



The NHLBI Strategic Vision

OBJECTIVES AND RESEARCH PRIORITIES

(Compelling Questions
and Critical Challenges)

NHLBI began the Strategic Visioning process with its four existing, mission-oriented goals that would most benefit from the Institute's sustained focus: understand human biology, reduce human disease, advance translational research, and develop the workforce and resources. Using a community-wide crowdsourcing methodology, NHLBI selected a set of strategic research priorities (Compelling Questions and Critical Challenges) that aligned with the established goals and resonated as high priorities for the Institute based on timeliness, feasibility, and potential to advance the fields of study. These 132 research priorities have been organized into eight objectives, all of which can be found within this brief.



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

OBJECTIVE 1 Understand normal biological function and resilience

Compelling Questions

- 1.CQ.01 How are normal cell functions regulated by complex gene networks and cell-to-cell interactions?
- 1.CQ.02 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?
- 1.CQ.03 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?
- 1.CQ.04 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?
- 1.CQ.05 What innate and adaptive immune system mechanisms promote HLBS health and prevent development of HLBS diseases?
- 1.CQ.06 How do specific lymphatic immune and nonimmune circulatory functions interact with and contribute to HLBS health and resilience?
- 1.CQ.07 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?
- 1.CQ.08 What are the basic pathways underlying the effects of circadian function, synchronization, and harmonization on HLBS health and resilience across the lifespan?
- 1.CQ.09 Does circadian regulation modify the effects of environmental exposures (e.g., cigarette smoke, particulates, pathogens, temperature, humidity) on mechanisms of HLBS function?
- 1.CQ.10 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?
- 1.CQ.11 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?
- 1.CQ.12 What are the normal molecular and cellular variations in specific regions of the lung, and what controls these variations?
- 1.CQ.13 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

- 1.CC.01 Reliable and diverse investigational models—from single cells to animals—that reflect individual variation as well as sex/gender-based differences are needed to reproduce normal functioning of HLBS systems and to reflect the activities of molecular targets in those systems and related diseases.
- 1.CC.02 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 and cells from female research subjects, expanding the number of HLBS cell lines, and improving reproducibility across studies are necessary.
- 1.CC.03 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.
- 1.CC.04 Advances in methods of and models for assessing and characterizing exposures (e.g., environmental, dietary, social) are needed to improve research on normal biologic function and resilience.
- 1.CC.05 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.
- 1.CC.06 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.
- 1.CC.07 New investigative tools and knowledge of structural and matrix biology are needed to better understand injury, regeneration, and repair of the normal (or developing) heart, lung, and blood tissues and to enable regenerative medicine.

OBJECTIVE 2 Investigate newly discovered pathobiological mechanisms important to the onset and progression of HLBS diseases

Compelling Questions

- 2.CQ.01 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?
- 2.CQ.02 What are the roles of RNAs (e.g., microRNAs, long non-coding RNAs) in HLBS systems' growth, adaptation, and injury-repair responses?
- 2.CQ.03 What biomarkers of acute and chronic environmental exposures (e.g., smoking) are predictive of disease onset or progression? What biologic effects measured by these biomarkers are irreversible responses and which are opportunities for intervention?
- 2.CQ.04 How do endogenous stem/progenitor cells and defects in these cells contribute to the onset and progression of chronic HLBS diseases?
- 2.CQ.05 What is the pathobiology of aberrant calcification of coronary arteries, heart valves, and peripheral arteries, and why is calcification associated with a poor prognosis?
- 2.CQ.06 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?
- 2.CQ.07 What are the mechanisms whereby social conditions and psychosocial stress contribute to the onset, progression, and morbidity of ischemic heart disease and peripheral arterial disease?
- 2.CQ.08 What are the mechanisms whereby congestive heart failure causes lung remodeling and leads, in end-stage disease, to right ventricular failure?
- 2.CQ.09 What pathobiology underlies vascular causes of cognitive decline? What early interventions could target this pathobiology to maintain cognitive function?
- 2.CQ.10 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?
- 2.CQ.11 What is the pathophysiology of heart failure with preserved ejection fraction (HFpEF), and how can this condition be better diagnosed and treated?
- 2.CQ.12 What is the relationship between angiogenesis and placental function in at-risk pregnancies?
- 2.CQ.13 How can a better understanding of the molecular and physiological mechanisms of hypothermia help differentiate beneficial hypothermia from uncontrolled shock-induced hypothermia?

Critical Challenge

- 2.CC.01 Understanding the pathobiologic mechanisms that govern the conversion of chronic HLBS conditions into acute disease is critically needed, specifically identifying biomarkers to predict and therapies to prevent these transitions.

OBJECTIVE 3 Investigate factors that account for differences in health among populations

Compelling Questions

- 3.CQ.01 What community-based effectiveness and implementation research strategies can help address HLBS health inequities?
- 3.CQ.02 How can we improve the representation of women, minority, and disadvantaged populations in clinical research studies and ensure that findings are applicable to these populations?
- 3.CQ.03 What are the environmental, genetic, and epigenetic factors and molecular, cellular, and systemic mechanisms that determine sex-related differences in HLBS health and disease?
- 3.CQ.04 Do the factors that render individuals or populations subjected to the same exposures (e.g., diet, smoking, other environmental and social exposures) resilient or susceptible to disease differ across the lifespan and by sex/gender?
- 3.CQ.05 How can cardiometabolic risk be managed to improve health trajectories in specific populations (e.g., according to race, ethnicity, sex/gender, socioeconomic status)?

Critical Challenges

- 3.CC.01 Sex/gender-specificity is needed in basic, translational, and clinical studies; data analyses; and management guidelines for HLBS conditions.
- 3.CC.02 Novel experimental strategies and tools are needed to evaluate the effect of sex differences on HLBS health, resilience, and disease.
- 3.CC.03 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).
- 3.CC.04 Advances in methods of and models for assessing and characterizing exposures (e.g., diet, smoking, other environmental and social exposures) are needed to understand differences in health among populations.

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

Compelling Questions

- 4.CQ.01 Which phenotypic, biomarker, and molecular characteristics predict outcome and, when applied in clinical studies, predict differential responses to therapy in individuals and in different populations with HLBS diseases?
- 4.CQ.02 What factors render individuals or populations subjected to the same exposures (e.g., diet, smoking, other environmental and social exposures) resilient or susceptible to disease?
- 4.CQ.03 What underlies secondary resilience, such that some people are protected from the complications of HLBS diseases?
- 4.CQ.04 Which patients benefit from rehabilitation treatments (e.g., cardiac, vascular, and pulmonary), and how can the benefits of rehabilitation treatments be sustained long term?
- 4.CQ.05 How does the pathobiology that underlies nonobstructive 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?
- 4.CQ.06 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?
- 4.CQ.07 What are biomarkers of pulmonary hypertension that could better identify individuals at high risk, reveal underlying mechanisms, and guide treatment?
- 4.CQ.08 What are the major determinants of individual and sex differences in breathing patterns in sleep, susceptibility to insomnia, and other sleep behaviors?
- 4.CQ.09 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

- 4.CC.01 Predictive modeling and prevention trials are needed in populations at high risk for highly prevalent HLBS diseases.
- 4.CC.02 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.
- 4.CC.03 Clinical evaluation tools are needed to differentiate patients with atherosclerotic heart disease who will progress to myocardial infarction or with sudden cardiac death from those with stable disease.

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

Compelling Questions

- 5.CQ.01 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?
- 5.CQ.02 Would interventions in pregnancy or early childhood designed to modulate immune development result in primary prevention of asthma?
- 5.CQ.03 How should the management of diseases that typically develop in childhood (including childhood interstitial lung disease, hemoglobinopathies, congenital heart disease, cystic fibrosis, and asthma) be modified as affected individuals mature into adulthood?
- 5.CQ.04 Would using multidisciplinary 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?
- 5.CQ.05 Would circadian-based strategies (e.g., sleep, timing of medication, meals) improve the efficacy of treatments for HLBS diseases (e.g., hypertension, asthma, thrombosis, obesity/diabetes)?
- 5.CQ.06 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?
- 5.CQ.07 What effective and implementable practices (e.g., recognition and initial response by the community, emergency medical response, hospital-based care) would reduce the rate of mortality associated with out-of-hospital cardiac arrest?
- 5.CQ.08 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?
- 5.CQ.09 What is the optimal clinical management approach for patients with severe calcific aortic stenosis but with minimal symptoms?
- 5.CQ.10 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?
- 5.CQ.11 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?
- 5.CQ.12 What are the optimal red blood cell transfusion thresholds and optimal plasma transfusion strategies in both pediatric and adult patients?
- 5.CQ.13 How can we optimize the effectiveness and safety of allogeneic hematopoietic stem cell transplantation in the treatment of nonmalignant blood and immune disorders and prevent both short-term and long-term complications?
- 5.CQ.14 What are the mechanisms for the late development of complications after hematopoietic stem cell transplantation? How can these consequences be predicted and prevented to reduce the high rates of mortality following HSCT?
- 5.CQ.15 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?
- 5.CQ.16 How can improved methods for hematopoietic cell transplantation or gene therapy approaches be used to cure certain hemoglobinopathies (e.g., sickle cell disease)?
- 5.CQ.17 How do we develop and implement novel strategies to prevent and treat minor and major hemorrhagic complications in males and females affected by acquired and inherited disorders?
- 5.CQ.18 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?
- 5.CQ.19 With increasing use of direct-acting oral anticoagulants for stroke prevention in atrial fibrillation and treatment of venous thromboembolism, what is the role of laboratory monitoring, and can the use of new technologies help better define those at risk of bleeding or thrombosis with use of direct-acting oral anticoagulants or warfarin?
- 5.CQ.20 How can imaging technology be leveraged to identify clinically useful markers of metabolic syndrome and cardiopulmonary disease?
- 5.CQ.21 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?
- 5.CQ.22 How can alterations of stem cell cycles and other therapies, as well as endogenous mechanisms, be harnessed to promote repair and regeneration of the heart, lung, and blood systems?
- 5.CQ.23 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

- 5.CC.01 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.
- 5.CC.02 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.
- 5.CC.03 Improved capabilities for responding rapidly and effectively to emerging infectious threats to the safety and availability of the nation's blood supply are needed.
- 5.CC.04 Robust tools and algorithms are needed to evaluate objective biomarkers of sleep health and dysfunction.
- 5.CC.05 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, glucose-responsive polymers that release insulin).
- 5.CC.06 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.
- 5.CC.07 Expanded research on bleeding risk in elderly patients with atrial fibrillation is needed to develop more accurate risk stratification that would enhance anticoagulation decision-making for the elderly population and reduce stroke incidence.
- 5.CC.08 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.
- 5.CC.09 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.
- 5.CC.10 A variety of "smart" devices are needed that both monitor physiology and assist, adjust, or intervene automatically to treat acute complications of cardio-vascular disease.
- 5.CC.11 A new generation of ventricular assist devices is needed to minimize platelet activation, thrombogenesis, and bleeding; to incorporate better percutaneous and transcutaneous systems; and to improve battery and charging-mechanism designs.
- 5.CC.12 More rapid translation of new discoveries about molecular, cellular, and tissue-based mechanisms of arrhythmia into better therapeutic and preventive strategies is needed.

OBJECTIVE 6 Optimize clinical and implementation research to improve health and reduce disease

Compelling Questions

- 6.CQ.01 What methods and technologies are effective for increasing awareness of and participation in clinical research, as well as awareness of and access to evidence-based diagnostics and therapeutics, including emerging approaches to care?
- 6.CQ.02 What clinical trial designs are best for studying the chronobiology of drug delivery?
- 6.CQ.03 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

- 6.CC.01 Synergy and collaboration among people at the MD and PhD level for; basic science; translational, patient-oriented researchers; community and population scientists; and individuals from multiple disciplines (e.g., engineers, clinicians, subspecialists, generalists, bioinformatics experts, academics, nonprofit organizations, industry) are needed to enhance and expedite advances in HLBS research.
- 6.CC.02 Improvements in clinical trial design, population estimations, project management, and other practices are needed to achieve timely trial completion.
- 6.CC.03 Skills development and training are needed to improve the navigation of pre-clinical new drug phases of translational science.
- 6.CC.04 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.

- 6.CC.05 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.
- 6.CC.06 Creative use 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.
- 6.CC.07 Creative approaches to clinical trials in rare HLBS diseases are needed to successfully test strategies that will expand preventive and therapeutic options.
- 6.CC.08 Standardized approaches and resources, including data and biospecimen repositories, should be developed to facilitate collaboration between basic, clinical, and population scientists in clinical trials and population studies.
- 6.CC.09 Creative approaches are needed to effectively transcend silos (e.g., perinatal, pediatric, and adult divides in clinical and translational research).
- 6.CC.10 Novel methodologies and improvements in existing methodologies are needed for implementation research that explores uptake of research findings into approaches, programs, and policies.
- 6.CC.11 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.

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

Compelling Question

- 7.CQ.01 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

- 7.CC.01 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 and the impact of environmental exposures on those networks.
- 7.CC.02 Novel integrative systems biology and analytical approaches are needed to exploit the wealth of knowledge coming from genetics, epigenetics, transcriptomics, metabolomics, proteomics, environmental exposures, electronic health records, and imaging to define disease subtypes, predict risks, and identify therapeutic targets.
- 7.CC.03 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.
- 7.CC.04 Advancements are needed in the organization, infrastructure, integration, and availability of “omics” data, including genetic, epigenetic, transcriptomic, metabolomic, proteomic, phenotypic, and ontologic information.
- 7.CC.05 Bold new bioinformatic and biostatistical methods and approaches are needed to improve the analysis of big data.
- 7.CC.06 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.”
- 7.CC.07 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.
- 7.CC.08 Integration of multidimensional data from a variety of sources (e.g., molecular, social, behavioral, environmental exposures, wearable sensor, self-reported 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.

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

Compelling Questions

- 8.CQ.01 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?
- 8.CQ.02 How can we foster diversity among trainees and in the HLBS scientific workforce so that our research community reflects the makeup of the population at large and has ample participation of individuals from disadvantaged and medically underserved communities?
- 8.CQ.03 How can clinical research training programs increase cultural competency about diseases or conditions that disproportionately affect underserved populations and attract and retain researchers who better understand the populations affected?
- 8.CQ.04 What are the best strategies to develop a highly competent and diverse scientific workforce—across the spectrum from basic to population science—to address domestic and international health inequities?
- 8.CQ.05 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, government)?
- 8.CQ.06 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?
- 8.CQ.07 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,” big data), but do not have the same cache and are thus on the decline?
- 8.CQ.08 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?
- 8.CQ.09 How can we harness virtual learning technologies (e.g., immersive learning simulations, serious games) to address the needs of the modern and future biomedical workforce?
- 8.CQ.10 How can we better incorporate interdisciplinary and team science in our training and career development programs to prepare scientists for collaborative research and for using emerging technologies and resources?
- 8.CQ.11 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

- 8.CC.01 Sufficient numbers of clinical scientists are needed, particularly those interested in pursuing translation of breakthroughs from basic science laboratories into clinical settings.
- 8.CC.02 Programs of training, professional development, and mentoring are needed to help create a more diverse cadre of senior leaders in science and medicine.
- 8.CC.03 Methods for encouraging medical students to choose research career paths are needed.
- 8.CC.04 Training that emphasizes rigorous scientific methods in the biomedical, behavioral, and social sciences is required to increase reliability and reproducibility of research findings.
- 8.CC.05 Better preparation of scientists for transitions between career stages (e.g., the graduate/medical education stage, the postdoctoral/fellowship period, the junior investigator stage) is needed.
- 8.CC.06 There is a need to develop and improve skills to communicate science to the public as well as among scientists of different specialties.
- 8.CC.07 Curricula and resources for education of health care workers in evidence-based care are needed.
- 8.CC.08 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.