

ADVANCING

Heart, Lung, Blood, and Sleep Research



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National Heart, Lung,
and Blood Institute

Director's Message

Advancing Heart, Lung, Blood,
and Sleep Research



NHLBI Director Gary H. Gibbons, M.D.

Last year, the National Heart, Lung, and Blood Institute (NHLBI) celebrated 75 years of funding biomedical research to prevent and treat heart, lung, blood, and sleep (HLBS) disorders, which continue to be the leading causes of death and disability in the United States. On October 17, 2023, the NHLBI Constituency Group, co-chaired by the American Heart Association and the American Thoracic Society, hosted a reception on Capitol Hill joined by representatives from health advocacy nonprofits, associations, and foundations, along with lawmakers who support NHLBI research. It was a night filled with inspiration and gratitude, capped by a performance by Caesar Sant, a violin prodigy who was born with sickle cell anemia and received a life-saving bone marrow transplant at the NIH Clinical Center.

Mr. Sant's performance was significant. As it turns out, 1948 was a banner year for NHLBI's birth. It was the year when sickle cell disease was first defined as a molecular disorder — the result of a single genetic mutation that causes life-threatening conditions. Seventy-five years later, 2023 was also momentous: At the end of the year, thanks to NIH-funded CRISPR technology, the biomedical community was able to announce a cure for sickle cell disease. Not just a better treatment. A cure.

NHLBI will continue to fund research into single-gene variant diseases and disorders. But our research portfolio is rich and complex, full of common diseases and disorders that are multifactorial, are chronic, and often worsen over time unless carefully managed. The beginning of the Framingham Heart Study (FHS) in 1948 was also a landmark event in the history of NHLBI. The FHS began as a bold effort to use broad, community-based health measures to identify common factors that contribute to cardiovascular disease. Since then, the FHS has evolved into a multigenerational study that analyzes family patterns of cardiovascular and other diseases, gathers genetic information from generations that followed the original study participants, and has expanded to include diverse populations and their unique patterns of risk factors.

Cardiovascular disease. High blood pressure. Lung diseases, such as asthma and pulmonary fibrosis. Sleep disorders. The incidence and outcomes of these common chronic diseases offer an eye-opening look into the stark discrepancies among people living in the United States who do much better at either avoiding them or living longer with better medical treatment and those who have significantly more disability and shorter life spans. For example, the enduring burden of heart failure is expected to increase significantly among Americans, yet it does not fall evenly across communities in the United States.

The persistence of these health inequities is as complex as the diseases' causes. Genetic disposition and health behaviors can combine to increase risks for everything from asthma to hypertension to heart failure and lung disease, reflecting a complicated dance between genes, socioeconomic status, and environmental exposure, among other factors. Resilience depends on who and where you are. For example, a simple

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lack of walkability in some neighborhoods creates barriers to behaviors that could increase resilience to disease and decrease vulnerability. An individual’s lived experience and health exist within that confluence of the individual, the community, and their socioeconomic structure.

Where you live matters, and your ZIP code may matter more than your genetic code. For example, the inequities in COVID-19 incidence and outcomes during the pandemic have laid bare other kinds of health vulnerabilities in all kinds of communities across the United States. As a consequence, NHLBI developed the Risk Underlying Rural Areas Longitudinal (RURAL) Cohort Study to address the high burden of chronic heart and lung disease in 10 rural counties in the heartland states of Alabama, Kentucky, Louisiana, and Mississippi by using community-engaged partners and high-tech mobile research units to collect data including medical histories, familial, lifestyle, and behavioral factors. These and other data from cohort studies will be fed into the analytic platform of NHLBI’s Trans-Omics for Precision Medicine (TOPMed) program to support discovery of genomic and other complex risk factors that influence health disparities wherever they are found.

It would be foolish to ignore the promise that biomedical research offers to create ways to preempt disease by using carefully targeted community-level interventions to help the most vulnerable before disease even has a chance to start. Fortunately, NHLBI has a long history of funding research that excels at approaching people where they are.

For example, the Maternal Health Community Implementation Project (MH-CIP) is a community-driven initiative that uses evidence-based interventions, such as regular blood pressure readings, to help reduce cardiac risk factors before and during pregnancy. Another initiative, Early Intervention to Promote Cardiovascular Health of Mothers and Children (ENRICH), is a partnership with other federal agencies and certified local home visiting programs to promote cardiovascular health in mothers and children up to 5 years old. ENRICH researchers work directly with communities that have a high burden of cardiovascular disease, including those of lower socioeconomic status and access to care and tribal nations.

These kinds of community-based efforts are now accelerated because of lessons learned from the COVID-19 pandemic. In 2020, the Community Engagement Alliance (CEAL) initiative was developed to reach out to communities across the country that bore disproportionate burdens of infection with the virus that causes COVID-19 by using meaningful engagement strategies to raise awareness about the risks of the disease and the value of mitigation strategies, including vaccination. CEAL created participatory space for all — patients, advocates, community leaders, scientific partners, and others — to leverage the power of community involvement to improve public health.

Because of the initiative’s success, CEAL funding has been sustained to strategically leverage the initiative as a platform to gather data and test interventions using uniform measures and analytic processes. Additional initiatives, including those from other NIH Institutes, have been incorporated into CEAL to strategically use the initiative’s model to tackle major public health issues. The Implementing a Maternal health and PRenancy Outcomes Vision for Everyone (IMPROVE) initiative and the Climate Change and Health (CCH) Initiative use the CEAL platform as a powerful research resource for NHLBI and other NIH Institutes to work effectively within communities.



NHLBI's Innovative Magnetic Resonance Imaging (MRI) Technology Program

NHLBI's innovative magnetic resonance imaging (MRI) technology program now makes it possible to maintain good image quality when testing for certain lung diseases while eliminating radiation exposure. To achieve this, NHLBI researchers **developed new techniques** to capture and process images with low-field MRI scanners. Researchers then applied novel, advanced reconstruction methods using contemporary computational power integrated into the clinical environment with the Gadgetron, an open-source tool for medical image reconstruction. The program emphasizes translation of new methods to clinical applications by collaborating with cardiologists, pulmonologists, radiologists, and critical care physicians.

However, we can't stop there. We have to look further. Now is the time to both sharpen and widen our focus and dive into the future embracing new technologies to tackle the most complicated and persistent public health challenges.

Artificial intelligence and machine learning technologies have been the focus of much discussion this past year. People fear that these new tools will make humans and our innate humanity not just irrelevant but unwanted. But as a scientist and a biomedical researcher, I believe that if we have the will, we have the power to harness these technologies for good as we have always done throughout history. Fire. Wheels. Telescopes. Microscopes. Computers that were once as big as a house but are now fitted onto microchips manufactured so inexpensively that anyone can buy one online.

We have to take that leap into these new technologies strategically and with deep thought about their opportunities and challenges. NHLBI has consistently funded data gathering and analysis initiatives. TOPMed. The Disparities Elimination through Coordinated Interventions to Prevent and Control Heart and Lung Disease Risk (DECIPHeR) Alliance. BioData Catalyst. The ability to analyze the functions of a single cell in its native environment has created the Human Lung Cell Atlas, an open-source resource of molecular and cellular maps of the organ.

With this kind of careful and strategic funding, we can accelerate our understanding of the activities and interactions of any cellular or molecular mechanism in the human body that contributes to HLBS diseases and disorders. We must fund initiatives that encourage slicing, dicing, and crunching data at levels both big and small to connect the dots between health and disease. Using this information, we will be able to assemble predictive models for any individual over the course of their lifetime. We will discover new targets for interventions that can unbend those unjust curves in outcomes that have been, up to now, resistant to budging.

People often say that if you have your health, you have everything. It's time to start thinking about and planning for what "having everything" might begin to look like for everyone.

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Highlights in Heart Health



Maternal Health

- Maternal morbidity and mortality have risen to crisis levels, an unacceptable indicator of health in the United States. According to the **Centers for Disease Control and Prevention**, more than 1,200 women died of causes related to pregnancy in the United States in 2021, the most recent year for which complete data are available. These numbers have steadily increased in the past few years, with 754 and 861 deaths in 2019 and 2020, respectively. Adverse pregnancy outcomes, including death, for Black women continue to be significantly higher than rates for other racial and ethnic groups. American Indian, Alaska Native, Native Hawaiian, and other Pacific Islander populations also experience increased risk.
- The **Early Intervention to Promote Cardiovascular Health of Mothers and Children (ENRICH)** initiative is a partnership with the Health Resources and Services Administration, the Administration for Children and Families, and certified local home visiting programs. The initiative promotes cardiovascular health in mothers and children up to 5 years old. ENRICH researchers work directly with communities that have a high burden of cardiovascular disease; these include communities of lower socioeconomic status, tribal nations, and people who live and work in low-resource areas. The initiative includes seven clinical centers around the country that investigate ways to lower the incidence of cardiovascular risk factors, including examining social determinants of health, obesity, hypertension, diabetes, and those at risk of developing preeclampsia or gestational diabetes.

“Maternal morbidity and mortality have risen to crisis levels, an unacceptable indicator of health in the United States.”

- NHLBI supports research that examines how to prevent or manage cardiovascular risk factors and disease in women across their lifespan. The **nuMoM2b Heart Health Study**, co-funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, is studying the effects of pregnancy complications on future cardiovascular health, including social factors that correlate with the future heart health of new parents, especially in communities of color.

Improving Access and Outcomes in Rural Populations

- According to the U.S. Census Bureau, approximately 60 million people, or **1 in 5 Americans**, live in rural areas. It is well-established that there is no higher burden of disease and disparities than in rural America. A recent study conducted by the HHS Healthy People initiative found that healthcare quality and access was the **top priority for health** in rural America. NHLBI strongly supports finding ways to bring care to where people are, which includes funding research to address health disparities experienced by rural populations.
- Lead exposure is known to harm the health of children by damaging the brain and nervous system and slowing growth and development. It has also been associated with increased risks for heart disease in adults. Exposure to elevated levels of lead and other metals has been disproportionately higher among American Indian communities. Through the **Strong Heart Family Study**, NIH-supported researchers found that adults who had the greatest reductions in blood lead levels saw their systolic blood pressure fall by about 7 mm Hg, an amount comparable to the effects of blood pressure-lowering medication. Public health policies and efforts implemented in recent decades have led to reduced lead exposure through paint, gasoline, water, plumbing, and canned items.
- In 2023, a study funded by NHLBI demonstrated that **parental history of obesity and smoking were associated with a higher risk of future cardiovascular disease** in offspring. However, some other parental modifiable risk factors (e.g., parental history of hypertension, diabetes, high cholesterol) were not associated with offspring's cardiovascular disease risk.



These findings suggest that the presence of parental obesity should prompt a focus on disease prevention in offspring of parents with cardiovascular disease and/or obesity. Future research should develop and test interventions before conception and during pregnancy to treat parental obesity and smoking to prevent obesity and cardiovascular disease risk in the offspring.

- A recent study by NHLBI-supported researchers used cardiovascular disease modeling to **estimate the long-term impact of adopting home blood pressure monitoring versus usual care on myocardial infarction, stroke, and healthcare costs**. Compared with usual care, adopting home blood pressure monitoring was estimated to reduce myocardial infarction cases by 4.9 percent and stroke cases by 3.8 percent, as well as saving an average of \$7,794 in healthcare costs per person over 20 years. Women, non-Hispanic Black people, and rural residents had more averted cardiovascular events and greater cost savings related to home blood pressure monitoring when compared with men, non-Hispanic White people, and urban residents. The study provides compelling evidence for healthcare systems and payers to support the broader implementation of this intervention.

Advancing Heart Disease Research

- In 2023, NIH supported studies related to postural orthostatic tachycardia syndrome (POTS), including a large **grant to the University of Texas Southwestern Medical Center** to further elucidate the disease. This study aims to improve scientists' understanding of POTS by comprehensively examining a large group of patients. It will be the first study to define the full picture of different POTS subtypes and the relationship between these subtypes, allowing clinicians to better evaluate and individualize treatment for POTS and guide future research. It is expected that the efforts will further stimulate interest in POTS research across a wider range of NIH Institutes, and NHLBI plans to seek participation from other these other Institutes.
- Hypertrophic cardiomyopathy (HCM) is a chronic disease and a well-recognized cause of sudden cardiac death in previously undiagnosed young individuals. There has been a long-standing, intense debate about whether vigorous intensity exercise is associated with an increase

in risk of ventricular arrhythmias in individuals with HCM. The prospective, multinational, **Lifestyle and Exercise in Hypertrophic Cardiomyopathy (LIVE-HCM) study** was designed to provide data to inform patient-clinician decisions around exercise. Results of this cohort study suggest that among individuals with HCM, vigorous exercise did not lead to a higher rate of death or life-threatening arrhythmias than among those exercising moderately or those who were sedentary. Given that individuals with HCM exercise less than the general population and report a higher prevalence of obesity, heightened anxiety, and reduced emotional well-being, these data may inform discussions between the patient and their expert clinician around exercise participation.

- As part of its broader commitment to research on heart and vascular diseases, NHLBI leads and supports research and programs on heart valve diseases in the United States and around the world. In December 2022, Congress authorized \$100 million over five years to NIH to support more research into the causes of and risk factors for valvular heart disease via the **Cardiovascular Advances in Research and Opportunities Legacy (CAROL Act)**. Through this funding, NHLBI is supporting expanded valvular heart disease research, including on risk factors for sudden cardiac arrest or sudden cardiac death from valvular heart disease, most commonly associated with mitral valve prolapse (MVP) and use of advanced imaging techniques. Research activities include basic science research aimed at addressing current knowledge gaps in valvular heart disease, development of artificial intelligence or machine learning techniques for comprehensive risk assessment and improved phenotypic characterization of individuals with MVP, and studies to establish ideal intervals for imaging and electrophysiological monitoring.
- Dilated cardiomyopathy is a type of heart disease in which the chambers of the heart thin and stretch, becoming enlarged. Current treatments aim to reduce symptoms and prevent further heart damage through medications or surgically implanted devices. Myocardial remodeling devices use a tether wrapped around a ventricle to reduce the chamber size and wall stress, but these surgeries have several significant limitations. NHLBI-funded researchers recently developed a new approach to reduce the circumference of the heart's left ventricle to overcome previous surgical limitations and increase survival rates,



an approach known as MIRTH (**myocardial intramural remodeling by transvenous tether**). The new method allows researchers to steer a guidewire through the coronary vein and uses EDEN (electrocardiographic radial depth navigation) electrocardiograms to direct the user to any location within the ventricular walls, increasing procedural accuracy and speed and allowing the user to integrate the tether within the heart's walls. MIRTH was performed on swine, resulting in positive measures of left ventricle performance, including increased contractility, efficiency, and reduced oxygen demand in cardiomyopathic animals. The technique may also have uses in the treatment of certain forms of acute myocardial infarction.

- NHLBI-funded scientists now utilize **innovative new stem cell-based technologies to grow highly complex 3D balls of heart cells** functioning much like a full-size heart — but in a dish. Termed organoids, these mini-organs develop from human stem cells and allow scientists to study the heart in ways they never have before. Isolating organoids from other organ systems will help researchers understand how organs such as the heart develop and function in both healthy and diseased states. Without other biological factors, such as blood, hormones, or signals from other organs, researchers can focus on elements like the genetic pathways that guide organ development or structural changes that happen during disease. This technology is a key step along the path to precision medicine.

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Dr. David Goff

✕ @NHLBI_HEARTDir

NHLBI's Division of Cardiovascular Sciences (DCVS) supports research to advance understanding of and interventions for promoting heart and vascular health across the lifespan. It also supports research aimed at preventing and treating pediatric and adult cardiovascular diseases, including heart attack, heart failure, stroke, and congenital heart disease. DCVS is led by David Goff, M.D., Ph.D.



Dietary Interventions to Reduce Cardiovascular Disease

- High-density lipoprotein (HDL) cholesterol, often called “good cholesterol,” removes extra cholesterol from the arteries by binding early-forming plaque and transporting it to the liver, which flushes it out of the body. Researchers recently **developed a quick and simple diagnostic test that measures HDL function** and have shown in clinical studies that their test can predict cardiovascular disease risk better than general levels of HDL cholesterol, which is currently used to assess such risk. The test is still years away from potential use in a medical setting, but it holds promise for physicians looking to gather additional information that could help inform their treatment decisions.
- Two NHLBI-supported diets, **Dietary Approaches to Stop Hypertension (DASH)** and **Therapeutic Lifestyle Changes (TLC)**, have collectively earned five top spots in the U.S. News & World Report's 2023 **“Best Diets”** rankings. To receive top rankings, a diet must be nutritious, safe, easy to follow, effective for weight loss, and protective against diabetes and heart disease. DASH, which supports overall heart health and helps lower blood pressure and cholesterol, ranked first in the “Best Heart-Healthy Diets,” “Best Diets for Diabetes,” and “Best Diets for Bone and Joint Health” categories. TLC, which focuses on lowering cholesterol, ranked first in the “Easiest Diets to Follow” and “Best Family-Friendly Diets” categories.
- A recent study explored the **impact of dietary sodium intake on blood pressure after one week on a low-sodium (500 mg) diet** compared with a high-sodium diet in middle-aged and elderly adults. The study found that, regardless of a person's starting blood pressure, a majority of individuals experienced an average 8 mm Hg reduction in systolic blood pressure after one week on a low-sodium diet, regardless of their hypertension status and use of antihypertensive medication.

Highlights in Lung Health



Increasing Odds of Successful Diagnostic and Therapeutic Procedures

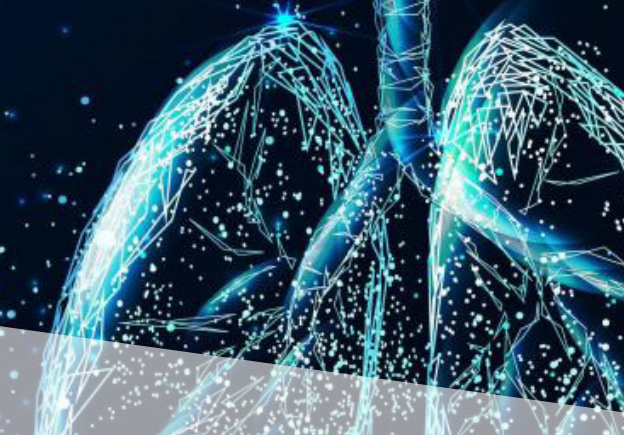
- Chronic obstructive pulmonary disease (COPD) remains underdiagnosed in primary care settings, particularly among African American patients and current or former smokers. Underdiagnosed patients experience impaired health and a greater risk of acute respiratory events and mortality. The diagnostic test for COPD is spirometry. However, disease symptoms of COPD (e.g., airway inflammation, airflow obstruction, emphysema, shortness of breath, exercise intolerance) are more complex and informative. Systematic failure to diagnose the disease may hamper understanding of disease manifestations and progression in populations more at risk of deprivation, as well as perpetuating health disparities. NHLBI-funded researchers have been working on **new tools** to mitigate missed COPD diagnoses. A recent NHLBI-funded study found that **participants with tobacco exposure and preserved spirometry (TEPS) and symptoms (symptomatic TEPS) had a similar rate of decline in lung function and similar incidence of COPD** defined by spirometry as those with TEPS without symptoms (asymptomatic TEPS), but participants with symptomatic TEPS experienced significantly more respiratory exacerbations over 2 to 10 years of follow-up.
- Some critically ill patients, such as those with ventilator-assisted pneumonia, are routinely prescribed empiric antibiotics with activity against anaerobic gut bacteria. Yet in other disease states and animal models, gut anaerobes are protective against pneumonia, organ failure, and mortality. Researchers studied **the effects of anti-anaerobic antibiotics on the risk of adverse clinical outcomes among critically ill patients receiving mechanical ventilation**, finding that the drugs are associated with increased mortality. The increased mortality, from both observational clinical data and animal modeling, is not completely explained by infections alone, and the protective effects of gut anaerobes are likely multifaceted. However, these results suggest that the widespread use of anti-anaerobic antibiotics in hospitalized patients should be reconsidered.
- Given their need for intense immunosuppressive regimens, lung transplant patients are at a significantly increased risk of infection and organ rejection soon after transplant.

Post-transplant monitoring typically involves routine bronchoscopies along with biopsies, especially during the first year post-transplant. In an effort to implement a less-invasive detection and monitoring approach during the COVID-19 pandemic, NIH researchers **tested levels of cell-free DNA (cfDNA) in the blood of lung transplant recipients**. Transplant recipients have cfDNA from both their own cells and the donated cells. Previous research has shown that the relative amounts of donor-derived cfDNA (dd-cfDNA) compared with recipient-derived cfDNA has the potential to be a useful biomarker of organ rejection, but this has not been tested as a method of routine clinical monitoring. NHLBI researchers periodically collected blood from patients within three years of their transplant and found that increased levels of dd-cfDNA indicated either rejection or infection of the donated tissue, suggesting that this method is a convenient and reliable way to monitor health. Additional testing is needed to establish clinical guidelines; the process may ultimately be used to monitor the health of other transplanted organs.

Exploring Biological Differences in Disease

- Puberty is a period marked by hormonal, metabolic, and immune changes. It also marks a shift in sex differences in susceptibility to asthma. Males have higher asthma prevalence in childhood, but starting from young adulthood, females are more affected. A recent NHLBI-funded study examined **pubertal development and leukocyte gene expression in a cohort of 163 children with asthma**; participants were between 10 and 17 years old when the study began and were followed annually for up to three

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years. The investigators used quantitative measures of asthma symptoms (e.g. chest tightness, coughing, wheezing) and severity to investigate whether changes in gene expression in immune cells during puberty were also associated with changes in disease status. In males, gene expression changes associated with puberty and age were inversely correlated with those associated with asthma symptoms and positively correlated with those associated with pulmonary function. Conversely, the opposite correlations were observed with gene expression changes linked to puberty and age in females. The study is the first to document these differences and also offers the first genome-wide characterization of patterns of gene expression changes in peri-pubertal males and females, adding to the knowledge base of epigenetic reprogramming of immune cells during puberty.

- Although studies have improved our understanding of idiopathic pulmonary fibrosis (IPF) disease development, effective therapeutics for IPF are still limited, and the molecular mechanisms of the development of fibrotic lesion remain poorly understood. Recently, a study in animal models showed that the circadian rhythm-regulating protein REV-ERB α , which is known for its roles in lung injury and repair, also **plays critical roles in the injury-induced fibrogenesis**. Interestingly, mouse lungs injured at night displayed exacerbated lung fibrogenesis. All these suggested a critical role for circadian rhythms in the development of IPF, and night shift workers could face a higher chance of fibrotic disease development. Therapeutics targeting REV-ERB α receptors might be one potential strategy to overcome the risk of fibrosis development.

Using Innovative Technology to Understand Lung Function

The human lungs face a slew of daily threats from airborne pathogens and pollutants and are also the site of many fatal diseases. Although procedures like magnetic resonance imaging (MRI) and computed tomography (CT) scans can shed critical light on what is going wrong when a patient has lung disease or illness, these techniques fail to provide the real-time information key to fully understanding the intricate workings of the lung at the cellular level. A new technological advancement called the crystal ribcage allows researchers to witness the moment-to-moment dynamics of respiration and circulation, the body's response to airborne pathogens, and what happens when tumor and immune cells move into the lungs. The system uses a ventilator and perfusion pump to keep the lung functioning outside the body while maintaining its natural shape. The **crystal ribcage** that encloses it then makes optical imaging of the organ possible, and researchers can capture everything from the entire lung to a single lung cell.

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Understanding the Causes and Consequences of E-Cigarette Use

- The use of electronic cigarettes (e-cigarettes, or vapes) has increased among adolescents and young adults in recent years. Use of these products produces aerosols that contain volatile chemicals, including flavorings and oxidant metals with known lung toxicity.
- It is important to understand why these young people start using e-cigarettes. Researchers recently **analyzed data from more than 12,000 participants in the 2019 National Youth Risk Behavioral Survey**, examining the association between stressors (e.g., bullying, sexual assault, depressive symptoms, weapon threats) and e-cigarette use in the month before the survey. There were significant links between participants with higher psychosocial stress scores and e-cigarette use. E-cigarette use was also positively associated with higher psychosocial stressor burden scores; the strength of the association is comparable to that of psychosocial stressors with combustible cigarette use.
- In a recent NHLBI-funded study, researchers evaluated the **associations of e-cigarette use with self-reported respiratory symptoms in a group of more than 2,000 U.S. teens** during a series of annual surveys across a four-year span. The participants were part of the University of Southern California Children's Health Study between 2014 and 2018. The odds of wheezing among the participants were 81 percent higher among those who had used e-cigarettes in the past 30 days than among those who had never vaped. Similarly, the odds of bronchitis-like symptoms were twice as high in users, while those of shortness of breath were 78 percent higher after adjustments for age, sex, race, and other factors. The findings remained statistically significant even after further adjustment for concurrent use of cigarettes and cannabis and secondhand exposure to e-cigarettes, cigarettes, and/or cannabis.

Dr. James Kiley

✕ @NHLBI_LUNGDir

NHLBI's Division of Lung Diseases (DLD) supports research on the causes, diagnosis, prevention, and treatment of lung diseases, including asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, acute lung injury, pulmonary complications of HIV/AIDS, pediatric lung diseases, and pulmonary fibrosis and other rare lung disorders. DLD is led by James Kiley, Ph.D.

“There were significant links between participants with higher psychosocial stress scores and e-cigarette use.

Improving Quality of Life for Those Who Use Supplemental Oxygen

- More than 1.5 million Americans use supplemental oxygen for a range of medical conditions. When asked, users consistently express a desire for a lighter, more portable oxygen supply that lasts longer and has flow rates that supply the appropriate amounts of oxygen for their needs. Through the **Air You Wear Challenge** competition, NHLBI aimed to broadly stimulate the research and development of processes and technologies designed to improve the accessibility, efficacy, and usability of supplemental oxygen. The competition had two phases: one that focused on the concepts and feasibility of solutions and a second 30-week phase during which teams developed working prototypes of their solutions. During the second phase, NHLBI helped finalists engage with subject matter experts from NIH, NHLBI's Catalyze Program, the National Science Foundation, the U.S. Food and Drug Administration (FDA), and the Centers for Medicare & Medicaid Services. In February 2023, NHLBI named three winning teams and one honorable mention. Since then, two teams successfully completed the competitive National Institute of Biomedical Imaging and Bioengineering Spring 2023 **Concept to Clinic: Commercializing Innovation (C3i) Education Program**, and all three winners have submitted small business applications to help conduct preclinical and/or clinical feasibility studies.





Highlights in Blood Health



Investing in a Multi-Pronged Approach to Address Sickle Cell Disease

- NHLBI was pleased to learn that on December 8, 2023, the FDA approved two gene therapies for the treatment of sickle cell disease in patients ages 12 years and older. NIH has long invested in basic genetics and genomics research, clinical trials, and translational medicine and social science studies to advance our understanding of this widespread illness and help develop effective therapies. However, these advances need to go hand in hand with scalable innovations that will ensure equitable access to life-altering care. To this end, NHLBI continues to engage in additional research endeavors that will minimize or eliminate potential risks that might be associated with such therapies.
- The **Cure Sickle Cell Initiative (CureSC)**, an NHLBI-led collaborative research effort, aims to transform the lives of many people affected by sickle cell disease by creating a collaborative, patient-focused research environment. CureSCi has identified and supports promising genetic therapies, which are currently being evaluated in multicenter clinical trials. Two therapies have been submitted to the FDA for review and approval by the investigational new drug sponsors; preliminary results from these clinical trials are expected within three to five years. CureSCi has focused on curative strategies that use genetic therapies to modify hematopoietic stem cells to prevent genetic mutations from making sickle-shaped red blood cells. This could make curative therapies available to a wider range of people with sickle cell disease. **One CureSC clinical trial** opened for enrollment in 2022, and enrollment in the second is expected to begin in the first half of 2024.
- In 2023, more than 20,000 people were diagnosed with acute myeloid leukemia (AML), a group of rare blood cancers associated with a five-year relative survival rate of 31.7 percent. One method of treatment for patients who are in remission is a stem cell transplant from a donor. Unfortunately, the disease recurs in approximately 30 percent of patients after allogeneic hematopoietic cell transplant and is the most common cause of post-transplant death. NHLBI researchers aimed to create a metric to determine whether a patient receiving an

allogeneic stem cell transplant was at increased risk for subsequent relapse and death. Research suggests that measuring the small number of cancer cells that remain post-treatment, or measurable residual disease (MRD), may provide information regarding risk for subsequent relapse and mortality. However, there is no standard method for AML MRD testing. Researchers used **targeted deep DNA sequencing** to look for disease-associated variants using the blood of AML patients. Among patients with AML in first remission before stem cell transplant, the presence of two genetic variants (FLT3-ITD or NPM1) above a certain level was associated with increased rates of relapse and worse survival compared with patients without variants detected. This strategy may also be applied to diagnose and understand the etiology of other chronic diseases, such as sickle cell disease.

Finding New Treatments for Blood Clotting Disorders

- Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is a rare genetic disorder that affects 1 in 5,000 people worldwide. Historically, there have been no effective medical therapies for HHT. People of all ages, sexes, genders, races, and ethnicities are affected and experience the problems associated with the disorder, some of which are life-threatening. The **Pomalidomide for the Treatment of Bleeding in HHT (PATH-HHT)** trial explored the use of an oral medication called pomalidomide, approved by the FDA for use in some cancers, for treating HHT symptoms at 11 research centers across the United States. NHLBI-funded researchers began to enroll adult patients with moderate to severe epistaxis in 2019; with the active support of the patient organization **Cure HHT**, researchers achieved a sufficient number of participating patients to conclude, earlier than expected, that pomalidomide is efficacious for treating HHT. The early conclusion of the trial for investigational drug efficacy is strong evidence that pomalidomide will become the first effective treatment option for patients with this rare disorder.
- Venous and arterial thrombotic disorders — such as pulmonary embolism, venous thromboembolism, myocardial infarction, and stroke — are major causes of global morbidity and mortality. Certain diseases and



conditions, including stroke, paralysis, chronic heart disease, high blood pressure, surgical procedure, or recent cancer treatment, can also raise a person's chances of thrombosis, commonly called a blood clot. Women who take hormone therapy pills or birth control pills, are pregnant, or are within the first six weeks after giving birth are also at higher risk for clotting disorders. People who smoke and older adults (age 60 and older) are also at increased risk. Improved therapeutic strategies that diminish bleeding risk due to anticoagulants and platelet antagonists would have a huge clinical impact. In a recent animal study funded by NHLBI, **researchers designed a new compound called macromolecular polyanion inhibitor (MPI-8)**. The compound prevented blood clots in mice, did not increase bleeding, and was tolerated well even at high doses. This finding may lead to significant changes in how doctors care for patients at risk for thrombosis without raising the risk of bleeding.

Improving the Lives of Those With HIV

- As people living with HIV age, they are at higher risk of various chronic medical conditions, including hypertension and other forms of cardiovascular disease. NHLBI's **Heart, Lung, and Blood Co-morbidities Implementation Models in People Living with HIV (HLB-SIMPLe)** program is a collection of research studies co-funded by the NIH Fogarty International Center. Researchers from African and American universities are working together with governments, community partners, and health facilities to test strategies for delivering effective hypertension detection, prevention, and treatment initiatives to affected individuals. There are currently studies in Botswana, Mozambique, Nigeria, South Africa, Uganda, and Zambia. These distinctive implementation clinical trials are designed to test and estimate costs for strategies to foster

sustainable and scalable uptake of effective interventions in routine clinical, public health, and community settings. These implementation studies will help ensure that all people living with HIV can access the care they need to maintain their health and well-being — beyond just medications to suppress HIV. Moreover, the ongoing methodological training opportunities supported by this program will increase the late-stage translation research workforce available to move discoveries into practice.

Improving the Availability and Safety of the Nation's Blood Supply

- NHLBI started the **Recipient Epidemiology and Donor Evaluation Study (REDS)** program in 1989 to protect the nation's blood supply from threats, improve the benefits of transfusions, and reduce the risks of transfusions. After 30 years, now in its fourth phase, REDS aims to evaluate and improve the safety and availability of the nation's blood supply, as well as the safety and effectiveness of transfusion therapies across the lifespan, with a new focus on understudied populations, including newborns, children, and pregnant women. This phase involves a seven-year multicenter program in the United States and Brazil and is charged with conducting epidemiologic and laboratory studies in blood donors and transfusion recipients.
- NHLBI funds the **BLOODSAFE** program, the goal of which is to enhance the availability and delivery of safe blood for transfusion into patients from low- or lower-middle-income countries in sub-Saharan Africa. BLOODSAFE supports projects that develop and test effective and sustainable strategies to increase the number of safe blood donors. It also aims to improve the **quality and safety of blood supplies** and enhance blood delivery to patients in need, especially in remote settings.

Dr. Julie Panepinto

✕ @NHLBI_BLOODir

NHLBI's Division of Blood Diseases and Resources (DBDR) leads research on the causes, prevention, and treatment of congenital and acquired blood diseases. The program also helps ensure the safety of the world's blood supply and supports stem cell biology and new gene- and cell-based therapies to repair and regenerate human tissues. DBDR is led by Julie Panepinto, M.D., M.S.P.H.





Highlights in Sleep Health

Studying Sleep Health Across the Lifespan

- In a recent NHLBI-funded study, researchers **gathered data from wearable devices, similar to Fitbits or Apple Watches, from more than 1,000 women during pregnancy.** Feeding the data into a new artificial intelligence algorithm, the researchers were able to detect even minute changes in sleep and physical activity during pregnancy. The algorithm also used the data to build a “clock” that was able to predict how far along a pregnancy was. In typical pregnancies, as the women advanced toward later-stage pregnancy, they became less physically active and their sleep more disrupted. However, some women’s sleep and activity patterns changed on a faster timeline relative to how far along they were in their pregnancies, with those women sleeping less and becoming more sedentary earlier in their pregnancies. The study found that these individuals were more likely to have a preterm birth. The results suggest that continuous monitoring of sleep and activity throughout pregnancy may enable doctors to better support patients who could be at higher risk of preterm birth.
- Researchers recently found that surgical removal of the tonsils and adenoids in children with snoring and mild breathing problems during sleep appears to **improve their sleep, quality of life, and blood pressure a year after surgery.** The study is believed to be the first large randomized trial to address the effects of adenotonsillectomy on children with mild sleep-disordered breathing (SDB). During the trial, half the participants received an adenotonsillectomy, and the other half received supportive care without surgery, including standardized education on healthy sleep and lifestyle and referral for untreated allergies or asthma. Researchers then evaluated neurodevelopmental, behavioral, health, and sleep-related outcomes in both groups, using measurements of attention and executive function, which

“Continuous monitoring of sleep and activity throughout pregnancy may enable doctors to better support patients who could be at higher risk of preterm birth.

includes a set of cognitive skills that help children manage everyday activities. Sleep outcomes were measured by polysomnography, a standard sleep test that measures breathing, heart rate, eye movement, and other factors. Secondary results showed several beneficial changes in the surgery group: less daytime sleepiness, reduced SDB, less snoring, fewer behavioral problems, better quality of life, and lower blood pressure. The children treated with surgery were also less likely to show disease progression into full-blown sleep apnea.

- According to a recent study, **chronic insufficient sleep can increase insulin resistance in otherwise healthy women,** with more marked effects in postmenopausal women. Previous studies have shown that sleep restriction can elevate risk for conditions such as cardiovascular disease, hypertension, and disordered glucose metabolism, which can lead to insulin resistance and type 2 diabetes. However, many of those studies were done only in men or focused on short-term, severe sleep restriction. The current study enrolled only women and sought to determine whether a prolonged, mild restriction of sleep — a reduction of just 1.5 hours each night — increased women’s blood glucose and insulin levels. The findings highlight the importance of adequate sleep in minimizing the risk for type 2 diabetes, which can develop when the body fails to effectively use a key hormone, insulin, to maintain healthy blood sugar levels.



Developing New Diagnostic Tools

Obstructive sleep apnea (OSA) is one of the most prevalent chronic sleep disorders, estimated to affect up to 30 million people in the United States. It is associated with an increased risk for cardiovascular disease and mortality. The primary diagnostic tool for OSA is the **apnea-hypopnea index (AHI)**, which measures the average number of times per hour breathing either partially or fully stops during sleep; however, the AHI has limitations. NHLBI-funded researchers have developed a **more accurate tool for diagnosing OSA**, using a metric called ventilatory burden (VB), that effectively captures breath-by-breath reductions in airflow and isolates the purely ventilatory burden of the disorder. The researchers leveraged data from four different NIH-funded cohorts to derive the normative range of VB from analysis of more than 34 million breaths. The team then assessed the relationship between the degree of upper-airway obstruction and VB and, using a unique algorithm, the relationship between VB and mortality risks, including cardiovascular disease and hypertension. Their method effectively assessed the severity of OSA and predicted mortality associated with cardiovascular diseases,

potentially making it a more successful diagnostic tool than the AHI. The team now plans to use an artificial intelligence algorithm along with the VB measure to identify patients who will benefit from continuous positive airway pressure treatment.

“OSA is one of the most prevalent chronic sleep disorders, estimated to affect up to 30 million people in the United States. It is associated with an increased risk for cardiovascular disease and mortality.”

Dr. Marishka Brown

The National Center for Sleep Disorders Research (NCSDR) supports research on the causes, diagnosis, prevention, and treatment of sleep disorders. NCSDR is led by Dr. Marishka Brown, Ph.D.





Highlights in Translation Research and Implementation Science



Working with Communities to Create Meaningful Change

- In July 2020, NHLBI and the National Institute on Minority Health and Health Disparities (NIMHD) started the **Community Engagement Alliance (CEAL)** to establish a research approach that ensured the participation of racial and ethnic minority communities in COVID-19 vaccine research trials that were underway. Moving forward, CEAL's successes provide a foundation for broadening its mission to address the host of health disparities that plague the very same communities. CEAL teams are located in 21 regions across the country, leverage existing relationships and partnerships, and recently expanded activities to address state and local concerns, including social determinants that challenge health within specific communities.
- NHLBI is leveraging this community engagement research platform to support scientific initiatives that address other major public health issues, including maternal health and the impact of climate on health in areas across the country. NHLBI is utilizing the lessons learned through CEAL to enhance research within American Indian, Alaska Native, Asian, Native Hawaiian, and Pacific Islander communities and is partnering with other NIH programs to address other research priorities, like the National Human Genome Research Institute's interest in improving understanding of and participation

in genomic research. Through meaningful community engagement, CEAL has the potential to transform discovery into health impact and reduce disparities.

- The **Maternal Health Community Implementation Project (MH-CIP)** is a community-driven initiative that uses evidence-based interventions, such as regular blood pressure readings, to help reduce cardiac risk factors before and during pregnancy. Through this program, NHLBI supports four community coalitions, consisting of research organizations and community partners, to engage communities and pilot-test the implementation of proven interventions in vulnerable populations. In addition to involving community coalitions, MH-CIP includes patient advocacy groups and subject matter experts in both governance and guidance roles.
- Because of CEAL's success, the program's funding has also been sustained in order to leverage it as a comprehensive research platform to address health disparities. Additional scientific initiatives have already been incorporated, and other NIH Institutes are also leveraging CEAL to address other major issues of public health. In addition to MH-CIP, examples include the **Implementing a Maternal Health and Pregnancy Outcomes Vision for Everyone (IMPROVE)** initiative and the **Climate Change and Health Initiative**. CEAL has become a powerful, strategic research resource that enables NHLBI and other NIH Institutes to work alongside and within communities to meet their missions.

NHLBI is leveraging this community engagement research platform to support scientific initiatives that address other major public health issues, including maternal health and the impact of climate on health in areas across the country.



Leveraging Data Science to Advance Health Disparities Research

- Heart and lung disease are the leading causes of illness and death in the United States, and the disease burden is unequal across groups defined by race, ethnicity, sex, gender, and socioeconomic status. Numerous programs have been proven to reduce heart or lung disease, but too often they are not put into practice in the communities where they are most needed. In September 2020, the **Disparities Elimination through Coordinated Interventions to Prevent and Control Heart and Lung Disease Risk (DECIPHeR) Alliance** was created, consisting of seven implementation research centers throughout the country.
- This seven-year (2020–2027) cooperative agreement has two phases. The first phase (2020–2023) was exploratory, including community engagement activities such as establishing community advisory boards and working

with high-burden communities to articulate locally relevant implementation strategies. The second phase, which began in 2023, builds on connections made and lessons learned in the first phase to test implementation strategies for optimally and sustainably delivering evidence-based multilevel interventions in clinical practice and community settings to reduce or eliminate cardiovascular and pulmonary health disparities.

“Heart and lung disease are the leading causes of illness and death in the United States, and the disease burden is unequal across groups defined by race, ethnicity, sex, gender, and socioeconomic status.”

Dr. George Mensah

✕ @NHLBI_TRANSLATE

NHLBI's Center for Translation Research and Implementation Science (CTRIS) supports research addressing both domestic and global health disparities and inequities and provides training and career development opportunities in these areas. CTRIS is led by George Mensah, M.D., FACC.





This document honors the legacy of **Dr. Claude Lenfant**, NHLBI's Director from 1982 to 2003. His years of dedication to research on heart, lung, blood, and sleep health paved the way for today's advances.

1928-2023

