

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

FY 2024 CONGRESSIONAL JUSTIFICATION

Significant Items

	<u>Page Number</u>
Alcohol-Associated Liver Disease.....	3
Alopecia Areata	4
Amyloidosis	5
Amyotrophic Lateral Sclerosis (ALS)	7
Autism Spectrum Disorder (ASD).....	10
Biomedical Research Workforce Diversity	13
Blepharospasm.....	17
Cardiovascular Disease (CVD).....	19
Cellular Immunity	22
Childhood Cancer Research Coordination.....	24
Childhood Cancer STAR Act	27
Childhood Post-Infectious Neuroimmune Disorders PANS and PANDAS.....	31
Chronic Kidney Disease (CKD)	33
Clinical Trial Diversity	35
Colorectal Cancer.....	39
Congenital Heart Disease (CHD).....	42
Deadliest Cancers.....	44
Diversity in NIH Kidney Disease Research Populations.....	54
Dystonia	56
Early-Career Pediatric Researchers	58
Early-Career Researchers.....	61
Endometrial Cancer	64
Geroscience.....	67
Gynecologic Cancers	69
Hearing Health Screening for Older Adults.....	71

Interstitial Cystitis.....	73
Marijuana Research	74
Melanoma	76
Metastatic Breast Cancer	80
Native Hawaiian Pacific Islander Health Research	82
Obstetric Fistula Research	85
Office of Behavioral and Social Sciences Research (OBSSR).....	87
Osteopathic Medical Schools.....	89
Overactive Bladder Treatment.....	92
Palliative Care.....	94
Pancreatic Cancer.....	97
Parkinson’s Disease	100
Parkinson’s Disease (PD)	102
Parkinson’s Disease and Dementia.....	104
Pelvic Floor Disorders	106
Polycystic Ovary Syndrome (PCOS).....	108
Prioritizing Black Youth Suicide Prevention.....	111
Pulmonary Fibrosis	113
Radiopharmaceutical Development	115
Rare Blood Cancers and Germline Mutations	120
Repeat Expansion Diseases.....	122
Spina Bifida	123
Suicide Prevention	126
Surveillance, Epidemiology, and End Results (SEER) Registry	129
Temporomandibular Disorders (TMD).....	131
Trans-NIH Pediatric Research Consortium (N–PeRC)	133

Alcohol-Associated Liver Disease

House Language

The Committee is aware that alcohol use disorder and alcohol-associated liver disease are distinct diseases. However, it is rare for patients to have the latter without first having the former. Combining the research in this area in a holistic approach could lead to advancements for both, which are needed urgently given the increased rates of alcohol consumption during the pandemic. The Committee requests an update in the fiscal year 2024 Congressional Justification on the viability of this approach, including NIAAA's capacity to award related grants and the field's capacity to develop scientifically valid research projects.

Action taken or to be taken

Closing the treatment gap for alcohol use disorder (AUD) as well its associated organ damage is a major priority for the National Institute on Alcohol Effects and Alcohol-Assisted Disorders (NIAAA).^{*} Alcohol misuse can lead to a spectrum of liver diseases, such as alcohol-associated hepatitis and cirrhosis, which are collectively known as alcohol-associated liver disease (ALD). Nearly half of deaths from liver disease each year are associated with alcohol misuse. From 2000 to 2019, ALD-related deaths increased 47 percent, and rates are increasing faster for women and young adults aged 25-34.

Currently, there are no treatments approved by the United States Food and Drug Administration (FDA) for ALD. Evidence-based treatments are available for AUD that could, in turn, prevent the development or recurrence of ALD or improve ALD-related outcomes. However, AUD treatments continue to be under-utilized. Less than 10 percent of people with AUD receive any treatment.

An emerging body of evidence, including studies funded by NIAAA, indicates that integrating treatment for AUD and ALD has the potential to improve health outcomes, promote recovery, and contribute to the long-term survival of patients. A recent NIAAA-supported study found that patients who received behavioral or medication-based treatment for AUD immediately following hospitalization for alcohol-associated hepatitis reduced hospital readmission, alcohol relapse, and death in this patient population that typically has high rates of morbidity and mortality.

A significant barrier to integrated treatment for AUD and ALD is the lack of supporting data from clinical trials. To advance research in this area, NIAAA is partnering with hepatologists, addiction medicine specialists, clinical trial design specialists, statisticians, FDA, and the private sector to lay the groundwork for optimizing trials to test integrated care. Ongoing NIAAA-supported ALD initiatives are poised to help advance a paradigm shift to integrated care. NIAAA's Alcohol-associated Hepatitis Network conducts translational and clinical research to develop potential therapies and identify risk factors for severe alcohol-associated hepatitis.

^{*}The FY 2024 President's Budget proposes to rename the National Institute on Alcohol Abuse and Alcoholism to the National Institute on Alcohol Effects and Alcohol-Associated Disorders.

Alopecia Areata

House Language

The Committee notes the importance of research into autoimmune skin conditions such as alopecia areata. The Committee requests an update in the fiscal year 2024 Congressional Justification on research initiatives into this condition and opportunities to advance research.

Action taken or to be taken

Alopecia areata (AA) is an autoimmune disease in which the immune system—which normally protects the body from foreign invaders such as viruses and bacteria—mistakenly attacks the hair follicles, the structures from which hairs grow. This can lead to hair loss on all parts of the body, but most noticeably on the scalp. As highlighted in the FY 2024 National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Congressional Justification, the U.S. Food and Drug Administration (FDA) approved baricitinib in 2022, the first whole-body treatment for AA.¹ Many current treatments for AA are not uniformly effective for all patients, and no AA treatments that can be taken orally had previously been FDA approved. In clinical trials conducted by a large pharmaceutical company, treatment with baricitinib, which belongs to a class of drugs called Janus kinase (a protein in cells also called JAK) inhibitors, caused substantial hair regrowth compared to placebo after 36 weeks.² While the clinical trial results led to the FDA's approval of baricitinib as the first oral medication available to AA patients, the groundwork for this approval was laid by previous NIAMS-funded research. NIAMS investigators showed that JAKs play a key role in the development of many autoimmune diseases—a finding that enabled the development of the JAK inhibitors.³ Subsequent NIAMS-supported translational research established the evidence base for using JAK inhibitors to combat hair loss in AA.⁴

NIAMS continues to support research to improve understanding of AA and develop new treatments since not all individuals with AA respond to JAK inhibitors. Within the intramural research program, NIAMS has recruited a pediatric dermatologist and expert in AA whose research background has focused on AA in children, including the natural history of pediatric AA as well as the epidemiology, associated co-morbidities, and response to therapy. Past NIAMS-funded research has uncovered genetic factors that are associated with AA, many of which have been implicated in other autoimmune diseases. Ongoing research is investigating the influence of immune abnormalities, environmental factors such as the microbiome, and the molecules that drive inflammation on AA development and severity. NIAMS-supported investigators continue to conduct basic, translational, and clinical research to identify and test the efficacy of potential AA therapies.

¹ www.fda.gov/news-events/press-announcements/fda-approves-first-systemic-treatment-alopecia-areata#:~:text=Today%2C%20the%20U.S.%20Food%20and,in%20the%20U.S.%20each%20year

² pubmed.ncbi.nlm.nih.gov/35334197/

³ www.nih.gov/sites/default/files/about-nih/impact/immune-cells-inflammation-case-study.pdf

⁴ www.nih.gov/sites/default/files/about-nih/impact/immune-cells-inflammation-case-study.pdf

Amyloidosis

House Language

The Committee strongly encourages NIH to expand its research efforts in amyloidosis, a group of rare diseases characterized by abnormally folded protein deposits in tissues. Although amyloidosis is often fatal, Federal and foundation support over the past years has given hope for successful new treatments. More efforts are needed to accelerate research and awareness of the disease and to help patients with amyloidosis related multi-organ dysfunction. The Committee also directs NIH to provide an update in the fiscal year 2024 Congressional Justification 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. There are several types of amyloidosis. Some forms of amyloidosis are hereditary, while others are sporadic (non-hereditary). Examples include AL amyloidosis, which is the most common form in the United States marked by an accumulation of “amyloid light chain” protein, AA amyloidosis, which is usually triggered by an inflammatory disease and characterized by accumulation of protein called “Serum Amyloid A,” and hereditary (or familial) amyloidosis, which most commonly occurs when a specific protein “transthyretin” builds up in organs. Some types of amyloidosis are characterized by a specific protein form and its location of buildup (e.g., transthyretin cardiac amyloidosis is associated with abnormal buildup of transthyretin specifically in the tissues of the heart).

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 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 and transthyretin. 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.⁵

Research has shown that amyloid- β protein is a natural antimicrobial synthesized by the body to help fight against infection. More specifically, research suggests that amyloid- β protects against infection by entrapping pathogens in insoluble amyloid deposits. This has led NIA to fund more research on how amyloidosis may be driven by pathogens, such as the herpes virus. For example, NIA funds a study testing whether chronic long-lasting viral infection in the brain accelerates amyloid generation and accumulation.⁶

NIH also supports 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. NHLBI is funding a study to develop a new approach to identify early changes in the structure and function of heart and blood markers in individuals with transthyretin cardiac amyloidosis.⁷ Another NHLBI-funded project is developing an artificial intelligence - based Clinical Decision Support Solution that will detect a form of amyloidosis called wild type transthyretin amyloid in individuals before they develop clinical manifestation. 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.⁸

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 amyloidosis, the most common systemic amyloid disease,⁹ using a compound that reduced secretion of the light chain 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.

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 in October 2020, with NIA support, and focused on natural history and endpoint development.

⁵ reporter.nih.gov/search/DSQ71snxa0ue1iPJkYWIAg/project-details/10467374

⁶ reporter.nih.gov/search/JC25TIK2tE2arTUvDRQ_hg/project-details/9638738

⁷ reporter.nih.gov/search/pl35fIG-c0-EOL4LjuaBJQ/project-details/9867084

⁸ reporter.nih.gov/search/wMN7Yjsb8UWVi5Lk2kRY5g/project-details/10100303

⁹ pubmed.ncbi.nlm.nih.gov/33599742/

Amyotrophic Lateral Sclerosis (ALS)

House Language

The Committee recognizes the devastating toll that ALS takes on those affected by the disease and their loved ones. ALS causes progressive and cumulative physical disabilities in patients, and leads to death due to respiratory muscle failure. The Committee strongly urges NINDS to expand support for research on ALS, including but not limited to its causes, diagnosis, and treatment. The Committee directs NIH to provide an update on NIH-supported research related to ALS in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

The National Institutes of Health (NIH) places a high priority on amyotrophic lateral sclerosis (ALS) research and has increased funding from \$52 million in FY 2016 to \$120 million in FY 2021 to support a broad, diverse research portfolio to identify the genetic and environmental causes of ALS, elucidate the cellular and molecular mechanisms by which the disease progresses, identify biomarkers, and develop and test treatments.

NIH funds and supports a wide-array of studies to understand the genetic and environmental causes and risk factors of ALS and cellular and molecular mechanisms by which the disease progresses. For example, NIH-supported studies have shown how mislocalization of a protein called TAR DNA-binding protein 43 (TDP-43) inside cells, which occurs in the vast majority of ALS patients, alters the genetic instructions for several other proteins and suggests that therapies that increase the levels of these other proteins may prevent the death of neurons in ALS¹⁰. This therapeutic approach is being studied in mice with the goal of eventually moving into humans.¹¹ To augment multi-disciplinary ALS research, NIH established the Accelerating Leading-edge Science in ALS (ALS²) initiative, part of the NIH Common Fund's Transformative Research Awards, which currently supports researchers to advance our understanding of what triggers ALS and what drives its rapid progression.

NIH is supporting several large natural history and biomarker studies that will help researchers to better track and understand disease progression and predict when people at risk for ALS might get the disease, which could allow them to begin treatment early, perhaps even before symptoms appear. The CReATe Consortium (The Clinical Research in ALS and Related Disorders for Therapeutic Development)¹² is a multi-component program for clinical research in ALS and related disorders that involves over 15 collaborative sites across the United States and abroad. The Pre-Symptomatic Familial ALS (Pre-fALS) Study¹³ follows people at risk for ALS (gene mutation carriers) and provides insights into the early stages of the disease.

To implement the Accelerating Access to Critical Therapies (ACT) for ALS Act (H.R. 3537), NIH is funding an expanded access study of intravenous trehalose¹⁴, a type of sugar that may help clear damaged proteins from cells, to investigate the safety of this investigational therapy,

¹⁰ www.ninds.nih.gov/news-events/press-releases/scientists-discover-new-molecular-pathway-shared-two-neurodegenerative-disorders

¹¹ reporter.nih.gov/search/bMx4WBOyyESXteuhfF7_5g/project-details/10317404

¹² www1.rarediseasesnetwork.org/cms/create

¹³ reporter.nih.gov/search/TZgLRrYueEy4LZHdQAP6EQ/project-details/10469619

¹⁴ reporter.nih.gov/search/ILgysESWb0GlhuncwObABA/project-details/10649756

measure levels of biomarkers that indicate nerve cell degeneration, and monitor disease progression and survival rates in people with advanced disease who are not otherwise eligible for clinical trials. NIH and the U.S. Food and Drug Administration (FDA) have launched the Critical Path for Rare Neurodegenerative Diseases (CP-RND)—as a first step in developing a public-private partnership aimed at establishing a framework for pre-competitive collaboration across academic, industry, government and organizations for people affected by ALS that will ensure all ongoing and future collaborative efforts emphasize diversity, equity, and inclusion with a goal to accelerate research and authorization for effective treatments. NIH has also partnered with the FDA Rare Neurodegenerative Disease Grant Program, which was established by ACT for ALS, to support a natural history study of ALS and an equivalency study to ensure reliability of a widely used physical assessment tool for ALS in telehealth applications. NIH-supported translational research projects are testing an extensive range of therapeutic targets and agents, including gene therapies and small molecule drugs, in experimental models of ALS, including animals or cells/tissues, to treat inherited and sporadic forms of ALS and ALS/frontotemporal degeneration (FTD). As an example, NIH-funded researchers found that a gene-based therapy designed to silence a gene called FUS that is implicated in a rare, aggressive form of ALS may treat ALS by reducing the number of disease-causing proteins. These studies yielded promising results when initially conducted in mice, and this gene-based therapy is now being tested in an industry-sponsored, multi-center Phase III clinical trial in ALS patients who carry FUS gene mutations.

Despite these advances, substantial gaps in our understanding into the causes of ALS and how it progresses remain a barrier to developing effective therapies. To help close those gaps, NIH led a strategic planning effort to identify high priority research that will lead to improvements in the diagnosis, prevention, management, and identification of highly effective therapies. The Draft ALS Strategic Plan, which is available on the NINDS website¹⁵, represents the combined input and expertise of 53 committee members, including people affected by ALS, and hundreds of members of the ALS community who provided input through the initial public request for information¹⁶ and at the public meeting. These priorities span the spectrum of basic, translational, clinical, and quality of life research, and identify opportunities for partnerships and collaborations. The overarching priorities within this plan are:

1. **Enhance understanding of basic biology of ALS.** In particular, there is wide consensus that we must do more to understand the cellular and molecular events that underlie non-familial, sporadic ALS (around 85 percent of all cases).
2. Translate **novel disease pathways into clinical therapeutic development.**
3. **Optimize clinical research** and the design and performance of trials for people living with ALS at all stages of the disease, including pre-symptomatic gene carriers.
4. Improve the **quality of life** of people living with ALS and their caregivers.
5. Expand and **improve existing collaborations and partnerships between all ALS stakeholders:** people living with ALS, caregivers, researchers, clinicians, and industry partners.

¹⁵ www.ninds.nih.gov/about-ninds/strategic-plans-evaluations/strategic-plans/amyotrophic-lateral-sclerosis-als

¹⁶ [www.ninds.nih.gov/sites/default/files/documents/NINDS ALS Strategic Plan RFI Response Summary_Webpage_508C.pdf](http://www.ninds.nih.gov/sites/default/files/documents/NINDS%20ALS%20Strategic%20Plan%20RFI%20Response%20Summary_Webpage_508C.pdf)

Additionally, NIH has commissioned a study from the National Academy of Science, Engineering, and Medicine (NASEM) to identify and recommend actions for the public, private, and nonprofit sectors to undertake to make ALS a livable disease within a decade. Building upon the research priorities identified in the NIH Strategic Plan for ALS, this study will span research, clinical care, and healthcare services for ALS, and people affected by ALS will have a central role in the study. The NASEM study is expected to be completed before October 2024.

These planning efforts provide a roadmap for future investments in ALS research to identify interventions that will prevent, slow, stop, or reverse ALS and to improve the lives of people living with the disease.

Autism Spectrum Disorder (ASD)

House Language

Recent reports indicate that an estimated one in 44 children in the U.S. is diagnosed with an ASD. While early intervention affords the best opportunity to support healthy development, many children with an autism diagnosis lack access to quality care and interventions. The Committee is encouraged by the growing evidence that caregiver-mediated early intervention can lead to improved child developmental outcomes, improved caregiver-reported skills and knowledge, and reduced stress. The Committee encourages NIH to invest in implementation-focused research that targets caregiver-mediated interventions, including caregiver skills training and naturalistic developmental behavioral interventions. The Committee strongly encourages NIH to work collaboratively across Institutes and Centers in this effort to ensure culturally competent approaches. Furthermore, the Committee is supportive of the research recommendations included in the Interagency Autism Coordinating Committee's (IACC) Strategic Plan for ASD. The Committee urges the NIH to provide an update on its investment across the priority areas outlined in the IACC Strategic Plan in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

Autism spectrum disorder (ASD) research, including research on health disparities and co-occurring conditions, is a priority for the National Institutes of Health (NIH). Through coordination and collaboration with the Interagency Autism Coordinating Committee (IACC), the Federal Interagency Workgroup on ASD (FIWA), and the Trans-NIH Autism Coordinating Committee, the National Institute of Mental Health (NIMH) plans and supports research focused on areas in need of growth, outlined in the *IACC Strategic Plan*. These areas include: research on lifespan issues to address the needs of transition-age youth and adults on the spectrum; research to enable development of evidence-based interventions and services; and, research to support the development and delivery of screening and diagnostic tools. The *2016-2017 IACC Strategic Plan for ASD* outlines an agenda for ASD research and services development, and the *2018-2019 Strategic Plan Update* provides details on Committee activities related to this agenda.^{17,18} The IACC is currently drafting a new Strategic Plan, as required by the Autism CARES Act of 2019. NIH is committed to addressing the budget priorities as identified in the 2016-2017 IACC Strategic Plan for ASD. The NIH Institutes and Centers (ICs) involved in funding the majority of autism research at NIH will continue to make awards to outstanding researchers, while considering the priorities identified by the IACC.

To advance the priority areas currently outlined by the IACC Strategic Plan, NIH supports basic, translational, and clinical research on ASD across the lifespan, including research on the biological mechanisms underlying ASD, early screening and intervention in children, the impact of screening on outcomes, and co-occurring conditions across the lifespan. NIMH research support emphasizes early identification, behavioral and other types of interventions for children and adults, co-occurring conditions, and services. Additionally, other NIH ICs with funding for ASD research include: the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), which focuses on early identification and pediatric health; the

¹⁷ iacc.hhs.gov/publications/strategic-plan/2017/

¹⁸ iacc.hhs.gov/publications/strategic-plan/2019/

National Institute of Environmental Health Sciences (NIEHS), which focuses on environmental factors; the National Institute of Neurological Disorders and Stroke (NINDS), which focuses on genetic syndromes that cause autism; and, the National Institute on Deafness and Other Communication Disorders (NIDCD), which focuses on language development and communication interventions and technologies. As one example of research that spans multiple areas of focus, the Autism Centers of Excellence (ACE) Program – funded by NIMH, NICHD, NIDCD, NINDS, and NIEHS – currently supports research on: the genetic etiology of autism; the neurodevelopmental underpinnings of the disorder; improving cognitive and developmental outcomes; how boys and girls with ASD differ in their brain circuitry; improving screening and diagnosis; improving access to services for minority children; and, developing novel interventions and services through new delivery methods.¹⁹ One ACE Center is focused on using artificial intelligence and computer vision approaches to develop new screening tools for ASD.²⁰ Another Center is investigating the effects of aging in a longitudinal cohort study of autistic adults.²¹

Research shows that children who receive early ASD diagnosis and intervention tend to have better daily functioning skills and well-being over the long-term. However, many families may not receive early screening and diagnosis due to disparities in access to these services. Researchers in the NIH-funded ASD Pediatric, Early Detection, Engagement and Services Research (PEDS) Network found that implementing an evidence-based, multistage screening procedure at federally funded early intervention sites could help address site-to-site variation and reduce disparities in ASD screening and diagnosis.²² NIH also supports research to examine the impact of universal screening on child behavioral and functional outcomes. NIH-funded researchers are using biostatistical and machine learning methods to examine long-term outcomes among school-aged children whose autism was detected early (12-24 months) compared to children with ASD who did not participate in an early detection program. Recently completed studies suggest that early screening in universal and targeted settings increases access to autism services and may be particularly beneficial for families from historically marginalized populations.^{23,24} Findings suggest that utilizing “family navigators” to engage caregivers in recommended services improved the likelihood of diagnostic ascertainment among children from racial/ethnic minority, low-income families who were detected in primary care as at-risk for ASD.²⁵

In addition to research focused on early diagnosis, NIH also supports efforts to improve the efficacy and availability of services and interventions, and to understand and reduce health disparities. For example, NIH is funding research to understand how best to support paraprofessionals (such as teacher assistants) and other school-based care providers who work with children with autism who have high service needs in elementary school settings. NIH-funded researchers are also testing the effectiveness of theater-based programs to enhance social

¹⁹ www.nimh.nih.gov/news/science-news/2022/nih-awards-100-million-for-autism-centers-of-excellence-program

²⁰ reporter.nih.gov/search/fQP-TbFDV0--ZbsPziwETA/project-details/10523403

²¹ reporter.nih.gov/search/sAGOL0_pLk-W-9710Yn0vQ/project-details/10523387

²² www.nimh.nih.gov/news/research-highlights/2022/multistage-autism-screening-in-early-intervention-settings-may-reduce-disparities

²³ pubmed.ncbi.nlm.nih.gov/33427861/

²⁴ pubmed.ncbi.nlm.nih.gov/34982099/

²⁵ pubmed.ncbi.nlm.nih.gov/33427861

abilities and peer interactions in youth with autism.²⁶ Importantly, intervention research projects like these have potential to address the issues that individuals on the autism spectrum and their families care deeply about, such as maximizing educational and social opportunities. Additionally, NIMH aims to support research on the socioeconomic, racial, and ethnic health disparities associated with ASD, in collaboration with the National Institute on Minority Health and Health Disparities (NIMHD), the National Institute on Aging (NIA), NICHD, NIDCD, NIEHS, and NINDS. For example, the NIH-wide ACE Program mentioned above currently supports a project that aims to study underserved populations with autism to determine their use of medical services, factors impacting health inequities, and resulting effects on health outcomes.²⁷

²⁶ reporter.nih.gov/search/yUfCjJsTOUOqvb0tflFSJw/project-details/10063050

²⁷ reporter.nih.gov/search/5LQKIGeANUW5CFStnG4jdw/project-details/10523859

Biomedical Research Workforce Diversity

House Language

The Committee is concerned with the impact of COVID–19 on the diversity of the biomedical research workforce, particularly women and women of color across career stages. The Committee strongly encourages NIH to study the race/ethnicity and sex/gender breakdown of the impact of COVID on participation in the workforce by monitoring the sex/ gender and race/ethnicity of principal investigators designated on applications from and awards to institutions for two years. If the data demonstrate that fewer women are designated on applications from institutions for grants, then it is imperative that NIH take steps to address this disparity. The Committee requests a status update in the fiscal year 2024 Congressional Justification as well as a description of the steps being taken to maintain and strengthen the diversity of the biomedical research workforce.

Action taken or to be taken

The National Institutes of Health (NIH) has long recognized that the most critical assets in the biomedical research enterprise are the scientists who comprise its workforce. The biomedical research enterprise relies upon a continuum of highly trained investigators to convey new insights, develop innovative ideas, and advance the translation of scientific research into improved health for all. NIH also remains deeply concerned and mindful of how the spread of coronavirus disease 2019 (COVID-19) has negatively affected the biomedical research workforce, particularly members of underrepresented groups.^{28,29} NIH understands these challenges and continues to invest in the future through initiatives that strengthen and diversify the biomedical research workforce.

Analyses of the Impact of COVID-19 on the Biomedical Research Workforce

NIH regularly assesses the demographics (sex/gender, race, and ethnicity) of designated principal investigators designated on Research Project Grant applications submitted before and after the onset of the COVID-19 pandemic. The first four analyses did not show any marked changes in the high-level demographics of designated principal investigators.^{30,31,32,33} The most recent analyses, which focused on understanding the gender distribution by career stage (reported in June 2022 and October 2022), did show that the proportion of applications designating either female or underrepresented minority early-stage investigators (ESIs) increased over the most recent 6-year period.^{34,35} NIH will continue to analyze the data on the impact of the COVID-19 pandemic on the biomedical research community, and its potential impact on NIH budget and grant activities.

²⁸ nexus.od.nih.gov/all/2020/11/04/continued-impact-of-covid-19-on-biomedical-research/

²⁹ nexus.od.nih.gov/all/2021/03/25/the-impact-of-the-covid-19-pandemic-on-the-extramural-scientific-workforce-outcomes-from-an-nih-led-survey/

³⁰ nexus.od.nih.gov/all/2022/04/08/another-look-at-applications-submitted-during-the-pandemic-part-4/

³¹ nexus.od.nih.gov/all/2021/10/20/more-data-on-applications-submitted-during-the-pandemic/

³² nexus.od.nih.gov/all/2021/06/01/an-updated-look-at-applications-submitted-during-the-pandemic/

³³ nexus.od.nih.gov/all/2020/07/28/an-early-look-at-applications-submitted-during-the-pandemic/

³⁴ nexus.od.nih.gov/all/2022/06/28/another-look-at-applications-submitted-during-the-pandemic-part-5-a-focus-on-career-stage/

³⁵ nexus.od.nih.gov/all/2022/10/13/follow-up-career-stage-analyses-of-applications-submitted-during-the-pandemic-part-6/

NIH recognizes and appreciates that the effects of the pandemic have not been equally felt across all institutions, investigators, and research areas. As such, NIH conducted two large-scale surveys, one of institutional leaders and one of scientists (opened in the fall of 2020 with results published in March 2021) to objectively document COVID-19's impact.³⁶ The results provided valuable insights into the well-being of the extramural biomedical research workforce, including as it relates to underrepresented and vulnerable groups. Institutional leaders reported concerns about research functions, research productivity, and financial challenges.³⁷ Scientists, especially those at earlier career stages, reported concerns about career trajectory, mental well-being, and research productivity.³⁸ NIH will continue to solicit input from the research community and devise new or repurpose existing strategies to mitigate potential career-related pandemic impacts on the biomedical workforce.

To date, several initiatives have been launched to help mitigate the impact of COVID-19 on biomedical careers,³⁹ including the implementation of numerous opportunities for ESIs to address COVID-19-related research delays. Because initial research and evidence indicate that COVID-19 may be disproportionately impacting engagement, experience, and retention of women scientists, especially those from underrepresented groups, NIH is focusing on developing programs and policies specifically to promote the continued advancement of women in biomedical research careers.⁴⁰

Steps to Diversify the Biomedical Research Workforce

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. 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.⁴¹ 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 enhance workforce diversity.⁴² NIH is analyzing NGRI policies to ensure that our efforts continue supporting career development for women and individuals from underrepresented backgrounds in biomedicine.

³⁶ nexus.od.nih.gov/all/2020/10/05/encouraging-participation-in-upcoming-nih-surveys-to-identify-impacts-of-covid-19-on-extramural-research

³⁷ nexus.od.nih.gov/all/2021/03/25/the-impact-of-the-covid-19-pandemic-on-the-extramural-scientific-workforce-outcomes-from-an-nih-led-survey

³⁸ The "scientists" who responded to the survey are individual researchers at domestic institutions who logged into eRA Commons within two years prior to the survey, and who identified as having a scientific role (e.g., principal investigators, trainees, sponsors, undergraduate students, graduate students, postdoctoral researchers, scientists, and project personnel).

³⁹ nexus.od.nih.gov/all/2020/11/04/continued-impact-of-covid-19-on-biomedical-research/

⁴⁰ orwh.od.nih.gov/career-development-education/nih-working-group-on-women-in-biomedical-careers

⁴¹ grants.nih.gov/ngri.htm

⁴² nexus.od.nih.gov/all/2021/07/12/data-on-implementing-nih-next-generation-researchers-initiative/

In FY 2021, NIH supported an all-time high of 1,513 new ESIs as first-time principal investigators designated on R01-equivalent awards, a 7.2 percent increase over FY 2020.⁴³ The FY 2021 NGRI data are also broken down by aggregate demographic information voluntarily self-reported by the researchers, including their sex, race, and ethnicity. As Dr. Michael Lauer, NIH Deputy Director for Extramural Research, wrote in the July 2022 blog post, “We are pleased to see the large number of ESIs entering the NIH system. It gives us a renewed focus on the future, a sentiment we share with what Acting NIH Director Dr. Lawrence Tabak mentioned at a recent Congressional hearing.⁴⁴ Our work is far from over though, and we will continue working with the research community to enhance support for the next generation of biomedical scientists.”

NIH has several programs aimed at promoting diversity and enhancing progress to an independent career, such as:

- BRAIN Initiative Advanced Postdoctoral Career Transition Award to Promote Diversity⁴⁵
- Maximizing Opportunities for Scientific and Academic Independent Careers program⁴⁶
- Building Infrastructure Leading to Diversity program⁴⁷
- National Research Mentoring Network⁴⁸
- Faculty Institutional Recruitment for Sustainable Transformation program⁴⁹
- New Investigators to Promote Workforce Diversity in Genomics, Bioinformatics, or Bioengineering and Biomedical Imaging Research⁵⁰
- Cancer Moonshot Scholars Diversity Program⁵¹
- Building Interdisciplinary Research Careers in Women’s Health⁵²
- Advancing Gender Inclusive Excellence⁵³

In addition, NIH has developed and implemented a range of approaches to improve the representation of women in biomedical research. NIH implemented automatic extensions of ESI status for childbirth within the ESI period in 2018.⁵⁴ In FY 2020, an automatic extension of one year was also implemented for childbirth within the 4-year K99 (Pathway to Independence award) eligibility window.⁵⁵ Additionally, NIH offers support for ESIs with high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying

⁴³ nexus.od.nih.gov/all/2022/07/18/more-early-stage-investigators-supported-in-fy-2021/

⁴⁴ www.appropriations.senate.gov/hearings/a-review-of-the-presidents-fy-2023-funding-request-and-budget-justification-for-the-national-institutes-of-health

⁴⁵ grants.nih.gov/grants/guide/rfa-files/rfa-ns-19-043.html

⁴⁶ www.nigms.nih.gov/training/careerdev/Pages/MOSAIC.aspx

⁴⁷ www.nigms.nih.gov/training/dpc/pages/build.aspx

⁴⁸ nrmnet.net/

⁴⁹ commonfund.nih.gov/first

⁵⁰ grants.nih.gov/grants/guide/rfa-files/RFA-HG-21-041.html

⁵¹ grants.nih.gov/grants/guide/rfa-files/RFA-CA-22-050.html

⁵² orwh.od.nih.gov/career-development-education/building-interdisciplinary-research-careers-in-womens-health-bircwh

⁵³ grants.nih.gov/grants/guide/rfa-files/rfa-od-21-010.html

⁵⁴ grants.nih.gov/grants/guide/notice-files/NOT-OD-18-235.html

⁵⁵ grants.nih.gov/grants/guide/pa-files/pa-18-592.html

circumstances.^{56,57} Finally, the Re-integration Program addresses the critical need to provide individuals, including predoctoral students, who are adversely affected by unsafe or discriminatory environments resulting from unlawful harassment, to rapidly transition into new safer, and more supportive research environments. The goal is to provide these individuals a timely and seamless continuation of their research training programs and to safely reintegrate into the biomedical workforce.⁵⁸

NIH also began providing funding for Childcare Costs for Ruth L. Kirschstein National Research Service Awards for Individual Fellows and Trainees.^{59,60} NIH issued 228 childcare cost awards in FY 2021, totaling \$572,083, and 196 awards in FY 2022 (as of July), for a total of \$509,687.⁶¹ NIH plans to report similar data on NRSA childcare requests from trainees at a later date.

In October 2021, NIH hosted a forum recognizing the winners of the NIH Prize for Enhancing Faculty Gender Diversity in Biomedical and Behavioral Science.⁶² The winning institutions implemented systemic and transformative policies to address gender inequities and enhance gender diversity.⁶³ A companion report outlined the successful strategies to encourage other institutions.⁶⁴

Lastly, NIH established the UNITE initiative to identify and address structural racism and promote equitable representation and inclusion at NIH and throughout the larger NIH-supported biomedical research community. To reach this goal, UNITE is facilitating research to identify opportunities, make recommendations, and develop and implement strategies to accelerate efforts to address racism and discrimination in science and to develop methods to promote diversity and inclusion across the biomedical research enterprise. The latest progress report was released in October 2022.⁶⁵

⁵⁶ grants.nih.gov/grants/guide/notice-files/NOT-OD-20-054.html

⁵⁷ grants.nih.gov/grants/guide/notice-files/NOT-OD-20-055.html

⁵⁸ grants.nih.gov/grants/guide/notice-files/NOT-OD-21-134.html

⁵⁹ grants.nih.gov/grants/guide/notice-files/NOT-OD-21-074.html

⁶⁰ grants.nih.gov/grants/guide/notice-files/NOT-OD-21-177.html

⁶¹ nexus.od.nih.gov/all/2022/08/10/preliminary-data-on-childcare-cost-support-for-national-research-service-award-nrsa-individual-fellows/

⁶² www.challenge.gov/?challenge=nih-prize-for-enhancing-faculty-gender-diversity

⁶³ orwh.od.nih.gov/about/newsroom/events/effective-approaches-to-fostering-faculty-gender-diversity-equity-and

⁶⁴ orwh.od.nih.gov/sites/orwh/files/docs/Meeting%20Summary_PrizeCompetitionWebinar_508c.pdf

⁶⁵ www.nih.gov/ending-structural-racism/announcing-inaugural-unite-progress-report

Blepharospasm

House Language

The Committee continues to encourage NEI to expand research into blepharospasm, a form of dystonia, and requests an update on collaborative efforts amongst stakeholders and other Institutes and Centers in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

Blepharospasm (also called benign essential blepharospasm, or BEB) is involuntary blinking or other eyelid movements, like twitching, that individuals are unable to control. Eyelid twitching usually goes away on its own. However, people with BEB can develop severe and chronic (long-term) eyelid twitching and eyelid closure, impacting vision. While the cause of BEB is unknown, researchers think it involves an interaction of genetic and environmental factors. BEB can run in families, but some affected individuals have a history of local eye disease, like eye trauma, or it can be secondary to other diseases.

Blepharospasm research involves the portfolios of multiple institutes at the National Institutes of Health (NIH). The National Eye Institute (NEI) supports research to understand how blepharospasm or potential therapies for blepharospasm impact vision. In November 2021, NEI issued its Strategic Plan for 2021-2025: Vision for the Future, in which it recognized that neurological conditions such as blepharospasm, ocular pain, and itch require interdisciplinary research initiatives. NEI has supported studies on therapies such as botulinum toxin (BOTOX), including their impacts on the cornea and dry eye. NEI recently launched the Anterior Segment Initiative (ASI) to focus on conditions at the front of the eye. Relevant to blepharospasm, ASI has focused research on dry eye disease, as well as peripheral and central neurological mechanisms of ocular pain and other disorders. The ASI Ocular Surface Innervation Consortium came together for its first meeting on October 25, 2022; the collaboration of eight newly funded project teams will explore the nerves and nerve damage at the front of the eye and in the brain that underlie pain, itch, tearing reflexes, and migraines.

Complementing NEI research, the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Dental and Craniofacial Research (NIDCR) fund research on dystonia, which is a movement disorder that causes involuntary muscle contractions, including blepharospasm. NINDS projects funded in 2022 include a deep phenotyping study, characterizing the specific manifestations of blepharospasm in different patients, such as spasms in muscles around the eyes, excessive blinking, eyelid fluttering, impaired eyelid opening, and dystonia spread to the lower face and jaw. This research could determine if there are specific patterns to distinguish different subtypes of the condition to improve diagnosis and to personalize treatment. Another project will study the role of specific neurons in adult-onset dystonia, and a final project aims to understand the early development of brain regions that mediate pediatric dystonia. NIDCR research aims to identify genes present in families with craniofacial dystonias, including blepharospasm, and to test the function of identified genes using a stem cell model of dystonia.

NINDS also funds the Dystonia Coalition, a large collaborative research effort across the United States, Canada, Australia, Italy, Germany, France, and the United Kingdom to study four types

of dystonias in patients: blepharospasm, cervical dystonia, laryngeal dystonia, and limb dystonia. The goal of the Coalition is to provide better understanding of these disorders to develop and evaluate novel treatments. The consortium collects demographic, clinical, and video data and facilitates collaboration and secure data sharing with investigators and other stakeholders including patient advocacy groups.

Cardiovascular Disease (CVD)

Conference Language

Recognizing that CVD remains the leading cause of death and most expensive condition in the United States, the agreement supports cutting-edge cardiovascular research and drug discovery across the disciplines of medicine, immunology, imaging, chemistry, biomedical engineering, physics, statistics, mathematics, and entrepreneurship to design new therapies and strategies that are more effective. The agreement directs NHLBI to highlight the areas with the greatest potential for transformative progress in CVD research in the fiscal year 2024 Congressional Justification and to prioritize funding that reduces cardiovascular disease among the hardest-hit - African Americans living in the rural South.

Action taken or to be taken

With heart disease being the leading cause of death in the United States, the National Heart, Lung, and Blood Institute (NHLBI) continues to amplify its efforts to reduce cardiovascular disease (CVD) especially among disproportionately affected and underserved communities including African Americans in the rural South and American Indians and Alaska Natives. The following are areas within the NHLBI's cardiovascular disease research portfolio that hold the greatest potential for transformative progress.

The Jackson Heart Study, the largest community-based epidemiologic study of CVD among African Americans, continues its focus on research, training, and community outreach. NHLBI's Risk Underlying Rural Areas Longitudinal (RURAL) cohort, established in 2019, is identifying the frequency of and risk factors for heart and lung diseases by following 4,000 people in low-income rural communities in Alabama, Kentucky, Louisiana, and Mississippi. The program is reaching rural communities by leveraging community engagement digital strategies, utilizing trusted online messengers and in person visits to pop-up clinics for vital needs. In 2021, the study began deploying a mobile exam unit equipped with the latest diagnostic technologies to collect medical data and uncover disease risk factors. The study will also collect socioeconomic and environmental data and is expected to inform disease prevention strategies for rural Americans.

NHLBI also co-funds the Southeastern Collaboration to Improve blood pressure (BP) Control trial with the Patient-Centered Outcome Research Institute (PCORI), as part of the Hypertension Disparities Reduction Program Partnership. This intervention trial compares three novel strategies (practice facilitation, peer coaching, and integrated peer coaching and practice facilitation) to standard of care for improving BP control in 80 primary care practices serving rural Southeastern African Americans with low socioeconomic status living in Alabama and North Carolina.

Although progress has been made in the treatment of many forms of heart disease, death due to heart failure (HF) continues to rise nationally. HF is when the heart contracts normally, but fills with blood too slowly, limiting treatment options. Developing precision treatment strategies for HF is critical. NHLBI's innovative new HeartShare program aims to improve our understanding of HF with preserved ejection fraction (HFpEF) through data science. HeartShare is supporting large-scale analysis of clinical data, images, and omics from patients to characterize mechanisms

of disease and identify therapeutic targets. Building on HeartShare’s data science capacity, on September 29, 2022, NHLBI and the Foundation for the National Institutes of Health (FNIH), launched a new project of the Accelerating Medicines Partnership® (AMP®) to investigate the syndrome of heart failure with preserved ejection fraction (HFpEF).⁶⁶ Utilizing cutting edge technologies, including digital measurements and artificial intelligence analytic methods, the AMP® Heart Failure Program is designed to find novel proteins or genes that could mitigate this disease when altered by therapeutics.

Through study of the genetic underpinnings of heart and vascular disease, NHLBI-funded researchers are finding new ways to screen, diagnose, and treat patients for a variety of heart conditions, including sudden cardiac death. Researchers have recently focused on identifying patients with a genetic risk for sudden cardiac death so doctors can monitor and ensure that lifesaving therapies and tools – like defibrillators – go to those who may need them the most. In 2022, an NHLBI-supported study investigating the genetic connection between coronary artery disease and sudden cardiac death using a polygenic risk score for coronary artery disease, found that individuals with coronary artery disease and higher genetic risks had a 77 percent increased risk for sudden cardiac death.⁶⁷

NHLBI is working to improve survival after out-of-hospital cardiac arrest, which has a 90 percent fatality rate. The Advanced REperfusion STRategies for Refractory Cardiac Arrest (ARREST) trial is examining the potential to treat such patients with extracorporeal membrane oxygenation (ECMO). Researchers recently found that compared to standard care, those given ECMO as soon as they arrived at the hospital had better survival rates and neurologic function at 6 months.⁶⁸

NHLBI’s Cardiothoracic Surgical Trials Network (CTSN) is moving research from the proof-of-concept stage into clinical trials. A recent CTSN trial offers hope for people with mitral and tricuspid valve regurgitation (leaky heart valves), which is typically treated with surgery to repair the mitral valve or, in severe cases, surgery to also repair the tricuspid. The new trial found that patients who had tricuspid and mitral repair at the same time were less likely to die or advance to severe tricuspid regurgitation 2 years out, compared with those who had mitral repair alone.⁶⁹ However, patients who had both procedures were also more likely to need a pacemaker.

CVD is the leading cause of pregnancy-related deaths, and NHLBI is playing a lead role in research to reduce the nation’s alarming rates of maternal mortality and morbidity. NHLBI’s innovative programs take a life course approach that focuses on improving women’s heart health before, during, and after reproductive age, with an emphasis on the significant disparities in maternal health that affect communities of color. These programs include the Nurses Study, which recently showed that women who developed high blood pressure after 20 weeks, post pregnancy, or had preeclampsia, had a 63 percent increased risk for future heart attack or stroke. Another NHLBI initiative, the Chronic Hypertension and Pregnancy Project (CHAP) trial, found

⁶⁶ www.nih.gov/research-training/accelerating-medicines-partnership-amp

⁶⁷ www.nhlbi.nih.gov/news/2022/genetic-paths-predicting-heart-disease

⁶⁸ pubmed.ncbi.nlm.nih.gov/33197396/

⁶⁹ www.nhlbi.nih.gov/news/2021/researchers-find-benefits-and-drawbacks-two-step-surgical-approach-leaky-heart-valves

in 2021 that pregnant individuals treated for high blood pressure early in pregnancy were 20 percent less likely to have pregnancy complications related to hypertension. Additionally, the nuMoM2b Heart Health Study, co-funded with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), has found that women who experience adverse pregnancy outcomes have worse cardiovascular outcomes, including higher risk for hypertension, as late as 2 to 7 years after delivery.

NHLBI recognizes that many promising early research ideas fail to reach the clinic and commercialization because investigators have gaps in expertise with regulations, product development, toxicology, marketing, commercialization, and other areas related to bringing products to market. NHLBI's Catalyze program and Small Business Innovation Research and Small Business Technology Transfer (SBIR/STTR) programs provide research funding as well as a suite of support and services in these gap areas to facilitate the translation of basic scientific discoveries into viable therapeutics, devices, diagnostics, and services ready for human testing.^{70,71} An example from the Catalyze program is a project to isolate human induced pluripotent stem cells from the patient's own blood as a therapeutic agent for treating severe peripheral artery disease (PAD).^{72,73} PAD can lead to critical limb ischemia (CLI), characterized by severe resting pains and ulceration, and up to one-half of CLI patients face amputation of the affected limb within one year. This Catalyze project will develop and characterize a cell-based therapy to grow new blood vessels in the ischemic areas, thus preventing the progression into CLI.

Another project funded by the NHLBI small business program supported an artificial intelligence platform that integrates with electronic health record systems to recommend optimal hypertension medications since nearly half of all hypertension patients do not have their blood pressure at the recommended goal.^{74,75,76} In a recent clinical trial, this platform demonstrated that it can outperform physician-recommended prescriptions and that hypertension can be safely managed within 6 months. This system has been subsequently enhanced to manage high-risk patients diagnosed with heart failure and hypertension and is being commercialized and implemented in clinical care in the University of California, San Francisco healthcare system.

⁷⁰ nhlbicatalyze.org/

⁷¹ www.nhlbi.nih.gov/grants-and-training/funding-opportunities-and-contacts/small-business-program

⁷² reporter.nih.gov/search/zHgWsYRV6k-hYJouXPxUsw/projects

⁷³ reporter.nih.gov/search/hm6GhaQsNki4hVs_LxVjIQ/projects

⁷⁴ reporter.nih.gov/search/padd-YStCkS3oeAJQRSf_w/projects

⁷⁵ reporter.nih.gov/search/8grjKatNKUuJpx5VbtmJVA/projects

⁷⁶ reporter.nih.gov/search/kddUFjoiBU2FsYIAWV1suw/projects

Cellular Immunity

House Language

To better understand diseases like COVID-19, the Committee is aware of the enormous value in assessing cellular immunity, in addition to antibodies, which may help us answer questions about the efficacy of vaccines, the need for boosters, and the degree to which they prime the body to protect against future variants, as well as the role of cellular immune response diagnostics. With more comprehensive immune response data, the Committee understands that it may be possible to identify features of immune responses to viruses like SARS-CoV-2 that make some people more susceptible to severe disease, long COVID, and reinfection. The Committee believes enhanced cellular immunity assessment will help to generate deeper insights into the immune response, and may help identify new strategies to improve countermeasures, including cellular immune response diagnostics, for SARS-CoV-2 and other potential pathogens in the future. The Committee encourages NIAID to incorporate cellular immunity assessment into the wide range of intramural and extramural COVID-19 and other disease studies conducted and supported by NIH, including but not limited to vaccine schedule studies and understanding post-acute sequelae of SARS-CoV-2 infection (PASC/ long COVID). The Committee requests that NIAID provide an update on these efforts in the fiscal year 2024 Congressional Justification.

Conference Language

The agreement directs NIH to include updates on the following research, projects, and programs in the fiscal year 2024 Congressional Justification: metastatic breast cancer; 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) has a longstanding portfolio of research that includes the characterization of cellular immune responses to pathogens and vaccines. While the role of antibodies in immunity has been well studied, the contribution of cellular immunity, and T cells (a type of immune system cell) specifically, remains an active area of inquiry. Since the beginning of the SARS-CoV-2 pandemic, NIAID has supported research to understand all aspects of the immune response to the virus. NIAID leveraged existing programs, including the Human Immunology Project Consortium (HIPC), to provide critical resources for investigators and help characterize cellular responses to SARS-CoV-2 infection and COVID-19 vaccination. NIAID-supported research also facilitated the development of the first test to assess T cell responses to SARS-CoV-2. In addition, NIAID scientists investigating causes for severe COVID-19 disease and multisystem inflammatory syndrome in children (MIS-C) identified distinctive signatures that characterize cellular immune responses, disease severity, and secondary complications of infection in these two groups of affected children. NIAID scientists also used a systems immunology approach to identify a timeframe following SARS-CoV-2 infection in adults when specific host immune responses correlate with disease severity and predict fatal outcomes. Knowledge of these markers, and the ability to test for them, may help monitor the course of infection and inform the use of interventions.

NIAID also investigates cellular immunity prompted by COVID-19 vaccines to understand its durability and to inform the use of boosters. The NIAID Vaccine Research Center (VRC) recently demonstrated the importance of booster vaccines in enhancing broadly protective antibody responses. NIAID-supported HIPC scientists are conducting systems biology analyses of the responses to different SARS-CoV-2 vaccines. These studies will assess the durability of T cell responses after booster immunizations with different COVID-19 vaccines. NIAID also has integrated analysis of cellular immune responses into COVID-19 vaccine trials, including examining B and T cell responses after vaccination of individuals who have and have not been previously infected, as well as people experiencing breakthrough infections or re-infection. NIAID will continue to study the durability and evolution of cellular immunity to SARS-CoV-2 infection and following COVID-19 vaccination, in people recovered from mild to moderate disease. This will include assessments in key populations, including post-acute sequelae of SARS-CoV-2 (PASC) patients.

NIAID also investigates the ability of SARS-CoV-2-specific cellular immune responses to protect against new variants. NIAID supports real-time assessments of variants through the SARS-CoV-2 Analysis of Viral Evolution (SAVE) program. SAVE investigators evaluate factors including the durability of B and T cell responses to emerging variants. Additional NIAID-supported investigators are evaluating cellular immune responses to COVID-19 vaccination with novel vaccine adjuvants to mimic natural viral infection, aiming to induce robust cellular responses and enhance vaccine efficacy, against variants. NIAID also is supporting efforts to incorporate immunogen design in the development of vaccine candidates that provide broad cell-mediated immunity to multiple SARS-CoV-2 variants and multiple coronaviruses.

NIAID continues to support research to understand cellular immunity to SARS-CoV-2 to help refine use of existing COVID-19 vaccines and therapeutics and develop next-generation countermeasures. NIAID also will build on multidisciplinary and systems biology-based approaches to generate new strategies to prepare for, and respond to, emerging and re-emerging pathogens of public health concern.

Childhood Cancer Research Coordination

Conference Language

The agreement directs NIH to include updates on the following research, projects, and programs in the fiscal year 2024 Congressional Justification: metastatic breast cancer; 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) continues to support basic, translational, and clinical research to increase our understanding of all pediatric cancers; develop safe, effective treatments for children with cancer; and address the late effects of cancer and its treatment in childhood and adolescent and young adult (AYA) cancer survivors. NCI is pleased to continue to serve as a partner with the National Institutes of Health (NIH) Common Fund in scientific leadership of the Gabriella Miller Kids First Research Program,⁷⁷ which is helping to foster new discoveries and biological insights, including the discovery of new genetic causes for childhood neuroblastoma and Ewing sarcoma. From 2015-2022, the Kids First program selected 63 childhood cancer and structural birth defects cohorts for whole genome sequencing, representing 20,000 patients (plus family members) and 48,000 genomes. In FY 2023, NIH anticipates supporting another round of cohorts for sequencing.⁷⁸ The Gabriella Miller Kids First Data Resource Portal provides access to Kids First data and is one of the largest pediatric data resources of its kind. Data from 21 Kids First projects are currently publicly available through the portal.

NIH is dedicated to supporting research to understand the healthy development of children as well as the causes of and treatment for diseases, illnesses, and conditions affecting them. The NIH Pediatric Research Consortium (N-PeRC), led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), was established in 2018 to harmonize pediatric research efforts across Institutes, Centers, and Offices (ICOs).⁷⁹ Nearly all NIH ICOs have appointed senior level representatives to N-PeRC. Among the issues of interest across ICOs are those faced by adolescents as they transition to adult health care, pediatric medical device development, and pediatric research workforce training. In 2022, a N-PeRC subgroup on pediatric medical devices published a Request for Information to seek comments and input on challenges, gaps, clinical needs, and research opportunities related to pediatric medical devices (PMD) to inform priorities for a potential public-private partnership (PPP) to advance the national ecosystem in PMD development.⁸⁰ A PPP could help optimize the translation of technological advancements into medical devices designed, evaluated, and approved for pediatric populations to improve quality of life in this population, including pediatric cancer patients. Moving forward, N-PeRC plans to continue to explore PPP opportunities for PMD development as well as embark on new efforts to benefit children with cancer and other pediatric diseases and to further develop the pediatric research workforce.

⁷⁷ commonfund.nih.gov/KidsFirst

⁷⁸ grants.nih.gov/grants/guide/pa-files/PA-22-054.html

⁷⁹ www.nichd.nih.gov/research/supported/nperc

⁸⁰ www.federalregister.gov/documents/2022/06/15/2022-12833/request-for-information-inviting-comments-and-suggestions-from-stakeholders-on-pediatric-medical

NCI is also maintaining important investments in the Pediatric MATCH precision medicine trial and the broader NCI-supported National Clinical Trials Network infrastructure (including the Children’s Oncology Group, or COG); the NCI Pediatric Oncology Branch and key cohort and natural history studies supported through the NCI intramural research program; and several pediatric and AYA research efforts supported through the Cancer Moonshot. The Pediatric MATCH trial⁸¹ has shown that it is possible for a nationwide screening protocol to successfully identify actionable genetic mutations and assign pediatric and young adult patients to trials for targeted therapies. It has also emphasized the importance of performing tumor molecular screening early on in pediatric patients with cancers that don’t respond to the standard of care treatments.⁸² However, the first arm to be completed in the MATCH trial showed that mutation status alone was not enough to predict efficacy of a single therapy.⁸³ All of the efforts described above contribute to a diverse pediatric oncology research portfolio at NCI and across NIH.

NCI also continues to lead the Childhood Cancer Data Initiative (CCDI), currently in its fourth year. One part of this Initiative is the National Childhood Cancer Registry (NCCR), a rapidly growing public health surveillance data resource.⁸⁴ The NCCR contributes to the CCDI data ecosystem by serving as a linked infrastructure of central cancer registry data that will integrate various other childhood cancer data—from hospitals, research centers, health care administrations, and other sources—to enhance access to and utilization of childhood cancer and survivorship data. Statistics based on the NCCR can be viewed through NCCR*Explorer.⁸⁵ Additionally, NCI launched the CCDI Molecular Characterization Initiative in FY 2022 to develop and provide detailed clinical and molecular data to help doctors determine treatments and help researchers learn more about childhood cancers. This effort represents a collaboration between CCDI and biospecimen collection projects that NCI is supporting through its implementation of the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act.

NCI also continues to conduct and support childhood and AYA cancer survivorship research that advances goals of the STAR Act. For example, a STAR Act-associated funding opportunity announcement⁸⁶ released in 2019 has funded 8 projects, including *Using information technology to improve outcomes for children living with cancer*,⁸⁷ *An Open-Label Intervention Trial to Reduce Senescence and Improve Frailty in Adult Survivors of Childhood Cancer*,⁸⁸ and another project that led to the development of the *Interactive Survivorship Program for the Improvement of Healthcare Resources in Adolescent and Young Adult Cancer Survivors (INSPIRE-AYA)* clinical trial;⁸⁹ all of these projects are currently recruiting participants. Additionally, in FY 2021-2022, NCI supported 23 projects in the second round of awards for the funding opportunity “Research to Reduce Morbidity and Improve Care for Pediatric, and Adolescent and Young

⁸¹ clinicaltrials.gov/ct2/show/NCT03155620

⁸² pubmed.ncbi.nlm.nih.gov/35353553/

⁸³ pubmed.ncbi.nlm.nih.gov/35363510/

⁸⁴ nccrexplorer.ccdi.cancer.gov/about/nccr.html

⁸⁵ nccrexplorer.ccdi.cancer.gov/about/

⁸⁶ grants.nih.gov/grants/guide/rfa-files/RFA-ca-19-033.html

⁸⁷ clinicaltrials.gov/ct2/show/NCT04789720

⁸⁸ clinicaltrials.gov/ct2/show/NCT04733534

⁸⁹ clinicaltrials.gov/ct2/show/NCT04593277

Adult (AYA) Cancer Survivors,”^{90,91} which aligns with survivorship research priorities emphasized in the STAR Act. NCI is also supporting several biobanking projects through awards to the COG and the Childhood Cancer Survivor Study (CCSS). These projects will enhance and expand NCI’s pediatric biospecimen collection efforts.

Childhood cancer research supported and conducted by the NCI continues to lay a foundation for practice-changing advances. For example, the United States Food and Drug Administration (FDA) recently approved a drug to reduce hearing loss in infants, children, and adolescents with cancer who are treated with cisplatin, a common chemotherapy medication that can cause hearing loss, based on results from clinical trials led by COG and United Kingdom researchers.⁹² This new approval is expected to lead to an update in the standard of care and can positively impact hundreds of pediatric patients each year. Another example of a study that could potentially change the standard of care is one supported by NCI and other organizations that developed a test to detect specific genomic changes in DNA shed from medulloblastoma (brain) tumor cells in the fluid surrounding the brain and spinal cord.⁹³ Recurrent disease is common in medulloblastoma patients and is usually found at an advanced stage, leading to poor prognosis for patients. This test allows detection of fast-growing recurrent disease earlier, which could lead to improved treatment outcomes. More research is needed to validate the results of the study, but these findings could eventually lead to the test being incorporated into standard of care for medulloblastoma pediatric patients.

⁹⁰ grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-027.html

⁹¹ grants.nih.gov/grants/guide/rfa-files/rfa-ca-20-028.html

⁹² www.cancer.gov/news-events/cancer-currents-blog/2022/fda-sodium-thiosulfate-cisplatin-hearing-loss-children

⁹³ www.sciencedirect.com/science/article/pii/S1535610821005018?via%3Dihub

Childhood Cancer STAR Act

Conference Language

The agreement includes no less than \$30,000,000 for continued implementation of sections of the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act (P.L. 115-180). The agreement directs NIH to provide an update in the fiscal year 2024 Congressional Justification on opportunities to enhance childhood cancer research efforts and the actions NCI has taken to ensure pediatric cancer expertise is included on all panels, as appropriate.

Action taken or to be taken

The Childhood Cancer STAR Act, which includes provisions directed toward the National Cancer Institute (NCI), has enhanced childhood cancer research since its enactment in 2018. In the United States in 2022, an estimated 10,470 new cases of cancer will be diagnosed among children from birth to age 14. Children's cancers are not the same as adult cancers, and hence NCI seeks specialized expertise to help steer the direction of its research to better prevent, diagnose, and treat cancer in children, adolescents, and young adults (AYA) and to help survivors of childhood cancer have healthier and longer lives.

NCI is pleased to continue to serve as a partner with the NIH Common Fund in scientific leadership of the Gabriella Miller Kids First Research Program,⁹⁴ which is helping to foster new discoveries and biological insights, including the discovery of new genetic causes for childhood neuroblastoma and Ewing sarcoma. From 2015-2022, the Kids First program selected 63 childhood cancer and structural birth defects cohorts for whole genome sequencing, representing 20,000 patients (plus family members) and 48,000 genomes. In FY 2023, NIH anticipates supporting another round of cohorts for sequencing.⁹⁵ The Gabriella Miller Kids First Data Resource Portal provides access to Kids First data and is one of the largest pediatric data resources. Data from 21 Kids First projects are currently publicly available.

NIH is dedicated to supporting research to understand the healthy development of children as well as the causes of and treatment for diseases, illnesses, and conditions affecting them. The NIH Pediatric Research Consortium (N-PeRC), led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), was established in 2018 to harmonize pediatric research efforts across NIH.⁹⁶ Nearly all NIH Institutes, Centers, and Offices (ICOs) have appointed senior level representatives to N-PeRC. Among the issues important across ICOs are those faced by adolescents as they transition to adult health care, pediatric medical device development, and pediatric research workforce training. In 2022, a N-PeRC subgroup on pediatric medical devices published a Request for Information to seek comments and input on challenges, gaps, clinical needs, and research opportunities related to pediatric medical devices (PMD) to inform priorities for a potential public-private partnership (PPP) to advance the national ecosystem in PMD development. A PPP could help optimize the translation of technological advancements into medical devices designed, evaluated, and approved for pediatric populations to improve quality of life in this population, including

⁹⁴ commonfund.nih.gov/KidsFirst

⁹⁵ grants.nih.gov/grants/guide/pa-files/PAR-22-054.html

⁹⁶ www.nichd.nih.gov/research/supported/nperc

pediatric cancer patients. Moving forward, N-PeRC plans to continue to explore PPP for PMD development and further develop the pediatric research workforce.

NCI is also maintaining important investments in the Pediatric MATCH precision medicine trial and the broader NCI-supported National Clinical Trials Network infrastructure (including the Children’s Oncology Group, COG); the NCI Pediatric Oncology Branch and key cohort and natural history studies supported through the NCI intramural research program; and several pediatric and AYA research efforts supported through the Cancer Moonshot. The Pediatric MATCH trial⁹⁷ has shown that a nationwide screening protocol is possible to successfully identify actionable genetic mutations and assign pediatric and young adult patients to trials for targeted therapies. It has also emphasized the importance of performing tumor molecular screening early on in pediatric patients with cancers that don’t respond to the standard of care treatments.⁹⁸ However, the first arm to be completed in the MATCH trial showed that mutation status alone was not enough to predict efficacy of a single therapy,⁹⁹ but showed the effectiveness of the trial molecular screening protocol in identifying patients eligible for screening, and other trial arms are still ongoing or have shown some clinical promise for treatment of pediatric cancer with a different mutation.¹⁰⁰ All of the efforts described above contribute to a diverse pediatric oncology research portfolio at NCI and across NIH.

NCI also continues to lead the Childhood Cancer Data Initiative (CCDI), currently in its third year. One part of this initiative is the National Childhood Cancer Registry (NCCR), a rapidly growing public health surveillance data resource.¹⁰¹ The NCCR contributes to the CCDI data ecosystem by serving as a linked infrastructure of central cancer registry data that will integrate various other childhood cancer data—from hospitals, research centers, health care administrations, and other sources—to enhance access to and utilization of childhood cancer and survivorship data. Statistics based on the NCCR can be viewed through NCCR*Explorer.¹⁰² Additionally, NCI launched the CCDI Molecular Characterization Initiative in FY 2022 to develop and provide detailed clinical and molecular data to help doctors determine treatments and help researchers learn more about childhood cancers. This effort represents a collaboration between CCDI and biospecimen collection projects that NCI is supporting through its implementation of the STAR Act.

NCI also continues to conduct and support childhood and AYA cancer survivorship research that advances goals of the STAR Act. For example, a STAR Act-associated funding opportunity announcement¹⁰³ released in 2019 has funded eight projects, including *Using information technology to improve outcomes for children living with cancer*,¹⁰⁴ *An Open-Label Intervention Trial to Reduce Senescence and Improve Frailty in Adult Survivors of Childhood Cancer*,¹⁰⁵ and another project that led to the development of the *Interactive Survivorship Program for the*

⁹⁷ clinicaltrials.gov/ct2/show/NCT03155620

⁹⁸ pubmed.ncbi.nlm.nih.gov/35353553/

⁹⁹ pubmed.ncbi.nlm.nih.gov/35363510/

¹⁰⁰ pubmed.ncbi.nlm.nih.gov/35133871/

¹⁰¹ nccrexplorer.ccdi.cancer.gov/about/nccr.html

¹⁰² nccrexplorer.ccdi.cancer.gov/about/

¹⁰³ grants.nih.gov/grants/guide/rfa-files/RFA-ca-19-033.html

¹⁰⁴ clinicaltrials.gov/ct2/show/NCT04789720

¹⁰⁵ clinicaltrials.gov/ct2/show/NCT04733534

Improvement of Healthcare Resources in Adolescent and Young Adult Cancer Survivors (INSPIRE-AYA) clinical trial;¹⁰⁶ all of these projects are currently recruiting participants. Additionally, in FY 2021-2022, NCI supported 23 projects in the second round of awards for the funding opportunity “Research to Reduce Morbidity and Improve Care for Pediatric, and Adolescent and Young Adult (AYA) Cancer Survivors,”^{107,108} which aligns with survivorship research priorities emphasized in the STAR Act. NCI is also supporting several biobanking projects through awards to the COG and the Childhood Cancer Survivor Study. These projects will enhance and expand NCI’s pediatric biospecimen collection efforts.

Childhood cancer research supported and conducted by the NCI continues to lay a foundation for practice-changing advances. For example, the United States Food and Drug Administration (FDA) recently approved a drug to reduce hearing loss in infants, children, and adolescents with cancer who are treated with cisplatin, a common chemotherapy medication that can cause hearing loss, based on results from clinical trials led by COG and United Kingdom-based researchers.¹⁰⁹ This new approval is expected to lead to an update in the standard of care and can positively impact hundreds of pediatric patients each year. Further, a study supported by NCI and other organizations developed a test to detect specific genomic changes in DNA shed from medulloblastoma (brain) tumor cells in the fluid surrounding the brain and spinal cord.¹¹⁰ Recurrent disease is common in medulloblastoma patients and is usually found at an advanced stage, leading to poor prognosis for patients. This test allows detection of fast-growing recurrent disease earlier, which could lead to improved treatment outcomes. More research is needed to validate the results of the study but could eventually lead to the test being incorporated into standard of care for medulloblastoma pediatric patients.

To guide the NCI’s efforts in pediatric oncology research, the rosters of NCI’s advisory boards and committees are carefully developed to ensure that members with adequate pediatric expertise are included. These advisory groups include the National Cancer Advisory Board (NCAB), Board of Scientific Advisors (BSA), Clinical Trials and Translational Research Advisory Committee (CTAC), Board of Scientific Counselors (BSC), Frederick National Laboratory for Cancer Research (FNLCR), Clinical Trials Steering Committees, and Childhood Cancer Data Initiative (CCDI) Working Groups, as well as peer reviewers for study sections involving pediatric research applications.

In accordance with Sections 111 and 112 of the STAR Act, members on the advisory boards include pediatric oncologists, scientists with pediatric expertise, and patient advocates. For example:

- **National Cancer Advisory Board**¹¹¹: Dr. Francis Ali-Osman, Duke University; Dr. Andrea Hayes, Howard University

¹⁰⁶ clinicaltrials.gov/ct2/show/NCT04593277

¹⁰⁷ grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-027.html

¹⁰⁸ grants.nih.gov/grants/guide/rfa-files/rfa-ca-20-028.html

¹⁰⁹ www.cancer.gov/news-events/cancer-currents-blog/2022/fda-sodium-thiosulfate-cisplatin-hearing-loss-children

¹¹⁰ www.sciencedirect.com/science/article/pii/S1535610821005018?via%3Dihub

¹¹¹ deainfo.nci.nih.gov/advisory/ncab/ncabpublicroster.pdf

- **Board of Scientific Advisors**¹¹²: Dr. Suzanne Baker, St. Jude Children’s Research Hospital; Dr Mary Beckerle, Huntsman Cancer Institute; Dr. Leslie Robison, St. Jude Children's Research Hospital
- **Clinical and Translational Research Advisory Committee**¹¹³: Dr. Smita Bhatia, University of Alabama at Birmingham; Dr. Carolyn Muller, The University of New Mexico Health Sciences Center
- **Board of Scientific Counselors** (Clinical Sciences & Epidemiology and Basic Sciences now combined)¹¹⁴: Dr. Ralph Deberardinis, University of Texas Southwestern Medical Center; Dr. David Malkin, University of Toronto; Dr. Anna Moscicki, University of California, Los Angeles
- **National Council of Research Advocates**¹¹⁵: Vickie Buenger, Coalition Against Childhood Cancer (CAC2)
- **Frederick National Laboratory Advisory Committee**¹¹⁶: Dr. Catherine Bollard, Children’s National Health System; Dr. Nilsa Ramirez Milan, Nationwide Children's Hospital
- **National Clinical Trials Network Steering Committees**: Eighty (80) subject matter experts with pediatric expertise serve across three relevant steering committees (Pediatric and Adolescent Solid Tumors, Brain Malignancies, Pediatric Leukemia and Lymphoma), including a patient advocate serving on each committee.
- **Study sections**: 238 reviewers with pediatric oncology expertise participated in up to 25 study section meetings during FY 2021-2022.

In addition, researchers with pediatric expertise are engaged in NCI’s Childhood Cancer Data Initiative (CCDI), which is building a community centered around childhood cancer care and research data. In 2021, a CCDI Steering Committee was established and currently includes 11 extramural pediatric cancer research experts, as well as 14 NCI childhood cancer research and/or informatics experts. NCI has also convened five CCDI working groups involving more than 50 experts outside of the Institute, including patient advocates. NCI was also pleased to welcome Dr. Gregory Reaman to the Institute in the fall of 2022 as the Scientific Director of CCDI. Dr. Reaman joins NCI following prior roles as the Associate Director for Pediatric Oncology at the Food and Drug Administration’s Oncology Center of Excellence, and he is also a former Chair of the NCI-supported Children’s Oncology Group.

¹¹² deainfo.nci.nih.gov/advisory/bsa/members.pdf

¹¹³ deainfo.nci.nih.gov/advisory/ctac/roster.pdf

¹¹⁴ deainfo.nci.nih.gov/advisory/bsc/roster.pdf

¹¹⁵ deainfo.nci.nih.gov/advisory/ncra/NCRApublicRoster.pdf

¹¹⁶ deainfo.nci.nih.gov/advisory/fac/roster.pdf

Childhood Post-Infectious Neuroimmune Disorders PANS and PANDAS

House Language

The Committee strongly encourages NIH to advance research and education related to the devastating diseases of Pediatric Acute-Onset Neuropsychiatric Syndromes (PANS) and Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS). Although NIH has undertaken some research in this area, more research is necessary to fully understand causes, diagnosis, and treatment. Training the medical community is essential to early identification and intervention, reducing the risk of chronic illness and associated costs to families, school systems, health care 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 prioritize research in this area, and report to the Committee in the fiscal year 2024 Congressional Justification on the progress being made on the understanding of the costs, causes, diagnostic criteria, and treatment of these conditions.

Conference Language

The agreement encourages NIH to prioritize research in this area, and include an update in the fiscal year 2024 Congressional Justification on the progress being made on the understanding of the costs, 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 two 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 stakeholders to share information about NIMH programs and NIMH-supported advances.¹¹⁷

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.¹¹⁸ Children

¹¹⁷ www.nimh.nih.gov/health/publications/pandas

¹¹⁸ pubmed.ncbi.nlm.nih.gov/15820236/

with PANS- or PANDAS-related OCD symptoms may also benefit from standard OCD treatment, which includes medication and behavioral therapy.¹¹⁹

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 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-2.¹²⁰ Another NIMH-funded investigator 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.¹²¹ Building on the finding from this initial small clinical study, the research team is now studying a larger cohort of patients to determine whether their PANDAS symptoms correlate with the binding of immune proteins to this type of neuron. In another NIMH-funded project, scientists are investigating how T helper cells – critical components of a typical immune response – contribute to brain inflammation and dysfunction following strep infection.¹²² 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.¹²³ 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.

¹¹⁹ pubmed.ncbi.nlm.nih.gov/25978743/

¹²⁰ pubmed.ncbi.nlm.nih.gov/33969321/

¹²¹ pubmed.ncbi.nlm.nih.gov/32539528/

¹²² reporter.nih.gov/project-details/9989906

¹²³ clinicaltrials.gov/ct2/show/NCT01778504

Chronic Kidney Disease (CKD)

House Language

The Committee urges NIDDK to continue support for kidney research. 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 is encouraged to prioritize research into endogenous filtration markers, activities that spur the adoption of new equations for estimating GFR that do not include race as a modifier, and interventions to eliminate racial and ethnic disparities. Finally, the Committee encourages NIDDK to continue investment in research that bridges existing deficits in CKD management and treatments to reduce incidence and progression, increases the number of CKD clinical trials and diversity of participants, improves the delivery of evidenced-base care in underrepresented populations, and improves patients' quality of life. The Committee requests an update on these priorities in the fiscal year 2024 Congressional Justification.

Action taken or to be taken:

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has a robust and diverse research portfolio that is making significant advancements in the diagnosis and treatment of kidney disease. Notably, NIDDK-funded research, published in the *New England Journal of Medicine*, improves accuracy of equations for estimating glomerular filtration rate (a critical measure of kidney function) through use of cystatin C as a biomarker and removing race as a factor.¹²⁴ Another ground-breaking stride came from NIDDK's Kidney Precision Medicine Project (KPMP), which aims to ethically obtain and evaluate human kidney biopsies from participants with acute kidney injury or chronic kidney disease (CKD). KPMP scientists recently published "A reference tissue atlas for the human kidney," revolutionizing our understanding of kidney physiology at the single-cell level and providing an invaluable, publicly available resource for catalyzing future advances in the diagnosis, monitoring, prevention, and treatment of kidney disease.¹²⁵

Developing new, superior biomarkers for the assessment of kidney health remains a critical research priority. NIDDK has therefore made a long-term investment in the Chronic Renal Insufficiency Cohort Study, which is examining a broad range of risk factors (from molecular markers of filtration and other biomarkers of disease pathways to clinical, demographic, and behavioral characteristics) on the progression of CKD and other health consequences in a diverse, 4,000-participant cohort. The study is developing and carrying out novel approaches with cutting-edge technologies to characterize CKD, which may provide the basis for improving markers and assessing kidney function. Additionally, the CKD Biomarkers Consortium is collaboratively pursuing the development and validation of novel biomarkers for CKD by assaying biological specimens and utilizing data from the Nation's largest epidemiological studies of kidney disease. The Consortium has produced extensive data resources that provide investigators with many potential areas for future research on biomarkers in clinical trials and drug development.

¹²⁴ pubmed.ncbi.nlm.nih.gov/34554658/; pubmed.ncbi.nlm.nih.gov/34554660/

¹²⁵ pubmed.ncbi.nlm.nih.gov/35675394/

NIDDK's Hemodialysis Opioid Prescription Effort (HOPE) is a key effort aimed at improving patient care and quality of life while reducing opioid dependency in individuals with end-stage renal disease (ESRD), a condition that must be treated with dialysis until a kidney suitable for transplant becomes available. Because more than half of people who are treated with dialysis experience significant pain and traditional opioid therapy increases risk of death and lowers quality of life, HOPE is testing alternatives for pain management. Because ESRD disproportionately affects people of color, particularly Black Americans, and NIDDK is committed to reducing disparities and advancing health equity in all its mission diseases, half of HOPE participants are Black. Importantly, NIDDK also recently released two novel initiatives focused on reducing disparities in care and outcomes for people living with kidney disease by addressing the effects of structural racism.¹²⁶

¹²⁶ grants.nih.gov/grants/guide/rfa-files/rfa-dk-22-014.html; grants.nih.gov/grants/guide/rfa-files/RFA-DK-22-015.html

Clinical Trial Diversity

House Language

The Committee recognizes NIH's efforts to increase meaningful participation across the lifespan of ethnic and racial minority populations and underrepresented communities in clinical trials. The Committee encourages NIH to continue improving clinical research diversity, equity, inclusion, and accessibility by engaging in proactive outreach efforts to people including women and racial and ethnic minority groups, underrepresented communities, and health care organizations serving these populations, to improve awareness of clinical research, including trials, and understanding of how people can participate. The Committee requests an update on these activities in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

The National Institutes of Health (NIH) has been committed to inclusion in clinical research for over 3 decades.¹²⁷ Appropriate inclusion of research participants ensures that NIH is supporting sound science that will ultimately inform clinical practice to benefit all who are affected by the disease or condition under study. NIH amended its policy on the inclusion of women and minorities to include additional reporting requirements for certain clinical trials in late 2017.¹²⁸ NIH also revised its Inclusion Across the Lifespan Policy and Guidelines on the Inclusion of Children to expand requirements to individuals of all ages.^{129,130}

In FY 2021, 31 percent of participants in NIH-funded clinical research identified as members of a racial or ethnic minority group, while female participants in NIH-funded clinical research represented 59 percent.¹³¹ As it relates to age of participants in NIH supported research during FY 2021, children under 18 years represented 20 percent, adults between 18 and 65 represented 58 percent, and adults older than 65 represented 19 percent.¹³²

NIH will continue its outreach efforts to women as well as members of racial and ethnic minority groups to strengthen awareness of how to participate in NIH-supported clinical research. Below are some examples of how NIH is currently addressing this issue:

Application Development and Review

- NIH provides reviewers with specific guidance on assessing inclusion of participants based on sex/gender, race, ethnicity, and age. Scientific Review Groups are instructed to focus on scientific considerations when assessing the enrollment for a proposed study described in an NIH grant application, considering the applicant's plans for outreach, recruitment, and enrollment. Unacceptable inclusion plans must be reflected in the priority score of the application and documented in the summary of the review session. Applications with unacceptable inclusion plans cannot be funded until concerns are resolved.

¹²⁷ grants.nih.gov/policy/inclusion.htm

¹²⁸ grants.nih.gov/grants/guide/notice-files/NOT-OD-18-014.html

¹²⁹ grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html

¹³⁰ grants.nih.gov/policy/inclusion/lifespan.htm

¹³¹ orwh.od.nih.gov/sites/orwh/files/docs/05-Corbett_508c.pdf

¹³² nexus.od.nih.gov/all/2022/04/11/fy-2021-data-on-age-at-enrollment-in-clinical-research-now-available-by-rcdc-category/

- An NIH All About Grants podcast mini-series discussed considerations for inclusion plans in applications, and what researchers should know, including for outreach programs.¹³³
- The NIH Minority Health and Health Disparities Strategic Plan¹³⁴ represents a commitment by NIH to support research aimed at addressing the risk and protective factors that operate and interact on multiple levels to impact the well-being of populations with health disparities. Relevant goals of note include promoting and enforcing accountability for inclusion of diverse populations as well as promoting inclusion of racial/ethnic minorities and other populations with health disparities in big data sets, clinical research, and future big science initiatives.

Training

- In September 2020, NIH held its second Inclusion Across the Lifespan Workshop.¹³⁵ Among the themes discussed at the meeting was the need for more researcher training and resources. Beginning in November 2020, NIH incorporated enhanced inclusion training opportunities at its annual NIH Virtual Seminar, including a training session called Including Diverse Populations in NIH-funded Clinical Research, booth resources, and opportunities to discuss inclusion one-on-one with NIH staff. To get a sense of its scope and reach, over 15,000 participants attended the 2021 Virtual Seminar.
- NIH regularly conducts training for NIH staff on consideration of sex, gender, race, and ethnicity in review and monitoring of awards.
- The NIH Office of Research on Women’s Health hosts a public NIH Inclusion Outreach Toolkit with information and training resources to help principal investigators and research teams fulfill their responsibilities in including women in clinical research.¹³⁶ The toolkit includes Inclusion Across the Lifespan modules to educate researchers on the policies to include women of all ages in studies.

Reporting

- Related to implementing inclusion Across the Lifespan activities, in April 2022, NIH began reporting data on the age of participants in NIH-supported clinical research.¹³⁷ The newly available information on age adds to already reported data on participant sex or gender, race, and ethnicity.¹³⁸
- ClinicalTrials.gov provides template tables that facilitate responsible parties’ reporting of clinical trial participant demographic information including age, sex, gender, race, and ethnicity.

Outreach to Communities

- NIH supports outreach and engagement efforts in ethnic and racial minority communities disproportionately affected by the coronavirus disease 2019 (COVID-19) pandemic as

¹³³ nexus.od.nih.gov/all/2022/04/15/nih-all-about-grants-podcast-miniseries-inclusion-plans-from-application-to-post-award/

¹³⁴ www.nimhd.nih.gov/about/overview/strategic-plan.html

¹³⁵ nexus.od.nih.gov/all/2020/12/10/some-thoughts-following-the-nih-inclusion-across-the-lifespan-2-workshop/

¹³⁶ orwh.od.nih.gov/toolkit

¹³⁷ nexus.od.nih.gov/all/2022/04/11/fy-2021-data-on-age-at-enrollment-in-clinical-research-now-available-by-rcdc-category/

¹³⁸ nexus.od.nih.gov/all/2019/05/06/nih-inclusion-data-by-research-and-disease-category-now-available/

part of the NIH Community Engagement Alliance (CEAL) effort.¹³⁹ In June 2022, CEAL launched the Community Engagement Alliance Consultative Resource (CEACR), established to elevate best practices throughout CEAL and provide customized expertise to optimize inclusive participation across the research ecosystem.

- The Rapid Acceleration of Diagnostics Underserved Populations (RADx-UP) program leverages existing community partnerships to build community-engaged implementation projects focused on understanding factors associated with COVID-19 testing disparities.¹⁴⁰
- The NIH National Institute on Aging's Outreach Pro online research tool helps researchers and local communities increase participation of traditionally underrepresented populations in clinical trials on Alzheimer's disease and related dementias. The website allows users to create customized outreach materials such as handouts, websites, and social media posts.¹⁴¹
- The NIH INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome) project¹⁴² aims to increase participation of people with Down syndrome and their families in clinical research, expand knowledge about Down syndrome and its links to other health conditions, and improve the health of this important population. In September 2022, NIH held a workshop that brought together members of the Down syndrome community, governmental and agency partners, healthcare and service providers, researchers, and experts in diversity and inclusion to inform efforts to enhance diversity and inclusion in Down syndrome research.
- The NIH Clinical Research Trials and You¹⁴³ website provides information on participation in clinical research to the public, health care providers, and researchers. The site includes basic information on clinical trial participation, personal stories, and educational resources. The website also includes promotional materials to raise public awareness about clinical trials, available in English and Spanish. The National Library of Medicine (NLM) provides information in plain language on the Learn about Clinical Studies¹⁴⁴ website. Additionally, the Beta.ClinicalTrials.gov website, which was recently launched as part of the NLM effort to modernize ClinicalTrials.gov, makes it easier to search for, compare, and read information about clinical studies of interest.
- The Network of the National Library of Medicine (NNLM) brings trusted health information to communities, including underrepresented populations from medically underserved areas, and provides highly respected community anchors to support awareness and engagement in major NIH initiatives such as the *All of Us* Research Program.¹⁴⁵ In the past year, the NNLM hosted more than 40 educational events specifically focused on the importance of diversifying clinical research.

¹³⁹ covid19community.nih.gov/about

¹⁴⁰ www.nih.gov/research-training/medical-research-initiatives/radx

¹⁴¹ www.nih.gov/news-events/news-releases/nih-unveils-new-online-tool-improve-alzheimers-clinical-trials-recruitment

¹⁴² www.nih.gov/include-project

¹⁴³ www.nih.gov/health-information/nih-clinical-research-trials-you

¹⁴⁴ clinicaltrials.gov/ct2/about-studies/learn

¹⁴⁵ www.nnlm.gov/initiatives/all-of-us

Other

- As directed in the FY 2020 omnibus appropriations conference report, NIH funded a \$1.2 million contract with the National Academies of Science, Engineering, and Medicine (NASEM) on Improving the Representation of Women and Underrepresented Minorities in Clinical Trials and Research. The NASEM committee examined the research on barriers to participation, highlighted programs that address issues of underrepresentation in clinical trials and identified more inclusive institutional and informational policies and procedures to increase the likelihood of improved health outcomes for women and racial and ethnic minorities.¹⁴⁶
- NIH and the United States Food and Drug Administration are working with external stakeholders through the Clinical Trial Transformation Initiative's project, called The Value of Increasing Diversity in Clinical Trials.¹⁴⁷ In October 2021, this ongoing project held an expert meeting called Increasing Diversity in Clinical Trials to review evidence and tools generated by the project and identify strategies to increase the participation of women and members of racial and ethnic minority groups in clinical trials. Forthcoming recommendations and resources will help stakeholders adopt new organizational-level practices that increase diversity in clinical trials and thereby, better identify population-level differences in treatment response, safety, and efficacy.

NIH remains dedicated to ensuring inclusion throughout our supported clinical research activities. Inclusion of diverse populations in clinical research requires a sustained commitment from the entire scientific community to design trials that answer questions important to diverse populations and that provide those affected by the condition under study the opportunity to participate. NIH continues to engage external stakeholders such as researchers, patients, their advocates, journals, and industry to address barriers to inclusion of participants in NIH-supported clinical research.

¹⁴⁶ nap.nationalacademies.org/catalog/26479/improving-representation-in-clinical-trials-and-research-building-research-equity

¹⁴⁷ www.ctti-clinicaltrials.org/projects/diversity

Colorectal Cancer

Conference Language

The agreement directs NCI to include an update in the fiscal year 2024 Congressional Justification on opportunities to advance progress against colorectal cancer with an emphasis on: (1) opportunities to develop more effective therapeutics; (2) rising rates in people under the age of 50, including rapidly increasing rates in the 20 to 39 year old age range; and (3) the persistent health disparities in prevalence, screening, and outcomes. The update should describe how NCI plans to play a role in addressing these challenges and what existing and future innovative research opportunities can be leveraged to advance progress.

Action taken or to be taken

Research on the causes, prevention, screening, diagnosis, and treatment of colorectal cancer, including research to address disparities and the recent rising rates of early onset disease, is a priority for the National Cancer Institute (NCI). To better understand the racial and ethnic disparities in colon cancer rates, NCI supports a number of activities, including funding development of comprehensive translational research programs focused on addressing cancer health disparities through its NCI Specialized Program of Research Excellence (SPORE) program. NCI-supported gastrointestinal SPORE researchers recently found biological evidence of differences in colon cancer in African American patients.¹⁴⁸ In the first study to find race and side-specific differences in cellular aging of the colon, the researchers showed that the right-side of the colon ages significantly faster in African Americans than it does in Americans of European ancestry. NCI is also working with the colorectal cancer advocacy community to create new patient derived xenograft¹⁴⁹ models of early-onset colorectal cancer by connecting with patients across the nation who are being treated at institutions that already submit specimens to the Patient Derived Models Repository.¹⁵⁰ The repository stores and distributes models generated from primary and metastatic tumor tissues and blood samples collected from patients. Pre-clinical testing using patient derived models can better predict treatment outcomes. Additionally, the NCI-supported Detroit Research on Cancer Survivors (ROCS) study,¹⁵¹ the largest study to date of African American cancer survivors in the United States, is working to understand the major factors affecting the poor outcomes of African Americans after a cancer diagnosis, including cancer progression, recurrence, mortality, and quality of life, with a focus on lung, breast, prostate, and colorectal cancers.¹⁵² ROCS aims to provide long-term outcomes data along with biospecimens for research to improve outcomes for this population; researchers have already started to analyze how clinical and socioeconomic stressors impact long-term survivorship¹⁵³ and how the novel coronavirus disease 2019 (COVID-19) pandemic is impacting these patients.¹⁵⁴

¹⁴⁸ pubmed.ncbi.nlm.nih.gov/33377907/

¹⁴⁹ Xenografts are organs, tissue, or cells transplanted to an individual of another species, such as a human tumor tissue on a mouse.

¹⁵⁰ pdmr.cancer.gov/

¹⁵¹ reporter.nih.gov/search/0Zlyd_IUEkKNmKXRaV_xpw/project-details/10387147

¹⁵² www.cancer.gov/news-events/press-releases/2017/detroit-cancer-survivors-study

¹⁵³ pubmed.ncbi.nlm.nih.gov/35655423/

¹⁵⁴ www.ncbi.nlm.nih.gov/pmc/articles/PMC8652865/

Education about the importance of screening and health behavior changes to help prevent colorectal cancer is another important prevention method. One example of this work is the CHURCH (Community Health workers United to Reduce Colorectal cancer and Cardiovascular disease among people at Higher risk) program, which is putting together a culturally relevant program to help reduce colon cancer risk among African Americans.¹⁵⁵ Community health educators are working across the United States and its territories, as part of this effort, to help educate populations on screening methods and their importance. Through the Cancer Moonshot, NCI continues to fund the Accelerating Colorectal Cancer Screening and Follow-Up Through Implementation Science (ACCSIS) program, launched in 2018.¹⁵⁶ The goal of ACCSIS is to help increase rates of screening, follow-up, and referral to care across the United States. Current studies include finding ways to improve access to screening for Americans in rural Appalachia¹⁵⁷ and in tribal communities.¹⁵⁸ Additionally, the NCI-funded Screen to Save (S2S): NCI Colorectal Cancer Outreach and Screening Initiative aims to increase colorectal screening rates among men and women aged 45 and older from racially and ethnically diverse communities and rural areas.¹⁵⁹

With the recent rise in early-onset colon cancer, there is a need to identify which patients should undergo screening for colon cancer at an earlier age. In 2020, NCI and the National Institute of Environmental Health Sciences held an “Early-Onset Colorectal Cancer Think Tank” meeting to address this concerning trend. Over 400 participants from various sectors presented and discussed emerging evidence on risk factors, mechanisms, and translational approaches for screening and treatment.¹⁶⁰ An NCI SPORE¹⁶¹ study found multiple genetic risk variants were associated with a higher risk of early-onset colorectal cancer.¹⁶² They determined that analyses of polygenic risk score (PRS), a score that estimates the genetic risk of a disease for an individual, along with environmental and modifiable risk factors can help determine patients who would benefit from preventative measures. Additionally, in May 2021, the U.S. Preventive Services Task Force (USPSTF) released new guidelines that recommend screening for colorectal cancer in adults starting at age 45, 5 years earlier than previously recommended. The new draft recommendation is largely informed by a report USPSTF commissioned from NCI, which included new analyses by race and with elevated risk scenarios to reflect population incidence trends.¹⁶³

There is a need for more effective treatment options for colon cancer. A number of NCI-funded clinical trials are looking at the use of immunotherapy or combination therapy for treatment of colon cancer. Two NCI-funded phase III trials are currently studying combination therapy for treatment of patients with a certain kind of advanced or metastatic colorectal cancer to see if the addition of monoclonal antibodies to chemotherapy helps the body’s immune system attack the

¹⁵⁵ reporter.nih.gov/search/dTrMIBBg2UqyzKh6WIXqhQ/project-details/10494230

¹⁵⁶ grants.nih.gov/grants/guide/rfa-files/rfa-ca-17-038.html

¹⁵⁷ reporter.nih.gov/search/mXBxOi-V00u6ymcwxT1wVw/project-details/10245119

¹⁵⁸ cancercontrol.cancer.gov/hdhe/native-american-health/colorectal-cancer-screening-american-indian

¹⁵⁹ www.cancer.gov/about-nci/organization/crchd/inp/screen-to-save

¹⁶⁰ www.futuremedicine.com/doi/10.2217/crc-2020-0028

¹⁶¹ reporter.nih.gov/search/T2YoiU3P_EGpDfzWznLM5A/project-details/10005904

¹⁶² www.ncbi.nlm.nih.gov/pmc/articles/PMC7103489/

¹⁶³ jamanetwork.com/journals/jama/fullarticle/2779986

cancer and possibly interfere with its ability to grow and spread.^{164,165} Another trial, the SOLARIS trial, is looking at the addition of high-dose vitamin D3 to combination therapy in colorectal cancer patients to determine whether it is more effective at shrinking and stabilizing colorectal cancer.¹⁶⁶ Other trials are also looking into treatment of conditions, such as the heritable Lynch syndrome, that increases risk of developing colorectal cancer. Additionally, a clinical trial testing a possible vaccine for patients with Lynch syndrome is currently recruiting participants.¹⁶⁷ By using a vaccine containing antigens that are produced by the cancerous cells of patients with Lynch syndrome, researchers hope that tumors will be more susceptible to immune system attack, while healthy cells are spared.¹⁶⁸

¹⁶⁴ clinicaltrials.gov/ct2/show/NCT02997228

¹⁶⁵ clinicaltrials.gov/ct2/show/NCT02912559

¹⁶⁶ clinicaltrials.gov/ct2/show/NCT04094688

¹⁶⁷ clinicaltrials.gov/ct2/show/NCT05078866

¹⁶⁸ prevention.cancer.gov/news-and-events/blog/vaccine-prevent-hereditary

Congenital Heart Disease (CHD)

Conference Language

The agreement encourages NHLBI to prioritize CHD activities outlined in its strategic plan and directs NIH to provide an update in the fiscal year 2024 Congressional Justification on steps being taken to close research gaps.

Action taken or to be taken

There are two to three 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. The National Heart, Lung, and Blood Institute (NHLBI) 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.

The Bench to Bassinet program includes the Pediatric Cardiac Genomics Consortium (PCGC) and the Pediatric Heart Network (PHN). The PCGC has recruited 13,477 children with CHD, as well as 18,269 parents, to assemble one of the world's largest CHD registries. Whole genome sequence data from the PCGC have shed considerable new light on the causes of CHD and are helping inform clinically available genetic tests. These data sets are also being combined with clinical outcome data to help inform the development of precision medicine strategies for CHD.

The PHN's research is leading to the development of improved treatment and care of children with CHD. In 2021, NHLBI's PHN celebrated 20 years at the forefront of pediatric cardiology research. The PHN is currently enrolling participants in six clinical research studies that include children and adults living with CHD, including the PHN's first nurse-led clinical trial. The program just completed its participation in a global study in partnership with Bristol Myers Squibb. This trial, Safety of Apixaban on Pediatric Heart Disease in the Prevention of Embolism (SAXOPHONE) demonstrated that the blood thinner, apixaban, was safe in children with heart disease to use to prevent blood clots and is easier to administer than current medications.¹⁶⁹ This offers an important new medication option for children with CHD at risk of blood clots. The PHN recently launched the Comparison of Methods of Pulmonary blood flow Augmentation in neonates: Shunt versus Stent trial (COMPASS) which compares a surgical treatment strategy to a newer strategy of ductal arteriosus stenting in neonates with complex CHD.¹⁷⁰ This trial uses a novel approach of leveraging two CHD registries for data collection.

The PHN has also been a significant asset in the NIH COVID-19 pandemic 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 a study called The Long-Term Outcomes after Multi-system Inflammatory Syndrome in Children (MUSIC).^{171,172} MUSIC enrolled over 1,200 children and adolescent participants in about a year. MUSIC study participants will now be followed to evaluate any long-term issues through

¹⁶⁹ clinicaltrials.gov/ct2/show/NCT02981472?term=NCT02981472&draw=2&rank=1

¹⁷⁰ clinicaltrials.gov/ct2/show/NCT05268094?term=NCT05268094&draw=2&rank=1

¹⁷¹ covidmusicstudy.com

¹⁷² pubmed.ncbi.nlm.nih.gov/34418362/

the NIH RECOVER study.¹⁷³ The PHN is also partnering with Pfizer to conduct a United States Food and Drug Administration (FDA)-mandated study of post-COVID-vaccine myocarditis.¹⁷⁴

About half of children with Down syndrome have CHD. The PHN is partnering with the NIH INCLUDE program to conduct the Congenital Heart Disease: Impact on Learning and Development in Down Syndrome (CHILD-DS) study.¹⁷⁵ This study will help determine if having CHD and infant heart surgery affects the way children with Down syndrome develop and learn.

NHLBI has approved the renewal of the PHN through 2031. During the next grant cycle, beginning in 2024, the PHN will build on its scientific strengths and commitment to training the next generation of investigators by emphasizing studies that improve equity in CHD outcomes across the lifespan, and harness data science to identify precision therapies for CHD.

NHLBI continues to fund a significant portfolio of research on CHD beyond the Bench to Bassinet program. For example, complex genetic analyses in two studies published this year have provided new detail that could lead to personalized treatments for CHD.¹⁷⁶ In addition, NHLBI funds cutting-edge research for therapies for CHD, including two trials of stem cell therapy for infants with CHD^{177,178} and a trial of tissue engineered vascular grafts for children with single ventricle CHD.¹⁷⁹

In August 2021, NHLBI convened researchers and patients for the Future of Pediatric Cardiovascular Research workshop to identify research opportunities and optimal approaches to reduce morbidity and mortality related to CHD across the lifespan.¹⁸⁰ Results of the workshop were published as a Review Topic of the Week in the Journal of the American College of Cardiology to coincide with the American Heart Association Scientific Sessions in November 2022.¹⁸¹ Key research opportunities to improve outcomes in CHD were identified in the areas of diversity, equity, and inclusion for both study participants and investigator teams; data science; aligning pediatric cardiovascular research with patient priorities; integrating research within clinical care; and leveraging creative study designs.

¹⁷³ recovercovid.org

¹⁷⁴ clinicaltrials.gov/ct2/results?cond=&term=NCT05295290&cntry=&state=&city=&dist=

¹⁷⁵ clinicaltrials.gov/ct2/show/NCT05312177?term=NCT05312177&draw=2&rank=1

¹⁷⁶ nature.com/articles/s41586-022-04989-3#Abs1

¹⁷⁷ clinicaltrials.gov/ct2/show/NCT04236479?term=NCT04236479&draw=2&rank=1

¹⁷⁸ clinicaltrials.gov/ct2/show/NCT04925024?term=NCT04925024&draw=2&rank=1

¹⁷⁹ clinicaltrials.gov/ct2/show/NCT04467671?term=NCT04467671&draw=2&rank=1

¹⁸⁰ nhlbi.nih.gov/events/2021/future-pediatric-cardiovascular-research

¹⁸¹ www.jacc.org/doi/10.1016/j.jacc.2022.09.032?utm_medium=email_newsletter&utm_source=jaccjournals&utm_campaign=spub_aha22&utm_content=20211108&cookieSet=1

Deadliest Cancers

House Language

The Recalcitrant Cancer Research Act (RCRA) of 2012 focuses on cancers with a five-year survival rate below 50 percent, which account for 44 percent of all U.S. cancer deaths. In House Report 117–96, the Committee directed NCI to develop a scientific framework using the process outlined in the RCRA for gastric and esophageal cancers. The Committee also notes that NCI has taken an important step by receiving approval for a Program in Origins of Gastroesophageal Cancers from the National Cancer Advisory Board and Board of Scientific Advisors. Given the toll all recalcitrant cancers exact on society and the lack of diagnostic and treatment resources currently available to help patients, the Committee encourages NCI to continue to invest in the most promising research opportunities to advance progress against each of the deadliest cancers (gastric, esophageal, and GE junction; liver, including cholangiocarcinoma; lung, including mesothelioma; ovary; pancreas; and brain, including adult and pediatric brain tumors), and to provide an update on research focused on each of these areas in the fiscal year 2024 Congressional Justification.

Conference Language

The agreement directs NIH to identify the greatest obstacles and most promising research opportunities to advance progress against each of the deadliest cancers in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

Gastric, esophageal, and GE junction

The National Cancer Institute (NCI) is supporting several promising research efforts to address challenges in understanding and making progress against gastric and esophageal cancers. A key challenge continues to be the identification of actionable biomarkers and targets within the processes of gastric and esophageal cancer development and progression, as highlighted in the Gastric and Esophageal Cancers Working Group of NCI’s Clinical and Translational Research Advisory Committee’s (CTAC) report, presented at the November 9, 2022, CTAC meeting.¹⁸²

The NCI Program on the Origins of Gastroesophageal (GE) Cancers supports basic research to better understand how gastric and GE junction cancers initially evolve at the cellular level,¹⁸³ and aims to provide a foundation for the identification of new biomarkers and targets for further evaluation. In the fall of 2022, the program awarded several new grants. One study is examining the effects of bacterial metabolism in GE cancer development. Other research projects include evaluating the risk factors, precursors, and stem cell origins of distinct classes of gastric cancer, as well as mechanisms that control how cells change in the stomach leading to cancer. Important goals include addressing the biological mechanisms underlying increased prevalence of GE cancers in certain populations, which aligns with a critical focus of NCI research into diversity, equity, inclusion, and accessibility across its cancer research portfolio.

Another challenge area is lack of standard screening tests for gastric or esophageal cancers. This is an important research opportunity and an area of focus for NCI, and approaches for developing

¹⁸² deainfo.nci.nih.gov/advisory/ctac/1122/index.htm

¹⁸³ www.cancer.gov/about-nci/organization/dcb/research-programs/gej

and implementing non-invasive screening tests for both are being studied. Current research is focused on whether identifying biomarkers, largely through genomic sequencing to detect genetic changes,¹⁸⁴ may provide a strategy for future cancer screening, particularly in high-risk populations. For example, African Americans are disproportionately affected by esophageal squamous cell cancer, but because incidence in the United States is low, NCI-supported researchers are studying whether oral microbiomes can be used as a biomarker for the disease in a black South African population, which if validated could offer a non-invasive strategy for identifying high-risk patients in the United States.¹⁸⁵

Additionally, a recent study by NCI intramural researchers found that young women who carry antibodies against specific cells in the lining of the stomach have an elevated risk of gastric cancer.¹⁸⁶ The presence of these antibodies is a hallmark of autoimmune gastritis, an underdiagnosed chronic inflammatory disease of the stomach. This finding may help explain the recent rise in gastric cancer cases in younger people despite the declining rates of *H. pylori* infection, the main risk factor for gastric cancer. While the results need to be tested in a more diverse patient population, the findings indicate a potential new model for gastric cancer that could inform future screening and treatment approaches.

NCI's Gastrointestinal (GI) Specialized Programs of Research Excellence (SPOREs) include several translational research projects focused on gastric and esophageal cancers. The GI SPOREs span cancers of the digestive system that include gastric, esophageal, colon, rectal, pancreatic, and gallbladder, among other digestive organ sites. Gastric and esophageal research projects include work to identify molecular markers for early detection of the development of esophageal cancer.¹⁸⁷ One SPORE award is focused on health disparities in both lung and gastric cancers, and includes a project exploring potential racial differences in host immune response and the development of gastric cancer.¹⁸⁸ Another project is focused on characterizing and overcoming resistance to a particular targeted therapy in metastatic gastric and esophageal cancers.¹⁸⁹

NCI's National Clinical Trials Network (NCTN) supports steering committees with disease-specific strategic priorities. The Gastrointestinal Steering Committee (GISC) addresses the design, prioritization, and evaluation of concepts for phase II and phase III clinical trials in adult gastrointestinal cancers, including GE cancer subtypes. One ongoing NCTN trial, the CABINET study, is testing the efficacy of a kinase inhibitor as a treatment for patients with advanced neuroendocrine tumors that most commonly develop in the GI tract.¹⁹⁰ Among the strategic priorities for the GISC are a focus on biomarker-driven treatments and the use of new technologies to inform treatment strategies.

¹⁸⁴ reporter.nih.gov/project-details/10057357

¹⁸⁵ reporter.nih.gov/project-details/10249451

¹⁸⁶ pubmed.ncbi.nlm.nih.gov/34913949/

¹⁸⁷ trp.cancer.gov/spores/abstracts/case_gi.htm#h05

¹⁸⁸ trp.cancer.gov/spores/abstracts/duke_p20.htm#h04

¹⁸⁹ trp.cancer.gov/spores/abstracts/dfhcc_gi.htm#h06

¹⁹⁰ clinicaltrials.gov/ct2/show/NCT03375320

Liver, including cholangiocarcinoma

Hepatocellular carcinoma (HCC), the most common type of liver cancer, is among the leading causes of cancer-related deaths worldwide and is one of the few cancers with rising incidence and mortality rates. Health disparities in liver cancer are evident, including a significantly higher mortality rate in historically underrepresented groups and higher incidence among men. Liver cancer remains a difficult-to-treat disease with sub-optimal patient diagnosis and poor patient survival mainly due to the lack of screening tools, advanced stage of disease at diagnosis, and lack of effective therapies.

NCI intramural researchers recently discovered that mice with high levels of platelets (cell fragments that help the blood create clots) had a reduced risk of tumor growth from hepatocellular carcinoma associated with fatty liver disease.¹⁹¹ They linked this surprising result to a specific protein on platelets, called CD40, that can bolster an anti-tumor immune response. The researchers plan to study the mechanism further to determine if CD40 can be harnessed for therapeutic purposes.

NCI intramural researchers also identified a specific surface protein on hepatocellular carcinoma tumor cells that is not typically found in normal liver tissue or other organs. NCI is now supporting a phase I clinical trial for patients with a specific type of HCC using CAR T-cell therapy to take advantage of this specific cell surface protein expression to determine if this treatment is safe and effective.¹⁹² Another NCI intramural study found that levels of a specific protein found on cell surfaces leads to more genetic diversity in both HCC and intrahepatic cholangiocarcinoma (iCCA, bile duct cancer that occurs in the liver), and corresponds with lower treatment response to immune checkpoint inhibitor therapy.¹⁹³ This offers a potential alternative treatment target that could be given in combination with checkpoint inhibitors for HCC and iCCA patients to improve response rates.

The Fusion Oncoproteins in Childhood Cancers (FusOnC2) consortium, a Cancer Moonshot-supported program, is funding a project to understand pathogenesis of fibrolamellar hepatocellular carcinoma (FLC). FLC is a rare type of deadly liver cancer in children and adolescents and young adults (AYA) characterized by a deletion and subsequent fusion of two specific proteins. This award is focused on determining how the fusion protein leads to cancer and developing targeted therapies. Other examples of NCI initiatives in liver cancer basic research include funding opportunity announcements (FOAs) to enhance mechanistic and epidemiologic investigations addressing the role of viral co-infection in liver cancer development and emerging risk factors and liver cancer susceptibility.

Additionally, the Hepatocellular carcinoma Early Detection Strategy (HEDS) study, a multi-center initiative that is part of NCI's Early Detection Research Network (EDRN),¹⁹⁴ is a follow-up to a previous EDRN study investigating specific biomarkers for detecting HCC.¹⁹⁵ HEDS will longitudinally collect biospecimens and clinical data from patients who are high risk for

¹⁹¹ pubmed.ncbi.nlm.nih.gov/36055226/

¹⁹² cancer.gov/news/article/clinical-trial-targets-cell-surface-protein-gpc3-to-treat-advanced-hepatocellular-carcinoma

¹⁹³ ccr.cancer.gov/news/article/protein-that-drives-aggressive-liver-cancer-identified

¹⁹⁴ edrn.nci.nih.gov/

¹⁹⁵ edrn.nci.nih.gov/data-and-resources/protocols/316-hepatocellular-carcinoma-early-detection

HCC development, as well as examine effectiveness of biomarkers in preclinical HCC detection and for HCC patient prognosis. This is the largest biorepository and database for high-risk HCC patients in the United States.

NCI supports two liver cancer SPOREs that conduct translational research focused on high risk populations, and aim to understand and prevent progression of liver fibrosis to HCC.¹⁹⁶ The Liver SPOREs are also evaluating potential new therapeutic approaches, and a SPORE focused specifically on liver cancer health disparities in Alaska Native and American Indian people.¹⁹⁷ A GI cancer SPORE also includes a project focused specifically on cholangiocarcinoma, and understanding the role that a specific molecular characteristic present in more than 20 percent of cholangiocarcinomas plays in the development of drug resistance.¹⁹⁸

NCI also supports several clinical trials focused on cholangiocarcinoma, including a recently launched study examining the efficacy of chemotherapy delivered directly to the liver in combination with an immune system-stimulating drug in patients with liver-only bile duct cancer or colon cancer that has spread to the liver.¹⁹⁹ Another longitudinal study, a National Translational Science Network of Precision-based Immunotherapy for Primary Liver Cancer (PLC), will create a biorepository of HCC, liver cancer, and cholangiocarcinoma patient samples to better understand disease development and progression; patients will be studied for their lifetime.²⁰⁰

Lung, including mesothelioma

NCI supports a range of programs aimed at improving outcomes for lung cancer patients. While progress has been made in identifying specific lung cancer genes, there have been few advances towards targeting these genes in treatment approaches. For small cell lung cancer (SCLC) especially, one obstacle to progress is the fact that the risk of developing cancer remains even decades after patients stop smoking. Additionally, lung cancer is often found at a late stage when it is more difficult to treat and many patients develop resistance to therapy, emphasizing the critical importance of developing improved early detection methods. Examples of NCI programs to address these challenges include the Lung-MAP Screening Study that allows non-small cell lung cancer patients who have had previous treatment to be assigned to one of multiple treatment option sub-studies,²⁰¹ and the NCI Small Cell Lung Cancer Consortium that is focused on information and data exchange, database support, and development and access to preclinical models to improve patient outcomes.²⁰²

In 2020, the United States Food and Drug Administration (FDA) approved the immunotherapy drug pembrolizumab for adults and children with solid tumors containing a certain number of mutations in tumor DNA. However, little was known about how well the drug would work for this purpose in patients from diverse ancestries. A recent NCI-supported study discovered differences in patient outcomes based on patient ancestry following pembrolizumab treatment for

¹⁹⁶ trp.cancer.gov/spores/hepatobiliary.htm

¹⁹⁷ trp.cancer.gov/spores/abstracts/uwashington_p20.htm

¹⁹⁸ trp.cancer.gov/spores/abstracts/dfhcc_gi.htm#h04

¹⁹⁹ clinicaltrials.gov/ct2/show/NCT05286814

²⁰⁰ clinicaltrials.gov/ct2/show/NCT04145141

²⁰¹ clinicaltrials.gov/ct2/show/NCT03851445

²⁰² www.mskcc.org/research-programs/nci-small-cell-lung-cancer-consortium/specific-aims

non-small cell lung cancers.²⁰³ These findings underscore the need to validate how well a drug works in diverse patient populations to prevent the exacerbation of existing health disparities, especially for lung cancer.

The NCI Center for Cancer Research is supporting a phase I clinical trial for patients with malignant mesothelioma, a rare, fast-growing form of lung cancer that produces large amounts of a cancerous protein called mesothelin.²⁰⁴ Researchers are exploring the benefit of injecting a known anti-mesothelin drug, called LMB-100, directly into tumors. In previous studies, patients treated with LMB-100 developed resistance to the drug. The researchers hypothesize that injection of LMB-100 into the tumor, combined with immunotherapy to boost the immune system's response against cancer, will have greater anti-tumor effects leading to better patient outcomes.

NCI continues to support researchers in the United States and around the world who are seeking to address lung cancer more effectively. For example, NCI funds eight lung cancer SPORes 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.²⁰⁵ Multiple lung cancer projects are underway through this funding mechanism.

An additional challenge is in the prevention and early detection of lung cancer, including greater uptake of recommended lung cancer screening for populations at increased risk. NCI-supported research informed a 2021 revised recommendation from the United States Preventive Services Task Force (USPSTF), recommending annual screening for lung cancer with low-dose computed tomography (LDCT) in adults aged 50 to 80 years who have a 20 pack-year smoking history and currently smoke or have quit within the past 15 years, expanding the population originally recommended for annual screening in 2013.²⁰⁶ Uptake of lung cancer screening among the recommended population 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 and decrease deaths from lung cancer,²⁰⁷ including efforts to reduce disparities.²⁰⁸

Ovary

Ovarian cancer incidence and mortality rates have decreased substantially in the last few decades. The approval of targeted cancer drugs such as PARP inhibitors, which cause cancer cells to die by preventing repairs to their damaged DNA, have been transformative for patients with both primary and recurrent ovarian cancer. However, although PARP inhibitors may work for several years, cancer cells can eventually become resistant to them. There is a clinical trial currently under development through the NCI Experimental Therapeutics (NExT) Program to

²⁰³ pubmed.ncbi.nlm.nih.gov/36179682/

²⁰⁴ cancer.gov/news/article/clinical-trial-researches-drug-combination-with-immunotherapy-for-mesothelioma

²⁰⁵ trp.cancer.gov/spores/lung.htm

²⁰⁶ www.uspreventiveservicestaskforce.org/uspstf/recommendation/lung-cancer-screening

²⁰⁷ reporter.nih.gov/search/r7jzRv5kB0asIVM530kfcw/project-details/10449314;

reporter.nih.gov/search/r7jzRv5kB0asIVM530kfcw/project-details/10318171

²⁰⁸ reporter.nih.gov/search/r7jzRv5kB0asIVM530kfcw/project-details/10359685;

reporter.nih.gov/search/r7jzRv5kB0asIVM530kfcw/project-details/10383711;

reporter.nih.gov/search/r7jzRv5kB0asIVM530kfcw/project-details/10396512

test the efficacy of a new treatment in patients with ovarian (and breast) cancer resistant to PARP inhibitors,²⁰⁹ and another trial is underway testing the efficacy of a PARP inhibitor in combination with two other drugs in patients with recurrent ovarian cancer.²¹⁰

A long-standing challenge is the inability to detect ovarian cancer early when it may be more responsive to treatment and before it has spread to other parts of the body. Effective ovarian cancer screening and early detection tests are needed and advances in liquid biopsy-based testing are benefiting ovarian cancer. CancerSEEK, a blood test to detect multiple types of cancer at the earliest stage possible, has shown promise for non-invasive ovarian cancer detection and NCI is supporting development of a similar test called PapGene.²¹¹ Also, a new study funded in FY 2022 by EDNRN is seeking to use uterine lavage (saline wash of the uterus) samples for early detection of ovarian cancer.²¹² NCI also supports six ovarian cancer SPOREs, with translational research projects focused on early detection as well as several other research opportunities, including risk assessment, imaging technologies, immunosuppression, and novel therapeutic approaches for patients with newly diagnosed and relapsed ovarian cancer.²¹³

The identification of risk factors for ovarian cancer is important to establish populations of women who should be screened for ovarian cancer when screening tests are available. In an international study partially supported by NCI, researchers conducted the largest evaluation to date of whether a specific type of DNA variation between people—called copy number variation (CNV)—associates with ovarian cancer risk.²¹⁴ While previous smaller studies did not find strong evidence for CNV association with ovarian cancer risk, the more recent investigation identified several CNVs that linked to an increased risk for ovarian cancer. This work adds to the growing understanding of how to assess genetic risk and disease prevention for ovarian and other cancers.

Ovarian cancer patients may carry genes conferring cancer risk to family members; however, fewer than one-quarter of patients receive genetic testing. “Traceback” testing is a framework for identifying and genetically testing patients with cancer who could have a genetic predisposition but were not referred for genetic testing at time of diagnosis/treatment. NCI is supporting research to improve the detection of families at risk for breast or ovarian cancer to provide individuals with hereditary cancer syndromes genetic counseling, preventive services, and ongoing surveillance to lessen the burden of cancer.

In recent years, NCI-supported studies have provided valuable data about modifiable risk factors, showing that women who have used oral contraceptives have a 30 to 50 percent lower risk of ovarian cancer than women who have never used oral contraceptives. This protection has been found to increase with the length of time oral contraceptives are used and to continue for up to 30 years after a woman stops using oral contraceptives. A reduction in ovarian cancer risk with use

²⁰⁹ www.cancer.gov/news-events/cancer-currents-blog/2021/novobiocin-cancer-parp-inhibitor-resistance-1

²¹⁰ clinicaltrials.gov/ct2/show/NCT02484404

²¹¹ reporter.nih.gov/search/voTJZBMDEEq-s3jnrI9trw/project-details/10478843/

²¹² reporter.nih.gov/search/voTJZBMDEEq-s3jnrI9trw/project-details/10485564

²¹³ trp.cancer.gov/spores/ovarian.htm

²¹⁴ pubmed.ncbi.nlm.nih.gov/36210504/

of oral contraceptives is also seen among women who carry a harmful mutation in the BRCA1 or BRCA2 gene.

Pancreas

Most pancreatic cancer is diagnosed at a later stage when the cancer has already metastasized due to a lack of early detection and screening options. This continues to be an obstacle in making progress against the disease and has led to a very low survival rate (less than 10 percent) for the most common type of pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC). To address this challenge, one of the focuses of the recently renewed Pancreatic Cancer Detection Consortium (PCDC) is PDAC early detection research, including precursor lesion characterization, biomarker testing, and identification of patients at risk of developing cancer.²¹⁵

Ninety-five percent of pancreatic cancers are driven by mutations of the RAS family of genes, a longstanding challenge, and an area where we are beginning to see significant progress. Over the last several years, NCI's RAS Initiative has made significant advances by determining the structures of oncogenic KRAS, the gene that most commonly drives development and progression of PDAC.²¹⁶ This effort is leveraging NCI-funded resources and amplifying internal efforts through partnerships with multiple pharmaceutical and biotechnology companies, which are focusing on advancing seven drug discovery programs that target oncogenic KRAS gene mutations, including the predominant mutations present in PDAC. For example, the breakthrough FDA-approved drug sotorasib that inhibits G12C-mutated KRAS in non-small cell lung cancer is now being used in clinical trials for PDAC patients.²¹⁷ NCI-supported research illustrated how to develop an inhibitor against this KRAS target, playing an important role in making further drug development possible.

NCI also supports translational research focused on understanding the RAS family of genes through the SPOREs in general, and the Hyperactive RAS SPORE in particular.²¹⁸ Two Pancreatic SPOREs²¹⁹ also include projects focused on RAS, as well as other molecular targets, and gaining a better understanding of potential immunotherapy approaches for PDAC. Additionally, a project in a GI cancer SPORE is exploring opportunities to improve therapeutic approaches for the approximately 20 percent of PDAC patients who harbor mutations in genes responsible for DNA damage repair, such as BRCA1 and BRCA2.²²⁰ Another GI SPORE also has a strong focus on pancreatic cancer, including diagnosis and management of pancreatic cysts in an effort to prevent progression to cancer.²²¹

NCI regularly supports studies at the leading edge of clinical research to discover novel, more effective drugs for pancreatic cancer. Recently, NCI-supported researchers identified a small molecule drug that could stop the growth and metastasis of pancreatic cancer in mice.²²² The molecule works by dysregulating iron metabolism in pancreatic cancer cells, leading to cancer

²¹⁵ grants.nih.gov/grants/guide/pa-files/PAR-21-334.html

²¹⁶ www.cancer.gov/research/key-initiatives/ras

²¹⁷ www.cancer.gov/news-events/cancer-currents-blog/2021/fda-sotorasib-lung-cancer-kras

²¹⁸ trp.cancer.gov/spores/hyperactive_ras.htm

²¹⁹ trp.cancer.gov/spores/pancreatic.htm

²²⁰ trp.cancer.gov/spores/abstracts/dfhcc_gi.htm#h05

²²¹ trp.cancer.gov/spores/abstracts/johnshopkins_gi.htm#h06

²²² pubmed.ncbi.nlm.nih.gov/35131878/

cell death. Importantly, this activity occurs even in the presence of DNA mutations that typically leave pancreatic cancer resistant to current treatments. The study's findings introduce a novel way to target pancreatic cancer and create a foundation for further study of this molecule as a potential pancreatic cancer therapy.

In another NCI-supported study, researchers discovered that pancreatic cancer cells can produce a misshapen form of collagen, an essential protein for structural and functional support, that renders them less susceptible to some forms of cancer treatment.²²³ In experiments in mice, the researchers found that a commonly used immunotherapy drug became more effective when they blocked the pancreatic cancer cells from producing the abnormal collagen. The study has implications for new therapeutic targets in pancreatic cancer, as the abnormal collagen is only produced by the cancer cells.

Intramural NCI researchers are embarking on a first-in-human clinical trial to evaluate a drug for pancreatic cancer and other solid tumors that targets the tumor's blood vessels and support cells.²²⁴ The drug, called ProAgio, causes these cancer-supporting cells to die and prevents the growth of tumors. In the trial, the researchers are studying the safety of the drug in people and finding the most effective dose.

Brain, including adult and pediatric brain tumors

There are a number of different types of brain cancers in both adults and children, typically distinguished by the cell type of origin of the cancer. Challenges for brain cancer include improving diagnostic accuracy since many cancer cells look similar but require different treatment, developing personalized treatments and not limiting clinical trial participation, improving responses to radiation therapy, addressing issues such as the blood brain barrier and use of anti-inflammatory drugs that interfere with immunotherapy efficacy, improving quality of life for people with brain cancer, and minimizing the impact of treatment on childhood brain cancer patients.²²⁵ NCI-supported research spans the breadth of these challenges, including a clinical trial testing a radiation sensitizer drug in combination with chemotherapy and radiation to improve treatment outcomes,²²⁶ a study that found a combination therapy of targeted drug and chemotherapy for patients with a rare brain and spinal cord tumor led to a quality of life improvement and updated treatment guidelines,²²⁷ and more accurate diagnosis of brain cancer using patterns of DNA modifications through NCI-CONNECT.²²⁸

NCI supports six brain SPOREs that aim to improve prognostic testing and treatment.²²⁹ For example, one SPORE group is working on developing brain-penetrant targeted therapies for a type of pediatric brain cancer with specific BRAF mutations, which can promote tumor development in many cancers since BRAF is involved in cell growth. Immunotherapies offer a promising treatment option but have had limited success in brain cancer. Several SPORE groups are focused on immunotherapy approaches, including vaccines, to overcome the

²²³ www.cancer.gov/news-events/cancer-currents-blog/2022/pancreatic-cancer-collagen-treatment-target

²²⁴ ccr.cancer.gov/news/article/first-in-human-clinical-trial-evaluates-drug-for-pancreatic-cancer

²²⁵ www.cancer.gov/types/brain/research

²²⁶ clinicaltrials.gov/ct2/show/NCT04216329

²²⁷ www.cancer.gov/rare-brain-spine-tumor/blog/2021/ependymoma-trial

²²⁸ www.cancer.gov/rare-brain-spine-tumor/blog/2022/methylation-marks

²²⁹ trp.cancer.gov/spores/brain.htm

immunosuppressive environment of the brain tumor microenvironment, while another group is assessing the correlation of specific immune biomarkers with clinical response.

Gliomas are a type of tumor that begins in the supportive (or glial) cells of the brain. Two recent NCI-supported studies identified a vulnerability in gliomas that could make these cancers more susceptible to treatment.²³⁰ One study examined a type of glioma commonly found in children,²³¹ while the other study focused on gliomas harboring mutations in *IDH* genes,²³² genes important for energy production and respiration, which tend to occur in adults. In both cases, the researchers found that in mice these types of gliomas were sensitive to blocked production of one of the building blocks of DNA, which the researchers exploited with a drug called BAY 2402234. This selectively reduced the cancer's ability to divide or repair itself, which eventually led to cancer cell death. Now, NCI's Glioblastoma Therapeutics Network (GTN), an initiative to pursue the development of ready-to-test treatments for adult glioblastomas, is supporting a clinical trial of BAY 2402234 in *IDH*-mutant gliomas.²³³ Additionally, one of the Brain SPORE groups is focused on overcoming treatment-induced resistance and recently identified characteristics associated with recurrence in glioma patients. These findings offer potential targets that could reduce resistance and change disease progression.²³⁴

Medulloblastoma, a rare and aggressive brain cancer that affects children and AYAs, often returns after an initial response to treatment. Effective treatment options are limited after the initial therapy stops working. NCI is committed to improving pediatric cancer treatments, and cutting-edge research is underway to provide innovative treatment options for these patients. For example, an experimental treatment study in mice showed that using nanoparticles to deliver the cancer drugs palbociclib and sapanisertib improved the drugs' ability to reach and fight medulloblastoma tumors.²³⁵ Whether this approach will work in people remains untested while researchers assess the safety of the nanoparticle carrier. Another NCI study developed a test that detects specific changes in DNA fragments shed from medulloblastoma tumor cells in the fluid around the brain and spinal cord in children.²³⁶ This test could be used to identify children who still have evidence of cancer and are at risk of relapse following surgery, allowing doctors to treat more aggressively before cancer can return. 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.²³⁷ There are currently 10 open PBTC studies.

Meningiomas are the most common type of brain tumor. They form from the outermost tissue layer that surrounds and protects the brain and spinal cord. While many meningiomas grow slowly, about 20 to 30 percent are fast-growing and potentially deadly. Two new NCI-supported studies revealed novel ways to classify meningiomas based on molecular changes inside the

²³⁰ www.cancer.gov/news-events/cancer-currents-blog/2022/glioma-treatment-targeting-pyrimidine-synthesis

²³¹ pubmed.ncbi.nlm.nih.gov/35985342/

²³² pubmed.ncbi.nlm.nih.gov/35985343/

²³³ dctd.cancer.gov/NewsEvents/20210928_glioblastoma_therapeutics_network.htm

²³⁴ pubmed.ncbi.nlm.nih.gov/35649412/

²³⁵ cancer.gov/news-events/cancer-currents-blog/2022/medulloblastoma-nanoparticle-palbociclib-sapanisertib

²³⁶ pubmed.ncbi.nlm.nih.gov/34678152/

²³⁷ www.pbtc.org/index.html

tumor cells.^{238,239} Traditionally, meningiomas are classified by what tumors look like under the microscope. The new approach has the potential to give clinicians more information, such as if a patient's tumor is likely to return following treatment or even what is driving tumor growth.

²³⁸ pubmed.ncbi.nlm.nih.gov/35534562/

²³⁹ pubmed.ncbi.nlm.nih.gov/34433969/

Diversity in NIH Kidney Disease Research Populations

House Language

The Committee recognizes NIH's commitment to understanding, evaluating, and resolving racial and ethnic disparities in health outcomes and adverse social determinants of health for individuals with chronic kidney disease (CKD) and end stage renal disease. The Committee directs NIH to submit to the Committee an update in the fiscal year 2024 Congressional Justification on NIH research related to kidney disease, including research focusing on health disparities in the prevention, diagnosis, and treatment of kidney disease among racial and ethnic minority populations.

Conference Language

The agreement directs NIH to include an update in the fiscal year 2024 Congressional Justification regarding the NIH kidney disease research program, including research on health disparities in the prevention, diagnosis, and treatment of kidney disease among racial and ethnic minority populations.

Action taken or to be taken:

Research aimed at improving health equity is a key priority of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the lead NIH Institute for kidney disease research. In February 2022, NIDDK hosted a virtual, two-day workshop on "Designing Interventions that Address Structural Racism to Reduce Kidney Health Disparities," which informed two of the Institute's recent funding initiatives focused on catalyzing research in this critical area.

A broad range of ongoing NIDDK studies are also designed to understand, evaluate, and resolve racial and ethnic disparities in health outcomes and adverse social determinants of health for individuals with chronic kidney disease (CKD) and end stage renal disease (ESRD). NIDDK has made a long-term investment in the Chronic Renal Insufficiency Cohort (CRIC) study, which is characterizing a diverse cohort of nearly 4,000 individuals with CKD. AI-CRIC, an ancillary study with 500 American Indian participants, will improve understanding of risk factors for CKD progression and of the scope of CKD among American Indians. The System Interventions to Achieve Early and Equitable Transplants study is quantifying the effectiveness of interventions that harness and coordinate health-system resources to overcome the multiple roadblocks to receiving living-donor kidney transplants that contribute to disparities, particularly for African Americans. The Motivational Strategies to Empower African Americans to Improve Dialysis Adherence trial uses culturally tailored motivational interviewing in African American participants with ESRD to improve dialysis treatment adherence and reduce hospitalizations, morbidity, mortality, and costs. NIDDK-funded research helped end the inclusion of race as a factor in estimating glomerular filtration rates, a method for assessing kidney function; the discovery of new, superior kidney function biomarkers will further improve renal care and promote health equity.

NIDDK's commitment to striving for health equity includes recruiting a sufficiently diverse cohort of participants in its major clinical trials to ensure that results will be applicable to the most affected U.S. populations, and ensuring that individuals with the conditions being studied have a leadership role on the research team as patient advisors. For example, patient advisors are

a key feature of the *APOLI* Long-term Kidney Transplantation Outcomes Network, providing input and guidance on study design, including participant recruitment and retention, implementation of protocols, and return of results. The study will determine the effects of genetic variations in the *APOLI* gene, found in some people of African descent, on outcomes for people who donate a kidney or receive a kidney transplant. Until and unless a suitable kidney donor can be found, people with ESRD require three lengthy dialysis sessions each week, resulting in significant pain in more than half of people who receive such therapy. Therefore, the NIDDK's Hemodialysis Opioid Prescription Effort (HOPE), part of NIH's Helping to End Addiction Long-term® (HEAL) Initiative, is testing alternatives for pain management in dialysis patients, because traditional opioid therapy can increase risk of death and could lower quality of life. Because ESRD disproportionately affects Black Americans, the HOPE study design specifies that half of participants should be Black, and patient advisors on its steering committee have made invaluable contributions to achieving this participant recruitment goal. NIDDK will continue to fund and conduct research that advances health equity through prevention, diagnosis, and treatment of diverse populations in CKD and other mission areas.

Dystonia

House Language

The Committee requests an update in the fiscal year 2024 Congressional Justification on the status of the implementation of the recommendations from the NINDS workshop Defining Emergent Opportunities in Dystonia Research that was held in 2018.

Action taken or to be taken

As the Committee notes, the National Institute of Neurological Disorders and Stroke (NINDS) convened a workshop in October 2018 titled “Defining Emergent Opportunities in Dystonia Research.” Dystonia is a disorder characterized by involuntary muscle contractions that cause slow and sometimes painful repetitive movements or abnormal postures. This workshop was cosponsored by the Dystonia Medical Research Foundation and included representatives from academic research, industry, patient groups, and scientific staff from the National Institutes of Health (NIH). A report on the workshop, “Defining Research Priorities in Dystonia,” detailed the prioritization of research opportunities discussed and was published in the journal Neurology in 2020.

Prioritization of comprehensive data collection for continued target identification and clinical trial readiness was a key workshop recommendation. The Dystonia Coalition, a large research consortium funded by NINDS and the NIH Office of Rare Disease Research, within the National Center for Advancing Translational Sciences, is conducting natural history studies on focal dystonias, which have resulted in the identification of distinct sub-groups of one type of dystonia (adult-onset idiopathic, isolated, focal cervical dystonia) as well as updated guidelines for classifying and diagnosing two other types of dystonia (blepharospasm and cervical dystonia). The Dystonia Coalition also leads a biobanking effort for DNA and other patient specimens that are used by consortium members and collaborators to advance understanding of the genetics of dystonia. In 2021, researchers using these data published a large genome-wide association study (GWAS) of cervical dystonia, the largest GWAS for any type of dystonia, and confirmed that the genetic underpinnings of cervical dystonia are complex and likely due to variations in multiple genes.

Furthering our understanding of the molecular and cellular mechanisms of dystonia and bridging the gap between cellular and neuronal network dysfunction were also indicated as high priorities from the 2018 workshop. NINDS supports research to understand how genetic mutations contribute to dystonia, the brain circuits involved in movement control and how those circuits are altered in dystonia, how molecular and cellular processes contribute to the dysfunction of neuronal networks, and neuronal mechanisms underlying sex differences in dystonia.

NINDS also funds scientific research focused on identifying biomarkers for diagnosing dystonia and developing effective treatments. Scientists are clinically evaluating a platform that uses MRI brain images and artificial intelligence to diagnose dystonia in its early stages, enabling patients to receive treatment sooner. Multiple studies are currently investigating the pathophysiology of developmental dystonia to identify the brain regions that may be optimal locations for deep brain stimulation treatment. At the intersection of genetics and therapeutic response, NINDS supports research to understand how patients’ individual genetic differences impact the likelihood that

they will respond to deep brain stimulation. NINDS also supports a small business grant to develop a safer botulinum neurotoxin (BoNT, the active ingredient in Botox) to treat movement disorders such as dystonia. To invest in the future of dystonia research, NINDS also supports the development of the next generation of dystonia researchers through funding for early career scientists.

Early-Career Pediatric Researchers

House Language

The Committee remains concerned about the ongoing challenges in developing the next generation of researchers—including physician scientists—focusing their careers in pediatrics. Challenges to the pediatric research workforce include declining numbers of graduating medical students choosing to enter the field of pediatrics, declining numbers of pediatric residents choosing to enter most pediatric subspecialties, lower transition rates from early-career to full awards, increased clinical demands, and limited mentorship opportunities compared to other fields. If unaddressed, a contraction of the pediatric researcher pipeline will result in both limited breakthroughs in child health research and to diminished understanding of adult-onset conditions given the growing body of research that many such conditions have their roots in childhood. To begin addressing this problem, the Committee encourages NIH, through the Trans-NIH Pediatric Research Consortium (N-PeRC), to explore programs for NIH-wide early career development focused on early-career researchers in the field of pediatrics and encourages NIH to include efforts to recruit researchers from diverse backgrounds, including those that are from groups underrepresented in the biomedical research workforce. The Committee requests an update on progress in the fiscal year 2024 Congressional Justification.

Conference Language

The agreement encourages NIH, through the Trans-NIH Pediatric Research Consortium, to explore an NIH-wide early career development award that is focused on early-career researchers in the field of pediatrics that includes efforts to recruit researchers from diverse backgrounds, including those that are from groups underrepresented in the biomedical workforce. The agreement requests an update on progress in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

The National Institutes of Health (NIH) has long recognized that the most critical assets in the biomedical research enterprise are the scientists who comprise its workforce. The NIH knows that its ability to help ensure scientific discovery and innovation is dependent upon a pool of highly diverse talented scientists who will help to further NIH's mission. For example, NIH is co-sponsoring a National Academies of Sciences, Engineering, and Medicine (NASEM) study on how to ensure an adequate pediatric subspecialty workforce to support access to high-quality care and a robust research portfolio.²⁴⁰ The development of early career pediatric researchers is a priority for NIH.

N-PeRC is an NIH-wide initiative that capitalizes on pediatric research expertise and resources across NIH's 27 institutes and centers (ICs) through increased collaboration. Many NIH ICs support research training, career development, and loan repayment programs to train early career researchers, including investigators working in pediatrics. A small subset of examples of these NIH programs are listed below.

- **Environmental influences on Child Health Outcomes (ECHO) Program**²⁴¹ – An extramurally-funded program maintained within the Office of the Director at NIH, the

²⁴⁰ www.nationalacademies.org/our-work/the-pediatric-subspecialty-workforce-and-its-impact-on-child-health-and-well-being

²⁴¹ www.nih.gov/research-training/environmental-influences-child-health-outcomes-echo-program

mission of the ECHO Program is to enhance the health of children for generations to come. Since September 2018, each year the ECHO program has provided supplemental awards toward Opportunities and Infrastructure Funds (OIF). The OIF benefits the ECHO Program and the child health community by promoting the development of early career scientists to help foster their transition to research independence. To date, ECHO has funded 30 early career scientists. Moreover, ECHO funds at least one Early Career Investigator at each of its clinical sites.

- **Pediatric Scientist Development Program (PSDP)**²⁴² – Supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the PSDP provides scientific research experience, particularly in basic science areas, for pediatricians wishing to pursue careers in academic medicine. This program has provided research training for more than 175 scholars across the country.
- **Child Health Research Career Development Award Program**²⁴³ – Supported by NICHD, the program was created to fill the gap in training for junior faculty who intend to devote their careers to academic pediatrics. The program provides funding for sustained mentoring and laboratory-based training and offers the vital foundation to compete for grant funding.
- **Pediatric Clinical and Developmental Pharmacology Training Network (PCDPTN)**²⁴⁴ – Supported by NICHD and the National Institute of General Medical Sciences (NIGMS), the goals of the PCDPTN are to provide training in pediatric clinical pharmacology; stimulate interdisciplinary collaboration among clinical, translational, and basic researchers in pediatric therapeutics; and enable the development of a pediatric pharmacology section within the adult clinical pharmacology department.
- **Pediatric Critical Care and Trauma Scientist Development Program (PCCTSDP)**²⁴⁵ – Supported by NICHD, the PCCTSDP’s goal is to increase the number of highly trained, successfully funded, and sustainable pediatric critical care and pediatric trauma physician-scientists who will engage in research to enhance the scientific understanding, clinical management, and long-term outcome of critical illness and trauma in children.
- **Pediatric Heart Network (PHN) Scholars Program**²⁴⁶ – The National Heart, Lung, and Blood Institute (NHLBI)-funded Pediatric Heart Network (PHN) is training the next generation of pediatric cardiovascular clinical researchers through the Scholars Program. There have been 31 PHN Scholars to date.
- **Diabetes-Docs**²⁴⁷ – Supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the program emphasizes support for pediatric

²⁴² www.nichd.nih.gov/research/supported/PSDP

²⁴³ www.nichd.nih.gov/research/supported/chrda

²⁴⁴ www.nichd.nih.gov/research/supported/pcdptn

²⁴⁵ www.nichd.nih.gov/research/supported/pcctsdp

²⁴⁶ www.pediatricheartnetwork.org/

²⁴⁷ grants.nih.gov/grants/guide/rfa-files/rfa-dk-21-019.html

endocrinologists and physicians from other specialties conducting innovative research into the causes and consequences of diabetes and aims to increase the diversity of next generation physician-scientists in type 1 diabetes research.

- **Center to Reduce Cancer Health Disparities (CRCHD)**²⁴⁸ – Supported by the National Cancer Institute (NCI), CRCHD supports early-stage investigators, including pediatric researchers, through many types of funding opportunities.
- **Research Dissertation Fellowship for Audiologists (Au.D.)**²⁴⁹ – The National Institute on Deafness and Other Communication Disorders (NIDCD) supports this program. The goal is to train a pool of highly talented scientists from diverse backgrounds to do research on scientific health-related fields relevant to the mission of the NIDCD, including those that impact pediatric populations.
- **Research Career Development Support for Child Neurologists (CNCDP)**²⁵⁰ – Supported by the National Institute of Neurological Disorders and Stroke (NINDS), the CNCDP supports child neurologists who have made a commitment to independent research careers.
- **International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Early Career Investigator Mentored Research program**²⁵¹ – Supported by the National Institute of Allergy and Infectious Diseases (NIAID), the program aims to support the development of early career investigators to enter the field of maternal/child HIV research. NIAID also supports early career pediatric infectious diseases investigators through research training grants.
- **The Pediatric and Reproductive Environmental Health Scholars (PREHS) Program**²⁵² – Supported by the National Institute of Environmental Health Sciences (NIEHS), the program will bring together institutional expertise in environmental health science research with clinical and translational expertise at Pediatric Environmental Health Specialty Units (PEHSUs) to provide pediatric healthcare providers, obstetricians/gynecologists, nurses, and other interested healthcare professionals (PREHS Scholars) with research experiences that bridge clinical practice in environmental health, community-level engagement, and teaching.

These are a few examples of NIH research training and career development programs geared toward developing early career researchers, including investigators working in pediatrics.

²⁴⁸ www.cancer.gov/about-nci/organization/crchd

²⁴⁹ grants.nih.gov/grants/guide/pa-files/PAR-21-093.html

²⁵⁰ reporter.nih.gov/project-details/10014466

²⁵¹ www.niaid.nih.gov/research/impaaact-early-career-investigator-mentored-research

²⁵² grants.nih.gov/grants/guide/rfa-files/RFA-ES-20-007.html

Early-Career Researchers

House Language

The Committee notes that the mean age of a first R01 award has continued to increase over the past 25 years. Accordingly, the Committee directs NIH to examine existing efforts to expand early career research, including the Next Generation Researchers Initiative, and provide an update in the fiscal year 2024 Congressional Justification. The Committee requests that NIH consider additional actions, including larger payline differentials for new or early-stage investigator applications, to further prioritize early career research

Action taken or to be taken

The National Institutes of Health (NIH) agrees with the Committee's interest in expanding opportunities to support and prioritize researchers early in their career. The R01 (or R01-equivalent) grant has traditionally been a critical component to the launch of a research career. A number of academic leaders have described and expressed concerns about the age at which scientists are first supported on an R01 award ("age at first R01"). NIH shares the concerns raised about the age at which scientists are first supported on an R01 award and recognizes the potential impact it may have on the future biomedical workforce.

While the age at which principal investigators designated on their first R01-equivalent grant continuously increased between fiscal years (FYs) 1995 to 2020, the rate of increase has slowed over the last 10 years.²⁵³ Breaking the data down by degree type, investigators with an MD degree (either alone or with a PhD) have been consistently older at the age of first R01 compared to those without an MD degree, likely due to time spent in clinical training after receiving their degrees.

Additionally, the age of students receiving a PhD has increased over the years. As a point of reference, National Science Foundation data report that 44.1 percent of those receiving their doctorate in 2020 were between 26 to 30 years of age, 31.1 percent between 31 and 35 years of age, and 12 percent between 36 to 40 years of age.²⁵⁴ NSF maintains records of prior year's data tables for further reference.²⁵⁵

NIH will continue following these and other data going forward to better understand trends in the wider biomedical workforce. However, the mean age at being designated on one's first R01-equivalent grant is only one measure. NIH aims to expand the earlier paradigm beyond this to a more holistic view of the transition from obtaining a doctoral-level degree to time to becoming an independent investigator. Amongst other things, this helps account for differences in the age of matriculation, given that many more individuals may be starting a research career later in life.

Recognizing this view, NIH's Next Generation Researchers Initiative (NGRI) aims to cultivate and support talent entering the biomedical and behavioral research workforce.²⁵⁶ This initiative

²⁵³ nexus.od.nih.gov/all/2021/11/18/long-term-trends-in-the-age-of-principal-investigators-supported-for-the-first-time-on-nih-r01-awards/

²⁵⁴ nces.nsf.gov/pubs/nsf22300/data-tables

²⁵⁵ www.nsf.gov/statistics/doctorates/

²⁵⁶ grants.nih.gov/ngri.htm

aims to bolster opportunities for early-stage investigators (ESIs).²⁵⁷ ESIs are defined as those within 10 years of completing their terminal degree or postgraduate clinical training and who have not previously competed successfully for a substantial NIH independent research award. In addition, applications from ESIs are given special consideration during peer review as well as at the time of funding consideration.

NIH Institutes and Centers prioritize funding for ESIs as part of NGRI. The initiative also tracks the impact of funding decisions on ESIs, such as subsequent grant submission and success. As a result of this initiative, NIH has substantially increased support for ESIs, increasing from 978 in FY 2016 (before NGRI started) to 1,513 in FY 2021.^{258,259} This new all-time high level of support for ESIs represents a 7.2 percent increase over FY 2020. NIH remains strongly committed to the goals of NGRI to fund more early-career investigators, protect and retain meritorious at-risk scientists, and enhance the diversity of the biomedical research workforce.

In addition to NGRI, NIH has several other programs and initiatives developed with the intention to enhance career progression and funding opportunities for early career investigators.²⁶⁰ Selected examples are below:

- NIH Director's New Innovator Award Program²⁶¹
- Maximizing Investigators' Research Award²⁶²
- NIH Pathway to Independence Award²⁶³
- Director's Early Independence award²⁶⁴
- High Priority, Short-Term Project/Bridge Award²⁶⁵
- Maximizing Opportunities for Scientific and Academic Independent Careers program²⁶⁶
- Stephen Katz ESI Research Grant Program (no preliminary data allowed)²⁶⁷
- NIH loan repayment award amounts support up to \$50,000 per year, which can be competitively renewed^{268,269}
- Funding provided for Childcare Costs for Ruth L. Kirschstein National Research Service Award Individual Fellows and Trainees²⁷⁰

NIH will continue working with the research community to enhance support for the next generation of biomedical scientists. For instance, a new ad hoc group of the Advisory Committee to the NIH Director (ACD) was recently charged with re-envisioning NIH-Supported

²⁵⁷ grants.nih.gov/grants/guide/notice-files/NOT-OD-17-101.html

²⁵⁸ nexus.od.nih.gov/all/2022/07/18/more-early-stage-investigators-supported-in-fy-2021/

²⁵⁹ nexus.od.nih.gov/all/2021/07/12/data-on-implementing-nih-next-generation-researchers-initiative/

²⁶⁰ researchtraining.nih.gov/career/early-career

²⁶¹ commonfund.nih.gov/newinnovator

²⁶² www.nigms.nih.gov/research/mechanisms/mira/pages/default.aspx

²⁶³ grants.nih.gov/grants/guide/pa-files/PA-20-188.html

²⁶⁴ commonfund.nih.gov/earlyindependence

²⁶⁵ grants.nih.gov/grants/funding/r56.htm

²⁶⁶ www.nigms.nih.gov/training/careerdev/Pages/MOSAIC.aspx

²⁶⁷ nexus.od.nih.gov/all/2020/11/09/introducing-the-stephen-i-katz-early-stage-investigator-research-grant-program/

²⁶⁸ nexus.od.nih.gov/all/2019/09/20/dont-miss-out-nih-loan-repayment-applications-now-being-accepted/

²⁶⁹ nexus.od.nih.gov/all/2022/08/22/announcing-the-2023-nih-loan-repayment-program-application-cycle-and-a-new-lrp-director/

²⁷⁰ nexus.od.nih.gov/all/2022/08/10/preliminary-data-on-childcare-cost-support-for-national-research-service-award-nrsa-individual-fellows/

Postdoctoral Training. As mentioned in the December 2022 ACD meeting, NIH anticipates releasing a Request for Information in 2023 seeking feedback targeted on this critical early career group. Moreover, NIH issued a separate request for information seeking feedback on revising and simplifying the peer review framework for research project grant applications.²⁷¹ Amongst other things, the proposed changes will allow peer reviewers to focus on scientific merit by evaluating whether or not appropriate expertise and resources are available to conduct the research, thus mitigating the undue influence of the reputation of the institution or investigator.

It is a high priority for NIH to identify, grow, and retain investigators across these critical career stages, because they convey new insights, develop innovative ideas, and advance the translation of scientific research into improved health for all.

²⁷¹ nexus.od.nih.gov/all/2022/12/08/update-on-simplifying-review-criteria-a-request-for-information/

Endometrial Cancer

House Language

The Committee remains concerned about the significant racial and ethnic disparities in mortality rates for endometrial cancer that adversely impact Black women. The age-adjusted mortality rate for Black women with endometrial cancer is nearly twice the rate of White women, which is partly attributed to cancer stage at diagnosis. The Committee commends NCI's efforts to address these disparities through projects like the Discovery and Evaluation of Testing for Endometrial Cancer in Tampons (DETECT) Study, and encourages NCI to continue supporting research activities that will lead to the development of targeted interventions to improve early diagnosis among Black women with endometrial cancer. The Committee also encourages NCI to research innovative community-based outreach methods to improve access to high-quality care, with the goal of increasing enrollment and participation by Black women in clinical trials. The Committee requests an update on NCI's activities regarding endometrial cancer in the fiscal year 2024 Congressional Justification, including progress made in endometrial cancer early diagnosis, survival rates, and clinical trial enrollment by race and ethnicity.

Action taken or to be taken

Endometrial cancer, the most common type of uterine cancer, is the most common gynecologic cancer in the United States, with an estimated 65,950 new cases and 12,550 deaths in 2022.²⁷² The National Cancer Institute (NCI) remains dedicated to improving outcomes for all women with endometrial cancers and to better understanding endometrial cancer disparities.

NCI is aware of and concerned about the significant inequities in endometrial cancer mortality rates as confirmed by a recent NCI study.²⁷³ Previous analyses have made the uterine cancer disparities among ethnic and racial groups known, but the NCI study was the first nationally representative analysis that broke down their results by subtype and stage by race and ethnicity. The NCI study found that Black women are twice as likely to die of uterine cancer compared to other racial and ethnic groups. Most of the increase in mortality is attributable to non-endometrioid uterine cancer, an aggressive subtype, which disproportionately affects Black and Hispanic women. Non-endometrioid cancer mortality increased 3.5 percent per year for Black women and 6.7 percent for Hispanic women between 2010 and 2017.

NCI is addressing rising endometrial cancer rates by supporting gynecologic cancer prevention research.²⁷⁴ For example, a current clinical trial²⁷⁵ is testing whether the drug metformin, in combination with progestin, can prevent progression of endometrial precancer, and another trial²⁷⁶ is testing the success of an estrogen production-blocking drug to prevent low-grade or precancer progression. The trial is also investigating patient molecular markers that correlate with outcomes. Conversely, progesterone (a hormone produced by the ovaries) exposure has been shown to reduce endometrial cancer rates and the progesterone receptor is necessary for this protective impact. NCI-funded research²⁷⁷ is examining the mechanism for downregulation of

²⁷² seer.cancer.gov/statfacts/html/corp.html

²⁷³ jamanetwork.com/journals/jamaoncology/article-abstract/2792010

²⁷⁴ prevention.cancer.gov/news-and-events/blog/rising-endometrial-cancer?cid=eb_govdel

²⁷⁵ clinicaltrials.gov/ct2/show/NCT04576104

²⁷⁶ clinicaltrials.gov/ct2/show/NCT03300557

²⁷⁷ reporter.nih.gov/search/LdzKeiaf-EGrPL97_L89iA/project-details/10165666

the progesterone receptor in endometrial cancer patients and ways to potentially overcome this to improve outcomes for all patients.

Additionally, the Specialized Programs of Research Excellence (SPOREs) support research on gynecologic cancers. The Endometrial Cancer SPORE at MD Anderson Cancer Center conducts translational research for the prevention and treatment of endometrial cancer.²⁷⁸ Their research involves developing therapeutics for advanced and recurrent endometrial cancer, as well as for aggressive subtypes. NCI also funds planning grants for future SPORE programs in cancer health disparities. The aim is to build programs to improve the prevention, early detection, diagnosis, and treatment of cancers that disproportionately affect specific racial and ethnic minority populations that can compete for SPORE funding in future years. In FY 2020, Northwestern University was awarded a SPORE planning grant focused on racial differences in gynecologic cancers. The Northwestern University Cancer Health Equity Research SPORE (NU-CHERS) is focusing on endometrial and ovarian cancer disparities experienced by Black women.²⁷⁹ The information gained will help with understanding tumor biology differences between racial groups and predicting differences in treatment responses. This program also supports a biospecimen core, in conjunction with a local hospital, that will store samples and allow researchers improved access to gynecological samples from underrepresented groups.

NCI supports research to understand underlying causes of endometrial cancer, in order to help better predict risk and work toward prevention and early detection of this cancer. For example, the Epidemiology of Endometrial Cancer Consortium (E2C2) is an NCI-supported consortium dedicated to studying the etiology of endometrial cancer through collaboration among investigators.²⁸⁰ In FY 2021, Brigham and Women's Hospital was awarded NCI funding to use E2C2 to study genomic variation and distinct risk factor profiles across tumor subtypes and the role of underlying tumor biology that may contribute to disparities in mortality between Black and White women.²⁸¹ Additionally, the Carolina Endometrial Cancer Study is analyzing endometrial tumors for genetic and molecular information to help inform future therapeutic studies.²⁸² Researchers are aiming for at least half of the women enrolled to be Black women, and are also developing mouse models based on endometrial tumors from Black women to examine if there are differences in cancer progression compared to White women.

Uterine serous carcinoma (USC) is a rare but aggressive type of endometrial cancer. In about one-third of women with USC, their tumor cells overproduce a protein called HER2 (HER2 positive), which is associated with poor prognosis in women with endometrial cancer. Black women are more likely than White women to be diagnosed with USC and are more likely than women of other races/ethnicities to have HER2-positive USC tumors. An NCI clinical study for patients that have HER2-positive uterine serous cancer and carcinosarcoma is currently underway to determine if targeted treatments shrink tumor size better than chemotherapy.²⁸³

²⁷⁸ trp.cancer.gov/spores/abstracts/mdanderson_gyn.htm

²⁷⁹ trp.cancer.gov/spores/abstracts/northwestern_p20.htm

²⁸⁰ epi.grants.cancer.gov/eccc/

²⁸¹ reporter.nih.gov/search/kPH-0602jEm7TGH_Ju2fsQ/project-details/10156374

²⁸² unclineberger.org/cecs/

²⁸³ clinicaltrials.gov/ct2/show/NCT05256225?cond=Uterine+Serous+Carcinoma&fund=0&draw=2&rank=2

There are no validated screening tests for uterine or endometrial cancer currently, and the clinical work-up of patients with symptoms is invasive. The NCI-supported Discovery and Evaluation of Testing for Endometrial Cancer in Tampons (DETECT) Study is conducting research to demonstrate that tampons may be used to collect samples to detect molecular markers associated with uterine cancer.²⁸⁴ Early studies have been conducted in mainly white populations, but efforts are now underway to expand this work. NCI is collaborating with the University of Alabama at Birmingham to enroll a racially diverse population of people undergoing surgical removal of the uterus for endometrial cancer or benign reasons. This study will provide evidence to inform the development of early detection strategies based on self-collected samples for uterine/endometrial cancer screening, with the ultimate goal of reducing racial disparities. DETECT will also evaluate predictors of endometrial cancer recurrence and survival to better understand differences in uterine cancer deaths by race.

NCI remains committed to increasing underserved populations participation 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.

²⁸⁴ clinicaltrials.gov/ct2/show/NCT03538665

Geroscience

House Language

The Committee commends NIA for its support of geroscience, which 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. A growing body of research suggests it is possible to develop treatments that would address many late-life diseases, as opposed to solely tackling each disease individually, as under the current prevailing model. Significant advances in recent years highlight the need to develop a comprehensive strategy for addressing research gaps and opportunities. Therefore, the Committee urges NIA to convene a meeting of experts across NIH, other relevant Federal agencies, academic researchers, and the private sector to identify gaps and opportunities for this research field. The Committee also recognizes that there is a shortage of investigators who combine clinical, social, and behavioral research skills with a knowledge of aging biology and experience in the care of older adults and the processes of aging at the individual and societal level. The Committee encourages NIA to expand its translational geroscience training programs to support the pipeline of such investigators. The Committee requests an update on these topics in the fiscal year 2024 Congressional Justification.

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 that diminish the quality of life for older individuals. The National Institute on Aging (NIA) funds research on geroscience-related topics across all of its scientific divisions—Neuroscience, Aging Biology, Behavioral and Social Research, and Geriatrics and Clinical Gerontology — and the intramural research program. In order to identify gaps and opportunities to be explored to advance this research field toward translation to clinical applications, the NIH-wide Geroscience Interest Group, led by NIA and including participation by more than 20 NIH Institutes and Centers, is currently planning the fourth NIH Geroscience Summit, *Geroscience for the Next Generation*.²⁸⁵ The Summit will be held in a hybrid format in April 2023 on the NIH main campus in Bethesda, MD. This 3-day Summit will bring together a diverse group of 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 toward several goals, including spurring development of new, informative, precise, and reliable measures of aging, and determining how those measures might contribute to translating discovery into health. The Summit will include a focus on translation of geroscience to social and clinical applications.

NIA also recognizes the need for expanded translational geroscience training programs to support the pipeline of investigators into the geroscience research field. To address this need, NIA recently released a new funding opportunity to support creative educational programs aimed at enhancing and expanding broader awareness of geroscience research.²⁸⁶ This funding

²⁸⁵ www.nia.nih.gov/2023-fourth-geroscience-summit

²⁸⁶ grants.nih.gov/grants/guide/pa-files/PAR-22-214.html

opportunity is designed to support courses for skills development, research experiences, curriculum or methods development, and outreach programs on the topic of geroscience. These educational activities can be targeted to broad audiences, including basic, translational, or clinical researchers. NIA is looking to support innovative geroscience coursework and hands-on research experiences. This opportunity will also support networking with experts in the geroscience field, materials, and outreach to promote awareness of geroscience among the public, the curation of important geroscience publications and clinical trials, and the fostering of innovative approaches to enhancing diversity within the field.

NIA recognizes the importance of this growing field of research and is committed to leading efforts to advance the translation of findings. NIA will continue dedicating resources to push the field toward clinical applications with potential to improve the health and quality of life of the aging population.

Gynecologic Cancers

House Language

The Committee continues to be concerned about the growing racial, socioeconomic, and geographic disparities in gynecologic cancers. In contrast to most other common cancers in the U.S., relative survival for women with newly diagnosed advanced cervical or endometrial cancer has not significantly improved since the 1970s. Furthermore, historical data demonstrates that Black and Latina women with gynecologic cancers are not as likely to receive standard therapy and/or die more frequently. The current COVID-19 pandemic has only exacerbated the health care disparities that were already present in minority and underrepresented communities. For example, in early 2021, CDC published findings that cervical cancer screenings among women aged 21–29 in California decreased by as much as 78 percent during the pandemic. This is concerning because cervical cancer incidence and mortality rates are disproportionately higher in Hispanic women and non-Hispanic Black women. The Committee urges NCI to expand the number of clinical trials, research grants, and contract opportunities for investigators that focus on discoveries that will positively impact access to prevention, early detection, diagnosis, and treatment for gynecologic cancers and address these now well-documented disparities. The Committee requests an update on NCI’s research program for gynecologic cancers in the fiscal year 2024 Congressional Justification, including specific grants and strategies where the intent is to overcome these racial disparities in gynecologic cancers outcomes and opportunities to increase participation of minority women in gynecologic cancer clinical trials.

Action taken or to be taken

The National Cancer Institute (NCI) supports research across the cancer continuum to understand, prevent, and treat gynecologic cancers. Over half of the new cervical cancer cases in the United States each year are among women who have never been screened or who are infrequently screened, reflecting barriers presented by socioeconomic disparities, geographic inaccessibility, and other factors. NCI supports research to increase screening uptake and to develop new technologies for cervical cancer screening. The Last Mile Initiative²⁸⁷ is a public-private partnership between federal agencies, industry partners, and professional societies/clinical practice guideline organizations that is working to validate self-sampling-based human papillomavirus (HPV) testing as a comparable alternative to provider-collected cervical specimens for HPV testing in cervical cancer screening. Self-sampling allows women to obtain samples for HPV testing in the privacy of their own homes and has significant potential to expand screening to never screened or under-screened women, tackling a pressing public health concern of lack of access to cervical cancer screening.

NCI continues to support the ESCUDDO trial²⁸⁸ to determine if a one-dose HPV vaccination is as effective as two doses in young women. The trial has been extended by 1 year to mitigate the impact of the COVID-19 pandemic. Additionally, plans for clinical trials are underway in NCI's Cancer Prevention Clinical Trials Network (CP-CTNet) for a broad-spectrum HPV vaccine that offers protection against potentially all HPV-related diseases and could offer easier accessibility for low-resource settings. Expanding the number of HPV types targeted by a vaccine is important for addressing variation in worldwide prevalence of cervical cancer. For example,

²⁸⁷ prevention.cancer.gov/major-programs/nci-cervical-cancer-last-mile-initiative

²⁸⁸ clinicaltrials.gov/ct2/show/study/NCT03180034

NCI researchers found that African American women have more HPV 35 infections and HPV 35-associated cervical precancers than other races/ethnicities and identified multiple genetic variations associated with cervical precancer in African American women.²⁸⁹

In FY 2022, NCI released a funding opportunity announcement for the HIV/Cervical Cancer Prevention ‘CASCADE’ Clinical Trials Network to conduct pragmatic clinical trials to evaluate the effectiveness of clinically proven interventions with a goal to optimize the cervical cancer screening, management, and precancer treatment cascade for women living with HIV. CASCADE Network trials will be conducted in regions with health disparities in the United States and in low- and middle-income countries.

The NCI’s National Clinical Trials Network (NCTN) supports disease-specific steering committees, including the Gynecologic Cancers Steering Committee (GCSC).²⁹⁰ These committees increase information exchange at early stages of trial development, increase efficiencies of collaboration among trial sites, and reduce trial redundancy across programs. The GCSC develops, evaluates, and prioritizes concepts for Phase II and all Phase III clinical trials for cervical, ovarian, and uterine cancers. The 2022 strategic priorities for the GCSC include attending to the inclusion and special needs of diverse populations in clinical trials across all gynecological cancers.²⁹¹ This includes developing innovative treatment designs and more efficient treatment approaches to reach all patient populations.

NCI is 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 the NCTN and NCI Community Oncology Research Program clinical trials. In November of 2022, NCI will host 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.

For more information on endometrial cancer research, please see the separate *Endometrial Cancer* response; additional information on ovarian cancer research is included in the *Deadliest Cancers* response.

²⁸⁹ pubmed.ncbi.nlm.nih.gov/32363580/

²⁹⁰ www.cancer.gov/about-nci/organization/ccct/steering-committees/nctn/gynecologic

²⁹¹ www.cancer.gov/about-nci/organization/ccct/steering-committees/nctn/gynecologic/gcsc-2022-strategic-priorities-revised.pdf

Hearing Health Screening for Older Adults

House Language

The Committee recognizes the associated comorbidities and costs of untreated hearing loss and, with the growing aging population, the importance of hearing screening for older Americans. The Committee urges NIH to provide an update in the fiscal year 2024 Congressional Justification on hearing screening research for older adults across NIH. The Committee encourages NIDCD and NIA to support studies that address the research needs and gaps identified by the USPSTF in their review of hearing screening recommendations for older Americans.

Action taken or to be taken

Improving hearing health care for adults in the United States is an urgent public health problem and contributing to solutions is a priority for the National Institutes of Health (NIH). In 2021, NIH program staff, individuals from the Agency for Healthcare Research and Quality, and representatives from the United States Preventive Services Task Force (USPSTF) met to define an analytical framework to address the research needs and gaps identified by the USPSTF on hearing screening for older Americans. The USPSTF determined that the following areas need to be addressed through research to determine if routine hearing screening for older adults is warranted:

- The benefit of screening for and treatment of hearing loss in asymptomatic adults on health outcomes, such as quality of life and function, not just on hearing aid use or quality of hearing.
- The potential harms of screening and treatment, such as false-positive results and overtreatment.
- The role of over-the-counter assistive hearing devices compared with prescription amplification devices.
- Screening tools that identify not just adults with hearing loss by audiometry definition criteria, but adults with unrecognized hearing loss that would benefit the most from amplification.
- Consistent use of definitions of hearing loss to improve certainty about the accuracy of screening tests and improved generalizability of results to include a general adult population and diverse subpopulations.

The National Institute on Deafness and Other Communication Disorders (NIDCD) and the National Institute on Aging (NIA) support innovative clinical and translational research initiatives related to the screening for, and detection and treatment of, adult hearing loss. NIDCD has supported over 60 research projects focused on improving access and affordability in hearing health care for adults. This research covers a wide range of topics, including some of the research needs and gaps identified by the USPSTF. Funded projects include ways to predict, improve, and measure hearing health care outcomes; test ways to promote hearing health care access and use in primary care; investigate how to improve delivery of care in community settings to people with hearing loss; and reduce disparities in access to hearing health care. NIDCD's new 2023-2027 Strategic Plan contains themes that encourages new research that will further the development of diagnostic tools that can be used to screen older adults for hearing

loss.²⁹² The new plan also encourages the development of precision medicine, artificial intelligence/machine learning approaches, and the need for specialized imaging capabilities that can lead to innovative methods to screen and diagnose hearing loss.

NIA also supports a number of studies focused on hearing health, particularly as hearing relates to cognitive outcomes. For example, the Aging, Cognition, and Hearing Evaluation in Elders randomized trial will help establish whether a hearing intervention including hearing needs assessment, fitting of hearing devices, and education/counseling can reduce cognitive decline and the risk of Alzheimer’s disease and Alzheimer’s disease-related dementias in cognitively normal older adults.²⁹³ In another study, investigators are characterizing hearing loss and hearing care in a community setting and testing the effects of a communication intervention that integrates over-the-counter assistive technology on disruptive behavior in persons with dementia, as well as on caregiver burden.²⁹⁴ A third example is a study investigating the association between hearing loss, communication impairment, and hearing aid use with health care outcomes such as 30-day readmission, length of stay, and hospitalization in older adults.²⁹⁵ Additionally, NIA is supporting studies aimed at investigating brain changes in older adults that may underlie relationships between hearing loss and cognitive function.

²⁹² www.nidcd.nih.gov/about/strategic-plans

²⁹³ reporter.nih.gov/project-details/10236266

²⁹⁴ reporter.nih.gov/project-details/10400224

²⁹⁵ reporter.nih.gov/project-details/10318657

Interstitial Cystitis

House Language

The Committee notes the progress of interstitial cystitis research through the Multidisciplinary Approach to the Study of Chronic Pelvic Pain program and encourages NIDDK and stakeholders to continue collaboration on a scientific workshop to examine mechanisms for scientific opportunity. The Committee requests an update on the progress of the conference in the fiscal year 2024 Congressional Justification.

Action Taken or to be taken:

Interstitial cystitis, also called interstitial cystitis/bladder pain syndrome (IC/BPS), affects millions of Americans. The research efforts of the National Institute of Diabetes and Digestive Kidney Disease (NIDDK) on IC/BPS are focused on: understanding the cause(s) of this condition, improving diagnosis, finding ways to prevent onset, and finding more effective treatments for the pelvic pain and urinary frequency and urgency that affect people with this condition. The innovative, multi-site Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, supported by NIDDK and the National Institutes of Health (NIH) Office of Research on Women's Health (ORWH), has spearheaded the evolution in our understanding of urologic chronic pelvic pain syndrome (UCPPS), a research term that includes IC/BPS and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). The MAPP Research Network has completed its data collection, and study investigators are working collaboratively on data analysis and publication of results.

On October 17-18, 2022, NIDDK hosted a workshop on “Research Advances for Urologic Chronic Pelvic Pain Syndrome: Informing the Next Generation of Clinical Studies.”²⁹⁶ The workshop highlighted key findings from MAPP Network studies, including the use of brain imaging to gain a more detailed look into the physical characteristics of UCPPS, and the development of a new approach to assess pain severity in UCPPS patients. The workshop also featured presentations of other critical findings from the UCPPS field and lessons learned that could inform future UCPPS clinical studies. Participants also discussed important considerations for potential future clinical trials including strategies for targeted interventions and improved measurements of patient outcomes. During a patient forum, individuals with IC/BPS discussed their personal health journeys and provided input on ways to improve future clinical studies/trials. Discussions and findings from this workshop may help inform future UCPPS research opportunities.

²⁹⁶ www.nidDK.nih.gov/news/meetings-workshops/2022/research-advances-urologic-chronic-pelvic-pain-syndrome

Marijuana Research

House Language

The Committee supports the development of an objective standard to measure marijuana impairment to ensure highway safety. Essential to that development are high-quality scientific studies using marijuana and products containing marijuana lawfully available to patients or consumers in a State on a retail basis. The Committee notes that a majority of Federal research on marijuana has been limited to a single strain of marijuana that is not fully representative. The Committee emphasizes the need for research that encompasses the diversity, quality, and potency of products commonly available to patients or consumers in a State on a retail basis. The Committee requests an update on efforts to expand researcher access to different marijuana strains in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

Providing researchers with more diverse cannabis products would advance our knowledge of the health effects of cannabis, particularly if such products could reflect the potency and diversity of those available on the market. Until recently, National Institute on Drug Abuse (NIDA)²⁹⁷ Drug Supply Program (DSP) was the only source of cannabis for research authorized by the Drug Enforcement Administration (DEA). Through a contract with the University of Mississippi, the DSP provides cannabis plant material and products to National Institutes of Health (NIH)-supported and to non-NIH funded researchers free of charge. NIDA's DSP carries multiple strains, or cultivars, of cannabis plant material in a range of potencies and ratios of tetrahydrocannabinol (THC) to cannabidiol.²⁹⁸ In 2021, the DEA began to authorize additional cannabis growers to supply cannabis for research purposes.²⁹⁹ In addition, NIDA recompeted a contract that supports the production of consistent, high-quality cannabis material for research.³⁰⁰ Any DEA-approved grower will be permitted to bid on the DSP contract and multiple contracts could be awarded to meritorious applicants. As such, the DSP may be able to provide a wider range of products in the future. In December 2022, the Medical Marijuana and Cannabidiol Research Expansion Act (P.L. 117-215) was signed into law. Among other things, this law directs DEA to register entities to manufacture cannabis for medical research and to assess whether there is an adequate and uninterrupted supply of cannabis for research purposes. It is possible that this legislation could impact the diversity of research-grade cannabis products.

While increasing the diversity and potency of products available exclusively for research may be useful, it will not fully inform our understanding of the effects of cannabis available on the market. The DSP can provide cannabis plant material and extracts but is unable to provide researchers with representative examples of whole classes of widely used contemporary products, such as vape pens, edibles, or emerging products such as cannabis beverages that may affect the brain and body in different ways. Without the ability to procure and test commercially

²⁹⁷ In NIDA's FY 2024 CJ, the institute proposes that its name be changed to the "National Institute on Drugs and Addiction" as part of a broader move toward less stigmatizing language when describing drug use, dependence, and addiction. NIDA's new name is included in the FY 2024 President's Budget and NIDA will implement the name change when that budget is passed into law.

²⁹⁸ nida.nih.gov/research/research-data-measures-resources/nida-drug-supply-program-dsp/nida-drug-supply-program-dsp-ordering-guidelines/marijuana-plant-material-available

²⁹⁹ www.deadiversion.usdoj.gov/drugreg/marihuana.htm

³⁰⁰ sam.gov/opp/42462662ace24fb9b988b8bff64a6d64/view

available products, it is not possible to develop research-grade materials that match marketed proprietary product profiles, many of which vary by jurisdiction. Furthermore, when monitoring programs provide alerts about the emergence of a potential contaminant in products, only real-world sampling can identify the cause of such concerns. With public health and safety at stake, it is essential to enable research on cannabis dispensary products to determine and differentiate characteristics responsible for adverse and potentially therapeutic effects.

While NIDA supports a broad portfolio of research to better understand cannabis-induced cognitive, emotional, and motor impairments and how they affect a range of functions including driving performance, evaluating the effects of cannabis on individual performance is especially challenging. Cannabis produces its effects differentially for different people, and the amount required to produce impairment is highly dependent on the route of administration and a person's experience with the drug. Moreover, blood and plasma levels of delta-9 THC – the main compound that produces cannabis' euphoric effects – do not directly track with observable impairment and detectable levels can be found in certain biosamples long after acute effects have disappeared. To address the need for objective measures of cannabis-induced impairment, NIDA is working with companies to develop and test detection methods using breath, saliva, and digital technology through Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) awards under the statutory authority of Sec. 301 of the Public Health Services Act.

NIDA acknowledges the need to better understand the effects of cannabis products available on the market today, particularly given their increased availability, diversity, and potency. Because research is hindered by federal regulations that prohibit researchers from procuring or testing such products, NIDA is supporting innovative studies that enable researchers to conduct assessments immediately before and after participants consume their own cannabis in their homes. However, these studies must rely on participant self-reports and unverified dispensary labels for product information. As regulations around product labels vary across jurisdictions, it is difficult to confirm causal relationships between product characteristics and health effects. To meet this challenge, NIDA recently released a funding opportunity for a medicinal cannabis registry that would capture information on routes of administration, frequency and amount used, and health data from diverse sources including health records, prescribing providers, and participants.³⁰¹ To facilitate comparisons with other studies, the registry will measure and report THC based on the 5mg standard unit, as is now required for all NIDA-supported cannabis research.³⁰² If this study is successful, it will provide abundant information about outcomes from medicinal cannabis use, but a gap will remain in our understanding of cannabis procured from diverse sources or used for non-medicinal purposes.

³⁰¹ grants.nih.gov/grants/guide/rfa-files/RFA-DA-23-011.html

³⁰² nida.nih.gov/about-nida/noras-blog/2021/05/establishing-5mg-thc-standard-unit-research

Melanoma

House Language

As UV radiation is established as the primary carcinogen for melanoma, the Committee urges NCI to continue to support research directed at genomic and mechanistic characteristics of mutagenesis; optimization of prevention strategies; and early detection and risk declassification strategies that leverage artificial intelligence, access to large databases, noninvasive technologies, and molecular markers that will support precision medicine. Although SEER data show a decline in mortality with the advent of new categories of treatment, some patients do not respond to initial treatment, and many of the responders have disease that will recur. The Committee encourages NCI to expand research on mechanisms of primary and secondary drug resistance and validation of predictive biomarkers that allow selection of optimal therapy and prediction of comprehensive longitudinal monitoring. Basic and translational goals should be facilitated through development and use of ever-improving models of human melanoma. Building on the success of adjuvant therapies, and the promising results of neoadjuvant therapies, the Committee encourages NCI to continue support of research addressing tumor cell dormancy and metastases. 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 support research on novel targets, especially for rare subtypes. The Committee requests an update on these requests and the status of NCI- funded melanoma research in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

The National Cancer Institute (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.³⁰³ NCI is funding a collaboration of 12 institutions³⁰⁴ investigating the correlation between melanoma biology and survival identified the mutational landscape in early-stage melanoma. This includes the identification of four driver mutation sub-types through the InterMEL study,³⁰⁵ along with DNA modifications that contribute to a mechanism of melanoma metastasis³⁰⁶ and worse survival rates for patients with invasive primary melanoma.³⁰⁷ Additional work by this group in collaboration with investigators from an NCI-supported melanoma Specialized Program of Research Excellence (SPORE) project includes development of a discovery platform including reproducible models to identify mediators of melanoma metastasis.³⁰⁸

Only a few genes correlated with melanoma susceptibility have been identified. NCI is supporting a familial melanoma study in collaboration with the international Melanoma Genetics

³⁰³ reporter.nih.gov/search/UYSuBb8Ah02EH6AyUR0dJg/project-details/10486570

³⁰⁴ reporter.nih.gov/project-details/10188447

³⁰⁵ pubmed.ncbi.nlm.nih.gov/35876628/

³⁰⁶ www.ncbi.nlm.nih.gov/pmc/articles/PMC8856617/

³⁰⁷ www.ncbi.nlm.nih.gov/pmc/articles/PMC9135958/

³⁰⁸ pubmed.ncbi.nlm.nih.gov/35343960/

Consortium to find new candidate melanoma susceptibility genes in families.³⁰⁹ The trial is currently recruiting, and through analysis of those already enrolled, researchers have found that there is a benefit to screening in high-risk melanoma families.³¹⁰

While immunotherapy has shown great promise for cancer treatment, it is still unknown why some patients respond better than others. An NCI-sponsored clinical trial, DREAMseq, that included patients with metastatic melanoma with a specific mutation in a cancer-causing gene (*BRAF* V600) found that a combination of immunotherapies (immune checkpoint inhibitors) was more effective than a combination of targeted therapies for patient survival.³¹¹ Both options had been used for treatment of advanced melanoma, but the immunotherapy combination was found to be so effective for patients with this specific mutation that the trial was stopped early.³¹² Additionally, intramural NCI researchers led a study that found that a high-fiber diet could help patients with advanced melanoma treated with immune checkpoint inhibitors and taking probiotics could decrease effectiveness of the immunotherapy, indicating the importance of the gut microbiome in treatment response.³¹³

Cancer drug resistance remains one of the biggest challenges facing cancer therapy, as cancers have different mechanisms for evading targeted drugs. An NCI-funded study recently found that high levels of the androgen receptor, which binds hormones including testosterone, may lead to treatment resistance in patients with melanoma treated with inhibitors of BRAF and MEK, a protein kinase part of a signaling cascade that drives cell growth and survival that is often mutated in cancer, which are common therapy targets in melanoma and other cancers.³¹⁴ Androgen receptor levels especially jumped in male patients during treatment with the inhibitors and women in the study had significantly higher levels of tumor shrinkage and time before relapse compared to the men. This indicates a sex difference response to this treatment, and while more research needs to be done to understand the mechanism leading to these differences, this study has potential implications for updated treatment strategies to improve outcomes, such as adding androgen blockers to treatment and cautions around testosterone supplement use in patients undergoing treatment.³¹⁵

The amyloid beta protein is known to be linked to Alzheimer's disease development, but NCI-funded researchers recently discovered that melanoma cells that spread to the brain produce their own amyloid beta necessary for their survival.³¹⁶ While brain metastasis from melanoma is common, there are currently no treatment options to prevent or treat this complication. However, this study suggests a potential new treatment option using drugs developed for Alzheimer's that target amyloid beta, which could be useful for preventing and/or controlling metastasis in melanoma and other cancers.³¹⁷ Additionally, one of the Skin Specialized Programs of Research Excellence (SPoREs) groups is conducting research on metastatic

³⁰⁹ dceg.cancer.gov/research/who-we-study/families/familial-melanoma-study

³¹⁰ clinicaltrials.gov/ct2/show/NCT00040352

³¹¹ clinicaltrials.gov/ct2/show/NCT02224781

³¹² www.cancer.gov/news-events/cancer-currents-blog/2021/advanced-melanoma-braf-immunotherapy-first

³¹³ www.cancer.gov/news-events/press-releases/2021/high-fiber-diet-melanoma-immunotherapy

³¹⁴ www.nature.com/articles/s41586-022-04833-8#author-information

³¹⁵ www.cancer.gov/news-events/cancer-currents-blog/2022/melanoma-treatment-androgen-receptor

³¹⁶ pubmed.ncbi.nlm.nih.gov/35262173/

³¹⁷ www.cancer.gov/news-events/cancer-currents-blog/2022/melanoma-brain-metastases-amyloid-beta

melanoma. They found that the tumor microenvironment of melanoma-derived brain metastases has an impact on response to treatment with immune checkpoint inhibitors and identified unique features of the microenvironment that could be potential future therapeutic targets to improve patient outcomes.³¹⁸ NCI is also collaborating on a clinical trial investigating the effect of multiple immunotherapies on brain metastasis of BRAF-V600 mutant melanoma patients.³¹⁹

Adjuvant therapies are given after surgery to decrease the risk of disease recurrence, but often have serious side effects. One large multicenter NCI-sponsored clinical trial for advanced stage high-risk melanoma is exploring whether immunotherapy given after surgery could be more effective if also given pre-operatively (neoadjuvant),³²⁰ with early results showing a substantially lower risk of cancer return in patients who received the neoadjuvant therapy.³²¹ Another similar trial is comparing the two-year survival rate in advanced melanoma patients with a specific mutation (*BRAF* V600) using different treatment orders.³²² NCI is also interested in studying treatment reduction times to limit toxicity to patients. One such trial is determining if biomarkers seen on imaging tests and tumor biopsies can predict the effectiveness of a shorter dose of the standard therapy option in patients with advanced (stage III-IV) melanoma that cannot be removed by surgery.³²³

NCI is committed to supporting research on rare subtypes of melanoma. One such rare and highly aggressive subtype is Merkel cell carcinoma (MCC), which may be caused by the precursor Merkel cell polyomavirus (MCPyV). A recent NCI-funded study retrospectively analyzed advanced MCC patient response and progression-free survival after monoclonal antibody treatment and found that the treatment elicited a high response rate and prolonged survival in patients.³²⁴ This study gave real-world validation to previous clinical trials plus new evidence for effectiveness in patients with more advanced disease. Multiple NCI-funded studies are examining different aspects of MCC, including developing a mouse model³²⁵ and studying cancer-specific immune cell effects.³²⁶ Additionally, a clinical trial is underway that looks at the impact of immunotherapy on treating desmoplastic melanoma, a rare subtype that is difficult to diagnose and is usually found on areas of high sun exposure in older individuals.³²⁷ Another rare, but deadly, melanoma subtype is acral lentiginous melanoma (ALM) and it is disproportionately found in people with darker skin, including Black, Hispanic, and Asian populations. An NCI SPORE group prospectively analyzed multi-center data on ALM patients to better understand clinical features that can indicate the prognosis for survival and recurrence to help improve care and patient outcomes. Researchers found poor prognosis even in early

³¹⁸ aacrjournals.org/cancerimmunolres/article/10/8/996/707174/Microenvironmental-Landscape-of-Human-Melanoma

³¹⁹ clinicaltrials.gov/ct2/show/NCT04511013

³²⁰ clinicaltrials.gov/ct2/show/NCT03698019

³²¹ oncologypro.esmo.org/meeting-resources/esmo-congress/neoadjuvant-versus-adjuvant-pembrolizumab-for-resected-stage-iii-iv-melanoma-swog-s1801

³²² clinicaltrials.gov/ct2/show/NCT02224781

³²³ clinicaltrials.gov/ct2/show/NCT04462406

³²⁴ www.ncbi.nlm.nih.gov/pmc/articles/PMC9394192/

³²⁵ reporter.nih.gov/search/gcGlhWHO1kysdjOCnxmUlw/project-details/10330465

³²⁶ reporter.nih.gov/search/gcGlhWHO1kysdjOCnxmUlw/project-details/10432068

³²⁷ clinicaltrials.gov/ct2/show/NCT02775851

disease stages, with survival rates especially low in stage II patients, highlighting a special need for adjuvant therapies for this group.³²⁸

³²⁸ www.ncbi.nlm.nih.gov/pmc/articles/PMC8581784/

Metastatic Breast Cancer

Conference Language

The Committee is aware that clinical research is of utmost importance to those living with MBC, which is breast cancer that has spread to other organs and become incurable. An estimated 168,000 Americans live with MBC, and nearly all of the more than 43,000 deaths from breast cancer are attributed to this late stage of disease. Given the mortality associated with MBC and the lack of treatment options, research offers the best possibility of therapeutic advances and extended life for these patients. MBC is also associated with startling health disparities, since breast cancer mortality is about 40 percent higher for Black women in the U.S. than Caucasian women and breast cancer is the second most common cause of death by cancer for Black women. The Committee encourages a continued emphasis by NCI on research for MBC, especially in communities of color, to discover better treatments and a cure for MBC and to address health disparities in this population. The Committee requests an update on NCI's activities regarding MBC in the fiscal year 2024 CJ, including progress made with respect to inclusion of people of color in NCI-funded clinical trials in this area.

Action taken or to be taken

Basic research to understand the biology of and mechanisms that drive the spread of cancer lead to future advances in treatment for metastatic cancer patients. To stimulate greater understanding and discovery, the National Cancer Institute (NCI) launched the Metastasis Research Network (MetNet) in 2021.³²⁹ The network consists of five collaborative research centers using systems-level approaches to study multiple aspects of the metastatic process including response to therapy. One of the research centers focuses exclusively on breast cancer,³³⁰ while others are investigating aspects of metastasis in common for a number of cancer types including breast cancer. There is also a center focused exclusively on brain metastasis, which is a devastating consequence for some breast cancer patients. To augment the work conducted by the MetNet research centers, NCI released a funding opportunity announcement in 2022 for individual research projects focused on areas of metastasis that were underrepresented by the five centers.³³¹ These include research on tumor dormancy and understudied metastatic sites such as metastases to the bone. The overall goal of the MetNet is to advance our understanding of metastasis as a whole body, systems-level problem to develop a comprehensive understanding of all the processes involved.

NCI's Specialized Programs of Research Excellence (SPORes) also fund breast cancer-focused translational research centers. Currently, NCI supports six breast cancer SPORes and three health disparities SPORes planning projects that include breast cancer research. The latter projects are specifically focused on differences between women of African and European ancestry involving areas of immune response and microbiome composition.

Additionally, in 2021, the NCI Office of Cancer Survivorship held a virtual meeting to discuss gaps in knowledge and areas of unmet needs for individuals living with metastatic and advanced cancers. The meeting brought together experts in research and clinical care, as well as cancer

³²⁹ www.cancer.gov/about-nci/organization/dcb/research-programs/metnet

³³⁰ reporter.nih.gov/search/yoc2JaX_LU23-SGX943zLA/project-details/10272387

³³¹ grants.nih.gov/grants/guide/pa-files/PAR-22-234.html

survivors and advocates to explore areas of high priority in metastatic and advanced cancer survivorship research. Several opportunities for key areas of research were put forth including to investigate and address disparities among those living with advanced or metastatic cancer by including understudied, underserved, and vulnerable populations in studies and by collecting detailed and comprehensive data on social determinants of health.³³²

NCI supports many clinical trials for patients with metastatic breast cancer. A majority of these trials test combinations of therapies including the addition of novel targeted and immunotherapies with traditional therapies to improve survival. Recently published results³³³ from an ongoing trial³³⁴ indicate that an experimental form of immunotherapy that uses an individual's own tumor-fighting immune cells could potentially be used to treat people with metastatic breast cancer. Patients with hormone receptor-positive tumors, which make up most breast cancers, were able to mount an immune response and saw tumor shrinkage. While more studies need to be done with this treatment approach, the results so far offer a potential new treatment for metastatic breast cancer patients whose tumors do not respond to most available immunotherapies.

NCI remains committed to increasing underserved populations participation 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. On November 16, 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.

³³² pubmed.ncbi.nlm.nih.gov/34878107/

³³³ ascopubs.org/doi/full/10.1200/JCO.21.02170

³³⁴ www.clinicaltrials.gov/ct2/show/NCT01174121

Native Hawaiian Pacific Islander Health Research

House Language

The Committee encourages NIH to place a high priority on addressing Native Hawaiian and Pacific Islander (NHPI) health disparities as well as supporting the career pathways and research of NHPI investigators. NIMHD, working with other Institutes and Centers, is encouraged to develop partnerships with academic institutions with a proven track record of working closely with NHPI communities and NHPI-serving organizations and located in States with significant NHPI populations to support the development of future researchers from these same communities. The Committee directs NIMHD to provide an update in the fiscal year 2023 Congressional Justification on NIH research to advance NHPI health and faculty researcher development.

Action taken or to be taken

The National Institutes of Health (NIH) is continuously evaluating opportunities to increase health equity for Native Hawaiian and Pacific Islander (NHPI) communities. NHPI populations are one of the NIH-designated populations with health disparities as defined by the National Institute on Minority Health and Health Disparities (NIMHD), which leads these efforts through research, training, capacity building, outreach, and dissemination of evidence-based health information and resources. Last year, NIMHD coordinated efforts on developing the NIH Minority Health and Health Disparities Strategic Plan (2021-2025) that guides research priorities, research-sustaining activities, and outreach and dissemination on racial and ethnic disparities in health. This plan serves as a guide for NIMHD and NIH to foster collaborations and partnerships around the research and training needs of specific populations such as those from the NHPI communities. Through coordinated efforts among several NIH Institutes, Centers, and Offices (ICOs), highlighted below are some examples of NIMHD-specific and NIH community-based, multidisciplinary research projects that aim to understand and improve the health challenges and reduce inequities faced by NHPI populations.

Ola HAWAII, an NIMHD-funded Research Center in Minority Institutions Specialized Center at the University of Hawaii, is advancing minority health and health disparities research by fostering 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.³³⁵ Ola means “health” and “to heal” in Hawaiian and HAWAII designates both the state and acronym, “Health And Wellness Achieved by Impacting Inequalities.” A research project supported by Ola HAWAII has been exploring community-driven approaches to mitigate COVID-19 disparities in Hawaii’s vulnerable populations.³³⁶ Recent research outputs such as evaluating the impacts of the COVID-19 pandemic on Hawaii’s nursing workforce and vaccine updates provide novel insights to support customized interventions specific to this community.³³⁷

³³⁵ reporter.nih.gov/project-details/10556969

³³⁶ reporter.nih.gov/project-details/10233714

³³⁷ www.ncbi.nlm.nih.gov/pmc/articles/PMC9077570/; www.ncbi.nlm.nih.gov/pmc/articles/PMC9229995/

NIMHD is prioritizing population health research and building research capacity on health conditions that are impacting Pacific Islanders.³³⁸ A recently funded project from that initiative will establish a Micronesian Data Laboratory at the University of Guam to conduct the first Guam National Health Interview Survey to collect disease prevalence.³³⁹ Data collected will be essential to inform policies and programs that support population health for people living in that territory. In a separate project, researchers funded by the National Institute of General Medical Sciences and NIMHD are evaluating the effectiveness, scalability, and sustainability of culturally adapted, family-focused diabetes self-management education and support networks for reducing rates of diabetes.³⁴⁰ The Marshallese subpopulation of Pacific Islanders has some of the highest documented rates of type-2 diabetes in the world. The results of this intervention can potentially improve the diabetes health crisis faced by Marshallese immigrants and other Pacific Islander communities living in the United States. Pacific Islanders also experience disproportionate risks for mental health and substance use disorders, low mental health literacy, stigma, and barriers to accessing care exacerbate their health and well-being. Incorporating Pacific Islander partnerships and evidence-based best practices from mental health, substance use, stigma, and health communication literature, NIMHD-supported researchers are designing and testing culturally adapted interventions to promote treatment-seeking among Pacific Islanders.³⁴¹ An NIH project is also developing a tailored pilot intervention program to reduce opioid use disorders among Pacific Islanders.³⁴²

The NIH-funded Center for Biomedical Research Excellence at the University of Hawaii is leveraging a culturally diverse, multidisciplinary research team to explore basic science mechanisms underlying diabetes among the people of Hawaii and the Pacific region.³⁴³ By applying new technological resources such as *in vivo* (within the body) imaging systems to analyze clinical blood samples, research findings focused on diabetes and chronic kidney deficiencies among this population are providing foundational evidence to help reduce disparities in diabetes diagnosis, prevention, and treatment. Another NIH project is building on a partnership with the United States Department of Agriculture to guide interventions for hypertension and cardiovascular diseases among six NH communities.³⁴⁴ Researchers are working with NH community leaders to improve the understanding of complex interactions between individual, household, and community factors and cardiovascular health prevention. A thorough assessment and increased understanding of health factors are critical to support evidence-based, culturally relevant interventions that can improve cardiovascular health among Native Hawaiians. A separate NIH project is addressing disparities associated with Alzheimer's disease and related dementias among NHPI and other populations through the engagement of trusted partners such as community organizations, health clinics, and researchers who are members of these communities.³⁴⁵

³³⁸ grants.nih.gov/grants/guide/pa-files/par-20-048.html

³³⁹ reporter.nih.gov/project-details/10452324

³⁴⁰ reporter.nih.gov/project-details/9711305

³⁴¹ reporter.nih.gov/project-details/10197755

³⁴² reporter.nih.gov/project-details/10213686

³⁴³ reporter.nih.gov/project-details/10387025

³⁴⁴ reporter.nih.gov/project-details/10375444

³⁴⁵ reporter.nih.gov/project-details/10172079

NIH projects are also promoting strategic collaborations to enhance research infrastructure that will improve the health and well-being of NHPI communities. The Center for Pacific Innovations, Knowledge, and Opportunities at the University of Hawaii establishes a statewide network of stakeholders, including practice-based and community-based organizations and health care providers, and converts basic research discoveries into real-world solutions to reduce health disparities among Native Hawaiians, Pacific Islanders, and Filipinos.³⁴⁶ This Center also promotes research training for early career investigators, particularly integrating those from Native Hawaiian, Pacific Islander, and Filipino backgrounds. A recent study supported by the Center found a potentially cost-effective, culturally appropriate intervention to reduce blood pressure among Native Hawaiians, thereby providing an effective and less expensive option for patients with this condition.³⁴⁷

As NIH-designated populations with health disparities, the NHPI communities remain a priority for NIMHD along with other NIH ICOs. NIH will continue to support, improve, and enhance NHPI health through research, training, and partnerships.

³⁴⁶ reporter.nih.gov/search/q0DsGzLQDEyfH63HYVb7bQ/project-details/10474426

³⁴⁷ ncbi.nlm.nih.gov/pmc/articles/PMC8807791/

Obstetric Fistula Research

House Language

Worldwide, an estimated 500,000 women and girls live with obstetric fistula, with thousands more occurring annually. It occurs disproportionately among impoverished, vulnerable, and marginalized girls and women. Skilled health personnel at birth and emergency obstetric and newborn care can ensure obstetric fistula is prevented. The Committee is concerned that fistula repairs were widely halted due to COVID-19, as they were deemed non-urgent and unsafe during the pandemic. This may result in an increased backlog of fistula cases. The Committee is concerned that not enough funding is provided to support existing academic curricula for the education and training for health care providers on obstetric fistula. The Committee requests a report regarding the annual support level for this training funding over the past five years, including the types of grants supported, in the fiscal year 2024 Congressional Justification

Action taken or to be taken

Impacting women worldwide, obstetric fistula is a traumatic maternal morbidity resulting in severe urinary incontinence that reduces quality of life and increases stigma. Women with obstetric fistulas have uncontrollable leakage of urine and/or feces (among other physical symptoms), are heavily stigmatized, and experience high psychiatric morbidity.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is supporting research into a number of gynecological conditions, including obstetric fistula over the last decade, to develop more treatment methods and provide clinical and counseling interventions. Many women with obstetric fistula face substantial multi-level barriers to surgical repair. NICHD-funded researchers are studying a non-surgical option for therapeutic management of fistula-related urinary incontinence. They will study the effectiveness of an insertable vaginal cup to manage fistula urinary incontinence, examine user and implementer acceptability, and quantify fistula management cost. The research findings will further women's options for management of fistula-related urinary incontinence and will inform changes to clinical practice for fistula management in low- and middle-income countries. By expanding management options for women with obstetric fistula, it is likely to reduce stigma, improve economic opportunity, and have a transformative effect on quality of life.

Building upon previously funded research in this area, NICHD-funded researchers will study the complications following obstetric fistula repair, such as fistula recurrence, incontinence, and pregnancy complications to improve the physical and psychosocial quality of life for women affected by fistula. In a 2021 NICHD-funded study, researchers will identify predictors of post-repair fistula breakdown and recurrence, identify predictors and characteristics of post-repair incontinence, and engage key stakeholders to develop intervention strategies that will be feasible and acceptable within the community. This research will hope to inform counseling and clinical care models for optimizing post-repair outcomes for women following fistula repair. In another 2021 NICHD-funded study, researchers will investigate whether adverse pregnancy rates are elevated among women affected by genital fistula following surgical repair. They will seek to estimate the incidence of stillbirth, spontaneous abortion, and preterm birth in post-repair pregnancies, and understand the individual, interpersonal and systems-based contributors to adverse outcomes. This study will identify relevant targets for clinical and counseling

interventions to improve women's health and quality of life following fistula repair. NICHD will continue to support this important research.

Office of Behavioral and Social Sciences Research (OBSSR)

House Language

The Committee includes no less than the fiscal year 2022 enacted level for OBSSR. The Committee commends OBSSR for effectively coordinating and supporting essential basic, clinical, and translational research in the behavioral, social, and population sciences to advance the NIH mission and recognizes the critical role of OBSSR to integrate these sciences throughout the NIH research enterprise via OBSSR's leadership and coordination. The Committee urges NIH to provide an update on OBSSR's activities and progress in the fiscal year 2024 Congressional Justification. The Committee notes that multiple Surgeon General and NASEM reports have concluded that most diseases and health problems facing the Nation have significant behavioral components. Meanwhile, behavioral science issues surrounding the current pandemic, including vaccine hesitancy and health misinformation, have made clear that it is important to better understand healthy behavior and how to improve health communications. The Committee notes the OBSSR's mission to enhance NIH's behavioral sciences research enterprise across all Institutes and Centers, but that its direct authorities to meet its mission are limited. The Committee is pleased that an NIH working group was established to review how better to integrate and realize the benefits of overall health from behavioral research at NIH, and encourages NIH to consider appropriate OBSSR funding levels, resources, and organizational structure to support full implementation of the working group recommendations.

Action taken or to be taken

In May 2021 a working group of the National Institutes of Health (NIH) Council of Councils was created to examine behavioral and social sciences research (BSSR) integration. The working group approached this inquiry from two perspectives: assessing both the portfolio of behavioral and social science research across NIH and assessing practices and processes within NIH's Institutes and Centers (ICs). The working group examined BSSR integration in research funding, initiatives, staff expertise, review practices, Advisory Council representation, public communications, and strategic planning and policy implementation. Integration in these categories varied widely across the ICs. Some ICs had a high degree of integration, but several had nominal BSSR integration in some or all metrics examined. Even within ICs that overall had significant BSSR integration, the level of integration varied across metrics, suggesting room for improvement. The BSSR Integration Working Group's recommendations³⁴⁸ that were accepted by the Council of Councils are as follows:

Greater inclusion and integration in IC and NIH-wide Strategic Plans

- NIH leadership should support and encourage the ICs and NIH-wide groups to work with the OBSSR and/or BSSR staff within their ICs when they develop their next strategic plans to help identify important BSSR goals that are relevant to each IC mission.

Evaluate and monitor the distribution of BSSR staff across NIH

- BSSR cannot be well integrated and maximally contribute to the broader NIH research mission unless there is consistent representation of BSSR expertise.

³⁴⁸ dpcpsi.nih.gov/council/working-groups/nih-behavioral-and-social-sciences-research-bssr-integration-working-group

Bring IC Advisory Council BSSR representation into alignment with the policy

- A lack of high-level advisory representation will hamper an IC's ability to develop, consider, and advance BSSR-relevant initiatives and grant funding.

Ongoing monitoring to ensure review panels adequately reflect BSSR knowledge and expertise

- For BSSR to be well integrated into the broader biomedical research enterprise, NIH needs to ensure there is adequate BSSR expertise on study sections whose primary focus might not be BSSR but where BSSR factors, outcomes, and methods are included or should be included.

ICs with nominal BSSR portfolios should work with the OBSSR to identify opportunities to increase the application of BSSR in their research and training initiatives

- More BSSR should be encouraged for the ICs with nominal levels of funding.

Increase centers, resource grants, and trial networks that include BSSR capacity and focus

- Without dedicated resources and support, BSSR is at a relative disadvantage.

Increase resources allocated to the OBSSR for staff and initiatives

- OBSSR has had good success addressing crosscutting scientific, training, and methodology gaps.
- Increased resources would build on their success and accelerate the pace of integration.
- OBSSR could lead or facilitate the development of high priority and cross-cutting initiatives and resource initiatives.

Engage BSSR expertise throughout the development and implementation of new research policies and practices

- Involve BSSR experts and consider BSSR methods, measures, and practices as a part of research policy development and implementation.

These working group findings and recommendations were presented at the May 2022 NIH Council of Councils meeting. Council members were supportive of the report and its recommendations, adding they would like to see measurement of progress within the recommendations over time and communication to the research community and lay public about the role of BSSR to benefit human health. In June 2022, the recommendations and the report were delivered to and approved by Lawrence A. Tabak, D.D.S., Ph.D., performing the duties of the NIH Director, and activities to implement the recommendations of the report are underway.

Osteopathic Medical Schools

House Language

The Committee recognizes that increased access to research funding for the osteopathic profession will bolster NIH's capacity to support recovery from the COVID-19 pandemic, address health disparities in rural and medically-underserved populations, and advance research in primary care, prevention, and treatment. The Committee requests an update on the current status of NIH funding to colleges of osteopathic medicine and representation of doctors of osteopathic medicine on NIH National Advisory Councils and standing study sections in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

The National Institutes of Health (NIH) is dedicated to strengthening and diversifying the biomedical research workforce, including for physician scientists. As part of this effort, NIH continues to address recommendations described in a 2014 report focused on the physician-scientist workforce from the NIH Advisory Committee to the Director (ACD).³⁴⁹ As the report notes and NIH agrees with, "findings which lead to advances in practice are driven largely by the work of investigators with a variety of degrees, of whom those with clinical training contribute essential knowledge and skills." Physician-scientists represent vital investment in research discovery and innovation. These researchers help transform clinical observations into hypotheses and research findings into medical advances.

Strengthening the future workforce includes fostering opportunities for physician-scientists with osteopathic medical degrees. Physicians with a Doctor of Osteopathic Medicine (D.O.) degree represent an important component of the medical community. They are at the intersection of the complementary, integrative health, and allopathic medical communities and have historically been connected to the National Center for Complementary and Integrative Health (NCCIH), one of NIH's Institutes and Centers (ICs) through the practice of osteopathic manipulation. Osteopathic manipulation is a full-body system of hands-on techniques to alleviate pain, restore function, and promote health and wellbeing. This promising intervention is of interest to NCCIH, and the Center makes every effort to ensure that D.O.s have representation on its advisory council. NCCIH currently has two members with a D.O. degree on its 18-member council.³⁵⁰

The following three tables show data of interest for fiscal years (FYs) 2020 and 2021.

Table 1 shows the representation of D.O.s and researchers with other degrees who are employed at osteopathic medical schools serving on an NIH National Advisory Council (NAC),³⁵¹

³⁴⁹ acd.od.nih.gov/documents/reports/PSW_Report_ACD_06042014.pdf

³⁵⁰ www.nccih.nih.gov/about/naccih-member-roster

³⁵¹ NACs: perform the second level of peer review of grant and cooperative agreement applications; provide advice and recommendations on matters of significance to the policies, missions, and goals of the IC they advise; provide oversight of research conducted by each IC's intramural program; and serve as a forum whereby interested members of the public, in open session, may hear and comment on issues relevant to the overall mission of the IC.

Initial/Integrated Review Group (IRG), or Special Emphasis Panel (SEP).³⁵² Please note the following:

- Members are recorded as described in the United States General Services Administration Federal Advisory Committee Act (FACA) database.³⁵³
- Members could serve on more than one committee per year.
- Degree information is based on what the reviewer entered when they joined the committee.
- The FY is determined by the date the committee met, not the FY of the applications being reviewed.

Fiscal Year	D.O. Degree			Other Degree		
	IRG	NAC	SEP	IRG	NAC	SEP
2020	10	2	13	18	0	33
2021	7	2	12	18	0	28

Table 1

Table 2 lists the total funding and number of awards (both competing and non-competing) NIH made to osteopathic medical schools in FYs 2020 and 2021.

Fiscal Year	# Awards	Funding
2020	71	42,618,974
2021	58	35,426,785

Table 2

Table 3 shows the success rate for competing research project grant³⁵⁴ applications submitted by investigators in osteopathic medical schools during FYs 2020 and 2021. The success rate is an application-based metric that is calculated by dividing the number of awards made in a FY by the number of applications.³⁵⁵

Fiscal Year	Applications	Awards	Success Rate
2020	119	20	16.8
2021	70	18	25.7

Table 3

³⁵² IRGs and SEPs provide scientific and technical merit review, which is the first level of peer review of research grant applications and contract proposals. IRG members are appointed for multi-year terms of service. At any given meeting, usually, there are also a number of temporary members present to provide the expertise needed. SEP Membership is fluid, with individuals designated to serve for individual meetings rather than for fixed terms of service.

³⁵³ www.facadatabase.gov/FACA/apex/FACAPublicGovtwideReports

³⁵⁴ [grants.nih.gov/grants/glossary.htm#ResearchProjectGrant\(RPG\)](http://grants.nih.gov/grants/glossary.htm#ResearchProjectGrant(RPG))

³⁵⁵ nexus.od.nih.gov/all/2022/03/07/fy-2021-by-the-numbers-extramural-grant-investments-in-research/

NCCIH and other NIH ICs have specific opportunities for clinician-scientists, which includes D.O.s, who conduct research across a wide range of complementary and integrative health approaches. Examples of such programs include, but are not limited to:

- Mentored Clinical Scientist Research Career Development Awards.³⁵⁶
- Clinical Scientist Institutional Career Development program.³⁵⁷
- Academic Research Enhancement Award program.³⁵⁸
- Mentored Patient-Oriented Research Career Development Award³⁵⁹
- Loan Repayment Program³⁶⁰

³⁵⁶ researchtraining.nih.gov/programs/career-development/K08

³⁵⁷ researchtraining.nih.gov/programs/career-development/k12

³⁵⁸ grants.nih.gov/grants/funding/r15.htm

³⁵⁹ researchtraining.nih.gov/programs/career-development/K23

³⁶⁰ www.lrp.nih.gov/

Overactive Bladder Treatment

House Language

The Committee remains concerned about the safety of medications used to treat overactive bladder, which may be increasing risk of ADRD. Overactive bladder affects 38 million Americans, and one in three older adults in this country. Overactive bladder has a significant impact on quality of life and the health care system. The anticholinergic medications typically used first-line to treat overactive bladder have been shown to increase the risk of developing dementia. Dementia continues to grow as a prevalent and serious public health issue. The Committee urges NIA to study anticholinergic medications and alternative treatments to determine the safety and effectiveness of medications for overactive bladder, and their potential risks related to ADRD. The Committee requests an update on the status of research activities focused on this issue in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

Overactive bladder occurs when the bladder is triggered to empty at the wrong time, leading to a sudden urge to urinate that a person may have difficulty suppressing. The symptoms of overactive bladder include urinary frequency, urinary urgency, and urge incontinence.

The National Institutes of Health (NIH) supports studies on a range of issues related to the causes, prevention, and treatment of overactive bladder. This includes research on the safety of long-term use of anticholinergic medications commonly prescribed to treat overactive bladder and the associated risk of cognitive impairment and dementia as well as research to advance safe and effective alternative treatments for overactive bladder.

The National Institute on Aging (NIA) is currently supporting several studies on the safety of long-term use of anticholinergic medications and the risk of cognitive impairment and dementia in older adults with overactive bladder. These include studies to utilize a novel model to investigate anticholinergic drug-induced dementia³⁶¹ and assess severe adverse events associated with the interaction of cholinesterase inhibitors, which are used to treat Alzheimer's by increasing communication between neurons, with anticholinergic medications.³⁶² Other studies are evaluating extended cognitive, urinary, and functional trajectories in older incontinent women without pre-existing dementia who use anticholinergic medication³⁶³ and testing mechanisms of neurotoxicity from anticholinergics.³⁶⁴

NIA is also funding studies exploring strategies for and impact of discontinuing use of anticholinergics. This includes a clinical trial testing whether discontinuing use of anticholinergics improves cognition and lowers the risk of Alzheimer's disease and related dementias.³⁶⁵ NIA is also funding a clinical trial to test a mobile app that integrates a personalized anticholinergic risk calculator, targeted multimedia such as videos and blogs to educate users regarding anticholinergics, and a conversation starter to help a patient self-initiate

³⁶¹ reporter.nih.gov/search/0lm26jQsukuQXix5r_QvGw/project-details/10258975

³⁶² reporter.nih.gov/search/pZSsBABfW0K-DPFCtVqRcQ/project-details/10212709

³⁶³ reporter.nih.gov/search/0lm26jQsukuQXix5r_QvGw/project-details/10343015

³⁶⁴ reporter.nih.gov/search/Ggd69UkxpkGGqF5IAEfYrg/project-details/10168318

³⁶⁵ reporter.nih.gov/search/Shaj-qYerkm0U6DRn1S6tg/project-details/10129872

ending anticholinergic prescriptions in collaboration with a healthcare provider.³⁶⁶ This trial will explore the impact of the app on prescription anticholinergic exposure among older adults and on cognitive function and quality of life. Additional studies are seeking to improve how older adults living with dementia, their caregivers, and clinicians make decisions about using anticholinergic medicines³⁶⁷ and test electronic health record-based tools that engage caregivers to help primary care providers reduce medication overload and deprescribe medications that can worsen cognitive burden in patients with mild cognitive impairment, Alzheimer’s disease, and related dementias.³⁶⁸

A recent NIA-supported study found that exposure to strong anticholinergics increased the risk of transitioning from normal cognition to mild cognitive impairment.³⁶⁹ Another recent NIA-funded study that evaluated adverse outcomes of anticholinergic medicines in patients with dementia and overactive bladder³⁷⁰ found an increased risk of mortality associated with non-selective antimuscarinic (a subtype of anticholinergic drugs) medications in older adults with dementia.³⁷¹

NIA is also supporting several studies to advance safe and effective alternative treatments for overactive bladder. One NIA-funded research study is assessing brief mindfulness and non-invasive brain stimulation to reduce symptoms of urgency incontinence in women.³⁷² In addition, a recent NIA-funded study found that a slow-paced breathing intervention practiced over 12 weeks was associated with a modest improvement in perceived stress in women with overactive bladder symptoms, but it was no more effective than a control intervention (listening to calming music) for reducing urinary symptoms.³⁷³ NIA also recently supported a study testing a novel, non-invasive nerve stimulation device for in-home treatment of overactive bladder.³⁷⁴

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) continues research into the causes and treatment of overactive bladder. NIDDK-supported projects include those developing novel non-drug therapies for overactive bladder and investigating other prevention and intervention approaches, especially within high-risk groups. Other projects are aimed at finding ways to better assess bladder function, psychological contributors, and clinically useful patient subtypes.

NIH is committed to continuing to fund research to improve the lives of people living with overactive bladder and will continue to fund research towards prevention of cognitive impairment in this, and other, areas of investigation.

³⁶⁶ clinicaltrials.gov/ct2/show/NCT04121858

³⁶⁷ reporter.nih.gov/search/Ggd69UkxpkGGqF5IAEfYrg/project-details/9926791

³⁶⁸ reporter.nih.gov/project-details/10370471

³⁶⁹ www.ncbi.nlm.nih.gov/pmc/articles/PMC6036636/

³⁷⁰ reporter.nih.gov/search/-xMveMuhZUWqFIMIntQeIw/project-details/9377896

³⁷¹ pubmed.ncbi.nlm.nih.gov/32026255/

³⁷² reporter.nih.gov/search/PWzY007ysEW1d1WslGSukQ/project-details/10259722

³⁷³ www.ncbi.nlm.nih.gov/pmc/articles/PMC6842393/

³⁷⁴ reporter.nih.gov/search/rmFNoL91xkamsqkkLW-QEQ/project-details/10219001

Palliative Care

Conference Language

The agreement reiterates the need for NIH to develop and implement a trans-Institute strategy to expand and intensify national research programs in palliative care. The agreement urges NIH to ensure that palliative care is integrated into all areas of research across NIH and requests an update on plans to realize this coordination in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

Summary of Ongoing Activities

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.³⁷⁵ Palliative care has the potential to improve patient care, patient-clinician communication, and patient-centered outcomes while decreasing unwanted burdensome treatments and enhancing quality of life for people with serious illness, their loved ones, and their care partners. 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.

For example, the National Cancer Institute (NCI) supports palliative care research as an important component of its portfolio, including an active funding opportunity announcement focused on the survivorship needs of individuals living with advanced cancer, an announcement focused on the conduct of palliative care clinical trials, and a third announcement on the management of treatment toxicities.³⁷⁶ The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is committed to supporting palliative care research relative to 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. The National Institute of Nursing Research (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 care. Recent NINR awards are funding research on improving integration of palliative care in primary care for American Indians, as well as enhancing discussion of palliative care in American Indian communities.³⁷⁷ The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports research to adjust treatment approaches and improve patient quality of life in end-of-life care for people with diseases such as end stage renal disease (also called kidney failure) and severe cirrhosis that results in liver failure. In addition to these examples, several other ICOs support a broad range of palliative care research activities.

NIH complements basic and translational research in palliative care with support for several ongoing clinical trials in this area. As one example, the NCI Community Oncology Research Program (NCORP) is a national network that brings cancer clinical trials and care delivery

³⁷⁵ www.nia.nih.gov/health/what-are-palliative-care-and-hospice-care; www.ninr.nih.gov/newsandinformation/what-is-palliative-care

³⁷⁶ 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

³⁷⁷ reporter.nih.gov/search/Ohqmi4CpkUmZzqHLtjI5gg/project-details/10431092; reporter.nih.gov/search/VdgUN3-c2k25yyHieMw81Q/project-details/10504687

studies to people in their own communities.³⁷⁸ NCORP supports research in supportive care, symptom management, palliative care, and health-related quality of life. Further, the National Institute on Aging (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.³⁷⁹

NIH also supports large research cooperatives that work to benefit the entire field of palliative care. The Palliative Care Research Cooperative (PCRC), funded by NINR from FY 2010 through FY 2022, supports researchers who are developing an evidence base to ensure high-quality care and optimal well-being for persons with serious illness and their care partners.³⁸⁰ Recent activities of the PCRC have focused on reducing inequities through screening social need in pediatric palliative care, palliative care in chronic kidney disease, and the use of virtual reality for management of cancer pain. In addition, other ICOs have collaborated with NINR on PCRC activities. For instance, NIA recently supported an award focused on diversifying and strengthening dementia palliative care clinical trials, an effort that builds on work done by the PCRC under an NIA-supported supplement to develop a curriculum for palliative care clinical trials training.³⁸¹

NIH ICOs also coordinate and collaborate on funding opportunities in palliative care. For example, the National Heart, Lung, and Blood Institute (NHLBI) and NINR both currently participate in a Notice of Special Interest (NOSI) focused on improving quality of life for people with heart, lung, blood, and sleep diseases.³⁸² This notice was issued in September 2020 and will remain active through July 2023.

New Opportunities in Palliative Care Research

Multiple NIH ICOs – including NCI, NHLBI, NIA, NICHD, NIDDK, NINR, the National Institute of Mental Health (NIMH), the National Institute of Minority Health and Health Disparities (NIMHD), and the National Institute of Neurological Disorders and Stroke (NINDS) – have invested in research related to palliative care in the past and continue to support this area of research. In December 2022, several ICOs reissued a joint Notice of Special Interest to facilitate research on palliative care for older adults, including those with multiple chronic health conditions.³⁸³ Participating ICOs include NIA, NHLBI, NINR, NCI, NIMHD, and the NIH Office of Research on Women's Health. The next round of applications is expected in February 2023.

Moreover, NIH ICOs are carrying out efforts to identify new opportunities for research in palliative care. For example, NHLBI convened a workshop in December 2022 on care for people with advanced heart failure.³⁸⁴ The workshop brought together healthcare providers,

³⁷⁸ ncorp.cancer.gov/

³⁷⁹ www.nia.nih.gov/research/ongoing-AD-trials

³⁸⁰ palliativecareresearch.org/

³⁸¹ reporter.nih.gov/search/esFZZNTeDUi5mGiY4CktDw/project-details/10409239;

reporter.nih.gov/search/NaZBHvzsb0CnZ5O16o_rtQ/project-details/9880259

³⁸² grants.nih.gov/grants/guide/notice-files/NOT-HL-20-737.html

³⁸³ grants.nih.gov/grants/guide/notice-files/NOT-AG-22-048.html

³⁸⁴ www.eventbrite.com/e/advanced-heart-failure-trajectories-triage-for-ambulatory-pre-d-d-tickets-470574690567?keep_tld=1

researchers, policy makers with expertise in adult and pediatric cardiology, heart failure, clinical trials, outcomes research, transplantation, mechanical circulatory support, geriatrics, and palliative care. This workshop focused on identifying gaps and opportunities that will help spur research to improve access to palliative care for ambulatory patients with advanced heart failure, such as enhancing integration of palliative care across the continuum of illness. Additionally, NICHD is planning a 2023 State of the Science conference on pediatric palliative care in critically ill children. This conference will convene experts in pediatric palliative care and help identify key gaps and opportunities in this area.

Moving forward, NIA is leading efforts to convene subject matter experts from the ICOs listed above to expand and intensify the strategic coordination of palliative care research efforts as well as identify future research topics and questions that pertain to palliative care.

Pancreatic Cancer

Conference Language

The agreement encourages NCI to leverage the investment in NCI's National Clinical Trials Network to accelerate the survival rate for pancreatic cancer patients by maximizing the knowledge gained from every trial and suggests that trials for pancreatic cancer include parallel and concurrent correlative studies, as appropriate, to better understand what treatments work best for which patients. The agreement directs NCI to consider ways to maximize learning from pancreatic cancer trials and provide an update in the fiscal year 2024 Congressional Justification on next steps towards this goal.

Action taken or to be taken

The Alliance of Pancreatic Cancer Consortia (APaCC) was formed as a virtual consortia of National Cancer Institute (NCI)-supported researchers focused on expanding research and collaboration efforts for the early detection of pancreatic cancer across government, academia, and the private sector. The Consortia is comprised of researchers from multiple NCI-funded networks including the Pancreatic Cancer Detection Consortium (PCDC);³⁸⁵ the Early Detection Research Network (EDRN);³⁸⁶ the Consortium for the Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC);³⁸⁷ and the Translational and Basic Science Research in Early Lesions (TBEL).³⁸⁸ The Kenner Family Research Fund and Pancreatic Cancer Action Network advocacy groups and industry partners also participate in the consortium. Since the inaugural meeting in December 2016, the group has continued to work together, along with the NCI, meeting in December 2018, September 2020, and December 2021. The next APaCC meeting is planned for December 2022.

In March of 2021, in collaboration with the Kenner Family Research Fund, APaCC organized a workshop entitled: "Early Detection of Pancreatic Cancer: Opportunities and Challenges in Utilizing Electronic Health Records (EHR)." The workshop included a select group of panelists with expertise in pancreatic cancer, EHR data mining, and Artificial Intelligence (AI)-based modeling. The potential of AI applied to clinical data from EHRs to improve early detection for pancreatic and other cancers remains underexplored. Specific challenges (biology, limited data, standards, compatibility, legal, quality, AI chasm, incentives) were identified³⁸⁹ and a potential roadmap was summarized.

In December 2021, NCI's Pancreatic Cancer Detection Consortium (PCDC) had a joint virtual meeting with the Early Detection Research Network – Alliance of Pancreatic Cancer Consortia for Early Detection (EDRN– APaCC).³⁹⁰ Topics discussed included building useful cohorts through collaborations and how to better leverage each other's resources.

Additionally, the Prediagnostic and Early-Stage Imaging Repository for Pancreatic Cancer, an APaCC collaborative study, reported their progress at scientific meetings and in a joint

³⁸⁵ prevention.cancer.gov/major-programs/pancreatic-cancer-detection

³⁸⁶ edrn.nci.nih.gov

³⁸⁷ www.dmscro.org/cpdpc

³⁸⁸ prevention.cancer.gov/major-programs/tbel

³⁸⁹ pubmed.ncbi.nlm.nih.gov/34629446/

³⁹⁰ prevention.cancer.gov/news-and-events/meetings-and-events/pcdc-edrn-apacc-joint

manuscript.³⁹¹ The repository is stored at the National Aeronautical and Space Administration's (NASA) Jet Propulsion Laboratories, which serve as the informatics center for ERDN and have the expertise and equipment to host the images, under contract with NCI. Collectively, the group has approximately 1,200 prediagnostic cases, 1,200 controls, and 1,500 early-stage pancreatic ductal adenocarcinoma (PDAC) cases. The collaborative group is now working on phase 3 validation of promising imaging biomarkers.

Alongside early detection, better treatments to improve outcomes for pancreatic cancer patients is a high priority. NCI supports translational research and clinical trials to test new pancreatic cancer therapies and learn from patient experiences. For example, the NCI Experimental Therapeutics Clinical Trials Network and the National Clinical Trials Network (NCTN) conduct studies on immunotherapy agents and novel treatment combinations and consistently incorporate research on biomarkers into studies to better understand why therapies work for some patients and not others. These data have implications not only for precision medicine in specific cancer populations but may also be relevant to multiple trials across the cancer immunotherapy field. One study currently underway through NCTN is the DART study that compares two different immunotherapy treatment options in patients with a wide variety of rare cancers including pancreatic neuroendocrine tumors.³⁹² Additionally, NCI supports and oversees numerous early- and late-phase clinical trials to develop effective treatments for pancreatic cancer and improve patient care. The Cancer Immunotherapy Trials Network (CITN) has prioritized pancreatic cancer immunotherapy studies and conducts early-stage trials and strategically chooses high-priority treatment agents that meet a number of criteria in the hopes that the studies can lead to larger clinical trials and United States Food and Drug Administration (FDA) approval.³⁹³ Please also see the pancreatic cancer section of the *Deadliest Cancers* response for more information about NCI-supported translational research through the Pancreatic and Gastrointestinal Cancers Specialized Programs of Research Excellence (SPOREs).

Several NCI-supported researchers are examining the genetics of pancreatic cancer. The Pancreatic Cancer Genetic Epidemiology (PACGENE) study is a clinical trial that aims to identify genetic susceptibility genes in families that are at high risk for pancreatic cancer to improve risk assessment and early detection and to provide new insights into screening, prevention, and treatment approaches.³⁹⁴ Additionally, the Whole Genome Scan for Pancreatic Cancer Risk in the Pancreatic Cancer Cohort Consortium and Pancreatic Cancer Case-Control Consortium (PanScan) study consists of two genome-wide association studies to identify susceptibility markers for pancreatic cancer.³⁹⁵ The Specialized Programs of Research Excellence (SPOREs), which promote collaborative, interdisciplinary translational cancer research, include projects on pancreatic cancer.³⁹⁶ One project is focused on development of a personalized pancreatic cancer vaccine for PDAC patients.

NCI also continues to prioritize the incorporation of correlative studies as part of clinical trials through existing funded networks. For example, one Experimental Therapeutics Clinical Trials

³⁹¹ pubmed.ncbi.nlm.nih.gov/33344245/

³⁹² clinicaltrials.gov/ct2/show/NCT02834013?term=dart&draw=4

³⁹³ www.fredhutch.org/en/research/institutes-networks-ircs/cancer-immunotherapy-trials-network.html

³⁹⁴ clinicaltrials.gov/ct2/show/study/NCT00526578

³⁹⁵ www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000206.v3.p2

³⁹⁶ trp.cancer.gov/spores/pancreatic.htm

Network (ETCTN) trial is looking at the combination of a monoclonal antibody with other immunotherapies or chemotherapy in patients with advanced pancreatic cancer.³⁹⁷ One of the outcome measures is to look at levels of specific biomarker pre and post treatment and how that relates to clinical outcomes. Another ETCTN trial examining the combination of a chemotherapy drug and different anti-cancer drug is looking at levels of markers of DNA damage before and after treatment and will experimentally identify biomarkers that correlate with a clinical response to the treatment.³⁹⁸ The institute also continues to explore approaches that support and streamline the initiation of these studies to ensure they are carried out in a timeframe that aligns most efficiently with the corresponding trials, while also protecting the integrity of the peer review process.

³⁹⁷ clinicaltrials.gov/ct2/show/NCT03816358

³⁹⁸ clinicaltrials.gov/ct2/show/NCT04616534

Parkinson's Disease

House Language

Research suggests that Parkinson's disease (PD) is caused by a combination of genetic and environmental factors. Agricultural exposure to pesticides, including herbicides, has been associated with an increased risk of developing the disease, yet other exposures common to soldiers, firefighters, first responders, and others, such as burn pits, insecticides, solvents and heavy metals, need to be explored or should be considered. The Committee urges NIEHS to expand its research and collaborate with appropriate partners to understand the effects of these chemicals on PD development and progression. Research should include fundamental approaches to identify other environmental triggers and to understand the expression of PD traits that result from the interplay of genes and environment to advance the development of individualized precision environmental health strategies to prevent and treat PD. The Committee requests an update on these activities in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

More than 1 million people in the United States are living with Parkinson's Disease (PD), and this number is steadily increasing, along with associated health care, loss of productivity, and other economic costs, and human suffering. National Institutes of Health (NIH)-funded research is advancing understanding of PD to enable treatments and progress toward a cure. Ongoing studies are revealing how environmental exposures to agents such as metals, solvents, and pesticides interact with genetics to cause PD. For example, researchers developed a single-cell genetic sensor called PRISM that exploits the abilities of viruses to enter cells and cause DNA damage and used it to probe brain cells in mice exposed to the chemical paraquat, which has been strongly associated with PD. The sensor found evidence of high levels of genotoxic stress in dopaminergic neurons, the most affected cells in PD.³⁹⁹ This same team is working to unravel the protective mechanisms of caffeine and coffee consumption against PD. Other researchers working in the Parkinson's Disease, Environment, and Genes (PEG) study measured the accumulation of random mutations across the genes of individual patients and found associations between a high epigenetic mutation load and risk of PD, disease progression, and time to death, respectively.⁴⁰⁰

Other efforts are focused on approaches for detecting PD earlier, which is key to delaying significant effects of the disease. PD is typically not diagnosable until 60 percent of dopamine-generating neurons in a certain area of the brain are lost. NIH intramural scientists using a mouse PD model found that supercharging neurons in this area caused them to generate dopamine metabolites at levels detectable in blood when only 30 percent had been lost.⁴⁰¹ The researchers are working to determine if these findings could be used to develop blood tests for diagnosing PD in high-risk individuals well before symptoms appear.

Gastrointestinal dysfunction is a major symptom leading up to PD. Research aimed at uncovering how environmental exposures may interfere in bodily systems to contribute to PD continues to make progress toward treatment. A major focus of study has been signaling of the

³⁹⁹ pubmed.ncbi.nlm.nih.gov/35427151/

⁴⁰⁰ pubmed.ncbi.nlm.nih.gov/34842194/

⁴⁰¹ pubmed.ncbi.nlm.nih.gov/34916526/

gut-brain axis, which was explored in an NIH-hosted conference in September 2021.⁴⁰² Using cell and animal models, researchers have explored effects of exposure of certain GI cells to rotenone and tebufenpyrad, pesticides that induce death in dopaminergic neurons. This study demonstrated for the first time that such exposure worked similarly in the gut to impair the mitochondrial functions of enteric glial cells and induce inflammation leading to gut dysfunction.⁴⁰³ Manganese (Mn) induces parkinsonism at elevated levels. A study has provided insight into the mechanisms by which proteins called hypoxia-inducible factors (HIF) increase expression of another protein called SLC30A10, which is critical for excretion of Mn from the body. Researchers showed in a mouse study that stabilizing HIF protected cells against Mn toxicity and reduced neuromotor deficits. This research suggests that HIF-stabilizing drugs currently in clinical trials for other uses might be repurposed to manage Mn neurotoxicity in people.⁴⁰⁴

NIH grantees are continuing to build on these discoveries to set a path toward reducing the burden of this disease. A group of PD researchers long-funded by NIH Institutes NIEHS and NINDS came together in a recent commentary titled, “Preventing Parkinson's Disease: An Environmental Agenda.” The article identifies ten areas of basic and clinical research on PD they say need to be greatly expanded, along with funding and policy steps that should be taken, in order to make significant progress on the disease.⁴⁰⁵

⁴⁰² www.niehs.nih.gov/news/events/pastmtg/2021/ieemhh2_2021/index.cfm

⁴⁰³ pubmed.ncbi.nlm.nih.gov/35550926/

⁴⁰⁴ pubmed.ncbi.nlm.nih.gov/34446561/

⁴⁰⁵ pubmed.ncbi.nlm.nih.gov/34719434/

Parkinson's Disease (PD)

House Language

The Committee commends NINDS for taking critical steps in identifying priority research recommendations to advance research on PD, which impacts between 500,000 and 1,500,000 Americans and is the second most prevalent neurodegenerative disease in the U.S. The Committee recognizes that NINDS is prioritizing public health concerns with severe gaps in unmet medical needs and supports the research recommendations set forth by the NINDS planning strategy to bring us closer to better treatments and a cure for PD. The Committee also encourages NINDS to submit an update on its progress on implementing these recommendations in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

The National Institute for Neurological Disorders and Stroke (NINDS) is using an array of approaches to address the basic, translational, and clinical Parkinson's disease (PD) research recommendations from the *Advancing Research, Improving Lives* conference.

Investigator-initiated basic research projects and the NINDS Morris K. Udall Centers of Excellence for Parkinson's Disease Research program are characterizing symptomatic, pathophysiologic, and genetic heterogeneity in people with PD, identifying the genetic and environmental risk factors for PD, increasing our understanding of the molecular and cellular mechanisms of disease process, improving animal and cell models for PD, developing imaging technologies to observe pathologic changes in people with PD, testing digital biomarkers of disease progression, and characterizing the brain circuits involved in PD. Studies to increase our understanding of PD dementia and find ways to prevent or treat PD dementia are an important component of the NINDS-led Alzheimer's Disease-Related Dementia initiatives.

NINDS-funded investigators are translating these disease mechanism studies into novel therapies. NINDS is funding development of a novel microbiome-based platform for the continuous delivery of levodopa (a drug used to increase levels of neurotransmitter dopamine) in relieving motor symptoms without inducing severe, involuntary muscle movements, which are a common side effect of levodopa therapy. NINDS-supported small business researchers are conducting preclinical studies to evaluate the potential of a novel oral formulation of carbon monoxide as a neuroprotective agent for PD, to develop an RNA-based therapy that reduces iron levels as a means to prevent iron-mediated neurodegeneration, to develop small molecules that can increase dopamine receptor activity and improve cognitive function without unwanted side effects, and to identify potential drug candidates to treat levodopa-induced dyskinesia, a debilitating side effect of levodopa treatment, based on biomolecular signatures associated with specific motor behaviors.

NINDS is also funding a number of studies to optimize current therapies for PD. NINDS-funded studies are testing different forms of exercise (treadmill walking and stationary bicycling) to determine whether high-intensity exercise alter disease progression and to facilitate patient-specific exercise prescriptions. Another study is investigating whether combining noninvasive brain stimulation with physical therapy can improve balance in people with PD. The NIH Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative is funding

several projects to improve deep brain stimulation (DBS) technology, which is currently used to treat motor symptoms in people with PD. A separate project is developing neuroimaging technologies to help surgeons individually customize electrode placement and stimulation strategies to improve DBS results. Other NINDS-funded studies are mining Medicare data and large multi-study clinical research datasets to identify treatment strategies that minimize adverse events and to develop methods for creating individualized PD treatment plans. NINDS is also funding studies to understand health disparities and improve clinical management of PD in Black and Latino individuals.

NINDS is also supporting research studies to develop and test new tools to diagnose PD and monitor disease progression, which will facilitate clinical trials and help physicians optimize individual treatment strategies. The NINDS PD Biomarkers Program (PDBP) and Accelerating Medicines Partnership for PD (AMP-PD) are identifying and validating novel biomarkers that can be used to improve diagnosis, monitor disease progression, or tailor treatments to individuals. These investigators have shown it is possible to diagnose PD by assaying small skin samples as well as cerebrospinal fluid. NINDS-funded small business awardee is validating a test to detect abnormal PD-linked proteins in blood and cerebrospinal fluid, which could aid in PD diagnosis. Other studies are developing neuroimaging tools and technologies that will allow clinicians to detect brain changes in people with PD, which may facilitate improved diagnosis and disease monitoring. NINDS Udall Center at the University of Rochester is developing telehealth tools and digital technologies for PD, including clinical studies demonstrating the value of non-invasive monitoring of activity and breathing patterns, as well as telemedicine visits and smartphone platforms for measuring PD progression. Another project is designing augmented reality environments to systematically evaluate motor and cognitive function and the performance of instrumental activities of daily living to ultimately advance PD treatment strategies.

Parkinson's Disease and Dementia

House Language

The Committee recognizes that although PD is often thought of only as a movement disorder, most PD patients also develop dementia. Common symptoms include difficulty with problem solving and speed of thinking, memory, and other cognitive skills. Because people with PD usually develop these symptoms several years after their diagnosis, PD represents an under-explored opportunity to study the onset and progression of dementia. Therefore, the Committee strongly urges NIA and NINDS to put a higher priority on PD, both before and after onset of dementia, within their overall dementia research portfolios. The Committee requests an update on these activities in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

The dementia portfolios at the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA) include studies and programs that are relevant to Parkinson's disease (PD) at all stages of the disease, including before the onset of dementia. Lewy body dementia (LBD) is an overarching term that includes both PD dementia and dementia with Lewy bodies (DLB), which shares certain clinical and pathological features with both PD and Alzheimer's disease. National Institutes of Health (NIH) funding of LBD research, including PD dementia, has increased more than seven-fold since 2015.

In PD, a brain region that plays a key role in movement is affected early in the disease, but as the disease advances, areas of the brain that are important for memory and the ability to think clearly also begin to degenerate, causing PD dementia. Many of the underlying cellular and molecular mechanisms of disease are the same for PD, PD dementia, and DLB. What differs is the time course over which various brain regions become affected. Projects within the NIH dementia portfolio are focused on understanding the normal function of alpha-synuclein, a protein linked to PD and PD dementia, as well as how it contributes to degeneration of neurons including what causes accumulations of abnormal alpha-synuclein to occur in both PD and PD dementia. NIH-funded studies are also aiming to understand how other genes that have been linked to PD, such as GBA1, LRRK2 and PINK1, contribute to the disease process including dementia. NIH-supported studies are also examining how altered cellular metabolism contributes to PD and PD dementia. Other NIH-funded studies are investigating factors that predict the risk of people with PD developing dementia.

NIH currently funds a number of large projects on PD and PD dementia, both before and after the onset of dementia.

- A Center Without Walls is identifying how protein interactions and genetics contribute to the unique symptoms, progression, and underlying pathology of LBD.
- The Proteinopathy Consortium is characterizing the structures of protein aggregates found in LBD and other dementias as a first step to developing brain imaging tools that could improve understanding of the disease and help identify biomarkers.
- The NIA-funded Alzheimer's Disease Research Centers (ADRCs) support basic, clinical, and biomarker research in PD dementia and DLB.

- The NINDS Parkinson’s Disease Biomarker Program (PDBP) is enhancing biomarker discovery for PD, LBD, and related disorders by collecting standardized, longitudinal clinical data and biospecimens for sharing with the research community.
- The Accelerating Medicines Partnership®-Parkinson’s Disease (AMP-PD) is a public-private partnership that is utilizing data and specimens from the NINDS PDBP and other biomarkers studies to identify and validate PD and LBD biomarkers. These biospecimens and data are also available for analysis by the broader PD and PD dementia research community.
- The Global Parkinson’s Genetics Program (GP2), supported in part by NIA, is an ambitious program to dramatically expand understanding of the genetic basis of PD across diverse populations by using cutting-edge techniques to determine the genetic makeup of more than 150,000 volunteers around the world, most of whom are living with PD. This work is being extended to include a significant component that focuses on PD dementia.

In addition to these ongoing studies, NIH has recently issued a funding opportunity announcement explicitly soliciting clinical trials for LBD, including PD dementia, to translate basic science discoveries into meaningful therapies.⁴⁰⁶

⁴⁰⁶ grants.nih.gov/grants/guide/rfa-files/RFA-NS-22-056.html

Pelvic Floor Disorders

House Language

Pelvic floor disorders, including urinary incontinence, accidental bowel leakage, and pelvic organ prolapse, negatively impact the quality of life of more than 25 million U.S. women each year. There are socioeconomic disparities amongst women suffering from pelvic floor disorders, with differences in symptoms, knowledge, access to care, availability of treatments, and treatment outcomes noted in patients from different backgrounds. The Committee urges NICHD to prioritize research activities into underrepresented patient populations and pelvic floor disorders. Such activities may include the development of educational programs for general practitioners, the evaluation of effectiveness of screening protocols for pelvic floor disorders in the primary care setting, investigating medical literacy amongst minority women as it pertains to pelvic floor disorders, as well as assessing socioeconomic and socio-cultural disease perspectives by designing qualitative studies using focus groups of women with varying socio-economic, cultural, and ethnic backgrounds, evaluating current educational resources, determining gaps in patient knowledge, and designing culture-specific educational materials and resources. The Committee requests an update on this research in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

Pelvic floor disorders, 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 sponsored research on pelvic organ prolapse is through the Pelvic Floor Disorders Network (PFDN), a multi-center network which was established by the NICHD in 2001 in response to increasing awareness by the public and by 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 between 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. For example, PFDN research published within the past year has demonstrated that:

- vaginal mesh used to lift the uterus proves superior to native tissue repair for the surgical treatment of pelvic organ prolapse at five years follow up examination;
- pain with sexual activity improves after surgical treatment of pelvic organ prolapse;
- the ability to fabricate support tissue from vaginal biopsies of the patient could be incorporated into surgical repairs;
- further identification of risk factors for failure of pelvic organ prolapse surgery based on patient characteristics and MRI findings;
- current definitions of success or failure may result in the overestimation of surgical failure rates following pelvic organ prolapse, potentially explaining, in part, the low retreatment rates after pelvic organ prolapse surgery; and

- percutaneous tibial nerve stimulation (PTNS) a non-invasive, low-risk neuromodulation treatment approved for urgency urinary incontinence, showed no significant difference in symptom severity, incontinence events, or most quality-of-life measures at the end of the 12 weeks of treatment for fecal incontinence when compared to another method.

In addition, ongoing PFDN research includes a comparative effectiveness study that is evaluating three surgical treatments for prolapse. This study will determine the advantages and/or disadvantages, risks and benefits, and the effect on quality of life of each surgery when used to repair vaginal vault (apical) prolapse. Another study is examining the long-term efficacy and safety outcomes (up to 10-years) of a native tissue repair and a mesh hysteropexy, a method used to lift the uterus. NICHD has also funded non-network research on pelvic organ prolapse. Ongoing NICHD funded studies include understanding the mechanisms and impact of pregnancy-induced adaptations in pelvic floor muscles, improving the outcomes of urogynecologic meshes in diabetic women, developing a new non-surgical treatment option 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.

NICHD will continue to support this important research, as well as the work of PFDN, which was renewed for another five-year cycle which began in July 2022. The inclusion of under-represented patient populations is a priority for NICHD and the PFDN. Within this cycle, sites were strategically chosen to increase access to and potential recruitment of underrepresented women. Moreover, the PFDN Steering Committee has committed to forming a diversity, equity, and inclusion committee to specifically address disparities in pelvic floor research by understanding why the disparity exists and developing efforts to dissipate it. NICHD is also working with stakeholders to increase awareness of these disparities and to educate providers so that these disparities may be better addressed.

Polycystic Ovary Syndrome (PCOS)

House Language

PCOS affects up to 15 percent of women and is a significant risk factor for multiple cardio-metabolic conditions, such as type 2 diabetes, lipid disorders, high blood pressure, obesity, sleep disorders, and others which may significantly increase risk for adverse COVID–19 outcomes. The Committee encourages NIH to increase investments into research on the metabolic, cardiovascular, psychosocial, maternal-fetal, oncologic, pediatric, dermatologic, and reproductive aspects of PCOS. Fifty percent of PCOS patients become diabetic or prediabetic before age 40, and are at higher risk for hypertension, stroke, nonalcoholic fatty liver disease, and non-alcoholic steatohepatitis, independent of, but exacerbated by obesity. There is also evidence of racial and ethnic differences that disproportionately increase the risk for cardiovascular and metabolic disease in PCOS. The Committee urges NIH to continue to support fundamental laboratory science, patient-directed research, clinical trials, and large longitudinal studies focused on the cardiometabolic features and endocrinopathy of PCOS throughout the lifespan. The Committee also encourages NIH to provide an update on research that has been conducted on PCOS and its impact on cardio-metabolic health to date in the fiscal year 2024 Congressional Justification. Additionally, the Committee requests that PCOS—one of the most common human disorders—be added to the NIH Research, Condition, and Disease Categories reporting

Action taken or to be taken

Polycystic ovary syndrome (PCOS) is a hormone disorder in women characterized by irregular or missing menstrual periods, high levels of male hormones (androgens), and small cysts on the ovaries. In addition to infertility, women with PCOS have an increased risk of developing type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease. The National Institutes of Health (NIH) has a broad portfolio of PCOS research supported by multiple Institutes and Centers.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is committed to understanding and using advanced technologies to inform prevention and treatment strategies to uncover factors leading to gynecologic conditions such as PCOS. For example, PCOS is also associated with changes in the gut microbiome—a community of microorganisms (such as fungi, bacteria, and viruses) that are important for the function of body systems including immunity, metabolism, and neurology. Using a mouse model, NICHD-funded research identified specific bile acid metabolites that were associated with both the gut microbiome and the metabolic changes of PCOS.⁴⁰⁷ This may help scientists explore how to prevent the long-term increases in the risk of chronic diseases associated with PCOS. In another study, NICHD-funded researchers found that women with a history of PCOS had a greater risk of gestational diabetes and a greater risk of preeclampsia compared to women without a diagnosis of PCOS.⁴⁰⁸ In addition, neonates born to women with a history of PCOS were more likely to be born preterm and more likely to have a prolonged hospitalization after delivery. This research suggests the importance of obstetricians' awareness of their patients' PCOS status, and

⁴⁰⁷ pubmed.ncbi.nlm.nih.gov/34519532/

⁴⁰⁸ pubmed.ncbi.nlm.nih.gov/36149255/

that they should closely monitor for potential pregnancy complications to improve maternal and infant perinatal health outcomes.

The National Heart, Lung, and Blood Institute (NHLBI) is committed to understanding and reducing the impact of PCOS on cardiovascular health. In recent years, NHLBI-funded research has focused on the mechanisms by which excess androgens associated with PCOS cause underlying detrimental cardiovascular effects. NHLBI-funded researchers are examining the intersection of testosterone and the sympathetic nervous system in the development of hypertension in women with PCOS.⁴⁰⁹ Other studies are investigating the relationship between prenatal androgens and adult cardiometabolic outcomes in human and animal models.^{410 411}

On October 13 and 22, 2021, NHLBI, in collaboration with the Office of Research on Women’s Health (ORWH), NICHD, the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), and the NIH Office of Disease Prevention (ODP), led a virtual workshop titled, “Cardiovascular Risk Across the Lifespan for PCOS,”⁴¹² to evaluate current PCOS-related research needs and opportunities. This NIH workshop brought together a multidisciplinary team of scientists and practitioners to address critical research needs and highlight research questions at the interface between PCOS and cardiovascular disease (CVD) risk across the lifespan. The leadership and members of the PCOS Challenge, a patient advocacy group, also participated and provided important stakeholder input for the workshop. Knowledge gaps and research opportunities were identified, including those in PCOS-related CVD research. Those have been summarized in the Executive Summary of the workshop published on the NHLBI website.⁴¹³ A working group of NHLBI staff is planning next steps in follow-up of the workshop. Moreover, a summary manuscript is in progress for publication in the peer-reviewed medical literature to stimulate PCOS research.

Recent evidence shows that women with PCOS might be at higher risk for SARS-CoV-2 infection. Importantly, the “Cardiovascular Risk Across the Lifespan for PCOS” workshop⁴¹⁴ and the June 16 and 17, 2022, NHLBI workshop on Sex/Gender-Specific COVID-19 Outcomes and Management Relevant for Heart, Lung, Blood, and Sleep Disorders: From Bench to Bedside, recognized these risks and discussed research needs and opportunities to improve COVID-19 outcomes in women with PCOS.⁴¹⁵ Crosscutting themes in the October 2021 and June 2022 meetings are sex-specific risks that seem related to 1) hormonal and/or inflammatory influences that may protect or trigger metabolic abnormalities, inflammation, obesity, depression, and cardiovascular risks with hypertension and diabetes; and 2) that women, especially women of color, have a high level of adverse social determinants of health leading to low health literacy and impaired healthy lifestyle, health care access and utilization.

⁴⁰⁹ reporter.nih.gov/project-details/9619086

⁴¹⁰ reporter.nih.gov/search/xn706Jwi0UaIDvJZVx4F9w/project-details/9898427

⁴¹¹ reporter.nih.gov/search/efaPOxfz-ESOX2V0qk7oyA/project-details/9971301

⁴¹² www.nhlbi.nih.gov/events/2021/cardiovascular-risk-across-lifespan-polycystic-ovary-syndrome-workshop

⁴¹³ www.nhlbi.nih.gov/events/2021/cardiovascular-risk-across-lifespan-polycystic-ovary-syndrome-workshop

⁴¹⁴ www.nhlbi.nih.gov/events/2021/cardiovascular-risk-across-lifespan-polycystic-ovary-syndrome-workshop

⁴¹⁵ www.nhlbi.nih.gov/events/2022/sexgender-specific-covid-19-outcomes-and-management-relevant-heart-lung-blood-and-sleep

Lastly, ORWH developed an informative PCOS Booklet⁴¹⁶ to educate the public and health care providers and to improve understanding and diagnosis of this syndrome. The PCOS booklet informs women about their chances of having PCOS, suggests how to manage symptoms, and describes how the syndrome affects women across their life course. The booklet also describes the etiology and symptoms of PCOS, disease definitions, and NIH initiatives related to the disease.

These are just a few examples of PCOS research and other initiatives supported by NIH.

⁴¹⁶ orwh.od.nih.gov/sites/orwh/files/docs/PCOS_Booklet_508.pdf

Prioritizing Black Youth Suicide Prevention

House Language

The Committee commends NIMH for consistently expanding resources for suicide screening and prevention research over the last four fiscal years and strongly encourages the Institute to provide additional increases for this purpose in fiscal year 2023, with special emphasis on producing models that are interpretable, scalable, and practical for clinical implementation, including utilization of healthcare, education and criminal justice systems that serve populations at risk. Specifically, this includes Black youth, whose suicide death rate is increasing faster than any other racial/ethnic group. In addition, the Committee encourages NIMH to prioritize research efforts related to primary care settings to evaluate suicide prevention interventions, strategies, and programs, including assessments of the effects of the COVID–19 epidemic. The Committee requests that NIMH provide an update on all of these efforts in the fiscal year 2024 Congressional Justification

Action taken or to be taken

The National Institute of Mental Health (NIMH) is committed to reducing suicide and supports research aimed at increasing knowledge about suicide, implementing scalable and practical preventive interventions across a variety of settings, and supporting underserved and at-risk populations. After increasing for nearly 2 decades, the national suicide rate decreased from 2018 to 2020; however, rates are increasing for some racial and ethnic groups. For example, suicide rates among Black youth more than doubled between 1999 and 2017, and Black youth under 13 years of age are now approximately twice as likely to die by suicide as their White counterparts.^{417,418} Supporting research to address disparities in suicide rates across minority groups, including Black youth, is a priority for NIMH.⁴¹⁹

To address the alarming rise in suicide among Black youth,⁴²⁰ NIMH is supporting research to understand suicide risk and protective factors, including studies focused on risk detection and interventions to reduce suicidality in Black children and adolescents. For example, NIMH-funded researchers are testing the effectiveness of a systems-level approach, *WeCare*, to assess and intervene in emergency departments (EDs) with Black youth identified as being at risk for suicide.⁴²¹ *WeCare* combines the NIMH-supported Computerized Adaptive Screen for Suicidal Youth (CASSY)⁴²² with Safe Alternative for Teens and Youth – Acute (SAFETY-A), a family-oriented suicide prevention intervention. Black youth who screen positive on CASSY during an ED visit will receive the SAFETY-A intervention, a brief (4-week) intervention that includes safety planning, referral to outpatient mental health care, and culturally adapted text messages which will also be sent to caregivers. A system of care that links Black youth at risk for suicide with quality mental health services has the potential to increase risk identification, treatment referral and engagement, and, in turn, reduce suicide. Additionally, NIMH has awarded research supplements to adapt evidence-based interventions for youth and young adults to be delivered

⁴¹⁷ www.cdc.gov/nchs/data/hestat/suicide/rates_1999_2017.htm

⁴¹⁸ pubmed.ncbi.nlm.nih.gov/29799931/

⁴¹⁹ www.nimh.nih.gov/about/organization/od/odwd/nimhs-approach-to-mental-health-disparities-research#nimh-priorities-for-mental-health-disparities-research

⁴²⁰ watsoncoleman.house.gov/imo/media/doc/full_taskforce_report.pdf

⁴²¹ reporter.nih.gov/project-details/10440864

⁴²² www.nimh.nih.gov/news/science-news/2021/adaptive-screener-may-help-identify-youth-at-risk-of-suicide

via telehealth during the Coronavirus Disease 2019 (COVID-19) pandemic; two of these supplements were awarded to ongoing studies focused on suicide among Black youth.^{423,424}

Detecting suicide risk in educational settings represents a critical opportunity for suicide prevention, as schools are often a primary source of mental health care for youth and young adults. NIMH is funding several suicide prevention studies in educational settings, including those that primarily serve Black youth. In one of these studies, researchers will test the effectiveness of a culturally adapted, school-based suicide prevention intervention for low-resourced, urban-dwelling, Black ninth grade students.⁴²⁵ This study has the potential to inform procedures for scaling up effective, high quality, and culturally grounded suicide prevention programs among Black adolescents.

Additionally, youth in publicly funded systems of care (e.g., Medicaid, child welfare, juvenile justice, and behavioral health) are often at heightened risk for suicide, and Black youth are overrepresented in many of these systems of care.^{426,427} NIMH-funded researchers aim to identify periods of high risk and predictors of suicide for youth in these settings by creating an integrated database that links nine years of data across multiple systems of care in Ohio.⁴²⁸ NIMH is also supporting research on interventions to reduce suicide risk among youth during transitions into or out of the juvenile justice system.⁴²⁹ Evidence from these studies may help inform the development of targeted suicide prevention efforts for youth in these settings.

⁴²³ reporter.nih.gov/project-details/10206479

⁴²⁴ reporter.nih.gov/project-details/10189928

⁴²⁵ reporter.nih.gov/project-details/10144019

⁴²⁶ www.ojjdp.gov/ojstatbb/njcda/pdf/jcs2013.pdf

⁴²⁷ www.sciencedirect.com/science/article/pii/S019074092032137X

⁴²⁸ reporter.nih.gov/project-details/10163914

⁴²⁹ reporter.nih.gov/project-details/10406228

Pulmonary Fibrosis

House Language

Many 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 3–5 years. The Committee urges NHLBI to support research into biomarkers that can aid in earlier, safer diagnosis of pulmonary fibrosis, as well as tools that can help predict which patients will experience disease progression. The Committee also encourages NHLBI to support the development of novel outcome measures for clinical trials in pulmonary fibrosis, such as imaging, and to continue to fund research involving early phase clinical assessment of novel drugs and personalized approaches to therapies. The Committee requests an update on PF research in the fiscal year 2024 Congressional Justification.

Conference Language

The agreement directs NIH to include updates on the following research, projects, and programs in the fiscal year 2024 Congressional Justification: metastatic breast cancer; 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 Heart, Lung, and Blood Institute (NHLBI) remains committed to providing support across a spectrum of basic, translational, and clinical research involving pulmonary fibrosis (PF). NHLBI continues its support for five collaborative projects to validate a set of model systems that reproduce essential disease-defining features of idiopathic pulmonary fibrosis (IPF), the most progressive and fatal form of PF.^{430,431} By developing several complementary model systems in parallel, these scientists are poised to identify common fibrotic pathways ripe for therapeutic intervention. In turn, these model platforms could be used to test novel treatments more meaningfully and efficiently. Early returns from this program include a now-published model using patient-derived inducible pluripotent stem cells carrying a specific gene mutation associated with IPF that can be used to test potential drug therapies.⁴³²

In recently completed translational studies supported by NHLBI, investigators highlighted the therapeutic potential of a compound known as saracatinib to treat IPF.^{433,434} This compound has now been advanced to a Phase 1b/2a clinical trial that is being supported by the National Center for Advancing Translational Sciences (NCATS).⁴³⁵ In another translational development that derived early support from 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, recently completed an industry-sponsored Phase 2 clinical trial

⁴³⁰ reporter.nih.gov/search/rogvFefYq0G8b7Nv5ArIgA/projects

⁴³¹ grants.nih.gov/grants/guide/rfa-files/RFA-HL-20-007.html

⁴³² pubmed.ncbi.nlm.nih.gov/34469722/

⁴³³ pubmed.ncbi.nlm.nih.gov/35998281/

⁴³⁴ pubmed.ncbi.nlm.nih.gov/36163190/

⁴³⁵ clinicaltrials.gov/ct2/show/NCT04598919

and showed promising results.^{436,437} NHLBI also recently initiated support for a Phase 1 clinical trial to test whether use of epigallocatechin-3-gallate is safe for use in IPF patients.⁴³⁸

NHLBI is continuing its support for a longitudinal natural history study that aims to observe PF at its inception. This study is enrolling individuals who are at high risk for developing PF based on family history as a means to better characterize how this disease manifests in its early stages and to aid in biomarker discovery that could enable earlier diagnosis and intervention. Advances in the use of novel imaging modalities to better and more readily detect PF are encouraging. 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.⁴³⁹ In an effort to improve the quality of life for patients with PF and other chronic lung diseases, NHLBI's Air You Wear Challenge is set to enter its second phase in early FY 2023. Phase I finalists have submitted applications to advance their ideas for the development of lighter, more portable oxygen devices to better serve the more than 1.5 million Americans who use supplemental oxygen.

The Institute's Prospective Treatment Efficacy in IPF Using Genotype for CAC Selection (PRECISIONS) study, a 5-year clinical trial aiming to enroll 200 IPF patients, is designed to apply the principles of precision medicine to the treatment of IPF.⁴⁴⁰ This pioneering trial seeks to enroll participants who carry a particular gene variant to potentially increase the likelihood that they benefit from treatment with a drug known as N-acetylcysteine and has recently surpassed the 50 percent enrollment mark on-schedule. The trial involves a partnership between NHLBI, investigators at 24 domestic academic centers, the Pulmonary Fibrosis Foundation (PFF), and the Three Lakes Foundation (TLF), and includes molecular analyses on biospecimens obtained from the PFF's Patient Registry. These analyses are intended to uncover novel genetic risk factors that will improve IPF diagnosis, prediction of progression, and understanding of its underlying mechanisms. The data will be made available to the broader research community through NHLBI's Trans Omics for Precision Medicine (TOPMed) and BioData Catalyst platforms upon study completion.^{441,442}

Lastly, to chart a path for the future of PF research, NHLBI co-sponsored and hosted a November 8-9, 2022, workshop entitled "The PF Stakeholder Summit" with the PFF and the TLF. This collaborative workshop provided a platform for sponsors, researchers, physicians, and patients to share innovative ideas for synergizing collective efforts in support of the PF research and patient communities. The summit identified current scientific gaps and will guide future research directions related to PF.

⁴³⁶ reporter.nih.gov/search/49ZPn-qrUUeVT2NUiqgTKQ/projects

⁴³⁷ pubmed.ncbi.nlm.nih.gov/35931801/

⁴³⁸ reporter.nih.gov/search/dFIWGOPUKEGAP23LCVYWdQ/project-details/10418169

⁴³⁹ reporter.nih.gov/search/VCQp5IEF5UqRB_TzyE4HIA/project-details/10054488

⁴⁴⁰ reporter.nih.gov/project-details/9822535#details

⁴⁴¹ topmed.nhlbi.nih.gov/

⁴⁴² biodatacatalyst.nhlbi.nih.gov/

Radiopharmaceutical Development

House Language

Recognizing the promise of radiotherapy treatments and other diagnostic uses, NCI has organized a Radiopharmaceutical Development Initiative (RDI), which is a specialized infrastructure for the clinical evaluation of novel theranostic radiopharmaceutical cancer therapies and which complements academic and industry development of these agents with early phase combination studies to test tolerability and early signs of efficacy. While clinical trials for radiopharmaceuticals are presently ongoing, domestic production of such drugs relies on a very small number of reactors, and the future loss of such reactors would not only deal a significant blow to domestic patients due to the short half-life of many of these drugs but would also limit NCI's ability to continue to support and conduct this important research. The Committee is aware of alternative technologies to produce radionuclides by accelerators, such as the one located at Brookhaven National Laboratory; however, some radionuclides can be produced only in nuclear reactors. Therefore, the Committee requests NIH, in conjunction with the Department of Energy, to provide an update in the fiscal year 2024 Congressional Justification regarding the impact shortages of medical isotopes and radiopharmaceuticals have on the ability to conduct cancer research.

Conference Language

The agreement directs NIH, in conjunction with the Department of Energy, to provide an update in the fiscal year 2024 Congressional Justification on the impact shortages of medical isotopes and radiopharmaceuticals have on the ability to conduct cancer research, including an analysis of infrastructure necessary to do so.

Action taken or to be taken

The shortage of radioisotopes limits the ability of the National Cancer Institute (NCI)-funded investigators to conduct important research. The United States Department of Energy (DOE) is the lead federal agency responsible for mitigating the shortage of critical isotopes. The DOE Isotope Program (DOE IP)⁴⁴³ has a multi-pronged mission to: (i) produce and distribute radioisotopes and enriched stable isotopes that are in short supply; (ii) maintain the required infrastructure to enable production and processing; (iii) conduct R&D on new and improved isotope production and processing techniques; (iv) build up the related workforce; and (v) ensure robust domestic supply chains to reduce United States dependency on foreign supply to maintain national preparedness. DOE IP works with United States industry to promote the availability of an adequate and high-quality isotope supply for continued stability, planned growth, and to facilitate commercialization of isotope production by the domestic private sector. These actions have enabled more robust radiopharmaceutical (RPT) supply chains and reduced United States dependency on foreign supplies. However, interest in radiopharmaceuticals is increasing; therefore, transient shortages and constrained availability are expected in the coming years until the DOE IP can increase capabilities. The DOE IP is pursuing several chemical processing initiatives to increase capacity and isotope availability (the Radioisotope Processing Facility and the Clinical Alpha Radioisotope Producer), as well as an initiative to develop enriched stable isotope capabilities in the United States (the Stable Isotope Production and Research Center).

⁴⁴³ science.osti.gov/Isotope-Research-Development-and-Production

Enriched stable isotopes are needed to produce the radionuclides, and currently the United States relies primarily on Russia for new inventories of feedstock.

The increased interest in RPT use and research is a sign of success of NCI's efforts to support research that aims to improve control of metastatic cancers not previously possible. NCI grants and contracts continue to contribute to the advance of RPT. Particularly, NCI's Small Business Innovation Research (SBIR) program supports several small businesses in the RPT arena. One of them is RadioMedix™, a clinical-stage biotechnology company focused on innovative targeted radiopharmaceuticals for diagnosis, monitoring, and therapy of cancer, that has recently initiated a Phase 2 clinical trial evaluating the safety and effectiveness of ²¹²Pb-DOTAMTATE (AlphaMedix™) in RPT of naïve patients with somatostatin receptor-expressing neuroendocrine tumors. Another is Radiopharmaceutical Imaging and Dosimetry, LLC (Rapid), which is using the expertise from a combined 45-plus years of NIH-funded research to provide expert dosimetry analysis accompanied by the advice needed to address regulatory requirements, design appropriate imaging protocols, select patients mostly likely to respond, reduce toxicities to normal organs, and optimize patient outcomes. The field is also encouraged by the United States Food and Drug Administration (FDA) approval of the radiopharmaceutical ¹⁷⁷Lu-PSMA (Pluvicto®), which is a substantial advance in the treatment of prostate cancer, as well as ¹⁷⁷Lu-DOTATATE (Lututhera®) approved for treatment of gastrointenteropancreatic neuroendocrine tumors. Both recent approvals are based upon the results of clinical trials conducted internationally, including several United States academic centers, and this progress continues to generate further RPT research, supported by various NCI funding mechanisms and supply chain efforts supported by DOE IP.

A critical point regarding supply chain is that the medically relevant isotopes required for these innovative radiopharmaceuticals cannot be stockpiled due to their intrinsic short half-lives (ranging from hours to days). Hence, this supply chain is “on demand” for patient need rather than through implementation of a “strategic stockpile.” This absolutely requires preservation of feedstock materials and highly specialized chemical processing facilities that interact to process the isotopes throughout the entire production chain to the clinical end users.

The DOE IP continually works on advancing the supply of radiopharmaceutical agents, as their production is challenging. Since FDA approval of ²²³RaCl₂ (Xofigo®) for treatment of metastatic prostate cancer, radionuclides emitting extremely cytotoxic alpha-particles became an attractive alternative to beta-emitters like ¹⁷⁷Lu. Actinium-225 (²²⁵Ac) is a medically relevant alpha-emitter in several active clinical trials; the demand for ²²⁵Ac exceeds the present production capacity (see the table below). Other promising alpha-emitters being tested in clinical trials are Astatine-211 (²¹¹At), Lead-212 (²¹²Pb), and Thorium-227 (²²⁷Th). Production methods for these isotopes are complex and can be complicated by any number of other challenges including feedstock supply, facility requirements and capabilities, and very short half-life (such as 6.72 hours in the case of ²¹¹At). DOE IP is supporting research on the production of new medically relevant radioisotopes (Cerium-134 (¹³⁴Ce), Lead-203 (²⁰³Pb), Antimony-119 (¹¹⁹Sb), Titanium-44 (⁴⁴Ti), etc.), the development of new production methods, and establishing strategic redundant capabilities to alleviate stress in the supply chain of these radioisotopes. Additionally, recent R&D investments have been focused on the development of new imaging

analog, or “theranostic pairs,” for existing alpha-emitting therapeutic radionuclides like ^{134}Ce for ^{225}Ac or ^{203}Pb for ^{212}Pb .

The NCI and DOE IP also cooperate on translational research associated with advancing novel isotopes for readiness in clinical trials. Such research includes toxicity and dosimetry studies, as well as radiolabeling.

Following are a few recent examples of the impact of radioisotope shortages on research:

1. A team of researchers from University of California in San Francisco and Los Angeles was not able to obtain ^{225}Ac for a phase 1/2 clinical trial of a new prostate-specific radiopharmaceutical. The trial was cancelled.
2. A molecular imaging and therapy clinic, participating in a clinical trial using ^{203}Pb as a diagnostic isotope for the evaluation of Gastrin-releasing peptide receptor (GRPR) expression in various common cancers including breast, prostate, lung, colon, melanoma, and cervical cancer, to predict the susceptibility of a patient's disease to ^{212}Pb radiopharmaceutical therapy using the same target, was not able to obtain ^{203}Pb . Therefore, the sponsor of the study made the very difficult decision to go ahead with the radiopharmaceutical therapy clinical trial using ^{212}Pb -GRPR without the ^{203}Pb -GRPR radiotracer for imaging. This unfortunate delay meant that two patients with advanced stages of cancer who had previously consented to participate had no other treatment options available and unfortunately, they succumbed to their disease in the interim. Further, patients now that are being evaluated for treatment with ^{212}Pb -GRPR in the absence of an appropriate pre-treatment non-invasive imaging test using an appropriate corresponding theranostic radiotracer are required to undergo a biopsy to prove GRPR expression of their disease prior to imaging.
3. A research group at University of Wisconsin lost several hundred mice and approximately two months of mouse model development time because of a several months delay of ^{90}Y delivery.
4. Researchers at Washington University, St. Louis, experienced a several months delay of ^{225}Ac and ^{227}Th . They had to push back in vitro chemical, cell and in vivo experiments. As many of the tumor models take months to develop, these delays are significant in particular for therapeutic efficacy studies with limited time period when the tumor size is appropriate for treatment. Additionally, the issues with ^{225}Ac and ^{227}Th delivery and uncertainty about future reliability of supply chain, make the researchers reluctant about planning larger studies that rely on these isotopes for fear that they will not be able to do the work.

The table below provides additional background regarding the supply status of several radionuclides as of October 2022 and represents robust coordinated efforts across the biomedical research community, with the DOE IP playing an important role in mitigating the impact of shortages on research.

Radionuclide	# Active Clinical Trials in the US (as of October 2022)	Indications	Additional Background and Supply Status
¹⁷⁷ Lu	56	prostate, breast, lung, kidney, head and neck, colorectal, pancreatic, ovarian, esophageal cancers, neuroendocrine tumors, pheochromocytoma, paraganglioma, thymus carcinoid, pheochromocytoma, paraganglioma, gliomas, meningioma, FAP-expressing solid tumors, advanced solid tumors overexpressing Gastrin-Releasing Peptide Receptor (GRRP), lymphoma	Currently the most popular therapeutic radioisotope. Commercially available through several providers.
²²⁵ Ac	16	lymphoma, colorectal cancer, prostate cancer, myeloma, neuroendocrine tumors, uveal melanoma, adenocarcinoma, FGFR3-expressing solid tumors	Produced using U-233 feedstock and accelerators at several DOE facilities. New accelerator-based production methods are being developed. Demand currently exceeds production capacity.
²¹¹ At	5	brain and central nervous system tumors, myeloma, lymphoma, nonmalignant disease treatable by allogeneic hematopoietic cell transplantation	Limited production site combined with a half-life of 7 hours makes the logistics challenging. DOE is establishing a production network to improve availability.

^{212}Pb	2	neuroendocrine tumors	Can be obtained for a generator, which makes it relatively easily available at academic centers.
^{227}Th	2	Prostate cancer, HER2-expressing cancers	Its application is currently limited and current supply is sufficient. Radiation decay “daughters” released from the targeting agent might lead to toxicity.

Rare Blood Cancers and Germline Mutations

House Language

The Committee commends NCI for collaborating with NHGRI in running natural history studies of patients with germline mutations and their families, which frequently lead to blood cancers including acute myeloid leukemia (AML). More research on how genetic dispositions, such as RUNX1 familial platelet disorder (RUNX1–FPD), lead to rare blood cancers will ultimately support the discovery of treatments that could prevent malignancy through advances in early detection and early treatment for all blood cancers. Interest in this field has grown significantly in recent years, and the Committee strongly urges NCI to initiate new and expanded funding opportunities related to germline predispositions to rare blood cancers. The Committee is pleased to hear that NCI will soon be launching a precision medicine clinical trial for AML and myelodysplastic syndromes and requests an update in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

The National Institutes of Health (NIH), including the National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), remain committed to understanding how genetic predispositions contribute to the development of myelodysplastic syndromes (MDS, a group of disorders where immature bone marrow blood cells do not mature or function properly) and acute myeloid leukemia (AML, a type of blood cancer), as well as identifying best practices for managing the care of patients with these conditions.

Expected to launch in the first half of calendar year 2023, the NCI-supported myeloMATCH precision medicine initiative is a trial that will screen patients with MDS and AML to identify molecular and clinical features of their disease.⁴⁴⁴ Participants will then be assigned to treatment sub-studies based on these features and enroll in sequential randomized phase II clinical trials of novel therapies. Investigators will follow patients from initial diagnosis throughout their treatment and test for meaningful improvements in their disease, such as minimal residual disease (MRD)-negative remissions (i.e., patients have no cancer symptoms, and cancer cells are not detected).

Additional features of the MyeloMATCH trial include:

- Testing of blood and bone marrow samples for specific cancer markers with a rapid 72-hour lab turnaround (currently takes 2-3 weeks in standard treatment)
- Tumor mutational profiling, including detection of RUNX1 mutations, before treatment starts to guide treatment protocol (sub-study) assignments
- Ongoing re-evaluation of tumor mutational profiles over the sequence of treatment sub-protocols to help determine how to target remaining disease more effectively
- A tier-advancement protocol: a potential participant can start with standard (approved) treatment and advance to a study, if medically appropriate based on molecular profiling
- Once screened, a person may be re-evaluated for possible participation in other MyeloMATCH sub-studies

⁴⁴⁴ clinicaltrials.gov/ct2/show/NCT05564390

NCI and the five NCI-supported National Clinical Trials Network (NCTN) groups are leveraging their existing informatics and clinical trials infrastructure to coordinate myeloMATCH. NCI's Molecular Diagnostic Network (MDNet) will perform the molecular testing for myeloMATCH and other NCI precision medicine trials for the purpose of assigning patients to treatment studies.

In addition to myeloMATCH, upcoming research for AML includes the Leukemia & Lymphoma Society (LLS) PedAL (Pediatric Acute Leukemia) project aimed at pediatric patients. LLS PedAL will be a precision medicine trial taking place at clinical sites around the world that simultaneously test multiple targeted therapies and is currently in development.⁴⁴⁵ For the North American implementation, LLS is partnering with the NCI supported Children's Oncology Group clinical trials network.

⁴⁴⁵ www.lls.org/dare-to-dream/pedal

Repeat Expansion Diseases

House Language

The Committee recognizes the rapidly emerging science on DNA repeat expansions, which causes over 50 distinct diseases. Myotonic dystrophy (DM1 and DM2) is one of these repeat expansion diseases and has served as paradigm for a class of diseases caused by repeat instability and toxic RNA, which includes C9ORF72/amyotrophic lateral sclerosis/frontotemporal dementia, Huntington's disease, and many common forms of dominantly inherited ataxias. Due to recently developed molecular and cell biological tools, a common thread has recently emerged, that repeat expansions may underlie multiple neurodegenerative conditions. The Committee encourages NIH to explore the most effective approaches to support trans-NIH research on repeat expansions and consider new funding mechanisms across multiple Institutes and Centers to support scientific discoveries that will lead to treatments and cures for these genetic disorders and related conditions. The Committee requests an update on these activities in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

Multiple Institutes and Centers within the National Institutes of Health (NIH) support a broad portfolio of research on diseases caused by DNA repeat expansions including myotonic dystrophy, and many of these are at the forefront of trials of genomic therapies. As part of the cross-NIH Senator Paul D. Wellstone Muscular Dystrophy Specialized Research Centers⁴⁴⁶, NIH funds a collaborative research center at the University of Rochester and University of Florida to clarify the cellular and molecular mechanisms by which repeat expansions cause myotonic dystrophy, to strengthen the pipeline of preclinical therapeutic agents, and to generate the tools and knowledge for conducting highly informative clinical trials for myotonic dystrophy. The center is also training the next generation of myotonic dystrophy researchers and maintains the National Registry for Myotonic Dystrophy.

In addition to a focus on the mutant proteins coded by DNA repeat mutations, recent NIH-funded studies are examining how the repeat expansions in RNA induce toxic effects by disturbing movement of RNA within a cell and causing widespread changes in the timing, amounts, and types of protein that is produced from messenger RNA (mRNA). NIH-funded projects are also developing gene-based therapies, such as antisense oligonucleotides and RNA interference, or small molecule drugs that reduce disease-causing, repeat expansion-containing mRNA, or disrupt disease-associated binding of the messenger RNA with RNA-processing proteins. These approaches are also being developed as treatment strategies for other repeat expansion diseases. For example, NIH-funded studies of Huntington's disease, amyotrophic lateral sclerosis (ALS), and frontotemporal degeneration caused by a repeat expansion in C9orf72 are optimizing the technologies for gene-based therapies to deliver therapies more safely and effectively to the brain and spinal cord, to improve their ability to silence the harmful copy of a gene, and to reduce their effects on the healthy copy of a gene. Another study is developing innovative strategies to develop small molecules that bind and degrade disease-causing RNA repeat expansions. These advances may facilitate development of gene- or small molecule-based therapies for myotonic dystrophy.

⁴⁴⁶ wellstonemdcenters.nih.gov/

Spina Bifida

House Language

The Committee encourages NIA, NIDDK, NICHD, and NINDS to study the causes and care of the neurogenic bladder and kidney disease in order to improve the quality of life of children and adults with spina bifida; to support research to address issues related to the treatment and management of spina bifida and associated secondary conditions, such as hydrocephalus and sudden death in the adult spina bifida population; and to invest in understanding the myriad comorbid conditions experienced by individuals with spina bifida, including those associated with both paralysis and developmental delay. The Committee requests and update in the fiscal year 2024 Congressional Justification on research findings on spina bifida and issues related to it. The Committee supports the specific efforts of NICHD to understand early human development; set the foundation for healthy pregnancy, and lifelong wellness of women and children; and promote the gynecological, andrological, and reproductive health for people with spina bifida. Additionally, NIH is encouraged to identify sensitive time periods to optimize health interventions; improve health during transition from adolescence to adulthood; and ensure safe and effective therapeutics and devices for adults as well as children.

Action taken or to be taken

The National Institutes of Health (NIH) is currently funding studies to understand and treat neurogenic bowel and bladder to improve the quality of life of children and adults with spina bifida. For example, researchers funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) are studying advances in neuromodulation therapies to improve bowel and bladder function. In addition, the National Institute of Neurological Disorders and Stroke (NINDS), supports research relevant to paralysis and neurogenic bladder in spina bifida, within a broader portfolio on spinal cord injury and repair. Current NINDS-funded studies are pursuing multiple strategies to restore bladder function, including a surgical approach to reestablish neural connectivity to the bladder and urethral sphincter, a method to promote regeneration of brainstem nerve fibers that control urination, electrical stimulation of spinal cord reflex pathways involved in bladder control, and a novel drug to induce “on-demand” bladder voiding.⁴⁴⁷ The National Institute of Diabetes and Digestive Kidney Diseases (NIDDK) supports investigators working to better understand the urologic and kidney complications of spina bifida. For example, NIDDK funds research focused on the development of methods to assess and address the impact of urinary incontinence and fecal incontinence on quality of life of youth and adults with spina bifida.⁴⁴⁸ Additionally, NIDDK supports research on strategies to improve adherence to treatment in youth with spina bifida and neurogenic bladder.⁴⁴⁹ In August 2022, NIDDK hosted a meeting to identify gaps in the understanding of interactions between the nervous system and the genitourinary system.⁴⁵⁰

⁴⁴⁷ reporter.nih.gov/search/8HewT1oQdEKTmqIXTpmhrA/projects; reporter.nih.gov/search/J6PIOw1qNk-qzIn9_W81Kg/projects; reporter.nih.gov/search/MF3bsMDpSki1yYXdVvaC-w/project-details/10259668; reporter.nih.gov/search/kSJMwG7AvU2jW60DwOEVZw/project-details/10114336

⁴⁴⁸ reporter.nih.gov/search/XvooGcYioU2Hz2NWasWnUw/project-details/10380173; reporter.nih.gov/search/XvooGcYioU2Hz2NWasWnUw/project-details/10017967

⁴⁴⁹ reporter.nih.gov/search/XvooGcYioU2Hz2NWasWnUw/project-details/9951035

⁴⁵⁰ www.nidDK.nih.gov/news/meetings-workshops/2022/neurourology-bridging-basic-clinical-science-understand-urologic-disease

Many of the research needs discussed could help inform future research directions in understanding and treating the urological complications of spina bifida.

NIH also supports research to address issues related to the treatment and management of spina bifida and associated secondary conditions. For example, NICHD-funded researchers found that prenatal repair of myelomeningocele, a severe form of spina bifida where the spinal cord protrudes out of the body, reduces the incidence and severity of associated orthopedic conditions.⁴⁵¹ In addition, NINDS researchers are developing novel therapies for treating myelomeningocele before birth, including bioengineered scaffolds⁴⁵² with neuroprotective and structural functions and an easily deployed “smart patch”⁴⁵³ to close the spinal defect that automatically degrades with healing, minimizing surgical follow-up and improving outcomes. There is also an ongoing clinical trial, developed from NINDS-supported research, in which placental stem cell patches are used to treat myelomeningocele that has shown promising results. NINDS also funds research to understand the normal development of the neural tube, including studies to identify the mechanisms of action of folate⁴⁵⁴ and neurotransmitter activity⁴⁵⁵ during neural tube development. Other related NINDS-funded projects target hydrocephalus, which often affects people with spina bifida. For example, ongoing studies are using non-invasive imaging methods, including ultrasound⁴⁵⁶ and optical⁴⁵⁷ approaches to detect elevated intracranial pressure and inadequate brain blood flow to enable timely and accurate intervention to improve hydrocephalus-associated neurologic outcomes, including cerebral palsy and developmental delay. NINDS-funded investigators are also working to understand and prevent complications linked to the infection and failure of shunts,⁴⁵⁸ the most common treatment for hydrocephalus. Furthermore, NINDS continues to encourage research on the mechanisms involved in prenatal and pediatric hydrocephalus and to develop new research tools and therapies through Notices of Special Interest.⁴⁵⁹ Lastly, the National Institute on Aging (NIA) supports research on systems to improve pressure-reducing in-seat body movement in adults with spinal cord injury and related disorders, which can improve the management of skin health of adults who use or sit in wheelchairs for long periods of time.⁴⁶⁰

NIH is also investing in research that identifies the variety of factors that cause spina bifida, including genetics. NIH-funded researchers compiled a list of candidate genes that may underlie the development of spina bifida by examining genes known to cause spina bifida in mice and genes that occur in families of individuals with spina bifida or related conditions.⁴⁶¹ Genetic sequencing of a group of individuals with spina bifida revealed genes that may cause spina bifida. Future work that focuses on the prevalence of these genes in a larger group of individuals with spina bifida will help determine which of these genes have the potential to cause spina

⁴⁵¹ pubmed.ncbi.nlm.nih.gov/33165214/

⁴⁵² reporter.nih.gov/search/kl_61Yabk0a1mfcxB66t0g/projects

⁴⁵³ reporter.nih.gov/search/FH63djA3FkWo4phOp2H2WA/project-details/10380758

⁴⁵⁴ reporter.nih.gov/search/8QQ_Gpd0CEay--_tZqlgAw/projects

⁴⁵⁵ reporter.nih.gov/search/g9FLGyqrr0-w-w0v8x_aUQ/projects

⁴⁵⁶ reporter.nih.gov/search/5wG0ItqEPES_W_h6hX-e7g/projects

⁴⁵⁷ reporter.nih.gov/search/njOryQhUMkaiVat7H_ly4A/projects

⁴⁵⁸ reporter.nih.gov/search/xbMKxI6Su0S_qSueqvKOig/projects

⁴⁵⁹ grants.nih.gov/grants/guide/notice-files/NOT-NS-23-004.html; grants.nih.gov/grants/guide/notice-files/NOT-NS-23-003.html

⁴⁶⁰ reporter.nih.gov/search/phUbOKYBd0GF9zwR5kTQjg/project-details/10289178

⁴⁶¹ reporter.nih.gov/search/wHRjtlDf8EiZWYrYMXJinsw/projects

bifida in humans. In another study, researchers looked at whether variants of the CIC gene, which is involved in transporting folate to the nervous system, are associated with the presence of neural tube defects.⁴⁶² Insufficient folate levels increase the risk of neural tube defects due to folate's role in neural development. Each variant was found to change the functioning of the gene in a way that could reduce folate levels in individuals, suggesting that the CIC gene variants may contribute to the risk of developing spina bifida and other neural tube defects.

NIH also supports research on the reproductive health of young people with spina bifida. For example, NICHD-funded researchers are developing a user-centered online sexual health curriculum for girls with spina bifida that is tailored to their learning style and addresses their sexual health topics.⁴⁶³

These are a few of the research examples supported by NIH to study the causes and care of the neurogenic bladder and kidney disease and improve the quality of life of children and adults with spina bifida.

⁴⁶² pubmed.ncbi.nlm.nih.gov/36054333/

⁴⁶³ reporter.nih.gov/project-details/10523587

Suicide Prevention

House Language

The Committee is encouraged that 2020 was the second year in two decades in which the suicide rate decreased. However, suicide was the 12th leading cause of death overall in the U.S. in 2020, and third among youth and young adults ages 10–24. The Committee remains committed to providing the resources necessary to address the current youth mental health crisis. The Committee commends NIMH for consistently expanding resources for suicide screening and prevention research in recent years and strongly encourages the Institute to continue to prioritize suicide prevention research in fiscal year 2023, with special emphasis on producing models that are interpretable, scalable, and practical for implementation. In addition, the Committee encourages NIMH to prioritize research efforts related to school-based suicide prevention models to evaluate suicide prevention interventions, strategies, and programs, including assessments of the effects of the COVID–19 epidemic on young adults and children. The Committee requests that NIMH provide an update on these efforts in the fiscal year 2024 Congressional Justification.

Action taken or to be taken

Suicide prevention research is a top priority for NIMH. Although the national suicide rate decreased from 2018 to 2020, suicide remains the second leading cause of death in youth ages 10-14 and third leading cause of death for youth ages 15-24.^{464,465} Additionally, in early 2021, emergency department visits for suspected suicide attempts were 51 percent higher for adolescent girls and 4 percent higher for adolescent boys compared to the same time period in early 2019, raising concerns about youth mental health and possible impacts of the COVID-19 pandemic.⁴⁶⁶ Research to better understand the mental health impacts of the pandemic, including concern about oneself or loved ones being infected and becoming seriously ill, responses to grief and instability that may have been caused by a death or a job loss in the family, or indirect consequence of public health measures, remains an urgent and significant priority.⁴⁶⁷

Detecting suicide risk in educational settings represents a critical opportunity for suicide prevention, as schools are often a primary source of mental health care for youth and young adults.⁴⁶⁸ As an example of NIMH-funded research in this area, one current project is adapting Youth Aware of Mental Health (YAM), an established school-based mental health promotion program, for a racially diverse middle school population.⁴⁶⁹ Researchers are exploring the feasibility of implementing YAM, as well as its effectiveness on reducing suicidal ideation and improving mood symptoms in the 3 months following the program.⁴⁷⁰ Other NIMH-funded researchers are leveraging existing data to understand the impact of childhood universal prevention programs on suicidal behaviors, depression and anxiety symptoms and diagnoses, and

⁴⁶⁴ www.cdc.gov/nchs/products/databriefs/db433.htm

⁴⁶⁵ wisqars.cdc.gov/data/lcd/home

⁴⁶⁶ www.cdc.gov/mmwr/volumes/70/wr/mm7024e1.htm?s_cid=mm7024e1_w

⁴⁶⁷ pubmed.ncbi.nlm.nih.gov/33353380/

⁴⁶⁸ pubmed.ncbi.nlm.nih.gov/30883761/

⁴⁶⁹ www.y-a-m.org/

⁴⁷⁰ reporter.nih.gov/project-details/10338185

psychosis symptoms in early adulthood.⁴⁷¹ NIMH also recognizes that COVID-19-related school closures and remote schooling may have limited access to resources, leaving many youth disconnected from their primary sources of mental health treatment during the pandemic. To address this challenge, NIMH provided research supplements to adapt school-based interventions for youth to be delivered via telehealth during the COVID-19 pandemic,⁴⁷² and plans to support school-based studies to understand and reduce the mental health impacts of the pandemic.⁴⁷³

NIMH is also supporting studies on family-based interventions, such as Family Check-up, an intervention originally designed to prevent the development of substance use and behavioral problems in youth. NIMH-funded researchers found that Family Check-up effectively reduced suicide risk in a racially, ethnically, and gender diverse sample of youth, even nine years after the initial intervention.⁴⁷⁴ Suicide prevention strategies that leverage community strengths and social networks can also be effective. For example, sexual and gender minority (SGM) youth often seek mental health services from SGM-focused community organizations; however, staff in these organizations may not have specialized training needed to provide care. With support from NIMH, researchers aim to train staff at two organizations to effectively deliver Behavioral-Health Works, an evidence-based youth suicide prevention program.⁴⁷⁵ The research team will subsequently measure whether the program effectively increases risk identification and referrals to care, as well as the program's feasibility.

In 2021, NIMH launched the Practice-Based Suicide Prevention Research Centers program, which is focused on developing, testing, and refining effective and scalable interventions at key points in the chain of care.⁴⁷⁶ The centers aim to reduce suicide across a range of at-risk groups, including people who experience disparities in mental health services and outcomes. In one center, NIMH-funded researchers are expanding the capacity of pediatric primary care to identify, refer, and manage youth at risk for suicide, particularly Black youth.⁴⁷⁷ In addition to research supported at the centers, NIMH-funded researchers are developing integrative approaches that place trained community health workers in pediatric primary care settings to improve the capacity to detect suicide risk and coordinate care for Latinx youth, particularly those in immigrant families with parents who have limited English proficiency.⁴⁷⁸

In addition to funding research,⁴⁷⁹ NIMH continues to collaborate with researchers, mental health practitioners, and members of the public to advance the understanding of suicide risk in youth and to enhance the real-world impact of research findings. In 2021, NIMH hosted a series of research roundtables to review the state of the science, identify research priorities, and discuss

⁴⁷¹ reporter.nih.gov/project-details/10144019

⁴⁷² reporter.nih.gov/project-details/10206479

⁴⁷³ grants.nih.gov/grants/guide/pa-files/PAR-21-287.html

⁴⁷⁴ www.nimh.nih.gov/news/research-highlights/2022/family-based-intervention-lowers-long-term-suicide-risk-in-youth

⁴⁷⁵ reporter.nih.gov/project-details/10440817

⁴⁷⁶ www.nimh.nih.gov/research/research-funded-by-nimh/research-initiatives/practice-based-suicide-prevention-research-centers

⁴⁷⁷ reporter.nih.gov/project-details/10435003

⁴⁷⁸ reporter.nih.gov/project-details/10440113

⁴⁷⁹ www.nimh.nih.gov/news/research-highlights/2021/understanding-the-characteristics-of-suicide-in-young-children

challenges and opportunities in identifying children and preteens at risk for suicide.⁴⁸⁰ Further, researchers in the NIMH Intramural Research Programs are collaborating with the American Academy of Pediatrics (AAP) to expand pediatric depression screening to identify suicide risk after studies found that depression screening alone failed to capture many at risk for suicide.⁴⁸¹ NIMH experts also collaborated with AAP and the American Foundation for Suicide Prevention to produce a Blueprint for Youth Suicide Prevention for pediatric health providers.⁴⁸²

⁴⁸⁰ www.nimh.nih.gov/news/events/2021/understanding-suicide-risk-among-children-and-pre-teens-a-synthesis-workshop

⁴⁸¹ pubmed.ncbi.nlm.nih.gov/33712380/

⁴⁸² www.aap.org/suicideprevention

Surveillance, Epidemiology, and End Results (SEER) Registry

Conference Language

The agreement directs NIH to include updates on the following research, projects, and programs in the fiscal year 2024 Congressional Justification: metastatic breast cancer; 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 United States cancer registry system represents a considerable investment toward establishing the infrastructure needed to collect information on individuals diagnosed with cancer. Data from cancer registries are often used to identify observed disparities in incidence, treatment, and outcomes. The National Cancer Institute (NCI)'s Surveillance, Epidemiology and End Results (SEER) Program, which is preparing for the celebration of its 50th anniversary in collecting and releasing cancer statistics, is the primary source of reports on trends in cancer mortality rates and sets national benchmarks for incidence and survival rates.⁴⁸³ SEER is the only population-based source of long-term cancer incidence and survival data in the United States. The objective of this program is the collection of high-quality cancer surveillance data while addressing the challenges of a rapidly evolving cancer care environment.

Cancer registries represent a sampling of cancer patients and contain considerable information on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for mortality outcomes. As researchers have learned more about the complexities of cancer, SEER registries have expanded to collect additional data to inform surveillance research. Currently, SEER registries collect information on several key predictive and prognostic factors, such as HER2 for breast cancer, PSA for prostate cancer, and HPV status for some cancers including cervical. Many registries can identify cases soon after diagnosis (called rapid case ascertainment) for inclusion in studies.⁴⁸⁴

In FY 2022, SEER made awards to three new CORE registries and nine new Research Support registries. These awards increased SEER Program coverage to 48 percent of the United States population, which allows for more refined data on important cancer sites and subsites (for example, leukemia = site, acute myeloid leukemia = subsite). This also increased SEER Program coverage of minority/underserved populations to now include 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. The SEER Program also designated two additional Core registries as SEER*Data Management Systems (SEER*DMS).⁴⁸⁵ This infrastructure supports all core cancer registry functions, improves cost efficiency, improves data quality and consistency, increases efficiency, and increases the sharing of knowledge and experience among registries.

⁴⁸³ seer.cancer.gov/

⁴⁸⁴ grants.nih.gov/grants/guide/notice-files/NOT-CA-21-020.html

⁴⁸⁵ seer.cancer.gov/seerdms/index.html

SEER has continued to expand its collaboration with the United States Department of Energy (DOE), including putting into production DOE Application Programming Interfaces (APIs) in 13 registries to move towards “real-time” incidence reporting.

The SEER Program is focusing on childhood cancer in collaboration with the NCI Childhood Cancer Data Initiative (CCDI). This includes the development of an infrastructure for statistical information for pediatric cancer, called NCCR*Explorer.⁴⁸⁶ In addition, migrating SEER Research Support registries and non-SEER registries to SEER*DMS Lite has broadened the coverage of U.S. pediatric cancers to include approximately 70 percent of children with cancer.

Additional achievements by the SEER Program in FY 2022 include the following:

- Enhanced data collection for cancer cases by expanding and continuing multiple SEER data linkages, including with pharmacy and genomic data companies.
- Completed the Virtual Tissue Repository (VTR) pilot. The VTR will supply cancer researchers with access to clinical data and deidentified tissue, obtained through clinical care, for secondary use in population-scale research.
- Continued/expanded the Virtual Pooled Registry (VPR) pilot to include 45 U.S. registries and other federal entities. The VPR seeks to utilize template applications, linkage software, and a centralized Institutional Review Board (IRB) to remove inefficiencies and redundancies investigators encounter when working on a multi-site study.
- Developed a SEER data access and authorization system that enables access but provides increased protection for patient privacy and confidentiality (even for de-identified datasets). Data set requests initiated by investigators will be assigned a tier based on the nature of the request and will determine how the request is handled (e.g., require use of a Central IRB).
- Contracted with a Central IRB that supports the new data access and authorization system, as well as enhancing efficiency for data access to other projects such as the VPR.

As part of the plan to expand and enhance the clinically relevant data incorporated into SEER, a Request for Information for cancer data acquisition was released as a first step towards identifying and contracting with new data owners.⁴⁸⁷ In FY 2022 NCI invested approximately \$45 million in the core operations of the SEER Program and anticipates continued enhancement of the SEER registries in the future.

⁴⁸⁶ nccrexplorer.ccdi.cancer.gov

⁴⁸⁷ sam.gov/opp/83cb460ca0e84277920d08e62eaa0e6b/view

Temporomandibular Disorders (TMD)

Conference Language

The agreement encourages NIDCR to maintain a patient-centered approach in the implementation of the TMD-IMPACT Concept and to seek collaborators from other government agencies such as the Department of Veterans' Affairs (VA) and the Department of Defense (DOD), as well as from within NIH itself. The agreement directs NIH to provide an update in the fiscal year 2024 Congressional Justification on efforts to implement the next phase of the initiative, including the recruitment of other NIH ICs as partners, the role of the patient perspective, and NIDCR's use of the National Academies of Sciences, Engineering, and Medicine (NASEM) Report on TMDs and the TMJ Patient-led Roundtable.

Action taken or to be taken

The National Institute of Dental and Craniofacial Research (NIDCR) is working with other NIH Institutes, Centers, and Offices (ICOs) to establish a national, interdisciplinary patient-centered research Collaborative, called the Temporomandibular Disorders Collaborative for Improving Patient-Centered Translational Research (TMD IMPACT).⁴⁸⁸ Recommendations from the recent National Academies of Sciences, Engineering, and Medicine (NASEM) consensus study report on TMDs⁴⁸⁹ and the Temporomandibular Joint Disorder (TMJ) Patient-led Round-Table efforts, including consideration of the patient perspective, helped to inform the TMD IMPACT concept. A Multi-Council Working Group⁴⁹⁰ was also convened from January 2020 to August 2021 to consider the recommendations of the NASEM report, from which a general framework for the TMD IMPACT concept was derived. TMD IMPACT will use a cohesive and coordinated, interdisciplinary approach to advance TMD basic and clinical research, research training, and translation to evidence-based treatments and improved clinical care for TMDs.

The TMD IMPACT concept was unanimously approved by the National Advisory Dental and Craniofacial Research Council in January 2022⁴⁹¹ and is currently under development in two stages. The first stage will consist of a planning grant funding opportunity announcement (FOA) and planning grant awards in preparation for the release of the TMD IMPACT Collaborative FOAs in the second stage. The planning grant awards will enable institutions to develop partnerships, infrastructure, and capabilities needed to address the major goals of the subsequent TMD IMPACT Collaborative. The planning grant FOA is anticipated to be released in FY 2023 and the ensuing awards are expected to be funded in FY 2024. The FOAs that will solicit applications for the subsequent TMD IMPACT Collaborative are anticipated to be released approximately 9 to 12 months after the planning grant awards are made.

Advances in TMD research and translation to patient care have not been as rapid as advances for other musculoskeletal disorders, partly due to the variety of underlying causes, complexity, sex and gender differences, and multi-system involvement in TMDs. To address this challenge, NIDCR is collaborating with several NIH ICOs, including the National Center for

⁴⁸⁸ www.nidcr.nih.gov/grants-funding/funding-priorities/future-research-initiatives/tmd-collaborative-improving-patientcentered-translational-research-tmd-impact

⁴⁸⁹ www.nationalacademies.org/our-work/temporomandibular-disorders-tmd-from-research-discoveries-to-clinical-treatment

⁴⁹⁰ www.nidcr.nih.gov/news-events/news/statement-on-tmd-report

⁴⁹¹ www.nidcr.nih.gov/about-us/advisory-committees/advisory-council/january-2022

Complementary and Integrative Health (NCCIH), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Biomedical Imaging and Bioengineering (NIBIB), National Institute of Neurological Disorders and Stroke (NINDS), Office of Behavioral and Social Sciences Research (OBSSR), and Office of Research on Women's Health (ORWH), to ensure that the Collaborative will use interdisciplinary approaches and strategies to advance research and translation to patient care. NIDCR anticipates that additional NIH ICOs will participate in the development of the FOAs and implementation of the Collaborative during the course of the planning stage. NIDCR is also in discussions with the United States Food and Drug Administration (FDA) regarding their participation in the development and implementation of the Collaborative.

Trans-NIH Pediatric Research Consortium (N-PeRC)

House Language

The Committee is aware of the N-PeRC that was established in 2018 to better coordinate pediatric research activities across multiple Institutes and Centers. The Committee supports the goals and objectives of N-PeRC and requests that NIH update the Committee on its activities and focus of multi-Institute or -Center pediatric research projects implemented as a result of N-PeRC. Additionally, the Committee requests a report in the fiscal year 2024 Congressional Justification on how N-PeRC plans to encourage longitudinal studies of the physical, mental, and behavioral health impacts of COVID-19 on children, including multisystem inflammatory syndrome in children (MIS-C), as well as plans for N-PeRC's focus over the coming three years.

Action taken or to be taken

The National Institutes of Health (NIH) is dedicated to supporting 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; in FY 2021, NIH spent more than \$5.5 billion in this area.⁴⁹² The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) provides approximately 16 percent of the total amount of pediatric research funding, joined by 23 other NIH Institutes and Centers (ICs). The NIH Pediatric Research Consortium (N-PeRC), led by NICHD, was established in 2018 to harmonize pediatric research efforts across NIH ICs.⁴⁹³ Nearly all NIH ICs and Offices have appointed senior level representatives to N-PeRC. Among the issues important across ICs that have provided areas of focus for the first several years of N-PeRC are those faced by adolescents as they transition to adult health care, pediatric medical device development, the effects of the COVID-19 pandemic on children, and pediatric research workforce training. Nearly every IC invests in pediatric research training and career development.

Developing pediatric medical devices poses unique challenges compared to adult devices. For example, children's bodies grow and change rapidly, so designs need to be adaptable. Additional ethical considerations also arise when working with pediatric populations. Responding to NIH-wide interest in improving and stimulating development of pediatric medical devices, N-PeRC formed a Pediatric Medical Devices (PMD) working group. This group has spearheaded efforts to develop a public-private partnership (PPP) for PMD development. To that end, a Request for Information (RFI) was published (NOT-EB-22-008)⁴⁹⁴ in June 2022 to seek public input on research gaps, needs, best practices, innovative study designs and measurement, resources and data resources, and opportunities to inform a PPP to enhance the PMD development space. Respondents were asked to comment on potential partners to ensure the success of PMD development; involvement of the private industry; priorities in PMD innovation, research, and commercialization; measures to evaluate program success; clinical trial infrastructure, data sharing, and protocol standardization; and reimbursement challenges. Comments were also encouraged to address unique challenges facing health disparity

⁴⁹² report.nih.gov/funding/categorical-spending/

⁴⁹³ www.nichd.nih.gov/research/supported/nperc

⁴⁹⁴ grants.nih.gov/grants/guide/notice-files/NOT-EB-22-008.html

populations in the use of PMD. The comment period concluded on September 21, 2022, and the input will be used to inform future steps in N-PeRC's public-private engagement in PMD development.

N-PeRC has also played a pivotal role in developing and sustaining pediatric Coronavirus Disease 2019 (COVID-19) research efforts. In March 2020, N-PeRC rapidly formed a working group with representation from 18 NIH ICs, led by NICHD and the National Institute on Drug Abuse (NIDA), to address pediatric issues related to COVID-19. The working group facilitated supplemental funding for projects in FY 2020 and FY 2021, totaling more than \$5 million. Some of these projects, funded by ICs and the Office of the Director, include:

- Augmenting a large cohort study including more than 10,000 children to examine pandemic-related perturbations in developmental trajectories of brain functioning, cognition, substance use, academics, social functioning, and physical and mental health.⁴⁹⁵
- A study assessing the impact of a universal intervention on the mental health of adolescent Black children during COVID-19 and identifying longitudinal multi-level risk and protective factors that predict adolescent mental health during the pandemic. The assessment examines multiple domains of mental health, including emotional wellness, and uses geographic information systems (GIS) data to explore neighborhood factors.⁴⁹⁶
- Testing a coping intervention in preadolescent urban youth designed to prevent the onset of anxiety, depression, and post-traumatic stress symptoms in children facing chronic stress.⁴⁹⁷
- A study to examine COVID-related changes in substance use and relationships between substance use and psychosocial and other variables that may be affected by the pandemic among American Indian adolescents who live on or near reservations.⁴⁹⁸

The N- PeRC COVID-19 working group also aided other NIH-wide research efforts, supporting the inclusion of children in the Rapid Acceleration of Diagnostics (RADx)⁴⁹⁹ programs and the REsearching COVID to Enhance Recovery (RECOVER) effort.⁵⁰⁰ In particular, the RADx-RadicalSM program includes the Predicting Viral-Associated Inflammatory Disease Severity in Children with Laboratory Diagnostics and Artificial Intelligence (PreVAIL kIDs) study, which aims to develop innovative approaches for understanding the underlying factors that influence the range of symptoms present in children infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), including multisystem inflammatory syndrome in children (MIS- C). The PreVAIL kIDs program is part of the Collaboration to Assess Risk and Identify loNG-term outcomes for Children with COVID (CARING for Children with COVID),⁵⁰¹ a cooperative NIH effort to improve understanding of the effects of SARS-CoV-2 infection and MIS-C on children.

⁴⁹⁵ reporter.nih.gov/project-details/10307028

⁴⁹⁶ reporter.nih.gov/project-details/10229056

⁴⁹⁷ reporter.nih.gov/project-details/9893921

⁴⁹⁸ reporter.nih.gov/10321039

⁴⁹⁹ www.nih.gov/research-training/medical-research-initiatives/radx

⁵⁰⁰ recovercovid.org

⁵⁰¹ caring4kidswithcovid.nih.gov/research.html

Although the PreVAIL kids studies will be ongoing through 2024, many investigators have already published early results of some of their research. For example, one research group compared severity of disease in hospitalized patients with MIS-C between the alpha COVID-19 strain and the Delta variants and found that patients with MIS-C associated with the Delta variants had lower severity during hospitalization compared with the alpha variant.⁵⁰² Another group of researchers focused on the effectiveness of SARS-CoV-2 mRNA vaccines in children with inflammatory bowel disease (IBD). They found that the durability of immunity was lower against SARS-CoV-2 Omicron BA.1, BA.2, and BA.3 variants after a second and third vaccine dose in children and young adults with IBD receiving biologics, compared to healthy children.⁵⁰³ Finally, a group of researchers compared Kawasaki disease (KD) with MIS-C, as the two diseases have many similar clinical manifestations. The scientists harnessed the power of artificial intelligence to identify a four-gene signature that distinguish MIS-C and KD, although they share similar host immune response pathways.⁵⁰⁴ The study further identified potential targets for MIS-C treatment and laboratory parameters that can be useful to monitor disease severity. To facilitate additional and long-term research on the physical, mental, and behavioral health impacts of COVID-19 on children, in 2022 NIH also released Notices of Special Interest (NOT-HD-22-002, NOT-HD-22-003)^{505, 506} to provide an avenue for researchers to pursue funding to conduct research addressing emerging and existing COVID-related issues among pregnant and lactating people, infants, children and adolescents, and individuals with physical and/or intellectual disabilities. One of the funded supplements is supporting a Pediatric COVID Dashboard, which conveys publicly accessible information to help assess trends in pediatric COVID infection, including geographic distribution and disease severity over time (associated with different variants). This funding opportunity is available until 2024.

During the next three years, N-PeRC plans to continue efforts described above as well as to embark on new areas of research collaboration. Led by the PMD working group, N-PeRC will consider ways to enhance NIH support for pediatric device development, including a potential new public-private partnership. Understanding the full and long-term impacts of the COVID-19 pandemic will continue to be a top priority for N-PeRC. The pandemic has highlighted the value of infrastructure that can be harnessed to study emergent public health crises. Information also will soon be added to N-PeRC's website to catalog many pediatric research training opportunities across NIH. We anticipate that collecting this information in a single location will be particularly valuable to fellows and trainees in pediatric research. A new N-PeRC effort will include discussions around how best to coordinate and align pediatric clinical trial and other research networks. N-PeRC is dedicated to working collaboratively to coordinate and support pediatric research activities across NIH.

⁵⁰² www.ncbi.nlm.nih.gov/pmc/articles/PMC9345524/

⁵⁰³ pubmed.ncbi.nlm.nih.gov/35963365/

⁵⁰⁴ pubmed.ncbi.nlm.nih.gov/33880476/

⁵⁰⁵ grants.nih.gov/grants/guide/notice-files/NOT-HD-22-002.html

⁵⁰⁶ grants.nih.gov/grants/guide/notice-files/NOT-HD-22-003.html