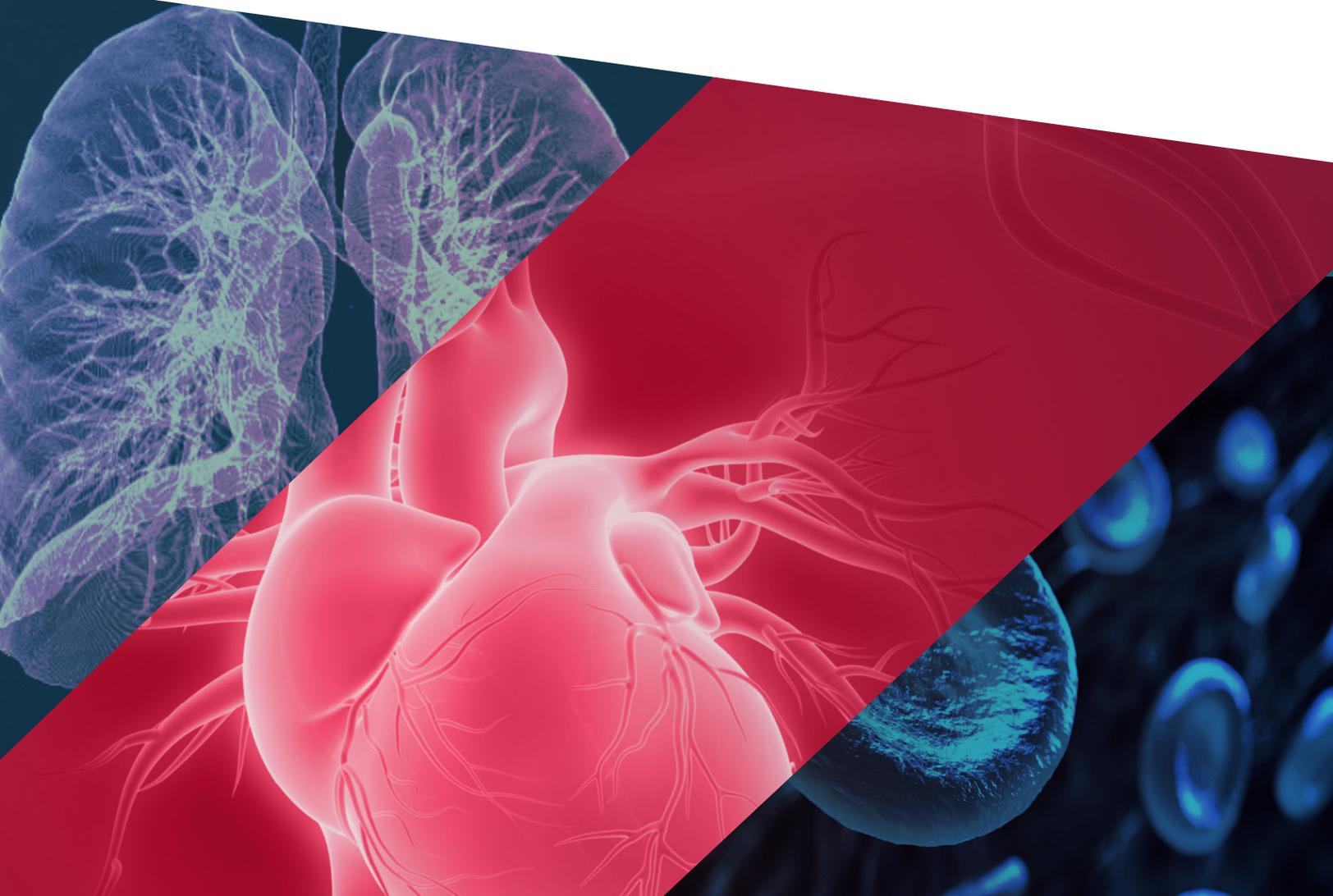


ADVANCING

Heart, Lung, Blood, and Sleep Research



National Heart, Lung,
and Blood Institute

January 2021 | WWW.NHLBI.NIH.GOV

Director's Message

Advancing Heart, Lung, Blood, and Sleep Research



NHLBI Director Gary H. Gibbons, M.D.

The COVID-19 pandemic has reinforced the importance of the public health mission that the NHLBI and its partners serve and support to foster lifesaving science. Since reaching the United States in January 2020, the novel coronavirus SARS-CoV-2 has infected more than 23 million people, causing over 394,000 deaths as of January 2021. Some of us have lost loved ones to COVID-19. All of us have had to adjust the way we live and work and care for our loved ones.

The NHLBI has taken an all-hands-on-deck approach to address the pandemic, especially to understand risk factors that affect susceptibility and outcomes in COVID-19, and to develop treatments to stop its punishing effects on the heart, lungs, and blood vessels. Within the biomedical field, the NHLBI community has stretched its capacity for innovation — conducting lifesaving research at an unprecedented speed in a new, largely virtual workspace. COVID-19 has also laid bare the health inequities that have long affected communities of color in the United States. Cases, hospitalizations, and deaths from COVID-19 remain higher among African Americans, American Indians/Alaska Natives, Hispanics/Latinos, and Asian Americans and Pacific Islanders, compared with whites. These disparities have prompted swift, trans-NIH efforts to reduce the burden of COVID-19 on our hardest-hit populations through community-engaged research.

As we enter 2021, the NHLBI will continue to be nimble in our response to the scientific demands of the pandemic, even as we remain committed to the research priorities outlined in our **Strategic Vision**. Despite the toll of COVID-19, we are optimistic that our research and engagement efforts will “pay it forward” and help us overcome or even avert future public health challenges for years to come.

NHLBI COVID-19 Efforts

Key to the NHLBI's response has been swiftly leveraging our existing assets, including our talented investigators around the country and at the NIH. For example, in July, we mobilized our clinical trial networks to refocus a portion of their efforts on COVID-19 studies under the **Collaborating Network of Networks for Evaluating COVID-19 and**

Therapeutic Strategies (CONNECTS). CONNECTS includes more than 30 such networks supporting trials that can adapt quickly as promising new treatments emerge. And in September, we launched the **Community Engagement Alliance (CEAL) Against COVID-19 Disparities**, which aims to reach the hardest-hit communities with vital information about COVID-19 research, prevention, testing, and treatment. Long before COVID-19, our staff and extramural investigators had been working to address health disparities in these communities, effectively laying the foundation for CEAL. Additional efforts are described in the COVID-19 fact sheet included in this “2021 Advances” report.

Meeting NHLBI Strategic Vision Objectives 1, 2, 7

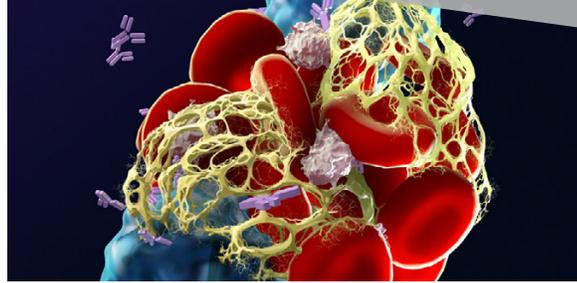
For a complete list of objectives, visit: www.nhlbi.nih.gov/about/strategic-vision.

NHLBI Data Science Initiatives

We have continued to invest in the **Trans-Omics for Precision Medicine (TOPMed)** program, which has amassed nearly four petabytes of de-identified genomic, clinical, imaging, and environmental data from more than 161,000 participants in 80 diverse studies, including the NHLBI's landmark Framingham Heart Study, the Jackson Heart Study, the Hispanic Community Health Study/Study of Latinos, and many others.

TOPMed and other datasets are now available to qualified researchers through a secure, cloud-based platform called the **BioData Catalyst**. The BioData Catalyst includes tools for analyzing large datasets and sharing results among users in real time. It also provides a virtual collaborative workspace that makes data findable, accessible, interoperable, and reusable to all qualified researchers, the vast majority of whom lack their own data science resources.





Meeting NHLBI Strategic Vision Objective 8

For a complete list of objectives, visit: www.nhlbi.nih.gov/about/strategic-vision.

Supporting the Next Generation

The NHLBI has continued to prioritize investigator-initiated research and to provide targeted support for early-stage investigators (ESIs). Under our funding and operating guidelines, we have consistently set a higher payline for ESIs than for established investigators, which has enabled us to maintain ESI success rates near 30 percent. In 2019 and 2020, we developed new opportunities for ESIs and trainees to conduct research on heart, lung, and blood disorders. For example, our **BioData Catalyst Fellows Program** is

supporting more than 30 uniquely skilled individuals, many of them ESIs, to explore this new data ecosystem and refine it for future users.

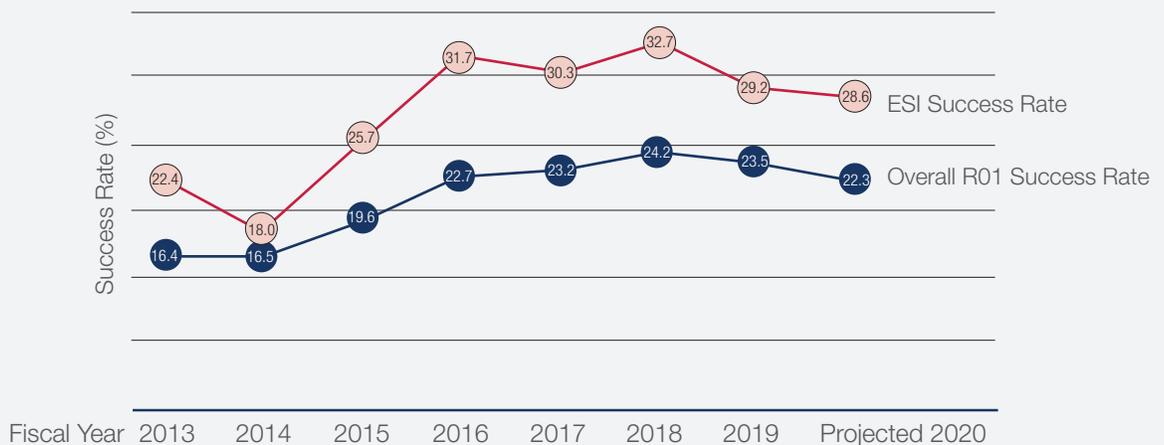
The NHLBI also has initiated Challenge competitions to encourage researchers from diverse fields and different career stages to address pressing needs in heart, lung, blood, and sleep research. For example, the NHLBI **Big Data Analysis Challenge in heart failure** called upon researchers to mine data from past and ongoing heart failure studies in an effort to define subtypes of adult heart failure, and identify new subtype-specific approaches to managing the disease.

As we begin a new year, we continue to address the high rates of maternal morbidity and mortality among American women of all ages, and look for ways to move evidence-based interventions into communities where the burden of chronic disease is high. Our efforts in these and other areas are described elsewhere in our “2021 Advances” report.

Throughout this difficult time, I have been heartened by the resolve and ingenuity of the NHLBI community, and grateful

for close collaboration with our partner organizations. The NHLBI has relied on your expertise and activities to keep policymakers, researchers, patients, and the public informed about the latest NHLBI findings and broader NIH efforts to fight this pandemic. We appreciate your tireless efforts to keep us informed about the challenges your communities face, as well as your suggestions for the best ways to remain responsive. Thank you for your partnership in this extraordinary time.

Success Rates for NHLBI R01 Applications: 2013 to 2020



Left masthead image: NHLBI scientists found that ~50% of inpatients with COVID-19 have autoantibodies (purple) that activate immune cells (blue), inducing them to release net-like structures (yellow) that trap red blood cells and cause clots. Credit: Yogendra Kanthi, M.D., NHLBI, and Erina He, NIH Medical Arts

The Impact of COVID-19 on Heart, Lung, and Blood Systems

The NHLBI's Research Strategy to Understand and Treat COVID-19

The COVID-19 pandemic touches nearly all aspects of the NHLBI research portfolio. People with chronic diseases such as certain lung conditions, cardiovascular disease, obesity, sickle cell disease, or diabetes are known to be at higher risk for severe outcomes from infection with SARS-CoV-2, the virus that causes COVID-19. Moreover, COVID-19 affects multiple organs, with potentially life-threatening effects on the heart, lungs, and blood/blood vessels.

A Responsive, Robust Research Strategy

Bolstered by \$103.4 million in additional support from the Coronavirus Aid, Relief, and Economic Security (CARES) Act, the NHLBI rapidly mobilized to support research on COVID-19 by leveraging existing NIH-funded studies and infrastructure.

The NHLBI's COVID-19 response has focused on research aiming to:

- Understand the factors that influence risk and resilience for infection and for severe illness
- Understand how COVID-19 attacks the body's vital organs
- Develop therapies to stop the disease and reduce the potential for long-term health effects
- Test behavioral, social, and community-based interventions to improve disease prevention and recovery
- Examine the prevalence of SARS-CoV-2 antibodies in the blood, their ability to protect against future infection, and their utility as a therapeutic

Integral to the NHLBI's approach is the **Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies (CONNECTS)**, which brings together more than 30 clinical trial networks to identify potential therapies for COVID-19. CONNECTS allows researchers to test a variety of interventions simultaneously, easily share their data, and quickly identify the most promising treatments.

Masthead image: A highly magnified image of SARS-CoV-2 virions (red) produced by human airway epithelial cells in the lungs. Credit: Camille Ehre, Ph.D., University of North Carolina School of Medicine.

COVID-19 Clinical Trials

- **The Outcomes Related to COVID-19 treated with hydroxychloroquine among In-patients with symptomatic Disease (ORCHID) Study** evaluated an anti-malaria drug in hospitalized COVID-19 patients. There was no evidence of benefit.
- **The Colchicine Coronavirus SARS-CoV-2 (COLCORONA) trial** is evaluating the gout drug colchicine to see whether it limits inflammation in the heart and lungs in patients with COVID-19.
- **The Clinical Trial of COVID-19 Convalescent Plasma of Outpatients (C3PO)** is evaluating the use of convalescent plasma to treat nonhospitalized patients with mild COVID-19.
- **The Accelerating COVID-19 Therapeutic Interventions and Vaccines 3 (ACTIV-3) trial** is evaluating whether monoclonal antibodies and other immune-modulating therapies can improve recovery in hospitalized patients.
- **ACTIV-4** includes three trials evaluating whether anticoagulants or antiplatelet drugs can reduce life-threatening blood clots in patients with various stages of COVID-19.
- **The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE)** is evaluating complications of SARS-CoV-2 infection among people living with HIV and whether statins can help.

COVID-19 Observational Studies

- **The COVID-19 Observational Study (CORAL)** is examining the pathobiology and outcomes among more than 3,000 adults hospitalized with COVID-19 for up to six months after discharge.
- **The Collaborative Cohort of Cohorts for COVID-19 Research (C4R)** is combining existing diverse population studies to look at long-term COVID-19-related outcomes and factors that affect risk and resilience.
- **The Recipient Epidemiology and Donor Evaluation Study (REDS)**, an NHLBI program that monitors threats to the U.S. blood supply, has launched **REDS RESPONSE** to analyze the prevalence of SARS-CoV-2 antibodies (seroprevalence) among blood donors in six cities with high COVID-19 rates, setting up a framework for a nationwide seroprevalence survey.





Establishing Partnerships to Address Health Disparities

COVID-19 has taken its toll on almost every community, but some groups have been hit especially hard. Compared with whites, there are higher rates of COVID-19 among Asian Americans, Blacks, Latinos, American Indians/Alaska Natives, and Pacific Islanders. These groups also tend to be at higher risk for severe illness. Research increasingly shows that **social determinants of health** — conditions in the places where people live, work, and play — have a large impact on these disparities.

Building on their history of engaging communities in research, the NHLBI and the National Institute on Minority Health and Health Disparities (NIMHD) are co-leading the NIH **Community Engagement Alliance (CEAL) Against COVID-19 Disparities Initiative**. CEAL connects researchers to trusted community-based organizations, minority professional societies, and faith-based organizations in communities impacted by COVID-19. Together, they will address misinformation, work to increase preventive practices (e.g., wearing face masks, hand washing), and ensure the inclusion of people of color in trials of vaccines and new treatments. More information and resources are at [covid19community.nih.gov](https://www.covid19community.nih.gov).

In addition, the NHLBI participates in the **NIH Rapid Acceleration of Diagnostics in Underserved Populations (RADx-UP) initiative**, which is developing community-based projects to increase reach, access, uptake, and impact of COVID-19 testing among hard-hit populations.

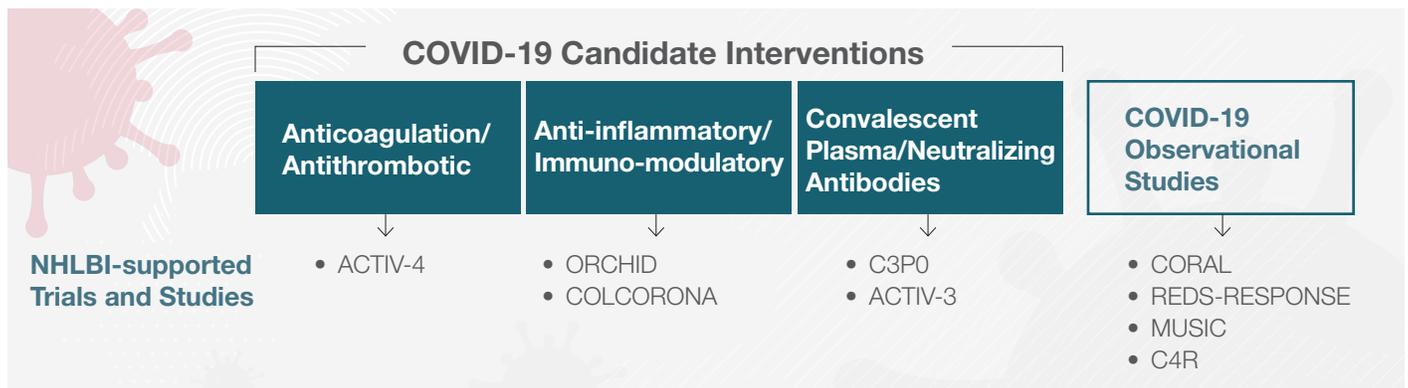
Evolving Data, Evolving Research

The NHLBI remains poised to adapt and shift its focus as new information about the virus emerges. For example, we now know that some children infected with COVID-19 later develop a severe inflammatory response that requires hospitalization, with most experiencing cardiovascular complications.

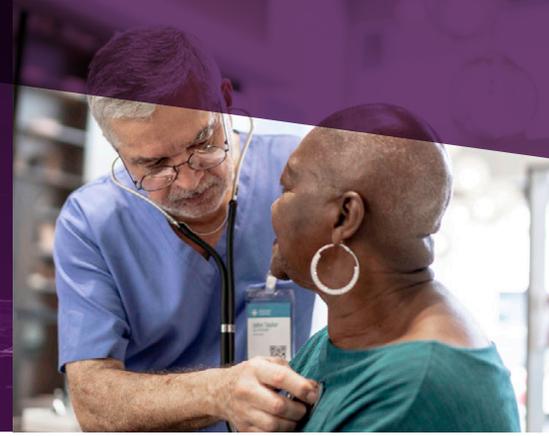
In response, the NHLBI is partnering with other NIH Institutes to leverage multiple networks, such as the NHLBI's 29-hospital Pediatric Heart Network, to gain a better understanding of this rare **multisystem inflammatory syndrome in children (MIS-C)**. Through the 5-year **Long-Term Outcomes after the Multisystem Inflammatory Syndrome In Children (MUSIC)** study, clinicians will collect data from pediatric hospitalizations and medical visits to guide diagnoses and treatment. This aggregated information will support long-term evidence-based management guidelines for MIS-C.

In addition, some people who have had COVID-19 — and even asymptomatic SARS-CoV-2 infection — have continued to struggle with symptoms months later. Those with **post-acute COVID-19** have developed serious conditions such as heart failure or myocarditis (heart inflammation), stroke, progressive lung disease such as pulmonary fibrosis, or kidney failure. Contingent on sufficient resources, the NHLBI plans to leverage the C4R study, as well as our data science platforms, to understand what causes these lingering health impacts of COVID-19 and to intervene early to prevent them.

The NIH is also developing a COVID-19 clinical trial data hub, which is integrating existing databases — including those housed within the NHLBI's BioData Catalyst — that contain clinical, lab, and imaging data from COVID-19 patients. The data hub will enable more rapid responses to COVID-19 surges, as well as to subsequent emerging threats.



Highlights in Heart Health



Supporting Clinical Trial Networks

NHLBI-supported clinical trial networks are testing interventions, devices, and procedures to improve treatment of heart and vascular diseases.

- The **International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA)** compared two common approaches for managing ischemic heart disease among more than 5,000 patients. About half were treated with invasive procedures, including stenting, bypass surgery, and medications. The other half were treated with lifestyle changes and medications in lieu of surgery. After three years of follow-up, both approaches produced similar outcomes, but patients with chest pain who received the more invasive approach had better symptom relief and quality of life.^{1,2} These results will help inform treatment decisions for patients and their physicians.
- The NHLBI renewed its commitment to the **Cardiothoracic Surgical Trials Network (CTS)**, which brings together scientists and surgeons across the country to move research from the proof-of-concept stage into clinical trials. As part of the CTS, the Anticoagulation for New-Onset Post-Operative Atrial Fibrillation After CABG (PACES) trial is evaluating whether adding blood thinners to antiplatelet therapy can further reduce the risk of heart attack and stroke in patients who develop AFib after undergoing coronary artery bypass surgery.³

Leveraging New Technologies

New **cardiac imaging** tools and technologies are enabling clinicians to more rapidly diagnose and treat patients with a number of heart disorders.

- An NHLBI-funded team recently developed a technique called electromechanical wave imaging (EWI) that uses

ultrasound to see electrical waves moving through the heart with each beat. In a study of 55 patients, the researchers found that EWI pinpointed the origin for 96 percent of arrhythmias (abnormal heartbeat) — an important step in treatment. In contrast, standard electrocardiography had a success rate of 71 percent.⁴

- NHLBI intramural investigators developed a new type of magnetic resonance imaging (MRI) called quantitative myocardial perfusion mapping that can improve identification of patients with heart disease who have two or more blocked coronary arteries.⁵
- **3D printing technologies** are being developed that can repair damaged heart or vascular tissue, or be used to engineer bioartificial hearts. NHLBI-supported researchers designed a 3D bioprinting device to build complex tubular networks that mimic human vascular networks.⁶ Others have printed 3D collagen, the main protein in the body's fibrous tissues, and then embedded cells within it to produce several complex heart tissues, including capillaries, valves, and ventricles.⁷
- A new approach using **artificial intelligence** to examine ultrasound images of the heart (echocardiogram) can identify subtle signs of heart disease that may be missed by expert eyes.⁸

Addressing Heart Failure

The NHLBI is working to improve outcomes for those living with **heart failure (HF)**. In HF with preserved ejection fraction (HFpEF), which accounts for about 50 percent of all HF cases but for which there are limited treatment options, the heart contracts normally but fills with blood too slowly. **HeartShare** is a new initiative to conduct large-scale analysis of clinical, laboratory, and imaging data from patients with HFpEF to characterize mechanisms of disease and identify potential therapeutic targets.





Meeting NHLBI Strategic Vision Objectives 2, 4, 5

For a complete list of objectives, visit: www.nhlbi.nih.gov/about/strategic-vision.

Improving the Heart Health of Young Women and Mothers

Adverse health conditions and death from pregnancy and delivery are more common in the United States than in other developed countries, with women of color two to four times more likely than white women to die from a pregnancy complication. Cardiovascular disease is the leading cause of pregnancy-related death, and an increasing number of young American women have one or more cardiovascular risk factors, such as obesity, sleep apnea, or high blood pressure. Moreover, blood pressure elevation occurs earlier in life and progresses more rapidly in women, compared with men.⁹ For these reasons, we need to address **maternal morbidity and mortality** throughout a woman's life, not just during her reproductive years.

The NHLBI supports studies that aim to understand the impact of sex as a biological variable and to improve women's heart health across the lifespan.

- The **Chronic Hypertension and Pregnancy (CHAP)** trial is examining the safety and effectiveness of using medication to treat mild hypertension in pregnancy, treatment of which is typically deferred unless a woman has severe high blood pressure.¹⁰ Enrollment of 2,400 women of diverse race and ethnicity from 62 sites across the United States is underway, and study results are expected by the end of 2021.
- A study of 1.4 million maternal and newborn records found that children born to mothers who had **sleep apnea** during pregnancy were more likely to have birth defects, be admitted to the neonatal intensive care unit, or require resuscitation at birth.¹¹ A trial funded in part by the NHLBI is now investigating whether treating sleep apnea during pregnancy can improve outcomes for both mother and newborn.¹²
- In 2021, the NHLBI is inviting applications for clinical research on **Early Intervention to Promote Cardiovascular Health of Mothers and Children (ENRICH)**. The goal is to determine whether cardiovascular health interventions delivered through home visiting programs can enhance maternal and early childhood outcomes, especially in low-resource or underserved communities.

Dr. David Goff

 @NHLBI_HEARTDir

The NHLBI's Division of Cardiovascular Sciences (DCVS) supports research on the causes, prevention, and treatment of cardiovascular diseases, including heart attack and heart failure, high blood pressure, stroke, arrhythmias, adult and pediatric congenital heart disease, cardiovascular complications of diabetes and obesity, and other cardiovascular diseases. DCVS is led by David Goff, M.D., Ph.D.



¹ pubmed.ncbi.nlm.nih.gov/32227755/

² pubmed.ncbi.nlm.nih.gov/32227753/

³ clinicaltrials.gov/ct2/show/NCT04045665

⁴ pubmed.ncbi.nlm.nih.gov/32213631/

⁵ pubmed.ncbi.nlm.nih.gov/33011115/

⁶ pubmed.ncbi.nlm.nih.gov/31048486/

⁷ pubmed.ncbi.nlm.nih.gov/31371612/

⁸ pubmed.ncbi.nlm.nih.gov/32269341/

⁹ pubmed.ncbi.nlm.nih.gov/31940010/

¹⁰ clinicaltrials.gov/ct2/show/NCT02299414

¹¹ pubmed.ncbi.nlm.nih.gov/31981755/

¹² clinicaltrials.gov/ct2/show/NCT02086448

Highlights in Lung and Sleep Health



Personalizing Asthma Treatment

The NHLBI continues to support research to more precisely tailor interventions based on growing knowledge about the variable symptoms, severity, and underlying mechanisms of asthma. For example, the **Precision Interventions for Severe and/or Exacerbation-Prone Asthma (PrecISE) clinical trial network**, with 30 locations across the country, is evaluating several novel and approved treatments for asthma by targeting them to defined groups of patients who share similar characteristics, such as genetic factors or biomarkers. The need for more personalized treatments is especially important in light of new findings showing that a variety of patient characteristics — such as ethnicity, overweight/obesity, and sensitivity to household allergens — can influence susceptibility to asthma as well as the severity of the disorder.^{1,2}

In December 2020, the NHLBI announced focused **updates of the 2007 national asthma management guidelines**, which help providers and patients make treatment decisions. The updated recommendations include guidance on the use of a new inhaled medication, reducing indoor allergens, and immunotherapy (injections of an allergen to desensitize the body, often called allergy shots).³

Maintaining Momentum Against Chronic Obstructive Pulmonary Disease (COPD)

As part of the **COPD National Action Plan**, several NHLBI research efforts are addressing the high burden of COPD in rural and underserved communities. For example, efforts are underway to improve the use of **pulmonary rehabilitation (PR)**, especially in rural and remote areas. Although PR has been shown to reduce hospitalizations and improve quality of life among people with COPD, only about 4 percent of eligible patients use it.⁴ NHLBI-funded researchers are studying a variety of approaches to increase access and adherence to PR, including through home-based visits, coaching, and telehealth. In 2019, the NHLBI also formed

Meeting NHLBI Strategic Vision Objectives 1, 2, 5

For a complete list of objectives, visit: www.nhlbi.nih.gov/about/strategic-vision.

Addressing the Health Effects of Vaping

In 2019, reports began to emerge of **e-cigarette, or vaping, product use-associated lung injury (EVALI)**, with more than 2,800 people hospitalized and nearly 70 dead as a result. In November 2019, data from the Centers for Disease Control and Prevention (CDC) had linked many EVALI cases to use of vaping liquids containing tetrahydrocannabinol (THC) — the active ingredient in marijuana — as well as vitamin E acetate, which is an agent used to dilute THC.⁸ NHLBI-funded researchers later confirmed that e-cigarette vapor containing vitamin E acetate causes lung injury in mice similar to that seen in EVALI patients.⁹ In response, the U.S. Food and Drug Administration (FDA) advised that vitamin E acetate should not be used in vaping products. EVALI cases declined in late 2019, but the NHLBI continues to support robust research on the long-term health consequences from vaping. The Institute has proposed resources to help speed progress, including the use of patient questionnaires to better characterize vaping behaviors, and collaborative systems to allow researchers to share data and specimens.¹⁰

a cooperative agreement with the American Lung Association to conduct the **Lung Health Cohort study**.⁵

In 2021, the NHLBI is also launching a web-based platform that will allow partners in the COPD National Action Plan to share their activities and collectively track their progress as they implement the plan.





Improving Lung Transplantation

Although organ transplant outcomes have steadily improved in recent years, the mortality rate for lung transplants remains nearly twice as high as for heart, liver, and kidney transplants. To improve outcomes, the NHLBI is establishing a multisite **Lung Transplant Consortium** that will harmonize clinical studies across lung transplant centers.

An NHLBI-funded study is also following more than 3,000 patients who have undergone a lung transplant to understand **chronic lung allograft dysfunction (CLAD)**, a condition in which the transplanted lung does not function properly.⁶ Other researchers are conducting a trial to determine whether a biologic approved for use in kidney transplants will help reduce CLAD and improve outcomes for lung transplants.⁷

Meeting NHLBI Strategic Vision Objectives 2, 7

For a complete list of objectives, visit: www.nhlbi.nih.gov/about/strategic-vision.

Advancing Sleep Health

Studies funded in part through **NIH's National Center on Sleep Disorders Research (NCSDR)** continue to show that sleep deficiency and sleep disorders are important risk factors for diabetes, hypertension, obesity, and other life-threatening conditions. In 2020, a study of nearly 2,000 middle-aged adults showed that compared with people with regular bedtimes and sleep duration, people with the most irregular sleep patterns had more than twice the risk of cardiovascular disease after five years of follow-up.¹¹ In addition, a large, prospective study found that sleeping less than six hours a night

due to chronic insomnia is associated with a higher risk for cognitive impairment.¹²

As new sleep findings emerge, they are added to the NHLBI's BioData Catalyst cloud-based data platform to allow researchers to share and analyze the data and speed advances in sleep research.

In November 2020, Marishka K. Brown, Ph.D., was named as the new NCSDR director. Dr. Brown first joined NCSDR in 2016 as a program director for sleep disorders medicine. She also led NCSDR's coordination of trans-NIH sleep research and chaired the working group responsible for national sleep health objectives as part of the U.S. Department of Health and Human Services' Healthy People 2030 initiative.

Dr. James Kiley

 @NHLBI_LUNGDir

The NHLBI's Division of Lung Diseases (DLD) supports research on the causes, diagnosis, prevention, and treatment of lung diseases and sleep disorders, including asthma, COPD, cystic fibrosis, sleep-disordered breathing, 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.



¹ pubmed.ncbi.nlm.nih.gov/32369487

² pubmed.ncbi.nlm.nih.gov/32479111

³ www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines

⁴ pubmed.ncbi.nlm.nih.gov/32396181

⁵ projectreporter.nih.gov/project_info_description.cfm?aid=9711058

⁶ projectreporter.nih.gov/project_info_description.cfm?aid=9952409

⁷ projectreporter.nih.gov/project_info_description.cfm?aid=9948711

⁸ cdc.gov/mmwr/volumes/68/wr/mm6845e2.htm

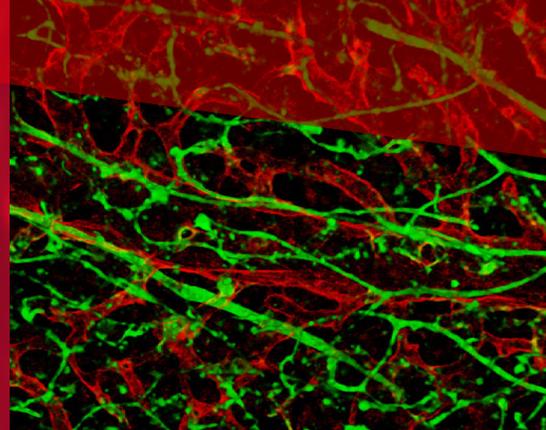
⁹ pubmed.ncbi.nlm.nih.gov/32101656

¹⁰ pubmed.ncbi.nlm.nih.gov/32243764

¹¹ pubmed.ncbi.nlm.nih.gov/32138974

¹² pubmed.ncbi.nlm.nih.gov/32968796

Highlights in Blood Health



Advancing Treatments and Cures for Sickle Cell Disease

The NHLBI launched the **Cure Sickle Cell Initiative** in 2018 to support the development of gene-based cures for sickle cell disease (SCD) that will work for all patients, including those ineligible for bone marrow transplants. Researchers involved in the Cure Sickle Cell Initiative helped develop an accurate, affordable, and easy-to-use device for point-of-care diagnosis of SCD in low-resource areas.¹ In early 2020, the NHLBI also became an integral part of a **collaboration between NIH and the Bill & Melinda Gates Foundation** to develop affordable, safe, and effective gene-based cures for SCD in sub-Saharan Africa. The Cure Sickle Cell Initiative also includes an analysis to ensure that new therapies will be beneficial to patients in ways that matter to them, including affordability and accessibility.

Also in 2020, NHLBI-supported researchers discovered that SCD causes abnormal twists and turns in the blood vessels that supply bone marrow, where red blood cells are made. These disorganized blood vessels deprive the bone marrow of oxygen and could complicate efforts to restore normal red blood cells to patients, such as through bone marrow transplantation or gene therapy. However, in studies on mice, these researchers found that six weeks of blood transfusion restored normal blood vessel architecture in the bone marrow, suggesting a similar protocol could be used as part of cell- and gene-based therapies in patients.²

In late 2020, NHLBI-funded researchers reported promising results in a pilot trial of gene therapy to restore the body's hemoglobin, the red blood cell protein altered in people with SCD. At birth, the body normally switches from making fetal hemoglobin (HbF) to making only adult hemoglobin (HbA). The trial is testing a **gene therapy** to turn off the switch—a molecule called BCL11A—turning on HbF to replace HbA. Over a median of 18 months,

six participants with severe SCD who received this therapy had robust HbF induction, fewer crises and other disease-related events, and less need for transfusions.³

Healthcare barriers continue to be an issue for people with SCD. The NHLBI's **Sickle Cell Disease Implementation Consortium** surveyed 440 adolescents and adults with SCD and found that most were pleased with their primary care but had negative experiences with emergency care during a sickle cell crisis.⁴ To address this challenge, one study is embedding each patient's individualized pain treatment plan in their electronic health records so that it can be accessed quickly by emergency care providers. In another study, researchers are collaborating with patients to develop and test a smartphone app that helps patients who are prescribed hydroxyurea remember to take it regularly. Hydroxyurea can help reduce the frequency of sickle cell crises.⁵

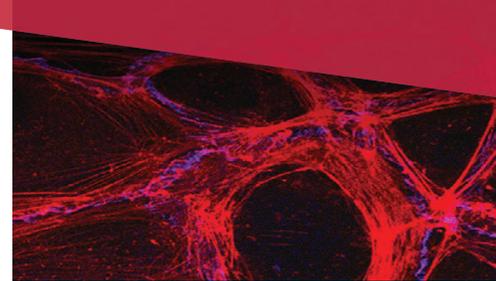
Improving Blood Storage and Transfusion Medicine

Refrigerated storage of red blood cells (RBCs) leads to a series of biochemical changes, referred to as storage lesion, that eventually causes damage to the RBCs and a breakdown of their antioxidant systems. Ongoing NHLBI-funded studies aim to better understand the aging of stored RBCs to evaluate how to reduce storage lesion or potentially mitigate its effects. One NHLBI-funded team has developed a cocktail of four chemicals—phosphate/inosine/pyruvate/adenine (PIPA)—to “rejuvenate” stored RBCs by giving them a boost of antioxidants. After showing that PIPA can improve the function of RBCs in the lab, the researchers compared blood transfusion using RBCs treated with PIPA versus use of standard RBC products in patients with SCD. They found that after transfusion, blood from patients with SCD who received the rejuvenated RBCs had markers for higher antioxidant and energy metabolism than blood from patients who received standard exchange transfusions.⁶

Right masthead image: Bone marrow in a mouse model of sickle cell disease, showing disorganized blood vessels (arteries in green, sinusoids in red). Credit: Shin-Young Park, Ph.D., Boston Children's Hospital and Harvard Medical School, Boston.



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The **NHLBI Recipient Epidemiology and Donor Evaluation Study (REDS)** is also examining aspects of blood processing that could affect RBC metabolic changes during storage. For example, recent findings show that additives used in the RBC storage bag can affect RBC metabolism.⁷

In addition, the RBC-Omics study, which was developed under the REDS program, is looking at blood samples from 13,400 healthy individuals to examine donor characteristics, such as genetics and diet, that are associated with

metabolic aging and breakdown of stored RBCs. RBC-Omics will shed light on how genetic or biological variations in donors, including iron levels, affect the metabolic age of stored RBCs, as well as transfusion outcomes in recipients.⁸ Other REDS studies recently found that iron supplements can help correct iron deficiencies in people who donate whole blood frequently⁹ and that a donor's health-related habits (such as smoking, or drinking caffeine or alcohol) can affect the quality of stored donated blood and transfusions.¹⁰

Meeting NHLBI Strategic Vision Objectives 1, 2, 4

For a complete list of objectives, visit: www.nhlbi.nih.gov/about/strategic-vision.

Examining the Blood-Brain Barrier

The blood-brain barrier (BBB) is made up of tightly joined cells that protect the brain from pathogens and toxins in the blood. But it can also prevent brain access to potentially helpful drugs, such as those under study for dementia and brain injuries. A new program, jointly funded by the NHLBI and the Department of Defense Joint Program Committee-6, Combat Casualty Care Research Program, is investigating the **crosstalk between the BBB and the blood** — the first time this has been attempted on a large scale. The program aims to build tiny bioengineered BBB models that can

help reveal mechanisms of neurological disease and injury, characterize the role of individual blood components, and potentially identify new therapies and diagnostic tools.



An illustration of blood flowing through the blood-brain barrier landscape. Courtesy of Edward Neuwelt, M.D., Oregon Health & Science University.

Dr. Keith Hoots

 @NHLBI_BLOODir

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 Keith Hoots, M.D.



¹ pubmed.ncbi.nlm.nih.gov/32123889/

² pubmed.ncbi.nlm.nih.gov/31990287/

³ pubmed.ncbi.nlm.nih.gov/33283990/

⁴ pubmed.ncbi.nlm.nih.gov/32469413/

⁵ pubmed.ncbi.nlm.nih.gov/32383683/

⁶ pubmed.ncbi.nlm.nih.gov/31385330/

⁷ pubmed.ncbi.nlm.nih.gov/30353560/

⁸ pubmed.ncbi.nlm.nih.gov/31184580/

⁹ pubmed.ncbi.nlm.nih.gov/32243609/

¹⁰ pubmed.ncbi.nlm.nih.gov/32385854/

Right masthead image: Endothelial cells that line the inside of blood vessels are held together by specialized proteins including actin (red) and cadherin (blue). Courtesy of Christopher V. Carman, Ph.D., and Roberta Martinelli, Ph.D., Harvard Medical School.

Highlights in Translation Research and Implementation Science



Delivering New Interventions in Underserved Communities

To date, there have been very few studies focused on the implementation, scale-up, and maintenance of delivering new interventions to communities where they are needed, and even fewer studies focused on underserved high-need communities. To address this gap, the NHLBI launched the **Disparities Elimination through Coordinated Interventions to Prevent and Control Heart and Lung Disease Risk (DECIPHeR)** program and awarded the first projects in September 2020.

Seven DECIPHeR grantees in different areas of the country will begin working with local communities to evaluate a variety of proven interventions for conditions such as asthma, cardiovascular disease (CVD), and hypertension. For example:

- In Louisiana, community health workers will partner with local churches to reduce CVD risk in African Americans by promoting lifestyle interventions that align with current CVD guidelines (e.g., healthy diet, physical activity, smoking cessation, weight loss).¹
- In rural Colorado, researchers will work with school-based asthma care navigators and nurses to test a team approach to asthma control in children.²
- In Los Angeles, 51 adult primary care clinics will implement culturally tailored multilevel evidence-based strategies to improve blood pressure control in this large and diverse city.³

Meeting NHLBI Strategic Vision Objective 3, 6 • For a complete list of objectives, visit: www.nhlbi.nih.gov/about/strategic-vision.

Dr. George Mensah

 @NHLBI_Translate

The NHLBI's Center for Translation Research and Implementation Science (CTRIS) supports research that addresses 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.



¹ projectreporter.nih.gov/project_info_description.cfm?aid=9931807
² projectreporter.nih.gov/project_info_description.cfm?aid=10063661

³ projectreporter.nih.gov/project_info_description.cfm?aid=10064593

