Improving the Nation's Evidence Generation System in the Context of the US FDA

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Commissioner of Food and Drugs

NIH Pragmatic Trials Collaboratory Steering Committee Meeting

April 21, 2022

The Opportunity

- Biomedical science and technology are in an amazing period of discovery and development.
- Yet these advantages are not resulting in superior health and outcomes for the U.S. population or for most individuals.
- The intersection of biomedical science, technology and communication, if handled with good policies, investment and communication, could usher in a new era of better health for the U.S. and the world.
- Previous policies and infrastructure investment provide a solid base from which to build an effective system for evaluation and implementation across the spectrum of development, pivotal trials and post-market evaluation.

Evidence Generation & FDA 2022

- FDA mission and priorities.
- Why do we need to improve the evidence generation system?
- What have we learned about evidence generation in the pandemic?
- Hopes for the future.

Societal Motivation

When possible, it is best to develop a concept, generate the evidence, implement strategies that are proven effective, and reassess for gaps and areas of improvement.

“Selfish Motivation”

The amount of heat generated about an FDA decision is inversely proportional to the quality of the evidence on the topic.

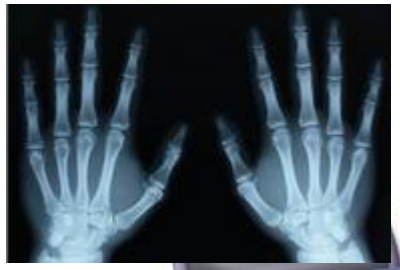
The FDA: Big Picture

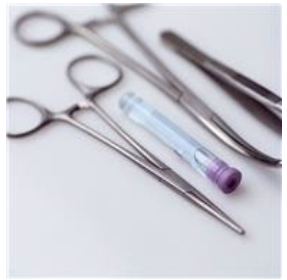
- Regulatory Agency
- Science Agency
- Public Health Agency
- Multiple disciplines always in play
  - Science/Medicine/Public Health
  - Policy
  - Law

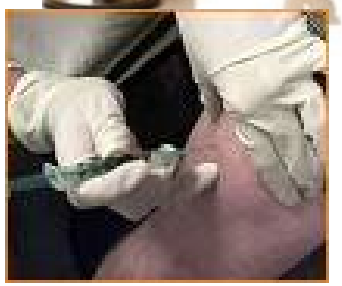
FDA Regulates a Spectrum of Health Products : 20-25 cents of every GDP dollar

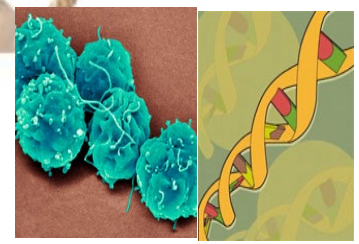








FDA Mission

FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

https://www.fda.gov/about-fda/what-we-do

FDA Mission

FDA is also responsible for advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health.

https://www.fda.gov/about-fda/what-we-do

FDA Mission

FDA also has responsibility for regulating the manufacturing, marketing, and distribution of tobacco products to protect the public health and to reduce tobacco use by minors.

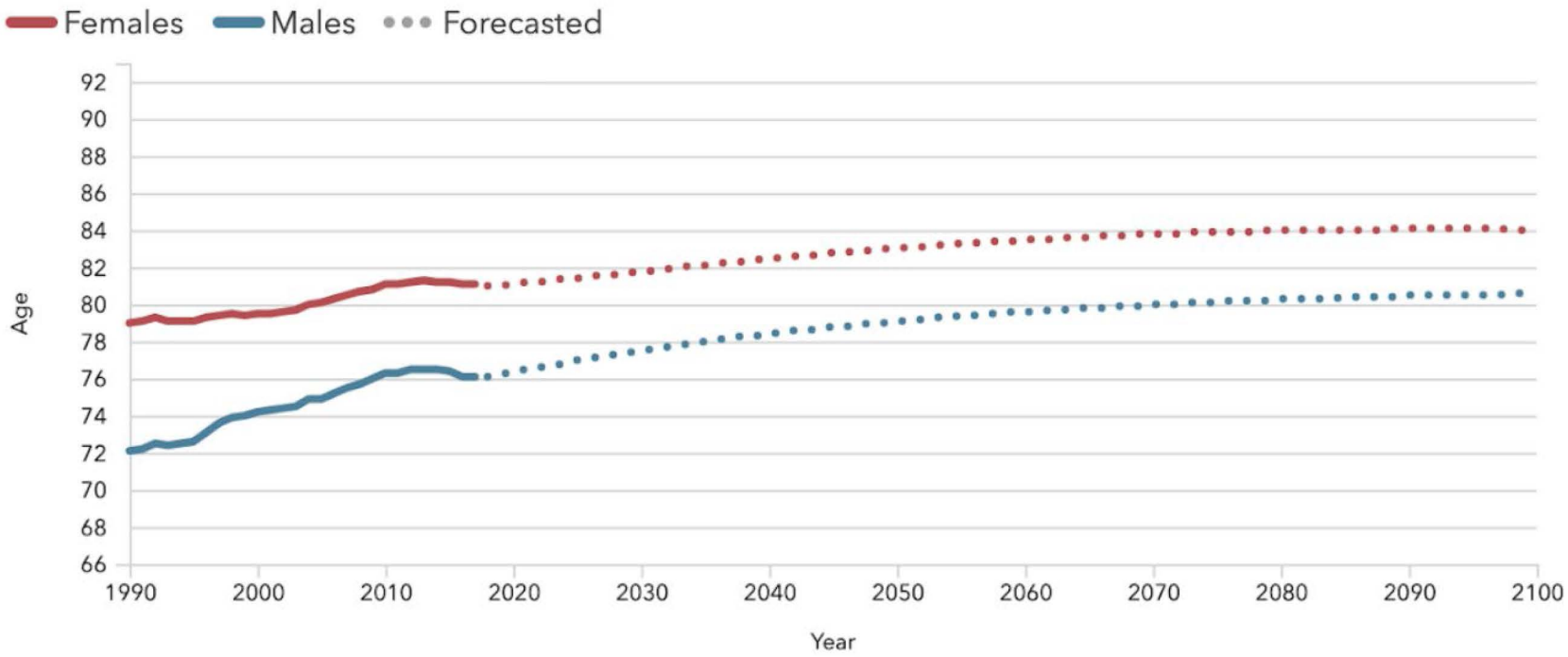
https://www.fda.gov/about-fda/what-we-do

FDA Mission

Finally, FDA plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.

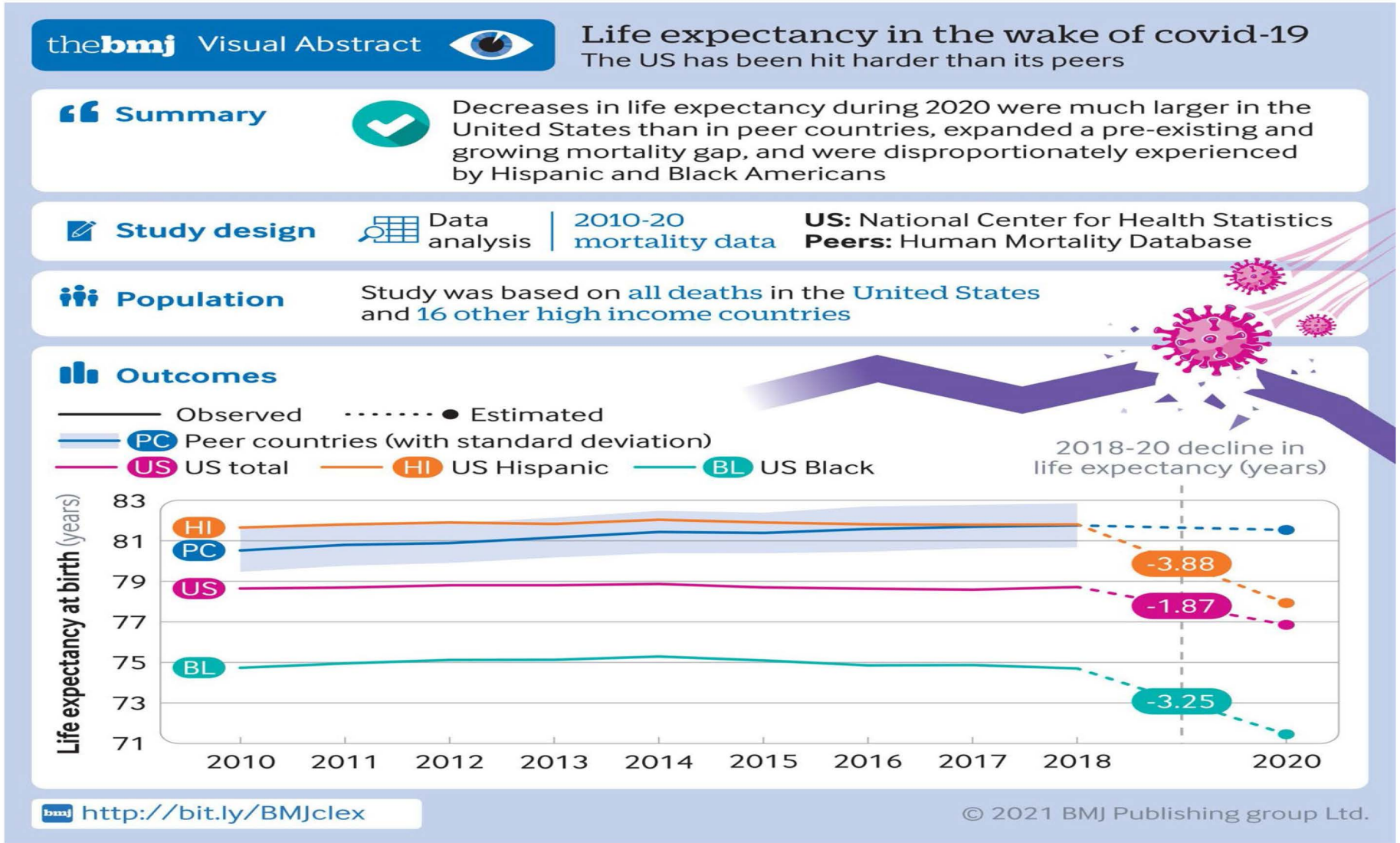
https://www.fda.gov/about-fda/what-we-do

How long do people live, and how will that change?



	1990	2017	2100
Females	79	81.1	84
Males	72.1	76.1	80.6

Life expectancy at birth, 1990–2100. Forecasted data based on Global Burden of Disease 2017 results.


thebmj Visual Abstract
Life expectancy in the wake of covid-19
The US has been hit harder than its peers
Summary
Decreases in life expectancy during 2020 were much larger in the United States than in peer countries, expanded a pre-existing and growing mortality gap, and were disproportionately experienced by Hispanic and Black Americans
Study design
Data analysis
2010-20 mortality data
US: National Center for Health Statistics
Peers: Human Mortality Database
Population
Study was based on all deaths in the United States and 16 other high income countries
Outcomes
Observed
Estimated
PC Peer countries (with standard deviation)
US US total
HI US Hispanic
BL US Black
2018-20 decline in life expectancy (years)
Life expectancy at birth (years)
83
81
79
77
75
73
71
HI
PC
US
BL
-3.88
-1.87
-3.25
2010
2011
2012
2013
2014
2015
2016
2017
2018
2020
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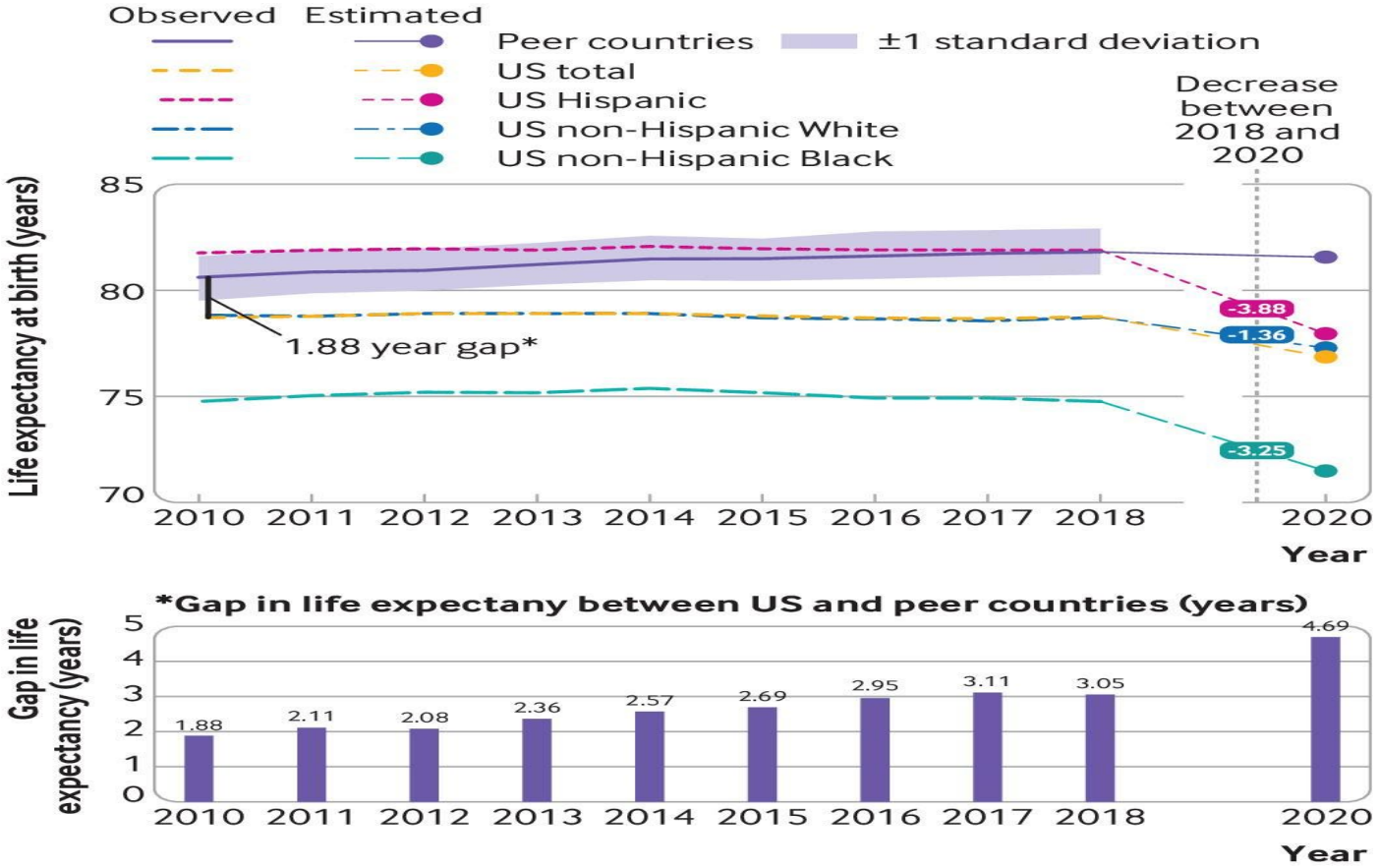
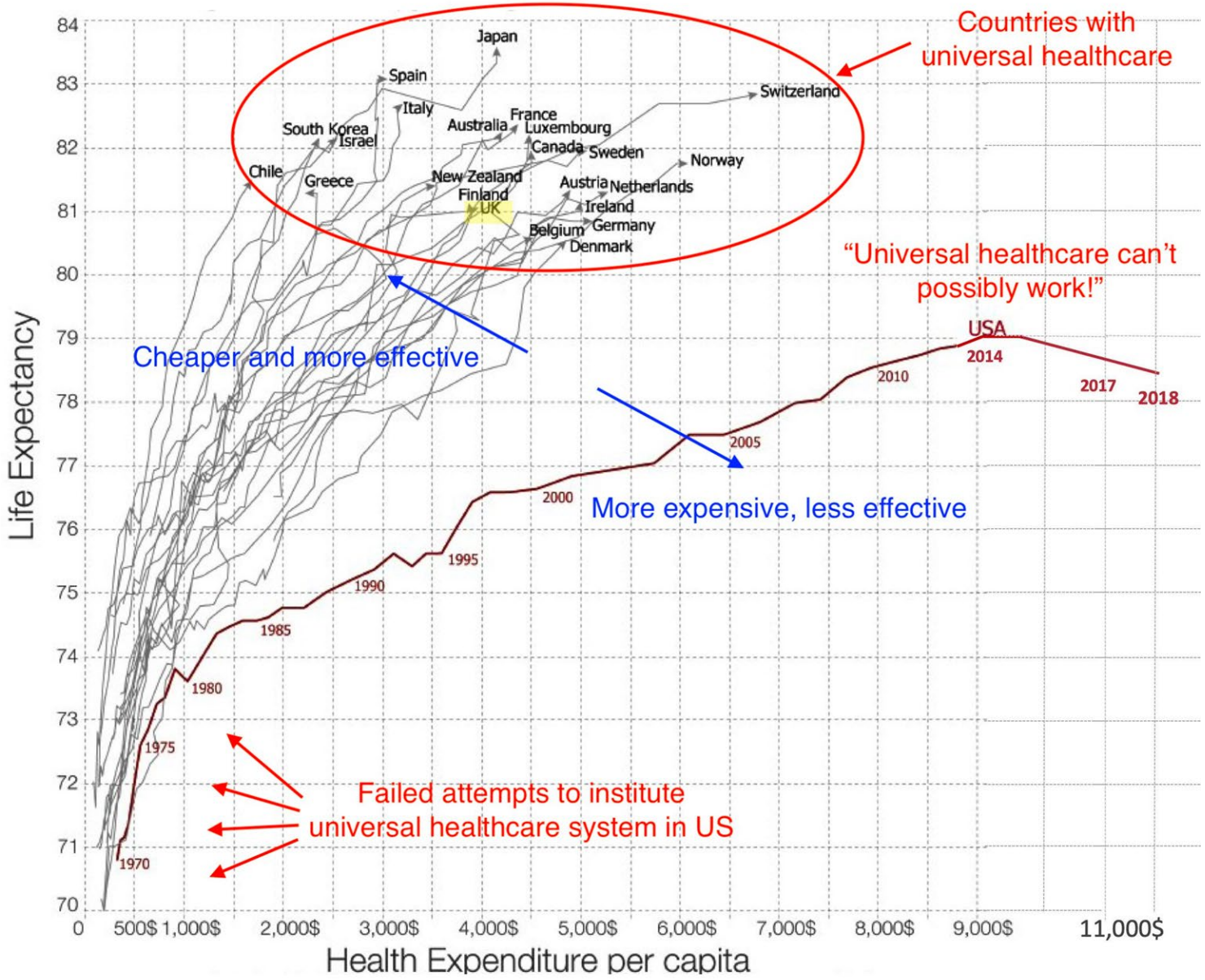
Life expectancy at birth in the United States, by race and ethnicity, and in peer countries for years 2010-18 and 2020.

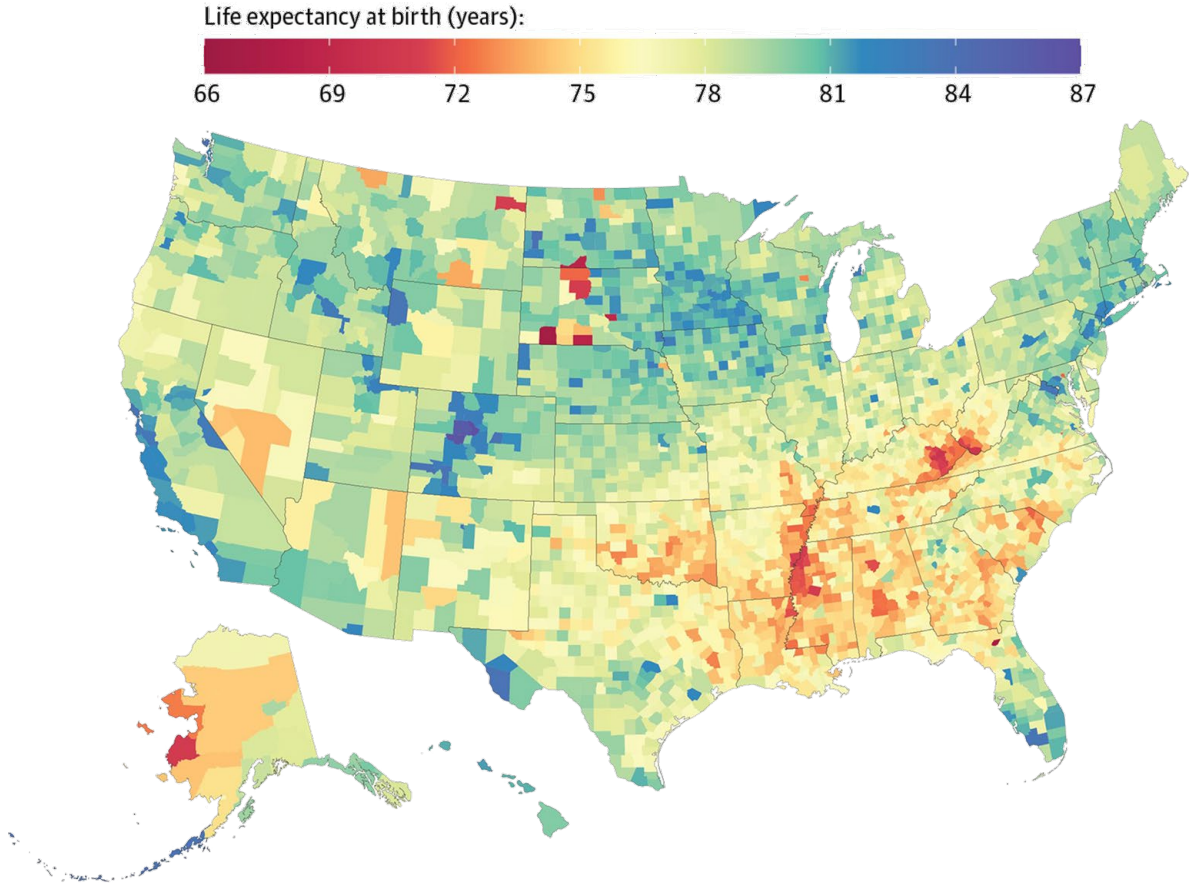



Countries with universal healthcare
Japan
Spain
Italy
Switzerland
France
South Korea
Israel
Australia
Luxembourg
Canada
Sweden
Norway
Chile
Greece
New Zealand
Finland
Austria
Netherlands
UK
Ireland
Belgium
Germany
Denmark
"Universal healthcare can't possibly work!"
Cheaper and more effective
USA
2014
2017
2018
2010
2005
2000
More expensive, less effective
1995
1990
1985
1980
1975
1970
Failed attempts to institute universal healthcare system in US
Life Expectancy
84
83
82
81
80
79
78
77
76
75
74
73
72
71
70
0
500$
1,000$
2,000$
3,000$
4,000$
5,000$
6,000$
7,000$
8,000$
9,000$
11,000$
Health Expenditure per capita

Life Expectancy at Birth by County, 2014

Counties 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

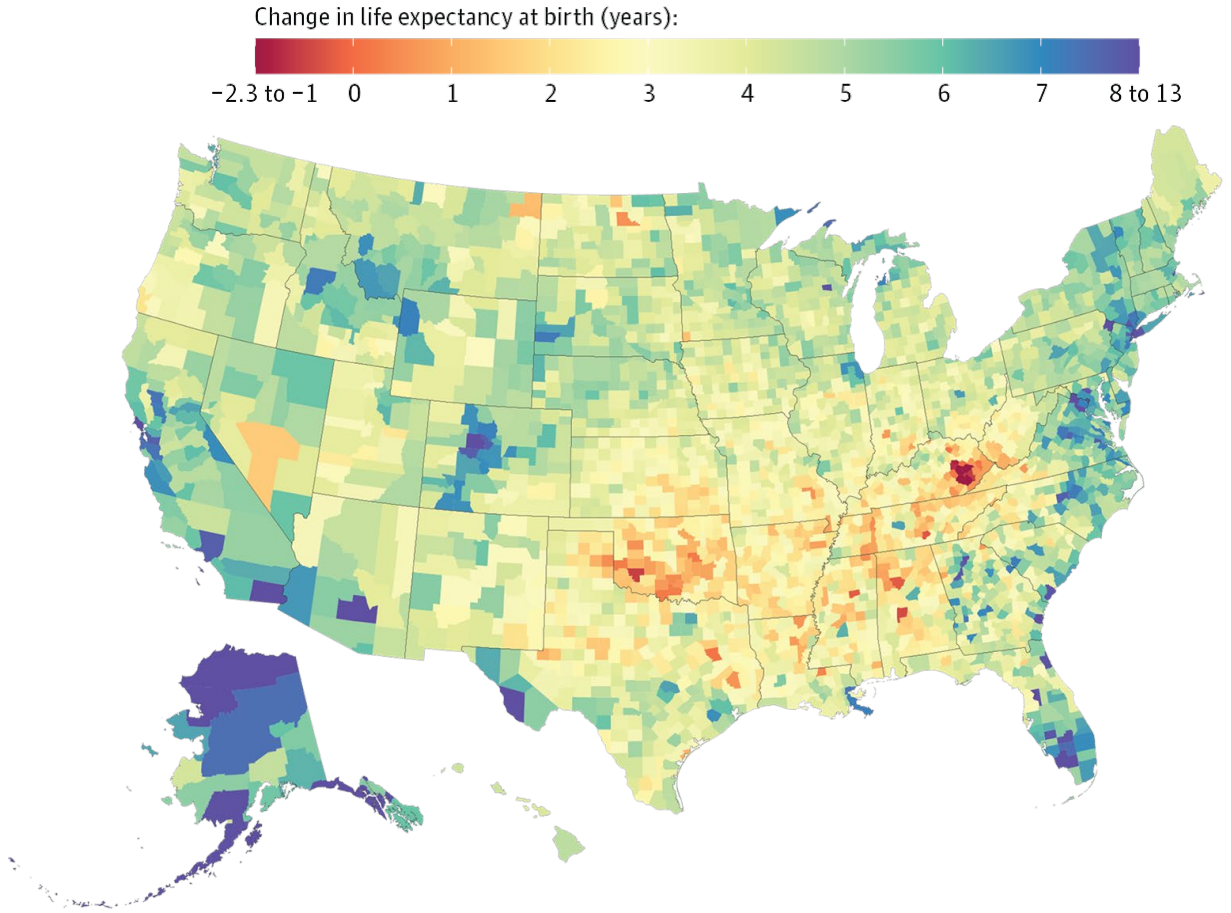
Counties in central Colorado had the highest life expectancies



Source: Dwyer-Lindgren L, et al. Inequalities in life expectancy among US counties, 1980 to 2014 - temporal trends and key drivers. JAMA Intern Med. 2017;177:1003-11. doi:10.1001/jamainternmed.2017.0918

Change in Life Expectancy at Birth by County, 1980 to 2014

Compared 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



Source: Dwyer-Lindgren L, et al. Inequalities in life expectancy among US counties, 1980 to 2014 - temporal trends and key drivers. JAMA Intern Med. 2017;177:1003-11. doi:10.1001/jamainternmed.2017.0918

From: **Inequalities in Life Expectancy Among US Counties, 1980 to 2014 Temporal 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

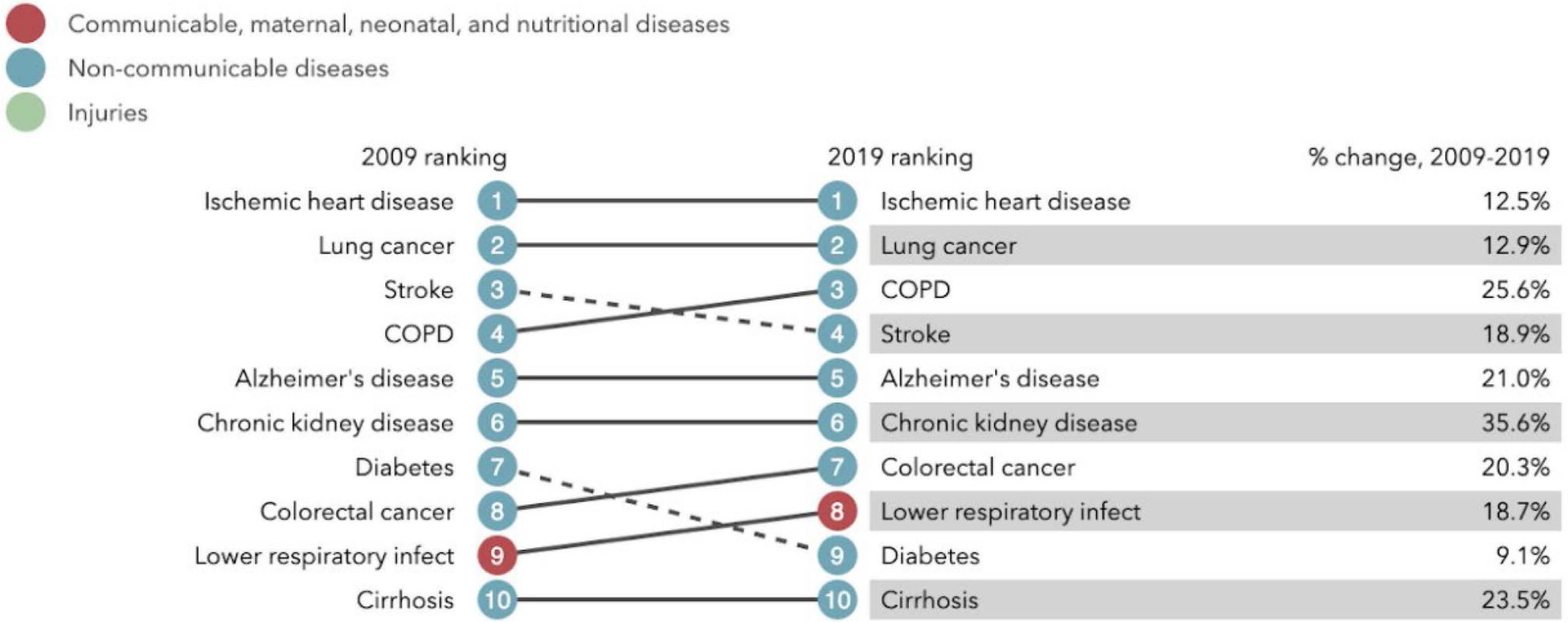
Abbreviation: SE, standard error.

Source: American Medical Association.2017.

Table Title:

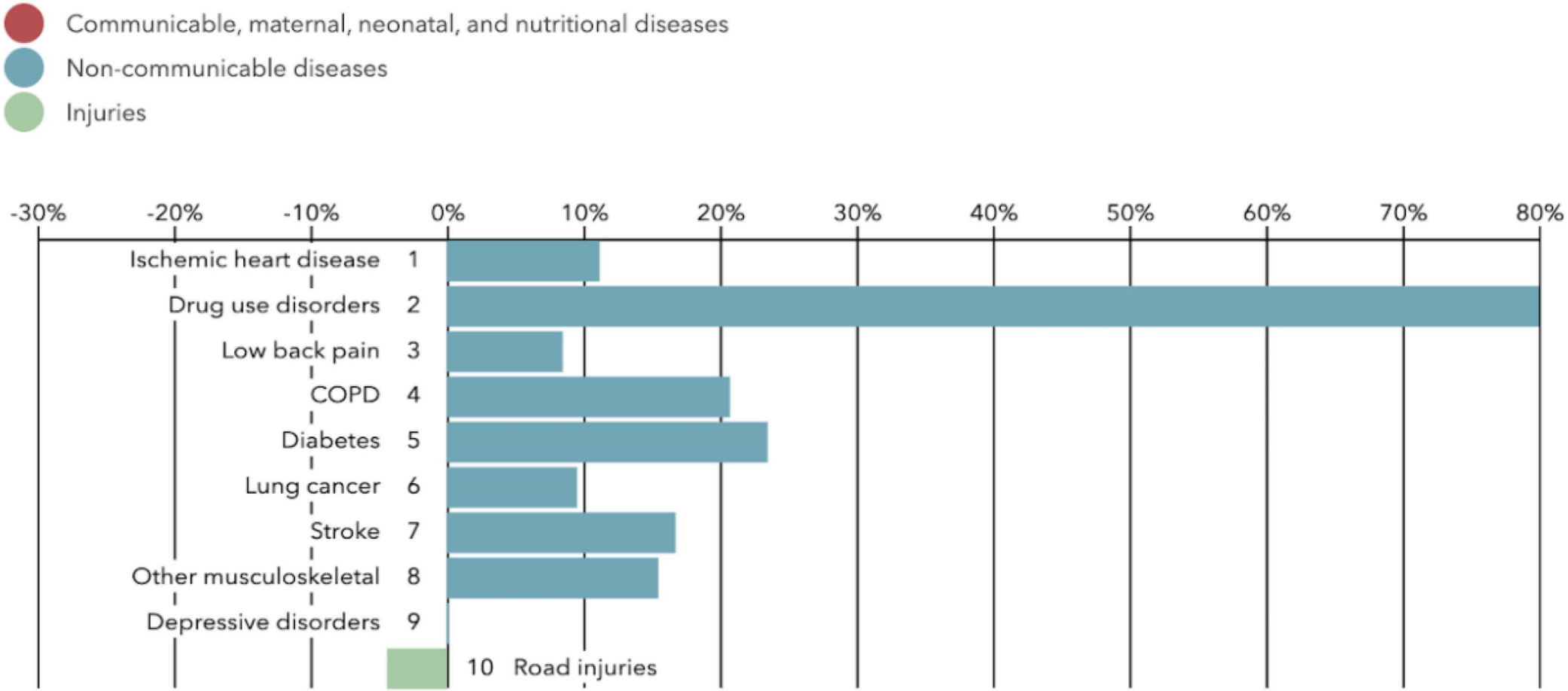
Variables Included in the Regression Analysis With Summary Statistics and Bivariate Regression Results

What causes the most deaths?



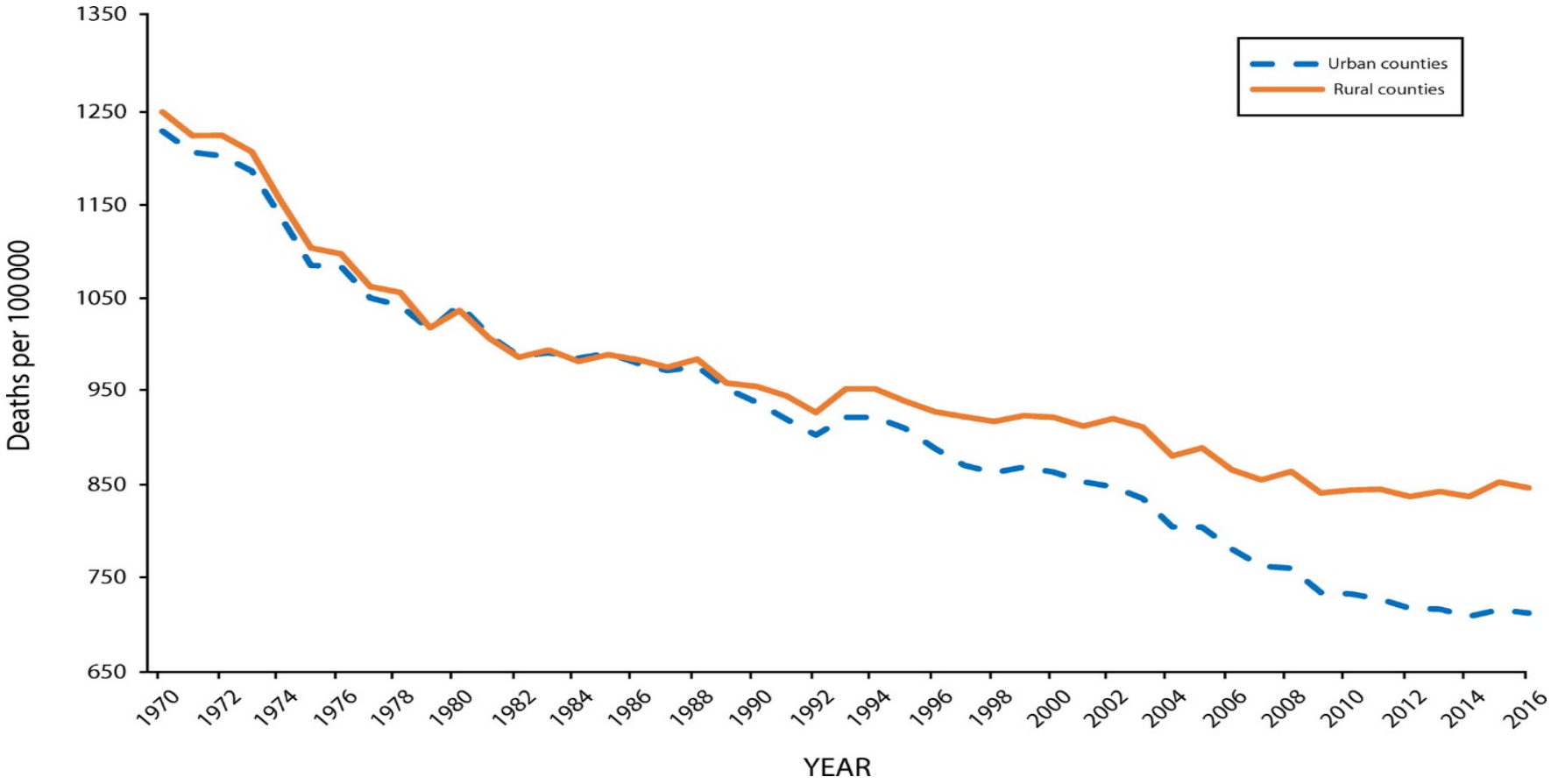
Top 10 causes of total number of deaths in 2019 and percent change 2009–2019, all ages combined

What causes the most death and disability combined?



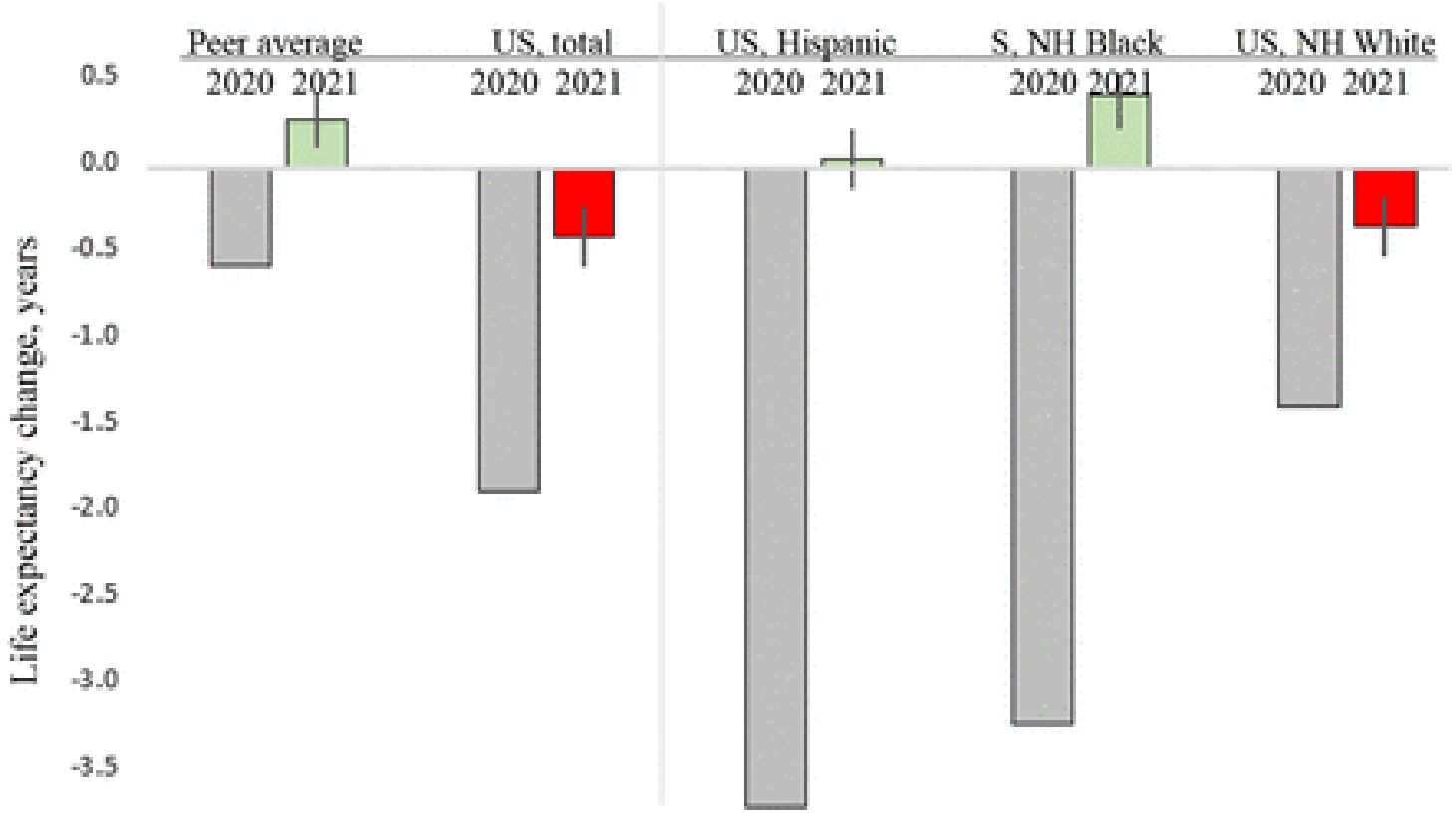
Top 10 causes of death and disability (DALYs) in 2019 and percent change 2009–2019, all ages combined

Mortality in Rural America



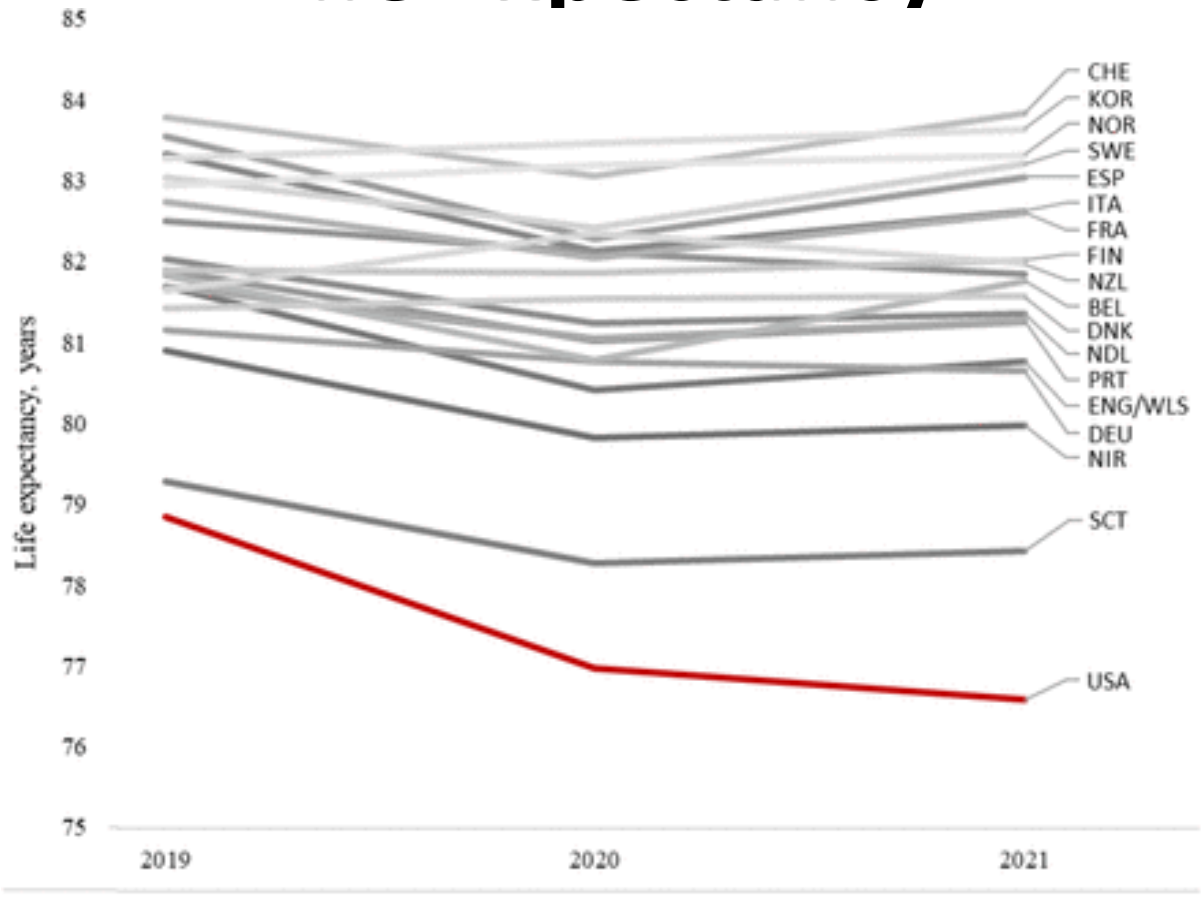
- In Mid '80s: Rural and urban death rates were approximately equal
- 2016: 134.7 excess deaths/100,000 in rural - a nearly 20% disparity
- Life expectancy is approximately 3 years lower
- Higher stroke and CV mortality
- Higher maternal mortality (much of which is cardiovascular)

The Impact of the Pandemic on US Life Expectancy has not been Uniform



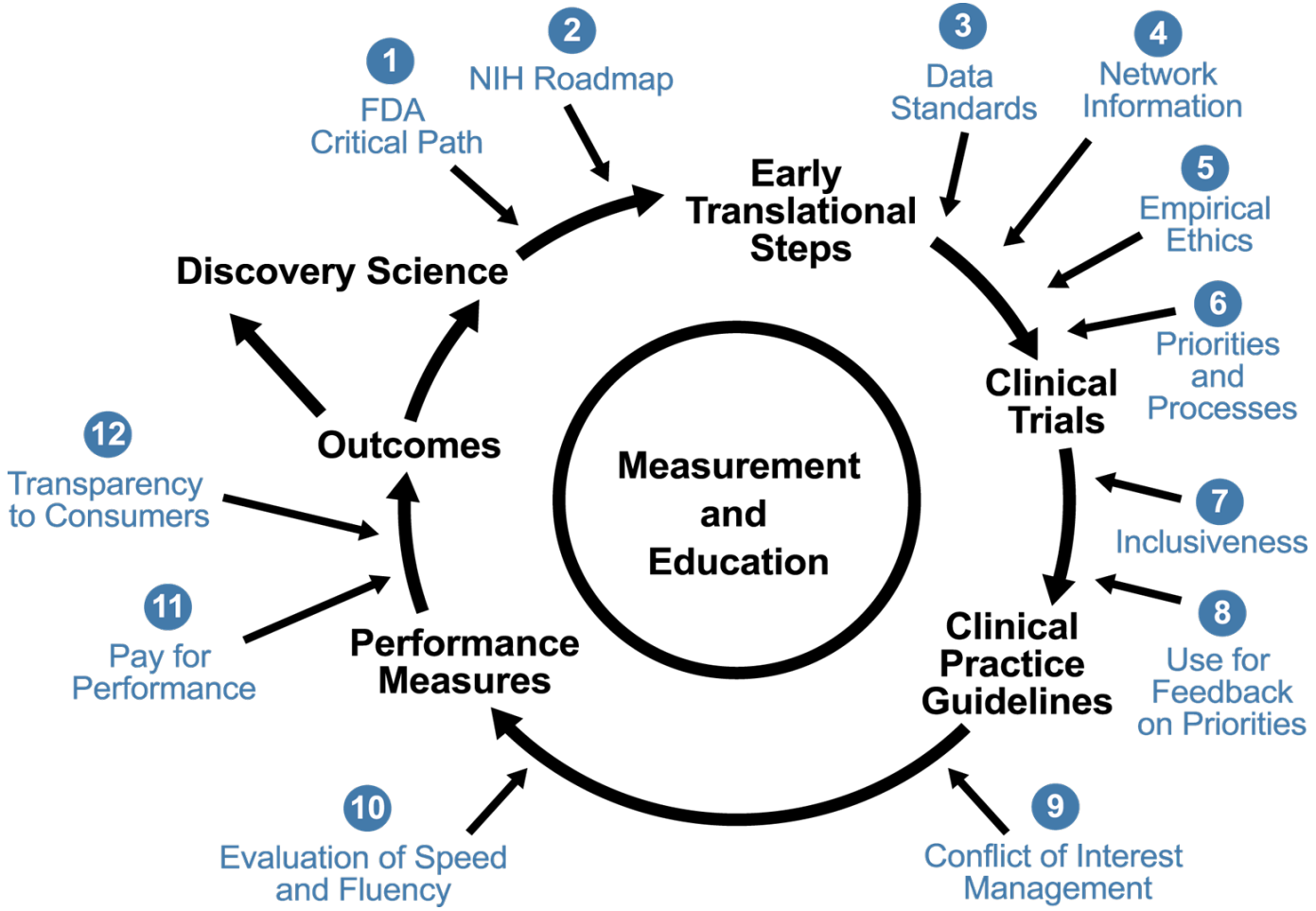
Source: medRxiv preprint DOI: https://doi.org/10.1101/2022.04.05.22273393

U.S. Continues to Lose Ground in Life Expectancy



Source: medRxiv preprint DOI: https://doi.org/10.1101/2022.04.05.22273393

Generating Evidence to Inform Decisions

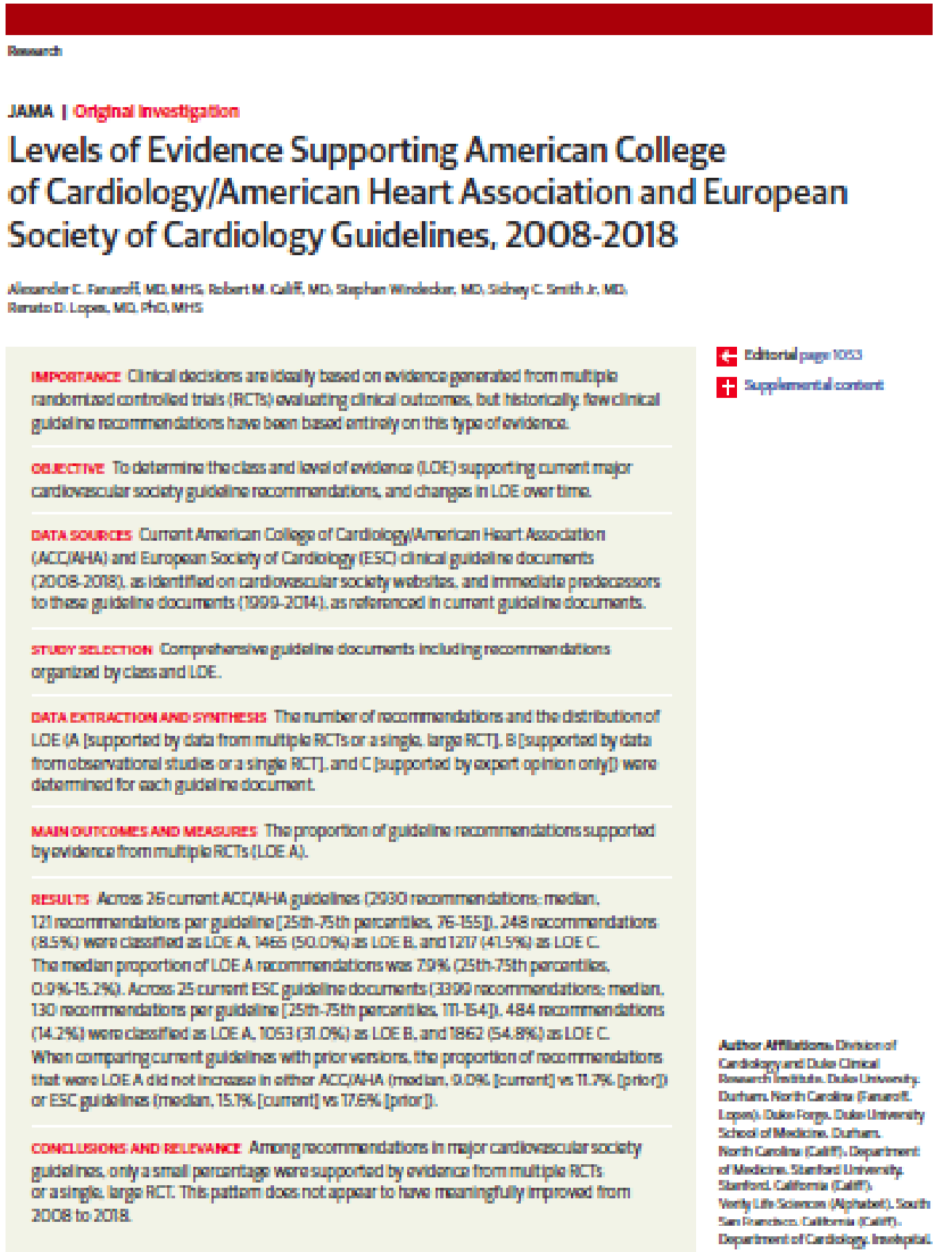


Our National Clinical Research System is Well-intentioned But Flawed

- 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.

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



Research

JAMA | Original Investigation

Levels of Evidence Supporting American College of Cardiology/American Heart Association and European Society of Cardiology Guidelines, 2008-2018

Alexander C. Fanaroff, MD, MHS; Robert M. Califf, MD; Stephan Windecker, MD; Sidney C. Smith Jr, MD; Renato D. Lopes, MD, PhD, MHS

Editorial page 1053
Supplemental content

IMPORTANCE Clinical decisions are ideally based on evidence generated from multiple randomized controlled trials (RCTs) evaluating clinical outcomes, but historically, few clinical guideline recommendations have been based entirely on this type of evidence.

OBJECTIVE To determine the class and level of evidence (LOE) supporting current major cardiovascular society guideline recommendations, and changes in LOE over time.

DATA SOURCES Current American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) clinical guideline documents (2008-2018), as identified on cardiovascular society websites, and immediate predecessors to these guideline documents (1999-2014), as referenced in current guideline documents.

STUDY SELECTION Comprehensive guideline documents including recommendations organized by class and LOE.

DATA EXTRACTION AND SYNTHESIS The number of recommendations and the distribution of LOE (A [supported by data from multiple RCTs or a single, large RCT], B [supported by data from observational studies or a single RCT], and C [supported by expert opinion only]) were determined for each guideline document.

MAIN OUTCOMES AND MEASURES The proportion of guideline recommendations supported by evidence from multiple RCTs (LOE A).

RESULTS Across 26 current ACC/AHA guidelines (2930 recommendations; median, 121 recommendations per guideline [25th-75th percentiles, 76-155]), 248 recommendations (8.5%) were classified as LOE A, 1465 (50.0%) as LOE B, and 1217 (41.5%) as LOE C. The median proportion of LOE A recommendations was 7.9% (25th-75th percentiles, 0.9%-15.2%). Across 25 current ESC guideline documents (3396 recommendations; median, 130 recommendations per guideline [25th-75th percentiles, 111-154]), 484 recommendations (14.2%) were classified as LOE A, 1053 (31.0%) as LOE B, and 1862 (54.8%) as LOE C. When comparing current guidelines with prior versions, the proportion of recommendations that were LOE A did not increase in either ACC/AHA (median, 9.0% [current] vs 11.7% [prior]) or ESC guidelines (median, 15.7% [current] vs 17.6% [prior]).

CONCLUSIONS AND RELEVANCE Among recommendations in major cardiovascular society guidelines, only a small percentage were supported by evidence from multiple RCTs or a single, large RCT. This pattern does not appear to have meaningfully improved from 2008 to 2018.

Author Affiliations: Division of Cardiology and Duke Clinical Research Institute, Duke University, Durham, North Carolina (Fanaroff, Lopes); Duke Forge, Duke University School of Medicine, Durham, North Carolina (Califf); Department of Medicine, Stanford University, Stanford, California (Califf); Verily Life Sciences (Alphabet), South San Francisco, California (Califf); Department of Cardiology, Inselspital,

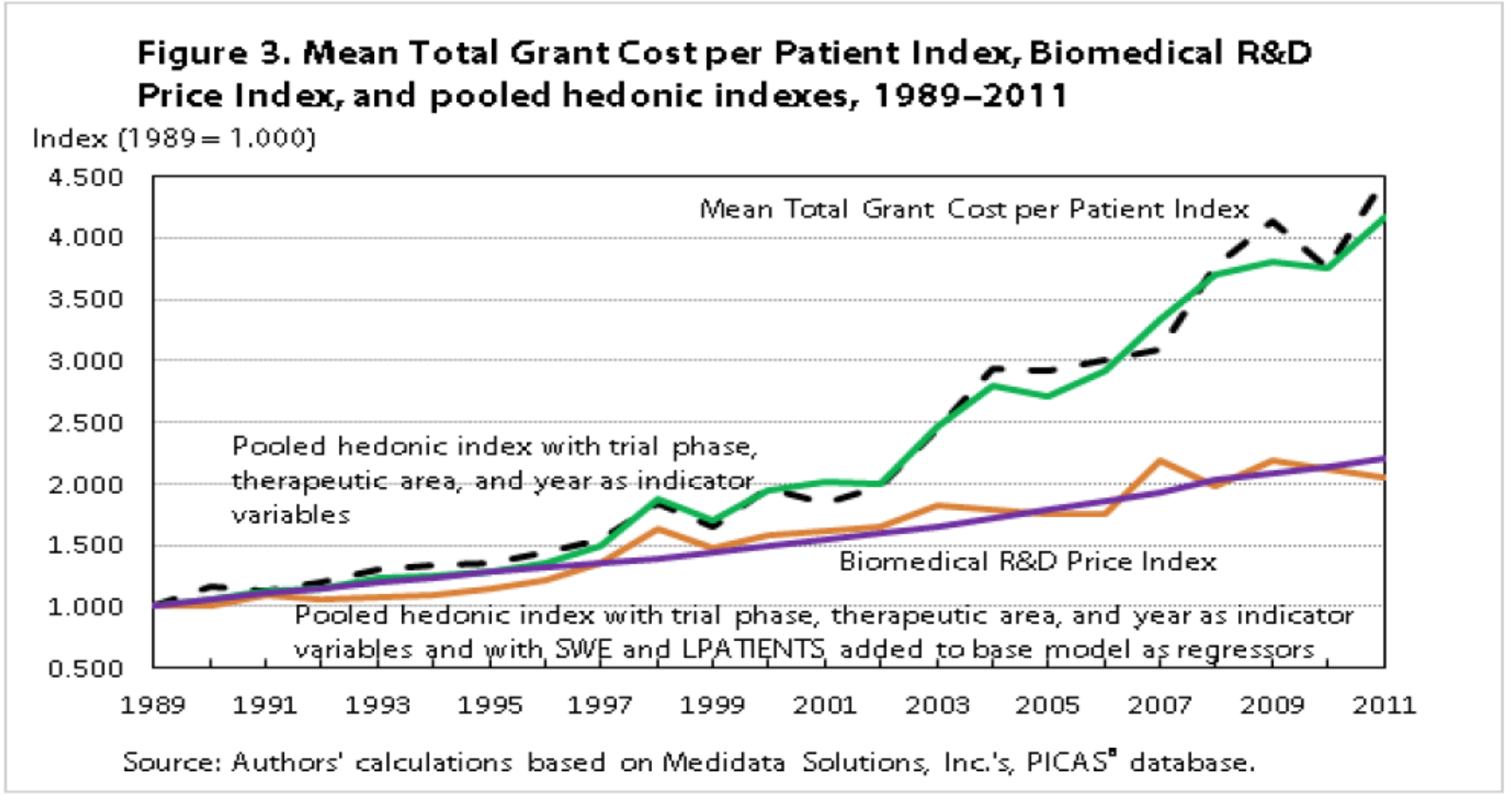
Across 26 current ACC/AHA guidelines, 8.5% of recommendations were LOE A

Across 25 ESC guidelines, 14.2% of recommendations were LOE A

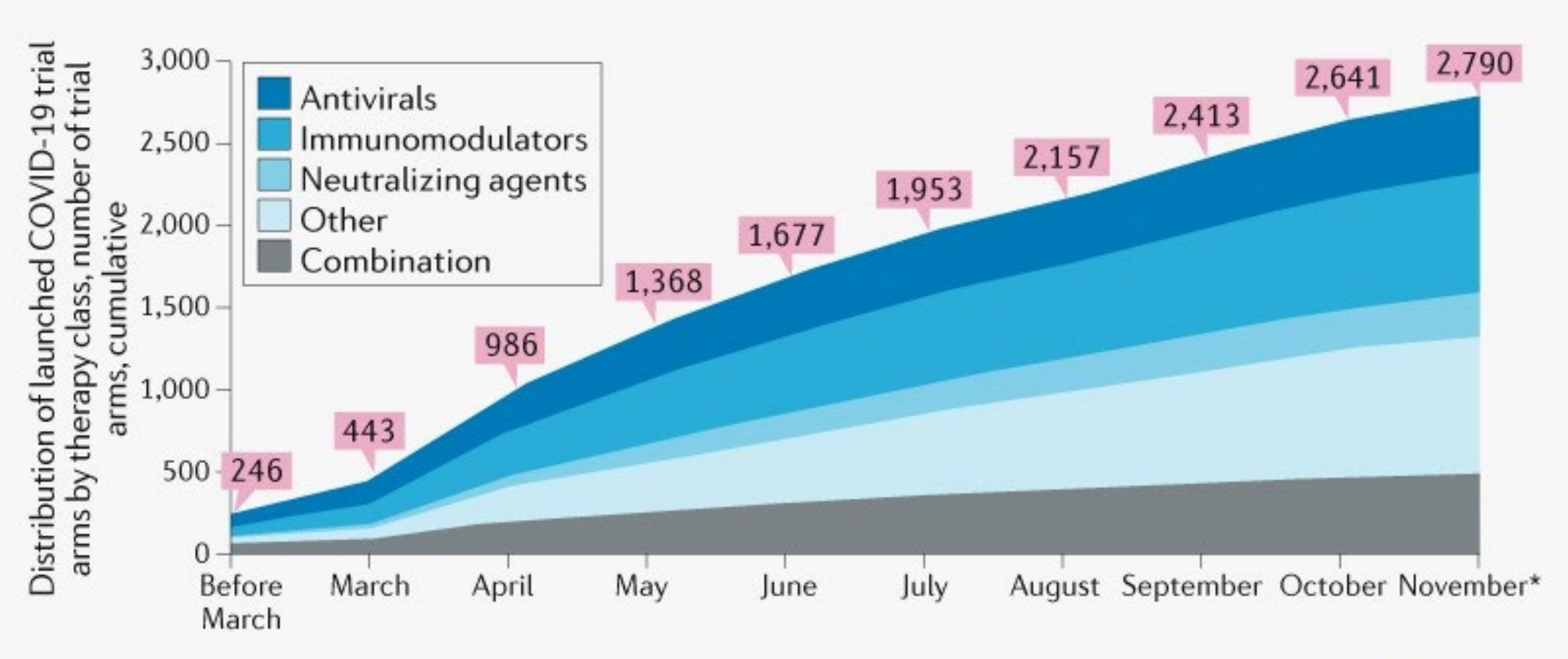
This pattern does not appear to have meaningfully improved from 2008 to 2018

Source: Fanaroff AC, Lopes RD, et al. JAMA 2019;321:1069

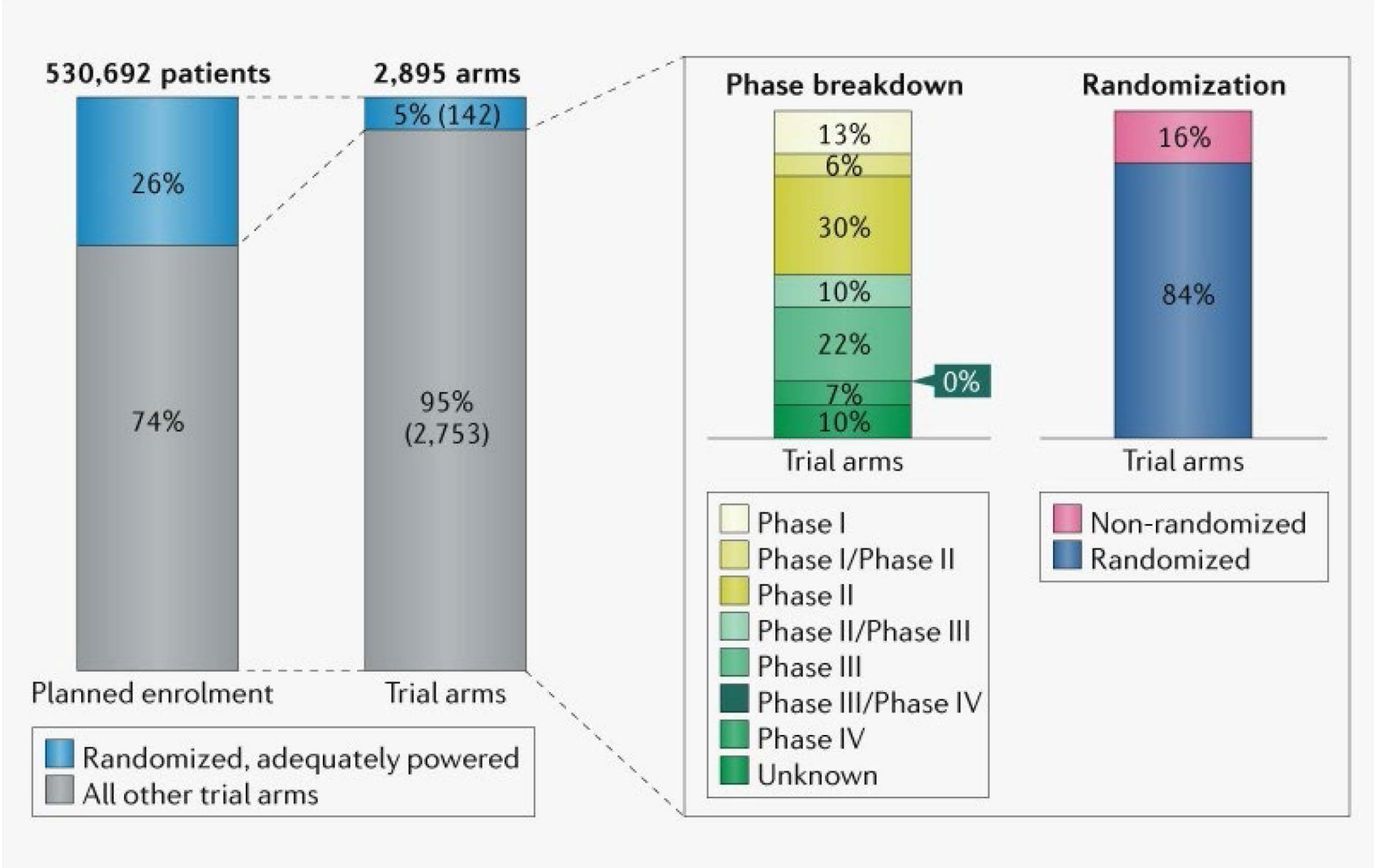
Trial Hyperinflation



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



Source: Nature Reviews Drug Discovery



Source: Nature Reviews Drug Discovery

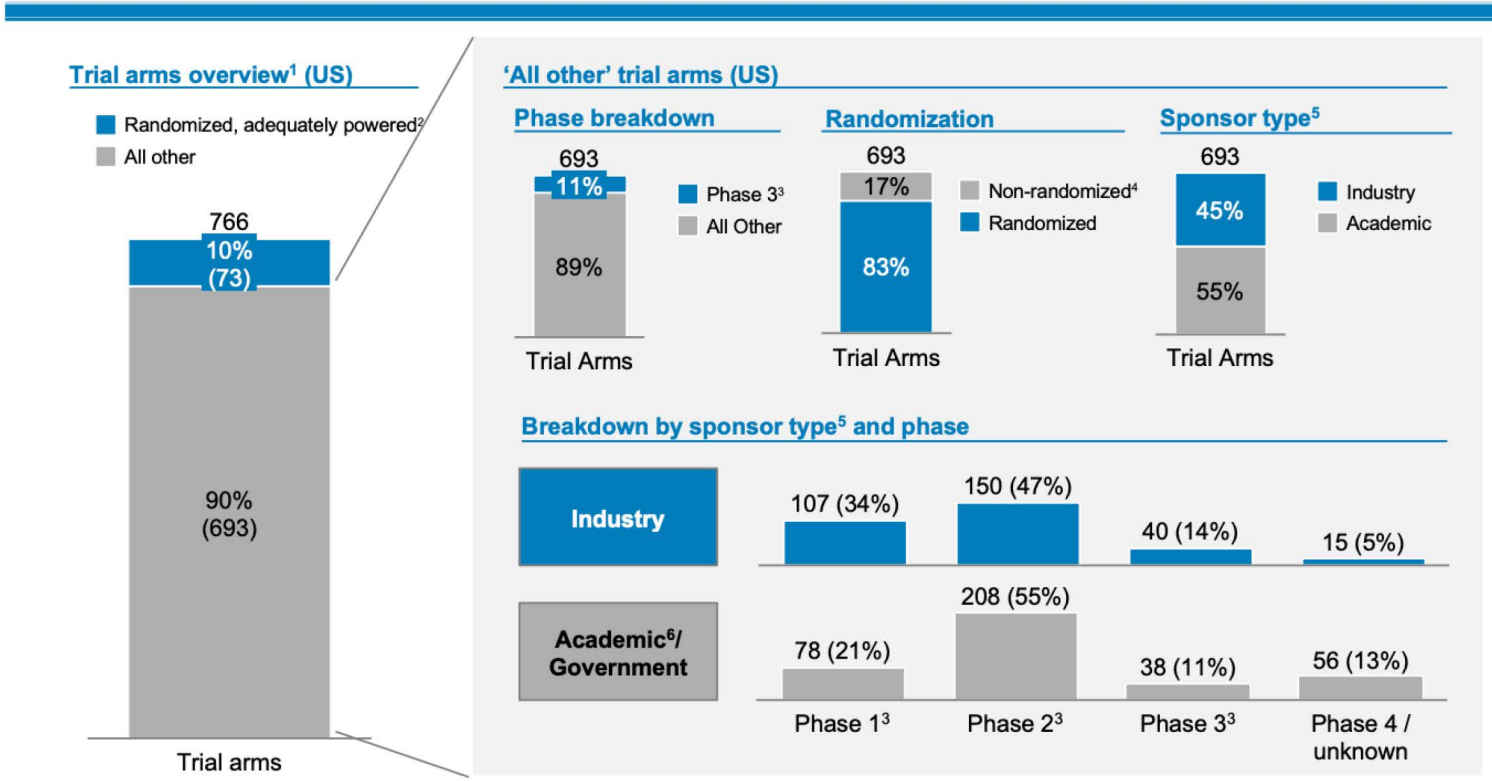


Figure S4: Characteristics of non- 'randomized, adequately powered' trial arms (US)

1 Corresponds to number of global investigational trials recruiting or completed. Excludes trials that have been terminated (or equivalent). Separates out multi-arm trials into distinct counts, including arms testing the same intervention in different doses or durations. May not be fully comprehensive. Excludes Traditional Chinese Medicine and vaccine trials.
2 Randomized, adequately powered trials are defined as randomized controlled trials in Phase 2 or beyond with expected enrollment of 250+ per arm for ventilated ICU, 500+ for hospitalized LRI, 1,000+ for early mild or asymptomatic, and 5,000+ for post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP).
3 Multi-phase trials grouped with earliest phase involved: Ph 1/2 trials grouped with Ph 1 trials, Ph 2/3 trials grouped with Ph 2 trials, Ph 3/4 trials grouped with Ph 3 trials.
4 Includes trials with unknown randomization design.
5 If multiple sponsors are involved, trial is categorized by lead sponsor type.

U.S. FOOD & DRUG ADMINISTRATION

Source: Clinicaltrials.gov accessed 11/20/2020 and WHO clinical trial registry accessed 11/20/2020

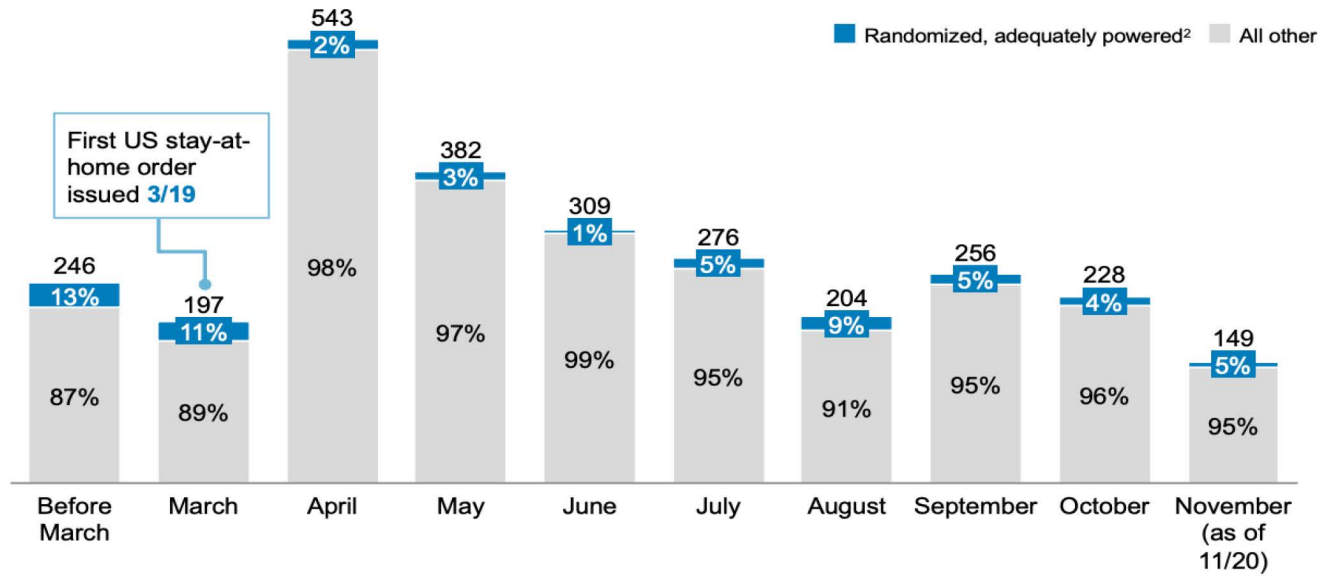


Figure S3: The total number of trial arms[1] started and randomized, adequately powered per month

1 Corresponds to number of global investigational trials recruiting or completed. Excludes trials that have been terminated (or equivalent). Separates out multi-arm trials into distinct counts, including arms testing the same intervention in different doses or durations. May not be fully comprehensive. Excludes Traditional Chinese Medicine and vaccine trials. Placebo arms are not included in arm counts.
2 Randomized, adequately powered trials are defined as randomized controlled trials in Phase 2 or beyond with expected enrollment of 250+ per arm for ventilated ICU, 500+ for hospitalized LRI, 1,000+ for early mild or asymptomatic, and 5,000+ for post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP).

FDA U.S. FOOD & DRUG ADMINISTRATION

Source: Clinicaltrials.gov accessed 11/20/2020 and WHO clinical trial registry accessed 11/20/2020

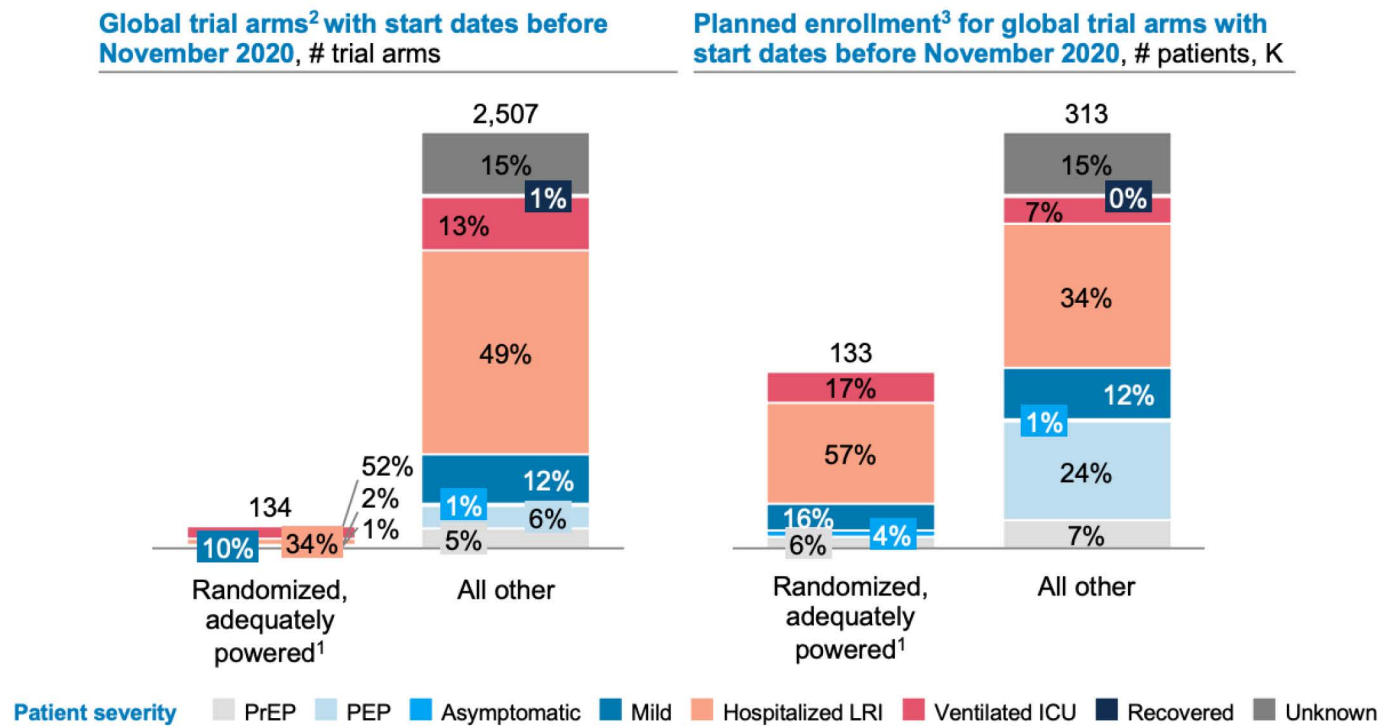


Figure S5: Randomized, adequately powered trial arms[1] and target patient enrollment for trials started before November 2020

1 Randomized, adequately powered trials are defined as randomized controlled trials in Phase 2 or beyond with expected enrollment of 250+ per arm for ventilated ICU, 500+ for hospitalized LRI, 1,000+ for early mild or asymptomatic, and 5,000+ for post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP).
2 Corresponds to number of global investigational trials recruiting or completed. Excludes trials that have been terminated (or equivalent). Separates out multi-arm trials into distinct counts, including arms testing the same intervention in different doses or durations. May not be fully comprehensive. Excludes Traditional Chinese Medicine and vaccine trials.
3 Planned enrollment defined as enrollment per arm estimated from total enrollment by assuming even distribution of patients across all arms. It is not reflective of actual enrollment. Total planned enrollment does not include planned enrollment in placebo arms.

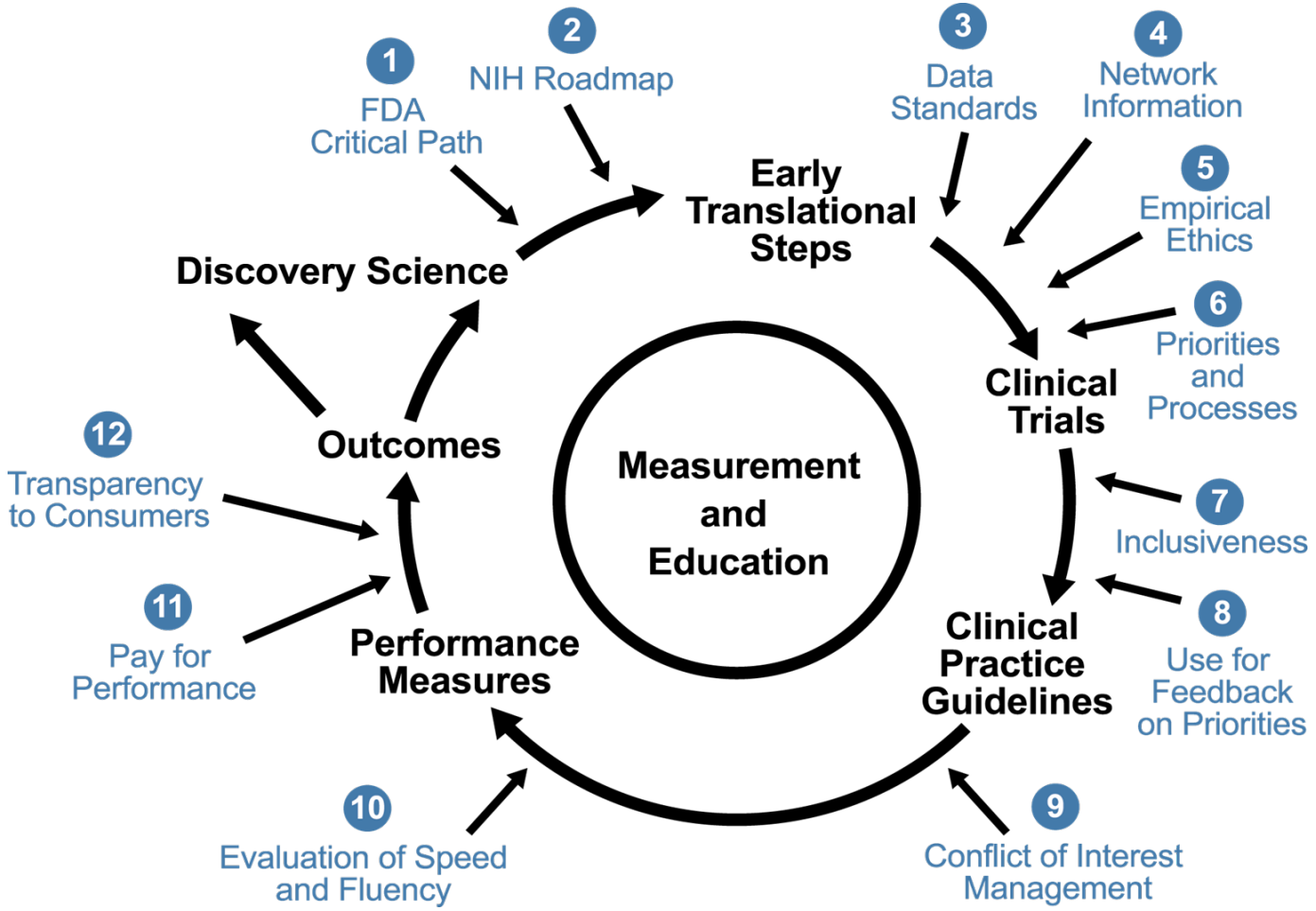
U.S. FOOD & DRUG ADMINISTRATION

Source: Clinicaltrials.gov accessed 11/20/2020 and WHO clinical trial registry accessed 11/20/2020

Evidence to Practice

- Clinical outcomes are improved most when interventions are planned and evaluated in a reasonable sequence.
- Most interventions, despite good intentions, fail to provide benefits that exceed the risks.
- For this reason, the law requires evidence that benefits outweigh risks for the intended use of the product.
- The need for evidence generation continues for the life cycle of the product.

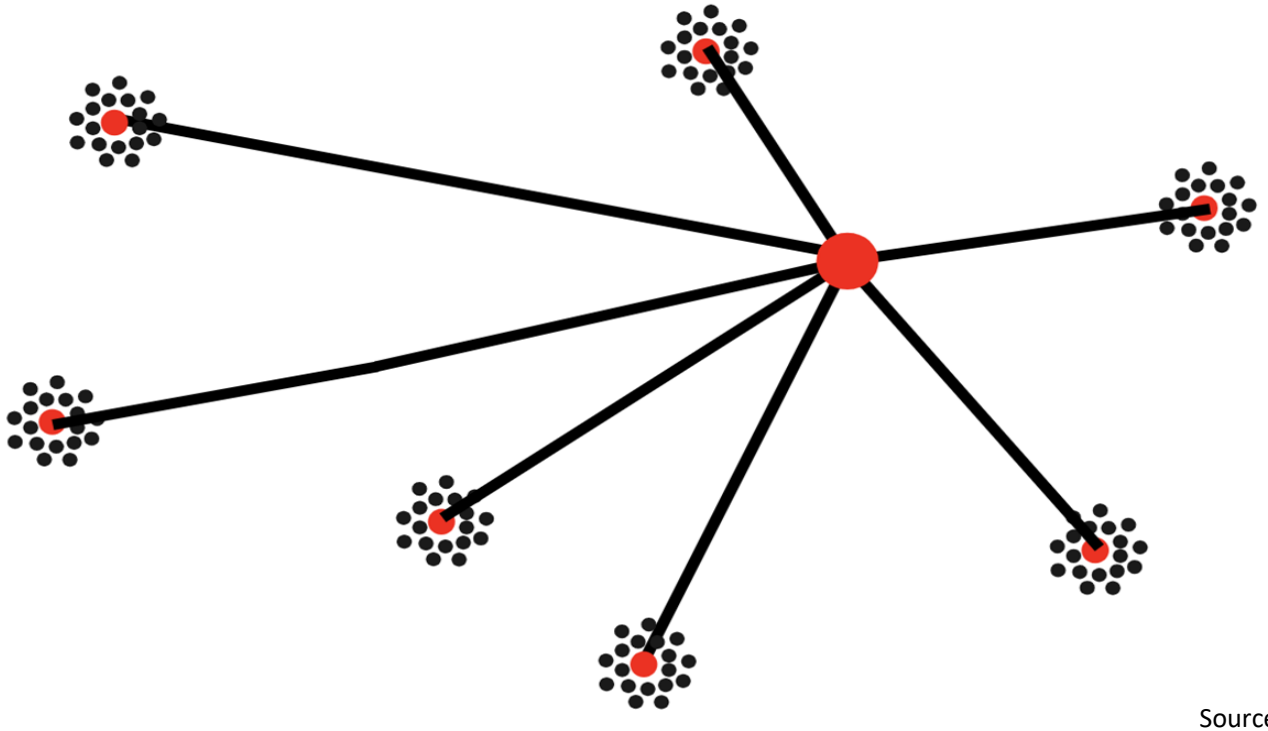
Generating Evidence to Inform Decisions



An Evidence Generation Infrastructure

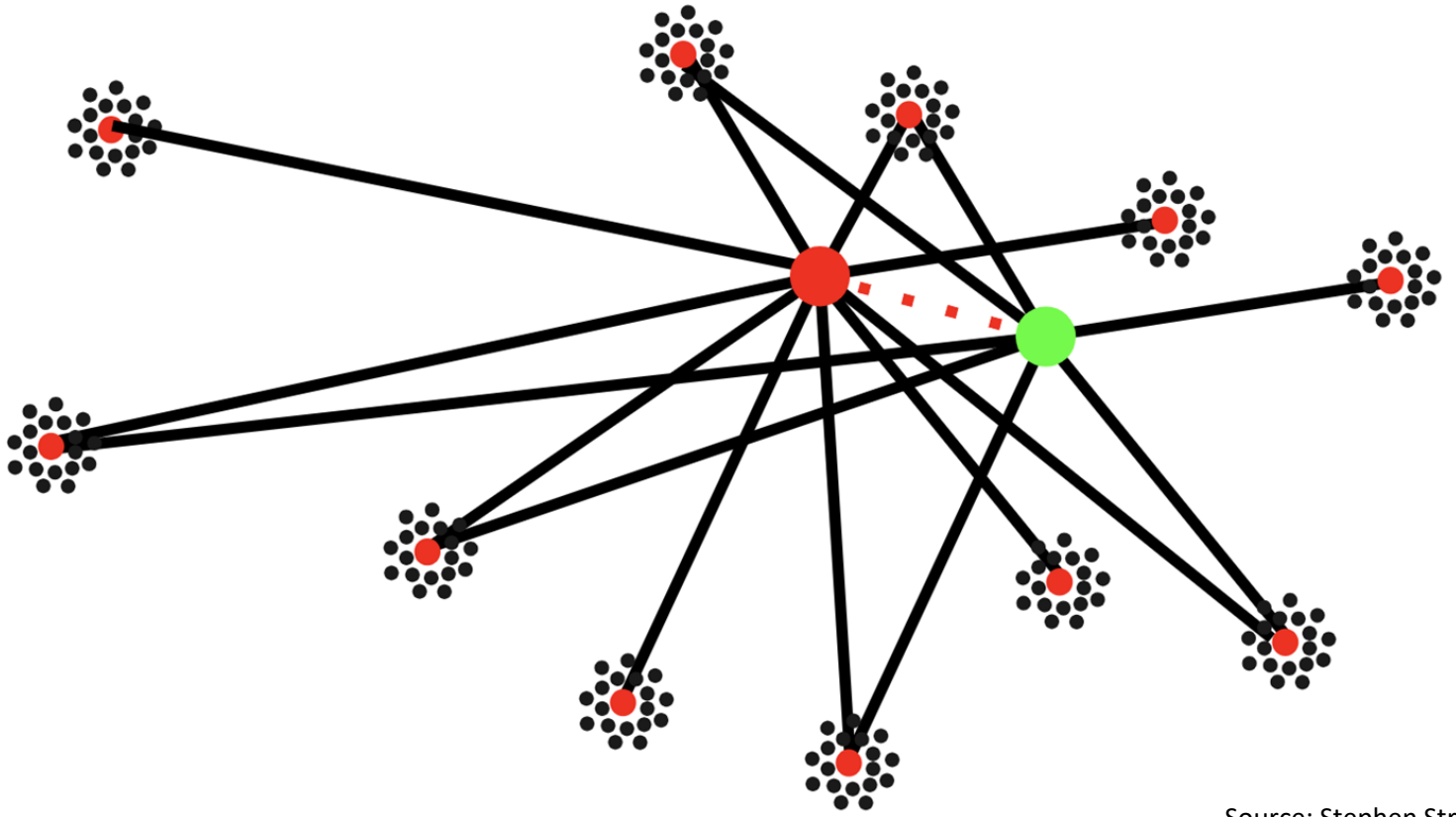
- Engaged participants and clinicians.
- Outcome measurement and payment that aligns ecosystem with better participant/patient outcomes.
- Inclusive communication tailored to the needs of diverse research participants.
- Transparent, shared information across the ecosystem.
- Quality by design to have the right amount of oversight/bureaucracy tuned to optimize useful research results.
- Data quality and prospective design are critical.
- Societal norms for data sharing and reciprocal obligations of data aggregators.

Typical NIH Network Academic Health Center Sites and Data Coordinating Center



Source: Stephen Strauss, NIH Roadmap 2004-2005

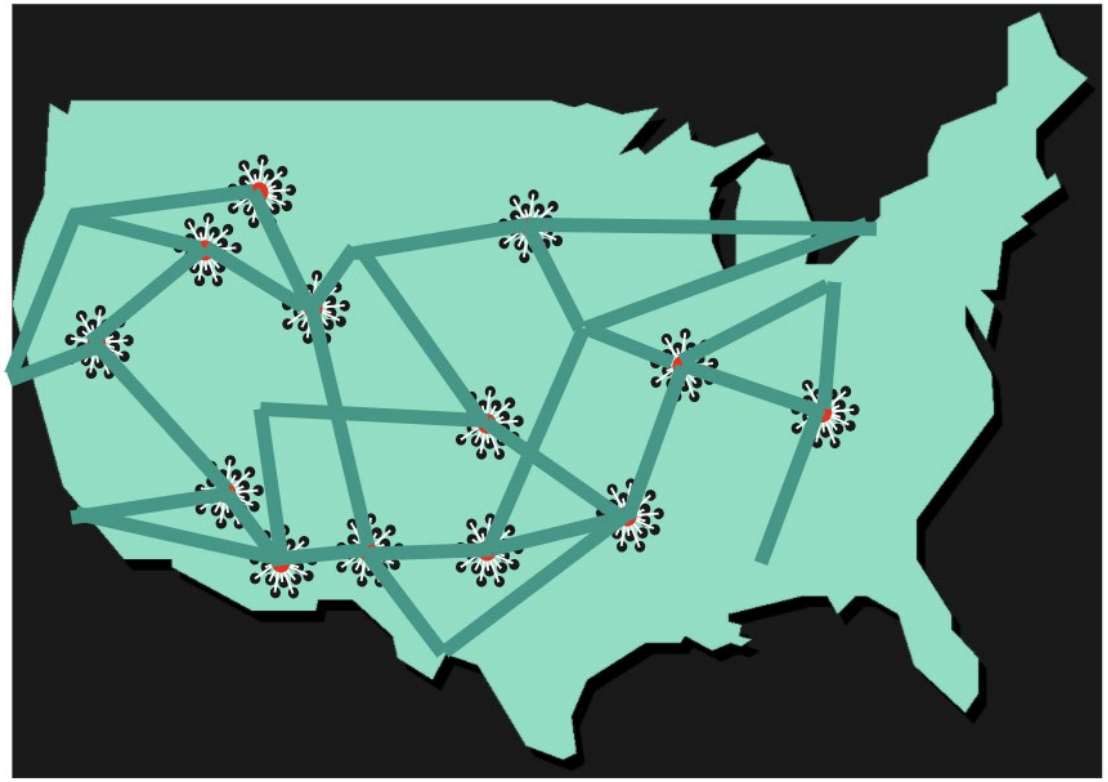
Networks Share Sites Interoperable and Data



Source: Stephen Strauss, NIH Roadmap 2004-2005

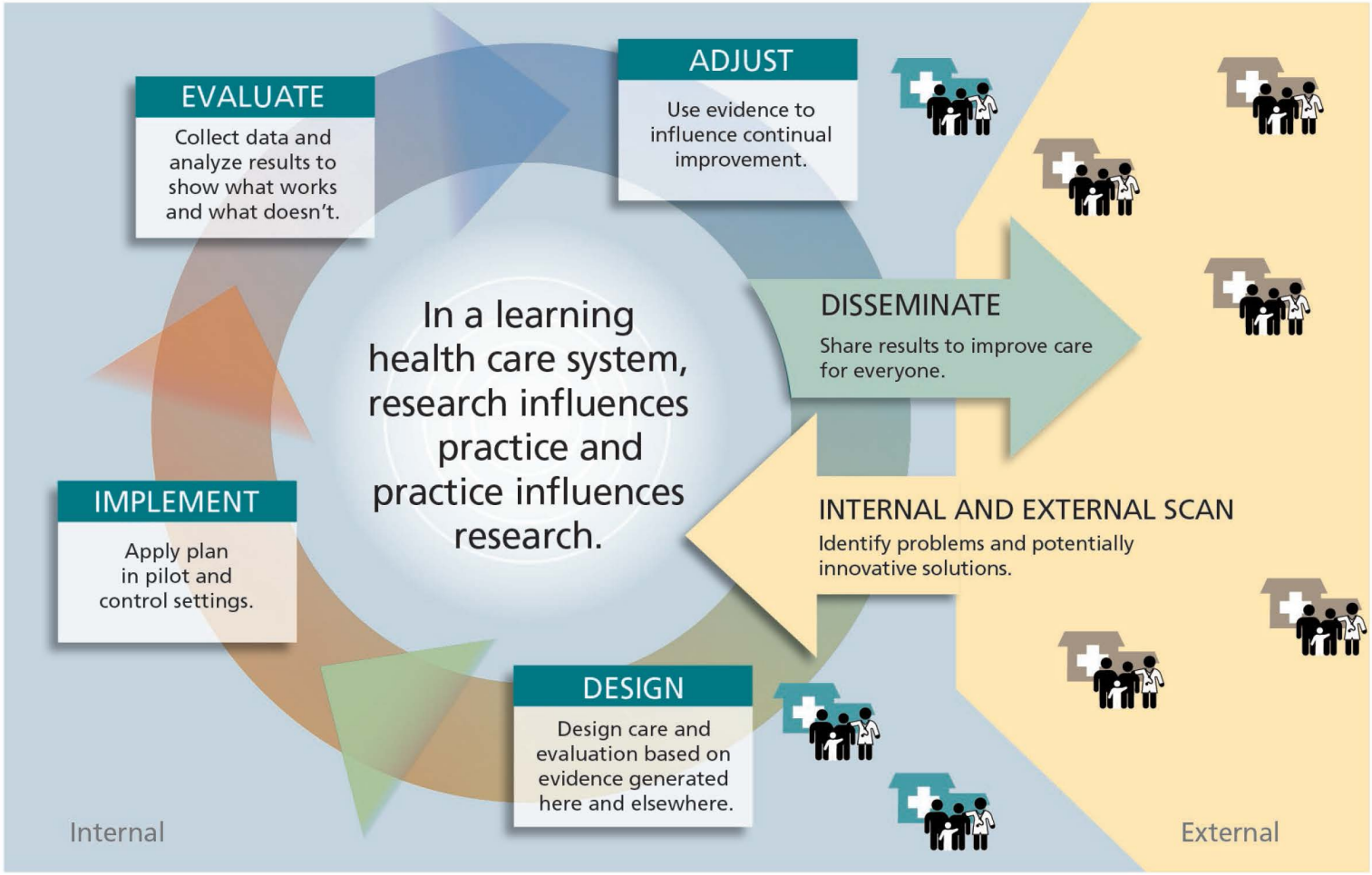
Integration of Clinical Research Networks

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

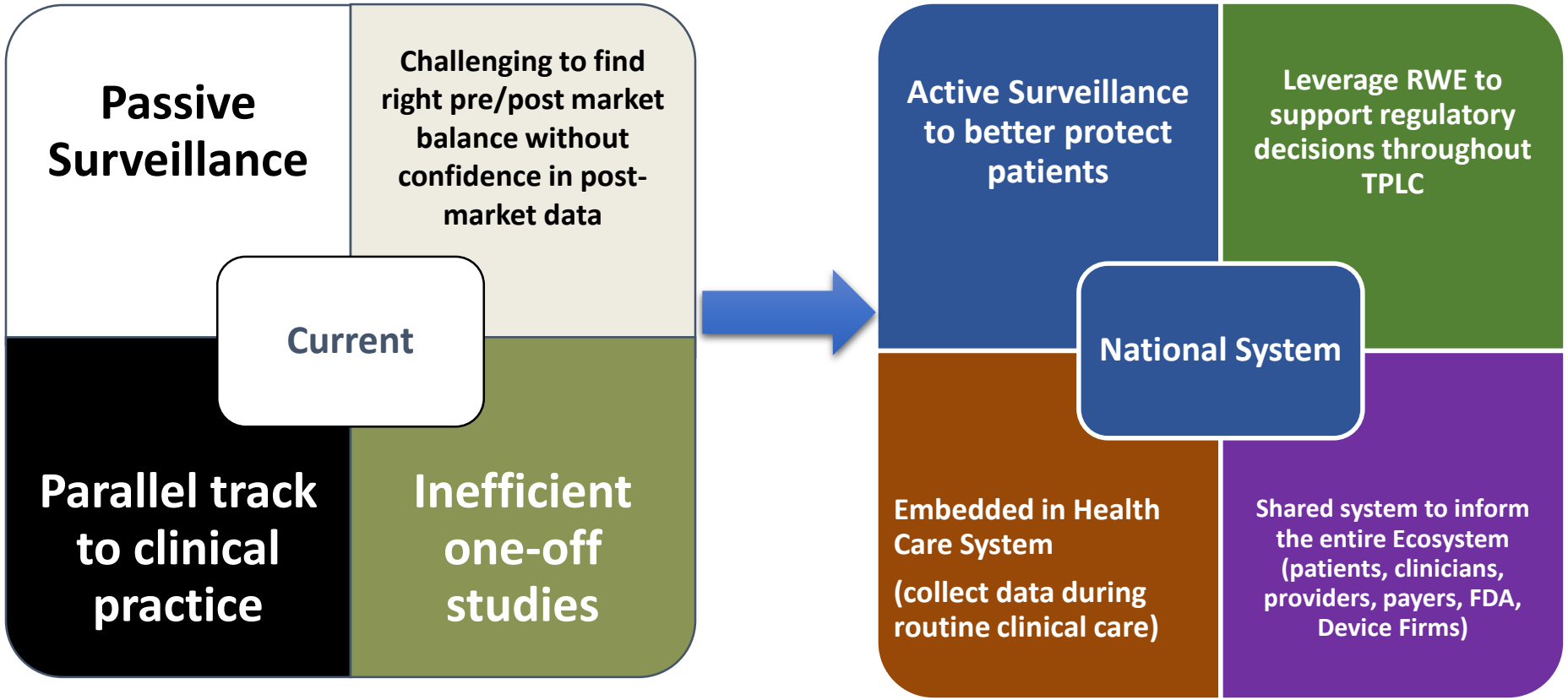


Stephen Strauss, NIH Roadmap 2004-2005

Learning Health Care Systems

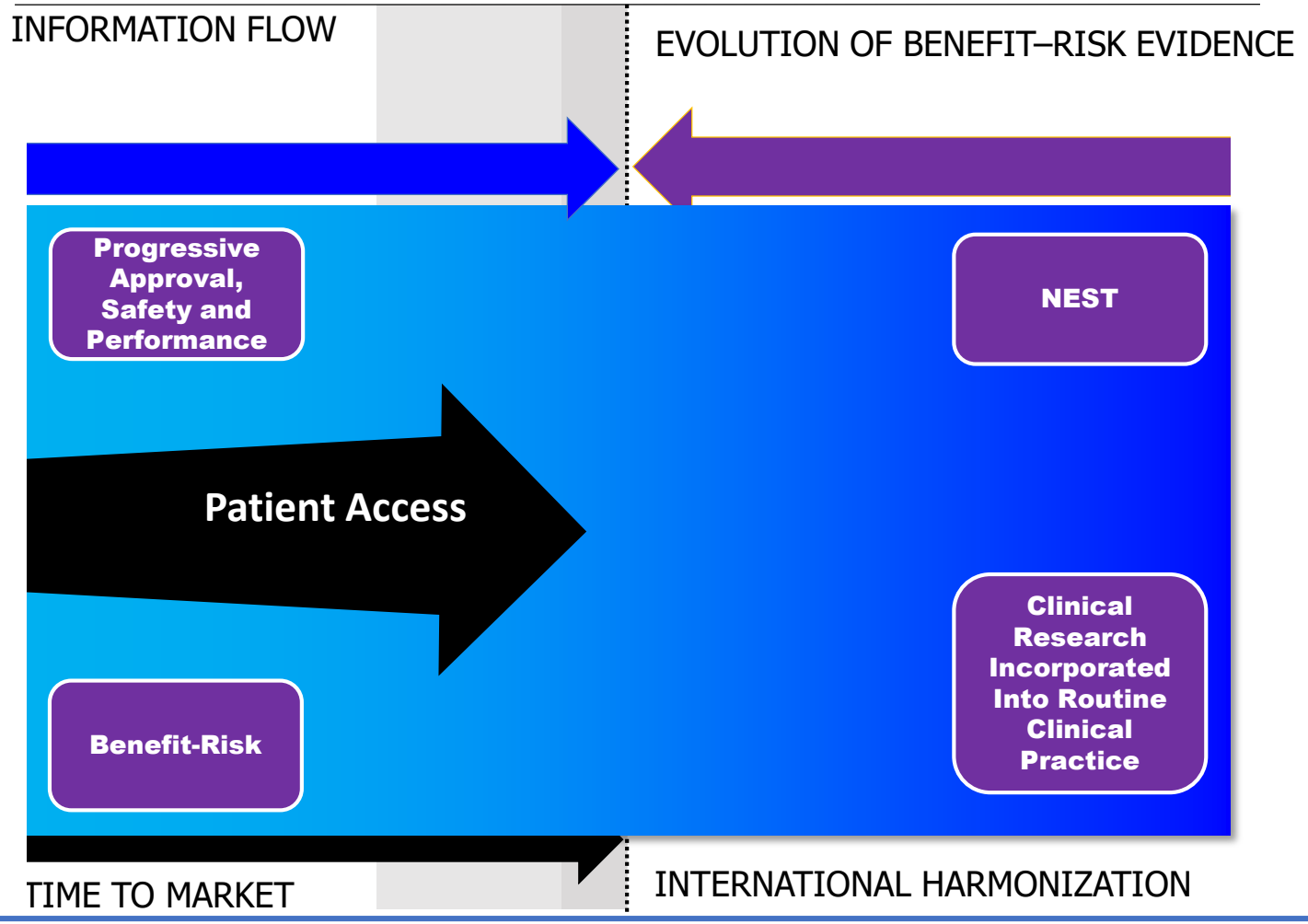


National System Paradigm Shift

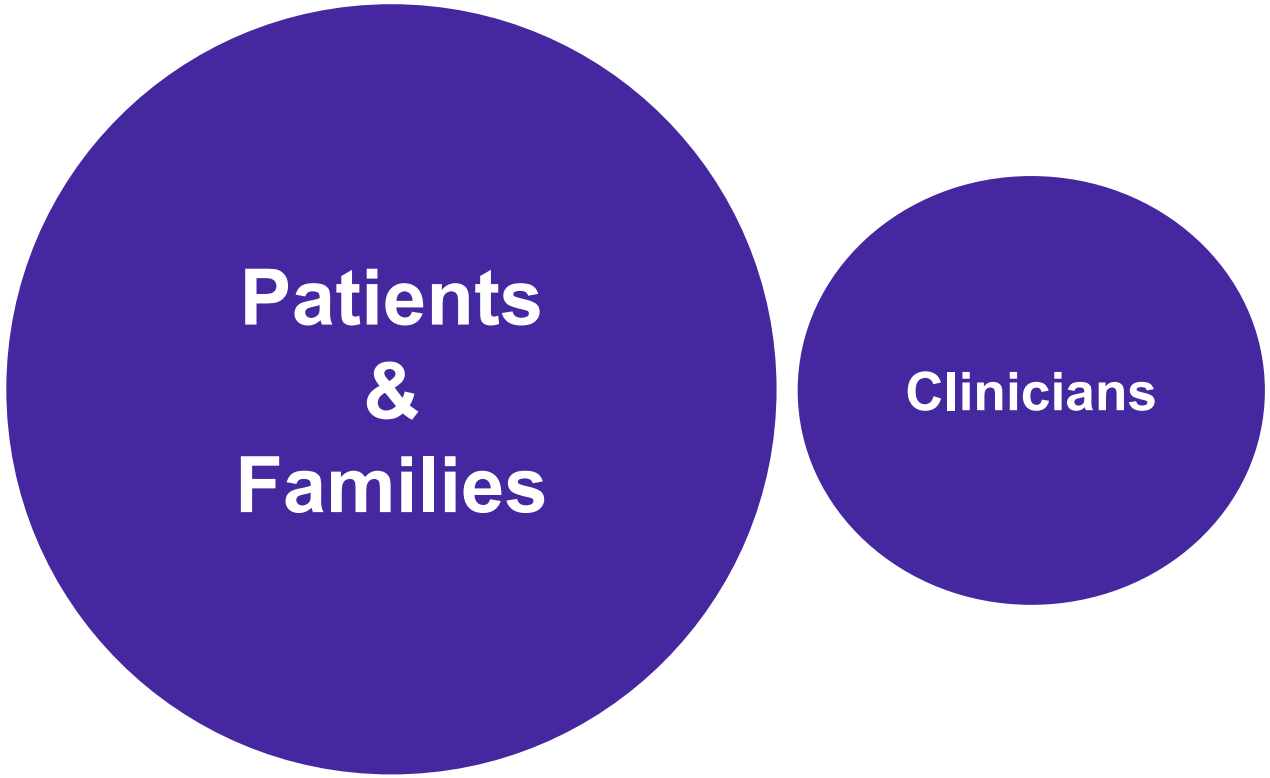


Learning Medical Device Ecosystem

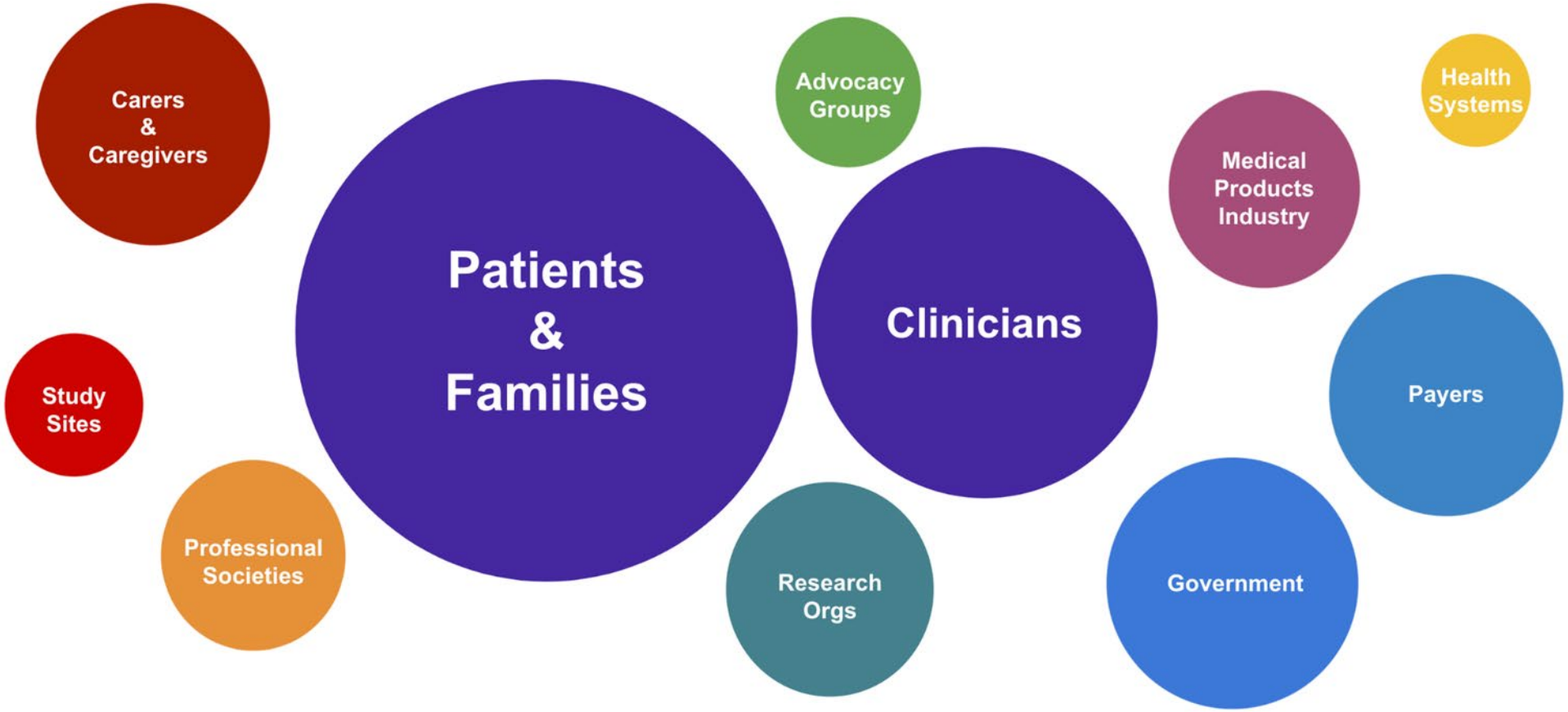
Total Product Life Cycle (TPLC) Framework



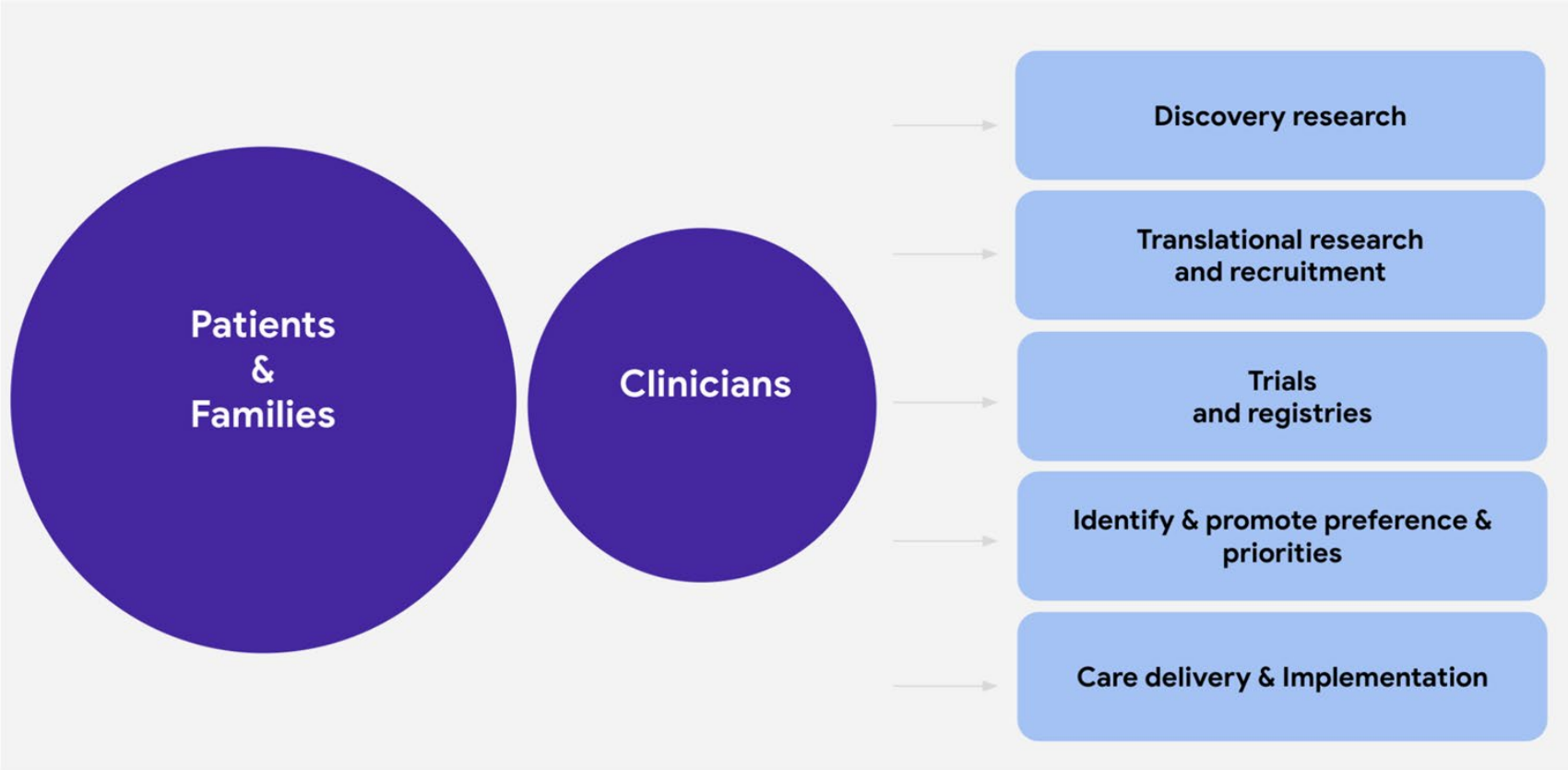
Patients and their families are at the center. And most patients with a disease highly value a happy, trusted clinician(s) & team.



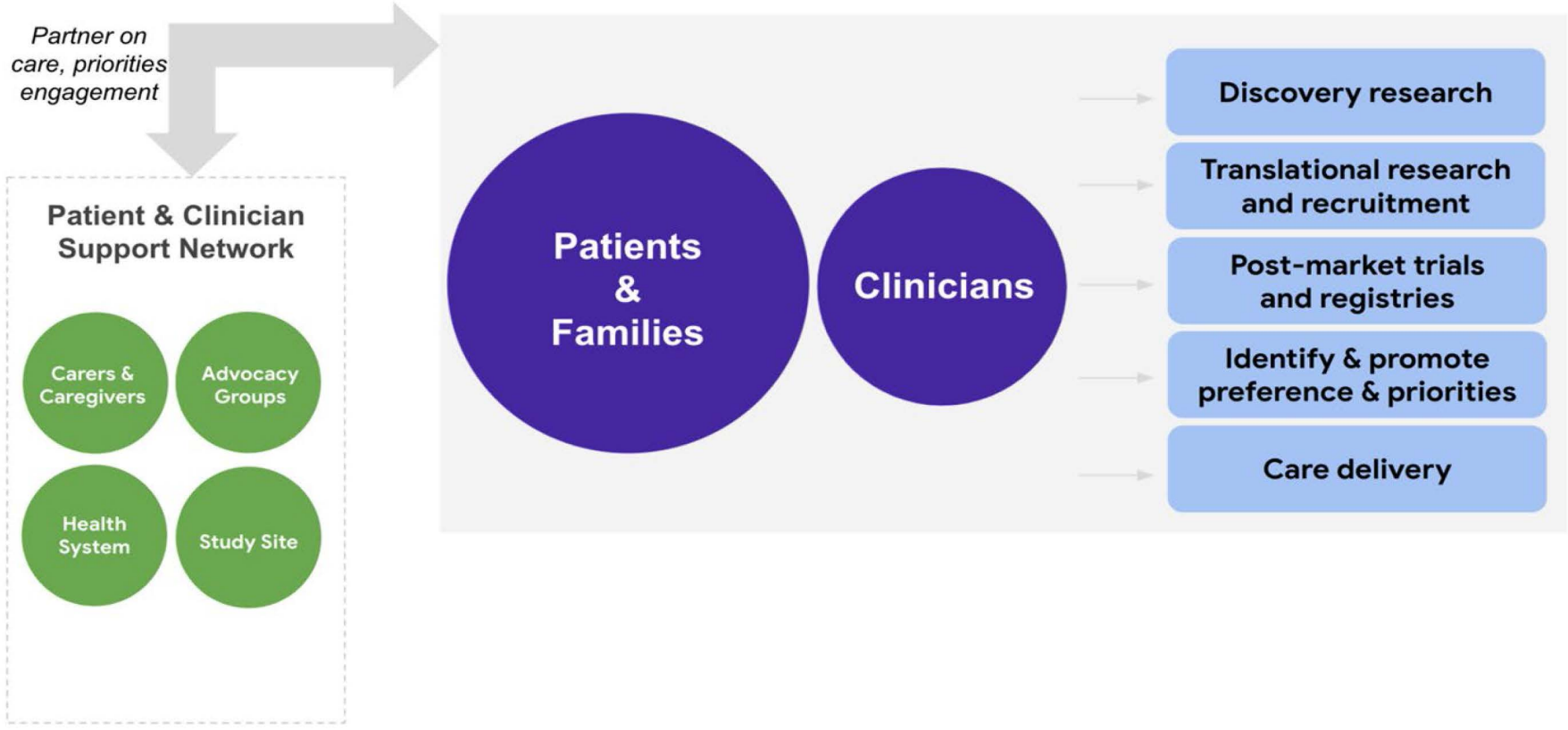
The reality is we have is a disaggregated, fragmented system with lack of organization around common, transparent high-quality information



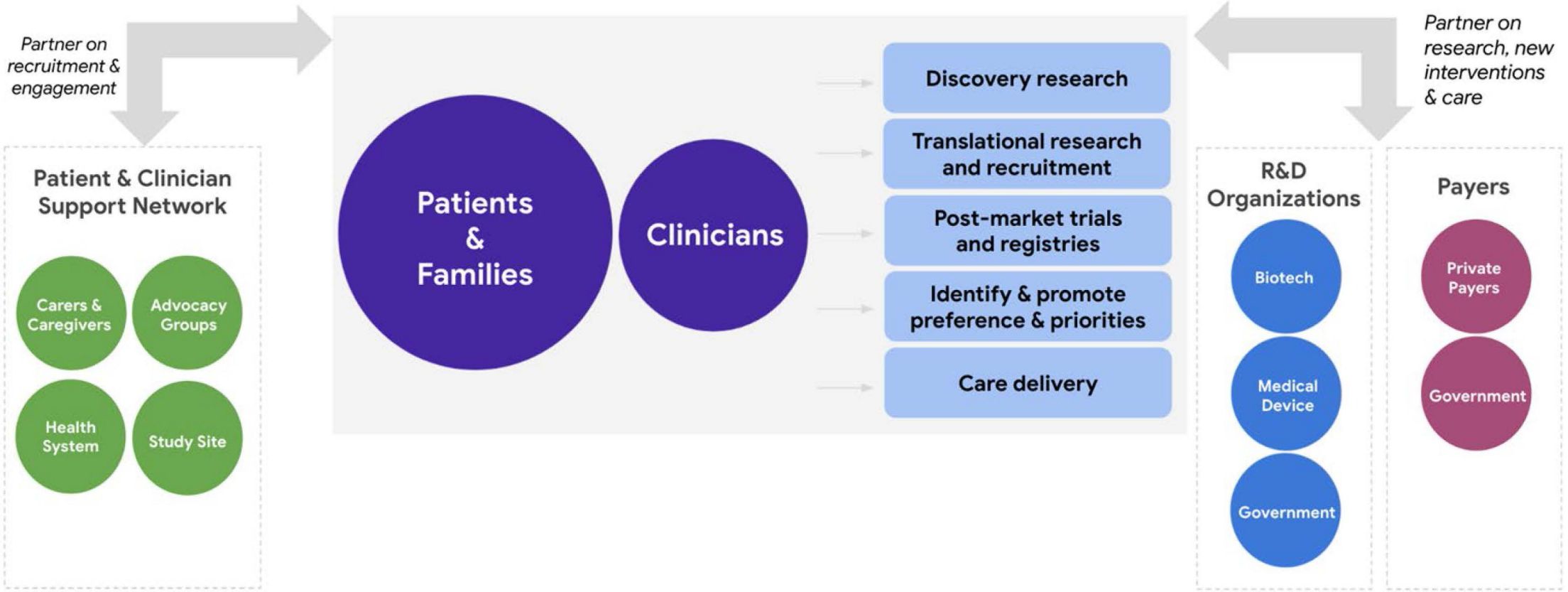
If patients and clinicians banded together to optimize the information base for high-quality, evidence-based care…



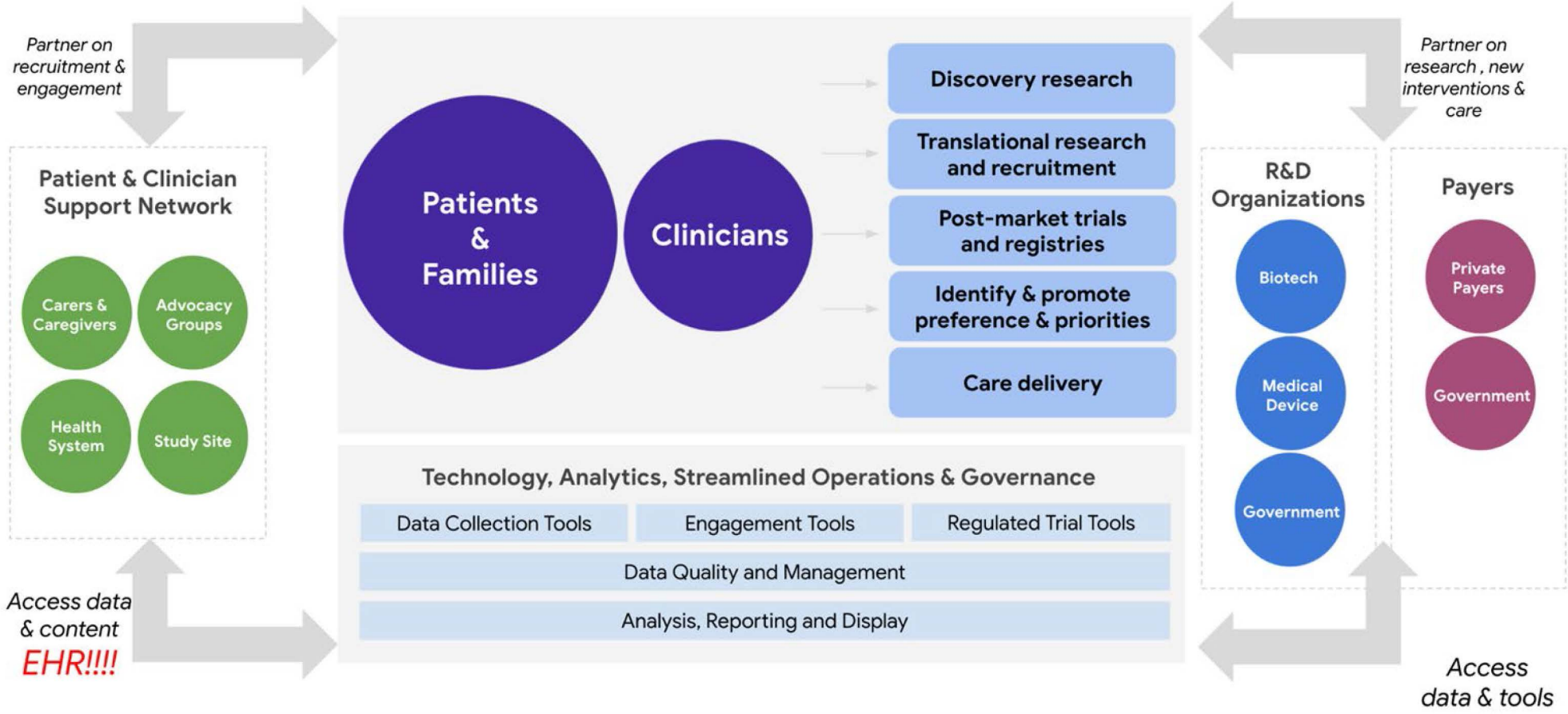
Organizations that support the patient-clinician dyad would do better with common goals



The medical products industry & payers would benefit from higher quality information and participation



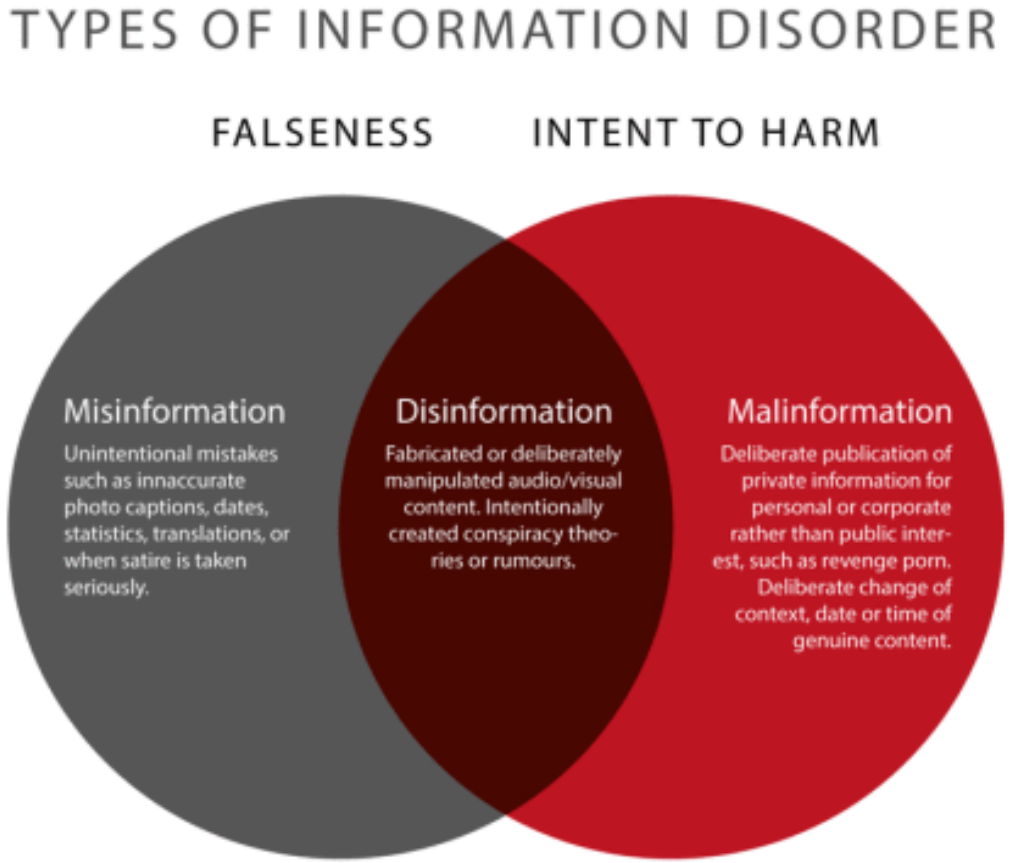
Given common goals, current technology could support a common information base that could support the primary mission: better outcomes for patients



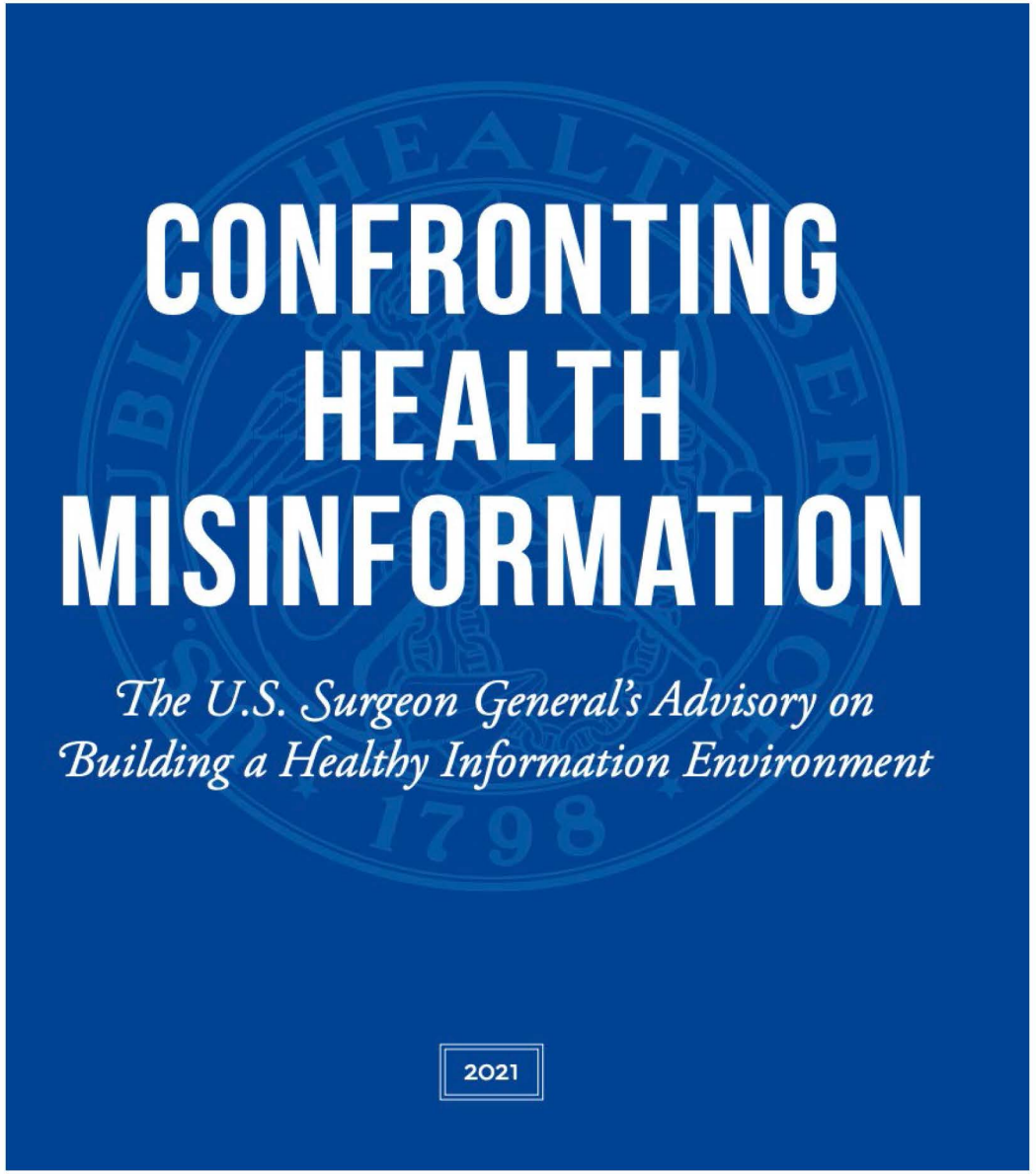
Varying forms of misinformation carry different levels of threat

"Disinformation," is intended to mislead and is disseminated with knowledge that those who succumb to it could be harmed

"Malinformation" is which represents a purposeful effort to harm others directly by spreading incorrect information.



https://flowersforsocrates.com/2018/08/12/disinformation-misinformation-malinformation-involves-framing/


CONFRONTING
HEALTH
MISINFORMATION
The U.S. Surgeon General's Advisory on
Building a Healthy Information Environment
2021

I am urging all Americans to help slow the spread of health misinformation during the COVID-19 pandemic and beyond. Health misinformation is a serious threat to public health. It can cause confusion, sow mistrust, harm people's health, and undermine public health efforts. Limiting the spread of health misinformation is a moral and civic imperative that will require a whole-of-society effort.

Vivek H. Murthy, M.D., M.B.A.
Vice Admiral, U.S. Public Health Service
Surgeon General of the United States

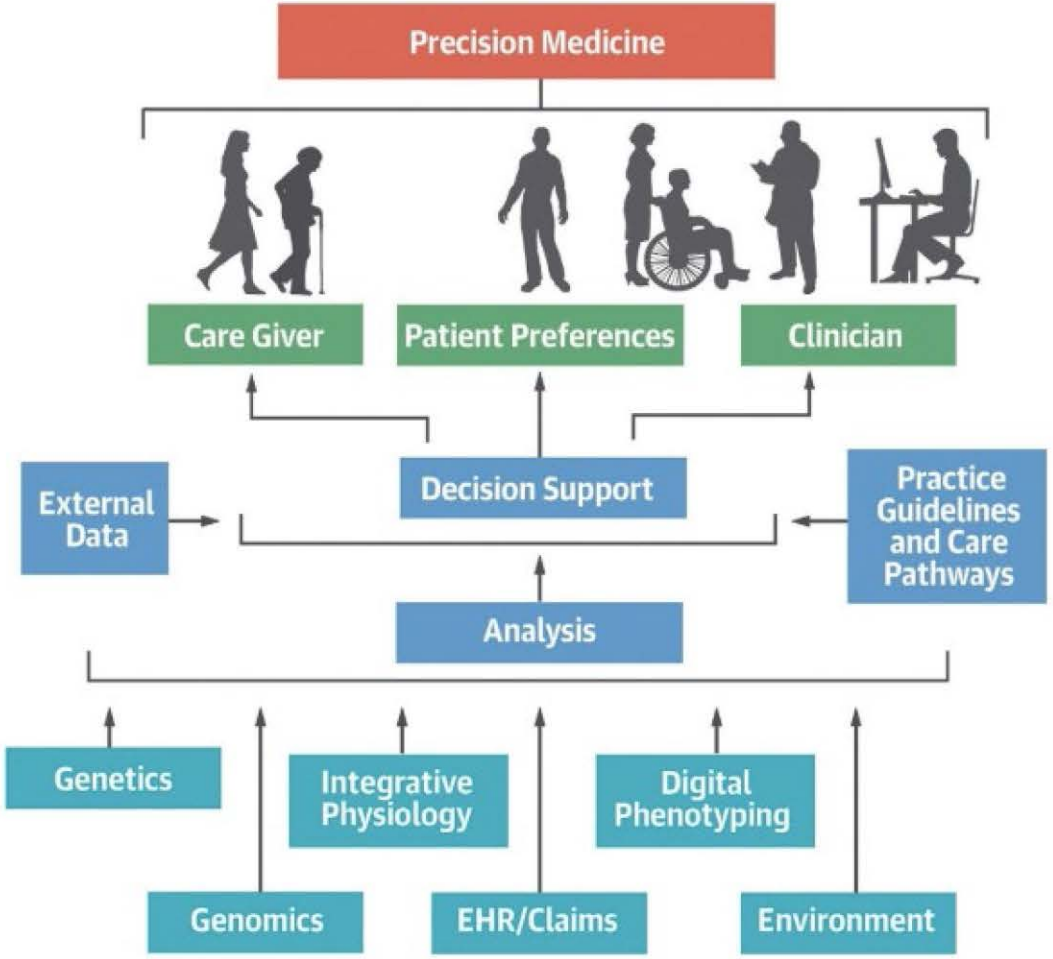
U.S. FDA
@US_FDA

You are not a horse. You are not a cow.
Seriously, y'all. Stop it.

fda.gov
Why You Should Not Use Ivermectin to Treat or Prevent COVID-19
Using the Drug ivermectin to treat COVID-19 can be dangerous and even lethal. The FDA has not approved the drug for that ...

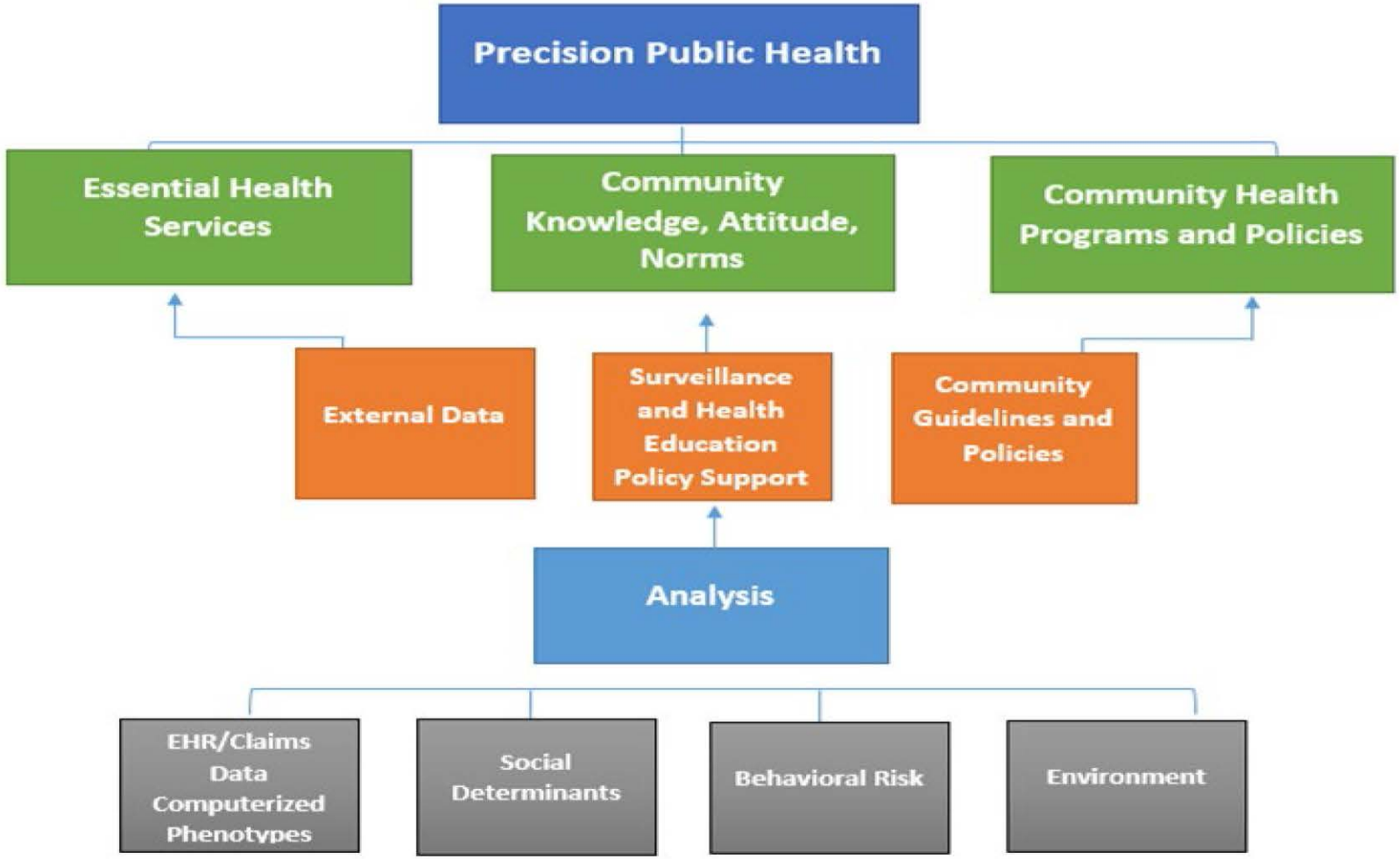
7:57 AM · Aug 21, 2021 · Twitter Web App

Central Illustration: Precision Medicine



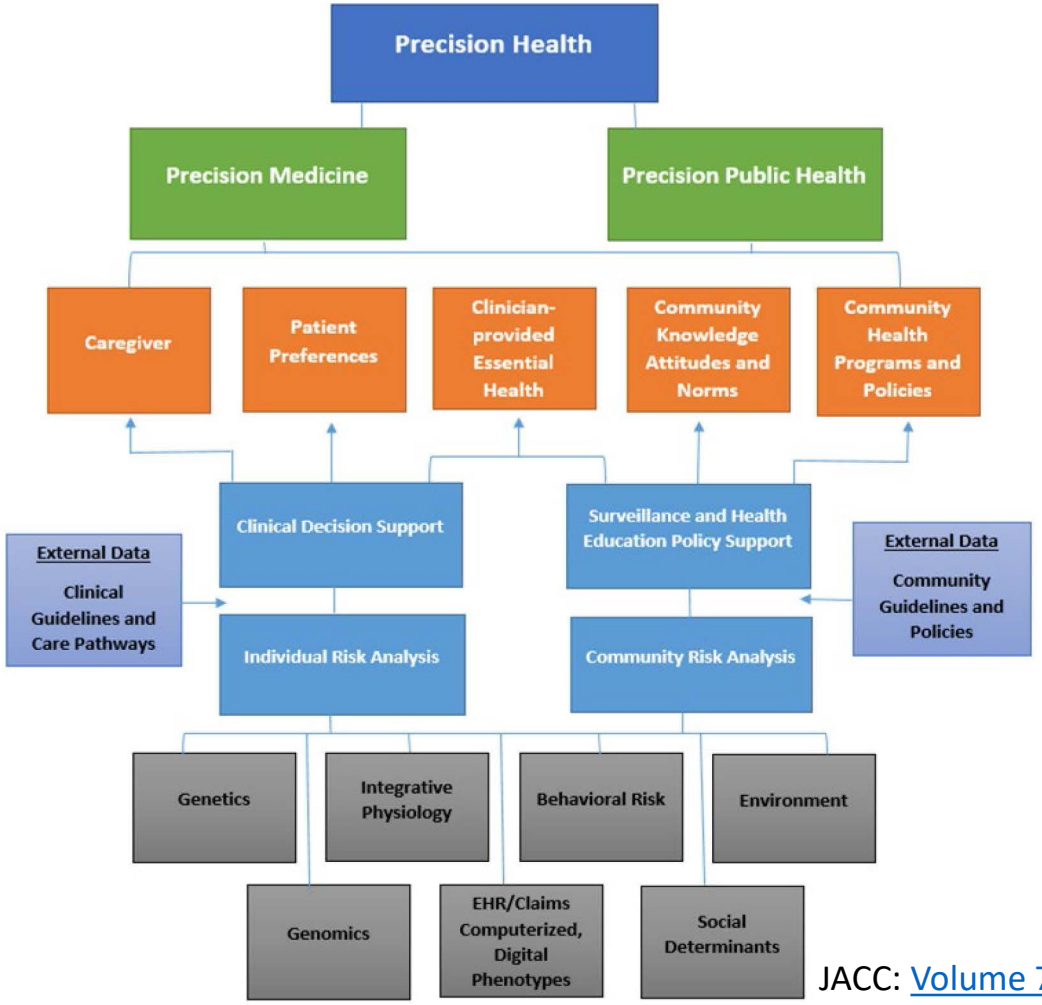
Califf, R.M. J Am Coll Cardiology. 2018;72(25):3301-9

Central Illustration: Precision Public Health



JACC: Volume 76, Issue 3, 21 July 2020, Pages 306-320

Data-driven Merger of Precision Medicine & Precision Public Health



JACC: Volume 76, Issue 3, 21 July 2020, Pages 306-320

The Opportunity

- Biomedical science and technology are in an amazing period of discovery and development.
- Yet these advantages are not resulting in superior health and outcomes for the U.S. population or for most individuals.
- The intersection of biomedical science, technology and communication, if handled with good policies, investment and communication, could usher in a new era of better health for the U.S. and the world.
- Previous policies and infrastructure investment provide a solid base from which to build an effective system for evaluation and implementation across the spectrum of development, pivotal trials and post-market evaluation.


NAVAL ORDNANCE LABORATORY