DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

FY 2023 CONGRESSIONAL JUSTIFICATION

Significant Items

All of Us Research Program/Precision Medicine Initiative

The Committee provides a total of $541,000,000 for the All of Us precision medicine initiative, $41,000,000 above the fiscal year 2021 enacted level and consistent with the fiscal year 2022 budget request. The total includes $150,000,000 authorized in the 21st Century Cures Act (Public Law 114–255) to be transferred from the NIH Innovation Account. The Committee directs NIH to continue its efforts to recruit and retain participants from historically underrepresented populations in biomedical research, and to expand its efforts to enroll participants from geographically diverse communities. To achieve this diversity, NIH is encouraged to support additional avenues for enrollment from the Midwest and Great Plains regions that facilitate participation from both rural and urban communities. These efforts will help ensure that All of Us scientific resources reflect the rich diversity of our country and that advances made from this program will benefit the health of all Americans.

Action taken or to be taken

The *All of U*s Research Program's mission is to accelerate health research and medical breakthroughs to enable individualized prevention, treatment, and care for all of us. *All of Us* is on its way to enrolling one million or more participants, and as of November 2021, more than 434,000 participants had consented to join the program and more than 309,000 participants had completed all steps in the initial protocol. The program's participants continue to reflect the rich diversity of the United States and are from different races, ethnicities, age groups, and from all regions in the country Nearly 50 percent of *All of Us* participants who have shared health information and biosamples are from racial and ethnic minority communities, and nearly 80 percent are from communities historically underrepresented in biomedical research – including people living in rural areas, older adults, economically disadvantaged, and sexual and gender minority populations. A*ll of Us* remains committed to community engagement for both urban and rural populations. In 2021, the program funded the next iteration of engagement work, which includes adding three additional partners, the American Association of Health and Disability, the National Baptist Convention USA, Inc., and Baylor College of Medicine to the program's robust network of engagement partners.[1]

Currently, individuals over the age of 18 who are living anywhere within the United States can join the *All of Us* Research Program by enrolling on the program's website.[2] Once enrolled online, participants can complete enrollment by donating biosamples through the program's network of Healthcare Provider Organizations (HPO), including Regional Medical Centers, Federally Qualified Healthcare Centers, and alternative enrollment locations, and through the program's long-term partnership with Veterans Affairs Hospitals (VA). The program currently has a network of enrollment locations covering several states in the Midwest and Great Plains including HPOs located in Colorado, Illinois, Michigan, Minnesota, North Dakota, and Wisconsin, and additional VA enrollment locations located in Indiana, Iowa, Kansas, and Minnesota. The program also anticipates opening additional VA locations in Colorado. The program continues to explore more enrollment options to meet participants where they are, and this includes providing enrollment opportunities for interested individuals who are not close to an existing enrollment center. Starting in 2021, participants who are unable to join at an existing enrollment center may request a mailed saliva kit to fulfill the initial sample contribution from anywhere in the United States. As of November 2021, more than 12,000 additional participants donated biosamples through saliva kits. In the future, the program aims to offer additional opportunities that allow biosample donation for participants outside of an enrollment center. This could include home visits or mailed kits for blood collection at clinical phlebotomy laboratories. Diversity, equity, inclusion, and accessibility are core values within the

[1] allofus.nih.gov/news-events-and-media/announcements/all-us-research-program-awards-funding-seven-community-partners

[2] allofus.nih.gov/

All of Us Research Program, and the program will continue to explore additional enrollment methods that ensure the program's participants reflect the rich diversity of our country and that advances made from this program will benefit the health of all Americans.

ALS Research Coordination and Acceleration

The Committee is aware of the significant need to expand scientific understanding of amyotrophic lateral sclerosis (ALS) and to translate ALS science more rapidly into effective treatments that can make ALS a livable disease. To achieve these outcomes as soon as possible, the Committee directs NIH to organize a trans-agency initiative to develop an ALS research strategic plan. The plan, which should be developed in collaboration with the nation's leading ALS patient and biomedical research organizations, should: identify the most promising areas of research and the specific NIH activities where additional funding could lead to more rapid translation of discoveries for treatments, prevention, and interventions or technologies that can reduce the burden of ALS; identify which Institutes and Centers are undertaking ALS and ALS-related research and which are not but have a role to play; and uncover any impediments to ALS research. As part of this effort, NIH should hold at least one public meeting at which stakeholders can provide testimony. This effort should include, but not be limited to: NINDS, NIA, NIEHS, NIMH, NHGRI, NIAMS, and NCATS.

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) is the lead National Institutes of Health (NIH) Institute for amyotrophic lateral sclerosis (ALS) research. NINDS has begunorganizing a strategic planning effort for ALS research. As part of this effort, NINDS will solicit broad input from the public via public Requests for Information and a public meeting, and will engage relevant NIH Institutes and Centers, federal agencies, and non-governmental organizations to develop research recommendations for advancing research on ALS as described by the Committee.

NINDS currently supports a broad, diverse research portfolio on ALS, including investigator-initiated research projects to understand the genetic and environmental causes of ALS and to elucidate the cellular and molecular mechanisms by which the disease progresses. To augment this investigator-initiated research program, NIH established the Accelerating Leading-edge Science in ALS (ALS^2) initiative, part of the NIH Common Fund's Transformative Research Awards, which will dramatically advance our understanding of what triggers ALS and what drives the rapid progression of this disease. NINDS is also supporting several large natural history and biomarkers studies that aim to identify biomarkers that predict when people at risk for ALS might get the disease, allowing them to begin treatment early, perhaps even before symptoms appear. NINDS supported preclinical research projects are testing a 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. Finally, several promising industry-funded clinical trials are proceeding based upon NIH-supported basic and preclinical research findings.

ALS Research Coordination and Acceleration

Additionally, The Committee strongly supports the Transformative Research Award program for ALS and directs the Director to continue to fund this critical initiative in fiscal year 2022.

Action taken or to be taken

The National Institutes of Health (NIH) Common Fund's Accelerating Leading-edge Science in ALS (ALS^2), part of the Transformative Research Award initiative, aims to stimulate innovative research and answer critical scientific questions about ALS. Research supported through ALS^2 is intended to be exceptionally creative, with the potential to transform research on the molecular causes of ALS, describe how the disease progresses, and develop possible therapeutic strategies. The hope is that ALS^2 will introduce new ideas into the field to rapidly advance progress towards safe and effective therapies. These awards also encourage attracting new talent from a range of scientific disciplines, including cell biology, bioengineering, chemistry, biophysics, environmental health sciences, and computational science, as well as formation of new multi- and interdisciplinary collaborations.

The first funding opportunity announcement for ALS^2 was issued in June 2020. Applications were received by September 2020, and the first round of awards were announced in fall 2021. NIH issued four Transformative Research awards[3] for the ALS^2 initiative in fiscal year 2021. These awards are addressing how the disease works at the cellular level by identifying the genetic and cellular factors that drive nerve cell death; determining how environmental exposures that may contribute to ALS disease risk interact with molecular and immune features also associated with ALS; investigating the restoration of the balance among key proteins that impact ALS as a treatment option; and determining how changes associated with the disease are linked to dysfunction in specific cell types in ALS. These awards represent a 5-year, $25 million investment by the NIH. This initiative is managed collaboratively by the Common Fund, the National Institute of Neurological Disorders and Stroke, the National Institute on Aging, the National Institute of Environmental Health Sciences, and the National Institute of General Medical Sciences.

[3] commonfund.nih.gov/TRA/recipients

Amyloidosis

The Committee directs NIH to continue its expansion of research efforts in amyloidosis, a group of rare diseases characterized by abnormally folded protein deposits in tissues. Amyloidosis is often fatal, and there is no known cure. Current methods of treatment are risky and unsuitable for many patients. Average survival without treatment is in months. The Committee directs NIH to provide an update in the fiscal year 2023 Congressional Budget 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. This buildup often leads to compromised organ function. For example, researchers supported by the National Institute on Aging (NIA) have 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 National Institutes of Health (NIH) support, and the investigator who led this work was recently awarded the Breakthrough Prize—one of the world's largest science prizes—for his efforts. NIH also supported a subsequent study demonstrating that tafamidis is equally effective against hereditary and sporadic forms of the disease.

Basic research on amyloid and amyloidosis is supported across the NIH. For example, investigators supported by the NIA and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) are working to determine why and how misfolded proteins clump together to cause disease. Other research from NIDDK and the National Institute of General Medical Sciences (NIGMS) has clarified the unique biochemical properties of various familial forms of transthyretin amyloidosis that lead to their becoming amyloidogenic, discoveries that could ultimately lead to better treatment or prevention of this disease.[4]

Early and accurate diagnosis of amyloidosis remains an active area of study. For example, NIA-supported investigators have developed a highly accurate diagnostic and screening tool for cardiac amyloidosis. Elsewhere, investigators supported by the National Heart, Lung, and Blood Institute (NHLBI) are using artificial intelligence approaches with digital echocardiographic images to create a completely automated method for diagnosing and tracking rare heart diseases, including cardiac amyloidosis. NHLBI also supports research investigating whether genetic risk factors can be used to guide radiologic imaging of cardiac amyloidosis, especially among older African American and Hispanic/Latino patients, in whom amyloidosis may be underdiagnosed.

NIH supports clinical treatment trials using a range of drugs, including small molecule inhibitors, monoclonal antibodies, biological therapies, and agents commonly used in cancer chemotherapy. Recent NIDDK- and NIA-funded research has identified a promising potential strategy for treating light chain (LC) amyloidosis, the most common systemic amyloid disease, typically occurring when amyloidogenic

[4] pubmed.ncbi.nlm.nih.gov/33645214/

antibody LCs are secreted by certain types of abnormal blood cells.[5] The compound reduced secretion of the LC amyloid precursors and was found to be effective in cells isolated from LC amyloidosis patients and to be non-toxic to mice.

To advance drug development for these diseases, the Amyloidosis Forum was created through a public/private partnership between the Amyloidosis Research Consortium and the U.S. Food and Drug Administration (FDA) to discuss the challenges, address the obstacles, and find pathways towards accelerating drug development in light chain amyloidosis. The most recent meeting was held October 2020 with NIA support, and focused on natural history and endpoint development.

[5] pubmed.ncbi.nlm.nih.gov/33599742/

Antiviral Drugs and Pandemic Preparedness

The Committee strongly encourages NIAID efforts to establish a public-private partnership focused on global pandemic preparedness and antiviral drug discovery, in coordination with BARDA. Such a partnership could leverage the best of academia and pharmaceutical manufacturers to develop broad-spectrum antiviral drugs to address rapidly emerging public health threats, helping our nation be better prepared for the next global pandemic. The Committee directs NIAID to provide an update on this and any related efforts in the fiscal year 2023 Congressional Budget Justification.

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) supports research to better understand, treat, and prevent infectious diseases as well as to respond to emerging public health threats. NIAID and the National Center for Advancing Translational Sciences (NCATS), in collaboration with the Biomedical Advanced Research and Development Authority (BARDA), have initiated the Antiviral Program for Pandemics (APP), which supports the development of broad-spectrum antiviral drugs to address rapidly emerging public health threats through public-private partnerships. The APP will develop antivirals to combat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), build sustainable platforms for drug discovery, and develop a pipeline of antivirals against select viruses with pandemic potential. The APP will focus on accelerating development of direct-acting antivirals—particularly against RNA viruses of pandemic potential such as SARS-CoV-2—from discovery to early development. Of particular interest are oral or intranasal antiviral candidates that could be taken at home early in the course of infection. These antivirals could prevent transmission of the virus and help to stem overwhelming surges in hospitalizations resulting from viral infections.

Through the APP, NIAID will utilize existing research resources and preclinical services, which include a full suite of early-stage drug development activities, and provides in-kind support for the development of promising antiviral candidates. NIAID will also continue to support basic research that will feed into the development pipeline for antiviral candidates.

As part of the APP drug discovery effort, NIAID released a funding opportunity announcement to establish Antiviral Drug Discovery (AViDD) Centers for Pathogens of Pandemic Concern in FY 2022.[6] AViDD will be comprised of multidisciplinary centers focused on discovering and developing new antiviral candidates targeting SARS-CoV-2 and other viruses with pandemic potential.

NIAID also plans to utilize public-private partnerships and award product development contracts to support the development of promising antiviral candidates from late-stage preclinical studies through clinical testing. These efforts will help advance candidate antivirals into clinical trials and facilitate late-stage development by industry or BARDA. BARDA will support the manufacturing of drug candidates for clinical trials and the development of analytical assays needed for drug substance and drug product release.

In addition, NCATS will be a key partner in APP alongside NIAID and BARDA to accelerate antiviral drug development through early discovery and preclinical development. NCATS will coordinate with potential partners to develop candidates and take them into clinical development with APP partners. NCATS will apply its proficiency in drug discovery and development and its cutting-edge technologies, such as high-throughput screening, Artificial Intelligence/Machine Learning/Deep Learning, and advanced biological testing (including tissue models of infection), to drive preclinical drug

[6] grants.nih.gov/grants/guide/rfa-files/RFA-AI-21-050.html

discovery that will fill critical needs of the APP. NCATS' expertise in preclinical development will complement the mechanisms for supporting drug development at NIAID and BARDA.

NIAID will continue to coordinate with NCATS and BARDA on the APP to help prepare for and respond to existing and newly emerging infectious disease threats.

Artificial Intelligence/Big Data

NIH continues to expand its efforts to develop its capacity to leverage the potential of machine learning [ML] to accelerate the pace of biomedical innovation. The Office of Data Science Strategy [ODSS], collaborating with NLM, has been working to ensure new research datasets meet the international Fast Healthcare Interoperability Resources [FHIR] standard requirements and provide opportunities for data experts to work in the field of biomedicine. It is also developing a governance structure for the rapidly develop field, including principles for con- sent and privacy, fairness and equity, security and accountability. While encouraging, making full use of these opportunities, which rely on scale and collaboration across areas of expertise, presents unique challenges to NIH's massive federation of institutes and centers. Controlled access mechanisms, for example, as required by the NIH Genomic Data Sharing Policy, are the primary means through which NIH protects the privacy and respects the wishes of research participants whose data are stored and shared for secondary research. However, investigator access to data stored and managed in NIH-supported repositories continues to be burdensome and inconsistent, despite numerous incremental improvements implemented by past working groups. The inefficiencies presented by NIH's federated data sharing landscape will likely become intractable as data access requests continue to increase, new NIH Institute, Center and Office [ICO]-supported data repositories proliferate, and innovative data access processes are piloted and implemented across NIH. Moreover, a lack of harmonized data access processes across NIH will stymy the goal of the emerging NIH data science infrastructure to make data more Findable, Accessible, Interoperable, and Reusable [FAIR]. Given these developments, it is imperative for NIH to develop more efficient, streamlined data access and control processes that are standardized and scalable across the agency to enable timely and secure access to research data while preserving participant protections. To achieve this goal, the Committee directs NIH to engage stakeholders across the agency to develop best practices to standardize controlled data access processes. Such an effort will streamline access, support the emerging NIH data science infrastructure, and meet the needs of the research community in a manner that preserves the original protections agreed to when the data were collected, taking into account potential cost and burden. It should consider lessons learned from past efforts, review emerging processes and technologies currently being piloted by ICO repositories, and develop new potential solutions that leverage technological advancements, while continuing to support policies for appropriate privacy protections and respect the wishes of research participants. Potential participant re-identification risks associated with the aggregation of disparate data, including data in controlled access, should be considered. The Committee directs NIH, no later than 1 year after enactment of this Act, to develop and present recommendations for: potential common solutions for streamlining and centralizing controlled access mechanisms through implementation improvements (e.g., more efficient workflows or Data Access Committee processes, including a single, centralized DAC process) and use of emerging technological advancements (e.g. automation, single sign-on); making controlled-access data (e.g., human data that may contain sensitive information such as health conditions, including genomic data) stored in NIH-operated and supported repositories more readily findable and accessible; and assess the extent to which increased interoperability of controlled access repositories (e.g., permitting combining disparate data sets, aggregating data across time) leads inadvertently to gaps in oversight and control, including explicit consideration of increased re-identification risk. To support NIH's continued efforts, the Committee recommendation includes $122,000,000, including $50,000,000 for the Bridge2AI initiative and other ML-focused investments and $72,000,000 for ODSS. The Committee directs ODSS and NLS to continue to provide quarterly updates on its efforts.

Action taken or to be taken

The National Institutes of Health (NIH) efforts in data science include artificial intelligence (AI) and machine learning (ML) to accelerate the pace of biomedical innovation; advancing the use of the Fast Healthcare Interoperability Resources (FHIR) standard in research; and developing a governance structure for this rapidly developing field. The NIH has initiated strategies to address many of the challenges outlined here, which are all foundational to building a Findable, Accessible, Interoperable, and Reusable (FAIR) data ecosystem for NIH's controlled access and open data.

As part of the Office of Data Science Strategy's (ODSS) efforts in collaboration with the National Library of Medicine (NLM), NIH is developing new capabilities to streamline access to controlled data across the agency's managed and supported data repositories and platforms, while simultaneously enhancing NIH's position with respect to data integrity and research participant protections. NIH will engage stakeholders to develop best practices for centralizing controlled data access implementation for more efficient data access to meet the needs of the research community and the NIH-supported data science infrastructure.

The NIH also is addressing the challenges of findability though a community-wide workshop planned for early 2022. Interoperability of data and tools also is being advanced through coordinated efforts with partnerships across multiple NIH Institutes and Centers. These activities will focus on oversight and stewardship; preserving original protections; and potential costs and burdens.

All of these efforts will inform the development of recommendations to address the critical capabilities outlined in this response. The ODSS will continue to provide quarterly updates on these and related activities to the Committee.

Biomedical Research Workforce Diversity

The Committee is concerned with the impact of COVID–19 on the diversity of the biomedical research workforce, particularly women and women of color at risk across career stages. The Committee strongly encourages NIH to study the race and gender breakdown of the impact of COVID on participation in the workforce by monitoring the types of awards applied for and granted by gender, race, and ethnicity for two years. If the data demonstrate that fewer women are applying for grants, then it is imperative that NIH take steps to address this disparity. The Committee requests a status update from NIH on this research in the fiscal year 2023 Congressional Budget Justification as well as the steps being taken to maintain and stabilize 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. Intense competition for funding, however, can pose a challenge for researchers trying to embark upon and sustain independent research careers. Moreover, 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 and vulnerable populations.[7,8] NIH understands these challenges and, as such, is continuing 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 has begun assessing the gender distribution of designated principal investigators of R01 and Research Project Grant (RPG) applications submitted before and after the onset of the COVID-19 pandemic.[9,10] Furthermore, an NIH survey of institutional leaders and scientists (open in the Fall of 2020 with results published in March 2021) provided valuable insights into the well-being of the extramural biomedical research workforce, including as it relates to underrepresented and vulnerable groups. Going forward, NIH will continue assessing our efforts when designing, testing, and implementing future policies and programs to enhance the success and diversity of the next generation of talented biomedical researchers.[11]

To date, several initiatives have been launched to help mitigate the impact of COVID-19 on biomedical careers,[12] including the implementation of numerous opportunities for early-stage investigators to address COVID-19-related research delays. NIH will continue to solicit input from the research community and devise new strategies or repurpose existing ones to mitigate the devastating effects of the pandemic on the biomedical workforce. Because initial research and evidence indicate that COVID-19 may be disproportionately impacting engagement, experience, and retention of women scientist, especially those from underrepresented groups, NIH, via the Working Group on Women in Biomedical Sciences Careers is focusing on developing strategies (including programs and policies) specifically to promote the continued advancement of women in biomedical research careers.

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[7] nexus.od.nih.gov/all/2020/11/04/continued-impact-of-covid-19-on-biomedical-research/
[8] 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/
[9] nexus.od.nih.gov/all/2020/07/28/an-early-look-at-applications-submitted-during-the-pandemic/
[10] nexus.od.nih.gov/all/2021/06/01/an-updated-look-at-applications-submitted-during-the-pandemic/
[11] extramural-diversity.nih.gov/
[12] nexus.od.nih.gov/all/2020/11/04/continued-impact-of-covid-19-on-biomedical-research/

Steps to Diversify the Biomedical Research Workforce

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.[13] As a part of its offerings, 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.**[14] 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. NIH is analyzing NGRI policies to ensure our efforts continue supporting career development for women and individuals from diverse backgrounds in biomedicine.

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 Diversity (K99/R00)[15]
- Maximizing Opportunities for Scientific and Academic Independent Careers (MOSAIC) program[16]
- Building Infrastructure Leading to Diversity (BUILD) program[17]
- National Research Mentoring Network (NRMN)[18]
- Faculty Institutional Recruitment for Sustainable Transformation (FIRST) program[19]

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 early stage investigator (ESI) status for childbirth within the ESI period.[20] In fiscal year 2020, an automatic extension of one year was also implemented for childbirth within the four-year K99 eligibility window.[21] Additionally, NIH offers support for early-career investigators with high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying circumstances.[22,23] NIH also provides funding for Childcare Costs for Ruth L. Kirschstein National Research Service Award Individual Fellows.[24] 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.[25]

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[13] grants.nih.gov/ngri.htm
[14] nexus.od.nih.gov/all/2021/07/12/data-on-implementing-nihs-next-generation-researchers-initiative/
[15] grants.nih.gov/grants/guide/rfa-files/rfa-ns-19-043.html
[16] www.nigms.nih.gov/training/careerdev/Pages/MOSAIC.aspx
[17] www.nigms.nih.gov/training/dpc/pages/build.aspx
[18] nrmnet.net /
[19] commonfund.nih.gov/first
[20] grants.nih.gov/grants/guide/notice-files/NOT-OD-18-235.html
[21] grants.nih.gov/grants/guide/pa-files/pa-18-592.html
[22] grants.nih.gov/grants/guide/notice-files/NOT-OD-20-054.html
[23] grants.nih.gov/grants/guide/notice-files/NOT-OD-20-055.html
[24] grants.nih.gov/grants/guide/notice-files/NOT-OD-21-074.html
[25] grants.nih.gov/grants/guide/notice-files/not-od-21-134.html

Lastly, NIH recently 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. These efforts are part of an overall effort by the U.S. Department of Health and Human Services (HHS) to respond to the *Executive Order*[26] *On Advancing Racial Equity and Support for Underserved Communities Through the Federal Government* to improve equity, diversity, and inclusion in the Federal workplace.

[26] www.whitehouse.gov/briefing-room/presidential-actions/2021/01/20/executive-order-advancing-racial-equity-and-support-for-underserved-communities-through-the-federal-government/

Biosafety Labs

The Biosafety in Microbiological and Biomedical Laboratories (BMBL) recommends as a special practice the reporting of all laboratory incidents and near misses in Biosafety Lab (BSL) BSL-3 and BSL-4 laboratories. The Committee directs NIH to ensure all funding for BSL-3, BSL-4, high containment laboratory, or any entity involved in managing Hazardous Biological Agents both foreign or domestic maintains up to date, comprehensive policies, to promote optimal Biosafety and Biosecurity practices. Such policies must reference (1) incident reporting, (2) roles and responsibilities, (3) training, (4) inventory control, and (5) inspections and must be reported to NIH and/or related agencies.

Action taken or to be taken

The National Institutes of Health (NIH) has a comprehensive biosafety oversight system for our laboratories and our grantee institutions that is designed to protect both laboratory workers and the public health and which rests on a foundation of federal and institutional regulations, guidelines, and policies. The NIH Grants Policy Statement (GPS),[27] which outlines the terms and conditions for which awardees must comply, codifies several of these policies and expectations. For instance, the NIH GPS explicitly recommends institutions use the Biosafety in Microbiological and Biomedical Laboratories[28] (BMBL) in developing and implementing procedures and practices for both personnel and facilities. The BMBL is guidance detailing best practices for the safe conduct of work in laboratories from a biosafety perspective, which allows for flexibility for institutions to evaluate the risks associated with research and implement appropriate mitigation measures specific to that institution.

In addition to the BMBL, NIH requires institutions to follow the Federal Select Agent Regulations[29] (SAR), which specify stringent biosafety, biocontainment, and biosecurity requirements for the possession, use and transfer of biological select agents and toxins that have the potential to pose a severe threat to public, animal or plant health or to animal or plant products. The Federal Select Agent Program[30] (FSAP), monitors compliance with the SAR through an inspection program. Institutions are required to have biosafety, security, and incidence response plans. Institutions must report any theft or loss, occupational exposures, or release of a biological select agent or toxin to the FSAP. Institutions are also required to provide and document training and must maintain an accurate, current inventory for each select agent.

Additional oversight for research conducted with a broader range of infectious agents by our supported scientists is provided by the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*[31] (*NIH Guidelines*), which detail safety practices and containment procedures for research including the creation and use of organisms and viruses containing recombinant or synthetic nucleic acid molecules. Compliance with the *NIH Guidelines* is a term and condition of NIH funding. The *NIH Guidelines* articulate the roles and responsibilities of institutions and individuals involved in the conduct and oversight of such research and require institutions to implement policies for the establishment of Institutional Biosafety Committees, to oversee research at the local level. The *NIH Guidelines* also articulate training responsibilities and require the development of incident response plans and reporting of significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses to NIH, for any and all activities funded by the NIH.

[27] grants.nih.gov/policy/nihgps/index.htm
[28] www.cdc.gov/labs/BMBL.html
[29] www.selectagents.gov/regulations/index.htm
[30] www.selectagents.gov/
[31] osp.od.nih.gov/wp-content/uploads/2019_NIH_Guidelines.htm

NIH-funded high containment laboratories conducting research covered by these existing regulations and policies are already required to establish and maintain up-to-date, comprehensive biosafety and biosecurity policies. NIH will continue to implement these policies to ensure that important biomedical research with pathogens is conducted safely and securely. NIH is strongly committed to biosafety and biosecurity oversight and continually re-evaluates its policies to ensure that they remain scientifically responsive to emerging agents and technologies.

Black Men and Women Pursuing Medicine and Science

The Committee supports the efforts of the National Academies Roundtable on Black Men and Black Women in Science, Engineering, and Medicine and its efforts to develop specific programs to increase the numbers and effectiveness of Black Men and Women pursuing medicine and science. The Committee directs the Director to allocate increased resources from the Common Fund of the diversity program consortium to the National Academies Roundtable on Black Men and Black Women in Science, Engineering, and Medicine to address the increasing underrepresentation of Black Men in medical schools and the biomedical research profession.

NIH Response

Despite the nation's changing demographics and a growing appreciation for diversity and inclusion as drivers of excellence in science, engineering, and medicine, Black Americans are severely underrepresented in these fields. Black Americans constitute 13 percent of the U.S. population but make up less than 7 percent of medical students and less than 3 percent of practicing physicians.[32] In the science and engineering disciplines, Black Americans represent 4.8 percent of employed professionals.[33] As documented in several key reports, including Altering the Course: Black Males in Medicine[34] and An American Crisis: The Growing Absence of Black Men in Medicine and Science (National Academies of Sciences, Engineering, and Medicine (NASEM), 2018)[35], racism and bias are significant reasons for this disparity, with detrimental implications on individuals, health care organizations, and the nation as a whole. In 2017, the Health and Medicine Division of the NASEM (or the National Academies) and the Cobb Institute organized a national workshop that resulted in the publication of An American Crisis. The shortage of Black men and Black women that persists in science and medicine threatens the quality of the biomedical research enterprise. It hinders progress in science, medicine, and public health as we seek to address health disparities and achieve the National Institutes of Health mission.

The NIH Chief Officer for Scientific Workforce Diversity (COSWD) is working with the NIH Common Fund and the National Academies to provide expertise and focus on Black Men and Women Pursuing Medicine and Science, including serving on and providing funding to the NASEM Roundtable on Black Men and Black Women in Science, Engineering, and Medicine ("the Roundtable"). In addition, NIH funded the NASEM effort "Addressing Diversity, Equity, Inclusion, and Anti-Racism in 21st Century Science, Technology, Engineering, Mathematics, and Medicine (STEMM) Organization: A Summit". Building on the insights gained in the Summit and the Roundtable, the NIH recently funded a NASEM Study on the same topic that will launch in early 2022.

In addition, the Common Fund invests in the Diversity Program Consortium (DPC), a resource that supports the goals to enhance Black Men and Black Women in Science, Engineering, and Medicine. The DPC consists of three primary integrated initiatives, which aim to enhance diversity in the biomedical research workforce through the development, implementation, assessment, and dissemination of innovative and effective approaches for (a) student outreach, engagement, training and mentoring, (b) faculty development, and (c) institutional research training infrastructure. The Building Infrastructure

[32] National Academies of Sciences, Engineering, and Medicine (NASEM). 2018. An American Crisis: The Growing Absence of Black Men in Medicine and Science: Proceedings of a Joint Workshop. 2018. Washington, DC: The National Academies Press. www.nap. edu/catalog/25130/an-american-crisis-the-growing-absence-of-black-men-in.
[33] National Science Foundation. 2015. Employed Black Scientists and Engineers, as a Percentage of Selected Occupations: 2015. www.nsf.gov/statistics/2017/nsf17310/ digest/occupation/blacks.cfm.
[34] Association of American Medical Colleges. 2015. Altering the Course: Black Males in Medicine. Washington, DC. store.aamc.org/altering-the-course-black-males-in-medicine. html.
[35] www.nap.edu/catalog/25130/an-american-crisis-the-growing-absence-of-black-men-in

Leading to Diversity (BUILD) initiative, a component of the DPC, includes research training programs intended to support undergraduate trainees in pursuit of biomedical research careers.

The BUILD initiative includes significant support for the biomedical research training of undergraduates. This initiative directly supports the goal of increasing Black Men and Women pursuing medicine and science. The lessons learned about what factors increase the persistence of Black Men and Women in biomedical fields will allow institutions to implement inclusive practices that should result in the number of Black Men and Women who maintain a career path in science, engineering, and medicine. Approximately 25 percent of BUILD undergraduate students who received full financial assistance (BUILD trainees) were Black. Of the 1,704 BUILD trainees funded since the initial awards in FY 2014, 113 were Black Men (or approximately 7 percent of the total), and 306 were Black Women.

The DPC is conducting a large-scale evaluation of the interventions developed by funded sites. The outcomes from this evaluation are intended to address knowledge gaps about workforce development, and findings will be disseminated to the broader community as they become available. At this time, BUILD awardees are in the process of implementing their 10-year long programs while collecting data for analysis. Some interim results have been shared; however, none of the publications focus specifically on Black Men, as these interventions are aimed at students from various racial, ethnic, and socio-economic backgrounds.

Two new initiatives were added to the DPC during FY 2019-FY 2023: the DPC Dissemination and Translation Awards (DPC DaTA), which focus on the effectiveness of biomedical research training, mentoring, and research capacity building interventions aimed at enhancing diversity in the biomedical research workforce; and the Sponsored Programs Administration Development (SPAD) Program which focuses on establishing Offices of Sponsored Programs (OSPs) or enhancing the services of existing OSPs or similar entities at domestic institutions of higher learning.

One of the lessons learned from the early years of the DPC was the importance of a robust, efficient, consistent, and responsive Office of Sponsored Programs. The objective of the SPAD program is to increase the productivity of sponsored programs activities to enhance biomedical research and/or training. The objective may be determined by short-term metrics such as an increase in the number of grant application submissions, awards, and subcontracts, and longer-term metrics, such as enhanced research activity (e.g., publications, presentations, awards), and/or an increase in the number of students who pursue biomedical careers. This award helps those institutions that do not have an OSP, or those with limited capacity for programs administration or even those with limited NIH research project grant awards. Funded institutions are expected to develop offices that facilitate the development of a culture of biomedical research or research training by providing services such as professional development in targeted areas, pre- and post-award services, and certification-guided training of sponsored program staff and leadership. As mentioned, a major goal of the program is to enhance the faculty and student participation in biomedical research and research training programs.

These awards are cooperative agreements, meaning that there is substantial federal scientific or programmatic involvement. NIH scientific and/or program staff assist, guide, coordinate, or participate in the project activities.

The awardees for the DPC DaTA program and the first round of SPAD awardees began implementation in 2019. The second and final round of SPAD awardees began implementing their interventions in 2020. The funded institutions include many Minority-Serving Institutions: one Asian Americans and Native American Pacific Islanders-Serving Institution (AANAPISI), six Historically Black Colleges and Universities (HBCUs), five Hispanic-Serving Institutions (HSIs), and one Native American-Serving

Nontribal Institution (NASNTI); thus, the DPC initiatives at these institutions will reach a large and diverse group of participants.

All DPC-funded initiatives implement program evaluations and collect data on outcomes of interest. It is expected that awardees will publish on their interventions as they near the completion of their awards. Funding for all DPC initiatives concludes in FY 2023.

Buildings and Facilities

The Committee recommendation includes $275,000,000 for NIH buildings and facilities, an increase of $75,000,000 above the fiscal year 2021 enacted level and $25,000,000 above the budget request. This funding will remain available for obligation for 5 years. Once again, the Committee has not included authority for NIH to transfer up to 1 percent of its research funding to Buildings and Facilities. This would be highly unusual authority for a Federal agency and the Administration has provided no explanation for why this mechanism would be appropriate for NIH, but not other Federal agencies. The recommendation also increases the flexibility available to NIH through section 216 of the General Provisions, which has not been revised since fiscal year 2012. The bill would increase the amount of funding appropriated to Institutes and Centers that may be used for repairs and improvements from $45,000,000 to $100,000,000 and raise the per project cap from $3,500,000 to $5,000,000. The Committee supports NIH's efforts to develop a centralized and disciplined capital planning process that can guide and inform agency decision-making. While capital planning remains fragmented and inconsistent, the agency is making steady progress in developing best practices in use elsewhere in the Federal and private sector. The Committee continues to support the use of the Research Facilities Advisory Committee [RFAC] to consistently evaluate and rank all projects, regardless of their funding source. As NIH's portfolio management capabilities mature, the Committee expects the agency will develop the policies and practices to assess whether construction, purchase, or leasing is the most cost-effective approach. The Committee directs NIH to continue to provide quarterly updates of its efforts to develop best practices and its maintenance and construction plans for projects whose cost exceeds $3,500,000, including any changes to those plans and the original baseline estimates for individual projects. It also directs NIH to describe in its fiscal year 2023 and future CJs how the projects requested in its budgets tie to its capital planning process, including the RFAC's role in determining which projects are selected for inclusion in the budget.

Action taken or to be taken

All projects requested in the National Institutes of Health (NIH) budgets go through a capital planning process which has three phases:

1. **Early Planning Documents:** Projects are sorted into three categories depending on the completeness of three documents:

   Section A – COMPLETE:

   a. Program of Requirements (POR)
   b. Environmental Impact Statement (EIS)
   c. Independent Government [Cost] Estimate (IGE)

   Section B – INCOMPLETE: POR, EIS or IGE

   Section C – MINIMAL DEFINITION

   Only projects in Section A proceed to the next phases. In addition, most projects have completed the U.S. Department of Health and Human Services (HHS) Facility Project Approval Agreement (FPAA), a Construction Request has been put into the ORF tracking system, and a "C" number issued for the project.
2. **Scoring:** All projects are scored in three areas. The maximum total score is 1,000 points.
   a. Mission Dependency: The Research Facility Advisory Committee (RFAC), composed of selected Scientific Directors, plus two or three Executive Officers, award up to 450 points based principally on scientific merit and the criticality of the program to NIH's mission.

b. **Facility Condition:** The Office or Research Facilities (ORF) staff awards 350 points based on the physical condition, code compliance, and functionality of existing facilities that are being replaced.
c. **Executability:** ORF staff awards 200 points based on shovel readiness, completeness of enabling projects, permitting, and approvals.

3. **Prioritization:** In parallel, but independent, of the scoring effort, ORF Office of the Director and Division of Budget and Financial Management prepare the HHS five-year, projected, capital request plan. This five-year projection also determines the source of funds, such as whether the money is coming from Building and Facilities (B&F) or Nonrecurring Expense Funds (NEF). Considering the project score, budget timing, best professional judgement, and other considerations, such as predecessor projects, all projects are prioritized from 1 to approximately 30. Priority, therefore, is not bottom up and not driven by the score; it is top down and driven by NIH's goals, professional judgement, and backed-up by the score. The expectation is that score and priority are correlated. The last step of the capital planning process is for the RFAC and ORF Staff to review both the scores and priorities and agree upon the final list.

As directed by Congress in the Consolidated Appropriations Act of 2017, NIH entered into a contract with the National Academies of Science, Engineering, and Medicine (NASEM) to assess the condition of the facilities on the Bethesda Campus. An ad hoc committee comprised of medical, architectural, engineering, planning, and maintenance experts was established to conduct the analysis. On August 26, 2019, the committee's report was made public.[36]

The report found that "The buildings and facilities at the NIH Bethesda Campus are in need of significant improvement and upgrading to sustain their current mission and ongoing functionality." The report highlights pressing campus-wide infrastructure needs and recommends improvements to NIH's capital planning and funding processes, including updating the Buildings and Facilities (B&F) prioritization model and developing an annual budget request for Backlog of Maintenance and Repair (BMAR) reduction. It also suggests that NIH strengthen internal governance process by assigning and empowering a senior leader to manage capital planning.

NIH is taking steps to address all 14 recommendations of the NASEM report. Twelve of those recommendations were procedural, and NIH is moving forward with implementation of these procedural and governance recommendations. Also as directed by Congress, NIH has been providing quarterly briefings to the Appropriations Staff regarding the facilities project backlog, project prioritization, and overall governance. It should be noted that the NASEM recommendations were related to the Bethesda backlog and did not address the backlog at other NIH sites. While the scope of the report was limited to the Bethesda Campus, the NIH also has facilities at other sites in Maryland, Montana, and North Carolina.

Recognizing the criticality of providing a plan to manage the backlog to HHS, OMB, and Congress, NIH awarded a consultant contract to Deloitte to assist NIH in its Capital Planning processes.

This effort identified six strategic improvements: 1) Improve Project Prioritization; 2) Develop Improved Backlog Reduction Strategies; 3) Improve Planning and Cost Control; 4) Make Training and Documentation Improvements; 5) Improve Master Plan Communications; and 6) Improve Data Driven Decision Making. One of the key findings from this effort has been a recognition that not all backlog is equally risky. To illustrate, a roof leak over operating rooms in the Clinical Center could have more serious consequences than a roof leak in an office building. Therefore, the strategy must consider the

[36] www.nap.edu/read/25483/chapter/1

need to attack the high-risk backlog. Another observation is that there are often advantages to developing projects with large economies of scale, involving an entire wing or floor of a building, as opposed to narrowly targeted, room-level repairs and improvements that incur high costs per square foot and suffer inefficiencies associated with working adjacent to active science, because of the need to avoid or minimize utility shutdowns, noise, vibration, and dust generation.

In fiscal year (FY) 2021, NIH provided to Congress quarterly updates on November 18, 2020; March 30, 2021; June 30, 2021; and September 27, 2021; the first quarterly update for FY 2022 was held on December 13, 2021. NIH will continue to provide these updates as long as Congress requests them.

Cancer Data Sharing

The Committee applauds NIH for creating the National COVID Collaborative (N3C), a commercial solution leveraged to create a centralized and secure database that researchers in academic institutions can use to study COVID–19 and identify potential treatments. The Committee encourages NIH to continue pursuing similar approaches to other critical areas of research, including cancer, where data sharing continues to be a barrier to progress. The Committee commends NCI's data sharing efforts through the Cancer Moonshot, the Childhood Cancer Data Initiative, and other programs, and requests an update in the fiscal year 2023 Congressional Budget Justification on NCI's continued progress toward adopting a centralized, secure, national platform to share cancer research data to drive new insights and speed research efforts across the country.

Action taken or to be taken

The National Cancer Institute (NCI) has taken significant action toward building the cancer research data component of a National Cancer Data Ecosystem that consists of a secure infrastructure of standards, methods, and portals with enhanced cloud-computing platforms and services that link clinical, imaging, and molecular data. An update on the Childhood Cancer Data Initiative is provided in a separate Significant Item on page 22.

NCI, in part with funds provided through the Cancer Moonshot, has developed the Cancer Research Data Commons (CRDC), a secure cloud-based data science infrastructure that connects data sets with analytics tools to allow users to share, integrate, analyze, and visualize cancer research data to drive scientific discovery. The CRDC provides access to data-type specific repositories (genomic, proteomic, comparative oncology, imaging, and others) and is growing to include a wider range of data.

Currently, the accessible repositories within the CRDC include:

- The Genomic Data Commons[37]—a unified repository that supports hosting, standardization, and analysis of genomic, clinical, and biospecimen data from cancer research programs and includes data from The Cancer Genome Atlas and its pediatric equivalent, the Therapeutically Applicable Research to Generate Effective Treatments program, as well as Foundation Medicine, the Cancer Cell Line Encyclopedia, and a growing number of other sources.
- The Proteomic Data Commons[38]—an actively growing repository that currently offers access to highly curated and standardized biospecimen, clinical, and proteomic data including those from the Clinical Proteomic Tumor Analysis Consortium program.
- The Integrated Canine Data Commons[39]—a repository of genomics, proteomics, and imaging data from naturally occurring cancer in canine cancer patients.
- The Imaging Data Commons[40]—a repository that provides cloud-based access to a wide variety of medical imaging and metadata from The Cancer Imaging Archive and other NCI projects. Its connection to a wide variety of analytical tools allows researchers and data scientists to train and explore imaging models without downloading data.
- The Cancer Data Service[41]—a repository for cancer research data generated by NCI-funded programs that do not meet submission criteria or are on the waitlist for a specific CRDC Data Repository.

[37] gdc.cancer.gov/
[38] proteomic.datacommons.cancer.gov/pdc/
[39] caninecommons.cancer.gov/
[40] portal.imaging.datacommons.cancer.gov/
[41] datacommons.cancer.gov/repository/cancer-data-service

Additionally, several repositories are currently planned or under development, including the Clinical Trial Data Commons and others related to immuno-oncology and population science data such as large-scale cohort study data.

NCI recognizes that pooling of data in CRDC from numerous sources strengthens the power of the information only if it can be meaningfully connected. In order to connect data from separate, non-interoperable repositories, NCI has established the Center for Cancer Data Harmonization[42] (CCDH) which will serve to facilitate and assure interoperability of data across the CRDC repositories and data coordinating centers through a variety of logistical operations, services, and technical assistance. NCI is also developing the Cancer Data Aggregator (CDA) to allow researchers to aggregate diverse data types generated by NCI-funded programs. Through CDA and a harmonized data model developed by CCDH, users will be able to discover, query, retrieve, and aggregate data according to a variety of search parameters.

As part of a comprehensive data sharing vision and strategy for NCI and the cancer research community, NCI's recently established Office of Data Sharing (ODS) facilitates the proper balance of open-access and broad data sharing policies to enable reproducibility, secondary use, and knowledge sharing. ODS respects the rights of the public to participate in and benefit from publicly funded research while considering the critical importance of intellectual property concerns for individuals and organizations to support a healthy commercial marketplace.
NCI's ongoing and future investments in this endeavor will greatly aid in achieving the goal of enabling all participants across the cancer research and care continuum to contribute, access, combine, and analyze diverse data that will enable new discoveries and reduce the burden of cancer.

The National Center for Advancing Translational Science's (NCATS) National Covid Cohort Collaborative (N3C) represents one of the largest, most secure clinical data resources for accelerating research on coronavirus disease 2019 (COVID-19). The N3C is utilizing both commercially available tools and platforms in addition to open-source resources and translates the different ways that contributing hospitals store patient data into a single, common format to enable combined "apples-to-apples" analyses. The N3C includes a powerful analytics platform for online discovery, visualization, and collaboration. NCI is collaborating with NCATS and providing valuable COVID-related data and scientific expertise to the N3C; particularly exploring methods and approaches to connect different types of data or datasets together to enrich the abilities to share data. NCATS is partnering with NCI on the N3C resource for exploring two key questions 1) how COVID-19 diagnoses are affecting cancer outcomes (and vice versa), and 2) how the data can be used to explore novel privacy-preserving approaches for data sharing and better integration.

[42] harmonization.datacommons.cancer.gov/

Cancer Vaccines

The Committee recognizes that the success of the COVID–19 vaccines—which became available less than a year from the outset of the pandemic and now deliver up to 95 percent protection rates—is due to the fact that these vaccines were built on messenger RNA technology, or mRNA, an approach that had been initiated for cancer research. While most traditional vaccines use inactivated viruses to stimulate an immune response, a complicated process that can take several years, mRNA vaccines use the body's own genetic material, and can be developed much more quickly. The Committee understands that with further research, mRNA cancer vaccines could potentially be among the most cost-effective methods of preventing recurrences and the high costs of cancer care. The Committee commends the work of NCI, which is currently supporting multiple research projects focusing on the use of mRNA vaccines, and encourages its continued commitment to moving the field forward for mRNA vaccines as an approach for cancer immunotherapy treatment and prevention. To better understand NCI's progress to date and the potential of new breakthroughs with mRNA, the Committee requests an update in the fiscal year 2023 Congressional Budget Justification on NCI's work on mRNA vaccines, noting existing barriers or challenges, if any.

Action taken or to be taken

The National Cancer Institute (NCI) is supporting research projects on mRNA cancer vaccines focused on glioma,[43] melanoma,[44] and prostate cancer,[45] as well as research that may lead to therapies for other cancer types.[46] The ability to safely deliver mRNA into the human body, which instructs the body to manufacture a protein of interest and to elicit an immune response to the said protein, can potentially be used to create personalized cancer vaccines based on mutated proteins found in a patient's tumor. Generally, the cell fragments proteins into small pieces, known as peptides, which end up on the surface of cancer cells and, theoretically, can elicit a specific immune response. Due to advances in sequencing tumor genomes, it is possible to detect these mutations and engineer mRNA molecules to contain the said mutations. Such mRNA, when introduced into the body, would instruct the body to produce mutation-bearing peptides, known as neoantigens. In addition to the highly personalized nature of this approach, an mRNA vaccine based on neoantigens is likely to be less toxic than traditional chemotherapies.

However, for mRNA cancer vaccines to be successful, several biological barriers must be overcome. One significant barrier is poor tumor immunogenicity; that is, a reduced ability to induce an immune response that would prevent tumor growth. This occurs in part because only a small fraction of mutated proteins within a cancer cell become neoantigens on the cell surface.[47] Moreover, only a subset of these are capable of eliciting an immune response. Several studies funded by the NCI suggest that combining neoantigen vaccines with immune checkpoint inhibitors may produce clinical benefit.[48] Ongoing NCI-funded research is testing a neoantigen vaccine in combination with an immune checkpoint inhibitor to improve outcomes for patients with advanced melanoma.[49]

To address the paucity of neoantigens, NCI is funding research to induce production of more neoantigens that could lead to a broadly applicable vaccination strategy.[50] Because tumors have thousands of mutated

[43] reporter.nih.gov/project-details/10122019
[44] reporter.nih.gov/project-details/9991198
[45] reporter.nih.gov/project-details/10269186
[46] reporter.nih.gov/project-details/10050026
[47] ncbi.nlm.nih.gov/pmc/articles/PMC7954132/
[48] ncbi.nlm.nih.gov/pmc/articles/PMC6549688/; ncbi.nlm.nih.gov/25409260/; ncbi.nlm.nih.gov/pmc/articles/PMC4993154/
[49] reporter.nih.gov/project-details/9575177
[50] reporter.nih.gov/project-details/10265108

proteins, and because so few of these proteins result in immunogenic neoantigens, it is difficult to predict which neoantigens to use in mRNA cancer vaccines. In addition, each patient's neoantigens are unique to their tumor, so a neoantigen successfully targeted in one patient may not work for another patient with a similar cancer type. To address these challenges, NCI is investing in bioinformatics technology to predict which mutated proteins in a given patient would result in neoantigens capable of eliciting an immune response.[51] Additionally, NCI intramural researchers have developed an experimental method to identify immunogenic neoantigens and package them into an mRNA vaccine.[52] In an initial trial, the vaccine induced neoantigen-specific T cell (immune) responses in patients with gastrointestinal tumors, but did not result in clinical benefit, prompting the research team to initiate a new clinical trial combining the vaccine with immune checkpoint inhibitor therapy.

Another major obstacle for mRNA cancer vaccines is the inhospitable nature of the tumor microenvironment, which resists infiltration by neoantigen-specific T cells. NCI is funding many research projects that aim to alter the tumor microenvironment permissiveness, including one project that combines therapies to activate an innate antitumor response in pediatric solid tumors.[53] This project is part of the Pediatric Immunotherapy Discovery and Development Network, funded through the Cancer Moonshot[SM].

In addition to mRNA cancer vaccines, NCI supports many research projects on cancer peptide vaccines. One NCI-funded project with a potential application to immunotherapy for triple negative breast cancer is based on the fact that certain chemotherapies lead to DNA damage, resulting in the generation of neoantigens. This project aims to identify a common set of neoantigens for a peptide vaccine that could be used to immunize patients prior to chemotherapy treatment, which may contribute to tumor eradication.[54] NCI is also investing in creative approaches to cancer vaccination, such as fusing patient-derived tumor cells with a specific type of immune cell to produce a personalized vaccine against acute myeloid leukemia.[55] This approach has shown clinical results for some patients, and NCI is supporting further research to expand the benefit to other patients.[56]

[51] reporter.nih.gov/project-details/9507415
[52] pubmed.ncbi.nlm.nih.gov/33016924/
[53] reporter.nih.gov/project-details/9839928
[54] reporter.nih.gov/project-details/10198213
[55] ncbi.nlm.nih.gov/pmc/articles/PMC5800949/
[56] reporter.nih.gov/project-details/10277055

Childhood Cancer Data Initiative (CCDI)

The Committee includes $50,000,000 for the second year of the CCDI, as proposed in the fiscal year 2022 budget request. The development of new therapies is important to finding a cure for childhood cancers, many of which have not seen new therapies in decades. The Committee commends NCI for its support of the establishment of the National Childhood Cancer Registry as a part of the Childhood Cancer Data Initiative. Data sets for childhood cancers are often small and spread out across institutions or aggregated into State-wide or Federal registries where the particulars of incidence rate by cancer are lost. Traditional disease registries such as the Federally-supported Surveillance Epidemiology and End Results Program (SEER) and the CDC's National Program for Cancer Registries (NPCR) aggregated into the U.S. Cancer Statistics (USCS) do not yet include all of the data relevant to cutting-edge pediatric cancer research, such as the molecular characteristics of each child's cancer. The Committee urges NCI to use available resources to ensure all relevant data needed to assist childhood cancer researchers in developing innovative treatments for childhood cancer are made available through the National Childhood Cancer Registry and other integrated CCDI programs. The Committee requests an update on the progress made to increase available childhood cancer data in the fiscal year 2023 Congressional Budget Justification.

Action taken or to be taken

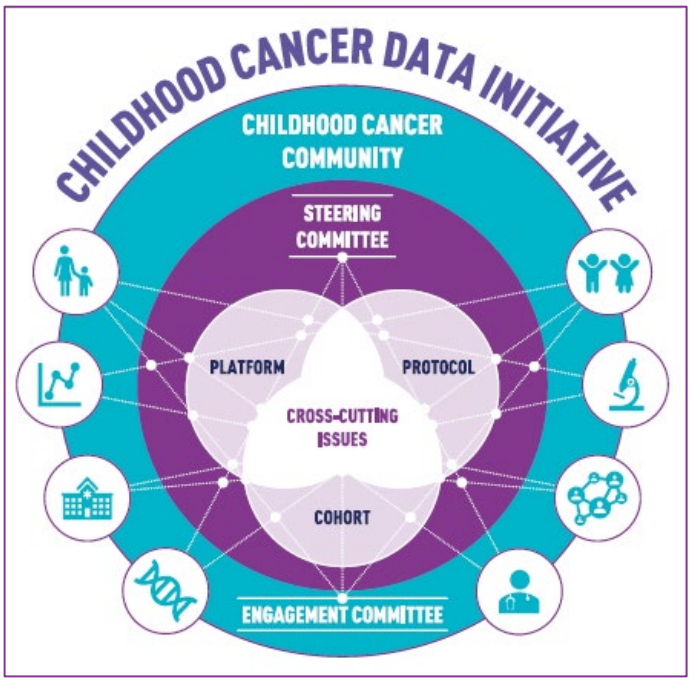
NCI launched CCDI in 2020 to enable greater data sharing among the childhood cancer community to ensure data from each child with cancer is captured and stored in a way that cancer researchers can easily access to learn from and inform future preventative, clinical, and survivorship care.[57]

For CCDI's first year, NCI focused largely on strengthening existing childhood cancer research programs, developing data systems, and convening a multidisciplinary working group of the NCI's Board of Scientific Advisors (BSA) to guide and inform the priorities and structure of CCDI. At a June 2020 joint meeting of the BSA and the National Cancer Advisory Board, the working group presented its recommendations for implementing CCDI.[58] NCI also allocated CCDI funds to a range of childhood cancer and survivorship research activities through grants and supplements to build a foundation for data sharing, analysis, and access. This includes investing in the molecular characterization of germline and tumor samples (both diagnostic and relapse) from ongoing NCI studies such as Pediatric Molecular Analysis for Therapy Choice (Pediatric MATCH) and the Childhood Cancer Survivor Study.

Based on the BSA working group guidance, three foundational goals were established: (1) gather data from every child, adolescent, and young adult diagnosed with a pediatric cancer, regardless of where they receive their care; (2) create a national strategy of appropriate clinical and molecular characterization to speed diagnosis and inform treatment for all types of pediatric cancers; and (3) develop a platform and tools to bring together clinical care and research data that will improve preventive measures, treatment, quality of life, and survivorship for pediatric cancers.

[57] www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative
[58] deainfo.nci.nih.gov/advisory/bsa/sub-cmte/CCDI/CCDI%20BSA%20WG%20Report_Final%20061620.pdf

NCI has organized the CCDI to ensure maximum participation from the entire childhood cancer research and care community. This structure includes a Steering Committee, an Engagement Committee, a Data Platform working group, a National Childhood Cancer Cohort working group, a Molecular Characterization Protocol working group, and a Cross-Cutting Issues team. The steering committee will provide strategic direction and feedback on working group activities and will collaborate with the community through the engagement committee.



The National Childhood Cancer Cohort working group is charged with developing a set of strategies to gather data from every child diagnosed with cancer in the United States. This strategy began with the launch of the National Childhood Cancer Registry (NCCR).[59] 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, heath care administrations, and other sources—to enhance access to and utilization of childhood cancer and survivorship data. The NCCR benefits from NCI's experience leading the Surveillance, Epidemiology and End Results (SEER) Program and the SEER registry infrastructure.

The Data Platform working group is defining the approach to create infrastructure to federate, aggregate, and integrate all relevant data. The infrastructure will also include tools to analyze the data and will support a central portal to make the data easy to find and use. This data will include the comprehensive clinical and molecular characterization data of every child. The Molecular Characterization Protocol group is designing and implementing a national strategy to ensure that every pediatric cancer patient receives the comprehensive characterization of their cancer as a standard of care regardless of where they receive care.

Additional activities underway include but are not limited to: developing and refining computational methods and pipelines that can be shared to analyze a variety of data, creating frameworks to harmonize pediatric cancer data, investing in pilot projects to enhance efficiency of clinical trials data collection, and building a searchable online catalog of the data, tools, and resources available through the CCDI. NCI strongly believes in harnessing the power of data as a driver of progress in all childhood cancers and is bringing together the entire childhood cancer community, including advocates, clinicians, researchers, and data scientists to realize this goal.

[59] seer.cancer.gov/statistics/nccr/

Childhood Cancer Star Act

The Committee includes $30,000,000, the same as the fiscal year 2021 enacted level, for continued implementation of the Childhood Cancer Survivorship, Treatment, Access, and Research [STAR] Act to expand existing biorepositories for childhood cancer patients enrolled in NCI-sponsored clinical trials to collect and maintain relevant clinical, biological, and demographic information on all children, adolescents, and young adults with cancer. The Committee has also included sufficient funding to carry out childhood cancer survivorship research and programs as authorized in the STAR Act, such as developing best practices for the treatment of late effects of childhood cancers, improving collaboration among providers so that doctors are better able to care for this population as they age, and creating innovative models of care for childhood cancer survivors. The STAR Act calls on NCI to ensure that all applicable study sections, committees, advisory groups, and panels at NCI include one or more qualified pediatric oncologists, as appropriate. Therefore, the Committee requests an update on the actions NCI has taken to ensure appropriate pediatric cancer expertise is included on all panels.

Action taken or to be taken

See response in Pediatric Cancer Expertise

Childhood Post-Infectious Neuroimmune Disorders

The Committee continues to be concerned that some children, following streptococcal and other infections, may experience the onset of neuropsychiatric and behavioral disorders. These auto-inflammatory encephalopathic conditions include Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS). Due to a paucity of research and limited avenues of treatment, children continue to encounter significant delays in identification and treatment, resulting in escalation of mental health symptoms and associated costs. The incidence of neurological and psychiatric symptoms associated with SARS–CoV–2 underscores the need for research that expands our understanding of neuropsychiatric illness following infection. Because these complications lie at the nexus of medical and mental health, investigations into their mechanisms have far-reaching implications. The Committee encourages NIH to explore cross-disciplinary research in this area, including neurobiology, neurology, immunology, rheumatology, infectious disease, and mental health, and report to the Committee in the fiscal year 2023 Congressional Budget Justification on the understanding of the incidence, 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 PAN Disorder Associated with Streptococcal infection (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.

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.[60] In the case of PANDAS, this immune response is associated specifically with Group A streptococcal (strep) infections, such as strep throat and scarlet fever.[61] Researchers found that strep-related PANDAS episodes can be managed by prescribing antibiotics to eliminate the strep infection and ameliorate symptoms. Children with PANS- or PANDAS-related OCD symptoms may also benefit from standard OCD treatment, which includes medication and behavioral therapy.

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 anti-neural antibodies collected from a large and diverse cohort of patients with idiopathic encephalitis.[62] These researchers recently reported that antibodies from patients diagnosed with coronavirus disease 2019 (COVID-19) reacted to neural tissue in an animal model, suggesting a possible mechanism for the association of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with neurological and psychiatric

[60] projectreporter.nih.gov/project_info_description.cfm?aid=9790789&icde=46937455
[61] www.nimh.nih.gov/health/publications/pandas
[62] reporter.nih.gov/project-details/10146485

symptoms.[63] 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.[64] 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.[65] These multidisciplinary approaches aim to provide a more precise understanding of the link between autoimmune encephalitic processes and PANS/PANDAS, and may clarify diagnosis and identify new targets for treatment to ultimately improve outcomes for individuals with these conditions.

[63] pubmed.ncbi.nlm.nih.gov/33969321/
[64] pubmed.ncbi.nlm.nih.gov/32539528/
[65] reporter.nih.gov/project-details/9726837

Chronic Diseases and Health Disparities

In fiscal year 2021, NIMHD undertook an initiative to support regional comprehensive research and coordinating centers on the prevention, treatment, and management of multiple chronic diseases associated with health disparities. The Committee remains strongly supportive of this effort and is pleased the awards emphasized support for regional based, multi-institutional consortia that will produce collaboration and research that can be easily translated into sustainable community and health system changes that promote chronic disease treatments long after research projects have concluded. The Committee recommendation reflects sufficient funding for NIMHD to continue this effort in fiscal year 2022.

Action taken or to be taken

In FY 2021, the National Institute on Minority Health and Health Disparities (NIMHD) issued a funding opportunity announcement entitled, *Centers for Multiple Chronic Diseases Associated with Health Disparities: Prevention, Treatment, and Management (P50 Clinical Trial Required).*[66] The purpose of this initiative is to support regional comprehensive research centers on the prevention, treatment, and management of chronic diseases associated with health disparities. These centers will conduct research on chronic diseases that disproportionately affect populations with health disparities, including, but not limited to, obesity, diabetes, hypertension, coronary heart disease, congestive heart failure, asthma, chronic kidney disease, chronic liver disease, stroke, osteoarthritis, and certain cancers.

Pursuant to directives in FY 2021 appropriations, the NIMHD awarded funds to 11 research institutions to establish and support regional comprehensive research centers on the prevention, treatment, and management of comorbid chronic diseases that disproportionately affect populations with health disparities. These Multiple Chronic Disease (MCD) Centers received grants totaling almost $205 million including funds committed over a 5-year period. Research projects from each MCD Center are expected to address determinants of health at two or more levels of influence (individual, interpersonal/organizations, community, and societal). In addition, interventions may address one or more of the following: prevention of chronic diseases by addressing risk factors and early stages of a condition (e.g., pre-diabetes); increasing access to or quality of health care to detect or treat chronic diseases; enhancement of treatment quality or adherence; and self-management to manage chronic diseases and improve or maintain quality of life across different life course stages.

In addition, an Investigator Development Core supported by a required allocation for a Pilot Project Program provides research opportunities for post-doctoral fellows, early-career faculty, or other early-stage investigators, with an emphasis on those from backgrounds underrepresented in the biomedical research workforce. Community engagement efforts of each MCD Center will facilitate the development and nurturing of bi-directional working relationships with consortium partners within the region to develop relevant and actionable information and findings and disseminate them to the community.

Lastly, to coordinate activities across all the MCD Centers, the NIMHD also awarded $4.5 million and committed $18 million more over a five-year period to establish a Research Coordinating Center (RCC). The scope of activities for the RCC is to coordinate common activities and meetings, harmonize data as appropriate, agree on data sharing principles, facilitate cross-MCD Center research resources, provide opportunities for mentoring of early-career investigators, and disseminate research project findings.

[66] grants.nih.gov/grants/guide/rfa-files/RFA-MD-21-007.html

Clinical and Translational Science Awards (CTSA) Program

The Committee includes $616,183,000 for the CTSA Program, an increase of $29,342,000 above the fiscal year 2021 enacted level and $14,683,000 above the fiscal year 2022 budget request. The Committee notes that while the CTSA program works to advance the full spectrum of medical research and modernize our research enterprise, as demonstrated by the CTSAs being a driving force behind the Federal effort to rapidly develop COVID–19 treatments, diagnostic tools, and vaccines. Central to the ongoing success of the CTSA consortium are individual CTSA hubs that form a nationwide network. The Committee directs NCATS to maintain the current size of the core awards supporting CTSA hubs, including the institutional partners that are part of the hubs, and historic structure of the CTSA program. This ongoing approach reflects the central role of the hubs, including each hub's partners, as critical national research infrastructure and the core of the CTSA Consortium. The Committee reiterates previous guidance that NCATS duly inform the Committee of any planned changes to the size of awards, scope of the program, or strategic direction of emerging or ongoing CTSA initiatives. Further, NIH is encouraged to further integrate the CTSA program into cross-agency initiatives that can leverage the full spectrum of medical research for progress on a variety of contemporary topics.

Action taken or to be taken

The National Center for Advancing Translational Sciences' (NCATS) Clinical and Translational Science Awards (CTSA) Program supports the full spectrum of medical research on local, regional, and national levels, to improve and accelerate the research enterprise. The CTSA Program has the capacity to address significant public health problems, and it has been a key partner in the Federal effort to rapidly develop coronavirus disease 2019 (COVID-19) treatments and diagnostic tools. The importance of the CTSA program goals has never been clearer than over the course of the COVID-19 pandemic, in addition to the existing opioid public health crisis.

Over many years that included many programmatic and administrative innovations, NCATS and CTSA awardees have made great progress together in building a program that can address critical challenges to the nation's clinical and translational research and infrastructure; and improve the efficiency, quality, and impact of the process for turning observations into interventions that improve the health of individuals and communities.

Over the last few years, NCATS undertook a significant effort to solicit public feedback, much of which was provided by the CTSA-funded hub institutions and investigators, on the CTSA Program goals, structure, and operations (including application reviews and awards management). Many of the insights gleaned from that process were further borne out in the experience of the COVID-19 pandemic. A few examples of feedback received include:

- Partners to the hubs in the network do not all possess strong clinical research assets;
- There is a gap in the capacity of the network to carry out clinical research in populations underrepresented in research;

The formula in the prior Funding Opportunity Announcement creates a large disparity in the size of awards across the hubs; and there is significant administrative burden reported in the CTSA application, budget development, and awards process.

Per the Notice of Intent to Publish (NOT-TR-21-030[67]), NCATS' planned changes are to benefit applicants and support program objectives by: allowing institutions to prioritize their strengths; providing streamlined application and award management processes; emphasizing the importance of clinical partnerships critical to achieving the objectives of this national program; incorporating research to tackle

[67] grants.nih.gov/grants/guide/notice-files/NOT-TR-21-030.html

health disparities; and stabilizing funding provided to the hub institutions by allowing up to seven years of hub funding (rather than the typical five-year award period for NIH awards). Changes are also designed to ensure the CTSA Program's sustainability by stabilizing and standardizing budget projections and numbers of hub awards, which the current award formula does not provide. The changes intend to avoid reductions in the number of hubs and negative impacts on hub budgets.

NCATS will continue to work closely with applicant and awardee institutions and Principal Investigators to enhance the program's ability to achieve its mission.

The growing success of the CTSA Program has been recognized and rewarded through several cross-agency collaborations that utilize the Program's extensive expertise, geographical reach, and resources. The Biomedical Advanced Research and Development Authority (BARDA), U.S. Food and Drug Administration (FDA), and U.S. Department of Veterans Affairs (VA) collaborate with NCATS to leverage the CTSA national network of clinical trial infrastructure and trial readiness in support of two NIH Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) trials: the ACTIV-1 Phase III clinical trial evaluating the safety and efficacy of three immune modulator drugs in hospitalized adults with COVID-19 and the ACTIV-6 Phase III clinical trial to test several existing medications for people to self-administer to treat symptoms of COVID-19. The National COVID Cohort Collaborative (N3C) involves many CTSA institutions and investigators working together to study COVID-19 using electronic health record-derived data. NCATS has engaged FDA, BARDA, the Office of the National Coordinator for Health Information Technology (ONC), and the Centers for Disease Control and Prevention (CDC) on this program. CTSA investigators are working with FDA and the White House's National Strategy for the COVID-19 Response and Pandemic Preparedness on the randomized clinical trial for anti-SARS-CoV-2 convalescent plasma treatment for hospitalized patients.

NCATS will work to ensure these cross-agency collaborations continue and expand beyond the COVID-19 pandemic with the goal of positioning the CTSA Program at the forefront of future public health endeavors.

Congenital Heart Disease [CHD]

The Committee commends NHLBI for its continued work to better understand causation, improve treatments and outcomes, support the growth of the clinical workforce, and integrate registry data and research datasets to facilitate research on congenital heart disease across the lifespan, including through the Pediatric Health Network and the Pediatric Cardiac Genomics Consortium. The Committee encourages NHLBI to prioritize CHD activities outlined in its strategic plan, including improving understanding of outcomes and co-morbidities, modifying treatment options across the lifespan, and accelerating discovery, analysis, and translation by leveraging CHD registries and networks. The Committee requests NHLBI include an update in its fiscal year 2023 CJ on steps being taken to close these research gaps.

Action taken or to be taken

There are between 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 over 13,300 children with CHD, as well as many parents, to assemble one of the world's largest CHD registries. Whole genome sequence data from the PCGC have shed light on the causes of CHD and are helping inform clinically available genetic tests; those data are also being combined with clinical outcome data to help inform the development of precision medicine for CHD.

The PHN is currently enrolling five clinical research studies that cover CHD populations from infancy through adulthood, and two more studies are nearing launch. Several studies include industry collaboration. The PHN also has proven to be an asset in the National Institutes of Health (NIH) coronavirus disease 2019 (COVID-19) response and is conducting an observational study to better understand multi-system inflammatory syndrome in children (MIS-C). This is a rare condition that follows severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, infection in some children, and often includes cardiac complications. To date, the study has enrolled more than 1,000 children, or about 20 percent of affected children nationally.

In partnership with the NIH Office of the Director and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), NHLBI co-leads the trans-NIH INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) Project. Approximately 50 percent of all children born with Down syndrome have CHD. Through the INCLUDE Project, NHLBI is expanding the PCGC to conduct genome sequencing that will shed light on the genetic factors that contribute to CHD in people with and without Down syndrome. Nearly 100 whole-genome sequences have been completed to date. In addition, the PHN is conducting an INCLUDE-funded study comparing surgical outcomes after common types of CHD surgery in people with and without Down syndrome.

In August 2021, NHLBI convened researchers and patients for a workshop to identify research opportunities and optimal approaches to reduce morbidity and mortality related to CHD across the lifespan. Aligning with NHLBI's commitment to increase diversity among research participants, the workshop identified opportunities to expand diversity through engagement of family-based advocacy organizations and community groups to advise researchers on participant recruitment and retention

strategies. These community engagement efforts will be incorporated into the PHN and other CHD clinical research projects. The workshop also identified a number of key research opportunities that could transform CHD research. These include expanding knowledge of pathways by which genetic and environmental factors cause CHD and understanding mechanisms of CHD comorbidities. There is also potential to leverage the PHN with other registries and platforms to screen infants early in life for the genetic cause of their CHD and follow them over the lifespan. Such an effort may enable researchers to characterize genetically defined subtypes of CHD, and to collect observational data on outcomes of different CHD treatment strategies in a large, diverse population.

The PHN's research is leading to the development of improved treatment and care of children with CHD. For example, the Fontan Udenafil Exercise Longitudinal (FUEL) trial tested udenafil, a drug that increases blood flow to the lungs, in children who have only one working heart ventricle. Although surgery in early childhood can stabilize heart function in these children, they often face a decline in exercise capacity and an increased risk of heart failure over time. The trial found that udenafil improved exercise capacity in teenagers with single-ventricle defects.[68] The drug manufacturer has submitted these data to the U.S. Food and Drug Administration (FDA) as part of a request to approve udenafil for use in this population.

Additional avenues of potential CHD treatment are stem cell therapy and tissue engineering. NHLBI is currently funding an early phase clinical trial of stem cell therapy for infants undergoing two-ventricle repair surgery (creating two functional ventricles from one) within the first six months of life.[69] In addition, NHLBI is funding a safety and efficacy trial of tissue engineered vascular grafts (TEVG) for single-ventricle CHD, created from the patient's own cells; unlike conventional grafts would be able to grow and remodel with growth or other structural changes of the patient's heart.[70]

[68] pubmed.ncbi.nlm.nih.gov/31736357/
[69] clinicaltrials.gov/ct2/show/NCT04467671?term=NCT04467671&draw=2&rank=1
[70] clinicaltrials.gov/ct2/show/NCT04236479?term=NCT04236479&draw=2&rank=1

COVID-19

COVID–19 has shown the importance of FIC's essential role in global infectious disease health research training, pandemic preparedness, and global health security by assisting low- and middle-income countries (LMICs) in advancing their own research and health solutions and tools. The FIC has developed important partnerships in countries to not only fight infectious diseases, but also to build their capabilities to detect and treat infectious diseases. The COVID–19 pandemic illustrates the importance of FIC's efforts to strengthen country capacity to enable cutting edge research at the origin of outbreaks, improving the likelihood that emerging diseases can be addressed at their source—ultimately protecting American health security. The Committee believes these long-standing relationships and unique capabilities position FIC to play an important and expanded role in pandemic preparedness, including developing a network of modeling hubs and joint research programs to engage LMIC investigators to collaboratively train for pandemic preparedness. The Committee requests information from FIC in the fiscal year 2023 Congressional Budget Justification about how FIC training programs and research collaborations have, and with additional resources can, increase efforts to advance global health security and pandemic preparedness. The Committee is particularly interested in understanding FIC's unique capabilities and capacities as well as coordination with other Federal government agencies engaged in these efforts.

Action taken or to be taken

When infectious diseases emerge, limited research capacity in many countries heightens the global risk. This was clear when Ebola ravaged West Africa and has been reinforced by coronavirus disease 2019 (COVID-19). Progress has been made to build up these capabilities, yet much remains to be done.

For over 5 decades, the Fogarty International Center (FIC) has invested in research and capacity strengthening and is uniquely poised to advance global health security and pandemic preparedness due to its 1) unique experience in developing global networks; 2) outstanding in-house expertise in mathematical modeling; and 3) key role in facilitating partnerships across the U.S. government and worldwide.

Existing Networks That Can Be Leveraged

- In recent years, scientists in FIC's global infectious disease training network pivoted to tackle urgent threats such as Ebola and Zika. Now many grantees and former trainees are leading critical international COVID-19 clinical trials supported by the National Institutes of Health (NIH); however, many countries are still not able to conduct high-quality clinical trials or other countermeasure research.
- FIC has invested in research ethics capacity for decades and supports the Global Forum for Bioethics in Research, which developed a framework for a global ethics response network for public health emergencies, utilized by the World Health Organization (WHO) for COVID-19.
- FIC has trained over 160 researchers in 23 countries on pathogen sequencing. Grantees in NIH's Human Heredity and Health in Africa program, a network of genomics centers co-led by FIC, were the first institutions in Africa to implement sequencing of SARS-CoV-2.
- With funds from the United States President's Emergency Plan for AIDS Relief (PEPFAR), FIC supports the African Forum for Research and Education in Health (AFREhealth), an association of African institutions training a clinical research workforce that can confront future outbreaks.

Preparedness Research Training Program. FIC plans to establish a program to train low- and middle-income country (LMIC) investigators in diverse areas of pandemic research, such as transmission dynamics, social factors, countermeasures, supply chain analysis, vaccine development, and implementation science.

Modeling and genomic surveillance. FIC plans to establish a global network of mathematical modeling and epidemiological analysis to conduct research and build capacity for modeling of potential outbreaks and interventions. FIC also plans to expand pathogen sequencing and analytic capacity to address a lack of COVID-19 genomic information in most countries.

Technology. FIC plans to leverage its technology research networks to support digital health projects specifically focused on pandemic preparedness, including repurposing of technologies or information systems for COVID-19 and future pandemic threats; affordable, rapid diagnostic development; and implementation research associated with digital technology integration.

Coordination with federal agencies and others. FIC plays an essential role representing NIH on various interagency and White House working groups and is engaged with the Global Health Security Agenda Task Force on Research and Development. FIC engages all NIH Institutes and Centers on international issues and coordinates with Centers for Disease Control and Prevention (CDC), the U.S. Department of Health and Human Services (HHS) Office of Global Affairs, the State Department, the U.S. Agency for International Development, the White House Office of Science and Technology Policy, the National Science Foundation, and others. FIC also works closely with foreign governments, the WHO, the Africa CDC, the Bill and Melinda Gates Foundation, and other NGOs.

Deadliest Cancers

The Recalcitrant Cancer Research Act (RCRA) of 2012 (P.L. 112–239) focuses on cancers with a five-year survival rate below 50 percent, which account for 44 percent of all U.S. cancer deaths. While advances in some cancers have made it possible to reduce the overall rate of cancer deaths over the last two decades, there has been limited progress reducing mortality for these diseases. For fiscal year 2020, Congress directed NCI to develop a scientific framework using the process outlined in the RCRA for stomach and esophageal cancers. The Committee notes that in addition to the ongoing framework development, NCI has also developed and received approval from its Board of Scientific Advisors to launch a Program in Origins of Gastroesophageal Cancers. Alongside the research and advocacy communities, the Committee appreciates NCI's efforts to keep the Committee apprised of continued research progress informed by the pancreatic, lung, glioblastoma, esophageal, and stomach cancer frameworks. The Committee encourages NCI to consider a similar process, as appropriate, for primary liver cancer, including cholangiocarcinoma. Given the toll all recalcitrant cancers exact on society and the lack of diagnostic and treatment resources currently available to help patients, the Committee also requests an update in the fiscal year 2023 Congressional Budget Justification on research goals to advance progress for the deadliest cancers (brain, esophagus, liver, lung, ovary, pancreas, stomach and mesothelioma).

Action taken or to be taken

Cancer is not one disease but hundreds of diseases; the complexity extends well beyond just considering the organ site where it originated, including molecular characteristics (e.g., specific gene mutations) that may be shared between cancers originating in different organs. This complexity necessitates planning on many levels to make continued progress. The National Cancer Institute (NCI) sets scientific priorities to build on the progress that has been made in long-established areas of research and to seize new opportunities in emerging areas of science across the cancer research continuum.

NCI's research portfolio includes investigator-initiated research grants, specifically targeted networks and special programs, and infrastructure support such as the Cancer Centers program. Investigator-initiated grants support ideas from scientists who propose research projects based on their area of expertise and receive funding for those projects after they are deemed meritorious in a rigorous peer-review process. Targeted networks and programs arise from identifying opportunities in emerging areas and recognizing unmet needs and research gaps. The most effective horizon-scanning activities are conducted in real-time, based on scientific opportunity and are flexible in format so that efforts can be tailored to the subject, whether basic, translational, or clinical in focus. Flexible approaches allow NCI to revise its activities based on the needs of the science and the needs of patients.

Many of the cancers with high mortality rates noted by the Committee are not only the subject of investigator-initiated research but are also the focus of NCI networks and consortiums with specific research goals. A few examples include:

- Glioblastoma Therapeutics Network (GTN)[71] which is pursuing ways to improve the treatment of adult glioblastoma (GBM) by developing novel and effective agents to overcome the blood-brain barrier and GBM heterogeneity and eventually evaluate drugs in Phase 3 clinical trials
- Program on the Origins of Gastroesophageal Cancers[72] which seeks to understand the earliest cellular changes that take place prior to the development of cancer

[71] grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-047.html
[72] grants.nih.gov/grants/guide/rfa-files/rfa-ca-21-026.html

- Translational Liver Cancer Consortium[73] which supports research to better stratify patients at risk of developing liver cancer, improve the surveillance of liver cancer in high-risk populations, and increase the fraction of liver cancer detected at an early stage
- Small Cell Lung Cancer Consortium[74] which focuses on both prevention and treatment by expanding understanding of the critical molecular changes that precede the development of small cell lung cancer and developing therapeutic approaches for treatment while understanding the mechanisms of drug resistance
- Ovarian Cancer Specialized Program of Research Excellence (SPORE)[75] which includes six programs with individual goals including reducing incidence and mortality, developing novel therapies, and understanding drug resistance (note there are also brain, gastrointestinal, liver, lung, and pancreatic cancer SPOREs[76])
- Pancreatic Cancer Microenvironement Network[77] which aims to improve therapeutic outcomes for pancreatic cancer patients by understanding the tumor-microenvironment interactions
- NCI's Intramural Research Program plays in important role as a leader of mesothelioma research, conducting clinical trials of novel immunotherapy approaches[78], studing early detection approaches among patients and families with a genetic predisposition to the disease[79], and leading natural history study with tissue procurement of patients with malignant mesothelioma that serves as a resource for the broader research community[80].

Networks and programs with broader themes such as the Early Detection Research Network also support projects focused on particular types of cancer such as mesothelioma[81] while supporting research that will benefit all patients with cancers and those at risk of developing the disease.

[73] prevention.cancer.gov/major-programs/translational-liver-cancer-consortium
[74] prevention.cancer.gov/major-programs/small-cell-lung-cancer-consortium
[75] trp.cancer.gov/spores/ovarian.htm
[76] trp.cancer.gov/spores/bylocation.htm
[77] dctd.cancer.gov/NewsEvents/20200102_PaCMEN.htm
[78] clinicaltrials.gov/ct2/show/NCT04840615; clinicaltrials.gov/ct2/show/NCT03907852
[79] clinicaltrials.gov/ct2/show/NCT03830229
[80] clinicaltrials.gov/ct2/show/NCT01950572
[81] reporter.nih.gov/project-details/10463892

Diversity in NIH Clinical Trials

While 40 percent of Americans belong to a racial or ethnic minority, 80 to 90 percent of participants in clinical trials are White. Patients in underserved communities are often less comfortable enrolling in clinical trials or are unaware of how to do so, excluding them from the opportunity to access potentially lifesaving treatment. Further, it is essential that NIH researchers develop a comprehensive understanding of how treatments impact various populations. The Committee encourages NIH to increase proactive outreach efforts to patients in minority and underrepresented communities and providers serving these populations, to improve awareness of clinical trials and understanding of how patients can participate.

Action taken or to be taken

The National Institutes of Health (NIH) has been committed to inclusion in clinical research for over 3 decades.[82] NIH amended its policy on the inclusion of women and minorities to include additional reporting requirements for certain clinical trials in late 2018. NIH also revised its inclusion of children policy to expand requirements to individuals of all ages.[83] In fiscal year (FY) 2020, 32 percent of participants in NIH-funded clinical research identified as members of a racial or ethnic minority group.

NIH will continue its outreach efforts to minority and underrepresented communities to strengthen awareness of how to participate in NIH-supported clinical research. Below are some examples of how NIH is currently addressing this issue:

- NIH provides reviewers specific guidance on reviewing inclusion based on sex/gender, race, ethnicity, and age. Scientific Review Groups (SRGs) 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.

- NIH supports outreach and engagement efforts in ethnic and racial minority communities disproportionately affected by the coronavirus disease 2019 (COVID-19) pandemic as part of the NIH Community Engagement Alliance (CEAL) effort.[84] CEAL supports research inclusion through engagement, outreach, and education focused on correcting misinformation about COVID-19 and addressing mistrust in the research process. These efforts focus on populations hardest hit by the COVID-19 pandemic, including Black or African Americans, Hispanic or Latinos, American Indian or Alaska Natives, Asians, Native Hawaiians, and Pacific Islanders, with the goal of building long-lasting partnerships. Embedded in the foundation of CEAL is the importance of engaging trusted community-based organizations and leaders to serve as champions who disseminate information about the importance of participating in COVID-19 research.

- In September 2020, NIH held its second Inclusion Across the Lifespan Workshop.[85] The workshop brought together individuals with a variety of backgrounds in clinical study development and execution, with focus on pediatric and geriatric populations, and consideration of special populations (e.g. racial/ethnic minorities, people with disabilities, rural/isolated

[82] grants.nih.gov/policy/inclusion.htm
[83] grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html
[84] covid19community.nih.gov/about
[85] www.nia.nih.gov/Inclusion-Across-Lifespan-2020

populations, language minority individuals, pregnant and lactating people, people with co-morbidities, sexual and gender minorities, and other groups), across the life course to examine the state of the science, discuss lessons learned, and share evidence-based practical advice to consider going forward.

- NIH is funding 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.[86] The NASEM committee will examine the research on barriers to participation, highlight programs that address issues of underrepresentation in clinical trials, and identify more inclusive institutional and informational policies and procedures to increase the likelihood of improved health outcomes for women and racial and ethnic minorities.

- NIH and the U.S. Food and Drug Administration (FDA) are working with external stakeholders through the Clinical Trial Transformation Initiative's "The Value of Increasing Diversity in Clinical Trials" project.[87] This ongoing project held a public webinar Engaging Racial and Ethnic Minority Patient Populations in COVID-19 Clinical Trials on June 18, 2020.[88] 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.

- The NIH's National Institute on Aging (NIA) recently launched its Outreach Pro online research tool, designed to help increase participation by traditionally underrepresented populations in clinical trials on Alzheimer's disease and related dementias.[89]

- The NIH Clinical Research Trials and You[90] website provides information on participation in clinical research to the public, health care providers, and researchers, including 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 NIH Minority Health and Health Disparities Strategic Plan 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 from the strategic plan include: 1) standardizing the collection of demographic data by all Principal Investigators; 2) providing guidance, recommendations, and technical assistance for NIH-funded researchers in appropriate study design and best practices for recruitment; 3) promoting and enforcing accountability for inclusion of diverse populations; and 4) promoting inclusion of racial/ethnic minorities and other populations with health disparities in big data sets, clinical research, and future big science initiatives.

Inclusion of diverse populations in clinical trials requires a sustained commitment from the entire scientific community to design trials that answer questions important to diverse populations and that

[86] www.nationalacademies.org/event/03-29-2021/overcoming-barriers-to-diversifying-clinical-trial-workshop
[87] www.ctti-clinicaltrials.org/projects/diversity
[88] ctti-clinicaltrials.org/briefing-room/webinars/engaging-racial-and-ethnic-minority-patient-populations-covid-19-clinical
[89] www.nih.gov/news-events/news-releases/nih-unveils-new-online-tool-improve-alzheimers-clinical-trials-recruitment
[90] www.nih.gov/health-information/nih-clinical-research-trials-you

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.

Diversity of the Biomedical Research Workforce

The Committee is concerned with the impact of COVID–19 on the diversity of the biomedical research workforce, particularly early stage and midcareer investigators who are women and women of color. The Committee directs NIH to study, to the extent possible, the race, ethnicity, age, gender, disability status and career stage breakdown of the impact of COVID–19 on participation in the workforce by monitoring the types of awards received from and awarded to institutions for 2 years beginning 90 days after enactment of this Act. If pre-pandemic data on these demographics are not available, the Committee directs the NIH to collect them going forward. If the data demonstrate that fewer women are applying for grants, then it is imperative that NIH take steps to address this disparity. The Committee requests a status update from NIH on this research in the fiscal year 2023 CJ, as well as the steps being taken to maintain the diversity of the 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. Intense competition for funding, however, can pose a challenge for researchers trying to embark upon and sustain independent research careers. Moreover, the 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 and vulnerable populations.[91,92] The NIH understands these challenges and, as such, is continuing 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

The NIH has begun assessing the gender distribution of designated principal investigators of R01 and Research Project Grant (RPG) applications submitted before and after the onset of the COVID-19 pandemic.[93,94] Furthermore, an NIH survey of institutional leaders and scientists (opened in the fall of 2020 with results published in March 2021) provided valuable insights into the well-being of the extramural biomedical research workforce, including as it relates to underrepresented and vulnerable groups. Going forward, the NIH will continue assessing its efforts when designing, testing, and implementing future policies and programs to enhance the success and diversity of the next generation of talented biomedical researchers.[95]

To date, several initiatives have been launched to help mitigate the impact of COVID-19 on biomedical careers,[96] including the implementation of numerous opportunities for early-stage investigators to address COVID-19-related research delays. The NIH will continue to solicit input from the research community and devise new strategies or repurpose existing ones to mitigate the devastating effects of the pandemic on the biomedical workforce. Because initial research and evidence indicate that COVID-19 may be disproportionately impacting engagement, experience, and retention of women scientists, especially those

[91] nexus.od.nih.gov/all/2020/11/04/continued-impact-of-covid-19-on-biomedical-research/
[92] 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/
[93] nexus.od.nih.gov/all/2020/07/28/an-early-look-at-applications-submitted-during-the-pandemic/
[94] nexus.od.nih.gov/all/2021/06/01/an-updated-look-at-applications-submitted-during-the-pandemic/
[95] extramural-diversity.nih.gov/
[96] nexus.od.nih.gov/all/2020/11/04/continued-impact-of-covid-19-on-biomedical-research/

from underrepresented groups, the NIH is focusing on developing strategies (including programs and policies) specifically to promote the continued advancement of women in biomedical research careers.

Steps to Diversify the Biomedical Research Workforce

In September 2017, with support from the 21st Century Cures Act (P.L. 114-255), the NIH launched the Next Generation Researchers Initiative (NGRI) to cultivate and support talent entering the biomedical and behavioral research workforce.[97] NGRI promotes opportunities for new researchers and fosters earlier research independence through policies **that increase opportunities for new researchers to receive funding**, enhance training and mentorship programs and **enhance workforce diversity.**[98] Scientists and trainees from diverse backgrounds and life experiences bring different perspectives and creative approaches to solving the scientific problems we face as a nation. The 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. The NIH is analyzing NGRI policies to ensure our efforts continue supporting career development for women and individuals from diverse backgrounds in biomedicine.

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

- Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative Advanced Postdoctoral Career Transition Award to Promote Diversity (K99/R00)[99]
- Maximizing Opportunities for Scientific and Academic Independent Careers (MOSAIC) program[100]
- Building Infrastructure Leading to Diversity (BUILD) program[101]
- National Research Mentoring Network (NRMN)[102]
- Faculty Institutional Recruitment for Sustainable Transformation (FIRST) program[103]

In addition, the NIH has developed and implemented a range of approaches to improve the representation of women in biomedical research. The NIH implemented automatic extensions of early-stage investigator (ESI) status for childbirth within the ESI period.[104] In FY 2020, an automatic extension of one year was also implemented for childbirth within the four-year K99 eligibility window.[105] Additionally, the NIH offers support for early-career investigators with high potential to re-enter an active research career after an interruption for family responsibilities or other qualifying circumstances.[106,107] The NIH also provides funding for Childcare Costs for Ruth L. Kirschstein National Research Service Awards for Individual Fellows and Trainees.[108,109] Finally, the Re-entry and 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

[97] grants.nih.gov/ngri.htm
[98] nexus.od.nih.gov/all/2021/07/12/data-on-implementing-nihs-next-generation-researchers-initiative/
[99] grants.nih.gov/grants/guide/rfa-files/rfa-ns-19-043.html
[100] nigms.nih.gov/training/careerdev/Pages/MOSAIC.aspx
[101] nigms.nih.gov/training/dpc/pages/build.aspx
[102] nrmnet.net /
[103] commonfund.nih.gov/first
[104] grants.nih.gov/grants/guide/notice-files/NOT-OD-18-235.html
[105] grants.nih.gov/grants/guide/pa-files/pa-18-592.html
[106] grants.nih.gov/grants/guide/notice-files/NOT-OD-20-054.html
[107] grants.nih.gov/grants/guide/notice-files/NOT-OD-20-055.html
[108] grants.nih.gov/grants/guide/notice-files/NOT-OD-21-074.html
[109] grants.nih.gov/grants/guide/notice-files/NOT-OD-21-177.html

continuation of their research training programs and to safely reintegrate into the biomedical workforce.[110]

Lastly, the NIH recently 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. These efforts are part of an overall effort by the U.S. Department of Health and Human Services (HHS) to respond to the *Executive Order*[111] *On Advancing Racial Equity and Support for Underserved Communities Through the Federal Government* to improve equity, diversity, and inclusion in the Federal workplace.

[110] grants.nih.gov/grants/guide/notice-files/not-od-21-134.html

[111] whitehouse.gov/briefing-room/presidential-actions/2021/01/20/executive-order-advancing-racial-equity-and-support-for-underserved-communities-through-the-federal-government/

Drug Impairment Standards for Marijuana

The Committee is concerned that development of a drug impairment standard for marijuana remains unlikely in the near term and encourages NIH to continue supporting a full range of research on the health effects of marijuana and its components, including research to understand how marijuana policies affect behaviors that impact public health, such as drug-impaired driving. The Committee is aware that due to Drug Enforcement Administration restrictions on registered growers, the majority of Federal research using marijuana has been limited to marijuana produced by a single grower and encourages NIH, when possible, to undertake research that encompasses the diversity, quality, and potency of commonly available cannabis products.

Action taken or to be taken

As cannabis gains wider availability and social acceptability, it is increasingly important to understand the drug's effects on individual and public health, including the impact of cannabis on driving. Such research continues to be a high priority for the National Institute on Drug Abuse (NIDA). NIDA is supporting research to examine the effects of cannabis on driving simulator tasks that are predicting of on-road ability. One of these projects is aimed at elucidating specific, driving-related cognitive impairments caused by acute cannabis use, their persistence over time, associations with underlying functional brain anatomy, and relationship to driving performance.[112] Another is exploring how high-potency smoked cannabis, commonly used for medical and recreational purposes, affects driving performance.[113] Other efforts focus on how cannabis use impacts motor learning in general, and how this is related to memory and motor performance.[114] Researchers are also developing devices to help measure cannabis impairment with a goal of improving public safety. A portable device is being used to identify impaired driving through psychomotor and oculomotor measures, and blood biomarkers.[115] In addition, a breath analyzer and a sweat-based screening device are being developed for real-time, quantitative, point-of-use detection of cannabis use.[116,117,118]

Other NIDA-supported studies are assessing the social, behavioral, and public health impacts of cannabis policies. These include research on the effects of recreational cannabis advertising on adolescent cannabis use and its consequences, including vehicular risk behaviors;[119] the effects of state medical cannabis laws on the prevalence of cannabis use, cannabis use disorder, and their consequences, such as arrest rates and emergency department visits;[120] and the health and social consequences of cannabis legalization in other countries.[121] NIDA is also supporting research on the relationship between cannabis use, cannabis use disorder, and other drug use;[122,123] and the impact of cannabis use on, and comorbidity

[112] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9698917
[113] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9735170
[114] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9785495
[115] reporter.nih.gov/search/KtuS4m0PnUq3480JxJpzTg/project-details/10190878
[116] reporter.nih.gov/search/nQdjuGT8fky4VeAOEgPP0A/project-details/10059295
[117] reporter.nih.gov/search/KtuS4m0PnUq3480JxJpzTg/project-details/9852598
[118] reporter.nih.gov/search/KtuS4m0PnUq3480JxJpzTg/project-details/10137820
[119] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9656892
[120] eporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9527798
[121] reporter.nih.gov/search/sme-z3YD4ke0a78NbFHKxQ/project-details/9693697#history
[122] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9784768
[123] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9788381

with, mental illnesses.[124,125,126] Through the Adolescent Brain Cognitive Development (ABCD) Study,[127] the Healthy Brain Child Development (HBCD) Study,[128] and other NIDA supported projects, researchers are also examining the impact of cannabis exposure on the developing brain, including fetal exposure during pregnancy.[129,130,131] .[132,133,134] The ABCD Study is following nearly 12,000 children who were aged 9-10 at enrollment, through adolescence and into young adulthood. The recently launched HBCD Study will follow approximately 7,500 children from the prenatal period through ages 9-10. By longitudinally tracking biological and behavioral development, these studies will help us understand how substance use - including marijuana exposure - influences brain development and other outcomes. In addition to assessing adverse consequences of cannabis exposures, NIDA research is evaluating the therapeutic effects of cannabinoids, including for opioid use disorder,[135]tobacco cessation,[136] pain,[137] and HIV.[138]

To facilitate cannabis research, NIDA's drug supply program provides cannabis to researchers in a range of potencies. Still, the diversity of products is limited and does not necessarily reflect the range of products that consumers are using. For example, higher potency products are available on the market yet inaccessible to researchers due to their Schedule I status. Some researchers have taken novel approaches to conducting research relevant to real-world cannabis use, such as using mobile laboratories to draw blood immediately before and after a participant uses their cannabis in their own home, and to collect self-report, interview, and neurobehavioral measures without any delay.[139]

Another limitation to cannabis research has been the lack of a standard unit by which to measure cannabis intake and compare its effects across studies. Existing data are often hard to interpret due to the wide variability in potency of cannabis plant material and extracts, the lack of standard measures of use, and the wide variety of ways people consume cannabis. To help overcome this barrier, NIDA, the National Cancer Institute (NCI), the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Mental Health (NIMH), recently published a notice directing researchers to measure and report their findings from clinical research on cannabis using a standard unit of THC of 5 milligrams.[140] Similar standard measures have been applied for other substances, and having a standard unit of measurement for cannabis will make it easier to compare the influence of these factors on how individuals respond to the drug.

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[124] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9388982
[125] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9388982#sub-Projects
[126] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9458154
[127] www.drugabuse.gov/drug-topics/adolescent-brain/longitudinal-study-adolescent-brain-cognitive-development-abcd-study
[128] heal.nih.gov/research/infants-and-children/healthy-brain
[129] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9749068
[130] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9505868
[131] reporter.nih.gov/search/OKRlN12af0OE4PK0OjDCCA/project-details/10224159
[132] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9749068
[133] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9505868
[134] reporter.nih.gov/search/OKRlN12af0OE4PK0OjDCCA/project-details/10224159
[135] reporter.nih.gov/search/FpE_ivA7BUm6tUSfzG2yqA/project-details/10117221
[136] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9741114
[137] reporter.nih.gov/search/q7b_yh0rCk6kITjZ0-Cf4Q/project-details/9700089
[138] reporter.nih.gov/search/sAblhM5NDU2GNlbKbzpn0A/project-details/9696827
[139] reporter.nih.gov/search/n2ynguNbqUK_OSOS7lSaFQ/project-details/10307408.
[140] grants.nih.gov/grants/guide/notice-files/NOT-DA-21-049.html

Duchenne Muscular Dystrophy

In light of improvements in care leading to patients living into their third decade, the leading cause of death in Duchenne Muscular Dystrophy patients is heart failure. The Committee urges NHLBI to support research that characterizes cardiomyopathy in Duchenne and Becker Muscular Dystrophy. There is a gap in the ability to develop novel cardiac therapeutics for Duchenne Muscular Dystrophy due to a lack of accepted cardiac outcome measures. The Committee encourages NHLBI to continue its work towards establishing viable cardiac outcome measures for the development of therapeutic agents to combat cardiomyopathy and to report on its progress in the fiscal year 2023 CJ.

Action taken or to be taken

Duchenne Muscular Dystrophy (DMD) is the most common form of muscular dystrophy among children, and there is currently no cure. DMD primarily affects boys, and the average life expectancy is 27 years of age. DMD and the less severe Becker Muscular Dystrophy, which are both caused by mutations in the *DMD* gene encoding a muscle protein called dystrophin, are associated with cardiomyopathy (weakness in the heart muscles). Dystrophin is part of a group of proteins that strengthen muscle fibers and protect them from injury as muscles contract and relax. Loss of dystrophin function causes muscle cell damage, as well as buildup of scar tissue over time.

Together with the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the National Institute of Neurological Disorders and Stroke (NINDS); the National Heart, Lung, and Blood Institute (NHLBI) co-funds the Senator Paul D. Wellstone Muscular Dystrophy Research Centers Program, the National Institutes of Health's (NIH) flagship program for muscular dystrophy research. The Centers promote collaborative basic, translational, and clinical research and provide resources including outstanding training environments, community outreach, and shared core facilities. Center funding, combined with additional NIH support, has enabled significant advances in gene therapy approaches for DMD. For example, one challenge in applying gene therapy to this disease is that the *DMD* gene is too large to fit commonly used viral vectors. NHLBI-funded researchers have engineered smaller *DMD* genes, preserving the parts that are critical to the functions of dystrophin.[141] After showing promise in animal models, one of these micro-dystrophins is currently being evaluated in a clinical trial.[142] NHLBI investigators also have developed CRISPR-mediated gene editing technology that can restore dystrophin in patient-derived cells and in animal models of DMD.[143]

In addition to supporting the Wellstone Centers, NHLBI funds basic research to understand the basis of cardiac muscle disease in the muscular dystrophies, including the role of dystrophin in coronary blood flow, the effects of dystrophin mutations on cardiac muscle cell function, and how other genes and proteins needed for the dystrophin complex affect cardiac function and pathology in DMD. For example, recent NHLBI-funded research shows that without dystrophin, cell-to-cell connections called gap junctions become destabilized in cardiac muscle cells, suggesting that these structures may be a therapeutic target for preventing or slowing cardiomyopathy in DMD patients.[144]

The Institute is funding clinical and preclinical studies to develop therapeutic approaches to have the greatest impact on reducing death and disability in patients with DMD. For example, a 2019 NHLBI-

[141] ncbi.nlm.nih.gov/30718090/
[142] clinicaltrials.gov/ct2/show/NCT03368742
[143] ncbi.nlm.nih.gov/34748394/
[144] ncbi.nlm,nih,gov/pubmed/31910160/

funded study found that early therapy with aldosterone blockers— spironolactone and eplerenone – is safe and effective at preserving cardiac function in boys with DMD with high cardiomyopathy risk.[145]

Other studies seek to optimize treatment of DMD with corticosteroids, which can help reduce inflammation and promote muscle repair, but also have side effects, including weight gain and osteoporosis. For example, one study is exploring how corticosteroid responses change with the circadian clock and the potential for optimal timing of dosing. The project aims to produce evidence for time-restricted intermittent corticosteroid dosing to trigger glucocorticoid action in heart metabolism, converting these drugs from "pro-diabetic" to "anti-diabetic" in cardiometabolic health. In addition, findings from NHLBI-funded preclinical studies have shown promise that the vasodilatory drug nicorandil may be cardioprotective for DMD-associated cardiomyopathy.[146]

[145] ncbi.nlm.nih.gov/pmc/articles/PMC6806050/
[146] pubmed.ncbi.nlm.nih.gov/34130633/

Environmental Influences on Child Health Outcomes [ECHO]

The Committee provides $180,000,000, the same level as fiscal year 2021, for the ECHO Program. ECHO currently funds the Navajo Birth Cohort Study. This funding will allow the Program to continue. The Committee encourages OD to consider expanding the study to include a larger representation of indigenous children into the national cohort. This would allow for a better understanding of the impacts of environmental exposure in these unique populations, benefiting the current goals of ECHO-wide efforts as well as indigenous communities across the U.S. OD is directed to provide an update in the fiscal year 2023 CJ on progress made by ECHO-funded research.

Action taken or to be taken

In 2019, the National Institutes of Health (NIH) facilitated a data-sharing and use agreement between the Navajo Nation and Environmental Influences on Child Health Outcomes (ECHO) Program grantees. The first Tribal data-sharing agreement for a nationwide research consortium creating a large-scale database lays the groundwork for discussion with other Tribal Nations considering participation in biomedical research programs.

Please see below for a discussion of:

- The ECHO Program's goals
- How the next phase of the ECHO Cohorts will include a focus on diversity—inclusive of indigenous communities—as it extends and expands the ECHO-wide Cohort
- The Navajo Birth Cohort and its contributions to ECHO science
- Relevant publications that help contribute to the understanding of these unique populations
- An overview of ECHO research related to indigenous populations

Program Goals. The ECHO Program has implemented an evaluative planning approach to ensure success in developing a consortium-wide high-quality data platform and biorepository with data and specimens from over 50,000 children and their families, which it will make available to the research community as a national resource for studying child health. The ECHO Program established goals and objectives based on markers of successful observational studies: successful enrollment and retention of study populations – including metrics on participant diversity; fidelity to the research protocol; and sound data analysis, publication, and dissemination.

As of November 2021, the ECHO cohorts had data from 96,049 participants from 72 cohort studies, including 58,863 children, with 27,244 in active follow up. The Program has 40,650 biospecimens collected from 19,900 participants. ECHO participants are diverse in age, socio-economic status, geography, and race/ethnicity, with 26 percent Hispanic, 43 percent non-Hispanic White, 12 percent Black, 4 percent Asian, 3 percent American Indian or Alaska Native, 4 percent more than one race, and 8 percent unknown/not reported/other.

Diversity and Indigenous Populations in Next Phase of Echo Cohorts. The next phase of the ECHO Cohorts—which will begin in FY 2023—will extend and expand the ECHO-wide Cohort to further investigate the roles of a broad range of early exposures on ECHO's five key child health outcomes among diverse populations. The ECHO Program is planning on expanding the Program using community engaged strategies to enhance diverse populations, including indigenous populations.

Navajo Birth Cohort Study (NBCS). The goal of this study, a large-scale assessment of metal mixtures exposures on children's neurodevelopment and immune function in tribal populations. To date the Navajo Birth Cohort has helped to raise questions on the appropriateness of assessment tools,

understanding the potential variability in developmental trajectories, and continuing to remain sensitive to the appropriateness of research measures and methods for indigenous children before interpreting data and generalizing results.

The Navajo Nation was greatly affected by the coronavirus disease 2019 (COVID-19) pandemic, and as a result the NBCS faced many challenges including high prevalence of infection and death, lack of supplies available to the Navajo staff and participants; shut-down of hospitals, clinics, and office space to conduct research; the need for different approaches to convey culturally informed public health recommendations; and given the lack of broadband access, the difficulty in transitioning to remote enrollment, resulting in time-intensive delivery of materials to participants' houses. However, research operations are now starting to resume.

Relevant Publications. The ECHO Program investigators have published over 700 peer-reviewed scientific articles. Even in the face of the COVID-19 challenges listed above, the NBCS released many publications over the last year and a half, related to diet quality among pregnant Navajo women,[147] assessing the impact of chemical exposures on neurodevelopment,[148] exposure to uranium and other metals among pregnant women,[149] and the effect of indoor fine particulate matter in homes heated with wood fuel.[150]

Additionally, this past year, the ECHO Program published *Best Practices for Conducting Clinical Trials with Indigenous Children in the United States.*[151] This article provides guidance for conducting clinical trials with Indigenous children in the United States, drawing on extant literature and experiences to describe best practices for the ethical and effective conduct of clinical trials with Indigenous children. Case examples of pediatric research conducted with American Indian, Alaska Native, and Native Hawaiian communities are provided to illustrate these practices. Indigenous children must be included in clinical trials to reduce health disparities and improve health outcomes in these pediatric populations. Establishment of the Environmental Influences on Child Health Outcomes Institutional Development Award States Pediatric Clinical Trials Network (ECHO ISPCTN) in 2016 and renewal in 2020 creates a unique and timely opportunity to increase Indigenous children's participation in state-of-the-art clinical trials.

Sample of ECHO Research Involving Indigenous Populations. In 2020, the ECHO Program released a Notice of Special Interest (NOSI): Administrative Supplements to Existing NIH ECHO Cooperative Agreements (Admin Supp - Clinical Trial Not Allowed) for Coronavirus Disease 2019 (COVID-19) – related Research.[152] One project entitled "Impact of COVID-19 and associated stressors on neurodevelopment in marginalized populations" focused on indigenous populations. This project examined the relative pandemic-induced stress across multiple cohorts differing with respect to marginalization, COVID-19 population prevalence, and experience with historical trauma/systemic racism. This comparison included the NBCS, the Prenatal Alcohol in Sudden Infant Death Syndrome (SIDS) and Stillbirth (PASS-ECHO) cohorts (Indigenous and non-Indigenous populations in South Dakota), and the Atlanta ECHO cohort of urban Black participants. This was an innovative study exploring the impact of increased stress across communities already affected by historical trauma and facing a disaster like COVID-19 to address whether collective stress affects long-term child neurodevelopment through changes in parenting and the home environment, and ensured that minority

[147] pubmed.ncbi.nlm.nih.gov/32026554/
[148] pubmed.ncbi.nlm.nih.gov/32526495/
[149] pubmed.ncbi.nlm.nih.gov/32750552/
[150] pubmed.ncbi.nlm.nih.gov/33620109/
[151] Am J Public Health. 2021 Sep;111(9):1645-1653. doi: 10.2105/AJPH.2021.306372. Epub 2021 Aug 26.
[152]grants.nih.gov/grants/guide/notice-files/NOT-OD-20-107.html

cohorts are represented in the time-sensitive datasets in sufficient numbers to evaluate and compare impacts to develop mitigation interventions, rather than simply by population proportional representation.

An NBCS early-stage investigator was awarded a grant supplement using ECHO funds to perform a research project entitled: "Attentional mechanisms underlying information processing in a sample of Navajo children." This study examined the relationship between attentional biases and children's anxiety and depression symptoms of Navajo children as compared to those observed in children from another ECHO cohort with the aim to test whether attentional biases are associated with metal exposure. This will be done in part by checking children's anxiety/depression symptoms as assessed through biomonitoring of blood and urine collected, in addition to assessing internalizing behavior problem in children from NBCS. This project is still in the process of analyzing data and plan to publish results in the near future.

While the Navajo Birth Cohort is not the only source of tribal participants in ECHO, their recruitment across Tribal lands and by tribal members makes this cohort the most representative of an indigenous population as a whole still living on tribal land. An additional source of tribal participants is the PASS-ECHO cohort. The aim of this cohort is to answer questions relating to the impact of prenatal and early childhood environmental exposures on later health outcomes. This study consists of over 1,700 American Indian participants, roughly 18.5 percent of the total number of participants. This unique cohort provides a wealth of prenatal and infant data that can expand the capability of the ECHO study in areas of neurodevelopment, neurophysiology, and asthma, particularly among rural and American Indian youth. The PASS-ECHO investigative team has a proven track record in conducting complex and high-quality studies while maintaining longitudinal participant and community engagement in the region, helping the ECHO Program to retain diverse participants.

Firearm Injury and Mortality Prevention Research

The Committee includes $25,000,000 to support research on the prevention of gun violence, $12,500,000 above the fiscal year 2021 enacted level and the same as the fiscal year 2022 budget request. The Committee also requires NIH and CDC to collaborate with the National Institute of Justice to compile, share, and improve firearm violence data. Such data must include the Uniform Crime Report (UCR) and include data from hospitals treating victims of nonfatal gunshot wounds.

Action taken or to be taken

In fiscal year (FY) 2020, the National Institutes of Health (NIH) Office of Behavioral and Social Sciences Research (OBSSR) and the Office of Extramural Research (OER), in collaboration with multiple NIH Institutes and Centers (ICs), developed two Funding Opportunity Announcements (FOAs), released on March 20, 2020, intended to build upon the existing NIH research portfolio and address emerging opportunities on firearm injury and mortality prevention. From these FOAs, NIH funded nine grants with multi-year funding.

- PAR-20-143[153]: Two-year R61 awards for pilot, exploratory, or developmental projects
    - Seven awards were funded
- NOT-OD-20-089[154]: One-year administrative supplements to active R01 or R21 grants to incorporate firearms research with the scope of the project.
    - Two awards were funded

In FY 2021, OBSSR, in collaboration with multiple NIH ICs, developed two FOAs, released on March 5, 2021, that had a similar broad and comprehensive approach to research on firearm injury and mortality prevention, and provided for longer multi-year funding periods to allow for more comprehensive and longer-term research evaluation of firearms violence prevention interventions.

- PAR-21-191[155]: Two-year R21 awards, with the option of a subsequent third year through an R33 award, for pilot, development, or exploratory projects
    - Two awards were funded
- PAR-21-192[156]: Three-year R01 awards
    - Eight awards were funded

Consistent with the White House and Congressional efforts to support Community Violence Interventions (CVI), these FOAs took a broad public health approach to firearm injury and mortality prevention, encouraging research on interventions delivered in healthcare systems and community settings, as well as research that integrated individual, family, interpersonal, community, and structural or system (e.g., criminal or juvenile justice, child welfare, drug courts) approaches to firearm injury and mortality prevention. Violence research, including community violence intervention research, provides the basis for new evidence-informed approaches (or strategies) that communities can implement to improve their ability to reduce violence.

Based on in-depth analysis of NIH-funded violence research across the ICs, NIH is prepared to use funds provided by Congress in FY 2022 to fund important violence research questions such as how to optimize violence prevention strategies, tailor strategies to the unique needs of various communities, improve the

[153] grants.nih.gov/grants/guide/pa-files/PAR-20-143.html
[154] grants.nih.gov/grants/guide/notice-files/NOT-OD-20-089.html
[155] grants.nih.gov/grants/guide/pa-files/PAR-21-191.html
[156] grants.nih.gov/grants/guide/pa-files/PAR-21-192.html

prediction of those at risk of violent acts, identify the combination of neurobiological mechanisms and contextual factors that predispose individuals to violent acts, increase implementation and adoption of effective violence reduction strategies, and assist the recovery of victims of non-fatal violence.

NIH has established collaborations with Centers for Disease Control and Prevention (CDC) and the National Institute of Justice (NIJ), as well as coordinated with CDC and NIJ on prior firearm violence initiatives. As new firearm injury and mortality prevention research programs are developed, NIH will continue to collaborate with CDC and NIJ to compile, share, and improve firearm violence data using information from the Uniform Crime Report (UCR) and hospitals treating victims of nonfatal gunshot wounds.

Foreign Animal Research

The Committee requests additional information in the fiscal year 2023 Congressional Budget Justification about how NIH monitors and ensures foreign institutions' compliance with applicable laws, regulations, and policies governing NIH-funded animal research.

Action taken or to be taken

As described in the National Institutes of Health (NIH) Guide for Grants and Contracts Notice NOT-OD-12-081,[157] the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (Policy)[158] requires that institutions in foreign countries receiving PHS support for activities involving animals shall have an approved Foreign Assurance on file with the NIH Office of Laboratory Animal Welfare (OLAW).[159] Foreign Assurances submitted to OLAW are evaluated for compliance with the PHS Policy or evidence that acceptable standards for the humane care and use of animals in PHS-supported activities will be met.[160] OLAW approves Foreign Assurances for periods up to five years and will only renew a Foreign Assurance if the institution has current direct or indirect PHS funding for activities with animals.

The Foreign Assurance documents that the foreign institution agrees to follow the International Guiding Principles for Biomedical Research Involving Animals[161] and comply with all laws, regulations, and policies listed in the Assurance regarding the humane care and use of laboratory animals in the country of origin.[162] Lack of an Assurance will not adversely affect the institution's ability to apply for future funding.[163] An Assurance does not determine whether an organization can or will receive a grant.

As it relates to oversight, all funded grant recipients are required to submit an annual Research Performance Progress Report.[164] Assured institutions are subject to review by OLAW at any time to assess the adequacy or accuracy of the institution's compliance.[165]

NIH takes seriously the humane care and use of animals used in NIH-funded research. Likewise, NIH takes seriously all noncompliance with the PHS Policy,[166] either self-reported by the institution or received from other sources. Compliance with the Policy is a collaborative effort between the NIH and research institutions, including both foreign and domestic collaborating institutions. By law, OLAW affords NIH award recipients the reasonable opportunity to take corrective action for cases of noncompliance. For situations of reported noncompliance by an institution, an OLAW compliance officer considers the nature of the incident and determines whether the corrective and preventive measures offered by the institution appropriately address the problem and have a reasonable expectation of preventing recurrence.[167,168] If all factors are met, then the institutional official is informed and the case for the incident is closed. OLAW maintains records of such cases for both domestic and foreign Assured institutions.

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[157] grants.nih.gov/grants/guide/notice-files/NOT-OD-12-081.html
[158] olaw.nih.gov/policies-laws/phs-policy.htm
[159] grants.nih.gov/grants/foreign/animal_welfare.htm
[160] olaw.nih.gov/policies-laws/phs-policy.htm
[161] olaw.nih.gov/sites/default/files/Guiding_Principles_2012.pdf
[162] olaw.nih.gov/resources/tutorial/terms.htm#3c
[163] grants.nih.gov/grants/guide/notice-files/NOT-OD-12-081.html
[164] grants.nih.gov/grants/rppr/index.htm
[165] olaw.nih.gov/policies-laws/phs-policy.htm
[166] olaw.nih.gov/policies-laws/phs-policy.htm
[167] olaw.nih.gov/sites/default/files/ComplianceOversightProc.pdf
[168] olaw.nih.gov/guidance/reporting-noncompliance.htm

Gynecologic Cancers

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. Therefore, the Committee urges NCI to expand the number of programs, projects, 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 2023 Congressional Budget Justification, including specific grants and strategies where the intent is to over-come these racial disparities in gynecologic cancers outcomes, including the underrepresentation of minority women in gynecologic cancer clinical trials.

Action taken or to be taken

The National Cancer Institute (NCI) supports a robust research program in women's cancers (cervical, endometrial, ovarian cancers, and other gynecologic cancers) including research aimed at addressing disparities for women from racial/ethnic and underserved populations who disproportioantly suffer from these cancers for a number of reasons. NCI's commitment to expanding clinical trial participant demographics to better represent the American population and better reflect broad health outcomes is reflected in NCI's fiscal year (FY) 2023 Annual Plan: "Clinical Trials: Bringing Cancer Research to All Possible Participants."[169] Over the last two decades, the proportion of racial and ethnic minority patients enrolled in NCI-funded National Clinical Trials Network (NCTN) and National Community Oncology Research Program clinical trials has nearly doubled.

The NCTN supports steering committees with disease-specific strategic priorities, including steering committees for women's cancers. The steering committees increase information exchange at early stages of trial development, increase efficiencies of collaboration among trial sites, and reduce trial redundancy across programs. The Gynecologic Cancers Steering Committee (GCSC)[170] develops, evaluates, and prioritizes concepts for large Phase II and all Phase III clinical trials for cervical, ovarian, and uterine cancers. The 2021 strategic priorities for the GCSC include endeavoring to address health equity across all barriers and advance diversity in the treatment of people with gynecological cancers. All of the strategic priorities are publicly available on the NCI website.[171] In addition to annual planning meetings, in 2021, the GCSC held a meeting titled "Defining and Targeting Molecular Pathways to Direct Personalized Value-added Treatments for Patients with Epithelial Ovarian Cancer" to identify and prioritize novel and existing therapies to target specific ovarian cancer subtypes.[172]

NCI is dedicated to eradicating cervical cancer through prevention and early detection.[173] Current human papillomavirus (HPV) vaccines can prevent 90 percent of HPV-related cancers, and NCI continues to research efforts to increase HPV vaccine uptake and understand vaccine hesitancy. Over half of the new

[169] cancer.gov/research/annual-plan/scientific-topics/clinical-trials
[170] cancer.gov/about-nci/organization/ccct/steering-committees/nctn/gynecologic
[171] cancer.gov/about-nci/organization/ccct/steering-committees/nctn/gynecologic/2021-gynecologic-strategic-priorities
[172] cancer.gov/about-nci/organization/ccct/steering-committees/nctn/gynecologic/gcsc-otf-ctpm-feb-execsum-2021
[173] cancer.gov/news-events/nca50/stories/cervical-cancer-prevention

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 has developed the 'Last Mile Initiative'[174] as a public private partnership between federal agencies, industry partners, and professional societies/clinical practice guidelines organizations. This Initiative aims to validate self-sampling-based HPV testing as a comparable alternative to provider-collected cervical specimens for HPV testing in cervical cancer screening. As part of this Initiative, the NCI will support a nationwide, multicentric screening trial in diverse delivery settings. 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 supports research to advance our understanding of how to prevent, detect, and treat uterine cancers (endometrial cancer and uterine sarcoma). 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.[175] While investigators from NCI's Early Detection Research Network designed the PapSEEK test for early detection of endometrial cancers.[176] This test is a type of liquid biopsy that identifies cancer-related alterations in DNA obtained from fluids collected during a routine Pap test to detect some endometrial cancers at earlier, more treatable stages. Similarly, the DETECT (Discovery and Evaluation of Testing for Endometrial Cancer in Tampons) Study is developing ways to detect endometrial cancer in samples of uterine tissue collected using tampons.[177] By comparing uterine tissue from women who are having a hysterectomy for endometrial cancer with tissue from women having a hysterectomy for an unrelated benign condition, scientists in NCI's intramural research program hope to find biomarkers that may eventually lead to noninvasive early detection approaches.

It is well documented that African American women with ovarian cancer do not survive as long as non-Hispanic White women with the disease. Studies suggest that multiple factors, including access to care and socioeconomic factors, result in the disparity. NCI is funding three separate but complementary studies to better understand why certain groups of patients with ovarian cancer have worse outcomes than others. One of the studies uses a comprehensive approach to examine the interplay among patient, health care, socio-contextual, and biological factors from data collected on approximately 4,500 women to understand racial disparities in survival.[178] A second study is focused on factors that contribute to poor ovarian cancer suvival in African American women. This study will recruit 350 newly diagnosed African American women and intergrate information regarding their social and physical environments with data on inflammationi-related exposures and inflammatory markers from their tumor tissues.[179] The third study is surveying women who recently completed initial treatment for ovarian cancer to determine barriers to access to quality cancer care.[180] This study will investigate five dimensions of health care: access, afforability, availability, accommodation, and acceptability. Together these studies will help develop new strategies to improve outcomes for all ovarian cancer patients.

The Specialized Programs of Research Excellence (SPOREs), a key component of NCI's Translational Research Program, also supports research on women's cancers including five ovarian cancer SPOREs and

[174] prevention.cancer.gov/major-programs/nci-cervical-cancer-last-mile-initiative
[175] epi.grants.cancer.gov/eecc/
[176] cancer.gov/news-events/cancer-currents-blog/2018/liquid-biopsy-screening-test-endometrial-ovarian
[177] clinicaltrials.gov/ct2/show/NCT03538665
[178] reporter.nih.gov/project-details/9998465
[179] reporter.nih.gov/project-details/9887475
[180] reporter.nih.gov/project-details/9831150

one endometrial cancer SPORE.[181] NCI has also been funding planning grants for future SPORE programs in cancer health disparitites.[182] 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 fiscal year 2020, Northwestern University in Chicago was awarded a SPORE planning grant focusing on racial differences in gynecologic cancers.[183]

The National Institute on Minority Health and Health Disparities (NIMHD) also supports research in gynecologic cancers with known increased rates in racial and ethnic minority populations. One NIMHD-funded study found that patients at high-performing hospitals were more likely to receive treatment consistent with standard ovarian cancer guidelines and had a longer average survival time after treatment compared to patients treated at medium and lower performing hospitals.[184] Another NIMHD-funded study aims to characterize cervical cancer screening coverage, failures in cervical cancer screening, diagnosis and treatment, and correlation of cervical screening with HPV vaccination among American Indian and Alaska Native (AI/AN) women. The overarching goal of this study is to elucidate the specific pathways through which failures to screen for cervical cancer occur to inform cost-effective and data-driven strategies for interventions that can mitigate the pervasive health disparities witnessed among AI/AN women.[185]

[181] trp.cancer.gov/
[182] grants.nih.gov/grants/guide/rfa-files/RFA-CA-19-034.html
[183] reporter.nih.gov/project-details/9961257
[184] pubmed.ncbi.nlm.nih.gov/31923082/
[185] reporter.nih.gov/project-details/10020805

Harassment Policies

The Committee is deeply frustrated by NIH's failure to implement its direction to address harassment in extramural research settings. Both the Statement of managers accompanying the Further Consolidated Appropriations Act, 2020 (Public Law 116–94) and the Consolidated Appropriations Act, 2021 (Public Law 116–260) directed NIH to revise its guidance to make clear that grantees must identify any changes to key personnel on an award that are related to concerns about harassment. The Committee has included a new general provision to require institutions that receive NIH funding to notify the agency when key personnel are removed from their position for harassment.

Action taken or to be taken

The National Institutes of Health (NIH) takes harassment and discrimination very seriously, including sexual harassment and racial discrimination. NIH has made it clear that the agency will not tolerate behaviors contributing to an unsafe or hostile work environment affecting personnel on NIH-funded projects.[186] The biomedical research community can and must do better. Since 2015, NIH has taken various substantive steps to enhance our ability to learn of, assess, and address allegations of harassment.[187]

To encourage institutions to identify any changes to key personnel on an award that are related to concerns about harassment, NIH issued a Guide Notice in June 2020 (NOT-OD-20-124) which stated that organizations should inform the agency of concerns about safe working conditions (including concerns about harassment) when they seek prior approval for changes in principal investigators or key personnel.[188] This expectation has since been incorporated into the NIH Grants Policy Statement, which is a Term and Condition of award (see Section 8.1.2).[189]

At the time of this notice, NIH did not have the legal authority to require that institutions report this information and implemented an "expectation" that we be given this information, which is the most NIH could do within existing law. As the world's largest funder of biomedical research, it has been our experience that NIH-funded institutions take NIH expectations seriously.

Also, NIH senior leadership reiterated the policy expectation in a related blog post,[190] stating "…when requesting changes in either investigators … or movement of a grant to a new recipient institution … grantees are expected to mention if there are related concerns about the safety and/or work environments … The new guidance marks critical progress in NIH's efforts to foster a culture of safety and respect for all those working in science and sends a clear message that sexual harassment and other inappropriate behaviors are unacceptable and will not be tolerated."

NIH will move expeditiously to implement the General Provision included in the FY 2022 appropriations bill.

Other policies and approaches which may be of interest that NIH developed to address sexual harassment in extramural environments include:

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[186] nexus.od.nih.gov/all/2019/02/28/update-on-nihs-efforts-to-address-sexual-harassment-in-science/
[187] grants.nih.gov/grants/policy/harassment.htm
[188] grants.nih.gov/grants/guide/notice-files/NOT-OD-20-124.html
[189] grants.nih.gov/grants/policy/nihgps/HTML5/section_8/8.1.2_prior_approval_requirements.htm?Highlight=HARASSMENT
[190] nexus.od.nih.gov/all/2020/06/11/new-steps-to-help-ensure-safe-work-environments-for-nih-supported-research/

- February 2019: The NIH Director issued a detailed statement[191] which described steps the agency had already begun, at the suggestion of both an internal Anti-Harassment Steering Committee and the newly formed Advisory Committee to the Director (ACD) Working Group on Changing the Culture to End Sexual Harassment.[192] These steps included clarifying expectations of organizations to ensure a safe workplace and inform the agency, and to provide clear channels of communications to NIH whereby anyone can report concerns. At that time NIH established a dedicated mailbox, granteeharassment@nih.gov.

- March 2019: The Director of the NIH Center for Scientific Review (CSR) issued a statement that, out of an abundance of caution, the Center would proactively exclude some reviewers from committees until concerns had been resolved.[193]

- December 2019: The NIH Director accepted the recommendations of the ACD working group which includes steps that NIH should take to address sexual harassment as seriously as it takes other types of misconduct.[194]

- June 2020: NIH issued[195] a detailed description of its processes for handling sexual harassment allegations.[196] The processes are centralized (mainly within the NIH Office of Extramural Research, which is organizationally located directly under the immediate Office of the Director) and as such has the direct authority to remove individuals from NIH committees (usually peer review committees which can be located in the CSR or in NIH Institutes or Centers).

- September 2020: NIH and the U.S. Department of Health and Human Services (HHS) Office of Civil Rights signed a memorandum of understanding whereby the two entities would share information and work with each other on addressing specific allegations.

- June 2021: NIH provided the ACD with an update of its approaches to addressing harassment, along with results to date.[197,198]Since 2018, the Office of Extramural Research had handled extramural harassment allegations involving over 300 individuals. A large proportion of these individuals were removed from peer review committees, at least temporarily while allegations were being assessed as well as some have been removed from grants depending on the severity of the case and the actions taken by NIH as well as the recipient institutions. The updates in this area have been well-received by the ACD.

- December 2021: NIH leadership informed the Institute and Center Directors and the ACD members about the general provision being considered by Congress and foreshadowed the swift implementation process NIH will take if the provision becomes law.

Over the last few years, NIH has taken substantive steps in enhancing its ability to learn about, assess, and address allegations of sexual harassment. Our steps have led to results, with certain individuals removed

[191] www.nih.gov/about-nih/who-we-are/nih-director/statements/update-nihs-efforts-address-sexual-harassment-science
[192] acd.od.nih.gov/working-groups/sexual-harassment.html
[193] www.csr.nih.gov/reviewmatters/2019/03/25/ensuring-integrity-impartiality-in-peer-review/
[194] acd.od.nih.gov/documents/presentations/12122019ChangingCulture_Report.pdf
[195] nexus.od.nih.gov/all/2020/06/24/how-we-handle-allegations-of-sexual-harassment/
[196] grants.nih.gov/grants/policy/harassment/actions-oversight/allegation-process.htm
[197] www.acd.od.nih.gov/documents/presentations/06102021_Lauer.pdf
[198] nexus.od.nih.gov/all/2021/06/29/an-update-on-implementing-acd-recommendations-on-changing-the-culture-to-end-sexual-harassment/

from NIH-funded activities, including from NIH committees. Going forward, NIH will continue to address recipient requirements related to harassment, such as through new and/or revised grant policies, as well as potential actions for noncompliance. The biomedical research community can and must do a better job of keeping our scientists safe, and NIH remains committed to doing its part.

Hearing Health Screening for Older Americans

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 2023 Congressional Budget Justification on hearing screening research for older adults across the NIH. The Committee encourages NIDCD and NIA to support studies that address the research needs and gaps identified by the U.S. Preventive Services Task Force (USPSTF) 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). Early in 2021, NIH program staff, individuals from the Agency for Healthcare Research and Quality, and the U.S. 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.
- USPSTF staff noted that research in this area would benefit from 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. As of 2021, the NIDCD has supported over 40 research projects focused on improving access and affordability in hearing healthcare 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; testing ways to promote hearing health care access and use in primary care; investigating how to improve delivery of care in community settings to people with hearing loss; and reducing disparities in access to hearing health care.

The 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 an intervention including hearing needs assessment, fitting of hearing devices, education/counseling can reduce cognitive decline and the risk of Alzheimer's disease and Alzheimer's disease-related dementias in cognitively normal older adults. In another study, investigators are characterizing hearing loss and care in a diverse community 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. A third study is 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.

Hepatitis B

The Committee recognizes the estimated $4 billion of annual medical costs associated with the care and treatment of those infected with the hepatitis B virus and urges NIH to redouble its efforts to identify more effective treatments for the disease. While there are treatments available to control HBV, they must be taken for years if not for life. Without treatment, one in four of those infected will die prematurely from cirrhosis, liver failure, and/or liver cancer. This serious public health threat results in over 800,000 worldwide deaths each year, making it the tenth leading cause of death in the world. The Committee commends NIH for it support in the development of the 2019 Strategic Plan for Trans-NIH Research to Cure Hepatitis B and urges NIH to help implement the plan by issuing new targeted calls for research. The Committee requests that NIH support an update of the Strategic Plan for Trans-NIH Research to Cure Hepatitis B and that it submit it to the Committee, within 180 days of enactment of this Act, a specific plan to pursue a cure for hepatitis B in coordination with the Trans-NIH Hepatitis B Working Group. [p. 154 of House Report]

The Committee recognizes the estimated $4,000,000,000 of annual medical costs associated with the care and treatment of those infected with the hepatitis B virus and urges NIH to redouble its efforts to identify more effective treatments for the disease. While there are treatments available to control HBV, they must be taken for years if not for life. Without treatment, 1 in 4 of those infected will die prematurely from cirrhosis, liver failure and/or liver cancer. This serious public health threat results in over 800,000 worldwide deaths each year, making it the 10th leading cause of death in the world. The Committee commends NIH for it support in the development of the 2019 Strategic Plan for Trans-NIH Research to Cure Hepatitis B and urges NIH to help implement the plan by issuing new targeted calls for research. The Committee requests that NIH support an update of the Strategic Plan for Trans-NIH Research to Cure Hepatitis B to be completed before the end of fiscal year 2022 and submit within 180 days of enactment of this bill into law, a specific plan to pursue a cure for hepatitis B in coordination with the Trans-NIH Hepatitis B Working Group. [pp. 152-153 of draft Senate Report]

Action Taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) is leading the Trans-National Institutes of Health (NIH) Hepatitis B Working Group in updating the *Strategic Plan for Trans-NIH Research to Cure Hepatitis B*.[199] This group includes the National Institute on Minority Health and Health Disparities (NIMHD), National Institute on Drug Abuse (NIDA), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Cancer Institute (NCI), National Institute on Alcohol Abuse and Alcoholism (NIAAA), and NIH Office of the Director. NIH also participates in the U.S. Department of Health and Human Services (HHS) National Viral Hepatitis Plan Steering Committee. In January 2021, HHS published the *Viral Hepatitis National Strategic Plan for the United States: A Roadmap to Elimination 2021-2025*,[200] which focuses on eliminating viral hepatitis as a public health threat in the United States by 2030 and will inform the NIH Plan.

NIAID implements the NIH plan by supporting basic, translational, and clinical research on hepatitis B virus (HBV) to identify new drug targets and treatment strategies for hepatitis B. NIAID provides a suite of resources to the research community, including screening candidate therapeutics for potential anti-HBV activity. In FY 2020, NIAID awarded four contracts to explore innovative approaches to develop a cure for chronic hepatitis B. NIAID also issued the *Research Towards Developing a Cure for HBV in HIV/HBV Co-Infection* Funding Opportunity Announcement (FOA), and an FY 2022 Notice of Special Interest is planned on this topic.

[199] www.niaid.nih.gov/sites/default/files/Trans-NIH-Hep-B-Strategic-Plan-2019.pdf
[200] www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf

NIMHD supports research to improve early detection and prevention of diseases that disproportionately affect racial and ethnic minority communities. NIMHD-supported research found that HBV screening by community health workers was feasible among Haitian immigrants living in South Florida. NIMHD also is evaluating how chronic HBV infection relates to chronic liver disease and health disparities. NIMHD supports 11 regional research centers focused on prevention, treatment, and management of chronic diseases, including chronic liver disease. In FY 2022, NIMHD plans to release a FOA on optimal management of chronic diseases, including chronic liver disease, to help reduce health disparities.

NIDA funds implementation research to assist rural communities with approaches to prevent and treat consequences of injection drug use, including HBV infection. NIDA projects examine factors affecting injection practices to inform harm reduction services and interventions; identify approaches to implement syringe service programs (SSPs) in rural areas; and enhance prevention services in SSPs. NIDA also supports training for clinical researchers to more effectively understand and manage infectious consequences of substance use, including HBV.

NIDDK is continuing funding of the Hepatitis B Research Network to complete and publish analyses of three trials of combination therapy (peginterferon and an oral nucleoside analogue) in children and adults with different clinical patterns of chronic hepatitis B. Early results indicate that major factors in achieving a "functional cure" were the HBV strain and the Hepatitis B e-antigen (HBeAg) status of the infection. A functional cure is typically defined as the sustained loss of hepatitis B surface antigen (HBsAg), ideally with the presence of antibodies against HBsAg and undetectable HBV DNA in serum, after treatment.

NIH will continue to coordinate activities in this area of research through the Trans-NIH Hepatitis B Cure Working Group and HHS National Viral Hepatitis Plan Steering Committee as it pursues a cure for hepatitis B.

Indoor Amplified Microbial Growth Research

The Committee believes that a more robust and focused NIH commitment to research relating to mold and amplified microbial growth in damp and water-damaged buildings would yield significant advancements of knowledge and insight regarding how fungi, mycotoxins, actinobacteria, and endotoxins within indoor environments affect public health. The Committee urges NIH to expedite planned and ongoing studies already nominated and established through the National Toxicology Program (NTP). The Committee is concerned that some of these studies were nominated in 2001 but have yet to be conducted. The Committee also urges NIH to prioritize new research, explore the causal links, and interventions to the potential neurotoxic, immunosuppressive, immunoreactive, autoimmune, nephrotoxic, carcinogenic, and inflammatory responses due to inhalation of indoor amplified microbial growth in damp and water-damaged indoor environments. The Committee encourages NIH to improve applied research, communication and education, and coordination with other Federal, State, and local health and environmental agencies regarding mold and microbial growth in damp and water-damaged indoor environments. The Committee requests an update in the fiscal year 2023 Congressional Budget Justification on its efforts.

Action taken or to be taken

The National Institute of Environmental Health Sciences (NIEHS) agrees that exposure to molds, including fungi and other potentially pathogenic organisms that thrive in damp and water-damaged buildings represents, an important and increasing health hazard. The growing frequency and severity of extreme weather events and related flooding will only increase people's exposure, particularly in communities where heat, humidity, and under-resourced homes and building are prevalent. As part of its Disaster Research Response (DR2) program, NIEHS funds studies on the health effects of mold and other flooding-related exposures resulting from events such as Hurricane Harvey. Through its Worker Training Program, NIEHS provides workers engaged in post-disaster and public health emergency cleanup and remediation with training in how to protect themselves from exposure to hazards such as mold to avoid adverse health outcomes.

In support of the interagency National Toxicology Program (NTP), NIEHS is conducting studies on molds commonly found in damp indoor environments or on food products to better understand how exposure may cause disease. A list of related publications is below. As part of the NTP mold research program, the National Institute of Occupational Safety and Health (NIOSH) has collaborated with the NIEHS to develop an inhalation exposure system, which it is using to conduct short-term toxicology studies of different fungi using rodents. These studies are in different phases of completion.

An interagency briefing on study findings on the toxicity of *Aspergillus fumigatus* (a fungus that can cause disease in immunocompromised individuals) was held on June 25, 2021; the NTP report was published in July 2021. Studies on *Stacybotrys chartarum* (a type of black mold) are finished and the results are under review by the NTP. Studies of *Aspergillus versicolor* (a fungus commonly found in damp environments or on food) were delayed due to the coronavirus disease 2019 (COVID-19) pandemic but got underway in July. External peer review and publication of the final reports on *Aspergillus versicolor* and *Stacybotrys chartarum* are anticipated in fiscal year (FY) 2022-23.

NIEHS also conducts toxicology studies of mycotoxins that infect grains in the field or during storage under damp conditions. Chronic dietary exposure to aflatoxin, produced by the fungus *Aspergillus flavus*, which is frequently found on grains, combined with hepatitis virus infection, leads to liver cancers that are one of the leading causes of cancer deaths worldwide. NIEHS studies continue to explore how aflatoxin damages DNA systems. Deoxynivalenol (a toxin frequently found on grains), which is produced by the common fungal plant pathogen *Fusarium graminearum,* has been detected globally in food and human

urine. Human exposure occurs at low levels and throughout life and is associated with gastrointestinal symptoms. NIEHS's studies focus on understanding the effects of low-level exposure of rodents to deoxynivalenol on the health of dams and their offspring. Two journal articles were published in December 2020, and an NTP report on the findings of a multigenerational toxicology study is in preparation.

NIEHS will continue to fund studies on the health effects of indoor mold and other flooding-related exposures.

Related Publications

Deoxynivalenol

Huang MC, Furr JR, Robinson VG, Betz L, Shockley K, Cunny H, Witt K, Waidyanatha S, Germolec D. Oral deoxynivalenol toxicity in Harlan Sprague Dawley (Hsd:Sprague Dawley® SD®) rat dams and their offspring. *Food Chem Toxicol*. 2020 Dec 31;148:111963. doi: doi.org/10.1016/j.fct.2020.111963. Epub ahead of print.

Rehder Silinski MA, Gilliam JA, Fernando RA, Robinson VG, Germolec D, Cunny H, Huang MC, Furr J, Waidyanatha S. Development of an analytical method for quantitation of deoxynivalenol by UPLC-MS-MS: a preliminary assessment of gestational and lactational transfer in tats. *J Anal Toxicol*. 2020 Sep 4:bkaa119. doi: doi.org/10.1093/jat/bkaa119. Epub ahead of print.

Mold

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Interstitial Cystitis

The Committee notes the progress of interstitial cystitis research through the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Program and encourages NIDDK and stakeholders to continue collaboration on a comprehensive state of the science conference to examine mechanisms for scientific opportunity. The Committee requests an update on the progress of the conference in the fiscal year 2023 Congressional Budget Justification.

Action taken or to be taken

The research efforts of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) on interstitial cystitis, also called interstitial cystitis/bladder pain syndrome (IC/BPS), are focused on understanding the cause(s) of this condition, which affects millions of Americans; improving diagnosis; finding more effective treatments for the pelvic pain and urinary frequency and urgency that affect people with this condition; and finding ways to prevent onset. 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, has spearheaded the evolution in our understanding of IC/BPS and another urologic chronic pelvic pain syndrome, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Active since 2009, the MAPP Research Network is now nearing the end of a final 3-year continuation period supported by the NIDDK. With this support, the Network has pursued additional, critical opportunities and comprehensive data analyses; the Network will sunset in summer 2022, with publication of results likely to continue for a few years thereafter.

Following delays imposed by the COVID-19 pandemic, NIDDK is planning to hold a multi-day, in-person scientific conference in fall 2022 focused on research advances in urologic chronic pelvic pain syndromes—including consideration of how to leverage Network insights and resources into new studies and how they can inform the next generation of clinical studies. It is anticipated that the conference will serve as a forum for the exchange of key scientific insights from both MAPP Research Network and non-Network studies, as well as from other pain studies that may inform the urologic pain field. Participants will also be asked to help identify improved strategies for disseminating Network findings, and to initiate development of new research definitions for urologic pain conditions, based upon the evolving insights into patient characteristics that have emerged from Network and other studies.

Research opportunities important for IC/BPS should be identified through this effort. At this time, meeting planning is in its early stages, but will expand to include representatives from patient advocacy groups, such as the Interstitial Cystitis Association, that have been active partners in various aspects of Network activities, as well as additional NIH and external scientific experts.

Kratom

The Committee recognizes that NIDA-funded research has contributed to the continued understanding of the health impacts of kratom, including its constituent compounds, mitragynine and 7-hydroxymitragynine. The Committee is aware of the potential promising results of kratom for acute and chronic pain patients who seek safer alternatives to sometimes dangerously addictive and potentially deadly prescription opioids and of research investigating the use of kratom's constituent compounds for opioid use disorder. The Committee directs NIDA to continue to invest in this important research, especially considering the increase in overdose deaths during the COVID–19 pandemic.

Action taken or to be taken

Kratom can cause effects similar to that produced by both opioids and stimulants.[201] Two compounds in kratom leaves, *mitragynine* and *7-hydroxymitragynine,* interact with opioid receptors in the brain -- albeit with much lower efficacy than heroin or fentanyl -- producing sedation, pleasure, and decreased pain, especially when consumed in large amounts. Mitragynine also interacts with other receptor systems in the brain to produce stimulant effects when taken in small amounts, such that people report increased energy, sociability, and alertness instead of sedation. Kratom additionally contains a number of other mitragynine-analogs whose pharmacologic properties are not well understood. While some people report using kratom to reduce opioid use or treat pain,[202] the potential therapeutic effects of kratom have not been tested rigorously. There are some concerns that kratom may be addictive and potentially dangerous. A few deaths involving kratom have been reported; however, most appear to have resulted from adulterated products or taking kratom with other potent substances.[203,204,205] Additional research is needed to determine the health effects of kratom and its constituent compounds.

The National Institute on Drug Abuse (NIDA) is addressing the need for further research by supporting studies on the pharmacology of kratom's constituents, their toxicity and addictive liability, and their potential therapeutic benefits. For example, researchers are studying the chemistry and pharmacology of mitragynine and 7-hydroxymitragynine[206] to evaluate their potential addiction liability.[207] Preclinical studies supported by NIDA and the National Institutes of Health (NIH) Helping to End Addiction Long-Term (HEAL) Initiative are exploring the potential for kratom's constituents in the treatment of opioid use disorder.[208,209] Researchers are also developing a method to make mitragynine derivatives so they could be developed into medications that could be tested as analgesics with reduced addiction liability.[210] In addition, the National Center for Complementary and Integrative Health (NCCIH) and National Center for Advancing Translational Sciences (NCATS) support research on kratom's potential therapeutic use for pain.[211,212]

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[201] pubmed.ncbi.nlm.nih.gov/31308789/
[202] pubmed.ncbi.nlm.nih.gov/28950240/
[203] www.fda.gov/media/111148/download
[204] www.tandfonline.com/doi/pdf/10.1080/15563650.2019.1569236?needAccess=true
[205] www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-scientific-evidence-presence-opioid-compounds
[206] reporter.nih.gov/project-details/10203899
[207] eporter.nih.gov/project-details/10117220
[208] reporter.nih.gov/project-details/10403754
[209] reporter.nih.gov/project-details/10118159
[210] reporter.nih.gov/project-details/10209056
[211] NIDA grant R21AT010404
[212] NCATS grant ZIATR000375

Lung Cancer in Women

The agreement requests an update on the status of research on women and lung cancer and the disparate impact of lung cancer in women who have never smoked in the fiscal year 2023 Congressional Justification.

Action taken or to be taken

Overall lung cancer incidence and mortality rates continue to decrease in the United States, but important gender and race differences persist. For example, Black women have comparable lung cancer incidence and mortality rates to white women, despite lower smoking rates. For nonsmokers, research has shown that approximately 20 percent of women who develop lung cancer have never smoked compared with about 9 percent of nonsmoking men. The reasons for these disparities are not well understood. The National Cancer Institute (NCI) supports research to understand and eliminate cancer disparities, to increase our understanding of sex differences in cancer, and to advance cancer prevention, detection, and treatment for women.

In 2019, NCI launched the Sherlock-lung study, a comprehensive study that aims to trace lung cancer etiology in never smokers by analyzing genomic data in tumor and surrounding lung tissue.[213] This molecular characterization will identify exogenous and endogenous processes involved in lung tumorigenesis. The molecular landscape will be integrated with histological and radiological features to develop a more refined understanding of lung cancer in never smokers and provide insights into prognosis and treatment strategies. The study will collect data from approximately 2,500 never smokers. The first results from Sherlock were published in September of 2021 and showed that a majority of the lung tumors analyzed from never smokers arise from the accumulation of mutations caused by natural processes in the body (endogenous).[214]
Importantly, the study identified three novel molecular subtypes of lung cancer in people who never smoked. These subtypes were identified from 232 patient samples, 75 percent of whom were women. The study also identified mutations that independently had negative effects on survival, providing information that could lead to personized treatments in the future.

Ongoing NCI-supported research is investigating the role of female hormones in the development of lung cancer. An estrogen metabolite (4-hydroxyestrogen, 4-OHE) is a known carcinogen and was found to exist in higher quantities in lung tumors compared to normal tissue in small cell lung cancer patients. An NCI- funded project is using cell lines and mouse models to determine potential mechanisms for 4-OHE to lead to lung cancer, which could help to identify possible therapeutic inhibitors to prevent lung cancer development for female never-smokers.[215] Another project is studying the effects of estrogen signaling and related inflammation on the development of lung cancer with the goal of developing targeted treatment and prevention options depending on sex and other unique biomarkers.[216] A project that recently concluded studied the association between exposure to a type of estrogen (phytoestrogen) and lung cancer risk in women who had never smoked. In this case-control study with long term follow up of approximately 15 years, the researchers found that moderately increasing intake of foods that contain phytoestrogen (foods with soy) had an association with lower lung cancer risk in women who have never smoked.[217]

[213] dceg.cancer.gov/research/cancer-types/lung/sherlock-lung-study
[214] pubmed.ncbi.nlm.nih.gov/34493867/
[215] reporter.nih.gov/search/IWt72di6wUGBSocZrHU53A/project-details/10338105
[216] reporter.nih.gov/search/dG20M9F3IUiAhnAsz8Iykg/project-details/10114231
[217] pubmed.ncbi.nlm.nih.gov/34673927/

Eighty percent of lung cancers among women can be attributed to smoking. Along with research in this area, NCI has ongoing efforts to reduce the uptake and use of tobacco. These efforts remain paramount to lung cancer prevention in females. NCI continues to support *Smokefree Women*, part of the larger Smokefree.gov website,[218] and remains committed to supporting research and resources to prevent lung cancer and advance progress for all cancer patients, whether their diagnosis is tobacco-related or not.

Key NCI-supported programs such as the Specialized Programs of Research Excellence (SPOREs) and the Cancer Intervention and Surveillance Modeling Network (CISNET) focus on lung cancer. There are currently four lung cancer SPORE Programs and three cancer disparities SPORE pilots that include lung cancer as one of the pilot projects.[219] CISNET conducts research on the impact of tobacco control policies and screening in lung cancer with a focus on disparities.[220] A recently awarded CISNET lung cancer disparities supplement seeks to: use an existing CISNET lung cancer model to study lung cancer incidence and mortality in the non-Hispanic Black (NHB) population; determine the contributions of various factors along the cancer control continuum to disparities in lung cancer mortality in the NHB population relative to the whole population; and evaluate the potential impact of screening and other interventions to reduce lung cancer burden and existing disparities in the NHB population.

NCI continues to support a portfolio of research into ways to increase cancer screenings. A newly funded project is specifically focused on multilevel interventions to increase adherence to lung cancer screening.[221] Additionally, results from CISNET and the NCI-supported National Lung Screening Trial (NLST) along with other randomized clinical trials and cohort studies lead to the 2021 U.S. Preventive Services Task Force recommendation that lowered the age of starting annual screening exams for lung cancer from 55 to 50 years of age. This will double the number of people eligible for annual computerized tomography (CT) scans to screen for lung cancer and is expected to lead to higher screening rates among women and Black patients, who are at higher risk of lung cancer.

[218] smokefree.gov
[219] trp.cancer.gov/spores/lung.htm
[220] cisnet.cancer.gov/lung/
[221] reporter.nih.gov/search/EmHMXPNGO0i8Ndp8p3DdeA/project-details/10274176

Lyme Disease and Related Tick-Borne Illnesses

The Committee includes a $20,000,000 increase for Lyme Disease and other tick-borne illnesses research. The Committee encourages NIAID to use these funds to prioritize the support of meritorious research that informs a better understanding of Lyme disease pathogenesis and encourages the development of improved diagnostics and vaccines. The Committee directs NIH to leverage this understanding to develop new tools that can more effectively prevent, diagnose, and treat Lyme disease, including long-term effects, and other tick-borne diseases. The Committee encourages the promotion and development of potential vaccine candidates for Lyme disease and other tick-borne diseases. The Committee directs NIH to conduct research to better understand modes of transmission for Lyme and other tick-borne diseases, including vertical transmission. The Committee urges NIH to incentivize new investigators to enter the field of Lyme disease and other tick-borne disease research. The Committee directs NIH to coordinate with CDC on publishing reports that assess diagnostic advancements, methods for prevention, the state of treatment, and links between tick-borne disease and psychiatric illnesses.

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic, translational, and clinical research on Lyme disease and other tick-borne diseases (TBDs) to better understand the diseases and inform the development of medical countermeasures.

The *National Institutes of Health (NIH) Strategic Plan for Tickborne Disease Research*[222] includes focus on Lyme and TBDs in all populations, including women and children, and multiple aspects of Lyme and other TBDs, including neuropsychiatric complications. NIH implements the plan by supporting research to improve knowledge of TBDs and to develop tools for diagnosis, prevention, and treatment. The NIH, Centers for Disease Control and Prevention (CDC), and key stakeholders participate in the Health and Human Services (HHS) Tick-Borne Disease Working Group (TBDWG), which collaborates to publish reports on diagnosis, treatment, prevention, and clinical manifestations of TBD, including psychiatric illnesses.

In June 2021, NIAID convened a meeting of scientific experts titled *Understanding Persistent Symptoms Attributed to Lyme Disease* to discuss manifestations and potential causes of persistent symptoms that some patients experience after Lyme disease treatment. NIAID also participates in the NIH Notice of Special Interest (NOSI) titled *Advancing Research for Tickborne Diseases*[223] to encourage new research focused on priorities in the TBD strategic plan, including diagnosis, treatment, prevention, and fundamental knowledge of TBD. In FY 2021, NIH released the NOSI *Small Business Initiatives for Innovative Diagnostic Technology for Improving Outcomes for Maternal Health*,[224] which includes a call for applications on improved Lyme disease diagnostics.

In FY 2020-2021, NIAID funded 16 awards focused on vaccines to prevent Lyme and other TBDs under the funding opportunity *Targeted Prevention of Tickborne Diseases.*[225] NIAID is supporting a clinical study to assess treatments for children experiencing neuroborreliosis, a neurological manifestation of infection with *Borrelia burgdorferi,* the bacteria that cause Lyme disease. NIAID also supports research on new treatments and vaccines; Lyme disease transmission and persistent symptoms; and interventions to block transmission of *B. burgdorferi* from ticks to humans or from animal reservoirs to ticks. In addition, NIAID is conducting clinical trials to identify biomarkers to improve Lyme disease diagnostics

[222] www.niaid.nih.gov/sites/default/files/NIH-Strategic-Plan-Tickborne-Disease-Research-2019.pdf
[223] grants.nih.gov/grants/guide/notice-files/NOT-AI-20-005.html
[224] grants.nih.gov/grants/guide/notice-files/NOT-EB-21-001.html
[225] grants.nih.gov/grants/guide/rfa-files/RFA-AI-19-037.html

and vaccines. NIAID recently expanded its intramural Lyme disease research portfolio by hiring three tenure-track scientists focused on vector-host-pathogen interactions to identify new targets for intervention.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) actively supports a large portfolio related to prevention of mother-to-child transmission of infectious diseases. NICHD studies their impact on the pediatric nervous system and on reproductive and overall health, with the goal of developing and advancing safe and effective treatments. NICHD published a NOSI[226] titled *Advancing the Understanding, Prevention, and Management of Infections Transmitted from Women to their Infants*, which is aimed at stimulating research by extramural researchers that would lead to improved health and well-being of mothers' infants and families. NICHD welcomes grant applications for research to address questions related to a broad range of congenital infections, including Lyme disease.

NIH will continue to support research to better understand, treat, and prevent Lyme and other TBDs, including through coordination with partners on the TBDWG, such as the CDC.

[226] grants.nih.gov/grants/guide/notice-files/NOT-HD-19-021.html

Lymphedema (LE)

LE is a chronic, debilitating, and incurable swelling that can be a result of damage to the lymphatic system due to surgery, cancer treatment, or injury, and that can also be inherited. An estimated 10,000,000 Americans suffer from LE. Additional research is necessary to improve our understanding of this condition and expand the treatment options available. The Committee directs NHLBI to increase support for research on LE and to establish a Research Condition Disease Categorization category for research related to lymphedema.

Action taken or to be taken

The National Institutes of Health (NIH) supports and is strongly committed to advancing a robust, trans-disciplinary portfolio of research on the lymphatic system. Established in 2002, the Trans-NIH Lymphatic Coordinating Committee (TNLCC) brings together representatives from the NIH Office of the Director and eight Institutes and Centers (ICs). The TNLCC works collaboratively utilizing IC-specific resources and expertise on lymphatic diseases and conditions to help set priorities in lymphatic research.

The lymphatic system plays a significant role in a broad spectrum of diseases and conditions, including infectious diseases, inflammation, cancer, obesity, and cardiovascular disease. One disease of the lymphatic system that has high public interest is lymphedema.

Tracking NIH annual support levels is critical to measuring progress, gaps, and opportunities in various research areas. Research, Condition, and Disease Categorization (RCDC) category development for Lymphedema, as well as a broader category for Lymphatic Research, began in March 2021. Since then, IC subject matter experts have been working to establish trans-NIH definitions for and an automated algorithm for capturing relevant NIH-funded projects.

NIH anticipates that fiscal year (FY) 2021 data for these new Lymphedema and Lymphatic Research categories will be finalized and ready for public reporting in spring 2022. After FY 2021, NIH will continue to report the annual funding level for each subsequent fiscal year.

Maternal Health Research

The Committee includes an increase of $30,000,000 for the Implementing a Maternal Health and Pregnancy Outcomes Vision for Everyone (IMPROVE) Initiative, as requested in the fiscal year 2022 budget. Maternal mortality in the U.S. is higher than in other industrialized nations, and there are disparities in maternal outcomes across the country. For example, Black women experience maternal mortality at nearly four times the rate of White women. The IMPROVE Initiative advances research to reduce preventable causes of maternal deaths and improve health for pregnant and postpartum individuals before, during, and after delivery. The initiative uses an integrated approach to understand biological, behavioral, sociocultural, and structural factors that affect severe maternal mortality and maternal mortality (SMM/MM) by building an evidence base for improved care and outcomes in specific regions of the country. IMPROVE will target health disparities associated with SMM/MM by (1) implementing and evaluating community-based interventions for disproportionately affected women (e.g., African American, American Indian/Alaska Native, advanced maternal age, low socioeconomic status, and rural populations), and (2) identifying risk factors and the underlying biological mechanisms associated with leading causes of SMM/MM, including cardiovascular disease, infection and immunity, and mental health.

Action taken or to be taken

Tackling the challenge of reducing maternal morbidity and maternal mortality requires strong partnerships with and among local communities and resources, particularly with racial and ethnic minority populations that experience stark health disparities. To that end, several National Institutes of Health (NIH) Institutes, Centers, and Offices (ICOs) held community engagement activities to hear firsthand how patient communities can inform future research and what engagement strategies might enhance local efforts to improve maternal health. A common refrain was that such research should be developed in partnership with, and be responsive to, communities to ensure success and improved maternal health outcomes.

These engagement activities informed the development of the IMPROVE (**I**mplementing a **M**aternal health and **PR**egnancy **O**utcomes **V**ision for **E**veryone) Initiative, which aims to build an evidence base that will improve maternal care and outcomes from pregnancy through one year postpartum. IMPROVE is co-led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the NIH Office of the Director, including the NIH Office of Research on Women's Health (ORWH), and engages over 30 NIH ICOs to research the leading causes of maternal mortality in the United States—cardiovascular disease, infection, and immunity—as well as contributing health conditions or social factors, such as mental health disorders, diabetes, obesity, substance use disorders, and structural and healthcare system issues that disproportionately affect Black pregnant and postpartum individuals.

This initiative complements NIH's existing investments in maternal morbidity and mortality research, which totaled $224 million in FY 2020. IMPROVE awarded more than $7 million in FY 2020 and more than $13 million in FY 2021 for research in areas related to maternal heart disease, hemorrhage or bleeding, and infection which are the leading causes of U.S. maternal deaths; contributing conditions, such as diabetes, obesity, mental health disorders, and substance use disorders; the impact of structural racism and discrimination on maternal health outcomes; and the effects of SARS-CoV-2 infection and the COVID-19 pandemic on maternal mental health, well-being, functioning, and quality of life.

IMPROVE prioritizes comprehensive, interdisciplinary research that engages communities with high rates of maternal deaths and complications including detecting and intervening when risk for poor

outcome is increased. By employing a life course perspective, these efforts will help create tailored, evidence-based solutions for pregnant and postpartum individuals.

Maternal Infections

The Committee requests an update on research to better understand and prevent congenital cytomegalovirus in the fiscal year 2023 Congressional Budget Justification.

Action taken or to be taken

Cytomegalovirus (CMV) is a common virus that causes few symptoms in healthy people but can cause death and serious health effects when transmitted to fetuses during pregnancy. Newborn CMV infection affects as many as 40,000 U.S. infants each year. The infection is linked to stillbirth, newborn death, deafness, and cognitive and motor delays. Among pregnant women with CMV infection, 30 to 45 percent of their fetuses can become infected, with 10 percent having symptoms at birth. For infants born to infected mothers, 20 percent have no signs of infection at birth but develop deafness and other neurologic effects later in life.

There is no licensed vaccine for CMV and treatment of CMV infection is challenging because of the side effects of antiviral drugs and the emergence of drug-resistant strains. New approaches for both prevention and treatment will have a substantial public health impact. In September 2018 the *Eunice Kennedy Shriver* National Insitute of Child Health and Human Development (NICHD) held a workshop to explore research gaps and opportunities in this space which led to new awards on CMV.[227]

For example, a recent study supported by NICHD's Maternal Fetal Medicine Units Network found that an antibody treatment in early pregnancy for women infected with CMV does not appear to reduce the risk of infection or death among their newborns.[228] The findings contradict several smaller studies on the treatment, known as hyperimmune globulin, that suggested the treatment was effective.

Another NICHD grant is exploring whether CMV is acquired by women during pregnancy secondary to exposures to household contacts. The research team will test this by identifying sources of CMV exposure in the household, implementing a behavioral modification trial to interrupt virus exposure, and then determining if behavior modifications can limit the rate of intrauterine CMV infections.

[227] www.nichd.nih.gov/about/meetings/2018/090418
[228] www.nichd.nih.gov/newsroom/news/082421-maternal-antibody-treatment

Melanoma

As UV radiation is established as the primary carcinogen for melanoma, the Committee urges NCI 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 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 support multicenter trials that will determine whether shorter courses of therapy will decrease toxicity and costs while maintaining benefit, the role of adjuvant therapy and whether patients with earlier disease should receive adjuvant therapy and that further determine the role of adjuvant therapy in both treatment and drug development.

The Committee encourages NCI to support research on novel targets, especially for rare subtypes, and support development of registries where populations are not adequate for randomized trials. The Committee requests an update on these requests and a status of NCI-funded melanoma research in NCI's fiscal year 2023 Congressional Budget Justification.

Action taken or to be taken

For all cancers, it is important to understand the underlying genomic contributors and mechanisms of mutagenesis that lead to disease. Ultraviolet (UV) radiation has been studied for decades; its relationship to skin cancer (and cancer in general) has been well established and multiple mechanisms of mutagenesis are known. The National Cancer Institute (NCI) dedicates significant resources to developing and implementing prevention strategies and improving early detection for melanoma, including supporting research using technology to expand training programs for groups more likely to be in the sun,[229] research that informs sun safety policies,[230] and an exploratory project tapping into an app that tracks physical activity and location to offer geographically relevant sun safety advice to users.[231] It is important to note that rarer skin cancers such as acral lentiginous melanoma are more common in communities of color and less likely to be caused by UV radiation than the common cutaneous melanoma. See the *Skin Cancer in Communities of Color* Significant Item response for more details on prevention, detection, and risk factors.

In addition to sun safety prevention strategies, 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 developing better models to evaluate therapeutics.[232] An NCI-funded grant that is a collaboration of

[229] reporter.nih.gov/project-details/9986720
[230] pubmed.ncbi.nlm.nih.gov/33393708/
[231] reporter.nih.gov/project-details/10057198
[232] ncbi.nlm.nih.gov/pmc/articles/PMC8378471/

12 institutions[233] investigating the correlation between melanoma biology and survival identified risk factors for various melanoma sites and sensitivity of genes to UV, and developed tools to better stratify patient data and identify biomarkers.[234] Additional work by this group in collaboration with a melanoma Specialized Program of Research Excellence (SPORE) project developed gene network models for more informed clinical decision making.[235] NCI is also supporting a familial melanoma study in collaboration with the Melanoma Genetics Consortium to find new candidate melanoma susceptibility genes in families.[236]

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 a rare melanoma subtype is exploring whether an immunotherapy given after surgery could be more effective if also given pre-operatively, while another similar trial is comparing the two-year survival rate in advanced melanoma patients with a specific mutation using different treatment orders. Other research supported by NCI is using databases from two large and geographically distinct melanoma treatment centers to develop a guide for clinical surveillance strategies based on timing and risk of central nervous system (CNS) metastasis. Melanoma patients were tracked for multiple years post diagnosis; their data extracted and analyzed for metastatic incidence and correlated with numerous factors. The framework developed for this study can be applied to future analyses of the impact adjuvant therapies have on risk potential for CNS metastasis.[237]

While immunotherapy has shown great promise for cancer treatment, it is still unknown why some patients respond better than others. NCI-supported research recently investigated why some metastatic melanoma patients respond to a certain type of immunotherapy treatment (adoptive cell transfer, or ACT), while others do not, identifying the presence of specific populations of antitumor T-cells associated with persistent tumor cell killing and cancer regression.[238] This is valuable information for improving immunotherapy outcomes in cancer patients. A recent clinical trial co-led by intramural NCI researchers found that some advanced melanoma patients resistant to a certain immune checkpoint inhibitor were able to positively respond to the drug after receiving a fecal transplant from a patient who responded to the drug;[239] more research and expansion of the trial will be needed to identify the specific microbes and biomarkers correlated with positive fecal transplant. Importantly, immune checkpoint inhibitors are increasingly used as treatment for many types of cancers, including potentially for rare melanoma subtypes,[240] but their long-term side effects are not known. In a study across eight medical centers, researchers found that more than 40 percent of patients treated with an immune checkpoint inhibitor developed a related long-term side effect, but the majority were mild.[241] This information should be incorporated in clinician discussions with patients when talking about the benefits and drawbacks of different treatment options.[242]

Cancer drug resistance remains one of the biggest challenges facing cancer therapy, as cancers have different mechanisms for evading targeted drugs. Understanding the multiple pathways to resistance is a

[233] reporter.nih.gov/project-details/10188447
[234] ncbi.nlm.nih.gov/pmc/articles/PMC7641988/; pubmed.ncbi.nlm.nih.gov/32643855/; ncbi.nlm.nih.gov/pmc/articles/PMC7716509/; ncbi.nlm.nih.gov/pmc/articles/PMC7933297/
[235] ncbi.nlm.nih.gov/pmc/articles/PMC7900178/
[236] dceg.cancer.gov/research/who-we-study/families/familial-melanoma-study
[237] ncbi.nlm.nih.gov/pmc/articles/PMC7193747/
[238] pubmed.ncbi.nlm.nih.gov/33303615/
[239] pubmed.ncbi.nlm.nih.gov/33542131/
[240] clinicaltrials.gov/ct2/show/NCT02775851
[241] pubmed.ncbi.nlm.nih.gov/33764387/
[242] cancer.gov/news-events/cancer-currents-blog/2021/immune-checkpoint-inhibitors-melanoma-long-term-side-effects

key aspect of NCI-supported research to overcome or prevent drug resistance in patients. Cutaneous malignant melanoma (CMM) patients with advanced disease often develop resistance to immunotherapy or targeted therapies. A study in cell lines found that combining two drugs currently used for non-small cell lung cancer (afatinib and crizotinib) could be a potential treatment for CMM by silencing multiple signaling pathways and offers more clinical options to CMM patients.[243]

[243] ncbi.nlm.nih.gov/pmc/articles/PMC7576205/

Metastatic Breast Cancer

The Committee is aware that clinical research is of utmost importance to those living with metastatic breast cancer (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 White women, and breast cancer is the second most common cause of death by cancer for Black women. The Committee believes that a renewed emphasis by NCI on research for MBC, especially in communities of color, is needed 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 2023 Congressional Budget Justification, 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

The National Cancer Institute (NCI) supports a robust breast cancer research portfolio, including metastasis research, across the cancer continuum from basic mechanistic studies to clinical research and cancer survivorship. In fiscal year (FY) 2021, NCI launched the Metastasis Research Network (MetNet), which seeks to develop a comprehensive understanding of cancer metastasis as a whole body, systems-level disease. The network expects to fund four multi-project awards in FY 2021, and a second round of applications are being reviewed for funding in FY 2022. Several of the projects focus on aspects of breast cancer metastasis including how breast cancer cells travel to particular organs in the body during the metastatic process. Additionally, NCI funded over 20 new research project grants (R01 awards) focused on metastatic breast cancer in FY 2021.

Immunotherapy is a type of treatment that had early success in the treatment of a specific subtype of metastatic breast cancer termed Her2 amplified (Her2+) breast cancer. Tastuzumab (Herceptin) is an antibody drug that has been U.S. Food and Drug Administration (FDA) approved to treat metastatic Her2+ breast cancer since 1998. In a highly publicized case in 2018, researchers from the NCI intramural program reported the use of adoptive cell therapy with tumor infiltrating lymphocytes for the treatment of a patient with estrogen receptor positive metastatic breast cancer that was refractory to multiple chemotherapies.[244] More recently, immune checkpoint inhibitor drugs have been FDA approved for the treatment of metastatic triple negative breast cancer (TNBC). Decades of NCI-supported basic research played a role in bringing these drugs to patients. In April of 2021, the FDA granted approval for the drug sacituzumab govitecan (Trodelvy) for patients with locally advanced or metastatic TNBC.[245] This drug is an antibody coupled to the chemotherapy agent irinotecan to deliver the irinotecan directly to the breast cancer cells. The NCI Small Business Innovation Research program supported the small biotechnology company that developed the drug and funded the first in human clinical trials of the drug.

Black women are at higher risk for getting more aggressive types of breast cancer. A research study funded by the National Institute on Minority Health and Health Disparities (NIMHD) investigated the role of neighborhood social determinants of racial disparities in TNBC in Louisiana. Researchers found that Black women had 2.2 times the incidence of TNBC incidence compared to White women, were more likely to be initially diagnosed at a later stage (i.e., higher chance of metastasized breast cancer), and had lower survival rates when neighborhood disadvantage was taken into account.[246] To improve overall

[244] pubmed.ncbi.nlm.nih.gov/29867227/
[245] cancer.gov/news-events/cancer-currents-blog/2021/sacituzumab-govitecan-tnbc-regular-approval
[246] pubmed.ncbi.nlm.nih.gov/30834239/

survival, additional research is needed to explore the mechanisms through which social determinants affect the promotion and progression of TNBC. In another study funded by NIMHD, researchers looked at specific genetic regulators in a group of breast cancer patients in rural North Carolina, and found differences between survival rates in African American patients compared with those of European descent even though levels of gene regulators were similar.[247] This research indicates that other factors in the genetic pathway for breast cancer development and progression may differ between racial groups and contribute to the observed differences, and more research is needed to understand the biological processes that may contribute to racial disparities in breast cancer survival.

NCI also supports survivorship studies to help address the challenges faced by cancer survivors, including those living with metastatic disease. For example, the University of Wisconsin Carbone Cancer Center is conducting a study of long-term survivors of metastatic breast cancer to identify habits, medical care, and genes that help people with metastatic cancer live longer.[248] The study has enrolled over 700 participants to date including many who have lived more than 10 years with metastatic breast cancer. NCI is also supporting large cohort studies in Black populations including the Detroit Research on Cancer Survivors (ROCS) study, which is the largest study to date of Black cancer survivors. Results published to date include findings on genetic heritability of cancer and factors that affect quality of life for Black cancer survivors.

The exact reasons for persistent disparities between Black and White women with breast cancer are unclear, although studies supported by NCI and others suggest that they are the result of a complex interplay of genetic, environmental, and societal factors, including access to health care. Recently, several studies have pointed to access to health care as a major contributor of disparate outcomes. One study focused on metastatic breast cancer survival funded by the NCI SEER program and others concluded, "Access to appropriate, timely, and up-to-date diagnosis, care, treatment, and surveillance could turn this fatal disease into a chronic and treatable phenomenon, depending on patient factors, molecular subtype, and insurance capacity to pay for treatment."[249]

[247] pubmed.ncbi.nlm.nih.gov/31911546/
[248] outliers.cancer.wisc.edu/
[249] pubmed.ncbi.nlm.nih.gov/31639221/

Multiple Sulfatase Deficiency

The agreement directs NIH to include updates on the following research, projects, and programs in the fiscal year 2023 Congressional Justification: Multiple Sulfatase Deficiency.

Action taken or to be taken

Multiple Sulfatase Deficiency (MSD) is an ultra-rare disease with an estimated prevalence of one in 1.4 million people. MSD results from mutations in the *SUMF1* gene, which encodes a protein required for activating enzymes called sulfatases that degrade complex carbohydrate and lipid molecules inside cells. Insufficient sulfatase activity in MSD leads to a wide range of clinical symptoms affecting multiple organ systems.

In 2021, the National Center for Advancing Translational Sciences (NCATS) awarded a grant to the United MSD Foundation to support a scientific and family conference which will help build upon existing clinical and scientific knowledge and engage both scientists and patient families to inform new research initiatives. This conference, currently in the planning stages, will have a primary focus on preparedness to move forward with gene therapy.

Beyond this conference grant, the National Institutes of Health (NIH) supports a broad portfolio of research on lysosomal storage disorders, the family of disorders to which MSD belongs. For example, NCATS, the National Institute for Neurologic Disorders and Stroke (NINDS), and the National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) support the Lysosomal Disease Network (LDN), part of the NIH Rare Diseases Clinical Research Network (RDCRN) led by the Office of Rare Diseases Research within NCATS. The LDN conducts multiple clinical studies, works closely with patient advocacy organizations, and supports scientific conferences and research training to grow the pool of investigators focused on lysosomal storage disorders, including MSD. The LDN and other research to understand and develop treatments for lysosomal storage disorders may inform further progress in MSD, given that this family of disorders shares overlapping clinical symptoms and similar treatment approaches.

NIH also supports research programs and resources applicable to broad range of rare and ultra-rare disorders, including MSD. For example, NCATS leads several cross-cutting NIH programs that aim to address many rare diseases at one time through gene-targeted therapies and that have the potential to expedite therapeutic development for many rare diseases. The Bespoke Gene Therapy Consortium, which is a public-private partnership involving the U.S. Food and Drug Administration (FDA), Foundation for NIH, and several NIH Institutes, is exploring novel collaborative approaches related to gene therapy for rare diseases. These approaches will be applicable to expediting treatments for many diseases, including, potentially, MSD. NCATS, in partnership with the National Human Genome Research Institute (NHGRI), also serves as a home for patient and clinician information on rare diseases through its support of GARD: the Genetic and Rare Diseases (GARD) Information Center.[250]

Additionally, NINDS supports a suite of translational research initiatives designed to move therapies toward clinical trials, including programs for developing model systems for testing and biomarkers for measuring disease progression or response to treatment. In late 2021, NINDS launched the Ultra-Rare Gene Therapy (URGenT) program to support the development of gene-based and transcript-directed therapies for ultra-rare neurological diseases. URGenT is a late-stage preclinical therapy development program that aims to address challenges of gene-targeting technologies, de-risk these approaches for industry adoption, and coordinate their entry into clinical trials. The program will facilitate ways to

[250] rarediseases.info.nih.gov

standardize and share resources, data, and best practices across diseases to make therapy development for ultra-rare diseases like MSD more efficient and accessible.

National Laboratories

NIH funding supports investments which are collaborative with the ongoing work of the Department of Energy. The Committee directs NIH to provide an update in the fiscal year 2023 Congressional Budget Justification on the work to coordinate its efforts with DOE and the National Laboratories, and in more strategic ways to leverage NIH's research needs in the next generation of cancer research, brain mapping, drug development or other emerging ideas in biomedical research that would benefit from DOE's instrumentation, materials, modeling simulation, and data science. In 2015, the Secretary of Energy established the Energy Advisory Board (SEAB) to evaluate the prospects for increased collaboration between DOE researchers and biomedical scientists supported by other agencies, especially NIH. Increased and more effective coordination could be instrumental to assist in the development of the Nation's health, security, novel biomedical technologies, and in the development of more strategic enabling technologies. The Committee supports NIH's collaboration with DOE and the National Laboratories in an effort to maximize utilization of DOE's capabilities, particularly for NIH's rapidly growing data and computational challenges, and encourages NCI to build off the success of previous initiatives and consider additional pilots to address key computation and imaging bottlenecks in cancer research.

Action taken or to be taken

The National Institutes of Health (NIH) is enthusiastic about continuing to grow its collaboration with the Department of Energy's (DOE) National Laboratories. There are many opportunities at the intersection of high-performance computing, big data, and biomedical research that the NIH is actively leveraging in the next generation of brain mapping, emerging technologies, cancer research, and many other areas. Selected examples of ongoing partnerships are described below but are far from a complete list of NIH's coordination with DOE and the National Laboratories.

Brain Mapping

The NIH Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative is a coordinated program of 10 NIH Institutes and Centers to develop and apply innovative technologies to understand brain circuits. In 2021, the NIH BRAIN Initiative partnered with the DOE Office of Science to organize and convene five virtual scientific workshops on brain connectivity mapping. The workshops brought together scientists and engineers with broad expertise to discuss challenges in mapping brain circuits and to consider opportunities that state-of-the-art technologies present for creating detailed maps of brain connectivity, i.e., "wiring diagrams," spanning the entire mammalian brain.[251]

DOE expertise in areas such as large-scale project management, computational science, and data science for handling exceptionally large and complex data sets complement NIH expertise. Conversely, past research on brain circuits has inspired major advances in artificial intelligence (AI) and computing architecture, and the human brain is still superior in performance to computers for many tasks while using dramatically less energy. Hence, both scientific advances from the brain mapping project and progress stimulated by the technical challenges will stimulate and accelerate progress in data science, AI, and computer design. The participants have prepared a comprehensive report of insights from the workshops that is guiding planning of a BRAIN Initiative "transformative project" on brain connectivity mapping and potential DOE collaborations.[252]

[251] braininitiative.nih.gov/News-Events/event/brain-connectivity-workshop-series-032021
[252] braininitiative.nih.gov/sites/default/files/pdfs/brain-connectivity-workshop-series_rpt-080421_508c.pdf

Emerging Technologies
DOE and NIH, represented by the National Institute of Biomedical Imaging and Bioengineering (NIBIB) and the National Cancer Institute (NCI), held a joint virtual workshop in July 2021, titled *Advancing Medical Care through Discovery in the Physical Sciences*. The purpose of the workshop was to bring together DOE scientists, NIH scientists and extramural staff and NIH grantees, with two main goals: to identify opportunities for DOE and NIH communities to collaborate on projects and to identify opportunities for the NIH community to take advantage of existing state-of-the-art DOE technologies.

The DOE Science Council Offices of Basic Energy Sciences and Biological and Environmental Research, and NIH, specifically NIBIB and the National Institute of General Medical Sciences (NIGMS), are also working together to raise awareness within the biomedical research community of existing DOE- and NIH-supported bioimaging capabilities and identify the gaps in capabilities that must be addressed to support current and future research needs. In addition, the NIGMS and National Eye Institute (NEI) have led the NIH Common Fund program: Transformative High Resolution Cryo-Electron Microscopy.[253] This initiative has established national service centers to increase research capacity for molecular structure determination by high resolution cryo-electron microscopy (cryo-EM) and cryo-electron tomography (cryoET).

Finally, the National Institute on Deafness and other Communication Disorders (NIDCD) provides funding support for the Implantable Microsystems Group at the Lawrence Livermore National Laboratory to develop precise and rapid construction micromachining techniques and construct arrays of microelectrodes suitable for recording and stimulating neural tissue. NIDCD-funded investigators are allowed access to this unique microfabrication facility that can take computer aided design (CAD) files and deliver devices for use in animal studies that provide preclinical data. Ultimately, this facility can be used to make devices suitable for use in human research under an innovate software design environment. In the meantime, investment in this inter-agency agreement accelerates the pace of innovation for neural prosthesis designs using micromachined features in the electrode array that are beyond the reach of the handcrafted processes used by industry today.

Cancer Research
NCI, through the Frederick National Laboratory for Cancer Research, and DOE have been collaborating since 2016 on three broad initiatives: Joint Design of Advanced Computing Solutions for Cancer (JDACS4C),[254] Accelerating Therapeutic Opportunities for Medicine (ATOM),[255] and Cancer Distributed Learning Environment (CANDLE).[256]

The NCI-DOE collaborative initiatives have yielded numerous accomplishments in the initial five years, including the development of software tools and computational models made freely available to the research community to extend the reach of the program to advance cancer research. Of note, the JDACS4C population project has advanced the NCI Surveillance, Epidemiology, and End Results (SEER)[257] program to include using artificial intelligence approaches for the extraction of data from novel sources, such as pharmacy records, and the integration of this data with existing and newly collected data to increase the breadth and depth of information related to cancer patients, their treatments, and outcomes. As part of this project, deep learning algorithms were developed to extract tumor features automatically from pathology reports, saving thousands of hours of manual processing time. Also, a process for

[253] commonfund.nih.gov/CryoEM
[254] cbiit.cancer.gov/ncip/hpc/jdacs4c
[255] atomscience.org/
[256] cbiit.cancer.gov/ncip/hpc/candle
[257] seer.cancer.gov/

obtaining real-time feedback from SEER state cancer registries was established through an application programming interface, commonly referred as an API. In the future, real-time data analysis will allow for individuals newly diagnosed with a cancer to be linked with clinical trials that may benefit them.

Future Directions for Cancer Research

There are external scientific and technical oversight committees that work with initiative project leads and NCI and DOE agency leadership to monitor the progress, plan the future directions, and capture emerging opportunities. Two areas for future collaboration currently under discussion are: AI co-design and precision radiation oncology. Both areas present significant opportunities to advance the missions of both agencies and benefit the cancer community. AI co-design refers to the goal of driving more effective experimental design through advanced computing and AI. AI co-design has the potential to greatly advance multiple areas of predictive oncology. There is also an opportunity to meaningfully impact radiation oncology practice by using computational-enabled modeling to make radiation treatment more personalized and adaptive. This includes using advanced computing to achieve dynamic, multiscale, data-informed, clinically actionable predictions to inform decision making and treatment planning. Both of these potential new collaboration areas have emerged from numerous interactive workshops and discussions co-led by the NCI and DOE with the extramural cancer research and data science communities.

National Center on Sleep Disorders Research [NCSDR]

The Committee notes the appointment of a new NCSDR Director as well as the release of a long-overdue strategic plan. The Committee requests the Center provide an update in the fiscal year 2023 CJ on plans and stakeholder collaboration efforts to effectively advance the Center's mission. This update may include information on the Center's work to promote cross-agency collaboration, participate in emerging efforts (such as addressing health disparities), and lead a variety of impactful research projects.

Action taken or to be taken

The National Center on Sleep Disorders Research (NCSDR), housed at the National Heart, Lung, and Blood Institute (NHLBI), administers the Institute's research projects related to the biology of sleep and the body's internal clock (circadian rhythm), and the diagnosis, treatment, and prevention of sleep disorders, including sleep apnea. NCSDR also funds studies to understand how poor sleep health contributes to the risk of heart, lung, and blood diseases. The Trans-National Institutes of Health (NIH) Sleep Research Coordinating Committee, which comprises representatives from 17 NIH Institutes and Centers and the NIH Office of the Director, is working to foster research on biomarkers to measure, predict, and manage sleep disorders and sleep deficiency.[258]

In December 2021, NHLBI released the NIH Sleep Research Plan, which was developed in consultation with the Sleep Disorders Research Advisory Board (SDRAB), the Trans-NIH Sleep Research Coordinating Committee, and external stakeholders. NHLBI solicited external stakeholder input to inform the development of the Plan through two Requests for Information (RFI) published in the NIH Guide, from public discussions at national meetings, at the public SDRAB meetings and meetings with stakeholder organizations, as well as an open online crowdsourcing campaign. The goals of the Plan are to: 1) elucidate sleep and circadian mechanisms underlying health and disease; 2) improve treatment of sleep and circadian disorders, reduce the risk associated with sleep deficiency; 3) identify gaps and opportunities to accelerate the clinical implementation of sleep and circadian research and protect the health of the public; 4) advance the understanding of the role of sleep and circadian contributions in health disparities in diverse populations and their impact on public safety and; 5) foster the development of a strong and diverse workforce for sleep and circadian research.

In line with the NIH-Wide Strategic Plan, NCSDR is already prioritizing research to reduce disparities in sleep health. In FY 2018, the NHLBI, the National Institute on Minority Health and Health Disparities (NIMHD), and NIH Office of Behavioral and Social Sciences Research (OBSSR) convened a workshop on sleep, circadian rhythms, and health disparities to forge connections among experts in these fields and to explore the future of research on sleep health disparities. The workshop identified opportunities to better define the causes of sleep health disparities and to integrate circadian-related mechanisms and measures into sleep study designs. In FY 2020, NIH reissued a funding opportunity announcement to support research to understand the underlying mechanisms of sleep disparities among U.S. racial/ethnic minority and other populations, and how sleep deficiencies may contribute to other poor health outcomes.[259] NHLBI, NIMHD, the National Institute on Aging (NIA), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Cancer Institute (NCI) participate in this funding opportunity, which is open until July 15, 2022. In FY 2021, NCSDR also hosted several webinars in partnership with the Department of

[258] The Trans-NIH Sleep Research Coordinating Committee consists of NHLBI, the National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute of Allergy and Infectious Diseases (NIAID), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Nursing Research (NINR), National Cancer Institute (NCI), Office of Behavioral and Social Sciences Research (OBSSR), Office of Research on Women's Health (ORWH).
[259] grants.nih.gov/grants/guide/pa-files/par-17-234.html

Housing and Urban Development, including a roundtable on sleep health as a marker for healthy homes and healthy communities.

NHLBI and partner NIH Institutes and Centers also continue to investigate how sleep deficiency and abnormal sleep patterns, such as shift work, affect the risk of disease and poor health outcomes throughout the lifespan. For example, a study funded in part by NHLBI and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) explored the relationship between sleep and overweight during infancy. The study found that infants who slept longer through the night with fewer interruptions were less likely to become overweight by six months of age.[260] Past studies have shown that night shift workers have increased risk for diabetes, heart disease, and obesity. A recent NHLBI-funded clinical trial helps explain why and offers a potential solution. The trial, which simulated night work conditions in a controlled setting, found that eating during the night—like many shift workers do—can increase glucose levels, a risk factor for diabetes. In contrast, restricting meals to daytime prevented this effect. The study could lead to novel behavioral interventions aimed at improving the health of shift workers, including first responders and other essential service providers.

NHLBI also continues to support research on sleep during pregnancy. Such research has shown that women who experience sleep-disordered breathing during pregnancy are at greater risk for gestational hypertension and preeclampsia. In partnership with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), NHLBI is supporting a phase III clinical trial to assess whether treatment with continuous positive air pressure (CPAP) can reduce this risk.[261]

Finally, NCSDR is leveraging the power of data science to accelerate sleep and circadian research. Advances in sleep research, including the use of wearable sensors that can record sleep patterns without disturbing sleep—are helping researchers collect vast amounts of real-time, real-world data on sleep. The NCSDR supported National Sleep Research Resource, an open-access platform for eligible researchers to share data and collaborate. NCSDR currently includes de-identified data from more than 40,000 individuals, with representation throughout the lifespan and across racial/ethnic groups. This resource will help accelerate discovery of sleep and circadian pathways, mechanisms of sleep disorders, and new targets therapy.

Future sleep research directions outlined in the NIH Sleep Research Plan focus on 1) discovery of biomarkers to identify sleep and circadian disorders and sleep deficiency; 2) identification of neurobiological mechanisms underlying perception of sleepiness and fatigue; 3) development of chronotherapeutic approaches to prevent and treat chronic diseases and; 4) development of tools and/or methods for early prediction, detection, and treatment of sleep deficiency in pediatrics and adolescents to promote health and prevent disease.

[260] pubmed.ncbi.nlm.nih.gov/34676870/
[261] clinicaltrials.gov/ct2/show/NCT03487185

National Dental Practice-Based Research Network [NDPBRN]

The Committee recommends that the NIDCR continues funding support of National Dental Practice-Based Research Networks.

Action taken or to be taken

The National Institute of Dental and Craniofacial Research (NIDCR) supports research conducted within a practice-based setting, the main goals of which are: to streamline the implementation of national oral health research studies in dental practices on topics of importance to practitioners and their patients, to provide evidence useful in daily patient care, and to facilitate the translation of research findings into clinical practice. One of the most prevalent challenges in dentistry is the amount of time it takes private practices to adopt new, evidence-based treatments and protocols. On average, the journey from the laboratory bench to the dental chair can take almost a decade before patients benefit from more effective or durable treatments. One of the most successful ways to shorten this lag time is to conduct research in a practice-based setting, which is designed to bring together patients and practitioners in the study of oral health issues within the real-world environment of a dental practice. The results from studies conducted in this setting have been accepted and adopted much more quickly into clinical practice.

Over 16 years ago, NIDCR launched the National Dental Practice-Based Research Network (National Dental PBRN) to study and answer questions of everyday relevance to dental practitioners and their patients. Since that time, more than 7,000 dental practitioners and 60,000 patients in all 50 states have participated in more than 60 studies. The studies, conducted in participating dental offices with consenting patients, have helped to exponentially expand the profession's evidence base. Overall, the findings have provided robust evidence to better inform oral health treatment decisions. Completed research has covered a wide range of topics, including a study of cracked teeth to record tooth symptoms and treatment outcomes over time, assessing opioid prescribing practices among dental providers, managing pain and functional outcomes involved in temporomandibular joint disorder (TMD), screening for oral human papillomavirus (HPV) positivity in dental offices, leveraging electronic health record data for clinical research, and assessing the prevalence of persistent pain after root canals.[262]

The current cycle of the National Dental PBRN received funding in 2019 and has built on the momentum of the previous two cycles of investment. It has maintained a geographically diverse network comprising all 50 U.S. states and has added a Specialty Node to recruit and engage practitioners within dental specialties, as well as a unique Patient Population Node to link practitioners with similar practice types or practitioners who treat patients with disease-specific conditions that affect oral health. The National Dental PBRN infrastructure is supported through 2026 via: a) the National Administrative and Resource Center,[263] which provides study-specific support to practitioners and office/clinic staff and coordinates study deployment across dental practices across the country, and b) the National Coordinating Center,[264] which is the central locus for data coordination/management and maintains the practitioner membership database.

The National Dental PBRN has been instrumental in addressing critical knowledge gaps related to the delivery of dental care during the Coronavirus pandemic.[265] For example, aerosol measurement studies performed during aerosol-generating procedures in a variety of specialty and general dentistry practices with different clinic configurations found that aerosols were rapidly dispersed within minutes of completing the aerosol-generating procedure, and that standard aerosol mitigation strategies were

[262] nationaldentalpbrn.org/study-results/
[263] reporter.nih.gov/search/UnOs19c1OUC0N6A_hq0csg/project-details/10188501#description
[264] reporter.nih.gov/search/UZXg2pRENES-5963Qzps7A/project-details/10187547#description
[265] nidcr.nih.gov/research/covid19/studies-grantee-institutions

effective in mitigating risk during routine dental clinical practice.[266] Other research topics currently being supported and implemented in the National Dental PBRN include studies using mobile technology to improve patient pain experience following dental procedures,[267] testing the effectiveness of nicotine replacement sampling in dental practices,[268] assessing the biologic and prosthetic outcomes of dental implants,[269], and evaluating procedures for integrating mental health screening and referral into dental care workflows and dental management of patients with special healthcare needs.[270] NIDCR's steady and strategic support of the National Dental PBRN will ensure that evidence-based interventions are more rapidly integrated into clinical practice and bring large-scale benefits to dental patients across the country. NIDCR has maintained long-term support of the National Dental PBRN and continues to propose new initiatives to support clinical research conducted in the practice-based setting. [271]

[266] medrxiv.org/content/10.1101/2021.07.30.21261399v1
[267] reporter.nih.gov/search/QUEGajkRwUWYdwcJH55HvA/project-details/10405312#description
[268] reporter.nih.gov/search/4Cf8zCMNU0qKn-KErDTovg/project-details/10221673
[269] reporter.nih.gov/search/xlkZZS8WdUOLVQMg7MKIXw/project-details/10101988
[270] nationaldentalpbrn.org/recruiting-ongoing-upcoming-completed/
[271] nidcr.nih.gov/grants-funding/funding-priorities/future-research-initiatives/conducting-dental-practicebased-research-dental-schools-provide-clinical-research

National SARS–CoV–2 Genomic Surveillance Program

New SARS–CoV–2 variants continue to emerge across the globe, including variants that may have increased transmissibility and potential to evade vaccines. This dire situation demonstrates the need for a comprehensive genomic sequencing and surveillance program to discover and track the spread of these variants and devise appropriate public health countermeasures. The Committee directs NIH and CDC, in coordination with other HHS agencies as appropriate, to continue to expand national genomic surveillance to rapidly scale up sequencing of viral samples and dissemination of SARS–CoV–2 genomic data.

Action taken or to be taken

The National Institutes of Health (NIH) is fully engaged in efforts to mitigate the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants. The National Institute of Allergy and Infectious Diseases (NIAID), National Human Genome Research Institute (NHGRI), National Library of Medicine (NLM), and Fogarty International Center (FIC) participate in the SARS-CoV-2 Sequencing for Public Health Emergency Response, Epidemiology, and Surveillance (SPHERES) initiative led by the Centers for Disease Control and Prevention (CDC). NIAID, NLM, and other Federal partners also participate in the U.S. Department of Health and Human Services (HHS) SARS-CoV-2 Interagency Group (SIG), which conducts genomic surveillance to monitor emerging variants and address their impact on medical countermeasures. As part of SIG, NIAID coordinates the SARS-CoV-2 Assessment of Viral Evolution team to rapidly prioritize variants for characterization and evaluation of potential impact to SARS-CoV-2 vaccine effectiveness. NIAID scientists collaborate with domestic and international partners to obtain, sequence, and test variants; in addition, they have established a library of variants and developed methods to track SARS-CoV-2 evolution within infected individuals.

Beginning with the Human Genome Project, NHGRI supported the research that reduced the cost and increased the speed of genetic and genomic sequencing. This foundation enabled the rapid pivot towards coronavirus disease 2019 (COVID-19)-focused research, development, and viral surveillance. The Human Genome Project also set the standard for the unprecedented rapid and open data sharing that has been critical in the response to the COVID-19 pandemic. For example, the NHGRI Genomic Data Science Analysis, Visualization and Informatics Lab-space (AnVIL) has been used as the genomics data repository for various NIH COVID-19 host genetics studies and for the international COVID-19 Host Genetics Initiative, a consortium studying the genomic determinants of COVID-19 susceptibility, severity, and outcomes. In addition, NHGRI will continue to develop the PhenX Toolkit, which includes a robust library of measurement protocols for COVID-19 research, and to drive the development of foundational genomic technologies.

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) and the Rapid Acceleration of Diagnostics (RADx^{SM}) Tech and RADx^{SM} Advanced Technology Platforms programs are collaborating with the CDC to collect samples and identify variants of the SARS-CoV-2 virus. Collected samples enable the independent verification and validation of RADx-developed diagnostic tests. All RADx-funded tests undergo performance testing with each new variant. RADx also is funding a pilot project to develop a low-cost, fast, flexible, and comprehensive variant surveillance system. The goal of this pilot is to pre-screen positive samples to efficiently identify novel or low-prevalence variants. In addition, RADx has funded the development of a software package to model the impact of variants on RADx-funded diagnostic tests. RADx also has collaborated with the U.S. Food and Drug Administration (FDA) to assess the impact of variants on diagnostic systems.

NLM facilitates the deposit, access, and use of SARS-CoV-2 sequence data through its publicly available databases GenBank® and Sequence Read Archive (SRA). NLM also is continually updating its SARS-

CoV-2 Data Resources webpage, developing a SARS-CoV-2 data analysis and visualization webpage, developing a new rapid submission pipeline and public sequence quality control tools, making data available via cloud platforms, engaging in outreach with potential new data submitters, and developing new data analysis and processing tools. In addition to SPHERES, NLM also is helping to facilitate standards development by the Public Health Alliance for Genomic Epidemiology (PHA4GE), and analyzing sequencing data and generating reports to support the NIH Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Tracking Resistance and Coronavirus Evolution (TRACE) project. NLM, in collaboration with federal partners and other stakeholders, will continue to facilitate SARS-CoV-2 data submission and access, and enable variant data gathering and distribution.

NIH is committed to supporting genomic surveillance of SARS-CoV-2, including research to advance the rapid sequencing, analysis, and dissemination of SARS-CoV-2 genomic data. NIH Institutes and Centers will continue to coordinate with partners across HHS and the research community in this effort.

NIH Division of Police

The Committee supports vigorous action to improve training for all Federal, State, and local law enforcement officers on racial profiling, implicit bias, procedural justice, the use of force, and the duty for officers to intervene when witnessing the use of excessive force against civilians. The Committee therefore directs the Director to work with the Attorney General and the Federal Law Enforcement Training Centers to implement improved, mandatory training on these topics for all Federal law enforcement officers, along with the development of related standards that can be applied in hiring and performance assessments. These training requirements and standards should be based on the related provisions in H.R. 1280, as passed by the House of Representatives in March 2021.

Action taken or to be taken

NIH has taken several steps toward addressing implicit bias and racial injustice, including within the NIH Division of Police. For example, NIH police officers take full advantage of the courses offered to all agency employees addressing implicit bias, anti-harassment, equity diversity and inclusion. These courses are not specific to law enforcement but as a practical matter introduce officers to sociocultural factors that may be unfamiliar. NIH police instructors use scenario-based simulations to re-enforce the principles of conflict management and de-escalation techniques for incidents requiring law enforcement intervention. Following each scenario, officers are de-briefed on their response(s) and when necessary, provided alternative solution(s) to resolving the incident without the use of force. The senior NIH training coordinator communicates with FLETC (Federal Law Enforcement Training Centers) on a continual basis to ensure NIH officers are receiving the most up to date training that incorporates the lessons learned from recent events that have received national attention. Additionally, NIH provided feedback to the Director of the FLETC and the Assistant Attorney General for Civil Rights asking them to consider revising the Uniformed Police Officer Training curriculum by including a single module of instruction dedicated to the use of force and the broader areas of de-escalation, implicit bias, and procedural justice. NIH continues to stand ready to implement new trainings after they are approved.

Office of Behavioral and Social Sciences Research (OBSSR)

The Committee includes $49,827,000 for OBSSR, an increase of $20,000,000 above the fiscal year 2021 enacted level and $19,523,000 above the fiscal year 2022 budget request. The Committee notes that OBSSR has the mission to enhance NIH's behavioral science research enterprise across all Institutes and Centers. As multiple Surgeons General and NASEM have declared that most health problems facing the nation have significant behavioral components, the Committee strongly supports the continued strengthening of the behavioral science enterprise at NIH and urges OBSSR funding be increased to accomplish this mission. In this regard, the Committee is pleased that an NIH working group has been established to review how better to integrate and realize the benefits of overall health from behavioral research at NIH, and directs that appropriate OBSSR funding levels, authority, and organizational structure be included in this review.

Action taken or to be taken

A Behavioral and Social Sciences Research (BSSR) Working Group of the National Institutes of Health (NIH) Council of Councils was established in 2021 to fulfill this Congressional directive. The Working Group is co-chaired by the NIH's Office of Behavioral and Social Sciences Research (OBSSR) Deputy Director, Christine Hunter, Ph.D., ABPP, CAPT, USPHS, and Council of Councils' member Paul J. Kenny, Ph.D. (Icahn School of Medicine at Mount Sinai). Working Group members include behavioral and social science experts serving on the various NIH Institute and Center Councils and Advisory Boards. These members are well-respected leaders in behavioral and social sciences research, understand its relevance to the NIH mission, and are familiar with the processes through which NIH operates to achieve its mission.

The group is currently assessing examples of behavioral and social science research capacity, integration, and collaboration across the NIH through multiple types of reviews and analyses. These include review of strategic plans; patterns and types of NIH-funded awards in the past 10 years; current organizational structure, processes, and practices at OBSSR; NIH peer review processes and ongoing or planned changes to those processes; and collaborations, initiatives, expertise, and integration across individual NIH Institutes and Centers.

The Working Group will consider the results of these various analyses to develop recommendations about improved processes, organizational practices and resources that will strengthen and enhance NIH's integration of behavioral and social sciences and its benefits for overall health. While the Working Group will be able to make general recommendations about funding needs in NIH's behavioral and social sciences research portfolio, it is not within the scope of or charge to the Working Group to make specific OBSSR funding or funding authority recommendations.

Expected Timeline:

- The Working Group began in April 2021 after approval at the NIH Council of Councils in January 2021. The Working Group has met five times as of October 2021 and is writing the draft Report from November 2021 to March 2022. The Working Group plans to present the draft Report to the NIH Council of Councils in May 2022.
- February 2021: Initiated contract for support; invited members
- March 2021: Developed introductory materials, scheduled meetings for the year
- April – October 2021: Working group met
- November 2021: Report outline written; action items identified
- March 2022: Working Group Report finalized

- May 2022: Presentation of final draft of the Working Group Report to the NIH Council of Councils

Osteopathic Medical Schools

The Committee supports access to NIH research funding for osteopathic medical schools. The Committee is concerned by the historical disparity in NIH funding as osteopathic professionals receive only 0.1 percent of NIH grants, yet osteopathic medicine is one of the fastest growing healthcare professions in the country and osteopathic medical schools educate 25 percent of all medical students. The Committee understands that osteopathic medical students receive 200 hours of additional training in the musculoskeletal system and learn the value of osteopathic manipulative treatment as a non-pharmacological alternative to pain management. Over half of osteopathic physicians practice in the primary care specialties of family medicine, internal medicine, and pediatrics, and a disproportionate share of osteopathic medical graduates locate in rural and underserved areas. The Committee recognizes that increased access to research funding for the osteopathic profession will significantly bolster the NIH's capacity to support robust 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 urges NIH to report to the Committee 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 2023 CJ.

Action taken or to be taken

Table 1 lists the total funding and number of awards the National Institutes of Health (NIH) made to osteopathic medical schools in fiscal years (FYs) 2020 and 2021.

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

Table 2 shows the representation of Doctors of Osteopathic medicine (D.O.s) and researchers with other degrees who are employed at osteopathic medical schools serving on a National Advisory Council (NAC)[272], Initial/Integrated Review Group (IRG), or Special Emphasis Panel (SEP).[273] Please note the following:

- Members are recorded as described in the U.S. General Services Administration FACA database.[274]
- 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.

[272] 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 Institute and Center (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.

[273] 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, there are also usually 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.

[274] www.facadatabase.gov/FACA/apex/FACAPublicGovtwideReports

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

NIH is dedicated to strengthening and diversifying the biomedical research workforce. This includes fostering opportunities for physician-scientists with osteopathic medical degrees, a group of researchers NIH recognizes as being underrepresented in the biomedical workforce. 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.[275] 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 [including D.O.s], of whom those with clinical training contribute essential knowledge and skills."

Physicians with a D.O. degree represent an important component of the medical community. They straddle 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 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 2 members with a D.O. degree on its 18-member council.[276]

NCCIH along with other NIH ICs has 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.[277]
- K12 career development award program.[278]
- Academic Research Enhancement Award (AREA) program.[279]

[275] acd.od.nih.gov/documents/reports/PSW_Report_ACD_06042014.pdf
[276] www.nccih.nih.gov/about/naccih-member-roster
[277] researchtraining.nih.gov/programs/career-development/K08
[278] researchtraining.nih.gov/programs/career-development/k12
[279] grants.nih.gov/grants/funding/r15.htm

Overactive Bladder and Cognitive Impairment Treatment

The Committee is concerned that anticholinergic medications commonly prescribed to treat overactive bladder, a condition that affects one in three older Americans, have been shown in recent studies to increase the risk of developing ADRD. The Committee believes that further research of anticholinergic medications as well as on alternatives to these treatments is urgently needed to establish certainty regarding the safety of these medications as a treatment option for overactive bladder in older adults. The Committee urges NIA to prioritize research grants and contracts that study the long-term use of anticholinergic medications and the risk of cognitive impairment and ADRD. The Committee requests an update on this issue and on research activities to advance safe and effective alternative treatments for overactive bladder in the fiscal year 2023 Congressional Budget 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 Institute on Aging (NIA) 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.

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. This includes a clinical trial testing whether discontinuing use of anticholinergics improves cognition and lowers the risk of Alzheimer's disease and related dementias.[280] 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 ending their anticholinergic prescriptions in collaboration with a healthcare provider.[281] This trial will explore the impact of the app on prescription anticholinergic exposure among older adults and on cognitive function and quality of life. Other research studies currently funded by NIA seek to evaluate adverse outcomes of anticholinergic medicines in patients with dementia and overactive bladder;[282] assess severe adverse events associated with the interaction of cholinesterase inhibitors used to treat Alzheimer's with anticholinergic medications;[283] test mechanisms of neurotoxicity from anticholinergics;[284] and improve how older adults living with dementia, their caregivers, and clinicians make decisions about using anticholinergic medicines.[285] In addition, a recent NIA-supported study found that exposure to strong anticholinergics increased the risk of transitioning from normal cognition to mild cognitive impairment.[286]

NIA is also supporting several studies to advance safe and effective alternative treatments for overactive bladder. Ongoing NIA-funded research studies include testing a novel, non-invasive nerve stimulation device for in-home treatment of overactive bladder[287] and in a separate study, assessing brief mindfulness

[280] reporter.nih.gov/search/Shaj-qYerkm0U6DRn1S6tg/project-details/10129872
[281] reporter.nih.gov/search/xezgy1EkF0O1us1_5CJpMA/project-details/10127545
[282] reporter.nih.gov/search/-xMveMuhZUWqFIMIntQeIw/project-details/9377896
[283] reporter.nih.gov/search/pZSsBABfW0K-DPFCtVqRcQ/project-details/10212709
[284] reporter.nih.gov/search/Ggd69UkxpkGGqF5IAEfYrg/project-details/10168318
[285] reporter.nih.gov/search/Ggd69UkxpkGGqF5IAEfYrg/project-details/9926791
[286] ncbi.nlm.nih.gov/pmc/articles/PMC6036636/
[287] reporter.nih.gov/search/rmFNoL91xkamsqkkLW-QEQ/project-details/10219001

and non-invasive brain stimulation to reduce symptoms of urgency incontinence in women.[288] 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.[289]

In addition, 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 evaluating the efficacy of interventions and treatment approaches for urinary incontinence in older and minority women, including group-based, community-based, and online approaches. Other projects are aimed at finding ways to better assess bladder function, psychological contributors, potential biomarker signatures, and clinically useful patient subtypes.

The National Institutes of Health (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.

[288] reporter.nih.gov/search/PWzY007ysEW1d1WslGSukQ/project-details/10259722
[289] ncbi.nlm.nih.gov/pmc/articles/PMC6842393/

Pancreatic Cancer

Pancreatic cancer is the third leading cause of cancer-related death in the U.S. In 2020, over 60,000 Americans will be diagnosed with pancreatic cancer; more Americans than ever before. The five-year survival rate for pancreatic cancer remains at just over ten percent. The Committee appreciates that NCI has adhered to and completed all reporting requirements of the Recalcitrant Cancer Research Act of 2012 (RCRA) as it pertains to the Pancreatic Cancer Scientific Framework. The Committee looks forward to updates and progress made on the action items identified in the pancreatic cancer focus areas. The Committee is encouraged to hear that NCI is building upon the RCRA's Strategic Framework and taking steps to integrate research efforts across the NCI, and that several NCI-supported consortia focused on early detection have formed the Alliance of Pancreatic Cancer Consortia as a virtual network of researchers, clinicians, and advocacies to provide a platform and coordinate resources to discover and validate biomarkers and imaging methods for early detection. The Committee applauds this effort and requests an update in the fiscal year 2023 Congressional Budget Justification on progress made within the Alliance since its inaugural meeting in December 2016.

Action taken or to be taken

The Alliance of Pancreatic Cancer Consortia (APaCC) was formed to expand 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 National Cancer Institute (NCI) funded networks including the Pancreatic Cancer Detection Consortium;[290] the Early Detection Research Network;[291] the Chronic Pancreatitis, Diabetes and Pancreatic Cancer Consortium;[292] and Molecular and Cellular Characterization of Screen-Detected Lesions Consortium.[293] 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 and met again in December 2018 and September 2020.

At the inaugural meeting, attendees participated in a "Data Jamboree" and reviewed the current literature on biomarkers for early detection of pancreatic cancer. While none of the biomarkers evaluated were deemed ready for large-scale clinical validation trials, several of them had sufficiently high sensitivity and specificity to warrant additional research. The concept of a biomarker panel was of particular interest, combining a number of individual biomarkers for a more robust diagnostic assay. The group also discussed collaborative opportunities to facilitate validation studies and move the best biomarkers to the clinic. Since this workshop, there have been several reports of new pancreatic cancer biomarkers by Alliance members and others. A conference report was published in the *Pancreas* journal.[294]

The 2018 APaCC meeting focused on four research topics considered vital by the investigators for improving early detection of pancreatic ductal adenocarcinoma (PDAC): (1) current molecular characterization of PDAC; (2) development and utilization of new methods; (3) applications based on existing methods; and (4) biospecimen science and resources. The APaCC members concurred that development and utilization of new methods for early detection of pancreatic cancer is a top research priority across the consortia. A particular opportunity for further research and collaboration is the use of computed tomography (CT), artificial intelligence (AI), and related computational techniques to uncover subtle patterns in CTs, improve image interpretation, and streamline diagnostic workflow. The meeting

[290] prevention.cancer.gov/major-programs/pancreatic-cancer-detection
[291] edrn.nci.nih.gov
[292] cpdpc.mdanderson.org/index.html
[293] prevention.cancer.gov/news-and-events/news/consortium-molecular
[294] ncbi.nlm.nih.gov/pmc/articles/PMC5777224/

participants agreed that the APaCC would develop a repository for images collected prior to the diagnosis of pancreatic cancer. These images will be a shared resource and useful for the development of imaging biomarkers. The Alliance also formed an Imaging Working Group to tackle the challenges associated with the use of AI and to develop AI systems for early detection. In addition, NCI staff and Alliance researchers have begun establishing the common data elements needed to develop the repository of pancreatic cancer images to maximize its usefulness. A conference report was published in the *Pancreas* journal.[295]

On September 1, 2020, the APaCC met virtually to discuss pre-diagnostic and early stage PDAC imaging. The Imaging Working Group provided an update on the progress of developing the image repository and discussed current approaches across institutions for processing CT images.
Finally, the Early Detection Research Network-APaCC held a joint meeting with the NCI's Pancreatic Cancer Detection Consortium in December 2021, where the group discussed cohort studies focused on early detection of pancreatic cancer, mechanisms to share biospecimens and associated data, and biomarkers for early detection. Overall, the APaCC provides a valuable forum for investigators and collaborators to discuss and address early detection of pancreatic cancer.

[295] pubmed.ncbi.nlm.nih.gov/32675784/

Parkinson's Disease

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 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 2023 Congressional Budget Justification.

Action taken or to be taken

The National Institute of Environmental Health Sciences (NIEHS) is taking a multi-faceted approach to increase our understanding of environmental links to Parkinson's disease (PD), with the overarching goal of helping to identify what may cause or help prevent the disease. Current efforts include increased investment in advancing basic, epidemiological, and clinical research, along with expanded collaboration across the National Institutes of Health (NIH) to ensure full consideration of environmental triggers and mechanisms of gene-environment interaction in the study of PD.

NIES has expanded the existing 45 studies of links between PD and environmental exposures (including pesticides) to include industrial solvents (e.g., trichloroethylene), heavy metals (e.g., manganese, lead), air pollutants, infectious agents such as viruses, and dietary factors (e.g., iron). These new studies have used transgenic animal models to explore regulation of gene expression by these agents to help identify novel gene-environment interactions in PD.

Collaboration will continue to be a key component in advancing the NIEHS PD research program. Because age is a significant factor in PD disease progression, it is essential when considering relevant pre-clinical models. NIEHS has joined the trans-NIH Geroscience Interest Group to plan the "Animals for Translational and Preclinical Geroscience Symposium," to be held in FY 2022. NIEHS also participated in organizing two workshops on September 22-23[296] and September 30-October 1, 2021[297] that explored the impact of environmental exposures on gut-brain signaling in PD. Identifying research gaps and opportunities in this understudied area may have important implications for designing effective early intervention strategies prior to PD diagnosis, as well as treatments. Given the growing need for mechanistic research with which to assess the clinical relevance of the exposure-disease linkages observed in human studies, NIEHS has joined several NIH Institutes and Centers including the National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Mental Health (NIMH), *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), National Institute on Drug Abuse (NIDA),to form the NIH Environmental Neuroscience Working Group, which will work to facilitate research collaboration and raise awareness of the impact of environmental exposures on brain-related conditions such as PD.

[296] www.niehs.nih.gov/news/events/pastmtg/2021/ieemhh2_2021/index.cfm
[297] www.niddk.nih.gov/news/meetings-workshops/2021/brain-gut-axis-neurodegenerative-diseases

Parkinson's Disease (PD)

The Committee commends NINDS for taking critical steps in identifying priority recommendations to advance research on PD, which impacts between 500,000 and 1,500,000 people in the U.S. and is the second most prevalent neurodegenerative disease in this country. 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 of its progress on implementing these recommendations in the fiscal year 2023 Congressional Budget 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 Parkinson's disease (PD) research recommendations from the *Advancing Research, Improving Lives* conference.[298]

Investigator-initiated basic research projects and the NINDS Morris K. Udall Centers of Excellence for Parkinson's Disease Research program are expanding our knowledge of the genetic and environmental risk factors for PD, connecting the molecular clues of PD pathology to mechanisms of disease process, characterizing symptomatic, pathophysiologic and genetic heterogeneity in people with PD, improving animal and cell models for PD, developing imaging technologies to observe pathologic changes in people with PD, and characterizing the brain circuits involved in PD. For example, recent studies to elucidate the role of the immune system early in the disease process suggest that certain types of immunotherapies might slow or stop the disease process and that monitoring immune cells might aid in early diagnosis and treatment. Other studies have shown that the gut microbiome may affect the initial accumulation of alpha-synuclein protein (a pathologic signature of PD) in the nerves that line the gut and that these aggregates of alpha-synuclein may travel from the gut to the brain via the vagal nerve, suggesting that altering the gut microbiome might help prevent PD.

NINDS is also supporting clinical studies to test therapies and to improve methods of monitoring PD. The COVID-19 pandemic has demonstrated the importance of developing telemedicine technologies that can allow people with PD to be monitored by physicians in their homes. The Udall Center at the University of Rochester is developing telehealth tools and technologies for PD, and a clinical study is testing telemedicine and smartphone platforms for measuring PD progression. NINDS-funded researchers have shown that gene therapy can restore function of AADC, an enzyme that is essential for the production of dopamine and other neurotransmitters, in children with a genetic AADC deficiency. This result opens the possibility that AADC gene therapy may be used to restore dopamine levels in PD. NINDS is funding two large clinical trials of different forms of exercise (treadmill walking and stationary bicycling) to determine whether high-intensity exercise alters disease progression and to facilitate patient-specific exercise prescriptions. NINDS is also funding a clinical trial that aims to determine the most effective dose of light therapy to improve sleep in people with PD. The National Institutes of Health (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. Studies to increase our understanding of PD dementia and finding ways to prevent or treat PD dementia are an important component of the NINDS led Alzheimer's Disease-Related Dementia initiatives.

Identifying biomarkers was a high priority in the recommendations from the *Advancing Research, Improving Lives* conference. The NINDS PD Biomarkers Program (PDBP) data management, clinical,

[298] www.ninds.nih.gov/sites/default/files/2014-PD-Recommendations_0.pdf

biospecimen and cell line resources have aided in identifying a potential PD biomarker that is based upon measuring clumped aggregates of misfolded alpha-synuclein protein in the spinal fluid and skin punch biopsy, and these resources continue to be essential tools for researchers as they further develop and validate this biomarker in spinal fluid, blood, and skin samples. The NIH Accelerating Medicines Partnership for Parkinson's Disease (AMP PD) is a public-private partnership that is utilizing existing cohorts and biomarkers resources, including PDBP resources, to perform large scale analyses of genes, gene transcription and proteins to identify and validate biomarkers and new therapeutic targets for PD. AMP PD has harmonized clinical and genomic data from more than 3,500 people with PD and 4,300 controls. AMP data and analyses are being used by the broad biomedical community to identify biological pathways and genes associated with PD risk.

Parkinson's Disease (PD) and Dementia

The Committee recognizes that although Parkinson's is often thought of only as a movement disorder, most PD patients also develop dementia; common symptoms include difficulty with problem solving, speed of thinking, memory and other cognitive skills. Because people with PD usually develop these symptoms several years after their diagnosis of Parkinson's, PD represents an under-explored opportunity to study the onset and progression of dementia. The Committee strongly urges NINDS and NIA 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 2023 Congressional Budget Justification.

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA) dementia portfolio contains research studies that are relevant to Parkinson's disease (PD) both before and after the onset of dementia. Lewy body dementia (LBD) is an umbrella 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. The National Institutes of Health (NIH) funding of LBD research, including PD dementia, has increased more than 5-fold since 2015 due to funds made available by Congress for Alzheimer's disease and related dementias research.

In PD, neurons degenerate in a brain region that plays a key role in movement, but as the disease advances, areas of the brain that are responsible for a person's memory and ability to think clearly also begin to degenerate, causing PD dementia. Although different brain regions are affected by PD and PD dementia, many of the underlying cellular and molecular mechanisms of disease are the same. For example, a key finding in the brain tissue of people with PD and PD dementia is an accumulation of abnormal alpha-synuclein protein (these accumulations are called Lewy bodies), and genetic mutations in the alpha-synuclein gene have been shown to cause PD and PD dementia. Projects within the NIH dementia portfolio are focused on understanding what causes abnormal alpha-synuclein to accumulate in neurons and how this process contributes to degeneration of neurons. Other projects are aiming to understand how other genes that have been linked to PD contribute to the disease process, are elucidating the role of inflammation, and are developing animal and cell models that can be used to study the cellular processes that contribute to PD before and after dementia and to test potential therapies.

NIH is funding several projects to understand the similarities and differences among PD, PD Dementia, DLB, and Alzheimer's. One major project is the Lewy Body Disease Center Without Walls, which is a collaboration between six research institutions to determine why both alpha-synuclein and the Alzheimer's-related beta-amyloid protein accumulate in DLB brain tissue, whether the protein structures are unique to DLB versus Alzheimer's, PD dementia or PD, and how these proteins lead to tissue damage and dementia. In addition, the NIA-funded Alzheimer's Disease Research Centers (ADRCs) support basic, clinical and biomarker research in PD dementia and DLB. ADRC research led to one of the first tests for alpha-synuclein.

Discovering biomarkers, such as imaging or blood tests, that can aid with diagnosis or tracking disease progression is a top priority. 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 biomarkers studies funded by non-governmental organizations to identify and validate PD and LBD biomarkers. These data are available for secondary analysis by the general research community. A recent study, which included an NIA intramural research team and used

samples provided by the NIA-funded ADRCs, used AMP-PD data to demonstrate that the genetic risk profile for LBD overlaps with Alzheimer's and PD risk profiles. Understanding genetic risk profiles will help pave the way for precision medicine. NIH is also supporting a Center Without Walls to visualize, at atomic-level resolution, the structures of protein aggregates found in LBDs and other dementias as a first step to developing imaging biomarkers that could enhance differential dementia diagnosis and serve as markers of disease progression in future clinical trials.

Pediatric Cancer Expertise

The Committee recognizes that the Childhood Cancer STAR Act (P.L. 115–180) calls on NCI to ensure that all applicable study sections, committees, advisory groups, and panels at NCI include one or more qualified pediatric oncologists, as appropriate. The Committee requests an update in the fiscal year 2023 Congressional Budget Justification on the actions NCI has taken to ensure appropriate pediatric cancer expertise is included in such groups.

Action taken or to be taken

The National Cancer Institute (NCI) continues to support implementation of the Childhood Cancer STAR Act. In the United States in 2021, an estimated 10,500 new cases of cancer will be diagnosed among children from birth to 14 years, and about 1,190 children are expected to die from the disease.[299] Children's cancers are not the same as adult cancers, and hence NCI seeks specialized expertise to help steer guide the direction of its research support to better help prevent, diagnose, and treat cancer in children, adolescents, and young adults and to help survivors of childhood cancer have healthier and longer lives.

To guide the NCI's efforts in pediatric oncology research, including biorepositories and childhood cancer survivorship, 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**[300]: Dr. Peter Adamson, Sanofi; Dr. Francis Ali-Osman, Duke University; Dr. Andrea Hayes-Jordan, University of North Carolina Children's Hospital
- **Board of Scientific Advisors**[301]: Dr Mary Beckerle, Huntsman Cancer Institute; Dr. Leslie Robison, St. Jude Children's Research Hospital; Dr. Martine Roussel, St. Jude Children's Research Hospital; Dr. Kevin Shannon, University of California San Francisco; Dr. Cheryl L. Willman, Mayo Clinic
- **Clinical and Translational Research Advisory Committee**[302]: Dr. Smita Bhatia, University of Alabama at Birmingham; Dr. Anne-Marie Langevin, University of Texas Health Science Center at San Antonio
- **Board of Scientific Counselors** (Clinical Sciences & Epidemiology and Basic Sciences now combined)[303]: Dr. Paul Spearman, Cincinnati Children's Hospital Medical Center; Dr. Gail E. Tomlinson, University of Texas Health Science Center at San Antonio
- **National Council of Research Advocates**[304]: Danielle Leach, National Brain Tumor Society

[299] cancer.gov/types/childhood-cancers
[300] deainfo.nci.nih.gov/advisory/ncab/ncabpublicroster.pdf
[301] deainfo.nci.nih.gov/advisory/bsa/members.pdf
[302] deainfo.nci.nih.gov/advisory/ctac/roster.pdf
[303] deainfo.nci.nih.gov/advisory/bsc/bs/roster.pdf
[304] deainfo.nci.nih.gov/advisory/ncra/NCRApublicRoster.pdf

- **Frederick National Laboratory Advisory Committee**[305]: Dr. Catherine Bollard, Children's National Health System; Dr. Nilsa Ramirez Milan, Nationwide Children's Hospital; Dr. Cheryl Willman, Director, University of New Mexico Comprehensive Cancer Center
- **National Clinical Trials Network Steering Committees**: More than 40 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**: 120 reviewers with pediatric oncology expertise participated in up to 25 study section meetings in FY 2020.

NCI's Cancer Moonshot Initiative continues to support several activities to accelerate research addressing pediatric cancer. These include a Pediatric Immunotherapy Discovery and Development Network (PI-DDN), and the Fusion Oncogene Consortium, the latter of which engages an external panel of pediatric cancer experts to guide activities.

In addition, researchers with pediatric expertise are engaged in NCI's Childhood Cancer Data Initiative (CCDI),[306] which is building a community centered around childhood cancer care and research data. This includes 15 pediatric experts who participated on a BSA *ad hoc* Working Group on CCDI and contributed to a report on this topic provided to the BSA in June 2020. In 2021, a CCDI Steering Committee was established and includes 13 pediatric cancer research experts, along with five working groups involving 54 experts, including patient advocates.

[305] deainfo.nci.nih.gov/advisory/fac/roster.pdf
[306] cancer.gov/research/areas/childhood/childhood-cancer-data-initiative

Pediatric Nephrology Research Awards

The Committee recognizes the importance of research funded by NIDDK to advance innovations in kidney care, including research on pediatric kidney disease. The Committee remains concerned about the lack of pediatric nephrology clinical trials and the small pediatric nephrology biomedical research workforce. The Committee requests an update in the fiscal year 2023 CJ detailing its efforts to encourage pediatric nephrology research.

Action taken or to be taken

Note: Because the report language on Pediatric Nephrology Workforce Diversification and Pediatric Nephrology Research Awards covers similar topics, the response provided to each item is identical.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) acknowledges the need to expand the pediatric nephrology biomedical workforce, which is small and widely dispersed geographically. While junior faculty and trainees in pediatric nephrology are strikingly more diverse than their older counterparts, NIDDK continues to invest time and funds toward developing them as a resource for the future through such programs as its Kidney, Urologic, and Hematologic (KUH) R25 Summer Undergraduate Research Program and cognate symposium. For example, 14 institutions currently participate in the R25 Program; most of them support programs focused on nephrology, and many have tailored recruitment plans aimed at engaging a diverse group of students each year. The NIDDK has also used funded consortium studies, such as the Chronic Kidney Disease in Children Study (CKiD), to develop this diverse workforce—for example, by providing support for workshops that teach junior investigators how to use CKiD data, both expanding the use of this resource and the number and diversity of investigators who are aware of it and can use it with skill. Complementing these efforts, the NIDDK expects that its new "Institutional Network Award for Promoting Kidney, Urologic, and Hematologic Research Training (U2C/TL1—Clinical Trial Not Allowed)" training mechanism, while more broad-based, will help bolster the number and diversity of pediatric nephrologists in research.

In response to the dearth of clinical trials enrolling children with chronic kidney disease, the NIDDK funded a new clinical trial, "Ferric Citrate and Chronic Kidney Disease in Children (FIT4KiD) Trial." This trial also represents a workforce opportunity. Supplemental funding provided by the NIDDK will help advance the shared goal of incorporating a diverse group of junior faculty in all aspects of FIT4KiD clinical trial development and implementation, enabling these individuals to attend steering committee meetings that might otherwise only had representation from more established faculty.

NIDDK scientific program staff continue to hold regular meetings with the American Society of Pediatric Nephrology (ASPN) Research Committee to provide information and guidance to junior faculty as they work towards funded research projects and career advancement. Moving forward, discussions at these meetings will expand to cover strategies NIDDK and ASPN are employing to diversify as well as enlarge the cadre of pediatric nephrology trainees and investigators. The NIDDK also maintains a strong presence on the NIH–Pediatric Research Committee (N-PeRC) and advocates for targeted efforts to enhance research careers for junior pediatric nephrology faculty. N-PeRC recently sponsored a workshop on "Navigating Pediatric to Adult Health Care: Lost in Transition," and NIDDK representation helped to ensure that diverse speakers from pediatric nephrology and pediatric urology were featured. The NIDDK will continue efforts to help encourage junior researcher and diversity in this field as well as other fields within its mission.

Pediatric Nephrology Workforce Diversification

The Committee recognizes that the COVID–19 pandemic caused unprecedented disruption in biomedical research, delaying awards and dissuading applications for pediatric nephrology research. The Committee is concerned that these disruptions have disproportionately impacted researchers from traditionally underrepresented groups, resulting in even fewer researchers from communities of color. Pediatric nephrology studies continue to suffer from low enrollment, due in part to the disproportionate impact of kidney disease on children of color and longstanding challenges of clinical trial recruitment within those communities. Because children and families of color are more likely to enroll in studies where the research team is from the same community, the diversity of pediatric nephrology biomedical workforce is paramount to the success of this research. The Committee requests that NIDDK consult with stakeholder groups to identify barriers to increasing the diversity of the pediatric nephrology workforce and identify ways to incentivize researchers from traditionally underrepresented groups to enter this field. The Committee requests that NIDDK include information in the fiscal year 2023 Congressional Budget Justification on the progress made to bolster the diversity of the pediatric nephrology biomedical research workforce

Action taken or to be taken

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Pediatric Research

The Committee encourages NCI and NIH to continue to prioritize pediatric cancer research. The Committee recognizes NCI's efforts to implement sections of the Childhood Cancer STAR Act (Public Law 115–180), develop a new Childhood Cancer Data Initiative, and continue to support and expand new and innovative research efforts to advance progress for children with cancer. These include the Pediatric MATCH precision medicine trial and a pediatric immunotherapy translational science network established through the Cancer Moonshot, in addition to NCI's long-standing support for the Children's Oncology Group, the Childhood Cancer Survivor Study, the Pediatric Preclinical Testing Consortium, and several other critical programs. The Committee also commends NIH for its efforts to coordinate pediatric research across its Institutes and Centers through the recently established Trans-NIH Pediatric Research Consortium. The Committee understands NCI participates in the Consortium, and that childhood cancer research is an important part of the pediatric research portfolio across NIH. The Committee requests an update in the fiscal year 2023 CJ on opportunities to enhance childhood cancer research efforts, including coordination 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 NIH Common Fund in scientific leadership of the Gabriella Miller Kids First Research Program,[307] which is helping to foster new discoveries and biological insights, including the discovery of new genetic causes for childhood neuroblastoma and Ewing sarcoma. From 2015-2021, the Kids First program selected 44 childhood cancer and structural birth defects cohorts for whole genome sequencing, representing 20,000 patients and 48,000 genomes. In FY 2022, NIH anticipates supporting another round of cohorts for sequencing.[308] 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. There are more than 2,400 registered portal users, and data from 23 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. NCI continues to partner with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development as a member of the Trans-NIH Pediatric Research Consortium (N-PeRC) that was established in 2018 to harmonize pediatric research efforts across NIH.[309] Nearly all NIH institutes, centers, and offices have appointed senior level representatives to N-PeRC. Important common issues across NIH are those faced by adolescents as they transition to adult health care, pediatric medical device development, and pediatric research workforce training. During the next 3 years, N-PeRC plans to embark on new efforts and continue efforts for common issues, which will benefit children with pediatric diseases, including pediatric cancer, as well as the pediatric cancer research workforce. A forthcoming publication outlining the support available across NIH to develop and grow the pediatric research workforce will help educate potential applicants and facilitate diversifying the field of pediatric researchers. Additionally, in partnership with the National Institute of Environmental Health Services and the National Heart, Lung, and Blood Institute, NCI helped establish the Human Health Exposure Analysis Resource (HHEAR),[310] a

[307] commonfund.nih.gov/KidsFirst
[308] grants.nih.gov/grants/guide/pa-files/PAR-22-054.html
[309] www.nichd.nih.gov/research/supported/nperc
[310] www.niehs.nih.gov/research/supported/exposure/hhear/index.cfm

consortium that works to characterize all human environmental exposures. By integrating datasets across the lifespan (including early stages), researchers can better understand the developmental origins of health and disease.

NCI is maintaining important investments in the Pediatric Molecular Analysis for Therapy Choice (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. In fact, the MATCH trial[311] is exceeding expectations for rate of study enrollment because of more frequent actionable tumor mutation detection and treatment assignment than pre-study projections.[312] In addition to gaining important information from the MATCH trial about clinically relevant cancer susceptibility genes across a wide variety of genes the trial can also be used as a model for similar precision oncology trials.[313] 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 second year. Please see the House Significant Item for updates on that initiative, including the launch of the National Childhood Cancer Registry (NCCR) and the CCDI Molecular Characterization Protocol.

NCI also continues to conduct and support childhood and AYA cancer survivorship research that advances goals of the Childhood Cancer STAR Act. For example, a STAR Act-associated funding opportunity announcement released in 2019 has funded over 10 projects, including *Using information technology to improve outcomes for children living with cancer*, which is in the process of recruiting participants for a clinical trial[314] and another project that led to development of the Interactive Survivorship Program for the Improvement of Healthcare Resources in Adolescent and Young Adult Cancer Survivors (INSPIRE-AYA) clinical trial that will start recruiting patients in early 2022.[315] Additionally, in FY 2021, NCI supported 10 projects[316,317] in response to the funding opportunity "Research to Reduce Morbidity and Improve Care for Pediatric, and Adolescent and Young Adult (AYA) Cancer Survivors," which aligns with survivorship research priorities emphasized in the STAR Act. A second round of awards for this announcement is anticipated to be funded in the spring of 2022. 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, including through collaboration with the CCDI Molecular Characterization Protocol.

Childhood cancer research supported and conducted by the NCI and other NIH Institutes continues to lay a foundation for practice-changing advances. For example, a recent clinical trial[318] conducted by the NCI-supported COG found a new combination of drugs is highly effective in children with acute promyelocytic leukemia (APL) and will become the new standard of care for pediatric APL. This treatment also caused fewer short- and long-term side effects due to shorter (or no) chemotherapy doses. The largest ever international rhabdomyosarcoma (RMS) study,[319] led by NCI scientists, found mutations in several genes that seem to be associated with a more aggressive form of RMS, a rare pediatric cancer that impacts muscles and other soft tissues. These findings will inform new clinical approaches, including research into developing new therapies that target these mutations. Additionally, researchers at

[311] www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match
[312] ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.10007
[313] cancerres.aacrjournals.org/content/81/13_Supplement/631
[314] clinicaltrials.gov/ct2/show/NCT04789720
[315] clinicaltrials.gov/ct2/show/NCT04593277
[316] reporter.nih.gov/search/NndNJ2EFJ0mYSG8iU47JTw/projects?fy=2021&agencies=NCI
[317] reporter.nih.gov/search/LyZqcweWD0iGvXMVkflXDQ/projects?fy=2021&agencies=NCI
[318] www.cancer.gov/about-cancer/treatment/clinical-trials/search/v?id=NCT02339740&r=1
[319] www.cancer.gov/news-events/press-releases/2021/childhood-cancer-rhabdomyosarcoma

the National Institute on Deafness and Other Communications Disorders are working on ways to prevent hearing loss from cisplatin, a common chemotherapy medication. In an observational study, patients who are already taking cholesterol lowering medications (statins) had reduced cisplatin-induced hearing loss compared to those who are not. If these results are confirmed in a new study, this approach could potentially be used to protect the hearing of children with metastatic cancer.

Polycystic Kidney Disease

The Committee commends NIDDK for its continued commitment to Polycystic Kidney Disease Research and Translation Centers and the Pediatric Centers of Excellence in Nephrology, which improve our understanding of the causes of autosomal dominant polycystic kidney disease and autosomal recessive polycystic kidney disease. The Committee encourages NIDDK to ensure that funds previously committed for polycystic kidney disease research centers remain dedicated to funding other PKD research efforts.

Action taken or to be taken

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) maintains its commitment to Polycystic Kidney Disease (PKD) research through the newly formed PKD Research Resource Consortium, which develops and shares investigative resources, reagents, and expertise with the broader scientific research community to accelerate innovation and discovery in the field of PKD. In addition, NIDDK recently issued a Notice of Special Interest[320] entitled Advancing Polycystic Kidney Disease Research through Catalytic Tool and Technology Development, which aims to stimulate technological innovation that will enable researchers to close knowledge gaps in PKD pathophysiology and disease progression, and ultimately improve outcomes for people with the disease. All funds previously committed for PKD research centers remain dedicated to funding innovative research to understand, prevent, and treat polycystic kidney disease.

[320] grants.nih.gov/grants/guide/notice-files/not-dk-20-034.html

Polycystic Ovary Syndrome (PCOS)

PCOS affects up to 15 percent of women and is a significant risk factor for multiple cardiometabolic 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. Emerging data also link the risk of severe COVID–19 with certain factors such as low vitamin D levels, hyperandrogenism, inflammation, and ethnicity predisposition, all of which are directly associated with PCOS. The Committee encourages NHLBI, NICHD, ORWH, and NIDDK to support research investigating the risk of severe SARS–CoV–2 infection in the PCOS patient population and the strong overlap of risk factors for both worse PCOS cardio-metabolic manifestations and severe COVID–19. Findings should be disseminated to health care providers, PCOS patients, and the public, as well as highlighted for clinical practice. The Committee also encourages NIH to report on research that has been conducted on PCOS and its impact on cardio-metabolic health to date in the fiscal year 2023 Congressional Budget Justification. Finally, the Committee requests that PCOS 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. Women with PCOS are also at higher risk of diabetes and heart disease. The National Institutes of Health (NIH) has a broad portfolio of PCOS research supported by multiple Institutes and Centers (ICs).

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is committed to expanding the genomic understanding, phenotypic characterization, and use of advanced technologies to inform new prevention and treatment strategies to uncover factors leading to gynecologic conditions such as PCOS. NICHD funds a range of research on PCOS, including trainee grants, career development awards, and large multi-investigator research projects. For example, a recent NICHD and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funded study suggests that PCOS may have at least two different subtypes. The findings could provide important information on the possible causes of PCOS and for developing more effective ways to treat the condition. In addition, other NICHD research projects are investigating the genetic and pathophysiologic underpinnings of PCOS, including studies on specific genetic determinants and the biologic mechanisms that may cause PCOS and co-occurring clinical conditions.

In September 2020, NICHD published a Notice of Special Interest (NOSI) entitled, "Optimizing Precision Treatment of Gynecologic, Reproductive and Obstetrical Outcomes in Adolescents and Adults with PCOS and Associated Comorbid Conditions."[321] The goals of this initiative are to stimulate interdisciplinary scientific collaborations between gynecologists, reproductive endocrinologists, obstetricians, and other specialists in diverse medical fields to advance individualized treatments consistent with women's health care needs; promote translational and clinical research to increase understanding of the effects of various therapies on gynecologic, reproductive, and obstetric outcomes; and discover and develop novel safe and more effective therapies for adolescents and women with PCOS along with underlying co-occurring conditions. Ultimately, this research could advance precision therapeutics for adolescents and adults with PCOS who have concomitant medical conditions.

The National Heart, Lung, and Blood Institute (NHLBI) is committed to understanding and reducing the impact of PCOS on cardiovascular health. Recent studies suggest that elevated androgen levels have a negative impact on cardiovascular function in women, independent from other comorbidities of

[321] grants.nih.gov/grants/guide/notice-files/NOT-HD-20-026.html

cardiovascular disease.[322] For example, in NHLBI's Coronary Artery Risk Development in Young Adults (CARDIA) study, low levels of sex hormone-binding globulin, a protein that helps regulate androgens circulating in the body, were associated with higher risk of subclinical cardiovascular disease in young to middle-aged women.[323]

Current NHLBI-funded research focuses on understanding how excess androgens impair the cardiovascular system and increase the long-term risk of cardiovascular disease. To investigate mechanisms of PCOS, as well as potential therapeutic interventions, one NHLBI-funded group has developed a rodent model of PCOS by implanting female rats with a testosterone pump.[324] By studying this model as well as women with PCOS, the researchers are investigating a theory that excess androgen in the female body activates the sympathetic ("fight or flight") nervous system, leading to high blood pressure.[325]

To inform the development of future PCOS research initiatives, NHLBI, NICHD, NIDDK, and other NIH components sponsored a workshop in October 2021 on "Cardiovascular Risk Across the Lifespan for Polycystic Ovarian Syndrome" to bring together PCOS experts to review current knowledge of cardiovascular risk factors associated with PCOS and to identify research gaps needed to improve prevention, intervention, and implementation strategies. The workshop agenda included a presentation by researchers who have reported a higher risk of coronavirus disease 2019 (COVID-19) among women with PCOS.[326]

In light of the factors associated with PCOS and the overlap of these factors with an increased risk of severe severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2) infection, NIH is exploring additional research in this space. NICHD plans to publish a Notice of Special Interest to stimulate research to investigate and understand the biological basis of the risk of severe SARS–CoV–2 infection in the PCOS patient population. NIDDK is supporting research to understand the relationship between SARS-CoV-2/COVID-19 and chronic metabolic diseases and conditions, including type 2 diabetes and obesity, to find improved approaches to prevention and/or treatment of both severe COVID-19 and worse outcomes or new onset of metabolic disease potentially triggered by infection. Findings from this research could help people with PCOS.

NHLBI's Collaborative Cohort of Cohorts for COVID-19 Research (C4R) may help shed light on the potential association between PCOS and COVID-19 risk. C4R combines 14 diverse established population studies—including CARDIA, the Framingham Heart Study, and the Jackson Heart Study—to examine risk factors and outcomes related to COVID-19.[327] The rich historical and ongoing health data from these cohorts include measures of high blood pressure, obesity, and insulin resistance, as well as androgen levels and other PCOS-relevant data collected in some ancillary studies. Such data may help researchers further explore the reported association between PCOS and COVID-19.

NIH supports a robust PCOS research portfolio and is in the process of adding PCOS to the NIH Research, Condition, and Disease Categories (RCDC) reporting.

[322] pubmed.ncbi.nlm.nih.gov/32727622/
[323] pubmed.ncbi.nlm.nih.gov/20554712/
[324] academic.oup.com/endo/article/157/7/2920/2423013
[325] projectreporter.nih.gov/project_info_description.cfm?aid=9619086
[326] pubmed.ncbi.nlm.nih.gov/33635829/
[327] pubmed.ncbi.nlm.nih.gov/33758891/

Pulmonary Fibrosis (PF)

The agreement recognizes that pulmonary fibrosis encompasses more than 200 different lung diseases that have many similarities despite having a variety of causes. This heterogeneity presents significant challenges for diagnosis and treatment. Accordingly, the agreement is pleased that the Institute-funded PRECISIONS study, which is testing a potential new treatment and aims to identify genetic variants for certain forms of PF, has moved ahead notwithstanding the challenges posed by the COVID-19 pandemic. Given the grim prognosis for most PF patients, the agreement also recognizes the critical need for other areas of research, particularly on common fibrosis pathways, as well as patient-centered clinical research. With additional resources and focus, additional disease mechanisms can be identified, which would allow for enhanced patient-centered care for all of those affected by PF. The agreement requests an update in the fiscal year 2023 Congressional Justification.

Action taken or to be taken

The National Heart, Lung, and Blood Institute (NHLBI) is committed to supporting basic, clinical and translational research on pulmonary fibrosis, which leads to progressive scarring of the lungs that makes it increasingly more difficult to breathe. PRECISIONS[328] is a five-year study which aims to enroll 200 patients with idiopathic pulmonary fibrosis (IPF),and will use genetic testing to identify those patients most likely to respond to an experimental treatment, an antioxidant known as N-acetylcysteine or NAC. This first-of-its-kind precision medicine trial builds on an earlier study suggesting that a gene called TOLLIP influences how patients respond to NAC, such that it might be helpful only for a subgroup of patients who have a particular version of the gene. The trial will enroll only that subgroup in order to increase the likelihood of detecting a benefit.

During coronavirus disease 2019 (COVID-19) related delays and uncertainty regarding the feasibility of in-person lung function assessments (spirometry), PRECISIONS initiated an ancillary study to understand the utility of home spirometry to monitor patients with IPF. The study added a COVID-19-specific questionnaire to baseline and follow-up visits in the clinical trial as a means of leveraging this existing patient cohort to capture additional data on the epidemiological and clinical characteristics of COVID-19.

NHLBI is now supporting five collaborative research projects to establish a set of complementary model systems that reproduce essential disease-defining features of human idiopathic pulmonary fibrosis (IPF) in order to advance our understanding of the pathogenesis of IPF from its onset through disease progression and to serve as a clinically relevant resource for identifying and testing novel therapies to treat IPF.[329] By developing several model systems in unison, this program is poised to better model disease heterogeneity and thus identify common underlying pathways that lead to fibrosis. Two of these projects have now co-developed and published a model using individual patient-derived lung cells that carry a specific gene mutation associated with IPF, showing that these cells undergo molecular changes in the lab that are consistent with changes observed in IPF patient lungs and therefore may be useful for testing new drug therapies for IPF.[330]

NHLBI is also supporting several clinical studies aimed at testing novel treatments for PF. For example, in addition to the PRECISIONS trial, NHLBI is currently funding clinical trials of compounds that target different oxidant pathways associated with the development of IPF, as well as a therapy intended to lessen the severity of acute disease exacerbations in IPF patients. Another recent NHLBI-funded study

[328] eporter.nih.gov/project-details/9822535
[329] reporter.nih.gov/search/fJnh4i6dokero_a9iGbg7g/projects
[330] pubmed.ncbi.nlm.nih.gov/34469722/

suggests that targeting and treating elevated concentrations of Muc5b, a major gel-forming mucin in the lung that plays a key role in mucociliary clearance and host defense, may prevent the progression of preclinical pulmonary fibrosis.[331]

NHLBI is also supporting initiatives to improve patient outcomes and quality of life. NHLBI has embarked on a new two-phase **Air You Wear Challenge** to stimulate the development of lighter, more portable oxygen devices for the more than 1.5 million Americans who use supplemental oxygen for pulmonary fibrosis and other conditions. Phase I winners were announced in December 2021.[332]

NHLBI continues to fund observational studies with the potential to yield new insights into disease mechanisms that lead to pulmonary fibrosis. For example, a large natural history study of preclinical pulmonary fibrosis in currently unaffected but at-risk individuals who have two or more close family members with confirmed cases of idiopathic interstitial pneumonia will provide us with a better understanding of the etiology and heterogeneity of preclinical pulmonary fibrosis, before the lungs become irreversibly scarred.[333] Defining genetic and environmental risk factors that predispose to the eventual onset and progression of pulmonary fibrosis could enable earlier diagnosis, improve monitoring of disease progression, and may uncover novel biological targets for clinical intervention. In addition, this study may reveal unique biomarkers that can be used to direct treatment and evaluate responsiveness to existing or new anti-fibrotic therapies. Another group of NHLBI-funded researchers identified blood gene expression signatures with the capability to reveal new signaling targets for precision therapeutics. These findings could also pave the way for patient outcome prediction tools.[334]

[331] pubmed.ncbi.nlm.nih.gov/30560893/
[332] www.nhlbi.nih.gov/grants-and-training/air-you-wear-challenge/finalists-and-honorable-mentions
[333] reporter.nih.gov/search/LTo8hNlxNkaiwrndj5x0Vg/project-details/10219354
[334] pubmed.ncbi.nlm.nih.gov/33689671/

Prostate Cancer Disparities

Nearly 250,000 men will be diagnosed with and 34,000 men will die from prostate cancer in 2021. Incidence of prostate cancer is almost 80 percent higher in non-Hispanic Black men, and prostate cancer mortality among Black men is more than double that of men in every other racial or ethnic group, representing a stark example of health inequity in cancer outcomes. The Committee supports NCI and NIMHD research on Prostate Cancer in Men of African American Ancestry: Defining the Roles of Genetics Tumor Markers, and Social Stress (RESPOND) Study, intended to identify the underlying causes of disparities in prostate cancer incidence and mortality. The Committee requests an update on the study in the fiscal year 2023 Congressional Budget Justification.

Action taken or to be taken

Research on the diagnosis, treatment, and prevention of prostate cancer remains a priority for the National Cancer Institute (NCI), especially as it relates to health disparities. The Institute coordinates and collaborates across the National Institutes of Health (NIH), as well as with other Federal agencies, private research organizations, and advocacy groups to improve detection and treatment, and decrease the discrepancies in diagnosis and mortality rates between different population groups.

In July of 2018, NCI launched the Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Tumor Markers, and Social Stress (RESPOND) study.[335] This $26.5 million study is the largest coordinated research effort to study biological and nonbiological (social) factors associated with aggressive prostate cancer in African American men, who disproportionally experience aggressive disease and mortality compared with men of other racial and ethnic groups. The study is expected to last 5 years and hopes to recruit 10,000 African American men to participate across the country. RESPOND is supported by NCI, the National Institute on Minority Health and Health Disparities (NIMHD), and the Prostate Cancer Foundation, a philanthropic organization dedicated to funding and accelerating prostate cancer research. NCI's support is provided through the Cancer Moonshot[SM].

Since the RESPOND study began, several results have been released. In 2020, researchers published a study[336] identifying an inherited genetic variant associated with a higher risk of prostate cancer in men of African descent. In general, about 12 percent of African American men have this genomic variation, which increases their risk of prostate cancer two-fold, and the variant is not seen in any other populations. This variant is more likely to be found in individuals with a family history of prostate cancer (32 percent of the men with a family history had this variant in the study) and is strongly associated with prostate cancer diagnosis at an earlier age and a more aggressive disease. This variant can be used in the future to identify African American men who are at higher risk of developing prostate cancer and would benefit from more targeted and frequent screening.

In addition, other results from the RESPOND study published in 2020[337] found that the genomic profiles of prostate cancer differ between men of African and European descent, emphasizing the importance of having African American men included in future prostate cancer molecular studies and clinical trials for new therapies. However, the researchers found that there were similar rates of mutations in common genes targeted by current prostate cancer therapies, indicating that these therapies should be as successful in patients of African American ancestry as men of European descent if they are applied equitably. These results also highlight that more research is needed into how environmental and social factors interact with

[335] reporter.nih.gov/search/SJhRb5lw40KsGhSq-YJqdA/project-details/9417919, respondstudy.org/StudyDetails.aspx
[336] pubmed.ncbi.nlm.nih.gov/32409115/
[337] pubmed.ncbi.nlm.nih.gov/32651179/

genetic and biological tumor characteristics of prostate cancer in African American men to influence clinical outcomes.

The RESPOND study aims to examine the factors contributing to the increased burden of prostate cancer in African American men. This includes environmental factors like stress, inherited genetic profiles, and tumor characteristics. By the end of the study, the thousands of samples that have been gathered and analyzed will hopefully lead to more effective preventative interventions, earlier diagnosis, and new and more targeted treatment options for African American men.

Rare Disease Research

The Committee is aware that nearly one in ten individuals in the U.S. is affected by a rare disease, and that rare diseases frequently are genetic or have a genetic component. The Committee urges NIH to expand research on rare genetic and chromosomal abnormalities, such as 7q11.23 Duplication Syndrome and Hereditary Spastic Paraparesis 49 (TECPR2). The Committee directs NIH to provide an update on these two conditions in the fiscal year 2023 Congressional Budget Justification.

Action taken or to be taken

The National Center for Advancing Translational Sciences (NCATS) is working on several platform approaches for finding treatments for rare diseases, as well as studying specific rare disease syndromes, such as 7q11.23 Duplication Syndrome and Hereditary Spastic Paraparesis 49 (TECPR2). Collaborations with other National Institutes of Health (NIH) Institutes and Centers are essential to how NCATS addresses rare disease research needs. To promote therapy development for rare diseases such as Hereditary Spastic Paraparesis 49 (TECPR2), and all Hereditary Spastic Paraparesis disorders (HSPs), the National Institute of Neurological Disorders and Stroke (NINDS) and NCATS support an initiative called Clinical Trial Readiness for Rare Neurological and Neuromuscular Diseases, which funds biomarker development and other types of studies aimed at preparing for successful clinical trials to test emerging treatments. As part of the NIH Rare Diseases Clinical Research Network, NINDS and NCATS also co-fund the Clinical Research in ALS and Related Disorders for Therapeutic Development (CReATe) Consortium, which focuses on disorders characterized by degeneration in motor systems, including amyotrophic lateral sclerosis (ALS) and HSP. The goals of the CReATe Consortium are to support collaborative research on these disorders and promote clinical trial readiness by developing and disseminating research resources, increasing patient participation in clinical research, enhancing training of new investigators, and engaging stakeholders in partnerships that foster therapeutic development.

Studies by intramural NINDS investigators and others have found that many genes linked to HSPs, including TECPR2, are associated with components of the endoplasmic reticulum (ER), a cellular organelle involved in producing, transporting, and disposing of proteins inside cells. One study funded by NINDS is examining the protein coded by the TECPR2 gene and its role in a cellular pathway that clears misfolded proteins from the ER. Other NIH-supported studies on HSPs focus on finding genetic causes, understanding disease mechanisms across different types of HSPs, and identifying targets for treatments to prevent or slow disease progression. Findings from these studies will aid in the discovery of treatments that may work for various types of HSPs, including Hereditary Spastic Paraparesis 49 (TECPR2).

It is important to note that rare genetic diseases that affect larger pieces of chromosomes, such as 7q11.23 Duplication Syndrome, impact many different genes at the same time and tend to cause severe illness in affected patients. A good deal of work still needs to be done to better understand these disorders and to develop new approaches that may impact these syndromes.

NCATS leads several important cross-cutting NIH programs that aim to address many rare diseases at one time through gene-targeted therapies and that have the potential to expedite therapeutic development for many rare diseases. Such programs include:

- The NIH Somatic Cell Genome Editing program is working to find better ways to deliver genome editors into the relevant cell type(s).

- The Platform Vector Gene Therapy (PaVe-GT) pilot project seeks to increase the efficiency of clinical trials by testing a commonly used gene delivery system.

- The Bespoke Gene Therapy Consortium and Coordinating Center, which is a public-private partnership involving the U.S. Food and Drug Administration (FDA), Foundation for NIH, and several NIH Institutes, is exploring novel collaborative approaches related to gene therapy for rare diseases.

- A new NCATS-led multistakeholder project, involving collaborations with other NIH Institutes, academic groups, biopharmaceutical companies, and the FDA, seeks to substantially streamline and accelerate the development of antisense oligonucleotide drugs for rare genetic diseases—even as rare as those affecting only a single patient—and including gene mutations such as those that give rise to HSP.

Lastly, NCATS supports work to broadly address early identification of, and interventions for, rare genetic and chromosomal disorders. For example:

- A project titled "Precision Medicine in the Diagnosis of Genetic Disorders in Neonates" is examining the use of whole genome sequencing to rapidly diagnose newborns with undiagnosed diseases in neonatal intensive care units. The overarching goal is to examine the clinical utility of a neonatal gene panel in high-risk neonates to determine if it will provide 1) faster detection of gene and chromosomal abnormalities, and 2) enable earlier diagnosis that leads to better clinical care.

- NCATS hosted a three-day workshop in June 2021 focused on early diagnostic strategies for rare genetic diseases. The goal of the workshop was to engage stakeholders on approaches that will impact many rare diseases. This virtual workshop had almost 2,000 participants, and it featured about 50 speakers on about 25 topics relevant to early identification of patients who may benefit from gene targeted (precision or personalized medicine) treatment approaches. A meeting summary and a related publication in a scientific journal are being compiled. The meeting also generated a great deal of interest in the patient and industry communities, and NCATS is exploring potential additional avenues for further discussion with rare diseases stakeholders.

Research on Cancer Disparities

The Committee encourages NCI to continue its commitment to support the NCI Community Oncology Research Program and the activities of the Center to Reduce Cancer Health Disparities, two key efforts that contribute to building a cadre of community stakeholders and medical researchers prepared to engage in transdisciplinary approaches to address cancer, including its disparate impact on some communities nation-wide. Although there have been significant advances in the prevention and treatment of cancer, evidence shows persistent differences in cancer incidence, late-stage diagnosis, and mortality in many States depending on socioeconomic status, geography, race, ethnicity, and other factors. The Committee encourages NCI to continue to prioritize research and training programs aimed at reducing health disparities in cancer, including through NCI's continued support of its integrated training, education, and outreach networks between communities and medical research centers. The Committee encourages NCI to prioritize partnerships with community groups and other stakeholders to explore the issues associated with cancer disparities as identified by local communities and include activities to develop curriculum to inform health professions education to reduce medical mistrust in targeted groups and to highlight relevant research questions to address cancer disparities. Additionally, NCI efforts should support the development of a cancer research infrastructure to identify relevant research questions related to disparities and to develop integrated and sustainable approaches to reducing cancer disparities, including examining social determinants of health and their impacts on such disparities.

Action taken or to be taken

The National Cancer Institute's (NCI) scientific priorities span the cancer continuum and include ending cancer disparities and making health equity a priority, while building a diverse and inclusive workforce. NCI's equity and inclusion efforts are led by an Equity Council of diverse leaders from across the Institute with a passion and commitment to ensuring NCI has a robust research portfolio to effectively address cancer disparities and nurturing a workforce at all career levels that is wholly representative of the people who NCI serves.

NCI's Community Oncology Research Program (NCORP) and the Center to Reduce Cancer Health Disparities (CRCHD) are key to NCI efforts. In fiscal year (FY) 2019, NCORP was renewed, which included an expansion in the number of Minority/Underserved Community Sites. There are currently seven NCORP Research Bases and 46 Community Sites, 14 of which are designated as Minority/Underserved Sites. In September of 2020, NCI's Division of Cancer Prevention held an inaugural workshop of Primary Care Alliance in Research Trials Involving NCORP Sites (PARTNRS) to encourage and forge partnerships between oncologists, primary care providers, and medical specialists to promote accrual to clinical cancer control and prevention trials conducted by NCORP. Strategies generated at the workshop are outlined in an executive summary as suggestions for consideration by stakeholders to overcome accrual barriers.[338]

In FY 2021, CRCHD launched a new program, Connecting Underrepresented Populations to Clinical Trials (CUSP2CT),[339] to increase referral and accrual of historically underrepresented populations to NCI-supported clinical trials in NCORP and other NCI networks through implementation and evaluation of culturally tailored outreach and education. NCI's commitment to expanding trial participant demographics to better represent the American population and better reflect broad health outcomes is also reflected in NCI's FY 2023 Annual Plan highlighted opportunity "Clinical Trials: Bringing Cancer Research to All Possible Participants."[340]

[338] ncorp.cancer.gov/d/partnrs_executive_summary.pdf
[339] grants.nih.gov/grants/guide/rfa-files/RFA-CA-21-057.html
[340] cancer.gov/research/annual-plan/scientific-topics/clinical-trials

NCI supports a variety of training opportunities aimed at reducing cancer health disparities and supporting a diverse workforce. The Continuing Umbrella of Research Experience (CURE) program is a seminal program run by CRCHD.[341] Through professional development and unique training opportunities, the CURE program enhances workforce diversity in the cancer and health disparities fields, offering funding and support from middle school through the junior investigator level. NCI also reissued the Funding Opportunity Announcement (FOA), NCI Mentored Research Scientist Development Award to Promote Diversity, in FY 2021. These awards seek to enhance the diversity in the NCI-funded cancer research workforce by supporting eligible individuals from diverse backgrounds, including groups that have been shown to be nationally underrepresented in the biomedical, behavioral, social, and clinical sciences.[342]

In addition to the CURE programs, CRCHD also supports the Partnerships to Advance Cancer Health Equity (PACHE) program.[343] Established in 2001, PACHE provides funding to connect institutions that serve underserved populations and underrepresented students with NCI-designated Cancer Centers. The grants administered through PACHE target cancer research, education, and outreach to develop stronger cancer programs and better understand and reduce cancer disparities. There are 23 active partnerships being funded.

The Division of Cancer Control and Population Sciences currently has 13 FOAs that address cancer disparities research on topics including cancer risk factors in rural populations and mechanisms for chronic liver diseases and cancer disparities.[344] Also, a long-standing and recently renewed NCI FOA for basic research in cancer disparities,[345] encourages applications interested in conducting basic, mechanistic research into the biological causes of cancer disparities. NCI also supports planning grants for future Specialized Programs of Research Excellence (SPORE) in cancer disparitites[346] to build programs to improve the prevention, detection, diagnosis, and treatment of cancers that disproportionately affect underserved populations that can compete for future SPORE funding. NCI has awarded 10 planning grants over the past 3 years.

Bringing underrepresented communities into the decision-making process helps ensure that research will benefit the target population, contribute to alleviating the unequal cancer burden, and create workforce diversity among health disparities researchers. An example of this is the trans-NIH initiative, Native American Research Centers for Health (NARCH), that supports biomedical research and career development opportunities for American Indian and Alaska Native (AI/AN) communities, plus research infrastructure development and capacity building. Research areas for this initiative are selected by AI/AN Tribes, allowing the impacted communities to have some control over research directions and career opportunities.

[341] cancer.gov/about-nci/organization/crchd/diversity-training/cure
[342] grants.nih.gov/grants/guide/pa-files/PAR-21-295.html; grants.nih.gov/grants/guide/pa-files/PAR-21-296.html
[343] cancer.gov/about-nci/organization/crchd/diversity-training/pache
[344] grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-051.html; grants.nih.gov/grants/guide/pa-files/PAR-20-088.html
[345] grants.nih.gov/grants/guide/pa-files/PAR-21-322
[346] grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-033; grants.nih.gov/grants/guide/rfa-files/RFA-CA-19-034

Research Transparency

As demonstrated over the past several years, the Committee remains committed to funding NIH research and ensuring that our nation's researchers, particularly our young scientists, have the support to make the scientific breakthroughs that may transform healthcare. However, it is critical that NIH can ensure funds are used for the best possible research that fulfill the core research mission of NIH. Over the last 6 fiscal years, Members have provided several examples of questionable spending stemming from research grants awarded by NIH, showing the need for enhanced oversight in the review and approval process. Therefore, NIH is directed to justify, in writing made available on a publicly accessible website, that each grant or agreement promotes efforts to seek fundamental knowledge about the nature and behavior of living systems and/or the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.

Action taken or to be taken

The National Institutes of Health (NIH) takes seriously its mission to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. Applications submitted to the NIH for grants or cooperative agreements are evaluated for scientific and technical merit through the NIH peer review system,[347] and reviewers provide an overall impact score to reflect their assessment of the likelihood for the project to exert a sustained, powerful influence on the research field(s) involved.

NIH has also included the following language prominently on the main Research Portfolio Online Reporting Tool – Expenditures and Results (RePORTER) homepage[348] to address this request: "Each award supported by NIH promotes efforts to seek fundamental knowledge about the nature and behavior of living systems and/or the application of that knowledge to enhance health, lengthen life, and reduce illness and disability." The RePORTER system is a publicly accessible, electronic tool that allows users to search a repository of both intramural and extramural NIH-funded research projects and access publications since 1980, and patents resulting from NIH funding.

[347] grants.nih.gov/grants/peer-review.htm
[348] reporter.nih.gov/

SARS–CoV–2

The Committee thanks NIDCR for its commitment to prioritizing research to answer critical research questions related to the novel coronavirus. The Institute's research into high-impact areas such as transmission risk in dental environments is critical for the nation to continue fighting COVID–19 and to ensure everyone is as safe as possible.

Action taken or to be taken

The National Institute of Dental and Craniofacial Research (NIDCR) is committed to its unique role at the National Institutes of Health (NIH) in responding to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus by focusing on oral health and safety in the dental clinic. NIDCR provided approximately $4 million in supplemental support to current grantees to shift focus to SARS-CoV-2 research,[349] and administers six Rapid Acceleration of Diagnostics Radical (RADx-rad) initiative grants.[350] The institute is also involved in the NIH REsearching COVID to Enhance Recovery (RECOVER) Initiative, which seeks solutions to the long-term health effects of coronavirus disease 2019 (COVID-19).[351] NIDCR published two papers highlighting the institute's response to the pandemic outlining its nimble, rapid scientific response[352] and shedding light on the impacts of the pandemic on NIDCR staff and researchers.[353]

One of the most critical tools in ending the ongoing COVID-19 pandemic is rapid, sensitive, inexpensive diagnostic methods. NIDCR-funded researchers are developing a "smart mask" that changes color in the presence of the virus.[354] Another group of researchers is in the process of developing a portable biosensor that utilizes disposable cartridge strips and shows promise as a fast, easy, and low-cost detection method.[355] Also, a RADx-rad project is developing a fast cellphone camera-based SARS-CoV-2 RNA detection method for rapid diagnosis.[356]

NIDCR is investing in research to understand the biology of the SARS-CoV-2 virus, with a focus on transmission and infection. NIDCR intramural scientists discovered that SARS-CoV-2 infects the cells in the mouth as well as saliva.[357] NIDCR-funded investigators are exploring the mechanisms that the virus uses to gain entrance into the host cell[358] and the role that specific cell receptors located in the oral cavity, called P2Y2 receptors, play in infecting the cell.[359] Another study is assessing the effectiveness of certain compounds called probiotics, that are produced by the normal bacteria found in the mouth, in inhibiting the infectivity of SARS-CoV-2.[360]

NIDCR-supported investigators are also examining ways to keep dental health professionals and patients safe in dental practices. Several of these studies are conducted by members of the National Dental

[349] www.nidcr.nih.gov/research/covid19/studies-grantee-institutions
[350] www.nidcr.nih.gov/research/covid19/nidcr-supported-radx-awards
[351] recovercovid.org/
[352] pubmed.ncbi.nlm.nih.gov/34044965/
[353] pubmed.ncbi.nlm.nih.gov/33906484/
[354] pubmed.ncbi.nlm.nih.gov/34309356/
[355] pubmed.ncbi.nlm.nih.gov/34309356/
[356] onlinelibrary.wiley.com/doi/full/10.1002/admt.202100602
[357] www.nidcr.nih.gov/news-events/nidcr-news/2021/scientists-find-evidence-novel-coronavirus-infects-mouths-cells; pubmed.ncbi.nlm.nih.gov/33767405/
[358] reporter.nih.gov/project-details/10221894
[359] reporter.nih.gov/project-details/10176830
[360] reporter.nih.gov/project-details/10175495

Practice-Based Research network (PBRN).[361] One is testing the feasibility of several risk-mitigation strategies in dental offices to increase safety in dental office settings,[362] while others are evaluating proper usage of personal protective equipment (PPE)[363] and assessing aerosol mitigation strategies in dental environments to limit virus transmission.[364] Also, the PBRN COVID-19 Research Registry (CORE) is currently surveying dental practitioners about their approaches to reducing transmission risk, and the associated costs of these approaches.[365]

[361] www.nidcr.nih.gov/research/clinical-trials/national-dental-practice-based-research-network
[362] www.nationaldentalpbrn.org/recruiting-ongoing-upcoming-completed/#1599667173484-701a56f0-7843
[363] www.nationaldentalpbrn.org/recruiting-ongoing-upcoming-completed/#1595865482318-42bc47a4-441b
[364] www.medrxiv.org/content/10.1101/2021.07.30.21261399v1
[365] www.nationaldentalpbrn.org/recruiting-ongoing-upcoming-completed/#1627438270053-0d10a7b2-94c1

Skin Cancer in Communities of Color

Research has shown that skin cancer in patients with skin of color is often diagnosed in its later stages, making treatment more difficult and decreasing the chances for survival. The Committee requests an update in the fiscal year 2023 Congressional Budget Justification regarding research that assesses factors contributing to later diagnoses of skin cancer among patients with skin of color, as well as research focused on measures to raise awareness of risk factors for skin cancer and to encourage activities that promote prevention and early detection of skin cancers among patients with skin of color and other underserved populations.

Action taken or to be taken

People of color more frequently have higher instances of certain types of melanoma, including melanoma of the palms, soles, and nailbeds (known as acral lentiginous melanoma), while White individuals and Hispanics most frequently have superficial spreading melanoma (known as cutaneous), the most common form of melanoma. Additionally, Black patients are more than three times as likely to be diagnosed with late-stage melanoma as non-Hispanic White patients. Some of the factors that contribute to the lower frequency of skin cancer but worse outcomes for communities of color include lower public awareness of the risks of skin cancer for communities of color, less regular full-body skin exams due to lower cancer incidence, and more difficult detection of skin cancer because it tends to be on less sun-exposed areas and melanoma on dark-skinned people doesn't match the ABCDE (asymmetry, border, color, diameter, evolving) guidelines for examining moles. Much less is known about acral than cutaneous melanoma, as ultraviolet (UV) radiation from the sun does not appear to be as much of a factor in this type of skin cancer.

The National Cancer Institute (NCI) has supported skin cancer research and prevention for many years and is dedicated to improving health equity for all. In 2021, the NCI funded a grant[366] to understand the factors contributing to later-stage melanoma diagnosis of Hispanic populations compared to non-Hispanic White populations, which can potentially lead to an increased likelihood of metastasis and worse survival rates. After identifying these factors, targeted clinic-based health education can be tested to achieve earlier diagnosis and reduce the melanoma burden in the Hispanic population. This study will take place in Los Angeles County, CA, which has high melanoma rates among Hispanics.

Additionally, NCI-funded researchers conducted a pilot study[367] as part of a Comprehensive Partnerships to Advance Cancer Health Equity (CPACHE) study to improve cancer care outcomes for Hispanics in Puerto Rico and Florida. Researchers found variants of a gene known to increase the risk of skin cancer in over half of the participants. Even Hispanics with stronger African or Native American genetic ancestry (darker skin and hair) could still have an elevated skin cancer risk due to the gene variants. This study indicates the need for future work with diverse populations regarding both genetics and physical characteristics, and that the genetic variants identified in this study could be a future tool for risk assessment, prevention, and early detection in Hispanic populations.

The MelaNostrum Consortium, convened through the NCI intramural research program, consists of collaborations with researchers and clinicians from Italy, Spain, Greece, Croatia, southern France, and Cyprus.[368] They collect data and biospecimens from individuals of Mediterranean descent, creating a growing database and sample repository for melanoma research. This population is often underrepresented in research studies as they are thought to have lower risk of developing skin cancer due

[366] reporter.nih.gov/search/wUqAqLlOPUOb-C6NajivtA/project-details/10210925
[367] ncbi.nlm.nih.gov/pmc/articles/PMC7190662/
[368] dceg.cancer.gov/research/cancer-types/melanoma/melanostrum/research

to their darker pigmentation, and therefore there is a lack of knowledge of skin cancer risk factors and disease progression in these populations.[369] Another project focuses on acral lentiginous melanoma, a common skin cancer found in Black populations that is not linked to sun exposure and will characterize the genomic profile of this cancer. The researchers also aim to look at the processes that lead to tumor development and their correlation with patient factors. This study will also include patients from the United Kingdom and Mexico, among other countries, to expand the sample size for this rarer melanoma subtype in the general population.

NCI is supporting multiple studies focused on education and prevention of skin cancer in communities of color. One recently awarded study[370] will develop a virtual Sun Safe Workplace (SSW) learning environment to increase employee actions in sun safety and employee sun protection practices. The material included will be adjusted for African American and Hispanic audiences to help overcome identified barriers, attitudes, and sun safety practices. Another study will use multiple methods to better assess psychosocial sun protection factors in the Latino population. This will contribute to the limited literature focused on predictors of skin cancer prevention for this group, helping to better inform future prevention and dissemination efforts to help decrease disparities in skin cancer morbidity and mortality. Additionally, NCI funding opportunity announcements focused on behavioral research have included skin cancer prevention and control as an area of interest, including funding opportunities related to rural health[371] and Intervention Research to Improve Native American Health.[372]

Finally, NCI contributes to multiple reports and tools that track skin cancer rates in different demographic groups, including the Cancer Trends Progress Report (CTPR) – which recently began reporting information by race and skin type for skin cancer prevention behaviors and sunburn, the Annual Report to the Nation on the Status of Cancer that contains information on melanoma rates including information relevant to communities of color and historically underserved populations, and the NCI SEER (Surveillance, Epidemiology, and End Results program) Explorer tool that contains information on skin cancer incidence and mortality rates for a variety of demographic characteristics.

[369] dceg.cancer.gov/research/cancer-types/melanoma/melanostrum
[370] reporter.nih.gov/search/olTspWVyx0aRIFY0h1VocA/project-details/10324860
[371] grants.nih.gov/grants/guide/rfa-files/RFA-CA-19-064.html
[372] cancercontrol.cancer.gov/native-american-intervention

Spasmodic Dysphonia

The Committee notes the research NIDCD continues to facilitate on spasmodic dysphonia. The Committee requests an update in the fiscal year 2023 Congressional Budget Justification on collaborative efforts with related Institutes, Centers, and stakeholders to advance critical research into all forms of dystonia, including spasmodic dysphonia.

Action taken or to be taken

Laryngeal dystonia (LD), also referred to as spasmodic dysphonia, is a voice disorder that belongs to a family of neurological disorders called focal dystonias. When a person with LD attempts to speak, the muscles in the larynx spasm involuntarily and cause the voice to break up and sound strained or breathy. It is a rare disorder, and more women than men are affected. Currently, there is no cure for LD, and the most common treatment is repeat injections of very small amounts of botulinum toxin directly into the affected muscles of the larynx every few months to lessen the muscle spasms. Surgical procedures, like the selective laryngeal adductor denervation-reinnervation have yielded good results in people with adductor spasmodic dysphonia. Voice therapy can also be helpful, especially when a patient has developed compensation techniques.

In 2018, the National Institute on Deafness and Other Communication (NIDCD) participated in a National Institute of Neurological Disorders and Stroke (NINDS)-organized Dystonia meeting. Public stakeholders, grantees, and National Institutes of Health (NIH) scientific program staff discussed a range of research topics, including LD. In 2019, the NIDCD convened a multidisciplinary panel of experts for a one-day workshop to examine the current progress in understanding the causes of LD and to delineate research priorities for improving clinical care.[373] The panel was comprised of experts from the fields of neurology, otolaryngology, speech-language pathology, neurosurgery, genetics, and neuroscience. Experts recognized LD as a multifactorial form of isolated dystonia that has heterogeneous characteristics. Why an individual may develop LD remains unknown, and the experts agreed the pathology of the disorder likely involves large-scale functional and structural brain network disorganization. Clinical challenges include the lack of validated diagnostic markers and outcome measures and the paucity of therapies that address the disordered pathology. The panel recommended supporting research that identifies biomarkers to develop diagnostic tools and standardized measures of treatment outcomes. Also needed is research support to better understand the underlying neurobiology of the disorder, which could lead to targeted therapies.

NIDCD currently funds research to better understand LD, determine its causes, and develop new diagnostics and better treatment options. NIDCD-supported scientists are conducting research to identify brain abnormalities and genes that cause LD. NIDCD-funded scientists are also pursuing several new areas for future therapies and surgical interventions, including locating specific brain areas involved in regulating abnormal laryngeal muscle activity and looking for new oral medications that affect the abnormal brain activity underlying LD. Through this research program, NIDCD is directly addressing the need for more accurate detection, prediction, and diagnosis.

[373] pubmed.ncbi.nlm.nih.gov/33858994/

Suicide Prevention

The Committee is encouraged that 2019 was the first year in two decades in which the suicide rate decreased. However, death by suicide remains the tenth leading cause of death in the U.S., and the Committee remains committed to providing the resources necessary to address this alarming crisis. 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 continue to prioritize suicide research in fiscal year 2022, with special emphasis on producing models that are interpretable, scalable, and practical for clinical implementation, including utilization of health care, education, and criminal justice systems that serve populations at risk. 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 pandemic. The Committee requests that NIMH provide an update on these efforts in the fiscal year 2023 Congressional Budget Justification.

Action taken or to be taken

The National Institute of Mental Health (NIMH) is committed to reducing the national suicide rate and has invested in actionable research that could swiftly make an impact, while not losing sight of longer-term prevention strategies. NIMH-supported studies, in combination with concerted federal efforts and increasing interest among stakeholders in healthcare (e.g., medical professionals and the societies to which they belong, professional guilds, and healthcare systems) to translate research into practice, may be making an impact; for the first time in two decades, the national suicide rate dropped from 2018 to 2019.[374]

NIMH supports research aimed at implementing scalable and practical interventions across a variety of settings, including primary healthcare. Healthcare settings are a key location for suicide prevention, as most people who die by suicide access healthcare services within 12 months of their death.[375] To support healthcare providers, researchers in the NIMH Intramural Research Program (IRP) partnered with the American Academy of Child and Adolescent Psychiatry to publish suicide risk screening tools that can be used in multiple healthcare settings and age groups;[376,377] these tools have also been adapted in response to the coronavirus disease 2019 (COVID-19) pandemic.[378] Further, NIMH recently solicited research to develop and test the effectiveness and feasibility of service-ready tools and technologies to be used in healthcare settings and beyond for identification, prevention, and treatment of individuals at risk for suicide.[379] NIMH is also supporting research in emergency departments[380] and primary care settings[381] to improve outcomes for persons at risk for suicide. For example, to address rising rates of suicide ideation and behaviors among youth, NIMH is funding practice-based research in pediatric primary care aimed at testing developmentally focused assessments and interventions that may improve mental health outcomes and reduce suicide risk.[382,383] These studies are part of a larger effort to understand risk trajectories in children and preteens, particularly among health disparity populations. NIMH recently hosted a series of

[374] www.cdc.gov/nchs/data/databriefs/db395-H.pdf
[375] pubmed.ncbi.nlm.nih.gov/24567199/
[376] pubmed.ncbi.nlm.nih.gov/30384966/
[377] www.nimh.nih.gov/research/research-conducted-at-nimh/asq-toolkit-materials/youth-asq-toolkit
[378] www.nimh.nih.gov/sites/default/files/documents/research/research-conducted-at-nimh/asq-toolkit-materials/inpatient/pdfs/covid-19_adult_suicide_risk_screening_pathway.pdf
[379] grants.nih.gov/grants/guide/rfa-files/RFA-MH-21-110.html
[380] reporter.nih.gov/search/NANZUjdGaE6ydV4oFow7-w/project-details/10102469
[381] reporter.nih.gov/search/xUC0JuSeGk2_P_9RsRCzRQ/project-details/10218442
[382] reporter.nih.gov/search/JA_i3wb2wkuIZHj9sP87dQ/project-details/10104075
[383] reporter.nih.gov/search/m_5uRYFcCkO_I87ZT5ZGxA/project-details/10136092

meetings on this topic[384] and has solicited research to address systems-level risk detection and interventions to reduce suicidality among Black youth[385] and other underserved populations.[386]

NIMH also plans to support the development of Suicide Prevention Research Centers where transdisciplinary teams will focus on the rapid development of scalable approaches to identify and treat high-risk individuals and improve continuity of care across healthcare, education, and criminal justice settings.[387] Youth commonly access mental health services through school, making education an important setting for suicide prevention. NIMH is supporting a number of school-based studies with students ranging from adolescents to college-age.[388,389,390] Additionally, NIMH is supporting research to adapt evidence-based interventions for youth and young adults to be delivered via telehealth during the COVID-19 pandemic.[391,392] Individuals involved in the justice system are at increased risk for suicidal behavior, particularly during transitions into or out of incarceration. NIMH is supporting research on interventions to reduce risk among youth[393,394,395,396] and adults[397,398,399] during such transitions.

NIMH continues to work with public and private partners to advance the Institute's suicide prevention research agenda. During the COVID-19 pandemic, NIMH partnered with the National Action Alliance for Suicide Prevention (NAASP) and other public and private partners to lead a coordinated, national mental health and suicide prevention response.[400] NIMH representatives also participate in a number of NIH- and HHS-wide working groups, such as the Behavioral Health Coordinating Council, which was re-established in 2021 to facilitate interagency collaboration on behavioral health research, including suicide prevention research.

[384] www.nimh.nih.gov/news/events/2021/understanding-suicide-risk-among-children-and-pre-teens-a-synthesis-workshop
[385] grants.nih.gov/grants/guide/rfa-files/RFA-MH-21-185.html
[386] grants.nih.gov/grants/guide/rfa-files/RFA-MH-21-187.html
[387] grants.nih.gov/grants/guide/pa-files/PAR-20-286.html
[388] projectreporter.nih.gov/project_info_description.cfm?aid=9487307
[389] projectreporter.nih.gov/project_info_description.cfm?aid=10005477
[390] projectreporter.nih.gov/project_info_description.cfm?aid=9996789
[391] reporter.nih.gov/project-details/10206479
[392] reporter.nih.gov/search/DGYnKhTuQkClj07JYV5HVw/project-details/10189928
[393] reporter.nih.gov/search/bWDP0-FMok2cTmczypIKQg/project-details/9988500
[394] reporter.nih.gov/search/ACYaKZXBtkCL_19GzMSInA/project-details/9768575
[395] reporter.nih.gov/search/_1BSkuLFLk6d9dajYlUffA/project-details/9929655
[396] reporter.nih.gov/search/eiMPrThgDUizLlwl29YKxg/project-details/10110165
[397] reporter.nih.gov/search/S8rvD4CNN0eyOPrWHj2DsQ/project-details/10123624
[398] reporter.nih.gov/search/TVvomPMHRUqd4w1_cGyGvQ/project-details/9523227
[399] pubmed.ncbi.nlm.nih.gov/32304829/
[400] theactionalliance.org/covid19

Surveillance, Epidemiology, and End Results [SEER] Registry

The Committee encourages NCI to continue to advance efforts to modernize the SEER Registry and better capture key data points, such as metastatic recurrence and cancer migration. The Committee requests an update in the fiscal year 2023 CJ on these efforts and the recent expansion of the SEER program.

Action taken or to be taken

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) is an authoritative source of information on cancer incidence and survival in the United States. As of June 1, 2021, SEER collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 48 percent of the U.S. population. This is an expansion from 35 percent of the population in 2020 and represents more than 850,000 incident cancers reported annually. The expanded coverage increased representation of population subgroups in the United States to include 44.6 percent of African Americans, 69.2 percent of Hispanics, 55.7 percent of American Indians and Alaska Natives, 72.2 percent of Asians, and 73.5 percent of Hawaiian/Pacific Islanders. Overall, the expanded population coverage will allow researchers to better understand how cancer affects different patient subgroups and inform the development of interventions intended to address cancer disparities.

The increased U.S. population coverage was aided by the addition of three new Core SEER Registries in Illinois, New Jersey, and Texas, which submit data annually to the SEER program. Also in 2021, nine Research Support Registries were added to the SEER network to participate in specific activities that include a Virtual Pooled Registry (VPR), Virtual SEER-Linked Biorepository, National Childhood Cancer Registry (NCCR), special research projects and pilots, and linkages with external data partners.

NCI continues its efforts to enhance SEER with the objective of collecting high-quality cancer surveillance data while addressing the challenges of a rapidly evolving cancer care environment. This includes meeting real-world data needs to address the changes in cancer patient diagnosis and disease management, the lack of data collected and shared outside of clinical trials, and treatment guidelines that are based on data that doesn't reflect the diversity of the population. Population level data is critical to meeting these needs and SEER enhancements are expanding the data and methods for population data capture through linkages with external partners that hold key clinical data and using automated methods for data capture that exploit deep learning and natural language processing techniques.

Data traditionally collected by SEER includes demographics, geospatial data, characterization of the tumor at diagnosis, initial course of treatment, and survival. Recent data enhancements include collection of more detailed information on treatments received and capturing both initial and subsequent courses of treatment. Capturing this data will provide important information about patient outcomes from recurrent disease. Previous enhancements included linking pharmacy data to SEER to expand the depth and breadth of information on treatment of oral and infused drugs.

Other recent enhancements include, SEER capturing expanded tumor characteristics such a genomic profiling data, tumor biomarker information, and multigene panel test results for specific cancers (e.g., Oncotype diagnosis for breast cancer). Importantly, SEER is currently integrating data on metastatic disease recurrence by leveraging multiple data sources such as pathology reports, insurance claims, and hospital reports. Finally, longitudinal residential history data is also now being linked to SEER data to minimize loss of follow up data as cancer patients may move from the geographic coverage area of the registry where their initial cancer diagnosis and associated data were originally captured.

An ongoing collaboration between the NCI and the Department of Energy developed automated methods to extract information from pathology reports, saving thousands of hours of human time. These methods are currently being used in six registries and have been shown to be able to automatically extract data from 20 percent of all pathology reports. The use of these methods is being expanded across all registries and are being adapted for use with radiology reports. Information from both types of reports (pathology and radiology) is essential to tracking cancer recurrence, including metastatic disease. In the future, SEER hopes to capture pathology and radiology images, too. The automated extraction of data from pathology reports will help reach the goal of near real-time cancer incidence reporting.

The NCCR is also an important component of the SEER modernization effort. This is a centralized data system for 23 registries across the United States that currently collects information on 77 percent of all childhood cancer patients. NCCR is a component of the Childhood Cancer Data Ecosystem that seeks to link data from various sources, aggregate it, and make it available to the research community.

Telehealth-Based Services for Vulnerable Patients

The COVID–19 pandemic significantly exacerbated the physical, emotional, and mental toll on cancer patients and families. Providing clinical and psychosocial services to address these challenges is an essential component of comprehensive cancer care across a patient's lifespan. Cancer centers across the U.S. quickly pivoted to providing patient support and related health services by telehealth, although the extent to which all patients and families had equitable access to these services and the impact for those who have attended them is unknown. For example, both rural and urban underserved areas disproportionately lack reliable home-based Internet service, creating barriers for patients to access telehealth-based clinical and psychosocial support services. To overcome this, many cancer centers provided technical assistance to patients during the pandemic to support their use of telehealth. The Committee urges NCI to increase its support of research on the delivery and evaluation of telehealth-based clinical and psychosocial services, particularly among vulnerable patients and disadvantaged communities. This enhanced research would lead to evidence-based best practices, so that all patients can benefit from the most effective cancer care at all stages of the disease.

Action taken or to be taken

The National Cancer Institute (NCI) is dedicated to advancing a national telehealth research agenda focused on improving cancer-related care and outcomes across the cancer control continuum in a rapidly changing healthcare, policy, technology, and communication environment. In 2021, NCI released the funding opportunity announcement (FOA) "Centers on Telehealth Research for Cancer-Related Care"[401] that aims to establish three Centers. Funded Centers are expected to generate and disseminate a robust evidence base for patient-centered, sustainable telehealth models of cancer care delivery, fostering innovations to improve cancer care delivery by researching real-time, patient-provider telehealth communication using new tools, research methods, and technologies. Each Center will focus on one overarching cancer-focused telehealth research theme that will frame the Center's scientific activities, leveraging a clinical practice network able to support multiple cancer-focused telehealth research studies. A centerpiece of each Center is the completion of a pragmatic trial that will evaluate the integration of telehealth-delivered cancer care into a real-world clinical environment designed to yield improvements in patient access, quality of care, patient-provider communication, and health outcomes. Centers are expected to disseminate evidence-based approaches to telehealth-focused cancer care to the broader clinical care and cancer control communities. Importantly, this FOA requires that Centers emphasize opportunities to identify and address disparities in access to and receipt of telehealth services and/or cancer-related care among disparate populations. Centers are also expected to build research capacity, collaborate on common data elements, exchange measures and metrics, and disseminate findings, tools, and resources with other funded centers and across the broader clinical care and cancer control research communities. Collectively, the Centers on Telehealth Research for Cancer-Related Care will represent a national initiative at the forefront of cancer-related telehealth research committed to improving access to care, care quality, patient-provider communication, and health outcomes across the cancer control continuum.

In 2021, NCI also released the Notice of Special Interest "Telehealth in Cancer Care"[402] as a companion announcement to the FOA listed above. This Notice highlights NCI's interest in receiving investigator-initiated R01 and R21 grant applications for conducting research on the use of telehealth in cancer-related care. The scope of telehealth research encompassed by this announcement includes synchronous and asynchronous communications and other digital interactions between clinicians and patients (including family members and other caregivers) as well as communications and other digital interactions between

[401] grants.nih.gov/grants/guide/rfa-files/RFA-CA-21-029.html
[402] grants.nih.gov/grants/guide/notice-files/NOT-CA-21-043.html

and among clinicians. The proposed telehealth research can focus on any part of the cancer care continuum (ranging from cancer prevention to end-of-life care) for patients of all age groups in all types of care settings. This research may use either observational or interventional study designs, or a combination of both. NCI encourages research on populations that experience inequities in access to care, have limited access to broadband and digital technologies, have low health and/or digital literacy, and have worse cancer outcomes compared to the general population, especially those accessing care in community oncology practices, including those in rural areas or serving under-served populations. NCI is also strongly encouraging research that examines how telehealth can be implemented without creating or exacerbating health disparities, as well as research that examines how telehealth can be used to address health disparities and promote health equity.

The development of these two FOAs was informed by a 2020 NCI Request for Information (RFI), "Seeking Stakeholder Input on Scientific Gaps and Research Needs Related to Delivery of Cancer-related Care via Telehealth,"[403] intended to identify gaps in the evidence base related to telehealth for cancer care. Topics explored by the RFI included:

- What outcomes should be used to evaluate the delivery of telehealth care, what types of appointments and care delivery models are best suited to telehealth, what influences positive patient-provider communication, and what are additional areas of respondent interest?
- Topics related to access and equity in telehealth delivery models included: who can benefit from telehealth care, is access to telehealth care equitable, and is delivery of telehealth care equitable?

Analysis of the 46 RFI responses showed that scientific gaps and opportunities related to rural populations had the most mentions, including the benefit of telehealth care, and the removal of time and travel burdens, particularly for patients who live in rural and geographically remote areas.

In recognition of the possible benefits of and barriers to telehealth care in rural areas, NCI's FOA "Social and Behavioral Intervention Research to Address Modifiable Risk Factors for Cancer in Rural Populations"[404] solicits applications to develop, adapt, and test individual, community, or multilevel interventions to address modifiable risk factors for cancer in rural populations. One of the specific research challenges to be addressed in this FOA is "health care and technology access barriers that may contribute to rural cancer disparities."

In addition to encouraging and funding research, NCI is focused on sharing the latest evidence and research efforts related to the use of telehealth across the cancer control continuum. The NCI Telehealth and Cancer Care Deliver Webinar Series[405] was established to highlight important topics related to transitioning from in-person health appointments to telehealth services as a way for multidisciplinary care teams to provide uninterrupted care to their patients during the coronavirus disease 2019 (COVID-19) pandemic. While team-based care using telehealth is appealing, it can be challenging to implement. This series highlights some of what is known about telehealth in general and multidisciplinary telehealth services specifically. Implications for telehealth in care delivery across the cancer control continuum are discussed, and challenges and opportunities for value-based, patient-centered approaches are highlighted.

NCI will continue to work closely with agency partners and a wide variety of experts to analyze the current evidence and scale our research efforts accordingly, particularly for underserved, vulnerable and disadvantaged populations, to help ensure effective and equitable use of telehealth for improved access to evidence-based delivery of cancer-related care.

[403] grants.nih.gov/grants/guide/notice-files/NOT-CA-20-080.html
[404] grants.nih.gov/grants/guide/rfa-files/RFA-CA-20-051.html
[405] healthcaredelivery.cancer.gov/cyberseminars/telehealth.html

Tobacco Regulatory Science Program

The Committee supports the Tobacco Regulatory Science Program and encourages NIH to increase funding for research into the understanding of nicotine addiction and to spur the development of better prevention and treatment strategies. Of particular importance is funding for research for effective interventions to help youth and young adults to quit tobacco use or vaping, and to understand the interrelationship between the vaping of tobacco and marijuana. The Committee directs NIDA to conduct interdisciplinary research on this topic with an emphasis on risk perceptions, decision-making and neuroscience.

Action taken or to be taken

The National Institutes of Health (NIH) supports a robust portfolio of research on vaping and other tobacco product use among youth and young adults, including large observational studies aimed at understanding the trajectory of tobacco product and marijuana co-use and their consequences. For example, the National Institute on Drug Abuse (NIDA) funds the Monitoring the Future survey, an annual survey of substance use behaviors and attitudes among 8th, 10th, and 12th graders, and young adults. NIDA also leads the trans-NIH Adolescent Brain Cognitive Development (ABCD) Study, a longitudinal study that is collecting data on nearly 12,000 adolescents beginning at ages 9-10 (the cohort is currently ages 12-15) and extending over a 10-year period, to determine how childhood experiences, including tobacco, marijuana, and other substance exposure, interact to affect brain development and other child health outcomes.

The National Cancer Institute (NCI) continues to support a substantial and diverse portfolio of research to better understand trends in e-cigarette use behavior, and to advance tobacco cessation and prevention among youth. One currently funded study is assessing trajectories of e-cigarette use and how e-cigarette use influences other tobacco product use from adolescence to young adulthood (R01CA239097). The project is also exploring the determinants of co-use of nicotine and tetrahydrocannabinol (THC) via vaping devices and assessing self-reported respiratory conditions and symptoms. Another NCI-supported longitudinal study among adolescents is examining what environmental factors contribute to progression from e-cigarette experimentation to regular use, and how adolescents' e-cigarette use influences other tobacco use, particularly conventional cigarette smoking (R01CA202262).

The National Heart, Lung, and Blood Institute (NHLBI) supports research to understand how e-cigarette use affects heart and lung health. For example, NHLBI's Lung Health Cohort is an observational study of young adults designed to better understand predictors of lung health, including whether chronic vaping is associated with lung disease or reduced lung function (U01HL146408).[406] A recent series of NHLBI-led state-of-the-science workshops suggest that e-cigarettes and inhaled nicotine have various potentially deleterious effects on both the heart and lungs.[407] NHLBI also has a robust portfolio of basic, clinical, and population research to further address these questions. For example, ongoing NHLBI-funded studies are examining the cardiovascular and pulmonary effects of chronic e-cigarette exposure in model systems and in humans (R01HL144258, R01HL139348, R01HL139358).

NIH also supports research aimed at developing interventions to prevent tobacco product use. In 2020, NIH released a request for applications (RFA) to test the effectiveness of interventions to prevent initiation and/or escalation of electronic nicotine delivery systems (ENDS)/e-cigarette use among

[406] Study Protocol for a National Cohort of Adults Focused on Respiratory Health: the American Lung Association Lung Health Cohort (ALA-LHC) Study
[407] E-cigarettes and Cardiopulmonary Health

adolescents, as well as research on the impact of tobacco control policies on adolescent ENDS/e-cigarette use behavior (RFA-DA-21-009).

Complementing prevention intervention research investments, NCI leads the Smokefree.gov Initiative[408], a suite of online cessation resources for all ages and all types of tobacco use, with the SmokefreeTeen website developed specifically to support cessation among teens and young adults. NCI's Smokefree.gov Initiative has a long-standing partnership with the U.S. Food and Drug Administration's (FDA) Center for Tobacco Products to provide digital cessation resources in support of FDA's youth and adult public education campaigns. In 2019, Smokefree.gov launched a new vaping cessation content collection on the SmokefreeTeen website, to address the growing epidemic of youth vaping and unmet needs around cessation support.[409] This collection, developed in support of FDA's The Real Cost e-cigarette prevention campaign, provides information and support to teens on how to quit vaping and deal with nicotine addiction and cravings. In 2020, an interactive quit plan builder tool was added to the content collection to guide teens through a series of steps to create a personalized plan for quitting vaping.[410]

NIDA supports research on behavioral and pharmacologic treatments for smoking and e-cigarette cessation. One study is assessing the use of mobile peer-driven tools for adolescents (R34DA050992-01A1) and a phase II study that assessed the usability and feasibility of a mobile app aimed at facilitating tobacco smoking cessation and preventing smoking initiation in young adults (NCT04009590). A NIDA-funded trial examining the efficacy and safety of varenicline for smoking cessation among adolescents and young adults found that while varenicline was well tolerated and did not result in serious adverse events, it did not improve measures of abstinence at the end of treatment.[411,412] The study also found a high prevalence of cannabis or alcohol and tobacco co-use among participants, highlighting the need for research that targets tobacco and substance co-use.[413] To this end, NIDA is exploring the effects of comorbid cannabis and tobacco use on adolescent neurodevelopment (R21DA047953); the perceptions, patterns, and symptoms of vaping nicotine and cannabis in youth and young adults (R21DA051943, R01DA051157); and a behavioral intervention to treat cannabis and tobacco co-use in adults (R34DA051051).

NIH also supports a broad portfolio of tobacco research through the Tobacco Regulatory Science Program (TRSP), a collaborative research partnership with the FDA Center for Tobacco Products.[414] Through TRSP, NIH supports a comprehensive research agenda to inform FDA's regulation of tobacco products. The program generates important research on tobacco product chemistry and engineering, toxicity, addiction, health effects, use behavior, communication, and marketing of tobacco products, as well as understanding the potential impact of FDA regulatory actions. Additionally, NIH supports the Population Assessment of Tobacco and Health (PATH) Study,[415] a national longitudinal cohort study examining the relationship between tobacco product—including e-cigarette—use and health, in partnership with the FDA.

[408] smokefree.gov/
[409] teen.smokefree.gov/quit-vaping
[410] teen.smokefree.gov/vaping-quit-plan
[411] Efficacy and Safety of Varenicline for Adolescent Smoking Cessation: A Randomized Clinical Trial
[412] High-dose and low-dose varenicline for smoking cessation in adolescents: a randomized, placebo-controlled trial
[413] Cannabis and Alcohol Co-Use in a Smoking Cessation Pharmacotherapy Trial for Adolescents and Emerging Adults
[414] Tobacco Regulatory Science Program
[415] Population Assessment of Tobacco and Health

Trans-NIH Pediatric Research Consortium

The Committee is aware of the Trans-NIH Pediatric Research Consortium (N–PeRC) that was established in 2018 to better coordinate and support 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 as to multi-Institute or Center pediatric research projects implemented as a result of N–PeRC and projects in the planning stage. Additionally, the Committee requests a report in the fiscal year 2023 Congressional Budget Justification on how N–PeRC plans to support 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 2020, NIH spent more than $5.3 billion in this area.[416] The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) provides approximately 17 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 ICs.[417] Nearly all NIH ICs and offices have appointed senior level representatives to N-PeRC. As an initial objective, the group identified areas of common interest and potential collaboration. Among the issues important across ICs are those faced by adolescents as they transition to adult health care, pediatric medical device development, and pediatric research workforce training.

N-PeRC leaders held a scientific workshop in September 2020 to identify research gaps and opportunities that arise when adolescents with chronic conditions transition to adult health care. These transitions can raise research questions that are applicable across many conditions, such as defining outcome measures for successful transition; consent and shared medical decision-making; use of technologies and telehealth; and, for those with mental illness, increasing youth engagement in personalized recovery-oriented services. The virtual environment and free videocast enabled more than 900 participants to view the Lost in Transition workshop, and a workshop summary is publicly available.[418] N-PeRC efforts to support research gaps in this area continued with a related Notice of Special Interest (NOSI) for grant applications, released in June 2021 and initially supported by eight NIH Institutes, Centers, and Offices. The NOSI encourages applications in high-priority research areas related to pediatric health care transition (HCT) for youth with chronic physical/medical conditions or intellectual or developmental disabilities, with the ultimate goal of improving care quality and patient and family outcomes during and after HCTs.[419]

Support for pediatric training and career development programs spans NIH ICs. N-PeRC conducted a preliminary analysis to better understand the support for such programs across NIH. The analysis showed that nearly every IC invests in pediatric training and career development. A publication is in preparation to educate and inform the research community about these funding opportunities.

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

[416] report.nih.gov/funding/categorical-spending#/
[417] www.nichd.nih.gov/research/supported/nperc
[418] web.cvent.com/event/1861c38c-e953-4ffa-a0f1-1688840fb295/summary
[419] grants.nih.gov/grants/guide/notice-files/NOT-HD-21-027.html

considerations also arise when working with pediatric populations. Responding to trans-NIH interest in improving and stimulating development of pediatric medical devices, N-PeRC recently formed a Pediatric Medical Devices (PMD) subgroup. The group's initial task is to undertake a landscape analysis to inventory current NIH efforts in this area. This analysis will help identify research gaps that could benefit from collaboration and coordination. In addition, the group plans to cultivate a public webpage to serve as a central location for stakeholders to find information and relevant resources about NIH's PMD research, including funding opportunities and funded studies.

N-PeRC has 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, to address pediatric issues related to COVID-19. The working group facilitated supplemental funding for four projects in FY 2020 and 18 projects in FY 2021. The FY 2021 funding (approximately $4.8 million total) included support from seven ICs with matching funds from the NIH Office of the Director. Many of these supplements enable current and ongoing projects to pivot to address urgent COVID-19 research needs, including studies of the physical, mental, and behavioral health impacts of COVID-19 on children. For example, one study will assess potential learning loss as a result of COVID-19 restrictions and school closures in children with and without a heightened risk of developing reading difficulties. Another study will examine effects of an intervention to promote adolescent mental health among a low-income, urban community as well as assess longitudinal risk and protective factors that shape adolescent mental health during the pandemic. Recognizing that the pandemic exacerbated effects of poverty and systemic racism on disparities in early child development, another study will test the ability of a preventive intervention to promote parent-child relational health and child development and foster resilience in a group of Latinx and Black families with young children.

The N-PeRC COVID-19 subgroup also aided other NIH-wide research efforts, persistently advocating to include children in Rapid Acceleration of Diagnostics (RADx)[420] programs and the REsearching COVID to Enhance Recovery (RECOVER) effort.[421] N-PeRC members served as application reviewers for these efforts and provided expertise to inform protocol development and scientific program management. In particular, the RADx-Radical[SM] 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),[422] a cooperative NIH effort that aligns multiple cohort studies to improve understanding of the effects of SARS-CoV-2 infection and MIS-C on children. Subject to available appropriations, this program aims to study the immediate and long-term health effects of MIS-C on children up to 5 years after diagnosis.

During the next 3 years, N-PeRC plans to continue efforts described above as well as embark on new areas of research collaboration. A publication outlining the support available across NIH to develop and grow the pediatric research workforce will help educate potential applicants and facilitate diversifying the field of pediatric researchers. Led by the PMD subgroup, N-PeRC will consider ways to enhance NIH support for pediatric device development. The COVID-19 pandemic continues to significantly impact children in the United States and 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. A

[420] www.nih.gov/research-training/medical-research-initiatives/radx
[421] recovercovid.org
[422] caring4kidswithcovid.nih.gov/research.html

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.

Valley Fever

The Committee is encouraged by NIAID's recent announcement to establish collaborative coccidioidomycosis (Valley Fever) research centers. To guide this continuing work, the Committee requests, within 180 days of enactment of this Act, a 10-year strategic plan from NIH with the objective of producing a Valley Fever vaccine by 2031. This plan should include, but not be limited to: (1) a statement of science on Valley Fever, including disease burden in the U.S.; (2) identifiable and achievable benchmarks for Valley Fever vaccine development, including vaccine market viability; (3) identifying or developing funding priorities and opportunities that actively support the development of a Valley Fever vaccine; and (4) any recommendations to Congress on policy reforms designed to help develop a Valley Fever vaccine. Furthermore, the Committee directs NIAID to convene a stakeholder and researchers conference in an endemic region to help guide the strategic plan's development. The Committee requests an update in the fiscal year 2023 Congressional Budget Justification on progress towards achieving goals in this strategic plan.

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic, translational, and clinical research to better understand Valley fever, an infection caused by Coccidioides fungi, and to develop vaccines, diagnostics, and therapeutics to combat it. NIAID support for Valley fever research includes targeted program announcements and funding opportunities. NIAID also plans to engage researchers and other stakeholders as appropriate while we continue to develop a Strategic Plan to support the advancement of a Valley fever vaccine.

NIAID pursues research to prevent Valley fever, including through support for basic research that may inform the development of vaccines. NIAID is supporting the development of two promising Valley fever vaccine approaches: a live, attenuated vaccine candidate and an adjuvanted recombinant protein vaccine candidate. In March 2019, NIAID hosted a workshop entitled Vaccine Strategies for Endemic Fungal Pathogens to identify scientific gaps and discuss strategies to develop a Valley fever vaccine. The workshop included community members and Valley fever researchers, including those new to the field. As a result of the discussions at this workshop, in fiscal year (FY) 2022, NIAID plans to establish Coccidioidomycosis Collaborative Research Centers, a network of research centers to conduct translational and clinical research for improved diagnosis, treatment, and prevention of Valley fever, including through the development of vaccine candidates against Coccidioides.

NIAID also is supporting the development of improved diagnostics for Valley fever. This includes characterization of proteins from Coccidioides that may be targets for the development of a diagnostic that could identify multiple Coccidioides species. Improved diagnostics could help to better understand the rates of disease in the community in order to identify populations more effectively for testing and use of vaccines. NIAID encourages researchers to submit applications in response to the Program Announcement, Advancing Development of Rapid Fungal Diagnostics, which aims to support the development of rapid, sensitive, specific, and cost-effective diagnostics for primary healthcare settings.[423]

In addition, NIAID is supporting research on Coccidioides life cycle and disease prevalence; pathogenesis and the molecular events that contribute to infection; host response to infection; and Coccidioides transmission, natural history, and environmental factors. Improved understanding of these topics will inform the development of Valley fever vaccines and may help to identify populations that would benefit most from a vaccine. In addition, NIAID is working to support the development of improved therapeutics for Valley fever for those who currently are infected. NIAID encourages researchers to submit

[423] grants.nih.gov/grants/guide/pa-files/PA-19-081.html

applications in response to the Program Announcement, Novel Approaches to Understand, Prevent, Treat, and Diagnose Coccidioidomycosis (Valley Fever) and Other Select Endemic Fungal Infections.[424]

Through its Vaccine and Treatment Evaluation Units, NIAID supports an observational clinical study to provide data on the prevalence of Valley fever in endemic areas among persons with community acquired pneumonia, the clinical course of disease, and the response to antifungal treatment compared to the standard of care. As of September 2021, this study has enrolled 393 patients at six sites in California and Arizona. NIAID anticipates this study will continue to increase public awareness of the disease, support early diagnostic testing and treatment, and may also identify factors that impact disease outcomes as well as specific regions or populations that would benefit most from a safe and effective vaccine.

NIAID also currently is leading a Valley fever observational cohort study. This research aims to understand mechanisms of the disease and inform the development of novel treatment strategies. This study has uncovered novel genetic variants of *Coccidioides* that increase susceptibility to disseminated coccidioidomycosis, a more severe form of the disease where infection spreads from the lungs to other tissues. Enrollment for this study remains open, and 142 participants are enrolled.

NIAID will continue to support a diverse portfolio of basic, translational, and clinical Valley fever research in addition to advancing the development of candidate vaccines and the NIAID Valley fever vaccine Strategic Plan.

[424] grants.nih.gov/grants/guide/pa-files/PA-19-082.html; grants.nih.gov/grants/guide/pa-files/PA-19-083.html