

ADVANCING

Heart, Lung, Blood, and Sleep Research



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Working in Partnership to Advance Research and Improve Health

In 2018, NIH's National Heart, Lung, and Blood Institute (NHLBI) culminated its 70th year of support for fundamental discovery science and translational and clinical research. Researchers, clinicians, and patient advocates led the charge to establish the National Heart Institute in 1948 and to later expand its scope to encompass lung, blood, and sleep disorders. Today, these partners continue to play a vital role in guiding NHLBI's mission, helping us recognize areas of need and opportunity, setting priorities, and finding new ways to accelerate research and improve health.

Thousands of individuals and dozens of allied organizations have helped us develop and implement the Strategic Vision—our plan for guiding Institute-led initiatives over the next 5 to 10 years.

Implementation of the Strategic Vision includes the patient-focused *Cure Sickle Cell Initiative*, which launched in September 2018 after extensive engagement and planning by the NHLBI, the research community, and patient advocacy groups. It is only by continuing to work together that we can achieve our ambitious goal of bringing curative genetic therapies to people who have sickle cell disease.

With our partners, we are implementing the first-ever *COPD National Action Plan*, released in 2017. The thoughtful insights of patients and their families, healthcare providers, investigators, and others in the chronic obstructive pulmonary disease (COPD) community were essential in developing the plan. Our joint ownership and engagement in the plan will remain essential to making it a success by empowering patients and families; enhancing research;

improving COPD diagnosis, treatment, and management; and reducing its public health burden.

We also value our partners in combating heart disease. Together, we have propelled research advances to better understand the causes of heart disease, to improve medical care, and to educate people to take better care of their hearts through programs such as *The Heart Truth*®. Although heart disease remains the leading cause of death among Americans, our work has helped bring about a 70 percent decline in heart disease deaths over the past half century.

What follows is a sampling of the many exciting research advances in heart, lung, blood, and sleep research over the past year, made possible through our shared commitment and collaboration with researchers, patients, providers, and policymakers. ●

NHLBI STRATEGIC VISION: EIGHT OBJECTIVES TO ADVANCE OUR SCIENCE



- 1 Understand normal biological function and resilience.
- 2 Investigate newly discovered pathobiological mechanisms important to the onset and progression of HLBS (heart, lung, blood, and sleep) diseases.
- 3 Investigate factors that account for differences in health among populations.
- 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.



CARDIOVASCULAR DISEASE RESEARCH



Catalyzing progress in congenital heart disease research

Congenital heart disease (CHD) is the most common birth defect in the United States. With advances in medicine, many children who have CHD are living well into adulthood, and the NHLBI continues to support research on the causes of CHD as well as its effects across the lifespan. NHLBI's Bench to Bassinet Program leads these efforts, with the Pediatric Heart Network as its clinical cornerstone.

- Network researchers recently completed a study to improve postsurgical management for two common heart defects, tetralogy of Fallot and coarctation (narrowing) of the aorta. Through a collaborative learning approach, five centers in the network examined and updated their practices for breathing tube removal after surgery. The new practices cut the typical

amount of time infants spent with a breathing tube by nearly 80 percent and helped reduce medical costs by an estimated 27 percent—or \$13,500 per surgery.

- CHD occurs in about half of all babies who have Down syndrome. To address heart disease and other conditions associated with Down syndrome, the NHLBI is coleading the trans-NIH INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) Project with the goal of improving health and quality of life. These efforts will leverage the Bench to Bassinet Program's Pediatric Cardiac Genomics Consortium and the Gabriella Miller Kids First Pediatric Research Program cohort. Recently funded research is designed to identify genes that contribute to CHD in babies who have Down syndrome. •

Evaluating surgical procedures and devices for the heart

The NHLBI-supported Cardiothoracic Surgical Trials Network (CTSN) addresses

Legacy Studies Continue to Drive Discovery

NHLBI's long-running population-based cohort studies have made major contributions to understanding the causes of and prevention strategies for heart and vascular diseases. These studies continue to drive discovery by uncovering new links between cardiovascular health and brain health.

The Framingham Heart Study, which turned 70 in 2018, led the way in discovering risk factors for heart disease, thus empowering the development of treatment and prevention strategies that continue to save lives. This multigenerational study offers an unprecedented ability to study age-related cognitive decline as the participants, including the grandchildren of the original cohort, grow older.

Researchers recently found that high blood pressure in midlife increases the risk of age-related dementia, suggesting that managing blood pressure early in life may help provide protection from cognitive decline later.

In 2018, the NHLBI renewed its support for the **Jackson Heart Study**, the nation's largest study of cardiovascular disease in African Americans. NHLBI's investment in the study has helped identify genetic and environmental risk factors that contribute to the high prevalence and mortality rates of cardiovascular diseases among African Americans in the Jackson, Mississippi, area and nationwide. This funding phase adds a new dimension to the study by exploring risk factors for cognitive impairment and dementia. ●

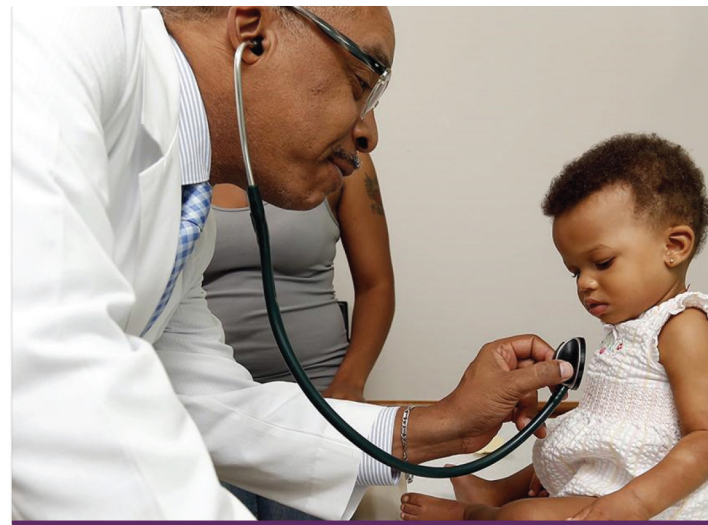
important questions in cardiac surgery and conducts clinical trials on new devices and procedures.

In 2018, the NHLBI renewed support for and expanded the CTSN to conduct implementation research along with clinical trials to facilitate adoption and sustainability of CTSN findings. The renewal also



expanded the network's training for early-stage investigators (ESIs), extended its reach to areas with high disease burden, and enabled outside investigators and industry to access the network. The CTSN currently supports studies to:

- Comparing long-term outcomes of mitral heart valve repair versus replacement
- Evaluating the benefit of injecting mesenchymal precursor cells, a type of stem cell, during implantation of a left ventricular assist



device in people who have advanced heart disease

- Assessing whether repairing a tricuspid valve with a small amount of leakage during a planned mitral valve surgery leads to improved outcomes. ●

Strategic Vision Objectives

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Transforming Lives in Sickle Cell Disease

The NHLBI continues to be a leading scientific force in working toward improved treatments for sickle cell disease, a blood disorder caused by a mutation in the beta globin gene.

- The NHLBI is leading the Cure Sickle Cell Initiative, with the aim to bring curative genetic therapies for sickle cell disease into clinical trials in 5 years. The Initiative is engaging patients and their caregivers, patient advocates, academic and private sector researchers, and state and federal agencies.
- NHLBI intramural researchers continue to pursue groundbreaking research on sickle cell disease that intersects with this Initiative. One pressing question is the level of normal globin gene needed for gene therapy to work. By monitoring patients after bone marrow transplant, these researchers estimate that at least 20 percent of a patient's blood cells must have normal levels of hemoglobin to cure the disease.
- The NHLBI also strives to have a more immediate impact on patients' quality of life. In addition to supporting research to expand use of hydroxyurea to relieve sickle cell pain, the NHLBI is leveraging the NIH HEAL (Helping to End Addiction Long-term) Initiative to understand pain mechanisms in sickle cell disease. ●

Improving bone marrow transplants to treat blood disorders

Transplants of the blood-forming stem cells in bone marrow can be lifesaving for patients who have a range of blood disorders from sickle cell disease to aplastic anemia. But not all donors tolerate the injections needed to mobilize these cells in the bloodstream.

- The NHLBI supports efforts to improve stem cell collection, including a recent study showing that a single injection of the molecule GRObeta efficiently mobilized the cells and was well tolerated. The results could potentially increase the number of stem

cell donors and provide a safer, less painful way to isolate these cells from patients so that they can be repaired and reimplanted. ●

Unlocking the secrets of the blood-brain barrier

The blood-brain barrier provides the brain with essential nutrients while protecting it from toxic chemicals in the blood, and its breakdown during a stroke or traumatic brain injury can be devastating. NHLBI-funded researchers are making progress in understanding how the blood-brain barrier is regulated by proteins in the blood.

- Recent studies have focused on activated protein C (APC), which inhibits blood clotting. Previous studies tested APC as a potential stroke therapeutic agent but found that it increases the risk of bleeding. NHLBI-funded researchers recently discovered that APC also has signaling functions and can act on cells in the blood-brain barrier to stabilize it. Boosting these signals could provide an alternative, potentially safer, route to stroke therapy. ●



A Quarter Century of Federal Coordination and Research Investment in Sleep

Strategic Vision Objectives

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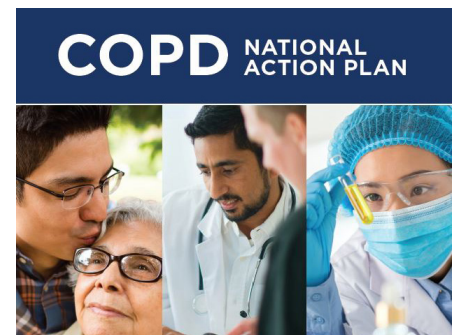
For 25 years, the NHLBI National Center on Sleep Disorders Research has led foundational research on sleep and circadian biology across the NIH and has worked with federal and private organizations to disseminate sleep health information.

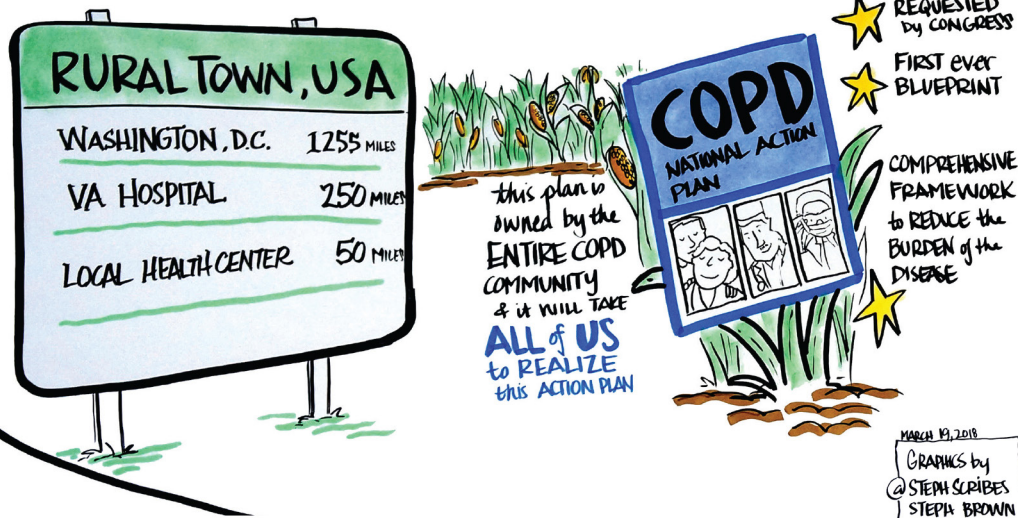
- The Center co-hosted the 2018 Research Conference on Sleep and the Health of Women to highlight advances in understanding how sleep disorders affect women’s health. Other goals of the conference were to stimulate translation of findings to improve health and to identify knowledge gaps where more research is needed.
- As part of the NIH HEAL Initiative, an effort to speed scientific solutions to stem the opioid crisis, the Center is funding projects to understand the role of sleep and circadian rhythms in opioid use disorder, including their roles in dependence, addiction, and response to treatment.
- Sleep apnea disproportionately affects people who have Down syndrome. Through the INCLUDE program, the Center is leveraging NHLBI’s sleep cohort studies, the NHLBI’s Pediatric Cardiac Genomics Consortium, and the Gabriella Miller Kids First Pediatric Research Program to improve sleep apnea treatment for children who have Down syndrome. ●

Implementing the COPD National Action Plan

COPD is a leading cause of death in the United States. Yet many Americans are not aware of COPD, and some may not realize they have it.

In 2017, the NHLBI and its federal and nonfederal partners developed the first-ever *COPD National Action Plan* with the goal of providing a comprehensive, unified framework for fighting the disease. In the year since, the NHLBI has been working closely with patient





advocacy groups, professional organizations, and other agencies to implement the plan.

- In 2018, NHLBI's *COPD Learn More Breathe Better*[®] program awarded six subcontracts to state and local organizations to advance outreach and education through innovative community-level programs that support implementation of the *COPD National Action Plan*.

New data from an ongoing collaboration between the NHLBI and the Centers for Disease

Control and Prevention (CDC) show that COPD is almost twice as common in rural areas as in urban settings. To address this disparity, the NHLBI initiated new efforts with the CDC as well as the Health Resources and Services Administration and the Federal Office of Rural Health Policy.

- The NHLBI and its partners convened two workshops on COPD and rural health in 2018. These workshops addressed how to better meet the challenges of diagnosing

and treating COPD in rural America, such as through telemedicine. The NHLBI also recently funded several projects that are evaluating the effectiveness of home-based pulmonary rehabilitation programs for patients in rural settings who have COPD. ●

Pursuing innovative, tailored therapies for pulmonary fibrosis

NHLBI-funded researchers are working to better understand mechanisms of disease in pulmonary fibrosis to develop more effective therapies and to improve lung transplantation, which remains the only treatment option for many patients.

- A recent study found higher levels of the PD-1 protein in a type of immune cell in people who have idiopathic pulmonary fibrosis (IPF). Blocking PD-1 and a related signaling pathway reduced fibrosis in a mouse model. A number of drugs that block this pathway have been approved for other conditions, suggesting that similar drugs may be effective for treating pulmonary fibrosis.
- Without a lung transplant, IPF often takes a fatal course in 3 to 4 years. However, people who have the disease also can be stable for long periods, making treatment decisions difficult. In a large genetic study, researchers found a gene expression pattern in blood cells that can predict a



Driving Precision Medicine Through Data Science

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The ultimate goal of precision medicine is to provide the right treatment, at the right time, tailored to a patient's individual needs. To support this goal, the NHLBI Trans-Omics for Precision Medicine (TOPMed) program is collecting genomic and other -omics data from a vast number of diverse study participants. The NHLBI is also supporting development of new ways to share and analyze these data to drive scientific discoveries for heart, lung, blood, and sleep disorders.

- Genomic data from the NHLBI TOPMed program make up one of three massive datasets that researchers will be able to access and analyze during a pilot phase of the NIH Data Commons, a cloud-computing environment that is part of the NIH Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES) Initiative.
- Concurrently, TOPMed and other datasets will be integrated into the NHLBI Data Storage, Toolspace, Access and analytics for biG-data Empowerment (DataSTAGE), a cloud-based platform with analytical tools to add computing power for precision medicine research. Through DataSTAGE, NHLBI-funded investigators will be able to pursue innovative research questions by obtaining data from the NIH Data Commons and many other databases that were previously inaccessible.

NHLBI's investment in creating and analyzing large, diverse, health-related datasets is already revealing new findings to advance precision medicine for lung diseases.

- Recently, investigators with NHLBI's COPDGene® Study analyzed lung imaging, genomic, and clinical data from nearly 15,000 people. They found that a gene variant improved risk prediction for fibrotic lung disease when it was added to a risk calculator that included age, sex, and smoking status. ●

patient's response to therapy. This work—which involved people with IPF who are participating in clinical trials—could help guide the choice of treatment, including when lung transplant remains the best option. ●

Advancing high-quality precision care for asthma

NHLBI-supported research on asthma has led to better treatment and prevention options. But given that many people continue to have poorly controlled asthma, there is a significant need to improve adoption of current

evidence-based interventions and to develop new ones.

- The NHLBI is supporting updates to the 2007 national guidelines for asthma care. The Institute has supported completion of rigorous systematic evidence reviews addressing critical issues in asthma diagnosis and management. The NHLBI has also established a federal advisory committee that will chart the path for translating new evidence into improved care guidelines for people who have asthma.

- The NHLBI-funded Precision Interventions for Severe and/or Exacerbation Prone Asthma Network (PreclSE) is designed to identify precision medicine-based approaches to treat severe asthma more effectively. Recently, 10 centers were established to test a series of treatments approved by the Food and Drug Administration based on each patient's specific biology or biomarkers. ●



8 Supporting the Brightest Minds, From Early Career Onward

In the final days of September 2018, Congress passed and the President signed legislation that funds NIH and other agencies within the Department of Health and Human Services through fiscal year (FY) 2019. NHLBI's appropriation is \$3.49 billion, a 3.1 percent increase over FY 2018.

NHLBI will continue to dedicate the majority of its funding to investigator-initiated research. Over the past several years, the Institute has been able to steadily improve our support for R01 research project grants, with R01 application success rates climbing from 16.5 percent in FY 2014 to a projected 24.2 percent in FY 2018.

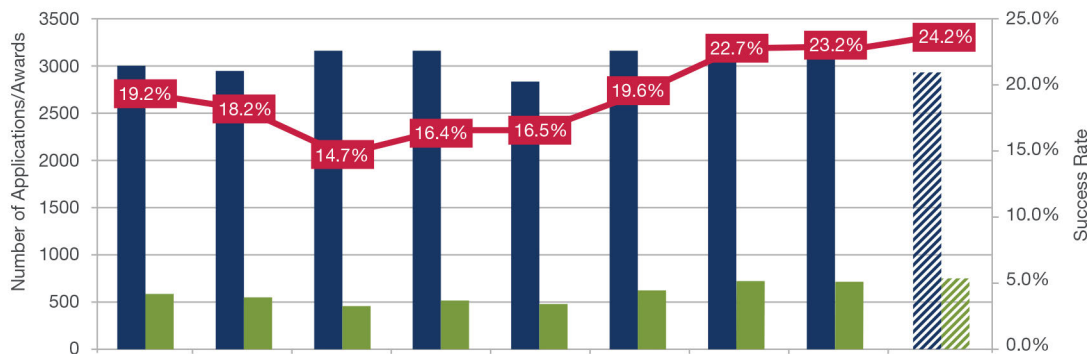
In alignment with the NIH Next Generation Researchers Initiative, we also continue to enhance our support for early-stage investigators (ESIs). By setting higher paylines for ESIs, we increased R01 applications success rates among ESIs from 18 percent in FY 2014 to a projected 32.7 percent in FY 2018.

NHLBI is also expanding innovative training and career development programs to support the Nation's brightest minds and empowering them to fill critical scientific and public health needs. For example, in FY 2018, the Institute launched the Stimulating Access to Research in Residency (StARR) program, which funds research

institutions to provide the tools, mentorship, and training needed to put medical residents on a research career path; so far, we have made awards to seven institutions.

While the Strategic Vision helps guide our priorities, our investments will continue to focus on robust support for investigator-initiated research—and a workforce to sustain the research pipeline. ●

Success Rates for R01 Applications from 2010 to 2018



	2010	2011	2012	2013	2014	2015	2016	2017	2018 Projected
# Applications	3019	2966	3,161	3168	2839	3164	3129	3055	2942
# Awards	581	539	464	518	468	619	710	708	711
Success Rate	19.2%	18.2%	14.7%	16.4%	16.5%	19.6%	22.7%	23.2%	24.2%

■ # of Applications ■ # of Awards ■ Success Rate