introduced on a national scale
- Recognition that speed and cost of generating evidence not acceptable
- NIH takes a bold step to change paradigm for evidence generation
- Where are we today?

Today

- We all have electronic health records
- Tremendous growth of biomedical measurement capability
- Consolidation of health systems
- Cloud computing, arrays of processors
- Silicon Valley with cash and desire to invest in health issues
- Cost of generating evidence and speed still unacceptable
- Are we making progress?

RFA-RFM-23-012

- “to strengthen the national capacity to implement cost-effective large-scale research studies that engage health care delivery organizations and patients as research partners”

Top 3 Things for Collaboratory (IMHO)

1) Get results and publish
2) Develop approach to broader dissemination and implementation
3) Develop “metaknowledge”
   A. What is working?
   B. What are the toughest hurdles for those hoping to do pragmatic trials?
      i. What are solutions to overcoming the hurdles?
   C. Turn metaknowledge into policy

Our National Clinical Research System is Well-intentioned But Flawed

- High percentage of decisions not supported by evidence*
- Health outcomes and disparities are not improving
- Current system is great **except**:
  - Too slow, too expensive, and not reliable
  - Doesn't answer questions that matter most to patients
  - Unattractive to clinicians & administrators

We are not generating the evidence we need to support the healthcare decisions that patients and their doctors have to make every day.

Tricoci P et al. JAMA 2009;301:831-41

Which Treatment is Best for Whom?

High-Quality Evidence is Scarce

< 15% of Guideline Recommendations Supported by High Quality Evidence

ORIGINAL CONTRIBUTION

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

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Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

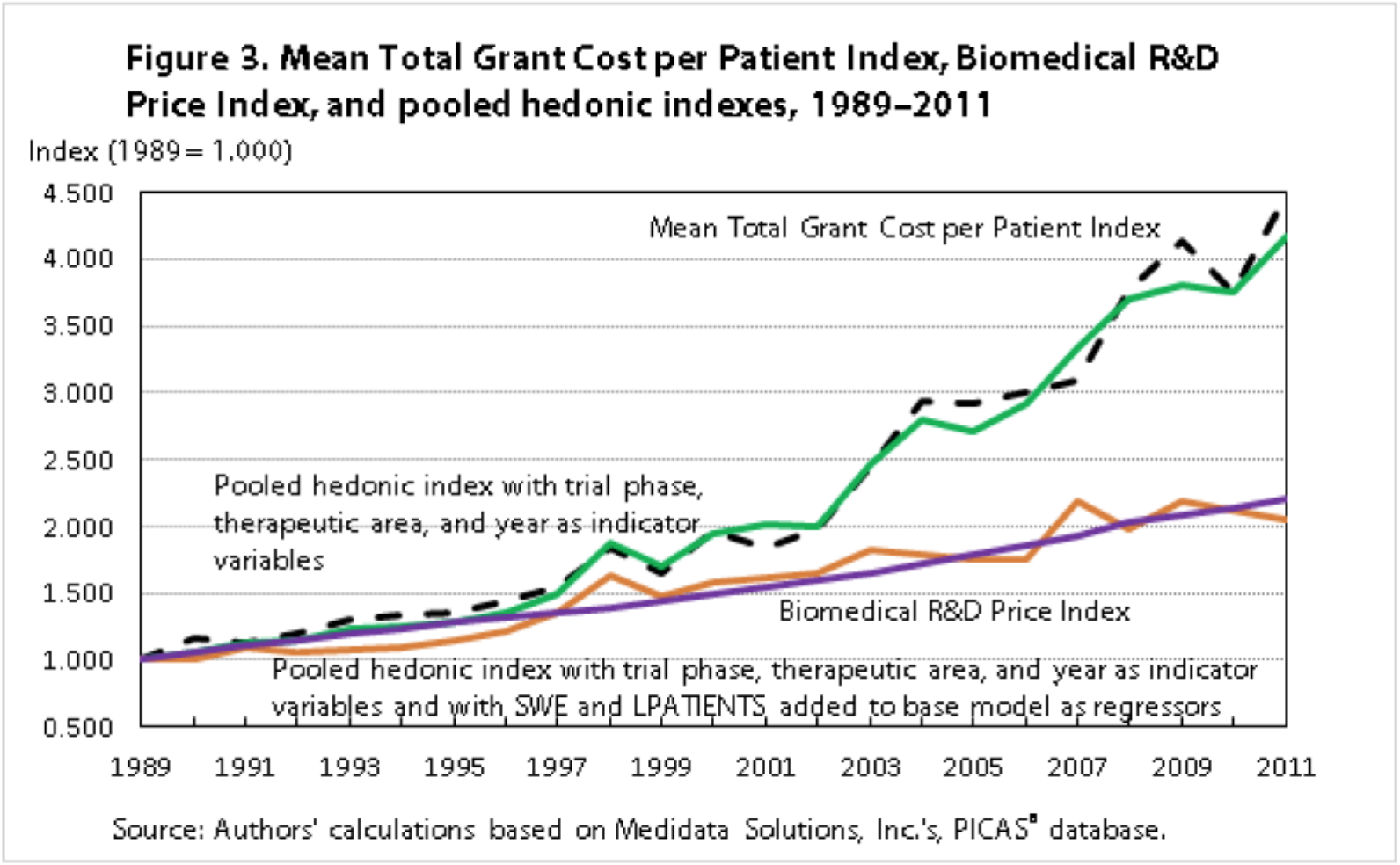
CLINICAL PRACTICE GUIDELINES are systematically developed statements to assist practitioners with decisions about appropriate health care for spe-

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.

Trial Hyperinflation



Berndt E, Cockburn I. Monthly Labor Review, June 2014

From: **Inequalities in Life Expectancy Among US Counties, 1980 to 2014Temporal Trends and Key Drivers**

JAMA Intern Med. Published online May 08, 2017. doi:10.1001/jamainternmed.2017.0918

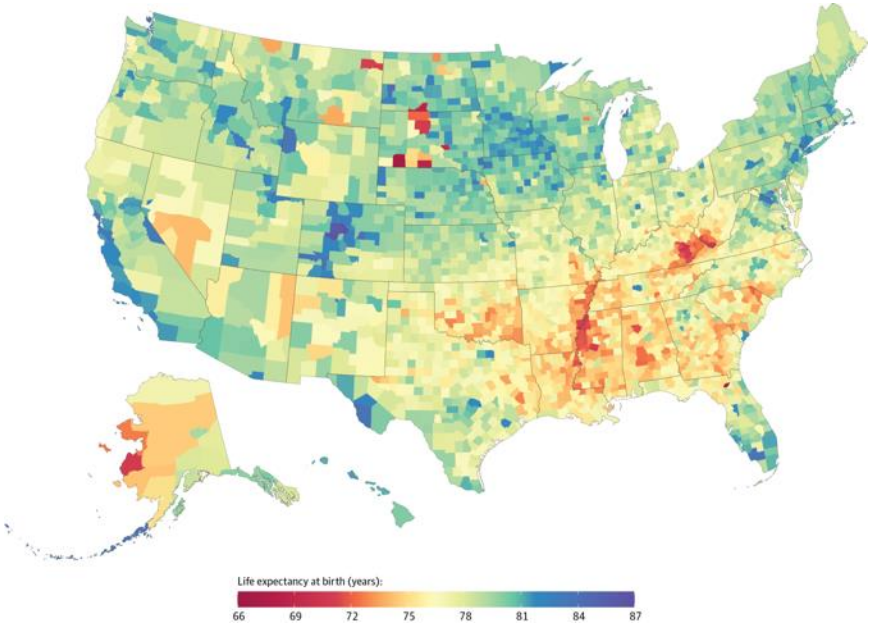


Figure Legend:

Life Expectancy at Birth by County, 2014Counties in South Dakota and North Dakota had the lowest life expectancy, and counties along the lower half of the Mississippi, in eastern Kentucky, and southwestern West Virginia also had very low life expectancy compared with the rest of the country. Counties in central Colorado had the highest life expectancies.

From: **Inequalities in Life Expectancy Among US Counties, 1980 to 2014Temporal Trends and Key Drivers**

JAMA Intern Med. Published online May 08, 2017. doi:10.1001/jamainternmed.2017.0918

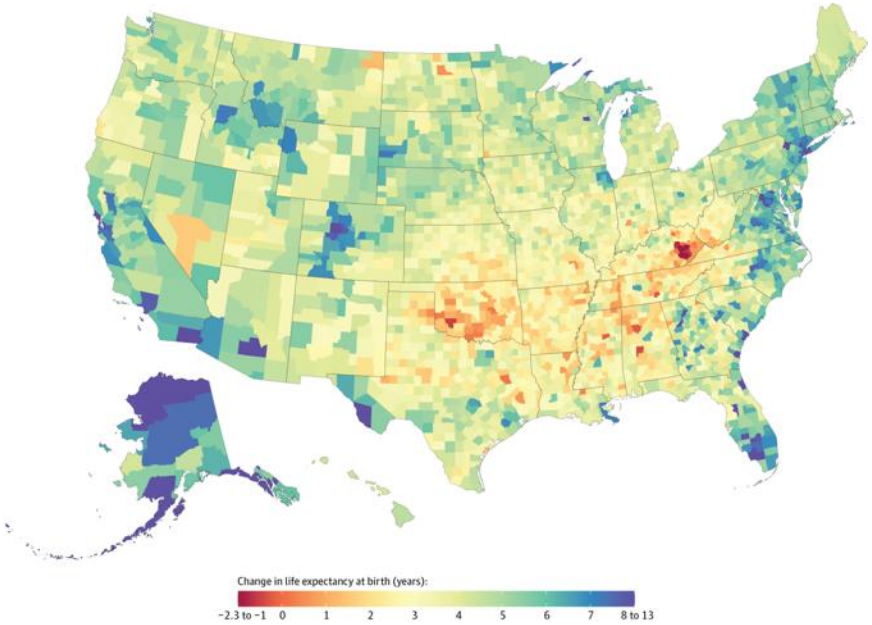


Figure Legend:

Change in Life Expectancy at Birth by County, 1980 to 2014Compared with the national average, counties in central Colorado, Alaska, and along both coasts experienced larger increases in life expectancy between 1980 and 2014, while some southern counties in states stretching from Oklahoma to West Virginia saw little, if any, improvement over this same period.

From: **Inequalities in Life Expectancy Among US Counties, 1980 to 2014Temporal Trends and Key Drivers**

JAMA Intern Med. Published online May 08, 2017. doi:10.1001/jamainternmed.2017.0918

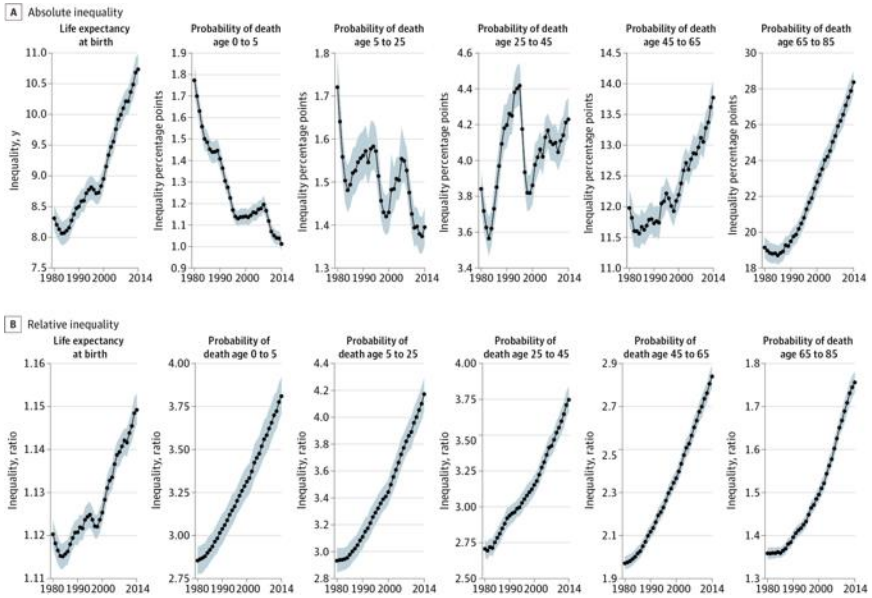


Figure Legend:

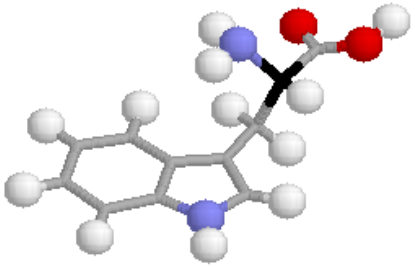
Absolute and Relative Inequality Among Counties in Life Expectancy and Age-Specific Mortality Risks, 1980–2014Shaded areas along the plotted data represent 95% uncertainty intervals. Absolute geographic inequality was quantified as the difference between the 99th and first percentile level, and relative geographic inequality was quantified as the ratio of the 99th to the first percentile level.

Precision Medicine Initiative: Modernizing FDA Regulation of Genomic Laboratory Tests

Traditional testing

Next generation sequencing

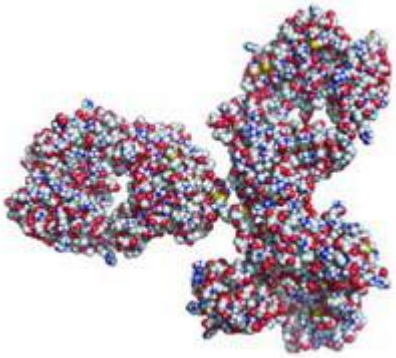
Relative Complexity of Therapies



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

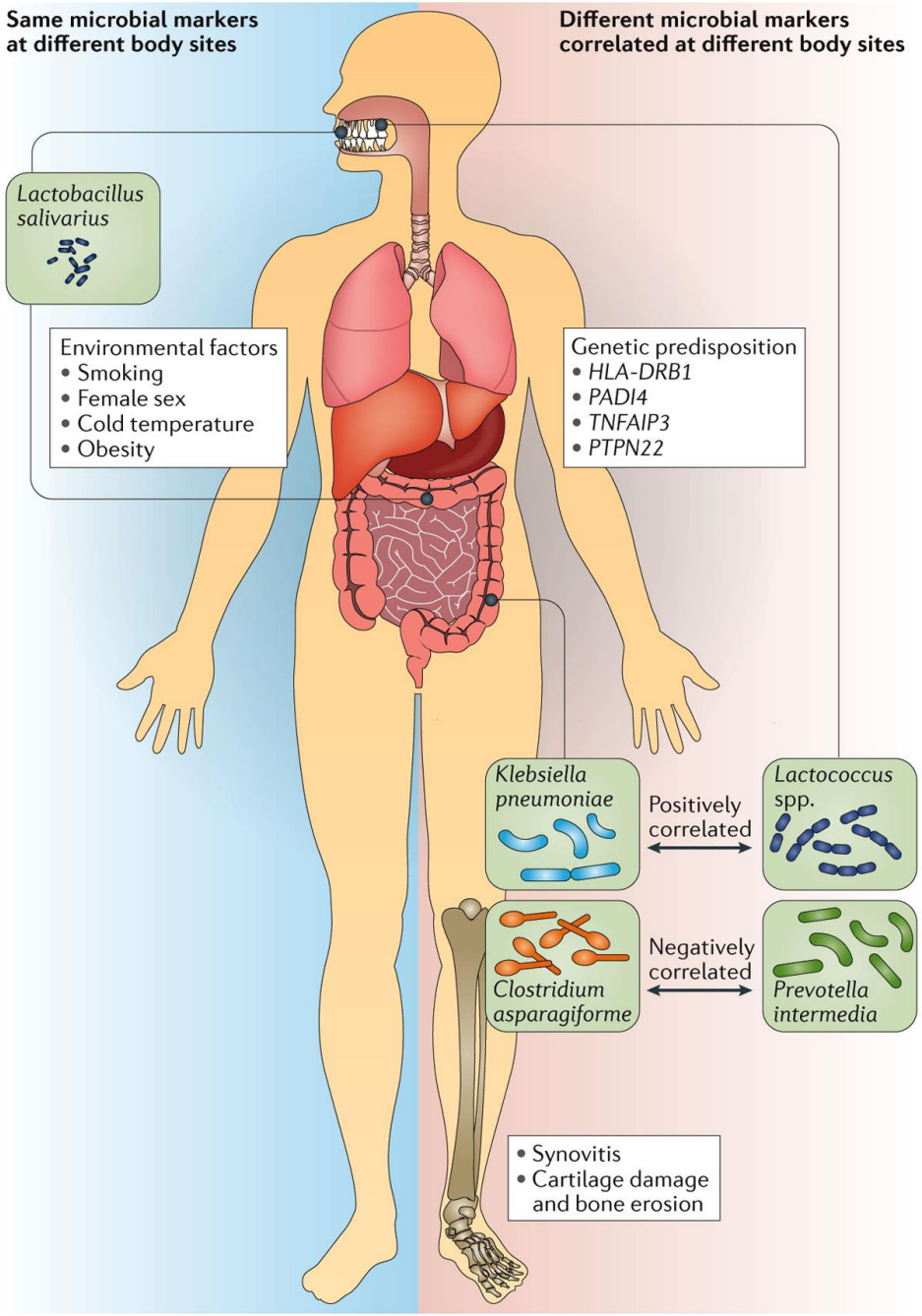
Cell composed of about 3.6×10^6 proteins

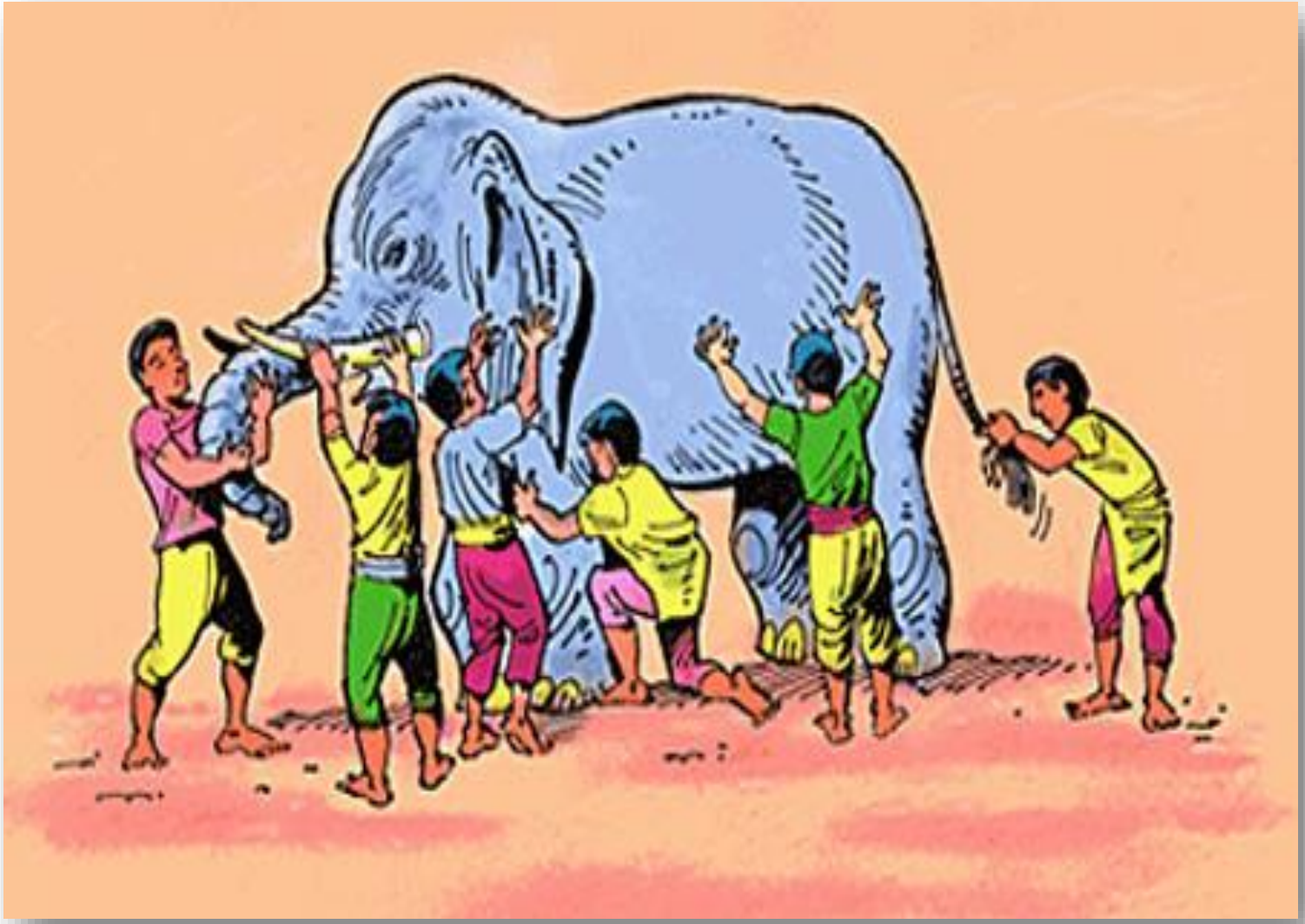
10^{14} Atoms

Mesenchymal stem cell
Cellular Biologic

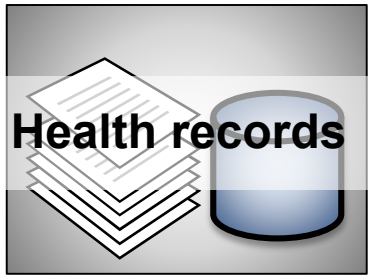
CRISPR/Cas9 Gene Editing

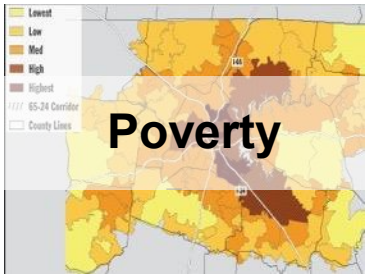
- Cas9 nuclease can be directed to cut at specific locations designated by guide RNAs
- Though there is some concern for off-target effects, CRISPR/Cas9 is a powerful technique for altering genes

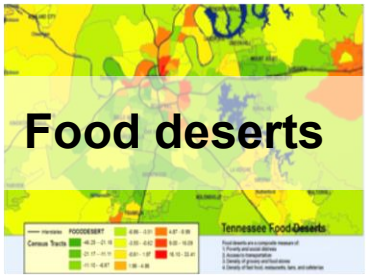

Same microbial markers at different body sites
Different microbial markers correlated at different body sites
Lactobacillus salivarius
Environmental factors
• Smoking
• Female sex
• Cold temperature
• Obesity
Genetic predisposition
• HLA-DRB1
• PADI4
• TNFAIP3
• PTPN22
Klebsiella pneumoniae
Positively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

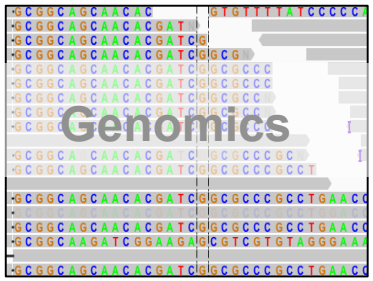


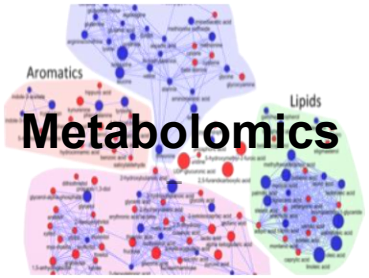
Many tools to dissect individualized health

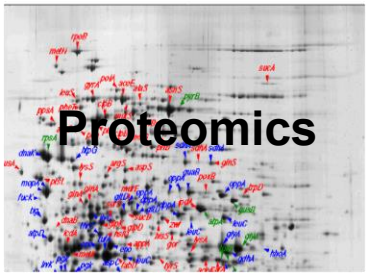


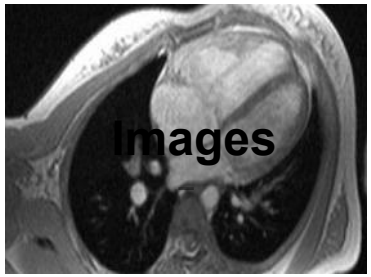


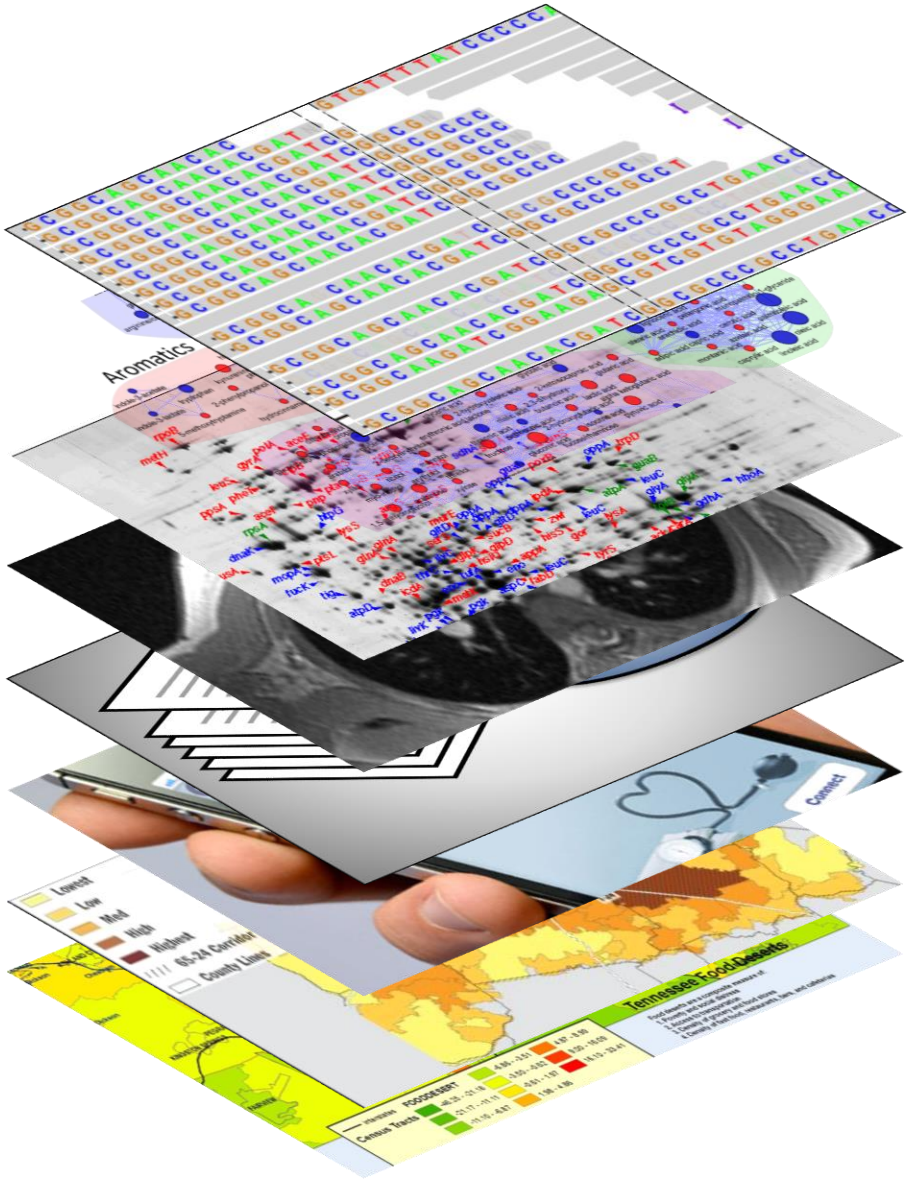






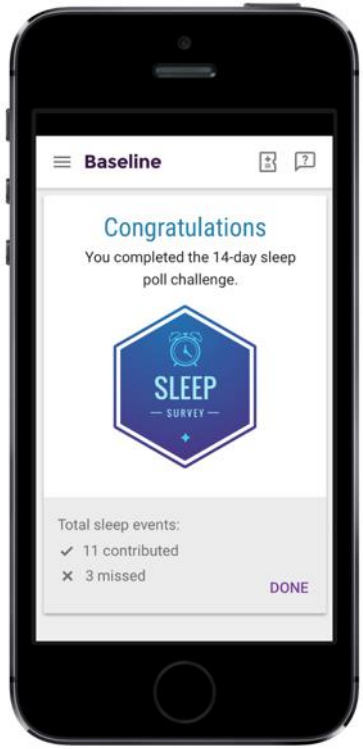






The challenge:
integrating multiple datasets for discovery and implementation

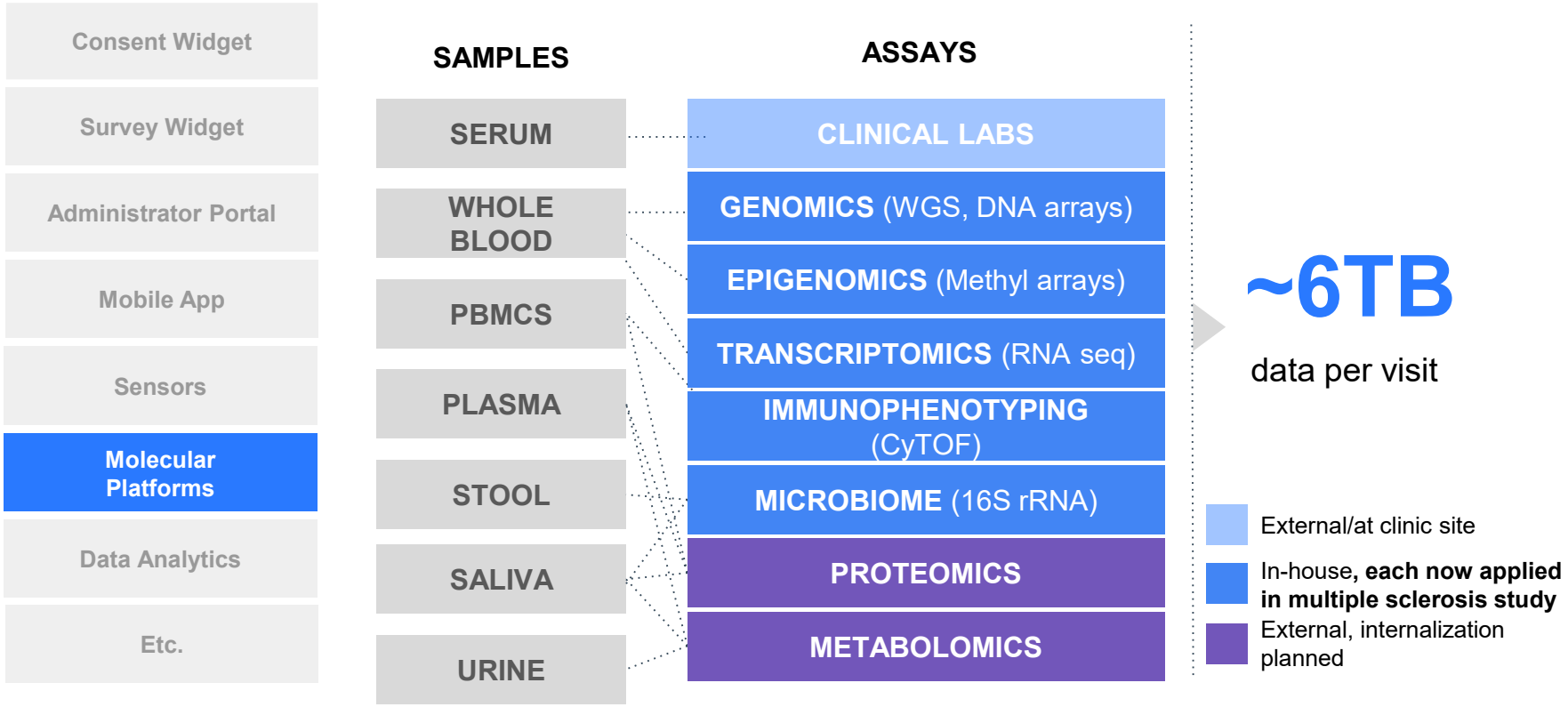
Smartphone

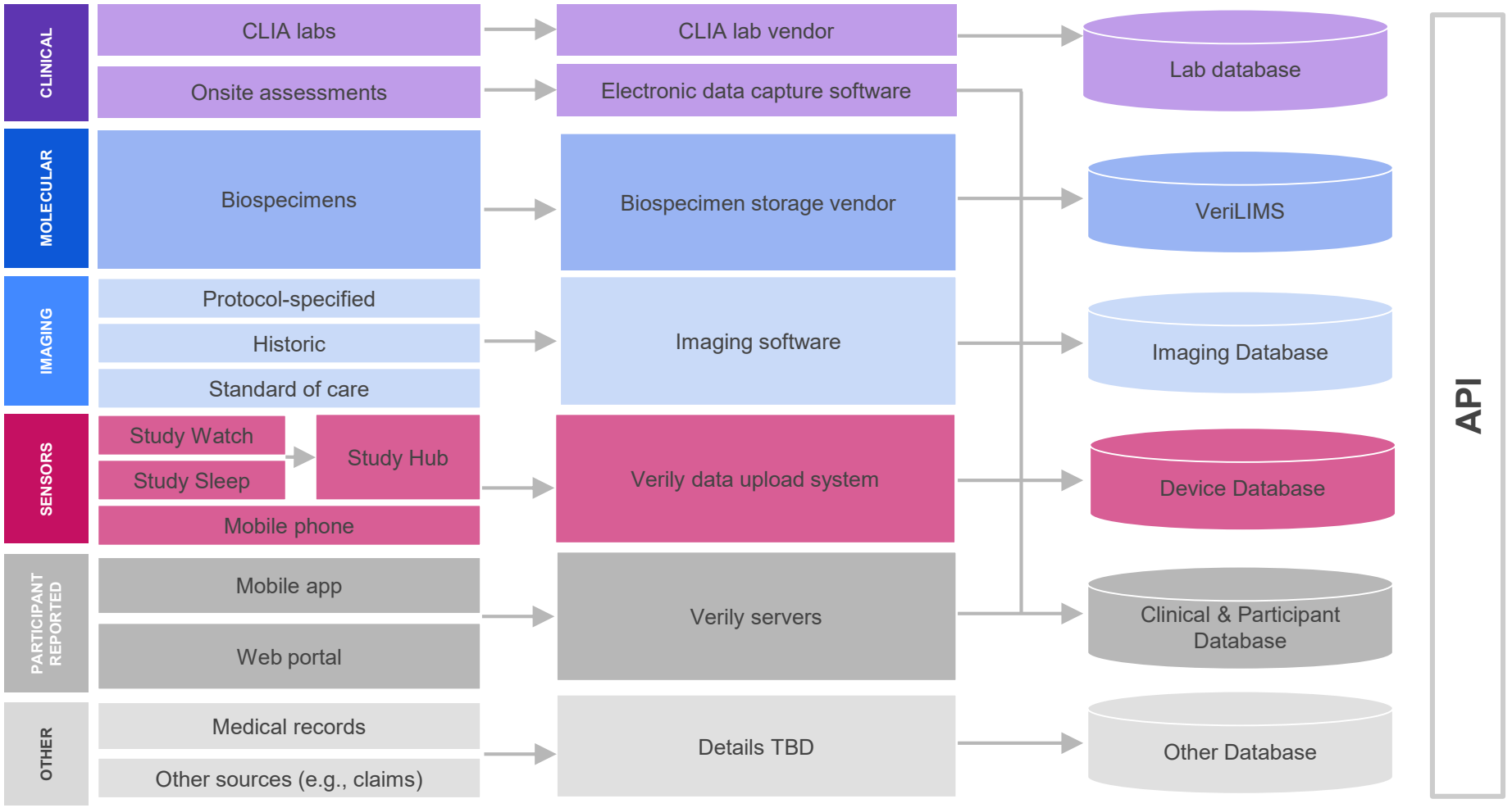


Cardiac and Activity Monitor

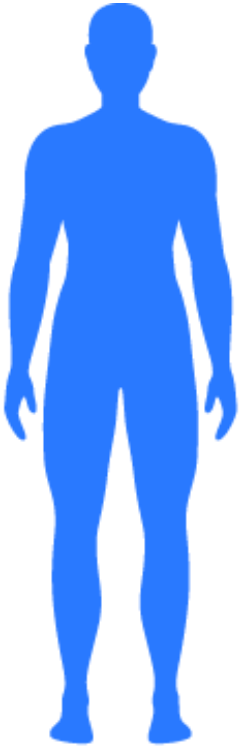
Sleep Sensor

Scalable & Standardized Tools

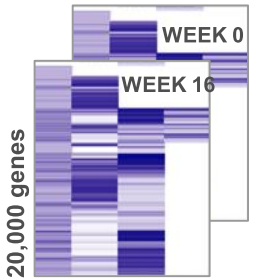



CLINICAL
CLIA labs
Onsite assessments
CLIA lab vendor
Electronic data capture software
Lab database
MOLECULAR
Biospecimens
Biospecimen storage vendor
VeriLIMS
IMAGING
Protocol-specified
Historic
Standard of care
Imaging software
Imaging Database
SENSORS
Study Watch
Study Sleep
Study Hub
Mobile phone
Verily data upload system
Device Database
PARTICIPANT REPORTED
Mobile app
Web portal
Verily servers
Clinical & Participant Database
OTHER
Medical records
Other sources (e.g., claims)
Details TBD
Other Database
API

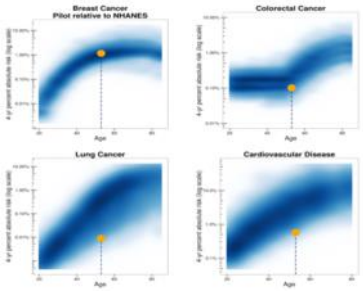
Aggregated & Searchable Participant Data



-OMICS DATA

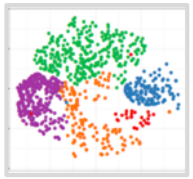


CLINICAL DATA



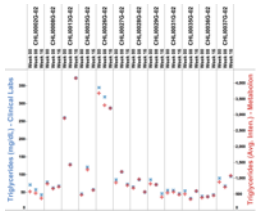
IMAGING DATA

IMMUNOPROFILING DATA



DEVICE DATA

LAB DATA



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.

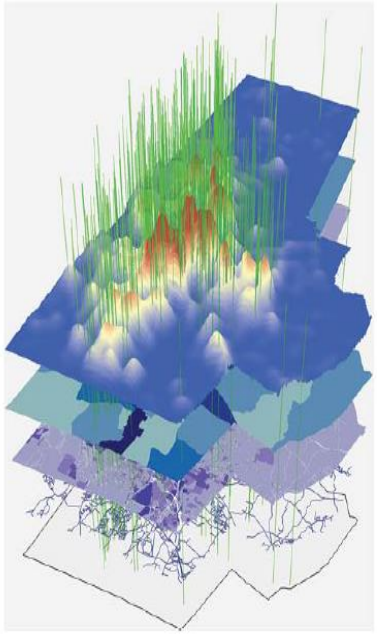
ABSTRACT **Despite the rapid growth of electronic health data, most data systems do not connect individual patient records to data sets from outside the health care delivery system. These isolated data systems cannot support efforts to recognize or address how the physical and environmental context of 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

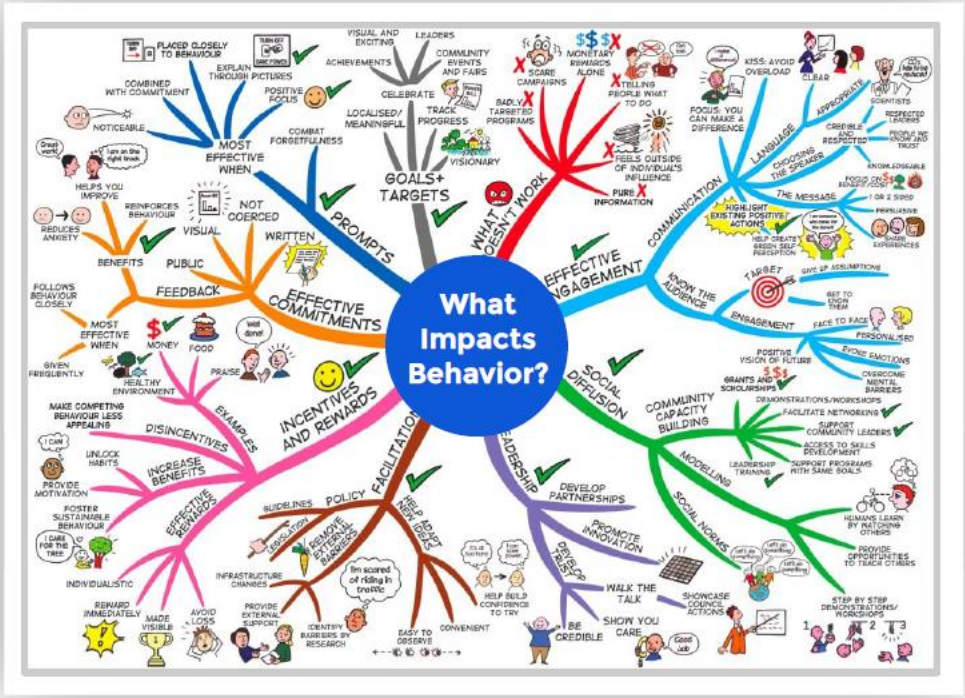
EXHIBIT 1

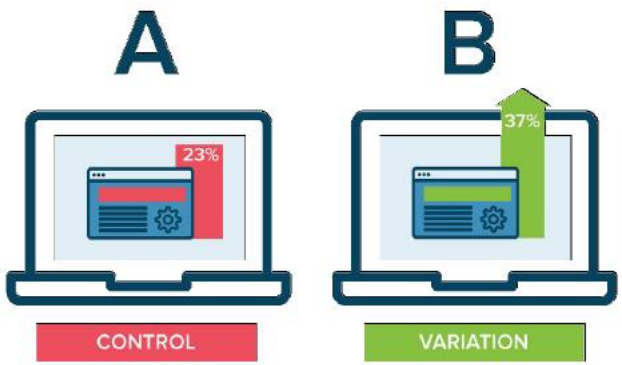
Example Of Geographic Health Information Systems (GHIS) For Mapping The Terrain Of Diabetes In Durham County, North Carolina



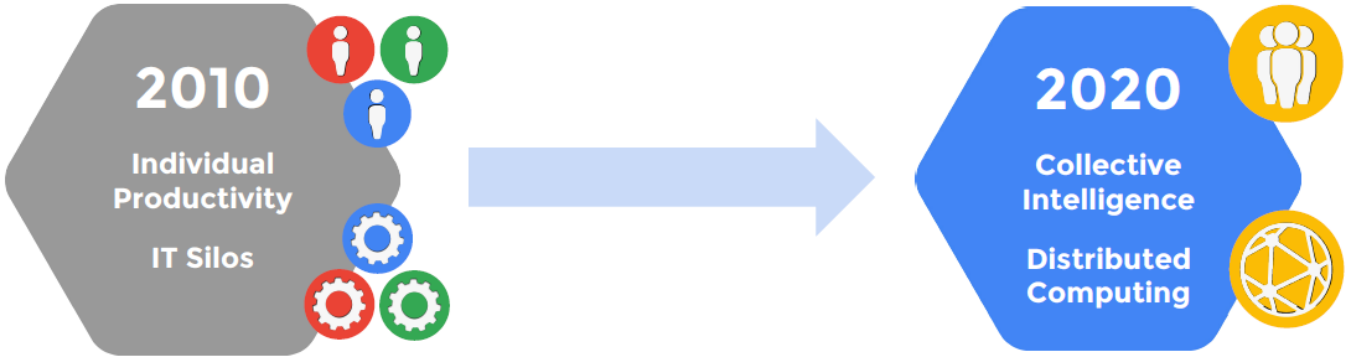
SOURCE Duke Health Technology Solutions Decision Support Repository (DSR), using information on boundaries and streets layers from the US Census Bureau Geography Division, census 2010; and tax-parcel data from the Durham County Tax Assessor. NOTE The elements of this GHIS map are ex-

Data Activation and Testing Outcomes





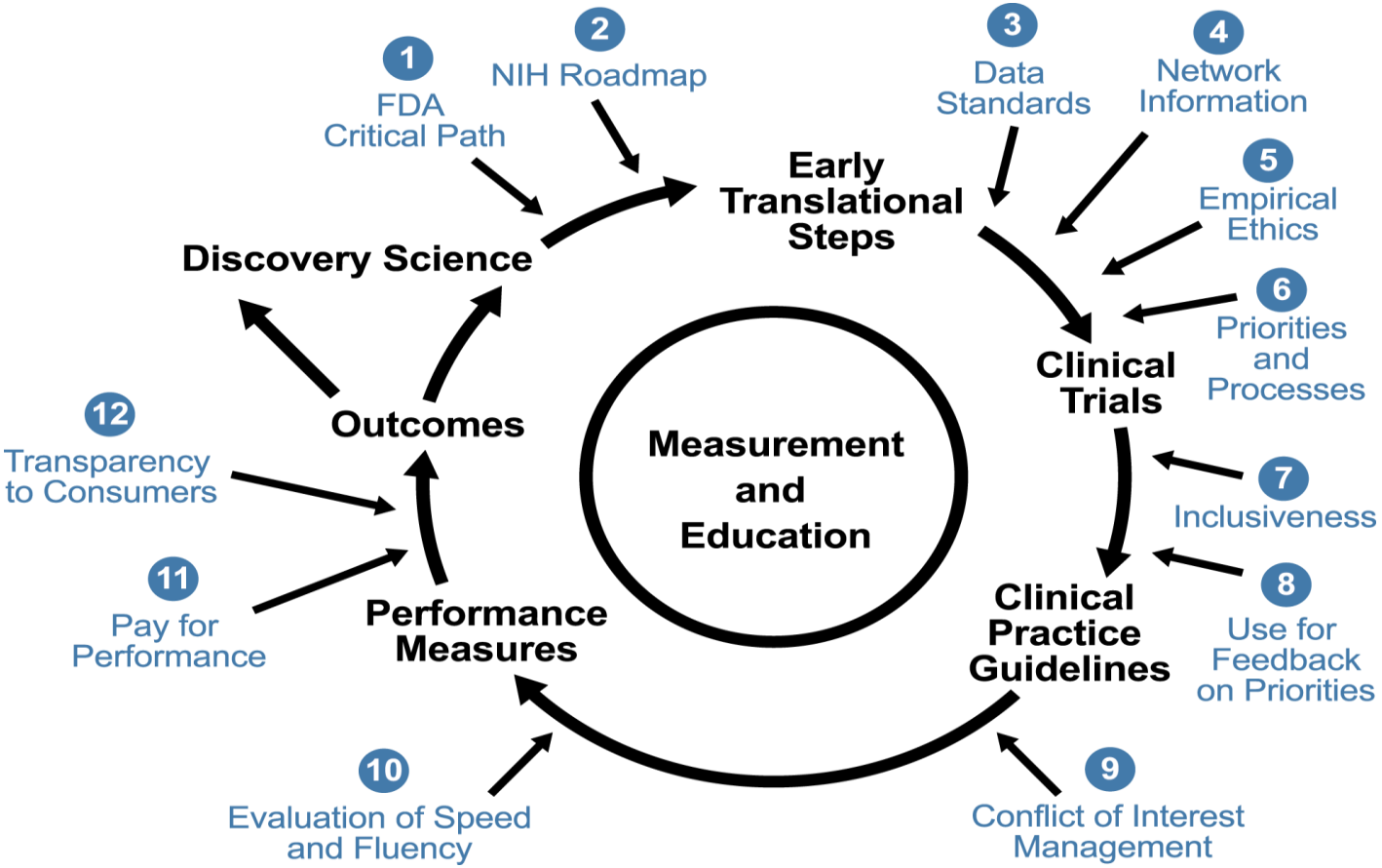
Digital Transformation



- 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

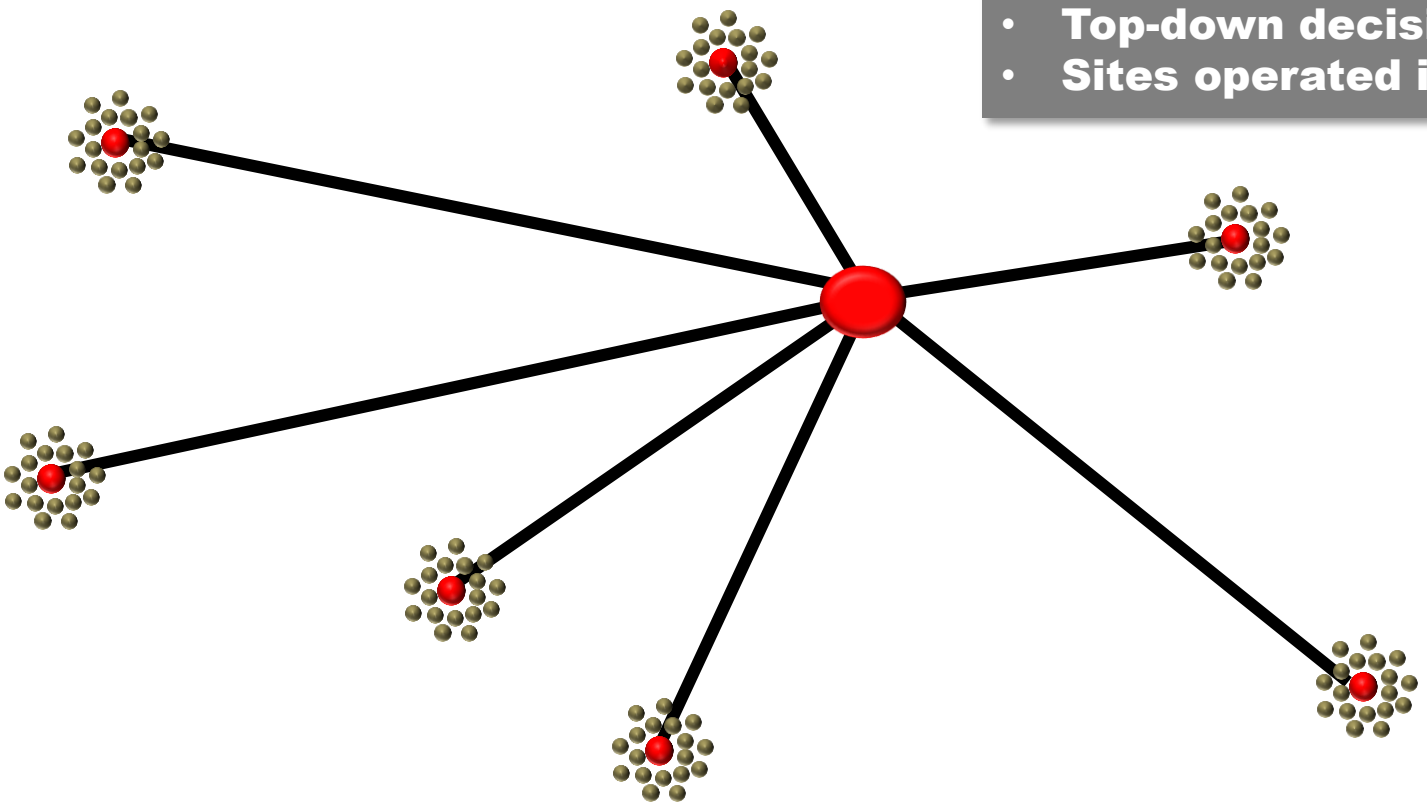
Generating Evidence to Inform Decisions



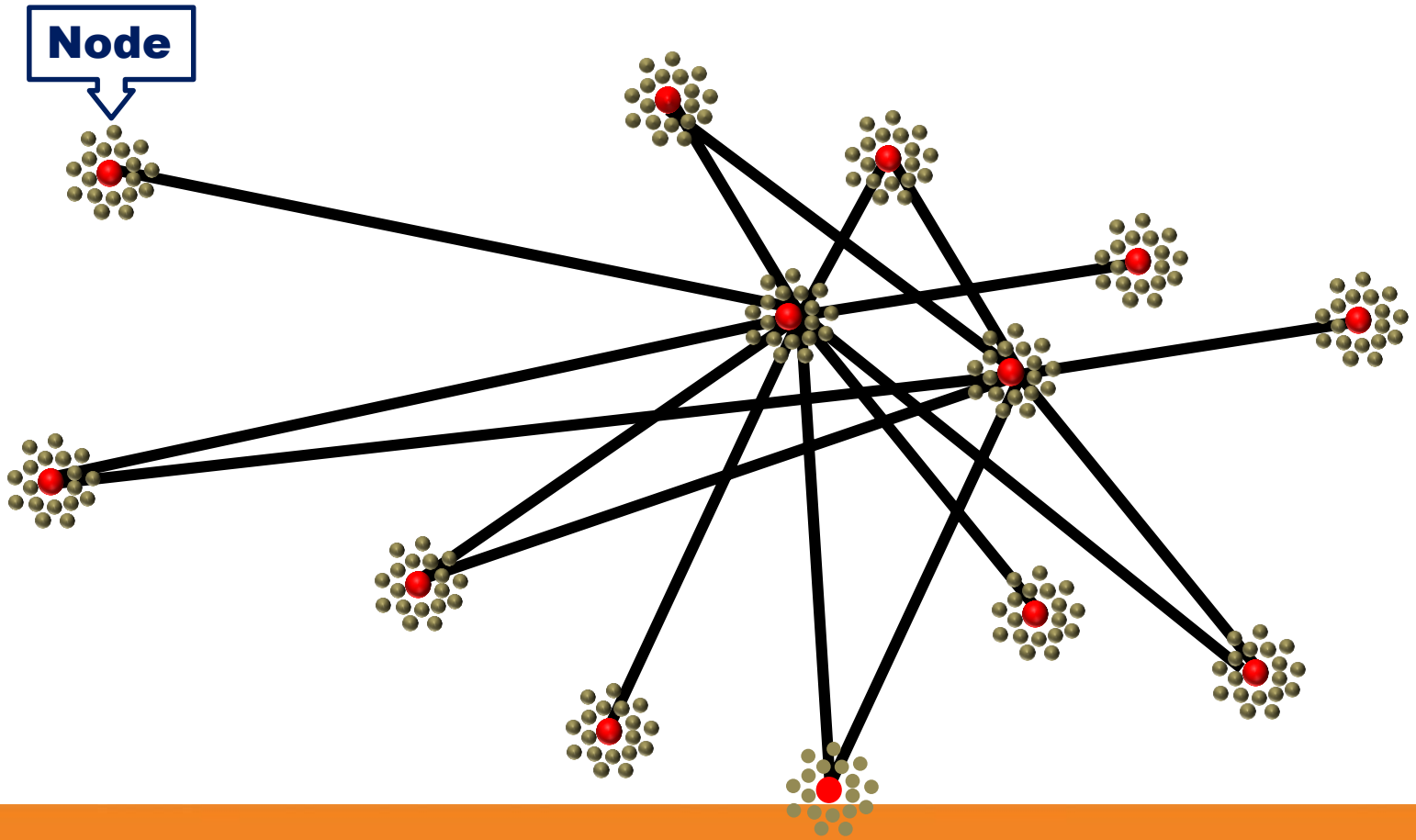
Learning health care systems

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



The “Biomedical Academic System”

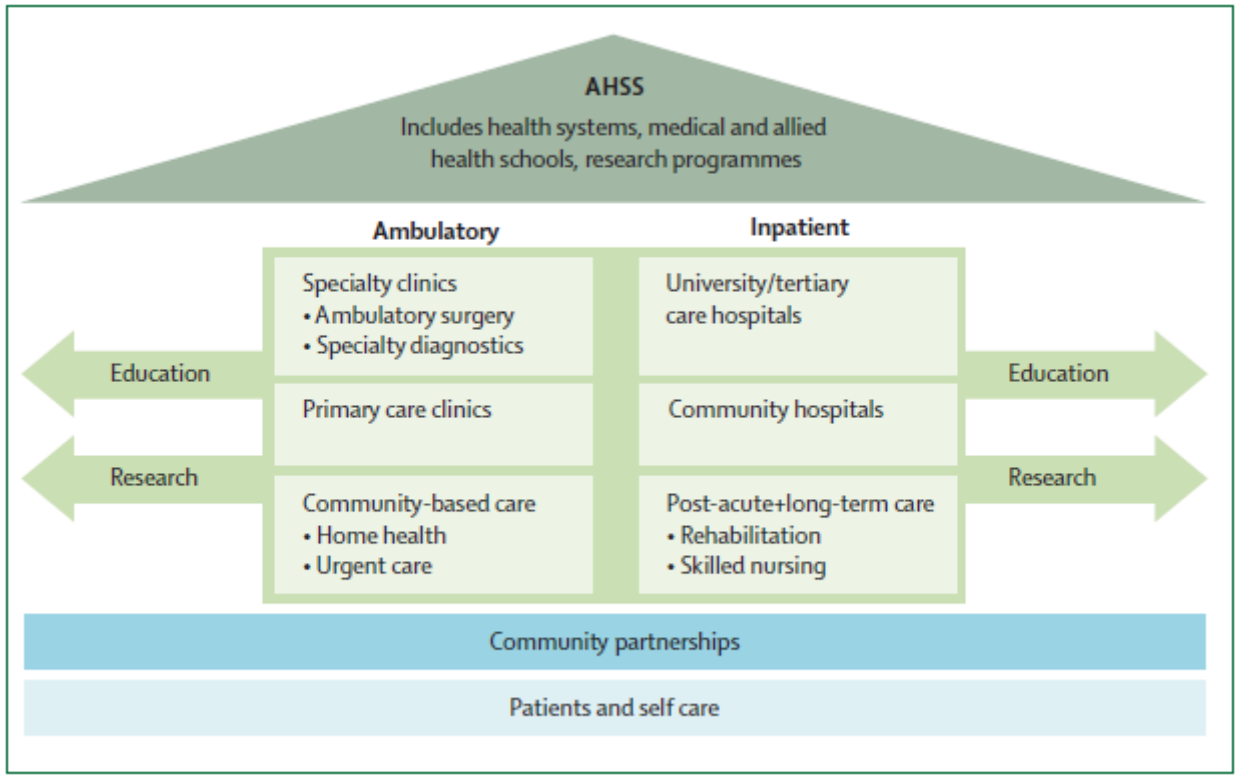
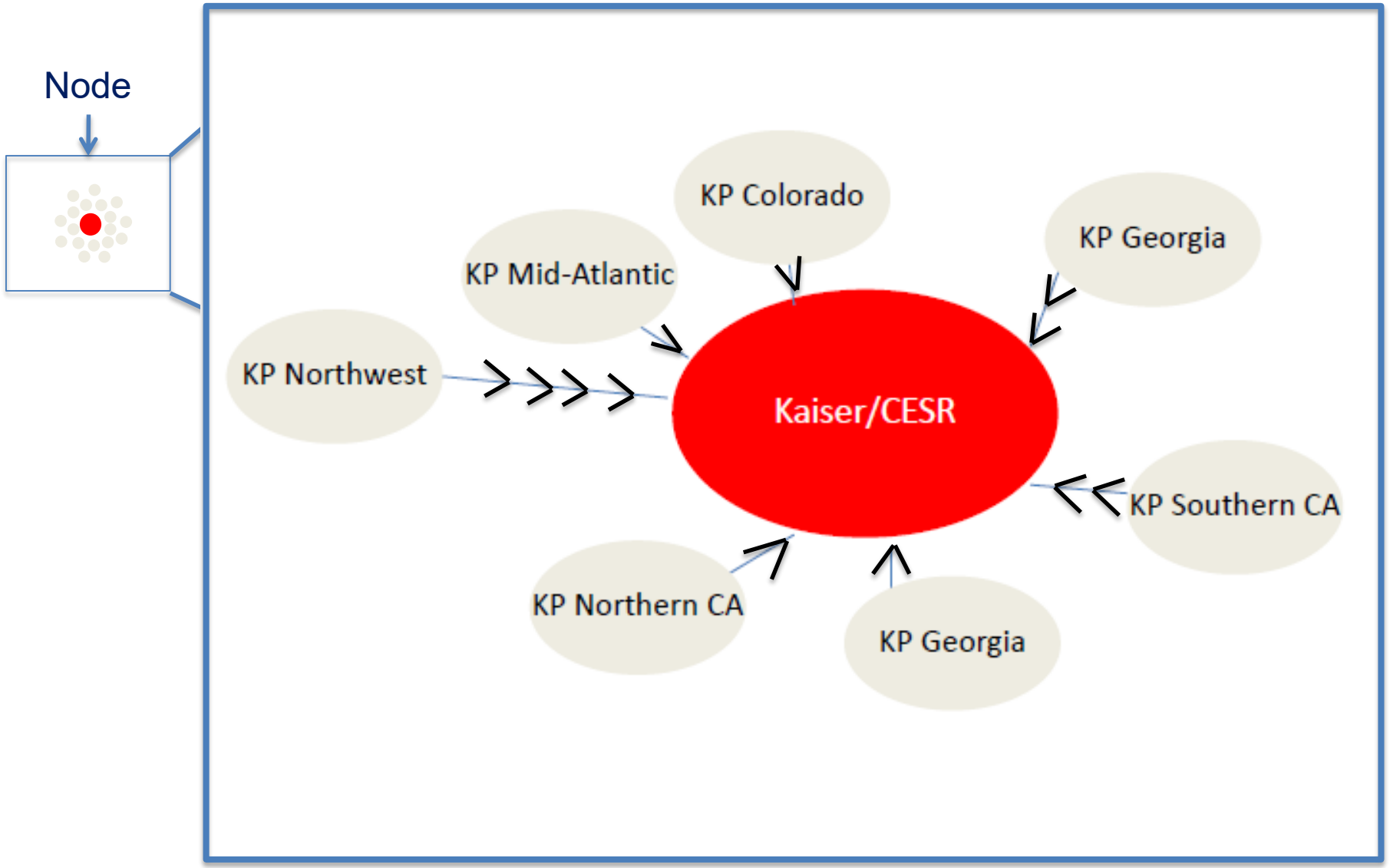


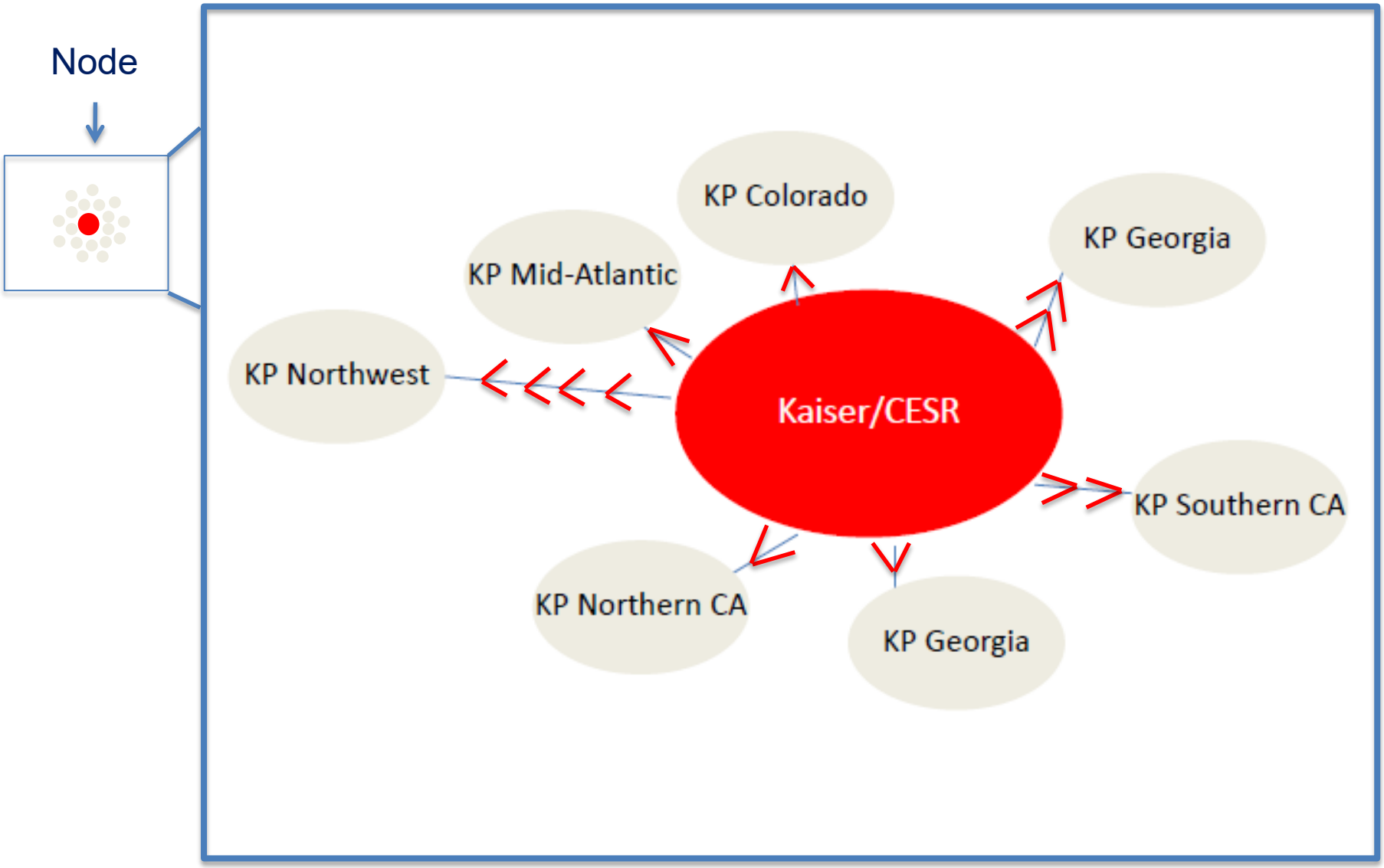
***Figure 2:* Academic health sciences system (AHSS) as a vertically integrated care-delivery system**

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

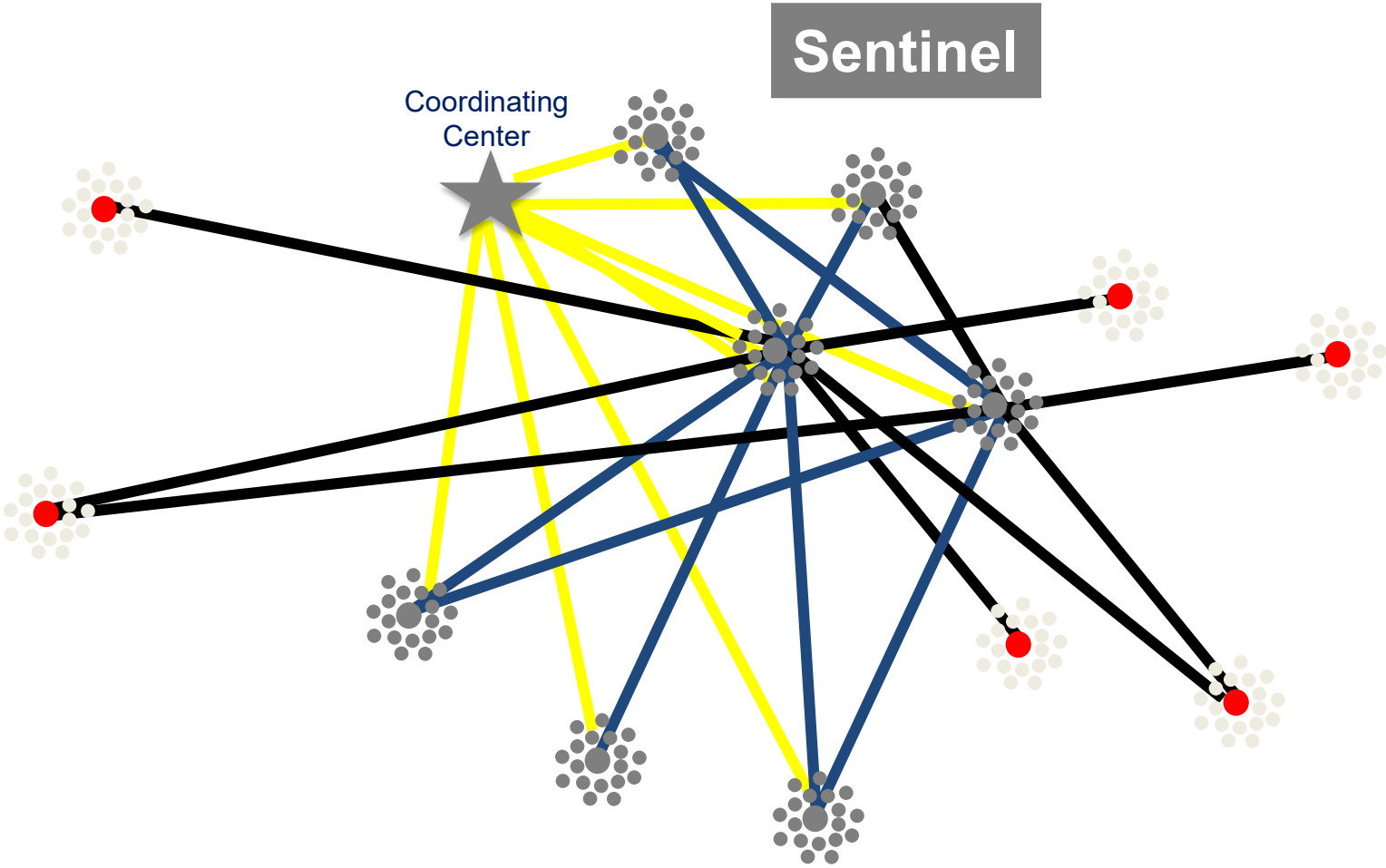
Previously independent sites now part of large integrated health systems increasingly sophisticated data warehouses



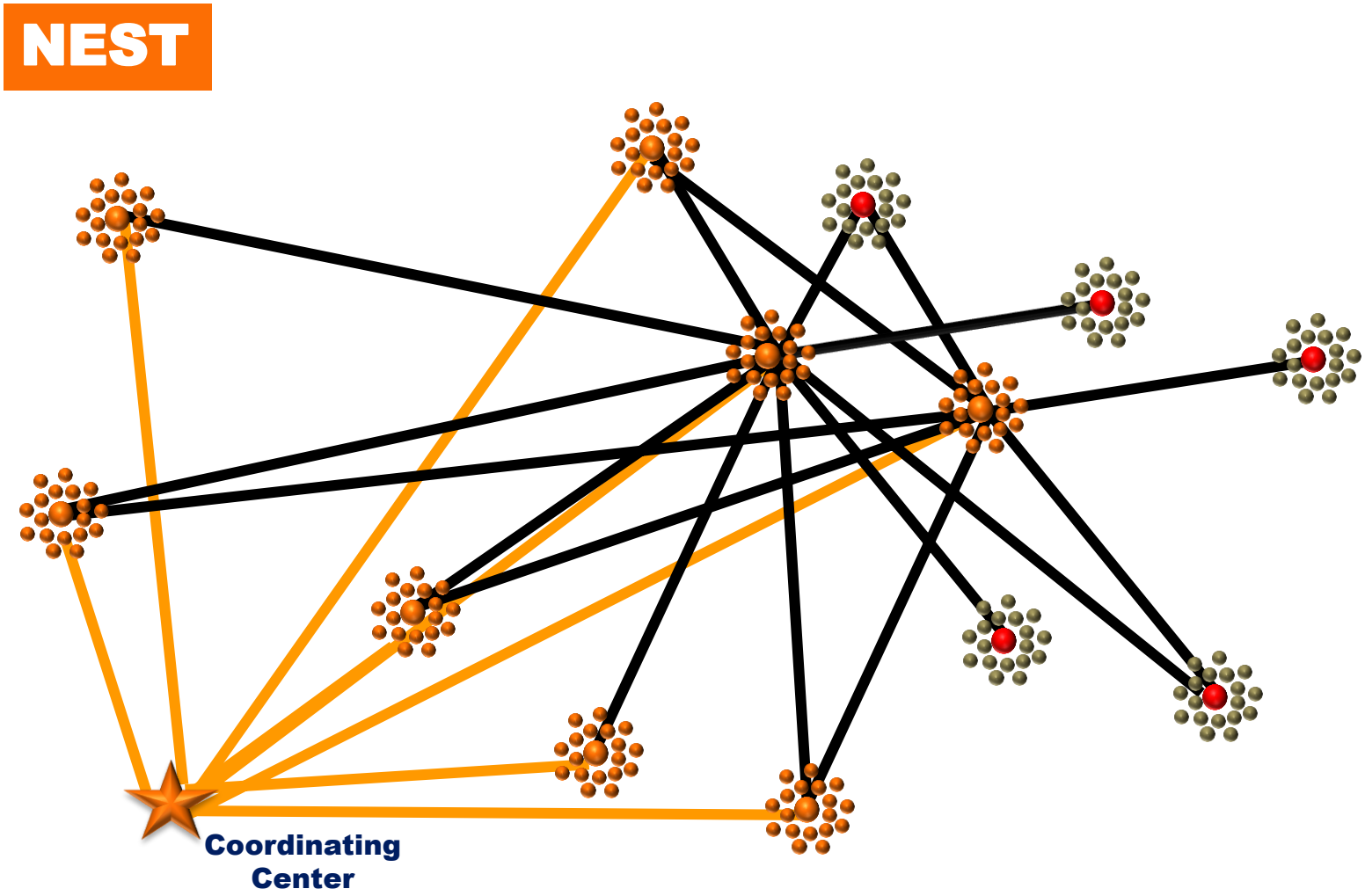
Nodes are operational clusters using common data



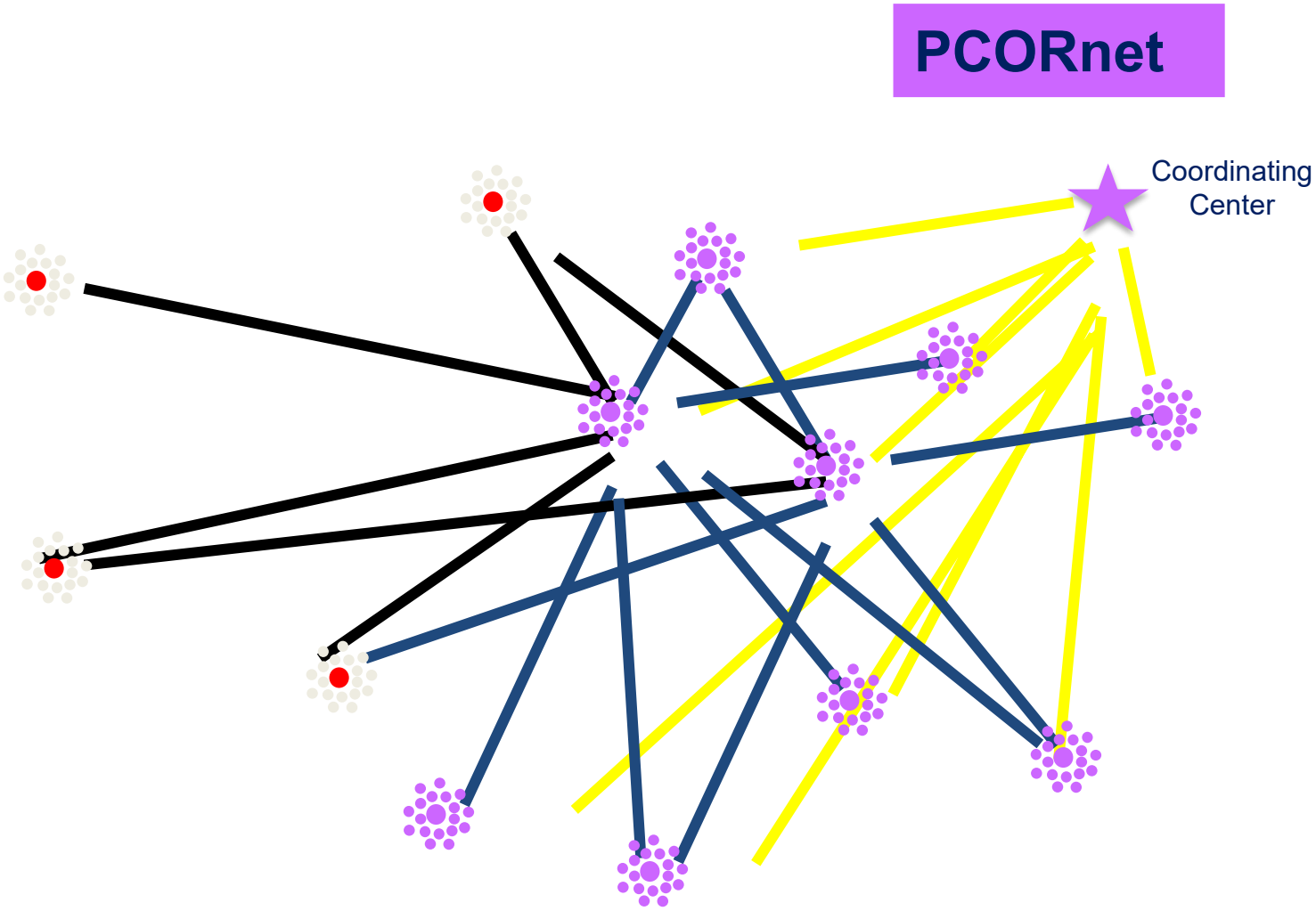
Drug & Biologic Surveillance and Trials



Device Surveillance and Trials

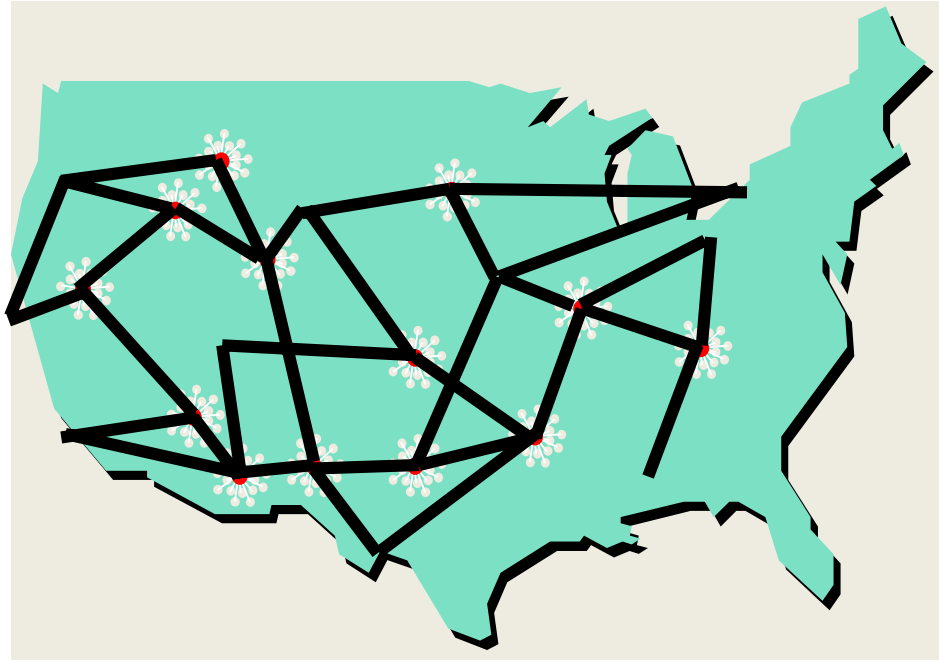


Post Market Studies, including comparative effectiveness



Integration of Clinical Research Networks ? CTSA Trial Innovation Network

- Link existing networks so clinical studies and trials can be conducted more effectively
- Ensure that patients, physicians, and scientists form true “Communities of Research”



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**)

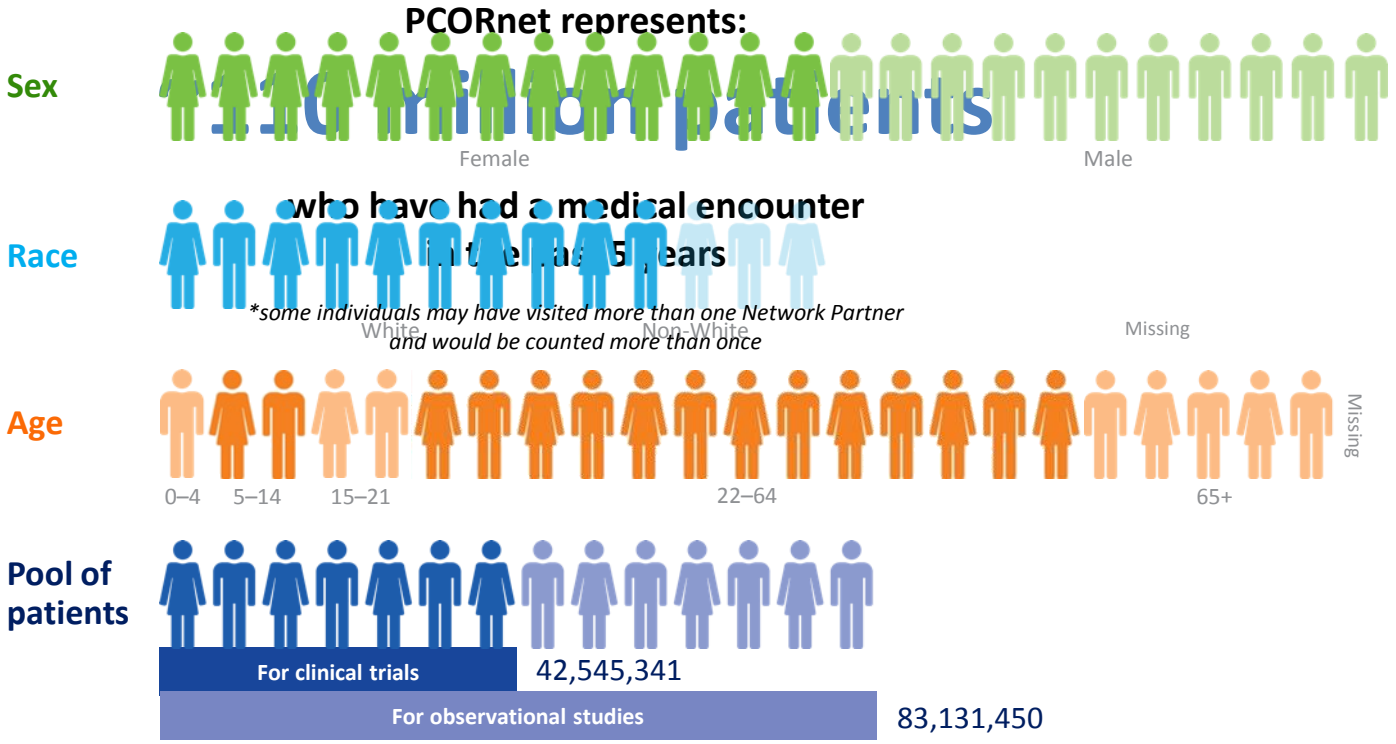
+

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

=

PCORnet
A national infrastructure for people-centered clinical research

Resulting in a national evidence system with unparalleled research readiness



People-Centered Research Foundation

- Launched March 21st

Mission to engage patients, families, research participants, clinicians, scientists, and health system leaders in the design, conduct, dissemination, and implementation of research and analysis that leads to improvements in the health and well-being of individuals and populations and the performance of health care delivery systems

People-Centered
RESEARCH FOUNDATION

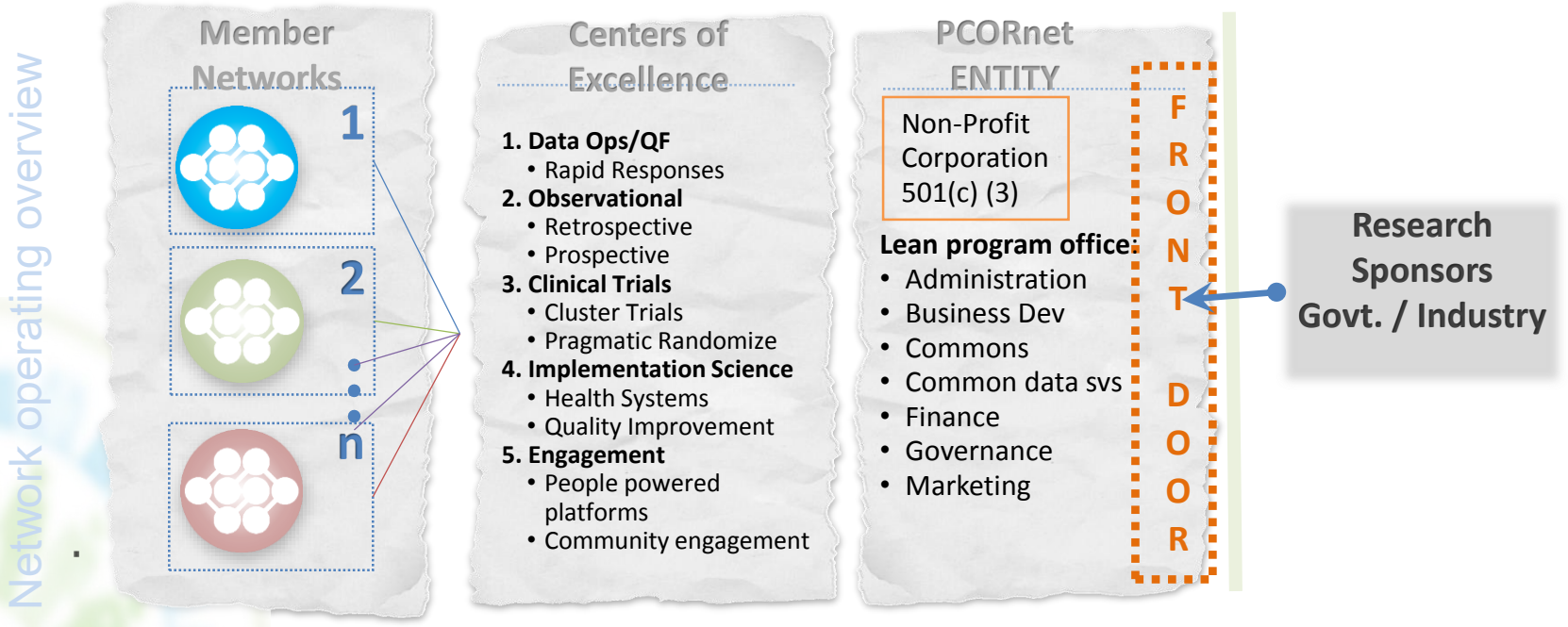
Inaugural Board

- Chair – Robert Califf, MD, former FDA Commissioner and Professor of Medicine, Duke University
- Board –
  - Richard Bankowitz, MD, MBA, FACP, Executive Vice President, Clinical Affairs, America's Health Insurance Plans (AHIP)
  - Josephine P. Briggs, MD, Director, National Center for Complementary and Integrative Health (NCCIH)
  - Marc M. Boutin, JD, Chief Executive Officer, National Health Council (NHC)
  - Donna Cryer, President & CEO of the Global Liver Institute
  - Craig Lipset, MPH, Head of Clinical Innovation, Global Product Development, Pfizer
  - Joanne Waldstreicher, MD, Chief Medical Officer, Johnson & Johnson
  - Reed Tuckson, MD, Managing Director of Tuckson Health Connections

People-Centered
RESEARCH FOUNDATION

New entity for continued operations: NewCo.

A non-profit corporation to be established to facilitate transition of current operations and to execute mission-aligned strategy toward sustainability



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

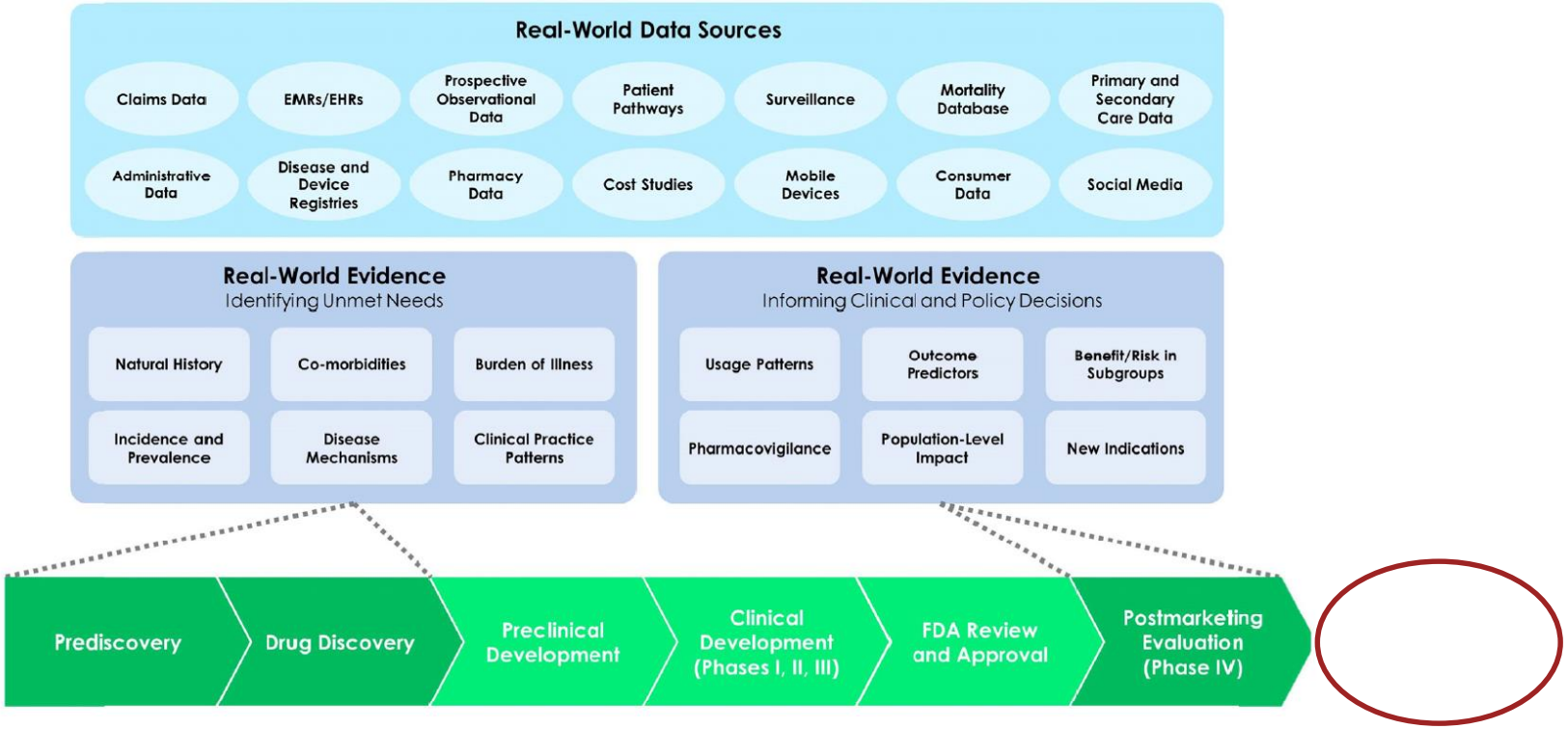
PDUFA RWE provisions

- 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?

Rachel E. She
Gerald J. Dal Pan, M.
Nina L. Hunter, Ph
Peter W. Marks, M.D.
Robert Temple, M.D., Ja

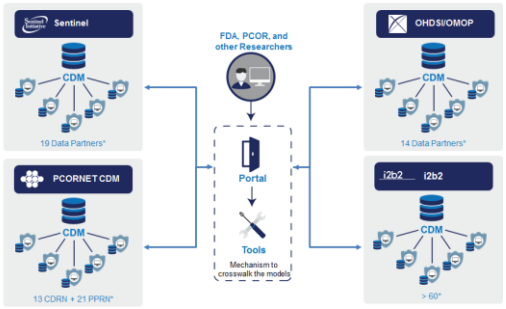
- Real-world evidence can be used across a wide spectrum of research, ranging from observational studies to studies that incorporate planned interventions, whether with or without randomization at the point of care.
- Incorrect to contrast the term “real-world evidence” with the use of randomization 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

Demonstratio: Electronic Source Data in Clinical Investigations

Use of Electronic Informed Consent

Call to Action

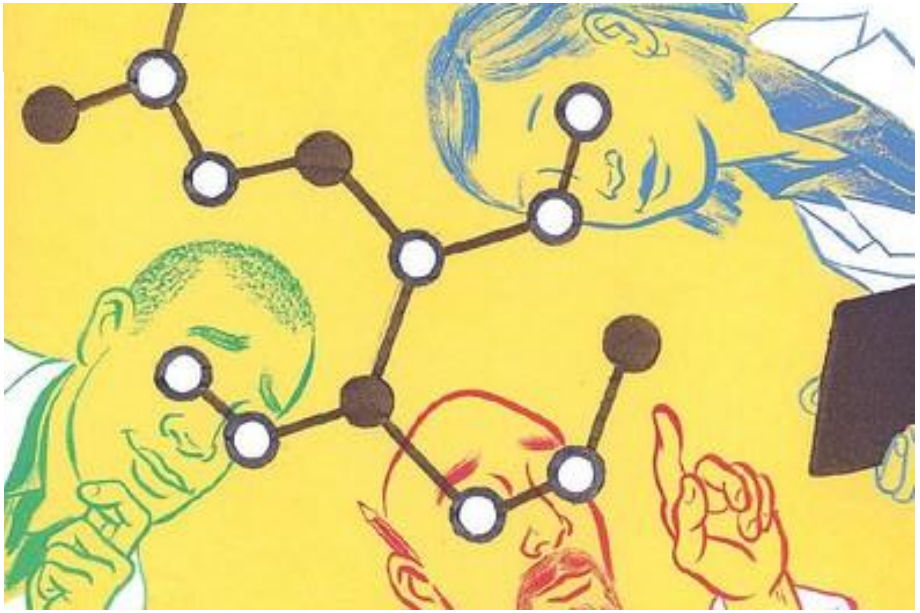
- **Organize operational systems that bring together research networks embedded in practice**
  - to enable patients, consumers, clinicians, industry, government, and health care systems to participate in prospective trials and observational studies
  - Develop operational/regulatory approaches to facilitate 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?**

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.



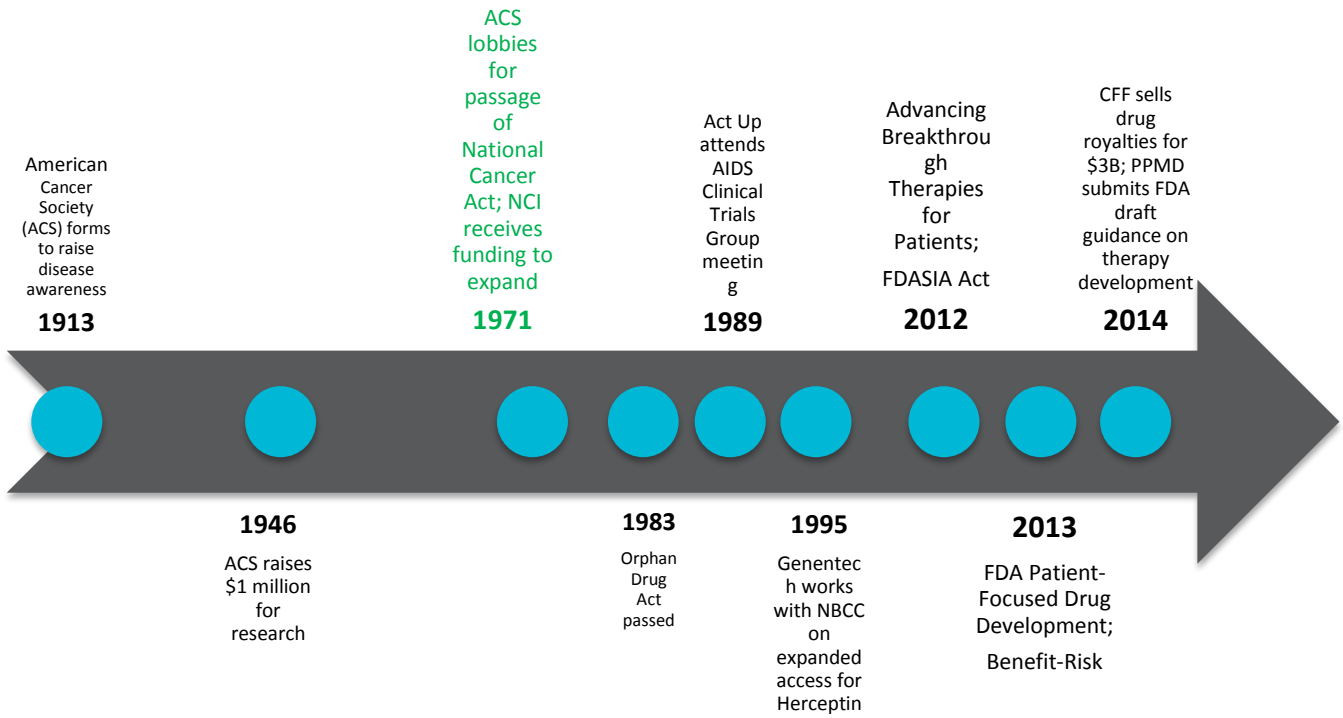
Several hours after Mr. Gowers opened up his blog for discussion, a Canadian-Hungarian mathematician posted a comment. Fifteen minutes later, an Arizona high-school math teacher chimed in. Three minutes after that, the UCLA mathematician Terence Tao commented. The discussion ignited, and in just six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

THE WALL STREET JOURNAL.

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?**

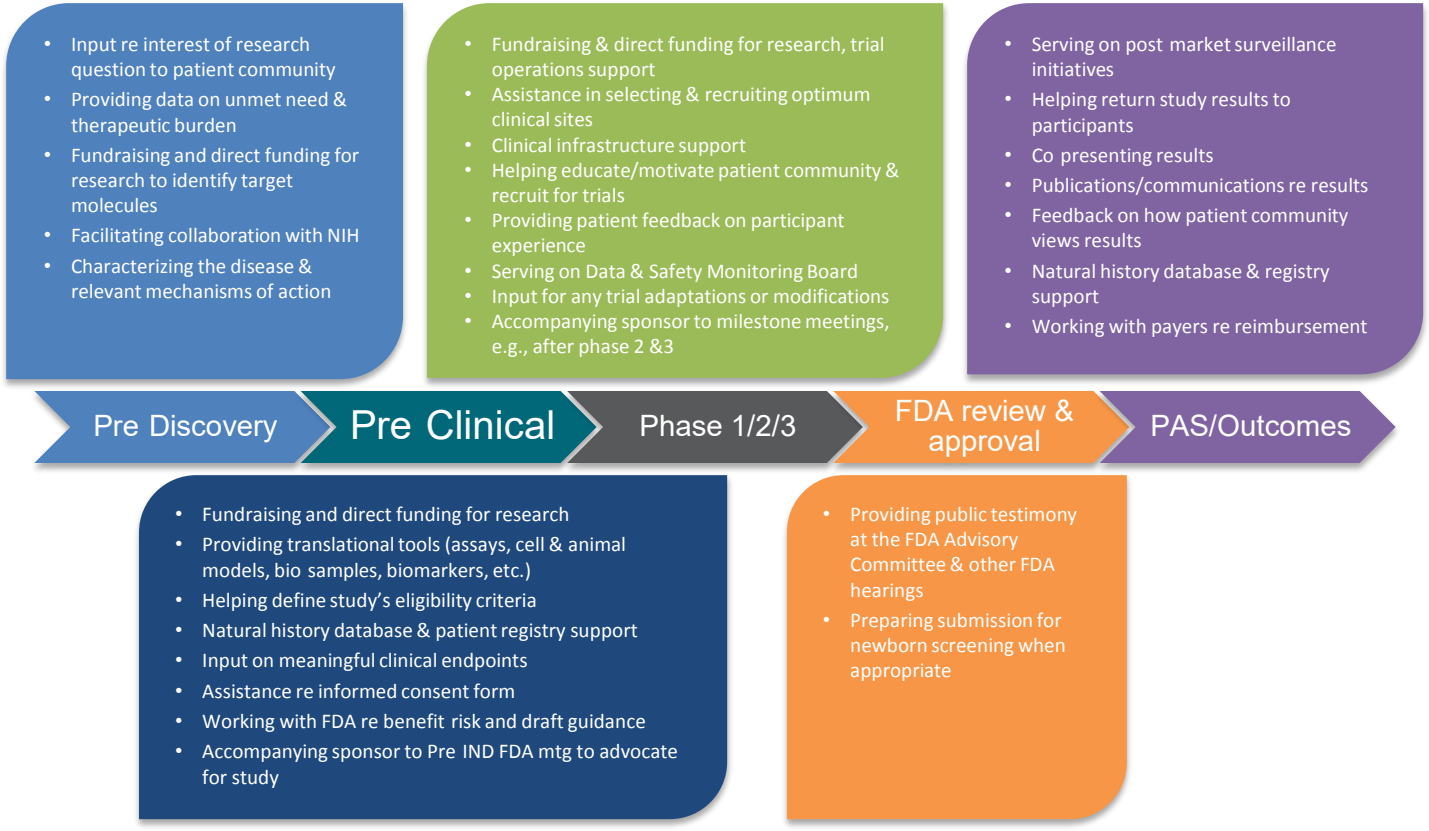
Background-Activated Participants



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

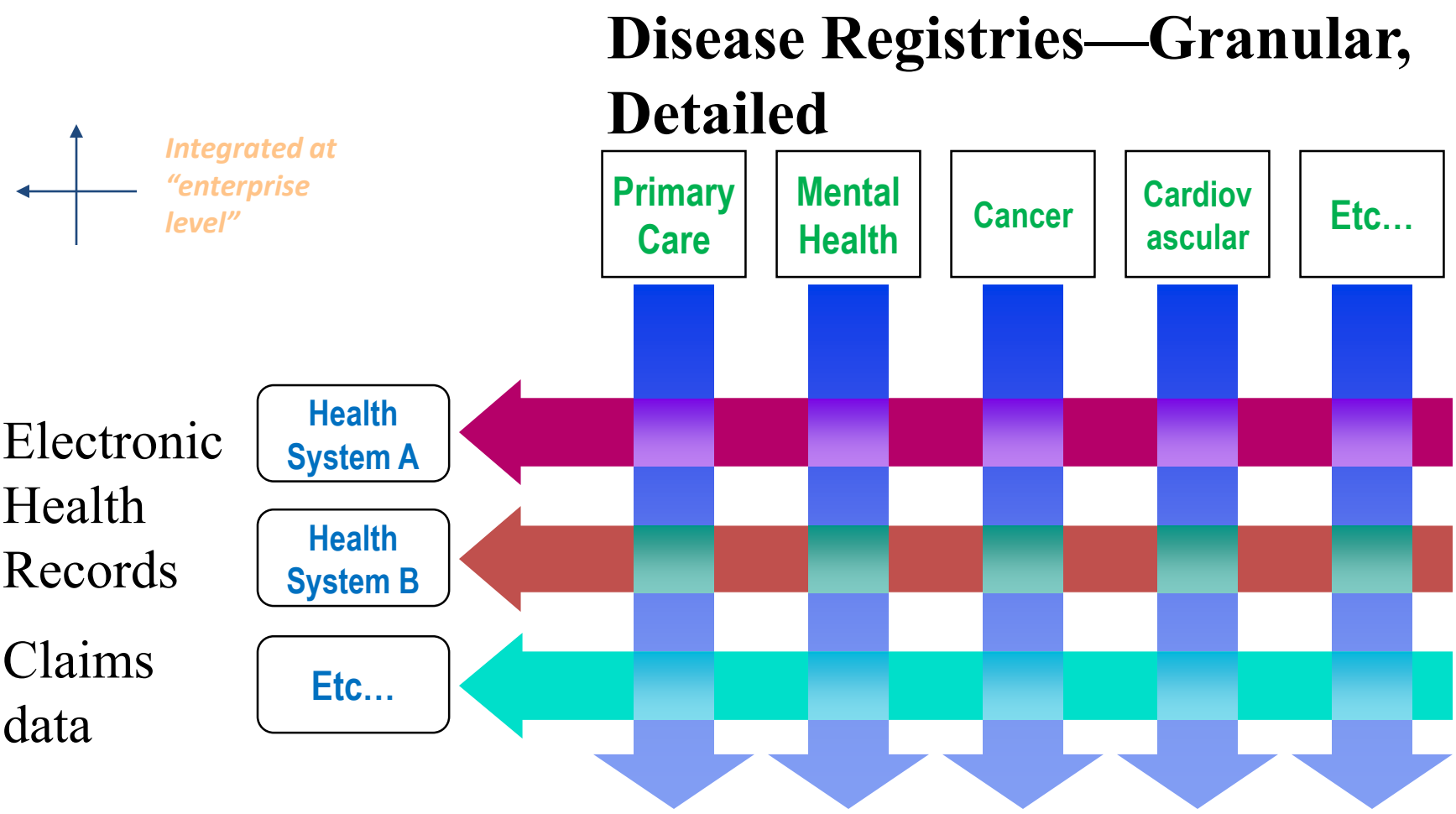


**Adapted from Parkinson's Disease Foundation materials for CTTI's Patient Groups & Clinical Trials Project*

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?**

Fundamental Informatics Infrastucture--Matrix Organizational Structure



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

TECHNOLOGY

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

By STEVE LOHR AUG. 17, 2014

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?**

Top 3 Things for Collaboratory (IMHO)

1) Get results and publish
2) Develop approach to broader dissemination and implementation
3) Develop “metaknowledge”
   A. What is working?
   B. What are the toughest hurdles for those hoping to do pragmatic trials?
      i. What are solutions to overcoming the hurdles?
   C. Turn metaknowledge into policy

Summary

- We have become complacent with lack of knowledge about best course of action for individuals and populations
- Consequences are substantial
  - Individual health
  - Population health
- Collaboratory is at the leading edge of a new way of learning in health care
- How do we move this along?