Implementing the NHLBI Strategic Vision in the Division of Cardiovascular Sciences

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This material represents my personal views and does not necessarily represent the official views of the NHLBI, NIH, DHHS, or US Federal Government.
Charting the Future Together: The NHLBI Strategic Vision, 2016

Accelerating our journey towards scientific and health advances in the next decade

- Understand Human Biology
- Develop Workforce and Resources
- Reduce Human Disease
- Advance Translational Research
NHLBI Strategic Objectives

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
Turning discovery into cardiovascular health

Current major initiatives map to NHLBI’s Strategic Vision

New initiatives for strategic investments guided by Strategic Vision, complemented by Big Goals
CVD in the US: Recent stagnation and enduring disparities

Sustaining DCVS Leadership with Big Goals

- Addressing social determinants of CVH and health inequities
- Enhancing resilience
- Promoting CVH and preventing CVD across the lifespan
- Eliminating hypertension-related CVD
- Reducing the burden of heart failure
- Preventing vascular dementia

Addressing Social Determinants of CVH Equity: DECIPHER

- Disparities Elimination through Coordinated Interventions to Prevent and Control Heart & Lung Disease Risk
  - High Burden Communities
    - Geographic Region (e.g., Appalachia, Mississippi Delta, Stroke Belt, Oklahoma to Eastern Kentucky)
    - Rural or Inner-city locales
    - Racial/Ethnic Groups (e.g. Blacks or African Americans, American Indian and/or Alaska Natives)
    - Low socioeconomic status
    - Sex
  - Creative academic-community partnerships
  - Creative use of health metrics

DECIPHeR Awards

- **DECIPHeR RCC**
  Stevens (U24 HL151308) University of North Carolina at Chapel Hill
  Coordinating Center for the DECIPHeR Network

- **UG3/UH3 Awards**
  He (UG3 HL151309) Tulane University
  Community Health Worker-Led Church-Based Intervention for Eliminating Cardiovascular Health Disparities in African Americans

  *Brown (UG3 HL154302) UCLA
  Multi-ethnic Multi-level Strategies and Behavioral Economics to Eliminate Hypertension Disparities in LA County

  Daumit (UG3 HL154280) Johns Hopkins University
  Achieving Cardiovascular Health Equity in Community Mental Health: Optimizing Implementation Strategies

  *Kho (UG3 HL154297) Northwestern University at Chicago
  Community Intervention to Reduce Cardiovascular Disease in Chicago (CIRCL-Chicago)

  *Ogedegbe (UG3 HL151310) NYU School of Medicine
  Actions to Decrease Disparities in Risk and Engage in Shared Support for Blood Pressure Control (ADDRESS-BP) in Blacks

  Matthews (UG3 HL151302) University of Illinois at Chicago
  Mi QUIT CARE (Mile Square QUIT Community-Access-Referral-Expansion)

  Szefler (UG3 HL151297) University of Colorado Denver
  Reducing Asthma Attacks in Disadvantaged School Children with Asthma

*Studies focused on hypertension prevention, treatment, and/or control
Social Determinants of CV Health Workshops

- Social Determinants of Health: Contributions of Early Life Adversity to Cardiovascular Disparities in Adulthood, 2018

- Social Determinants of Cardiometabolic Health, Disease, and Health Disparities: Setting an Agenda for Research, 2019

- Harnessing Novel Data Sources and Technologies for the Study of Social Determinants of Health in HLBS Disorders, 2020
Advancing Health Equity by Addressing Health Disparities and Predict, Prevent and Preempt Disease

- Partnering with **key stakeholders** to engage and better understand community needs
- Build **sustainable** community **collaborations**
- **Embedding trainees**/community partners into large, existing clinical studies
- Expand opportunities for **transdisciplinary research**
- Engage **less research-intensive** institutions
Promoting CVH and preventing CVD across the lifespan: focus initially on younger ages
Challenges and opportunities for the prevention and treatment of cardiovascular disease among young adults. 2017

Promoting Cardiovascular Health in Early Childhood (0-5 years) and Transitions in Childhood through Adolescence. 2018

Social Determinants of Health: Contributions of Early Life Adversity to Cardiovascular Disparities in Adulthood. 2018

AHA Scientific Sessions 2019: 50x50x50 - Transforming the Cardiovascular Health of Youth for Generations to Come

Notice of Intent to Publish a Funding Opportunity Announcement for Early Intervention to Promote Cardiovascular Health of Mothers and Children (ENRICH).
Seeking applications to test the effectiveness of an implementation-ready intervention designed to determine if a cardiovascular health (CVH) promotion module delivered within the context of a home visiting program can enhance maternal and early childhood CVH and address CVH disparities in both mothers and children (0-5 years).

Topics of interest are available in this link:
Notice of Special Interest (NOSI): Understanding Factors in Infancy and Early Childhood (Birth to 24 months) That Influence Obesity Development. Notice Number: NOT-HL-19-695

Children’s [Human] Health Exposure Analysis Resource (CHEAR/HHEAR)

https://www.niehs.nih.gov/research/supported/exposure/chear/index.cfm

Adolescent Brain Cognitive Development®
Testing new ways of
1. treating HTN in clinical practice (G3: Optimize Patient Care)
2. improving HTN care in clinical practice (G3: Optimize Patient Care)
3. taking HTN care to people outside clinical settings with a focus on health disparities communities (G2: Ensure That the Places Where People Live, Learn, Work, and Play Support Hypertension Control)
4. implementing evidence-based care in the community: DECIPHeR, our signature program! (G2: Ensure That the Places Where People Live, Learn, Work, and Play Support Hypertension Control)
5. Educating the public on Heart Health (G1: Make Hypertension Control a National Priority)
6. Setting the research agenda through workshops
Achieving healthy behaviors
- Addressing root causes of obesity- and aging-related increases in BP

Managing chronic conditions in healthcare systems
- Creating systems of team care & simplified treatment strategies
- Enabling more effective IT resources/tools
- Evidence-based incentives for sustained organizational commitment to HTN control

Engaging patients
- Addressing social determinants
- Improving adherence and expanding community engagement
- Removing barriers to control (telemedicine, home blood measurement)
Reducing the burden of Heart Failure

Moving from Heart Failure to Heart Healthy
Heart Failure with Preserved Ejection Fraction (HFpEF) is a critical public health problem

- 6.2 M Americans with HF
- 40-50% with HFpEF
- 46% increase by 2030
- Disparities among Blacks, LatinX
- Diagnostic limitations
- Lack of a single biomarker
- Underuse of stress testing
- Barriers for research
- Drug intervention trials for ace inhibitors, ARBs, aldosterone antagonists, ARNIs have been neutral
- The current understanding of HFpEF suggests chronic systemic inflammation unique from HFrEF

Tromp J, JACC, 2018
HFpEF is a diverse clinical syndrome for which a phenotype-specific treatment strategy is necessary.

There are many potential therapeutic targets for HFpEF.
HeartShare initiative

Conduct large-scale analysis of phenotypic data, images, and omics from patients with heart failure with preserved ejection fraction (HFpEF) in order to characterize mechanisms of disease and identify therapeutic targets.

Define sub-phenotypes of HFpEF by integrating existing phenotypic data on HFpEF subjects and controls from NIH cohorts and trials.
Understand mechanisms of disease by integrating existing omics data across cohorts, including TOPMed, and generating new omics data.

Investigate sub-phenotypes of HFpEF through deep phenotyping of a new cohort of recently diagnosed HFpEF subjects and controls.
Identify and validate biologic targets through multi-omics evaluation of blood, urine, tissue.

RFA-HL-21-015 HeartShare: Next-Generation Phenomics to Define Heart Failure Subtypes (U01 Clinical Trial Not Allowed)

RFA-HL-21-016 HeartShare: Next Generation Phenomics to Define Heart Failure Subtypes and Treatment Targets Data Translation Center (U54 Clinical Trial Not Allowed)
Rising to the Public Health Challenge of COVID-19: The Community-Engaged Research Imperative

**HEART**
- Cardiovascular Complications

**LUNG**
- Acute Respiratory Distress Syndrome (ARDS)
- Acute Respiratory Failure

**BLOOD**
- COVID-19–Associated Coagulopathy (CAC)

**SLEEP**
- Sleep Quality Impact on Complications

Those with underlying health conditions, such as chronic lung disease, cardiovascular disease, and diabetes mellitus, appear to be at higher risk for severe COVID-19–associated disease.

COVID-19 Cases in the U.S. as of October 20, 2020

<table>
<thead>
<tr>
<th>Total Cases</th>
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<tbody>
<tr>
<td>&lt;14K</td>
</tr>
<tr>
<td>&lt;39K</td>
</tr>
<tr>
<td>&lt;90K</td>
</tr>
<tr>
<td>&lt;163K</td>
</tr>
<tr>
<td>&lt;347K</td>
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<tr>
<td>&lt;867K</td>
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</table>

23 CDC COVID Data Tracker
Full Court Press Framework Addressing Near and Long-Term Impact of COVID-19

**Goals**

- Reduce case severity/fatality, speed recovery
- Understand short- and long-term trajectory
- Enable risk stratification, precision interventions
- Identify biomarkers and therapeutic targets
- Target populations most severely affected

**Host-Directed Therapeutics Clinical Trials**

**Observational/Longitudinal Studies**

**Translational/Pre-Clinical Studies**

**Data Resources and Platforms**

**Community-Engaged Research**
NHLBI Clinical Research Portfolio: Therapeutic Targets Across the Clinical Course of COVID-19

Host-Directed Therapeutics Clinical Trials & Case Registries

Patient Populations

**Pre-hospital Outpatient**

- **Anti-Thrombotic**
  - ACTIV – 4B

- **Passive Immunity**
  - C3P0 – Convalescent Plasma

- **Anti-Inflammatory**
  - COLOCORONA
    - Colchicine

**Hospitalized Patients (+/- ventilatory support)**

- **Anti-Thrombotic**
  - ACTIV – 4A

- **Passive Immunity**
  - ACTIV – 3
    - Monoclonal Antibodies

- **Anti-Inflammatory**
  - ORCHID
    - Hydroxychloroquine* (closed)

**Post-hospital Convalescent Patients**

- **Anti-Thrombotic**
  - ACTIV – 4C

**Observational Studies**

- Understand disease pathobiology and long-term outcomes
- Assess blood safety and sero-surveillance

*Trial ended in June 2020 following 4th DSMB determined drug unlikely to be beneficial to Hospitalized COVID-19 patients

25
Collective Response to a Global Pandemic: Leveraging NHLBI Resources Through CONNECTS

“Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies”

- Comprehensive, expandable platform linking trial network, registries and cohorts
- Leveraging existing assets, data and studies
- Facilitating case finding, clinical trial accrual, longitudinal studies, and community engagement
Advancing Comprehensive Understanding of Multisystem Inflammatory Syndrome in Children with COVID-19 (MIS-C)

MIS-C Cases in the U.S.
- >1,000 cases in U.S.
- >70% cases in children who are Hispanic or Black
- 80% required ICU and Cardiovascular involvement also seen in 80%
- Launched long-term observational study (MUSIC) 9/30/20 - Clinical-physio-molecular characterization and follow-up for 5 yrs.

https://www.cdc.gov/mis-c/cases/index.html
Feldstein et al. NEJM. 2020
Impact of COVID-19 Across the U.S.: Disproportionately Affecting Communities of Color

Disparities in case rates and risk of hospitalization and death from COVID-19 in minority communities

CDC COVIDView

https://ehe.amfar.org/
Reducing the Burden of COVID-19 on Our Hardest-Hit Communities Through Engagement

Community Engagement Alliance Against COVID-19 Disparities (CEAL)

- Community-engaged research and outreach focused on COVID-19 awareness and education
- Addressing misinformation and mistrust
- Promoting and facilitating inclusion of diverse racial and ethnic populations in clinical trials
- Targeting populations disproportionately affected by the pandemic

11 states identified as part of the alliance

https://ehe.amfar.org/
NIH Community Engagement Alliance (CEAL) Against COVID-19 Disparities

Establish Partnerships within the Community

Address Misinformation within Communities of Color

Foster an Understanding and Trust in Science

Accelerate Inclusive Participation and Uptake of Beneficial Treatments

Trans-NIH initiative leading outreach, engagement and inclusive participation efforts in ethnic and racial minority communities disproportionately affected by the COVID-19 pandemic
Creating Partnerships that Share Trustworthy Information

CEAL Teams: Addressing the adverse impact of misinformation and distrust in COVID-19 research

Work with trusted messengers within communities

Create mechanisms and tools to support community-engaged research

“Recruiting Black volunteers for vaccine trials during a period of severe mistrust of the federal government and heightened awareness of racial injustice is a formidable task.”

“Recruiting Black volunteers for vaccine trials during a period of severe mistrust of the federal government and heightened awareness of racial injustice is a formidable task.”

“I Won’t Be Used as a Guinea Pig for White People,” The New York Times, October 7, 2020
“Resilience is the ability of living systems to successfully maintain or return to homeostasis in response to physical, molecular, individual, social, societal, or environmental challenges or stresses.”
The Concept of Resilience
Current NHLBI Portfolio Landscape

Search terms:
- Resist
- Recover
- Withstand
- Re-adjust
- Adaptive
- Challenge
- Healthy-aging
- Resilience
- Elasticity
- Recovery
- Adaptability
- Positive psychology
- Psychological-resilience
- Physiologic-resilience
- Well-being
- Positive-deviants
- Adaptation
- Health-maintenance
- Coping
- Self-efficacy
- Mastery
- Collateral
- Restoration
- Reperfusion
- Susceptibility
- Resistance
- Neoangiogenesis
- Vasculogenesis
- Revascularization, Immune response, lymphangiogenesis

Resilience intersects with all other DCVS SVIP

NIH
National Heart, Lung, and Blood Institute
Resilience Workshops

- Enhancing Resilience for Cardiovascular Health and Wellness, 2018

- Exerkines in Health, Resilience and Diseases, 2020
  - Discovery of exerkines is only beginning and more to be discovered
  - Mechanisms of how exerkines work are largely unknown
  - Better understanding of interorgan communication of exerkines in humans is needed
  - Data of the roles of genetics, gender, race, and ethnicity on effects of exerkines is lacking
  - Development in phenotypic measures and biomarkers for resilience in health and disease state is warranted
  - No guidance is currently available on how to best use large databases (i.e. [http://www.metamex.eu/](http://www.metamex.eu/)) for future studies
Exploring the Role of Endothelial Cell Resilience in Cardiovascular Health and Disease

Gao & Galis, Oct 2020
https://www.ahajournals.org/doi/abs/10.1161/ATVBAHA.120.314346
Vascular Dementia: Where can we be in 10 years?

- What vascular pathologies contribute to cognitive impairment or dementia?
  How?
- Noninvasive biomarkers (including imaging tools) for early diagnosis of dementia
- When to intervene and how? Who to treat?

Can we bend the curve?

Adapted from https://www.alzsd.org/resources/other-dementias
Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Treatment Group</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Standard</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. With Outcome/Person-Years</td>
<td>149/20 569</td>
<td>176/20 378</td>
<td>Cases per 1000 Person-Years</td>
<td>7.2</td>
<td>8.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.83 (0.67-1.04)</td>
<td>0.81 (0.69-0.95)</td>
<td>P Value</td>
<td>.10</td>
<td>.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild cognitive impairment&lt;sup&gt;b&lt;/sup&gt;</td>
<td>287/19 690</td>
<td>353/19 281</td>
<td>Cases per 1000 Person-Years</td>
<td>14.6</td>
<td>18.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite of mild cognitive impairment or probable dementia</td>
<td>402/19 873</td>
<td>469/19 488</td>
<td>Cases per 1000 Person-Years</td>
<td>20.2</td>
<td>24.1</td>
<td>0.85 (0.74-0.97)</td>
<td>.01</td>
</tr>
</tbody>
</table>

<sup>a</sup> Intensive treatment group vs standard treatment group based on Cox proportional hazards regression.

<sup>b</sup> Participants adjudicated as having probable dementia at the first follow-up visit (year 2) do not contribute to the analyses of mild cognitive impairment.
Workshop on future clinical trials to test promising mechanisms for reducing vascular contributions to cognitive impairment and dementia, November 2019

Purpose
- To identify compelling research opportunities for clinical trials to test single or combined interventions for the primary and secondary prevention of vascular contributions to VCID.

Summary of Discussions
- Presentations and discussions were centered around:
  - What are the most important unanswered scientific questions from the current epidemiological studies and recently completed trials that address VCID risk factors for the prevention of cognitive impairment and dementia?
  - What questions are being answered by some of the ongoing trials, including the rrAD, U.S. POINTER, MIND, and SMARRT trials?
  - What is known about mechanisms of VCID that can inform VCID trials, and what are the opportunities to address mechanistic hypotheses in future VCID trials?

- Several important challenges and research opportunities.
  - In future trials of younger participants who are at lower risk for MCI and dementia, validated surrogate markers of MCI and dementia with good correlation to clinical outcomes would be useful trial endpoints. Although there has been progress in developing validated biomarkers, currently there are limitations for their use as primary outcome measures in efficacy trials.
  - In future trials involving high-risk participants, it may be useful to combine MCI and dementia endpoints.
  - Continuous measures of cognitive function have been used in observational studies, but their utility in efficacy trials has not yet been established.
One of the Largest Studies in Adults 75 Years or Older

PREVENTABLE is one of the largest research studies in older adults. The purpose is to learn if taking a statin could help older adults live well for longer by preventing dementia, disability, or heart disease. A statin is a commonly used drug to lower cholesterol.

Help us find out.

https://preventabletrial.org/home.cfm