Challenges and Opportunities for Personalized and Precision Nutrition: A Regulatory Perspective

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Overview

- FDA's mission is to preserve and protect the public **health**
- **Now is a good time to talk about precision nutrition**
  - By all measures, health of the U.S. public is deteriorating
  - Biology provides the underpinning for understanding how products (food, supplements, drugs, devices, biologics) lead to better or worse health
  - We are in a period of new capability to understand biology and behavior and to transmit information that is **truthful and not misleading**
- Except in cases of of specific nutritional deficiency, individual biomarkers are unlikely to predict the effect of food on health
- **The pipeline of precision nutrition requires multiple levels of quality systems and validation**

The FDA: Big Picture

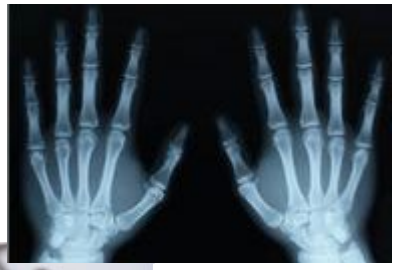
- Regulatory Agency
- Science Agency
- Public Health Agency
- Multiple disciplines always in play
  - Science/Medicine/Public Health
  - Policy
  - Law

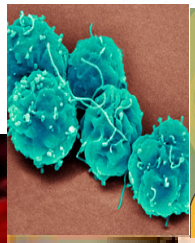
FDA Regulates a Spectrum of Health Products : 20-25 cents of every GDP dollar

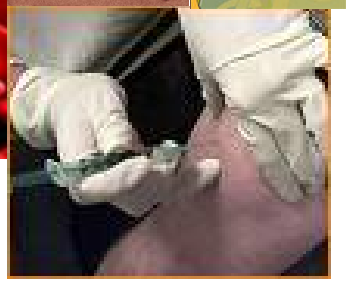
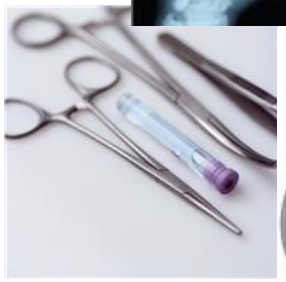









FDA Mission

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.

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

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.

FDA Mission

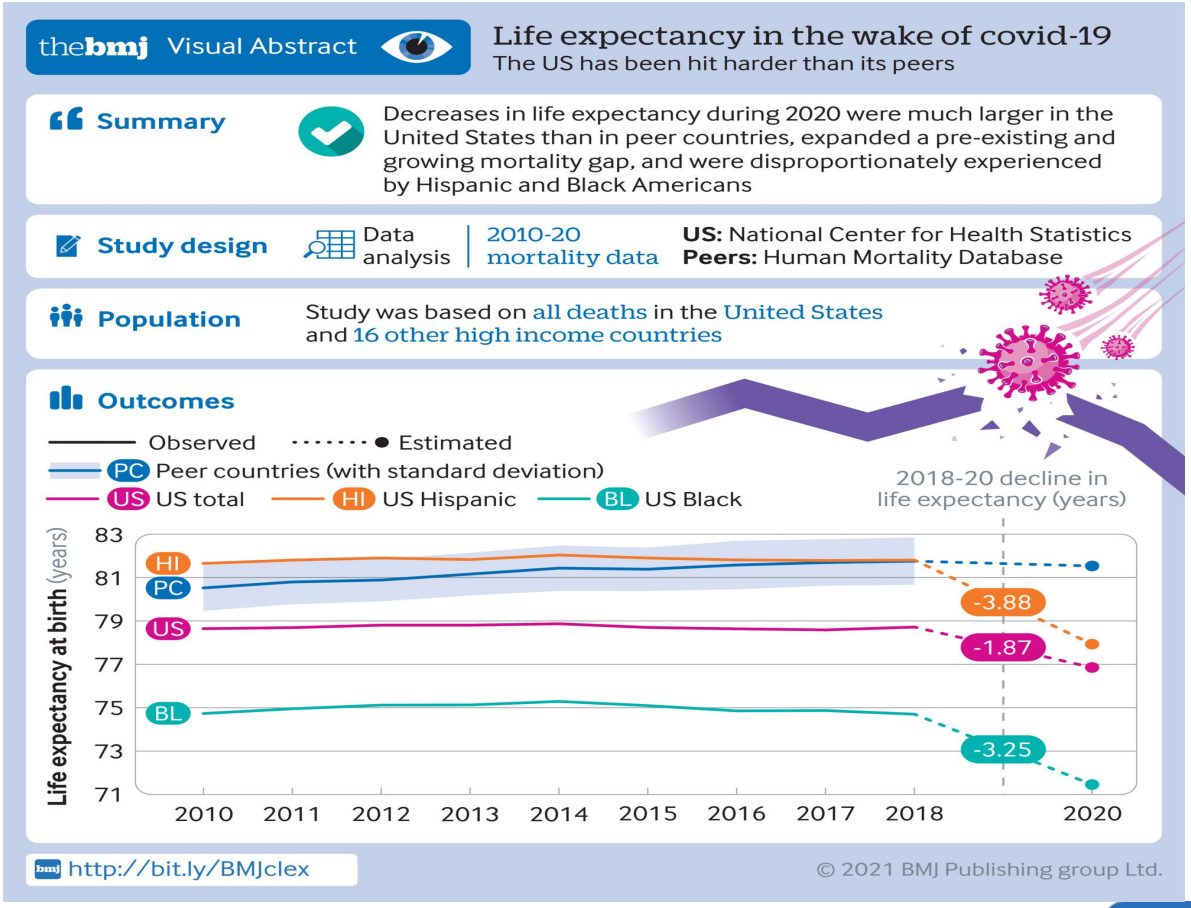
Finally, FDA plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats.

Decision Making

- While FDA is a science based organization, in the end it must make decisions
  - Cannot just say “more research is needed”
- Analogy to a referee making decisions with guidance of rulebook
- Consequences profound
  - Public health and well being of patients
  - Economy

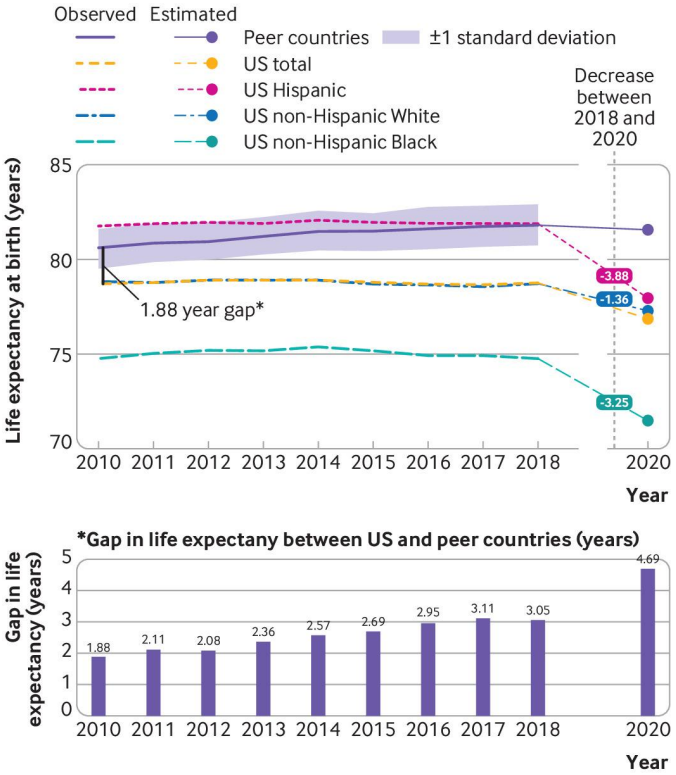
Life expectancy at birth (years) in 18 high income countries for women and men during 2010-16 and 1990-2015

 Jessica Y Ho, and Arun S Hendi BMJ 2018;362:bmj.k2562



Steven H Woolf et al. BMJ 2021;373:bmj.n1343

Life expectancy at birth in the United States, by race and ethnicity, and in peer countries, for years 2010-18 and 2020.

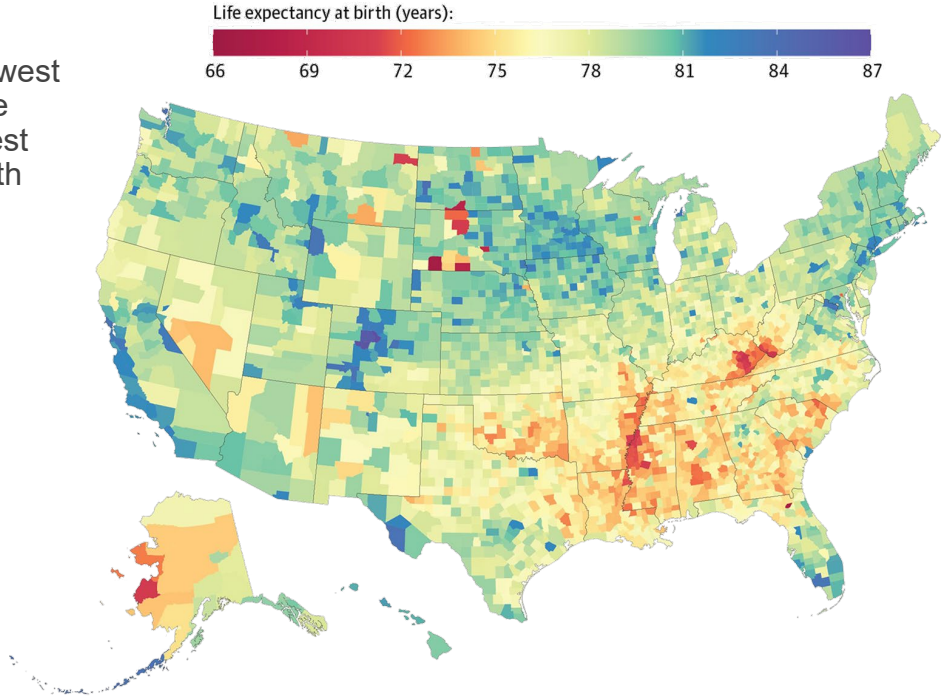


Steven H Woolf et al. BMJ 2021;373:bmj.n1343

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



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

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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

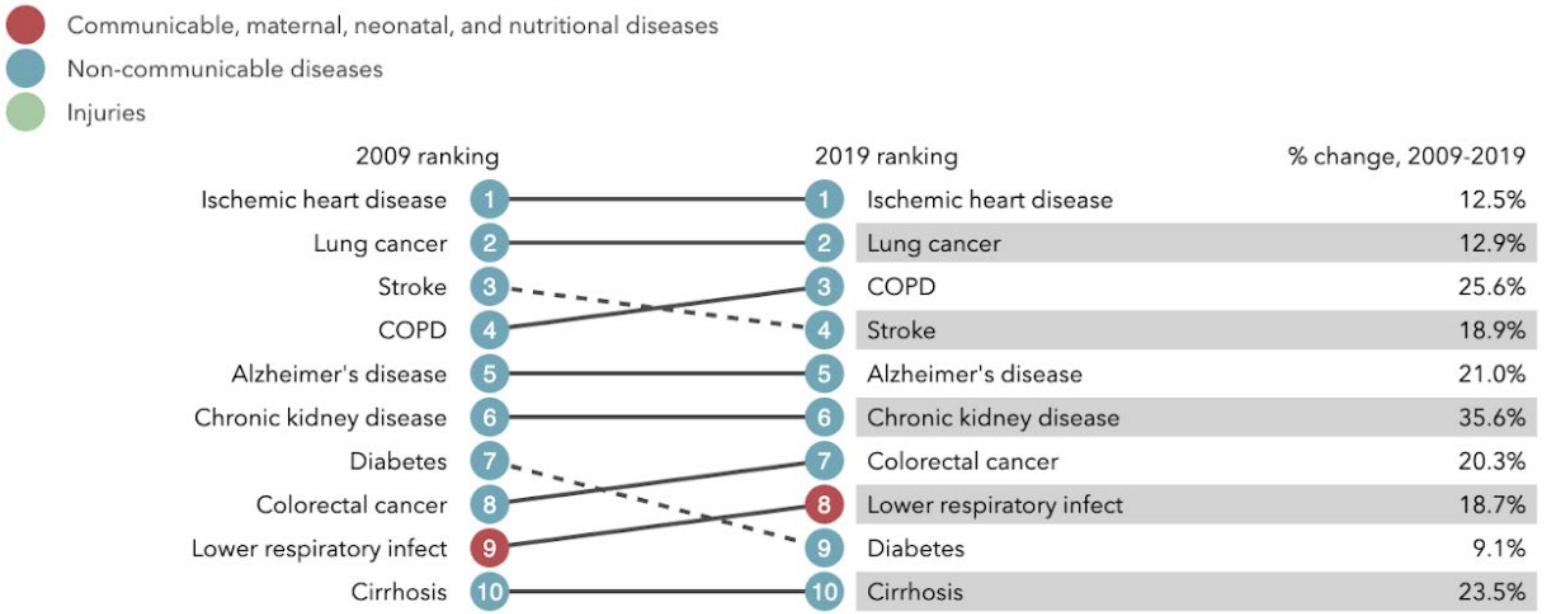
Variable	Summary Statistics, Mean (SD) [Range]	Bivariate Regression Results	
		Coefficient (SE)	R^2
Socioeconomic and race/Ethnicity factors			
Population below the poverty line, %	16.3 (6.4) [3.1-62.0]	−0.24 (0.005)	0.47
Median household income, log $	10.6 (0.2) [9.8-11.6]	6.06 (0.130)	0.41
Graduates, 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.

Table Title:

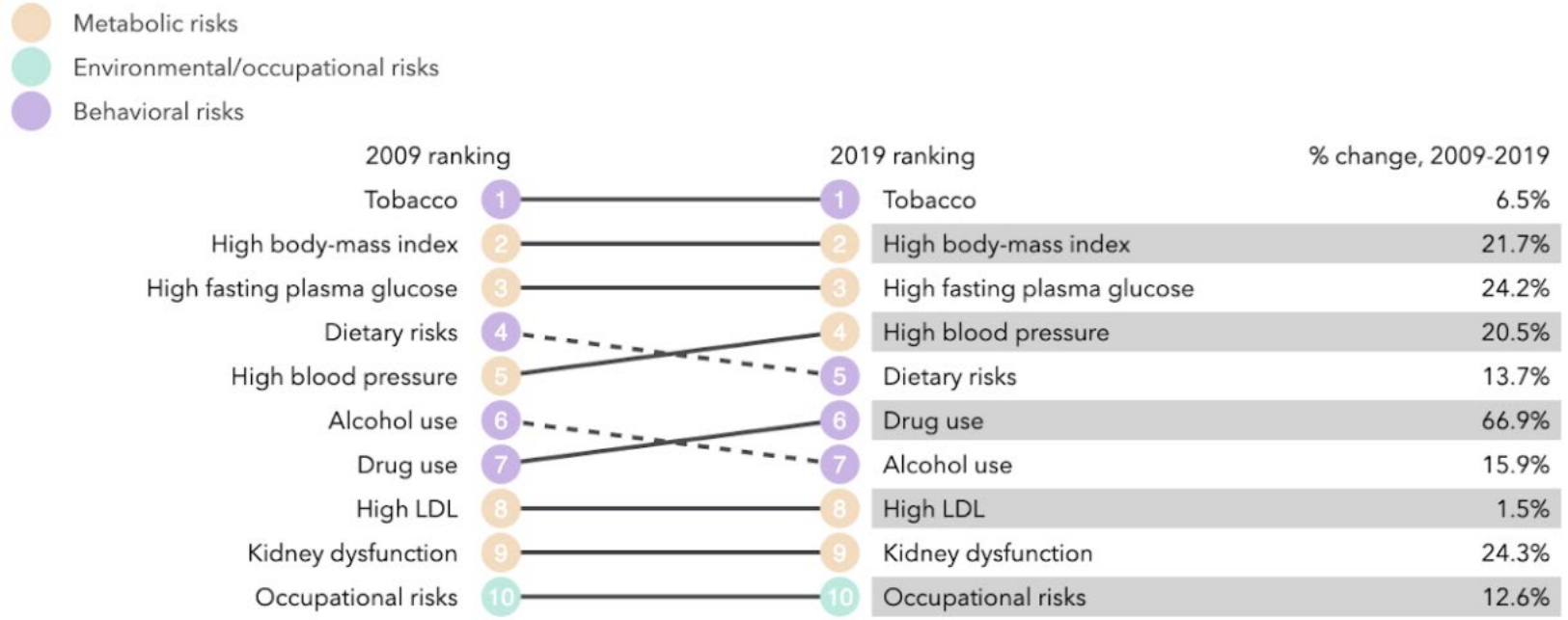
Variables Included in the Regression Analysis With Summary Statistics and Bivariate Regression Results

What causes the most deaths?



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

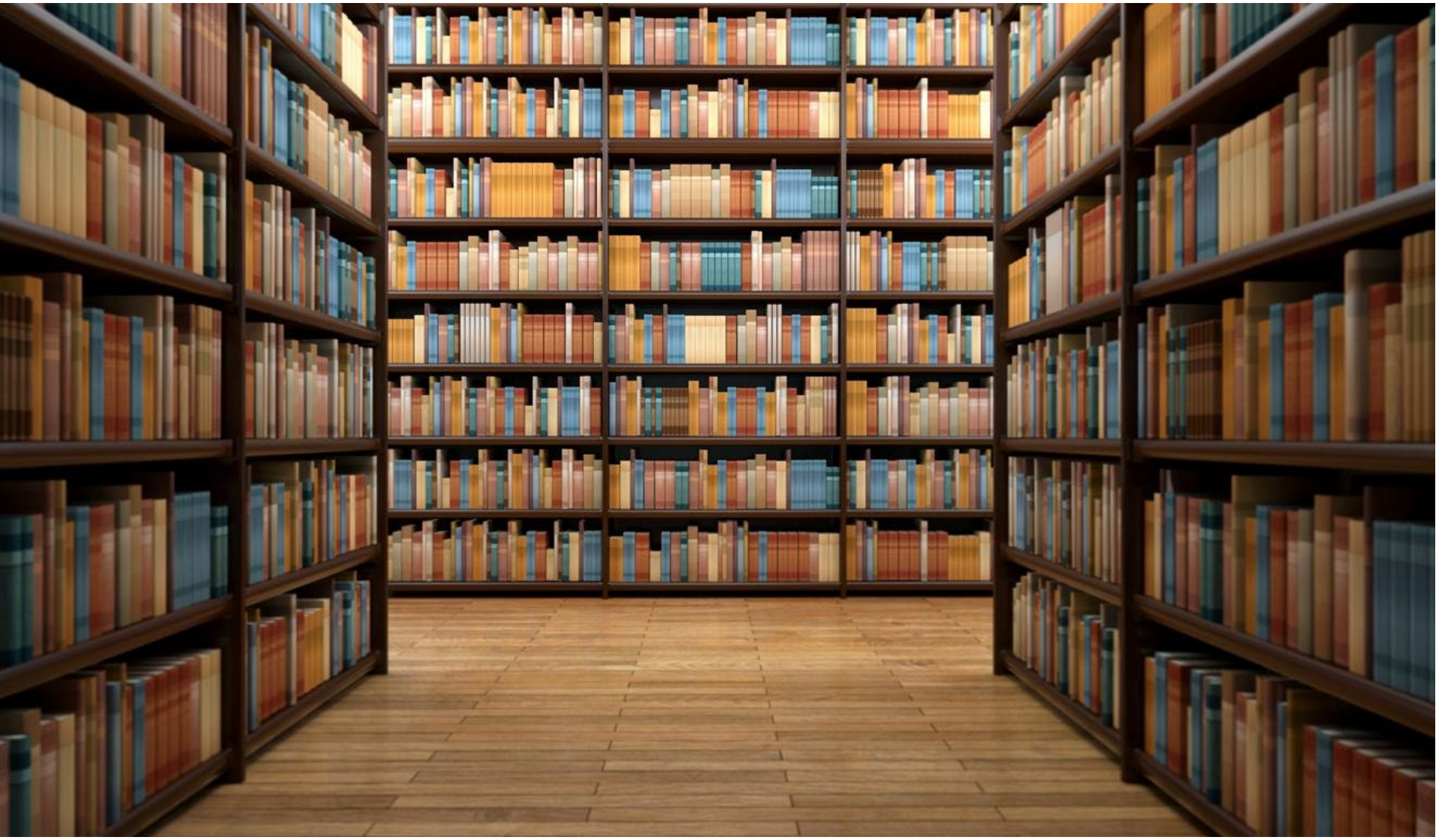
What risk factors drive the most death and disability combined?



Top 10 risks contributing to total number of DALYs in 2019 and percent change 2009–2019, all ages combined

Qualities of the New Data Environment

- **Volume**
  - **New methods of data storage allow access to huge amounts of data**
- **Ubiquity/Liquidity**
  - **Data are available anywhere across geography, social and economic classes**
- **Latency**
  - **There is no delay in access to data inherent in the technology**
- **Analysis**
  - **Data, information, knowledge, wisdom continuum is being shifted to the right**

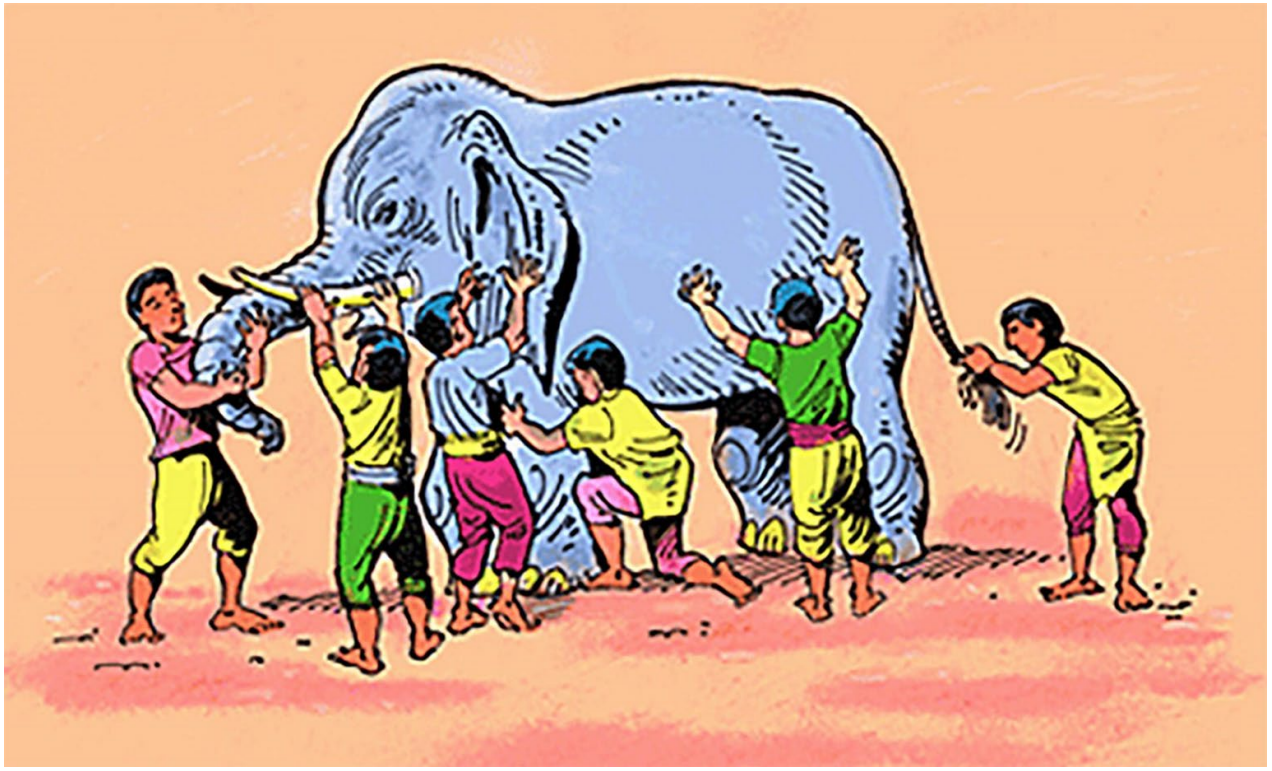


16.3M results

in 0.57 second

You Tube Covid impressions:
500 Billion

The Blind Men and the Elephant




“To learn the truth, we must put all the parts together.”

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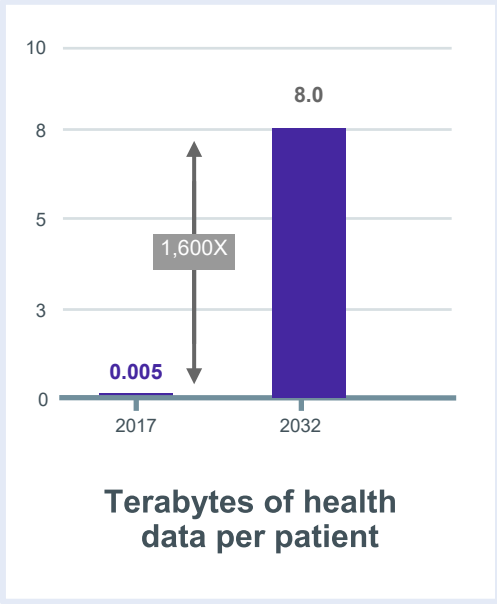
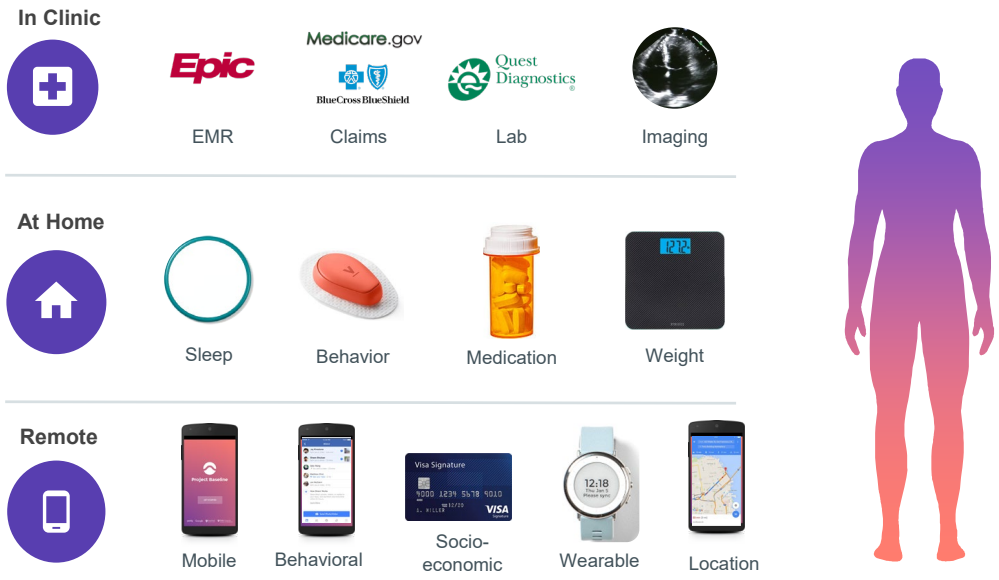
Collecting comprehensive health data

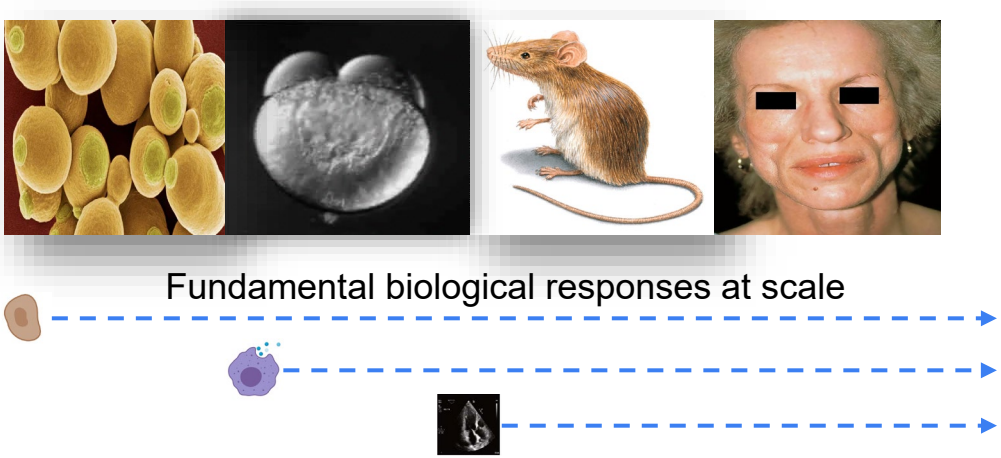
Generate tools and technologies to collect diverse, comprehensive health data in-clinic, at-home, and remotely.

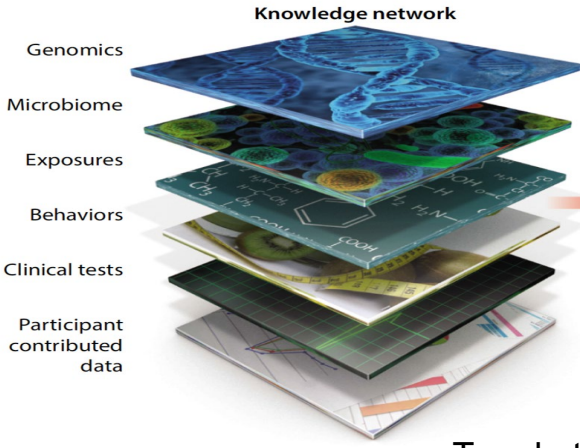


6 TB of collected data on each Project Baseline participant per year



Phenotype stack: novel interconnecting latent phenotypes

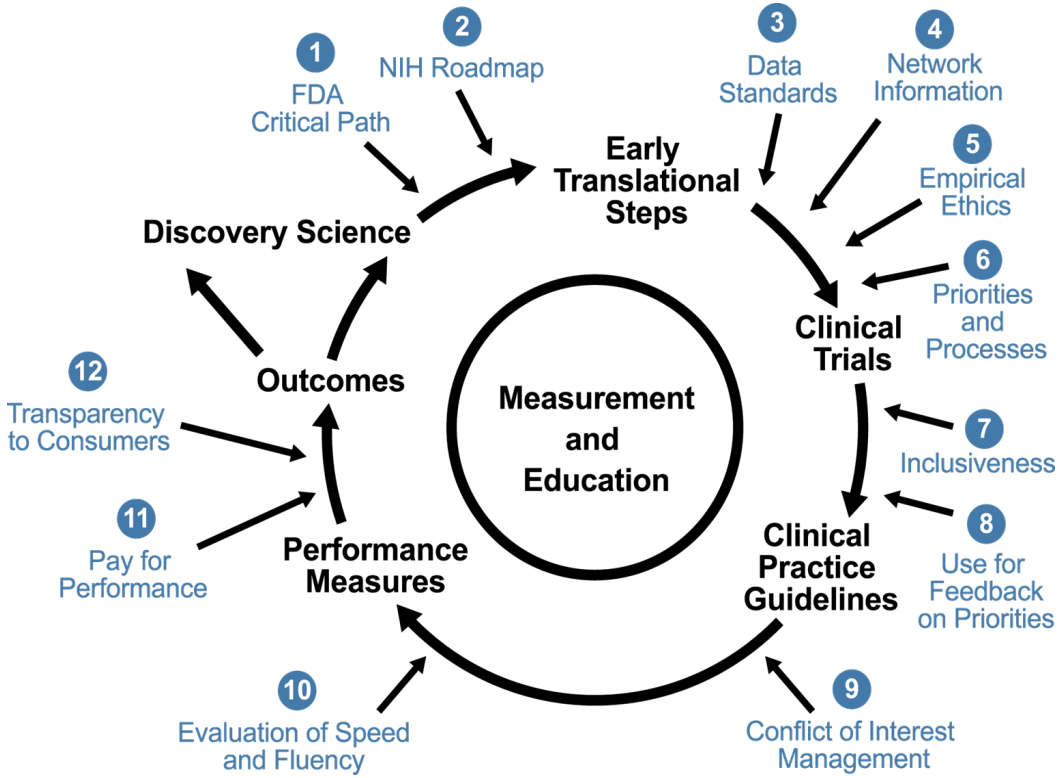




Topol et al.

- Adding new dimensions to biomedical measurement
  - Inexpensive: reproducible, scalable
  - Expressive: can reflect diverse disease processes
  - Derivation and validation: empiric
  - Trainable: can validated
  - Treatment responsive: changes with disease status
  - Interpretable: can be understood mechanistically
- Linked by shared perturbations (metadata): **small molecules, biophysical stimuli**

Generating Evidence to Inform Decisions



FDA Defined Claims for Food Labels

Claim and Definition	FDA Requirements
Health claim: characterizes the relationship of a substance to a disease or health related condition; must base on a "significant scientific agreement" standard	1. Preapproval required through petition 2. Food may not meet or exceed disqualifying nutrient levels of total fat, saturated fat, cholesterol or sodium
Qualified health claims: "credible evidence supporting the claim" of a relationship between a food and reduced risk of a disease or health related condition; evidence does not meet the more rigorous "significant scientific agreement" standard	1. Manufacturer must apply for preapproval 2. FDA issues a Letter of Enforcement Discretion 3. Claims required to use a disclaimer or qualifying language to accurately communicate level of scientific evidence 4. Food may not meet or exceed disqualifying nutrient levels
Nutrient content claims: expressly or implicitly characterize the level of a nutrient of the type required to be disclosed in nutrient labeling	1. Must be made in accordance with Reference Amounts Customarily Consumed or the Recommended Daily Value of a food or nutrient 2. No disqualifying nutrient list applies 3. If food meets disqualifying standards for health claims, label must state "See nutrition information for [subject nutrient] content
Structure/Function Claims: describe the role of nutrient or dietary ingredient intended to affect the normal structure or function of the human body	Do not need preapproval and there are no specific requirements for their use

Pomeranz, JL; Lurie PG; Am J Prev Med 2018

Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease

Authored by the Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease

Edited by Christine M. Micheel and John R. Ball

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Definitions - Biomarker

Biomarker: “a characteristic that is objectively* measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a[n]…intervention.” Example: cholesterol level.

*The committee defines “objectively” to mean “reliably and accurately.”

Biomarkers Definitions Working Group. 2001. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clinical Pharmacology and Therapeutics* 69(3):89–95.

Definitions – Surrogate Endpoint

Surrogate Endpoint: “a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.” Example: blood pressure for trials of several classes of antihypertensive drugs.

Biomarkers Definitions Working Group. 2001. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clinical Pharmacology and Therapeutics* 69(3):89–95.

Definitions – Clinical Endpoint

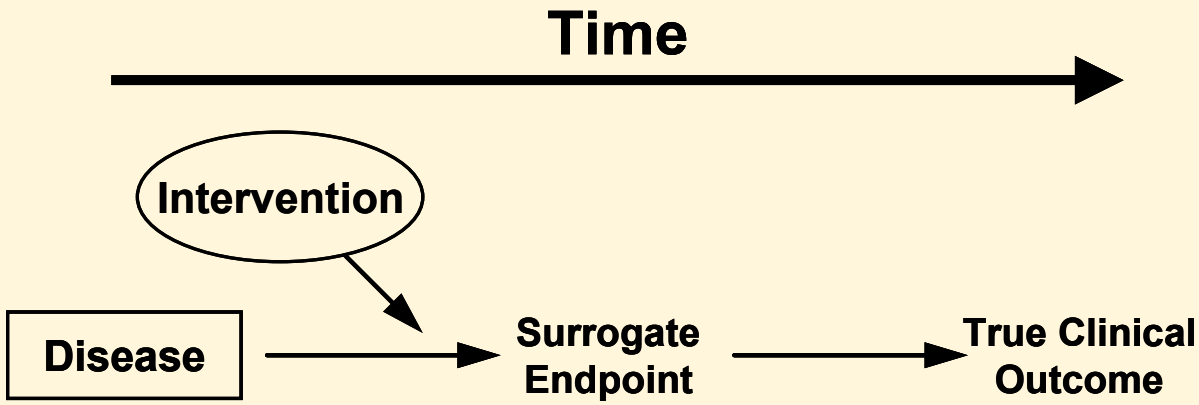
Clinical Endpoint: “a characteristic or variable that reflects how a patient [or consumer] feels, functions, or survives.” Example: death.

Biomarkers Definitions Working Group. 2001. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clinical Pharmacology and Therapeutics* 69(3):89–95.

Product of the Biomarker Working Group charged by the **FDA-NIH Joint Leadership Council** to develop a glossary of harmonized terminology for biomarkers and endpoints

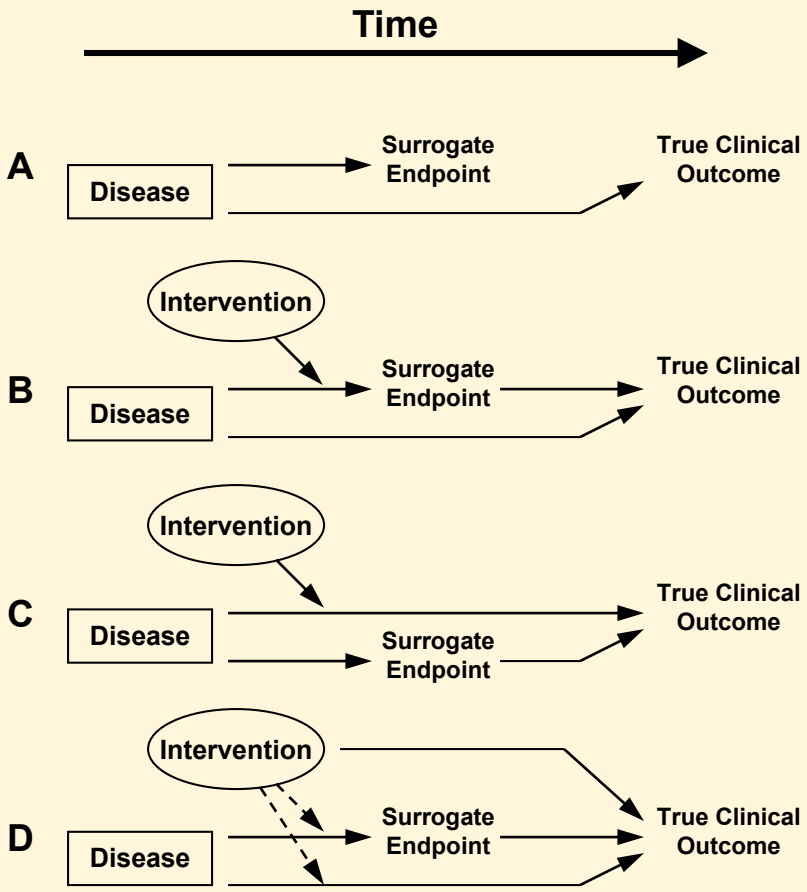
http://www.ncbi.nlm.nih.gov/books/NBK326791/

"Even in the best of circumstances, it is possible for surrogate endpoints to be misleading by either overestimating or underestimating an intervention's effect on clinical outcomes."



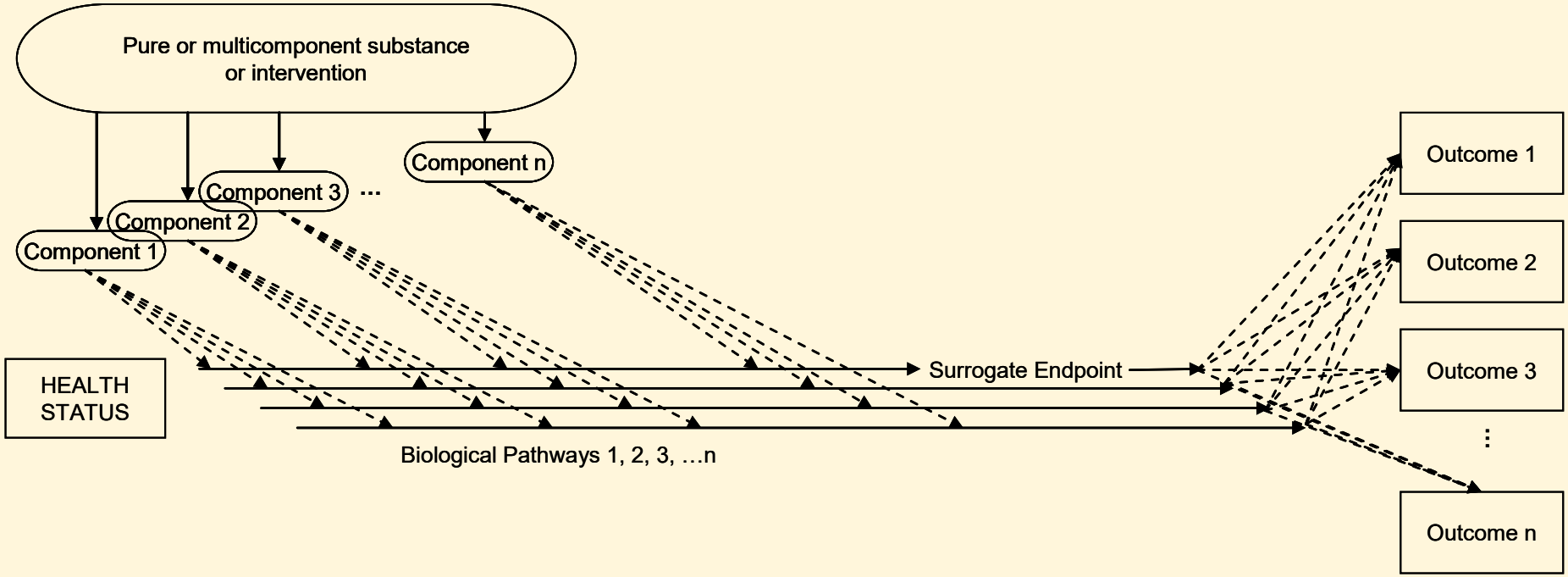
Fleming, T. R., and D. L. DeMets. 1996. Surrogate end points in clinical trials: Are we being misled? *Annals of Internal Medicine* 125(7):605–613.

Failures of Surrogate Endpoints

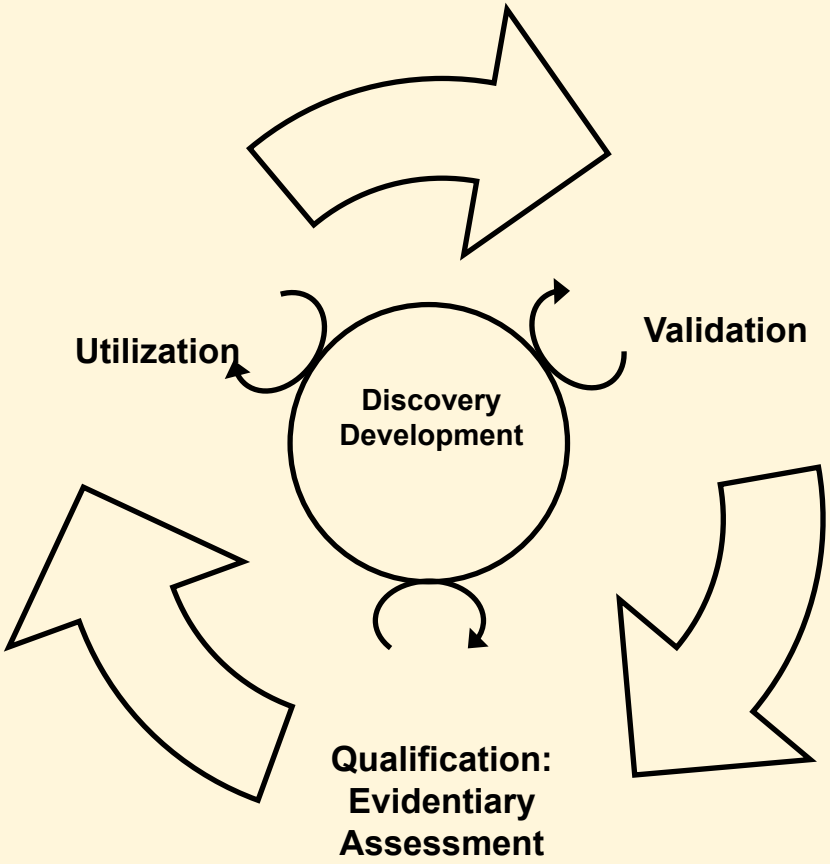


Fleming, T. R., and D. L. DeMets. 1996. Surrogate end points in clinical trials: Are we being misled? *Annals of Internal Medicine* 125(7):605–613.

Biological Complexity Leads to Many Opportunities for Error



Biomarker Evaluation Framework



Recommendation: Biomarker Evaluation Framework

The biomarker evaluation process should consist of the following three steps:

- Analytical validation: analyses of available evidence on the analytical performance of an assay;
- Qualification: assessment of available evidence on associations between the biomarker and disease states, including data showing effects of interventions on both the biomarker and clinical outcomes; and
- Utilization: contextual analysis based on the specific use proposed and the applicability of available evidence to this use. This includes a determination of whether the validation and qualification conducted provide sufficient support for the use proposed.

Biomarker Evaluation Framework: Analytical Validation

TABLE 3-1 Sources of Variability in Biomarker Measurements

Preanalytical Sources of Variability		Analytical Sources of Variability
Biological	Sample Collection	
Sociodemographics (including age and gender)	Mislabeling	Purity of reference standards
Posture	Duration of tourniquet application	Lot-to-lot variation in reagents
Exercise	Strength of collection vacuum	Antibody crossreactivity
Meals/fasting status	Size of needle gauge	Loss during extraction
Diet	Dead volume in catheters/collection tubes	Mislabeling of processing tubes
Diurnal biorhythm	Anticoagulants	Pre-assay incubation time and temperature
Seasonal biorhythm	Local effects of indwelling catheter	Pre-assay amplifications
Concurrent disease	Ambient temperature prior to centrifugation	Chemical interference by endogenous substances
Concurrent medications	Centrifugation speed, duration, temperature	Chemical interference by drugs
Overall health/preexisting disease	Evaporation/biomarker volatility	Analyte or reagent instability in light
Gastrointestinal motility	Preservatives/biomarker stability	Time between intermediate steps
Anesthesia/surgical intervention	Storage temperature	Fluctuations in instrument performance
Stress	Transport temperature	Correction for baseline/background levels
Pregnancy	Completeness of urine collection	Post-run calculation errors
Menstrual cycle	Hemolysis	Matrix effects
Dehydration	Effect of glass and plastic collection tubes	Reproducibility of sample
Kidney function	Exposure to light	
Body composition (obesity)	Type of sample	
	Time of clotting	

Biomarker tests need to be reliable, reproducible across multiple laboratories and clinical settings, and maintain adequate sensitivity and specificity before data based on them can be used in subsequent evaluation steps.

Summary

- FDA's mission is to preserve and protect the public **health**
- **Now is a good time to talk about precision nutrition**
  - By all measures, health of the U.S. public is deteriorating
  - Biology provides the underpinning for understanding how products (food, supplements, drugs, devices, biologics) lead to better or worse health
  - We are in a period of new capability to understand biology and behavior and to transmit information that is **truthful and not misleading**
- Except in cases of of specific nutritional deficiency, individual biomarkers are unlikely to predict the effect of food on health
- **The pipeline of precision nutrition requires multiple levels of quality systems and validation**