NHLBI Strategic Visioning Framework
Release Date: February 6, 2015

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I. Message from the Director

As Director of the National Heart, Lung, and Blood Institute (NHLBI), I would like to invite you to participate in a Strategic Visioning process that will shape the scientific priorities for the Institute and guide our funding strategies over the next decade.

The NHLBI community has made tremendous progress in meeting the NHLBI mission across the entire spectrum of heart, lung, blood, and sleep (HLBS) diseases. Despite these advances, few families are left untouched by HLBS disorders, which continue to exact an exorbitant toll on the public's health.

I am asking the NHLBI community to identify the most compelling questions (CQs) and critical challenges (CCs) that we must tackle in the coming years if we are to take full advantage of emerging scientific opportunities and bold new approaches for actively promoting human health, as well as significantly reducing and preventing disease.

Please join us as we embark on a collective endeavor to chart our future research path together.

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

II. Strategic Visioning Process

The Strategic Visioning process is designed to engage the entire NHLBI community in developing the Institute's Strategic Vision, which will ultimately guide the NHLBI in setting priorities, making decisions, and allocating resources over the next decade.

This dynamic process will identify scientific priorities and ensure that our NHLBI community and partners have a voice in framing the Institute's future direction. It involves (1) fostering an iterative dialogue to identify CQs and CCs in HLBS research, (2) charting an actionable path for pursuing these questions and challenges, and (3) measuring and evaluating our progress in realizing the NHLBI's priorities.

The NHLBI community is invited to propose CQs and CCs that will be considered and discussed by the NHLBI and its scientific advisory committees. The questions and challenges will be evaluated using the Prioritization Considerations listed in Table 1, Section V below, and those deemed to be the most pressing and relevant for advancing the NHLBI mission will comprise the Strategic Visioning Scientific Priorities. To jumpstart the discussion of CQs and CCs, we solicited ideas from the National Heart, Lung, and Blood Advisory Council (NHLBAC), the NHLBI Board of Extramural Experts, and the NHLBI staff. Their ideas have been collected for consideration, and a few are provided below as illustrative CQs and CCs. It is important to note that these examples are not intended to circumscribe your thinking in any way, nor have they been designated as a priority by the NHLBI leadership.

There are several methods for participating in the Strategic Visioning process. All modes will allow you to submit new CQs and CCs and/or to comment on what is posted.

- Enter the CQs and CCs at the crowdsourcing website: http://strategicvisioning.nhlbi.nih.gov
- Email CQs and CCs: nhlbi_vision@mail.nih.gov
- Send a letter containing CQs and CCs:
  National Heart, Lung, and Blood Institute
  Attn. Strategic Visioning Team
  Building 31, Room 5A48
  31 Center Drive MSC 2486
  Bethesda, MD 20892

You will have additional opportunities in 2015 to contribute to the Strategic Visioning process. As outlined in Figure 1, Section III below, the input received in response to the Strategic Visioning Framework will be reviewed and synthesized by the NHLBI leadership, publicly discussed with the NHLBAC, and incorporated into the Draft Strategic Visioning Scientific Priorities, which will be released for Public Comment in mid-2015. Public comments, as well as the key prioritization considerations outlined in this document, will help to guide the ranking of the CQs and CCs within each Strategic Goal and to generate the Strategic Visioning Scientific Priorities, which is anticipated to be released publicly by early 2016.

III. Getting Started!

Here are the immediate next steps that you need to take to contribute your ideas and help shape the future of HLBS research:

1. Visit the Strategic Visioning website (http://strategicvisioning.nhlbi.nih.gov) to learn more about the process.
2. Submit CQs or CCs using one of the methods outlined above (i.e., crowdsourcing website, email, or mail). You may also review the CQs and CCs already submitted into the crowdsourcing platform (http://nhlbivisioning.ideascale.com/a/index) and comment or vote on them.

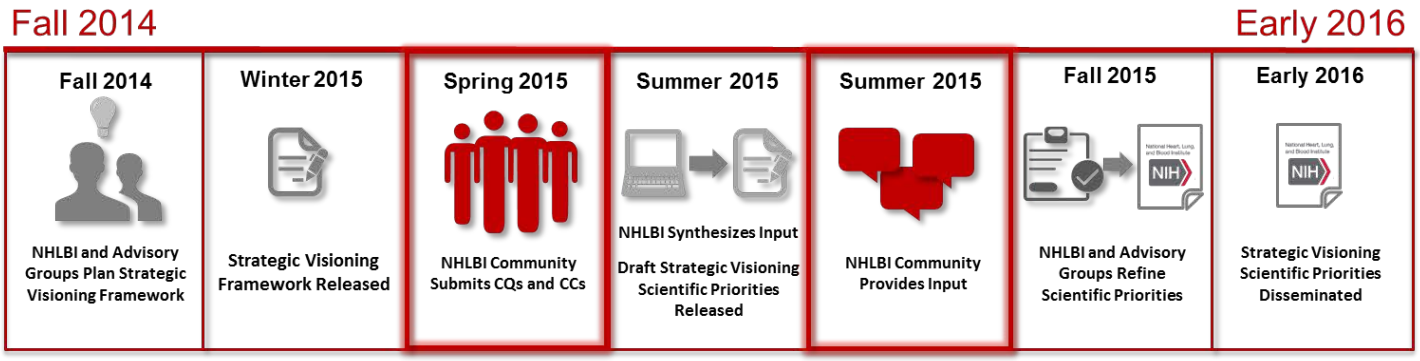

Figure 1: The Strategic Visioning process timeline for community engagement. The National Heart, Lung, and Blood Advisory Council (NHLBAC) and the Board of External Experts (BEE) met jointly in September 2014 to create the initial outline for the Strategic Visioning process. The NHLBI staff then developed the Strategic Visioning Framework to elicit and collect scientific Compelling Questions (CQs) and Critical Challenges (CCs) from the NHLBI community. In Spring 2015, the NHLBI community will contribute CQs and CCs. These CQs and CCs will be used to develop a Draft Strategic Visioning Scientific Priorities that will be released for public comment for mid-2015. The NHLBI, working with its scientific advisory groups, will select a final prioritized list of CQs and CCs and publish them as part of a Strategic Visioning Scientific Priorities document by early 2016 that will describe the strategic priorities of the NHLBI.

IV. Strategic Goals and Illustrative CQs and CCs

The four Strategic Goals for the Strategic Visioning process span the NHLBI mission and include research on normal health and disease in HLBS systems, the translation of research for prevention, diagnosis, and treatment of HLBS diseases, and the support of training and resources for biomedical researchers across the HLBS landscape.

We welcome CQs and CCs within any or all of the NHLBI Strategic Goals.

Goal 1: Promote Human Health	To expand knowledge of the molecular and physiological mechanisms governing the normal function of heart, lung, blood, and sleep systems as essential elements for sustaining human health.
Goal 2: Reduce Human Disease	To extend our knowledge of the pathobiology of heart, lung, blood, and sleep disorders and enable clinical investigations that advance the prediction, prevention, preemption, treatment, and cures of human disease.
Goal 3: Advance Translational Research	To facilitate innovation and accelerate research translation, knowledge dissemination, and implementation science that enhances public health.
Goal 4: Develop Workforce and Resources	To develop and enable a diverse biomedical workforce equipped with the essential skills and research resources to pursue emerging opportunities in science.

Figure 2: The Strategic Goals of the NHLBI.

- A CQ should relate to a specific line of inquiry and address a crucial scientific knowledge gap or opportunity. The scope of a CQ should be broad; i.e., it should transcend an individual investigator-initiated program and require the NHLBI to facilitate and coordinate an approach that might answer the question. The timeframe for addressing the CQ should be within the next decade.
- A CC is a barrier to an unexplored area or an impediment that hinders scientific progress in a mission-critical area. CCs will generally identify needed resources, infrastructure, or tools that could catalyze major scientific advances.

The section below describes each Strategic Goal. Illustrative CQs and CCs are provided as examples within each goal area to demonstrate how to frame and draft your own CQs and CCs. CQs and CCs should address specific, targeted issues, make bold connections, and propose inventive, tangible approaches.

Goal 1 – Promote Human Health: To expand knowledge of the molecular and physiological mechanisms governing the normal function of heart, lung, blood, and sleep systems as essential elements for sustaining human health.
Goal 1 recognizes the intrinsic value of an in-depth understanding of the molecular mechanisms and other key determinants of normal biology and physiology as essential to sustaining and enhancing human health. The intent of this goal is to explore normal human physiology at all levels, spanning the molecular, cellular, individual, and population levels. This goal encompasses basic, preclinical, and clinical research.

Compelling Questions

- **Compelling Question 1.1:** What are the "protective" genetic variants that are associated with a resilient, healthy phenotype or that mediate an intrinsic "resistance" to the influence of risk factors that accelerate HLBS diseases throughout the human lifespan?

  Rationale: *The onset of chronic heart, lung, and blood disorders is accelerated by exposure to certain "risk factors" (e.g., tobacco smoke), yet there is a sub-set of "resilient" individuals who defy conventional "at-risk" predictions and exhibit long, disease-free lives. Scientific advances have made it feasible to sequence an individual's whole genome and discover "protective" genetic determinants of "resilient longevity" that sustain the normal HLBS system functions essential for health.*

- **Compelling Question 1.2:** What is the lineage map of each cell type within normal HLB tissues?

- **Compelling Question 1.3:** What are the genetic programs and molecular networks that orchestrate cell differentiation and normal HLB tissue development in accordance with the lineage map?

  Rationale: *It is now feasible to trace and map the lineage of every cell within a complex tissue, such as the heart, from the earliest stages of embryonic development until adulthood. Moreover, advances in single-cell analytical tools and sub-cellular imaging make it feasible to define the molecular networks that orchestrate cell differentiation and tissue development.*

Critical Challenges:

- **Critical Challenge 1.1:** There is a need for the NHLBI to catalyze the development of tools and shared data resources – the "Heart, Lung, and Blood Systems Biology Connectome" – that facilitates the systematic characterization of the dynamic changes in complex molecular interactions that sustain normal HLB system functions under various physiological conditions. This open resource would comprehensively catalogue these genomic, epigenomic, and metabolic pathways, as well as provide tools to systematically probe them.

  Opportunity: *Advances in high-throughput "-omic" technologies and sub-cellular imaging make it feasible to systematically characterize the complex molecular networks that govern normal cellular and HLB tissue function. However, the in-depth characterization of complex cellular systems is often beyond the scope and capability of individual investigators working in isolation. The NHLBI research community lacks an openly accessible, shared tissue-specific systems biology framework resource that would accelerate the progress of individual, investigator-initiated research.*

- **Critical Challenge 1.2**: There is a critical need to establish a data resource that systematically characterizes and catalogs the epigenome and histone markers associated with the transcriptome in normal HLB cells and tissues.

  Opportunity: *The Human Genome Project and subsequent sequencing projects are characterizing the structural architecture of the human genome; but the biological significance of the human genome and the characterization of functional elements that mediate gene-environment interactions and influence tissue-specific gene expression remain to be further defined. It has become clear that tissue-specific, epigenetic modifications of nucleic acids (e.g., DNA methylation) and dynamic changes in the histone code and chromatin remodeling are important determinants of the transcriptome within HLB tissues. Although the NIH ENCODE project has made important contributions, a major barrier to progress in HLBS science is the lack of systematic, comprehensive characterization of the distinct epigenome and histone code associated with the transcriptome in normal HLB cells and tissues.*

Goal 2 – Reduce Human Disease: To extend our knowledge of the pathobiology of heart, lung, blood, and sleep disorders and enable clinical investigations that advance the prediction, prevention, preemption, treatment, and cures of human disease.
Goal 2 focuses on elucidating the fundamental mechanisms and molecular pathways of disease to enable interventions that alter the development and natural progression of disease. The approaches to achieve this goal may span basic, preclinical, and clinical research, including clinical trials.

Compelling Questions

- **Compelling Question 2.1:** What are the earliest cellular events and changes in the molecular profile of HLB cells during the transition from health to disease in humans and pre-clinical models of HLBS disorders?

  Rationale: *Progress in pre-clinical and clinical science has extended our understanding of the pathobiological processes that precede the onset of clinically manifested symptoms or signs of HLBS disorders. Advances in "-omic" technologies and imaging modalities are making it feasible to perform in-depth characterization of*

complex biological events at the single cell level in health and disease.

- **Compelling Question 2.2:** What are the most promising biomarkers and imaging modalities with the greatest predictive value in identifying HLBS patients at risk for adverse outcomes?

  Rationale: *Advances in precision medicine have the potential to revolutionize how we define disease phenotypes, identify high-risk patient subsets, and approach the diagnosis and treatment of disease. There is an ongoing need in clinical science for biomarker discovery and the characterization of reliable, well-validated surrogate markers of clinical outcomes.*

Critical Challenges:

- **Critical Challenge 2.1:** There is a need for the NHLBI to convene stakeholders and facilitate the creation of registry databases comprised of potential clinical research protocol participants that are sufficiently phenotyped to accelerate protocol eligibility screening and clinical study recruitment. The creation of these research participant registries could involve leveraging EHRs and patient-centered social media and web portals as data sources and involve the outreach and coordination by patient-interest organizations, CTSAs, clinical research organizations, professional organizations, and academic health systems.

  Opportunity: *A major impediment to progress in clinical science relates to the current limitations of traditional clinical trial design, innovative clinical trial methodologies, and barriers to effective clinical trial launch and conduct (e.g., efficient and sufficient participant accrual). Strategies are needed to enable timely, efficient, and broadly inclusive trials that are able to inform clinical practice. For example, protocol launch and execution could be significantly accelerated by the establishment of pre-existing databases with potential research study participants with sufficient phenotyping to facilitate screening. Such a resource could also facilitate the creation of synthetic cohorts and usage of common control groups.*

Goal 3 – Advance Translational Research: To facilitate innovation and accelerate research translation, knowledge dissemination, and implementation science that enhances public health.
Goal 3 aims to facilitate and accelerate activities that promote the progression of research findings and technologies from the bench into clinical practice (e.g., commercialization and dissemination science). Goal 3 encompasses translation across the entire research spectrum (sometimes characterized as T0-T4), bridging basic to clinical, clinic to practice, and population to public health impact.

Compelling Questions

- **Compelling Question 3.1:** What are the most effective trans-disciplinary and multi-level strategies for accelerating the long-term sustained adoption and translation of robust evidence into clinical practice domestically and globally?

  Rationale: *Biomedical research advances over the last half-century have produced many safe and effective drugs, devices, and interventions for the prevention and treatment of HLBS diseases. As a result, most premature deaths from HLBS diseases can be prevented through recommendations for prevention and treatment based on high-quality evidence from these advances. However, widespread adoption of these recommendations in clinical practice to maximize population health impact is lacking or typically lags by as much as 17 years.*

- **Compelling Question 3.2:** What factors and drivers of effective quality care delivery can be identified through natural experiments in health care for the prevention and treatment of HLBS diseases?

Rationale: *Chronic HLBS diseases are a major cause of rising health care costs in the United States. As a result, there is intense focus on understanding strategies that lead to cost-effective high-quality care at the individual level and broadly across populations. Differential implementation of the Affordable Care Act and other health care policies within different states and regions of the US are themselves natural experiments which could yield data on how best to deliver care within various healthcare systems efficiently and effectively for HLBS diseases.*

- **Compelling Question 3.3:** What are the features of an efficient translational research "test early"/"fail often" model that helps eliminate failures early while accelerating translation of promising therapeutics?

  Rationale: *It is well-recognized that many innovative and promising fundamental discovery science never makes it to clinical or public health practice for diagnostic evaluation, treatment, or cure for HLBS diseases. Initial NHLBI effort to address the gap in the commercialization pipeline between scientific discovery and company formation with a long-term goal of more rapidly and effectively moving breakthrough innovations to relevant products that will have health, economic, and societal impact is an important first step.*

Critical Challenges:

- **Critical Challenge 3.1:** The NHLBI community needs a research platform that spans the early and late translational research domains for advancing trans-disciplinary collaborations involving public- and private-sector expertise and knowledge/skills/resources beyond the biomedical science field in order to advance successful translation, dissemination, and implementation of advances in HLBS research.

  Opportunity: *Scientists engaged in the initial pursuit of bench-to-bedside "translational research" may quickly find themselves in need of different skills, tools and a distinct body of "real-world" tacit knowledge not accessible in the academic health center or that extends well beyond their training and experiences as biomedical scientists. Similarly, clinicians or patient advocates interested in improving HLBS disease outcomes in a high-risk community may find themselves without the evidence of which strategies could be most impactful in maximizing health impact.*

Goal 4 – Develop Workforce and Resources: To enable and develop a diverse biomedical workforce equipped with the essential research resources to pursue emerging opportunities in science.
Goal 4 focuses on enabling the biomedical workforce to fully capitalize on emerging scientific opportunities (1) by equipping today's workforce with new skills and the necessary tools and resources and (2) by cultivating a diverse next generation trained in cutting-edge science and the requisite multi-disciplinary skills. The intent of Goal 4 is to span all phases of research, including basic, clinical, translational, and population studies.

Compelling Questions

- **Compelling Question 4.1:** What are the essential elements of an *outstanding* 21st century training program that effectively prepares and empowers new investigators today to be the leaders of NHLBI science in 2050?

  Rationale: *The research training mission of the NHLBI is a fundamental core element of the Institute's stewardship of the biomedical research workforce. Over the past several decades, the NHLBI has developed an assortment of various training and career development award mechanisms that range from T32 training programs to F and K awards. Given the transformative changes that have occurred in science, the demographic profile of the population, and the career development ladder that has evolved over the past 35 years, it is appropriate for the NHLBI community to step back and assess what a training program in NHLBI-related science should look like in 2025 to create the scientific leaders of NHLBI science in 2050.*

- **Compelling Question 4.2:** What are the most compelling emerging areas of NHLBI-related science that represent gaps in the NHLBI-funded training program portfolio and/or lack effective tools, resources, and educational contexts for training NHLBI scientists?

  Rationale: *The rapid pace of scientific advances and technological breakthroughs creates a dynamic landscape that requires a training program to adapt its offerings to align with new emerging fields of inquiry. For example, there is a need for NHLBI training programs to facilitate the transition of investigators with skills in mathematics and physics in related "Big Data Science" to the re-calibration and application of those skills to NHLBI-related data science. Similarly, there is a need to ensure that the NHLBI community has the appropriate training in T4 translational research and implementation science to fulfill the NHLBI mission in this area.*

Critical Challenges:

- **Critical Challenge 4.1:** There is a need to recognize emerging trends in careers outside of traditional R01-funded faculty positions and adapt to the altered landscape with viable alternative career development pathways by convening and collaborating with key stakeholders (academia, private-sector employers, and public-sector employers) to develop better training and career development opportunities that embrace the changing labor market realities.

  Opportunity*: NHLBI provides substantial investments to support career development and training for its most promising young investigators, with the goal of preparing them for productive, independent careers in the NIH biomedical research enterprise. There is substantial evidence that a great number of these highly skilled scientists, both MD and PhD, elect not to pursue a conventional R01-funded academic career track, choosing instead to utilize their training in other sectors (e.g., pharmaceutical industry, government) or disciplines (e.g., patent law)*.

V. Prioritization Considerations

The CQs and CCs received in response to this Strategic Visioning Framework will be reviewed using the prioritization considerations below. All CQs and CCs that are evaluated and chosen for future NHLBI initiatives and activities in the Strategic Visioning Scientific Priorities (1) must align with the NHLBI mission and (2) must require the facilitation of the NHLBI. As you think about your CQs and CCs, consider these prioritization considerations.

Prioritization Considerations
Has significant and meaningful impact in HLBS biology, physiology, clinical practice, translational research, or workforce development
Demonstrates the timeliness of the scientific opportunity for tackling the CQ/CC now to accelerate innovation and transformation of HLBS research
Capitalizes on existing scientific approaches that could be used to make addressing the CQ/CC feasible within the next decade
Leverages, accesses, or supports NHLBI resources or ongoing research programs
Synergizes and leverages strategic partnerships from non-NHLBI sources

Table 1: The Prioritization Considerations for CQs and CCs submitted in the Strategic Visioning process.

VI. Initial CQs and CCs

The following are initial CQs and CCs generated by the NHBLI to facilitate the discussion with the NHLBI community.

Goal 1 – Promote Human Health		
1	CQ	What are the roles of RNAs (e.g., microRNAs, long non-coding RNAs, etc.) in myocardial growth, adaptation, and injury healing response?
2	CQ	What are the unknown elements of the human virome, and what host-virome interactions affect the heart, lung, and blood health and diseases?
3	CQ	What specific roles do protein glycosylation and protein complex formation on stable and activated cellular membranes play in inherent immunogenicity and antibody formation to life-saving therapies for rare blood disorders?
4	CQ	What is the level of population variation of gene regulatory networks in heart, lung, and blood and sleep disease mechanisms? Can we use different animal model strains to identify key factors in networks and modifier genes?
5	CQ	What is the measureable normal human variation at the -omic, cellular, organ, and system levels within the population and across the lifespan?
6	CQ	How does inflammation and cell injury induce the immune system during transplant rejection? How do we control immune responses to enable cell- and tissue-regenerative strategies?
7	CQ	What is the interplay of the micro- and macroenvironment and their effect on gene and protein expression and overall effect on phenotypes in HLBS systems?
8	CQ	Does the homeostasis and health of the lung depend on circadian-coupled genomic function?
9	CQ	What are the best tools/algorithms for robust and objective evaluations of sleep health biomarkers?
10	CQ	What are the regional variations in cellular and molecular characteristics (from epigenetics to microbiome) in the lung, and what controls these variations?
11	CQ	Is there a critical window of growth and development for maximizing lung function?
12	CQ	What is the influence of the microbiome on the immune system and other development processes across the normal human lifespan?
13	CQ	How do lung progenitors recognize stem cell niches, and what cell-cell interactions mediate normal repair?
14	CQ	What are the molecular and cellular responses in the lung that occur after environmental stimuli that predict homeostatic resilience or transition to disease, disorder, or aging?
15	CQ	What is the best method to develop an integrated map of the expression patterns of the vasculature (RNA, protein, and epigenome) within each organ system?
16	CQ	Is there a true "mechanome" affecting normal heart function that could be studied to uncover important mechanically-stimulated pathways relevant to tissue development, maintenance, and repair in vivo?
17	CQ	What is the level of intra-tissue variation of cardiac development gene regulatory networks at single cell resolution?
18	CQ	Can we "reprogram" the immune system to improve outcomes of heart, lung, and hematopoietic cell transplants?
19	CC	To eventually modulate pathologic communication processes employing new therapeutics, there is a need to better understand the transcellular communication between blood cells and components of the vascular layer in vivo.
20	CC	We need to improve the understanding of the molecular and physiological bases of paracrine signaling of heart, and use the knowledge gained to develop improved, effective approaches to diagnose, treat, and prevent cardiac disorders.
21	CC	There is a need to develop computational biology modeling approaches to study normal variation in HLBS

		systems.
22	CC	There is a need to better understand the biological basis for sex differences, particularly for identifying important basic factors that influence normal cardiovascular function and cardiovascular disease in males or females and explain differences in the overall prevalence, progression, and mechanism of cardiovascular disease.

Goal 2 – Reduce Human Disease		
1	CQ	In the US, what kind of diet(s) is/are best for preventing hard CV events?
2	CQ	What is the optimal management approach to severe asymptomatic calcific aortic stenosis (surgical aortic valve replacement (AVR) or deferred surgical AVR until development of symptoms (watchful waiting))?
3	CQ	What are optimal transfusion practices for acute coronary syndrome?
4	CQ	What innovative methodologies applicable to small cohorts and rare outcomes can better ensure the success of clinical and implementation studies in the rare diseases affecting heart, lung, blood, and sleep?
5	CQ	What are the primary molecules and cellular signals associated with prolonged hypertensive stress that cause adverse myocardial tissue remodeling, and what strategies that prevent or reverse adverse remodeling can be developed and tested?
6	CQ	What are the true risks of physical activity and competitive sports for children/young adults with congenital heart disease and arrhythmia syndromes?
7	CQ	Do patients with congenital heart disease have the same, higher, or lower risk for coronary artery disease as they age into adulthood?
8	CQ	Which phenotypic and molecular characteristics predict differential responses to therapy in individuals with chronic HLBS diseases?
9	CQ	What insights can be gathered from patients with single gene functional mutations to improve our understanding of the pathobiology of human disease?
10	CQ	Are the current methodologies for clinical trials still the best practices for conducting efficient clinical trials?
11	CQ	Will integration of behavior science in clinical research improve effectiveness of interventions for HLBS diseases associated with behavioral risk factors?
12	CQ	What are the genetic variants influencing complex HLBS traits and diseases in Asian American subgroups?
13	CQ	Do the etiology and vascular pathology of macrovascular disease differ in Type 1 and Type 2 diabetes?
14	CQ	How does insufficient sleep duration, irregular timed sleep schedules, and poor sleep quality contribute to the pathophysiology of lung, heart and blood diseases?
15	CQ	What are informative and clinically relevant biomarkers of pulmonary hypertension?
16	CQ	Using knowledge of matrix biology and lung development, what are useable methods to modify cadaveric donor lungs to provide a durable, effective organ replacement therapy?
17	CQ	What molecular and cellular pathways explain the sex-specific differences in the prevalence, severity, and progression of lung diseases?
18	CQ	What triggers decompensation of cellular and molecular pathways during exacerbations of chronic lung diseases?
19	CQ	What is the secret behind the “resilience” some people have to HLBS diseases?
20	CQ	What are the critical mechanisms that account for progression from reversible to irreversible ischemia and reperfusion injury?
21	CQ	In adults without diastolic hypertension (DBP ≥ 90 mm Hg), what is the best way to determine at what systolic blood pressure treatment should be initiated?

22	CQ	What approaches can utilize current knowledge on health literacy/health communications as a research development tool and/or strategy to enhance obesity prevention and treatment efforts?
23	CQ	What are the most effective weight loss/weight gain prevention strategies for high risk groups?
24	CQ	What types of newer patient-centered Q of L assessment tools can be employed in HLBS studies so that they can be validated and refined to improve our measurement of Q of L outcomes in populations of interest to NHLBI?
25	CQ	During this period of diminishing Federal resources and funding, what novel methods can be employed to effectively conduct clinical trials that address existing and emerging medical and public health issues?
26	CQ	Is there an optimal range of dietary sodium and potassium intake to lower risk of cardiovascular disease?
27	CQ	What are the metrics that can predict success of clinical trials?
28	CQ	What are the optimal strategies for transfusion of blood products in pediatric and neonatal population?
29	CQ	What is the effect of coconut oil (high in saturated fat) on blood lipids and cardiovascular disease risk?
30	CQ	Will sensitivity to the psychological aspects of obesity, including lifestyle priorities and motivations, improve the efficacy of long-term effectiveness of weight loss and obesity prevention interventions?
31	CQ	What should be the systolic blood pressure goal for pharmacological treatment, and should it vary by age or by CVD risk category?
32	CQ	How does the mechanism of pediatric heart failure differ from adult heart failure mechanisms?
33	CC	There is a need to educate the scientific community and program staff about the use of metrics, results-based accountability, and other business models to improve the science, productivity, and efficiency of clinical trials and clinical trial networks.
34	CC	There is a need to improve and optimize strategies for weight loss maintenance to make them more effective for more individuals.
35	CC	Critical challenges in the assessment of aortic aneurysms are: (1) Availability of reliable animal models that simulate the human pathology, (2) Availability of molecular imaging resources – identification of biomarkers, development of targeted imaging probes and pre-clinical imaging methods, and plasma markers that predict whether an aneurysm is prone to rupture or dissection, (3) Bringing together a wide array of multi-disciplinary experts (biologists, chemists, physicists, cardiologists, radiologists, and engineers) to focus on the common goal of aneurysm diagnosis to predict optimal timing of surgery or endovascular repair.
36	CC	It is essential to develop clinically viable, non-invasive, less expensive technologies for the surveillance of allograft rejection in heart transplant patients. Critical challenges that exist in the near term or long term surveillance after transplant is the unavailability of molecular and cellular level markers that can be non-invasively imaged and quantified detect rejection and thus improve patient survival. Development of molecular and cellular level imaging techniques is essential to address this critical question.
37	CC	There is a need to digitize, remove identifiers, and archive, and catalog physical images, and to promote their use in clinical investigations.
38	CC	There is a need for understanding of right heart failure and its consequences following LVAD support, as well as to develop devices to optimally support the right ventricle.
39	CC	There is a vital need for evidence-based clinical evaluation tools to assess operative risk and post-operative recovery in the elderly, including biomarkers of physiologic age and a simple/reliable clinical evaluation scheme to determine frailty as a risk factor for poor surgical outcomes.
40	CC	Clinical trials are at a crossroads. They are too expensive, take too long, and often can't recruit adequately. A critical challenge is to develop tools that can change the cost, time, and recruiting practices for clinical trials.
41	CC	There is a need to improve identification and surveillance of persons at risk for heart failure and pathological ventricular remodeling prior to development of clinically overt heart failure.

Goal 3 – Advance Translational Research		
1	CQ	What well-developed principles and lessons learned can be employed to improve the safety and availability of blood transfusions in developing countries?
2	CQ	What advancements in our understanding of hematopoietic stem cell differentiation can be combined with practical developments in novel processing and storage technologies to develop the next generation of transfused blood therapeutics?
3	CQ	How might the NHLBI effectively encourage and support its investigators to collaborate with strategic partners to pursue the early translation of their HLBS discoveries into new diagnostics and therapeutics?
4	CQ	What methodologies will best enhance the translation of technologies for gene and cell therapies into potential products for clinical application and commercial development?
5	CQ	What is needed to translate our knowledge of cardiac development and congenital heart disease genetics into novel diagnostic and/or therapeutic strategies for congenital or acquired heart disease?
6	CQ	How do we harness the ongoing “natural experiments” of quality improvement (QI) activities in various healthcare systems to facilitate hypothesis-driven research, improve scientific validity to address questions in clinical trials, and implement and disseminate research results?
7	CQ	What steps can the research community take to facilitate the translation of discovery science into proof of concepts in preclinical models and in humans for diagnosis, prevention, and treatment?
8	CQ	What incentives will encourage current and new NHLBI investigators to pursue late translation (T4) research of proven effective interventions in HLBS diseases?
9	CQ	What translational bioinformatics tools could be used in pulmonary medicine to allow multidimensional, multi-scale modeling of clinical and biomolecular data to assist clinical decision-making?
10	CQ	What are practical point-of-care diagnostic biomarkers that could be used for assessment of sleep/circadian health, sleep disorders, and the risk of sleep-related heart, lung, and blood diseases?
11	CQ	In what ways can researchers better collaborate with community representatives from populations with high prevalence/morbidity/mortality of cardiovascular disease (CVD) to enhance and sustain interventions and achieve improved health outcomes?
12	CQ	How do we go about leveraging existing infrastructure, such as PEPFAR, to reduce the risk of HLBS diseases among HIV patients and other vulnerable populations?
13	CQ	What are effective strategies and clinical decision support tools that can maximize pediatric care providers’ adoption of evidence-based recommendations for assessment and treatment of cardiovascular risk factors and/or asthma?
14	CQ	What are effective strategies for community-based participatory dissemination and implementation research initiatives in rural settings?
15	CQ	How might NHLBI assist its awardees to attract private sector funding or partnerships earlier in the product development process to help bridge the gap between academic discoveries and product commercialization?
16	CQ	What knowledge about health behavior change can be leveraged to design innovative and effective strategies for behavior change among the most vulnerable individuals?
17	CQ	What translational science approaches are best able to test individual, community, and environmental approaches for increasing adherence to heart-healthy dietary recommendations, such as DASH diet?
18	CQ	What are the best implementation strategies to improve adherence to clinical practice guidelines, protocols, and other evidence-based practices that actually lead to the elimination of inequities in preventable disability and death from HLBS diseases?
19	CC	There is a need to utilize bioinformatics to analyze EHR/EMR documentation of practice-based

		pulmonary and sleep medicine to better understand longitudinal care delivery patterns and outcomes, identify changes in evidence, inform practice, and foster reverse translation to integrate basic and clinical research.
20	CC	There is a need to utilize the vast data generated in -omics research to develop biomarker panels for better prediction of cardiovascular diseases risks.
21	CC	There is a need to identify effective interventions for HLBS diseases that could have a transformative population level impact on health inequities if expanded at the national level.
22	CC	There is a need to utilize insights gained from T4 translation research and implementation science to inform the design and execution of early-stage translational research and clinical trials.
23	CC	There is a need to improve accessibility of Bone Marrow Stem Cell Transplantation (BMSCT) for Sickle Cell Disease patients who are most likely to benefit from this treatment option.
24	CC	There is a need to develop a biological pacemaker for pediatric patients that would react to neurohumoral factors that normally modulate heart function, as well as adapt to the growing heart.
25	CC	There is a need to build a robust coordinated surveillance system on the incidence and prevalence of chronic diseases. Surveillance data are needed to: •Describe and monitor the burden, trends, and patterns of these diseases •Set parameters and metrics of research priorities •Identify where to target resources for prevention, treatment, and delivery of care •Track and monitor progress toward public health disease prevention/health promotion goals Existing data sources (i.e., population surveys, registries, cohort studies, administrative data, and vital statistics) do not individually provide nationally representative data, cannot be linked, and are not currently readily accessible to all levels of users. One potential way to build such a system is to integrate and expand existing data sources."
26	CC	Given the lack of outcomes data in the pediatric population, there is a need to develop a repository of data, including integrated electronic clinical data (outpatient, inpatient, laboratory, imaging, and prescription), on all CVD risk factors (e.g. hypertension, dyslipidemia) in children. One approach is to start with leveraging health care systems that have existent electronic clinical data, have infrastructure in place for conducting electronic health record (EHR)-based research, and have solid experience working with electronic data for research purposes.
27	CC	There is a need to identify and develop suitable animal models (e.g. larger, non-primate animal models) that faithfully predict the outcomes of new medicines and treatments in HLBS disorders prior to human clinical trials.
28	CC	There is little evidence about the best ways in which to effectively communicate ASCVD risk to patients so that they clearly understand the potential benefits and harms of treatments in order to make informed decisions about their care. A shift toward shared decision-making and tailored treatment makes it imperative that effective risk communication strategies be developed and implemented.

Goal 4 – Develop Workforce and Resources		
1	CQ	What are the best methods for NHLBI to contribute to reforms that make careers more attractive to people from disadvantaged backgrounds?
2	CQ	What kinds of incentives, reforms, and exposures would work best with students from diverse and disadvantaged backgrounds to pursue careers in science?
3	CQ	What are the best methods to identify future training areas and develop/adapt training and mentorship programs to address future critical needs?
4	CQ	What strategies should NHLBI use to pursue students at the K-12 level of their education and also to encourage their scientific interests through the undergraduate and graduate levels?

5	CQ	What is the best way for the mentoring effort of senior investigators to be encouraged, enhanced, and supported to develop early career investigators?
6	CQ	Are T32s doing a sufficient job of promoting interdisciplinary and team science? Should we change the way these programs are structured?
7	CQ	What can research institutions do to entice and support potential and actual K applicants to become independent scientists?
8	CQ	To ensure continuity of mentorship across generations, should we create incentives to encourage participation of younger, junior faculty in the leadership of our T32 programs?
9	CQ	How do we add communication skills to our training programs to improve scientists' communication with the public?
10	CC	There is a need to ensure that mentors have adequate skills, time, and incentives to mentor successfully.
11	CC	There is a need to establish markers that are predictive of future trainee success.
12	CC	We need to increase our base of T4 implementation research expertise among researchers, reviewers, and investigators.
13	CC	There is a critical challenge to retain highly trained basic and clinical scientists in the biomedical research enterprise and expediently promote their independence and capacity to produce innovative discoveries. There is a need to provide more funding opportunities for collaborative, team-science approaches to scientific investigation by interdisciplinary teams comprised of clinician scientists, basic researchers, and data scientists, as co-investigators, thereby recognizing and capitalizing on the unique training, strengths, and contributions of each.
14	CC	There is a need to develop training programs, mentorship, and collaborations that cross boundaries and prepare researchers for future transdisciplinary needs.