National Heart, Lung, and Blood Institute

Strategic Research Priorities [DRAFT]

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

National Heart, Lung, and Blood Institute (NHLBI)
Strategic Research Priorities – PUBLIC COMMENT VERSION

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Introduction

For more than 60 years, the NHLBI community has fostered a legacy of research excellence through groundbreaking fundamental discovery science, landmark clinical trials and population-based cohort studies, as well as innovative health education and dissemination efforts. However, despite the significant advances in treatment and prevention made during these decades, HLBS diseases still pose a major health and economic burden in the United States.

In order to sustain the NHLBI's legacy, the Institute must look beyond the horizon, anticipate and capitalize on emerging scientific opportunities, as well as foresee and identify approaches to overcome emerging barriers to progress. This Strategic Vision was initiated in recognition of these needs and in acknowledgement of the transformational scientific advances that are emerging at an accelerating pace. New scientific tools and the logarithmic expansion of the capacity to manage and analyze data present opportunities that are only limited by human imagination. Therefore, this is an especially opportune time for the NHLBI to partner with its scientific and patient communities to identify areas where NHLBI can help others harness new opportunities and overcome roadblocks to scientific success. This Strategic Vision is an unprecedented effort to engage NHLBI's stakeholder communities in identifying and prioritizing the most compelling science for which NHLBI leadership over the next decade could catalyze the closing of large gaps in knowledge and break down significant barriers to research progress in ways that adhere to the Institute's enduring principles.

This process included a broad circle of partners, including scientists, medical professionals, policymakers, patients and patient advocates, professional groups, and other interested members of the public. The Strategic Vision is unique in that, unlike a conventional strategic plan, it is dynamic and will be refreshed periodically with continuing input from the communities who are at the edge of scientific exploration and know the needs of our scientific and patient communities. This Vision will provide an

NHLBI Mission Statement

The National Heart, Lung, and Blood Institute (NHLBI) provides global leadership for a research, training, and education program 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.

NHLBI's Enduring Principles

- Value investigator-initiated fundamental discovery science
- Maintain a balanced cross-disciplinary portfolio (basic, translational, clinical, population science)
- Train and nurture a diverse new generation of leaders for the biomedical workforce
- Support implementation science that empowers patients and enables partners to improve health
- Value the health of all communities while working to eliminate health inequities in the United States and around the globe

ongoing source of scientific inspiration for NHLBI-solicited research programs and may also serve as inspiration for the scientific community at large.

Strategic Visioning Goals

NHLBI launched the Strategic Visioning process with four mission-oriented strategic goals to focus input on areas of HLBS research that would most benefit from sustained focus from the Institute. These goals cut across the Institute's research portfolio, which includes basic science, clinical translation, epidemiology, and implementation studies:

- **Understand Human Biology** — To expand knowledge of the molecular, cellular, and physiological mechanisms governing the normal function of HLBS systems as essential elements for sustaining human health.

- **Reduce Human Disease** — To extend our knowledge of the pathobiology of HLBS disorders and enable clinical investigations that advance the prediction, prevention, preemption, treatment, and cures of human diseases.

- **Advance Translational Research** — To facilitate innovation and accelerate research translation across the entire research spectrum, bridging basic to clinical, clinical to practice, and population to health impact.

- **Develop Workforce and Resources** — To enable and develop a diverse biomedical workforce equipped with the essential research resources to pursue emerging opportunities in science.

The NHLBI Strategic Visioning crowdsourcing forum served as an interactive platform that allowed the NHLBI community to submit, vote, and comment on *Compelling Questions* and *Critical Challenges* that mapped to these four strategic goals and were feasible to address in five to ten years with NHLBI facilitation.

- Compelling Questions are unanswered questions or poorly understood areas of research requiring NHLBI facilitation because their complexity exceeds the capacity of any one investigator-initiated program.

- Critical Challenges are barriers or impediments to scientific progress, and the overcoming of these obstacles will result in significant impact.

The Compelling Questions and Critical Challenges submitted touched on exciting and emerging areas of research and returned to many overarching themes, including resilience, data science, health disparities, sex as a biological variable, precision medicine, and nurturing the next generation of HLBS researchers.

With extensive input from the National Heart, Lung, and Blood Advisory Council and Board of External Experts, the NHLBI reviewed the submitted ideas and associated feedback to select the Compelling Questions and Critical Challenges that resonated most as high priorities for the Institute based on timeliness, feasibility, and overall potential to advance the fields of study.

Strategic Visioning Overarching Objectives

From this collaborative process, the following eight Objectives coalesced as an organizing framework and focus for the Compelling Questions and Critical Challenges submitted from the participants. The Objectives mesh with one or more of the mission-oriented strategic goals and serve to organize the Compelling Questions and Critical Challenges that best fit within their focus.

Over the next decade, these Objectives will serve as the Institute's guide for moving HLBS science forward, exploring research opportunities, and making investment decisions. While these Objectives are not meant to embody NHLBI's entire research portfolio, the Compelling Questions and Critical Challenges corresponding to the following eight Objectives will play a substantial role in helping the Institute to set a research agenda and priorities for the next decade.

Objective 1: Understand normal biological function and resilience

Understanding normal biology is the backbone of all biomedical science; it is essential for understanding homeostatic maintenance, for predicting how biological systems respond to their environment, and for recognition of disease and targets for intervention. Research on normal biological function, including emerging topics like circadian rhythms, the microbiome, and understanding how tissues develop from progenitor cells, can help us to better define health and to better understand disease. From single cell analytics to studies of entire healthy populations, research into normal biology can uncover the specific biological factors (e.g., aging) and social circumstances (e.g., environmental exposures) that enable resiliency or increase disease risk. For these reasons, understanding normal biology remains a cornerstone of NHLBI-funded research.

Potential Impact in the Next Decade:

- An improved understanding of the normal physiology of HLBS systems will enable researchers to more reliably pinpoint when normal function transitions to disease.
- Preparations of progenitor cells will be used for cell-based therapies and tissue engineering to repair damaged organs.
- The ability to identify biological and other specific factors that support resistance to disease will be advanced. New therapies based on these factors will be developed to promote health optimization and maintenance.

Objective 2: Investigate newly discovered pathobiological mechanisms important to the onset and progression of HLBS disease

Discovering new pathobiological mechanisms and studying them is critical for improving HLBS health. Such discoveries and research can potentially lead to clinical and implementation studies, which in turn can inform new therapeutic strategies or clinical practice. Important areas to focus on include undiscovered mechanisms in the pathogenesis of rare and common diseases, disease-related structural and functional changes, and the possible clinical significance of these changes. In addition, tracking of disease onset and progression across the lifespan is essential because it has the potential to inform our understanding of the conversion of chronic conditions into acute disease and the effects of early interventions and exposures.

Potential Impact in the Next Decade:

- Identification of novel targets for therapy will result from deep pathobiological exploration.
- Improved communication and collaboration between clinicians and basic scientists will lead to discovery of pathobiological mechanisms of HLBS diseases.
- The study of newly discovered pathobiological mechanisms underlying rare diseases will enable a deeper understanding of the disease process and provide insights into mechanisms of common disease.

Objective 3: Investigate factors that account for differences in health among populations

Variations exist between populations — grouped by such factors as age, sex, and race — in susceptibility and resilience to HLBS diseases and in disease course and outcomes. While some of these variations are caused by genetic and other biologic factors, health disparities driven by a wide range of behavioral factors and socioeconomic inequities can also contribute. Research is needed to better understand the causes of population health differences and to identify strategies to effectively address these differences. Investigations in this area may range from basic laboratory studies to community-centered implementation research.

Potential Impact in the Next Decade

- Critical factors will be identified that underlie sex differences in HLBS health and disease.
- Health inequities in certain HLBS diseases will be improved by novel therapeutic and implementation strategies.

Objective 4: Identify factors that account for individual differences in pathobiology and in responses to treatments

Research advances in areas such as genomics and other "omics" approaches have provided new opportunities to deepen our understanding of HLBS pathobiological processes and how these vary among individual patients. Research into factors that account for differences in pathobiology and unique responses to treatment will serve to accelerate progress toward precise, individualized prevention efforts and medical interventions, in which personal and clinical decisions, practices, and medical products are tailored to the individual patient to help optimize the outcome.

Potential Impact in the Next Decade

- Researchers will more precisely stratify patients using molecular and non-molecular characteristics for enrollment in clinical studies.
- Health professionals will more effectively monitor, diagnose, and provide treatment based on individual patient profiles using molecular and imaging biomarkers.

Objective 5: Develop and optimize novel diagnostic and therapeutic strategies to prevent, treat, and cure HLBS diseases

Recent scientific and technological developments offer especially promising opportunities to improve human health. These wide-ranging technologies include, but are not limited to, new gene editing techniques that could safely treat and prevent HLBS diseases, "smart" tools that could monitor and adjust biological processes, techniques that modulate stem cell or immune system signaling to reduce disease risk, and advances in materials science that could yield vastly improved implant devices. Other technologies may further facilitate diagnostic capabilities and improve approaches to the maintenance of continued health and wellness. It is critical to use these opportunities, many of which are the results of past investments in basic research.

Potential Impact in the Next Decade

- Enable early and effective interventions through new technologies for greater progress in preventing, ameliorating, or even curing certain HLBS diseases.

Objective 6: Optimize translational, clinical, and implementation research to improve health and reduce disease

New methodologies, research frameworks, and resources need to be developed to refine the conduct of translational, clinical, and implementation research, while also improving the overall efficiency and effectiveness of the research enterprise. Current challenges in translational research include difficulties in recruiting a diverse population for clinical trials and implementation research, gaps in the transparency of trial result publication, and the transition to smaller studies that will enroll more targeted groups of participants based on molecular data.

Potential Impact in the Next Decade

- Direct patient engagement and novel uses of patient health records will reduce recruitment times and streamline data collection for HLBS clinical trials.
- Strategic partnerships, novel pre-clinical research designs, and improved training of investigators will reduce the number of potential therapeutics and treatment strategies that fail in later-stage trials.

Objective 7: Leverage emerging opportunities in data science to open new frontiers in HLBS research

New technologies, from “omics” platforms to high-throughput screening, have generated vast amounts of data that have the potential to provide new insights into the preemption and precise treatment of HLBS disorders. Unfortunately, only a small portion of this data is being optimally assessed and incorporated into practice. It will be essential to develop innovative approaches to the integration, analysis, and interpretation of data from multiple sources so that this information can be effectively utilized to improve patient outcomes.

Potential Impact in the Next Decade

- Novel insights in HLBS biology, new understandings in clinical and population science, and the identification of new drug targets may result from integration and analysis of disparate data sources.
- Systems biology and bioinformatics approaches will promote our understanding of the integrated regulation of complex gene, protein, and metabolic networks.

Objective 8: Further develop, diversify, and sustain a scientific workforce capable of accomplishing the NHLBI's mission

New approaches are needed to ensure the continuing development of a diverse scientific workforce equipped with the relevant skills, knowledge, and resources to tackle future HLBS challenges. This goal will require strategic interventions all along the research career continuum, including K to 12 education, collegiate and postdoctoral studies, and career development from early investigator to senior scientist. It will be critical to expose young students to the wonders of science; to further encourage them during college and advanced studies to pursue not only scientific careers but also research endeavors that address problems affecting HLBS health; to provide beginning and mid-career investigators with appropriate support and resources to enable them to succeed in their investigations; and to enable senior scientists to effectively engage in mentoring activities.

Potential Impact in the Next Decade

- Larger numbers of students from diverse backgrounds will be interested in STEM education and careers.
- The future workforce will have an appropriate balance of scientists from traditional and emerging research fields.
- Scientists will be better prepared to communicate and engage in interdisciplinary research and participate in team science.
- An increasingly diverse, well-prepared cadre of researchers will pursue answers to scientific questions germane to HLBS research.

Conclusion

Investigator-initiated discovery science has been and will remain the bedrock of the NHLBI mission. However, NHLBI leadership can catalyze extramural investigations that take advantage of new scientific opportunities and close gaps in knowledge. One means by which this occurs is through Institute-solicited research initiatives supported through new Funding Opportunity Announcements (FOAs). This Strategic Research Priorities identifies important opportunities in science that will shape the development of future FOAs and other activities.

Initiatives to answer the Compelling Questions and overcome Critical Challenges will advance our progress in achieving the eight Objectives and will have profound impacts on the health and well-being of the American public. For example, these efforts will enable a deeper understanding of biologic processes; allow for more precise targeting of therapies to patients, leading to early interventions to prevent disease and reduce inequities in health outcomes; and foster a more diversified and integrated scientific workforce.

Success will be realized through effectively implementing the Strategic Vision and ensuring that the strategic priorities remain dynamic and responsive to the evolving scientific landscape and emerging opportunities. This ongoing iterative process will require the continued engagement of the varied stakeholders: the scientific community, medical professionals, patients and their advocates, professional organizations, policymakers, professional groups, and other interested members of the public, as well as the NHLBI advisory groups and staff. Harnessing the creative energy and marshaling the sustained participation and commitment of our stakeholders will enable achievement of the Strategic Vision described here.

As the Institute transitions to implementing the Strategic Vision, we will engage the scientific community through thinks tanks, workshops, and working groups to help us further pinpoint specific activities that will advance the strategic priorities in this Strategic Vision.

Compelling Questions and Critical Challenges

Compelling Questions for Objective 1: Understand normal biological function and resilience
How are normal cell functions regulated by complex gene networks and cell-to-cell interactions?
What are the key molecular and structural mechanisms that allow single cells and tissues to sense, integrate, and respond to mechanical cues and influences at local and systemic levels?
What are the molecular, developmental, hormonal, and behavioral mechanisms and psychological, social, and environmental factors — evaluated with a systems biology approach — involved in maintaining healthy weight across the lifespan?
What are the mechanisms and range of normal physiologic responses to environmental, neuropsychiatric, social, and other stimuli that predict homeostatic resilience or transition to disease across the lifespan?
What innate and adaptive immune system mechanisms promote HLBS health and prevent development of HLBS diseases?
How do specific lymphatic immune and non-immune circulatory functions interact with and contribute to HLBS health and resilience?
What is the influence of the microbiome (including virome and fungome) on the immune system and on HLBS health and resilience, including developmental processes, across the lifespan?
What are the basic pathways underlying the effects of circadian function, synchronization, and harmonization on HLBS health and resilience across the lifespan?
Does circadian regulation modify the effects of environmental exposures (e.g., cigarette smoke, particulates, pathogens, temperature, humidity) on mechanisms of HLBS function?
What are the mechanisms that underlie adaptation in HLBS systems in extreme conditions, and how can this knowledge be used to develop novel interventions that optimize health or prevent disease?

What are the basic mechanisms that direct the interactions of blood cells with each other and their environment, how do these interactions influence their function, and how can this understanding be used to optimize the handling of blood cells?
What are the normal molecular and cellular variations in specific regions of the lung, and what controls these variations?
What "omic" signatures describe the normal vasculome (gene expression patterns in the vascular endothelium) of the different vascular beds and different arteries (elastic vs. muscular) that supply HLBS tissues and organs?

Critical Challenges for Objective 1: Understand normal biological function and resilience
Reliable and diverse investigational models — from single cells to animals — that reflect normal individual variation are needed to reproduce normal functioning of HLBS systems and to reflect the activities of molecular targets in those systems and related diseases.
Standardized protocols are needed to establish and maintain cultured cell lines relevant to functional studies of HLBS systems. Specifically, facilitating the availability of hard-to-culture cell lines, expanding the number of HLBS cell lines, and improving reproducibility across studies is necessary.
Development and application of comprehensive single-cell biology analytics are needed to facilitate an integrated understanding of cellular diversity, cell-cell interactions, and cellular phenomena in HLBS health and disease risk.
Gaining fundamental knowledge of the glycome, its regulation, and its function in HLBS systems is needed to improve understanding of post-translational modifications of proteins.
Dietary assessment methodologies that combine objective measures and biomarkers of dietary intake are needed to identify dietary patterns and food constituents that contribute to healthy weight maintenance and to inform intervention strategies to lower cardiometabolic risks.
New investigative tools and knowledge of lung structural and matrix biology are needed to better understand injury, regeneration, and repair of the normal (or developing) lung and to enable regenerative medicine.

Compelling Questions for Objective 2: Investigate newly discovered pathobiological mechanisms important to the onset and progression of HLBS disease
What are the pathobiologic mechanisms that govern the conversion of chronic HLBS conditions into acute disease? How can we identify biomarkers to predict — and therapies to prevent — these transitions?
What are the molecular mechanisms underlying dysregulation of homeostasis, and how do these mechanisms vary from individual to individual, leading to development of HLBS diseases in some but not in others?
What are the roles of RNAs (e.g., microRNAs, lncRNAs) in HLBS systems' growth, adaptation, and injury-repair responses?
What biomarkers of acute environmental exposure are predictive of disease onset or progression? What biologic effects measured by these biomarkers are irreversible responses and which are opportunities for intervention?
How do endogenous stem/progenitor cells and defects in these cells contribute to the onset and progression of chronic HLBS diseases?
What is the pathobiology of aberrant calcification of coronary arteries, heart valves, and peripheral arteries, and why is calcification associated with worse prognosis?
What interdependencies between the brain/peripheral nervous system and the heart/vascular systems are important to the development, progression, manifestations, and treatment of cardiac and vascular disease?
What are the mechanisms whereby psychosocial stress contributes to the onset, progression, and morbidity of ischemic heart disease and peripheral arterial disease?
What are the mechanisms whereby congestive heart failure causes lung remodeling and leads, in end-stage disease, to right ventricular failure?
What pathobiology underlies vascular causes of cognitive decline? What early interventions could target this pathobiology to maintain cognitive function?

What is the pathobiology of fibrosis that accounts for its organ specificity (often affecting the lungs, heart, or bone marrow alone), its progression in the absence of apparent stimuli, and its resistance to drug therapy?
What is the pathophysiology of heart failure with preserved ejection fraction (HFpEF), and how can this condition be better diagnosed and treated?
What is the relationship between angiogenesis and placental function in at-risk pregnancies?
How can a better understanding of the molecular and physiological mechanisms of hypothermia help differentiate beneficial hypothermia from uncontrolled shock-induced hypothermia?

Compelling Questions for Objective 3: Investigate factors that account for differences in health among populations
What community-based effectiveness and implementation research strategies can help address HLBS health inequities?
How can we improve the representation of minority and disadvantaged populations in clinical research studies and ensure that findings are applicable to these populations?
What are environmental, genetic, and epigenetic factors and molecular, cellular, and systemic mechanisms that determine sex-related differences in HLBS health and disease?
Do the factors that render individuals or populations subjected to the same exposures resilient or susceptible to disease differ across the lifespan and by sex?
How can cardiometabolic risk be managed to improve health trajectories in specific populations (for example, according to race, ethnicity, gender, socioeconomic status)?

Critical Challenges for Objective 3: Investigate factors that account for differences in health among populations
Sex/gender-specificity is needed in clinical studies, data analyses, and management guidelines for HLBS conditions.
Novel experimental strategies and tools are needed to evaluate the effect of sex differences on HLBS health, resilience, and disease.
Integrated analysis of expanding collections of health information from individual patients — including genetic, epigenetic, and "omic" data — is needed to allow more precise medical management of patients at risk for or afflicted with an HLBS disorder, especially among groups that are understudied or have disparate morbidity and mortality (e.g., minorities, women).

Compelling Questions for Objective 4: Identify factors that account for individual differences in pathobiology and in responses to treatments
Which phenotypic, biomarker, and molecular characteristics predict outcome and, when applied in clinical studies, predict differential responses to therapy in individuals with HLBS diseases?
What factors render individuals or populations subjected to the same exposures resilient or susceptible to disease?
What underlies secondary resilience, such that some people are protected from the complications of HLBS diseases?
Which patients benefit from rehabilitation treatments (cardiac, vascular, and pulmonary), and how can the benefits of rehabilitation treatments be sustained long term?
How does the pathobiology that underlies non-obstructive ischemic heart disease and the associated risks for acute coronary syndrome and early mortality differ between subpopulations, and what are the targets for treatment and prevention?
What tests would identify individuals who are at high risk of venous thromboembolic events and would benefit from targeted risk factor modification and/or intensive prophylaxis?

What are biomarkers of pulmonary hypertension that could better identify individuals at high risk, reveal underlying mechanisms, and guide treatment?
What are the major determinants of individual and sex differences in breathing patterns in sleep, susceptibility to insomnia, and other sleep behaviors?
What genetic, biomarker, and environmental predictors of risk and outcome would inform and improve management of sickle cell disease and secondary prevention of its progression and complications?

Critical Challenges for Objective 4: Identify factors that account for individual differences in pathobiology and in responses to treatments
Predictive modeling and prevention trials are needed in populations at high risk for highly prevalent HLBS diseases.
In patients with an aortic aneurysm, better tools are needed to determine which patient phenotypes and disease characteristics could best predict who would benefit from a repair. Examples of such tools include animal models that reflect human pathology and biomarkers/molecular imaging tools that are predictive of rupture or dissection.
Clinical evaluation tools are needed to differentiate patients with atherosclerotic heart disease who will progress to myocardial infarction or sudden cardiac death from those with stable disease.

Compelling Questions for Objective 5: Develop and optimize novel diagnostic and therapeutic strategies to prevent, treat, and cure HLBS diseases
Would reduction of known cardiac and vascular risk factors during childhood and adolescence translate into the prevention or delayed development of atherosclerosis and other heart diseases?
Would interventions in pregnancy or early childhood designed to modulate immune development result in primary prevention of asthma?

How should the management of diseases that typically develop in childhood (including childhood interstitial lung disease, sickle cell disease, congenital heart disease, cystic fibrosis, and asthma) be modified as affected individuals mature into adulthood?
Would using multi-disciplinary teams (e.g., nutritionists, exercise physiologists, social workers, psychologists, nurses) be an effective approach to developing, testing, and ultimately applying lifestyle interventions as part of routine patient care in a variety of contexts, from community to patient care settings?
Would circadian-based strategies (e.g., sleep, timing of medication, meals) improve the efficacy of treatments for HLBS diseases (e.g., hypertension, asthma, thrombosis, or obesity/diabetes)?
What technical improvements in the collection, preparation, storage, and processing of blood products would improve their potency, safety, and lifetime? What biomarkers or other characteristics predict stability during storage and successful transfusion?
What effective and implementable practices (e.g., recognition and initial response by the community, emergency medical response, and hospital-based care) would reduce the rate of mortality associated with out-of-hospital cardiac arrest?
How can real-time, individual-level monitoring be used to detect and predict electrical instability of the heart and reduce risk for sudden cardiac death in low-risk patients?
What is the optimal clinical management approach for patients with severe calcific aortic stenosis but minimal symptoms?
What is the best strategy for reducing cardiac and vascular morbidity and mortality in cancer survivors who are at enhanced risk of cardiac and vascular events and whose clinical care may be complicated by both comorbidities and drug toxicity?
In patients with enhanced cardiovascular risk due to comorbidities from chronic diseases (e.g., HLBS disorders, diabetes) and multiple drug therapy, what is the best strategy for reducing cardiac and vascular morbidity and mortality?
What are the optimal red blood cell transfusion thresholds and optimal plasma transfusion strategies in both pediatric and adult patients?
How can we optimize the effectiveness and safety of allogeneic hematopoietic stem cell

transplantation (HSCT) in the treatment of non-malignant blood and immune disorders and prevent both short-term and long-term complications?
What are the mechanisms for the late development of complications after hematopoietic stem cell transplantation (HSCT)? How can these consequences be predicted and prevented to reduce the high rates of mortality following HSCT?
How can we “reprogram” the immune system to improve outcomes of allogeneic cell therapies, tissue and organ transplants, and regenerative strategies, and to diminish allogeneic responses to essential biologic replacement therapies?
How can improved methods for hematopoietic cell transplantation or gene therapy approaches be used to cure sickle cell disease?
Is targeted manipulation of epigenetic modifications (distinct from global suppression of histone acetylation or DNA methylation) a useful strategy for therapeutic intervention in chronic cardiopulmonary or blood diseases?
In the context of anticoagulation in atrial fibrillation, would warfarin therapy with INR self-testing and online "virtual clinic" monitoring and management yield lower rates of thromboembolism and major bleeding than are achieved with the newer oral anticoagulants?
How can imaging technology be leveraged to identify clinically useful markers of metabolic syndrome and cardiopulmonary disease?
Do interventions to improve ventilation during sleep decrease morbidity and mortality in individuals with either heart failure (or other diseases associated with chronic hypoxemia) and sleep-disordered breathing?
How can endogenous mechanisms and alterations of stem cell cycles be harnessed to promote repair and regeneration of the lung?
How can we better integrate palliative care concepts, such as respect for personal values, goals, and treatment preferences, in the management of patients with HLBS diseases?

Critical Challenges for Objective 5: Develop and optimize novel diagnostic and therapeutic strategies to prevent, treat, and cure HLBS diseases
A better understanding of the factors governing the safety and efficacy of therapeutic hemoglobin-based extracellular oxygen carriers (HBOCs) and improved animal models for HBOC studies are needed.
An understanding of the immune system from a systems biology perspective is needed to design more efficacious treatment strategies for chronic inflammatory and autoimmune HLBS diseases.
Improved capabilities for responding rapidly and effectively to emerging infectious threats to the safety and availability of the nation's blood supply are needed.
Robust tools and algorithms are needed to evaluate objective biomarkers of sleep health and dysfunction.
New materials and constructs that are electrically, chemically, and mechanically active are needed to enable the development of self-adjusting bioengineered implants (e.g., self-regenerating protective layers, biologics like vein grafts, and glucose-responsive polymers that release insulin).
Development of safe, well-functioning designer platelets and red blood cells from stem or progenitor cells, as well as the large-scale production of these products, is needed for therapeutic and diagnostic uses.
Clinical evaluation tools, such as biomarkers of physiologic age and a clinical score for frailty, are needed for assessing cardiopulmonary perioperative risk and predicting postoperative recovery in the elderly.
Better apheresis-based sickle cell disease treatments are needed to provide the benefits of blood transfusion without the risks and complications that are associated with both simple and exchange transfusions.
A variety of "smart" devices are needed that both monitor physiology and assist, adjust, or intervene automatically to treat acute complications of cardiovascular disease.
A new generation of ventricular assist devices (VADs) is needed to minimize platelet activation, thrombogenesis, and bleeding; to incorporate better percutaneous and transcutaneous systems; and to improve battery and charging-mechanism designs.

More rapid translation of new discoveries about molecular, cellular, and tissue-based mechanisms of arrhythmia into better therapeutic and preventive strategies is needed.

Compelling Questions for Objective 6: Optimize translational, clinical, and implementation research to improve health and reduce disease
What methods are effective for increasing patient participation in clinical research and patients' awareness of and access to evidence-based therapies, as well as to emerging new approaches to care?
What clinical trial designs are best for studying the chronobiology of drug delivery?
How can we engage relevant stakeholders, including patients, private entities, and Federal agencies, to improve the clinical research enterprise and address critical needs such as standardized informed consent and cost containment?

Critical Challenges for Objective 6: Optimize translational, clinical, and implementation research to improve health and reduce disease
Synergy and collaboration among M.D.s and Ph.D.s, basic science, translational, and patient-oriented researchers, and individuals from multiple disciplines (e.g. engineers, clinicians, subspecialists, generalists, bioinformatics experts, academics, and non-profit industries) are needed to enhance and expedite advances in HLBS research.
Improvements in clinical trial design, population estimations, project management, and other practices are needed to achieve timely trial completion.
Skills development and training are needed to improve the navigation of pre-clinical new drug phases of translational science.
Innovative approaches to private sector collaborations and partnerships are needed early in therapeutic and diagnostic product development to bridge the gap between academic discoveries and product commercialization.

Expanded resources for identifying therapeutic targets and agents, establishing proof of concept, and developing data for investigational new drug applications are needed to enable the early translation of research findings to clinical applications.
Creative utilization of the array of newly available data sources is needed in clinical trial design and conduct in order to improve efficiency, cost effectiveness, and generalizability.
Creative approaches to clinical trials in rare HLBS diseases are needed to successfully test strategies that will expand preventive and therapeutic options.
Creative approaches are needed to effectively transcend silos (e.g., perinatal, pediatric, and adult divides in clinical and translational research).
Novel methodologies and improvements in existing methodologies are needed for implementation research.
Multidisciplinary, multinational partnerships are needed to develop effective and sustainable strategies for combating chronic HLBS disorders in developing nations, which take into account the highly variable local epidemiology of HLBS disorders, the need for novel approaches to reducing disease burden, and the challenges of implementation in developing countries.

Compelling Questions for Objective 7: Leverage emerging opportunities in data science to open new frontiers in HLBS research
How do we encourage training in biostatistics, computer science, and bioinformatics to reach the entire biomedical community in this era of very large data sets?

Critical Challenges for Objective 7: Leverage emerging opportunities in data science to open new frontiers in HLBS research
The development, application, and sharing of robust and multidimensional data-analytical and theoretical methods, mathematical modeling, and computational simulation techniques are needed for understanding fundamental mechanisms of HLBS systems, including gene, protein, and metabolic regulatory networks.

Novel integrative analytical approaches are needed to exploit the wealth of knowledge coming from electronic health records, genetics, epigenetics, transcriptomics, metabolomics, proteomics, imaging, and systems biology to define disease sub-types, predict risks, and identify therapeutic targets.
Novel analytical approaches, coordinated access to data, well-planned sample analyses, and creation of a scientific data commons are needed to leverage existing deeply phenotyped cohorts to accelerate translational research and promote the discovery of key druggable targets and the development of novel and precise treatments for HLBS diseases.
Advancements are needed in the organization, infrastructure, integration, and availability of "omics" data, including genetic, epigenetic, transcriptomic, metabolomic, proteomic, phenotypic, and ontologic information.
Bold new bioinformatic and biostatistical methods and approaches are needed to improve the analysis of big data.
Creative and innovative methods to integrate and analyze data from population and cohort research are needed to generate hypotheses and to expedite bedside-to-basic “reverse translation.”
Integration of registry data and research datasets is needed to facilitate research on the molecular genomics and pathobiology of congenital heart disease, including the natural history of congenital heart disease across the lifespan.
Integration of multidimensional and multidisciplinary data is needed to develop predictive and actionable models of weight gain, weight loss, and weight loss maintenance and to clarify the role of obesity in the risk, prevention, and treatment of cardiopulmonary and sleep disorders.

Compelling Questions for Objective 8: Further develop, diversify, and sustain a scientific workforce capable of accomplishing the NHLBI’s mission
What kinds of exposures, beginning in early education, would stimulate and maintain students’ interest in and understanding of science, particularly students from diverse and disadvantaged backgrounds?
How can we ensure that the HLBS scientific workforce and trainees include adequate numbers of members of under-represented minority groups and individuals from disadvantaged and medically

underserved communities?
How can clinical research training programs increase cultural competency regarding diseases or conditions that disproportionately affect under-served populations and attract and retain researchers that better understand the populations affected?
What are the best strategies to develop a highly competent and diverse implementation science research workforce to address domestic and international health inequities?
How do we ensure that HLBS trainees across the career continuum are aware of and prepared for a variety of possible scientific career opportunities (e.g., careers in teaching, industry, or government)?
How do we best develop a scientific workforce that is fluent in product development and commercialization issues, including regulatory, intellectual property, and business issues, in order to bring products for HLBS indications to the market?
How do we attract more students/trainees into traditional research fields (e.g., physiology, integrative biology) that are as critical to advancing science as emerging fields (e.g., “omics” and big data) but do not have the same cache and are thus on the decline?
How do we add communication skills to our training programs to improve scientists’ communication with the public? How do we also improve the ability of basic and clinical scientists to understand each other’s scientific language and appreciate the importance of the other’s research questions and findings?
How can we harness virtual learning technologies (e.g., immersive learning simulations and serious games) to address the needs of the modern and future biomedical workforce?
How can we better incorporate interdisciplinary and team science in our training and career development programs to prepare scientists for collaborative research and for utilizing emerging technologies and resources?
How can senior scientists be encouraged to mentor young investigators and, in the later stages of their career, to entrust greater responsibility to emerging lab leaders (e.g., incrementally turning over their projects to more junior lab members)?

Critical Challenges for Objective 8: Further develop, diversify, and sustain a scientific workforce capable of accomplishing the NHLBI's mission
Sufficient numbers of clinical scientists are needed, particularly those interested in pursuing translation of breakthroughs from basic science laboratories into clinical settings.
Methods for encouraging medical students to choose research career paths are needed.
Training that emphasizes the rigorous scientific methods of biomedical and behavioral investigations is required to increase reliability and reproducibility of research findings.
Better preparation of scientists for transitions between career stages (e.g., the graduate/medical education stage, the postdoctoral/fellowship period, and the junior investigator stage) is needed.
There is a need to develop and improve skills to communicate science to the public as well as among scientists of different specialties.
Curricula and resources for education of health care workers in evidence-based care are needed.
Collection and analysis of education and employment data from HLBS scientists over the course of their careers is needed to define metrics and predictors of success at both individual and training-program levels.

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