# 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

**Dr. Gary H. Gibbons, M.D.**
Director, National Heart, Lung, and Blood Institute (NHLBI)

Over the past two years, we asked individuals and organizations with an interest in the NHLBI research mission to help refresh and update our **Strategic Vision** goals to ensure they remain timely, relevant, and reflective of the latest, most promising directions in biomedical research. Overall, the process affirmed that the institute was on the right path with its goals and aspirations. But two issues repeatedly emerged in our discussions: the need to adopt and leverage new scientific opportunities and emerging technologies, and to develop cross-disciplinary teams and partnerships. By continuing to invest in research across a broad range of scientific approaches, with an emphasis on the opportunities inherent in cross-disciplinary research, we can cultivate unique environments that encourage the development of precise, targeted treatments — especially for chronic conditions — that are available to every American, no matter where they live. Here's how we intend to get there.

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Since its inception, the NHLBI has understood the importance of population studies and the examination of how lifestyle and neighborhoods affect health and well-being. Leadership at what was then known as the National Heart Institute launched the **Framingham Heart Study** (FHS) in 1948 in Massachusetts to gather heart-related health information from a small, stable cohort of people to identify common factors or characteristics that contribute to cardiovascular disease (CVD). One of the first long-term cohort studies of its kind, the study has now encompassed three generations of participants and is considered the crown jewel of epidemiology. Thanks to the FHS, we learned that most CVD is influenced by modifiable risk factors such as smoking, high blood pressure, obesity, high cholesterol levels, and physical inactivity. The NHLBI has furthered its legacy of longitudinal cohort studies by looking south to Jackson, Mississippi, with the **Jackson Heart Study,** and west to Tribal communities in America's heartland with the **Strong Heart Study**.

The NHLBI's commitment to population studies goes far beyond cardiovascular health. Our studies collect data on sickle cell disease through the **Cure Sickle Cell Initiative**, lung diseases via the **Prevention and Early Treatment of Acute Lung Injury (PETAL) Network**, and sleep data using the **National Sleep Research Resource** within the **Hispanic Community Health Study/Study of Latinos**. The NHLBI will continue to gather important health-related data to create and make accessible to countless researchers rich, multivariate data resources designed to yield valuable insights into diseases and disorders across our research portfolio.

The NHLBI has worked for the past several years to establish the infrastructure needed to conduct exciting new analyses made possible through super intelligence and machine learning (SI/ML). The NHLBI's pioneering **Trans-Omics for Precision Medicine (TOPMed)** analytic platform, launched in 2024, integrates whole genome sequencing and other omics data such as metabolic profiles and epigenomics, with molecular, behavioral, imaging, environmental, and clinical data from our population-based studies. The NHLBI's **BioData Catalyst®** makes TOPMed data available in a cloud-based repository ecosystem that gives researchers raw data as well as the analytic tools, applications, and workflows needed to manipulate and build upon those data.

To guide the NHLBI in this space, we created the TOPMed Super Intelligence Coordinating Center, which acts as a central hub for coordinating research initiatives and supporting collaborations among scientific experts in the use of SI/ML methods to analyze and interpret the vast amounts of rich and varied data available. Additionally, we recently announced an SI Working Group within the Advisory Council to advise our research community about how to integrate SI technologies into our mission.

Finding ways to combine and mine disparate datasets is now within our capacity. It will be vital to help us understand chronic disorders, whose origins are multifactorial and may have as much to do with lifestyle, health and diet choices, and environmental influences as they do with inherited predispositions. Now that data can be shared widely through cloud-based platforms, we are opening the playing field to broader groups of scientists, including those from smaller research institutions whose limited resources may impede their participation in cutting-edge research.

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Expanding access to data offers opportunities for previously untapped talent to bring a wider range of points of view to the research enterprise.

Developing new treatments, especially for chronic disorders, is always top of mind for the NHLBI. But having implementation strategies to ensure that the right treatment gets to the right person at the right time is critical to public health. Not all communities have benefitted equally from turning scientific advances into better health care, including Tribal nations, people who live in rural areas, and those with a lower socioeconomic status. For example, heart disease is the leading cause of death in the United States. However, there is a lack of available diagnostic tools to monitor and treat diseases and disorders in certain populations, such as those living in rural areas. One study found that providing **home blood pressure monitors** to people with high blood pressure helped to prevent heart attacks and costly hospital stays. The development of a **low-field MRI** — a much cheaper, portable, and more readily available imaging tool — has provided another way to bring diagnostic capabilities to people living in areas with limited health care facilities.

The NHLBI's **RURAL (Risk Underlying Rural Areas Longitudinal) Cohort Study** has established **mobile examination units** with the aim of getting all the functions of an urban primary care office into the most remote areas of the country. This means that more people will know their health status and be able to better monitor any conditions they may have.

The NHLBI has always used every tool and method available to discover better ways to diagnose, treat, and ultimately cure diseases and disorders in our research portfolio. The NHLBI will continue to fund cutting-edge research that advances every aspect of care related to heart, lung, blood, and sleep disorders, always aiming to improve health across lifespans and generations. The research that starts in a laboratory or with a digital model may someday lead to breakthroughs in therapeutics and treatments for patients in clinical settings. The excitement that comes with seeing benefits in research participants from these breakthroughs accelerates advancement toward widely beneficial treatments for patients and public health. An exciting future in biomedical research lies further down the road. We are well on our way.

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## Leadership Changes

The NHLBI has cultivated a remarkable leadership team. In 2024, we had some changes to our leadership, including the retirement of stalwart Dr. Jim Kiley, who served as the Director of the Division of Lung Diseases for 24 years. He brought key perspectives, invaluable experience, and significant dedication during his 40 years of public health service.

**James P. Kiley, Ph.D., M.S.**

Another change to our leadership was the appointment of Dr. David Goff, formerly the Director of the Division of Cardiovascular Diseases, as the NHLBI's first Deputy Director for Precision Medicine and Data Science. This new role will be critical to our efforts to harness cutting-edge data science approaches to drive advancements in precision prevention, detection, and treatment of heart, lung, blood, and sleep conditions.

**David C. Goff, Jr., M.D., Ph.D.**

# Highlights in Heart Health

## Understanding heart health during and beyond pregnancy

The **Nulliparous Pregnancy Outcomes Study (nuMoM2b) Heart Health Study**, with support from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, studies the effects of pregnancy complications on future cardiovascular health. A 2024 analysis of data from this study found that **those with obesity early in pregnancy** are at significantly higher risk of adverse pregnancy outcomes, such as gestational hypertension, gestational diabetes, and preeclampsia. Another analysis from the nuMoM2b cohort found that mothers who experienced adverse outcomes during their first pregnancy had higher predicted 30-year risk of cardiovascular disease when measured **2 to 7 years after the pregnancy**. The risks compounded in cases with multiple adverse outcomes. These analyses show that pre-pregnancy health can affect pregnancy outcomes and future heart health.

## Delving into the science of cholesterol

Heart disease is **twice as high** in American Indian adults compared to the general U.S. population. However, the prevalence of elevated cholesterol, or fat levels, in the blood — a condition called dyslipidemia, a known risk factor for heart disease — in American Indian adolescents and young adults has been difficult to determine. A recent NHLBI-supported study found that more than 70 percent of American Indian young adults (between 20 and 39 years old) and 50 percent of American Indian teens (between 15 and 19 years old) **have dyslipidemia**, which, in some cases, is linked to plaque buildup in blood vessels and cardiovascular events, such as heart attack and stroke. The findings came from a 19-year review of data from more than 1,400 participants in the Strong Heart Family Study, part of the **Strong Heart Study**, which is the largest study of cardiovascular health outcomes and risk factors among American Indian adults. These findings highlight the importance of cholesterol screenings, education, and interventions, especially for teens and young adults who may be more likely to have underlying cardiovascular risks.

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In 2024, NHLBI scientists made a significant breakthrough in understanding how low-density lipoprotein-cholesterol, or LDL-C, builds up in the body. The researchers were able to show for the first time **how the main structural protein of LDL binds to its receptor** — a process that starts the clearing of LDL from the blood — and what happens when that process is impaired. Using an advanced imaging technique called cryo-electron microscopy, the researchers were able to see the entirety of the structural protein of LDL when it bound to the low-density lipoprotein receptor (LDLR).

Then, with super intelligence-driven protein prediction software, they were able to model the structure and locate the known genetic mutations that result in increased LDL. The researchers found that many of the mutations that mapped to the location where LDL and LDLR connected were associated with an inherited condition called familial hypercholesterolemia (FH). They found that FH-associated variants tended to cluster in particular regions on LDL. By knowing precisely where and how LDLR binds to LDL, the researchers may be able to target those connection points to design new drugs for lowering LDL in the blood.

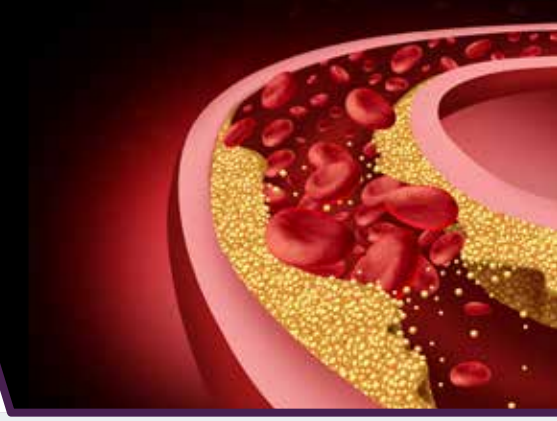
## Changing clinical guidelines for people living with HIV

Decades of research and advances in HIV treatment have **drastically reduced HIV-related complications and deaths**. As people with HIV live longer, premature heart disease and other chronic conditions have emerged as leading causes of morbidity and mortality, contributing to persistent gaps in lifespan between people living with HIV and the general population. However, there have been few interventions to help prevent adverse cardiovascular events in this population. The **Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) study** began in 2015 and enrolled 7,769 participants between 40 and 75 years old. The trial is co-funded by the National Institute of Allergy and Infectious Diseases and was conducted in 12 countries in Asia, Europe, North America, South America, and Africa. A planned interim analysis of study data found that participants who took **pitavastatin calcium**, a statin used to lower cholesterol, reduced the risk of major adverse cardiovascular events by 35 percent compared with those who received a placebo. These findings led the Department of Health and Human Services (HHS) Panel for the Use of Antiretroviral Agents in Adults and Adolescents to change its **clinical guidelines** to recommend that statin therapy be used as the primary prevention tool for cardiovascular disease in people living with HIV.

## Healing the heart

Treating cardiac disease requires new innovations to prevent and treat tissue damage. However, **healing heart damage** is extremely difficult due to the need for specialized cells that can both form new tissue and integrate with the pre-existing vasculature of the heart. Vascular endothelial cells (cells that line the inside of the heart and blood vessels) have various roles necessary for development, function, and regeneration, but they are not readily available at sites of injury in the body. To address this, researchers used cardiac fibroblasts (cells that produce connective tissue) from mice to modify the expression of the *Sox17* and *Erg* genes (which encode proteins that control gene expression), effectively instructing them to mature to be similar to endothelial cells. Researchers confirmed that the reprogrammed cells had similar properties as endothelial cells by examining various behaviors in culture. Then they injected the reprogrammed cells at the injury site of a mouse directly after a cardiac injury, and found that hearts treated with the cells healed with less scarring than untreated hearts. This method improves on previous attempts to develop endothelial-like cells because it produces cells that are more analogous to the body's mature endothelial cells, requires less cell modification, and works on both neonatal and adult cells. While this procedure has only been performed on mice thus far, this study demonstrates the potential for using reprogrammed cells to heal damaged heart tissue. Additional studies are needed to continue understanding these processes, and could possibly pave the way to creating therapeutic strategies for repairing injured tissue.

In December 2022, Congress enacted the **Cardiovascular Advances in Research and Opportunities Legacy (CAROL) Act**, which authorized $100 million over 5 years to the National Institutes of Health (NIH) to expand research into the causes of, risk factors for, and treatment of valvular heart disease (VHD). Through the CAROL Act, the NHLBI is supporting expanded VHD research in a range of areas, from determining risk factors for sudden cardiac arrest or sudden cardiac death from VHD to developing advanced imaging techniques. For example, CAROL Act funds supported a supplement to the **Percutaneous or Surgical Repair In Mitral Prolapse And Regurgitation for ≥60 Year-olds (PRIMARY)** clinical trial. The trial compares the long-term effectiveness and safety of two intervention strategies to repair faulty mitral valves in the heart that don't fully close, which allows blood to leak backward in the



heart. One intervention is surgical, which is more invasive but may lead to more complete repair; the second procedure (transcatheter edge-to-edge repair) is minimally invasive and doesn't require open-heart surgery. The goal of the PRIMARY trial is to determine which VHD treatments best target abnormalities that put patients at risk of irregular heartbeats and sudden death. These trials are part of the NHLBI's broader commitment to lead and support research and programs on heart valve diseases in the United States and around the world.

Atherosclerosis, a major cause of cardiovascular disease, is characterized by the narrowing of arteries due to the development of lesions and plaques along artery walls. The exact cause of this chronic inflammatory disease is unknown, but it is thought to be dependent on several factors. In a new study, researchers discovered that the smooth muscle cells (SMCs) that line arteries can transition into new cell types at sites of atherosclerotic lesions and **develop traits similar to cancer cells**. Using a combination of molecular techniques in mouse models and tissue samples from patients with atherosclerosis, researchers characterized the mechanisms that drive the SMCs to transition into cancer-like cells. They found substantial similarities with cancer cells when examining the converted SMCs of atherosclerotic plaques, including increased rates of DNA damage, signaling pathways (chemical reactions in a cell that allow it to interact with its environment) associated with cancer, and an increased likelihood of genetic mutations during cell division. Researchers treated mice that had atherosclerosis with the anti-cancer drug niraparib, which targets DNA damage; it showed potential for preventing and treating atherosclerosis. These findings could pave the way for the use of anti-cancer drugs to counteract the tumor-like mechanisms that drive the buildup of plaque in arteries, the major cause of cardiovascular disease.

*...this study demonstrates the potential for using reprogrammed cells to heal damaged heart tissue.*

## Improving MRI quality

Magnetic resonance imaging (MRI) is a common diagnostic tool that uses noninvasive radio waves and a powerful magnet to produce detailed images of the internal structures of the human body. Conventional MRIs collect diagnostic images over a fixed amount of time, optimized to provide acceptable image quality for most patients. However, cardiac imaging tends to have variable results, and image quality can depend on several factors (for example, a patient's size, movement, irregular breathing, or if the imaging coils are improperly positioned). Insufficient image quality can result in longer exams or require the patient to return for a repeat exam. In 2024, researchers in the NHLBI's Division of Intramural Research MRI Technology Program designed a method to computationally **assess image quality of a phase-contrast MRI** in real-time and to adjust imaging acquisition time accordingly. Image quality is periodically evaluated; once the quality requirement is met, the acquisition stops itself. This assessment combines novel computer vision programs with modern image-reconstruction techniques — specifically an open source medical image reconstruction framework called **Gadgetron** that was co-developed at the NHLBI. When implemented, the team observed a wide range of automatic stopping times in volunteer patients, revealing the value of individualized acquisition time for consistent image quality. Future research will likely focus on defining specific criteria for when to automatically stop imaging and investigating how the method could be applied to other types of MRIs.

## Examining the effects of heat on the heart

Extreme summer heat and heat waves have become common over the last several decades. While many people are able to adapt to the increased temperatures, some groups are particularly vulnerable (for example, children, older adults, people who work outdoors, communities of color). People with existing cardiovascular disease are at especially high risk. A recent study used statistical modeling to project a 162 percent increase in **excess cardiovascular deaths due to heat** by 2050. Older adults and non-Hispanic Black adults were projected to be particularly affected, with 3.5 and 4.6 times increased risk, respectively. As the United States experiences extreme summer heat, it will be essential for communities to effectively monitor vulnerable members for signs of cardiovascular distress.

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**Dr. Gina Wei (Acting)**
**https://www.linkedin.com/showcase/nhlbi-heart/**

The 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 Acting Director Gina Wei M.D., M.P.H.

# Highlights in Lung Health

## Using technology to map, model, and mend the lung

*The LungMAP Consortium recently reported the creation of the first molecular map of human newborn lung cells...*

A detailed, comprehensive understanding of organs and tissues is critical to identify novel treatment strategies tailored to each individual. The **Molecular Atlas of Lung Development Program (LungMAP)** uses cutting-edge technology and precision medicine to create an open source atlas of the lung that includes both molecular and cellular maps of the organ. The LungMAP Consortium recently reported the creation of the **first molecular map of human newborn lung cells** by using sophisticated laboratory techniques that determine the specific genes that are turned on in individual cells. Data from molecular maps of mouse lungs were also used to estimate the maturation states of the human cells. The findings from this study provide valuable insights into normal human lung development and will provide a foundation for the discovery of therapeutic targets for lung diseases.

Gas exchange in the lung occurs within tiny sacs, called alveoli, that contain highly specialized cell types. One type, called AT1 cells, flatten and connect to form a thin, continuous air-blood barrier that allows for the diffusion of oxygen and carbon dioxide, respectively, into or out of the surrounding blood vessels. Despite their critical role in normal lung function and disease progression, relatively little is known about **human AT1 cells**, in part due to technical challenges when attempting to isolate the cells and grow them in the laboratory. In a recent NHLBI-supported study, scientists sought to define a set of laboratory conditions where they could induce human adult stem cells to take on characteristics similar to AT1 cells. The researchers achieved this by using molecular techniques to force precursor cells to produce an active form of a protein called YAP and ensure its presence in the nucleus. The resulting cells flattened and connected to form thin sheets that could act as a barrier — as normal human AT1 cells do in alveoli. These reprogrammed adult stem cells will serve as a valuable new research tool for modeling human AT1 cell-based lung structures and functions in the laboratory, which could lead to advances in understanding normal lung biology and disease.

Cystic fibrosis (CF) is a life-shortening disease that is caused by genetic mutations in the *CFTR* gene. This disease affects many organs of the body, especially the lungs. In a recent study, NHLBI researchers optimized gene editing technology to **correct a gene mutation** that causes approximately 85 percent of CF cases. The technique, called prime editing, is a variation of CRISPR technology that makes precise and targeted modifications to DNA with minimal off-target errors. The mutation is particularly challenging to correct by prime editing. But researchers optimized the process by using six recent advances in prime editing technology, including improving the "guide RNA" that targets the correct gene. Researchers were able to increase successful gene correction efficiency from initial levels of 0.5 percent in cultured cells to 58 percent in immortalized bronchial

epithelial cells and 25 percent in patient-derived airway epithelial cells. In the patient cells, researchers also observed restored function of the CFTR protein to greater than 50 percent compared to cells without gene correction — similar to what is achieved with the best current therapeutic drugs. This study shows that prime editing is a promising method for future gene editing and treatment of CF. It also provides an optimization method that may be applied to other challenging genetic diseases.

## Addressing critical needs in sepsis care

Human blood contains three main components: red blood cells, white blood cells, and plasma. Red blood cells carry hemoglobin, a protein that helps transport oxygen to different parts of the body. In sepsis, red blood cells become injured and die at abnormally high rates, releasing cell-free hemoglobin into the blood. The body becomes overwhelmed and cannot remove this excess hemoglobin, which may lead to organ damage. The NHLBI funds the research network **Prevention and Early Treatment of Acute Lung Injury.** One of the network's clinical trials, **Acetaminophen in Sepsis: Targeted Therapy to Enhance Recovery** found that intravenous acetaminophen reduced sepsis patients' risk of organ injury or developing acute respiratory distress syndrome, a serious condition that allows fluid to leak into the lungs. Previously, acetaminophen (a common ingredient in pain relief medicines such as Tylenol) had been shown to block the harmful effects of cell-free hemoglobin on the lungs, which are at major risk of injury during sepsis. These findings show great promise for patients who become critically ill with sepsis.

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## Predicting risks for lung transplant patients

Lung transplantation is a life-saving intervention for many individuals, but this treatment risks serious complications, including infection and donor organ rejection. An estimated one-third to one-half of transplant patients develop treatable acute cellular rejection (ACR) in the first year after transplantation. ACR is a risk factor for death as well as development of chronic lung allograft dysfunction (CLAD), a progressive syndrome that is the most common cause of mortality and morbidity in lung transplant recipients. However, the link between ACR and CLAD was previously not well understood. NHLBI researchers studied patients who had lung transplants in order to identify **who was likely to develop CLAD after ACR**. They also evaluated levels of cell-free DNA (cfDNA) in recipients' blood, a helpful biomarker of patients' lung health. When a cell dies, it releases pieces of DNA into the bloodstream, collectively known as cfDNA; transplant recipients have cfDNA from both their own cells and the donated cells. An increase in the relative amounts of donor-derived cfDNA (dd-cfDNA)

indicates either rejection or infection of the donated tissue. In the study, researchers followed 188 transplant patients and found that 80 patients developed ACR over the course of the study. The researchers found that patients with a high concentration of dd-cfDNA at the time of their ACR diagnosis had an increased risk of both CLAD and death, independent of the severity of their ACR episode. These findings may have important implications for designating risk in patients with ACR and identifying who might benefit from additional preventative measures. They may also lead to additional insights into the pathophysiology of CLAD development.

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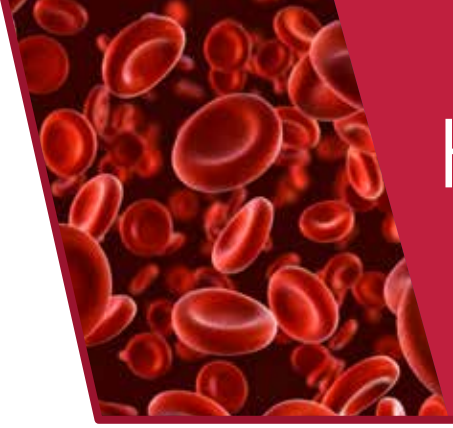
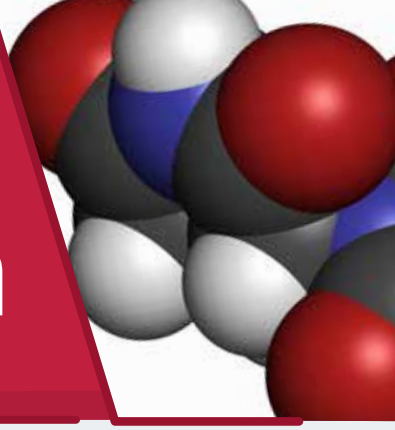
**Dr. Gustavo Matute-Bello (Acting)**
**https://www.linkedin.com/showcase/nhlbi-lung/**

The 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 Acting Director Gustavo Matute-Bello, M.D.



# Highlights in **Blood Health**



## Searching for cures to rare blood disorders

Hemophilia A is an inherited bleeding disorder marked by low levels or a lack of a certain clotting factor, which leads to unexpected and uncontrolled bleeding. Because the condition is associated with the X chromosome, it is far more prevalent in males than in females. It is estimated that as many as **33,000 males** are living with the condition in the United States. In November 2023, the NHLBI established the **Hemophilia A Analytical Cohort Research Program** as part of a public-private partnership to study the condition. The observational cohort study will follow mother-baby pairs where the mother has the severe hemophilia A genotype and the baby has the condition. The study will examine the development of anti-clotting antibodies, immune response to the condition, and causes of bleeding in females with the condition. Researchers will share these data in an online analytical portal, allowing the wider research community to learn from their findings.

Hereditary Hemorrhagic Telangiectasia (HHT), also known as **Osler-Weber-Rendu syndrome**, is a rare genetic disorder that affects 1 in 5,000 people worldwide. Malformed blood vessels cause excessive bleeding from the nose (epistaxis) and gastrointestinal tract, requiring medical treatment and blood transfusions and impairing quality of life. Historically, there have been **no effective medical therapies** for HHT. People with HHT experience problems associated with the disorder, some of which are life-threatening. The **Pomalidomide for the Treatment of Bleeding in HHT** trial explored the use of an oral medication called pomalidomide — approved by the U.S. Food and Drug Administration (FDA) to treat some cancers — to treat HHT symptoms at 11 research centers across the United States. Starting in 2019, the study's researchers enrolled adults who have HHT with moderate to severe epistaxis and require iron infusions or blood transfusions. With the active support of the patient organization, **Cure HHT**, the study achieved a sufficient number of participating patients to conclude, earlier than expected, that **pomalidomide is effective to treat HHT**. The early conclusion of the trial is strong evidence that pomalidomide may become an effective treatment option for patients with this rare disorder.

> *...the study achieved a sufficient number of participating patients to conclude, earlier than expected, that pomalidomide is effective to treat HHT.*

The **Cure Sickle Cell Initiative** is an NHLBI-led collaborative research initiative to accelerate the development of genetic therapies to cure sickle cell disease (SCD). The initiative aims to transform the lives of many people affected by SCD — an estimated 100,000 Americans and more than 20 million worldwide — by creating a collaborative, patient-focused research environment. In a widely celebrated announcement in December 2023, the FDA approved **two new curative gene therapies** for SCD. While it is still too early to tell, the new gene therapies can be transformative for people with this disease, but these treatments will not work for everyone and are currently cost-prohibitive. It is essential that advances go hand in hand with scalable innovations that will ensure widespread access to life-altering care. The NHLBI is **conducting clinical trials** for other potential curative therapies. Additionally, researchers are using the **Repurposing, Focused Rescue, and Accelerated Medchem (ReFRAME)** drug repurposing library, which looks at drugs that are already FDA-approved and have the potential to treat SCD pain in a cost-effective way.

## Addressing hypertension during pregnancy for patients with sickle cell disease

Hypertensive disorders occur in approximately 1 in 7 pregnancies in the United States. Elevated blood pressure during pregnancy may cause organ damage, preterm birth, and low birth weight. However, it was not previously known whether typical threshold measures of **hypertensive disorders during pregnancy** (blood pressure readings higher than 140/90 Hg after 20 weeks of gestation) were appropriate for women with SCD. An NHLBI-funded study found that those existing thresholds were, in fact, **too high for accurate diagnosis in those with SCD**. Researchers recommended a lower blood pressure threshold for these patients, considering the potential adverse events associated with hypertensive disorders during pregnancy.

## Examining the underpinnings of hematopoiesis

Hematopoiesis is the process of producing the cells that make up the blood, including red blood cells, immune cells, and platelets. Every type of blood cell is derived from hematopoietic stem cells, which primarily reside in bone marrow. Scientists recently developed a technique to **visualize the process of hematopoiesis** in the skeleton by genetically labeling six types of hematopoietic progenitor cells in mice. Progenitor cells come from hematopoietic stem cells but are more specialized and will only divide into their designated type of blood cells. Fluorescently labeling these cells allowed researchers to track different kinds of blood cells as they were being made in the bones of a living mouse, thereby mapping the anatomy of hematopoiesis. They found a sophisticated arrangement of different progenitor cells within the bones. Researchers then investigated the effects of common hematopoietic injuries, observing a resilient system that consistently produced cells, regardless of injuries, and used specific sites within the bone marrow to rapidly adjust specific types of blood cell output when under stress. The stress response varied across the skeleton, suggesting that certain bones may be specialized to respond to specific injuries. This study provides new tools and methods needed to study blood production in a live, native environment and helps defines hematopoietic anatomy under normal and stressful conditions.

*Scientists recently developed a technique to visualize the process of hematopoiesis in [the skeletons of living mice]... suggesting that certain bones may be specialized to respond to specific injuries.*

Understanding embryogenesis, the process of building a complex multicellular life from a single fertilized egg, is key to understanding many components of human diseases, including congenital diseases. However, very early stages of human development are extremely difficult to study. While some models of human embryonic development exist, none have been able to replicate the complex process of early hematopoiesis, the formation of blood cell components. Recently, NHLBI-funded researchers used induced, adult-derived pluripotent stem cells to create a **model of early human post-implantation development** that has many self-organizing cellular programs similar to embryogenesis, including a process similar to hematopoiesis. This model presents an easy-to-use, high-throughput, reproducible, and

scalable platform to investigate aspects of human development and blood formation at early stages. It will provide a useful human-based model for drug testing and disease modeling, in addition to helping scientists understand how to better create personalized regenerative therapies and stem cells.

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## Developing a new generation of treatment for bleeding after trauma

Uncontrolled bleeding after trauma is ideally treated with a transfusion of blood that contains platelets, which encourage clotting and stop the bleeding. However, donor platelets are frequently limited because they are difficult to store and transport and risk bacterial contamination. In a recent study, NHLBI researchers developed **synthetic, platelet-like particles** that can be stored under a variety of conditions and do not have any observed contamination risks. These synthetic particles are made from hydrogel nanoparticles, which allow them to mimic natural platelets. Additionally, they target the injured area with antibody fragments that bind fibrin, a protein naturally produced at wound sites. The synthetic platelets were tested in both rodent and pig models of trauma; they enhanced clotting and promoted healing after clotting. Importantly, the synthetic platelets did not cause a measurable allergic or immune system reaction in the pigs. These promising results support further study of the use of these therapeutics and may help improve patient outcomes through the development of new treatment options for emergency medicine.

**Dr. Julie Panepinto**
**https://www.linkedin.com/showcase/nhlbi-blood**

The 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

## Understanding the relationships among sleep, age, and diabetes

According to the Centers for Disease Control and Prevention, more than one-third of U.S. adults report that they do not get the recommended 7 or more hours of sleep per night, which may cause significant health problems. In a recent NHLBI-funded study co-funded by the National Institute of Diabetes and Digestive and Kidney Diseases, adult women between 20 and 75 years old who were at risk of heart disease and diabetes were randomly assigned to 6 weeks of either 7 to 9 hours of regular sleep per night, or restricted by 1.5 hours of sleep to determine how long-term limited sleep affects glucose metabolism. The study found that getting just 6.2 hours of sleep per night (the median for people in the United States who don't get enough sleep) impaired insulin sensitivity; this was particularly true for post-menopausal women. These results show that 7 or more hours of sleep per night on a consistent basis should be considered as part of a behavior change strategy to prevent diabetes.

A lack of quality sleep is a risk factor for obesity, and obesity is known to be a risk factor for poor sleep. Certain populations are at higher risk of obesity, such as those who are non-Hispanic Black or Hispanic, as well as people with lower incomes. NHLBI-funded researchers examined the relationship between obesity and sleep. They found that energy metabolism, which generally is lowest at night during sleep, is lowest during the day and while awake in people with obesity. This means that people with obesity showed heightened glucose intolerance during the day and produced less insulin at night, which may not align with biological energy needs. This research highlights new approaches, as described in the NIH Sleep Research Plan, that focus on circadian rhythms and chronobiology to prevent chronic disease and poor health outcomes.

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## Examining how air quality affects sleep

For children, limited sleep is linked to **stress, depression, anxiety, and impaired memory and learning**; it has also been associated with **worse daytime blood pressure**. Many environmental factors also affect sleep quality, such as light, noise, temperature, and safety. Recently, researchers studied **indoor air quality** in the homes of children between 6 and 12 years old in the Boston, Massachusetts, area. They compared levels of indoor fine particulate matter to sleep disordered breathing (for example, snoring and sleep apnea). After accounting for other factors, such as economic status and seasonality, children who slept in an environment with high levels of indoor fine particulate matter were 3.5 times more likely to have sleep disordered breathing compared to children in environments with low levels of indoor fine particulate matter. These findings suggest that poor indoor air quality in urban housing environments affects sleep quality and may contribute to disparities in sleep quality, even among children.

## Studying the effects of obstructive sleep apnea

Researchers recently found that people with obstructive sleep apnea (OSA) who slept fewer than 7 hours per night had a **higher risk of death** compared to those who sleep longer. OSA is linked to heart disease, diabetes, and other health problems. As part of the **Sleep Heart Health Study**, researchers included data for more than 2,500 people with OSA with a median of 11.7 years of follow-up. The researchers identified 688 all-cause deaths among the participants. Those who slept fewer than 7 hours had a significantly higher risk of all-cause death compared to those sleeping at least 7 hours. Experts recommend that adults sleep between 7 to 9 hours a night. Further studies are needed to identify the underlying causes in the link between OSA and risk of death, and to determine whether extending sleep in people with OSA and short sleep duration might improve their health.

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The National Center on 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 in, with, and for communities

In July 2020, the NHLBI and the National Institute on Minority Health and Health Disparities launched the Community Engagement Alliance (CEAL). Since then, CEAL has been dedicated to promoting participation in research as well as community engagement practices that support optimal health for all Americans. CEAL teams work with nearly 1,200 community-based organizations, among other groups, to conduct formative research in many settings, including local clinics and rural communities. CEAL also funds the **Health Knowledge Monitoring and Response System Pilot Program**, which leverages local community partnerships to understand information needs and ensure access to relevant, timely, and accurate health information. In 2024, CEAL received the **HHS Culturally and Linguistically Appropriate Services Champion Award** in the category of Outstanding Sustainability, which leverages local community partnerships to understand information needs and ensure access to relevant, timely, and accurate health information.

In addition to its own community engagement work through CEAL, the NHLBI has created a consultative resource for NIH-funded research teams that are interested in this type of work. The resource, called the **Community Engagement Alliance Consultative Resource (CEACR)**, was founded through a partnership between the University of Pittsburgh and Community-Campus Partnerships for Health. CEACR's primary goal is to help researchers build trust in the communities where they work. To accomplish this, CEACR hosts webinars and personalized sessions for individual teams. Since 2022, CEACR has completed more than 30 private consultations and reached more than 300 researchers via its webinars.

> *CEAL teams work with nearly 1,200 community-based organizations, among other groups, to conduct formative research in many settings, including local clinics and rural communities.*

## Redefining HIV as a chronic disease

Significant progress in the treatment of HIV over the last several decades has led to higher survival rates; overall, people with HIV are living longer. As a result, the challenges have now shifted to long-term diseases, such as coronary heart disease, chronic obstructive pulmonary disorder, and chronic anemia. Many studies have shown that people with HIV have a much higher risk of developing heart, lung, and blood conditions, and that these conditions may develop earlier in people with HIV compared to the general population. The NHLBI-funded **ImPlementation REsearCh to DEvelop Interventions for People Living with HIV (PRECluDE) Consortium** is conducting implementation research in communities where people who are living with HIV experience obstacles connecting to, participating in, and consistently accessing care to control their blood pressure and cholesterol. Some of the methods include nurse-led continua of care, trauma-informed behavioral change education, behavioral economics, and the systematic review of electronic health records. The consortium's work will provide an evidence-informed basis for improving quality of life for people living with HIV.

## Supporting chronic disease research around the world

The World Health Organization estimates that of the nearly **1.3 billion adults between 30 and 79 years old with hypertension globally**, approximately two-thirds live in low- and middle-income countries (LMICs). Unfortunately, only around one-third of people with hypertension in LMICs are aware that they have the condition, and less than 10 percent have their **blood pressure controlled**. The NHLBI, through NIH, is an associate member of the **Global Alliance for Chronic Diseases**, which invests in research on chronic diseases such as hypertension, cancer prevention, diabetes, and mental health. As a country, the United States also has high rates of elevated blood pressure; some of our discoveries can be shared internationally, and global findings may inform possible strategies to improve U.S. public health. To that end, the NHLBI has funded three hypertension-related research programs: the **NaSS study in Nigeria, the CATCH study in Jamaica and Colombia**, and the **ANDES study in Peru**. NaSS aimed to reduce sodium intake in Nigerian adults, nearly half of whom have hypertension. Researchers in Colombia and Jamaica worked in communities to implement a team-based care strategy to control hypertension. And researchers in Peru are conducting a multi-pronged health education campaign on the risks of hypertension and diabetes in vulnerable populations. These NHLBI-funded programs will help raise awareness and improve control of hypertension to help people with the condition lead healthy and productive lives.

### Dr. George Mensah

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

National Heart, Lung, and Blood Institute