Advancing Discovery Science for Public Health Impact

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Director
National Heart, Lung, and Blood Institute

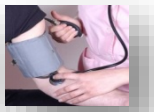
Council of Councils Meeting

May 17, 2019

National Heart, Lung, and Blood Institute

Turning Discovery Science Into Public Health Impact: Knowledge of Risk Factors to Prevent Heart Disease

Risk Factors
High blood pressure
Smoking
High blood cholesterol
Overweight/ Obesity
Physical inactivity
Diabetes
Family history
Age

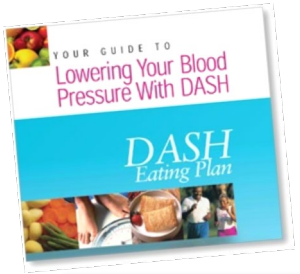


Framingham Risk Factors

Intramural Research Program: Frederickson, Stadtmans

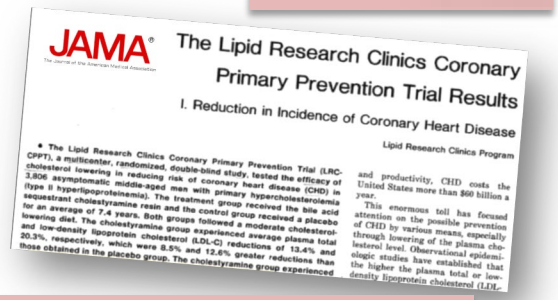
Clinical Research: Tangier's Disease (HDL Cholesterol)

Brown and Goldstein: Nobel Prize (LDL Cholesterol)



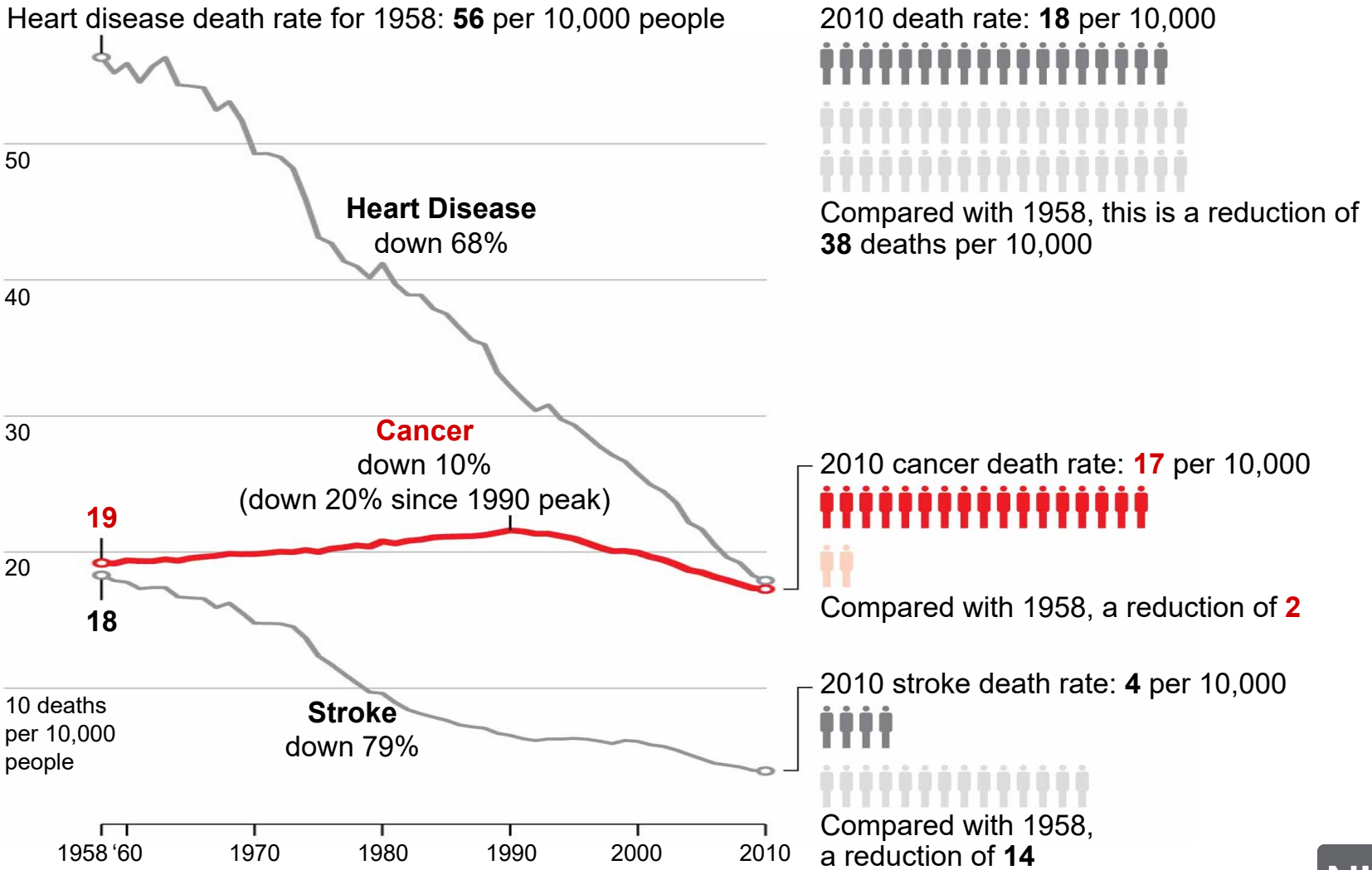
Value of Lifestyle Interventions

Roy Vagelos: Statins



NHLBI Trial: Lowering Cholesterol Cuts CHD Risk

Inheriting a Legacy of Excellence & Stewardship: The Public Health Impact of NHLBI Investments



Adapted from: New York Times, January 4, 2014
Data: Centers for Disease Control and Prevention; National Vital Statistics System

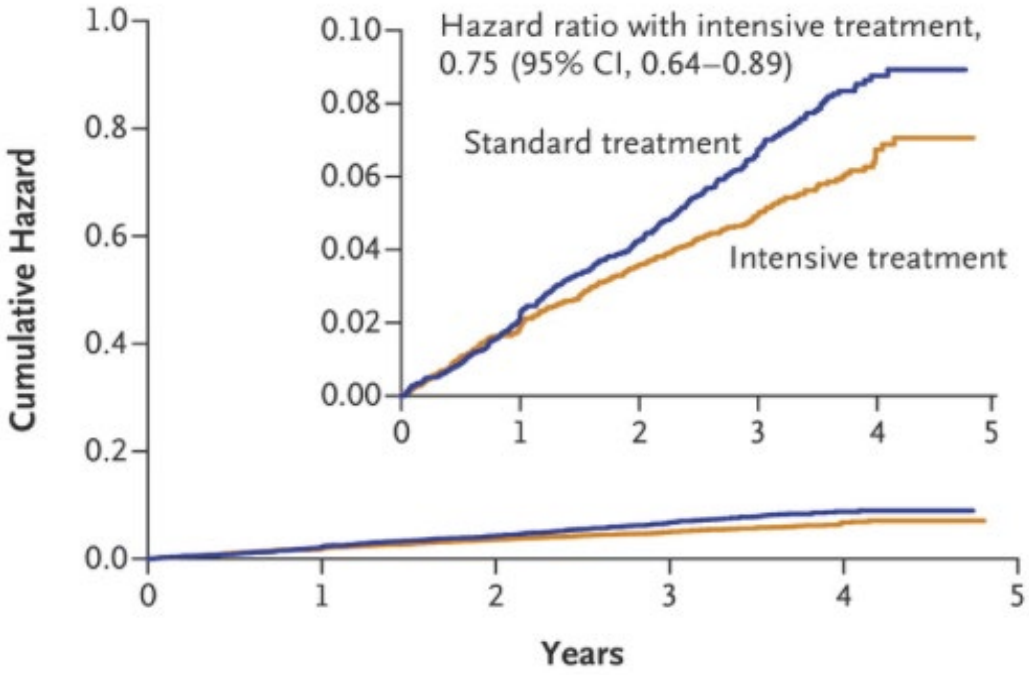
NIH National Heart, Lung, and Blood Institute

Guided from Observation to Intervention: Extending the Legacy in Hypertension to Management and Control

SPRINT

A Randomized Trial of Intensive vs. Standard BP Control

SPRINT-MIND
Memory and Cognition in Decreased Hypertension



After 3 yrs of intervention and 5 yrs follow-up, **intensive treatment reduced**:

- Incidence of mild cognitive impairment (MCI)
- Combined incidence of MCI or probable dementia
- Progression of cerebral white matter lesions

Intensive management of SBP to **target <120 mmHg** reduced complications of high BP by **25%** and death by **27%** as compared to SBP target <140 mm Hg.

NIH National Institute of Diabetes and Digestive and Kidney Diseases

NIH National Institute on Aging

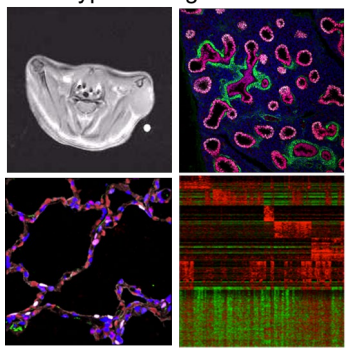
NIH National Institute of Neurological Disorders and Stroke

NIH National Heart, Lung, and Blood Institute

N Engl J Med 2015; 373:2103-2116; JAMA 2019;321:553-561; Blood Pressure 2018; 27:247-248.

Building Upon a Legacy of Excellence: Improving Lung Outcomes with Discovery Science

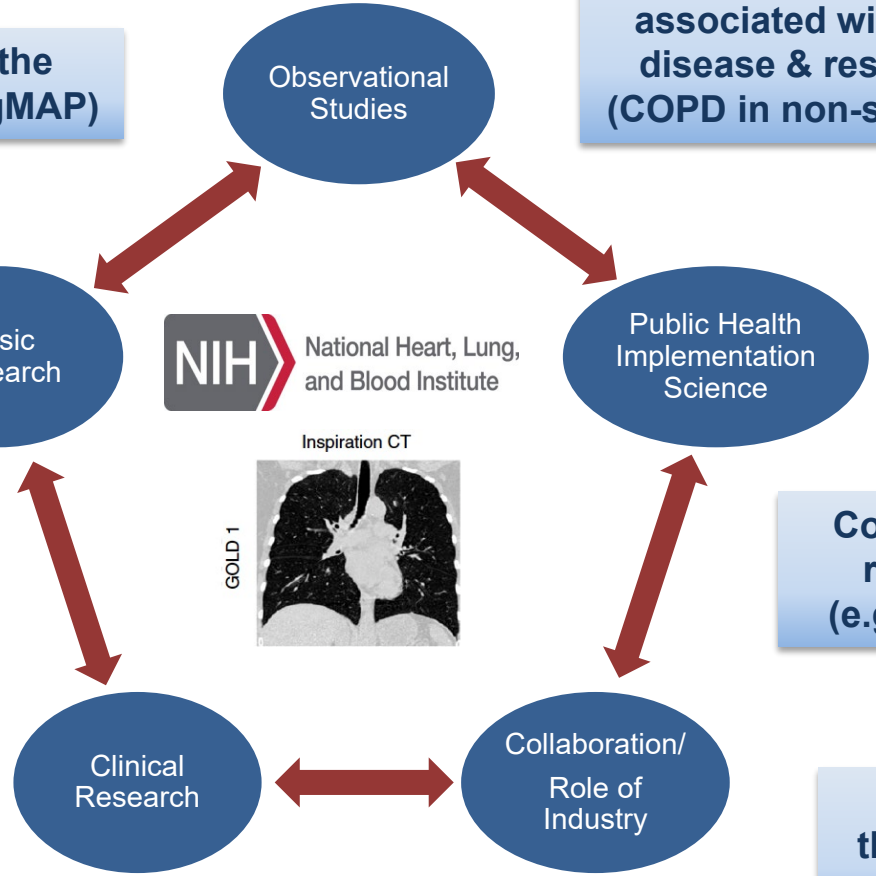
From Organ/Tissue to Cell Type to Single Cell



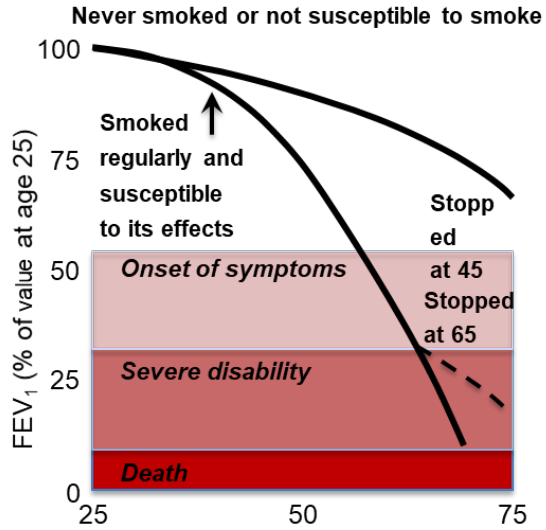
Building a lung atlas at the single cell level (e.g., LungMAP)

Identifying phenotypes, biomarkers (i.e. deep learning of COPDGene CT images to subphenotype disease)

Conducting adaptive trials and precision interventions for asthma (e.g., PreclSE)



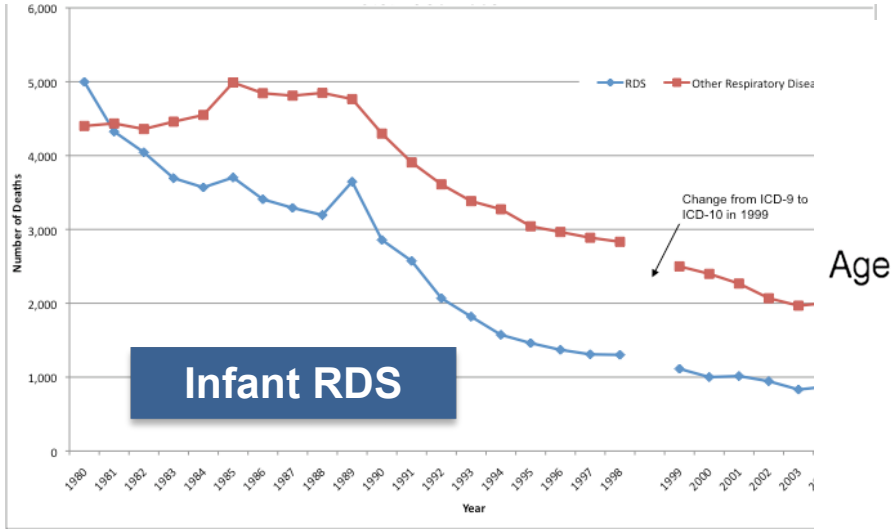
Identify risk factors associated with lung disease & resilience (COPD in non-smokers)

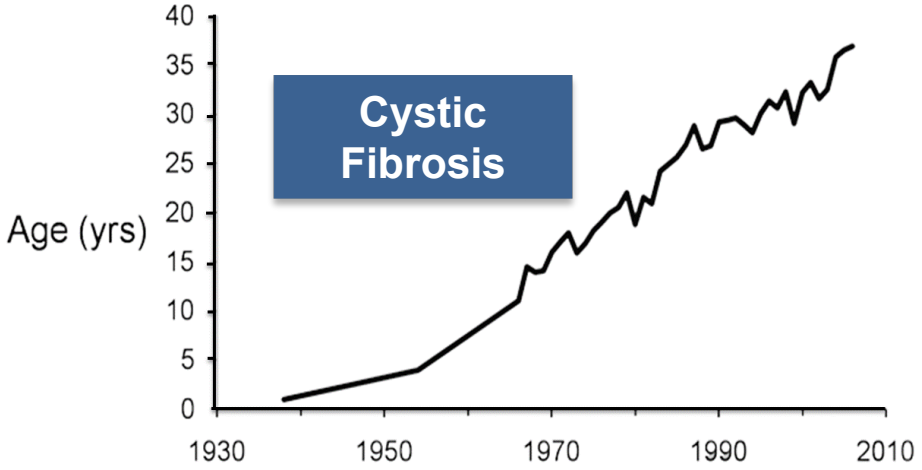


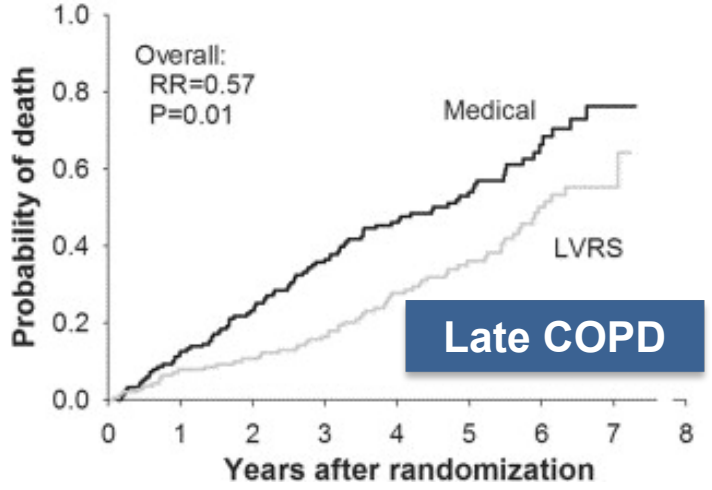
Conducting systematic evidence reviews and health education (e.g., COPD National Action Plan)

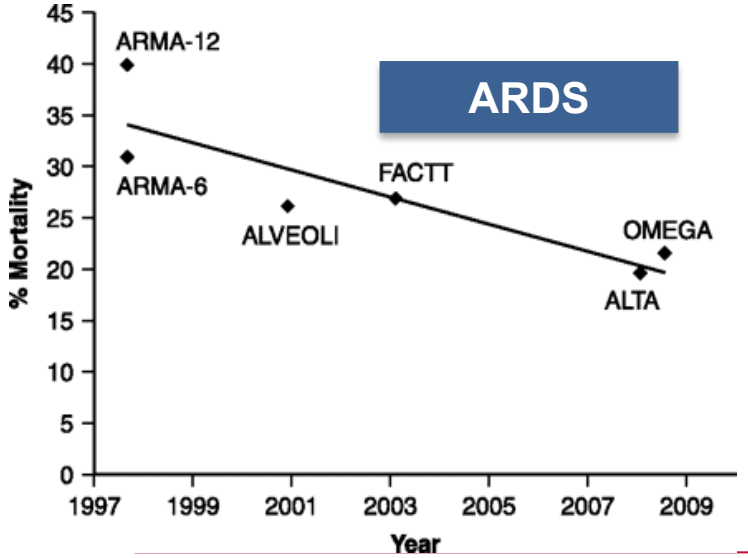
Developing novel therapeutics targeted to risk profiles or sub-phenotypes

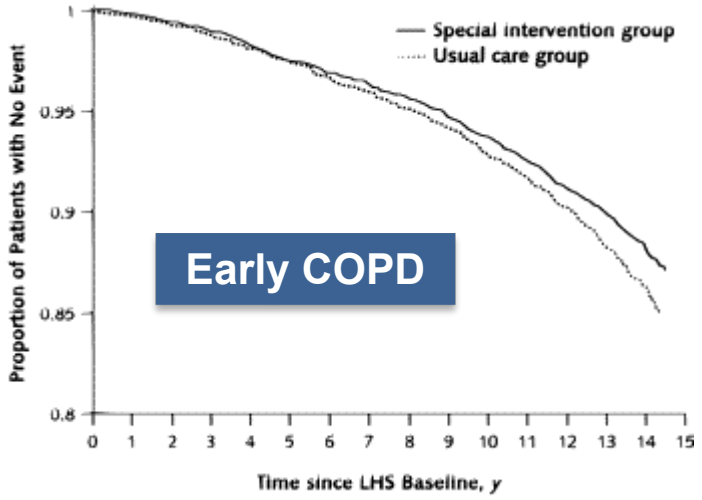
Turning the Curve in Pulmonary Disease
Innovating for Challenges Ahead

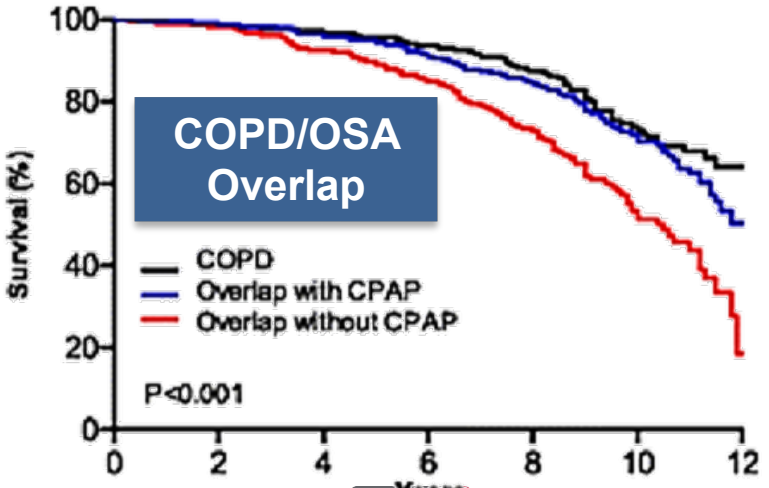












Navigating the Present and Charting Our Future…

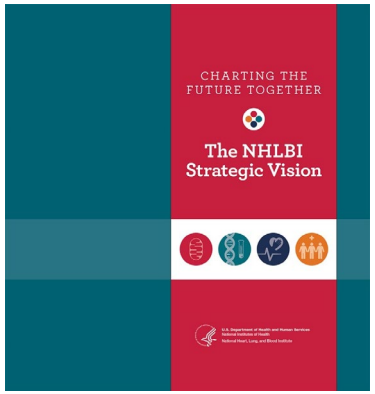
- **Accountable Stewardship**
  - Enduring Principles
  - Fiscal Update
    - Investing in Investigator-Initiated Science
    - Investing in People Not Projects
  - Strategic Vision: Addressing Research Priorities
- **Advancing Discovery for Public Health Impact**
  - Curing Sickle Cell Disease
  - Legacy of Excellence in Cardiovascular Research
  - Social and Behavioral Determinants of Heart Disease
- **Seizing Unprecedented Opportunities**
  - Precision Medicine and Prevention
  - Data Science

NHLBI Mission - *Discovery Science That Enhances Human Health:* Accountable Stewardship and the Privilege of Public Service

NHLBI Enduring Principles

- Value investigator-initiated fundamental discovery science.
- Maintain a balanced, cross-disciplinary portfolio (basic, translational, clinical, population science).
- Train a diverse new generation of leaders in science.
- Support implementation science that empowers patients and enables partners to improve the health of the nation.
- Innovate an evidence-based elimination of health inequities in the U.S. and around the world.

Aligning Institute-Solicited Science with the Strategic Vision Goals & Objectives

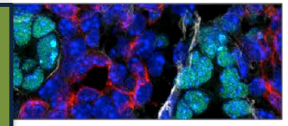
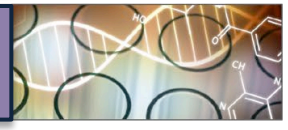
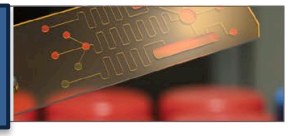


Understand **Human Biology**

Advance **Translational Research**

Reduce **Human Disease**

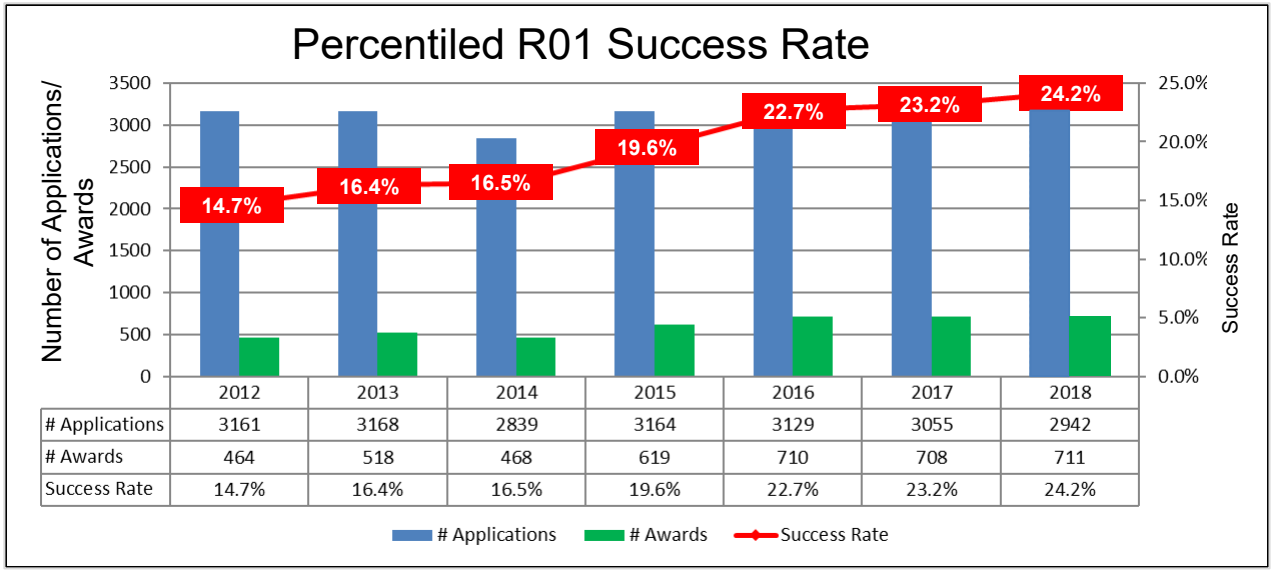
Develop **Workforce and Resources**

Objective 1: Normal Biology	
Objective 2: Pathobiology, Onset, & Progression of HLBS diseases	
Objective 3: Population Differences	
Objective 4: Precision Medicine	
Objective 5: Novel Diagnostics & Therapeutics	
Objective 6: Clinical & Implementation Research	
Objective 7: Data Science	
Objective 8: Workforce & Resources	

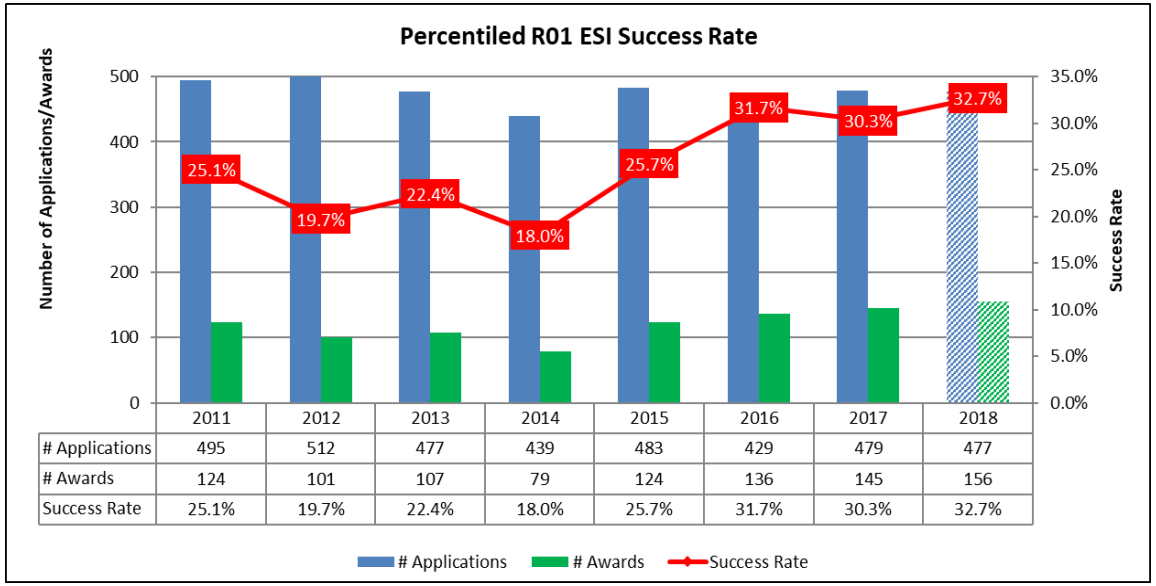
Prioritized Investments in Investigator-Initiated Science: Bending the Curve

Grant Program	FY17 Paylines	FY17 # Awards (Success Rate)	FY18 Paylines	FY18 # Awards (Success Rate)	FY19 Paylines
R01	15%ile	708 (23.3%)	15%ile	711 (24.2%)	16%ile
ESI	25%ile	145 (30.3%)	25%ile	156 (32.7%)	26%ile

FY2018 budget increase enabled NHLBI to make **more awards for investigator-initiated science.**



	2012	2013	2014	2015	2016	2017	2018
# Applications	3161	3168	2839	3164	3129	3055	2942
# Awards	464	518	468	619	710	708	711
Success Rate	14.7%	16.4%	16.5%	19.6%	22.7%	23.2%	24.2%



	2011	2012	2013	2014	2015	2016	2017	2018
# Applications	495	512	477	439	483	429	479	477
# Awards	124	101	107	79	124	136	145	156
Success Rate	25.1%	19.7%	22.4%	18.0%	25.7%	31.7%	30.3%	32.7%

Fulfilling the Mission: Goal for ESI R01 Success Rates Greater or Equal to General Pool

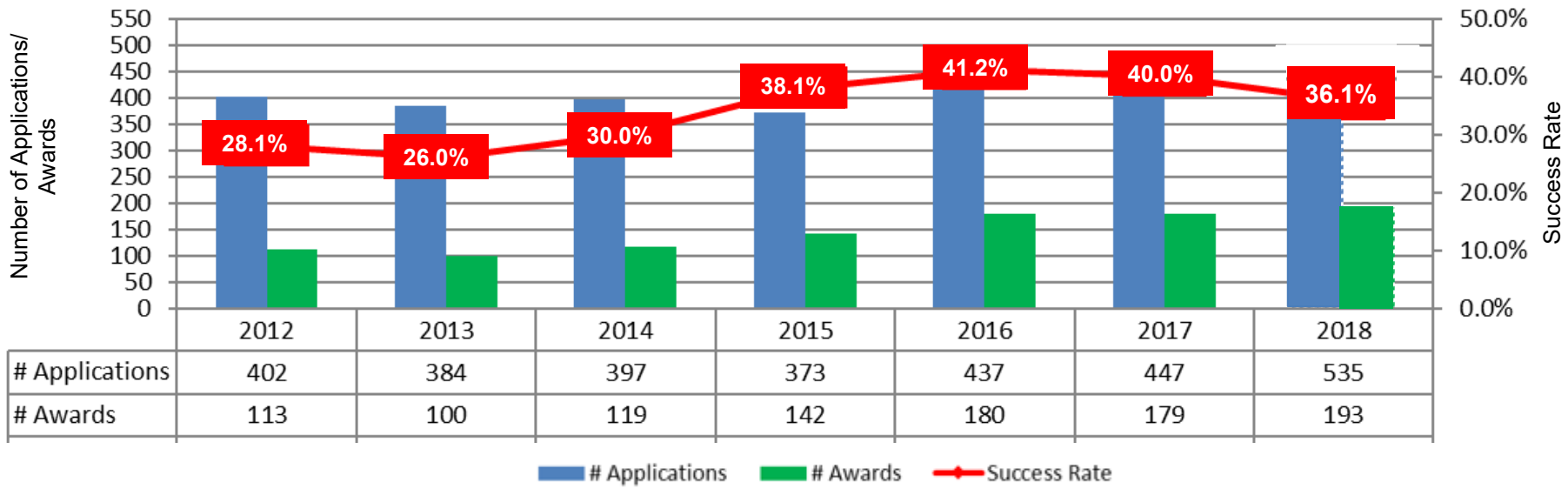
Nurturing a Diverse Next Generation of Leaders: Multi-level Strategies to Expand Opportunities

Current Activities

Diversity

- BUILD/Mentoring Networks
- R25/PRIDE
- Diversity K Awards
- Diversity Supplements

Career Awards Historical Success Rate (excl K-22)



	2012	2013	2014	2015	2016	2017	2018
# Applications	402	384	397	373	437	447	535
# Awards	113	100	119	142	180	179	193

Career Development

- ESI Bridge (R56) Awards
- Loan Repayment Program
- Mentored Clinician-Scientist (K08)
- K Awards: FY18 Success 36%
- ESI R01s: FY18 Success 33%

Focused Initiatives

- K-R03 awards
- R35 for Emerging Investigators
- R01 Physician-Scientist Award for ESIs
- Stimulating Access to Research in Residency (StARR) (R38) & StARR Transition Scholar (StARRTS) (K38)
- Career Pathway to Independence in Blood Science Award for Physician Scientists (K99/R00)

Investing in People and Not Projects: NHLBI's Approach to the R35 Program

NHLBI R35 Program

NIH National Heart, Lung, and Blood Institute

88 R35s awarded in FY17- FY19

Outstanding and Emerging Investigator Awards

To promote scientific productivity and innovation by providing stable and flexible funding

7 years of support at $600,000/per year

NIH National Institute of Neurological Disorders and Stroke

NIH NATIONAL CANCER INSTITUTE

NIH National Institute of General Medical Sciences

NHLBI Supports Trans-NIH and Trans-HHS Priorities

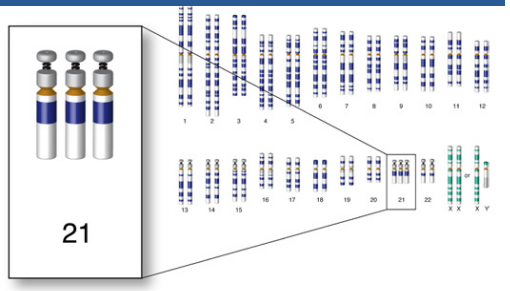
NHLBI-supported Research

HEAL Initiative: Sleep and Circadian-Dependent Mechanisms Contributing to Opiate Use Disorder (OUD) and Response to Medication Assisted Treatment (MAT)

RFA-HL-19-028 (R01- Clinical Trial Not Allowed)
RFA-HL-19-029 (U01 – Clinical Trial Optional)

THE INCLUDE PROJECT

Multiple systems involved in DS require a trans-NIH approach



NHLBI-supported DS Research

Mechanisms for Cell Signaling in the Control of Cardiomyogenesis

Genomic Analysis of Congenital Heart Defects and Acute Lymphoblastic Leukemia in Children with Down Syndrome

Data Fusion: A Sustainable, Scalable, Open Source Registry Advancing PVD Research

For full list of HEAL Funding Opportunities,
visit https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative

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Moving from Vision to Implementation: Highlights of NHLBI Strategic Priorities

Building on the Strategic Input from the Council of Councils

HMP

NIH The Common Fund

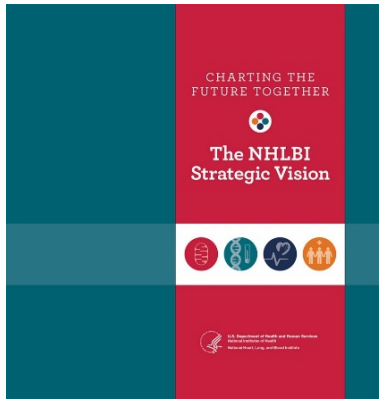
Gabriella Miller Kids First Pediatric Research Program

CGE Somatic Cell Genome Editing

GTEx

HuBMAP

ECHO Environmental influences on Child Health Outcomes
A program supported by the NIH



- Objective 1: Normal Biology
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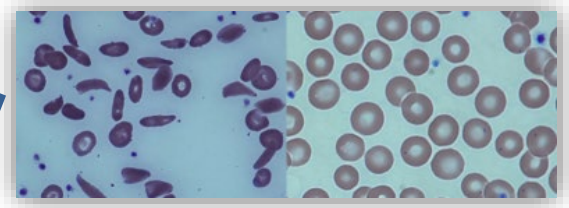
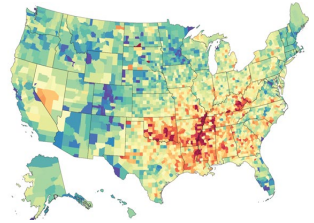


Novel Therapeutics: Sickle Cell Disease



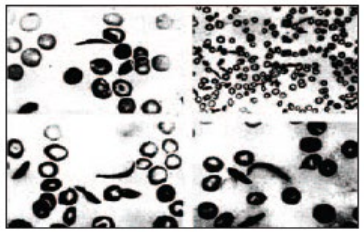
Cardiovascular Disparities

Leveraging Data Science: Omics & Imaging

NIH National Heart, Lung, and Blood Institute

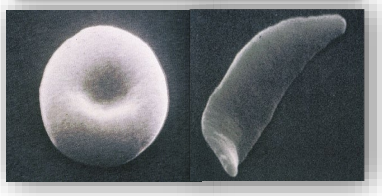
Building Upon a Legacy of Excellence: Improving Sickle Cell Disease Outcomes with Discovery Science

"Sickle Cell Anemia" Term Coined



Sickled cells from 1910 Herrick paper

Hemoglobin Cause for SCD Defined



Linus Pauling

Transfusion Therapy and Silent Infarct

Hydroxyurea improves HbF production

TWiTCH

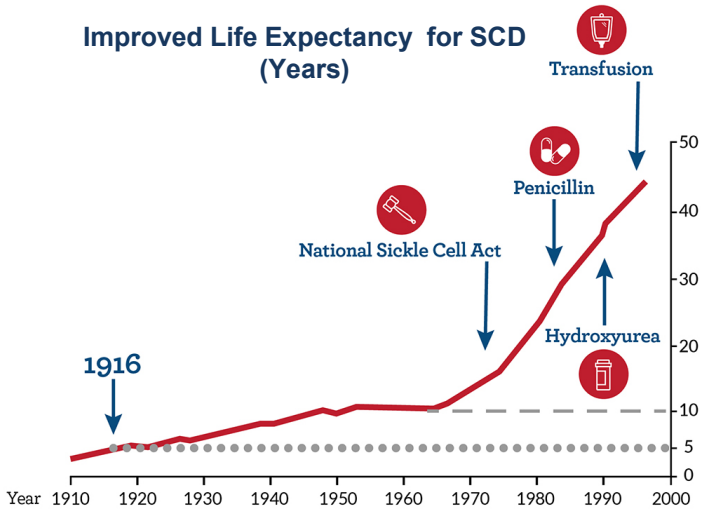
SIT

Excellence in Hemoglobinopathies

SC Trait Protects Against Malaria & HbF with more favorable course

SCDIC
Sickle Cell Disease Implementation Consortium

Improved Life Expectancy for SCD (Years)



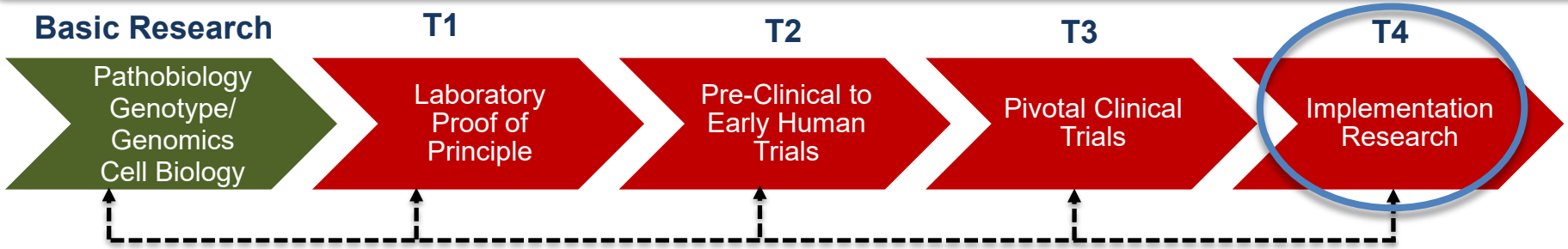
Gene Therapy for SCD

NIH National Heart, Lung, and Blood Institute

Ribeil, JA et al., *NEJM* 2017; Pauling, L., et al., *Science* 1949; Brawley OW, et al., *Ann Intern Med* 2008; Ware, RE et al., *Lancet* 2016; Aidoo, M et al., *Lancet* 2002.

Comprehensive SCD Implementation Science Strategy to Improve Health Outcomes in the US and Globally

Opportunity for **Implementation Science** strategies to improve treatment initiation and adherence

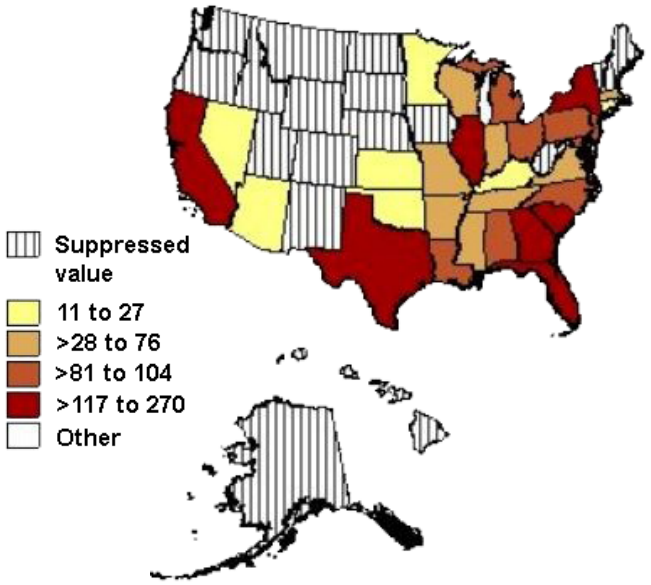


NHLBI Sub-Saharan Africa Initiative

SPARCo Sickle African Research Consortium

SADaCC Sickle Africa Data Coordinating Centre

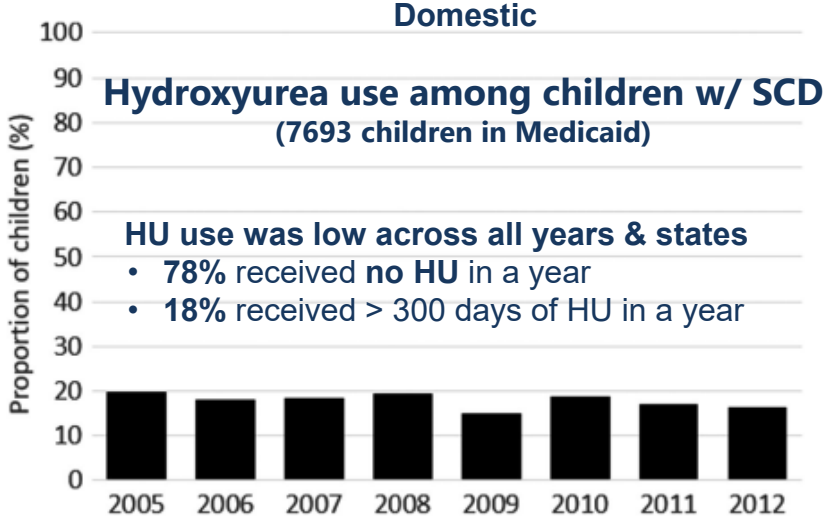
Sickle Cell Disease Deaths, U.S. (2013-2017)



SCDIC Sickle Cell Disease Implementation Consortium

Domestic

Hydroxyurea use among children w/ SCD
(7693 children in Medicaid)



HU use was low across all years & states

- **78%** received **no HU** in a year
- **18%** received > 300 days of HU in a year

SPAN Sickle Pan African Network

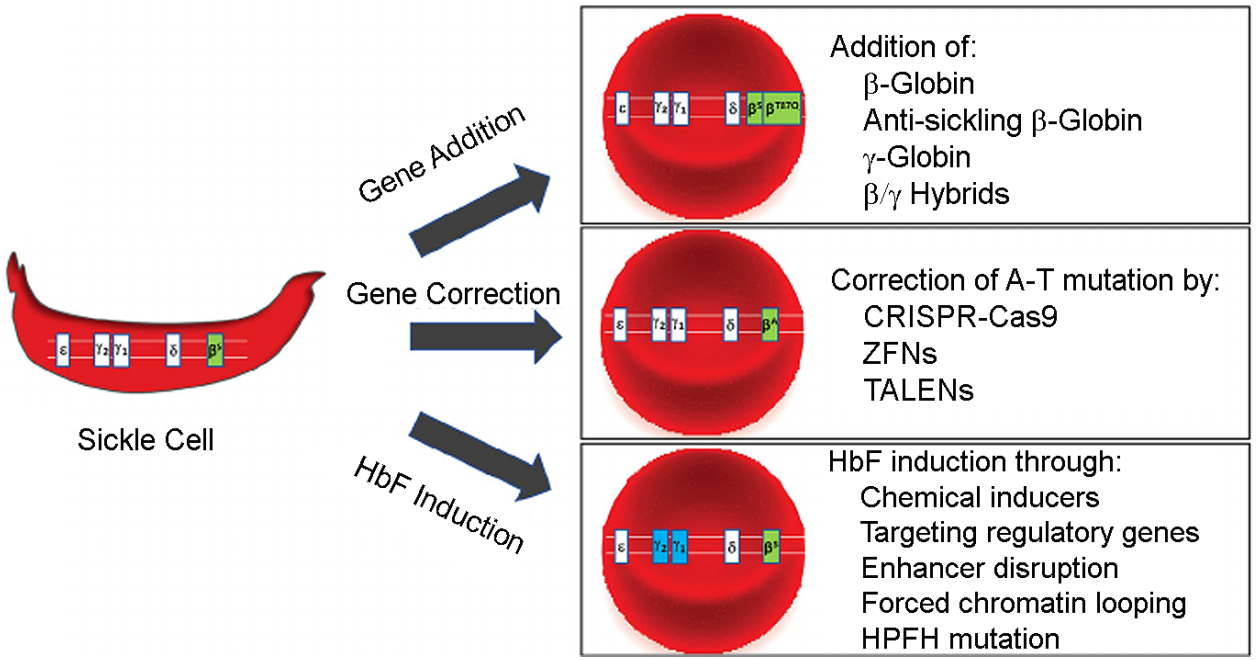
SICKLE CELL DISEASE ONTOLOGY SCDO

NIH National Heart, Lung, and Blood Institute

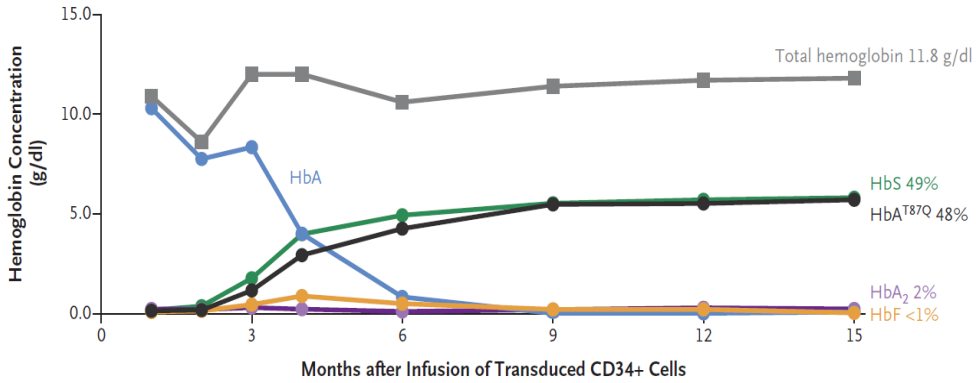
Reeves SL, et al. *Pediatric Blood & Cancer.* 2019

Is the Time Ripe for a Cure of the First 'Molecular' Disorder? New Technologies Toward Curative Strategies

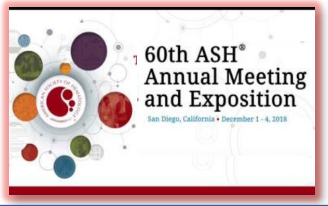
Gene therapy options to address SCD



LentiGlobin BB305 vector encodes human *HBB* variant and inhibits HbS polymerization.



- Patient attained normal blood cell counts.
- Engrafted stem cells were capable of long-term repopulation.



bluebirdbio™

➢ Total of 18 patients:
- **Stable Hemoglobin** production
- **Decreased** vaso-occlusive events

Demirci S, *Cytotherapy* 2018; 2019 ASH Annual Meeting, posters 1026 (Tisdale J et al.) and 1080 Kanter J et al.; Ribeil JA, et al. *NEJM.* 2017; BlueBirdBio press release, *Business Wire*, December 3, 2018

NIH National Heart, Lung, and Blood Institute

Leveraging Collaborative Partnerships on the Path to SCD Cures

Identify and support the most promising genetic therapies for scalable cures.

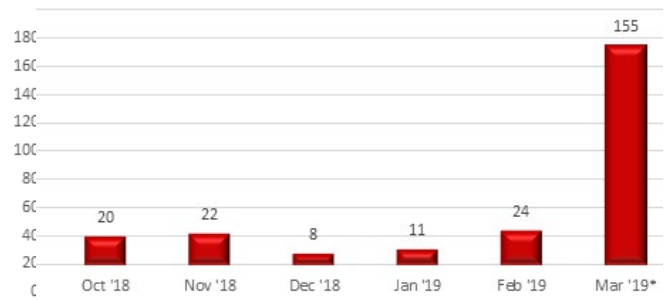
Areas of Focus

- Patient Engagement
- Therapeutics Development
- Date Repository
- Clinical & Econ Impact Analysis
- Clinical Platforms & Networks

Highlights from "60 Minutes"

Could Gene Therapy Cure Sickle Cell Anemia?

March 2019



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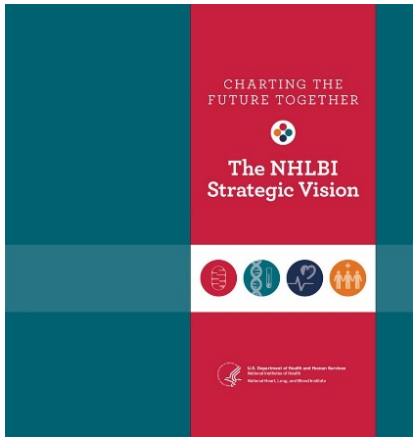
Moving from Vision to Implementation: Highlights of NHLBI Strategic Priorities



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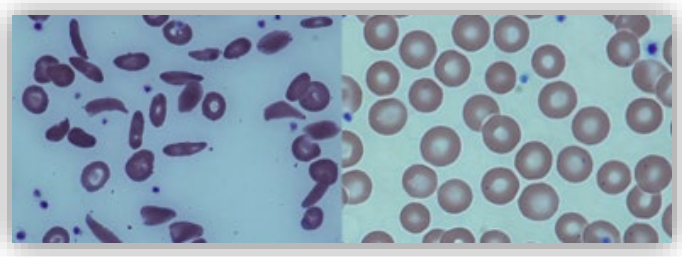
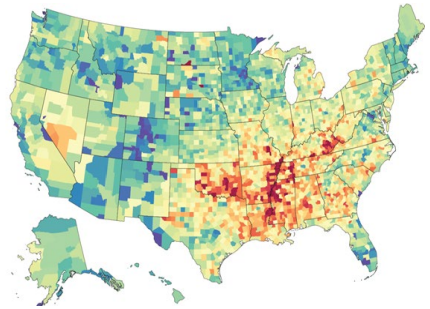


Novel Therapeutics: Sickle Cell Disease

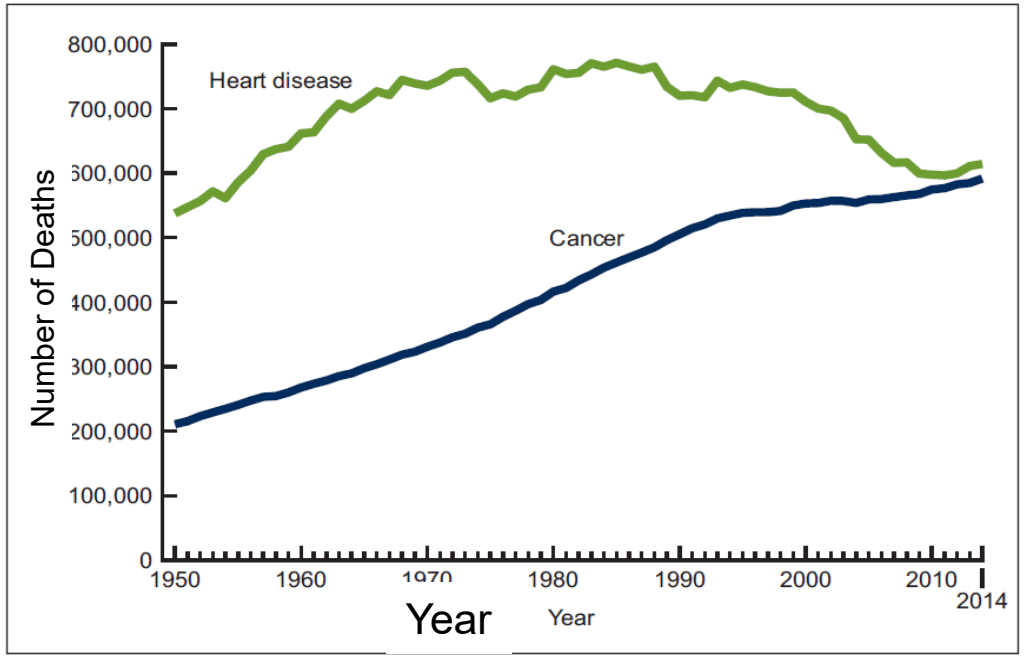


Cardiovascular Disparities

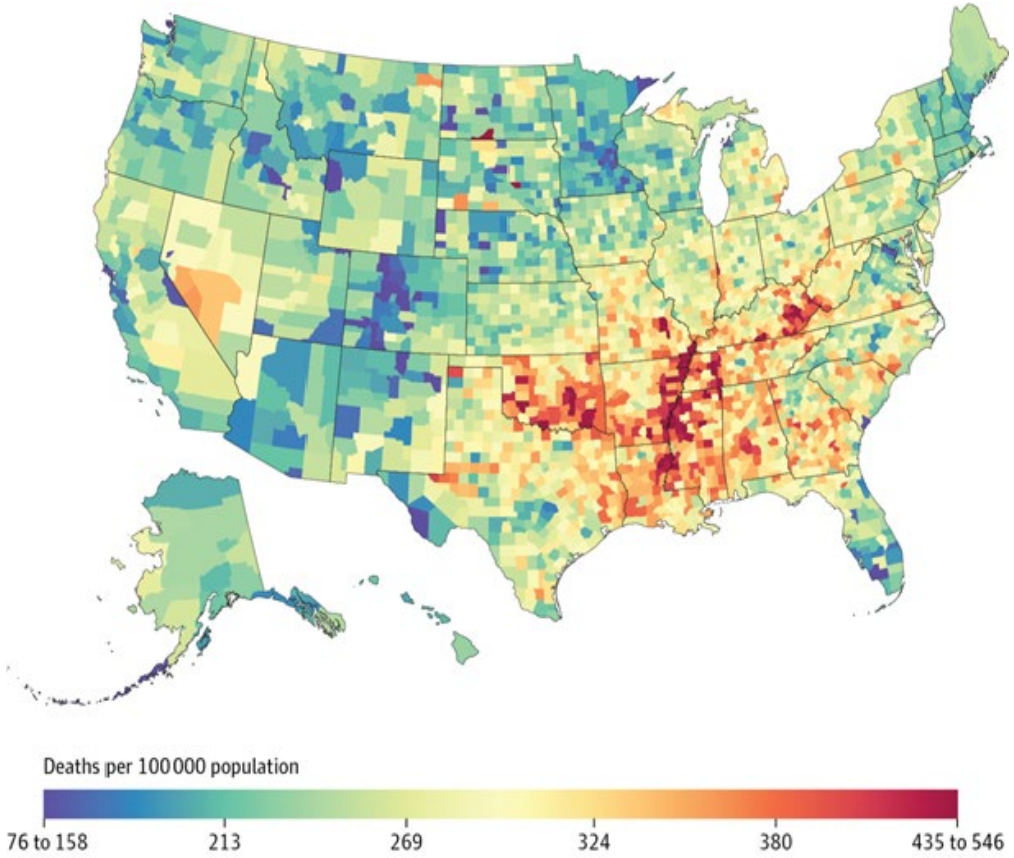
Leveraging Data Science: Omics & Imaging

Heart Disease Mortality: An Evolving Story
CVD Mortality Reveals Place Matters in Health Inequities

Overall, heart disease death rates down over 70% since 1950. However, progress has slowed.



U.S. County-Level Mortality From CVD (both sexes, 2014)

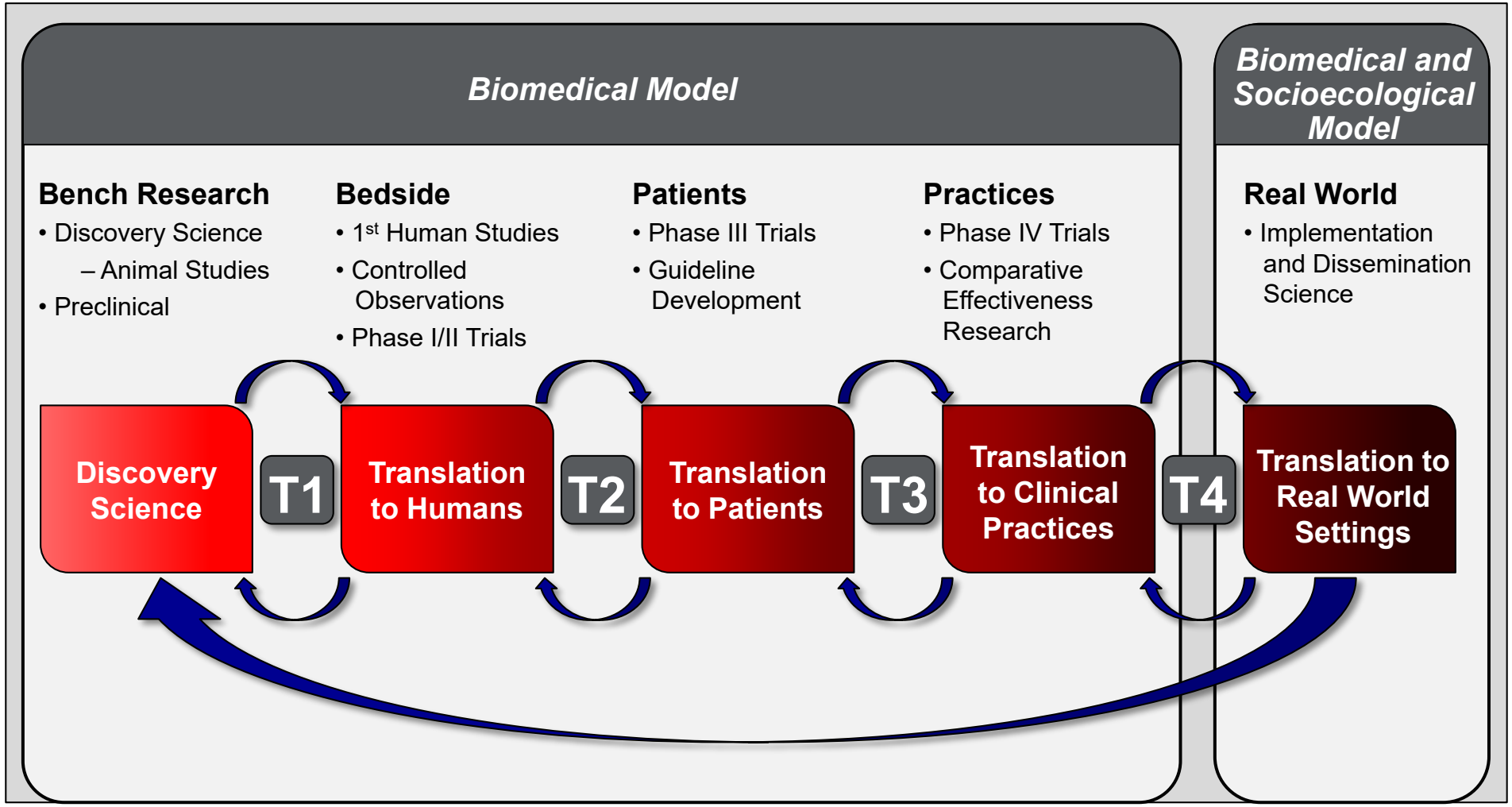


NCHS Data Brief No. 254. August 2016

Roth, et al. JAMA, May 16, 2017

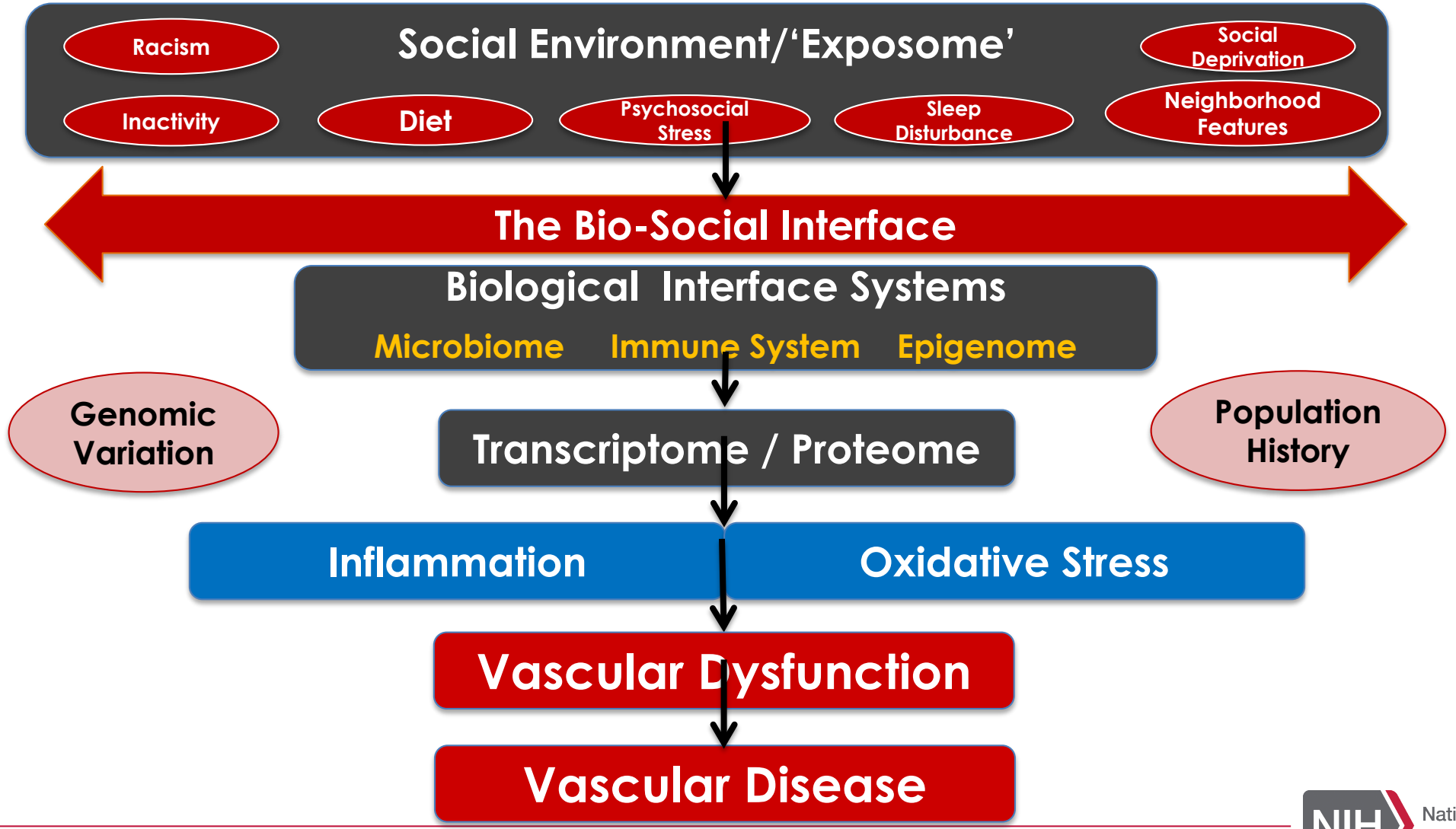
NIH National Heart, Lung, and Blood Institute

Translating Discovery Science into Public Health Impact: From 'Nucleotides-to-Neighborhoods'



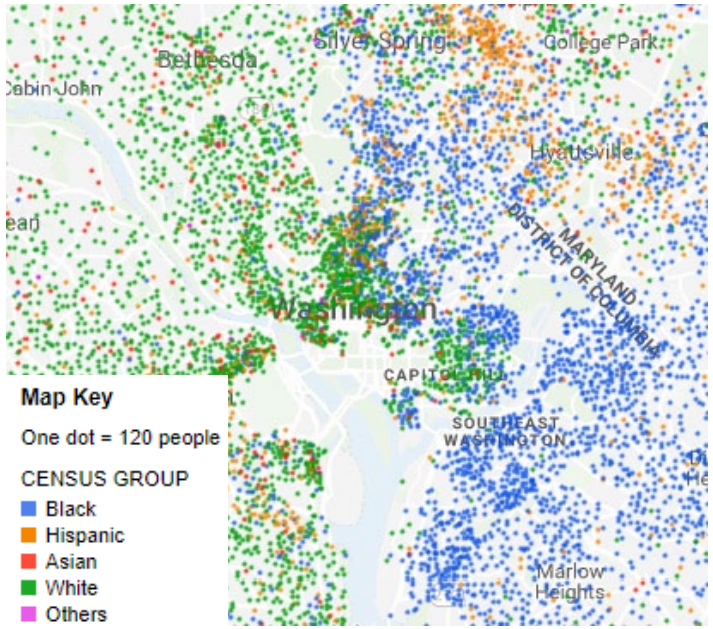
Modified/adapted from M Khoury et al Genet Med 2007 and Harvard Catalyst CTSA

Health Disparities: A Complex Multi-Level Challenge

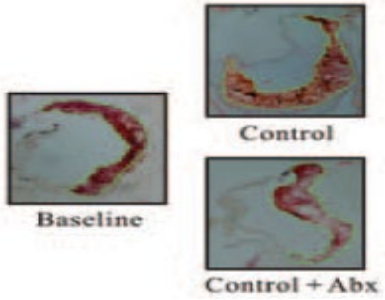


What does it mean locally? Social Determinants of Heart Disease: Interplay of Social and Biological Systems

Washington, DC Segregation



Anthocyanin and miRNA-10b



- Racial Segregation
- Socioeconomic Status
- Food Desert
  Unhealthy Diet
- Biosocial Interface
- Microbiome
- Immune System Activation
- Vascular Disease

New York Times: Mapping Segregation; 7/8/15

Wang D et al Circ Res. 2012 Sep 28;111(8):967-81

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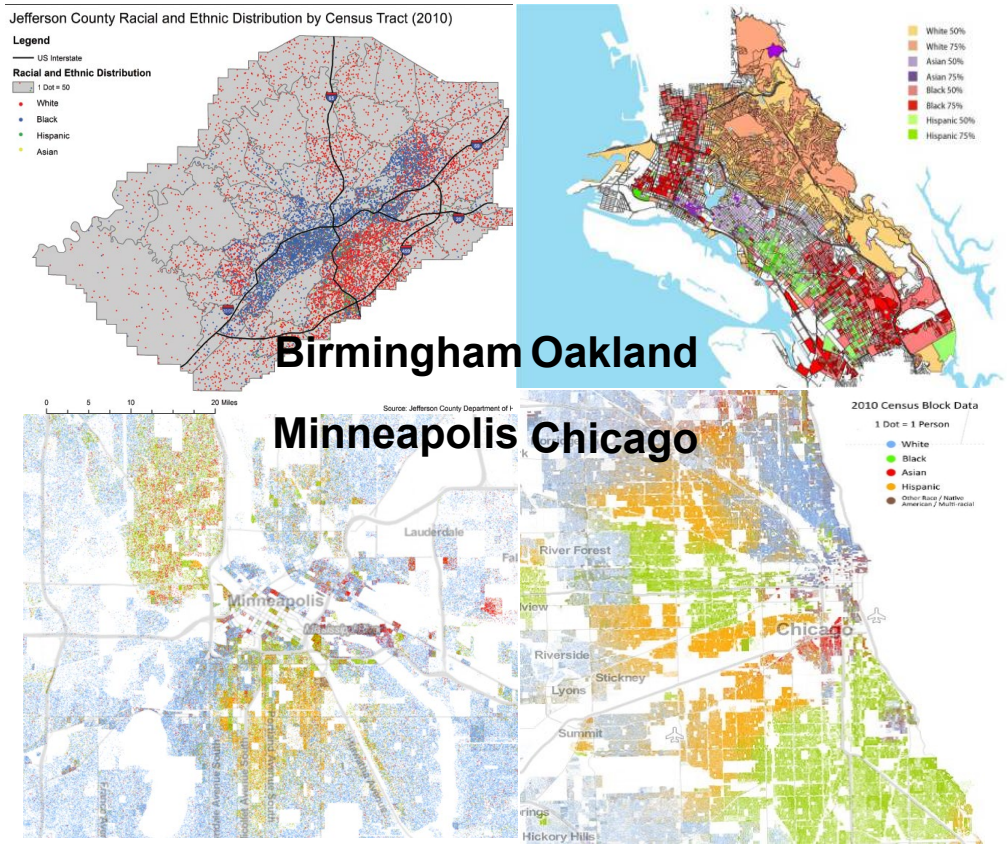
Addressing Persistent Disparities in Hypertension
"Place Matters" in Health Equity

CARDIA

Coronary Artery Risk Development in Young Adults



JAMA Internal Medicine | Original Investigation

Association of Changes in Neighborhood-Level Racial Residential Segregation With Changes in Blood Pressure Among Black Adults

In black participants of the CARDIA study, **reductions in systolic blood pressure** over 25 years were associated with **decreases in racial segregation** of participant's place of residence.

Kershaw KN, et al. JAMA Internal Medicine. 2017.

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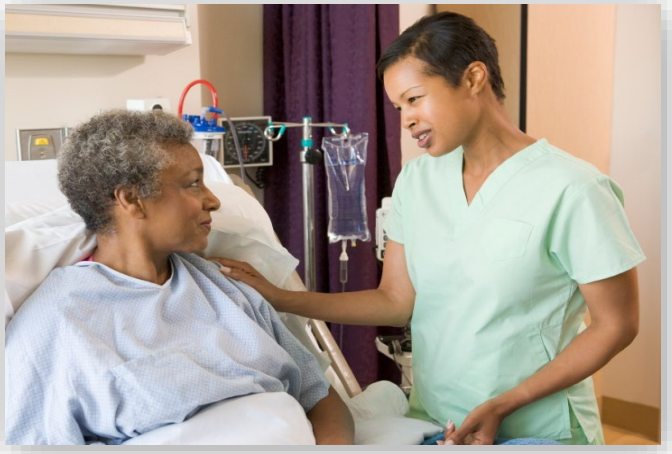
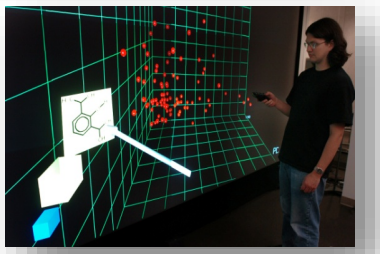
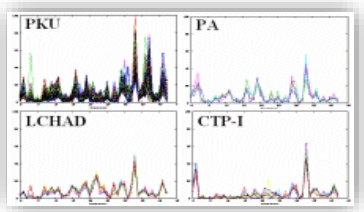
Systems Biology Framework for Developing Tailored Therapies: Harnessing New Technologies to Improve Health Outcomes







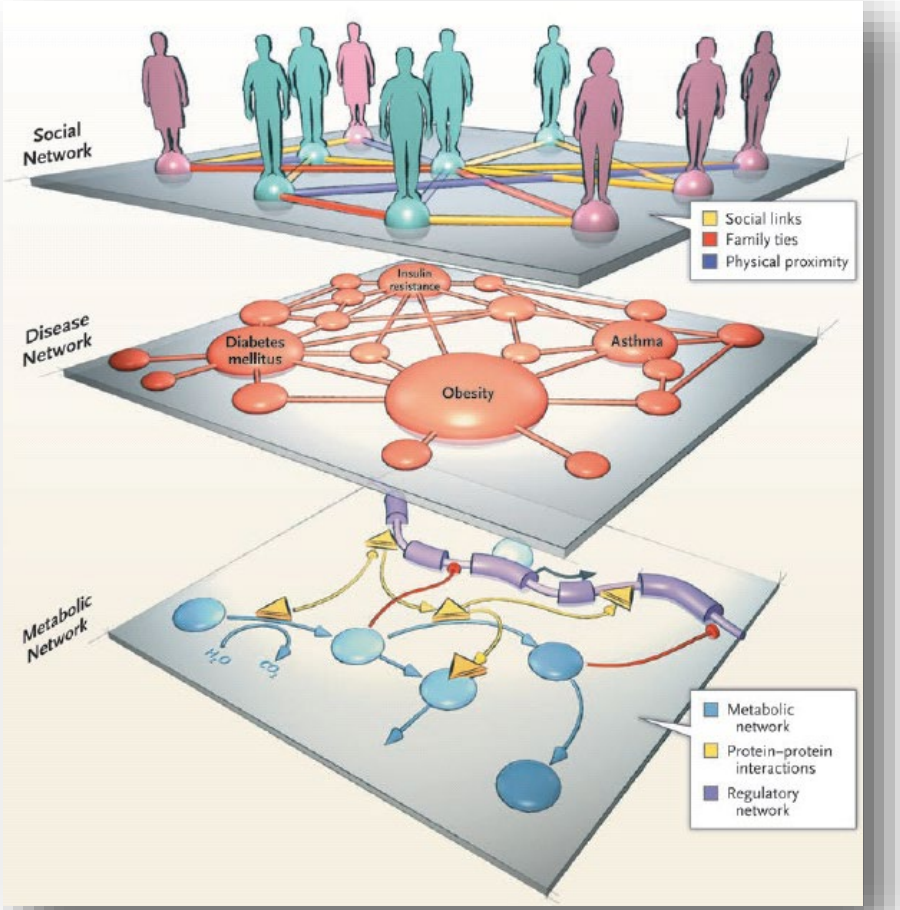
Leveraging New Technologies for HLBS Disorders

Data Science and AI

Identify behavioral contributors and molecular mechanisms of disease

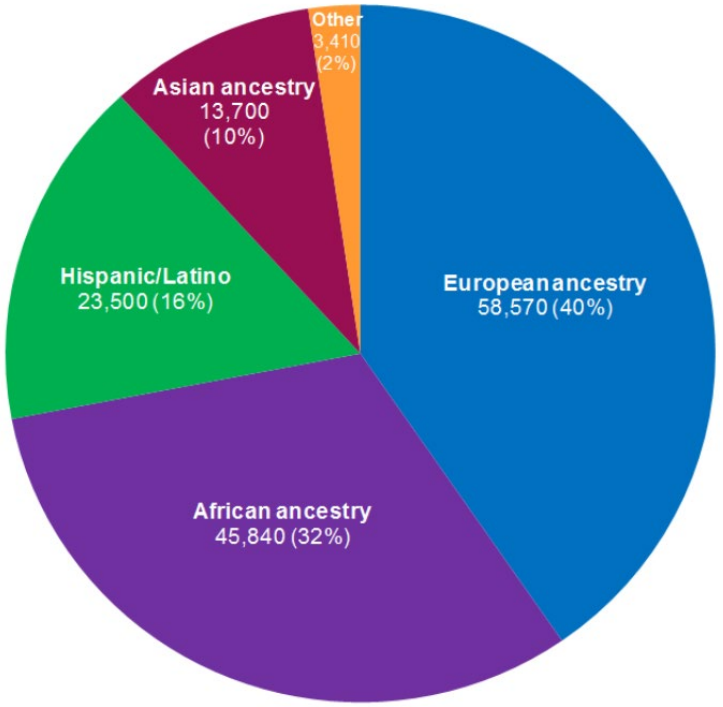
Precision Medicine

Tailor treatments across populations

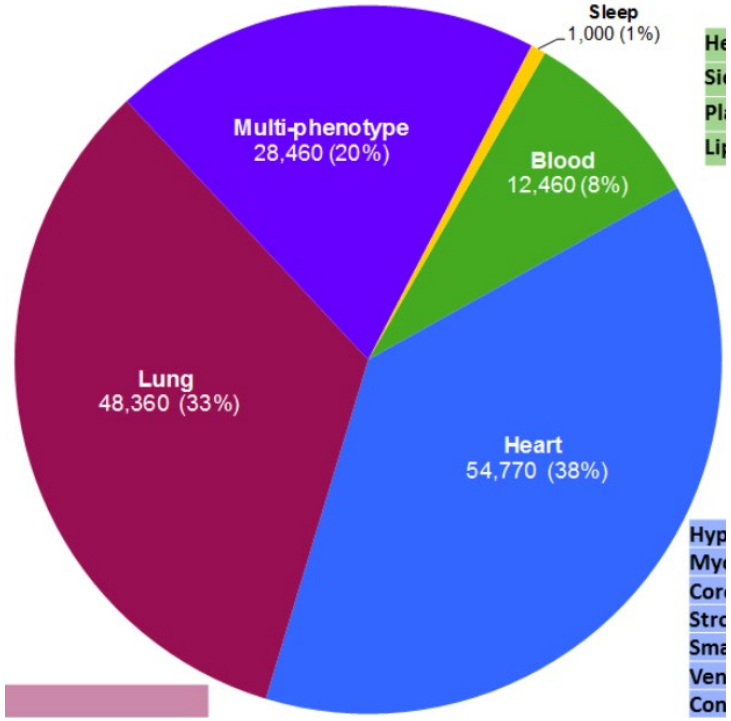


TOPMed: A Diverse Genome-Phenome Resource Enabling Data Science with Public Health Impact

Population Diversity



Phenotype Diversity



TOPMed

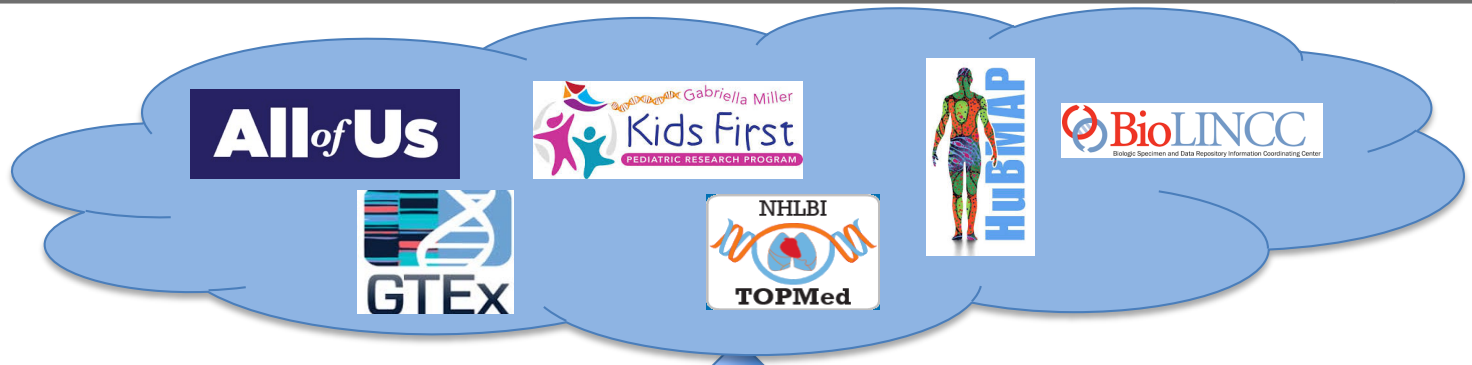
Hypertension MI CAD Stroke Small Vessel Disease CHD Afib CAC Adiposity CHF HCM	Hemophilia SCD Platelets Lipids VTE
	Asthma COPD IPF Sarcoidosis ILD Sleep

An expansive data resource for **integrated exploration** of multi-omics data with molecular, behavioral, imaging, environmental, and clinical data in heart, lung, blood, and sleep disorders.

NIH National Heart, Lung, and Blood Institute

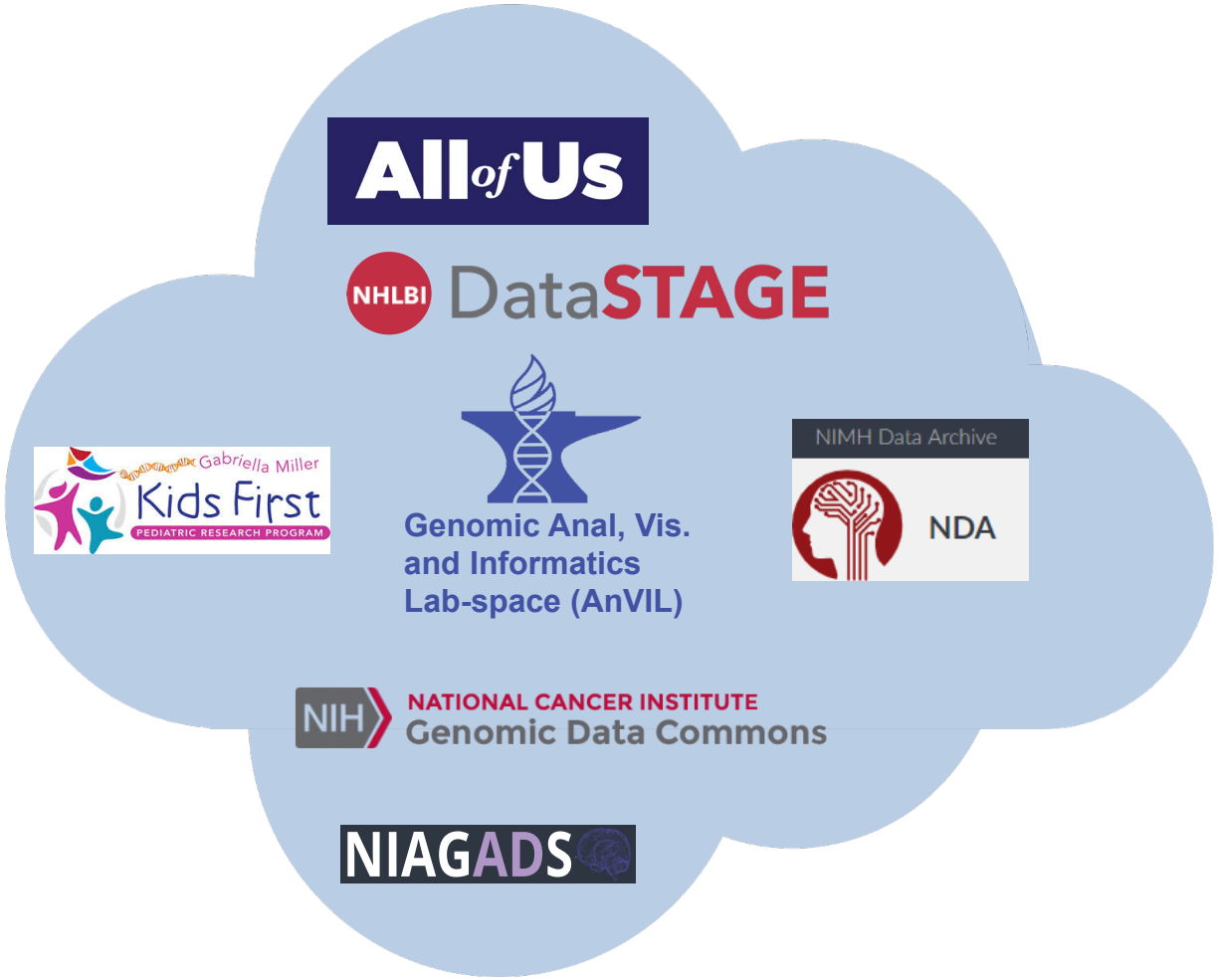
Phenotype Diversity represents 145K WGS samples from Phase 1-4 X01s.

Envisioning a Communal, Global Discovery Platform for Multi-Disciplinary Open Science



Registries	Data & Bio-Specimen Repositories	Population Cohort Studies	Clinical Trials	Genomics Sequencing
Registries with clinical data and biological samples (i.e. All of Us, GTEX)	Datasets & Biospecimen from over 100 Clinical & Epi studies (LungMap)	Longitudinal Phenotypic data from diverse populations (Personal Sensor Data)	Individual participant data from practice-changing clinical trials	Genomics and Phenomics data from diverse HLBS cohort/clinical studies

Building a Communal Trans-NIH Platform for Multi-Disciplinary Open Science



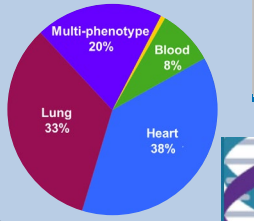
Accelerating Data to Knowledge and Knowledge to Discovery

- Make **data accessible** to medical, scientific community
- Ensure data **interoperability** with other data sets
- Drive **discovery**
- Enhance **tools** and treatments available for clinicians
- Revolutionize **prevention and treatment** of disease

Realizing the Promise of Precision Medicine: Harnessing Data Science to Improve Health Outcomes

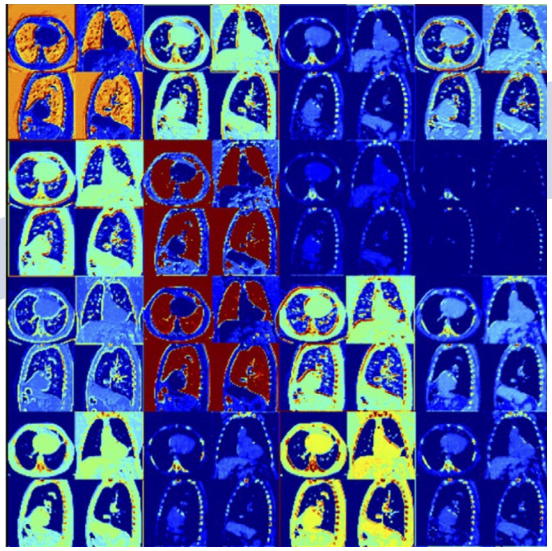
DataSTAGE

NHLBI TOPMed



COPDGene® COPD Genetic Epidemiology

Resource platforms enabling discovery of molecular pathways, subphenotypes, & treatment targets



Leveraging AI & deep learning of neural networks from CT in COPDGene to characterize disease severity and predict acute exacerbations and mortality

Public Health Impact

- Identifying COPD prior to symptom onset
- Linking structural, functional and biological changes
- Identifying high-risk subgroups in large populations

Predicting/Preventing/ Preempting Disease

Gonzalez G, et al. *AJRCCM*, 2018.

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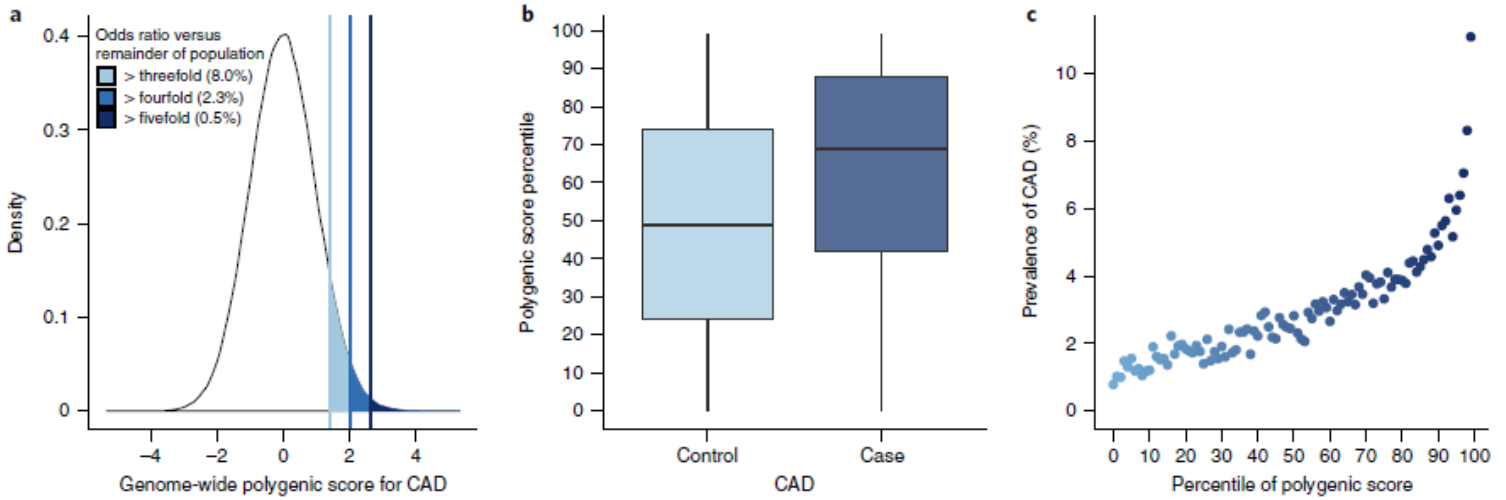
What if… We Employed Polygenic Risk Scores to Refine Risk and Optimize Therapy for Chronic Conditions?

Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations



"The polygenic score identified 20-fold more people at comparable or greater risk than were found by familial hypercholesterolemia mutations in previous studies."

Polygenic Risk Scores for Polygenic Diseases

High polygenic scores identify participants with 3X (or more) **higher risk for disease** compared to participants with lower scores for common diseases.

- Coronary Artery Disease
- Atrial Fibrillation
- Type 2 Diabetes
- Inflammatory Bowel Disease
- Breast Cancer
- Obesity

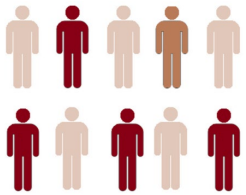
NIH National Heart, Lung, and Blood Institute

Khera & Kathiresan et al. *Nature Genetics*, 2018 375:2349-2358.

A Paradigm for Translating Discovery to Public Health Impact for Heart, Lung, Blood and Sleep Research

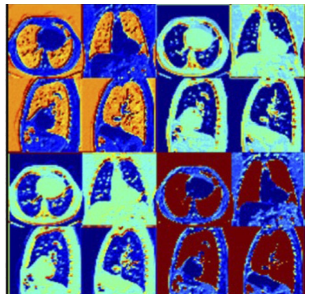
Identify Disease Risk

Track early risk, identify disease categories



Expand Diagnostic Capabilities

Novel use of artificial intelligence & machine learning



Perform Deep Phenotyping

Patient-centric data mining through discovery science (e.g., TOPMed and Data STAGE)

Conduct Clinical Research

Biomarkers & therapeutic targets identified through Omics

Develop Tailored Treatments

Improve disease management and health outcomes

Transform Health Outcomes

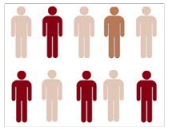
Improve health and quality of life

A Paradigm for Translating Discovery to Public Health Impact for Heart, Lung, Blood and Sleep Research

Building on the Strategic Input from the Council of Councils

Identify Disease Risk

Track early risk, identify disease categories



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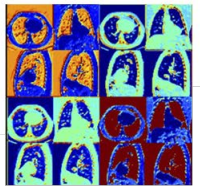

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National Institutes of Health

National Heart, Lung, and Blood Institute

NIH National Heart, Lung, and Blood Institute