Shaping the Future of Research

A Strategic Plan for the National Heart, Lung, and Blood Institute

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

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People Science Health

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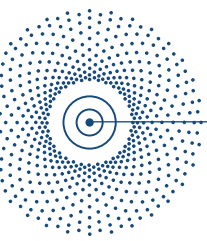

Welcome from the Director

I am delighted to present the Strategic Plan of the National Heart, Lung, and Blood Institute. This plan reflects the intellectual energy of over 600 individuals representing an international spectrum of expertise in areas of relevance to the Institute's mission. We are proud of the important role that the Institute has played historically in shaping the prevention and treatment of heart, lung, and blood diseases worldwide. We look forward with great enthusiasm to building upon this tradition and broadening our impact in the years to come. We invite you to join us in this grand adventure.

With best wishes,

Elizabeth G. Nabel, M.D.
Director

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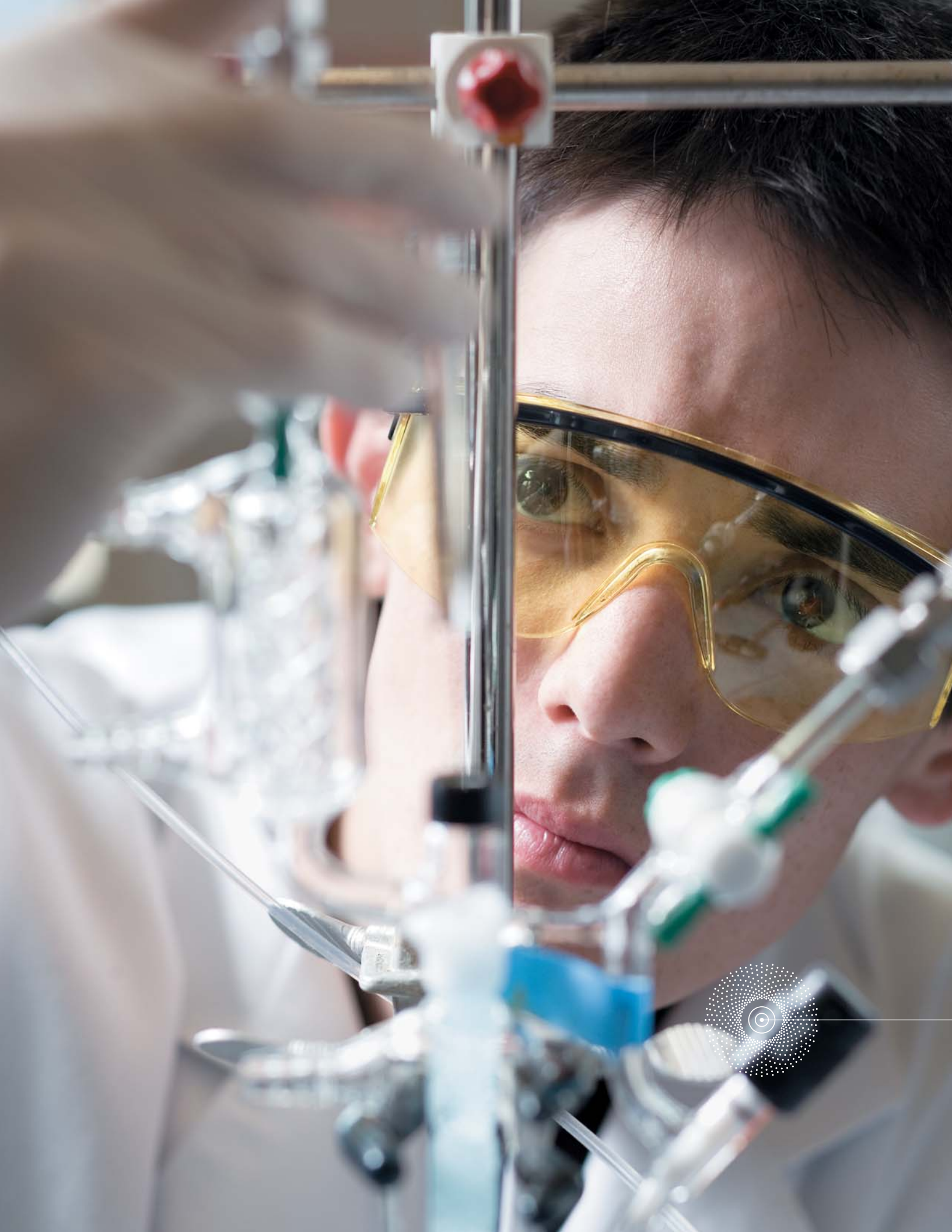
Introduction

The National Heart, Lung, and Blood Institute (NHLBI) has a distinguished record of supporting and guiding seminal advances in heart, lung, and blood research that have yielded unprecedented improvements in the Nation's health. Building on the Institute's numerous accomplishments, we now have an opportunity to develop a heart, lung, and blood research agenda for the United States that will lead to even greater successes. This is our challenge—and our obligation, as stewards of Federal research dollars.

Heart, lung, and blood research can be expected to change dramatically over the next several decades in response to the major drivers of research activity: information technologies that link scientists and their findings globally and instantaneously; accelerating health care costs; an aging population of baby boomers who can expect to live longer, more productive lives, even in the face of chronic diseases; and the development of increasingly sophisticated research tools and databases.

This strategic plan is intended to provide the NHLBI with a guide for its research and training programs over the next 5 to 10 years. It is not intended to provide a detailed implementation plan to address the challenges it identifies—that will be developed by the Institute over the life of the strategic plan in consultation with the National Heart, Lung, and Blood Advisory Council (NHLBAC) and with representatives from the research community and the public—and it is not intended to address matters that are beyond the scope of the Institute's mandate. We expect that implementation of the plan will require the Institute to continue to develop and explore effective ways to collaborate with other agencies of the Federal government; with other governmental agencies, both domestic and foreign; and with nongovernmental organizations, both public and private. Our success in implementing the plan will be evaluated on an ongoing basis by the Institute with advice and guidance provided by the NHLBAC.

This strategic plan reflects the wisdom, advice, and judgment of more than 600 individuals who participated in its preparation, all of whom are identified in the Appendix. We are indebted to them and to the scientific communities they represent for their commitment to the excellence and productivity of the Institute. Their further participation in the strategic plan will ensure its successful implementation and its continued evolution in response to new challenges and discoveries. We are also indebted to the many individuals and organizations that contributed their insights to the plan during the time that it was open for public comment.



Executive Summary

The National Heart, Lung, and Blood Institute provides global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood diseases and to enhance the health of all individuals so that they can live longer and more fulfilling lives. The breadth of the Institute's programs reflects the breadth of its mandate, which includes three of the four leading causes of death in the United States. To achieve its vision, the NHLBI stimulates basic discoveries about the causes of disease, speeds the translation of basic discoveries into clinical practice, fosters training and mentoring of emerging scientists and physicians, and communicates research advances to the public.

This strategic plan is intended to provide the NHLBI with a guide for its research and training programs over the next 5 to 10 years. Investigator-initiated research has long constituted the largest share of the NHLBI research portfolio, and it is our intention to maintain that historical commitment. In fact, we expect that much of the plan will be realized through our investment in investigator-initiated research. Institute investments guided by this plan will be directed largely toward programs that either will enable or complement investigator-initiated activities.

The plan consists of a set of goals that reflects the successive movement of scientific discovery from "form to function" (Goal 1), "function to causes" (Goal 2), and "causes to cures" (Goal 3), with research challenges identified for each of the goals and a set of strategies to address the plan as a whole.

The goals are as follows:

Goal 1: To Improve Understanding of the Molecular and Physiological Basis of Health and Disease, and To 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 pathological 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 and 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 2: To Improve Understanding of the Clinical Mechanisms of Disease and Thereby Enable Better Prevention, Diagnosis, and Treatment.

Challenge 2.1: To accelerate the 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 the 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.

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

2.3.a. Improve the understanding of 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 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 care 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.

The strategies that will be used to address the preceding goals and challenges are listed below:

Strategy 1: Develop and facilitate access to scientific research resources.

Strategy 2: Develop new technologies, tools, and resources.

Strategy 3: Increase the return from NHLBI population-based and outcomes research.

Strategy 4: Establish and expand collaborative resources for clinical research.

Strategy 5: Extend the infrastructure for clinical research.

Strategy 6: Support the development of multidisciplinary teams.

Strategy 7: Develop and retain human capital.

Strategy 8: Bridge the gap between research and practice through knowledge networks.

The NHLBI, Past and Present

The National Heart Institute was established in 1948 through the National Heart Act, with a mission to support research and training in the prevention, diagnosis, and treatment of cardiovascular diseases. Twenty-four years later, through the National Heart, Blood Vessel, Lung, and Blood Act, Congress directed the Institute to increase and coordinate its activities to improve understanding and reduce the public health burden of heart, blood vessel, lung, and blood diseases. As a result, the Institute expanded its scientific areas of interest, intensified its efforts related to research on diseases within its purview, and re-emphasized its commitment to training the next generation of investigators in heart, lung, and blood research. It also assumed responsibility for the conduct of educational activities, including the development and dissemination of materials for health professionals and the public, with an emphasis on prevention. During the 1990s, the Institute was directed to expand its mandate to encompass sleep disorders through its administration of the National Center on Sleep Disorders Research and was charged with administering the Women's Health Initiative.

Today, the NHLBI provides 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. The breadth of the Institute's programs reflects the breadth of its mandate, which includes three of the four leading causes of death in the United States. While necessarily focusing considerable effort and resources on diseases that affect large numbers of people, the Institute also recognizes its obligation to address those conditions that do not themselves constitute a major public health burden but do impose serious health burdens on affected individuals.

To achieve its vision, the NHLBI stimulates basic discoveries about the causes of disease, speeds the translation of basic discoveries into clinical practice, fosters training and mentoring of emerging scientists and physicians, and communicates research advances to the public. The NHLBI creates and supports a robust, collaborative research infrastructure in partnership with private and public organizations, including academic institutions, industry, and government agencies. The NHLBI collaborates with patients, families, health care professionals, scientists, professional societies, patient advocacy groups, community organizations, and the media to maximize the use of research results and leverage resources to address the public health needs of the Nation.

All activities of the NHLBI are conducted in a spirit of public service and with a commitment to excellence, innovation, integrity, respect, compassion, and open communication.

Goals and Challenges

The structure of this plan reflects a successive movement of scientific discovery from "form to function," "function to causes," and "causes to cures." Although research priorities are provided for each of the plan's major goals, the NHLBI recognizes that the relevant fields, available technologies, and emerging biological principles are evolving rapidly. As a result, the NHLBI is committed to remaining vigilant in identifying—and nimble in embracing—critical research opportunities as they arise. The Institute will continue to look to the NHLBAC and to the larger research community for guidance and assistance in implementing the plan and ensuring that it is updated as needed to reflect the latest scientific advances.

The Institute also will continue to look to the larger research community to develop the ideas and conduct the studies that will advance our knowledge of heart, lung, and blood diseases and will enable its application in ways that will improve public health. Investigator-initiated research has long constituted the largest share of the NHLBI research portfolio, and it is our intention to maintain that historical commitment. In fact, we expect that much of the plan will be realized through our investment in investigator-initiated research and, especially, through those innovative investigator-initiated research projects that entail a high risk but offer the promise of especially high returns. Institute investments guided by this plan will be directed largely toward programs that will either enable or complement investigator-initiated activities.

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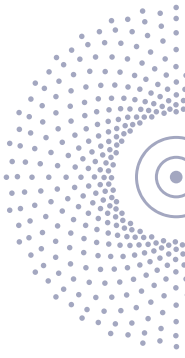


Goal 1: To Improve Understanding of the Molecular and Physiological Basis of Health and Disease, and To Use That Understanding To Develop Improved Approaches to Disease Diagnosis, Treatment, and Prevention.

To enhance understanding of the molecular and physiological basis of health and disease, the NHLBI has identified two priority objectives. The first is to delineate normal and pathological biological mechanisms. The second is to exploit the emerging understanding of these mechanisms to identify biomarkers of disease. The second challenge provides a natural link to the clinical and translational objectives that are considered subsequently in this plan because the goal of biomarker discovery is to identify markers that can be used to stratify diseases into distinct and clinically relevant molecular subtypes, monitor disease initiation and progression, and uncover potential therapeutic targets.

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

Recent technological advances offer new opportunities for investigating the molecular events associated with health and disease. The developing field of systems biology, for example, allows scientists to identify mechanistic relationships among the numerous individual molecules that constitute larger systems of cells, tissues, and organs and to generate predictive models of molecular, cellular, and physiological processes based on these mechanistic relationships. The models allow scientists not only to understand but also to anticipate the consequences of specific perturbations of molecular events. Such systems-level approaches have numerous applications to heart, lung, and blood investigations.

Since pathology and drug therapy represent medically relevant perturbations of normal biology, systems-level approaches are ideally suited for investigating and providing unique solutions to biomedical problems. Although already widely used in basic studies of health and disease, the combination of "-omics" technologies and integrative computational methods will increasingly play a major role in efforts to obtain a systems-level understanding of health and disease.

While a systems approach clearly will be important for pursuing Goal 1, many biological functions still are best studied using biochemical and biophysical methods applied at the level of individual or small numbers of molecules rather than at the systems level. Thus, if a complete understanding of normal and pathobiological conditions is to be achieved, future mechanistic investigations must strike a balance between highly reductionist and systems-level approaches, and integrate the two strategies to obtain a holistic view of health and disease.

In fact, no single strategy—however comprehensive—will be able to address every problem of biomedical interest to heart, lung, and blood investigators. More likely, investigational approaches will have to be customized based on the biological process or disease to be studied. Development and dissemination of new technologies throughout the research community will allow investigators the flexibility to draw on core experimental and computational methods that are suited to multiple applications.

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.

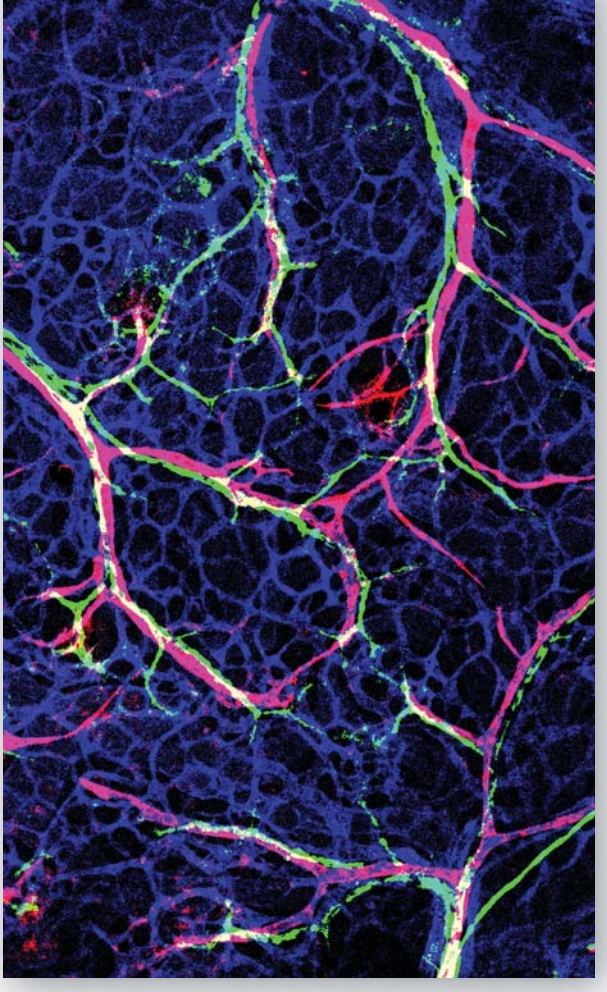
Developing a comprehensive understanding of the mechanisms involved in maintaining human health will require research approaches that are more multidisciplinary and integrative than those relied upon in the past. Scientists currently working in separate fields, such as tissue engineering and gene therapy, will need to work collaboratively to achieve an integrated understanding of relevant biological processes. Processes of interest to NHLBI investigators include tissue repair and regeneration; organ development (with an emphasis on stem cell biology, model organism genetics, and human congenital disorders); intrinsic and extrinsic mechanisms underlying the proliferation, differentiation, maturation, survival, and trafficking of stem and progenitor cells in different contexts; and roles played by growth factors, extracellular matrix, and cell-cell contact. The resulting information will be critical for understanding physiological mechanisms and applying the information to the development of cell-based therapies.

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

Research in model organisms and human systems has demonstrated that signaling and transcriptional pathways intersect to form higher order regulatory networks. Because the disruption of individual pathways may have adverse consequences that are manifested as disease, detailed characterization of regulatory networks at cellular, tissue, and whole-organism levels is essential. Research must progress beyond an understanding of static molecular relationships to the development of dynamic, quantitative models that are capable of predicting how subtle environmental or genetic perturbations alter normal function. Such models will help researchers to identify potential targets for therapeutic interventions and to anticipate not only the benefits but also the potential adverse effects of specific interventions. The new models also are expected to provide insights into variations among individuals in the response to interventions, a central goal of personalized medicine. Research to meet the challenge will require the use of emerging technologies such as high-throughput small-molecule gene and protein expression profiling, high-density genotyping, ribonucleic acid interference (RNAi) and chemical screening, protein interaction mapping, and computational methods that allow the integration and interrogation of disparate data sets relevant to heart, lung, and blood experimental systems.

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.

Most common diseases—including those of the cardiovascular, pulmonary, and hematopoietic systems—have a complex etiology that involves multiple genetic risk factors. Disease severity may vary greatly among affected individuals depending on the presence of genes that either enhance or suppress a disease phenotype. Researchers now are able to identify



disease susceptibility, resistance, and modifier loci using the completed human haplotype map in conjunction with new genomic mapping technology that permits cost-efficient detection of common polymorphic variants on a genome-wide scale in thousands of affected individuals and healthy controls. The NHLBI currently supports genetic association studies for a number of common heart, lung, and blood diseases and recognizes the importance of continuing its commitment to this promising area of research. However, conducting an association study is only the first step in identifying a disease gene. Researchers must independently replicate findings from an initial association study in a second cohort and then perform additional fine-mapping studies to select the causative gene from the possible candidates that maps to a chromosomal region of interest. Once researchers have determined that a gene variant contributes to disease susceptibility or resistance, additional research is required to determine its mechanism of action. Investigations that address mechanisms will intersect with other objectives of this strategic plan, notably those focused on gene and protein functions in health and disease. Finally, while some of the genetic variants associated with diseases relevant to the NHLBI mandate will be found at high frequency among affected individuals, rare variants also could be informative for understanding disease pathogenesis and for developing new treatments. The discovery of rare variants awaits the development of less expensive technology for high-throughput deoxyribonucleic acid (DNA) sequencing, and the NHLBI must be prepared to encourage the adoption of such technology as it becomes available. Similar genetic and genomic approaches also must be applied to pharmacogenomics—the study of individual variations in responses to particular drug therapies—a key element in the development of personalized medicine.

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.

Environmental influences can affect disease susceptibility and phenotypic heterogeneity through their interactions with genes and their effects on proteins and protein metabolites. Environment in this context includes not just toxic exposures but also diet, physical activity, sleep deprivation, psychosocial factors, and—in the case of the developing fetus—maternal factors, all of which may converge to alter the predisposition for developing a disease, the rapidity and degree of its progression, and the response to therapy. Determining the mechanisms by which non-genetic factors perturb normal biology and interact with genetic susceptibility is an important objective of future research. Suitable experimental systems that recapitulate adverse environmental effects and gene-environment interactions are needed for the study of disease development and evolution.

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

Systemic processes reflect an integration of genetic, infectious, toxic, ischemic, and metabolic insults in acute and chronic disease. Understanding how this integration of multiple stimulants contributes to disease initiation and progression remains an important challenge. Research in this area has the potential to profoundly alter approaches to disease prevention, diagnosis, and treatment.

Challenge 1.2: To discover biomarkers that differentiate clinically relevant disease subtypes and that identify new molecular targets for application to prevention and diagnosis—including imaging, and therapy.

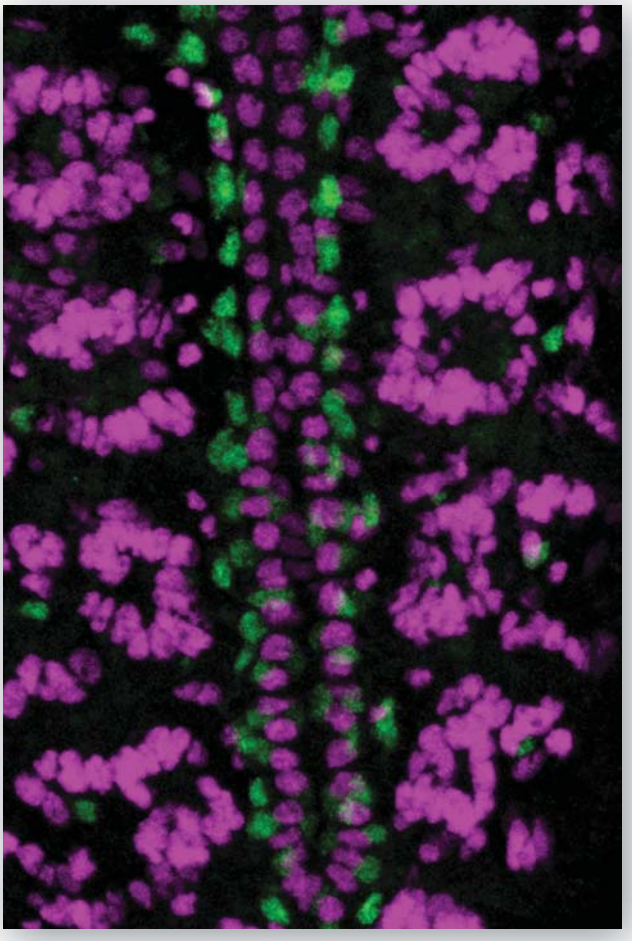
Broadly defined, biomarkers encompass any characteristic that is objectively measured and evaluated as an indicator of genotype, normal biological processes, pathological processes, or responses to therapeutic intervention. Investigations addressing Challenge 1.1 will expand the list of known biological components in numerous cellular and physiological contexts. More important, they will associate the components with specific context-dependent functions and will identify previously unrecognized interactions among individual genes and proteins. Finally, research addressing Challenge 1.1 will pinpoint molecules, pathways, and networks that are perturbed by particular disease processes. Collectively, the findings will enable the extension of basic science discoveries to the identification of markers with predictive, diagnostic, and prognostic power; to the validation of therapeutic targets; and to the characterization of pathways that are amenable to molecular imaging.

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

Traditional diagnostic criteria—including physical examination findings, gross and microanatomical features of affected tissues, or the combined results of conventional laboratory and radiological testing—may not reveal subtle differences among subtypes of a given disease. Because such distinctions can have important prognostic or therapeutic implications, more refined methods are needed to characterize what historically have been considered to be homogeneous disorders. It is becoming increasingly apparent that small sets of molecular markers can be used to subdivide related diseases into clinically meaningful classes. They also can be used to diagnose disease at an early stage, to predict disease progression or eventual regression, and to anticipate the occurrence of desirable or adverse therapeutic outcomes. Moreover, the biomarkers may themselves serve as effective drug targets or may be useful for monitoring and even titrating the response to specific therapies or prophylactic measures. Thus, the identification of new biomarkers forms an essential foundation for the development of personalized medicine.

1.2.b. Develop *in vivo* molecular imaging methods and probes for investigating the biology of disease processes.

The same knowledge base that will provide new insights into disease mechanisms and enable the identification of potential therapeutic targets also will enable the design of new molecular imaging probes and provide an impetus for the development of new imaging modalities. After initial development and testing in animal models, promising new imaging methods and reagents must be adapted for use in human subjects. Advances in imaging technology may enhance understanding of the natural history of disease and may have subsequent translational applications in routine clinical settings.



Goal 2: To Improve Understanding of the Clinical Mechanisms of Disease and Thereby Enable Better Prevention, Diagnosis, and Treatment.

To increase understanding of the clinical mechanisms of disease initiation and progression and to improve prevention, diagnosis, and treatment, the NHLBI has identified four priority objectives. The *first* is to enhance the transmission of knowledge between basic and clinical research so that findings in one arena rapidly inform and stimulate research in the other. The *second* is to apply new approaches and technologies to develop more precise methods of risk-stratification and diagnosis. The *third* is to advance the nascent field of personalized medicine. The *fourth* is to enhance the evidence available to guide the practice of medicine and improve public health.

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

Remarkable advances have been made in understanding the molecular, genetic, and cellular bases of heart, lung, and blood diseases, and opportunities now exist to uncover practical uses for this new knowledge. The application of the fundamental understanding of biological processes to prevention and management of disease requires creative insights into possible relationships and implications. It will be necessary to identify, measure, and validate targets and pathways that have been detected in basic studies. Improved animal models and new analytic approaches that bridge basic and clinical investigations will be needed to move this work along.

2.1.a. Integrate advances in regenerative biology to develop clinically feasible applications.

Allogeneic and autologous stem cells and cell-based therapies hold great potential for treating heart, lung, and blood diseases. Advances in hematopoietic stem cell biology and in the ability to manipulate such cells *in vitro*, including gene transfer, have moved the field closer to clinical application. Research is needed on the selection of cells and their propagation, production, dose, timing and method of administration; adjunctive pharmacology; viability after delivery; and effects on organ function, healing, and microvascular perfusion. Much work must

be done to define and overcome genetic and immunologic barriers to successful allogeneic stem cell transplantation. The feasibility of organ, tissue, blood vessel, and blood regeneration/restoration with xenogeneic and allogeneic cells also is ripe for further exploration.

Tissue engineering offers the possibility of improving function and host response in many heart, lung, and blood vessel diseases through the creation of durable, functional, biocompatible implants. Considerable basic research (e.g., the development of artificial scaffolds and other tissue constructs or the manipulation of growth factors to generate an adequate supply of blood vessels and nerves) has brought the field to a point where testing in humans may be feasible.

2.1.b. Apply discoveries in nanotechnology to the development of new diagnostic and therapeutic strategies.

Drug delivery and therapeutics, molecular imaging, diagnostics and biosensors, and tissue engineering and biomaterials are all areas in which nanotechnology is expected to play a key role in the future. Of relevance to the NHLBI is the potential application of nanotechnology to the diagnosis and treatment of vulnerable plaque; tissue repair, engineering, and remodeling for the restoration of blood vessels and heart and lung tissue; the diagnosis, treatment, and prevention of lung inflammatory diseases; the development of multifunctional devices to monitor the body for the onset of thrombotic or hemorrhagic events and precisely regulate the release of therapeutic drugs; and the development of *in vivo* sensors to monitor patients for sleep apnea. Clinical testing of nanoparticles and nanodevices is not likely to begin for 5 to 10 years, and another 5 years will probably be needed before materials could be used in clinical practice. However, applications of nanotechnology that are less invasive (e.g., diagnostic blood tests) could become available much sooner. Success in bringing nanotechnology to the bedside will depend on collaborations among biologists and physicians, materials scientists, physicists, and engineers. Particular emphasis should be placed on conducting the necessary preclinical and clinical studies to assess the potential health risks associated with nanotechnologies.

2.1.c. Integrate, analyze, and share extant and emerging genotypic and phenotypic data.

Biomedical research already has generated volumes of data from advances in "-omic" technologies and biomedical imaging, and an overwhelming amount of new information can be expected from such developments as affordable individual genome sequencing, real-time metabolomics, and electronic medical records. Realizing the full potential of these data will require a significant partnership between biomedical researchers, mathematicians, systems engineers, statisticians, and computer scientists. The NHLBI expects to play a key role in developing and supporting an information infrastructure that embodies comprehensive standards for biomedical information related to heart, lung, and blood diseases and sleep disorders, including controlled vocabularies, ontologies, data models, and data representation formats; that facilitates the integration of data from the molecular level to the systems level in health and disease; and that encourages and enables the broad sharing and use of research data with appropriate attention to privacy.

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

Over the past several decades, multiple observational and intervention studies supported by the NHLBI have identified and refined the definition of risk factors for heart, lung, and blood disorders. Opportunities now exist to improve the precision of risk estimates across the lifespan for individuals and populations, to identify abnormalities before disease is

clinically evident, and to develop strategies for preventing the development or progression of subclinical disease. Progress in this area hinges on the identification, measurement, and validation of biological pathways and targets for intervention.

2.2.a. Exploit noninvasive imaging methods to detect and quantify subclinical disease.

Many disease processes relevant to the NHLBI mission—plaque formation in atherosclerosis, destruction of alveoli in emphysema—are known to progress silently over the course of decades. The use of sensitive imaging technology would shed light on mechanisms of initiation, progression, and reversal of disease and would enable the measurement of the clinical outcomes of interventions. For example, a pressing need exists for advances in noninvasive imaging that can accurately assess risk for myocardial infarction before and after therapeutic intervention. Such advances not only could be of immediate benefit to patients but also could shorten the time required to test new therapeutic agents by reducing the need for clinical trials that rely on clinical end points. Similarly, better methods for imaging an evolving thrombus would markedly improve the diagnosis of patients with arterial and venous thrombosis. To make the most of opportunities in this area, magnetic resonance imaging, computerized tomography, the rapidly evolving techniques of molecular imaging, and other imaging modalities may be integrated with genomic technologies and biomarkers and validated in clinical trials.

2.2.b. Apply new discoveries in biomarkers to improve risk assessment, diagnosis, prognosis, and prediction of response to therapy.

As noted in Challenge 1.2, biomarkers are broadly defined to encompass any characteristic that is objectively measured and evaluated as an indicator of genotype, normal biological processes, pathological processes, or responses to therapeutic intervention. Biomarkers are needed in clinical medicine to detect early tissue injury and document disease progression. They may prove particularly valuable in providing clues to disease etiology. Focused and rapid biomarker discovery and validation have already yielded significant benefits for subgroups of patients identified as being at risk for a wide variety of disorders. Association studies using "-omic" technologies are expected to uncover many new biomarkers that may become useful tools for evaluating risk and individual responsiveness to interventions in populations and, ultimately, for identifying new therapeutic targets. An improved ability to detect subclinical diseases and monitor disease progression could potentially transform clinical decision-making and enhance the participation of patients in lifestyle choices and behaviors that affect clinical outcomes.

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

Personalized medicine is based on the concept that all individuals have unique characteristics defined by their genome and that human variability in health and disease is determined by genetic makeup in combination with environmental exposures. If the vision of personalized medicine becomes a reality, it will enable clinicians to select appropriate medications and dosages to achieve high efficacy and avoid adverse reactions, thereby improving outcomes and potentially reducing health care costs. More efficient drug development is also likely to result: testing new drugs only in patients likely to experience a benefit could speed the process of getting drugs to market.

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

Over the past 50 years, great advances have been made in understanding the roles of such environmental influences as diet, exercise, sleep, psychosocial factors, socioeconomic status (SES), and air and water quality on the development of disease. Environmental and lifestyle or behavioral factors are known to contribute to the initiation or progression of many common disorders of the heart, lungs, and blood. Even single-gene disorders are now acknowledged to have complex genetic and environmental modifiers of expression and severity. Exploration of the interactions between genetic and environmental factors has now become essential to explain the development, progression, and outcome of many diseases. Key to success in this area will be the development of more precise measures of environmental exposures and more robust definitions of clinical phenotypes.

The NHLBI will capitalize on its rich resource of studies that enable the association of whole-genome single-nucleotide polymorphisms with clinical phenotypes. The identification of such associations will enhance the understanding of complex traits and will permit investigators to explore the relationship between genetic variants, gene expression, and gene function. The application of these "-omic" approaches may lead to more sophisticated analyses of risk and individual responsiveness to interventions in populations.

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.

Disease development and progression are influenced not only by genetic factors but also by developmental and environmental exposures. In recent years, researchers have focused on identifying, measuring, and understanding the effects of such exposures to provide a basis for the development of new interventions. Systems biology approaches for modeling the complex interactions between genetic and environmental factors provide valuable information for identifying potential interventions. Basic researchers are developing *in vivo* systems and tools for preclinical testing of new therapies. They are also developing new cell and animal models based on knowledge of susceptibility genotypes and relevant exposures. Large cohort studies that include measures of exposure to drugs, allergens, and infectious agents, as well as information about diet, exercise, sleep duration and quality, and psychosocial factors, offer a wealth of information for generating hypotheses. In the future, the value of data from basic, clinical, and cohort studies will be enhanced by the standardization of definitions of phenotypes, diseases, exposures, and outcomes. In addition, the creation of shared databases with information from multiple studies will facilitate the integration and analysis of results. Clinical testing of new interventions will be informed not only by epidemiological and basic studies of the effects of particular exposures but also by results of genetic and genomic studies that allow researchers to sort patients into genetically defined subgroups. Such clinical tests are expected to enable developmental and environmental interventions that are tailored to individuals.

Challenge 2.4: To enhance the evidence available to guide the practice of medicine, and improve public health.

The NHLBI will continue to build upon a long and distinguished tradition of excellence in the conduct of clinical trials to generate new knowledge to improve the prevention, diagnosis, and treatment of heart, lung, and blood diseases. Many of the current rigorous standards of evidence upon which practice guidelines are based derive from NHLBI-supported randomized clinical trials. The Institute remains committed to continuing to generate new evidence that will inform disease prevention, diagnosis, and treatment.

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.

To realize its public health objective, the Institute must find ways to extend the full benefits of scientific advances to all of the diverse populations that constitute the American public. Many evidence-based approaches to prevent and treat heart, lung, and blood diseases have not been uniformly applied in clinical and community practice. Further research is needed on the translation process itself to expedite and expand the adoption of biomedical advances into clinical practice and individual health behaviors. The NHLBI will evaluate new ways to disseminate and implement proven prevention and treatment approaches to improve public health. Research to address issues that are directly relevant to clinical and community practice, such as how best to apply what is already known to be effective, is a priority.

Opportunities exist for the NHLBI to collaborate with community-based practice networks to conduct multidisciplinary research that would address important behavioral issues and facilitate the evaluation of new approaches to prevent, diagnose, and treat disease. The new Clinical and Translational Science Awards (CTSAs) of the National Institutes of Health (NIH) and the Practice-Based Research Networks of the Agency for Healthcare Research and Quality both offer the potential for leveraging Institute resources.

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

Behavioral and psychosocial factors are known to play an important role in the development and progression of heart, lung, and blood diseases. For example, diet and physical activity are critically involved in the development of cardiovascular disease risk factors, such as hypertension, dyslipidemia, obesity, diabetes, and untreated sleep apnea and reduced sleep duration, are risk factors for obesity, hypertension, and diabetes. The success of many therapeutic regimens, even highly effective ones, depends on patient adherence. Stress and depression are other behavioral factors known to be associated with cardiovascular disease risk and progression.

Despite widespread recognition of the importance of health behaviors, only a relatively small percentage of adults regularly follow relevant recommendations. Because influences on health behaviors are diverse, ranging from individual (e.g., knowledge and motivation), to familial (e.g., expectations and role models), to environmental (e.g., workplace and school policies, social and cultural norms, and physical environments), they are best studied in complex environments. In the clinical setting, a widely acknowledged "quality gap" exists in which proven effective preventive and therapeutic strategies are not consistently followed, a function of both patient behavior and provider practice. The gap is greater among Americans with limited resources and minority groups.

If research findings are to improve the public's health, they must be translated into practice. Because it is often not clear how best to do so, the translation process itself needs study. Methods especially are needed to adapt interventions to address the needs of minority populations.

3.1.a. Develop and evaluate new approaches to implement proven preventive and lifestyle interventions.

Although research has uncovered a number of preventive and lifestyle interventions that are effective in small, controlled studies, it is often not clear how to implement them on a larger scale. Family- and community-based approaches offer particular promise for reaching much of the population. Although major life events (e.g., school transitions, entry into the workforce, retirement) often result in increased risk, they also may present opportunities to implement effective preventive strategies. Research also is needed to evaluate the extent to which risk stratification and application of personalized approaches can improve effectiveness.

3.1.b. Develop and evaluate policy, environmental, and other approaches for use in community settings to encourage and support lifestyle changes.

The successful national effort to reduce tobacco use illustrates the efficacy of policy and environmental approaches to promote healthy lifestyles. Environmental factors may also affect health behaviors. Examples include the influence of public policy decisions on physical activity, nutrition (e.g., portion sizes, marketing practices, retail food choices), and adequate sleep in students and workers. Research is needed to identify factors that are important influences on behavior and health and to determine how they can be changed in a cost-effective way.

3.1.c. Develop and evaluate interventions to improve patient, provider, and health care system behavior and performance in order to enhance quality of care and health outcomes.

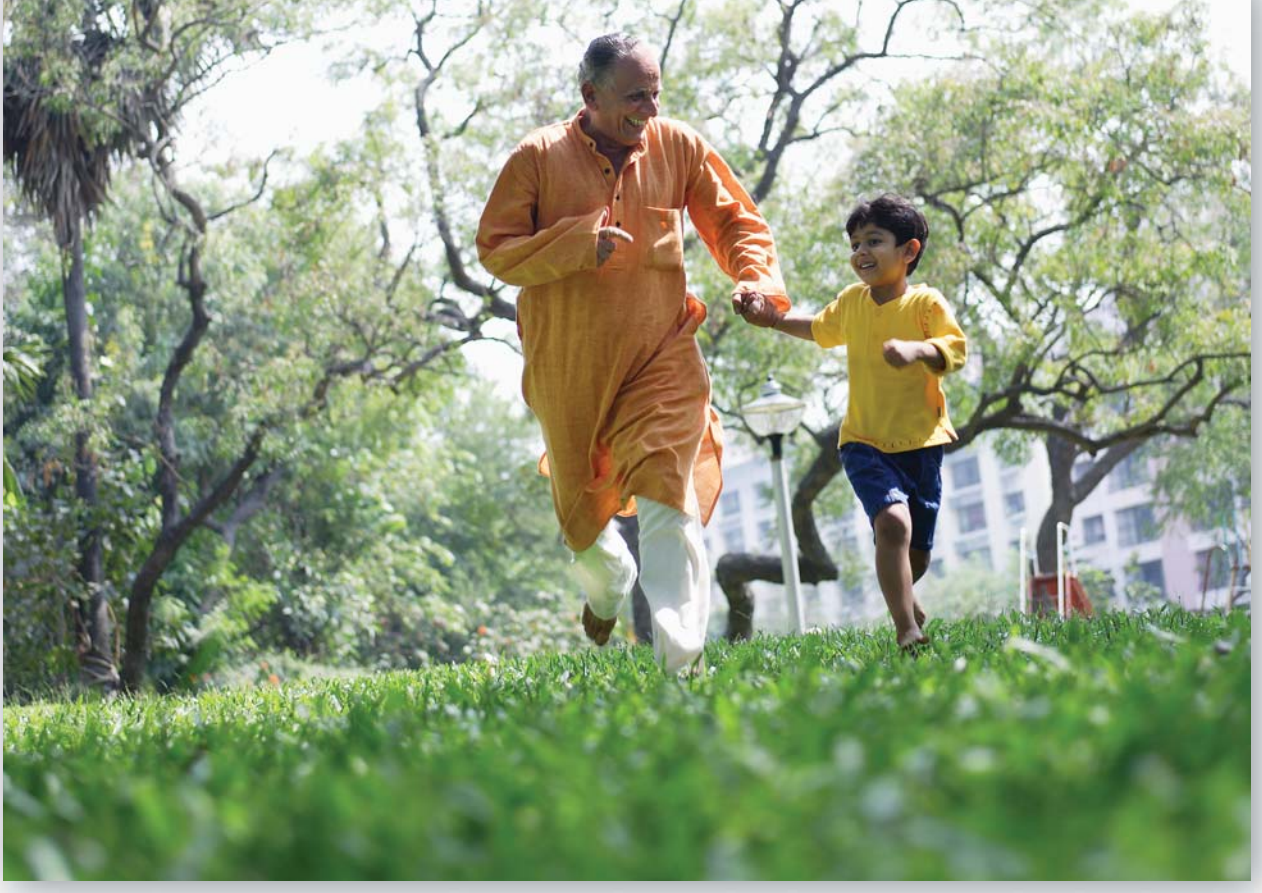
Integrating behavioral and social sciences research with clinical research is crucial for developing successful strategies to improve health care. An improved understanding of the factors that influence patient, provider, and health care system behaviors may facilitate the development of new approaches to reduce the "quality gap." A range of such interventions as economic incentives and performance measures for providers could be evaluated. Wide-scale adoption of electronic health records could enable tracking of the delivery and outcome of medical innovations, evaluation of factors that are associated with care-delivery patterns, and testing of new interventions. Studies are needed to identify and evaluate "patient-centered" approaches, such as incorporating patient preferences into clinical decision-making, and to reduce the inappropriate use of diagnostic tests and treatments.

Challenge 3.2: To identify cost-effective approaches for prevention, diagnosis, and treatment.

To achieve a substantial improvement in the health of the Nation, more cost-effective approaches to prevent, diagnose, and treat heart, lung, and blood diseases are needed. Research on community applications of evidence-based clinical practices will be undertaken to document current practice patterns and factors associated with high-quality clinical care; identify the relative contributions of secular trends and interventions; integrate data from rare diseases and newly emerging data on prevalent diseases to develop, evaluate, and revise evidence-based clinical best practices; and translate findings into educational messages for providers, patients, and the general public and assess their effects on behaviors and health status.

3.2.a. Evaluate the risks, benefits, and costs of diagnostic tests and treatments in representative populations and settings.

Surveillance systems that allow for the rapid analysis and communication of health status can provide data on the effectiveness of community-based and population-based interventions. Dissemination of results is the most critical part of the research effort, yet much remains to be learned about how to do so effectively. New disciplines such as bioinformatics may transform established public health education approaches. Social marketing approaches and diffusion-of-innovation models may provide insights that can help refine preventive and therapeutic efforts. The NHLBI will initiate collaborations and public-private partnerships to facilitate evaluations of new treatment approaches. The new CTSAs are models of interdisciplinary teams and streamlined, non-redundant core facilities that may transform translational research. Industry—including health plans, disease management companies, and purchasers—is a rich source of data and will be included in the research enterprise. Research on health services and outcomes can evaluate clinically feasible interventions to improve the delivery of evidence-based preventive and therapeutic approaches.



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.

New approaches are needed that can accommodate nontraditional family patterns, low SES, and immigrant status. The "microculture" of immigrant families, including their eating, drinking, and sleeping patterns, health literacy, and responses to major life events, can influence not only their interactions with the health care system but also their health. Successes over several decades have enabled people with congenital diseases to live beyond childhood, but too often inadequate data are available to guide their treatment as adults. Data systems that can characterize patient demographics, including SES, access to health care, patterns of health care use, family structure, work roles, quality of life, and clinical health status, could be used to identify clinical best practices and educate providers. Research designs and analytic methods are needed to enable valid analyses of interventions delivered at a "group" level (e.g., at worksites or in clinical practices) and to assess the efficacy of preventive interventions that seek to achieve long-term public health improvements through small individual changes. Evaluations of the cost-effectiveness of interventions require methods that are relevant to society as a whole and consider all relevant costs as well as quality of life.

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.

Too often, evidence-based guidelines that distill the best available scientific knowledge into recommended actions for individuals, communities, and health care systems to improve health outcomes are not fully adopted into practice. Addressing this challenge will require efforts to promote the implementation of evidence-based guidelines by individuals, communities, health care providers, and public institutions; to influence public policy by promoting and implementing evidence-based guidelines; and to reduce health disparities with attention to personalized, community, and health system-oriented approaches to increase the use of proven preventive interventions among vulnerable subgroups.

3.3.a. Establish evidence-based guidelines for prevention, diagnosis, and treatment and identify gaps in knowledge.

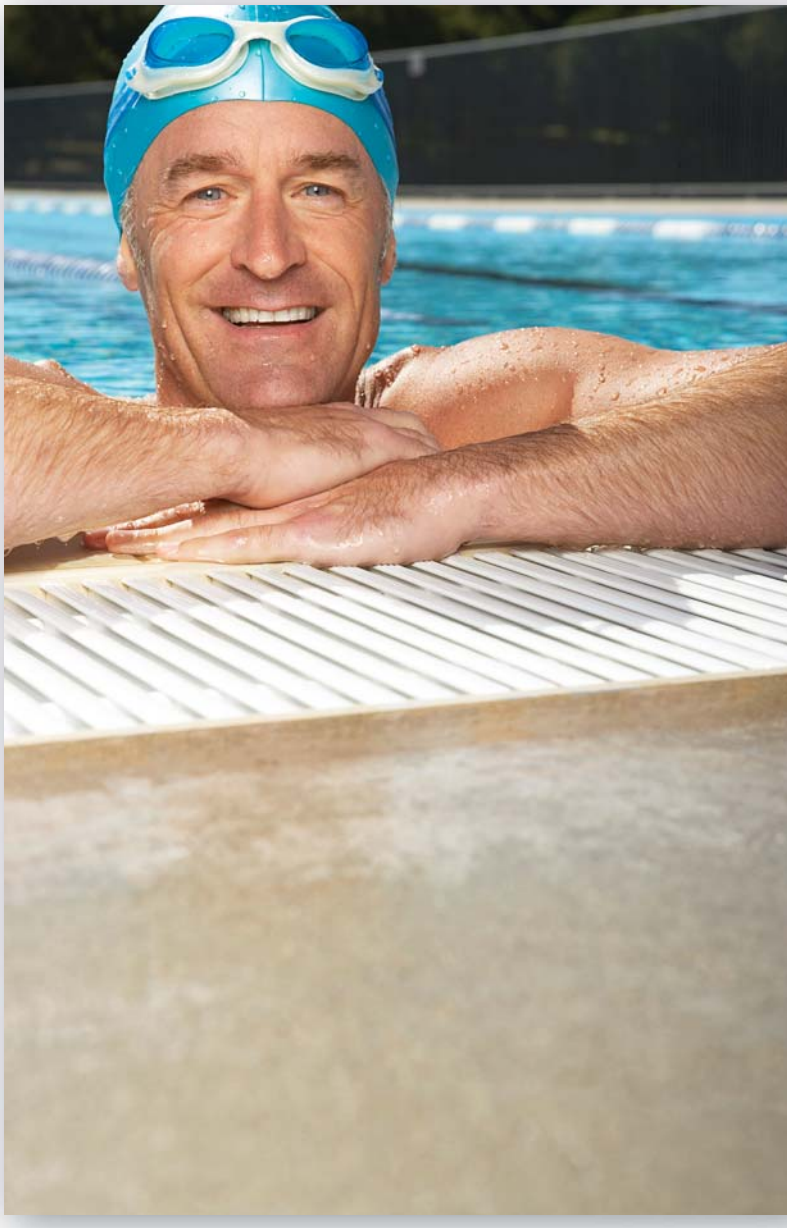
The NHLBI will continue to exert national leadership in the development of evidence-based guidelines and promote the concept of integrated guidelines that comprehensively address the known, modifiable risk factors associated with a disease. The NHLBI will continue to take a leadership role in, or serve as a knowledge broker for, guideline development efforts and support ongoing efforts to make the most current scientific evidence publicly available so that professional organizations can develop appropriate guidelines. The Institute will continually assess the nature of the available evidence and identify areas that need additional research to support clinical decision-making.

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.

Systems approaches will be developed to speed the implementation of knowledge in health care and community settings; foster partnerships among practitioners, patients, family members, community organizations, and community health workers; and create environments that support healthy choices and reduce known risk factors. Linkages among interested groups that previously operated independently will be encouraged to realize efficiencies through cooperation. As appropriate, the NHLBI will work with other government agencies and with private-sector organizations to encourage reliance on evidence-based guidelines in setting policies that affect health behaviors and care. Policy changes (e.g., regarding reimbursement practices, performance measures, and accreditation standards) can be highly effective in stimulating the development and implementation of evidence-based guidelines and influencing the behaviors of providers, patients, and health systems. School and worksite environments can foster improvements in lifestyle behaviors and risk factor screening practices.

Substantial evidence indicates that health, SES, and psychosocial factors are inextricably linked and that health disparities exist even among individuals at the same SES level who are from different population groups. Efforts to raise the health of minority groups to the level enjoyed by the majority population must recognize that discrimination in living conditions, educational systems, health care systems, and work settings can adversely influence health. Because they share an understanding of their local environment,

including an appreciation of prevalent psychosocial factors and cultural beliefs, community groups and local health providers must be involved in efforts to promote community acceptance of science-based health information. Outcomes from community health promotion and evaluation projects can inform the development of new dissemination models at the personalized/individual, community, and health care system levels. The Institute will support partnerships and linkages that enhance the understanding of contributions of individual health behaviors, community-based organizational and environmental policies, and health systems innovations to reducing health disparities.



3.3.c. Communicate research advances effectively to the public.

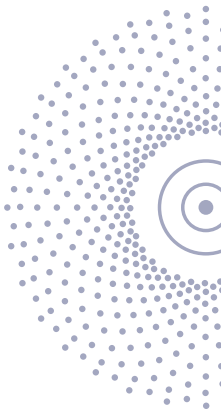
The objective of all NHLBI public education activities is to motivate the audience to become active users of health information. The Institute will continue to investigate and evaluate new communication and social-marketing approaches to communicate research advances with the goal of engaging all interested parties. They include members of the research community who generate new knowledge; governmental agencies, national voluntary and professional organizations, credentialing bodies, and foundations that translate and disseminate knowledge; individuals engaged in clinical practice and in community programs who apply the science to improve health outcomes and share their experiences with others; and workers in the knowledge technology field who develop and implement new systems that can link various knowledge communities and promote performance-focused and science-based approaches.

The Institute will continue to develop public education programs, as needed, to address areas of major public health concern, such as heart failure, partnering with professional societies, patient-advocacy groups, community-based organizations, and Federal entities to ensure that uniform health messages are disseminated. In addition to encouraging individuals and communities in health promotion and disease prevention efforts, the Institute will stress the importance of their involvement in the research process by emphasizing that new health-related information can be generated only with their cooperation and participation.

Strategies

Implementation of this plan will require a diversity of approaches to address the scientific challenges previously identified that will enable sharing of both knowledge and resources. This section presents the strategies that the NHLBI intends to employ to facilitate the conduct of research; enhance interdisciplinary work; speed early stage translation of basic discoveries; ensure cross-fertilization of basic, clinical, and epidemiologic discoveries; and maximize the resultant public health benefit of the information created. As the challenges identified in this plan are met and as new ones emerge, the NHLBI will identify and embrace new strategies. The Institute also will continue to look to the NHLBAC and to the larger research community for guidance to ensure that these strategies are updated as needed to reflect the rapidly changing environments of research and public health issues.

As the challenges identified in this plan are met and as new ones emerge, the NHLBI will identify and embrace new strategies.



Strategy 1: Develop and facilitate access to scientific research resources.

Lack of access to costly technologies often limits what individual investigators can accomplish. It is not practical for every laboratory, department, or even institution to develop many technical capabilities involving expensive equipment, scarce materials, large amounts of space, and specialized technical expertise. Such services can be more efficiently provided by centralized facilities that are dedicated to a single activity or a set of related functions and can ensure appropriate quality control oversight and realize economies of scale. Centralized facilities can also significantly enhance the productivity of individual investigators by allowing them to focus on pursuing hypothesis-driven scientific questions rather than on obtaining the resources needed to address them.

Support will be provided for core genomics, proteomics, chemical, and RNAi screening; small-animal imaging; and other technologies as they become available or are requested by the research community. Adoption of new and cheaper DNA sequencing methods for large-scale re-sequencing projects is one example of a need that is likely to arise in the very near future.

The Institute will strategically support tissue and animal repositories, databases, and information systems dedicated to the support of NHLBI projects. In creating such resources, careful attention will be paid to center capacity, regional distribution, and standardization of methods so that quality services are made available expeditiously to all who require them. Formal mechanisms will be established to ensure equitable access to the resources without imposing onerous requirements on investigators.

Strategy 2: Develop new technologies, tools, and resources.

In addition to making existing technologies widely available, the NHLBI will continue to invest in the development of new methods for laboratory investigations. Areas requiring attention include genomics; proteomics; metabolomics; bioinformatics (especially integrative computational tools); imaging probes and modalities (for studies at the level of whole animals, cells, and individual molecules); nanotechnology; tissue engineering; gene knock-out, knock-down, and knock-in methods in whole animals; and gene and cell-based therapies.

Animal models are a critical resource. Support is required for efforts to create new animal models that closely emulate the pathology of human disorders and that can be used not only for mechanistic investigations but also for evaluations of new therapies. The need for new animal models is certain to expand rapidly, as additional human disease susceptibility genes are discovered in genome-wide association studies. To accommodate the increased need, new experimental approaches for qualitatively and quantitatively perturbing model organism orthologs and for studying interacting genetic and non-genetic factors will be required.

Given that the new technologies, tools, and resources needed by NHLBI investigators also will be used by investigators who are supported by other funding sources, opportunities for their development through partnering arrangements—with other NIH components as well as with other government agencies and with private sector organizations—will be explored. The NHLBI also will undertake projects that complement and extend other resource development efforts, as exemplified by

such existing programs as the Pharmacogenetics Research Network and the Knockout Mouse Project, and perhaps enable the development of new collaborative networks or other approaches to stimulate preclinical efforts. By seeking involvement in additional research opportunities of this type, the NHLBI can both enhance community-wide activities and provide valuable resources for the benefit of its own investigators, thereby yielding benefits for all interested parties.

Strategy 3: Increase the return from NHLBI population-based and outcomes research.

The NHLBI has made extensive and highly productive investments in population-based and outcomes research that have not only addressed specific scientific questions but also provided real-world perspectives on disease burden, risk factors, and the effectiveness of medical care. If the full value of these studies is to be realized, however, the Institute must address several critical needs.

The Institute will take a leadership role in developing national standards for nomenclature and informatics to facilitate the sharing of phenotypic data. Common collection methods, definitions, and exchange formats for data are needed to enable linkages among studies of complex diseases. Data from studies that are not large enough individually to examine gene-environment interactions, risks and benefits of interventions, or risk factor associations in subgroups could be pooled to address those issues. Nomenclature standards that are easily implemented, universally accessible, broadly applicable, and yet flexible enough to accommodate advances in technology and science (e.g., newly identified risk factors and disease end points) are needed. Data repositories that include informatics tools for data analysis and promote data-sharing (while ensuring data security and participant confidentiality) are needed.

The Institute will selectively complement ongoing surveillance of local and national incidence, prevalence, practice patterns, and outcome measures in diverse populations. Up-to-date figures are critical for detecting important scientific and public health trends, and they also can be used to uncover health disparities and monitor efforts to reduce them. Documentation of the influence of sociocultural environments, psychosocial traits and stressors, lifestyles, economic resources, access to health care, and other factors can reveal pathways that contribute to disease burden and therapeutic response. Surveillance of practice patterns can enable assessment of the effects of clinical guidelines on physician prescribing practices and can facilitate the identification of barriers to implementing best practices. Efforts will focus on enhancing and combining data from existing data collection systems, partnering with public and private organizations that collect and use electronic health information (e.g., insurers, large health care systems, other government agencies), and developing new approaches to capture data in diverse populations.

The value of existing studies could be enhanced by adding new genetic, social, environmental, and psychological measures. Because even such well-defined environmental exposures as smoking have been difficult to measure, this effort may call for new technologies to enable accurate assessments of risk. New analytic methods are needed to integrate the large volumes of data obtained in population research to permit examinations of gene-environment and gene-gene interactions and of reversible heritable changes in gene function. Population studies can provide an appropriate context for evaluating and translating new technologies for imaging and "-omics" into clinical applications. The introduction of "-omics" technologies into population studies will require interactions among epidemiologists, geneticists, clinicians, bioinformaticians, statisticians, and "-omics" scientists and the creation of new resources to be shared with the scientific community in a manner consistent with participant consent. Large-scale "-omics" studies are likely to require new paradigms, including public-private partnerships.

Strategy 4: Establish and expand collaborative resources for clinical research.

Coordinated resources are needed to facilitate the conduct of disease-oriented studies and speed the application of basic science observations to clinical problems. The network approach to translational and clinical research has been successful and will be expanded to additional areas of science.

Disease-oriented Internet portals could enable access to information and tools for use in research and patient care. They would serve not only as an essential resource for integrative understanding of heart, lung, and blood disorders but also as a stimulus for community-wide collaborations. To be effective, portals must be interoperable with other data and information resources to allow users to develop a comprehensive understanding of relevant diseases, particularly multi-system and multi-organ syndromes. They also will facilitate the sharing and linking of disparate data types (e.g., sequences, single nucleotide polymorphisms, phenotypes, disease mechanisms) and the development of data-management tools, strategies for analysis, and data-visualization approaches.

The new NIH network of CTSAs offers great promise for investigators interested in conducting research in community settings, affording them access to an integrated and organized resource. A serious challenge for the NHLBI continues to be the delay typically experienced between the time that an intervention is shown to be effective and when it is broadly adopted by health practitioners, patients, and the public. One potential way to reduce the delay would be to encourage broader community involvement in research to increase the general awareness of ongoing studies and increase interest in research outcomes. The Institute views the CTSAs as an important resource for stimulating community involvement in clinical research whenever appropriate.

Strategy 5: Extend the infrastructure for clinical research.

The NHLBI will develop a comprehensive process for establishing priorities for large clinical trials. As part of the process, advice will be solicited from a broad range of interested parties, including individual investigators, expert panels, industry, other Federal agencies (e.g., Centers for Medicare and Medicaid Services, Food and Drug Administration), patients, and nonacademic medical practitioners through their professional societies. Also needed are explicit criteria to be used in deciding among proposed trials to ensure that the most pressing questions are addressed. Establishing standards for the design, conduct, and interpretation of clinical studies and trials will ensure that the answers are scientifically valid and applicable to diverse populations.

The process of initiating and conducting clinical trials will be refined. Templates and educational materials will be developed to guide clinical trial investigators as they pursue a research idea from study design to implementation. Standardized definitions of end points and adverse events, streamlined reporting procedures of adverse events, and improved methods for analyzing data from early-phase trials are also needed. Controlled vocabularies, ontologies, data models, and data representation formats will be developed for major areas within the Institute's mission to enable data sharing and study comparisons. NHLBI-supported researchers will be encouraged to adopt the same Federal standards already used by clinical systems in order to facilitate the research use of data stored in clinical databases within health care organizations. In addition, the NHLBI will work with other components of the NIH and the Department of Health and Human Services toward facilitating clinical research by reducing the regulatory burden associated with the initiation and conduct of clinical studies.

The scientific return from the Institute's substantial investments in time and resources represented by large-scale clinical trials can be increased by facilitating important ancillary studies. In addition to providing mechanisms for the timely funding of ancillary studies not included in the original trial protocol, efficiency may be gained by incorporating substudies of known broad interest and applicability into the initial funding action. Ancillary studies to validate imaging findings and biomarkers with clinical outcomes, studies that establish repositories for use by the research community, and biostatistical methodology development will be included in the initial design of trials whenever possible. The Institute also recognizes the value of community- and practice-based research and their potential for further increasing the return on its clinical trial investments, and it will continue to encourage and support such efforts.

Strategy 6: Support the development of multidisciplinary teams.

Interdisciplinary collaborations are becoming ever more critical to all areas of research related to the mission of the NHLBI. Increasingly, clinicians and biologists are requiring the expertise of individuals in quantitative disciplines, including computer science, mathematics, physics, and engineering. The NHLBI encourages this trend by including in research initiatives, wherever appropriate, a requirement that diverse groups of scientists be assembled to work together on a common problem. The Institute will consider supporting "virtual centers" to enable collaborations that are focused on expertise and are independent of geography. Given the currently available electronic and Web-based communication technologies, geography is no longer a barrier.

Development of multidisciplinary teams will require greater recognition in the research community, and especially in universities and medical schools, of the accomplishments of groups rather than individuals. It will also likely entail collaborations on research programs among the various Institutes and Centers of the NIH. To facilitate the transition to and acceptance of this new research paradigm, the NHLBI and other funding agencies will have to work closely with academic institutions to ensure that proper recognition is accorded to all participants. Acknowledging the value and appropriateness of a co-principal investigator in individual research project grants is a good start, but more needs to be done.

One approach to promoting interdisciplinary research is for the NHLBI to establish seed funding for Research Centers of Excellence. By providing infrastructure support, Centers can serve as a focal point within an institution for research in heart, lung, and blood diseases as well as attract the interest of investigators who are unaffiliated with the Center but who have potentially related skills and expertise. To ensure the greatest return on Research Centers of Excellence, eligibility could be limited to institutions that have been selected for the CTSA, with NHLBI funding provided to enhance the CTSA in areas relevant to the Institute's mission. Consideration will be given to limiting the period of NHLBI support for a Center, to requiring recipient institutions to provide some level of matching funds for the entire award term, and to requiring the institutions to present a plan for transition to continue funding of the Center beyond the period of NHLBI Center support.

Strategy 7: Develop and retain human capital.

The NHLBI and the heart, lung, and blood research community have experienced increasing challenges in the recruitment of young scientists. The Institute is committed to extending the reach of its educational efforts to elementary and high school students, and it will continue to expand its support of science education in the schools to ensure a steady supply of enthusiastic and creative young scientists.

To ensure the continued advance of knowledge related to heart, lung, and blood diseases, the NHLBI must enable a constant renewal of the research workforce. To that end, the NHLBI supports training and career development opportunities for scientists at all career stages. Scientists today are called upon to master increasingly complex technologies, including quantitative methods that may not have been part of their training. The Institute not only will encourage inclusion of courses in statistics and other types of mathematical analysis in postdoctoral training for scientists in biomedical disciplines but also will enable hands-on training experiences in relevant quantitative areas. To avoid extending what is already a lengthy training experience for most scientists, the added materials will be accompanied by measures to shorten the overall training period, such as providing incentives to both mentors and trainees who meet certain milestones.

To afford scientists with expertise in quantitative and analytical areas the opportunity to contribute to biomedical research, the Institute will offer programs to enable them to acquire relevant basic biomedical knowledge. One way of doing so would be to foster reciprocal cross-training during the postdoctoral years for individuals with predoctoral training in biomedical disciplines and quantitative disciplines. This could also serve as a stimulus for interdisciplinary studies among the next generation of scientists.

New investigators face the challenge of obtaining a first individual research project grant (R01) in competition with applications from more experienced individuals. The NHLBI will continue its policy of giving new investigators an advantage by funding them at higher pay scales and ensuring expedited re-review of applications that are highly meritorious but do not receive funding on first submission. The NHLBI recognizes the critical role of mentoring to ensure success in research careers and will work with host institutions to develop new approaches to foster mentoring for young faculty members. The Institute also recognizes that initial funding for a new investigator is often not sufficient to establish a research career; the first competing renewal is critical. Partial bridge funding, perhaps in a cost-sharing mechanism with host institutions, might provide adequate support for an unsuccessful applicant to maintain a research program, while a revised application is pending.

The Institute recognizes its obligation to established scientists. They often are required to develop new skills to respond to changes in research directions and new scientific opportunities. Training programs of "continuing biomedical education" and support for mini-sabbaticals are two possible approaches to aid established investigators in acquiring needed expertise.

Strategy 8: Bridge the gap between research and practice through knowledge networks.

The NHLBI has a long history of establishing and maintaining networks to fulfill its mandate to translate science-based information into clinical practice and public health behavior. The Institute will explore new network approaches to promote collaborations among researchers that enable them to develop evidence-based initiatives to improve public health.

The NHLBI will create individual knowledge networks focused on disease priorities—based on their burden to society—to connect researchers to health practitioners by facilitating interaction among those who generate new knowledge, those who translate and disseminate it, and those who use it. The networks will provide an avenue for identifying knowledge gaps that need to be addressed by future research and for speeding translation into practice through use of more effective approaches to synthesizing and organizing evidence. It is expected that knowledge networks will constitute a public resource that will enable research and prevention programs internationally as well as domestically. Development of a Cardiovascular Knowledge Network (CKN) is the first step. The knowledge network concept can then be expanded to encompass other diseases based on the lessons learned in the first 3 years of operation of the CKN.

The CKN will require a new informatics infrastructure that supports knowledge-sharing and rapid interaction between researchers and practitioners as well as close surveillance of cardiovascular health data to guide research and development of preventive efforts, particularly for selected populations. Other important aspects include community strategies that pool resources to create environments that support healthy choices and reduce known risk factors over the entire lifespan, incentives to stimulate the adoption of beneficial behaviors, personalized health care strategies that address individual needs, and social marketing communication strategies to promote social norms that improve cardiovascular health.

Broad scientific literacy is essential to enable full public participation in policy decisions posed and informed by scientific advances and full individual participation in the active maintenance and management of their own health. Citizens, patients, family members, and investors must be able to critically evaluate new information, assess areas of ambiguity, and appreciate the implications of personal and public decisions related to health. The NHLBI will participate in improving science education in elementary and secondary schools and in improving higher education for nonscientists as well as scientists.

Appendix—Participants

Edward Abraham, M.D.
University of Alabama at Birmingham

Michael Acker, M.D.
University of Pennsylvania

Christine M. Albert, M.D.
Brigham and Women's Hospital

Jean-Pierre Allain, M.D.
University of Cambridge

Laura Almasy, Ph.D.
Southwest Foundation for Biomedical Research

Garnet Anderson, Ph.D.
Fred Hutchinson Cancer Research Center

Margaret Anderson
The Center for Accelerating Medical Solutions

Mark E. Anderson, M.D., Ph.D.
University of Iowa

Derek C. Angus, M.D.
University of Pittsburgh

Elliot Antman, M.D.
Brigham and Women's Hospital

Lawrence J. Appel, M.D., M.P.H.
Johns Hopkins University

Andrea Apter, M.D., M.Sc.
University of Pennsylvania

Donna Arnett, Ph.D.
University of Alabama at Birmingham

Bruce J. Aronow, Ph.D.
Cincinnati Children's Hospital Medical Center

Mara G. Aspinall, M.B.A.
Genzyme Genetics

Larry Atwood, Ph.D.
Boston University

James AuBuchon, M.D.
Dartmouth-Hitchcock Medical Center

Grover C. Bagby, Jr., M.D.
Oregon Health and Science University

Raymond D. Bahr, M.D.
St. Agnes Healthcare System

James Baker, M.D.
University of Michigan

H. Scott Baldwin, M.D.
Vanderbilt University

Christie Ballantyne, M.D.
Baylor College

Tom Baranowski, Ph.D.
Baylor College of Medicine

Barbara E. Barnes, M.D.
University of Pittsburgh

Ted Barrett, Ph.D.
Lovelace Respiratory Research Institute

William A. Baumgartner, M.D.
Johns Hopkins University

Dan Beard, Ph.D.
Medical College of Wisconsin

Michael J. Becich, M.D., Ph.D.
University of Pittsburgh

John Belperio, M.D.
University of California, Los Angeles

Emelia J. Benjamin, M.D., Sc.M.
Boston University

Ivor J. Benjamin, M.D.
University of Utah

Susan Bennett, M.D.
George Washington University

Raymond L. Benza, M.D.
University of Alabama at Birmingham

Gordon R. Bernard, M.D.
Vanderbilt University

Donald Berry, Ph.D.
University of Texas

Ronald Bialek, M.P.P.
The Public Health Foundation

Celso Bianco, M.D.
America's Blood Centers

Joyce Bischoff, Ph.D.
Children's Hospital Boston

Peter B. Bitterman, M.D.
University of Minnesota

Henry R. Black, M.D.
Rush University

Henry W. Blackburn, M.D.
University of Minnesota

Judith Blake, Ph.D.
The Jackson Laboratory

Bruce Q. Blazar, M.D.
University of Minnesota

David A. Bluemke, M.D., Ph.D.
Johns Hopkins University

Neil Blumberg, M.D.
University of Rochester

Eric Boerwinkle, Ph.D.
University of Texas

Roberto Bolli, M.D.
University of Louisville

Robert Bonow, M.D.
Northwestern University

Jeffrey Borer, M.D.
Cornell University

Richard Boucher, M.D.
University of North Carolina at Chapel Hill

Janice Bowie, Ph.D., M.P.H.
Johns Hopkins University

Eugene Braunwald, M.D.
Harvard University

Bruce E. Bray, M.D.
University of Utah

Paul Bray, M.D.
Jefferson Medical College

Malcolm K. Brenner, M.D., Ph.D.
Baylor College of Medicine

Patrick Breysse, Ph.D.
Johns Hopkins University

James Bristow, M.D.
Joint Genome Institute

Michael Bristow, M.D., Ph.D.
University of Colorado

V. Courtney Broaddus, M.D.
University of California, San Francisco

Colleen Brophy, M.D.
Arizona State University

Ronald T. Brown, Ph.D.
Temple University

Hal E. Broxmeyer, M.D., Ph.D.
Indiana University

George Buchanan, M.D.
University of Texas Southwestern

Esteban E. Burchard, M.D.
University of California, San Francisco

Julie Buring, M.D.
Brigham and Women's Hospital

Gregory C. Burke, M.D., M.Sc.
Wake Forest University

John C. Burnett, Jr., M.D.
Mayo Clinic

Helen Burstin, M.D., M.P.H.
Agency for Healthcare Research and Quality

Michael Busch, M.D., Ph.D.
Blood Centers of the Pacific

William W. Busse, M.D.
University of Wisconsin Hospital

Robert Byington, Ph.D.
Wake Forest University

Michael Cabana, M.D.
University of California, San Francisco

Robert M. Califf, M.D.
Duke University

Blase A. Carabello, M.D.
Michael E. DeBakey Veterans Affairs Medical Center

James Casella, M.D.
Johns Hopkins University

Margaret O. Casey, R.N., M.P.H.
National Association of Chronic Disease Directors

Patricia Casey
Kaiser Permanente Medical Group

C. Thomas Caskey, M.D.
University of Texas Health Science Center

Mario Castro, M.D.
Washington University

Oswaldo Castro, M.D.
Howard University

Sule Cataltepe, M.D.
Children's Hospital Boston

Juan Celedon, M.D., Dr.P.H.
Brigham and Women's Hospital

David M. Center, M.D.
Boston University

Aravinda Chakravarti, Ph.D.
Johns Hopkins University

Peng-Sheng Chen, M.D.
Cedars-Sinai Medical Center

Linzhao Cheng, Ph.D.
Johns Hopkins University

Kenneth R. Chien, M.D., Ph.D.
Richard B. Simches Research Center

Aram V. Chobanian, M.D.
Boston University

David C. Christiani, M.D., M.P.H.
Harvard University

Douglas B. Cines, M.D.
University of Pennsylvania

William Clarke, M.D., M.Sc.
Cellectar, LLC

Alexander W. Clowes, M.D.
University of Washington

Thomas D. Coates, M.D.
Children's Hospital Los Angeles

Thomas M. Coffman, M.D.
Duke University

Alan R. Cohen, M.D.
Children's Hospital of Philadelphia

Larry Cohen
Prevention Institute

Barry S. Coller, M.D.
Rockefeller University

Alfred F. Connors, M.D.
Case Western Reserve University

Richard S. Cooper, M.D.
Loyola University

Janet M. Corrigan, Ph.D.
The National Quality Forum

Maria R. Costanzo, M.D.
Edward Cardiovascular Institute

Shaun R. Coughlin, M.D., Ph.D.
University of California,
San Francisco

Allen W. Cowley, Jr., Ph.D.
Medical College of Wisconsin

James Crapo, M.D.
National Jewish Medical and
Research Center

Michael H. Criqui, M.D., M.P.H.
University of California, San Diego

Jose Cruz, D.Sc.
Pan American Health Organization

Ronald G. Crystal, M.D.
Cornell University

Ann B. Curtis, M.D.
University of South Florida

William C. Cushman, M.D.
Memphis Veterans Administration
Medical Center

A. Jamie Cuticchia, Ph.D.
Duke University

Mark Daly, Ph.D.
Whitehead Institute

Stephen R. Daniels, M.D., Ph.D.
University of Colorado

Martha L. Daviglus, M.D., Ph.D.
Northwestern University

Barry Davis, M.D., Ph.D.
University of Texas

Ron Davis, Ph.D.
Stanford University

Robin L. Davisson, Ph.D.
University of Iowa

Pedro J. del Nido, M.D.
Children's Hospital Boston

Elizabeth DeLong, Ph.D.
Duke Clinical Research Institute

Dawn DeMeo, M.D., M.P.H.
Harvard University

David DeMets, Ph.D.
University of Wisconsin

Edward C. Dempsey, M.D.
University of Colorado
Health Sciences Center

Loren C. Denlinger, M.D., Ph.D.
University of Wisconsin

Richard Devereux, M.D.
Cornell University

Gregory Diette, M.D.
Johns Hopkins University

Ana V. Diez-Roux, M.D., Ph.D.
University of Michigan

John P. DiMarco, M.D.
University of Virginia
Health Sciences Center

Stephanie Dimmeler, Ph.D.
Johann Wolfgang Goethe
University Frankfurt

Robert S. Dittus, M.D.
Vanderbilt University

Roger Dodd, Ph.D.
Jerome H. Holland Laboratory

Claire M. Doerschuck, M.D.
Case Western Reserve University

Gerald Dorn II, M.D.
University of Cincinnati

Ivor Douglas, M.D., M.R.C.P.
University of Colorado
Health Sciences Center

Pamela S. Douglas, M.D.
Duke University Medical Center

George J. Dover, M.D.
Johns Hopkins University

Wonder Drake, M.D.
Vanderbilt University

Jeffrey M. Drazen, M.D.
New England Journal of Medicine

Dennis Drotar, Ph.D.
Case Western Reserve University

Victor J. Dzau, M.D.
Duke University Medical Center

Walter Dzik, M.D.
Massachusetts General Hospital

James Eckman, M.D.
Emory University

Kim A. Eagle, M.D.
University of Michigan

Jack A. Elias, M.D.
Yale University

Susan Ellenberg, Ph.D.
University of Pennsylvania

Mark C. Ellisman, M.D.
University of California at San Diego

John Engelhardt, Ph.D.
University of Iowa

Serpil C. Erzurum, M.D.
Case Western Reserve University

Thomas Eschenhagen, Ph.D.
University Hospital,
Eppendorf, Germany

Charles T. Esmon, Ph.D.
Oklahoma Medical
Research Foundation

David Evans, Ph.D.
Columbia University

Ronald M. Evans, Ph.D.
The Salk Institute

John V. Fahy, M.D.
University of California, San Francisco

Zahi Fayad, Ph.D.
Mount Sinai School of Medicine

Donald O. Fedder, Dr.P.H.
Society for Public Health Education

Ted Feldman, M.D.
Evanston Northwestern Healthcare

Keith Ferdinand, M.D.
Association of Black Cardiologists, Inc.

Victor Ferrari, M.D.
University of Pennsylvania
Medical Center

Patricia Finn, M.D.
University of California, San Diego

John R. Finnegan, Jr., Ph.D.
University of Minnesota

Adolfo Firpo, M.D.
Uniformed Services University

Garret FitzGerald, M.D.
University of Pennsylvania

Kevin R. Flaherty, M.D., M.S.
University of Michigan Health System

Kathy Foell, M.S., R.D.
Massachusetts Department of
Public Health

John Fontanesi, Ph.D.
University of California, San Diego

Myriam Fornage, Ph.D.
University of Texas Health Sciences
Center at Houston

Charles K. Francis, M.D.
Robert Wood Johnson Medical School

James Frank, M.D.
University of California, San Francisco

Paul S. Frenette, M.D.
Mount Sinai School of Medicine

Carol Lynne Freund, Ph.D.
Meharry Medical College

Felix Frueh, M.D.
Food and Drug Administration

Sherrilynne Fuller, Ph.D.
University of Washington

Barbara Furie, Ph.D.
Beth Israel Deaconess Medical Center

Bruce C. Furie, M.D.
Harvard University

Brian F. Gage, M.D., M.Sc.
Washington University

Patrick G. Gallagher, M.D.
Yale University

Joe G. N. Garcia, M.D.
University of Chicago

Daniel Gardner, Ph.D.
Cornell University

Thomas A. Gaziano, M.D., M.Sc.
Brigham and Women's Hospital

Adrian P. Gee, Ph.D.
Baylor College of Medicine

Bruce Gelb, M.D.
Mount Sinai School of Medicine

James N. George, M.D.
University of Oklahoma

James E. Gern, M.D.
University of Wisconsin

Hertzel Gerstein, M.D.
McMaster University

Robert E. Gerszten, M.D.
Massachusetts General Hospital

Saghi Ghaffari, M.D., Ph.D.
Mount Sinai School of Medicine

Patricia J. Giardina, M.D.
Cornell University

Gary H. Gibbons, M.D.
Morehouse School of Medicine

Richard Gibbs, Ph.D.
Baylor College of Medicine

Don Giddens, Ph.D.
Georgia Institute of Technology

Henry N. Ginsberg, M.D.
Columbia University

David Ginsburg, M.D.
University of Michigan Medical Center

Geoffrey Ginsburg, M.D., Ph.D.
Duke University

Christopher K. Glass, M.D., Ph.D.
University of California, San Diego

Alan Go, M.D.
Kaiser Permanente of
Northern California

David Goff, M.D., Ph.D.
Wake Forest University

Ary Goldberger, M.D.
Harvard University

Lee Goldman, M.D., M.P.H.
Columbia University

Pascal Goldschmidt, M.D.
University of Miami

Steven A. N. Goldstein, M.D., Ph.D.
University of Chicago

Steven Goodman, M.D., Ph.D., M.H.S.
Johns Hopkins University

Philip B. Gorelick, M.D., M.P.H.
University of Illinois

Robert C. Gorman, M.D.
University of Pennsylvania

Jerome Gottschall, M.D.
Blood Center of Wisconsin

Darryl T. Gray, M.D., Sc.D.
Agency for Healthcare Research
and Quality

David Green, M.D.
Northwestern University

Ronald M. Green, Ph.D.
Dartmouth College

Phyllis Greenberger
Society for Women's Health Research

A. Gerson Greenburg, M.D., Ph.D.
Brown University

Sheldon Greenfield, M.D.
University of California, Irvine

Philip Greenland, M.D.
Northwestern University

Bartley Griffith, M.D.
University of Maryland

Theresa Guilbert, M.D.
University of Arizona

Gordon Guyatt, M.D.
McMaster University

Neil R. Hackett, Ph.D.
Cornell University

Roger Hajjar, M.D.
Harvard University

Kasturi Haldar, M.D.
Northwestern University

John E. Hall, Ph.D.
University of Mississippi
Medical Center

Mary M. Hand, M.S.P.H., R.N.
Agency for Healthcare Research
and Quality

Richard Harding, Ph.D.
Monash University, Clayton Campus

Joshua M. Hare, M.D.
Johns Hopkins University

John Harlan, M.D.
University of Washington

Robert Harrington, M.D.
Duke Clinical Research Institute

David G. Harrison, M.D.
Emory University

Kevin Harrod, Ph.D.
Lovelace Respiratory Research Institute

Kathryn Hassell, M.D.
University of Colorado
Health Sciences Center

Barbara Hatcher, Ph.D., M.P.H., R.N.
American Public Health Association

Jack J. Hawiger, M.D., Ph.D.
Vanderbilt University

Robert P. Hebbel, M.D.
University of Minnesota

Adriana Heguy, Ph.D.
Cornell University

John A. Heit, M.D.
Mayo Clinic

Frances Henderson, R.N., Ed.D.
Consultant

Katherine A. High, M.D.
Children's Hospital of Philadelphia

Christopher Hillyer, M.D.
Emory University Hospital Blood Bank

Alan T. Hirsch, M.D.
University of Minnesota

Mark A. Hlatky, M.D.
Stanford University

Helen H. Hobbs, M.D.
University of Texas Southwestern
Medical Center

Judith S. Hochman, M.D.
New York University

Brigid Hogan, Ph.D.
Duke University Medical Center

David R. Holmes, M.D.
Mayo Clinic

Susan R. Hopkins, M.D., Ph.D.
University of California, San Diego

Keith Horvath, M.D.
Suburban Hospital

Edwin M. Horwitz, M.D., Ph.D.
St. Jude Research Hospital

Catherine L. Hough, M.D., M.Sc.
University of Washington

Thomas Howard, M.D.
University of Alabama Medical Center

Judith Hsia, M.D.
George Washington University

Leonard D. Hudson, M.D.
University of Washington

Peter J. Hunter, Ph.D., M.E.
University of Auckland, New Zealand

Steven Idell, M.D., Ph.D.
University of Texas

David H. Ingbar, M.D.
University of Minnesota

Silviu Itescu, M.B.B.S., M.D.
Columbia University

Howard J. Jacob, Ph.D.
Medical College of Wisconsin

Robert L. Jesse, M.D., Ph.D.
McGuire Veterans Affairs
Medical Center

Alan Jobe, M.D., Ph.D.
Children's Hospital
Research Foundation

Jennie R. Joe, Ph.D., M.P.H., M.A.
University of Arizona

Cage Johnson, M.D.
University of Southern California

Clinton H. Joiner, M.D., Ph.D.
University of Cincinnati

Hoxi J. Jones
Texas Health and Human
Services Commission

Robert Jones, M.D.
New York Blood Center

Wanda K. Jones, Dr.P.H.
Department of Health and
Human Services

Rudy Juliano, Ph.D.
University of North Carolina

Mark L. Kahn, M.D.
University of Pennsylvania

Robert Kaplan, Ph.D.
University of California, Los Angeles

George Karniadakis, Ph.D.
Brown University

David A. Kass, M.D.
Johns Hopkins University

Robert S. Kass, Ph.D.
Columbia University

Kathy Kastan, L.C.S.W., M.A.Ed.
The National Coalition for Women
with Heart Disease

David L. Katz, M.D., M.P.H.
Yale University

Steven Kawut, M.D., M.S.
Columbia University

Armand Keating, M.D.
Princess Margaret Hospital, Canada

Steven H. Kelder, Ph.D., M.P.H.
University of Texas
Health Science Center at Houston

Catarina Kiefe, M.D., Ph.D.
University of Alabama

Carla F. Kim, Ph.D.
Massachusetts Institute of Technology

Talmadge E. King, Jr., M.D.
San Francisco General Hospital

John P. Kinsella, M.D.
University of Colorado
Health Sciences Center

Richard N. Kitsis, M.D.
Yeshiva University

Michael Knowles, M.D.
University of North Carolina at
Chapel Hill

Kenneth Knox, M.D.
Indiana University

Walter J. Koch, Ph.D.
Thomas Jefferson University

Thomas Kodadek, Ph.D.
University of Texas
Southwestern Medical Center

Isaac Kohane, M.D., Ph.D.
Children's Hospital Boston

Donald B. Kohn, M.D.
Children's Hospital Los Angeles

Barbara Konkle, M.D.
University of Pennsylvania

Greg Koski, M.D., Ph.D.
Massachusetts General Hospital

Laura Koth, M.D.
University of California, San Francisco

Daryl N. Kotton, M.D.
Boston University

Mark Krasnow, M.D., Ph.D.
Stanford University

Jerry Krishnan, M.D., Ph.D.
Johns Hopkins University

Harlan M. Krumholz, M.D., S.M.
Yale University

Rita Kukafka, Dr.P.H., M.A.
Columbia University

Thomas Kulik, M.D.
C.S. Mott Children's Hospital

Shiriki K. Kumanyika, Ph.D., M.P.H.
University of Pennsylvania

Steve Kunkel, Ph.D.
University of Michigan

Peter Kurre, M.D.
Oregon Health and Science University

Rebecca Kush, Ph.D.
Clinical Data Standards
Interchange Consortium

Robert Kushner, M.D.
Northwestern University

Frans Kuypers, Ph.D.
Children's Hospital
Oakland Research Institute

Darwin R. Labarthe, M.D.,
Ph.D., M.P.H.
Centers for Disease Control
and Prevention

Peter Lane, M.D.
Emory University

Albert Lardo, Ph.D., F.A.H.A
Johns Hopkins Hospital

Eric B. Larson, M.D., M.P.H.
Center for Health Studies

Philippe Leboulch, M.D.
Brigham and Women's Hospital

Richard T. Lee, M.D.
Harvard University

Branka Legetic, M.D., Ph.D., M.P.H.
World Health Organization

Susan Leibenhaut, M.D.
Food and Drug Administration

Leslie Leinwand, Ph.D.
University of Colorado

Robert F. Lemanske, Jr., M.D.
University of Wisconsin at Madison

Kam W. Leong, Ph.D.
Duke University

Andrew Levey, M.D.
Tufts University

Sanford Levine, M.D.
University of Pennsylvania

Robert Levy, M.D.
Abramson Research Center

Peter Libby, M.D.
Brigham and Women's Hospital

Richard P. Lifton, M.D., Ph.D.
Yale University

Stephen B. Liggett, M.D.
University of Maryland

Karen Lipton, J.D.
American Association of Blood Banks

Peter Liu, Ph.D.
Canadian Institute of Health Research

Donald Lloyd-Jones, M.D., Sc.M.
Northwestern University

Jose A. Lopez, M.D.
Puget Sound Blood Center

Joseph Loscalzo, M.D., Ph.D.
Brigham and Women's Hospital

Douglas W. Losordo, M.D.
Caritas St. Elizabeth's Medical Center

Richard Lottenberg, M.D.
University of Florida

James E. Loyd, M.D.
Vanderbilt University

Naomi Luban, M.D.
Children's National Medical Center

Bertram Lubin, M.D.
Children's Hospital
Oakland Research Institute

Russell V. Luepker, M.D.
University of Minnesota

Nigel Mackman, Ph.D.
Scripps Research Institute

Richard T. Mahon, M.C., U.S.N.R.
Naval Medical Research Center

Marilyn J. Manco-Johnson, M.D.
University of Colorado

Douglas Mann, M.D.
Baylor College of Medicine

Kenneth Mann, Ph.D.
University of Vermont

Catherine Scott Manno, M.D.
Children's Hospital of Philadelphia

JoAnn Manson, M.D., Dr.P.H.
Brigham and Women's Hospital

Eduardo Marban, M.D., Ph.D.
Johns Hopkins University

Thomas A. Marciniak, M.D.
Food and Drug Administration

Victor Marder, M.D.
University of California, Los Angeles

Daniel B. Mark, M.D., M.P.H.
Duke University

Andrew R. Marks, M.D.
Columbia University

Thomas R. Martin, M.D.
University of Washington

Fernando D. Martinez, M.D.
University of Arizona

Donald J. Massaro, M.D.
Georgetown University

Barry Massie, M.D.
University of California, San Francisco

Michael Matthay, M.D.
University of California, San Francisco

Karen Matthews, Ph.D.
University of Pittsburgh

Paul Mazmanian, Ph.D.
Virginia Commonwealth University

Patrick E. McBride, M.D., M.P.H.
University of Wisconsin

Andrew McCulloch, Ph.D.
University of California, San Diego

Jeffrey McCullough, M.D.
University of Minnesota

Mary McDermott, M.D.
Northwestern University

Rodger McEver, M.D.
Oklahoma Medical
Research Foundation

Richard McFarland, M.D.
Food and Drug Administration

J. Michael McGinnis, M.D., M.P.P.
Institute of Medicine at the
National Academies

James M. McKenney, Pharm.D.
National Clinical Research

Ann McKibbon, Ph.D., M.L.S.
McMaster University

Bruce M. McManus, M.D., Ph.D.,
F.R.S.C., F.C.A.H.S.
St. Paul's Hospital, Canada

Elizabeth M. McNally, M.D., Ph.D.
University of Chicago

Robert McNellis, M.P.H., PA-C
American Academy of
Physician Assistants

Amy Melnick
Heart Rhythm Society

Michael E. Mendelsohn, M.D.
New England Medical Center
Hospitals, Inc.

Jay Menitove, M.D.
Community Blood Center

Mark Mercola, Ph.D.
The Burnham Institute

Takashi Mikawa, Ph.D.
University of California, San Francisco

Lisa A. Miller, Ph.D.
University of California, Davis

John Mittler, Ph.D.
University of Washington

Alicia Moag-Stahlberg
Action for Healthy Kids

David R. Moller, M.D.
Johns Hopkins University

Anne M. Moon, M.D., Ph.D.
University of Utah

Jonathan D. Moreno, Ph.D.
University of Virginia

David Morris, M.D.
Roche Pharmaceuticals

Heather Morris
National Association for Sport and Physical Education

Edward E. Morrisey, Ph.D.
University of Pennsylvania

Lori J. Mosca, M.D., Ph.D., M.P.H.
Columbia University

Arthur J. Moss, M.D.
University of Rochester

Jay Moskowitz, Ph.D.
Pennsylvania State University

Albert George Mulley, M.D.
Harvard University

William Munier, M.D.
Agency for Healthcare Research and Quality

David Murray, Ph.D.
Ohio State University

Thomas H. Murray, Ph.D.
The Hastings Center

Mark A. Musen, M.D., Ph.D.
Stanford University Medical Center

Robert J. Myerburg, M.D.
University of Miami

Joseph H. Nadeau, Ph.D.
Case Western Reserve University

Mohandas Narla, M.D.
New York Blood Center

Karen Near, M.D.
Office of the Surgeon General

James Neaton, Ph.D.
University of Minnesota

Enid R. Neptune, M.D.
Johns Hopkins University

Jeanne M. Nerbonne, M.D.
Washington University

Paul Ness, M.D.
Johns Hopkins Hospital

Ellis J. Neufeld, M.D.
Children's Hospital Boston

Jane W. Newburger, M.D., M.P.H.
Children's Hospital

Ngai X. Nguyen, M.D., F.A.C.C., F.A.C.P.
Private Practitioner

Deborah A. Nickerson, Ph.D.
University of Washington

Shuming Nie, Ph.D.
Emory University

Steven L. Nissen, M.D.
Cleveland Clinic

Paul W. Nobel, M.D.
Duke University

Garry Nolan, Ph.D.
Stanford University

Jan A. Nolta, Ph.D.
Washington University

Carole Ober, Ph.D.
University of Chicago

Ira Ockene, M.D.
University of Massachusetts

Judith Ockene, Ph.D.
University of Massachusetts

Christopher O'Connor, M.D.
Duke University

Peter J. Oettgen, M.D.
Harvard University

Kwaku Ohene-Frempong, M.D.
Children's Hospital of Philadelphia

Samuel C. Okoye, M.D., F.A.A.F.P.
Community Outreach for Health Awareness

Richard O'Reilly, M.D.
Sloan-Kettering Institute of Cancer Research

Stuart H. Orkin, M.D.
Children's Hospital Boston

Joseph P. Ornato, M.D., F.A.C.P., F.A.C.C., F.A.C.E.P.
Virginia Commonwealth University Medical Center

Jerome A. Osheroff, M.D., F.A.C.P., F.A.C.M.I.
University of Pennsylvania Health System

Betty Pace, M.D.
University of Texas at Dallas

Allan I. Pack, M.B., Ch.B., Ph.D.
University of Pennsylvania

Kristen Page, Ph.D.
Children's Hospital Medical Center

Scott Palmer, M.D., M.H.S.
Duke University Medical Center

Julie A. Panepinto, M.D., M.S.P.H.
Medical College of Wisconsin

Leslie Parise, Ph.D.
University of North Carolina at Chapel Hill

Robertson Parkman, M.D.
University of Southern California

Russell Pate, Ph.D.
University of South Carolina

Cam Patterson, M.D.
University of North Carolina at Chapel Hill

Kevin A. Pearce, M.D., M.P.H.
University of Kentucky

Thomas A. Pearson, M.D., M.P.H., Ph.D.
University of Rochester

Emerson Perin, M.D., Ph.D.
Texas Heart Institute

Eric D. Peterson, M.D., M.P.H., F.A.C.C.
Duke University

Irina Petrache, M.D.
Indiana University

Marc Pfeffer, M.D., Ph.D.
Brigham and Women's Hospital

Steven Piantadosi, M.D., Ph.D.
Johns Hopkins University

David Pinsky, M.D.
University of Michigan

Bertram Pitt, M.D.
University of Michigan

Charles G. Plopper, Ph.D.
University of California, Davis

Bruce Psaty, M.D., Ph.D.
University of Washington

Lynn Puddington, Ph.D.
University of Connecticut

Marlene Rabinovitch, M.D.
Stanford University

Daniel J. Rader, M.D.
University of Pennsylvania

Shahin Rafii, M.D.
Cornell University

Cynthia S. Rand, Ph.D.
Johns Hopkins University

Scott H. Randell, Ph.D.
University of North Carolina at Chapel Hill

Adrienne Randolph, M.D.
Children's Hospital Boston

Margaret M. Redfield, M.D.
Mayo Clinic

Susan Redline, M.D.
Case Western Reserve University

William Reed, M.D.
University of California, San Francisco

Bob Rehm, M.B.A.
America's Health Insurance Plans

Mary V. Relling, Pharm.D.
St. Jude Children's Research Hospital

Paul Ridker, M.D.
Brigham and Women's Hospital

John Roback, M.D., Ph.D.
Emory University

Robert C. Robbins, M.D.
Stanford University

Rose Marie Robertson, M.D.
American Heart Association

John W. Robitscher, M.P.H.
National Association of Chronic Disease Directors

Dan M. Roden, M.D.
Vanderbilt University

Veronique L. Roger, M.D.
Mayo Clinic

Sheila H. Roman, M.D., M.P.H.
Centers for Medicare and Medicaid Services

Eric A. Rose, M.D.
Columbia University

Hugh Rosen, M.D., Ph.D.
Scripps Research Institute

Michael R. Rosen, M.D.
Columbia University

Ellen Rothenberg, Ph.D.
California Institute of Technology

Sharon Rounds, M.D.
Providence Veterans Administration Medical Center

Gordon D. Rubenfeld, M.D.
University of Washington

George S. Rust, M.D., M.P.H.
Morehouse School of Medicine

David H. Sachs, M.D.
Massachusetts General Hospital

Frank Sacks, M.D.
Harvard University

J. Evan Sadler, M.D., Ph.D.
Washington University

James F. Sallis, Ph.D.
San Diego State University

Joel Saltz, M.D., Ph.D.
Ohio State University

Michael C. Sanguinetti, Ph.D.
University of Utah

Maurice E. Sarano, M.D.
Mayo Clinic

Rajabrata Sarkar, M.D., Ph.D.
University of California, San Francisco

David T. Scadden, M.D.
Harvard University

Andrew I. Schafer, M.D.
University of Pennsylvania

Robert P. Schleimer, Ph.D.
Northwestern University

Ann Marie Schmidt, M.D.
Columbia University

Lynn M. Schnapp, M.D.
University of Washington

Barbara Schneeman, Ph.D.
Food and Drug Administration

Michael Schneider, M.D.
Baylor College of Medicine

Mark A. Schoeberl
American Heart Association

Daniel Schuster, M.D.
Washington University

Mark A. Schuster, M.D., Ph.D.
University of California, Los Angeles

Richard J. Schuster, M.D., M.M.M.
Wright State University

Sanford J. Schwartz, M.D.
University of Pennsylvania

Lisa M. Schwiebert, Ph.D.
University of Alabama, Birmingham

Christine E. Seidman, M.D.
Harvard University

Jonathan Seidman, Ph.D.
Harvard University

Joseph Selby, M.D., M.P.H.
Kaiser Permanente

Robert M. Senior, M.D.
Washington University

William C. Sessa, Ph.D.
Yale University

Prediman K. Shah, M.D.
University of California, Los Angeles

Steven D. Shapiro, M.D.
University of Pittsburgh

Sanford J. Shattil, M.D.
University of California, San Diego

Gary M. Shaw, Dr.P.H., M.P.H.
California Birth Defects Monitoring Program

Dean Sheppard, M.D.
University of California, San Francisco

Richard Shiffman, M.D., M.C.I.S.
Yale Center for Medical Informatics

Ramesh A. Shivdasani, M.D., Ph.D.
Harvard University

Carol Shively, Ph.D.
Wake Forest University

Alan Shuldiner, M.D.
University of Maryland

Gerald J. Shulman, M.D., Ph.D.
Yale University

Stephen Sidney, M.D., M.P.H.
Kaiser Permanente

Don Siegel, M.D., Ph.D.
University of Pennsylvania

Leslie Silberstein, M.D.
Harvard University

Amy Simon, M.D.
Tufts University

Daniel Simon, M.D.
Case Western Reserve University

M. Celeste Simon, Ph.D., M.S.
University of Pennsylvania

David S. Siscovick, M.D., M.P.H.
University of Washington

Donna Skerrett, M.D.
Cornell University

Wally R. Smith, M.D.
Virginia Commonwealth University

Susan Smyth, M.D., Ph.D.
University of Kentucky

Edward Snyder, M.D.
Yale-New Haven Hospital

Edward J. Sondik, Ph.D.
National Center for Health Statistics

Frank E. Speizer, M.D.
Harvard University

Eliot R. Spindel, M.D., Ph.D.
Oregon Health and Science University

Kenneth W. Spitzer, Ph.D.
University of Utah

Deepak Srivastava, M.D.
University of California, San Francisco

George Stamatoyannopoulos, M.D., Dr.Sci.
University of Washington

Jonathan S. Stamler, M.D.
Duke University

Theodore J. Standiford, M.D.
University of Michigan

Patrick S. Stayton, Ph.D.
University of Washington

Chad Steele, Ph.D.
University of Pittsburgh

Marcia L. Stefanick, Ph.D.
Stanford University

Martin H. Steinberg, M.D.
Boston University

Kurt R. Stenmark, M.D.
University of Colorado

Lynne Warner Stevenson, M.D.
Brigham and Women's Hospital

Duncan J. Stewart, M.D.
University of Toronto, St. Michael's Hospital

Gregg W. Stone, M.D.
Columbia University Medical Center

Neil J. Stone, M.D.
Northwestern University

Rainer Storb, M.D.
University of Washington

Robert M. Strieter, M.D., R.R.T.
University of Virginia

Barry Stripp, Ph.D.
University of Pittsburgh

Marie Stuart, M.D.
Thomas Jefferson University

Sam Stupp, Ph.D.
Northwestern University

Shankar Subramaniam, Ph.D.
University of California, San Diego

Bruce A. Sullenger, Ph.D.
Duke University

Mary E. Sunday, M.D., Ph.D.
Duke University

E. Rand Sutherland, M.D., M.P.H.
National Jewish Medical and Research Center

Megan Sykes, M.D.
Harvard University

Robert Tarran, Ph.D.
University of North Carolina at Chapel Hill

Lynn M. Taussig, M.D.
University of Denver

Anne L. Taylor, M.D.
University of Minnesota

Herman Taylor, M.D., F.A.C.C.
University of Mississippi Medical Center

Jonathan Teich, M.D., Ph.D.
Harvard University

Robert Temple, M.D.
Food and Drug Administration

Robert S. Tepper, M.D., Ph.D.
Indiana University

Bernard Thebaud, M.D., Ph.D.
University of Alberta

Theodore J. Theophilos
RR Donnelley & Sons Company

George Thomas, M.D.
Bradenton Cardiology Center

B. Taylor Thompson, M.D.
Massachusetts General Hospital

Robert W. Thompson, M.D.
Washington University

Galen B. Toews, M.D.
University of Michigan

Gordon F. Tomaselli, M.D.
Johns Hopkins University

Allison Topper
Pennsylvania Advocates for Nutrition and Activity

Eric J. Topol, M.D.
Scripps Health

Sheryl Torr-Brown, Ph.D.
Spiral5 Consulting, LLC

Jeffrey A. Towbin, M.D.
Baylor College of Medicine

Russell P. Tracy, Ph.D.
University of Vermont

Natalia Trayanova, Ph.D.
Tulane University

Marsha Treadwell, Ph.D.
Children's Hospital and Research Center at Oakland

John Triedman, M.D.
Harvard University

Darrell J. Triulzi, M.D.
University of Pittsburgh

Daniel Tschumperlin, Ph.D.
Harvard University

Reed Tuckson, M.D.
United Health Foundation

Rubin M. Tuder, M.D.
Johns Hopkins University

Fred W. Turek, Ph.D.
Northwestern University

Steve Turner, M.D.
Mayo Clinic

Lynne Uhl, M.D.
Harvard University

Eleftherios (Stephen) Vamvakas, M.D., Ph.D.
Canadian Blood Services

Cees Van der Poel, M.D.
Sanguin Blood Supply Foundation, Netherlands

Jennifer Van Eyk, Ph.D.
Johns Hopkins University

Linda V. Van Horn, Ph.D., R.D.
Northwestern University

Donata M. Vercelli, M.D.
University of Arizona

Catherine Verfaillie, M.D.
University of Minnesota

Richard L. Verrier, Ph.D.
Harvard University

Marc Vidal, Ph.D.
Harvard University

Tuan Vo-Dinh, Ph.D.
Duke University

Thiennu Vu, M.D., Ph.D.
University of California, San Francisco

Gordana Vunjak-Novakovic, Ph.D.
Columbia University

Denisa Wagner, Ph.D.
Harvard University

Peter D. Wagner, M.D.
University of California, San Diego

Patricia W. Wahl, Ph.D.
University of Washington

Albert L. Waldo, M.D.
Case Western Reserve University

David Warburton, M.D., D.Sc., F.R.C.P.
Children's Hospital Los Angeles

Robert Waterland, Ph.D.
Baylor College of Medicine

Hartmut Weiler, Ph.D.
Blood Research Institute

William S. Weintraub, M.D., F.A.C.C.
Christiana Care Health System

Daniel J. Weisdorf, M.D.
University of Minnesota

Daniel Weiss, M.D., Ph.D.
University of Vermont

James N. Weiss, M.D.
University of California, Los Angeles

Scott T. Weiss, M.D.
Brigham and Women's Hospital

Nanette K. Wenger, M.D., M.A.C.P., F.A.C.C., F.A.H.A.
Emory University

Jennifer West, Ph.D.
Rice University

Laura F. Wexler, M.D., F.A.H.A., F.A.C.C.
University of Cincinnati

Alexander White, M.D.
New England Medical Center Hospitals

Samuel A. Wickline, M.D.
Washington University

David S. Wilkes, M.D.
Indiana University

James T. Willerson, M.D.
University of Texas Health Science Center

Marlene S. Williams, M.D.
Johns Hopkins Bayview Medical Center

Mary C. Williams, Ph.D.
Boston University

O. Dale Williams, Ph.D.
University of Alabama at Birmingham

R. Sanders Williams, M.D.
Duke University

Redford Williams, M.D.
Duke University Medical Center

Marsha Wills-Karp, Ph.D.
Cincinnati Children's Hospital Medical Center

Sandra R. Wilson, Ph.D.
Stanford University

Rena Wing, Ph.D.
The Miriam Hospital

Raimond Winslow, Ph.D.
Johns Hopkins University

Robert A. Wise, M.D.
Johns Hopkins Asthma and Allergy Center

Janet Wittes, Ph.D.
Statistics Collaborative, Inc.

Prescott G. Woodruff, M.D., M.P.H.
University of California, San Francisco

Steve Woolf, M.D.
Virginia Commonwealth University

Anne L. Wright, Ph.D.
University of Arizona

Jackson T. Wright, Jr., M.D., Ph.D., F.A.C.P.
Case Western Reserve University

Jo Rae Wright, Ph.D.
Duke University

Mark M. Wurfel, M.D., Ph.D.
Harborview Medical Center

George Yancopoulos, M.D., Ph.D.
Regenron Pharmaceuticals, Inc.

Clyde Yancy, M.D.
Baylor University Medical Center

John Yates, III, M.D., Ph.D.
Scripps Research Institute

Herbert F. Young, M.D., M.A., F.A.A.F.P.
American Academy of Family Physicians

David W. Zaas, M.D.
Duke University

Guy A. Zimmerman, M.D.
University of Utah

James Zimring, M.D., Ph.D.
Emory University

Douglas P. Zipes, M.D.
Indiana University

Leonard I. Zon, M.D.
Children's Hospital Boston

NIH Participants

David B. Abrams, Ph.D.
Office of Behavioral and Social Sciences Research
National Institutes of Health

Bishow Adhikari, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Matilde M. Alvarado, M.S., R.N.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Barbara Alving, M.D.
Office of the Director
National Center for Research Resources

Deborah Applebaum-Bowden, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Larissa Aviles-Santa, M.D.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Robert S. Balaban, Ph.D.
Division of Intramural Research
National Heart, Lung, and Blood Institute

Timothy Baldwin, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Susan Banks-Schlegel, Ph.D.
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Luiz H. Barbosa, D.V.M., M.P.H.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Winnie Barouch, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Peg Barratt, Ph.D.
Office of Science Policy
National Institutes of Health

John A. Barrett, M.D.
Division of Intramural Research
National Heart, Lung, and Blood Institute

Petronella A. Barrow
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Leslie A. Bassett
Office of Minority Health Affairs
National Heart, Lung, and Blood Institute

Glen C. Bennett, M.P.H.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Mary Anne Berberich, Ph.D.
Formerly with Division of Lung Diseases
National Heart, Lung, and Blood Institute

Diane E. Bild, M.D., M.P.H.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Olivier Bodenreider, M.D., Ph.D.
Lister Hill National Center for Biomedical Communications
National Library of Medicine

Robin E. Boineau, M.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Ebony Bookman, Ph.D.
Formerly with Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Douglas A. Boyd
Formerly with Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Judith A. Burk
Office of the Director
National Heart, Lung, and Blood Institute

Stephanie Burrows, Ph.D.
Office of Science and Technology
National Heart, Lung, and Blood Institute

Denis B. Buxton, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Richard O. Cannon, M.D.
Division of Intramural Research
National Heart, Lung, and Blood Institute

Henry Chang, M.D.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Donald P. Christoferson
Office of Administrative Management
National Heart, Lung, and Blood Institute

James I. Cleeman, M.D.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Francis S. Collins, M.D., Ph.D.
Office of the Director
National Human Genome Research Institute

Sandra Colombini-Hatch, M.D.
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Lawton S. Cooper, M.D., M.P.H.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Judy Corbett
Formerly with Office of Science and Technology
National Heart, Lung, and Blood Institute

Thomas L. Croxton, M.D., Ph.D.
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Jeffrey A. Cutler, M.D., M.P.H.
Formerly with Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Susan M. Czajkowski, Ph.D.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Darla E. Danford, M.P.H., D.Sc.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Camina L. Davis, M.S.H.P.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Janet de Jesus, M.S., R.D.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Elizabeth Denholm, Ph.D.
Formerly with Division of Lung Diseases
National Heart, Lung, and Blood Institute

Patrice Desvigne-Nickens, M.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Nancy L. DiFronzo, Ph.D.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Michael J. Domanski, M.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Karen A. Donato, S.M., R.D.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Jonelle Drugan, Ph.D., M.P.H.
Formerly with Office of Science and Technology
National Heart, Lung, and Blood Institute

Cynthia E. Dunbar, M.D.
Division of Intramural Research
National Heart, Lung, and Blood Institute

Sue A. Edington
Division of Extramural Activities Support
National Institutes of Health

Paula T. Einhorn, M.D., M.S.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Abby G. Ershow, Sc.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Frank J. Evans, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Gregory L. Evans, Ph.D.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Richard R. Fabsitz, Ph.D.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Kathryn P. Fain
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Lawrence J. Fine, M.D., M.P.H., Dr.P.H.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Toren Finkel, M.D., Ph.D.
Division of Intramural Research
National Heart, Lung, and Blood Institute

Jerome L. Fleg, M.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Vicki A. Freedenberg, R.N., M.S.N.
Division of Intramural Research
National Institute of Dental and Craniofacial Research

Lisa A. Freeny
Office of Administrative Management
National Heart, Lung, and Blood Institute

Charles P. Friedman, Ph.D.
Formerly with the Center for Research Informatics and Information Technology
National Heart, Lung, and Blood Institute

Robinson Fulwood, Ph.D., M.S.P.H.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Dorothy B. Gail, Ph.D.
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Pankaj Ganguly, Ph.D.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Timothy J. Gardner, M.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Nancy L. Geller, Ph.D.
Office of Biostatistics Research
National Heart, Lung, and Blood Institute

Mark T. Gladwin, M.D.
Division of Intramural Research
National Heart, Lung, and Blood Institute

Roger I. Glass, M.D., Ph.D.
John E. Fogarty International Center
National Institutes of Health

Simone A. Glynn, M.D.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Stephen S. Goldman, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

David J. Gordon, M.D., Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Jeanette Guyton-Krishnan, Ph.D., M.S.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Patricia Ann Haggerty, Ph.D.
Division of Extramural Research Activities
National Heart, Lung, and Blood Institute

Andrea L. Harabin, Ph.D.
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Jane L. Harman, D.V.M., Ph.D.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Liana Harvath, Ph.D.
Formerly with Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Ahmed AK Hasan, M.D., Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Keith L. Hewitt
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Carla Hines, PA-C
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Van S. Hubbard, M.D., Ph.D., CAPT
Division of Nutrition Research
National Institute of Diabetes and Digestive and Kidney Diseases

Carl E. Hunt, M.D.
Formerly with Office of the Director
National Heart, Lung, and Blood Institute

Della E. Jackson
Division of Extramural Activities Support
National Institutes of Health

Cashell E. Jaquish, Ph.D.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Mary M. Joyce, R.N.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Peter G. Kaufmann, Ph.D.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Rae-Ellen W. Kavey, M.D., M.P.H.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

James P. Kiley, Ph.D.
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Harvey G. Klein, M.D.
Clinical Center
National Institutes of Health

Chitra Krishnamurti, Ph.D.
Office of Minority Health Affairs
National Heart, Lung, and Blood Institute

Jennie E. Larkin, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

David A. Lathrop, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Vicki Nghi Le
Office of the Director
National Heart, Lung, and Blood Institute

Caron J. Lee
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Warren J. Leonard, M.D.
Division of Intramural Research
National Heart, Lung, and Blood Institute

Daniel Levy, M.D.
Center for Population Studies
National Heart, Lung, and Blood Institute

Isabella Y. Liang, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Michael Lin, Ph.D.
Formerly with Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Rebecca P. Link, Ph.D.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Barbara M. Liu, S.M.
Office of Science and Technology
National Heart, Lung, and Blood Institute

Stacey A. Long
Office of Administrative Management
National Heart, Lung, and Blood Institute

Theresa C. Long
Formerly with Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Catherine Loria, Ph.D.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Harvey S. Luksenburg, M.D.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Martha S. Lundberg, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Nicole M. Mahoney, Ph.D.
Formerly with Office of Science and Technology
National Heart, Lung, and Blood Institute

Alice Mascette, M.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Judith G. Massicot-Fisher, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Clement J. McDonald, M.D.
Office of the Director
National Library of Medicine

Alan M. Michelson, M.D., Ph.D.
Office of the Director
National Heart, Lung, and Blood Institute

Marissa A. Miller, D.V.M., M.P.H.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Helena O. Mishoe, Ph.D., M.P.H.
Office of Minority Health Affairs
National Heart, Lung, and Blood Institute

Phyllis I. Mitchell, M.S.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Stephen C. Mockrin, Ph.D.
Division of Extramural Research Activities
National Heart, Lung, and Blood Institute

Traci H. Mondoro, Ph.D.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

R. Blaine Moore, Ph.D.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Gregory J. Morosco, Ph.D., M.P.H.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Joel Moss, M.D., Ph.D.
Division of Intramural Research
National Heart, Lung, and Blood Institute

Elizabeth G. Nabel, M.D.
Office of the Director
National Heart, Lung, and Blood Institute

Aaron B. Navarro, Ph.D.
Lister Hill National Center for Biomedical Communications
National Library of Medicine

Cheryl R. Nelson, M.S.P.H.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

George J. Nemo, Ph.D.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Emily Newcomer
Office of Administrative Management
National Heart, Lung, and Blood Institute

Cuong T. Nguyen
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Hanyu Ni, Ph.D.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Patricia J. Noel, Ph.D.
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Christopher J. O'Donnell, M.D., M.P.H.
Office of the Director
National Heart, Lung, and Blood Institute

Christopher E. Olaes
Center for Research Informatics and Information Technology
National Heart, Lung, and Blood Institute

Victor R. Olano, M.P.H.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Susan E. Old, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Jean L. Olson, M.D., M.P.H.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Gloria A. Ortiz
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Dina N. Paltoo, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Sunil P. Pandit, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Gail D. Pearson, M.D., Sc.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Hannah H. Peavy, M.D.
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Charles M. Peterson, M.D., M.B.A.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Sheila Pohl, M.A.
Office of the Director
National Heart, Lung, and Blood Institute

Nancy J. Poole, M.B.A.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Charlotte A. Pratt, Ph.D.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Valerie L. Prenger, Ph.D.
Division of Extramural Research Activities
National Heart, Lung, and Blood Institute

Dennis A. Przywara, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Susan E. Pucie
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Frank Pucino, Pharm.D., B.C.P.S., F.A.S.H.P., F.D.P.G.E.C.
Pharmacy Department
National Institutes of Health Clinical Center

Pankaj Qasba, Ph.D.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Christina Rabadan-Diehl, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Matt Raschka
Center for Research Informatics and Information Technology
National Heart, Lung, and Blood Institute

Herbert Y. Reynolds, M.D.
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Thomas C. Rindflesch, Ph.D.
Lister Hill National Center for Biomedical Communications
National Library of Medicine

Nora I. Rivera
Formerly with Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Edward J. Roccella, Ph.D., M.P.H.
Formerly with Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Yves D. Rosenberg, M.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Jacques E. Rossouw, M.D.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Carl A. Roth, Ph.D., LL.M.
Office of Science and Technology
National Heart, Lung, and Blood Institute

Ann E. Rothgeb
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Ayana K. Rowley, Pharm.D.
Pharmacy Department
National Institutes of Health Clinical Center

Rita Sarkar, Ph.D.
Division of Blood Diseases and Resources
National Heart, Lung, and Blood Institute

Peter J. Savage, M.D.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Charlene A. Schramm, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Eleanor B. Schron, M.S., R.N., F.A.A.N.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

David A. Schwartz, M.D.
Office of the Director
National Institute of Environmental Health Sciences

Susan K. Scolnik
Office of Science and Technology
National Heart, Lung, and Blood Institute

Jane D. Scott, Sc.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Amy W. Sheetz
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Susan T. Shero, M.S.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

Phyliss D. Sholinsky, M.S.P.H.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Susan B. Shurin, M.D.
Office of the Director
National Heart, Lung, and Blood Institute

Denise Simons-Morton, M.D., Ph.D.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Sonia I. Skarlatos, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Robert A. Smith, Ph.D.
Division of Lung Diseases
National Heart, Lung, and Blood Institute

Ellen K. Sommer, M.B.A.
Division for the Application of Research Discoveries
National Heart, Lung, and Blood Institute

George Sopko, M.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Paul D. Sorlie, Ph.D.
Division of Prevention and Population Sciences
National Heart, Lung, and Blood Institute

Miriam C. Spiessbach
Office of the Director
National Heart, Lung, and Blood Institute

Pothur R. Srinivas, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Maria R. Stagnitto, R.N., M.S.N.
Office of Clinical Research
National Heart, Lung, and Blood Institute

Dennis V. Stanley
Division of Cardiovascular Diseases
National Heart, Lung, and Blood Institute

Louis M. Staudt, M.D., Ph.D.
Center for Cancer Research
National Cancer Institute

Virginia S. Taggart, M.P.H.
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

Ann M. Taubenheim, Ph.D., M.S.N.
Division for the Application of
Research Discoveries
National Heart, Lung, and
Blood Institute

Thomas J. Thom
Division of Prevention and
Population Sciences
National Heart, Lung, and
Blood Institute

John W. Thomas, Ph.D.
Division of Blood Diseases
and Resources
National Heart, Lung, and
Blood Institute

Xin Tian, Ph.D.
Division of Prevention and
Population Sciences
National Heart, Lung, and
Blood Institute

Nico Tjandra, Ph.D.
Division of Intramural Research
National Heart, Lung, and
Blood Institute

Eser Tolunay, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and
Blood Institute

Rachael L. Tracy, M.P.H.
Division for the Application of
Research Discoveries
National Heart, Lung, and
Blood Institute

Michael J. Twery, Ph.D.
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

Karen L. Ulisney, R.N., M.S.N.
Division of Cardiovascular Diseases
National Heart, Lung, and
Blood Institute

Ralph Van Wey, M.S.
Center for Research Informatics
and Information Technology
National Heart, Lung, and
Blood Institute

Jamie Varghese, Ph.D.
Formerly with Division of
Cardiovascular Diseases
National Heart, Lung, and
Blood Institute

Paul A. Velletri, Ph.D.
Division of Extramural
Research Activities
National Heart, Lung, and
Blood Institute

Carol E. Vreim, Ph.D.
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

Elizabeth L. Wagner, M.P.H.
Division of Blood Diseases
and Resources
National Heart, Lung, and
Blood Institute

Evelyn R. Walker, Ph.D.
Division of Prevention and
Population Sciences
National Heart, Lung, and
Blood Institute

Madeleine F. Wallace, Ph.D.
Division for the Application of
Research Discoveries
National Heart, Lung, and
Blood Institute

Lan-Hsiang Wang, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and
Blood Institute

Wanda R. Ware
Division of Extramural
Activities Support
National Institutes of Health

Lynford Warner
Formerly with Center for
Research Informatics and
Information Technology
National Heart, Lung, and
Blood Institute

Momtaz Wassef, Ph.D.
Division of Cardiovascular
Diseases National Heart, Lung,
and Blood Institute

Norbert D. Weber, Ph.D.
Office of Science and Technology
National Heart, Lung, and
Blood Institute

Gina S. Wei, M.D., M.P.H.
Division of Prevention and
Population Sciences
National Heart, Lung, and
Blood Institute

Gail G. Weinmann, M.D.
Division of Lung Diseases
National Heart, Lung, and
Blood Institute

Barbara L. Wells, M.D.
Division of Prevention and
Population Sciences
National Heart, Lung, and
Blood Institute

Connie G. Wells
Office of the Director
National Heart, Lung, and
Blood Institute

Ellen M. Werner, Ph.D.
Division of Blood Diseases
and Resources
National Heart, Lung, and
Blood Institute

Roy L. White, Ph.D.
Division of Extramural
Research Activities
National Heart, Lung, and
Blood Institute

Violet R. Woo, M.S., M.P.H.
Division for the Application of
Research Discoveries
National Heart, Lung, and
Blood Institute

Daniel G. Wright, M.D.
Division of Kidney, Urologic, and
Hematologic Diseases
National Institute of Diabetes and
Digestive and Kidney Diseases

Song Yang, Ph.D.
Office of Biostatistics Research
National Heart, Lung, and
Blood Institute

Jane X. Ye, Ph.D.
Division of Cardiovascular Diseases
National Heart, Lung, and
Blood Institute

Neal S. Young, M.D.
Division of Intramural Research
National Heart, Lung, and
Blood Institute

Zhi-Jie Zheng, M.D., Ph.D.
Division for the Application of
Research Discoveries
National Heart, Lung, and
Blood Institute

Information and Resources

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http://www.nhlbi.nih.gov/resources/index.htm

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http://www.nhlbi.nih.gov/health/indexpro.htm

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NIH Resources

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http://cms.csr.nih.gov/

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For More Information

The National Heart, Lung, and Blood Institute (NHLBI) Health Information Center is a service of the NHLBI of the National Institutes of Health. The NHLBI Health Information Center provides information to health professionals, patients, and the public about the treatment, diagnosis, and prevention of heart, lung, and blood diseases and sleep disorders. For more information, contact:

NHLBI Health Information Center
P.O. Box 30105
Bethesda, MD 20824-0105
Phone: 301-592-8573
TTY: 240-629-3255
Fax: 301-592-8563
Web site: http://www.nhlbi.nih.gov

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