Imagining The NHLBI at 75: Integrating Science and Public Service

Gary H. Gibbons, MD
Director
National Heart, Lung, and Blood Institute

Advisory Committee to the Director Meeting
December 6, 2012
**NHLBI Mission: Aligns with My Life’s Purpose**

**Mission**: Provide global leadership for research, training, and education programs to promote the **prevention and treatment** of heart, lung, and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives.
Joining the Legacy of Leadership Excellence

1948-1952
Cassius Van Slyke, M.D.

1952-1961
James Watt, M.D., D.P.H.

1961-1965
Ralph E. Knutti, M.D.

1965-1965
William H. Stewart, M.D.

1966-1966
Robert P. Grant, M.D.

1961-1965
Ralph E. Knutti, M.D.

1965-1966
Robert P. Grant, M.D.

1966-1968
Donald S. Frederickson, M.D.

1968-1974
Theodore Cooper, M.D., Ph.D.

1975-1981
Robert I. Levy, M.D.

1982-2003
Claude Lenfant, M.D.

2005-2009
Elizabeth G. Nabel, M.D.
“We do not inherit the land from our ancestors, we borrow it from our children.”

Native American Proverb
Refining Our “Recipe” for Successful Stewardship: NHLBI Enduring Principles

- Value and support investigator-initiated fundamental discovery science.

- Maintain a balanced, cross-disciplinary portfolio (basic, clinical, population science).

- Support implementation science that empowers patients and enables partners to apply knowledge that improves the health of the nation.
Refining Our “Recipe” for Success: NHLBI Enduring Principles

- Train and nurture a diverse new generation of leaders in science.
- Engage key thought-leaders to collectively identify and pursue high-yield opportunities that will advance the field.
- Value the health of all communities; elucidate and eliminate health inequities in the US and around the globe.
The NHLBI Community -- Circle of Partners
Co-Stewards of Science as a Public Good

- Catalysts of Scientific Innovation
- Future Scientist-Leaders
Race, ethnicity and NIH research awards

Ginther DK, Shaffer WT, Schnell J, Masimore B, Liu F, Haak LL, Kington R
The NIH Intramural Track Record on Diversity: The ‘Glass House’ Challenge

<table>
<thead>
<tr>
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“It ain’t easy being green”

-- Kermit the Frog
Promoting Diversity in the Next Generation: Leading the Biomedical Community

Minority Scientists

- Faith
- Opportunity
- Mentors
- Resources to Excel
- A Village

Promoting Diversity in the Next Generation:
Leading the Biomedical Community

Passion

Mentors

Resources to Excel

A Village

Opportunity

Faith

National Heart Lung and Blood Institute

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A Diverse Nation’s Next Generation: Investing in **ALL** of the available talent
“We do not inherit the land from our ancestors, we borrow it from our children.”

Native American Proverb

An Inheritance Built on a Legacy of Good Stewardship: Today’s Investments for Tomorrow’s Breakthroughs

Expected deaths from CHD in 2009 if rate remained constant at 1968 peak = 1,593,000

Deaths from CHD averted in 2009 = 1,207,000

Actual deaths from CHD in 2009 = 386,000
Building Upon a Legacy of Excellence: Lessons of One NHLBI Success Story

- NIH Leadership
- Next-Gen Scientists
- Multi-Level Balance
- Collaboration
- Public Impact

Observational Studies ↔ Public Health Application

Basic Research

Clinical Research

Framingham Risk Factors

Intramural Research Program: Frederickson, Stadtmans

Clinical Research: Tangier's Disease (HDL Cholesterol)

Brown and Goldstein: Nobel Prize (LDL Cholesterol)

NHLBI Trial: Lowering Cholesterol Cuts CHD Risk

Roy Vagelos: Statins

Value of Lifestyle Interventions
The Lipid Research Clinics Coronary Primary Prevention Trial

Deaths from CHD averted in 2009 = 1,207,000

Actual deaths from CHD in 2009 = 386,000

Source: CDC/National Center for Health Statistics
A Legacy of Catalyzing Transformational Change: Applying New Knowledge in All Communities
Creating Our Collective Future – NHLBI at 75: 21st Century, Unprecedented Opportunities

- Systems biology/medicine
- Reparative biology/medicine
- Predictive health; Pre-emption Trials
- Health Inequities (local & global)
- New tools and platforms
  - ‘Omics’
  - Imaging
  - Informatics / Computational Modeling
  - Stem cells
  - Nanotechnology/bioengineering
  - Collaborative Knowledge-Intervention Networks
Transformational Change and Chronic Diseases: The Science that ‘Bends the Curve’ -- An Economic Imperative

Medicare Expenditures for Chronic Kidney Disease

Total expenditures (\$, in billions)

- Part D
- Hospice
- Home health
- Skilled nursing
- Physician/supplier
- Outpatient
- Inpatient

Years:
- 92
- 94
- 96
- 98
- 00
- 02
- 04
- 06
- 08
- 10

National Heart Lung and Blood Institute
Racial Inequities in Health: Integrating Science and Public Service

Stroke Mortality

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<tr>
<th>Year</th>
<th>Black Men</th>
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<th>White Women</th>
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<td>80</td>
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<td>1970</td>
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<td>1985</td>
<td>120</td>
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<tr>
<td>1992</td>
<td>100</td>
<td>40</td>
<td>60</td>
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</table>

Incident Kidney Failure

- African American
- All
- American Indian
- Asian
- Caucasian
Health Inequities: A Complex, Multi-Level, Systems Problem

Barbabasi A. NEJM 2007;357:404-7
The Etiologies of Cardiovascular Health Inequities: Multi-Level, Bio-Social Determinants

The Bio-Social Interface

- Microbiome
- Immune System
- Epigenome

Biological Systems

- Obesity
- Diabetes
- Hypertension
- Stroke
- Kidney Failure

Factors:
- Racism
- Environment
- Social Deprivation
- Inactivity
- Diet
- Psychosocial Stress
- Social Network
- Behavior

Genetic Variation

Population History

Gibbons 2009
## The Ying-Yang of Transformational Change: Integrating New and Traditional Approaches

<table>
<thead>
<tr>
<th>Classical Research Approach</th>
<th>Systems Medicine Approach</th>
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<tr>
<td><strong>Reductionist</strong></td>
<td>Holistic/Systems-level</td>
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<tr>
<td><strong>Uni-dimensional data</strong></td>
<td>Multi-dimensional data requiring integration</td>
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<tr>
<td><strong>Single-discipline laboratories</strong></td>
<td>Multidisciplinary collaborative teams</td>
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<tr>
<td><strong>Focus on individual molecules</strong></td>
<td>Focus on pathways and networks</td>
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<tr>
<td><strong>Descriptive modeling</strong></td>
<td>Predictive modeling</td>
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<tr>
<td><strong>Largely qualitative</strong></td>
<td>Increasingly quantitative</td>
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<tr>
<td><strong>Low-throughput assays</strong></td>
<td>High-throughput assays</td>
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<tr>
<td><strong>Uni-scalar analysis in individual projects</strong></td>
<td>Multi-scalar, integrative analysis in individual projects</td>
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</tbody>
</table>

Molecules OR Cells OR Tissues/Organs /Organism OR Populations

Molecules AND Cells AND Tissues/Organs/Organism AND Populations

… AND Society
META-Health Study (Atlanta): Racial Difference in CVD Risk Profile

### African-American
- Age = 49
- BMI = 32
- SBP = 125 mmHg
- Hx of Diabetes = 13%
- Framingham Risk = 6.0
- Low physical activity
- Low fruit/vegetable diet

### White
- Age = 51
- BMI = 28
- SBP = 119 mmHg
- Hx of Diabetes = 5%
- Framingham Risk = 6.0

Din, Vaccarino, Gibbons, Quyyumi 2009
META-Health Study – The Social Determinants of Health: Where you live, work and play matters

My neighborhood offers many opportunities to be physically active”

Din, Vaccarino, Gibbons, Quyummi 2009

Caucasian <$35K
Caucasian >$35K
AA <$35K
AA >$35K

Fast Food Stores
Few Parks
Unsafe to Walk

Unhealthy Diet/Physical Inactivity
Obesity/Vascular Inflammation

CVD/STROKE

Din, Vaccarino, Gibbons, Quyummi 2009
‘Social Contagion’ of Cardiovascular Disease: Interplay of Social and Biological Systems


G D Wu et al. Science 2011;334:105-108
Social Determinants of Heart Disease: Interplay of Social and Biological Systems

Metro-Atlanta Food Access

Racism  Segregation
Socioeconomic Status
Social-Environment
Food Desert
Unhealthy Diet
Bio-Social Interface
Microbiome
Immune System Activation
Vascular Dysfunction/Disease
The Etiologies of Cardiovascular Health Inequities: Multi-Level, Bio-Social Determinants

Racism

Environment

Social Deprivation

Inactivity | Diet | Psychosocial Stress | Social Network | Behavior

The Bio-Social Interface

Microbiome | Immune System | Epigenome

Genetic Variation

Population History

Biological Systems

Obesity

Diabetes

Hypertension

Stroke

Kidney Failure

Genetic Variation

Population History

Microbiome

Immune System

Epigenome

Obesity

Diabetes

Hypertension

Stroke

Kidney Failure

Gibbons 2009
Addressing Health Inequities: Toward a Multi-Level, Systems Approach

Barbasi A. NEJM 2007;357:404-7
Racial Health Disparities & Genomic Variation: Footprints of Population History and Admixture

Representative African American

Recent admixture

Recent European ancestry

High degree of European ancestry

Chromosome

Position (Mb)

0 50 100 150 200 250

Chromosome

Position (Mb)

0 50 100 150 200 250

Chromosome

Position (Mb)

0 50 100 150 200 250

Chromosome

Position (Mb)

0 50 100 150 200 250

African ancestry

Shared African and European ancestry

European ancestry

Bustamonte  PNAS 2009
Association of Trypanolytic ApoL1 Variants with Kidney Disease in African-Americans

G Genovese, DJ Friedman…JB Kopp, E Pays, MR Pollack

- Variant > 5-fold increased risk of ESKD
- Hypertension, HIV, SCD
- 12% of AA have 2 risk alleles (G1/G2)

APOL1 Trypanolytic Activity (HDL;Immune Cells Vascular Cells)

- Wild Type
- Heterozygous Variant

*
WHAT IF: APOL1-Based Genomic Medicine Therapeutic Strategy to Reduce Racial Inequities in CKD

**APOL1 Risk Variant for Kidney Failure in African-Americans**

- **Risk prediction**
  - Rx: Start antihypertensive treatment at lower goal of 130/80 in at-risk APOL1 carriers

- **Pharmacogenomics**
  - Rx: Angiotensin Blockers in African-Americans with high-risk APOL1 genotype

- **New therapies**
  - Rx: New drugs targeting mediators downstream of APOL1 to prevent kidney failure

**Pharmacogenomics**

**New therapies**

**Risk prediction**

**Pharmacogenomics**

**New therapies**
Prediction, Pre-emption and Remission of Chronic Diseases: ‘Bending the Curves’ of Racial Inequities in Health:

Stroke Mortality

Incident Kidney Failure

CDC, 1996
Transforming ‘Big Data’: Towards Predictive Health and Systems Medicine

Nate Silver
A Systems Approach to the NHLBI Portfolio: Synergy with Scientific Community Resources:

“Scientific Commons”

- Diverse Cohort Study Datasets
- Clinical Research Registry-Biobanks
- Phenomics: Ontologies
- Bioinformatic Tools; Computer Modeling
- Open ‘Omic’ Data Repositories

Imagine the Future: The NHLBI at 75

- **Astute Clinicians**
- **Cohort Datasets**
- **Proteomics/Metabolomics**
- **Genomics**
- **Big Data- Ontologies**
- **Computational Models**
- **Imaging**
- **Biorepositories**

**From ‘Bench-to-Bassinet’: Phenomics Atlas of Congenital Heart Disease**
Stroke recurrence with chronic blood transfusions compared with historical controls.

“What If” Unprecedented Opportunities: Eliminating Stroke and Cognitive Impairment in Sickle Cell Disease?

What if
- Modifier genes?
- Vasculopathy targets?

Source: Verduzco L A, Nathan D G *Blood* 2009;114:5117-5125
A Systems Approach to the NHLBI Portfolio: Catalyzing Scientific Community Connectivity

Knowledge Networks
Community-based Networks
Diverse Cohort Study Networks
Clinical Trial Networks
Genomic Medicine Networks
System Biology Networks
Diverse, Cross-Disciplinary Trainees
An Exciting Legacy of Excellence

Recent NHLBI-Funded Nobel Prize Winners
“We do not inherit the land from our ancestors, we borrow it from our children.”

Native American Proverb