Therapeutics in Children: Great Progress, Now Let's Fill in the Gaps

Robert M Califf MD
Vice Chancellor for Health Data Science
Duke University
Advisor, Verily Life Sciences

FDA ADEPT Meeting

September 18th, 2017

Frontiers

- Human biology
  - Growth and development
  - Maternal Fetal systems biology
- Evidence generation with pragmatic outcome studies
- Implementation science
- Social determinants of health
- Ethics of information and data science in children

Historical Milestones and Legislation

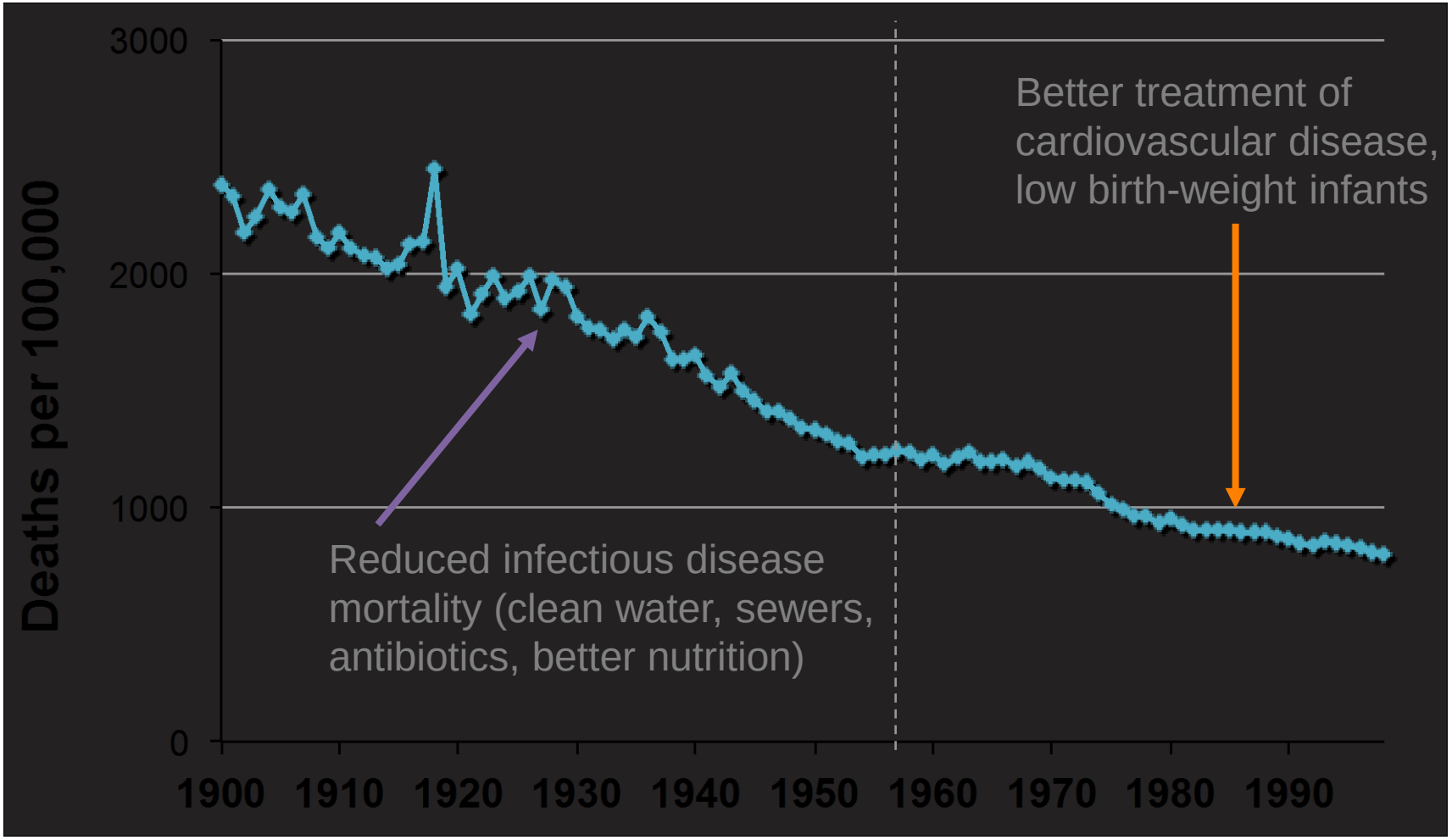
- **1902** The Biologics Control Act enacted following the death of 22 children from tainted anti-toxins
- **1938** FD&C Act: Drugs must be Safe: enacted after 100 deaths, many in children, after use of Elixir Sulfanilamide
- **1962** Following thalidomide tragedy in Europe; Kefauver–Harris amendments require effectiveness
- **1962** The FD&C Act amended: Drugs not tested in children should not be used in children
- **1974** AAP Committee on Drugs issues guidelines for evaluating drugs for pediatric use
- **1977** AAP issues guidelines for ethical conduct in pediatric studies
- **1979** FDA requires sponsors to conduct pediatric clinical trials before including pediatric information in the labeling
- **1992** Agency proposed Pediatric Labeling Rule and proposes extrapolation of efficacy from other data
- **1994** Final Rule on Pediatric Labeling. Formalizes Extrapolation of Efficacy; manufacturers to update labeling if pediatric data existed; HOWEVER, it allowed a disclaimer to the labeling for drugs not evaluated in children
- **1994** Pediatric Plan to encourage voluntary development of pediatric data
- **1997** FDAMA creates pediatric exclusivity provision **(voluntary**), provides 6-month exclusivity incentive
- **1998** Pediatric Rule **(mandatory):** products are required to include pediatric assessments if the drug is likely to be used in a ''substantial number of pediatric patients'' (50,000) or if it may provide a ''meaningful therapeutic benefit''
- **2002** Pediatric Rule declared invalid by DC Federal Court; the rule exceeded FDA's authority
- **2002** FDAMA reauthorized as BPCA. Maintains 6-month exclusivity added to patent life of the active moiety. Creates Office of Pediatric Therapeutics (including ethicist). Mandates pediatric focused safety reviews
- **2003** PREA re-establishes many components of the FDA's 1998 pediatric rule. Orphan products are exempted
- **2007** FDAA Reauthorizes BPCA & PREA for 5 years : Pediatric Review Committee (PeRC) formed.
  Studies submitted will result in labeling. Negative and positive results of pediatric studies will be placed in labeling
- **2012** FDASIA legislation makes **permanent** BPCA and PREA

Measures of Success

- 1997-2016: Over 620 products have been studied in pediatrics and have new pediatric information in the label
  - Of these, over 560 involved new pediatric studies
- First products submitted and labeled as a result of the BPCA "Docket" process involving FDA/NIH/investigators
  - 4 products have had a docket opened (sodium nitroprusside, meropenem, lorazepam, and ampicillin)
  - 3 products with finalized labeling (sodium nitroprusside, meropenem, and lorazepam)

The need for actionable evidence generation is urgent in the US

Mortality in the 20th Century



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

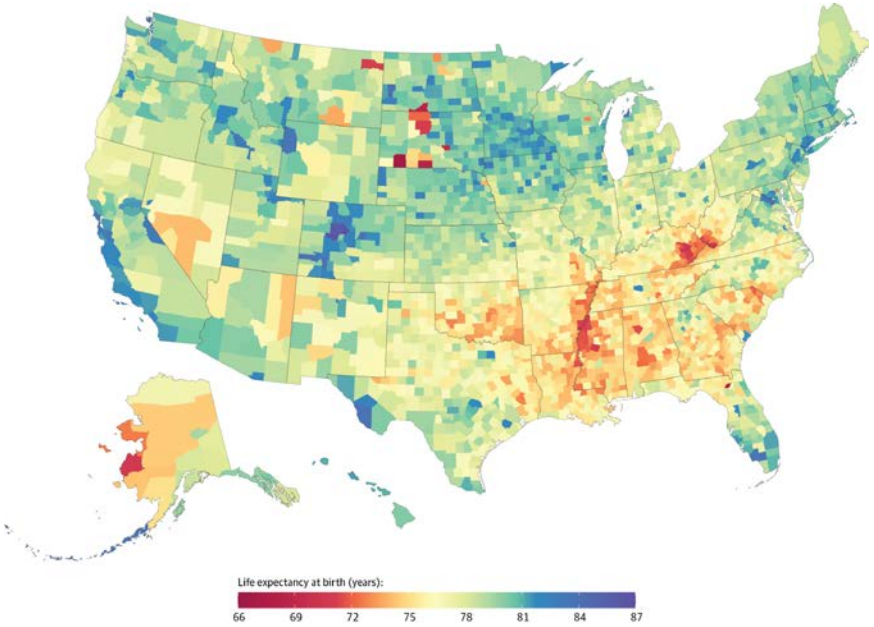


Figure Legend:

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

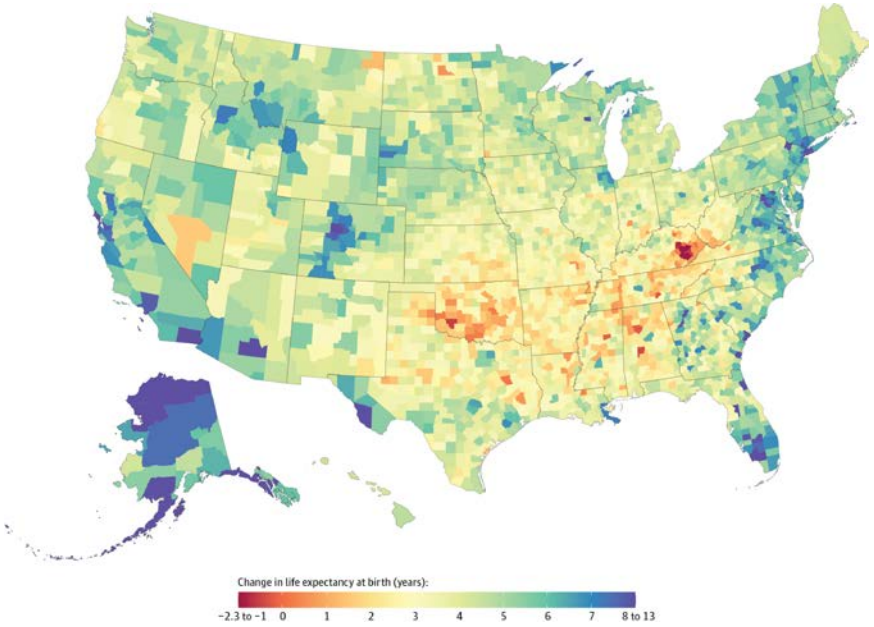


Figure Legend:

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

Table 1. Variables Included in the Regression Analysis With Summary Statistics and Bivariate Regression Results

Variable	Summary Statistics, Mean (SD) [Range]	Bivariate Regression Results	
		Coefficient (SE)	R^2
Socioeconomic and race/Ethnicity factors			
Population below the poverty line, %	16.3 (6.4) [3.1-62.0]	−0.24 (0.005)	0.47
Median household income, log $	10.6 (0.2) [9.8-11.6]	6.06 (0.130)	0.41
Graduates, age ≥25 y, %			
High school	83.7 (7.2) [46.3-98.6]	0.20 (0.004)	0.42
College	19.2 (8.6) [4.2-72.0]	0.15 (0.004)	0.34
Unemployment rate, age ≥16 y, %	9.1 (3.2) [2.1-27.4]	−0.29 (0.011)	0.18
Black population, %	9.4 (14.7) [0-85.8]	−0.07 (0.002)	0.24
American Indian, Native Alaskan, and Native Hawaiian population, %	2.3 (7.9) [0-97.2]	−0.06 (0.005)	0.04
Hispanic population, %	8.1 (13.1) [0-95.9]	0.02 (0.003)	0.01
Behavioral and metabolic risk factors, %			
Obesity prevalence, age ≥20 y	37.0 (4.3) [18.0-52.0]	−0.39 (0.006)	0.54
No leisure-time physical activity prevalence, age ≥20 y	27.0 (5.2) [11.7-47.2]	−0.34 (0.005)	0.62
Cigarette smoking prevalence, age ≥18 y	24.7 (4.1) [7.7-42.1]	−0.40 (0.007)	0.54
Hypertension prevalence, age ≥30 y	39.5 (3.6) [27.9-56.4]	−0.49 (0.007)	0.62
Diabetes prevalence, age ≥20 y	14.0 (2.4) [8.1-25.5]	−0.72 (0.011)	0.59
Health care factors			
Insured population, age <65 y, %	81.7 (5.7) [57.3-96.7]	0.15 (0.007)	0.14
Quality index	70.1 (11.5) [0-100]	0.10 (0.003)	0.28
Physicians per 1000 population, No.	1.1 (1.0) [0-4.4]	0.53 (0.039)	0.06

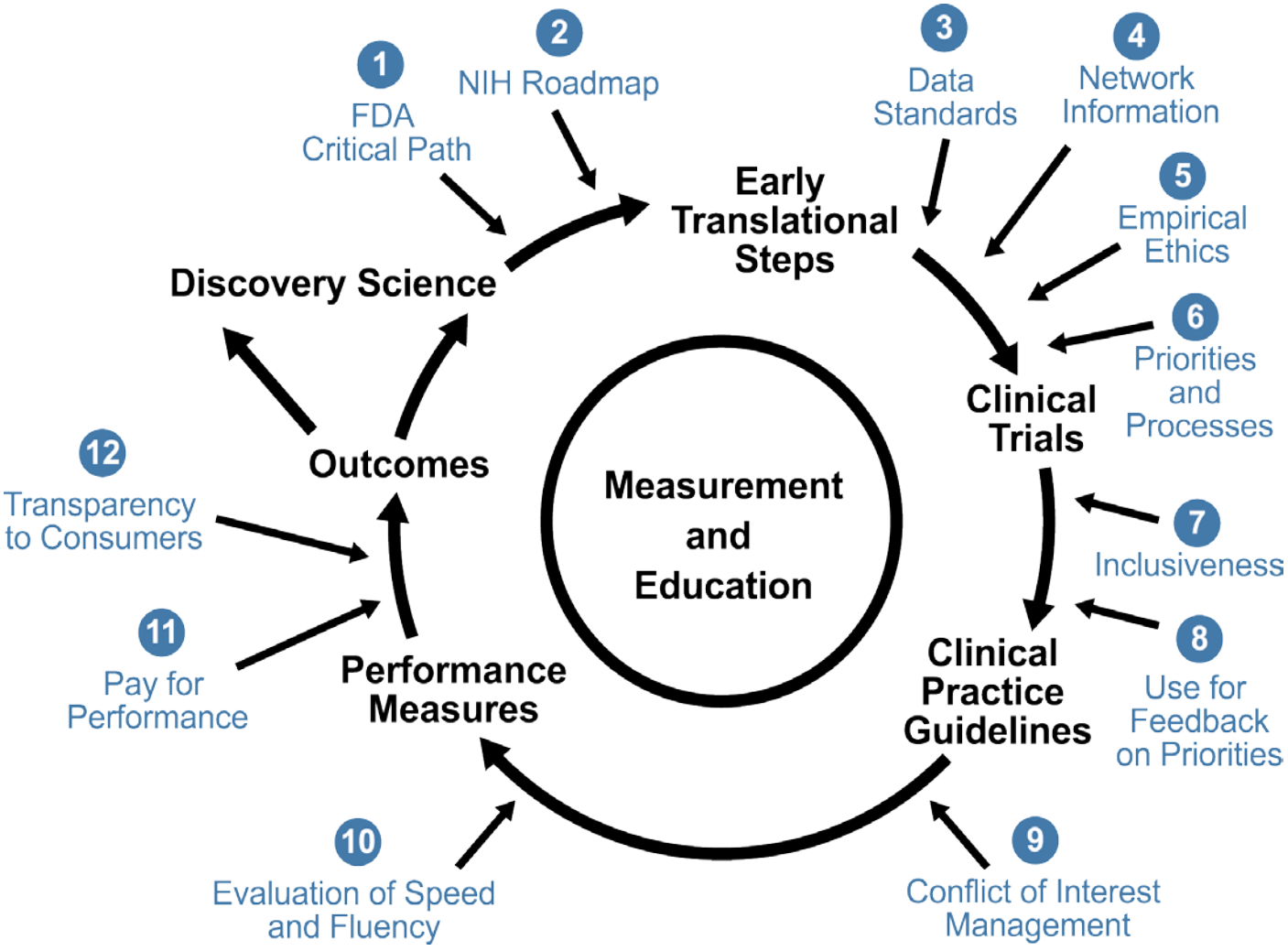
Abbreviation: SE, standard error.

Table Title:

Variables Included in the Regression Analysis With Summary Statistics and Bivariate Regression Results

Current system of evidence generation is inadequate

Generating Evidence to Inform Decisions



Our National Clinical Research System is Well-intentioned But Flawed

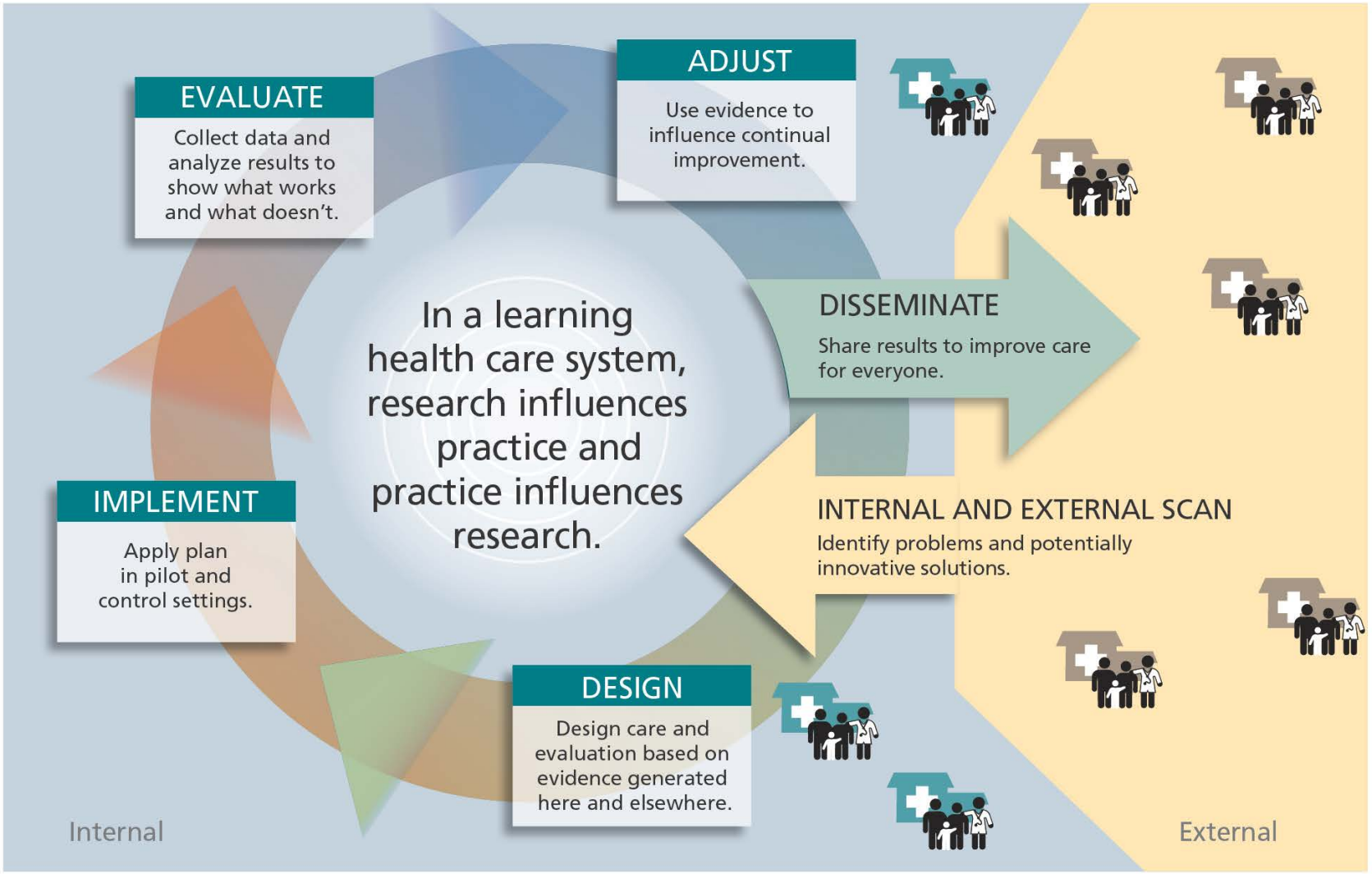
- High percentage of decisions not supported by evidence*
- Health outcomes and disparities are not improving
- Current system is great **except**:
  - Too slow, too expensive, and not reliable
  - Doesn't answer questions that matter most to patients
  - Unattractive to clinicians & administrators

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

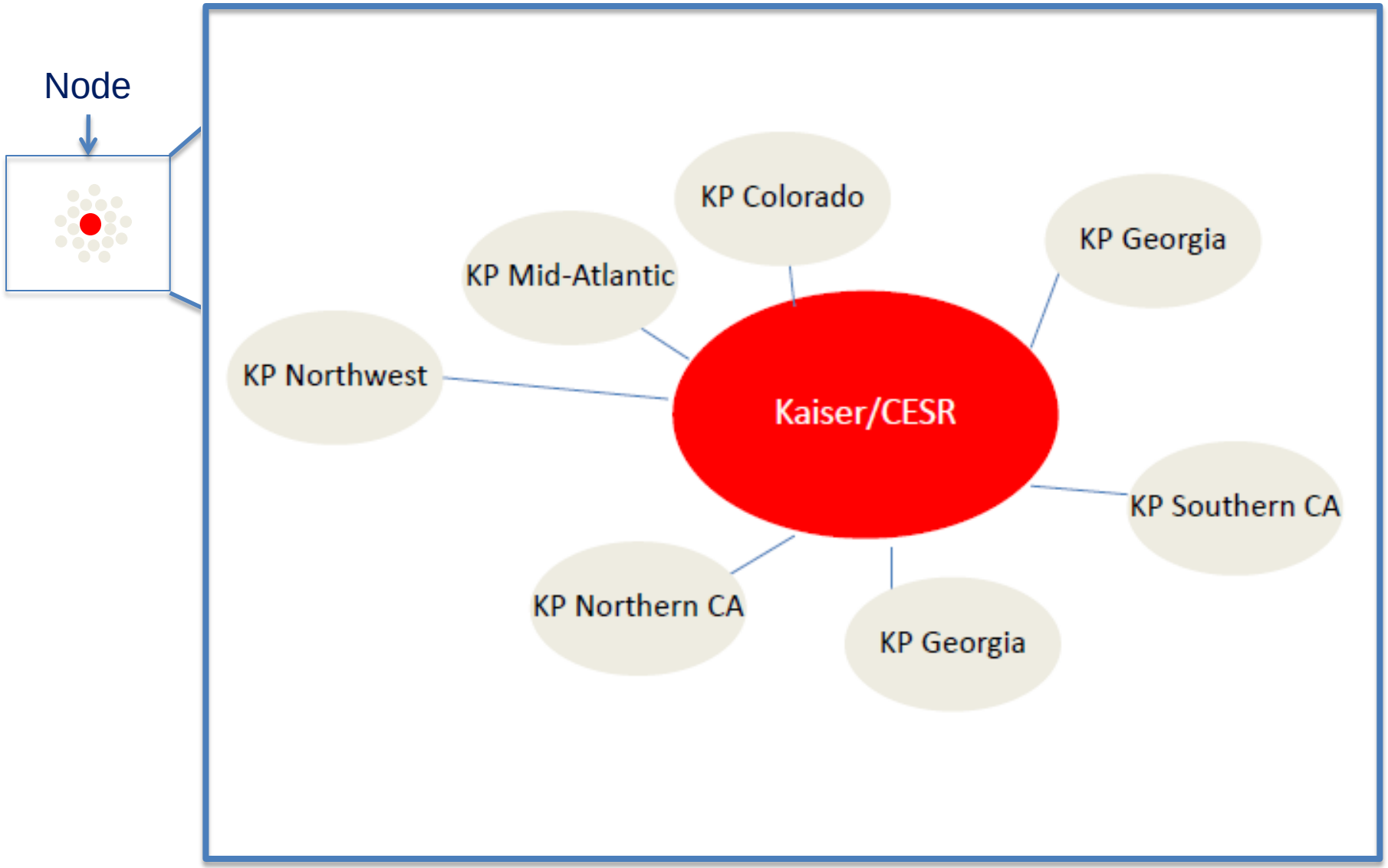
Tricoci P et al. JAMA 2009;301:831-41

Organizational substrate for far better system is developing rapidly

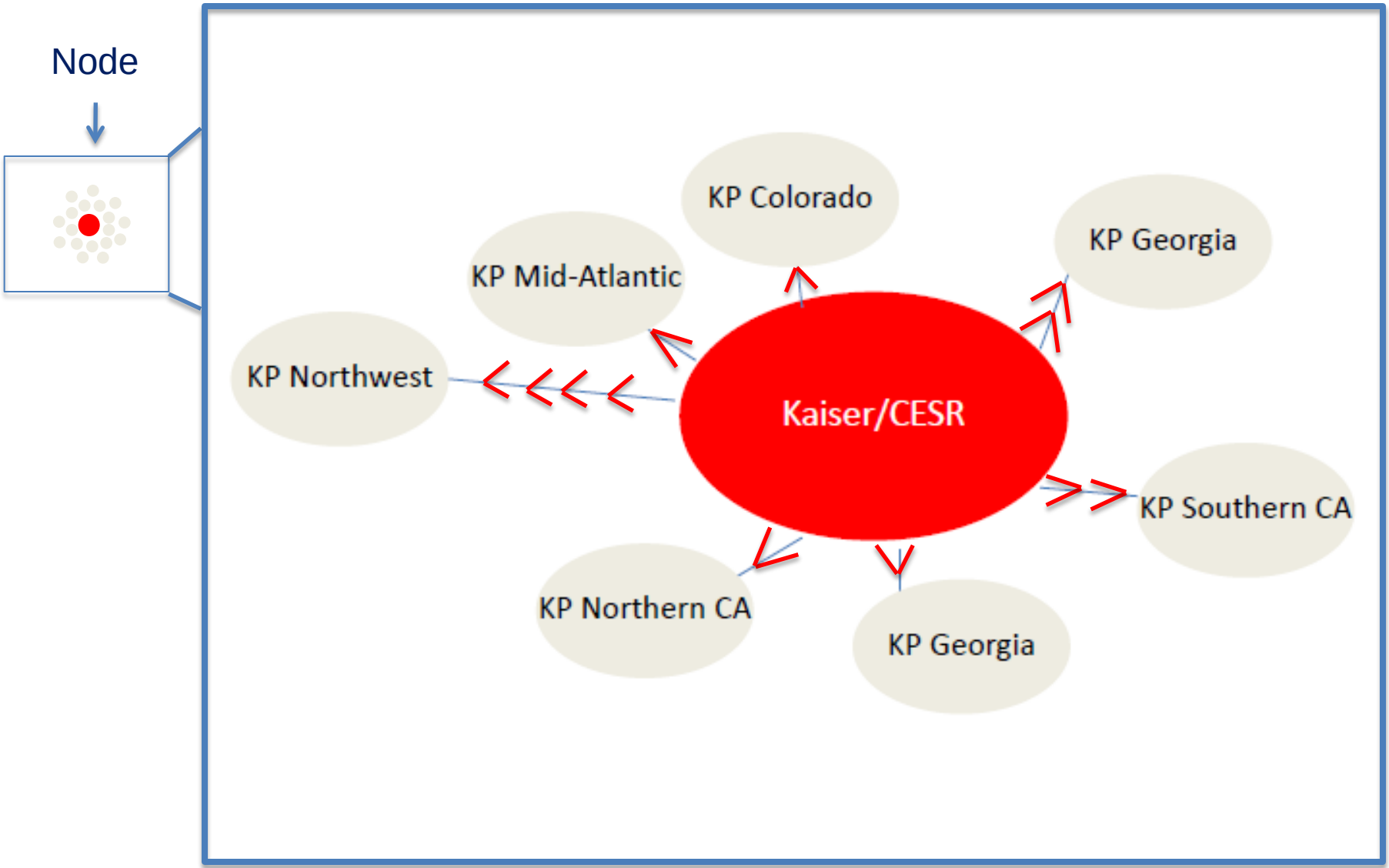
Learning health care systems



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

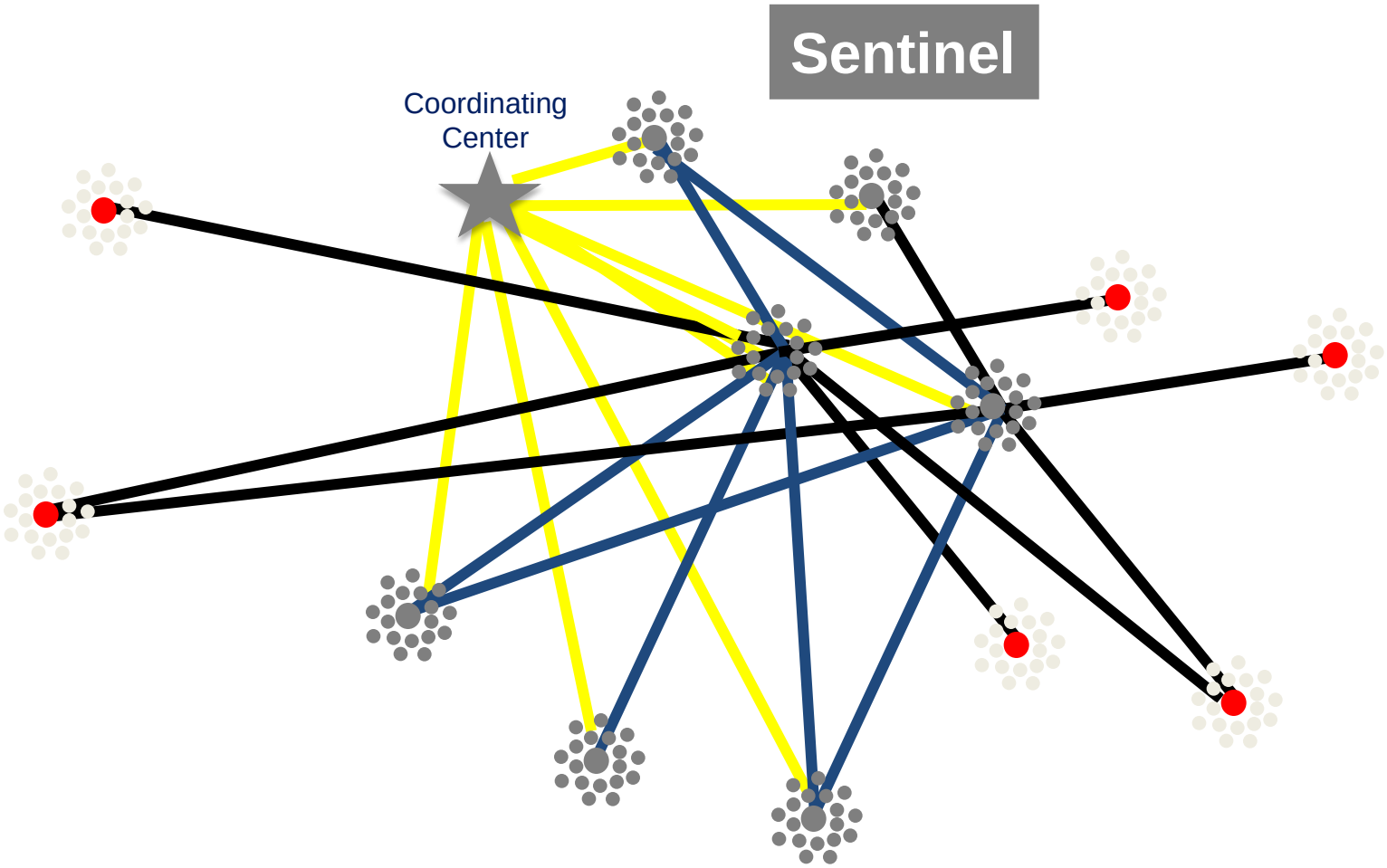


Nodes are Operational Clusters Using Common Data



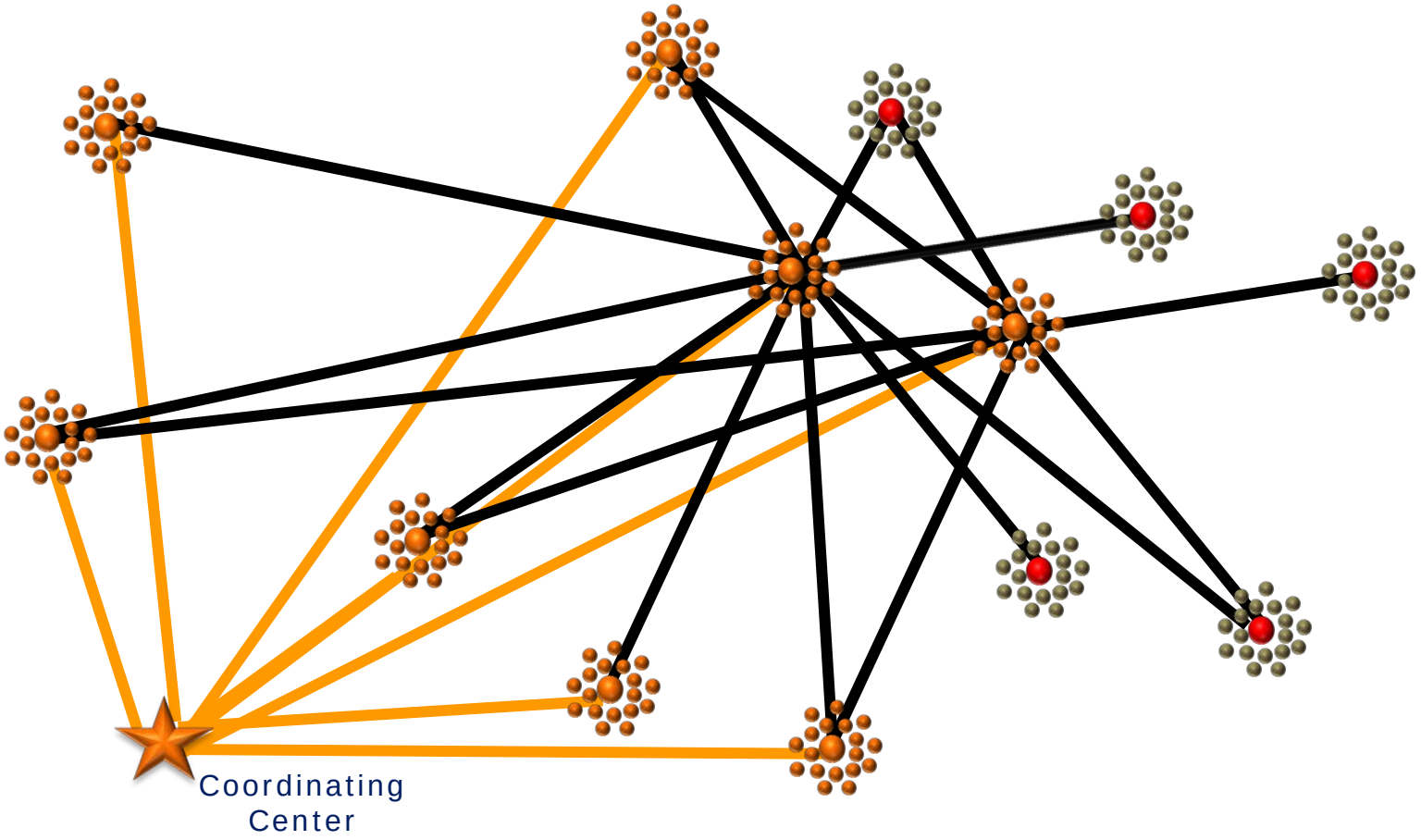
Public private partnerships are developing to generate reliable evidence rapidly

Drug Surveillance and Trials

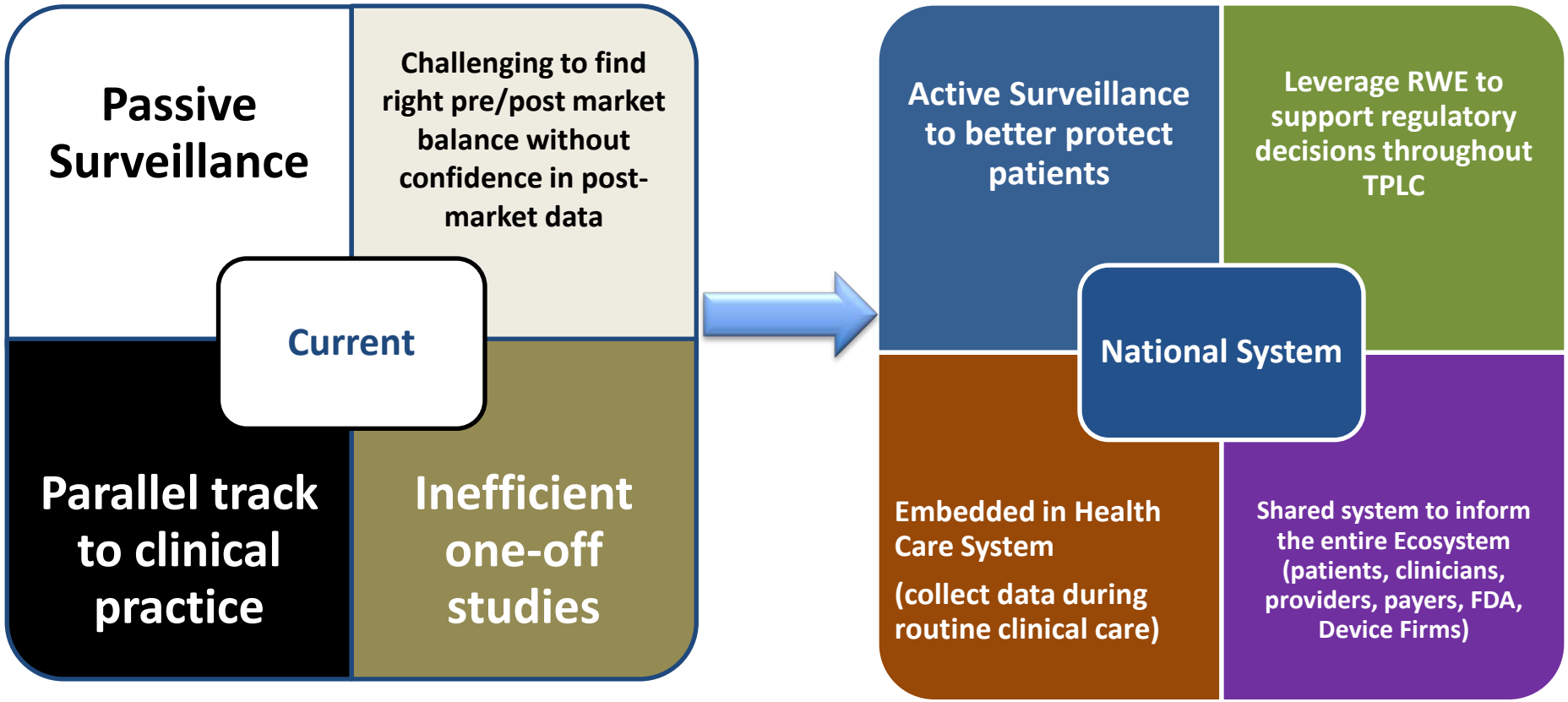


Device Surveillance and Trials

NEST

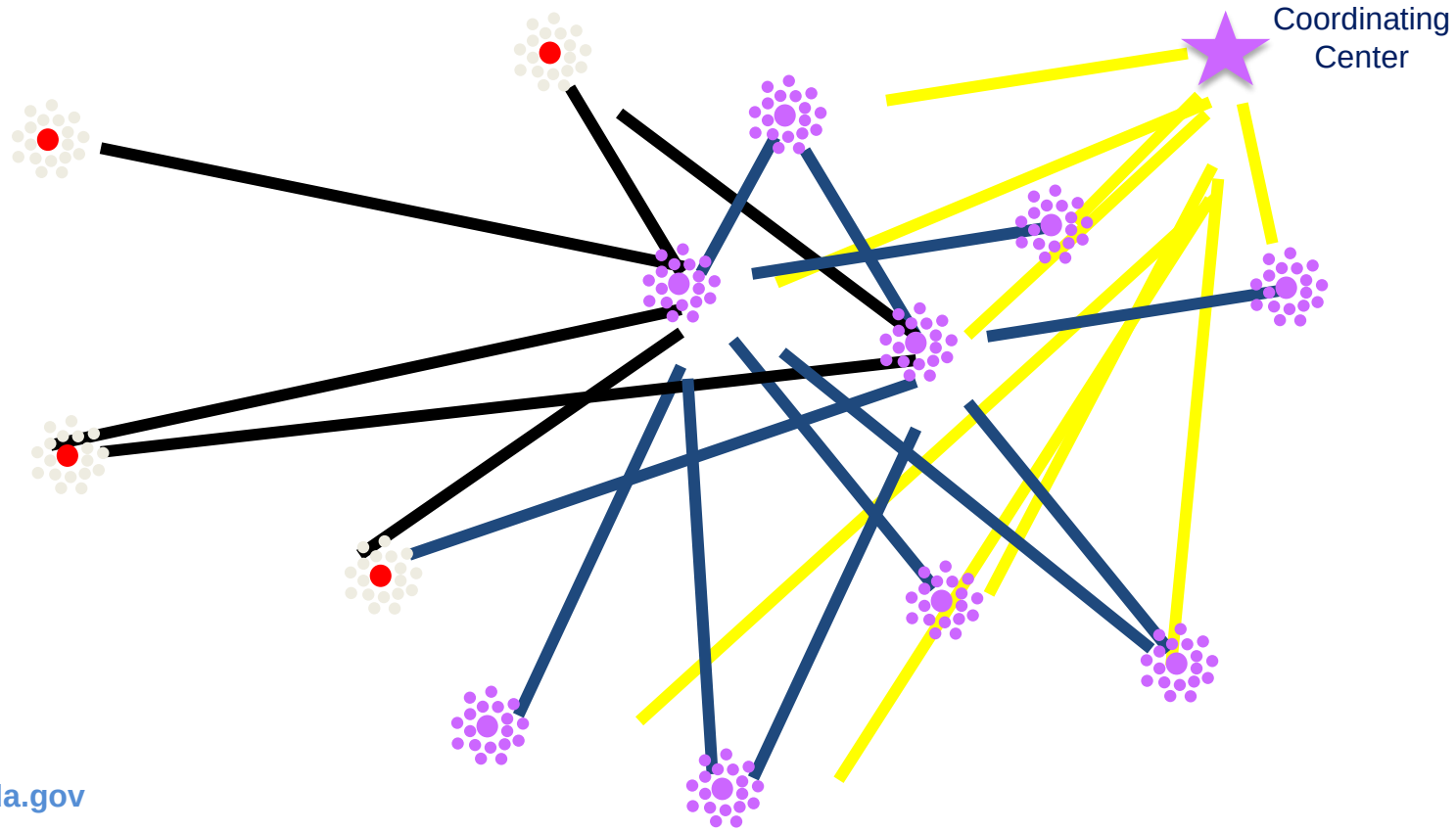


National System Paradigm Shift



Post Market Studies, including comparative effectiveness

PCORnet



Demonstration Project Overview-NIH Healthcare Systems Research Collaboratory

10 Demonstration Projects spanning 12 NIH institutes and centers

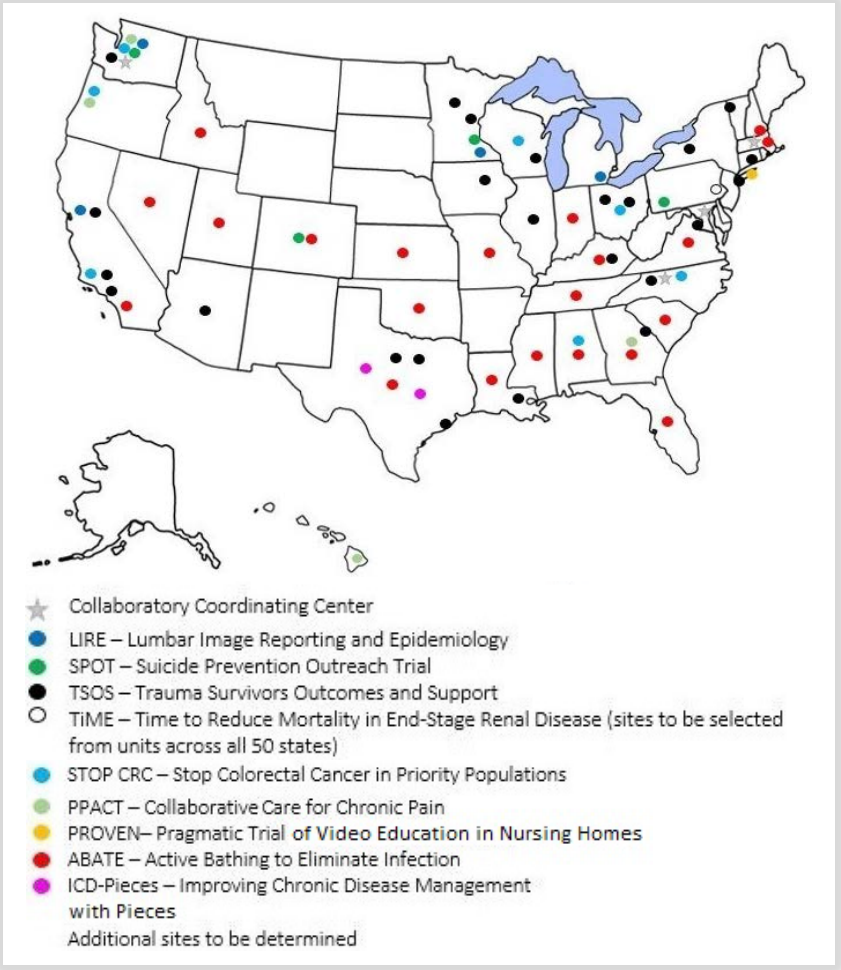
Major clinical outcome trials

1-year planning phase (UH2)

Implementation phase (UH3)

Using EHRs and minimal additional data collection

Log order reduction in cost



PCORnet/PCRF as an Example

People-Centered Research Foundation
PCORnet 2.0

People-Centered
RESEARCH FOUNDATION

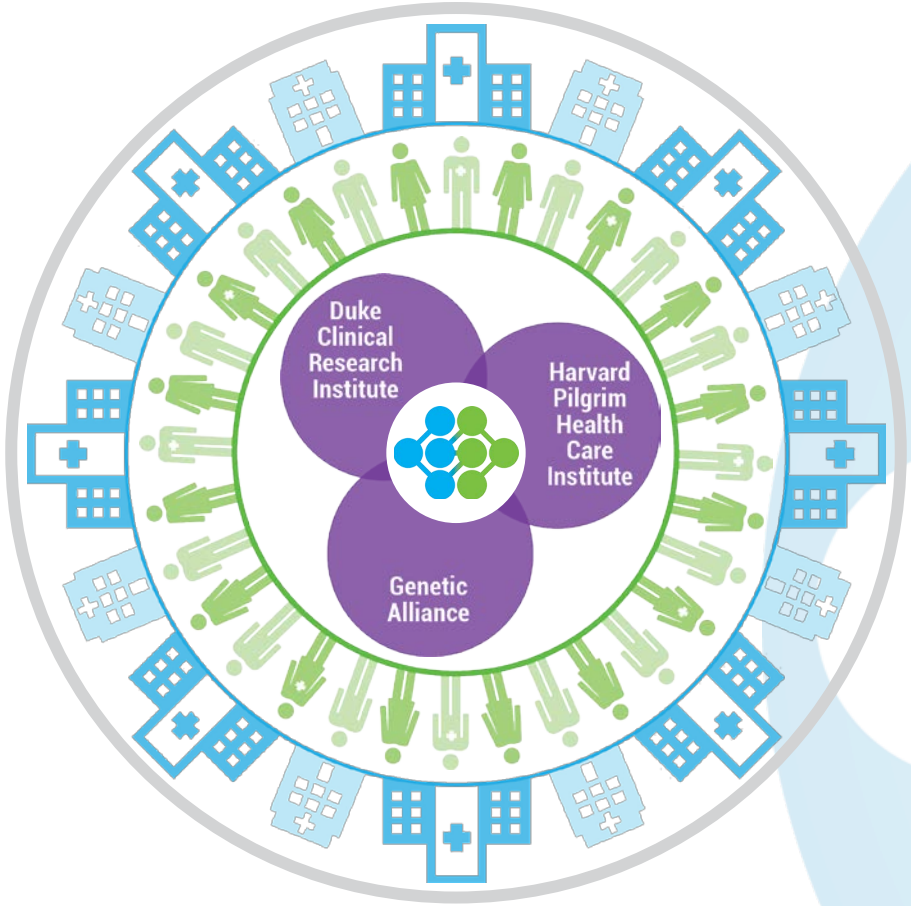
PCORnet® : the National Patient-Centered Clinical Research Network

An innovative initiative funded by the Patient-Centered Outcomes Research Institute (PCORI), PCORnet is **a large, highly representative, national patient-centered clinical research network**.

Our **vision** is to support a learning U.S. healthcare system and to enable **large-scale clinical research** conducted with **enhanced quality and efficiency**.

Our **mission** is to enable people to make informed healthcare decisions by efficiently conducting clinical research relevant to their needs.

PCORnet® embodies a "network of networks" that harnesses the power of partnerships



20 Patient-Powered Research Networks (**PPRNs**) + 13 Clinical Data Research Networks (**CDRNs**) + 1 Coordinating Center = pcornet®

A national infrastructure for people-centered clinical research

PPRNs

American BRCA Outcomes and Utilization of Testing Patient-Powered Research Network (ABOUT Network)
University of South Florida

ARthritis patient Partnership with comparative Effectiveness Researchers (AR-PoWER PPRN)
Global Healthy Living Foundation

CCFA Partners Patient Powered Research Network
Crohn's and Colitis Foundation of America

Collaborative Patient-Centered Rare Epilepsy Network (REN)
Epilepsy Foundation

Community and Patient-Partnered Centers of Excellence for Behavioral Health
University of California Los Angeles

Community-Engaged Network for All (CENA)
Genetic Alliance, Inc.

COPD Patient Powered Research Network
COPD Foundation

DuchenneConnect Registry Network
Parent Project Muscular Dystrophy

Health eHeart Alliance
University of California, San Francisco (UCSF)

ImproveCareNow: A Learning Health System for Children with Crohn's Disease and Ulcerative Colitis
Cincinnati Children's Hospital Medical Center

Interactive Autism Network
Kennedy Krieger Institute

Mood Patient-Powered Research Network
Massachusetts General Hospital

Multiple Sclerosis Patient-Powered Research Network
Accelerated Cure Project for Multiple Sclerosis

National Alzheimer's and Dementia Patient and Caregiver-Powered Research Network
Mayo Clinic

NephCure Kidney International
Arbor Research Collaborative for Health

Patients, Advocates and Rheumatology Teams Network for Research and Service (PARTNERS) Consortium
Duke University

Phelan-McDermid Syndrome Data Network
Phelan-McDermid Syndrome Foundation

PI Patient Research Connection: PI-CONNECT
Immune Deficiency Foundation

Population Research in Identity and Disparities for Equality Patient-Powered Research Network (PRIDEnet)
University of California San Francisco

Vasculitis Patient Powered Research Network
University of Pennsylvania

pcornet®

CDRNs

Accelerating Data Value Across a National Community Health Center Network (ADVANCE)
Oregon Community Health Information Network (OCHIN)

Chicago Area Patient Centered Outcomes Research Network (CAPriCORN)
The Chicago Community Trust

Greater Plains Collaborative (GPC)
University of Kansas Medical Center

Kaiser Permanente & Strategic Partners Patient Outcomes Research To Advance Learning (PORTAL) Network
Kaiser Foundation Research Institute

Research Action for Health Network (REACHnet)
Louisiana Public Health Institute (LPHI)

Mid-South CDRN
Vanderbilt University

National PEDSnet: A Pediatric Learning Health System
The Children's Hospital of Philadelphia

New York City Clinical Data Research Network (NYC-CDRN)
Weill Medical College of Cornell University

OneFlorida Clinical Data Research Network
University of Florida

Patient-Centered Network of Learning Health Systems (LHSNet)
Mayo Clinic

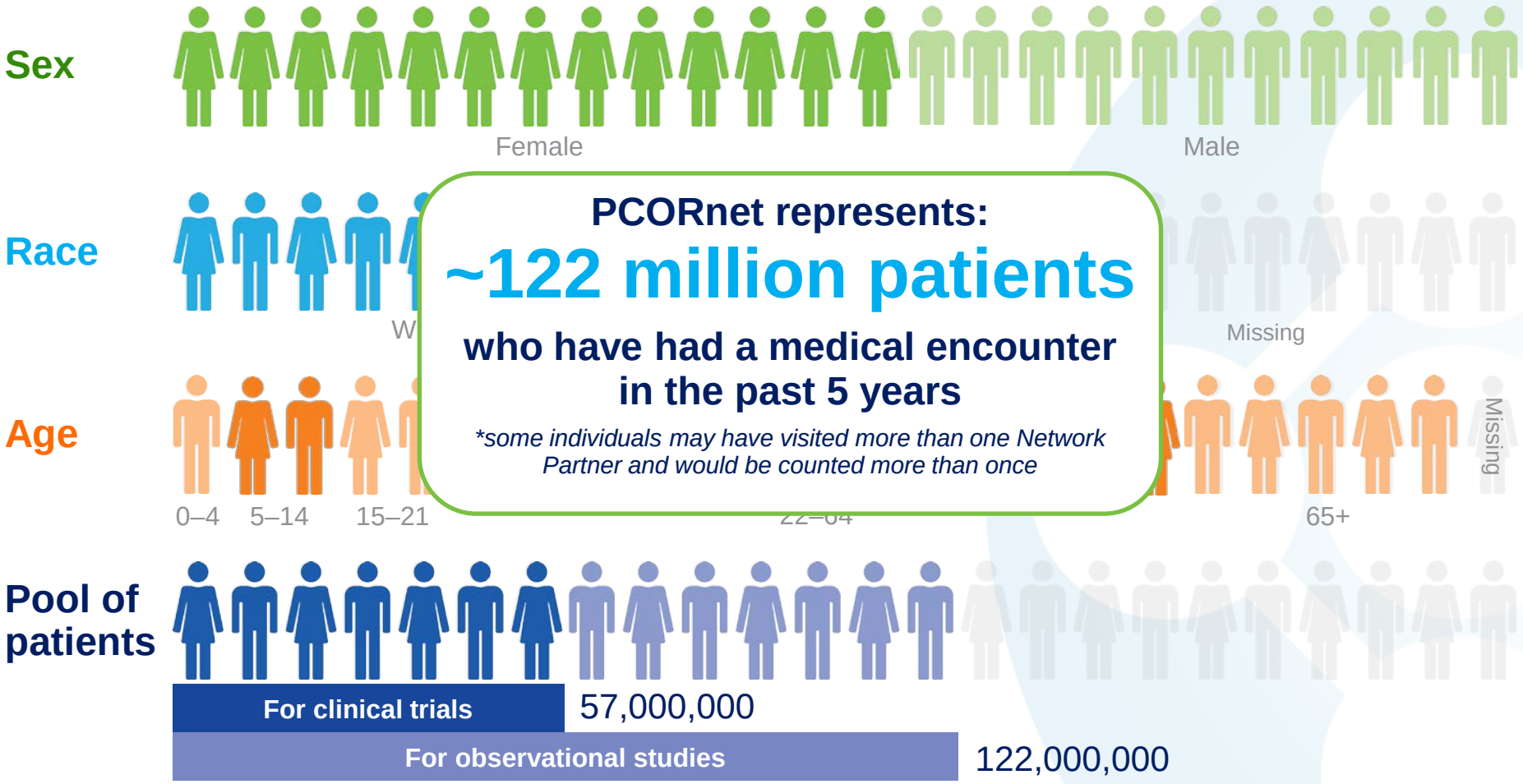
Patient-oriented SCAlable National Network for Effectiveness Research (pSCANNER)
University of California, San Diego (UCSD)

PaTH: Towards a Learning Health System
University of Pittsburgh

Scalable Collaborative Infrastructure for a Learning Healthcare System (SCILHS)
Harvard University

pcornet®

Resulting in a national evidence system with “research readiness”



pcornet®

Policy supports this evolution of real world evidence

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

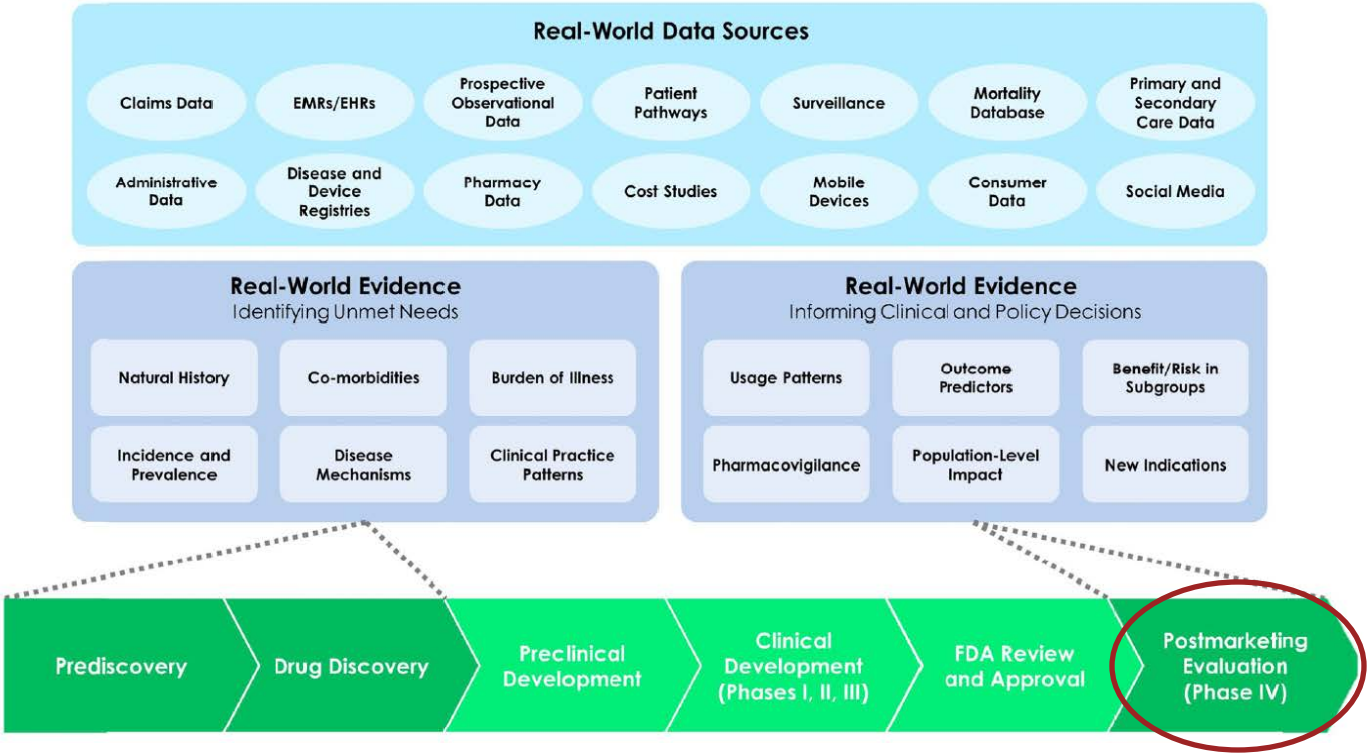
PDUFA RWE provisions

- 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

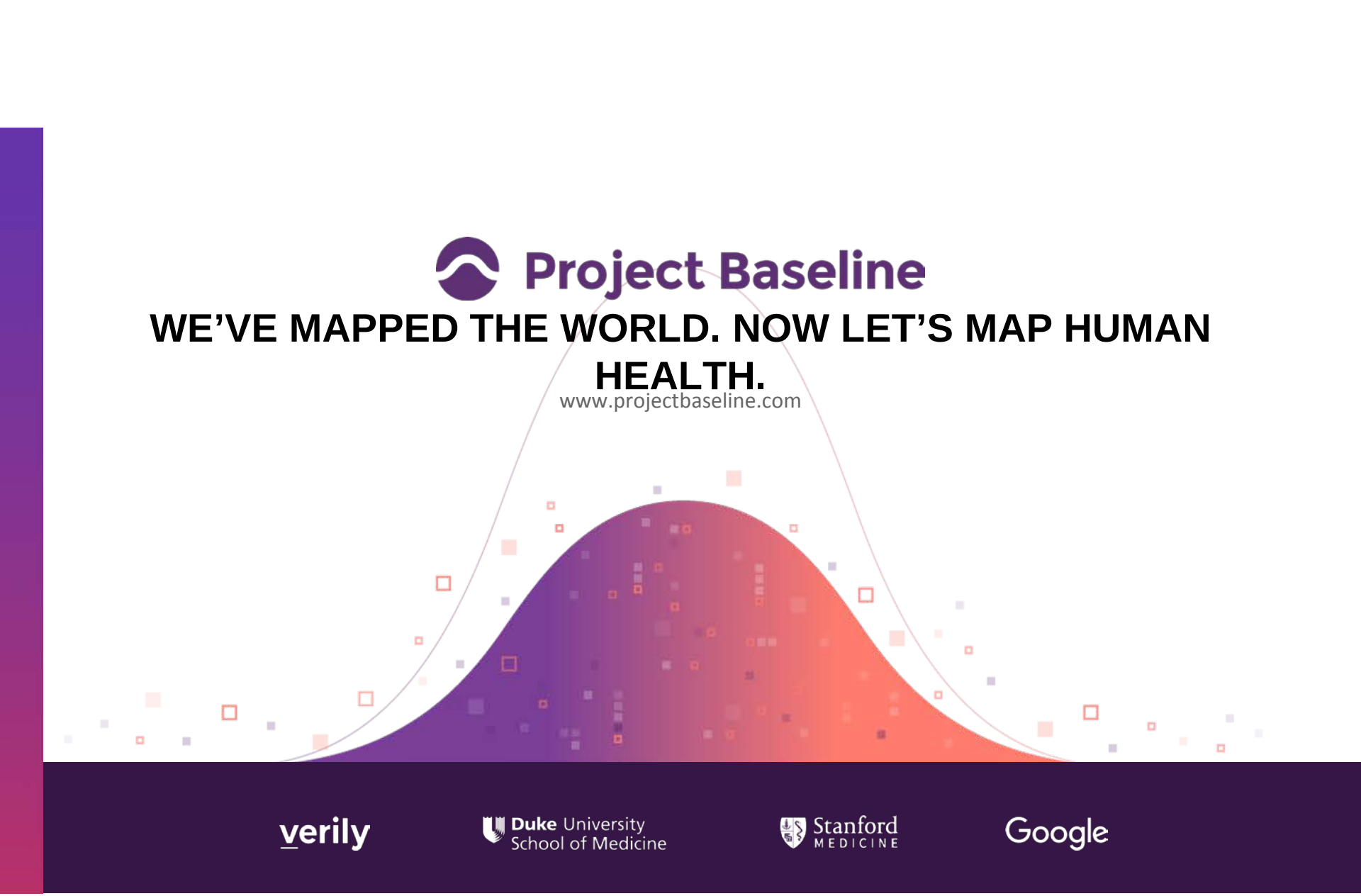
Real World Data and Efficacy

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.

Deeper Information about Mechanism will Soon be Available


Project Baseline
WE'VE MAPPED THE WORLD. NOW LET'S MAP HUMAN HEALTH.
www.projectbaseline.com
verily
Duke University School of Medicine
Stanford MEDICINE
Google

COMPREHENSIVE ONSITE ASSESSMENTS

"Omics"
- Genomics
- Proteomics
- Transcriptomics
- Metabolomics
- Microbiome
- Etc.

Eye exam, audiometry, PFT, etc.

Personal, family history surveys, etc.

Imaging
- Chest x-ray
- Coronary CT
- Echocardiography
- Etc.

Cognitive tests, physical performance tests, etc.

Blood, urine, stool, saliva, microbiome

Continuous monitoring
study watch, sleep sensor, app

CONTINUOUS MONITORING THROUGH PASSIVE SENSORS

Study watch

Investigational wrist-worn sensor for continuous recording of physiological and environmental data

App

Mobile interface for self-reported and passive data acquisitions

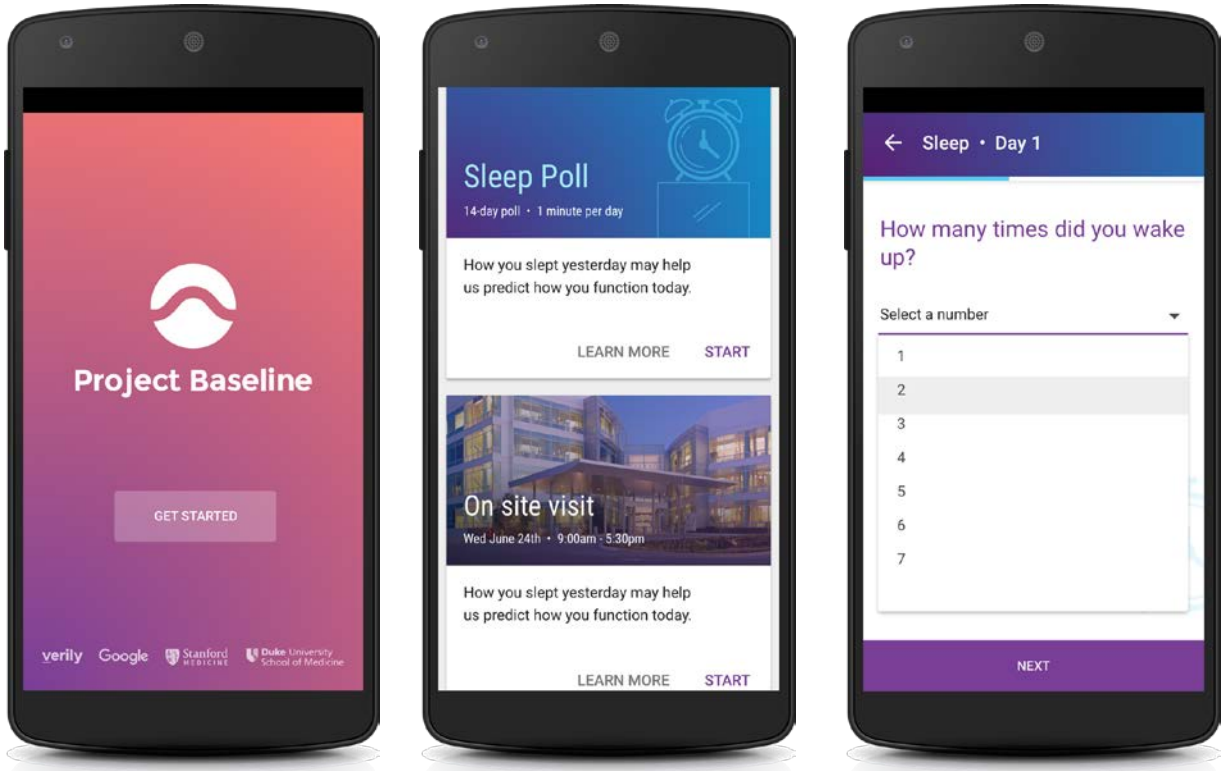
Sleep sensor

Commercially available, placed under mattress to passively monitor multiple physiologic data parameters

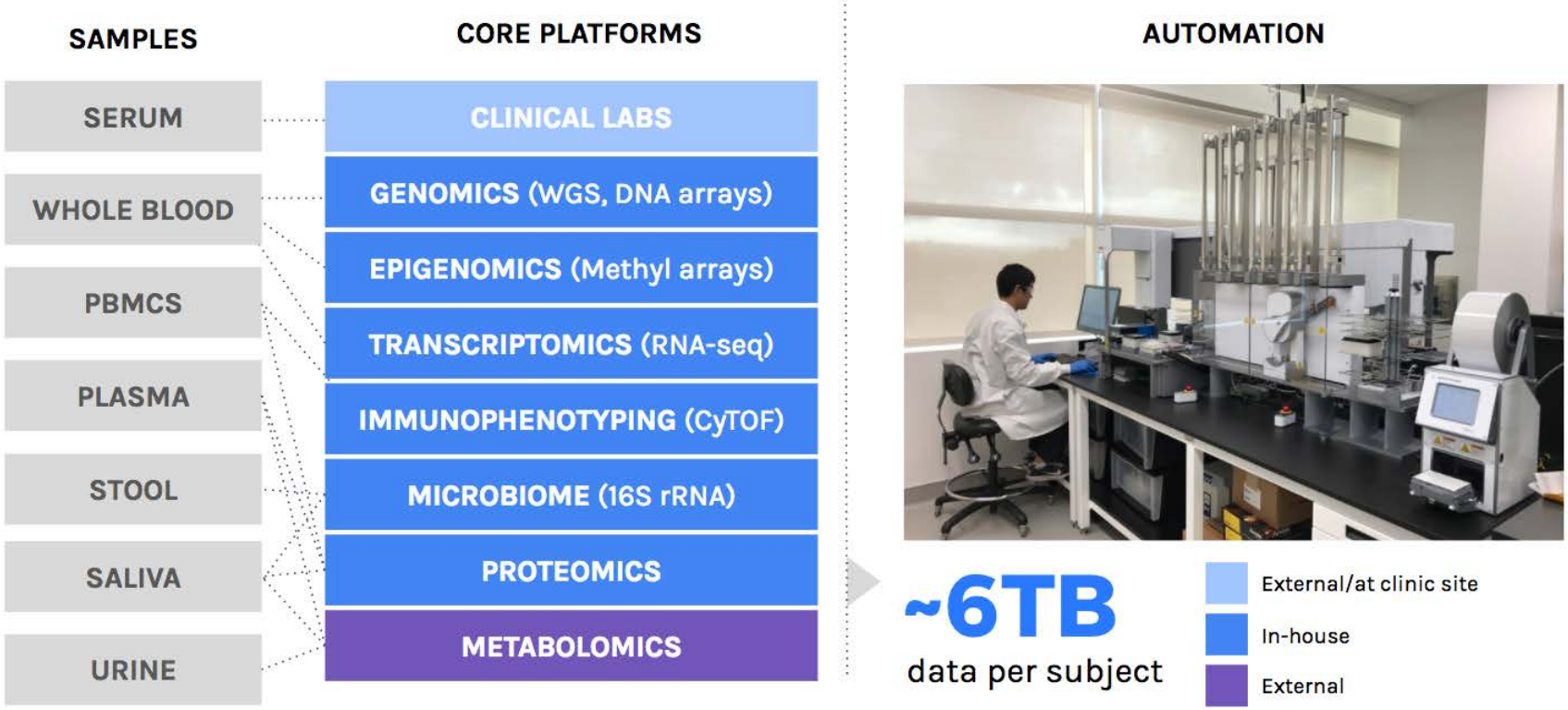
Study hub

Safely sends device data to secure, encrypted Baseline database

MOBILE APP


Project Baseline
GET STARTED
verily
Google
Stanford MEDICINE
Duke University School of Medicine
Sleep Poll
14-day poll • 1 minute per day
How you slept yesterday may help us predict how you function today.
LEARN MORE
START
On site visit
Wed June 24th • 9:00am - 5:30pm
How you slept yesterday may help us predict how you function today.
LEARN MORE
START
Sleep • Day 1
How many times did you wake up?
Select a number
1
2
3
4
5
6
7
NEXT

DEEP MOLECULAR PROFILING



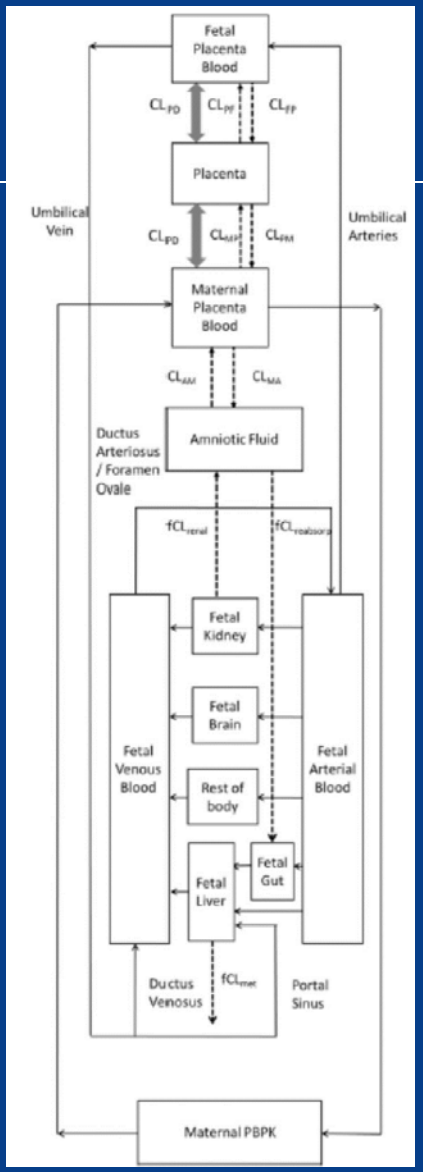
Novel approaches: examples

- Computational
  - Maternal-fetal physiologically-based pharmacokinetic (PBPK) models
- Non-invasive drug measurements
  - Raman technology
- Developmental fetal pharmacodynamics

Maternal-fetal PBPK models

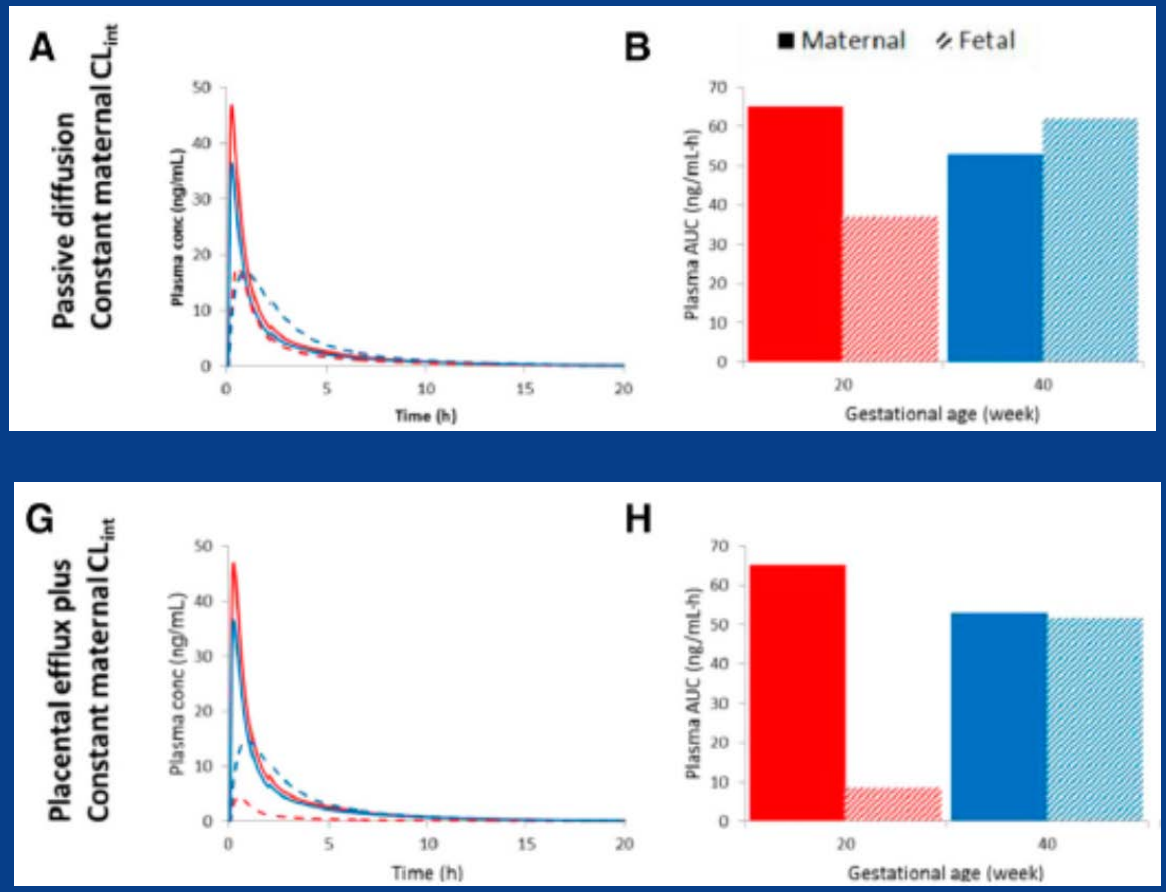
- Incorporate drug properties and maternal-fetal physiologic changes to predict drug disposition in mother and fetus
- Ex-vivo placental perfusion and animal models inform and help bridge PBPK models to humans
- Observed data is used to confirm predictions and reduce women enrolled in trials

Fetal PBPK model structure



Drug Metab Dispos 45:920 938, August 2017

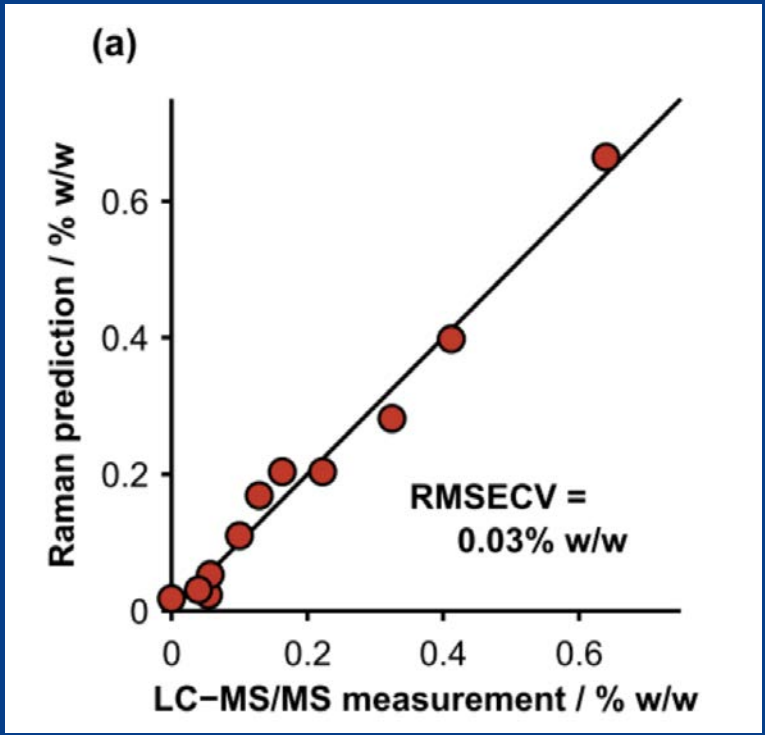
Maternal-fetal drug exposure simulations predicted with PBPK



Changes in maternal (solid) and fetal (dashed) exposure at 20 wk (red) and 40 wk (blue) GA under different placental drug disposition assumptions

Drug Metab Dispos 45:920 938, August 2017

Non-invasive drug concentration: preclinical



Figures shows good correlation between traditional tenofovir porcine vaginal tissue concentration measurements (HPLC/MS/MS) and Raman predictions

Information is already ubiquitous—how do we help people find accurate, truthful information that is scientifically based?

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

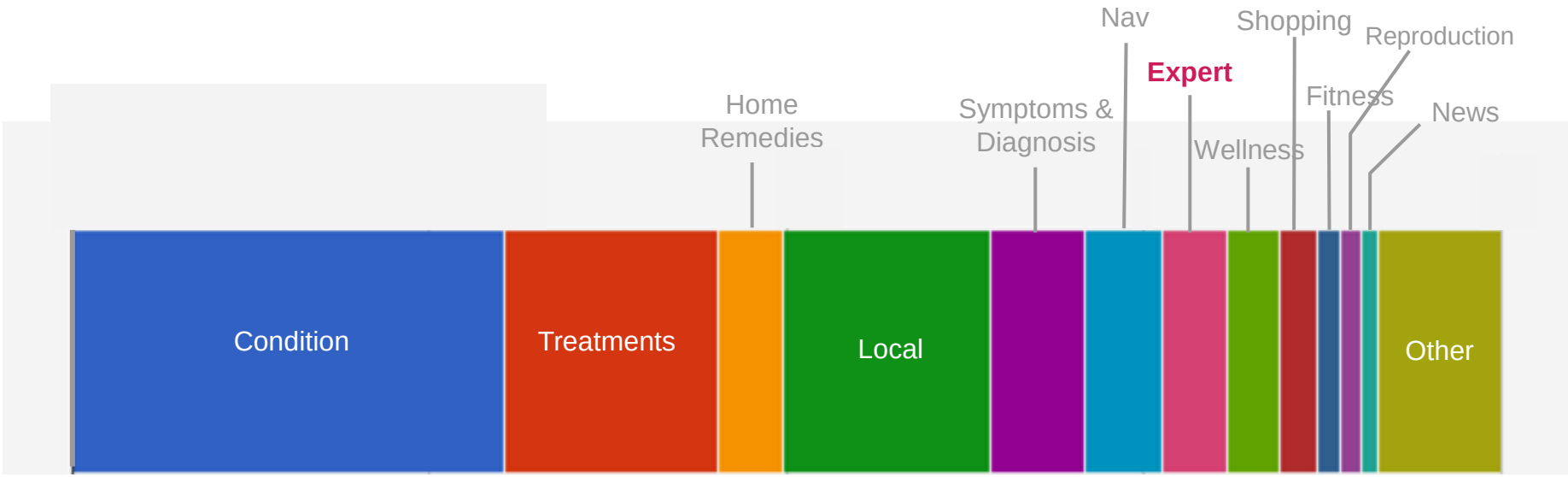

1 in 20
Google
searches are
health related

Our Mission:

Make health information universally accessible and useful.

Google

Categories of information needs



How do we help people find their way to useful action and behaviors?

WHY DEPRESSION?

DEPRESSION IS HIGHLY PREVALENT

300 M

people suffer from depression globally, WHO has declared it a leading cause of disability [WHO]

MANY PEOPLE DON'T GET TREATMENT

50%

of people with depression in the US did not get any treatment [JAMA]

TREATMENT IS OFTEN DELAYED

7 YRS

average time from onset to treatment in the US [JAMA]

TREATMENT IS EFFECTIVE

70%

of patients can improve, often in a matter of weeks [NIMH]

Google has the reach, scale and technology to help

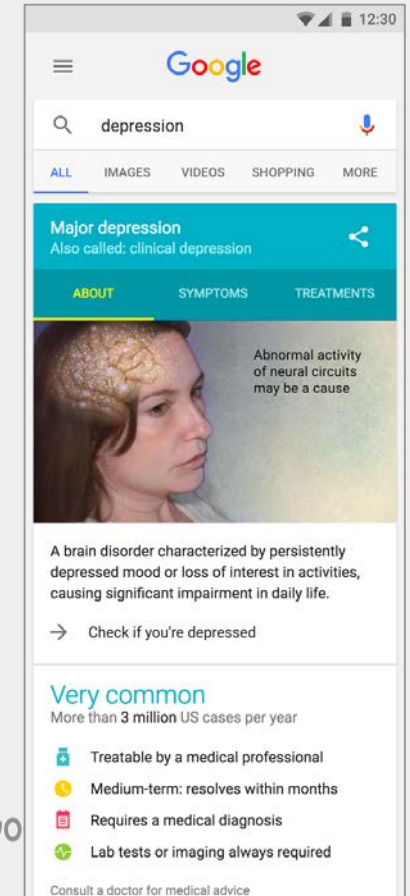
PRODUCT OVERVIEW: What is PHQ-9?

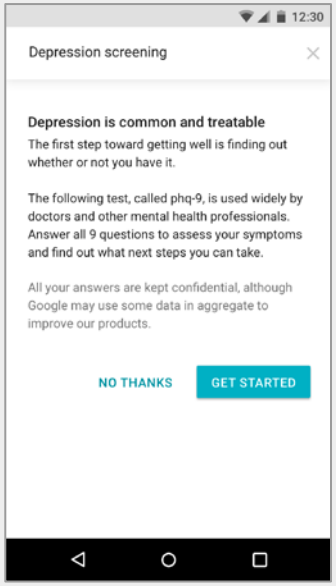
PHQ-9 is a Patient Health Questionnaire, with 9 questions, that is used to measure depression severity

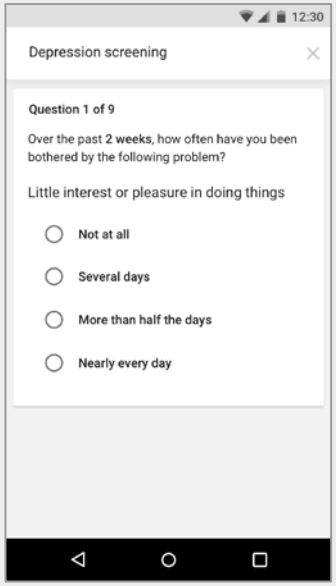
PATIENT HEALTH QUESTIONNAIRE-9				
Over the last 2 weeks, how often have you been bothered by any of the following problems?	**Not at all**	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

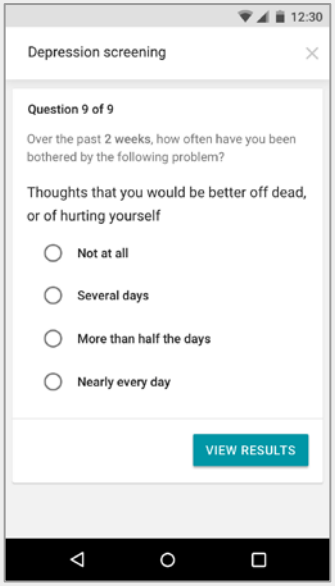
PRODUCT OVERVIEW: MVP Design & Demos

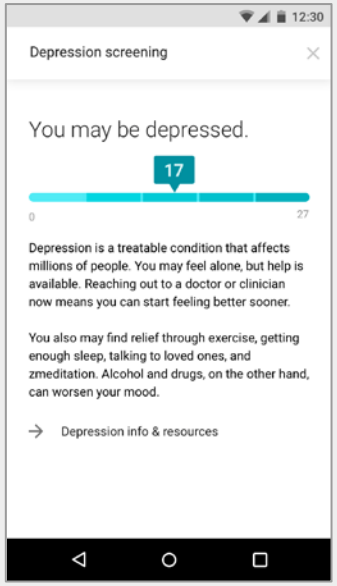
go/phq9-demo











We need a massive educational shift at all levels to take this gift of technology and optimize its use for better health for individuals and populations


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

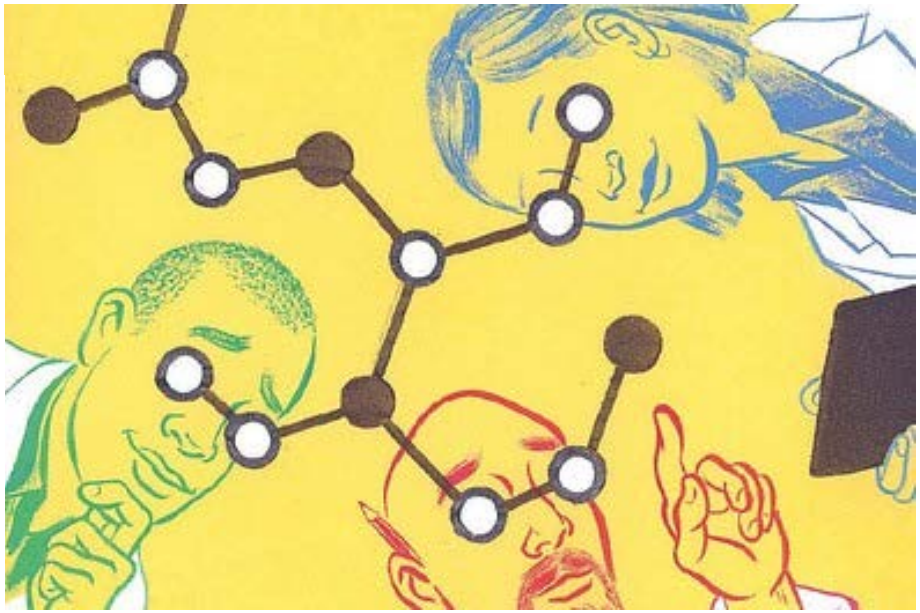
By STEVE LOHR AUG. 17, 2014

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

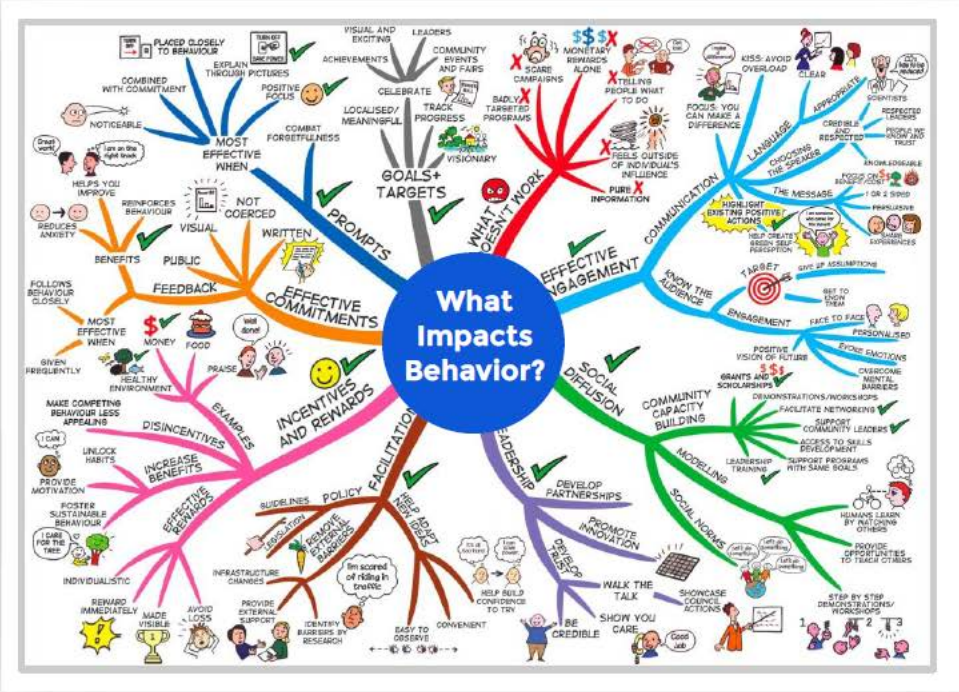
In January 2009, a mathematician at Cambridge University named Tim Gowers decided to use his blog to run an unusual social experiment. He picked out a difficult mathematical problem and tried to solve it completely in the open, using his blog to post ideas and partial progress. He issued an open invitation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

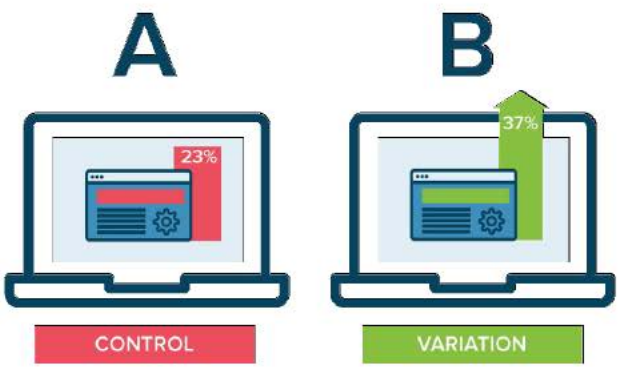


Several hours after Mr. Gowers opened up his blog for discussion, a Canadian-Hungarian mathematician posted a comment. Fifteen minutes later, an Arizona high-school math teacher chimed in. Three minutes after that, the UCLA mathematician Terence Tao commented. The discussion ignited, and in just six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

THE WALL STREET JOURNAL.

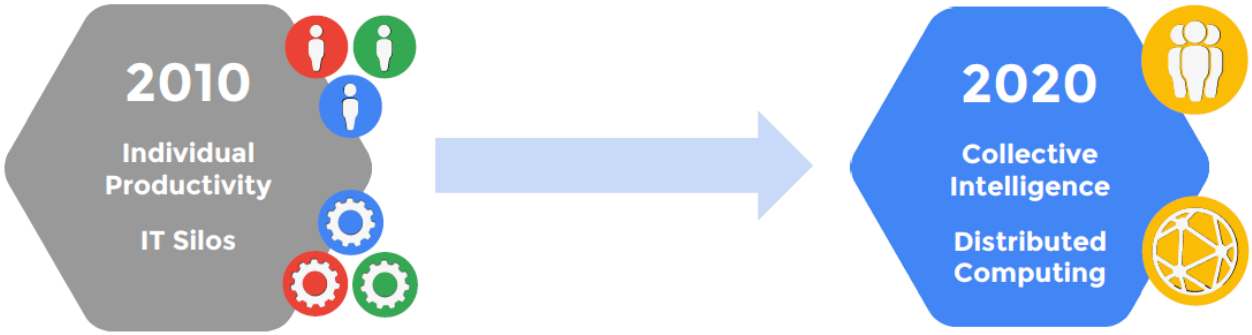
Data Activation and Testing Outcomes





Verily |

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

Verily

Frontiers

- Human biology
  - Growth and development
  - Maternal Fetal systems biology
- Evidence generation with pragmatic outcome studies
- Implementation science
- Social determinants of health
- Ethics of information and data science in children