CHARTING THE FUTURE TOGETHER

The NHLBI Strategic Vision

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

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National Heart, Lung, and Blood Institute
National Institutes of Health
www.nhlbi.nih.gov

NIH National Heart, Lung, and Blood Institute

ACKNOWLEDGEMENTS

The NHLBI appreciates the extensive input from its staff; the National Heart, Lung, and Blood Advisory Council and Board of External Experts, a working group of the Council; and the heart, lung, blood, and sleep community in the development of this Strategic Vision.

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Director's Message

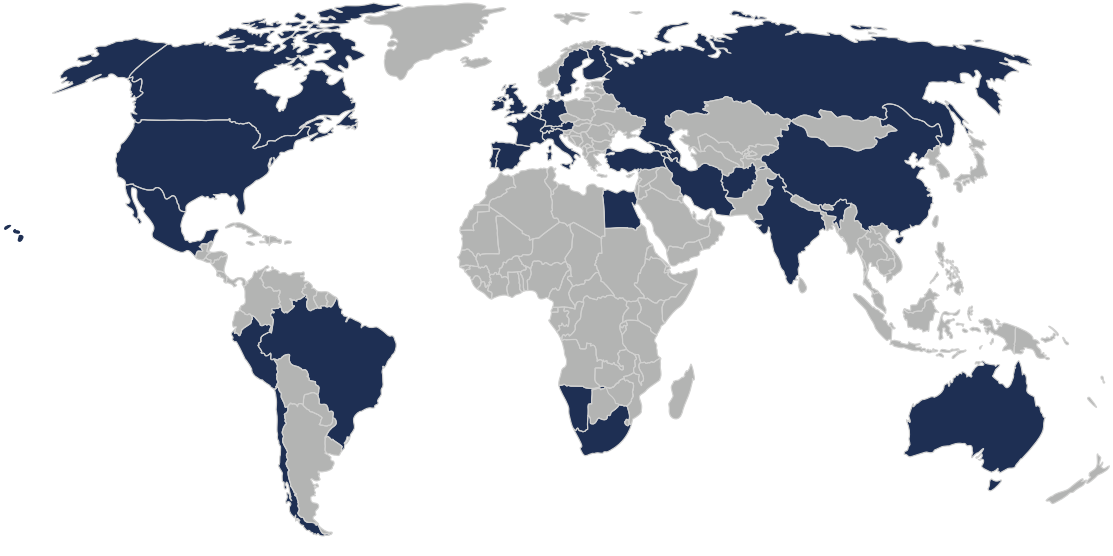
The National Heart, Lung, and Blood Institute (NHLBI) began the Strategic Visioning process with a bold challenge: Imagine a world where we are able to prevent the burden of cardiovascular, lung, and blood diseases; a world where we are able to capture the promise of personalized precision medicine, with each person receiving the right treatment, tailored to his or her needs, at the right time.

Through a dynamic and iterative process, we engaged diverse stakeholders from across the United States and around the globe **(figure 1)** and received an unprecedented number of ideas that have informed the development of this Strategic Vision. The research priorities in this Strategic Vision will enable us to accelerate our journey toward scientific and health advances over the next decade.

This is an exciting time for behavioral and biomedical research. The convergence of innovations in areas such as computational biology, data science, bioengineering, and high-throughput "omic" technologies holds promise for

Figure 1: Global Participation in Strategic Visioning

■ Participants came from 50 states and 42 countries. Registered Users on the Strategic Visioning Forum: 4,450; Ideas Supported: 42,000



major leaps forward in our understanding, at the most fundamental level, of human systems in both health and disease. With these developments and the help of our community, we have the opportunity to create a future in which we have an improved understanding of the complex interplay of environmental, behavioral, and molecular factors that promote health; a clearer picture of the earliest point of disease development; the ability to repair defective or damaged hearts with stem cell and tissue engineering techniques; a new generation of novel therapeutics for chronic conditions such as chronic obstructive pulmonary disease, heart failure, pulmonary fibrosis, hypertension, and asthma; and the ability to develop cures, through gene editing and stem cell technology, for sickle cell disease and other conditions.

The NHLBI will implement the Strategic Vision by developing specific activities and initiatives that are inspired by the strategic research priorities. We will leverage the research priorities for broad impact. Even if a particular disease or health concern is not cited by name, the scientific initiatives that emerge will be both crosscutting and targeted to ensure that we address pressing health concerns and conditions across our portfolio. In addition, investigator-initiated ideas will remain the principal way we support science. The ideas in this Strategic Vision are not intended to restrict or stifle creativity; rather, we hope that they stimulate and inspire scientists who are pursuing investigator-initiated ideas.

Strategic Visioning will remain a "living" process. As the NHLBI moves forward with implementation, our engagement with the community will continue. We will continue to foster ongoing dialogue through different forums, including webinars and workshops, to solicit and incorporate in our research program the best ideas of our community while keeping our strategic research priorities nimble and adaptive to scientific advancements and opportunities.

The NHLBI is grateful for all the input received to help develop this Strategic Vision. I look forward to working with you and welcome comments on all that we do together.

Sincerely,

/Gary H. Gibbons/

Gary H. Gibbons, M.D.
Director, NHLBI

Introduction

Investigator-initiated ideas will remain the principal way we support science.

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, and innovative health education and dissemination efforts. Despite the significant advances in treatment and prevention made during these decades, heart, lung, blood, and sleep (HLBS) diseases still pose a major health and economic burden on the United States. Through its broad research portfolio, the NHLBI is tasked with combating not only the major causes of death and disability but also rare disorders such as sickle cell disease, thalassemia, and pulmonary fibrosis. While these disorders are rare in the overall population, the burdens they place on those affected are enormous.

In order to sustain the NHLBI's legacy, we must anticipate and capitalize on emerging scientific opportunities, as well as foresee and identify approaches to overcome new barriers to progress. Strategic Visioning is a process that was initiated in recognition of these needs and in acknowledgment of the transformational scientific advances that are emerging at an accelerating pace. New scientific tools and an explosive 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 the Institute can help others harness new opportunities and overcome roadblocks to scientific success. Many of our research goals that once seemed remote are now within reach. For example, in the next decade, preventable cardiovascular disease deaths for all age groups could decline more than 30 percent with the greater adoption of proven prevention and treatment strategies. A stroke-free era for children worldwide with sickle cell disease is now imaginable.

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.

The Strategic Vision is the culmination of an unprecedented effort to engage NHLBI's communities in identifying and prioritizing the most compelling science for which NHLBI provides leadership. Over the next decade, these collective ideas could catalyze the closing of large gaps in knowledge and break through significant barriers to research progress in ways that adhere to the Institute's enduring principles. This Strategic Vision comprises over one hundred compelling questions and critical challenges aligned to eight scientific objectives. The objectives, questions, and challenges cut across the entire NHLBI scientific portfolio.

This Strategic Vision comprises over one hundred compelling questions and critical challenges aligned to eight scientific objectives.

A broad circle of partners participated in the Strategic Visioning process, 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 leading edge of scientific exploration and know the needs of our scientific and patient communities. The Strategic Vision is a "living" document, meaning it will be updated to respond to the changing needs of the HLBS research community. This will provide an ongoing source of scientific inspiration for NHLBI-solicited research programs and may also serve as inspiration for the scientific community at large.

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
- Innovate an evidence-based elimination of health inequities in the United States and around the world

Strategic Goals

The NHLBI launched the Strategic Visioning process with four mission-oriented strategic goals. These goals cut across the Institute's HLBS research portfolio and are rooted in a desire to understand and promote health and resilience, stimulate discoveries in the causes of disease, enable the translation of discoveries from basic research into clinical practice, and foster training and mentoring of emerging scientists and physicians.

The NHLBI Strategic Visioning crowdsourcing forum served as an interactive platform that allowed the NHLBI community to submit, vote, and comment on

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.

To enable and develop a diverse biomedical workforce equipped with the essential research resources to pursue emerging opportunities in science.

DEVELOP WORKFORCE AND RESOURCES

To facilitate innovation and accelerate research translation across the entire research spectrum, bridging basic to clinical, clinical to practice, and population to health impact.

ADVANCE TRANSLATIONAL RESEARCH

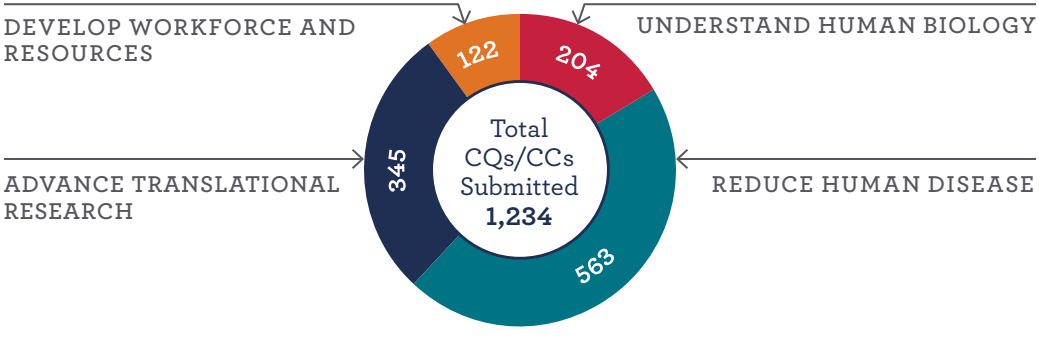
Compelling Questions and **Critical Challenges** that aligned with these four strategic goals **(figure 2)**. These questions and challenges could also be addressed in 5 to 10 years, with NHLBI facilitation.

- 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 overcoming these obstacles will result in significant impact.

With extensive input from the National Heart, Lung, and Blood Advisory Council and the Board of External Experts, a working group of Council, the NHLBI reviewed the submitted ideas and associated feedback and selected a set of Strategic Research Priorities (i.e., Compelling Questions and Critical Challenges) that resonated as high priorities for the Institute based on timeliness, feasibility, and potential to advance the fields of study. All submitted suggestions from the community have been retained and can be revisited as new opportunities or challenges arise as part of the dynamic Strategic Visioning process.

As the NHLBI moves forward with Strategic Visioning implementation, our engagement with the community will continue.

Figure 2: Strategic Visioning Participation
Compelling Questions (CQs)/Critical Challenges (CCs) Submitted: Breakdown by Goal



4 GOALS
8 OBJECTIVES

Strategic Objectives

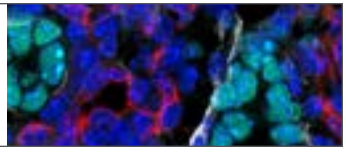
The following eight objectives resulted from this collaborative process and provide a framework for the strategic research priorities submitted by the participants. The objectives reflect one or more of the mission-oriented strategic goals and generally explore both biological and non-biological contributors to health and disease.

Over the next decade, these objectives will serve as the NHLBI's guide for moving heart, lung, blood and sleep science forward, exploring research opportunities, and making investment decisions. While these objectives are not meant to embody the NHLBI's entire research portfolio, the strategic research priorities corresponding to the objectives will play a substantial role in helping the NHLBI to set, and periodically refine, a research agenda and priorities for the next decade.

In the pages that follow, we elaborate on the objectives, explaining their importance and envisioning how achieving these aims could guide research and improve health.

1 **Understand normal biological function and resilience**

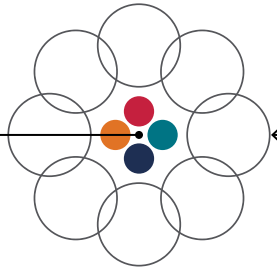
2 **Investigate newly discovered pathobiological mechanisms important to the onset and progression of HLBS diseases**



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

Figure 3: The NHLBI Strategic Vision Comprises 4 Goals, 8 Objectives and 132 Research Priorities

4 mission-oriented goals are at the center of the Strategic Vision



8 objectives provide a framework for moving HLBS science forward

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

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

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

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

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

STRATEGIC VISION OBJECTIVE 1: *Understand normal biological function and resilience*

STRATEGIC VISION 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, predicting how biological systems respond to their environment, and recognizing disease and targets for intervention. Research on normal biological function—including emerging topics such as circadian rhythms, the microbiome, and understanding how tissues develop from progenitor cells—can help us to better define health and understand the earliest origin of disease processes. The scope of research on normal biology can range from single cell analytics to studies of entire healthy populations. Using gold standard and emerging tools, methodologies, and technologies, such research can uncover the biological factors, behaviors, lifestyle factors, social circumstances, and environmental exposures that enable the resiliency essential for sustaining wellness in the face of the aging process, stressors, and adverse influences. Gaining new knowledge about the body's intrinsic reparative capacity will yield greater insight into the transition from health to disease. For these reasons, understanding normal biology must remain a cornerstone of NHLBI-funded research.

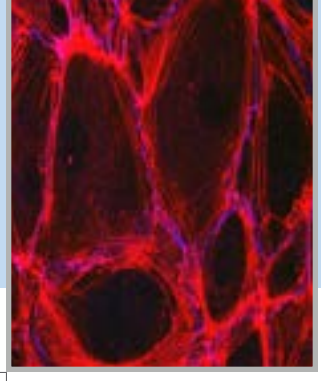
Envision a future in which we are able to...

- Promote resilience and healthy aging through the application of normal and reparative biology using cells (e.g., progenitor cells) that enable the regeneration and repair of heart, lung, blood, and sleep systems.
- Use emerging nanoscale imaging technologies (e.g., cryo-electron microscopy) and single-cell analytics to characterize the molecular signature of the homeostatic state of HLBS systems that sustain health and wellness.
- Generate a better understanding of how environmental exposures, social determinants, and behaviors (e.g., diet and physical activity) modulate biological systems such as the epigenome, microbiome, and immune system to sustain health and promote resilience.

STRATEGIC VISION OBJECTIVE 1: *Understand normal biological function and resilience*

Objective 1 Compelling Questions

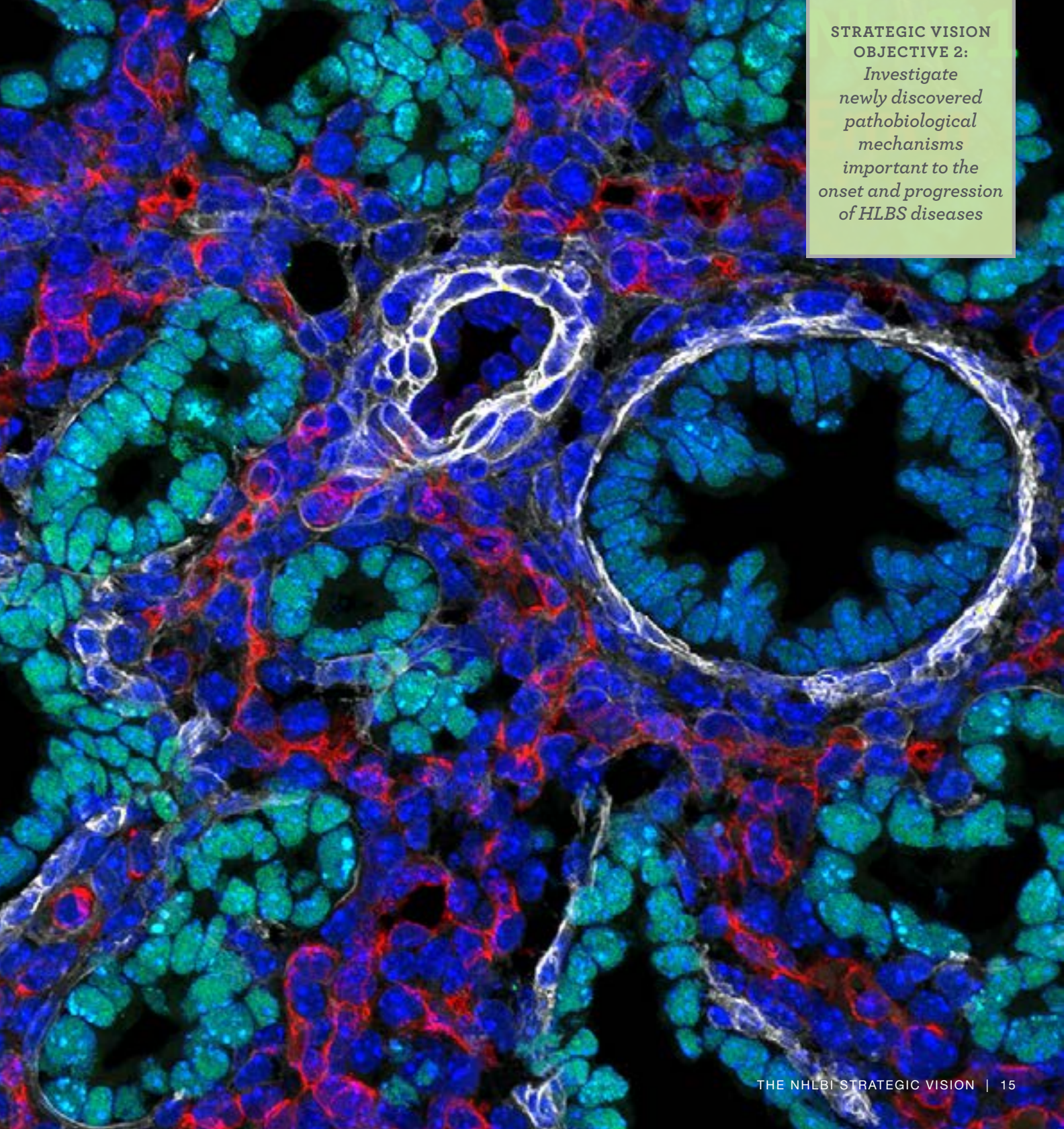
1.CQ.01	How are normal cell functions regulated by complex gene networks and cell-to-cell interactions?
1.CQ.02	What are the key molecular and structural mechanisms that allow single cells and tissues to sense, integrate, and respond to mechanical cues and influences at local and systemic levels?
1.CQ.03	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?



Objective 1 Compelling Questions	
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?

STRATEGIC VISION OBJECTIVE 1: *Understand normal biological function and resilience*

Objective 1 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.



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

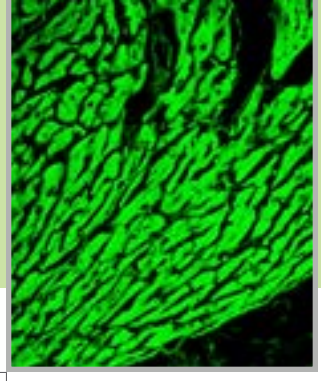
STRATEGIC VISION OBJECTIVE 2

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

Discovering new pathobiological mechanisms and understanding 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 and clinical practice. Important areas to focus on, with the help of emerging technologies such as molecular imaging and nanotechnology, include mechanisms involved in the pathogenesis of rare and common diseases, disease-related structural and functional changes, and the 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 exposures and interventions, including lifestyle changes.

Envision a future in which we are able to...

- Preempt the transition from health to disease and enable primary and secondary prevention through an enhanced understanding of the pathobiological mechanisms underpinning HLBS disorders.
- Leverage deep phenotyping and high-throughput "omic" technologies in NHLBI-supported cohort studies to define the functional significance of gain/loss-of-function genetic variants and gene knockouts on human pathobiology and the clinical outcomes of HLBS disorders.
- Gain new insights into modifier genes and molecular pathways that influence the clinical manifestations and severity of monogenic disorders (e.g., sickle cell disease and cystic fibrosis) as well as structural defects such as congenital heart disease, and thereby catalyze new therapeutic strategies.



Objective 2 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?

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

Objective 2 Compelling Questions

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?

Objective 2 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.

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

STRATEGIC VISION
OBJECTIVE 3

Investigate factors that account for differences in health among populations

Variations exist between populations—grouped by such factors as age, sex, race, and ancestry—in susceptibility and resilience to HLBS diseases and in disease course and outcomes. While some of these variations are caused by genetic and other biological factors, a wide range of behavioral factors and socioeconomic inequities also contribute to health disparities. 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 population science to community-centered implementation research.

Envision a future in which we are able to...

- Leverage a deeper understanding of biologic differences related to sex or ancestral groups (e.g., variation in ancestry leading to differences in asthma phenotypes among ethnic subgroups) to devise more precise, targeted intervention strategies and further improve clinical outcomes.
- Reduce health disparities and inequities in an era of information technology by leveraging epidemiology and the power of data science to understand and solve complex health problems.

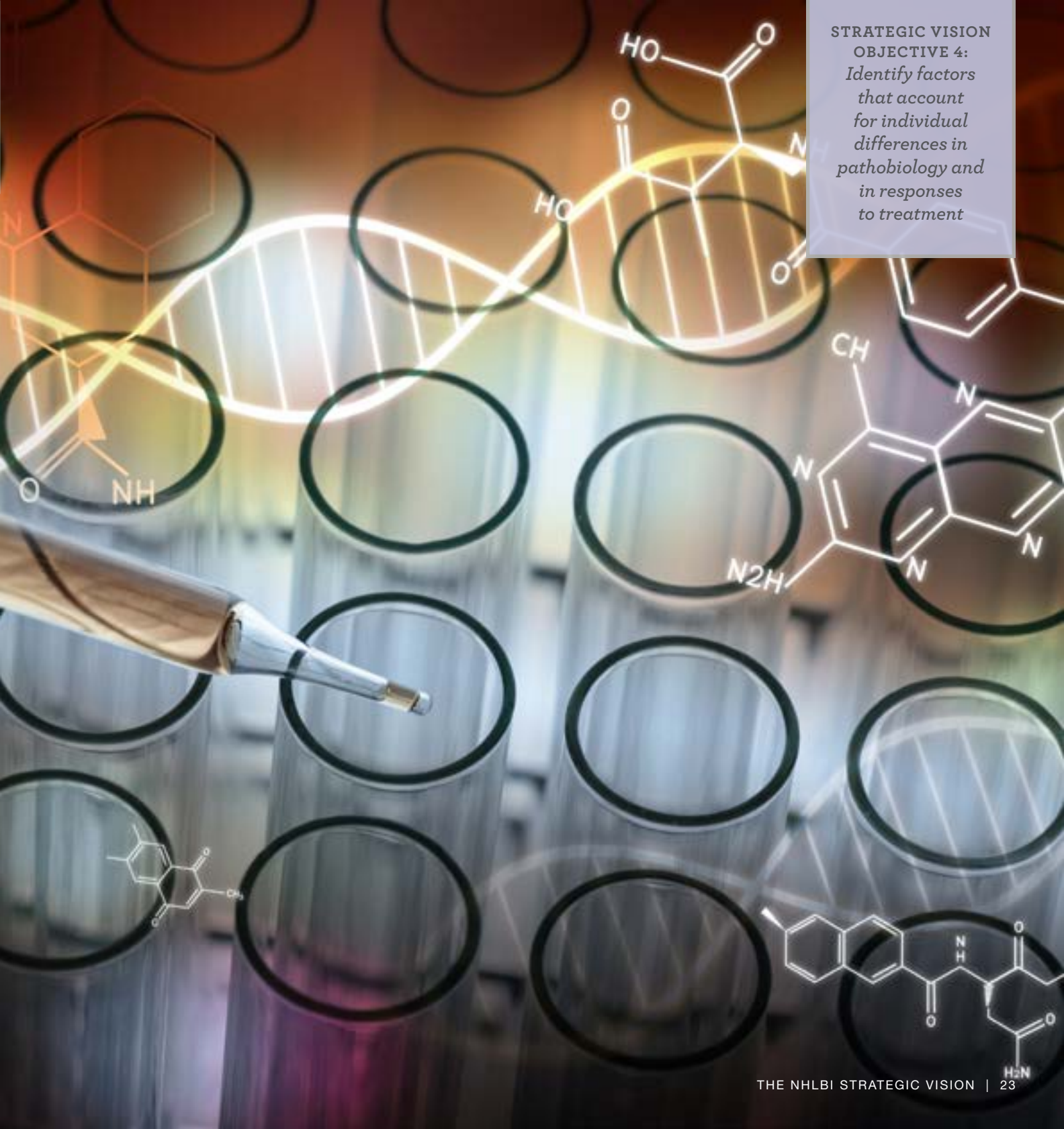
Objective 3 Compelling Questions

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)?

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

Objective 3 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.



STRATEGIC VISION OBJECTIVE 4:
Identify factors that account for individual differences in pathobiology and in responses to treatment

STRATEGIC VISION 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" (e.g., proteomics, metabolomics) have provided new opportunities to deepen our understanding of HLBS pathobiological processes and how these vary among individual patients. Accelerating progress toward precise, individualized prevention efforts and medical interventions will require research into biological factors, environmental exposures, and other influences that account for differences in pathobiology and unique responses to treatment (including drug reactions and other adverse events). This research will allow personal and clinical decisions, practices, and medical products to be tailored to the individual patient to help optimize outcomes.

Envision a future in which we are able to...

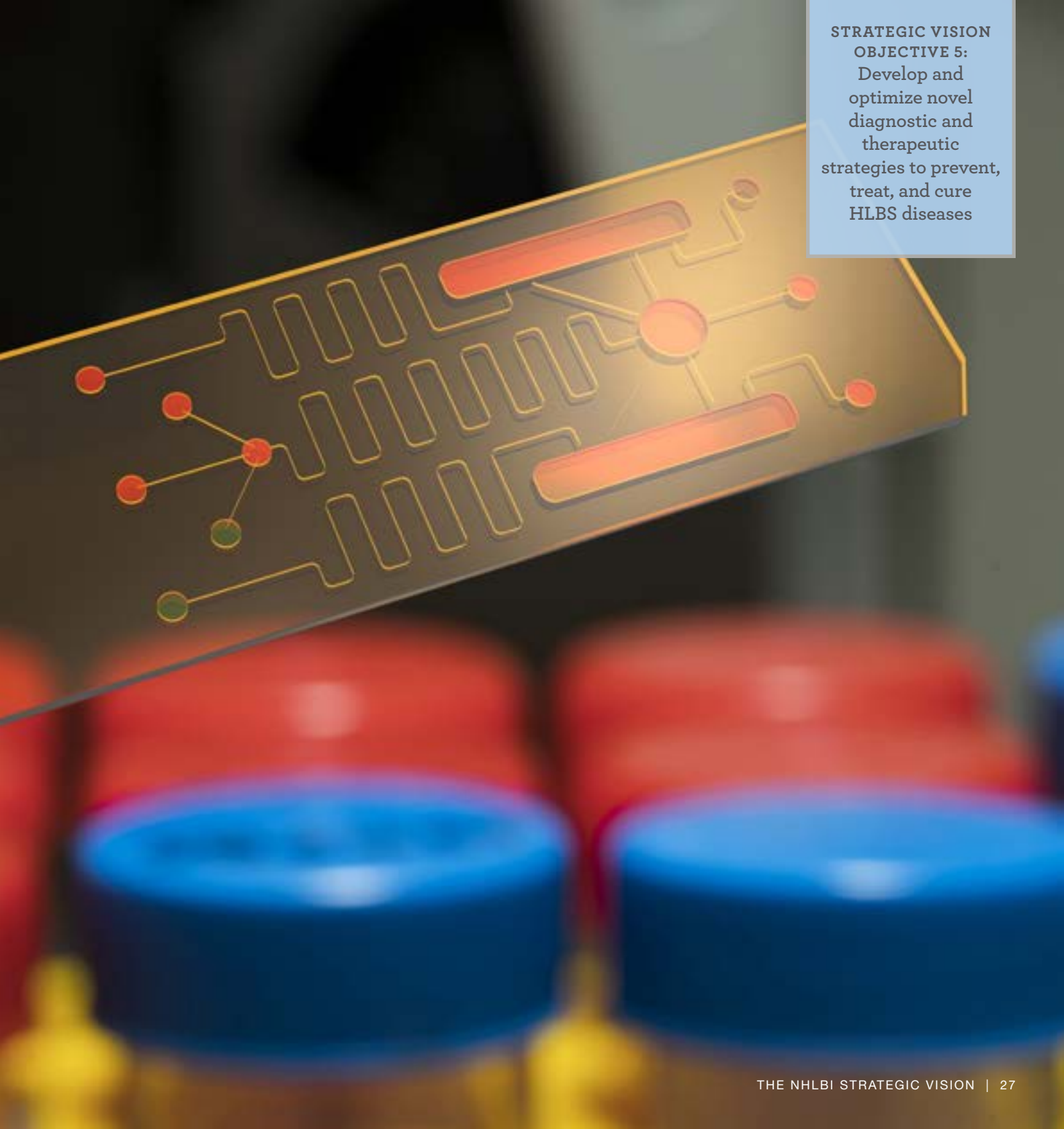
- Develop precise clinical interventions based on individual environmental exposures, behaviors, genotypes, and molecular-cellular phenotypes.
- Accelerate the incorporation of new imaging, omics, and sensor technologies with advanced data analytics to inform more precise clinical classification of chronic diseases (e.g., asthma, pulmonary fibrosis, chronic obstructive lung disease, heart failure) and thereby enable more accurate diagnosis and treatment.

Objective 4 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?

STRATEGIC VISION OBJECTIVE 4: *Identify factors that account for individual differences in pathobiology and in responses to treatment*

Objective 4 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.



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

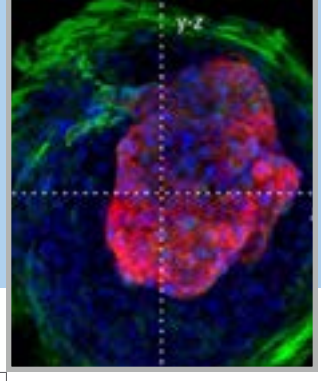
STRATEGIC VISION
OBJECTIVE 5

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 prevent disease, manage and treat illness, and promote resilience. These wide-ranging developments 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 and bioengineering developments may further facilitate diagnostic capabilities, and new lifestyle interventions may improve the maintenance of continued health and wellness and facilitate behavioral modification to prevent disease. Many of these advances, which are the results of past investments in basic research, are critical to developing and optimizing novel diagnostics and therapeutics strategies.

Envision a future in which we are able to...

- Develop surgical grafts (using stem cells, 3-D printing, and nanotechnologies) for children born with heart defects, such that the grafts grow as the child grows into adulthood, thereby avoiding multiple operations.
- Transform the safety and availability of the nation's blood supply by using genetically engineered stem cells to eliminate histo-incompatibility antigens and generate universal donor red blood cells that are available off the shelf by a high-throughput process.



Objective 5 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)?	

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

Objective 5 Compelling Questions

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?

Objective 5 Compelling Questions	
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?

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

Objective 5 Compelling Questions

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?

Objective 5 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.

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

Objective 5 Critical Challenges

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.

STRATEGIC VISION OBJECTIVE 6: *Optimize clinical and implementation research to improve health and reduce disease*

STRATEGIC VISION
OBJECTIVE 6

Optimize 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 clinical studies and implementation research, while also improving the overall efficiency and effectiveness of the research enterprise. Current challenges include difficulties in recruitment of research participants and effective translation of knowledge gained from these studies into programs and policies that improve health at the clinic and community levels.

Envision a future in which we are able to...

- Use novel platforms that link electronic health records and personal health data to facilitate the identification and enrollment of participants in clinical research and empower research volunteers to self-identify.
- Accelerate the translation of discovery into practice by embedding HLBS research platforms (e.g., clinical epidemiology registries, clinical trial networks, and implementation science programs) within "learning" health care systems, thereby engaging the clinical care and patient communities; leveraging electronic health records, patient registries, and existing datasets; and creating an integrative interface between clinical research and practice.

Objective 6 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?

STRATEGIC VISION OBJECTIVE 6: *Optimize clinical and implementation research to improve health and reduce disease*

Objective 6 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.

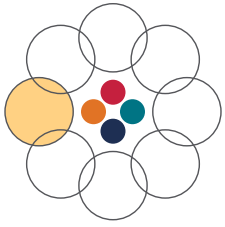
Objective 6 Critical Challenges

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.

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

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

STRATEGIC VISION OBJECTIVE 7



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 these data are being optimally assessed and incorporated into practice. Developing innovative approaches to the integration, analysis, and interpretation of data from multiple sources will be essential. This information can then be effectively used to understand biological, social, and behavioral determinants associated with HLBS health and disease and to improve patient outcomes.

Envision a future in which we are able to...

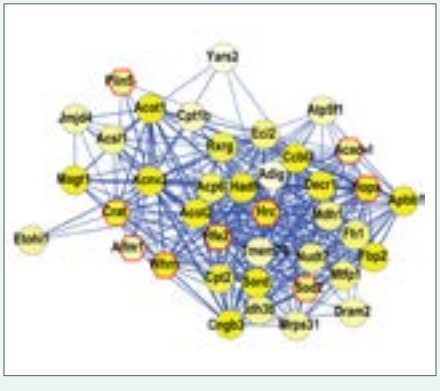
- Empower heart failure patients and their health care providers to co-manage care by using smartphone apps with personalized treatment algorithms that integrate electronic health record data, medication use monitors, and personal sensor data (e.g., body weight, heart rhythm, fluid balance) to sustain optimal function and quality of life.
- Accelerate the discovery of mediators of health and disease through the seamless and shared use of readily accessible cloud-based datasets that integrate genomics and other omics analyses with carefully phenotyped research participant data from diverse sources.
- Develop handheld devices to process and integrate genomics, clinical, and personal health data at the bedside to assist clinicians in their care of patients.

STRATEGIC VISION OBJECTIVE 7: *Leverage emerging opportunities in data science to open new frontiers in HLBS research*

Objective 7 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?

Objective 7 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.

Objective 7 Critical Challenges	
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.

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

STRATEGIC VISION 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. While this is relevant in all areas of development, particular attention is warranted for under-represented groups in science. Collaborative partnerships will be critical to collectively work toward the challenge of expanding the exposure of young students to the wonders of science and sustain that interest through college and graduate education. It is also critical to embrace research training as a lifelong exploration of scientific curiosity in which the NIH promotes the adoption of new disciplines, tools, and technologies as the scientific and public health landscape continually undergoes dynamic change.

Envision a future in which we are able to...

- Enable innovative solutions to pressing health problems by promoting the development of multidisciplinary teams capable of leveraging diverse skills and perspectives from crosscutting research fields such as data science, computational biology, quantitative population sciences, behavioral science, and implementation science.

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

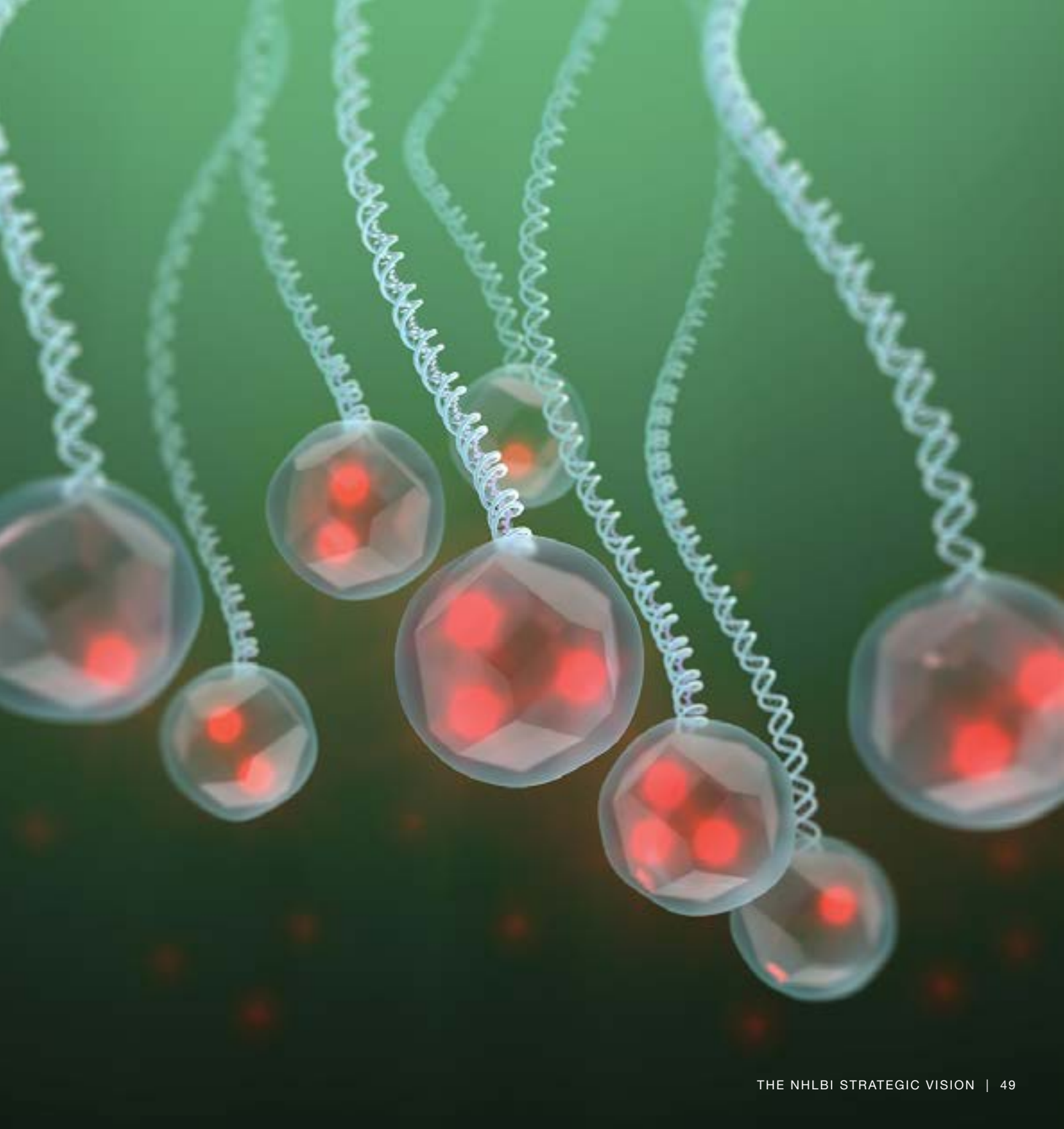
Objective 8 Compelling Questions	
8.CQ.01	What kinds of exposures, beginning in early education, would stimulate and maintain students' interest in and understanding of science, particularly students from diverse and disadvantaged backgrounds?
8.CQ.02	How can we foster diversity among trainees and in 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?

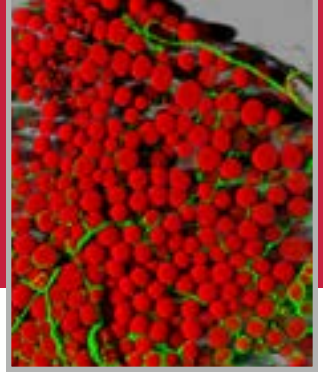
Objective 8 Compelling Questions

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)?

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

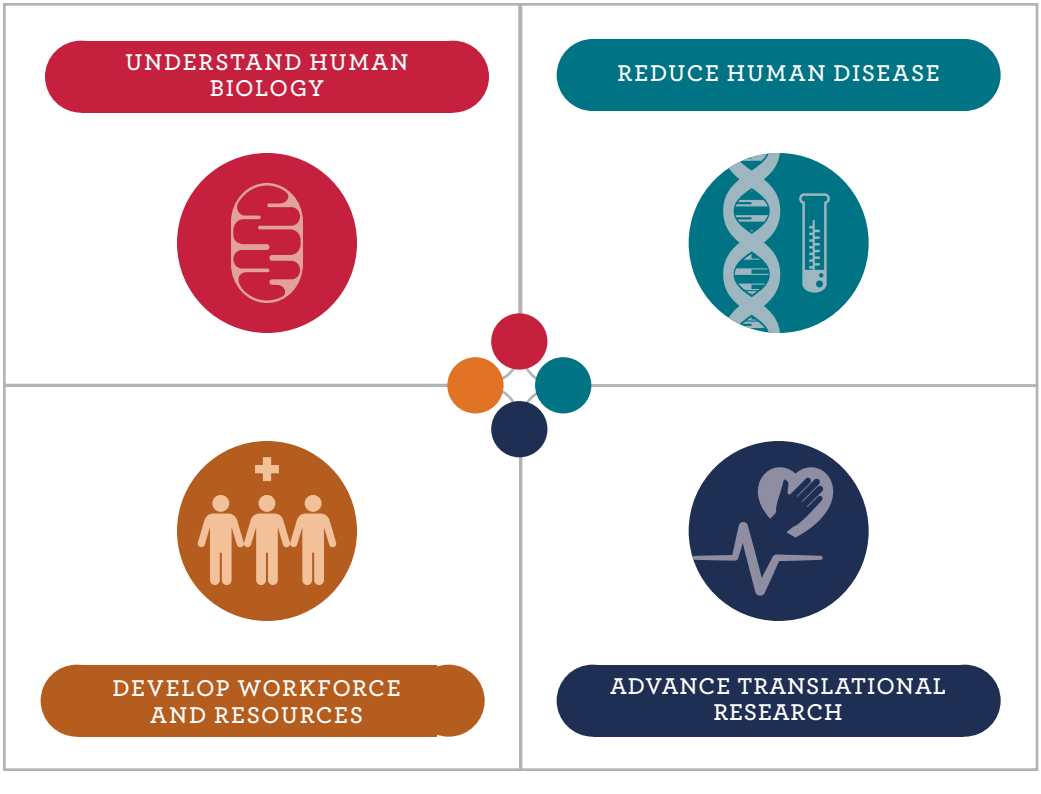
Objective 8 Critical Challenges	
8.CC.01	Sufficient numbers of clinical scientists are needed, particularly those interested in pursuing translation of breakthroughs from basic science laboratories into clinical settings.
8.CC.02	Programs of training, professional development, and mentoring are needed 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.





Conclusion

Investigator-initiated discovery science has been and will remain the bedrock of the NHLBI mission, and individual researchers will always be encouraged to pursue their ideas through investigator-initiated projects. 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 by new Funding Opportunity Announcements (FOAs). The Strategic Research Priorities identify important opportunities in science that will shape the development of future FOAs and other activities.



Initiatives that result from the Strategic Research Priorities will advance achievement of the eight Objectives and will have profound impacts on the health and well-being of the American public as well as the growing number of affected populations around the world. For example, these efforts will enable a deeper understanding of biological processes; allow for more precise targeting of therapies to patients, leading to approaches and early interventions to prevent disease and reduce inequities in health outcomes; and foster a more diversified and integrated scientific workforce.

Success will be realized by ensuring that our priorities remain dynamic and responsive to the evolving scientific landscape and emerging opportunities. This ongoing iterative Strategic Visioning 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 Council and staff. Harnessing the creative energy and marshaling the sustained participation and commitment of these stakeholders will enable achievement of the priorities in the Strategic Vision.

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

Success will be realized by ensuring that our priorities remain dynamic and responsive to the evolving scientific landscape and emerging opportunities.

Image credits:

pg 4: Open Heart Surgery, NIH. R. Perry, National Library of Medicine. 1955.

pg 13: Endothelial cells lining blood vessel walls. Christopher V. Carman and Roberta Martinelli, Harvard Medical School, Boston, MA "Life Magnified" exhibit. 2014.

pg 15: Confocal Immunofluorescence, mouse lung. Jeffrey A. Whitsett, Cincinnati Children's Hospital Medical Center, Cincinnati, OH. Generated by LungMAP Consortium [U01HL122642]. www.lungmap.net. 23 June 2016

pg 25: Confocal Immunofluorescence, mouse lung. Generated by LungMAP Consortium[U01HL122642]. www.lungmap.net. 23 June 2016 Jeffrey A. Whitsett, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.

pg 26: Clinical trial patient undergoing an echocardiogram. Albert Einstein College of Medicine, New York City, NY. 2016

pg 29: (top right) Beating human cardiac microchamber. Zhen Ma, Jason Wang, Peter Loskill, Nathaniel Huebsch, Sangmo Koo, Felicia L. Svedlund, Natalie C. Marks, Ethan W. Hua, Costas P. Grigoropoulos, Bruce R. Conklin and Kevin E. Healy, *Nature Communications*. 2015

pg 31 Sickled Cells. National Center for Advancing Translational Sciences (NCATS), National Institutes of Health. Accessed July 15, 2016.

pg 39 (upper right) Heart Disease Death Rates by County (2011-2013). National Center for Chronic Disease Prevention and Health Promotion, Division for Heart Disease and Stroke Prevention. Accessed June 16, 2016

Pg 42: Pathway visualization of genes involved in Heart Disease. Ma X, Gao L, Karamanlidis G, Gao P, Lee CF, Garcia-Menendez L, et al. *Plos Comput Biol.* 2015.

pg 43: Gene regulation of gene expression in Sickle Cell Disease patients. Quinlan, Idaghdour, Goulet, Gbeha, de Malliard, Bruat, Grenier, Gomez, Sanni, Rahimy and Awadalla. *Front. Genet* 2014

pg 47 (lower center) Researchers at the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health. 2012

pg 49 Functionalized silica-encapsulated fluorescent nanodiamonds (FNDs) attached to individual DNA molecules are excited by the evanescent field (green) in a total internal reflection microscope and emit red fluorescence. Susanta K. Sarkar, Neil Billington, Martin W. Brechbiel, and Keir C. Neuman. *J. AM. Chem Soc.* 2013.

pg 50 A mouse's fat cells (red) are shown surrounded by a network of blood vessels (green). Daniela Malide, National Heart, Lung, and Blood Institute, National Institutes of Health. 2015

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National Institutes of Health
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NIH Publication 16-HL-6150