Building on the NHLBI Legacy of Hypertension Research: Charting Our Future Together

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AHA Council on Hypertension

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Accountable Stewardship: NHLBI Enduring Principles
Health Inequities and Mission-driven Public Health Impact
Seizing Unprecedented Opportunities
Setting the Research Agenda with Our Partners
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 US and around the world.
Building Upon a Legacy of Excellence: NHLBI Success Story – A Balanced Approach

William B. Kannel, MD

Molecular Mechanisms of Hypertension


Chlorothiazide

Effects of Treatment on Morbidity in Hypertension

Results in Patients With Diastolic Blood Pressures Averaging 115 Through 129 mm Hg

Veterans Administration Cooperative Study Group on Antihypertensive Agents

JAMA 1967
Building on a Legacy of Excellence: Landmark Hypertension Trials
The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: The Systolic Blood Pressure Intervention Trial (SPRINT)

Is the age-related rise in systolic blood pressure normal?

Are ACEi and CCBs better than thiazide diuretics in preventing CVD?

In high risk T2DM patients, is targeting SBP<120 mmHg beneficial?

Is a target SBP<120 mmHg better than SBP<140 mmHg?

Prevention of Stroke by Antihypertensive Drug Treatment in Older Persons With Isolated Systolic Hypertension
Final Results of the Systolic Hypertension in the Elderly Program (SHEP)

Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus: The ACCORD Study Group

Building on a Legacy of Excellence: 25 Years of Hypertension Trials

SHEP

ALLHAT

ACCORD

SPRINT
Answering the Critical Questions to Improve Clinical Care

- **Purpose**: To determine whether reducing systolic blood pressure to <120 mm Hg is superior to commonly recommended target of <140 mm Hg

- **Primary Outcome**: CVD events (heart attack, non-MI ACS, heart failure, stroke, CV death)

- **Secondary Outcomes**: All-cause mortality, decline in kidney function or development of ESRD, incident dementia, decline in cognitive function, small-vessel cerebral ischemic disease

- **Participants**: 9,361 adults
  - Age ≥ 50 years
  - SBP ≥130 mm Hg and at least one additional CVD risk factor.
  - Women, Men, and Racial Minorities
  - 25% Elderly (age ≥ 75)
Intensive management of SBP to a target of <120 mmHg reduced composite primary endpoint by 30% and all-cause mortality by almost 25% as compared to an SBP target of <140 mm Hg. Interim results appear consistent for overall study population.
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The Health Inequity Challenge: “Unfinished Business” in Public Health Impact

Locally,

Eight Americas: Investigating Mortality Disparities across Races, Counties, and Race-Counties in the United States

Nationally,


Globally,

NIH
National Heart, Lung, and Blood Institute
Addressing Health Inequities – The Burden of Disease

978 million worldwide with hypertension

NIH National Heart, Lung, and Blood Institute
Health Inequities – A Complex, Multi-level Problem

Systems Science & the Socio-ecological Model

Barabasi A. NEJM 2007;357:404-7

Classic Approach | Systems Approach
--- | ---
Reductionist | Holistic; Integrated Systems
Uni-dimension data | Multi-dimensional data
Single-discipline lab | Multidiscipline teams
Individual molecules | Pathways & networks
Descriptive models | Predictive modeling
Molecular assays | High-output assays
Molecules OR Cells OR Tissues OR Populations OR Social Context | Molecules AND Cells AND Tissues AND Populations AND Social Context

NIH National Heart, Lung, and Blood Institute
The Ecosystems of Cardiovascular Health Inequities: Multi-Level, Bio-Social Determinants

Environment/ ‘Exposome’
- Racism
- Inactivity
- Diet
- Psychosocial Stress
- Social Network
- Social Deprivation
- Neighborhood Features

The Bio-Social Interface

Biological Interface Systems
- Microbiome
- Immune System
- Epigenome

Systems Biology/ Medicine/ Public Health
- Genomic Variation
- Population History

Hypertension
- Stroke
- Heart Failure
- Kidney Failure
- Obesity
- Diabetes

National Heart, Lung, and Blood Institute
A Systems Approach to Inequities in Hypertension:
What if we systematically leveraged a network of community partners and resources in knowledge exchange to reduce health inequities?

“You can’t educate a child who isn’t healthy, and you can’t keep a child healthy who isn’t educated.”
~ Former U.S. Surgeon General Joycelyn Elders
Translating Discovery Science into Public Health Impact: A ‘Beloved Community’ – From ‘Nucleotides-to-Neighborhoods’

‘Bending the Curves’ of Racial Inequities in Health: What If – Precisely, Predicted and Pre-empted CKD?

Rising Medicare Costs For CKD

Incident Chronic Kidney Failure By Race

Genomic Admixture Analysis: African American

African ancestry
Shared African and European ancestry
European ancestry

Genomics

CDC, 1996
The Ecosystems of Race-Ancestry Health Disparities: The ‘Exposome’, Population History and Genomic Variation

Environment /Exposome

Immune Defense Systems
Host Genomic Variation

Sickle Cell
Duffy Antigen
G-6-PD
APOL1 Risk Variant for Kidney Failure in African-Americans: Increased Risk of Chronic Kidney Disease and CVD

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

**Risk prediction**
Start anti-hypertensive and statin treatment at lower goal of <120/80 in at-risk APOL1/SCT carriers

**Pharmacogenomics**
Angiotensin Blockers in African-Americans with high-risk APOL1/SCT genotype

**New therapies**
New drugs targeting mediators downstream of APOL1/SCT to prevent kidney failure
Charting Our Future

- Accountable Stewardship: NHLBI Enduring Principles
- Health Inequities and Mission-driven Public Health Impact
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Advancing HLBS Science While Seizing Unprecedented Opportunities

**Genetics and Genomics Workshop (2014)**
- Whole Genome Sequencing (WGS)
- Functional studies of disease-associated genetic variants
- Clinical applications of basic research findings
- Establishment of scientific/data commons

**Trans-Omics for Precision Medicine**

**Precision Medicine**

**WGS Project**

**Building a Resource**

**Leveraging Our Cohorts**

**Gathering the Intelligence of Our Community**

**Scientific Opportunities**

**Seizing New Opportunities**

- **Whole Genome Sequencing (WGS)**
- **Functional studies of** disease-associated genetic variants
- **Clinical applications of** basic research findings
- **Establishment of** scientific/data commons
Toward an NHLBI Data Commons: Enabling Investigator-Initiated Precision Medicine Science

Toward HLBS Computational Medicine

WGS Existing Cohorts (60K WGS)

Clinical Phenotypes

Transcriptome

Bioinformatics

NHLBI Precision Medicine Data Commons

Genomics

Microbiome

Data Coordinating Centers

Proteomics Sequencing Centers

Shared Governance
(Extramural Community, Council, BEE, NHLBI)

Investigator-Initiated Science

NIH
National Heart, Lung, and Blood Institute
Toward Precision Medicine for ALL: Augmenting Diversity in the NHLBI Data Commons

First GWAS for hypertension in African Americans
- Identified multiple SNPs reaching genome-wide significance for hypertension
  - Two gene candidates for BP regulation (SLC24A4 and CACNA1H)

Under-represented Groups in Genomic Resources

- African Ancestry 7%
- European or Asian Ancestry 93%
### Studies with Hypertension Phenotypes

- San Antonio Heart Study (Mexican-Americans)
- Framingham Heart Study (3 generations, European Ancestry)
- Jackson Heart Study (African-Americans)
- Old Order Amish
- Samoan families with obesity
- Women’s Health Initiative (European, African, Hispanic, Asian Ancestry)
- Atherosclerosis Risk in Communities Study (African, European Ancestry)
- Multi-Ethnic Study of Atherosclerosis (African, Chinese, European, Hispanic Ancestry)
- HyperGen Study (African –American families)
- SAPPHIRE Study (Asia-Pacific Ancestry)
TOPMed and Planning for the Future: Evolving Next Steps

Additional Sequencing
(high impact diseases & populations, increase the sample size)

Layer on other “omics”
(Metabolomics, Epigenomics, Proteomics, RNA)

Develop analytic methods & pipelines
Bioinformatics
NHLBI Precision Medicine Data Commons
Proteomics Sequencing Centers
Data Coordinating Centers

WGS Existing Cohorts (60K WGS)

Develop data commons platform

Clinical Phenotypes
Genomics
Transcriptome
Microbiome

Layer on other “omics”
(Metabolomics, Epigenomics, Proteomics, RNA)
What if we completely re-imagined hypertension clinical research as we know it?

We enabled rich data collection that facilitates cohorts of HTN….

Big Data- Ontologies
Computational Models
Proteomics
Metabolomics

…and apply deep analytics to predict disease risk.

…and launch clinical trials with pre-determined eligibility, predictive risk profiles and embedded long-term follow-up.
Trans-Omic Approach to Elucidating Molecular Mediators of Hypertension

Systems biology approach integrating genome-wide genetic variation and transcriptome profiling data FHS participants identifies key BP regulatory genes and gene networks

“Pharmacologic treatment of prehypertension can prevent or postpone the development of hypertension."
Imagine a Precision Medicine Future: Carla’s Story in 2020

- 40 yo female volunteers to take part in National Research Cohort
- Cares for her mother who suffered a stroke; but Carla “feels fine.”
- Her DNA profile reveals a APOL1 variant that increases risk for kidney and cardiovascular disease.
- Offered opportunity to try out wearable sensor to continuously monitor blood pressure, physical activity, diet, sleep patterns, etc.
  - Finds her blood pressure is consistently high
Imagine a Precision Medicine Future: Carla’s Story in 2020

- Doctor confirms hypertension; prescribes diuretic drug, 7+ hrs sleep and DASH diet (low salt; rich in fruit/vegetables)
- Obtains “smart bottle” that notifies her smart phone if dose is missed
- mHealth App monitors BP, adherence to DASH diet and sleep hygiene.
- Blood pressure normalizes; Carla remains healthy
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Engaging the NHLBI Community’s Collective Intelligence: NHLBI Community Priority-Setting – Leveraging the Crowd

Phase I: Plan and Prepare
- Fall 2014: Framework Planned: NHLBI staff & BEE/NHLBAC

Phase II: Community Crowdsourcing
- Winter 2015: Strategic Visioning Framework Released
- Spring 2015: Community Input on CQs & CCs
- Summer 2015: Draft Strategic Research Priorities

Phase III: Community Update
- Summer 2015: Community Update
- Fall 2015: Draft Strategic Research Priorities Refined

Phase IV: Refine and Release
- Early 2016: NHLBI Strategic Research Priorities Disseminated

Research Priorities
(Compelling Questions & Critical Challenges)
## Preliminary, High-Priority Compelling Questions and Critical Challenges Relevant to Hypertension

<table>
<thead>
<tr>
<th>Goal 1: Promote Human Health</th>
<th>What if we understood mechanisms of resilience in aging to maintain blood pressure at &lt;120/80?</th>
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<tbody>
<tr>
<td>Goal 2: Reduce Human Disease</td>
<td>What if we leveraged genomics, phenotyping, and biomarkers to understand the molecular pathways of hypertension in order to predict risk, tailor treatment, and pre-empt complications?</td>
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<td>Goal 3: Advance Translational Research</td>
<td>What if we were able to leverage technology and systems to yield 100% awareness, treatment, and control rates of hypertension for <em>ALL</em> populations?</td>
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<td>Goal 4: Develop Workforce and Resources</td>
<td>What if we developed the next generation of scientists with the diversity of skills and disciplines (e.g., systems biology and data science) to advance the field?</td>
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NHLBI Mission - *Discovery Science That Enhances Human Health: Enduring Principles for Sustained Success*

**Enduring Principles**

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