NHLBI’s Strategic Plan Promotes Advances in Research Approaches

Research
- Informatics
- Systems analysis

Better Understanding

NHLBI
- Feedback

Improved Public Health
- Knowledge networks
- Education

Tools
- Infrastructure
- Technologies
- Teams
- Resources
- Workforce
Planning Principals

Our Approach
Work in partnership in an ever evolving environment.
NHLBI Strategic Plan Objectives

Develop a scientific blueprint for the next decade.

- A living, working plan from an inclusive and participatory process.
- Identify strategic priorities where NHLBI:
  - Initiates – does not happen unless the Institute takes a lead
  - Catalyzes – Institute facilitates the outcome
  - Supports – investigator-initiated research
NHLBI Strategic Plan Goals

Goal 1
Improve understanding of the molecular and physiologic basis of health and disease. Use that understanding to develop improved approaches to disease prevention, diagnosis and treatment. *Form → Function*

Goal 2
To develop personalized preventive and therapeutic regimens for cardiovascular, lung, and blood diseases. *Function → Cause*

Goal 3
Generate an improved understanding of the processes involved in translating research into practice and use that understanding to enable improvements in public health and to stimulate further scientific discovery. *Cause → Cures*
NHLBI Strategic Plan Leads Toward Personalized / Pre-emptive Medicine

Prevent Disease

Personalize Care

Cure Disease

Strategic Plan
### Need to Transform Medical Research in the 21st Century

#### 20th Century

- Treat disease when symptoms appear and normal function is lost
- Did not understand the molecular and cellular events that lead to disease
- Expensive in financial and disability costs

#### 21st Century

- Intervene before symptoms appear and preserve normal function for as long as possible
- Understanding preclinical molecular events and ability to detect patients at risk
- Orders of magnitude more effective
The Future Paradigm: Transform Medicine from Curative to Preemptive

Predictive ↔ Personalized ↔ Preemptive

Participatory
NHLBI Strategic Plan Goals

**Cohort Studies:**
- Heart
- Lung
- Blood
- Sleep

**Analysis:**
- ENDGAME
- GEI Analysis of GxE

**Pharm-genomics, Gene-Environment:**
- PGKB
- PROGENI
- GEI

**WGAS’s:**
- FHS, JHS SHARe
- STAMPEDE
- WHGS and WHI
- CARE WGAS
- GAIN and GEI

**Functional & Mechanistic Studies**
- CARE Genotyping
- NHLBI rsNg
- SHARe Follow-up Studies
- GEI and Other Resequencing

**Genomic Clinical Trials**
- PGAs
- Proteomics
- KOMP
- Animal Models

**Applications for Genomic Medicine**
- Training Programs
- Clinical Networks

**Predict**
**Prevent**
**Personalize**

- Genome-Wide Association
- Independent Replication
- Genotyping/Sequencing
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Programs of Genomic Applications

To develop information, tools, and resources to link genes to biological function on a genomic scale. To provide workshops, courses, and visiting scientist programs to facilitate the training of researchers in the use of the data and related technologies developed by the PGAs.
PGA Web Sites
NHLBI Resequencing and Genotyping Service

The National Heart, Lung, and Blood Institute (NHLBI) has funded the Resequencing and Genotyping (RS&G) Service to provide DNA resequencing and genotyping services at no charge to qualifying investigators seeking to identify a correlation to specific regions of the genome for heart, lung, blood, and sleep diseases and disorders. The RS&G Service only considers investigations using human DNA. Preference is given to researchers investigating the genetic components involved in the cause, variable outcome, and progression of heart, lung, blood, and sleep diseases and disorders.

Interested investigators must apply through this Web site for the service, which is provided free of charge to qualifying applicants.

Application Information

- Application Guidelines
  Visit our Application Guidelines page to learn more about the process and to see if your project qualifies.

- How to Apply
  You can learn about the application process by visiting our How to Apply page.
  For issues related to the application process or general comments regarding the website, please send email to nhlbi_rsg@nhlbi.nih.gov.
NIH Knockout Mouse Project

http://www.knockoutmouse.org/

Center for Fetal Monkey Gene Transfer for Heart, Lung, and Blood Diseases

- Evaluate the safety and efficiency of gene transfer strategies as they emerge
- Use established monkey models to explore fetal approaches for heart, lung, and blood diseases
- Provide NHLBI-funded investigators with essential expertise and resources - *annual call for proposals for studies with monkeys at no cost*

[www.CFMGT.ucdavis.edu](http://www.CFMGT.ucdavis.edu)
(also linked from NHLBI web site: [www.nhlbi.nih.gov/resources/resources.htm](http://www.nhlbi.nih.gov/resources/resources.htm))
NHLBI Proteomics Initiative
http://www.nhlbi-proteomics.org/

Welcome

The National Institute of Heart Lung and Blood has established a consortium of 10 highly interactive, multi-disciplinary Proteomic Centers to enhance and develop innovative proteomic technologies and apply them to relevant biological questions that will advance our knowledge of heart, lung, blood, and sleep health and disease.

This NHLBI Proteomics Initiative is intended to complement and enhance the NHLBI's ongoing research programs, which include a substantial investment in clinical research, genomic research, basic biology, technologies, and training and education programs.

"Visit the Proteomics Portal!"

Read about Dr. Semenza's lab at Johns Hopkins NHLBI Proteomics Center identifying role for RACK1 in oxygen-independent regulation of HIF-1α Spring 2007 NewsSpots
Highly interactive, multi-disciplinary Proteomic Centers to enhance and develop innovative proteomic technologies and apply them to relevant biological questions.
NHLBI Clinical Proteomics Program

Goals of the Clinical Proteomics Program

- Facilitate validation of protein panels that can be used to predict disease susceptibility
- To assist in differential diagnosis, disease staging, selection of individualized therapies, and monitoring of treatment responses
- To establish a high quality education and skills development program
- Design panels of candidate proteins for disease areas
- Develop high throughput analytic methodologies
- Assess predict value of proteomic measurements using biological and clinical information
- Establish procedures and standards for quality control

http://www.mc.vanderbilt.edu/root/vumc.php?site=proteomics
NHLBI Gene Therapy Resource Program (GTRP)

- Facilitate the translation of basic research in gene therapy to clinical application in heart, lung and blood diseases
- Provide the resources needed for gene therapy trials
- Provide support for gene therapy clinical protocols and assistance on regulatory issues

Gene Therapy image from Nikolaus Fiebiger Center of Molecular Medicine, University Erlangen-Nuernberg
NHLBI Production Assistance for Cellular Therapies (PACT)

- Manufacture a clinical grade product for PIs lacking a cGMP facility
- Work closely with FDA to facilitate translation to clinical studies
- Three Cell Processing Centers:
  - Baylor College of Medicine
  - University of Minnesota
  - University of Pittsburgh
- Application and Information at: http://www.pactgroup.net/
The goal of the Pediatric Circulatory Support program is to develop novel circulatory assist devices or other bioengineered systems for infants and children with congenital and acquired cardiovascular disease who experience cardiopulmonary failure and circulatory collapse.
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Imaging Plaque Using Nanotechnology

Target validation

Plaque regression in vivo

Circulation 114:1504, 2006 Nahrendorf et al
Developments of tools to reliably diagnose high risk atherosclerotic plaques that may cause clinical events at an early stage are critical. A multidisciplinary approach that combines state-of-the-art imaging technologies with a fundamental understanding of the cellular and molecular architecture of animal and human atherosclerotic plaques was used to detect and provide information on plaque pathology and the nature of its content. For the first time, high resolution imaging of atherosclerotic plaque components using intravascular magnetic resonance imaging (IVMRI) has been accomplished in humans. Improvement is shown in the next slide.
Shear Stress and Atherogenesis

Wall shear stress

Pro-atherogenic marker expression

Arterioscler Thromb Vasc Biol 2006 27:346 Suo et al
A mouse engineered to harbor a Marfan-associated mutation in the fibrillin-1 gene recapitulates the human phenotype.

<table>
<thead>
<tr>
<th>Bone Overgrowth</th>
<th>Emphysema</th>
<th>MVP</th>
<th>Myopathy</th>
<th>Aneurysm</th>
</tr>
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<tbody>
<tr>
<td>Nml</td>
<td>![Image]</td>
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<tr>
<td>MFS</td>
<td>![Image]</td>
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Neptune...and Dietz, *Nature Genetics*, 2003
Judge...and Dietz, *JCI*, 2004
Habashi...and Dietz, *Science*, 2006
Cohn...and Dietz, *Nature Medicine*, 2007

Marfan Syndrome: Bedside to Bench
Losartan Prevents Aortic Aneurysm and Attenuates Other Phenotypes in a Mouse Model of Marfan Syndrome

MFS

MFS + Los

Habashi…and Dietz, Science, 2006
Cohn…and Dietz, Nature Medicine, 2007
Marfan Syndrome: Bench to Bedside

- Pilot data in two children showed dramatic arrest of aortic root growth with Losartan
- NHLBI able to take advantage of Pediatric Heart Network (www.PediatricHeartNetwork.com)
- Randomized trial of losartan vs. atenolol in 600 patients 6 mos – 25 years old launched February 2007
- Reinventing the clinical research enterprise: unique partnership with National Marfan Foundation, FDA’s Orphan Drug Program, Merck, Novopharm
- Unique opportunity for pediatric translational research
National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Associated Cardiovascular Conditions

- To facilitate research to improve diagnosis and management of genetically induced thoracic aortic aneurysms
- Includes syndromes such as Marfan, Ehlers-Danlos, Loeyz-Dietz, and Turner Syndromes
- Will collect genetic and medical data, biospecimens, and DNA
- Will make data, biospecimens, and DNA available to investigators for research
Basic and Translational Research in Peripheral Arterial Disease (PAD)

Pathophysiology--genetic determinants, biomarkers, roles of inflammation, insulin resistance, and endothelial dysfunction.

Clinical studies--of exercise, endovascular intervention and lipid modification in PAD. Endpoints range from functional activity level to volume of arterial atherosclerotic plaque burden.

Imaging--development of noninvasive Magnetic Resonance, Intravascular Ultrasound, and hyperspectral technologies for diagnostic and serial follow-up applications in PAD.
Personalized Medicine for HLBS

Total Cavopulmonary Connection Flow With Functional Left Pulmonary Artery Stenosis
Angioplasty and Fenestration In Vitro
Kerem Pekkan, PhD; Hiroumi D. Kitajima, MSc; Diane de Zelicourt, MSc; Joseph M. Forbess, MD; W. James Parks, MD; Mark A. Fogel, MD; Shiva Sharma, MD; Kirk R. Kanter, MD; David Frakes, PhD; Ajit P. Yoganathan, PhD

Yoganathan and colleagues

- Use MRI to define total cavopulmonary connection (TCPC) anatomy in individual patients
- Use computational fluid dynamics to evaluate and predict resulting flow
- Goal of individualized surgical planning
Introduction of a New Optimized Total Cavopulmonary Connection
Dennis D. Soerensen, MS, Kerem Pekkan, PhD, Diane de Zelicourt, MS, Shiva Sharma, MD, Kirk Kanter, MD, Mark Fogel, MD, and Ajit P. Yoganathan, PhD

Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, Georgia; Carnegie Mellon University, Pittsburgh, Pennsylvania; Pediatric Cardiology Associates, Department of Surgery, Emory University, Atlanta, Georgia; and Division of Cardiology, The Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania

Yoganathan and colleagues
The individualized studies suggest a new design for the total cavopulmonary connection (TCPC)
Using new molecular and genetic approaches, the cause of high cholesterol levels in hypercholesterolemics was discovered as due to defects in the LDL receptor gene responsible for clearing cholesterol from plasma.

The extensive basic science knowledge gained led to the discovery of “statins” which inhibits the activity of a key enzyme in the biosynthetic pathway of cholesterol, and to the discovery of Ezetimibe that acts via a complementary pathway to statins.

Molecular genetic studies in humans identified a proprotein (PCSK9) that reduces the number of LDL receptors (LDLR) and lowered risk of developing atherosclerosis in affected individuals.

PCSK9 could be considered as a biological marker that can regulate the levels of LDL receptors.

Targeting PCSK9 in the bloodstream has the potential to control plasma cholesterol levels and could be explored for the treatment of hypercholesterolemia.
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NHLBI GWAS Related Programs

- SNP Health Association Resource (SHARe)
- Candidate Gene Association Resource (CARE)
- SNP Typing for Association with Multiple Phenotypes from Existing Epidemiologic Data (STAMPEED)
- Enhancing Development of Genome-wide Association MEthods (ENDGAME)
- Genetic Analysis Information Network (GAIN)
The greatest public benefit will be realized if data from GWAS are made available, under terms and conditions consistent with the informed consent provided by individual participants, in a timely manner to the largest possible number of investigators.
dbGaP
Variations in Drug Response

All patients:
- Same diagnosis,
- Same drug

Different Responses
- No Benefit
- + Benefit
- No Toxicity
- + Toxicity
- No Benefit
- No Toxicity
Pharmacogenetics and Gene-Environment Interactions

NHLBI Ancillary Pharmacogenetic Studies
https://www.pharmgkb.org/views/loadNhlbiMembers.action

Pharmacogenetics Research Network
http://www.nigms.nih.gov/pharmacogenetics

PROGENI Network
NHLBI GxE Interaction Studies
http://www.biostat.wustl.edu/progeni/
Randomized Trial of Genotype-Guided Dosing of Warfarin Therapy

Large, multicenter, double-blind, randomized trial comparing three possible approaches to guiding warfarin therapy initiation:

- initiation of warfarin therapy based on an algorithm using clinical information and the individual’s genotype relative to two genes known to influence warfarin metabolism (CYP2C9 and VKORC1 genes)
- initiation of warfarin therapy based on an algorithm using only clinical information
- standard, guideline-based initiation strategy

NHLBI-HV-08-03
Response Date: June 20, 2007

http://www.fbo.gov/spg/HHS/NIH/NHLBI/NHLBI%2DHV%2D08%2D03/listing.html
Randomized Trial of Genotype-Guided Dosing of Warfarin Therapy Draft Flowchart

Eligibility: Patients with > 3 months indication for warfarin therapy
Exclude: Patients with contra-indication to warfarin therapy

Randomized 1:1:1

Rapid (< 24 hours) Genotyping for 2C9 and VKORC 1 Genotypes

Clinical and Genotype Algorithm-Based Initiation Strategy
N = 655

Clinical Algorithm Based-Initiation Strategy
N = 655

Standard, Guideline-Based Initiation Strategy
N = 655

Subsequent doses adjustments based on INR response to the initial doses with dosage increments or decrements relative to first dose following a standardized protocol
Genes and Environment Initiative
http://genesandenvironment.nih.gov/

EXPOSURE BIOLOGY PROGRAM
- Develop technology and biomarkers
  - Nutrition
  - Physical Activity
  - Environmental Exposures

GENETICS PROGRAM
- Identify genetic variants
  - GWA Studies
  - Data Analysis
  - Replication
  - Sequencing
  - Database
  - Function
  - Translation

GXE
Improvements in Image-Guided Surgery

3D ultrasound in robotic surgery: performance evaluation with stereo displays

Del Nido and colleagues

Improved techniques in image-guided surgery reduce collateral trauma and enable earlier intervention before symptoms become established.
Investigation of Intensity Thresholds for Ultrasound Tissue Erosion

Zhen Xu,* J. Brian Fowlkes,*† Achi Ludomirsky,‡ and Charles A. Cain*

*Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA; †Department of Radiology, University of Michigan, Ann Arbor, MI, USA; ‡Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA

Cain and colleagues

Image-guided surgery can be performed using ultrasound directly to create tissue perforations, thus bypassing the need for even minimally-invasive surgical procedures.
Generate an improved understanding of the processes involved in translating research into practice and use that understanding to enable improvements in public health and to stimulate further scientific discovery. Cause → Cures

Intravascular magnetic resonance imaging (IVMRI) permitted the characterization of the fine structure and composition of arteries in the legs (iliac arteries) of human subjects. The individual components of the plaques were identified with adequate sensitivity and specificity to the extent that when a contrasting agent was used, the microvascular density and capillary permeability relative to surrounding tissues could be detected.

This represents an important advance in the field of atherosclerosis, with both clinical and research implications particularly for the assessment of plaque-stabilizing therapies and ultimately for reducing cardiovascular events.
Patch Replacement of Heart Muscle

PEUU scaffold

RVOT repair with PTFE or PEUU

Integration of tissue with PEUU

Thoracic Aortic Aneurysms
Bedside to Bench

National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Associated Cardiovascular Conditions

- To facilitate research to improve diagnosis and management of genetically induced thoracic aortic aneurysms
- Includes syndromes such as Marfan, Ehlers-Danlos, Loeyz-Dietz, and Turner Syndromes
- Will collect genetic and medical data, biospecimens, and DNA
- Will make data, biospecimens, and DNA available to investigators for research
DCVD Clinical Research Networks
Excel in Translational Research
Pediatric Heart Network

To help parents, patients, and healthcare professionals consider many aspects of joining a pediatric clinical study.
Resuscitation Outcomes Consortium

To conduct clinical research in out-of-hospital cardiopulmonary arrest & life-threatening trauma
Heart Failure Research Network

To expedite clinical research to evaluate the diagnosis, management, and treatment of heart failure
To promote and accelerate clinical research in the evaluation of novel cell therapy treatment strategies for individuals with cardiovascular disease.
Cardiothoracic Surgical Network

The goal is to inform the use of new interventions in surgical practice by moving promising therapies and techniques from the laboratory into clinical use.
# Cardiovascular Trials of Revascularization

<table>
<thead>
<tr>
<th>Trial</th>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BARI 2D</td>
<td>Type 2 Diabetes + CAD</td>
<td>CABG/PCI</td>
</tr>
<tr>
<td>CLEVER</td>
<td>Femoral Artery Stenosis</td>
<td>Femoral Artery Stent</td>
</tr>
<tr>
<td>CORAL</td>
<td>Renal Artery Stenosis + Hypertension</td>
<td>Renal artery stent</td>
</tr>
<tr>
<td>FREEDOM</td>
<td>Type 2 Diabetes + CAD</td>
<td>PCI versus CABG</td>
</tr>
<tr>
<td>STICH</td>
<td>Ischemic HF</td>
<td>CABG ± Surgical Ventricular Restoration</td>
</tr>
</tbody>
</table>
## Trials in Chronic CV Disease

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<thead>
<tr>
<th>Trial</th>
<th>Condition</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>AIM-HIGH</td>
<td>CHD + Atherogenic Dyslipidemia</td>
<td>Extended release niacin + statin vs statin</td>
</tr>
<tr>
<td>BARI 2D</td>
<td>Type 2 Diabetes + CAD</td>
<td>Insulin Sensitizing vs Insulin Providing</td>
</tr>
<tr>
<td>SANDS</td>
<td>Native Americans with Type 2 Diabetes</td>
<td>Intensive treatment of CV risk factors vs UC</td>
</tr>
<tr>
<td>TACT</td>
<td>CAD</td>
<td>Chelation Therapy (EDTA)</td>
</tr>
<tr>
<td>TOPCAT</td>
<td>HF with Preserved cardiac Function</td>
<td>Spirinolactone</td>
</tr>
</tbody>
</table>
## Trials in Acute CAD

<table>
<thead>
<tr>
<th>Trial</th>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMEDIATE</td>
<td>Acute Coronary Syndrome or MI</td>
<td>Glucose-Insulin-Potassium (GIK) Infusion</td>
</tr>
<tr>
<td>PACE-MI</td>
<td>Acute MI</td>
<td>Pacemaker-Facilitated Beta Blocker Therapy</td>
</tr>
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</table>
Training of New Clinical Investigators
Clinical Research Training Awards

- T32 Institutional pre- & post-doctoral training
- T35 Institutional short-term training
- K12 Institutional mentored clinical scientist program in vascular medicine (2007)
- NIH K99/ R00 Pathway to Independence award (2007)
- K08 Mentored early career clinical scientist award
- K23 Mentored early career patient-oriented research award
- K24 Mentored mid-career patient oriented research award
- K02 Independent scientist award
- K01 Mentored career development to promote diversity
- K07 Cultural competence & health disparities award
The goal is to offer comprehensive clinical research training for physicians wanting to specialize in the new & evolving discipline of vascular medicine.
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Partnering: Clinical Trials in Organ Transplantation (CTOT)

NIAID, NHLBI and NIDDK-sponsored Cooperative Research Network to conduct clinical and mechanistic studies with the goal of improving outcomes for recipients of solid organ transplants – heart, lung, kidney, liver.
Participatory Research

Deciding whether a child will participate in a clinical study can be especially difficult. This site was developed to help parents, patients, and healthcare professionals consider many aspects of joining a pediatric clinical study. The site was created and is maintained by the Pediatric Heart Network (PHN), which was established in 2001 by the National Heart, Lung, and Blood Institute to improve outcomes and quality of life in children who acquire or are born with heart disease.
Clinical trials have resulted in the everyday use of treatments and medication, often curing disease and making the management of healthcare conditions safer and more effective. Pediatric research is imperative to evaluate drugs and treatments in developing minds and bodies.

A Video For Parents

- The most important thing parents can do, when asked to participate in clinical research, is to get informed.
- Know all there is to know...about the child’s condition, the treatments available, the potential outcomes, the people involved, the risks and benefits...
- The answers are there – the questions just need to be asked. The more you know, the more you can feel good about your decision, whatever you decide.
Stay-in-Circulation Campaign

Peripheral Arterial Disease

The first national awareness campaign to increase public and health care provider awareness of PAD and its association with other cardiovascular diseases
NIH Core Strategic Vision

- Transform medicine and health from a Curative to a Preemptive paradigm
- Support basic research to identify the earliest molecular stages of disease in complex biological systems
- Accelerate translation of findings from the bench to the bedside to the community
- Provide the evidence and knowledge base to allow for a rational transformation of our healthcare system
Future Directions

- **Basic Discovery**
  - Genomics
  - Proteomics

- **Clinical**
  - Stem Cell Research
  - Tissuegenesis

- **Communication**
  - Cell Imaging
  - Translational
The Future Paradigm: Preempt Disease

- **Disease Burden**
  - Preclinical
  - Tolerable
  - Intolerable

- **Cost Savings**
- **Molecular preemption**
- **Symptom management**
- **Curative treatment**

- **Time**
- **Cost**
Goal One: Form to Function

Goal 1: To improve understanding of the molecular and physiological basis of health and disease and use that understanding to develop improved approaches to disease diagnosis, treatment, and prevention.

Challenge 1.1
To delineate mechanisms that relate molecular events to health and disease.

1.1.a Develop a detailed understanding of the molecular, cellular, and physiological mechanisms that maintain health from embryonic development to the end of the human lifespan.

1.1.b Identify intracellular targets of key signaling and transcriptional pathways in normal and pathologic states.

1.1.c Determine key genetic variants that are associated with specific diseases and delineate the molecular mechanisms that account for susceptibility or resistance to disease.

1.1.d Define molecular, cellular, and organ-specific responses to environmental challenges, and the mechanisms by which heritable and non-genetic factors interact in disease initiation and progression and in therapeutic response.

1.1.e Determine the role of systemic pathological processes, such as inflammation, immunity, and infection, in the development and evolution of disease.
**Challenge 1.2**

To discover biomarkers that differentiate clinically relevant disease subtypes and that identify new molecular targets for application to prevention, diagnosis – including imaging, and therapy.

1.2.a Identify molecular signatures that allow complex disease phenotypes to be stratified into clinically relevant categories.

1.2.b Develop in vivo molecular imaging methods and probes for investigating the biology of disease processes.
Goal Two: Function to Causes

**Goal 2:** To improve understanding of the clinical mechanisms of disease and thereby enable better prevention, diagnosis and treatment.

**Challenge 2.1**
To accelerate translation of basic research findings into clinical studies and trials and to promote the translation of clinical research findings back to the laboratory.

2.1.a Integrate advances in regenerative biology to develop clinically feasible applications.
2.1.b Apply discoveries in nanotechnology to the development of new diagnostic and therapeutic strategies.
2.1.c Integrate, analyze, and share extant and emerging genotypic and phenotypic data.

**Challenge 2.2**
To enable early and accurate risk stratification and diagnosis of cardiovascular, lung, and blood disorders.

2.2.a Exploit noninvasive imaging methods to detect and quantify subclinical disease.
2.2.b Apply new discoveries in biomarkers to improve risk assessment, diagnosis, prognosis, and prediction of response to therapy.
Goal Two: Function to Causes (continued)

**Challenge 2.3**
To develop personalized preventive and therapeutic regimens for cardiovascular, lung, and blood diseases.

- **2.3.a** Improve the understanding of the interactions between genetic and environmental factors that influence disease development and progression and response to therapy.

- **2.3.b** Identify and evaluate interventions to promote health and treat disease in genetically defined patient subgroups by altering developmental or environmental exposures including drugs, diet and exercise, sleep duration and quality, and infectious agents and allergens.

**Challenge 2.4**
To enhance the evidence available to guide the practice of medicine, and improve public health.
Goal Three: Causes to Cures

**Goal 3:** To generate an improved understanding of the processes involved in translating research into practice and use that understanding to enable improvements in public health and to stimulate further scientific discovery.

**Challenge 3.1**
To complement bench discoveries and clinical trial results with focused behavioral and social science research.

- **3.1.a** Develop and evaluate new approaches to implement proven preventive and lifestyle interventions.
- **3.1.b** Develop and evaluate policy, environmental, and other approaches for use in community settings to encourage and support lifestyle changes.
- **3.1.c** Develop and evaluate interventions to improve patient, provider, and health system behavior and performance in order to enhance quality of care and health outcomes.
**Challenge 3.2**

To identify cost-effective approaches for prevention, diagnosis, and treatment.

- **3.2.a** Evaluate the risks, benefits, and costs of diagnostic tests and treatments in representative populations and settings.
- **3.2.b** Develop research designs, outcome measures, and analytical methods to assess prevention and treatment programs in community and health-care settings across populations and lifespan.

**Challenge 3.3**

To promote the development and implementation of evidence-based guidelines in partnership with individuals, professional and patient communities, and health care systems and to communicate research advances effectively to the public.

- **3.3.a** Establish evidence-based guidelines for prevention, diagnosis, and treatment and identify gaps in knowledge.
- **3.3.b** Develop personalized and community- and health care system-oriented approaches to increase the use of evidence-based guidelines by individuals, communities, health care providers, public institutions, and, especially, by populations that experience a disproportionate disease burden.
- **3.3.c** Communicate research advances effectively to the public.