DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

FY 2025 CONGRESSIONAL JUSTIFICATION

Significant Items

Addressing All Rare Diseases

The Committee directs NCATS to host a public workshop convening rare disease expert stakeholders including scientists, Federal agency representatives including FDA, patient advocacy leaders, clinicians, therapy and diagnostics developers, and regulators. Developing a therapy for conditions occurring in very small populations involves overcoming unique regulatory and research hurdles due to their small patient populations. The workshop will address current research and treatment efforts for rare diseases, including focusing on commonalities across diseases and therapeutic platforms, the outcome of which would also be applicable for rare diseases with small patient populations, and rare diseases with no path to commercialization.

NCATS is in the process of planning a public workshop and will share the agenda and details with the Committee when available.

Action taken or to be taken

The National Center for Advancing Translational Sciences (NCATS) is committed to rare diseases research, and provides leadership, direction, and coordination for rare diseases research across NIH. NCATS supports innovations that can speed the diagnosis of rare diseases, as well as the development and delivery of therapies which can help millions of people affected by rare diseases, including those that are too rare to be of commercial interest. NCATS works collaboratively across NIH institutes and centers, and with partners outside of NIH, including patients and patient advocacy groups who partner with clinicians and scientists to meaningfully advance understanding of rare diseases and therapeutics development. The Rare Diseases Clinical Research Network (RDCRN),[1] Platform Vector Gene Therapy (PaVe-GT) pilot projects,[2] and grants supporting clinical trial readiness for rare diseases[3] are a few examples of how NCATS has sought to overcome research challenges faced by the rare diseases community. NCATS also regularly directly engages with patients and patient advocacy groups, such as outreach and information through the Genetic and Rare Diseases Information Center (GARD),[4] and annually hosting Rare Disease Day at NIH.[5]

NCATS recognizes the importance of bringing together and engaging multiple groups to discuss current research and treatment efforts for diseases which face unique regulatory and research hurdles, including rare diseases affecting small patient populations, and diseases with no path to commercialization. NCATS is in the process of planning a public workshop and will share the agenda and details with the Committee when available.

[1] ncats.nih.gov/research/research-activities/RDCRN
[2] ncats.nih.gov/research/research-resources/pave-gt
[3] ncats.nih.gov/research/research-activities/ctr
[4] ncats.nih.gov/research/research-resources/gard
[5] ncats.nih.gov/news-events/events/rdd

Amyloidosis

The Committee urges NIH to expand its research efforts in amyloidosis, a group of rare and often fatal diseases. Amyloidosis is characterized by abnormally folded protein deposits in tissues. Federal and foundation support over the past years has given hope for successful new treatments. However more efforts are needed to accelerate research and awareness of the disease and to help patients with amyloidosis related multi-organ dysfunction. The Committee directs NIH to provide an update in the fiscal year 2025 CJ on the steps NIH has taken to expand research into the causes of amyloidosis and the measures taken to improve the diagnosis and treatment of this devastating group of diseases.

Action taken or to be taken

Amyloidosis is a group of diseases in which an abnormal protein called amyloid builds up in the heart, kidneys, liver, or digestive organs, which often leads to compromised organ function. For example, researchers supported by the National Institute on Aging (NIA) identified cardiac amyloidosis as a risk factor for heart failure with preserved ejection fraction, a condition in which the heart's left ventricle is unable to fill properly, resulting in an insufficient supply of blood pumping throughout the body. Although amyloidosis remains largely incurable, advances in treatment have extended lifespan in many cases and improved quality of life for individuals with the condition. For example, in a recent phase III clinical trial, the drug tafamidis reduced all-cause mortality and improved quality of life in patients with transthyretin cardiac amyloidosis, a common form of the disease. Much of the basic, preclinical, and early clinical research leading up to this industry-funded trial received support from the National Institutes of Health (NIH). NIH also supported a subsequent study demonstrating that tafamidis is equally effective against hereditary and sporadic forms of the disease.

Basic research on amyloidosis is supported across the NIH. For example, the National Institute of General Medical Sciences (NIGMS) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) support research to better understand the properties of many of the key proteins involved in different forms of amyloidosis, including both Serum Amyloid A, which is involved in AA amyloidosis, and transthyretin, which can aggregate and result in transthyretin amyloidosis, a disorder characterized by abnormal buildup of transthyretin in organs and tissues such as the heart, kidneys, and nerves. Understanding how these proteins can lead to the aggregates may aid discovery of new drug targets and therapeutic approaches. As another example, the National, Heart, Lung, and Blood Institute (NHLBI) supports the Multi-Ethnic Study of Atherosclerosis (MESA) program which aims to determine the mechanisms by which cardiac transthyretin amyloidosis and progressive fibrosis separately contribute to age-related adverse cardiac changes in multi-ethnic older adults.[6] In addition, NIA supports research on amyloidosis driven by pathogens, such as herpes virus.

NIH also funds research on early and accurate diagnosis of amyloidosis. For example, NIA-supported investigators have developed a highly accurate diagnostic and screening tool for cardiac amyloidosis. NIA recently funded a new study aiming to improve early detection of transthyretin cardiac amyloidosis by systematically evaluating tissue specimens from older adults who underwent surgery for lumbar spinal stenosis, which can precede transthyretin cardiac

[6] reporter.nih.gov/search/DSQ71snxa0ue1iPJkYWIAg/project-details/10467374

amyloidosis onset.[7] In addition, NHLBI is funding a study to develop a new method to identify early changes in the structure and function of heart and blood markers in individuals with transthyretin cardiac amyloidosis.[8] Another NHLBI-funded project is developing an artificial intelligence (AI)-based Clinical Decision Support Solution that will detect a form of amyloidosis called wild type transthyretin amyloid before individuals develop clinical manifestation.[9] Another NHLBI-funded project leverages advances in machine learning to develop and validate fully-automated echo image analytic approaches to diagnose and track rare cardiomyopathies, focusing on cardiac amyloidosis.[10] Additional NHLBI studies are exploring the use of imaging and genetic/circulating biomarkers for diagnosis of transthyretin amyloidosis.[11] NHLBI is also studying populations at high genetic risk for amyloidosis, including African Americans and Hispanics/Latinos, using an approach to comprehensively study multi-systemic features and cardiac imaging findings to improve understanding of disease presentation and inform strategies for cardiac observation and earlier clinical diagnosis.[12]

NIH supports clinical trials using a range of drugs, including small molecule inhibitors, monoclonal antibodies, biological therapies, and agents commonly used in cancer chemotherapy. NIDDK- and NIA-funded research has identified a promising potential strategy for treating light chain (LC) amyloidosis, the most common systemic amyloid disease,[13] using a compound that reduced secretion of the LC amyloid precursors. In addition, one NIDDK-funded research team is developing an amyloid-binding reagent that can not only leverage the immune system to clear the amyloid buildup but also be used to visualize amyloid in patients.[14]

To advance drug development for these diseases, the Amyloidosis Forum was created through a public/private partnership between the Amyloidosis Research Consortium and the U.S. Food and Drug Administration (FDA) to discuss the challenges, address the obstacles, and find pathways towards accelerating drug development in light chain amyloidosis. The most recent meeting was held October 2020, with NIA support, and focused on natural history and endpoint development. In 2022, the Forum expanded to include transthyretin amyloidosis in recognition of the continuing challenges in therapeutic development. Another Amyloidosis Forum meeting is currently being planned focused on advancing drug development for transthyretin amyloidosis.[15]

[7] reporter.nih.gov/search/SvDcyPPbcU2ojfwvJLIgnA/project-details/10637491
[8] reporter.nih.gov/search/pI35fIG-c0-EOL4LjuaBJQ/project-details/9867084
[9] reporter.nih.gov/search/Wgm8Q0H9GkmBk5eOYhJivw/project-details/10481909
[10] reporter.nih.gov/search/vT-dOXyKVkmZUAylE6l9lA/project-details/10218258
[11] reporter.nih.gov/search/9MR7rPFllU-4lHsZCM1QKQ/project-details/9661914;
reporter.nih.gov/search/lH9dCvP3M0CJXneZqLFlCA/project-details/10520606
[12] reporter.nih.gov/search/wMN7Yjsb8UWVi5Lk2kRY5g/project-details/10100303
[13] pubmed.ncbi.nlm.nih.gov/33599742/
[14] reporter.nih.gov/search/6KHWed6P-kC0kMbKeNzWLQ/project-details/10579884
[15] reporter.nih.gov/search/BKEbDobgO06bfFKFafdUFA/project-details/10683562

Autoimmune and Immune Mediated Diseases

The Committee recognizes the important role the new Office of Autoimmune Disease Research within the Office of Research on Women's Health will play in coordinating and fostering collaborative research across Institutes and Centers. As the office develops a strategic research plan, the Committee strongly encourages it to seek input from external stakeholders particularly patient advocacy organizations that represent the populations affected by autoimmune and immune-mediated diseases.

Action taken or to be taken

The new Office of Autoimmune Disease Research[16] within the Office of Research on Women's Health (OADR-ORWH) was established and has begun coordinating and fostering collaborative research across NIH Institutes, Centers, and Offices (ICOs). In Fiscal Year 2023, OADR-ORWH funded six awards for applications received in response to a Notice of Special Interest (NOSI): EXposome in Autoimmune Disease Collaborating Teams PLANning Awards (EXACT-PLAN)[17] issued by ORWH and seven ICOs. This NOSI invited applications for exploratory, early, and conceptual stage research projects aimed at design, development, and implementation of a future national, interdisciplinary, collaborative, team science research network that will advance studies on the exposome in autoimmune diseases.

Additionally, a Notice of Funding Opportunity: Understanding Chronic Conditions Understudied Among Women[18] was issued by ORWH and six partnering ICOs to foster research on chronic conditions understudied among women and/or disproportionately affecting populations of women who are understudied, underrepresented, and underreported in biomedical research. Special areas of research interest for this funding opportunity announcement include autoimmune diseases. OADR-ORWH also co-funded 21 applications from nine Institutes with a focus on autoimmune disease research. OADR-ORWH also funded NIH intramural awards emphasizing autoimmune disease research and partially supported the Accelerating Medicines Partnership® Autoimmune and Immune-Mediated Diseases (AMP® AIM)[19] leadership program.

An NIH-wide Coordinating Committee for Autoimmune Disease Research (CCADR) was established to provide a structured forum to leverage the autoimmune disease research expertise across the ICOs and supports a streamlined process for expanding collaborations across both NIH intramural research programs and with the extramural community. OADR-ORWH has begun organizing the development of a NIH strategic plan on autoimmune disease research. A Request for Information (NOT-OD-24-049)[20] will obtain input from external partners from the scientific, clinical and public communities on key autoimmune disease research priority areas and existing research gaps. To date, OADR-ORWH has participated in engagements with external partners, including representatives of the Autoimmune Association, National Psoriasis Foundation, Arthritis Foundation, Crohn's and Colitis Foundation, Lupus Foundation of America,[21] Sjogren's Foundation, and the Celiac Disease Foundation. OADR-ORWH also has

[16] orwh.od.nih.gov/OADR-ORWH
[17] grants.nih.gov/grants/guide/notice-files/NOT-OD-23-112.html
[18] grants.nih.gov/grants/guide/rfa-files/RFA-OD-23-014.html
[19] orwh.od.nih.gov/in-the-spotlight/all-articles/new-pilot-program-will-mentor-and-advance-womens-health
[20] grants.nih.gov/grants/guide/notice-files/NOT-OD-24-049.html
[21] niams.nih.gov/about/working-groups/lupus-federal

presented at meetings that include patient advocates, such as the Lupus Federal Working Group, and the Office is planning additional engagements with partners from other community constituency groups.

Celiac Disease

The Committee commends NIH for issuing a Notice of Special Interest to spur additional research on the study of celiac disease. Today, the only known treatment is a gluten-free diet; however, recent public and private sector research confirms that such a ''treatment'' is insufficient for many who suffer from celiac disease. The Committee encourages NIH to devote focused research on the study of celiac disease and continues to urge NIH to: support new research on celiac disease; better coordinate existing research; and focus new research efforts toward causation, diagnosis, management, treatment, and, ultimately, a cure of this disease. The Committee directs NIH to include updates on research, projects, and programs for celiac disease in the fiscal year 2025 CJ.

Action taken or to be taken

Celiac disease is an autoimmune disease affecting about 1.5 percent of the United States population in which the immune system reacts to ingested gluten, a protein found in wheat, barley, and rye. This immune response takes place primarily in the small intestine and can result in diarrhea, fatigue, weight loss, bloating, anemia, and more serious complications. Celiac disease also can affect growth and development in children. Currently, there is no cure for celiac disease and patients must follow a strict gluten-free diet to help manage symptoms and promote intestinal healing.

NIH supports research to understand and address celiac disease. A Notice of Special Interest (NOSI): Accelerating Progress in Celiac Disease Research was published to solicit research on the etiology and pathogenesis of celiac disease, identification of therapeutic targets, and development of preventative or disease ameliorating therapies/strategies.[22] The National Institute of Allergy and Infectious Diseases (NIAID), the National Center for Complementary and Integrative Health, the National Cancer Institute, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases participated in this NOSI and NIH anticipates renewing it in Fiscal Year (FY) 2025. In FY 2023, Congress directed the NIH to establish an Office of Autoimmune Disease Research (OADR) within the NIH Office of Research on Women's Health to coordinate NIH research on autoimmune diseases and conditions, including celiac disease. OADR and NIAID jointly support awards to identify and validate genetic, immune, and microbial profiles that predict loss of tolerance to gluten in infants at risk for celiac disease.

NIAID supports a wide range of investigator-initiated basic research, clinical trials, and research collaborations to understand the development of celiac disease and to evaluate potential therapies to modulate the underlying immune response causing the disease. For example, NIAID is currently supporting a research project investigating the mechanisms by which gut-colonizing microbiota can boost tolerance to gluten in mouse models of celiac disease. The NIAID Autoimmunity Centers of Excellence conduct collaborative basic and clinical research on celiac and other autoimmune diseases. In addition, the NIAID Immune Tolerance Network clinically evaluates novel, tolerance-inducing therapies in immune-mediated diseases. NIAID also supports the Immune Drivers of Autoimmune Disease cooperative research program to improve the understanding of immune processes and events that drive autoimmune disease.

[22] grants.nih.gov/grants/guide/notice-files/NOT-AI-22-004.html

The long-term consequences of the intestinal inflammatory response during celiac disease can include damage in other organ systems, such as anemia, osteoporosis, dermatitis, peripheral nerve damage, heart disease, and cancer. NIAID also funds research to mitigate this immune-mediated inflammation and to promote intestinal healing. The NIAID Mucosal Immunology Studies Team conducts research to define immune mechanisms at mucosal surfaces, including the intestinal mucosal tissue. Additionally, NIAID supports a clinical trial to evaluate an enzyme treatment in celiac disease patients who remain symptomatic despite adhering to a gluten-free diet. As more than 30 percent of celiac-affected individuals who follow the diet have persistent intestinal damage, additional interventions are required to address their symptoms.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a robust research portfolio investigating potential causes of, and treatments for, celiac disease. For example, NIDDK supports a major new clinical trial that builds on the availability of novel technologies for gluten detection in food and urine. The trial will test the effectiveness of these technologies, when combined with telemedicine, to manage celiac disease and help facilitate gluten avoidance in newly diagnosed adults, helping to alleviate the disease's physical and psychological consequences. NIDDK also continues to support celiac disease research through The Environmental Determinants of Diabetes in the Young (TEDDY) study, a long-term, international study investigating environmental contributors (such as diet and the microbiome) to both type 1 diabetes and celiac disease, as these autoimmune diseases share many risk genes. Findings from the TEDDY study could pave the way to new disease prevention and treatment strategies. Other NIDDK-funded research includes investigating the role of immune cells in gut inflammation during celiac disease; determining the roles of genes involved in celiac disease susceptibility, which may provide therapeutic targets; understanding how the gut is damaged and heals across different individuals in celiac disease with an eye toward developing precision medicine approaches; and supporting early career investigators and scientific trainees who are studying celiac disease to help build the next generation of researchers.

NIH is committed to supporting research to understand the underlying causes of celiac disease and prevent them, as well as to develop new interventions and treatment strategies for individuals already living with celiac disease. Celiac disease has the capability of affecting many organ systems; therefore, this work is being conducted across multiple NIH institutes to address celiac disease in a holistic manner.

Cellular Immunity

The Committee directs NIH to include updates on the following research, projects, and programs in the fiscal year 2025 Congressional Justification: metastatic breast cancer; future goals for each of the deadliest cancers (brain, esophagus, liver, lung, ovary, pancreas, stomach and mesothelioma); the link between obesity and endometrial cancer; melanoma; neuroblastoma; pediatric immunotherapy clinical trials; congenital heart disease; kidney transplant disparities; lower urinary tract symptoms; celiac disease; Maternal-Fetal Medicine Units Network; pelvic organ prolapse; Usher syndrome; indoor pollutants; amyloidosis; Childhood Post-Infectious Neuroimmune Disorders/Pediatric AcuteOnset Neuropsychiatric Syndrome [PANS]/Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus [PANDAS]; Congenital Cytomegalovirus; Native Hawaiian Early Career Development; Von Hippel-Lindau Disease; NCI's plans to update the Surveillance, Epidemiology, and End Results Registry; pulmonary fibrosis; cellular immunity; and opportunities to enhance childhood cancer research efforts, including coordinating efforts already underway through the Trans-NIH Pediatric Research Consortium.

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) supports a robust portfolio of research examining the development of cellular immunity in response to pathogens and vaccinations, as well as in autoimmune conditions. The development of a cellular immune response that is protective of the host but is not overactive is a delicate balance. NIAID maintains several research programs to help advance our understanding of cellular immunity and support the development of new tools and technologies to advance research and address disease. NIAID-supported research efforts have been leveraged during outbreaks of influenza, Ebola, Zika, and COVID-19 to investigate the specificity, breadth, and durability of cellular immune responses to infection with, and vaccination against, these pathogens. NIAID also has invested in characterizing differences in cellular immunity among key populations, including children, pregnant people, the elderly, and immunocompromised or immunosuppressed individuals.

NIAID continues to focus on understanding the development of cellular immunity in response to COVID-19 vaccination. Since the emergence of COVID-19, researchers have discovered important nuances of cellular immune responses that will help us tailor new countermeasures and better prepare for future pandemics. The NIAID Vaccine Research Center (VRC), which was instrumental in the development of the Moderna Spikevax COVID-19 vaccine, also helped to identify the correlates of protection generated by the vaccine and continues to support the validated measurement of COVID-19 vaccine-elicited immune responses. The NIAID VRC also described a primary mechanism by which COVID-19 booster vaccines can enhance protective antibody responses. This work suggests that cellular responses boosted by additional vaccine doses can be broadly effective beyond the specific SARS-CoV-2 variant targeted by the vaccine. Additionally, analysis of T cell reactivity against a broad range of coronaviruses, including those that cause COVID-19 and the common cold, has provided critical insights for the development of pan-coronavirus vaccines. NIAID-supported clinical trials of Project NextGen COVID-19 vaccine candidates will include in-depth analyses of systemic and mucosal tissue cellular responses. NIAID also supports the development of vaccine adjuvants—components that can improve the efficacy of a vaccine by enhancing the immune response generated. It is known that

adjuvanted vaccines induce cellular immunity in a manner distinct from the immunity generated by natural infection. For example, an experimental SARS-CoV-2 vaccine with a specific adjuvant mixture can induce robust T cell immunity and protect from disease even in the absence of antibodies.

NIAID-supported investigators continue to characterize cellular immune responses to natural SARS-CoV-2 infection and examine the immune changes associated with post-acute sequelae of COVID-19 (PASC). Researchers supported by NIAID have shown that after SARS-CoV-2 infection, young children produce more robust and persistent antibody and mucosal tissue immune responses compared to adults. Importantly, in pediatric patients with severe COVID-19 and multisystem inflammatory syndrome in children (MIS-C), NIAID scientists have now identified distinctive signatures to characterize the cellular immune responses, disease severity, and secondary complications of infection. NIAID-supported scientists also have identified discrete immunological signatures that underlie PASC in older individuals. Knowledge of these markers in both protective and insufficient immune responses—coupled with the ability to detect them in patients—may help inform treatment strategies.

NIAID-supported research on the development of cellular immunity in response to SARS-CoV-2 infection and vaccination has helped improve our understanding of the re-establishment of baseline conditions after an immune response as well as the ability to mount responses to subsequent infections. Researchers have demonstrated that prior SARS-CoV-2 infection can alter antiviral T cell activity, which may influence an individual's immune response to future SARS-CoV-2 vaccination. NIAID scientists also have identified immune activation signatures in patients, months after recovery from mild COVID-19, suggesting that viral infections can establish new immunological set-points that can affect future immune responses. NIAID-supported investigators using systems biology approaches have developed a comprehensive database of immune signatures that characterize the complexity of the human immune system. The database details the interplay between the pathogen-specific and broadly applicable components of the immune response and enables comparative analysis of immunization-induced immunity. This database revealed a common predictor of vaccine-induced antibody responses and may help facilitate efforts to develop optimized vaccine candidates against a variety of pathogens.

NIAID also supports studies examining the effects of antimicrobial interventions and prior infections on cellular immunity. NIAID scientists identified the mechanism underlying enhanced susceptibility to secondary fungal infections resulting from the injuries to cellular immunity that can occur with antibiotic use. Additionally, NIAID investigators showed that an imbalance in the intestinal bacteria caused by the antibiotic vancomycin can alter T cells residing in the tissue and increase nonhuman primates' susceptibility to simian immunodeficiency virus (SIV) infection. Recently, NIAID researchers have identified critical signals derived from infected tissues that promote protective cellular responses during both *Mycobacterium tuberculosis* and influenza virus infections. NIAID scientists also discovered that people who experienced lung roundworm infections were protected from developing severe COVID-19 infection, due to immune surveillance cells being more readily primed to identify foreign agents and recruit antiviral T cells to the site of infection more rapidly. Research on the mechanisms

that underlie the complex relationships between immune cells, tissue environments, and therapeutics is essential and can help inform treatment strategies.

NIAID will continue to support innovative research to help better understand the development and nuances of cellular immunity. NIAID supports research programs to explore the role of stresses on host immunity and predisposition to inflammatory disorders; understand the crosstalk between immune cells and the microbiota; and characterize cellular dynamics, especially those associated with resistance to infection. An improved understanding of these relationships has significant implications for knowledge of cellular immunity and ability to address immunologic and infectious diseases.

Childhood Post-Infectious Neuroimmune Disorders (PANS/PANDAS)

The Committee is concerned that although NIH supports research on Pediatric Acute-Onset Neuropsychiatric Syndrome [PANS] and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus [PANDAS], significantly more needs to be done to fully understand causes, diagnosis, and treatment of these devastating disorders. Research and physician education are essential to early identification and intervention, thereby reducing the risk of chronic illness and associated costs to families, school systems, healthcare systems, and insurers. The association between neuropsychiatric illness and infections has become even more evident because of SARS CoV–2 and provides increasing opportunities for breakthroughs in research and treatment. The Committee encourages NIH to increase prioritization of research in this area, and report to the Committee in the fiscal year 2025 CJ on the progress being made on the understanding of the causes, diagnostic criteria, and treatment of these conditions.

Action taken or to be taken

Autoimmune encephalitic conditions are illnesses in which an inflammatory immune response triggers pathology in the brain, resulting in a sudden onset of obsessive-compulsive disorder (OCD) symptoms, other tic disorder symptoms, and/or other neuropsychiatric symptoms such as severe eating restrictions. For over 2 decades, the National Institute of Mental Health (NIMH) has supported a robust research portfolio on the full range of mental and neurodevelopmental disorders that emerge during childhood and adolescence, including autoimmune encephalitic conditions like Pediatric Acute Onset Neuropsychiatric Syndrome (PANS) and its subset Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS). Collectively, this research portfolio aims to identify the mechanisms leading to mental illnesses and to identify potential targets for the development of new and improved interventions. In addition, NIMH engages in educational outreach with the medical community and other external interested parties to share information about NIMH programs and NIMH-funded advances.[23]

Findings from NIMH-supported research have led to the development of new treatments to improve outcomes for individuals with autoimmune encephalitic conditions. For example, the NIMH Intramural Research Program was instrumental in identifying immune mechanisms that lead to brain dysfunction in PANS and PANDAS. In the case of PANDAS, this immune response is associated specifically with Group A streptococcal (strep) infections, such as strep throat and scarlet fever. Researchers found that strep-related PANDAS episodes can be managed by prescribing antibiotics to eliminate the strep infection and ameliorate symptoms.[24] Children with PANS- or PANDAS-related OCD symptoms may also benefit from standard OCD treatment, which includes medication and behavioral therapy.[25]

NIMH continues to support multidisciplinary approaches in which teams of researchers from multiple fields, including neurobiology, molecular biology, psychiatry, pediatrics, and clinical research, are exploring the biological pathways underlying autoimmune encephalitic conditions, which may lead to new therapies. For example, in one NIMH-funded project, researchers are

[23] nimh.nih.gov/health/publications/pandas
[24] pubmed.ncbi.nlm.nih.gov/15820236/
[25] pubmed.ncbi.nlm.nih.gov/25978743/

studying antibodies collected from the cerebrospinal fluid of a large and diverse cohort of patients with idiopathic encephalitis. The researchers recently reported that these antibodies may be associated with the neurological and psychiatric symptoms found in individuals with brain inflammation, including those infected with SARS-CoV-2.[26] This research contributes to the ongoing effort to better understand how neuropsychiatric symptoms may arise following infection.

Another NIMH-funded research team recently discovered that children with PANDAS produce antibodies that bind to and alter the activity of a specific type of neuron, providing a possible mechanistic explanation for PANDAS symptoms.[27] Building on the findings from this initial small clinical study, this research team is investigating whether antibody binding to cholinergic interneurons contributes to the pathophysiology of PANDAS.[28] In another NIMH-funded project, scientists are investigating how T helper cells – critical components of a typical immune response – contribute to both inflammation and dysfunction of the brain following strep infection.[29]

NIMH intramural researchers are also collecting medical, behavioral, and biological data to evaluate research participant characteristics that are associated with symptom profiles and responses to standard interventions for PANS/PANDAS and a variety of related childhood behavioral, psychiatric, and developmental disorders.[30] These multidisciplinary approaches aim to provide a more precise understanding of the link between autoimmune encephalitic processes and PANS/PANDAS, and may clarify diagnoses and identify new targets for treatment to ultimately improve outcomes for individuals with these conditions.

[26] pubmed.ncbi.nlm.nih.gov/33969321/
[27] pubmed.ncbi.nlm.nih.gov/32539528/
[28] reporter.nih.gov/project-details/10694079
[29] reporter.nih.gov/project-details/9989906
[30] clinicaltrials.gov/ct2/show/NCT01778504

Chronic Kidney Disease (CKD)

The Committee notes that NIH funding for kidney disease research has lagged far behind that of NIH overall. The Committee applauds recent changes to clinical practice in the diagnosis of kidney disease and concurs with recommendations for new markers for estimating kidney function. NIDDK should prioritize research into endogenous filtration markers, activities that spur the adoption of new equations for estimating glomerular filtration rate. Finally, the Committee encourages NIDDK to expand investment in research that bridges existing deficits in CKD management and treatments to reduce incidence and progression, increases the number of CKD clinical trials, improves the delivery of evidenced-base care in under-represented populations, and improves patients' quality of life. The Committee requests an update on these priorities in the fiscal year 2025 budget justification.

Action taken or to be taken

Key National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-funded research led to the removal of race as a factor in equations used to estimate glomerular filtration rate (eGFR), a critical measure of kidney function. This research developed race-neutral equations utilizing the biomarkers serum creatinine, cystatin C, or both together to assess kidney function. NIDDK-supported investigators have continued to build on this work. One study, for example, showed the potential benefits of more widespread use of cystatin C as a biomarker of kidney health. Another demonstrated that although eGFR is an imperfect measure, it remains a critical tool for tracking kidney health to help limit long-term loss of kidney function, which can otherwise lead to progression of cardiovascular disease, stroke, hospitalizations, and mortality.

Structural racism, which refers to macro-level conditions (e.g. residential segregation and institutional policies) that limit opportunities, resources, power, and well-being of individuals and populations based on race/ethnicity, is widely and increasingly recognized as a fundamental cause of the stark racial and ethnic disparities in health outcomes for individuals with Chronic Kidney Disease (CKD) and end-stage kidney disease in the United States. For example, historic redlining—which systematically denied home loans to Black people in the United States during a critical period of government-subsidized suburbanization—has shaped the racial and ethnic composition and relative access to resources in today's neighborhoods. As a result, people who live in these historically redlined communities often disproportionately suffer from CKD and experience greater barriers to practicing healthy behaviors and accessing quality health care, contributing to poor kidney health outcomes of Black people and other people of color.

To help address these disparities and to develop new interventions, the NIDDK established the Interventions that Address Structural Racism to Reduce Kidney Health Disparities Consortium. Launched in August of 2023, the Consortium has already initiated five clinical studies. One of the studies will assess the effectiveness of utilizing electronic medical records to connect patients from rural clinics in eastern North Carolina to community-based supports. This will help enable whole-person, integrated CKD care in improving management and slowing progression of CKD. Other studies focus on topics such as reducing disparities and bias in kidney transplant access. This consortium is a key addition to NIDDK's ongoing support of research toward improving kidney health by reducing kidney health disparities.

Clinical Trials

Although Alzheimer's disease and other dementias disproportionately affect Black Americans, Hispanic Americans, Asian American and Pacific Islanders, and Native Americans, they continue to be underrepresented in AD/ADRD clinical trials. The Committee directs NIA to work with the Alzheimer's Disease Research Centers and other organizations to promote participation in clinical trials within underrepresented populations and, to the maximum scientifically-feasible extent, reduce the burden of participating. These efforts should include expanding community engagement and outreach to these populations, incentivizing trial locations in areas of unmet need, encouraging the diversity of clinical trial staff, allowing appropriate flexibility in trial design and inclusion and exclusion criteria, and utilizing technology like remote patient monitoring, where appropriate, to facilitate clinical trial participation and retention.

Action taken or to be taken

In order to ensure treatments can be applied to a broad population, clinical trials need to be thoughtfully designed and inclusive, especially to individuals from communities traditionally underrepresented in biomedical research. A primary way the National Institute on Aging (NIA) has sought to enhance the recruitment and retention of participants in Alzheimer's Disease and Alzheimer's Disease-Related Dementias (ADRD) clinical trials is through the expansion of community engagement and outreach efforts.

The NIA-funded Alzheimer's Disease Research Centers (ADRCs) predominantly work with research volunteers as part of a long-term study on aging and brain health. These volunteers, or ADRC participants, are part of a longitudinal cohort who regularly undergo tests and assessments that help researchers gather valuable data to advance the scientific understanding of AD/ADRD. ADRC participants include individuals with and without cognitive impairment and represent a variety of racial and ethnic backgrounds and ages.

In addition to conducting a broad range of research, the ADRCs are charged with conducting tailored outreach to individuals living with dementia and their caregivers to promote participation in ADRC research as well as clinical trials conducted by other teams. Much of this robust outreach and engagement is performed through the Outreach, Recruitment, and Engagement (ORE) Cores located at each of the ADRCs. The ORE Cores interact with a Center's local community, work with NIA and non-governmental organizations to promote awareness of AD/ADRD among the public and clinicians, develop informational and research materials, and contribute to the Alzheimer's & Dementia Outreach, Recruitment, and Engagement (ADORE) resource database.[31] Successful activities include establishing community and participant advisory boards and community partnerships to build trust. To further support innovative ideas and opportunities for recruitment in AD/ADRD research, NIA included additional resources to support full time recruitment specialists at these Cores in the latest ADRC Request for Applications released in January 2023.[32] These specialists must have expertise in recruiting individuals from traditionally underrepresented communities and are responsible for outlining engagement, recruitment, and outreach plans for the research projects

[31] nia.nih.gov/research/alzheimers-dementia-outreach-recruitment-engagement-resources
[32] grants.nih.gov/grants/guide/rfa-files/RFA-AG-24-001.html

that leverages the resources of the Center. These activities reflect NIA's commitment to advance community engagement and outreach activities for AD/ADRD clinical trials and to develop a robust pool of community sites and providers supporting enrollment into AD/ADRD clinical trials.

The ADRCs promote participation in clinical trials by educating volunteers about research opportunities, performing screening procedures, and ultimately referring, or connecting, individuals to clinical trials for which they may be a potential good match for participation. While the ADRCs are not conducting these clinical trials, many of the trials are based at the same academic medical center or institution as the Center or at a nearby institution—and data indicate that the ADRCs, because of their longstanding relationships with ADRC volunteers and other individuals from their local community, are vital to the trial recruitment process. Evidence shows that ADRC engagement is extremely successful and has played a significant role in recruiting and retaining individuals into Alzheimer's clinical trials for decades, with participants recruited through commercial recruitment sites having significantly higher rates of study discontinuation than those recruited through the ADRCs.[33]

The ADRCs also each have local registries that include people living with dementia as well as other volunteers who are willing to participate in research studies. For all participants who wish to enroll in these registries, ADRCs obtain their consent to share their health information with other research teams. With the help of registries and other activities, ADRC researchers can refer participants to an array of clinical trials, including those funded by NIH, industry, universities, philanthropic organizations, and other federal agencies.

NIA also recognizes the need to invest resources to ensure the workforce now and in the future is capable of supporting clinical trials in all types of communities. NIH recognizes the value of a diverse scientific workforce for increasing the likelihood that traditionally underrepresented populations will participate in and benefit from research. [34] NIH UNITE[35] was established to identify and address structural racism in order to reduce barriers to racial equity in the intramural NIH workforce and the extramural biomedical research workforce, in addition to reducing health disparities and encouraging minority health research. A great deal of work has been done to strengthen the diversity of the workforce in the field of AD/ADRD. For example, all NIA ADRCs have a Research Education Component that specifically aims to enroll and educate a diverse set of trainees who will become the next generation of AD/ADRD researchers, and all ADRC Cores strive for a range of diversity in their staff.

Ensuring the diversity of AD/ADRD clinical trial participants, as well as diversity of participants in the preclinical work that enables clinical trials, is vital to ensuring that new treatments and prevention strategies work for all people. Over the last 40 years, the ADRCs have built trust within their communities and established partnerships to advance AD/ADRD research, including to enhance access to clinical trials. Acknowledging the importance of these community relationships, NIA will continue to engage the ADRC network to assist in supporting efforts in recruitment and retention, with the end goal of ensuring that the agency is funding rigorous

[33] ncbi.nlm.nih.gov/pmc/articles/PMC2922976/
[34] grants.nih.gov/grants/guide/notice-files/NOT-OD-20-031.html
[35] nih.gov/ending-structural-racism/unite

research that produces outcomes to inform the health and well-being of all individuals. NIA supports a myriad of other efforts focused on clinical trials recruitment and retention that complement these efforts.

Congenital Cytomegalovirus (cCMV)

cCMV is the most common viral infection infants are born with in the United States and the leading non-genetic cause of hearing loss. cCMV can cause stillbirth or miscarriage, visual impairment, developmental delays, and other health complications. Current anti-viral and prevention strategies for cCMV that have been clinically studied are based on outdated innovations. The Committee encourages NIH to support research on the development of lower-cost and high-sensitivity prenatal (fetal) diagnosis and newborn screening technologies; the design, evaluation, and acceleration of clinical trials for vaccines; strategies to prevent CMV-related stillbirth and miscarriages; cCMV disparities research; effectiveness studies of risk reduction measures during pregnancy; treatment trials for those who are pregnant to reduce transmission and fetal disease; and intervention trials to assist those infants born with CMV. The Committee directs NIH to submit an update in the fiscal year 2025 CJ on the development of this research.

Action taken or to be taken

The National Institutes of Health (NIH) recognizes the importance of research on newborn cytomegalovirus (CMV) infection, especially as the infection is linked to stillbirth, newborn death, deafness, and cognitive and motor delays. The *Eunice Kennedy Shriver* National Institute on Child Health and Human Development (NICHD) supports a number of key studies on CMV and research on newborn screening for CMV infection.

CMV-related clinical studies have been supported through clinical research networks, most notably NICHD's Maternal Fetal Medicine Units (MFMU) network. CMV research from the MFMU network has led to several key findings in the past year. MFMU scientists completed a phase III randomized, placebo-controlled clinical trial to test whether cytomegalovirus hyperimmune globulin treatment during pregnancy could be used to prevent CMV infections in newborns. Results showed that it did not decrease the likelihood of fetal or newborn cytomegalovirus infection or death, so researchers are now assessing new approaches for the prevention and treatment of CMV. Researchers were able to use data from that study to develop and validate a noninvasive method to predict the likelihood of congenital CMV infection when a pregnant person has primary CMV infection, even when ultrasound does not suggest fetal infection. The researchers found that combining four variables— three blood test measurements and the type of medical insurance held by the pregnant person—produced the best estimates of congenital CMV risk. Personalized estimates of risk for congenital CMV infection can help pregnant people and their healthcare providers make decisions about whether to undergo invasive testing to detect fetal CMV infection or whether to consider antiviral therapy. The calculator is freely available on the MFMU Network website.[36]

NICHD funded researchers are also examining the metabolic changes induced by maternal CMV infection during pregnancy and its effect on fetal development and immunity; the prevention of maternal CMV infections by increasing CMV risk-reduction behaviors in urban pregnant women; the development of infants from birth to 12 month of age with congenital CMV and the experiences of their mothers because infants with congenital CMV are at greater risk

[36] mfmunetwork.bsc.gwu.edu/

of developmental delays and disabilities; and whether CMV is acquired by women during pregnancy secondary to exposures to household contacts.

NICHD also collaborates with other institutes and centers on CMV research. For example, NICHD funded scientists are working with researchers funded by the National Institute of Allergy and Infectious Diseases (NIAID) to study the basic physiological mechanisms of CMV in animal models, with the goal of ultimately developing a broadly applicable CMV vaccine. In addition, clinical research networks and cohort studies focused on HIV have also included CMV research in several recent protocols. These groups are funded by multiple NIH Institutes and Centers, including both NICHD and NIAID.

Lastly, NICHD has issued funding opportunity announcements ~~is~~ to stimulate investigations including translational, epidemiologic and clinical studies and trials that improve the understanding, prevention and clinical outcomes of non-HIV infections, including CMV, transmitted from pregnant persons women to their offspring during pregnancy, labor and delivery, and breastfeeding.

Congenital Heart Disease (CHD)

The Committee commends NHLBI for its continued work to better understand causation, improve treatments and outcomes, support the growth of the clinical and research workforce, and integrate registry data and research datasets to facilitate research on congenital heart disease across the lifespan, including through the Pediatric Heart Network and the Pediatric Cardiac Genomics Consortium. The Committee encourages NHLBI to prioritize CHD activities outlined in its strategic plan, including improving understanding of outcomes and comorbidities, improving treatment options across the lifespan, and accelerating discovery, analysis, and translation by leveraging CHD registries and networks. The Committee requests NHLBI include in its fiscal year 2025 CJ a report on steps being taken to close these research gaps.

Action taken or to be taken

There are 2-3 million children and adults living with congenital heart disease (CHD) in the United States who face a high risk of early death and disability with increasing age. Guided by the National Heart, Lung, and Blood Institute (NHLBI) Strategic Vision's objective to investigate newly discovered pathobiological mechanisms important to the onset and progressions of heart, lung, blood and sleep diseases including congenital heart disease, the Institute's Bench to Bassinet program supports basic, clinical, and translational research focused on understanding the causes of CHD and its comorbidities and improving CHD diagnosis and treatment outcomes across the lifespan.[37]

The Bench to Bassinet program includes the Pediatric Cardiac Genomics Consortium (PCGC) and the Pediatric Heart Network (PHN). The PCGC has recruited 13,678 children with CHD, as well as 18,466 parents, to assemble one of the world's largest CHD cohorts for genomic analysis of CHD. The Consortium has made significant progress in improving our understanding of the genetic underpinnings of CHD and is now exploring more common heritable variants by combining study cohorts to increase power and leveraging data from NHLBI's flagship Trans-Omics for Precision Medicine (TOPMed) program for re-imputation, paving the way for development of precision medicine strategies for CHD. [38] In addition, findings from the PCGC have begun to elucidate the impact of genomics on clinical outcomes, including one of the most common co-morbidities, neurodevelopmental disability.[39]

The PCGC has expanded and refined its approach to deep phenotyping by harnessing big data from electronic health records and other existing databases and registries. In addition, the PHN works together with the PCGC to capture and analyze biospecimens and clinical phenotype data on all individuals enrolled in its studies and trials. The hope is to apply the findings from the PCGC to future PHN research protocols, thereby moving closer to applying personalized medicine to individuals affected with CHD across the lifespan.

PHN research, including clinical trials, is leading to the development of improved treatment and care of children with CHD. The Network is currently conducting six clinical research studies

[37] nhlbi.nih.gov/about/strategic-vision/goals-and-objectives/investigate-newly-discovered-pathobiological-mechanisms
[38] pubmed.ncbi.nlm.nih.gov/37026454/
[39] pubmed.ncbi.nlm.nih.gov/33084842/

that include children and adults living with CHD and acquired pediatric heart disease, including the PHN's first nurse-led clinical trial. The Safety of Apixaban on Pediatric Heart Disease in the Prevention of Embolism (SAXOPHONE) clinical trial, run in partnership with Bristol Myers Squib, recently demonstrated the safety of blood thinner, apixaban, in children with heart disease for prevention of blood clots.[40] The drug is easier to administer than current medications.

The Comparison of Methods of Pulmonary Blood Flow Augmentation in Neonates: Shunt versus Stent trial (COMPASS) is comparing a surgical treatment strategy to a newer strategy of ductal arteriosus stenting in neonates with complex CHD.[41] The trial uses an innovative approach of leveraging two CHD registries for data collection. The PHN's Multi-Institutional Neurocognitive Discovery Study in Adults with Congenital Heart Disease (MINDS-ACHD), is examining neurocognitive function and genetics in almost 500 young adults with congenital heart disease.[42] This important study has just successfully concluded recruitment, and data analysis is currently underway.

About half of children with Down syndrome have CHD. PHN is partnering with the NIH INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) program to conduct the Congenital Heart Disease: Impact on Learning and Development in Down Syndrome (CHILD-DS) study.[43] This study will help determine if having CHD and infant heart surgery affects the way children with Down syndrome develop and learn. In addition, the PHN has collaborated with INCLUDE to support six PHN Scholars career development awards. Two of those awards are for research on vascular health and risk factors in children with Down syndrome and analgesia in children with Down syndrome.

The PHN has also assisted in the NIH COVID-19 response. Shortly after multi-system inflammatory syndrome in children (MIS-C) was identified in the United Kingdom as a novel, serious condition arising after SARS-CoV-2 infection, the PHN launched The Long-Term Outcomes after Multi-system Inflammatory Syndrome in Children (MUSIC) study and recruited over 1200 children and adolescents.[44] MUSIC study participants are now being followed to evaluate any long-term issues through the NIH Researching COVID to Enhance Recovery (RECOVER) program. The PHN is also partnering with Pfizer on an FDA-mandated study of post-COVID-vaccine myocarditis, which launched in November 2022.[45]

NHLBI's CHD research portfolio CHD extends far beyond the Bench to Bassinet program. The Institute is funding cutting-edge trials of stem cell therapy for infants with CHD and tissue engineered vascular grafts for children with Fontan, and the development of a Fontan blood pump to improve circulation to the lungs. The Fontan procedure is a palliative surgical procedure used in children with single ventricle heart disease and diverts all oxygen-poor blood in a child's body to their pulmonary artery first to gather oxygen before going through their single heart ventricle to the body.

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[40] clinicaltrials.gov/study/NCT02981472
[41] clinicaltrials.gov/study/NCT05268094
[42] clinicaltrials.gov/study/NCT05270356
[43] clinicaltrials.gov/study/NCT05312177
[44] covidmusicstudy.com
[45] clinicaltrials.gov/ct2/results?cond=&term=NCT05295290&cntry=&state=&city=&dist=

NHLBI continues efforts to identify key scientific opportunities and address research gaps for improving CHD outcomes identified in the 2021 Future of Pediatric Cardiovascular Research workshop.[46] These include addressing diversity, equity and inclusion gaps in pediatric cardiovascular research by implementing targeted recruitment efforts to increase the diversity of participants in clinical trials, incorporating the perspectives of diverse communities more deeply into study design and performance and aligning pediatric cardiovascular research with patient priorities.

[46] nhlbi.nih.gov/events/2021/future-pediatric-cardiovascular-research

Deadliest Cancers

The Recalcitrant Cancer Research Act [RCRA] of 2012 (Public Law 112–239) focuses on cancers with a 5-year survival rate below 50 percent, which account for over 40 percent of all U.S. cancer deaths. While advances in some cancers have made it possible to reduce the overall rate of cancer deaths over the last several decades, there has been limited progress reducing mortality for these diseases.

In fiscal year 2020 (Public Law 116–94), Congress directed NCI to develop a scientific framework using the process outlined in the RCRA for stomach and esophageal cancers. In response, NCI formed a multi-disciplinary working group of its Clinical Trials and Translational Research Advisory Committee [CTAC] and has released a report listing suggested research focus areas. The Committee appreciates that NCI has transmitted its framework for gastric and esophageal cancers to Congress, emphasizing the important research efforts underway, as well as future opportunities.

The Committee requests to be kept informed of NCI's efforts on the pancreatic, lung, glioblastoma, esophageal and stomach cancer frameworks and directs NCI to start a similar process for primary liver cancer, including cholangiocarcinoma. Finally, given the devastating toll of all recalcitrant cancers and the lack of diagnostic and treatment resources currently available, the Committee urges NCI to identify future goals for each of the deadliest cancers (brain, esophagus, liver, lung, ovary, pancreas, stomach and mesothelioma) in the fiscal year 2025 CJ.

Action taken or to be taken

Gastric, esophageal, and GE junction

The National Cancer Institute (NCI) supports several promising research efforts to address challenges in understanding and making progress against gastric and esophageal cancers. In November 2022, the Gastric and Esophageal Cancers Working Group of NCI's Clinical and Translational Research Advisory Committee (CTAC) presented a report that highlighted three key goals for gastric and esophageal cancer research, including: 1) the identification of actionable biomarkers and targets within the processes of gastric and esophageal cancer development and progression, 2) the development of better assessment tools and therapies that are more tailored to the distinct characteristics of each person's disease, and 3) the development of improved tools for risk stratification, screening, early detection, and surveillance of gastric and esophageal cancers, as well as preventive interventions that are tailored to the characteristics of specific populations.

Knowledge generated through the NCI Program on the Origins of Gastroesophageal (GE) Cancers[47] provides a foundation for the identification of new biomarkers and targets for further evaluation. The program supports basic research to better understand how gastric and GE junction cancers develop at the cellular level, and to this end, several grants were awarded in the fall of 2022 to study the risk factors, precursors, and stem cell origins for distinct classes of gastric cancer, as well as mechanisms that control how cells change in the stomach leading to

[47] cancer.gov/about-nci/organization/dcb/research-programs/gej

cancer. Already, one study supported by the program found that distinct subsets of support cells in gastric tissue can influence the transition from inflamed tissue into the type of abnormal cells that can become precancerous.[48] In addition, an important goal of the program is to assess the biological mechanisms underlying increased prevalence of gastric and GE junction cancers in certain ethnic, racial, and gender populations.

The development of surveillance tools and preventive interventions that are tailored to the characteristics of specific populations is an important component of NCI's work to improve the prevention of and survival of gastric and GE cancers. For example, African Americans are disproportionately affected by esophageal squamous cell cancer (one of the two most common types of esophageal cancer), and NCI-supported researchers are studying whether oral microbiomes can be used as a biomarker for the disease in a Black South African population. Their work has revealed that the microbiome of the mouth is associated with the progression from a precancerous condition known as Barrett's esophagus to esophageal cancer,[49] a finding that could offer a non-invasive strategy for identifying high-risk patients in the U.S. population.

A major hurdle to treating gastric and GE cancers is the lack of standard or routine screening tests for these cancers, and once detected, the availability of precision treatment approaches. New approaches are underway to screen for increased risk of these cancers. For example, one NCI-supported study found that the presence of an unusual form of DNA in precancerous cells of people with Barrett's esophagus can indicate the likely transition into esophageal cancer.[50] In addition, researchers at the NIH Clinical Center are testing a new method for the detection of early-stage gastric cancer in people who have a mutation in the CDH1 gene, which is known to lead to stomach cancer. People who carry the CDH1 gene mutation are advised to get regular endoscopies with biopsies, even before symptoms appear.[51]

NCI's Gastrointestinal (GI) Specialized Programs of Research Excellence (SPOREs) have translational research projects that focus specifically on gastric and esophageal cancers.[52] This work includes establishing methods for early detection of esophageal cancer, studying potential racial differences in host immune response and the development of gastric cancer, and characterizing and overcoming resistance to a particular targeted therapy in metastatic gastric and esophageal cancers.

The Gastrointestinal Steering Committee (GISC), one of 13 disease-specific steering committees within NCI's National Clinical Trials Network (NCTN), addresses the design, prioritization, and evaluation of concepts for phase 2 and phase 3 clinical trials in adult gastrointestinal cancers and GE cancer subtypes. In particular, the committee emphasizes the importance of interdisciplinary research to develop biomarkers that can impact treatment selection and support scientific discovery. One NCTN trial is testing the efficacy of a drug that targets specific protein receptors that regulate cell growth, as a treatment for patients with advanced neuroendocrine tumors that most commonly develop in the GI tract.[53] This trial will end early, to enable a more rapid

[48] ncbi.nlm.nih.gov/pmc/articles/PMC10375042/
[49] ncbi.nlm.nih.gov/pmc/articles/PMC10327009/
[50] cancer.gov/news-events/cancer-currents-blog/2023/extrachromosomal-dna-barretts-esophageal-cancer
[51] clinicaltrials.gov/study/NCT04535414
[52] trp.cancer.gov/spores/gi.htm
[53] clinicaltrials.gov/ct2/show/NCT03375320

dissemination of results, due to a clear and dramatic improvement for patients who otherwise lack treatment options.

Liver, including cholangiocarcinoma

Liver cancer remains a difficult-to-treat disease with sub-optimal patient diagnosis and poor patient survival. Less than 20 percent of people with liver cancer that has spread to other sites in the body survive more than 5 years. Hepatocellular carcinoma (HCC), a type of liver cancer and one of the few cancers with rising incidence and mortality rates, is among the leading causes of cancer-related deaths worldwide. This is mainly due to the lack of screening tools, advanced stage of disease at diagnosis, and lack of effective therapies. In addition, health disparities in liver cancer are evident, including a significantly higher mortality rate in historically underrepresented groups. NCI-supported research aims to address these critical challenges, including tailored approaches for populations most affected by the disease.

One NCI-supported group of researchers developed a blood test that can accurately detect liver cancer, even in people with early stages of the disease.[54] In a preliminary study, the researchers used a type of artificial intelligence to analyze the differences in DNA fragments in the blood of people with and without liver cancer. Then, they used their findings to accurately identify samples from patients with the disease in another group of people with and without liver cancer. Ongoing research will see how well the blood test works in a large group of people who have not yet been diagnosed with the disease.

NCI intramural researchers have uncovered communication signals that liver tumor cells use to communicate with immune cells in the tumor microenvironment, potentially making liver tumors more aggressive.[55] They did this using a special method that provides genetic information at the single cell level. This work has important implications for designing effective therapies for liver tumors that have a mix of molecular characteristics.

Another group of researchers also used single cell technology to identify a niche of immune cells in HCC tumors that may be important for the tumor's response to immunotherapy.[56] The findings provide critical information on the underlying biology of how immunotherapy works in this type of cancer, which can impact future approaches to prevent or treat immunotherapy resistance.

Recent research by NCI intramural researchers revealed that liver cancer rates are almost three-fold higher in people with HIV than in the general population.[57] This is partially due to a higher prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) in this population. Based on these findings, an important future goal is to develop effective prevention and treatment strategies against HBV and HCV to reduce the incidence of liver cancer in people with HIV.

[54] cancer.gov/news-events/cancer-currents-blog/2023/liver-cancer-liquid-biopsy-fragmentomics
[55] ccr.cancer.gov/news/article/researchers-uncover-stable-molecular-networks-inside-liver-tumors
[56] pubmed.ncbi.nlm.nih.gov/37322116/
[57] dceg.cancer.gov/news-events/news/2023/liver-cancer-hiv

NCI supports two liver cancer SPOREs[58] that focus on new approaches to liver cancer diagnosis and therapy as well as the development of biomarkers for postoperative recurrence of the disease. In addition, the liver SPOREs aim to reduce deaths from liver cancer through research that explores novel early intervention and prevention strategies. For example, the Hispanic population in South Texas has one of the greatest increases in hepatocellular carcinoma rates, in part due to a high prevalence of obesity and diabetes. One liver SPORE project aims to establish the contributing factors and molecular drivers of liver fibrosis in this population, to identify and develop preventive interventions for those at risk of progression to liver cancer.

Cholangiocarcinoma is a type of liver cancer that begins in the bile ducts and is particularly hard to treat. Less than 10 percent of people who are diagnosed with cholangiocarcinoma survive for more than 5 years following the diagnosis. NCI-supported research is underway to better understand the biology and pathogenesis of this disease, in particular the immunosuppressive microenvironment of these tumors, and to identify new therapeutic options.[59,60]

Lung, including mesothelioma

NCI supports a range of programs aimed at improving outcomes for lung cancer patients. However, obstacles to progress include the long-term risk of lung cancer (even decades after a person stops smoking), the often-late stage at which lung cancers are discovered, and eventual resistance to therapy. Developing improved early detection methods is critical. In addition, while specific lung cancer genes have now been identified, there have been few advances in targeting these genes in treatment approaches. One example of an NCI program to address these challenges is the NCI Small Cell Lung Cancer Consortium, which is leading several research projects focused on understanding, screening for, and treating this disease with targeted approaches.

Other NCI-supported work focuses on non-small cell lung cancer (NSCLC). A large international clinical trial on early-stage NSCLC found that surgery to remove a piece of the affected lung lobe is as effective as removing the entire lobe for certain people.[61] This finding could mean better lung function for NSCLC survivors following surgery. NCI also launched the Pragmatica-Lung Study, a phase 3 randomized clinical trial of a two-drug combination to treat patients with advanced NSCLC.[62] This study is remarkable because it is one of the first NCI-supported clinical trials to use a trial design that removes many of the barriers that prevent people from joining clinical trials.

Lung adenocarcinoma, which is a type of NSCLC, is the most common lung cancer in the United States and represents the leading cause of cancer deaths in the country. While lung adenocarcinoma is strongly associated with a person's history of smoking, it is also the most common type of lung cancer in people who have never smoked. NCI-supported research aims to identify who is most susceptible to this devastating cancer. An international study, led by NCI intramural researchers, identified 12 new DNA variants that increase a person's risk of

[58] trp.cancer.gov/spores/hepatobiliary.htm
[59] reporter.nih.gov/search/s62z8e--tkWsZPT3WKRSVw/project-details/10590766
[60] reporter.nih.gov/search/s62z8e--tkWsZPT3WKRSVw/project-details/10711615
[61] cancer.gov/news-events/cancer-currents-blog/2023/early-stage-lung-cancer-sublobar-surgery
[62] cancer.gov/news-events/press-releases/2023/pragmatica-lung-study-begins-enrollment

developing lung adenocarcinoma.[63] The work increases the potential to identify individuals who may benefit from screenings for this cancer.

Another NCI study identified a gene signature associated with low survival rates for people with mesothelioma, a rare, fast-growing form of lung cancer.[64] The study's findings point to a subset of patients whose mesothelioma responds well to certain therapies, which has important implications for matching the most appropriate medicine to a person's cancer. NCI is also supporting a phase 1 clinical trial for patients with mesothelioma that has spread to other parts of the body.[65] In the trial, researchers are exploring the benefit of injecting a targeted medicine directly into tumors in combination with immunotherapy to boost the immune system's response against cancer.

NCI funds eight lung cancer SPOREs[66] to translate basic scientific findings into clinical applications and develop new and diverse approaches to the prevention, early detection, diagnosis, and treatment of lung cancer. Multiple lung cancer projects are underway through this funding mechanism, including research in underrepresented populations. For example, these studies include new therapeutic vaccination approaches in patients with certain types of lung cancer, research to understand the combined effects of environmental stress on lung cancer risk in Black men, the identification of racial differences in responses to immune checkpoint inhibition treatment, and new methods to counter specific types of treatment resistance.

An additional challenge is the greater uptake of recommended lung cancer screening for populations at increased risk. The uptake of lung cancer screening among recommended populations remains low, with rates in the single digits in many states across the country. NCI is supporting several research projects that aim to develop interventions to increase utilization of lung cancer screening, including patient-centered interventions, and personalized digital outreach interventions. In addition, NCI supports efforts to reduce disparities in lung cancer screening uptake. One study found that reducing racial disparities in early stage detection will require both individual level interventions as well as interventions aimed at structural-level factors.[67] Another study found that people who are eligible for lung cancer screening are less likely to receive that screening if they are enrolled in health plans with deductibles, and interventions at the health plan level may improve lung cancer screening uptake.[68]

Ovary

Despite the substantial decrease in ovarian cancer incidence and mortality rates in the last few decades, further research is needed to develop effective approaches for ovarian cancer prevention and early detection, and to establish biomarkers that can predict treatment response. In addition, Black and Hispanic women are less likely than white women to receive guideline-recommended treatment for ovarian cancer,[69] and therefore research is needed to understand how to address racial disparities in treating this disease.

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[63] dceg.cancer.gov/news-events/news/2023/lung-adenocarcinoma-gwas
[64] pubmed.ncbi.nlm.nih.gov/36773602/
[65] cancer.gov/news/article/clinical-trial-researches-drug-combination-with-immunotherapy-for-mesothelioma
[66] trp.cancer.gov/spores/lung.htm
[67] pubmed.ncbi.nlm.nih.gov/36435265/
[68] pubmed.ncbi.nlm.nih.gov/37582296/
[69] pubmed.ncbi.nlm.nih.gov/32142825/

A critical goal of NCI-supported ovarian cancer research is to develop effective prevention strategies. Given the low incidence of ovarian cancer in the general population, identifying these strategies is a major challenge. One study suggests that daily aspirin use may reduce the risk of non-mucinous ovarian cancer, regardless of the individual's genetic susceptibility to the disease.[70] Another recent NCI-supported study showed that women who have had fewer ovulatory years over their lifetime have a lower risk of certain types of ovarian cancer.[71] This finding matches the known protective effect against ovarian cancer by oral contraceptive use, which suppresses ovulation.

NCI funds six ovarian cancer SPOREs[72] that focus on early detection, risk assessment, imaging technologies, targeted therapies, and new therapeutic approaches for patients with newly diagnosed and relapsed ovarian cancer. For example, one project recently revealed that ovarian cancer may be linked to populations of disease-causing bacteria in the reproductive tract.[73] The findings, if confirmed in larger studies, could inform a novel approach of using the microbiome for the screening and early detection of ovarian cancer.

The identification of biomarkers for treatment response is important to establish populations of people who would benefit from certain treatments. PARP inhibitors, which prevent repair of damaged DNA, have been transformative for patients with certain types of primary and recurrent ovarian cancer. However, cancer cells can eventually become resistant to these treatments. NCI intramural researchers recently identified two genes whose activity could help determine which patients are the best candidates for another drug that may be beneficial for patients whose ovarian cancer has become resistant to PARP inhibitors.[74]

Another important goal of biomarker research is to identify biomarkers that indicate when a treatment should not be given, to spare patients from the sometimes-severe side effects of a therapy when it is unlikely to help in a meaningful way. One recent NCI-supported study focused on biomarkers that could help predict if a patient's cancer would respond well to chemotherapy. The researchers identified a group of proteins that can predict which tumors are unlikely to respond to platinum-based chemotherapy, a type of ovarian cancer treatment that disrupts DNA and causes cancers cells to stop growing and die.[75] Other researchers found that when given alongside chemotherapy, a drug called bevacizumab that starves tumors through prevention of new blood vessel growth, may be most effective only in patients whose ovarian cancer does not respond well to chemotherapy.[76]

Pancreas

Pancreatic cancer remains one of the most difficult to treat cancers for both men and women. It is responsible for 8 percent of cancer deaths in the United States, despite accounting for only 3 percent of new cancer diagnoses. With only modest improvements in pancreatic cancer

[70] ncbi.nlm.nih.gov/pmc/articles/PMC9958519/
[71] pubmed.ncbi.nlm.nih.gov/36688720/
[72] trp.cancer.gov/spores/ovarian.htm
[73] pubmed.ncbi.nlm.nih.gov/36639731/
[74] pubmed.ncbi.nlm.nih.gov/37343085/
[75] pubmed.ncbi.nlm.nih.gov/37541199/
[76] pubmed.ncbi.nlm.nih.gov/36252167/

survival—and an incidence rate that increased by 1 percent per year from 2001 to 2018—pancreatic cancer remains a major public health concern, and this is amplified by critical challenges to detect and treat early-stage disease. NCI supports a range of programs that aim to better understand pancreatic cancer biology, advance pancreatic cancer screening and detection technology, and develop more effective therapies.

Work is underway to investigate the early biological events that govern pancreatic cancer development and growth. The most common type of pancreatic cancer is pancreatic ductal adenocarcinoma (PDAC). The NCI-led Pancreatic Ductal Adenocarcinoma Stromal Reprogramming Consortium (PSRC) aims to understand how this cancer develops, with a particular focus on elements in the tumor microenvironment that drive PDAC progression and response to therapy.[77] PSRC projects[78] include research on cellular signaling networks that influence tumor growth and investigations into the cross-talk between tumor cells and surrounding elements. One study examined pancreatic tissue from brain dead donors who had no known pancreatic disease, allowing for molecular characterization of the cells prior to postmortem degradation of the tissue. Remarkably, most donors had abnormal pancreatic cells that were similar to cancer cells at the molecular level, the first-ever very-early characterization of its kind that sets the stage for efforts to better understand the surrounding biological factors that restrain or, conversely, promote the progression of these cells to cancer.[79]

Information about the underlying biology of pancreatic cancer aids the development of better pancreatic cancer screening and detection technology, as well as the identification of prognostic biomarkers. For example, one study found that the organization of different types of immune cells within pancreatic tumors may be associated with how well the cancer will respond to treatments and how long the patient is likely to survive.[80] Another group of NCI-supported researchers found a set of genetic markers that could help identify early pancreatic cancer risk by examining a specific type of precancerous cyst in the pancreas.[81] Now, they are working to identify those markers in the cyst fluid to aid clinical decision-making about cyst removal prior to cancer development.

Mutations in a single family of genes, known as the RAS family, drive 95 percent of pancreatic cancers. Over the last several years, NCI's RAS Initiative has made significant advances in targeting these genes in cancer treatments. The most prevalent mutations in the development of PDAC occur in the KRAS gene. The most common of these KRAS mutations is called G12D, which occurs in about 35 percent of pancreatic cancers. In a recent NCI-supported study in mice, researchers identified a promising experimental drug that directly targets the G12D mutation.[82] The new drug shrank or halted tumors in mouse models of pancreatic cancer that closely mimic the human disease.

[77] cancer.gov/about-nci/organization/dcb/research-programs/psrc
[78] cancer.gov/about-nci/organization/dcb/research-programs/psrc#funded-projects
[79] pubmed.ncbi.nlm.nih.gov/37021392/
[80] pubmed.ncbi.nlm.nih.gov/36112643/
[81] pubmed.ncbi.nlm.nih.gov/36930707/
[82] cancer.gov/news-events/cancer-currents-blog/2023/pancreatic-cancer-kras-g12d-mrtx1133

NCI also supports two pancreatic SPOREs[83] that are investigating new treatment approaches for PDAC. For example, one project is developing a new combination therapy to target a type of cell degradation, in the treatment of KRAS-mutant PDAC. Another project is investigating a completely new immunotherapy target to stimulate an immune response against PDAC tumors.

NCI regularly supports studies at the leading edge of clinical research to discover new, more effective drugs for pancreatic cancer. Recently, an NCI-funded research team tested a personalized mRNA vaccine against PDAC and found that it elicited a strong anti-tumor immune response in about half of the participants in a small study; the vaccine will be tested in a larger clinical trial soon.[84] Other NCI-supported researchers have successfully altered immune cells in the tumor microenvironment to improve pancreatic cancer response to treatment in preclinical testing of a triple immunotherapy combination. In addition, ongoing research is using microbes to degrade some of the structural components surrounding tumors to better expose tumors to therapies that require direct access, which could significantly improve efficacy and reduce toxicity for PDAC patients.

To date, surgery remains the only potentially curative treatment for pancreatic cancer. Finding and removing all cancerous tissue is critical to prevent the recurrence of disease following surgical treatment. NCI-supported researchers are developing a fluorescent probe that can bind to PDAC tumors and guide surgical removal of the cancer to improve treatment outcomes. Recently, researchers tested a human-specific version of the fluorescent probe in patient-derived pancreatic cancer tumors grafted onto mice and reported that it is safe and effective in this preclinical model.[85]

Brain, including adult and pediatric brain tumors

There are over 130 different types of adult and childhood brain cancers. This diversity, as well as the rarity of some types, creates unique challenges to brain cancer detection, diagnosis, and treatment. For example, many brain cancer cells look similar but may require different treatments, the blood-brain barrier poses a unique challenge for treatment delivery, and childhood brain cancer patients may face long-term impacts from treatment. In addition, the development of personalized treatments, enhanced clinical trial participation, better responses to immunotherapy and radiation therapy, and improved quality of life for people with brain cancer are all important goals to reach.

NCI supports research projects that span the breath of these goals. For example, researchers are investigating a targeted drug delivery system to overcome the blood-brain barrier and resistance to therapy in glioblastoma, an aggressive brain cancer that begins in brain support cells called astrocytes.[86] Other researchers aim to "reprogram" the tumor microenvironment in glioblastoma to improve the effectiveness of immunotherapy.[87] Additional research is exploring the identification of tumor-derived DNA in cerebral spinal fluid to track fast-growing gliomas, a

[83] trp.cancer.gov/spores/pancreatic.htm
[84] nih.gov/news-events/nih-research-matters/mrna-vaccine-treat-pancreatic-cancer
[85] pubmed.ncbi.nlm.nih.gov/35640060/
[86] reporter.nih.gov/search/WRWzcYU3OEaU_DstIJF6Dg/project-details/10659749
[87] reporter.nih.gov/search/LGIFzuSAvkeUVKBkzGJBpw/project-details/10595045

cancer of the brain's glial cells that support neurons, in hopes of forgoing invasive brain biopsies during disease management.[88]

NCI supports six brain SPOREs[89] that aim to improve prognostic testing and treatment, and to better understand brain cancer in underrepresented populations. Several brain SPORE groups are focused on immunotherapy approaches, including vaccines, to overcome the immunosuppressive surroundings of the brain tumor microenvironment. In cutting edge research, one group is exploring the use of oncolytic virus therapy, which uses genetically engineered viruses to seek out and destroy cancer cells, for the treatment of malignant glioma. Another group is characterizing the genetic landscape of gliomas in Blacks and Hispanics to better understand clinical outcomes in these underrepresented populations.

Meningiomas are tumors that form in the outermost tissue layer that protects the brain and spinal cord and represent the most common type of brain tumor. They are more prevalent in older adults, women, and African Americans, all of whom tend to be underrepresented in clinical trials. About 20 to 30 percent of meningiomas are fast-growing and potentially deadly. To date, there are no effective treatments for this disease. To meet this critical need, NCI supports research to understand druggable drivers of meningioma tumor formation. NCI-funded research is also exploring non-invasive liquid biopsy approaches for obtaining an accurate prognosis for this disease and other types of brain cancer. One such study measured certain DNA alterations in blood and tissue samples from patients with meningioma and used artificial intelligence to accurately identify and predict meningioma recurrence.[90]

Another type of brain cancer called papillary craniopharyngioma is rare but devastating. The disease, which is more likely to occur in adults, often requires surgery, radiation therapy, or both. While these craniopharyngiomas do not spread, their location near certain parts of the brain means that surgery and radiation treatments can damage healthy brain tissue and cause life-altering health problems. Recently, an NCI-funded clinical trial discovered that a combination of targeted drug therapies against specific proteins in the cancer cells can delay or even eliminate the need for additional treatments.[91]

Diffuse midline gliomas are the most aggressive brain tumors in children and young adults. NCI intramural researchers are leading a clinical trial to test a targeted anti-cancer drug for the disease. [92] As part of the trial, the researchers will closely monitor the ability for the drug to reach the brain.

Medulloblastoma is another aggressive brain cancer that affects children and young adults and is the most frequent malignant childhood brain tumor. NCI is committed to improving pediatric cancer treatments, and research is underway to identify the optimal treatment options for these patients. For example, an NCI-funded international study to improve neurocognitive outcomes in young children with low-risk medulloblastoma is the first ever randomized study that aims to

[88] reporter.nih.gov/search/65l2xvkVq0ezF5UKqyua2Q/project-details/10610117
[89] trp.cancer.gov/spores/brain.htm
[90] pubmed.ncbi.nlm.nih.gov/37704607/
[91] pubmed.ncbi.nlm.nih.gov/37437144/
[92] ccr.cancer.gov/news/article/clinical-trial-researching-therapy-for-aggressive-gliomas

compare two highly effective treatment regimens that were designed to avoid radiation therapy to the developing brain, which can lead to neurocognitive issues.[93]

Additionally, NCI supports the Pediatric Brain Tumor Consortium (PBTC) to develop and implement clinical trials to evaluate new agents and new treatment approaches for children with brain tumors, with a focus on children whose brain cancer has progressed or returned after their initial treatment.[94] There are currently 8 open PBTC therapeutic studies and 12 non-therapeutic studies. The participating academic centers and hospitals span the nation, and they are responsible for the diagnosis and treatment of a large number of children with brain tumors in the U.S. and Canada.

[93] reporter.nih.gov/search/LGIFzuSAvkeUVKBkzGJBpw/project-details/10720110
[94] pbtc.org/

Diet and Chronic Disease Research

The Committee recognizes the importance of ongoing activities to better understand the impact of food and diet on the development of mucosal immunity and the relevance of this topic to Crohn's disease and ulcerative colitis and to other digestive and autoimmune or immune-mediated diseases. The Committee encourages NIH to convene a scientific workshop, supported by multiple Institutes, Centers or Offices, including the Office of Nutrition Research, and to report to the Committee the outcomes of the workshop, including possible future research opportunities.

Action taken or to be taken

The NIH Office of Nutrition Research, in collaboration with the National Cancer Institute, the National Institute on Aging, the National Institute of Allergy and Infectious Diseases (NIAID), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Office of Dietary Supplements are in the process of developing a workshop in August 2024 focused on understanding the impact of early-life dietary exposures on the development of mucosal immunity and the relevance of this topic to digestive and autoimmune/immune-mediated digestive diseases, including inflammatory bowel disease (IBD) such as Crohn's Disease and ulcerative colitis. Understanding the impact of critical dietary factors modulating gut immune development and function will enhance our basic understanding of the development of autoimmune/immune-mediated diseases that result from dysregulated immune responses, such as IBD, food allergies, rheumatoid arthritis, cancer, metabolic syndrome, and obesity. This workshop will bring together experts with the aim of understanding the current knowledge and identifying scientific gaps in these areas and will focus on delineating the steps forward to address the gaps.

Moreover, NIDDK and NICHD support research on the fundamental contributions of diet and nutrition, including microbial metabolites, to mucosal immunity and chronic digestive diseases such as IBD, including Crohn's disease and ulcerative colitis. NIDDK has funded research in animal models associating lower fiber intake with intestinal inflammation due to gut microbial imbalances and breakdown of the protective mucus barrier lining the colon. Additional studies in humans have shown improvements with increased dietary fiber intake in biomarkers of gut-mediated inflammation throughout the body. Ongoing research is investigating immune-based mechanisms for improving intestinal health through microbial metabolites derived from dietary factors, and mapping components of intestinal inflammation due to dietary stress. NICHD has funded research bridging pharmacodynamic biomarkers to endoscopic and clinical outcomes in pediatric IBD, as well as characterizing disease trajectory to improve treatment in pediatric Crohn's Disease. Additional NICHD studies have focused on inflammatory mechanisms of puberty dysregulation in colitis. In addition, NICHD supports research with novel pharmacological approaches (e.g., 2′-Fucosyllactose) for the treatment of IBD in the pediatric population and continues to fund research evaluating sex differences in growth in pediatric patients with Crohn's Disease.

NIAID also supports research to help improve understanding of how nutrition and supplementation can directly and indirectly control immune function in health and disease. A

Phase II clinical trial led by NIAID-supported investigators found that supplementing the diet with a probiotic, *Bacillus subtilis*, eliminated more than 95 percent of *Staphylococcus aureus*, a common pathogenic bacterium that colonizes the human body, without altering the other microbiota. A NIAID-supported clinical study is being conducted to determine whether dietary intervention to increase fiber and decrease fat reduces infection recurrence by *Clostridium difficile*, a common pathogenic bacterium, in oncology patients. Another Phase II clinical trial led by NIAID-supported investigators is focused on using a restrictive diet to relieve gastrointestinal symptoms of patients with IBD and chronic granulomatous disease. The Mucosal Immunology Studies Team is conducting a study entitled, "Gut Intrinsic Inflammatory Responses," to investigate the capacity of the gut to switch from tolerance (an unresponsive state) to immune activation in response to infection, microbiota, and nutrition or food. NIAID also has hosted several widely attended virtual seminars focused on the impact of diet on the composition, function, and development of the gut microbiome. These were planned and co-hosted by the Trans-NIH Microbiome Working Group, the Strategic Plan for NIH Nutrition Research[95] Microbiome, Diet & Health Interrelationships Implementation Working Group, and other NIH institutes, centers, and offices.

[95] dpcpsi.nih.gov/onr/strategic-plan

Endometrial Cancer and Obesity

Endometrial cancer is the most common gynecologic cancer, and the fourth most common malignancy among women in the United States trailing only breast, lung, and colorectal. In fact, in 2023, it is estimated that 66,200 new cases of uterine cancer will be diagnosed, and about 13,030 women will die from the disease. Obesity is the strongest known risk factor for the most common type of endometrial cancer, and the disease is more than three times as common in people with obesity. The Committee recognizes that obesity is a growing public health issue, and as rates of obesity continue to increase, the number of women diagnosed with endometrial cancer is also expected to rise. Therefore, the Committee requests an update in the fiscal year 2025 CJ on collaborative research efforts across NIH, other NIH-supported extramural research projects, and research efforts focusing on the link between obesity and endometrial cancer.

Action taken or to be taken

The National Cancer Institute (NCI) is dedicated to better understanding underlying risk factors associated with the development and progression of endometrial cancers (EC) and to improving outcomes for all women with this disease. For example, NCI currently supports research investigating the underlying causes of EC to better predict risk and work toward improved prevention and early detection of this cancer.

While adult obesity has long been recognized as a strong risk factor for the development of EC, the associations of early life obesity and EC have been inconclusive. Recently, researchers in the Epidemiology of Endometrial Cancer Consortium (E2C2), an NCI-supported consortium dedicated to studying the etiology of EC through investigator collaboration,[96] showed that obesity in young adulthood is associated with EC risk (even after accounting for body mass index in adulthood).[97] Further, weight gain over the life course was shown to also be associated with EC risk, while weight loss was inversely associated. The results suggest that maintaining a healthy weight over a lifetime is important for EC prevention and reducing risk.

NCI also funds the Route 66 Endometrial Cancer Specialized Program of Research Excellence (SPORE) that includes interactive research teams in Missouri, Oklahoma, and New Mexico.[98] One of the projects in this SPORE is aimed at early prevention and uterine preservation (an important option for younger patients who wish to preserve fertility) in premenopausal women with obesity and EC.[99] Obesity is known to promote the development of atypical endometrial hyperplasia (AEH), a precursor of endometrial cancer. Researchers will test different therapeutic approaches in combination with behavioral weight loss interventions in two trials to determine the impact of each approach on uterine preservation and EC prevention. This could provide an important option for retaining fertility in EC patients.

NCI also conducts numerous preclinical and clinical studies to identify more effective treatments for endometrial cancer progression and recurrence. For example, an NCI-funded project is assessing the use of metformin, a drug commonly used to treat type 2 diabetes, in both mouse

[96] epi.grants.cancer.gov/eecc/
[97] pubmed.ncbi.nlm.nih.gov/37029916/
[98] trp.cancer.gov/spores/abstracts/wustl_endometrial.htm#h02
[99] reporter.nih.gov/search/xXDQvXGHG0aq-Xn_kzRTww/project-details/10711638

and human studies. The researchers have found that metformin increased efficacy against endometrial cancer in obese mice compared to non-obese mice,[100] and they are conducting a clinical trial of metformin as a potential treatment for endometrial cancer in obese compared to non-obese patients.[101]

In a separate NCI-funded study aimed at developing new therapeutic approaches for EC, NCI-supported researchers identified a molecular pathway that promotes the obesity-driven progression of endometrioid endometrial cancer (EEC), the most common subtype of EC.[102] In preclinical assays, the researchers found that inhibiting this pathway significantly reduced obesity-induced EEC progression in an animal model, offering a potential treatment option to improve outcomes for patients with EC driven by obesity.

Additionally, a recent NCI-funded award will study combination therapies targeting insulin signaling in EC.[103] Researchers are examining the role of hyperinsulinemia, a condition in which insulin levels in the blood are higher than a healthy level, in treatment approaches for EC. Hyperinsulinemia has been directly implicated in EC pathogenesis and can limit the efficacy of PI3K inhibitors, drugs commonly used to treat cancer patients by targeting mutations in a pathway that controls cell survival and proliferation. Using a combinatorial treatment approach, researchers will test strategies to lower insulin and blood sugar levels in conjunction with PI3K inhibition to limit EC progression. This research aims to identify approaches for mitigating the adverse effects of hyperinsulinemia that can be implemented in clinical practice.

[100] ncbi.nlm.nih.gov/pmc/articles/PMC6834476/
[101] projectreporter.nih.gov/project_info_description.cfm?aid=9869698&icde
[102] pubmed.ncbi.nlm.nih.gov/36358818/
[103] reporter.nih.gov/search/VO12-9kZpEeSyaa8ka0hzw/project-details/10637167

Equipping NIH Research Programs to Target HIV/AIDS Hotspots

The Committee directs the NIH Office of AIDS Research to coordinate NIH-wide resources to focus on areas with the highest prevalence of HIV/AIDS, for example, utilizing Centers for AIDS Research [CFARs] to develop targeted interventions that increase the use of pre-exposure prophylaxis [PrEP] and better protect those communities from HIV transmission and its consequences.

Action taken or to be taken

For almost 4 decades, the National Institutes of Health (NIH) Office of AIDS Research (OAR) has built strong partnerships with other government agencies, academia, and communities affected by HIV to catalyze, coordinate, convene, and communicate HIV/AIDS research across the NIH. OAR coordinates NIH-funded HIV/AIDS research to ensure optimal alignment with the highest scientific priorities. These efforts have translated innovative biomedical, behavioral, and social sciences research into highly effective HIV prevention, treatment, and care strategies which promise to yield maximal impact for the U.S. public. Protecting communities from HIV transmission relies not only on pre-exposure prophylaxis (PrEP), a very effective HIV prevention tool, for people at high risk of aquiring HIV, but also on rapid testing and expeditious treatment of anyone with HIV. NIH-funded research has shown that treating people with HIV effectively by reducing the virus to undetectable levels in the blood is highly effective at preventing sexual transmission of HIV to others--an approach known as "Undetectable = Untransmittable," or "U = U."

These advances addressing HIV transmission have not reached all of the people who may benefit from them. In the United States, more than half of new HIV diagnoses are concentrated in 50 local areas and jurisdictions (48 counties; Washington, D.C.; and San Juan, Puerto Rico). Focusing on these areas as well as the seven states with a substantial rural burden, the Ending the HIV Epidemic (EHE) initiative was launched by the United States Department of Health and Human Services (HHS) in 2019 to reduce new HIV infections in the United States by 75 percent by 2025 and 90 percent by 2030. While progress to date indicates a modest reduction in the overall estimated incidence in these areas (34,800 to 32,100 persons in 2019 to 2021, respectively[104]), more work is critical to achieve these ambitious goals. NIH strengthens the EHE initiative by funding implementation research—research on how best to use evidence-based interventions in real-world settings—in the geographic areas disproportionately affected by HIV, often focusing on minoritized populations who are at the highest risk. This crucial work at the community level is based on the four pillars of the EHE strategy—diagnose, treat, prevent, and respond—to end the HIV epidemic in the United States.

To achieve the aims of the EHE initiative, OAR coordinated across NIH to fund new research projects at existing Centers for AIDS Research (CFARs) and AIDS Research Centers (ARCs). Some of these Centers now serve as regional hubs supporting implementation research. To better protect communities with high HIV burden, NIH-funded researchers collaborate with local groups and institutions to explore which interventions are most effective. NIH also funds activities synthesizing lessons learned across EHE projects. Several CFARs and ARCs are participating in multi-site studies, such as developing a protocol to assess the rapid

[104] ahead.hiv.gov/

implementation of antiretroviral drugs for HIV prevention and treatment across six different EHE localities. This research will inform the development of generalizable best practices to improve HIV prevention, testing, treatment, and outbreak response – all four pillars integral to the success of the EHE initiative in the United States.

NIH is committed to supporting high priority research focused on lowering HIV transmission and ending the HIV/AIDS pandemic in the United States and globally.

Fund the Person, Not the Project

While many labs are funded by R01-equivalent grants, the R35 mechanism arguably allows scientists more flexibility and freedom to pursue the best possible science. At present, only NIGMS uses the R35 to a significant extent (more than four times as often as the rest of NIH put together), with its Maximizing Investigators' Research Award [MIRA] program. The Committee directs NIH to convene an expert panel on expanding the R35/MIRA grant type such that is more widely used across NIH Institutes and Centers, and to report back to the Committee within 1 year on NIH's plans for expanding the R35 along with its plans for evaluating the impact on scientific progress.

Action taken or to be taken

The NIH R35 grant type provides long-term support to investigators with an outstanding record of research productivity.[105] Per the Committee's request, NIH plans to consider options for expanding use of the R35 grant type across the agency, as appropriate. This may include convening an internal NIH group in fiscal year 2024 to begin assessing the feasibility and possible recommendations on expanding the use of R35s more widely across NIH. Any specific actions that may be taken must also align with existing grant policies and procedures, such as keeping in mind that NIH makes awards to institutions not individual researchers (with some notable exceptions for career development awards). [106,107,108]

An example of an R35 award is the National Institute of General Medical Sciences (NIGMS) Maximizing Investigators' Research Award (MIRA), which supports a scientific program of study within an established or early-stage investigator's laboratory rather than a series of individual projects.[109] MIRA provides investigators with:

- the flexibility to change directions to pursue novel insights and research questions;
- an enhanced stability of support through an additional year of funding and a high renewal success rate;
- separate peer review processes for established and early stage-investigators to maintain focus on the potential of research proposed by each group of investigators.

In addition to the NIGMS MIRA program, use of the R35 grant type to support outstanding investigators continues to expand across other NIH Institutes and Centers:

- National Institute of Dental and Craniofacial Research (NIDCR) Sustaining Outstanding Achievement in Research (SOAR) award provides up to eight years of support to NIDCR-funded investigators, who are in their mid-career stage, and have outstanding records of research productivity, mentorship, and professional service to the research

[105] grants.nih.gov/grants/funding/ac_search_results.htm?text_curr=r35&Search.x=0&Search.y=0&Search_Type=Activity
[106] grants.nih.gov/grants/who-is-eligible.htm
[107] nexus.od.nih.gov/all/2018/05/29/waitits-not-my-grant
[108] grants.nih.gov/grants/policy/nihgps/HTML5/section_12/12.2_types_of_career_development_awards.htm
[109] nigms.nih.gov/Research/mechanisms/MIRA

community.[110] It is expected that the SOAR Award will propel the investigator along this career trajectory and allow them to embark on ambitious longer-term projects of extraordinary potential within the NIDCR mission.

- National Cancer Institute (NCI) Outstanding Investigator Award provides up to seven years of support to accomplished investigators with outstanding records of cancer research accomplishments who propose to conduct exceptional research.[111] The award allows investigators the opportunity to take greater risks, be more adventurous in their lines of inquiry, or take the time to develop new techniques.

- National Institute of Neurological Disorders and Stroke (NINDS) Research Program Award provides principal investigators with up to eight years of support and the flexibility to redirect their time from grant administrative aspects to more engagement in the lab.[112] Researchers can advance their long-term research goals, rigorously explore exciting research opportunities, and mentor students and postdoctoral researchers.

In addition to the R35 grant type, NIH uses various other innovative funding approaches that provide some level of additional flexibility to support the most meritorious research possible beyond the traditional R01-equivalent grant. The Common Fund's High-Risk, High-Reward Research programs and funding through Other Transaction Authority as examples provide some level of additional flexibility when conducting and managing research. That said, NIH balances its use of the R35 grant type with R01-equivalent and other grant types to fund innovative research ideas based on various factors, like program balance, research needs, and budgetary resources.

[110] grants.nih.gov/grants/guide/rfa-files/RFA-DE-24-006.html#:~:text=The%20objective%20of%20the%20NIDCR,service%20to%20the%20research%20community.
[111] cancer.gov/grants-training/grants-funding/funding-opportunities/oia/award-recipients
[112] ninds.nih.gov/funding/about-funding/types-research-support/achievement-awards/ninds-research-program-award-r35

Geroscience

Recent advances in geroscience suggest it may be possible to prevent or treat a wide range of adult-onset health concerns, including functional declines such as frailty and lost resilience, and overt diseases such as Alzheimer's Disease, cancer, cardiovascular diseases and many others. This could be achieved by slowing or reversing certain genetic, molecular and cellular hallmarks of aging discovered through research on the basic biology of aging. The Committee strongly urges NIA to prioritize funding for geroscience research. The Committee also understands that the enormous promise of this field is limited by a shortage of investigators with expertise in the biology of aging and the clinical translation of basic research findings. Therefore, NIA should increase support for early career investigators, especially postdoctoral researchers and junior faculty, to help attract, retain, and develop top talent in the field of geroscience. Finally, the Committee encourages NIA to increase funding for basic and translational research in aging to provide more options and test more treatments as quickly as possible.

Action taken or to be taken

The field of geroscience seeks to understand the genetic, molecular, and cellular mechanisms that make aging a major risk factor and driver of numerous chronic conditions and diseases, including Alzheimer's disease, cancer, cardiovascular diseases, and many others. This growing field is focused on the discovery and translation of methods and interventions to prevent, minimize, or reverse age-related changes in the body that diminish health and quality of life for older people. Research on the biology of aging has shown that the course of aging can be altered in mammals. Geroscience interventions encompass ways to interrupt the molecular and cellular drivers of aging, such as through diet, physical activities, and pharmacology.

The National Institute on Aging (NIA) funds research on geroscience-related topics across its four extramural scientific divisions—Aging Biology, Behavioral and Social Research, Geriatrics and Clinical Gerontology, and Neuroscience — and its Intramural Research Program (IRP). NIA research includes studies investigating age-related molecular changes as well as those aimed at developing interventions for disorders and conditions related to aging. One example is the Translational Geroscience Network[113] through which NIA provides infrastructure for geroscience-based clinical trials of interventions that impact aging mechanisms to treat chronic conditions in older adults. NIA also conducts and supports large, long-term longitudinal studies to understand what biological mechanisms of aging are most relevant for the development of chronic diseases and therefore should be prioritized for interventions, as well as how those may be shaped by social, behavioral, and environmental factors. For example, NIA researchers are currently running the first mouse longitudinal cohort study to examine common metrics of aging across the entire lifespan in various mouse models, known as the Study of Longitudinal Aging in Mice (SLAM).[114] Similarly, NIA researchers are running the first longitudinal study of aging in rats (STARRRS—Successful Trajectories of Aging: Reserve and Resilience in RatS) aimed at understanding factors that contribute to cognitive aging. Using these studies, researchers are seeking to identify and characterize predictors of physical and cognitive function with aging and age-associated conditions in model organisms and assess whether these changes are consistent with those observed in human studies that assess the same variables, such as the Baltimore

[113] reporter.nih.gov/search/IRsDsUbYgk-uw6Vo3uXPTA/project-details/10539281
[114] reporter.nih.gov/search/3pt7CI96QUSbTqrby1dUGA/project-details/10473349

Longitudinal Study of Aging. Additionally, to understand the role of the behavioral and social sciences in geroscience, NIA convened a workshop[115] to examine the intersection of behavioral and social processes (including social determinants of health) and the biological mechanisms of aging to advance the discovery and validation of biomarkers of aging as well as more fully integrate evidence from the social sciences into geroscience research. To be able to provide information on funding levels of these and other geroscience research projects, NIH plans to establish a Research, Condition and Disease Categorization (RCDC) category for research related to geroscience.

NIA recognizes the need for expanded geroscience educational and training programs to support the pipeline of investigators into geroscience. To address these needs, NIA released a funding opportunity to support creative educational programs aimed at enhancing and expanding broader awareness of geroscience research.[116] This funding opportunity is designed to support courses for skills development, research experiences, curriculum or methods development, and outreach programs on the topics of geroscience. These educational activities involve undergraduates, postdoctoral fellows, and early-career scientists. This opportunity will support networking with experts in the geroscience field, outreach materials to promote awareness of geroscience among the public, the curation of important geroscience publications and clinical trials, and the fostering of innovative approaches to enhance diversity within the field. NIA is currently supporting three courses for education in geroscience that emphasize health disparities research in undergraduate training,[117] to develop a shared geroscience curriculum and educational materials for physicians,[118] and to create a geroscience coursework curriculum for training undergraduate students, including hands-on experiences in laboratories.[119] NIA also supports expanding existing training programs to bring in the next generation of geroscientists. For example, NIA recently supported Ruth L. Kirschstein National Research Service Awards (NRSA) for geroscience training at several institutions, including the University of Southern California,[120] the University of Oklahoma Health Sciences Center,[121] the University of Washington,[122] and the University of Texas Health Science Center.[123] Additionally, NIA is supporting an Academic Leadership Career Award[124] to assist with geroscience investigator faculty development and research at the University at Buffalo.

NIA remains a leader of the NIH-wide Geroscience Interest Group (GSIG), which includes participation by 16 NIH ICs and the NIH Office of the Director that are actively involved in this field. In order to identify gaps and opportunities to advance the field towards clinical applications, the GSIG held the fourth NIH Geroscience Summit, *Geroscience for the Next Generation*[125] in April 2023. This three-day Summit brought together a diverse group of

[115] nia.nih.gov/sites/default/files/2023-02/2022.10.31_geroscience_workshop_summary_final.pdf
[116] grants.nih.gov/grants/guide/pa-files/PAR-22-214.html
[117] reporter.nih.gov/search/U1kbzCoJEkWYq4gNVa7oLQ/project-details/10636912
[118] reporter.nih.gov/search/2NgT7vhGekeYVAB6s9g4eQ/project-details/10694061
[119] reporter.nih.gov/search/w8zeIiklwk-pYtS0p17XLQ/project-details/10729876
[120] reporter.nih.gov/search/d3-VKxAamESSf4757el1ow/project-details/10393601
[121] reporter.nih.gov/search/emY5bzjcgEC9HgHoVoKHFA/project-details/10411717
[122] reporter.nih.gov/search/UpliAFhpJUia21q39g9nig/project-details/10407664
[123] reporter.nih.gov/search/BWA0doL_4UOosJXAp8yYjw/project-details/10427178
[124] reporter.nih.gov/search/nokffltM9kCEtqMsRdMbSQ/project-details/10349503
[125] nia.nih.gov/2023-fourth-geroscience-summit

stakeholders, including federal, academic, and private sector representatives, to share perspectives and explore the state of the science and direction of the field to drive advances towards several goals, including spurring development of new, informative, precise, and reliable measures for rates of aging and determining how those measures might contribute to translating discovery into health for our growing population of older people. Leading into this Summit, the GSIG hosted a seminar series on frailty and resilience, which are important foundations to understand aging physiology. To continue scientific discussions following the Summit, NIA has organized a seminar series on molecular aging clocks, which are important tools to understand how much any intervention may slow aging and improve health at older ages. One such seminar will focus on developing and applying brain-specific measures of aging. Developing a clear understanding of the mechanisms driving aging processes in the brain is essential for combating age-related neurodegenerative diseases, including Alzheimer's and related dementias. Basic aging processes, such as cellular senescence— a process in which cells lose normal function but continue to release molecules that may damage neighboring cells— can drive age-related disease through the accumulation of senescent cells. Most published studies on cellular senescence were conducted in tissues outside of the brain, creating a gap in our understanding of the role of senescence in neurodegenerative disease. To address this, NIA hosted a workshop [126] followed by a funding opportunity supporting 15 awards stimulating further research in this area.[127] NIA also co-leads the trans-NIH working group for the NIH Common Fund Cellular Senescence Network (SenNet) Program that was established to comprehensively identify and characterize the differences in senescent cells across the body, across various states of human health, and across the lifespan.

NIA recognizes the importance of this growing field of research and is committed to leading efforts to fund basic research and to advance the translation of these findings from animal models to clinical trials, and their validation in nationally representative studies. NIA will continue dedicating resources to push the field towards clinical applications with potential to improve the health and quality of life of the aging population.

[126] ncbi.nlm.nih.gov/pmc/articles/PMC7206469/
[127] grants.nih.gov/grants/guide/rfa-files/RFA-AG-20-025.html

Indoor Air

Health outcomes from the use of combustion indoors depend on individual health characteristics, the fuel used, and mitigations. The Committee encourages NIEHS to research and collaborate with appropriate partners to understand effects of indoor emissions on health and the degree to which mitigation strategies reduce exposures and other impacts. Research should include the impacts of other indoor pollutants to fully understand the indoor air landscape. The Committee requests an update on these activities in the fiscal year 2025 CJ.

Action taken or to be taken

Household air pollution (HAP) or indoor air pollution (IAP) is a significant health hazard and poses risks for cardiovascular and respiratory conditions. NIH and NIEHS have been supporting research studies on HAP/IAP for many years. The source of these indoor air pollutants ranges from wildfire smoke, radon, household burning of plastic waste, smoke from cooking fires, biomass fuel combustion, burning of Fuel No. 4 in buildings, to ultrafine particles from highways and traffic. Particulate matter 2.5 (PM2.5) are tiny particles in the air that are 2.5 microns or less in width and are major pollutants in HAP. PM2.5 increases the incidence of cardiometabolic risk, atherothrombosis and heart failure. Indoor air pollution increases rehospitalization risk of chronic obstructive pulmonary disorder (COPD) patients. Poor indoor air quality has been shown to be a risk factor for bronchopulmonary dysplasia (BPD).

Research on effects of indoor air pollutants on children's health is also the subject of work funded by the NIH Environmental Influences on Child Health Outcomes (ECHO) Program. ECHO is funding an ongoing clinical trial in rural U.S. children under 12 months hospitalized with bronchiolitis, to see if the use of High Efficiency Particulate Air (HEPA) filters in their homes following hospitalization is effective in reducing respiratory symptoms. Other health outcomes are also under study with respect to effects of air pollutants. A systematic review on the effects of various indoor and outdoor air pollutants, including traffic-related air pollution, secondhand smoke, and formaldehyde exposure, has shown association with longer time to pregnancy, an indicator of a couple's reproductive health. ECHO researchers have also conducted a review of scientific literature presenting evidence that prenatal air pollution exposure affects neurodevelopment.

NIEHS is also supporting studies on the feasibility of using clean and subsidized cookstoves as a mitigation measure with respect to household air pollution-related anemia and hemoglobin concentration in pregnant women and infants, in Guatemala as well as in infants with pneumonia, in Uganda. Meanwhile, in the United States, research supported by ECHO showed household stove-use characteristics were associated with indoor PM2.5 concentrations, highlighting a need for effective intervention strategies in homes that use wood stoves for heating.

One of the mitigation measures to reduce household air pollution is to use low-cost HEPA purifiers. HEPA purifiers are being used in NIEHS-funded studies in India to see whether improved indoor air quality can reduce the incidence of heart failure due to acute indoor air pollution and the incidence of atherothrombosis (a blood clot in the arteries due to plaque development) due to PM2.5 exposure. HEPA air purifiers are also being used in NIEHS-funded

studies on patients with eosinophilic COPD, to assess their effects on the improvement of lung function and respiratory symptoms.

Other mitigation research is focused on the efficacy of different air cleaners to remove volatile organic compounds.

Researchers focused on community-engaged research in the Duwamish Valley near Seattle have begun a household-level intervention study supported by NIEHS to improve indoor air quality and reduce asthma symptoms in children. Low-cost box fans equipped with lower efficiency filters with greater air flow are being tested (in contrast to more expensive HEPA filters) to measure their effectiveness in follow-up indoor air quality assessments. In another NIEHS-funded study, the use of clean and sustainable household energy sources is being tested in Rwanda, to see if it helped in reducing household air pollution, leading to enhanced health benefits.

Kidney Transplant Disparities

The Committee appreciates the ongoing efforts of NIDDK's Health Disparities and Health Equity Working Group, particularly on disparities in the prevention, diagnosis, and treatment of kidney diseases through new studies to address disparities in kidney transplant care. The Committee reaffirms the importance of reducing health disparities and urges NIDDK to support health disparities research to improve kidney transplant care. The Committee requests an update on these efforts in the fiscal year 2025 CJ.

Action taken or to be taken

The optimal treatment for end-stage kidney disease (ESKD) is living donor kidney transplantation (LDKT). However, despite their nearly four-fold greater incidence of ESKD compared to Whites, African Americans have lower rates of LDKT. Health systems have numerous capabilities that could potentially be leveraged to address known roadblocks to transplant care and to reduce disparities. To test this possibility, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funded the System Interventions to Achieve Early and Equitable Transplants Study (STEPS). STEPS is a comparative effectiveness trial to quantify the benefits of a 'health system surveillance and outreach' approach compared to usual care to mitigate race disparities in LDKT. The study, which is being conducted in two large health systems in the southern United States, where disparities in kidney disease are extremely prevalent and where LDKT is most desperately needed, has succeeded in reaching 75 percent of its enrollment goal on schedule.

Fifteen years ago, NIH Intramural researchers discovered that variants of the *APOL1* gene found primarily in people of African descent are a major contributor to kidney health disparities. Questions arose whether kidneys donated by people with these genetic variants were any less likely to remain viable in the long-term. To find out, and with a further view toward addressing the need for equitable kidney transplantation, the NIDDK-supported APOL1 Long-term Kidney Transplantation Outcomes Network, which aims to determine the impact of *APOL1* gene variants on kidney transplant recipients who received a kidney from a Black kidney donor, has completed recruitment and is following up with participants.

Because structural racism is widely and increasingly recognized as a fundamental cause of the stark racial and ethnic disparities in health outcomes for individuals with ESKD in the United States and recognizing the need to move from observational studies to interventions, the NIDDK also established the Interventions that Address Structural Racism to Reduce Kidney Health Disparities Consortium. Launched in August of 2023, the Consortium has already initiated five clinical studies. These include interventions that connect patients with community-based supports such as a culturally concordant community health worker or care team with the goal of improving management and slowing progression of CKD; and reducing disparities and bias in kidney transplant access. This program is a key addition to NIDDK's ongoing support of research toward improving kidney health by reducing kidney health disparities.

Lower Urinary Tract Symptoms

Lower urinary tract symptoms [LUTS] describe symptoms related to the storage and voiding of urine. Conditions associated with LUTS include overactive bladder, stress urinary incontinence, as well as neurogenic and non-neurogenic voiding dysfunction. The effectiveness of treatment for these conditions varies depending on patient characteristics and symptoms.

Unfortunately, an established repository of patient phenotypes for LUTS does not exist. Knowledge in this area would enable the identification of symptom clusters to advance LUTS treatment. Therefore, the Committee urges NIDDK to conduct a workshop that will lead to the development of LUTS precision medicine approaches, including the characterization of LUTS clusters and their association to treatment responsiveness, identification of markers for phenotype clusters, development of functional and physiologic assessment measures specific to individual phenotype profiles to objectively correlate symptoms and treatment outcomes.

The Committee requests an update on research activities to advance LUTS prevention and treatment in the fiscal year 2025 CJ.

Action taken or to be taken

NIH is dedicated to furthering an understanding of the various causes and manifestations of lower urinary tract symptoms (LUTS) with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) as the lead institute for research in this area. NIDDK funds the Symptoms of Lower Urinary Tract Dysfunction Research Network (LURN) to increase understanding of LUTS and to help inform strategies to better measure and manage the condition and improve patients' lives. LURN is comprised of an interdisciplinary team of researchers, study coordinators, and medical facilities at six United States clinical sites and a data coordinating center. Through development and use of detailed questionnaires, LURN aims to measure patient experiences, assess the wide range of symptoms, and characterize different subtypes of LUTS in men and women as a first step to developing precision medicine approaches. Through the NIH-funded Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, NIDDK is working to better understand the underlying causes and distinct symptom profiles of urological chronic pelvic pain syndrome (UCPPS), which is characterized by chronic pain and diverse LUTS in men and women. Recognizing that bladder health is an important aspect in the development of LUTS, NIDDK also supports the Prevention of Lower Urinary Tract Symptoms (PLUS) Research Consortium, to develop tools and strategies to measure and promote bladder health in women. This knowledgebase will inform individualized strategies for the prevention of LUTS in women. Additionally, NIDDK supports basic, translational, and clinical research into LUTS through funding of various other programs, centers, and investigator-initiated research projects. For example, the O'Brien Urology Centers are studying the pathophysiology of urologic diseases and conditions, and the Stimulating Urology Interdisciplinary Team Opportunity Research program supports investigator-initiated projects, some of which are studying how neurologic dysfunction may impact various types of incontinence.

In Fiscal Year 2022, NIDDK held a workshop on benign prostatic hyperplasia (BPH) (an enlargement of the prostrate) and male LUTS, which highlighted research incorporating tissue

sampling and analysis to identify different characteristics of BPH and LUTS toward the goal of developing personalized approaches for management of urologic disease. NIDDK also supports research aimed at developing an openly accessible repository of tissue samples to assess cell-type specific molecular changes in male lower urinary tract dysfunction. In addition to these current initiatives, NIDDK continues to welcome investigator-initiated research in LUTS and seeks to identify new research gaps and opportunities for LUTS treatment and prevention.

Maternal Fetal Medicine Units

The Committee appreciates NICHD's continued support of research focused on improving maternal and infant health outcomes. A critical part of this work is the Maternal-Fetal Medicine Units Network [MFMU]. Since 1986, the MFMU Network has been performing multi-site clinical research focused on gathering data needed to ensure obstetric patients across the country and the world are receiving evidence-based and cost effective care. The Committee was pleased to see NICHD release a request for applications in 2022 for a new funding cycle for the MFMU Network that maintains the Network's existing infrastructure, ensuring high-quality, high-impact multi-site clinical studies continue. However, unlike the prior funding cycles, clinical study proposals for the MFMU Network will now undergo NIH peer review to assure greater rigor and transparency. In addition, the Network infrastructure will now be made available to the entire community of researchers. The Committee requests an update in the fiscal year 2025 CJ on the total funding for MFMU Network supported clinical trials awarded in each of fiscal years 2010—2022. This update should detail amounts spent on clinical trials and separately account for base funding for the MFMU Network clinical sites and data coordinating center. Further, NICHD should include in the update plans to ensure that NIH will continue to fund clinical research conducted by the MFMU at the appropriate levels based on scientific need.

Action taken or to be taken

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development's (NICHD) Maternal-Fetal Medicine Units (MFMU) is the largest clinical trials network at the National Institutes of Health (NIH) that focuses not only on the reduction of maternal mortality, and morbidity related to pregnancy, labor, and post-partum recovery, but also on expanding the evidence base regarding the safety and efficacy of therapeutic products used during pregnancy and lactation. One MFMU trial, ARRIVE, (A Randomized Trial of Induction Versus Expectant Management) helped fill evidence gaps on the effects of elective induction of labor at 39 weeks of pregnancy. It found a significantly lower risk of cesarean birth and no significant differences in neonatal complications after elective induction compared to expectant management. In another trial, researchers found that weekly injections of a natural progesterone resulted in a substantial reduction in the rate of recurrent preterm delivery among women who were at particularly high risk for preterm delivery and reduced the likelihood of several complications in their infants. During the pandemic, MFMU Network investigators quickly pivoted to studies of how COVID-19 affected maternal health and pregnancy to provide data to inform recommendations for maternal health care. For example, researchers found that those with moderate to severe SARS-CoV-2 infection are more likely to have a cesarean delivery, to deliver a premature baby, to need respiratory support such as a ventilator, to die around the time of birth, or to experience serious illness from hypertensive disorders of pregnancy, postpartum hemorrhage, or from infection other than SARS-CoV-2. They are also more likely to have a miscarriage or to have an infant die during the newborn period. Research that includes women during pregnancy and throughout the post-partum period is vital to informing health care, especially during national health emergencies.

Recently, NICHD ensured that the structure of the MFMU allowed for sites outside of the awarded clinical centers to propose clinical trials in cooperation with the network. This expands the reach and scientific focus of the network. The network trials are required to include diverse

populations in their recruitment and community partners aligned with the clinical center sites. The network structure also includes a Community Engagement Board that provides input on maternal-fetal research outcomes of highest interest to patients and families, as well as sharing feedback on recruitment and consent processes. The structure continues to allow the MFMU to grow, adapt, and respond rapidly to emerging issues. Moreover, the MFMU's Data Coordination Center is responsible for preparing and submitting protocol datasets to the NICHD Data and Specimen Hub and/or other NIH-approved repositories on behalf of the network.

The chart below provides a breakdown of the MFMU Network costs from FY 2010 through FY 2022, including site base costs, data coordinating center (DCC) costs, and capitation/trial cost. The NICHD funding for the MFMU, which includes the clinical sites and the data coordinating center, has been fairly consistent over the years. Some of the research studies performed by the MFMU have received co-funding from partner institutes. These costs include co-funding dollars from other institutes and specific research studies and are included in the totals for the capitation/trial costs below. For example, FY 2019-FY 2020 included dollars from the NIH HEAL Initiative (Helping to End Addiction Long-Term Initiative) for the PACT study (Opioid Prescription After Cesarean Trial), the ongoing SLEEP study (Continuous Positive Airway Pressure (CPAP) for Sleep Apnea in Pregnancy) received co-funding from the National Heart, Lung, and Blood Institute, NIH, while the GRAVID study (Gestational Research Assessments for COVID-19) received COVID-19 research dollars. It also includes dollars for studies that were to be performed while the new network structure was being finalized. Additionally, in the years where co-funding is included, the clinical trial costs may have increased.

MFMU Network Costs FY 2010-2022

Fiscal Year	Site Base Costs	DCC Base Costs	Capitation/Trial Costs
2010	$3,712,227	$3,935,339	$8,157,015
2011	$5,699,335	$4,141,585	$7,734,245
2012	$4,506,342	$5,651,646	$8,944,696
2013	$4,268,254	$5,388,798	$7,207,917
2014	$4,089,734	$5,442,314	$7,915,895
2015	$4,423,598	$4,417,946	$6,017,322
2016	$3,353,588	$5,449,355	$7,317,244
2017	$3,623,509	$5,449,355	$6,983,026
2018	$3,580,083	$5,457,083	$7,627,498
2019	$3,595,991	$5,852,856	$16,458,493
2020	$3,401,685	$5,749,061	$13,535,098
2021	$3,157,794	$7,029,442	$7,277,172
2022	$3,796,695	$4,562,801	$5,352,767

NICHD has been investing in maternal health research since its inception in 1962. Recognizing the need for well-designed clinical trials in maternal-fetal medicine and obstetrics, NICHD

established the MFMU Network in 1986. NICHD remains steadfast in its commitment to the MFMU Network, and the structural enhancements will ensure its sustainability into the future.

Melanoma

The Committee encourages NCI to continue support for research on mutagenesis, early detection and treatment. Continued study of gene expression profiling in melanoma and its precursors is needed to define patient subsets by their risk of melanoma and their prognosis, which will be able to guide management of early-stage disease as has been the case in breast cancer. Melanoma research over the last decade has produced groundbreaking advances in targeted therapy and immunotherapy that have not only led to a decline in melanoma mortality, but have been the foundation for advances in many other cancer types. The Committee encourages NCI to continue to support research on mechanisms of primary and secondary drug resistance, new drug targets and validation of predictive biomarkers that will allow selection of optimal therapy. Basic and translational goals should be facilitated through development and use of ever-improving models of human melanoma, including those involving rare subtypes. In addition, the Committee encourages NCI to explore opportunities for multicenter trials that will determine whether shorter courses of therapy will decrease toxicity while maintaining benefit, refine adjuvant therapies, and continue to develop neoadjuvant therapies. The Committee also encourages NCI to continue to further rare melanoma research through the use of patient data and biospecimen banks where populations are not adequate for randomized trials. The Committee requests an update on melanoma research efforts in the fiscal year 2025 CJ.

Action taken or to be taken

NCI supports a wide variety of research to improve the prevention, early detection, and treatment of melanoma. Much of this research hinges on a better understanding of melanoma biology in preclinical models being developed by NCI-supported researchers and the development of better melanoma models for evaluating therapeutic approaches. NCI is funding a collaboration of 12 institutions investigating the correlation between melanoma biology and survival.[128] This includes the identification of mutations that can lead to early melanoma development in targetable pathways through the InterMEL study[129] and examining repression of genes not needed by tumor cells so they can focus their energy and resources on growth and survival.[130] Additional work by this group in collaboration with investigators from an NCI-supported melanoma Specialized Program of Research Excellence (SPORE) project identified DNA modifications that control expression of a protein that they found drives melanoma metastasis, giving researchers an idea of how skin cells can transform into invasive melanoma cells.[131]

While immunotherapy has shown great promise for cancer treatment, it is still unknown why some patients respond better than others or what treatment combinations are most effective. An NCI-sponsored phase 3 clinical trial, DREAMseq, that included patients with metastatic melanoma with a specific mutation in a cancer-causing gene (*BRAF* V600) looked at the optimal treatment order of combination therapies.[132] Researchers found that a combination treatment of two checkpoint inhibitor immunotherapies followed by BRAF and MEK inhibitor therapy, which targets BRAFV600, upon disease progression is more effective than first giving the targeted

[128] reporter.nih.gov/project-details/10413854
[129] pubmed.ncbi.nlm.nih.gov/36926987/
[130] pubmed.ncbi.nlm.nih.gov/36805567/
[131] ncbi.nlm.nih.gov/pmc/articles/PMC10073109/
[132] ncbi.nlm.nih.gov/pmc/articles/PMC9839305/

therapies followed by the checkpoint inhibitors. Over 50 percent of patients with metastatic melanoma have *BRAFV*600 mutations, and these results provide a preferred treatment approach to help improve patient outcomes. NCI is also collaborating on a clinical trial investigating the effect of multiple checkpoint inhibitor immunotherapies on brain metastasis of BRAF-V600 mutant melanoma patients.[133] Another NCI-sponsored clinical trial is testing if the efficacy of an experimental cell therapy that extracts, grows, and reinjects certain white blood cells from a patient can be improved with the addition of a checkpoint inhibitor immunotherapy in patients with metastatic melanoma.[134] Additionally, a melanoma SPORE project used preclinical models to find that overexpression of a certain gene in melanoma cells resulted in a significant response to immunotherapy compared to melanoma cells that lacked that gene, offering a potential way to identify patients who would benefit most from this treatment.[135]

Adjuvant therapies are given after surgery to decrease the risk of disease recurrence, but they often have serious side effects. One large multicenter NCI-sponsored clinical trial for advanced stage high-risk melanoma is exploring whether an immunotherapy given after surgery could be more effective if also given pre-operatively (neoadjuvant),[136] with results showing a substantially lower risk of cancer return in patients who received the neoadjuvant therapy.[137] NCI is also interested in studying treatment reduction to limit toxicity to patients. One such trial currently recruiting participants is determining if biomarkers seen on imaging tests and in tumor biopsies can predict the effectiveness of a shorter dose of standard therapy in patients with advanced melanoma that cannot be removed by surgery.[138]

NCI is committed to supporting research on rare subtypes of melanoma. An NCI-led clinical trial found that patients with desmoplastic melanoma, a rare skin cancer subtype that is difficult to diagnose and is usually found on areas of high sun exposure in older individuals, could be treated effectively with a single immunotherapy drug instead of a combination, minimizing unnecessary side effects.[139] Patients with either inoperable desmoplastic melanoma or that which can be removed by surgery can both benefit from this single agent treatment; these findings could establish single-agent immunotherapy as the standard treatment for people with metastatic desmoplastic melanoma. While this is a small study, patients had a remarkable 90 percent response rate to the single agent treatment.

Another rare and highly aggressive subtype is Merkel cell carcinoma (MCC). Multiple NCI-funded studies are examining different aspects of MCC, including developing a mouse model and studying cancer-specific immune cell effects. The rare, but deadly, acral lentiginous melanoma (ALM) melanoma subtype is disproportionately found in people with darker skin, including Black, Hispanic, and Asian populations. NCI-funded researchers are working to identify the key factors contributing to later diagnosis of Hispanic patients with the goal of developing and delivering a clinic-based educational intervention that can reduce the melanoma

[133] clinicaltrials.gov/ct2/show/NCT04511013
[134] clinicaltrials.gov/study/NCT02621021
[135] pubmed.ncbi.nlm.nih.gov/36332624//
[136] clinicaltrials.gov/ct2/show/NCT03698019
[137] pubmed.ncbi.nlm.nih.gov/36856617/
[138] clinicaltrials.gov/ct2/show/NCT04462406
[139] clinicaltrials.gov/study/NCT02775851

burden in this population.[140] Another project that is exploring new treatment targets for melanomas resistant to many current therapies includes acral melanoma patient-derived models that will be used to help determine the best candidates for potential translation to future trials.[141]

[140] reporter.nih.gov/search/QnuIS8f-lESpfLSNqRxviw/project-details/10612918
[141] reporter.nih.gov/search/QnuIS8f-lESpfLSNqRxviw/project-details/10733197

Metastatic Breast Cancer

The Committee directs NIH to include updates on the following research, projects, and programs in the fiscal year 2025 Congressional Justification: metastatic breast cancer; future goals for each of the deadliest cancers (brain, esophagus, liver, lung, ovary, pancreas, stomach and mesothelioma); the link between obesity and endometrial cancer; melanoma; neuroblastoma; pediatric immunotherapy clinical trials; congenital heart disease; kidney transplant disparities; lower urinary tract symptoms; celiac disease; Maternal-Fetal Medicine Units Network; pelvic organ prolapse; Usher syndrome; indoor pollutants; amyloidosis; Childhood Post-Infectious Neuroimmune Disorders/Pediatric AcuteOnset Neuropsychiatric Syndrome [PANS]/Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus [PANDAS]; Congenital Cytomegalovirus; Native Hawaiian Early Career Development; Von Hippel-Lindau Disease; NCI's plans to update the Surveillance, Epidemiology, and End Results Registry; pulmonary fibrosis; cellular immunity; and opportunities to enhance childhood cancer research efforts, including coordinating efforts already underway through the Trans-NIH Pediatric Research Consortium.

Action taken or to be taken

The National Cancer Institute (NCI) supports a robust breast cancer research portfolio, including metastasis research, through a number of mechanisms including investigator-initiated research project grants (e.g., R01s), cooperative agreement research networks, and Specialized Centers of Research Excellence (SPORE) programs. In addition, NCI supports clinical trials to test new treatments for all types (estrogen receptor positive, HER-2 overexpressing, and triple negative) of metastatic breast cancer.

Metastatic breast cancer patients are benefiting from the numerous immunotherapies that have been approved by the U.S. Food and Drug Administration (FDA) over the last decade, including the use of immune checkpoint inhibitor drugs and antibody-drug conjugates for the treatment of metastatic triple negative breast cancer. It is important to note that decades of NCI-supported basic research played a role in bringing these drugs to patients, and this type of research continues to be critical for improving patient outcomes in response to these treatments. For example, a new NCI -funded study identified an enzyme (a type of protein that catalyzes a reaction) in a specific type of immune cells called neutrophils that can be targeted to improve immune checkpoint inhibitor drug efficacy in metastatic triple negative breast cancer.[142] The researchers identified this enzyme using sophisticated single cell sequencing methods to compare differences between tumor infiltrating neutrophils and neutrophils localized outside of the tumor.

Another recent NCI-funded study identified a mechanism whereby breast cancer cells mediate skeletal muscle dysfunction and may contribute to muscle weakness and loss.[143] About two-thirds of metastatic breast cancer patients experience reduced muscle mass and poor muscle quality. Furthermore, loss of skeletal muscle and poor muscle quality are associated with increased risk of death in patients with breast cancer. What makes this study remarkable is that it examined the effect of one of the most altered genes in human cancers, the p53 tumor suppressor, in non-cancer cells (i.e., muscle cells) and identified how factors secreted by breast

[142] pubmed.ncbi.nlm.nih.gov/37793345/
[143] pubmed.ncbi.nlm.nih.gov/37439436/

cancer cells affect the function of this protein in non-cancer cells, leading to morbidity and mortality.

Both studies illustrate how basic research to increase our understanding of cancer biology leads to improved outcomes for metastatic breast cancer patients. They also illustrate the importance of studying cells other than cancer cells to understand the systemic effects of cancer on the body. The NCI Metastasis Research Network (MetNet) seeks to develop a comprehensive understanding of cancer metastasis as a whole body, systems-level disease.[144] The network consists of five multi-project team awards and added two additional individual project awards in fiscal year 2023. Several of the projects focus on aspects of breast cancer metastasis, including how breast cancer cells travel to particular organs in the body during the metastatic process.

Exciting results from an international clinical trial that included several NCI-designated cancer centers as participating sites have changed the treatment recommendations for metastatic breast cancer patients with HER-2 low expressing tumors.[145] The trial tested the efficacy of the antibody-drug conjugate trastuzumab deruxtecan (T-DXd), which was previously approved by the FDA for the treatment of HER-2 overexpressing metastatic breast cancer. The results of the current trial led to the FDA approval of T-Dxd for metastatic breast cancer patients with HER-2 low expressing tumors. The use of this agent for both types of metastatic breast cancer provides a new and more effective treatment option for about half the people with metastatic breast cancer.

NCI remains committed to increasing the participation of underserved populations in clinical trials. Participation of racial and ethnic minority patients has increased from 14 percent at the beginning of this century to 25 percent in 2019 and is approaching 30 percent for NCI's National Clinical Trials Network and the NCI Community Oncology Research Program clinical trials. In November of 2022, NCI hosted a summit on increasing diversity, equity, and inclusion in early phase clinical trials. This is just one phase of NCI's long-term effort to meaningfully increase the participation of medically underserved populations in cancer clinical trials.

[144] cancer.gov/about-nci/organization/dcb/research-programs/metnet
[145] cancer.gov/news-events/cancer-currents-blog/2022/enhertu-her2-low-breast-cancer

Native Hawaiian Early Career Development

The Committee acknowledges the underrepresentation of Native Hawaiian health research-related activities across the agency and within the Native Hawaiian community. The Committee encourages NIH to continue to explore NIH-wide early career development awards that provide support for early-career investigators from populations underrepresented in the U.S. research enterprise, including Native Hawaiian investigators, and encourages outreach to entities with a proven track record of working closely with Native Hawaiian communities. The Committee requests an update on progress in the fiscal year 2025 CJ.

Action taken or to be taken

Scientists and trainees from diverse backgrounds and life experiences bring different perspectives and creative approaches to solving the scientific problems we face as a nation. The National Institutes of Health (NIH) recognizes that its ability to help ensure that the nation remains a global leader in scientific discovery and innovation is dependent upon a pool of highly talented scientists from diverse backgrounds who will help to further NIH's mission.

In September 2017, with support from the 21st Century Cures Act (P.L. 114-255), NIH launched the Next Generation Researchers Initiative (NGRI) to cultivate and support talent entering the biomedical and behavioral research workforce.[146] NGRI promotes opportunities for new researchers and earlier research independence, such as policies to increase opportunities for new researchers to receive funding, enhanced training and mentorship programs, and policies aimed at enhancing workforce diversity.[147] NIH is analyzing NGRI policies to ensure that our efforts continue supporting career development for women and individuals from underrepresented backgrounds in biomedicine.

In fiscal year (FY) 2022, NIH supported an all-time high of 1,609 new Early-Stage Investigators (ESIs) as first-time principal investigators designated on R01-equivalent awards, a 6.3 percent increase over FY 2021.[148] The referenced NIH Open Mike blog also provides data on the demographic breakdown of ESIs as part of NGRI efforts, and additional blog posts are available for further demographic analysis of the NIH-supported research workforce.[149,150]

NIH supports a number of programs to enhance diversity in the biomedical research workforce:

- Research Supplements to Promote Diversity in Health-Related Research have supported individuals from diverse backgrounds, including those from groups that have been shown to be underrepresented in health-related research and researchers with disabilities.[151] NIH renewed its support of these administrative supplements in June 2023 and expanded eligibility to three new grant types.

[146] grants.nih.gov/ngri.htm
[147] nexus.od.nih.gov/all/2021/07/12/data-on-implementing-nihs-next-generation-researchers-initiative/
[148] nexus.od.nih.gov/all/2023/06/05/more-early-stage-investigators-supported-in-fy-2022/
[149] nexus.od.nih.gov/all/2023/03/16/analyses-of-demographic-specific-funding-rates-for-type-1-research-project-grant-and-r01-equivalent-applications/
[150] nexus.od.nih.gov/all/2023/03/16/mentored-career-development-application-k-funding-rates-by-race-ethnicity-fy-2010-fy-2022/
[151] grants.nih.gov/grants/guide/pa-files/PA-23-189.html

- The Research Centers in Minority Institutions (RCMI) program aims to expand the national capacity for health sciences research. The program supports institutions that offer doctorate degrees in health-related science, have limited NIH research funding, promote biomedical workforce diversity, and serve underrepresented communities, including Native Hawaiian serving institutions.[152] For example, Ola HAWAII, a National Institute on Minority Health and Health Disparities (NIMHD)-funded RCMI Specialized Center at the University of Hawaii, fosters high-impact team-science research; strengthening a diverse research workforce, which includes training the next generation on data science skills; and enhancing, consolidating, and sustaining core research facilities and resources.[153]
- The Engagement and Access for Research-Active (EARA) initiative enhances outreach and connections between research-active institutions (RAIs) and NIH to share information regarding opportunities to work with NIH research programs or apply for NIH research funding. RAIs have a mission to serve historically underrepresented populations in biomedical and behavioral research, and award degrees in the health professions, the sciences related to health, or in STEM fields. The initiative includes Minority Serving Institutions, which include Native Hawaiian-Serving Institutions. The EARA initiative is expected to begin in FY 2024.

NIH has several other programs of interest aimed at promoting diversity and enhancing progress to an independent career.[154] Selected examples are below:

- BRAIN Initiative Advanced Postdoctoral Career Transition Award to Promote Diversity[155]
- Maximizing Opportunities for Scientific and Academic Independent Careers program[156]
- Faculty Institutional Recruitment for Sustainable Transformation program[157]
- Building Interdisciplinary Research Careers in Women's Health[158]

In FY 2024, using the $4 million included in the "Further Consolidated Appropriations Act, 2024" (P.L. 118-47), NIMHD will launch a new office in September 2024. The focus and mission of the office will be to advance NIH efforts in supporting research, training, community engagement, and academic-community partnerships to promote and improve health in Native Hawaiian and Pacific Islander (NHPI) communities in the U.S. and its territories. The NHPI Health Research Office will engage NHPI communities to prioritize research topics by conducting listening sessions with NHPI community leaders and workshops with investigators with experience in NHPI research. The NHPI Health Research Office will coordinate with established research initiatives such as the NIH Community Engagement Alliance, the Research Centers in Minority Institutions program, and other research projects focused on NHPI populations. Moreover, the NHPI Health Research Office will support efforts promoting career

[152] nimhd.nih.gov/programs/extramural/research-centers/rcmi/
[153] reporter.nih.gov/project-details/10556969
[154] extramural-diversity.nih.gov/guidedata/data
[155] grants.nih.gov/grants/guide/rfa-files/rfa-ns-19-043.html
[156] nigms.nih.gov/training/careerdev/Pages/MOSAIC.aspx
[157] commonfund.nih.gov/first
[158] orwh.od.nih.gov/career-development-education/building-interdisciplinary-research-careers-in-womens-health-bircwh

development-related outreach that fosters greater participation of NHPI individuals in NIH educational and training programs that target researchers who are in various stages of their careers.

Neuroblastoma

The Committee encourages NCI to continue to support research on high-risk neuroblastoma, including continued support for an innovative treatment consortium that tests new therapies for relapsed and refractory patients in early phase clinical trials. The Committee requests an update on neuroblastoma research efforts in the fiscal year 2025 CJ.

Action taken or to be taken

Neuroblastoma is a very rare extracranial (outside the skull) cancer that develops from immature nerve cells and occurs primarily in young children. Approximately 600-700 children in the United States are diagnosed each year with neuroblastoma. Genetic mutations in neuroblastoma tumors usually vary between patients, making targeted therapy a challenge. Treatment for high-risk patients includes a combination of chemotherapy, surgery, stem cell transplant, immunotherapy, radiation, and other therapies. Such aggressive treatment results in toxicity and severe side effects. Although most patients experience remission after the initial treatment, more than half relapse.

It is difficult to find druggable therapeutic targets in neuroblastoma because this cancer has relatively few mutations per tumor. The most commonly mutated protein (called ALK) in this cancer is only present in about 10 percent of the pediatric cases. However, the National Cancer Institute (NCI) scientists recently found a protein, GPC2, that is present in nearly half of neuroblastoma cases, which could help address this challenge. Importantly, they developed a CAR T cell therapy targeting GPC2, that inhibited neuroblastoma growth in mouse models, setting the stage for further clinical testing in children.[159]

NCI researchers are unraveling molecular mechanisms behind neuroblastoma development and relapse to find new molecular targets for therapy. There is a special emphasis on the MYCN oncogene, which is amplified (has a higher-than-normal number of copies of the gene) in half of the high-risk cases. Using pre-clinical models, NCI scientists found that *MYCN*-amplified neuroblastoma is sensitive to simultaneous inhibition of two metabolic drug targets, offering potential new therapeutic options.[160] In addition, the researchers discovered that a protein that modifies DNA to regulate gene expression is overexpressed in *MYCN*-amplified neuroblastoma and shuts down genes that are critical for successful therapy response. The next steps for advancing this finding will be to test inhibitors that target the specific protein in mouse models with an eye towards future clinical testing.

NCI has several consortia and programs that strive to find cures for neuroblastoma, covering the spectrum from basic research to clinical trials. For example, NCI-sponsored clinical trials conducted by the Children's Oncology Group (COG) led to a U.S. Food and Drug Administration (FDA) approval in 2015 of dinuximab, as first-line therapy for high-risk neuroblastoma.[161,162] NCI conducted initial preclinical studies on the drug, manufactured it through the Biopharmaceutical Development Program at NCI's Frederick National Laboratory

[159] pubmed.ncbi.nlm.nih.gov/36631162/
[160] ncbi.nlm.nih.gov/pmc/articles/PMC8020796/
[161] pubmed.ncbi.nlm.nih.gov/19047298/
[162] cancer.gov/news-events/cancer-currents-blog/2015/dinutuximab-neuroblastoma

for Cancer Research, and provided it to clinicians under a COG-led clinical trial. A long-term study showed that immunotherapy with dinutuximab, given in combination with two immune-boosting compounds, significantly increases 5-year survival. The study also identified potential predictive biomarkers for dinutuximab therapy success.[163] NIH researchers are finding molecular targets behind dinuximab resistance[164] and are combining dinuximab with other drugs to enhance anti-tumor activity in relapsed or resistant neuroblastoma patients.[165] Additionally, the success of the COG gave rise to NCI's Pediatric Early Phase Clinical Trial Network (PEP-CTN), which identifies and develops new therapeutic agents and conducts early phase clinical trials. PEP-CTN recently produced encouraging results for pediatric neuroblastoma patients with an experimental targeted agent[166] and an ALK inhibitor.[167]

The New Approaches to Neuroblastoma Therapy (NANT) pediatric cancer consortium tests promising new therapies for neuroblastoma through early phase (1/2) clinical trials.[168,169] Results from NANT trials are rapidly incorporated into larger COG phase 2/3 trials to test the potential of NANT therapies for patients with high-risk neuroblastoma. Results from a recent NANT trial funded by NCI found that a specific ALK inhibitor (lorlatinib) was safe and effective in pediatric patients.[170] Based on these findings, a COG trial changed the ALK inhibitor they were using to lorlatinib to improve patient outcomes.

Researchers from the NCI Pediatric Preclinical In Vivo Testing (PIVOT) consortium[171] have demonstrated that DNA shed by neuroblastoma tumors and circulating in the bloodstream can be used to track disease progression, to detect patient-specific cancer driver genes,[172] and to track how neuroblastoma tumors acquire resistance in patients treated with an ALK inhibitor.[173] The Consortium collaborates with industry partners to evaluate whether agents developed for adult cancers are applicable to treatment of pediatric cancers. The PIVOT research program in neuroblastoma uses a collection of patient-derived models to prioritize anti-cancer agents in development for early phase clinical trials, including testing an antibody-drug conjugate that showed significant anti-tumor activity.[174]

Finally, NCI has a Rare Tumor Patient Engagement Network to study and conduct clinical trials for treatment of rare tumors. One component of this Cancer Moonshot[SM]-funded endeavor, called MyPART,[175] collects samples from patients and shares rare cancer data with scientists around the world to find new treatments and improve patients' lives. Neuroblastoma is one of

[163] pubmed.ncbi.nlm.nih.gov/35839426/; pubmed.ncbi.nlm.nih.gov/33504555/
[164] pubmed.ncbi.nlm.nih.gov/37554309/
[165] pubmed.ncbi.nlm.nih.gov/32343642/
[166] pubmed.ncbi.nlm.nih.gov/37081608/
[167] pubmed.ncbi.nlm.nih.gov/33568345/
[168] ctep.cancer.gov/investigatorResources/childhood_cancer_resources.htm
[169] nant.org/home
[170] pubmed.ncbi.nlm.nih.gov/37012551/
[171] ctep.cancer.gov/MajorInitiatives/Pediatric_PIVOT_Program.htm
[172] pubmed.ncbi.nlm.nih.gov/36108156/
[173] pubmed.ncbi.nlm.nih.gov/37147298/
[174] ncbi.nlm.nih.gov/pmc/articles/PMC8127361/
[175] cancer.gov/pediatric-adult-rare-tumor/about/what-is-mypart

the rare tumor types being examined through patient participation in the MyPART natural history study.[176]

[176] clinicaltrials.gov/study/NCT03739827

NIH Support for Pediatric Research

The Committee commends NIH for its efforts to coordinate pediatric research across its Institutes and Centers through the recently established Trans-NIH Pediatric Research Consortium. The Committee understands NCI participates in the Consortium, and that childhood cancer research is an important part of the pediatric research portfolio across NIH. The Committee requests an update in the fiscal year 2025 CJ on efforts underway through the Trans-NIH Pediatric Research Consortium to enhance pediatric research across NIH, including efforts to strengthen the pediatric research workforce. The Committee desires NIH to maintain a robust pediatric research portfolio spanning basic, translational, and clinical research, to adequately support researchers at all career stages, particularly early career investigators focused in pediatrics, and to ensure pediatric components are included within larger NIH research priorities.

Action taken or to be taken

NIH supports research to understand the healthy development of children as well as the causes of and treatment for diseases, illnesses, and conditions affecting them. Funding for pediatric research has increased steadily over time, from nearly $3.3 billion in 2013 to nearly $6.2 billion in 2023. Spending on pediatric research spans basic, translational, and clinical research.[177] Pediatric research is supported across 24 of NIH's Institutes and Centers (ICs), with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) providing approximately 16 percent of the total amount. NIH established the NIH Pediatric Research Consortium (N-PeRC) in 2018, led by NICHD, to improve pediatric research collaboration and coordination across the agency's ICs and Offices (ICOs).[178] N-PeRC convenes representatives from nearly all ICOs to discuss pediatric research areas of interest NIH-wide.

Developing pediatric medical devices (PMDs) poses unique challenges compared to adult devices. Children undergo continuous developmental change, leading to a need for devices that must adapt to these changes or be replaced often, which decreases potential market for industry investors. Through the efforts of an N-PeRC subgroup on PMD development, in 2023 NIH launched the design phase of a public-private partnership to address the lack of medical devices designed and approved for children in the United States.[179] In this initial phase, NIH and partners will develop a detailed plan to build and launch a partnership that will bring together the resources of federal agencies and private sector organizations, including industry and non-profits. The non-profit Foundation for the NIH (FNIH) is leading the design phase, and key federal partners include the United States Food and Drug Administration (FDA) and the Biomedical Advanced Research and Development Authority (BARDA). Both agencies will provide scientific and regulatory insight and expertise, as well as funding. Additional funding and expertise will be provided by the private sector, including industry and nonprofit organizations working through FNIH. Within NIH, NICHD and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) are leading this effort, with multiple other ICs engaged through N-PeRC.

[177] report.nih.gov/funding/categorical-spending#/
[178] nichd.nih.gov/research/supported/nperc
[179] nichd.nih.gov/newsroom/news/092623-pediatric-medical-device-development

N-PeRC also plays a role in ensuring that pediatric research is included within larger NIH research priorities. An N-PeRC subgroup that focuses on pediatric pain research worked with the Helping to End Addiction Long-term (HEAL) initiative to develop funding opportunities in the new HEAL KIDS (Knowledge, Innovation and Discovery Studies) Pain program. The initial funding opportunities in this program will support large, multi-site clinical trials to better understand, measure, treat, and prevent acute pain in children, including those with disabilities and/or experiencing health disparities.[180] These awards are anticipated in July 2024.

The COVID-19 N-PeRC subgroup worked throughout the pandemic to ensure that children were included in broader NIH research efforts. The group's work continues today through advising the pediatric aims of the RECOVER (Researching COVID to Enhance Recovery) initiative that examines the effects and possible treatments for Long COVID.[181] As of October 2023, pediatric enrollment targets for RECOVER have nearly been met.

N-PeRC members are also serving on an ad hoc subgroup to consult with the NIH *All of Us* Research Program as they prepare to enroll pediatric participants. Many of the challenges for pediatric enrollment and participation in clinical trials are universal, and this is an opportunity for N-PeRC members and *All of Us* to draw on expertise across ICOs for mutual benefit.

Another area of interest across NIH is pediatric and maternal pharmacology. In 2002, the Best Pharmaceuticals for Children Act (BPCA) authorized research to improve the safety and efficacy of medication use for children. The goal of the act is to provide rigorous clinical data to improve drug label instructions. NICHD has been implementing the Act on behalf of NIH and with support from more than 20 other ICs with significant pediatric research portfolios.[182] In 2024, N-PeRC will launch a new subgroup to promote collaboration across ICs and to drive innovation in pediatric and maternal pharmacology. The group will provide a forum to promote awareness of pediatric pharmacology programs across NIH as well as a venue to discuss challenges, best practices, and potential new NIH-wide initiatives, subject to available appropriations.

N-PeRC will continue to convene NIH ICs to discuss crucial pediatric research topics, including the effects of social media and technology on child development and research efforts to understand late talking in children. NIH has also been considering ways to increase and enhance pediatric research at the NIH Clinical Center. In addition, nearly every NIH IC invests in pediatric research training and career development, particularly support for early career investigators. Cultivating a diverse pediatric research workforce is essential to moving science forward to optimize pediatric health.

N-PeRC also contributes to efforts to enhance childhood cancer research. For example, N-PeRC worked with the National Cancer Institute (NCI) to develop the HEAL Kids Pain program to ensure that children experiencing acute pain due to cancer disease or treatment could be included in proposed research. NIH supports a broad portfolio of efforts to bolster childhood cancer research led in large part by NCI, through both extramural and intramural research. In addition to clinical trials, research networks, and biobanking and data resources specifically focused on

[180] grants.nih.gov/grants/guide/rfa-files/RFA-HD-24-011.html; grants.nih.gov/grants/guide/rfa-files/RFA-HD-24-012.html
[181] recovercovid.org/
[182] nichd.nih.gov/research/supported/bpca/about

childhood cancer, NCI supports many investigator-initiated childhood cancer research projects, as well as an extensive portfolio of basic research projects that have the potential to lead to advances across cancer types. Beyond NCI, a number of other NIH ICs support advances relevant to childhood cancer, including research on brain cancers supported by the National Institute of Neurological Disorders and Stroke (NINDS), research on blood cancers funded by the National Heart, Lung, and Blood Institute (NHLBI), [183] as well as research funded through the Office of the NIH Director such as the Gabriella Miller Kids First Research Program.[184]

To advance preclinical testing of new treatments for pediatric cancers, NCI has established the Pediatric In Vivo Testing (PIVOT) Consortium, which builds upon two previous successful NCI programs.[185] The PIVOT Consortium is a public-private partnership that includes a coordinating center and seven academic research programs with expertise in the development, characterization, and testing of preclinical models of pediatric cancer.[186] The primary goal of PIVOT is to develop high quality preclinical data to help identify new therapeutic agents that are promising candidates for further testing in clinical trials.[187]

The Children's Oncology Group (COG), part of the NCI National Clinical Trials Network (NCTN), develops and coordinates childhood cancer clinical trials, with a focus on late-phase trials, available at more than 200 member institutions throughout the United States.[188] COG is carrying out several active and soon-to-open clinical trials, including trials to test the addition of immunotherapies to standard chemotherapy. For example, phase 3 clinical trials for children with standard-risk and high-risk acute lymphoblastic leukemia (ALL) are evaluating the addition of one of two immunotherapy agents to standard chemotherapy treatment.[189] A phase 3 clinical trial for children with neuroblastoma that is began enrollment in early 2024 is combining a different immunotherapy agent with standard chemotherapy drugs during the initial months of treatment to determine whether its addition can improve survival for children with high-risk neuroblastoma.[190] Other trials are seeking to reduce long-term adverse events while maintaining favorable outcomes for children, such as one trial testing treatment with a reduced dose of radiation therapy and chemotherapy for children who are newly diagnosed with a specific type of medulloblastoma, the most common type of pediatric brain tumor. Another trial for children with nasopharyngeal carcinoma (a rare head and neck cancer) is developing a new treatment regimen that adds a checkpoint inhibitor to standard chemotherapy to increase efficacy and that lowers the dose of radiation to reduce acute and long-term toxicity.

NCI's Pediatric Early Phase Clinical Trials Network (PEP-CTN) seeks to identify and develop effective new therapies for children and adolescents with cancer, including through early phase trials that often incorporate phase 2 expansion cohorts and through pilot studies to determine the

[183] NIH RePORTER, Pediatric Cancer research projects supported across NIH Institutes and Centers in FY22: eporter.nih.gov/search/ebUmCNvh5Uau9AMiSYn1QA/projects
[184] commonfund.nih.gov/KidsFirst
[185] preclinicalpivot.org/about-pivot/
[186] preclinicalpivot.org/
[187] ctep.cancer.gov/MajorInitiatives/Pediatric_PIVOT_Program.htm
[188] childrensoncologygroup.org/clinicaltrials-136
[189] clinicaltrials.gov/study/NCT03959085
[190] clinicaltrials.gov/study/NCT06172296?term=NCT06172296&rank=1

tolerability of promising new agents so they can proceed to phase 3 trials.[191] Both novel immuno-oncology agents (and new small molecule pathway inhibitors are under investigation by the PEP-CTN. In addition, the Pediatric Brain Tumor Consortium (PBTC), which was formed by NCI in 1999, now includes 15 academic centers and children's hospitals across the United States and Canada that are conducting clinical trials to evaluate new treatments for children with primary brain tumors, including checkpoint inhibitors, cancer-targeted vaccines, molecularly targeted agents, and CAR T-cells (chimeric antigen receptor T-cells).[192] Findings from PBTC trials are serving as the basis for COG phase 3 clinical trials for children with both high-grade and low-grade gliomas.

In addition to the above, NCI also supports additional neuroblastoma and pediatric immunotherapy trials, which are described in detail in Significant Item responses specific to those topics.

In accordance with the goals of the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act and STAR Reauthorization Act, NCI has also provided additional support to bolster and expand programs led by the COG Biobank,[193] including through projects to increase the collection of diagnostic, relapse, and autopsy specimens, as well as support for additional collection specimens from childhood cancer survivors through the Childhood Cancer Survivor Study (CCSS).[194] CCSS is an NCI-funded resource to promote and facilitate research among long-term survivors of cancer diagnosed during childhood and adolescence. Efforts are underway to further enhance the resource, including the collection of blood specimens to be banked and made available for researchers from participants with grade 3 and 4 chronic health conditions and the addition of methylation (a DNA modification) profiling of blood specimens.

To enhance data collection for biobanking and survivorship studies in alignment with the STAR Act, NCI's Childhood Cancer Data Initiative (CCDI) supports a dynamic and evolving infrastructure of data systems and user-friendly tools for finding, harmonizing, accessing, and analyzing childhood cancer data.[195] Data is added into the CCDI Data Ecosystem from within NCI and from other academic and health care institutions performing childhood cancer research. Additionally, CCDI encourages and supports organizations to share their data and incorporate these data into the ecosystem. The recently launched CCDI Hub serves as the entry point for researchers, data scientists, and citizen scientists to access the Data Ecosystem.

Childhood cancers are classified as rare cancers, and the efforts outlined above increase sample availability to researchers and clinicians, advancing research and improving patient outcomes, especially for children with the rarest cancer subtypes. For example, the Rare Tumor Populations Biobanking program supports tumor tissue and blood collection for specific groups of patients for which current tumor tissue collection is lacking or inadequate. This program collaborates closely with CCDI to analyze tumor tissue with the goal of obtaining clinically relevant molecular profiling through the CCDI Molecular Characterization Initiative.[196]

[191] /ctep.cancer.gov/initiativesPrograms/pep-ctn.htm
[192] pbtc.org/
[193] childrensoncologygroup.org/biorespository-for-the-children-s-oncology-group
[194] cancer.gov/types/childhood-cancers/ccss
[195] cancer.gov/research/areas/childhood/childhood-cancer-data-initiative
[196] cancer.gov/research/areas/childhood/childhood-cancer-data-initiative/data-ecosystem/molecular-characterization

Palliative Care Research

Palliative care is specialized medical care for people living with a serious illness and is focused on treating the discomfort, symptoms, and stress of such illness. Palliative care has the potential to improve patient care, patient-clinician communication, and patient-centered outcomes while decreasing unwanted and/or burdensome treatments and enhancing quality of life for people with serious illness, their loved ones, and their care partners. The Committee provides $12,500,000 for NIA to implement a trans-Institute, multi-disease strategy to focus, expand, and intensify national research programs in palliative care. NIH is directed to establish a comprehensive multi-Institute and multi-Center initiative aimed at a wide variety of palliative care research, training, dissemination, and implementation of projects to intensify the strategic coordination of palliative care research efforts. Funding is provided to establish an extramural-based palliative care research consortium with no less than three sites to provide technical assistance, pilot and exploratory grant funding, research dissemination, data repositories, data analytics, and career development support for interdisciplinary palliative care. NIH shall prioritize grantees with a recognized expertise and leadership in palliative care. The Committee encourages NIH to fund several multi-year, early-career development grants modeled after NIA's GEMSSTAR program. Appropriations provided in fiscal year 2024 for training are expected to cover 2 years of funding for career development awards.

Action taken or to be taken

NIH recognizes the importance of palliative care, with several NIH institutes, centers, and offices (ICOs) supporting a diverse set of research projects and initiatives focused on this essential area, including the National Cancer Institute (NCI), National Heart, Lung, and Blood Institute (NHLBI), National Institute on Aging (NIA), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Nursing Research (NINR), the National Institute of Minority Health and Health Disparities (NIMHD), the National Institute of Neurological Disorders and Stroke (NINDS), the Office of Behavioral and Social Sciences Research (OBSSR), and the Office of Research on Women's Health (ORWH).

These ICOs support research aligned with their mission, in addition to collaborations with other Institutes and Centers (IC). For example, NCI supports research projects[197] through multiple funding opportunities focused on the survivorship needs of individuals living with advanced cancer, the conduct of palliative care clinical trials, the management of treatment toxicities,[198] and recently released a funding opportunity to improve the cancer care of sexual and gender minority populations.[199] NICHD supports palliative care research involving children, pregnant and lactating people, and people with disabilities, with a particular focus on palliative care in critically ill or injured pediatric patients. NINR supports palliative care research that addresses issues of health equity, examines social determinants of health and their effects on individuals and families, and examines systems and models of care to improve access to quality palliative

[197] reporter.nih.gov/search/X3NAGiFNL0mYh_Wj4XCHHg/projects

[198] grants.nih.gov/grants/guide/rfa-files/RFA-CA-22-027.html; grants.nih.gov/grants/guide/pa-files/par-21-035.html; grants.nih.gov/grants/guide/pa-files/PAR-21-329.html

[199] grants.nih.gov/grants/guide/pa-files/PAR-23-292.html

care.[200] NIDDK supports research on palliative care for people with end stage renal disease (also called kidney failure), such as projects that address pain management in people receiving dialysis and develop informed decision-making strategies for patients and their caregivers. Multiple ICOs are also funding several ongoing clinical trials in palliative care. For example, the NCI Community Oncology Research Program (NCORP) is a national network that brings cancer clinical trials and care delivery studies to people in their own communities.[201] Further, the NIA currently funds more than a dozen clinical trials on palliative care, including those on dementia-specific palliative care and trials using telehealth to deliver palliative care, and a Palliative and Advanced Illness Research Roybal Center for Translational Research.[202]

Several ICOs are already collaborating in palliative care efforts. For example, NHLBI and NINR both currently participate in a Notice of Special Interest focused on improving quality of life for people with heart, lung, blood, and sleep diseases; several ICOs participated in multiple reissues of a Notice of Special Interest on advancing the science of geriatric palliative care.[203] To expand and intensify strategic coordination of these research areas across the agency, NIA convened a palliative care workgroup with subject matter experts from across the NIH Institutes and Centers. This workgroup is aimed at collaborating on a wide variety of palliative care research, training, dissemination, and implementation of projects to intensify the strategic coordination of palliative care research efforts. As one major step forward, in October 2023, the NIH Guide published a Notice of Intent to Publish a Funding Opportunity Announcement to support an NIH Consortium for Palliative Care Research Across the Lifespan.[204] The consortium is expected to be awarded by December 2024. The overall consortium goals include creating new scientific knowledge, in part through supporting pilot and exploratory studies; fostering development of early- and mid-career investigators; serving as a national platform to provide research resources and facilitate high-quality research; engaging health care systems and community-based organizations as research partners and settings; and disseminating research findings, best practices, data, and other impactful resources to the research and clinical communities. An important focus will be on supporting research that addresses disparities in access, quality, and use of palliative care services for underserved populations. This new consortium enables NIH to continue to prioritize strategic and collaborative research on palliative care across the agency.

[200] reporter.nih.gov/search/Ohqmi4CpkUmZzqHLtjI5gg/project-details/10709495; reporter.nih.gov/search/VdgUN3-c2k25yyHieMw81Q/project-details/10688290
[201] ncorp.cancer.gov/
[202] nia.nih.gov/research/ongoing-AD-trials; https://pair.upenn.edu/
[203] grants.nih.gov/grants/guide/notice-files/NOT-AG-22-048.html
[204] NOT-AG-23-050 grants.nih.gov/grants/guide/notice-files/NOT-AG-23-050.html

Pediatric Cancer Immunotherapy

The Committee encourages NCI to continue to support pediatric immunotherapy translational and clinical research. The Committee is aware of the transition from the Pediatric Immunotherapy Discovery and Development Network to the Pediatric Immunotherapy Network. The Committee requests an update on progress made in ensuring the continuation of multi-site pediatric immunotherapy clinical trials in the fiscal year 2025 CJ.

Action taken or to be taken

The National Cancer Institute (NCI) is dedicated to supporting pediatric clinical trials, particularly those testing immunotherapy treatment approaches, as they represent exciting new and less toxic treatment possibilities. NCI supports pediatric clinical trials networks that connect sites across the United States and abroad, including the Children's Oncology Group (COG). COG is the world's largest organization dedicated to childhood and adolescent cancer research and includes over 200 hospitals, universities, and cancer centers.[205] COG includes the Pediatric Early Phase Clinical Trials Network (PEP-CTN) that works to identify and develop effective new agents for children and adolescents with cancer through early-phase clinical trials at sites across the United States, Canada, and Australia. One currently open PEP-CTN clinical trial is evaluating the efficacy of an immunotherapy treatment combination in pediatric and adult patients with a specific genetic deficiency in their tumor cells that have returned or are resistant to treatment.[206]

The Cancer Moonshot^{SM} Pediatric Immunotherapy Discovery & Development Network (PI-DDN) is focused on developing new immunotherapies and improving the effectiveness of current immunotherapies to reduce the burden of cancer in children. Network researchers made significant advances in cell therapy for solid tumors including identifying new target antigens, engineering more effective T cell and natural killer (NK) cell immune cell-based therapies, overcoming T cell exhaustion to increase therapeutic effectiveness, and reducing side effects of immunotherapy. To leverage the successes of the PI-DDN, NCI established a new Pediatric Immunotherapy Network (PIN) focused on research with potential for clinical trials. Awards were made in FY 2023 for six projects.[207] Topic areas include anti-tumor vaccines and new immunotherapy approaches for pediatric neuroblastoma patients, immunotherapy approaches using chimeric antigen receptor (CAR) T-cells for treating pediatric Ewing sarcoma patients, and developing immunotherapy approaches that address immune evasion mechanisms in pediatric brain cancer patients.[208]

Currently, NCI is supporting several multi-site clinical trials focused on immunotherapy for various pediatric cancers. For example, one trial is looking at the use of a drug that inhibits an important pathway involved in the regulation of immune response in relapsed or newly diagnosed brain tumors that will potentially break immune tolerance to pediatric tumors.[209] Another trial is looking at using a vaccine made from a high-grade glioma patient's tumor to

[205] childrensoncologygroup.org/about
[206] clinicaltrials.gov/ct2/show/NCT05286801
[207] grants.nih.gov/grants/guide/rfa-files/RFA-CA-22-016.html
[208] cancer.gov/about-nci/organization/dcb/research-programs/pin
[209] clinicaltrials.gov/ct2/show/NCT04049669

stimulate T cells to kill tumor cells.[210] A different trial is examining the efficacy of using CAR T-cells with a new molecular target for a treatment in pediatric leukemia or lymphoma; new CAR targets are needed because not all patients respond to the most common treatment target, or disease can recur after treatment.[211] These three trials are all being conducted at multiple sites across the United States.

NCI is also manufacturing CAR T-cells for certain NCI-supported clinical trials at its Frederick National Lab for Cancer Research (FNLCR).[212,213] The goal of this program is to accelerate the ability to test these therapies in clinical trials to be conducted at multiple hospital sites. The initial clinical trial supported by this effort is the first trial to test a CAR T-cell therapy designed to target a specific protein on cancer cells in children and young adults with advanced forms of acute myeloid leukemia (AML). The trial started at one site but has been able to expand to enrolling patients at six sites across the country, including the NIH Clinical Center, with the help of this FNLCR program.[214]

NCI has also recently established the Cancer Adoptive Cellular Therapy (Can-ACT) Network. Through this network, NCI intends to foster innovation and promote early-stage clinical testing of novel state-of-the-art cell-based immunotherapies for solid tumors in pediatric and adult patients. Pediatric cancer awards are anticipated to be made in FY 2025 and will focus on preclinical, translational and investigational new drug (IND)-enabling studies that lay groundwork for early-stage clinical trials testing innovative immune cell therapies in pediatric patients with solid tumors.[215]

[210] clinicaltrials.gov/ct2/show/NCT03334305
[211] clinicaltrials.gov/ct2/show/NCT02315612
[212] cancer.gov/news-events/cancer-currents-blog/2020/car-t-cell-nci-manufacturing-clinical-trial
[213] frederick.cancer.gov/news/frederick-national-laboratory-produces-car-t-cell-immunotherapies-pediatric
[214] clinicaltrials.gov/study/NCT03971799
[215] grants.nih.gov/grants/guide/rfa-files/RFA-CA-24-021.html

Pelvic Organ Prolapse

Pelvic organ prolapse [POP] occurs when the pelvic floor muscles and connective tissue supporting the pelvic organs no longer support these organs, causing one or more of the pelvic organs to fall downward into the vagina. POP is a common problem, with 1 out of 8 women undergoing surgery for prolapse at some point in their life. Symptomatic POP is associated with urinary incontinence, depression, anxiety, sleep disturbance, sexual dysfunction, deteriorating physical function and diminished socialization. No effective preventative strategies for POP have been identified and the development of novel preventative strategies related to pregnancy is needed. Therefore, the Committee urges the NICHD to convene a workshop to assess peripartum, intrapartum, and postpartum preventative strategies for POP including ways to decrease pelvic floor trauma/denervation during delivery, with the goal of reducing the risk of subsequent POP and its complications. The Committee requests an update on this issue and on research activities to advance POP prevention and treatment in the fiscal year 2025 CJ.

Action taken or to be taken

Pelvic floor disorders (PFDs), including pelvic organ prolapse, are a common problem for women that the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is working to address. The majority of NICHD-supported research on pelvic floor disorders is through the Pelvic Floor Disorders Network (PFDN), a multi-center network established in 2001 in response to an increasing awareness by the public and health professionals of the need for more evidence-based data to guide both surgical and non-surgical care for this large and growing clinical problem. The overall objective of the PFDN is to facilitate interactions across a network of academic centers with the recruitment capabilities and research expertise needed to perform studies that will provide efficient, high quality, evidence-based clinical answers to both providers and women. PFDN research aims to inform healthcare providers about diagnosis, care, and treatment of women with PFDs, while improving the quality of life for women with PFDs and their families. Studies include both careful analysis of standard treatment outcomes as well as testing new therapies and approaches to move the research agenda forward in novel directions for clinical benefit. In the past cycle, the PFDN studied the following topics:

- Impact of pelvic organ prolapse surgery on pain with sexual activity;
- Fabrication of pelvic floor support tissue from vaginal biopsies;
- Identification of risk factors for failure of pelvic organ prolapse surgery based on patient characteristics and MRI findings;
- Evaluation of different treatments for the treatment of mixed urinary incontinence;
- Comparison of three surgical treatments to address post-hysterectomy pelvic organ prolapse.

The PFDN started a new cycle in 2022 and is developing multi-center clinical trials evaluating urinary incontinence treatments and prolapse. The network has initiated a Diversity, Equality, Inclusion committee to ensure enhanced consideration of underrepresented groups in the development of study protocols.

Furthermore, NICHD is currently funding non-PFDN studies examining the effects of mesh on vaginal tissue, the mechanisms and impact of pregnancy-induced adaptations in pelvic floor muscles, improving the outcomes of urogynecologic meshes in diabetic women, developing new non-surgical treatment options for pelvic organ prolapse, evaluating the use of stem cell-derived smooth muscle progenitor cells for vaginal wall prolapse, and tactile and ultrasound imaging fusion for functional assessment of the female pelvic floor.

In 2021, NIH held a workshop titled, *Advancing Bioprinting and Regenerative Medicine Solutions for Obstetric, Gynecologic, and Pediatric Applications Workshop***,** to stimulate a transdisciplinary discussion on the state of the art of tissue-construct manufacturing using 3D printing of biological, cellular, and tissue-based products (a.k.a., bioprinting) and regenerative medicine in the context of obstetric, gynecologic, and pediatric applications, including the functional restoration of anatomical structures for pelvic and reproductive organs. It brought together multidisciplinary experts and broad thinkers, including regulatory and manufacturing experts, 3D bioprinting and tissue-construct scientists, and bioengineers, as well as scientists and clinicians in regenerative medicine research. The goal was to explore the current state of knowledge, the key gaps and roadblocks that need to be addressed in the field, and actions to move the science forward. NICHD, in collaboration with the research community and stakeholders, will continue its efforts to understand the etiology of these conditions and improved treatment options. NICHD is also considering holding a future workshop on pelvic floor disorders.

Pulmonary Fibrosis

Many pulmonary fibrosis [PF] patients wait more than a year for diagnosis after symptom onset, and patients with some types of PF have a life expectancy of only three to 5 years. Therefore, the Committee encourages NHLBI to support research into biomarkers that can aid in earlier, safer diagnosis of PF, as well as tools that can help predict which patients will experience disease progression. The Committee commends NHLBI for hosting a Pulmonary Fibrosis Stakeholders Summit in November 2022 to develop a blueprint for PF-related research priorities over the next 5 years, and requests an update on the plan's implementation in the fiscal year 2025 CJ. The plan's priorities include a focus on early disease detection and improved diagnosis and innovative clinical trial designs. The Committee urges NHLBI to support the development of advanced research models and integrate these models into preclinical studies in order to facilitate faster drug development. The Committee also hopes the PF plan will lead to increased support for related research and coordination to address this deadly disease.

Action taken or to be taken

The National Heart, Lung, and Blood Institute (NHLBI) remains committed to supporting basic, translational, and clinical research focused on understanding the causes of pulmonary fibrosis (PF), and improving early detection, diagnosis, and treatment outcomes across the lifespan. In NHLBI-supported translational studies completed in 2022, investigators discovered the therapeutic potential of a compound known as saracatinib to treat idiopathic PF (IPF).[216, 217] This compound is now being studied in a Phase 1b/2a clinical trial supported by the National Center for Advancing Translational Sciences (NCATS).[218] In another translational development supported by NHLBI's Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Diseases (CADET) II program, a dual inhibitor targeting molecules on the cell surface, known as integrins, completed an industry-sponsored Phase 2 clinical trial and showed promising results.[219, 220] NHLBI is also supporting a Phase 1 clinical trial to test whether use of epigallocatechin-3-gallate is safe for use in IPF patients.[221] Repurposing drugs to treat conditions other than the one for which they were developed and/or approved can make effective, more affordable treatments available to patients sooner.

NHLBI continues its support for the IPF Models Consortium, which encompasses five cooperative projects that are developing animal and human models that better recapitulate disease-defining features of human IPF. Key resources affiliated with this program in addition to the models themselves will include transcriptomic profiling data across several models, and an interstitial lung disease (ILD) induced pluripotent stem cell (iPSC) Biorepository housed at Boston University that can be used to derive mouse or human organoids that carry mutations associated with the development of ILD including IPF and is currently available to all researchers.

[216] pubmed.ncbi.nlm.nih.gov/35998281/
[217] pubmed.ncbi.nlm.nih.gov/36163190/
[218] clinicaltrials.gov/ct2/show/NCT04598919
[219] reporter.nih.gov/search/49ZPn-qrUUeVT2NUiqgTKQ/projects
[220] pubmed.ncbi.nlm.nih.gov/35931801/
[221] reporter.nih.gov/search/dFIWGOPUKEGAP23LCVYWdQ/project-details/10418169

The Institute is supporting a longitudinal natural history study of individuals at high-risk for developing PF based on family history to better determine how the disease manifests in its early stages and help identify biomarkers that could enable earlier diagnosis and intervention. NHLBI continues to support studies to advance the use of novel imaging modalities to enable earlier detection of PF. For example, a grant project supported by NHLBI's Catalyze Program is developing a positron emission tomography (PET) imaging probe to detect early fibrotic changes in the lungs.

The Prospective Treatment Efficacy in IPF Using Genotype for NAc Selection (PRECISIONS) study, a partnership between NHLBI, 25 academic centers in the United States, the Pulmonary Fibrosis Foundation (PFF), and the Three Lakes Foundation (TLF) recently surpassed 90 percent enrollment. This innovative trial applies the principles of precision medicine to the treatment of IPF and is studying participants with a specific gene variant who may benefit from a drug known as N-acetylcysteine. Utilizing molecular analyses on biospecimens obtained from the PFF's Patient Registry, the trial also aims to discover novel genetic risk factors that will improve IPF diagnosis, prediction of progression, and understanding of underlying mechanisms.

In February 2023, NHLBI made awards to three teams through the Air You Wear Challenge to develop innovative concepts of lighter, more portable oxygen devices.[222] The three teams awarded are from the Vanderbilt University Center for Technology Transfer and Commercialization in Nashville, Tennessee, HealO Medical, LLC, in Sarasota, Florida and Advanced Interactive Response Systems (AIRS) and Michigan Technological University in Houghton, Michigan. The Challenge aims to improve quality of life for individuals with PF and other chronic lung diseases by incentivizing research and development of technologies designed to improve the accessibility, efficacy, and usability of supplemental oxygen to better serve the more than 1.5 million Americans who rely on it.

NHLBI is working with the cosponsors of the November 2022 Pulmonary Fibrosis Stakeholder Summit, the TLF and PFF, on publication of a framework to guide future research on PF. Key scientific opportunities that will be addressed include identification of early disease risk factors and methods to improve PF diagnosis, including increasing racial and ethnicity representation in studies, development of novel models and research tools to better study PF, uncovering new therapies and advancing innovative approaches to PF clinical trial design.

[222] nhlbi.nih.gov/grants-and-training/air-you-wear-challenge#

Research with Non-Human Primates

The Committee recognizes the critical role of non-human primate [NHP] research in virtually all areas of biomedical research. Research with unique animal models makes irreplaceable contributions to understanding the biological processes that cause disease, which is necessary for the development, safety and efficacy testing of new therapeutics before clinical trials. NHP research will be vital to studying both the underlying mechanisms and potential cures for costly and emergent diseases. The Committee is concerned about the condition and availability of critical Federal research assets outlined in the 2023 National Academies report on the State of the Science and Future Needs for Nonhuman Primate Models in Biomedical Research. In particular, the Committee is alarmed that NIH has no central data management or reporting structure for tracking the number of NHPs required to meet current and future research needs. The Committee directs NIH to develop a strategic management plan for NHP research resources to bolster cooperative efforts, data sharing, purposeful planning, and data-driven care and management methods. The Committee urges NIH to award funding to meritorious research proposals using NHPs to study neurological diseases as well as research into preventing the next pandemic. NIH is also encouraged to continue the development and validation of new approach methodologies that reduce the need for, enhance the utility of, and mitigate shortages and costs of NHP models in the future.

Action taken or to be taken

NIH-funded research with nonhuman primates (NHPs) has led to critical biomedical advancements that have saved countless human lives. NHPs remain essential models for advancing fundamental neurobiology and developing treatments for neurological disorders; providing crucial insights into reproductive health and fertility disorders; and developing new or improved therapeutics and vaccines for SARS-CoV-2, HIV, Ebola virus, Zika virus, and several other emerging or reemerging infectious diseases. NHPs will continue to be needed for progress at key stages of the research continuum in these and other areas of research for the foreseeable future.

In response to the ongoing NHP shortage, NIH began a new NHP evaluation and analysis study in 2023 to inform NIH's development of an updated strategic management plan for NHPs that builds on the analysis performed by NIH and reported in the 2018 Nonhuman Primate Evaluation and Analysis report.[223] This new study is characterizing major United States NHP providers, quantifying the latest 5-year trends in NHP usage by NIH-funded investigators, and forecasting NIH-supported investigators' needs for NHPs in the coming years. In support of this study, NIH released a Request for Information on Infrastructure for Research in Nonhuman Primates that closed September 7, 2023.[224] A report of the study's findings is expected in the first half of 2024 and will be made publicly available.

Identifying the best options for expansion of NHP breeding requires careful planning. Needs for NHPs must first be predicted to the extent possible. For rhesus macaques, the most used NHP species in NIH-funded research, there is generally a four-year delay before offspring mature to an age suitable for use in most research studies. Significant expansion of NHP breeding activity

[223] orip.nih.gov/nonhuman-primate-evaluation-and-analysis-part-1-analysis-future-demand-and-supply
[224] grants.nih.gov/grants/guide/notice-files/NOT-OD-23-150.html

will also require substantial investments in new animal housing infrastructure initially, followed by sustained increases in support for animal husbandry staff, veterinary care, infrastructure maintenance, and other animal care costs.

Each of the NIH Institutes, Centers, and Offices (ICOs) that supports NHP breeding colonies track the number of available NHPs from those colonies. In addition, ICOs involved in NHP research estimate the number of NHPs required to fulfill their current research needs. The ICOs that support NHP colonies and/or research using NHPs regularly share information and engage in planning discussions at monthly meetings of the NIH-wide Nonhuman Primate Resource Planning Working Group, formed in response to a 2018 expert panel forum.[225] A scientific advisor was hired in May 2023 to coordinate data and activities related to NIH-wide needs for, use of, and availability of NHPs. NIH is exploring options for expanding or supplementing NIH-supported breeding colonies and/or improving the efficiency of allocating NHPs from NIH-supported colonies as was accomplished during the response to COVID-19.[226]

NIH is actively engaged with the research community to identify and develop research methodologies that could improve the quality of research and minimize the use of animal models in general and NHP models in particular. NIH continues to invest in the development of "novel alternative methods" (NAMs) such as computational models, tissue chips, and cell-free methods to maximize research translation and potentially reduce reliance on animal models in certain areas. To identify the most promising areas of NAM development and use, NIH recently convened an Advisory Committee to the Director (ACD) Working Group on Catalyzing the Development and Use of Novel Alternative Methods to Advance Biomedical Research. One of the working group's goals is to articulate high-priority areas for NIH investment in NAMs to augment the tools and capabilities for biomedical research to complement and/or potentially replace traditional animal models.[227] NIH also is planning a potential Common Fund research program, entitled Complement Animal Research In Experimentation (Complement-ARIE), aimed at development, standardization, validation, and use of NAMs with improved capabilities for modeling human biology.[228] While progress on the development and validation of NAMs continues, NAMs currently cannot substitute for the use of NHP models. Nevertheless, NAMs are complementary tools that may help to narrow the types of studies that use NHP models and increase the translational value of those studies that still require NHPs. NIH will continue its development of NAMs as these alternative methods may eventually reduce, but not eliminate, reliance on NHPs. In addition, to optimize the stewardship and value of research that requires NHPs, NIH also will continue to enhance the rigor, transparency, and translatability of those studies for which NHPs remain the best model for progress in biomedical research.[229]

NIH will continue to support the crucial use of NHPs and development and validation of NAMs in biomedical and behavioral research for the ultimate goal of advancing safe and effective prevention and treatment strategies to improve public health in the United States and worldwide.

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[225] orip.nih.gov/about-orip/research-highlights/nonhuman-primate-evaluation-and-analysis-part-2-report-expert-panel
[226] grants.nih.gov/grants/guide/notice-files/not-od-21-080.html
[227] acd.od.nih.gov/working-groups/novel-alternatives.html
[228] commonfund.nih.gov/complementarie/strategicplanning
[229] acd.od.nih.gov/working-groups/eprar.html

Scientific Management Review Board

The Committee recognizes that under the NIH Reform Act of 2006 (Public Law 109– 482), a Scientific Management Review Board [SMRB] was created with the specific mission of reviewing the overall "research portfolio" of NIH, and advising on the "use of organizational authorities," such as abolishing Institutes or Centers, creating new ones, and reorganizing existing structures. Yet this Board has not met or issued a report since 2015, despite the obligation to do so every 7 years. The NIH Advisory Committee to the Director [ACD] does not have the statutory authority or mandate to serve as a substitute for the SMRB, and the Committee rejects any efforts to assign the ACD to undertake these efforts. The Committee directs NIH to reconvene the SMRB within 1 year of enactment in order to fulfill its statutory duty to advise Congress, the Secretary, and the NIH Director on how best to organize biomedical research funding.

Action taken or to be taken

The NIH is working to reestablish the SMRB and will reconvene the board to fulfill its role.

Surveillance, Epidemiology, and End Results (SEER) Program

The Committee recognizes NCI for recent efforts to modernize the SEER registry and bolster data collection, including innovative activities to better capture the prevalence and progression of metastatic cancers. NCI is directed to further support SEER modernization activities in a meaningful way, and to continue to update the Committee on progress and unmet needs in this area in the fiscal year 2025 CJ.

Action taken or to be taken

As the only population-based source of long-term incidence (including cancer stage at diagnosis) and survival data in the United States, the NCI Surveillance, Epidemiology and End Results (SEER) Program is continuing the collection of high-quality cancer surveillance data while addressing the challenges of a rapidly evolving cancer care environment.[230] The SEER Program consists of 18 Core registries covering 48 percent of the U.S. population and an additional 10 Research Support Registries that contribute data on more than 850,000 incident cancer cases annually. Program coverage of minority/underserved U.S. populations includes 44.7 percent of African Americans, 66.3 percent of Hispanics, 59.9 percent of American Indians and Alaska Natives, and 70.7 percent of Asians.

Several NCI-supported efforts are underway to enhance and expand the capabilities of, and data collected through, the SEER registries. In FY 2023, the SEER-Linked Pediatric Cancer Whole Slide Imaging Pilot was completed with six SEER registries. The registries tested the validity of a whole slide image (WSI) deidentification tool (DSA WSI DeID) on nearly 4,000 WSIs that will be linked to pediatric cancer cases in the National Childhood Cancer Registry (NCCR) as part of the Childhood Cancer Data Initiative (CCDI). This freely available tool deidentifies images of microscope slides generated through diagnosis and care so that they can be linked to SEER data and shared for cancer research. Most current collections of digital WSIs are not linked to disease outcomes, case characteristics, and other clinical data; the pilot aimed to address the limited availability of this type of data. In addition, the SEER Program developed a high-throughput version of DSA WSI DeID that autodetects and parses personal identifiers on slide labels and automatically matches WSIs to subjects prior to deidentification. Two academic healthcare systems are testing this version to determine if and how their digitally scanned clinical slides can be used in cancer research and education.

The SEER Program has also expanded collaborations with relevant cancer surveillance partners. Activities in FY 2023 include the following:

- The program continued collaboration with the Department of Energy (DOE), including putting into production DOE Application Programming Interfaces (API) as part of the default installation of SEER*DMS (SEER Data Management System), currently in use in 16 registries (including non-SEER registries that use SEER*DMS—these registries cover approximately 30 percent of the United States population). Two APIs are in a testing phase and one API is in a development phase.
- Data collection for cancer cases was enhanced by: (1) expanding and continuing multiple SEER data linkages, including with health insurance, clinical oncology, radiology,

[230] seer.cancer.gov/

pharmacy, and genomic data companies; (2) linking sociodemographic, residential history, and financial toxicity information about individuals diagnosed with cancer; and (3) conducting landscape assessments on potential linkages such as those with statewide claims processes and entities that hold data about the built environment and environmental exposures.
- In support of the PACT Act, SEER established agreements and project protocols with the United States Department of Veterans Affairs to enable data exchange on individuals diagnosed with cancer who are also veterans.
- A cloud-based data platform was initiated to hold and release deidentified data from the National Childhood Cancer Registry (NCCR). SEER also conducted data linkages with various data partners and performed analyses to characterize the population of children represented in the NCCR and in Children's Oncology Group (COG) clinical trials and the population of children represented in the NCCR but not in COG clinical trials.

The SEER Program's commitment to modernize its cancer registries and bolster data collection continues through the following ongoing efforts:

- After the successful analysis of the Request for Information responses for cancer data acquisition, the SEER Program began developing new acquisition(s) to pilot the support for Central Cancer Registries to have new direct connections with healthcare facilities within the geographical areas they serve. These pilots can provide increased technical and procedural assistance for Central Cancer Registries to acquire their state-mandated cancer data.
- SEER continues to update its current infrastructure, providing new capabilities for Central Cancer Registries to query their own data in a more user-friendly way, and providing NCI with a separate secure and direct way to access their own deidentified SEER datasets and other deidentified datasets. Also under development is a new data transfer system to reduce manual efforts to maintain individual connections to various data sources and improve security by creating a centralized hub for incoming data.
- The Virtual Pooled Registry (VPR) pilot has been expanded to include 45 U.S. registries and other federal entities. The VPR uses templated applications, linkage software, and a centralized Institutional Review Board (IRB) to remove inefficiencies and redundancies that investigators encounter when working on a multi-site data linkage study.

In celebration of the SEER Program's 50th anniversary in 2023, NCI hosted an in-person meeting with all SEER Principal Investigators, Registry Managers, as well as key invited guests and partner organizations (e.g., the Centers for Disease Control and Prevention). Additionally, SEER is working with the Journal of the National Cancer Institute to publish a special edition on SEER's history, current activities, and contributions to oncology.

Usher Syndrome

The Committee encourages NIH to enhance and prioritize Usher syndrome research at NEI. The Committee requests an update in the fiscal year 2025 CJ. The update should include efforts to stimulate the field and to accelerate viable human treatment options for those with Usher syndrome.

Action taken or to be taken

Usher syndrome (USH) is a set of rare genetic disorders that affect hearing, balance, and vision. USH affects between 4 to 17 per 100,000 people.[231,232] There are three types of USH (USH1, USH2, USH3), categorized based on symptoms, severity, and age of onset. Each USH type is further classified based on specific genetic mutations. NIH is committed to funding all investigator-initiated USH research that scores well in peer review. The National Eye Institute (NEI) and the National Institute on Deafness and Other Communication Disorders (NIDCD) lead the NIH in supporting USH research.

NEI researchers have developed animal models with genetic mutations corresponding to each of the forms of USH to study disease mechanisms and accelerate the development and validation of treatments to prevent blindness. Gene editing technology called clustered regularly interspaced short palindromic repeats (CRISPR) allows scientists to edit single mutations within a cell. NEI is supporting research by GeneToBe, a small business based in Michigan, which has recapitulated progressive vision and hearing loss in USH3 animal models and are using them to develop gene editing therapies for patients. NEI scientists are also using CRISPR technology to generate new models that specifically replicate the most prevalent mutations in the USH2A gene, with the ultimate goal of creating gene editing therapies to treat USH in patients. Another gene therapy targeting USH2A uses an RNA-based solution: ProQR Therapeutics received orphan drug designation from the United States Food and Drug Administration (FDA) for its RNA therapy and in 2021 announced the first USH2A patients had been treated.

To complement animal models, scientists working at NEI have created mini human retinas in a dish—retinal organoids—derived cells taken from patients with USH type 1 mutations. The development of retinal organoids provides a new platform to identify how USH develops in the retina. These organoids are also a valuable resource for the development and testing of gene therapy tools and have already demonstrated opportunities for potential future clinical trials.

While gene therapy continues to offer promising advances, NEI scientists are persistent in exploring alternative treatments to improve the lives of patients with USH. NEI is also prioritizing vision rehabilitation research to study and enhance peripheral vision in the context of disease progression. Patients with USH can maximize use of remaining vision to improve locomotive abilities and other activities of daily living. In 2022 NEI scientists demonstrated that a repurposed FDA approved drug with an established safety record was able to improve vision in an animal model of retinal degeneration, providing the opportunity for expediting a new treatment in patients.

[231] ncbi.nlm.nih.gov/pubmed/6885960
[232] ncbi.nlm.nih.gov/pubmed/20613545

Von Hippel-Lindau (VHL) Disease

The Committee recognizes that finding a treatment and cure for VHL disease, in which the VHL tumor suppressor gene is damaged or nonexistent, is key for treating and curing not only the rare disease of VHL but also many other forms of cancer. The role of the VHL gene is central in how cells sense and adapt to oxygen and nutrient availability and how this mechanism leads to abnormal cell or cancer growth. As a result, nearly a dozen medications currently used to treat various forms of cancer are the direct result of research in VHL biology. The Committee encourages NIH to continue to support research on VHL disease and biology, seeking both pharmacological and gene therapy treatments for VHL and other cancer patients. The Committee requests an update on VHL research efforts in the fiscal year 2025 CJ.

Action taken or to be taken

The rare inherited disorder von Hippel-Lindau disease (VHL) causes noncancerous tumors to grow and is associated with an increased risk of developing cancerous tumors in multiple organs, including the kidneys, pancreas, brain, and spine. Previous NIH-funded research into the underlying mechanisms of VHL disease found that mutations causing a loss of VHL protein results in accumulation of another protein involved in regulation of blood vessel formation and development, HIF-2α, leading to tumor formation.[233] Although therapeutically targeting VHL loss-of-function directly has proven challenging, fundamental research to identify other molecular players has led to drug discovery efforts targeting the activity of HIF-2α with a drug known as belzutifan. Researchers at the National Cancer Institute (NCI) conducted a phase 2 clinical trial to investigate the efficacy and safety of belzutifan in patients with VHL disease-associated renal cell carcinoma, a type of kidney cancer.[234] The outcome of that trial and others resulted in U.S. Food and Drug Administration (FDA) approval of belzutifan in August 2021, making it the first approved drug for the treatment of adults with tumors associated with VHL. NCI researchers continue to study belzutifan to better understand its effect on tumors and its long-term use with surgery. With more research, they hope that belzutifan will be approved for other types of VHL-associated tumors. A number of trials[235] are also now studying the effectiveness of belzutifan for sporadic clear cell kidney cancer, illustrating how basic research studies of a rare cancer can also have important implications for more common cancers.

Both NCI-supported Specialized Programs of Research Excellence (SPOREs) in Kidney Cancer include projects that are specifically aiming to advance translational research on VHL disease and its associated cancers. Researchers are testing several new potential HIF-2α inhibitor compounds[236] and are working to identify biomarkers that could potentially predict why some individual's tumors successfully respond to HIF-2α inhibitors, while others fail to respond or develop resistance over time.[237]

In addition to investigating new avenues for HIF-2α inhibition, NCI-supported researchers are also examining the tumor microenvironment around renal cell carcinoma cells lacking VHL

[233] directorsblog.nih.gov/2022/01/25/nci-support-for-basic-science-paves-way-for-kidney-cancer-drug-belzutifan/
[234] www.cancer.gov/news-events/cancer-currents-blog/2021/fda-belzutifan-vhl-tumors
[235] classic.clinicaltrials.gov/ct2/show/NCT04195750
[236] trp.cancer.gov/spores/abstracts/utsouthwestern_kidney.htm#h03
[237] trp.cancer.gov/spores/abstracts/dfhcc_gu.htm#h03

tumor suppressor function to understand the cancer cells' role in suppressing the anti-tumor activity of immune cells.[238,239] This research has the potential to pave the way for more effective immunotherapies.

At the National Institute of Neurological Disorders and Stroke (NINDS), intramural researchers are conducting a natural history study to learn more about the growth of brain and spinal cord tumors and cysts in individuals with VHL. Researchers will examine how fast the tumors grow and try to determine which factors (such as puberty, pregnancy, menopause, or blood proteins) affect tumor growth. Surgical removal of brain and spinal cord tumors is currently the treatment of choice when these lesions cause neurological problems. A better understanding of which tumors are likely to grow, and which will remain stable, may help guide physicians in treatment decisions and avoid unnecessary procedures.[240] NINDS intramural scientists are also conducting a clinical trial to learn if certain drugs can slow or stop the growth of VHL tumors. The researchers are using information from this natural history study to identify groups of individuals who may benefit from specific drugs.[241] If successful, these drugs might help individuals with VHL avoid surgery for these tumors.

Beyond understanding the role of VHL protein in tumor formation, researchers supported by the National Heart, Lung, and Blood Institute (NHLBI) are conducting studies to better understand the intricacies of the molecular pathways involving the VHL protein, as well as these pathways' potential implications for other diseases. For example, an NHLBI-supported study[242] is investigating whether a specific protein modification known as neddylation regulates the removal of damaged mitochondria (mitophagy) and if it could serve as a potential therapeutic target for treating age-related cardiac dysfunction; removing damaged mitochondria allows for regulation of cellular homeostasis and delays age-related disorders. The study has identified an inhibitor of neddylation that appears to effectively activate mitophagy by blocking the neddylation of a protein in the VHL protein complex, shedding light on the novel mechanistic link between neddylation and mitophagy and the potential of neddylation inhibition to modulate molecular pathways involving the VHL protein. In addition, other NHLBI-supported researchers[243] studying lung fibrosis, an irreversible and debilitating lung disease with no effective treatment options, have discovered a new function of a peptide (short amino acid chain) that targets the VHL protein for degradation and demonstrates therapeutic potential by reversing the pathogenic markers characteristic of lung fibrosis disease severity.

[238] reporter.nih.gov/search/kvkyMa_7dkSfGFBIBxDOeg/project-details/10607997
[239] reporter.nih.gov/search/kvkyMa_7dkSfGFBIBxDOeg/project-details/10532599
[240] clinicaltrials.gov/study/NCT00005902
[241] clinicaltrials.gov/study/NCT02108002
[242] reporter.nih.gov/search/d1hVZpcDW0SutyVCFUttVA/project-details/10419019
[243] reporter.nih.gov/search/pma0QFluAE6rh_7kPAvfJw/project-details/10292074

Youth E-Cigarette Use

The Committee understands that electronic cigarettes (e-cigarettes) and other vaporizing equipment remain popular among adolescents, and requests that NIDA continue to fund research on the use and consequences of using these devices. The Committee is pleased that NIDA continues to support the Monitoring the Future survey and Population Assessment of Tobacco and Health studies, which provide timely data on tobacco products and other drug use. Finally, with more than 4 million young people using e-cigarettes, there is a greater need for research into therapeutic options for nicotine cessation among youth who have developed addiction to nicotine. The Committee encourages NIDA to support research to develop therapies, including both pharmacologic and behavioral therapies, to combat nicotine addiction in pediatric populations.

Action taken or to be taken

For adults who smoke or vape nicotine and seek to quit, there are several effective cessation therapies available, including behavioral therapies (e.g., individual and group counseling, voucher- or prize-based incentives) and pharmacotherapies (e.g., varenicline, bupropion, nicotine replacement therapy). In contrast, there are currently no proven-effective cessation therapies for adolescents who smoke or vape nicotine. This is an urgent need, given that teens who vape are more likely to engage in subsequent smoking (Berry, et al. 2019) and are also more likely to experience wheeze, bronchitis, and shortness of breath, compared to teens who do not vape (Tackett, et al. 2023). Research also shows that among adolescents, there is a strong association between nicotine vaping and cannabis vaping (Trivers, et al. 2018), and that vaping of these substances has generally increased over that past several years while consumption by smoking has declined (Keyes, et al. 2022; MTF 2023). Thus, NIDA supports a robust research portfolio to develop and evaluate vaping cessation therapies for this age group, with many projects that aim to reduce both nicotine and cannabis use.

Past clinical trials of pharmacotherapy for *smoking* cessation among adolescents have yielded disappointing results. For example, trials of varenicline found it was well tolerated among adolescent and young adult smokers, but did not improve end-of-treatment smoking cessation compared to placebo (Gray, et al. 2019; Gray, et al. 2020). However, those trials had low retention rates, with about 40 percent of participants dropping out before end of treatment. An ongoing NIDA-funded placebo-controlled trial is testing whether varenicline can reduce nicotine vaping—as well as cannabis use—among adolescents who vape but do not smoke, have addiction to nicotine, and want to quit (Gray, et al. 2023). As in past trials of varenicline for smoking cessation, the participants receive cessation counseling. To improve retention, they also receive financial incentives for completing study assessments and taking their study medications daily, as confirmed by video recordings.

NIDA-funded research shows that vaping within adolescents' social networks, combined with misperceptions about its harms, has a significant impact on their odds of taking up vaping and their attempts to quit (Valente, et al. 2023; Dai, et al. 2023). Given that teens increasingly socialize through mobile devices, NIDA is investing heavily in research on behavioral digital therapies to support vaping cessation, especially those that leverage social interactions and norms around vaping, along with accurate information about its risks. For example, one project is

developing an app called Vaper2Vaper that connects teenage vapers with peers who are trying to quit and peer coaches who have successfully quit (5R34DA050992-02[244]). Another project will develop and pilot test the efficacy of a social media-based outreach and intervention system, quitSTART, targeted for individuals who report vaping and a desire to quit. Originally developed to support smoking cessation, quitSTART was customized to focus on vaping (5R34DA054725-02[245]).

Another innovative project will design a virtual reality system to provide cognitive behavioral therapy (CBT) to young vapers, taking it from feasibility studies through efficacy trials to assess its impact on nicotine vaping, as well as cannabis and alcohol use; this system will present participants with stressful situations known to trigger cravings while also prompting situation-specific CBT to help them learn to cope (1R44DA059018-01[246]). Because teens with depression are more likely to vape, researchers are developing and evaluating an app to support a customized form of behavioral activation therapy—which already has some support for treating smoking linked to depression (1R41DA053856-01[247]). Finally, NIDA and the National Cancer Institute recently launched a new program to further support development, testing, and implementation of behavioral interventions for tobacco cessation among adolescents, with a focus on e-cigarettes and other products popular with this age group (RFA-CA-22-043[248]). Studies may address tobacco and cannabis co-use and are expected to start as early as July 2024.

In addition to research on vaping cessation, NIDA also funds research on prevention interventions to deter youth from vaping in the first place. For example, in a feasibility study, high school students in Denver communities will be trained to deliver a vaping prevention program for middle school students (1R34DA058218[249]). Researchers are working with the New York public school system to train 8th-9th grade students as peer leaders in vaping prevention and examine the system-wide impact on student vaping (5R01DA050991-03[250]). Other researchers are working on a digital cannabis use prevention program intended for and co-designed by 8th graders (1R43DA055376-01[251]). Finally, NIDA supports efforts to develop and test comprehensive, community-based education and prevention programs to reduce tobacco, alcohol, and other drug use among youth (5R01DA050521-03).[252]

[244] reporter.nih.gov/search/phUdq1kEwkqi29-z7ia18A/project-details/10402794
[245] reporter.nih.gov/search/5Sa71EzDDE-Hzx-dUvs_XA/project-details/10671544
[246] reporter.nih.gov/search/UhUSV49_00CrODEVwcx2xw/project-details/10740956
[247] reporter.nih.gov/search/97jVp5wMbEGV_62byrvXEg/project-details/10250714
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