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3-D Retina Organoid Challenge

The Committee directs NIH to provide an update on the 3-D Retina Organoid Challenge authorized in the Consolidated Appropriations Act, 2016.

Action taken or to be taken:

The 3D-Retinal Organoid Challenge (3D-ROC)¹, is a two-part challenge conducted by the National Eye Institute (NEI) in order to accelerate cures for retinal disease. Robust disease models and appropriate platforms to screen and test potential treatments are needed. Organoids are miniature 3-D organs grown from stem cells in culture dishes, and have already been developed for liver, pancreas, gut, and other tissues for disease modelling and drug development for a number of other conditions. The development of an organoid model of the retina could mark a significant development for combating retinal disease.

The first part of the competition, launched in May 2017, focused on ideation—solvers were challenged to propose creative protocols that could replicate the structure and function of the human retina. Participants were encouraged to form interdisciplinary teams and integrate bioengineering, bioprinting, microfluidics, materials science, and other areas within vision biology to propose creative, outside-the-box ideas. NEI received 13 submissions involving more than 50 scientists and industry partners with expertise ranging from stem cell biology, tissue imaging, to retinal vascularization. Proposals were evaluated based on innovation, feasibility, solutions to scientific limitations, and the ability to model diseases or test therapies. The \$90,000 prize was awarded to a team at the University of Maryland, Baltimore County.

The second part of 3D-ROC, launched in November 2017 with a \$1 million prize, will yield organoid prototypes. Participants must submit data showing that their systems meet specified scientific criteria. In addition to the basic criteria, submissions will be judged on recapitulating normal retinal biology and on additional complexity, such as the duration of tissue survival and the potential for adoption by the broader research community. Inventors will retain their intellectual property and are encouraged to translate their work into commercially viable products. If funding allows, the prizes for part 2 will be awarded at two different checkpoints: an interim award in November 2018, will award up to \$100,000 to each of the six different teams, and the final prize will award the remainder of the \$1 million prize in May 2020 up to three winners. NEI has worked with over 10 industry partners, to provide additional support and incentives for solvers, such as seed money, pilot grants, discounts, or in-kind services. Upon completion of the challenge competition, NEI is planning to leverage retinal organoids to accelerate the development of therapeutics for retinal diseases.

¹ <https://nei.nih.gov/3droc>

Academic Research Enhancement Award (AREA) Program

The Committee believes that biomedical discoveries can occur anywhere, and continues to support programs that foster biomedical research and opportunities for students at institutions who may not receive significant NIH funding. The Committee continues its long-standing support of the IDeA program. However, the Committee notes that many institutions that may benefit from the IDeA program are ineligible because they reside in States that are not IDeA States. The Committee encourages NIH to enhance support for the AREA program and is urged to develop ways to improve ties between institutions that receive significant NIH funding and AREA-eligible institutions.

Action taken or to be taken:

NIH appreciates the Committee's support for the Institutional Development Award (IDeA) program and recognition of the importance of the R15/AREA program to support meritorious research, expose students to research, and enhance the research environment at institutions not receiving significant NIH support. NIH will continue to support the IDeA program and improve ties between NIH-funded institutions through the following initiatives:

- NIH staff present at national, professional meetings on topics ranging from grant application writing to time management tips for teaching and research. Of note, this includes the Council on Undergraduate Research, which seeks to enhance and provide undergraduate research opportunities for faculty and students at all institutions serving undergraduate students.
- NIH expanded and redesigned the AREA website for easier access to the most up-to-date information on the program, as many AREA investigators may lack the resources to attend meetings in person. Social media is also used to educate applicants about the AREA program and the NIH grants processes.
- The NIH AREA Program Advisory Committee, with staff from each Institute and Center, regularly discuss how best to reach out to the AREA-eligible community and to meet their needs. The NIH AREA Director regularly addresses questions from eligible investigators and will visit an AREA university to directly discuss needs identified by leadership, professors, administrators, and students.
- NIH organizes and participates in regional meetings across the country at least once per year to discuss preparing grant applications and developing undergraduate research. Participants learn how to prepare AREA R15 applications; receive responses to questions about collaborations, budgets, and scope of projects; and can join networking events held for investigators from AREA institutions.

NIH will continue to ensure the success of these programs. NIH aims to build active biomedical research environments in IDeA states and improve access to modern, state-of-the-art biomedical research for students and researchers. Collaborations will be encouraged among IDeA research resource centers when appropriate, as well as between research intensive institutions and AREA

universities. This will allow NIH to achieve research goals while preserving the goals of the R15/AREA program. For example, investigators could use R15 funds for equipment or involve collaborators at research intensive institutions.

By taking steps such as these, NIH will continue supporting activities across the nation to enhance the competitiveness of AREA-eligible investigators for research. Importantly, NIH will also provide opportunities through these programs for talented undergraduate students to participate in research training and careers in the biomedical sciences.

Addressing Hispanic Research Issues

The Committee is encouraged by NIH's efforts seeking to address health disparity research issues impacting the U.S. Hispanic population across various ICs. The Committee recognizes that the longitudinal Study of Latino Health research program being conducted by NHLBI, as well as the collaborative research efforts at NIMHD, are providing important progress in measuring more precisely the risk factors and outcomes and determining effective interventions among U.S. Hispanics. The Committee urges NIH to fill out key gaps in its translational research portfolio to include children and youth and reproductive-age young women, as well as older populations, in high-density areas to allow for broader research cohorts.

Action taken or to be taken:

Health disparities among Hispanics or Latinos in the U.S. are pronounced. For example, Hispanics or Latinos are more likely to die from diabetes and chronic liver disease than Whites. Hispanics or Latinos experience health disparities that are influenced by a complex interplay of social, environmental, and genetic factors including poverty, access to health care, and behavior. Hispanics or Latinos have the highest uninsured rate, almost three times the rate of Whites, making access to medical care including preventive care difficult or impossible, ultimately resulting in poor health outcomes.

NIH conducts research to increase understanding of the underlying pathways of health disparities among Hispanic or Latino populations. This knowledge can be used to design tailored treatment and behavioral interventions to reduce health disparities. For example, one National Institute on Minority Health and Health Disparities (NIMHD) grant brings together academic researchers and Hispanic or Latino community partners to test innovative and culturally appropriate interventions to prevent type 2 diabetes. Another NIMHD grant is studying the effect of acculturation among pregnant Mexican American women. The research measures the body mass composition of newborns and infants to determine any association with the increasing rates of obesity among Mexican Americans across generations. One study focused on improving asthma care among Hispanic or Latino children, and understanding the influence of social determinants of health, will link and examine data on asthma care for Hispanic or Latino children across multiple states.

Program and research activities at NIH address the health of Hispanics or Latinos across the life course, and encompass the full spectrum of the scientific continuum to facilitate the implementation of evidence-based practice and policy to improve Hispanic health. NIMHD supports research infrastructure and capacity building through the Endowment and the Research Centers in Minority Institutions programs at academic institutions serving Hispanic or Latino populations, to conduct innovative clinical and translational research in population health and health disparities, and train future Hispanic or Latino leaders in the sciences and medicine through programs that integrate multidisciplinary teams from health and human services, engineering, computer sciences, medicine, and health. Examples of NIMHD translational research to address Hispanic or Latino health include studies that use mobile technology to deliver personalized information about clinical trials, as well as studies with stroke patients that monitor blood pressure and provide tailored education messages to understand stroke risk factors to prevent a secondary stroke among Hispanics or Latinos.

NIMHD and the National Heart, Lung, and Blood Institute (NHLBI), continue to collaborate on research such as the Hispanic or Latino Community Health Study/Study of Latinos

(HCHS/SOL). The NHLBI-initiated HCHS/SOL study has served as a critical foundation to better understand the prevalence of chronic diseases, the associated risk or protective factors, and the relationship to changes in health in a cohort of Hispanics or Latinos. More than 16,000 locally representative participants, including 3,200 women of childbearing age, were recruited and observed from four U.S. sites. Observational and genetic data from the study have furthered our understanding of how health before pregnancy contributes to pregnancy-related complications as well as how genetics contribute to chronic conditions including asthma and type 2 diabetes in the Hispanic or Latino population. Additionally, the Hispanic or Latino community is represented in several other NHLBI studies. The Multi-Ethnic Study of Atherosclerosis (MESA) measures progression of subclinical cardiovascular disease and identifies risk factors that contribute to atherosclerosis in participants that included 22 percent Hispanic men and women up to 84 years old at enrollment. Also, Hispanic women in their first pregnancy make up 18 percent of the Nulliparous Pregnancy Outcomes Study-Monitoring Mothers-to-Be (nuMoM2b) and subsequent nuMoM2b Heart Health cohort study. The study's goal is to identify factors that may contribute to problems during pregnancy and later problems relating to cardiovascular health.

Adolescent and Young Adult Brain Development

The Committee recognizes and supports the NIH Adolescent Brain and Cognitive Development (ABCD) Study. The Committee recognizes that an individual's brain continues to develop into his or her mid- twenties. However, little is known about the dramatic brain development that takes place during adolescence and how the various experiences people are exposed to during this time interact with each other and their biology to affect brain development and, ultimately, social, behavioral, health, and other outcomes. The ABCD study addresses this knowledge gap.

Action taken or to be taken:

Adolescence is a period of intense brain and cognitive development. During this time, one's environments, experiences, and exposures shape brain structure and function, and ultimately adult identity. Brain research, particularly in the last decade, has opened new windows to understanding the adolescent brain, but there is much we still do not know about the normal trajectory of brain development during adolescence and the many experiences that may enhance or disrupt it, such as extracurricular activities (e.g., music, sports), concussions, unhealthy sleep patterns, and substance use.

To gain a better understanding of brain, cognitive, social, and emotional trajectories from childhood through adolescence, the National Institute on Drug Abuse (NIDA), in collaboration with the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Cancer Institute (NCI), the *Eunice Kennedy Shriver* National Institute on Child Health and Human Development (NICHD), the National Institute of Mental Health (NIMH), the National Institute of Neurological Diseases and Stroke (NINDS), the National Institute on Minority Health and Health Disparities (NIMHD), the Office of Behavioral and Social Sciences Research (OBSSR), the Office of Research on Women's Health (ORWH) and the CDC Division of Adolescent and School Health, is funding the landmark Adolescent Brain Cognitive Development (ABCD) Study², a multi-site, longitudinal investigation of 10,000 children from ages nine and ten into early adulthood.

The ABCD Study launched recruitment at 21 research sites across the country in September 2016. As of October 2017, 5,433 youth have enrolled in the study and have undergone baseline testing, including structural and functional brain imaging; physical and mental health questionnaires; behavioral and neurocognitive testing; and the collection of biospecimens for genetic, epigenetic, hormonal, environmental exposure, and substance use analysis. More than 2,100 youth have completed their six-month follow-up phone call, collecting recent substance use and some mental health information, and one-year follow-up visits have just begun.

To enrich the value of the study, ABCD is releasing anonymized data to the research community in an open science model to allow scientists from all over the world to pool resources to rapidly analyze the data, expanding the scientific questions that will be answered. Unprocessed neuroimaging data is already available, and regularly updated as more data is acquired. Curated

² <http://abcdstudy.org/index.html>

data, including all assessments and imaging data, for the first 4,500 participants is expected to be released in early 2018 and will be updated annually. The actionable information coming out of this study will be a foundation upon which to develop and refine substance use prevention and treatment as well as other health promotion interventions that are rooted in a deep understanding of the neurobiological and psychosocial factors that influence adolescent health and wellness to optimize the wellbeing and success of our Nation's children.

Adolescent Brain Development (ABCD)

The Committee recognizes and supports the ABCD study. This study will help the understanding of the dramatic brain development that takes place during adolescence and how the various experiences people are exposed to during this time interact with each other and their biology to affect brain development and, ultimately, social, behavioral, health, and other outcomes. The Committee requests an update be included in the fiscal year 2019 CJ on the ABCD study.

Action taken or to be taken:

Adolescence is a period of intense brain and cognitive development. During this time, one's environments, experiences, and exposures shape brain structure and function, and ultimately adult identity. Brain research, particularly in the last decade, has opened new windows to understanding the adolescent brain, but there is much we still do not know about the normal trajectory of brain development during adolescence and the many experiences that may enhance or disrupt it, such as extracurricular activities (e.g., music, sports), concussions, unhealthy sleep patterns, and substance use.

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To enrich the value of the study, ABCD is releasing anonymized data to the research community in an open science model to allow scientists from all over the world to pool resources to rapidly analyze the data, expanding the scientific questions that will be answered. Unprocessed neuroimaging data is already available and regularly updated as more data is acquired. Curated data, including all assessments and imaging data, for the first 4,500 participants is expected to be released in early 2018 and will be updated annually. The actionable information coming out of this study will be a foundation upon which to develop and refine substance use prevention and

³ <http://abcdstudy.org/index.html>

treatment as well as other health promotion interventions that are rooted in a deep understanding of the neurobiological and psychosocial factors that influence adolescent health and wellness to optimize the wellbeing and success of our Nation's children.

Adolescents and Medication-Assisted Treatment

The Committee applauds the ongoing coordinated efforts at NIH to understand and address substance use and substance use disorders among adolescents and young adults as a specific population. As part of those efforts, the Committee also encourages NIH to examine the effectiveness of medication assisted treatment in adolescents struggling with substance use disorder, and identify any barriers to treatment as well as potential unintended consequences.

Action taken or to be taken:

Adolescence is a period of significant vulnerability for substance use and substance use disorders. Early use of addictive substances is one of the strongest predictors of future substance use problems. NIH funds a broad portfolio of research to understand the unique characteristics of the adolescent brain that underlie this vulnerability, to develop improved strategies to prevent and treatment adolescent substance use disorders (SUD), and to improve the implementation of evidence based prevention and treatment strategies to ensure that scientific advancements translate to improvements in adolescent health. Research is a key element in the Department of Health and Human Service's 5-point strategy to fight the opioid crisis. Some examples include:

*The Adolescent Brain Cognitive Development (ABCD) Study*⁴. A trans-NIH coalition, in partnership with CDC, is funding this multi-site, longitudinal investigation of 10,000 children from ages nine and ten into early adulthood. The information coming out of this study will be a foundation upon which to develop and refine substance use prevention and treatment as well as other health promotion interventions that are rooted in a deep understanding of the neurobiological and psychosocial factors that influence adolescent health and wellness to optimize the wellbeing and success of our Nation's children. The ABCD Study launched recruitment at 21 research sites across the country in September 2016. As of October 2017, 5,433 youth have enrolled in the study and have undergone baseline testing.

NIDA's Monitoring the Future (MTF) epidemiological study measuring drug, alcohol, and tobacco use and related attitudes among 8th, 10th, and 12th grade students nationwide.

Fostering Healthy Mental, Emotional, and Behavioral Development Among Children and Youth Study. This consensus study, funded by NIH and conducted by the National Academies of Sciences, Engineering, and Medicine will inform future research directions related to mental, emotional and behavioral health among children and adolescents.

NIDA's Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS) program is working to improve prevention and treatment of SUD among criminal justice involved youth. The JJ-TRIALS cooperative was established in 2013 and is composed of six research centers and one coordinating center. The main study is a randomized trial that involves 36 sites in seven states and is testing the effectiveness of two implementation strategies for promoting system-wide improvements in SUD prevention and treatment services.⁵

⁴ <http://abcdstudy.org/index.html>

⁵ Knight DK, Belenko S, Wiley T, et al. Juvenile Justice—Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS): a cluster randomized trial targeting system-wide improvement in substance use services. *Implementation Science* : IS 2016;11:57

JJ-TRIALS has led to the development of the Juvenile Justice Behavioral Health Services Cascade, a framework for measurement of unmet substance use treatment needs that can be used to identify services delivery needs and develop strategies to address them.⁶

The Environmental influences on Child Health Outcomes (ECHO) is a seven-year initiative to understand the effects of environmental exposures, including drugs and alcohol, on child health and development.

The trans-NIH Childhood Screening Scientific Interest Group (SIG) coordinates research activities related to childhood screening including screening for substance use and related health consequences.

NIDA's clinician education and outreach program, NIDAMED. In July of 2017, NIDAMED released the clinician training tool “Adolescent Substance Use and Rx Drug Misuse Continuing Medical Education (CME)” that educates clinicians on how to address adolescent substance use from prevention through specialty treatment, and on the use of buprenorphine for the treatment of OUD in adolescents. As of October 2017, 1099 clinicians had completed the CME.

These studies and activities, among many others, demonstrate NIDA's continuing commitment to understanding and addressing substance use in adolescents and the effectiveness of medication assisted treatment, especially at this critical juncture in the nation's opioid crisis.

⁶ Belenko S, Knight D, Wasserman GA, et al. The Juvenile Justice Behavioral Health Services Cascade: A new framework for measuring unmet substance use treatment services needs among adolescent offenders. *Journal of Substance Abuse Treatment*;74:80-91.

Adolescents and Young Adults

The Committee encourages an NIH-wide emphasis on understanding and addressing substance use and substance use disorders among adolescents and young adults as a specific population. The Committee encourages NIH to identify and coordinate its efforts in this area and provide an update in the fiscal year 2019 Congressional Justification on these actions.

Action taken or to be taken:

Adolescence is a period of significant vulnerability for substance use and substance use disorders. Early use of addictive substances is one of the strongest predictors of future substance use problems. NIH funds a broad portfolio of research to understand the unique characteristics of the adolescent brain that underlie this vulnerability, to develop improved strategies to prevent and treatment adolescent substance use disorders (SUD), and to improve the implementation of evidence based prevention and treatment strategies to ensure that scientific advancements translate to improvements in adolescent health. Some examples include:

*The Adolescent Brain Cognitive Development (ABCD) Study*⁷. A trans-NIH coalition, in partnership with the Centers for Disease Control and Prevention, is funding this multi-site, longitudinal investigation of 10,000 children from ages nine and ten into early adulthood. The information coming out of this study will be a foundation upon which to develop and refine substance use prevention and treatment as well as other health promotion interventions that are rooted in a deep understanding of the neurobiological and psychosocial factors that influence adolescent health and wellness to optimize the wellbeing and success of our Nation's children. The ABCD Study launched recruitment at 21 research sites across the country in September 2016. As of October 2017, 5,433 youth have enrolled in the study and have undergone baseline testing.

The National Institute on Drug Abuse's (NIDA) Monitoring the Future (MTF) epidemiological study is measuring drug, alcohol, and tobacco use and related attitudes among 8th, 10th, and 12th grade students nationwide.

Fostering Healthy Mental, Emotional, and Behavioral Development Among Children and Youth Study. This consensus study, funded by NIH and conducted by the National Academies of Sciences, Engineering, and Medicine will inform future research directions related to mental, emotional, and behavioral health among children and adolescents.

NIDA's Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS) program is working to improve prevention and treatment of SUD among criminal justice involved youth. The JJ-TRIALS cooperative was established in 2013 and is composed of six research centers and one coordinating center. The main study is a randomized trial that involves 36 sites in seven states and is testing the effectiveness of two implementation strategies for promoting system-wide improvements in SUD prevention and treatment services.⁸

⁷ <http://abcdstudy.org/index.html>

⁸ Knight DK, Belenko S, Wiley T, et al. Juvenile Justice—Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS): a cluster randomized trial targeting system-wide improvement in substance use services. *Implementation Science* : IS 2016;11:57

JJ-TRIALS has led to the development of the Juvenile Justice Behavioral Health Services Cascade, a framework for measurement of unmet substance use treatment needs that can be used to identify services delivery needs and develop strategies to address them.⁹

The Environmental influences on Child Health Outcomes (ECHO) program, run centrally within the NIH Office of the Director, is a seven-year initiative to understand the effects of environmental exposures, including drugs and alcohol, on child health and development. ECHO also includes the IDeA States Pediatric Clinical Trials Network for supporting intervention studies of promising approaches among rural and underserved children.

The trans-NIH Childhood Screening Scientific Interest Group (SIG) coordinates research activities related to childhood screening including screening for substance use and related health consequences.

NIDA's clinician education and outreach program, NIDAMED. In July of 2017, NIDAMED released the clinician training tool “Adolescent Substance Use and Rx Drug Misuse Continuing Medical Education (CME)” that educates clinicians on how to address adolescent substance use from prevention through specialty treatment, and on the use of buprenorphine for the treatment of opioid use disorder in adolescents. As of October 2017, 1,099 clinicians had completed the CME.

⁹ Belenko S, Knight D, Wasserman GA, et al. The Juvenile Justice Behavioral Health Services Cascade: A new framework for measuring unmet substance use treatment services needs among adolescent offenders. *Journal of Substance Abuse Treatment*;74:80-91.

African American Males and Mental Health

The Committee is concerned with the prevalence of mental health issues which go undiagnosed, especially in African American males. Despite developments to diagnose and treat conditions, stigma allows many to go without the help that is needed. The Committee encourages the NIMH to work collaboratively with community partners to develop treatments for the populations that are in need.

Action taken or to be taken:

African American men experience a high rate of mental health issues, which often remain undiagnosed for several reasons including lack of understanding about mental health, lack of access to mental health services, lack of provider referral for mental health care or reluctance to seek mental health services, stigma associated with mental health, or cultural influences. African Americans have a higher rate of severe chronic and disabling mental health conditions compared to Whites. The most common forms of mental health conditions among African American men are major depression, suicide, and posttraumatic stress disorder (PTSD). Mental health disorders in African American men are sometimes a result of exposure to violence, stress, racism, discrimination, socioeconomic status, and some medical conditions, which if left untreated, could lead to incarceration, homelessness, substance abuse, or suicide.

NIH conducts research and outreach activities on mental health issues affecting African American men. The National Institute on Minority Health and Health Disparities (NIMHD) and the National Institute of Mental Health (NIMH) work to advance NIH's activities to raise awareness about mental health disparities and to address the mental health needs of African American men, through collaborations with community organizations, as well as mental health professional and advocacy groups. For example, NIMHD supports the Men of Color Health Awareness (MOCHA) Moving Forward program, a community-based participatory research collaboration between a university, local YMCA, and state Department of Public Health to address the physical, mental, social, and spiritual needs of African American men. The program examines strategies to lower stress levels and risk of chronic diseases in African American men, and includes an aerobic exercise program and a discussion forum on topics such as stress, violence, depression, and substance abuse.

NIMH funds studies that focus on advancing stigma-reduction interventions that are designed to improve physical and mental health outcomes among African American men confronted with HIV-testing and prevention stigma. NIMH also is funding a study that examines a community partnership approach to address major depression. Another NIMH-funded project is looking at a collaborative care intervention that uses a trauma-informed approach to address PTSD in an African American patient population in New Orleans. In 2016, NIMHD and NIMH co-hosted a Twitter Chat for National Men's Health Week. NIMHD is also working with Omega Psi Phi Fraternity, Inc. to promote national dialogue around mental health among African American men. NIMHD and NIMH collaborated to develop the Brother You're on My Mind Toolkit of materials on depression and stress for distribution within the African American community via Omega Psi Phi chapters and other community-based organizations. NIH will continue to conduct research and increase awareness about mental health disorders among African American men through its programs.

Age-Related Macular Degeneration (AMD)

The Committee recognizes NEI-funded research in which combinations of FDA-approved drugs used to treat a variety of conditions from lowering blood pressure to treating prostate disease may eventually offer an option for preventing vision loss associated with degeneration of cells in the retina from AMD and Stargardt disease, the most common form of inherited juvenile macular degeneration. Discovering new uses for these already-approved drugs-which act on G protein coupled receptors, a family of signaling proteins in various cell types throughout the body provides the quickest possible transition from bench to bedside.

Action taken or to be taken:

The National Eye Institute (NEI) is committed to finding ways to leverage knowledge about existing FDA-approved drugs and the pathways that they target to find new and accelerated therapy options for patients. One of the most impactful recent advances in vision care is the introduction of a class of drugs known as anti-Vascular Endothelial Growth Factor (VEGF) drugs. VEGF is a signaling protein that promotes the formation of blood vessels. Anti-VEGF drugs block abnormal growth of blood vessels in wet age-related macular degeneration (AMD), one type of AMD and the leading cause of blindness in the U.S. However, not all patients respond to these treatments, and therapies for the other type, dry AMD, are still needed. NEI basic research suggests that at the molecular level, AMD shares disease mechanisms with other conditions and it may be possible to repurpose FDA-approved drugs to treat AMD. For example, NEI researchers are testing FDA-approved compounds that target a common signaling pathway in the body for their effectiveness in treating AMD and related Stargardt disease in animal models. Others are testing HIV drugs which target inflammation mechanisms in dry AMD.

AMD is a complex disease, involving many genes and environmental influences. Genomic studies have started to identify genetic factors which lead to the disease, but progress will require multidisciplinary approaches including genetics, pharmacology, developmental biology, and computational science. In 2016, the National Advisory Eye Council created a working group focused on AMD pathobiology in order to conduct a critical evaluation of knowledge gaps and barriers to progress and identify a list of resources needed by the AMD research community. The working group developed recommendations that will be published in 2018. .

All of Us Precision Medicine Initiative

The Committee recommendation supports the *All of Us* Precision Medicine Initiative and has provided \$290,000,000 in support of this Initiative. The Committee is encouraged by the enormous potential of precision medicine for all populations, including children, since much of adult health is rooted in the earliest years. The Committee is aware that at an *All of Us* Research Program stakeholder briefing, NIH announced plans to develop working groups to address inclusion of the pediatric population and has also indicated plans to host a pediatric stakeholder convening. The Committee requests an update within 90 days after enactment of this act on the status and timeline for the working groups to release findings regarding pediatric enrollment in the *All of Us* Research Program and the expected timeline for beginning enrollment of children from diverse backgrounds in the program. The Committee expects NIH to ensure that the research cohort includes a sufficient number of children to make meaningful studies possible.

Action taken or to be taken:

The enrollment of children in the *All of Us* Research Program has been a consistent, important goal of the program. The Advisory Committee to the NIH Director (ACD) Precision Medicine Initiative Working Group, which developed the report that informs the program, strongly supported the inclusion of children in the cohort, recommending that the NIH work thoughtfully and carefully to “develop specific approaches to address the needs of [children] so that they may be included and retained in the cohort.”¹⁰ The program is pursuing the expansion of the cohort to include children with careful consideration to ensure that the program will enable a wide range of important precision medicine discoveries to improve children’s health, and in ways that are sensitive to the special concerns around data collection from and research with children in the long-term.

The Child Enrollment Scientific Vision Working Group of the *All of Us* Research Program Advisory Panel completed their work in early FY 2018 and finalized its report describing some of the types of research *All of Us* is uniquely positioned to enable through the enrollment of children. The consortium, comprising partners from all components across the program, is considering the information gathered by this working group. This includes ensuring any gaps in the report are identified and addressed to maximize the utility of the cohort to the wide range of pediatric research opportunities in the near-, medium-, and long-term, and to assess the practical implications of each option provided, including examples such as the impact on the broad range of pediatric research opportunities, cost, feasibility, and participant burden.

In addition, the consortium members have been evaluating all elements within the initial adult research protocol that need to be modified to accommodate the enrollment of children in the *All of Us* Research Program. The program is very cognizant of the need to maximize the long-term scientific utility of the pediatric data collected, ensuring that data from the pediatric protocol has the power to advance precision medicine and adds significant scientific value for participants who continue in the program as adults. The consortium is actively working on all components of the program (engagement, consent, assessments, return of information, etc.) to identify pediatric alternatives to the current adult versions.

¹⁰ https://acd.od.nih.gov/documents/reports/PMI_WG_report_2015-09-17-Final.pdf

The program's goal is to have a plan by national launch in the spring of 2018 that will describe how the program will enroll children, including a timeline.

Alopecia Areata Research

The Committee recognizes NIAMS for leadership on recent research breakthroughs that could potentially lead to effective treatments for alopecia areata and related conditions, and encourages NIAMS to continue to support research in this area.

Action taken or to be taken:

Alopecia areata (AA) is an autoimmune disease that leads to disfiguring hair loss on the scalp and elsewhere. The condition occurs when the immune system, which normally protects the body from foreign invaders such as viruses and bacteria, mistakenly attacks the hair follicles, the structures from which hairs grow. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports a wide range of studies on AA, from the genetic underpinnings of the disease, to the development and testing of new treatments. In addition, basic and translational research into the biology of the hair follicle can provide insights into how the disease occurs. Recently, NIAMS-funded researchers found that a subpopulation of immune cells, called T regulatory cells, control hair follicle stem cell activation and differentiation in mice. Other investigators are exploring strategies to prevent the development of AA by blocking cell signaling molecules that control migration of key immune cells. Although more research is needed to confirm these findings in humans, they may have significant implications for drug discovery to treat AA and other autoimmune skin diseases. These and other basic research projects complement clinical studies such as a pilot clinical trial of the oral JAK1/2 inhibitor ruxolitinib in the treatment of patients with moderate-to-severe AA. While larger randomized controlled trials are needed to further assess the safety and efficacy of ruxolitinib in the treatment of AA, 75 percent of treated patients in the pilot study experienced significant hair regrowth.

NIAMS continues to support the development of new AA treatments through the Alopecia Areata Center of Research Translation (AACORT) and a Skin Disease Resource-Based Core Center that provides researchers with state-of-the-art methods for modeling the disease and assists them with experimental techniques and approaches to study the AA disease process. Other NIAMS-funded projects include deep sequencing analysis of genes that contribute to AA and the development of the Alopecia Areata Disease Activity Index (ALADIN). In FY 2017, NIAMS funded a new career development award to an investigator who is exploring the role of immune signaling proteins in AA and a new Small Business Innovation Research project to develop vascularized 3-D skin models to generate engineered hair follicles. Results of these and other studies will advance the understanding of AA causes and manifestations and should aid the development of future AA treatments.

Alzheimer's Disease Centers

In recognition that Alzheimer's disease poses a serious threat to the nation's long-term health and economic stability, the Committee recommends an increase of \$400,000,000 within NIA to support a total of at least \$1,791,000,000 on Alzheimer's disease research. NIA should continue to address the research goals set forth in the National Plan to Address Alzheimer's disease, as well as the recommendations from the Alzheimer's Disease Research Summit in 2015. Additionally, the Committee encourages NIA to continue support for additional Alzheimer's Disease Centers in States with high patient incidences of Alzheimer's disease. Preference shall be given to centers demonstrating collaborative work among basic scientists and clinical scientists to expedite new treatment protocols, particularly among underrepresented areas.

Action taken or to be taken:

The National Institute on Aging's (NIA) plans for addressing the research goals set forth in the National Plan to Address Alzheimer's Disease (AD) and related dementias (ADRD) are outlined in its Research Implementation Milestones database¹¹. This database also includes input from other NIH Institutes and Centers, particularly the National Institute of Neurological Disorders and Stroke (NINDS). Many strategic planning efforts have informed the development of these milestones, including but not limited to the 2012 and 2015 AD Research Summits, the 2013 and 2016 Summits on ADRD, and the 2013 meeting on Advancing Treatment for Alzheimer's disease in Individuals with Down syndrome. A 2017 Dementia Care and Services Summit and AD and ADRD Summits planned for 2018 and 2019, respectively, will inform future iterations of these milestones.

NIA continues to support 31 Alzheimer's Disease Centers (ADCs) in 20 States, as well as the National Alzheimer's Coordinating Center, which coordinates data collection and fosters collaborative research among ADCs, and the National Cell Repository for Alzheimer's Disease, which provides a central repository for biological samples and associated data to be shared with the scientific community. States with large numbers of affected patients are well represented in the Centers program; among the 21 states with the highest projected incidence of AD through 2025, 17 are home to at least one ADC.

Each ADC includes an Outreach and Recruitment Core, as well as a network of Satellite Centers. The Centers work individually and collaboratively to ensure that basic, translational, and clinical research on Alzheimer's and related dementias is widely shared. Notably, several ADCs are enhancing coordination and collaboration with respect to their efforts to reach out to under-represented groups. The University of Washington and Wake Forest Centers continue to work with Native American communities, while multiple Centers in African-American communities with a long history of connecting with families facing Alzheimer's are more widely sharing strategies and best practices. Additionally, the Uniform Data Set collected across all the centers is available in Spanish and many centers have a focus on Latino populations. The ADCs will be active participants in the forthcoming Alzheimer's Clinical Trials Consortium and central to the soon-to-be-released national strategy for AD patient recruitment.

¹¹ <https://www.nia.nih.gov/sites/default/files/2017-08/FY2018-Alzheimers-Disease-Related-Dementias-Budget-Bypass-Milestones-508.pdf>.

Many ADCs are co-located with other NIA and NIH funded Centers, where they are able to leverage resources and work together to achieve common goals. For example, the UC Davis ADC works together with the Resource Center for Minority Aging Research at the same location to address cognitive health in older Latinos. The Wake Forest ADC works closely with the Older Americans Independence Center at the same institution, and several ADCs work with NINDS-funded Udall Centers for Parkinson's disease Research.

In 2017, NIA engaged experts from academia, industry, and the nonprofit world in a strategic planning process to help ensure that the next generation of AD Centers is poised to accomplish the goals of the National Alzheimer's Plan. The group's recommendations focus on the implementation of the new integrated translational research agenda promoted at the aforementioned Summits, and emphasize flexibility and collaboration.

Alzheimer's Disease

The Committee commends NIA for its leadership in supporting longitudinal, population-based cohort studies into the causes of dementia. Because rural, poor, and minority populations may be at enhanced risk for dementia, the value and application of these studies is enhanced when they include individuals from various geographic, ethnic, socio-economic, and generational backgrounds. Therefore, the Committee directs NIA to diversify its cohort studies, with the specific goal of capturing a diverse sample of Americans whose inclusion would promote a better understanding of the factors underlying variation and disparities in dementia risk and ultimately lead to improved diagnostic, treatment, and prevention strategies in high risk populations.

Action taken or to be taken:

The National Institute on Aging (NIA) recognizes the importance of diversifying its cohort studies and supports a number of cohort studies that include participants from a range of geographic, ethnic, socioeconomic, and generational backgrounds. NIA has planned additional substantive efforts to determine the diverse factors underlying variation in dementia risk.

For example, proposals to enhance the power of multi-ethnic cohort studies were specifically invited in a NIA issued 2016 Funding Opportunity Announcement (FOA) soliciting research applications addressing the epidemiology of Alzheimer's disease (AD) and protective factors for cognitive health and resilience. This FOA resulted in studies examining the role of neighborhood built and social environments for slowing progression of dementia; identifying factors influencing AD trends in a biracial population study; and exploring modifiable aspects of gene/environment (particularly socioeconomic status) interplay in later-life cognitive decline, among others

NIA also issued an FOA in FY 2017 for research aimed at leveraging existing cohort studies to clarify risk and protective factors for Alzheimer's and related dementias. Three projects have been funded to date, one of which draws information from the Honolulu-Asia Aging Study, the Nun Study, and the 90+ Study, which will allow the investigators to compare and contrast brain pathology associated with cognitive and motor impairment among people of differing age, sex, and race/ethnicity.

In addition, NIA supports the COhort Studies of Memory in International Consortium (COSMIC), an international consortium of prospective longitudinal population based cohorts examining the risk and protective factors for cognitive decline and the development of dementia. Established in 2012, COSMIC has developed into a consortium of 26 studies from 16 countries in five continents, with a combined sample size of >70,000, and is now uniquely placed to address some of the salient questions in relation to the epidemiology and biomarkers of neurocognitive disorders.

Cognitive impairment and dementia are frequently under-detected and under-diagnosed, particularly in minority and underserved populations. NIH recently established an interactive national consortium that will test and validate clinical tools and methods that can be used in primary health care settings to increase accurate detection of cognitive impairment and dementia

among high risk populations and lessen cultural and logistic barriers that currently impede both clinical care and research efforts.

To improve our understanding of geographic and racial disparities in cardio- and cerebrovascular risk factors that lead to cognitive impairment and dementia, NIH is supporting the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study and the Northern Manhattan Study (NOMAS), which are diverse longitudinal cohort studies of African-American and Hispanic participants. As the emerging scientific consensus recognizes the role of midlife cardio- and cerebrovascular health in cognitive outcomes, the research focus of these two studies has been expanded to include investigation of health disparities in risk factors for dementia, and how they relate to stroke risk factors.

Alzheimer's Disease and Vascular Dementia

The Committee recognizes the importance of well characterized, longitudinal, population-based cohort studies in providing insights into risk factors related to dementia, with special focus on minority populations where disease burden is greatest. As the participants in these studies have aged, much has been learned about cognitive decline and the role of mid-life risk factors, but key challenges remain, particularly in the identification of biomarkers and in understanding the role of environmental versus genetic factors. Therefore, within the provided funds, the Committee directs NHLBI to recruit and examine the subsequent generations of such cohorts, as studying the adult children of these extensively characterized cohort members may provide new insights into risk identification and accelerated prevention efforts. The project shall conduct clinical examinations, including brain imaging, of this second generation of participants.

Action taken or to be taken:

Cardiovascular disease (CVD) is increasingly recognized as an important contributor to cognitive impairment and dementia. The National Heart, Lung, and Blood Institute (NHLBI) continues to support epidemiological studies of CVD, and has expanded several such studies beyond the initial cohort of participants to include second and even third generations. As the participant's age, and with the advent of improved cognitive testing and brain imaging tools, these studies also have expanded to include epidemiological research on dementia.

NHLBI's Framingham Heart Study began in 1948 in Framingham, Mass., and has evolved over time to reflect the area's increasingly diverse population and to include several generations. The study has established that many risk factors for CVD – such as high blood pressure, cigarette smoking, lack of physical activity, obesity, diabetes, and aging – are also risk factors for vascular dementia. NHLBI-funded researchers also recently reported that among people with Alzheimer's disease, African Americans were twice as likely as Whites to have Alzheimer's disease mixed with other pathology, including more severe vascular pathology. This is consistent with evidence that African Americans have a higher dementia risk than Whites.

The Jackson Heart Study (JHS) in Jackson, Miss., the largest cohort study focused on CVD in African Americans, is well poised to conduct research to understand the links between CVD and dementia in this population. In its next phase, the study will investigate factors related to heart failure and impaired cognitive function. Over a span of nearly 20 years, researchers will examine changes in cardiac structure and function as well as cognitive function and signs of microvascular pathology on brain MRI findings. Additionally, the JHS Kids Study, funded through the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, has recruited 200 children and grandchildren (ages 12–19) of JHS participants to identify early life risk factors for CVD.¹² This pilot study may form the basis for a larger, long-term study of this generation.

The Atherosclerosis Risk in Communities (ARIC) study of African American and White adults provides 30 years of data on CVD risk factors, including data on change in cognitive function and incidence of dementia. The ARIC Neurocognitive Study, a large ancillary study funded by NHLBI and the National Institute on Neurological Disorders and Stroke (NINDS), the National

¹² <https://www.ncbi.nlm.nih.gov/pubmed/27129858>

Institute on Aging (NIA), and the National Institute on Deafness and Other Communication Disorders, is investigating whether midlife vascular factors predict dementia, mild cognitive impairment, and cognitive change. Another aim is to identify brain biomarkers and genome variants associated with cognitive decline.

NINDS supports additional projects to address the risk of dementia in minority populations. The Reasons for Geographic and Racial Differences in Stroke (REGARDS) study and the Northern Manhattan Study (NOMAS) were designed to improve our understanding of geographic and racial disparities in stroke burden and risk factors for stroke. NINDS is now leveraging data from these two longitudinal cohort studies of African American (REGARDS) and Hispanic participants (NOMAS) to fill gaps in our knowledge of vascular contributions to cognitive impairment and dementia in these populations.

There is increasing collaboration across NIH to further explore the connection between vascular risk factors and dementia. One such collaboration, which includes support from NHLBI, NINDS, NIA, and the National Institute of Diabetes and Digestive and Kidney Diseases, is the Memory and Cognition In Decreased Hypertension study, an add-on to the Systolic Blood Pressure Intervention Trial. This SPRINT-MIND study is testing whether lowering systolic blood pressure to less than 120 mm Hg has an impact on cognitive function and dementia in adults over age 50.

Other relevant ongoing NIA-supported cohort studies include the Kaiser Healthy Aging and Diverse Life Experience (KHANDLE) study and the Washington Heights-Inwood Community Aging Project (WHICAP). KHANDLE will examine dementia risk factors among African American, White, Asian, and Hispanic patients in this health system, in part by looking back at the results of clinical exams conducted from the 1960s to the 1980s. WHICAP has been studying aging and dementia – including identification of blood and imaging biomarkers – among African American, White, and Caribbean Hispanics since 1989. In addition, the Health and Retirement Study is examining the prevalence, predictors, and outcomes of cognitive impairment and dementia in a diverse cohort that includes African Americans and Hispanics at higher proportions than in the general population.

Amyloidosis

The Committee recommends that NIH continue to expand its research efforts into 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. The Committee directs NIH to keep the Committee informed on the steps taken to increase the understanding of 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:

NIH continues to support research into amyloidoses – an umbrella term for a variety of diseases in which normal human proteins misfold into an insoluble material called amyloid that can accumulate in various tissues, resulting in disease. For example, in response to a solicitation entitled “Systemic Amyloidosis: Basic, Translational, and Clinical Research,”¹³ NIH has funded two studies. One seeks to develop antibody-based methods to reduce amyloid deposits in mouse models of systemic amyloidosis.¹⁴ The other is employing a tissue culture approach to assess the utility of activating the cell’s unfolded protein response to reduce secretion of amyloidogenic proteins.¹⁵

In addition, NIH is supporting other relevant research, such as projects aimed at understanding the cellular events that contribute to formation of amyloid by the pancreatic protein amylin and to the toxicity of that amyloid in the pancreas; determining how cells can detect and eliminate misfolded proteins; evaluating potential treatments to remove the amyloid buildup in patients with light chain amyloidosis, a life-threatening disease that can arise when one of the protein components of antibodies (light chains), aggregate into amyloid; and gaining insight into how proteins may misfold, aggregate, and cause disease. NIH is supporting research projects that investigate pathological mechanisms that lead to amyloid accumulation within brain blood vessels to better understand what causes these deposits. For instance, researchers are studying distinct structural features of amyloid that builds up within brain vessels to understand the unique pathology of cerebral amyloid angiopathy (CAA) that contributes to cognitive impairment and dementia. Researchers are also conducting biomarker development and validation studies that would enable accurate detection and diagnosis of CAA in early stages of disease. The NIH is also supporting a study¹⁶ to assess how protein chaperones and protein partners called co-chaperones can promote either propagation or clearance of amyloid proteins in a yeast model system. Chaperones are proteins that assist with the folding or unfolding and the assembly or disassembly of other macromolecular structures, such as other proteins. For example, this effort recently demonstrated that the protein Hsp104 can work with other proteins to promote clearance of amyloids, and similar investigations are underway on Hsp70 and its co-chaperones.

Recent NIH-supported advances in amyloidosis research include: the identification of peptide probes (proteins made up of just a few amino acids) to detect misfolded protein associated with a hereditary type of amyloidosis that may be useful in early disease detection, monitoring of disease progression, and disease response to treatment—ongoing research seeks to determine whether other small molecules might be therapeutically capable of ameliorating secretion of

¹³ <https://grants.nih.gov/grants/guide/pa-files/PA-13-286.html>

¹⁴ https://projectreporter.nih.gov/project_info_description.cfm?aid=9292835

¹⁵ https://projectreporter.nih.gov/project_info_description.cfm?aid=9304206

¹⁶ https://projectreporter.nih.gov/project_info_description.cfm?aid=9565910

amyloid proteins; discovery that specific mutations cause changes in amyloid and accelerate the process of aggregation; discovery of a population of cells with the capacity to partially protect heart muscle cells from damage caused by amyloid deposits.

Angelman Syndrome

The Committee recognizes the promising scientific gains made in the pursuit of treatments for Angelman Syndrome. The Committee applauds the significant contributions of the Angelman Syndrome Natural History Study, funded by NIH, and the private partners working diligently to advance the growing body of Angelman Syndrome research towards practical treatments.

Because Angelman Syndrome is a single-gene disorder, specifically caused by a deleted *UBE3A* gene, the Committee believes that with recent advances in medical therapeutics and technology, the disorder is curable today. Further research in this area holds great promise for both Angelman Syndrome and forms of autism also linked to misexpression of the *UBE3A* gene. With two innovative new treatments poised for clinical trials, the Committee urges NIH to dedicate available resources to Angelman Syndrome research, and specifically to advance research in the roles of the *UBE3A* gene in brain functions. In this challenging budget environment, the Committee also believes public-private partnerships should be further encouraged as translational research progresses in the areas of Angelman Syndrome, autism, and *UBE3A* related disorders.

Action taken or to be taken:

Angelman syndrome is a neurodevelopmental disorder due to the loss of activity of the *UBE3A* gene on one copy of the mother's chromosome 15. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) has supported the Angelman, Rett, and Prader-Willi Syndrome Consortium¹⁷ that helped establish data on the natural history of all three of these conditions. Over a 10-year period, this consortium enrolled over 300 individuals with Angelman syndrome (AS) to assess the natural history of the disorder and further characterize its clinical features, which often include seizures, autism, and limited verbal abilities. About a third of these individuals participated in a sub-study on sleep issues; those with AS were found to have more sleep problems than the general population, which also affects the sleep quality of family members.

NICHD currently supports a range of basic research studies related to AS. NICHD-funded investigators are examining the underlying genetic alterations in the *UBE3A* gene that affect neuronal function by studying cells derived from individuals with AS and reprogramming them to develop into different types of neurons. These experiments are shedding light on which of several forms of the *UBE3A* protein is most critical for normal brain function and, in the future, these cell lines may also serve as a model system to screen potential drugs for those that are most effective. Other researchers are using mouse models of AS to determine the best timing for using genetic therapies to activate the missing gene during brain development and rescue the abnormal neural circuits and behavioral problems. Studies being led by one of the NICHD-funded Intellectual and Developmental Disabilities Research Centers are developing targeted molecular therapies to genetically correct the condition using special pieces of DNA that activate the normally silent copy of the *UBE3A* gene inherited from the affected individual's father. With engagement of patient advocacy groups, and in some cases, exploring potential partnerships with pharmaceutical companies interested in developing genetic therapies, these studies may help correct the loss of *UBE3A* protein. These efforts will improve understanding of the underlying

¹⁷ <https://www.pwsctc.org/>

defects in AS and may help identify strategies to help understand and treat certain forms of autism.

In addition, the National Institute on Neurological Disorders and Stroke (NINDS) is funding research projects focused on revealing the mechanisms by which loss and misexpression of *UBE3A* in the brain give rise to intellectual disability and motor impairments. Several ongoing projects are using mouse models of AS to restore *UBE3A* expression in specific cell types and brain circuits to identify critical periods for treatment. NINDS also funds preclinical research focused on identifying novel drug targets for mitigating learning and memory deficits in AS, such as components of signaling pathways involved in learning and memory mechanisms that are normally modulated by the UBE3A protein, and supports efforts to identify therapeutic biomarkers of AS, which would enable clinicians to assess the effectiveness of future treatments. One ongoing project is assessing how motor function delays in AS correlate to structural deficits in the fibers connecting relevant brain regions, and another found that specific brain waves are consistently increased among children with AS compared to age-matched healthy children. NINDS is collaborating with NICHD, other NIH Institutes, and several non-profit organizations to hold a workshop on biomarker development for neurodevelopmental disorders including AS in December 2017. This workshop will focus on physiological and functional biomarkers that can enable clinical trial readiness and success.

Angiogenesis

The Committee recommends that NIH study the regulation of vascular growth and its interactions with the immune system, stem cells, DNA repair, and microbiome. Further, the Committee urges the NIH to research the impact of metabolism and dietary factors on endothelial cells, specifically to support normal physiology and oppose disease, and to study biomarkers of vascular health.

Action taken or to be taken:

NIH supports comprehensive research on the mechanisms regulating vascular growth and remodeling. These processes, known as angiogenesis, occur during early development, in tissue growth and regeneration, and in disease contexts such as tumor vascularization.

Researchers are making progress in understanding the various molecular pathways that regulate angiogenesis. One recent National Heart, Lung, and Blood Institute-funded (NHLBI-funded) study found that small sugars called xylosides promote angiogenesis, making them ideal drug candidates for a broad spectrum of diseases and conditions that involve blood vessel injuries or abnormalities.¹⁸ NHLBI-funded scientists also are studying how the immune system and inflammatory responses influence angiogenesis. For example, ongoing research suggests that the immune signaling factor interleukin-19 may have complementary effects on endothelial cells and immune cells to help couple angiogenesis with other aspects of wound repair.¹⁹ A 2017 trans-NIH workshop explored similar areas of research, including the role that inflammation and the microbiome may play in influencing angiogenesis.²⁰

Metabolic diseases associated with lifestyle and dietary factors can affect vascular health. For example, diabetes may lead to peripheral artery disease. NHLBI-funded researchers are investigating how metabolic diseases affect endothelial cell function. For example, one project is focused on the activity of a gene regulator called PGC-1 α , which is known to suppress angiogenesis. PGC-1 α levels are elevated in diabetes, and this may reduce the ability of endothelial cells to migrate and create new blood vessels.²¹

In the eye, blood vessel abnormalities underlie the leading causes of blindness. Clinical trials supported by the National Eye Institute (NEI) have established that drugs targeting vascular endothelial growth factor (VEGF) can prevent and even reverse vision loss from these diseases.²² New research is exploring new therapeutic targets that regulate vascular growth. In diabetic retinopathy, where there is a loss of blood vessels that supply the retina, researchers are exploring endothelial cell-based therapy.²³

Angiogenesis is also necessary for tissue regeneration. A consortium funded through the NEI Audacious Goals Initiative is working to uncover factors that promote regeneration in the visual system, including pro-angiogenesis factors.²⁴ Other researchers have found that endothelial and

¹⁸ <https://www.ncbi.nlm.nih.gov/pubmed/28763512>

¹⁹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9043942

²⁰ <https://www.ncbi.nlm.nih.gov/pubmed/29044245>

²¹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9286870

²² <https://www.ncbi.nlm.nih.gov/pubmed/28837425>

²³ <https://www.ncbi.nlm.nih.gov/pubmed/21611766>

²⁴ <https://nei.nih.gov/audacious/omic-projects>

retinal cells grown together in a dish can form the eye's blood-retinal barrier.²⁵ This may be a useful model for testing the capacity of potential new drugs to cross the blood-retinal barrier.

²⁵ <https://www.ncbi.nlm.nih.gov/pubmed/28800962>

Antimicrobial Resistance

The Committee recommendation includes an increase of \$30,000,000 within NIAID for combating anti-microbial resistance. The Committee continues to support research on mechanisms of drug resistance, bacterial pathogenesis, and infection control; developing new or repurposing existing antimicrobials; and exploring approaches to prevention including bacterial vaccines and other strategies. The Committee encourages NIH to coordinate with CDC to determine how data in the CDC resistant pathogens database can be leveraged to improve future research. The Committee requests an update in the fiscal year 2019 Congressional Justification on how NIAID is working with CDC and other Federal partners in this field of research.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) is an active participant in the National Strategy for Combating Antibiotic-Resistant Bacteria (CARB) and pursues research on novel antimicrobial strategies in collaboration with other Federal agencies, international organizations, academia, and industry. Key Federal partners in this effort include the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the Biomedical Advanced Research and Development Authority (BARDA), the Department of Agriculture, and the Department of Defense.

NIAID continues its longstanding work with CDC, FDA, and other NIH partners to develop the National Database of Resistant Pathogens as a global repository for genomic data on drug-resistant pathogens. NIAID is sequencing high-priority reference strains for the Database to facilitate research on drug resistance mechanisms and to advance the development of new diagnostics, therapeutics, vaccines, and other antimicrobial strategies. NIAID scientists also are working with colleagues from CDC, NIH, and other institutions to improve our understanding of bloodstream infections caused by Gram-negative bacteria. The collaboration has fostered an ongoing NIH research initiative to analyze trends in antimicrobial resistance, including factors affecting mortality from these bloodstream infections. In addition, NIAID supports the Antibacterial Resistance Leadership Group, which oversees clinical research to reduce the public health threat of antibacterial resistance.

NIAID, along with BARDA, participates in the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator, (CARB-X), a global public-private partnership to advance early discovery and development of novel antibiotics, vaccines, and rapid diagnostics. NIAID is providing preclinical services and technical support to CARB-X awardees. NIH also has partnered with BARDA, with technical and regulatory expertise from CDC and FDA, to launch the Antimicrobial Resistance Diagnostic Challenge.²⁶ The NIH and BARDA have selected ten semifinalists for Phase 1 of this competition. This Challenge competition may award up to \$20 million in prizes for innovative, rapid, point-of-need *in vitro* diagnostic tests to combat the emergence and spread of drug-resistant pathogens. Final awards following three phases of the Challenge are expected in 2020.

NIAID will continue to collaborate with national and international partners to conduct research and support the antimicrobial resistance research community. These efforts include investigation of the mechanisms of drug resistance and pathogenesis via foundational basic research and cutting-edge genomic sequencing technologies; detection and tracking of pathogens with simple

²⁶ <https://dpcpsi.nih.gov/AMRChallenge>

and accurate diagnostics; development of next-generation vaccines to prevent bacterial infections; and identification of novel antibacterial drugs and treatment regimens.

Asthma

The Committee notes with concern the evidence suggesting a causal link between air pollution and the development of asthma. The Committee urges NHLBI and the NIEHS to explore this potential causal link and any interventions necessary to prevent the development of asthma.

Action taken or to be taken:

Both the National Institute of Environmental Health Sciences (NIEHS) and the National Heart, Lung, and Blood Institute (NHLBI) support a wide variety of studies related to the link between air pollution and asthma as well as interventions that may reduce or prevent asthma. Below are examples of such studies.

- NIEHS-supported research indicates that small increases in same day particulate matter (PM_{2.5}) concentrations were associated with emergency department (ED) visits for children living in a metropolitan area. These results suggest that pediatric ED visits for asthma are associated with PM_{2.5} concentrations.²⁷
- NIEHS grantees conducted research showing that declining air pollution levels over time were associated with improvements in respiratory health among children with and without asthma in Southern California.²⁸
- NIEHS has pioneered the development of several sensor systems for measuring personal exposure to environmental triggers of asthma such as particulate matter²⁹, gases such as ozone,³⁰ and volatile organic compounds associated with multiple sources such as traffic,³¹ personal care products, or incomplete combustion.
- NIEHS is funding clinical intervention research to help prevent asthma episodes such as a study using air cleaners in the home to determine if they offer an adequate intervention for asthma by reducing indoor air pollution,³² and a separate clinical trial that is evaluating removal of harmful nitrogen dioxide concentrations and asthma reduction.³³
- NIEHS is also funding the first multi-city study of asthma ED visits and air pollution across the lifespan. This study is also examining ED visits and air pollution between cities. This research will develop new methods to combine different types of environmental data for estimating air pollution exposures and help foster interventions to better treat asthma.³⁴

²⁷ <https://www.ncbi.nlm.nih.gov/pubmed/26452298>

²⁸ <https://www.ncbi.nlm.nih.gov/pubmed/25738666>

²⁹ <https://www.ncbi.nlm.nih.gov/pubmed/27354176>

³⁰ <https://www.ncbi.nlm.nih.gov/pubmed/?term=ES016925>

³¹ <https://www.ncbi.nlm.nih.gov/pubmed/?term=ES024718>

³² <https://www.ncbi.nlm.nih.gov/pubmed/28063655?dopt=Citation>

³³ <https://www.ncbi.nlm.nih.gov/pubmed/28063655?dopt=Citation>

³⁴ https://projectreporter.nih.gov/project_info_description.cfm?aid=9291306&icde=37753607&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

- NHLBI collaborates with NIEHS as part of the President's Task Force on Environmental Health Risks and Safety Risks to Children which has a subcommittee focused on reducing asthma disparities in children.³⁵
- NIEHS and NHLBI are also active collaborators with the NIH Environmental Influences on Child Health Outcomes study (ECHO) which is investigating the contribution of environmental exposures to child health, including airway diseases such as asthma. This NIH-wide effort is considering primary prevention efforts to eliminate or reduce deleterious environmental exposures.³⁶
- NHLBI served in a consultative role for a cooperative agreement led by the National Institute of Biomedical Imaging and Bioengineering called Pediatric Research Using Integrated Sensor Monitoring Systems (PRISMS). PRISMS allows investigators to develop wearable biosensors to measure exposures, such as pollution.³⁷
- NHLBI-supported investigators are using publicly available data on pollution to assess the impact of the pollution on responses of patients to drug therapies in multiple asthma clinical trials.³⁸
- Research funded by NIEHS, NHLBI, and the National Institute of Allergy and Infectious Diseases has demonstrated the importance of healthy school environments. A study of students from inner-city schools, published in January 2017, linked airborne mouse allergens at schools to increased symptoms and decreased lung function in asthmatic children. This suggests there are interventions schools can take to improve air quality and potentially benefit children with asthma.³⁹

³⁵ <https://ptfceh.niehs.nih.gov/>

³⁶ <https://www.nih.gov/echo>

³⁷ <https://www.nibib.nih.gov/research-funding/prisms>

³⁸

https://projectreporter.nih.gov/project_info_description.cfm?aid=9111935&icde=37744237&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball

³⁹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5349325/>

Audacious Goals Initiative (AGI)

The Committee commends NEI's leadership through its AGI, which aims to restore vision within the next decade through regeneration of the retina by replacing cells that have been damaged by disease and injury and restoring their visual connections to the brain. The Committee is pleased that NEI has proceeded with two rounds of grants to date that relate to novel imaging technologies to help clinicians observe the function of individual neurons in human patients and follow them over time as they test new therapies, as well as identifying new factors that control regeneration and comparing the regenerative process among model organisms, rodents, and non-human primates.

Action taken or to be taken:

The National Eye Institute (NEI) Audacious Goals Initiative (AGI) has surveyed the state of the science in neuroregeneration by convening five experts' workshops around the country to discuss and report on topics related to retinal neuron regeneration and reconnection, outlining barriers to progress and gaps in knowledge that need to be addressed for retinal cell replacement strategies to become effective therapies for disease. Additionally, NEI organized open town halls targeting the clinical community to gain insights regarding which diseases and patient populations would be amenable to cell replacement. The findings from these expert workshops and town halls were published in a series of articles to widely disseminate them to the vision science community.

The first two funding opportunity announcements (FOAs) arising from the AGI are to support research on new tools and technologies to monitor transplanted cells and to identify important new factors involved in retinal regeneration and reconnection. The next AGI FOA solicits applications to address the critical need for better animal models of diseases that can be used to evaluate regenerative medicine strategies. These new projects will build upon findings from the previous two rounds of grants to generate the necessary data to support the development of clinical trials in future years.

In addition, many researchers with current grants on regenerative medicine that are funded by NEI, are well positioned to take advantage of the additional funding that the NIH Regenerative Medicine Innovation Project offers towards supporting clinical studies involving adult stem cells.

Autism Spectrum Disorder Funding (ASD)

The Committee encourages NIH's continued funding of ASD research. The estimated lifetime cost of supporting an individual with autism and intellectual disability is \$2,400,000, and the cost of supporting an individual with autism without intellectual disability is \$1,400,000. Based on these estimates, the yearly cost of ASD to the United States is \$236,000,000,000. Medicaid covers autism treatments for nearly half of all children with autism and pays for the majority of residential and day programs serving adults with developmental disabilities. NIH-funded research presents an opportunity to mitigate the disabling effects of autism and reduce the Federal costs associated with it in the future for children and adults.

Action taken or to be taken:

NIH is committed to supporting innovative and high impact biomedical research on autism spectrum disorder (ASD), including research on services and interventions for children and adults with ASD that may mitigate disabling effects and reduce the cost of care.

Since 2007, the National Institute of Mental Health (NIMH), the Eunice Kennedy Shriver National Institutes of Child Health and Human Development (NICHD), the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Deafness and Other Communication Disorders (NIDCD), and the National Institute of Environmental Health Sciences (NIEHS) have supported the NIH Autism Centers of Excellence (ACE) Program. The ACE Program is an integrative multidisciplinary, coordinated research effort focused on ASD causes, trajectories, and interventions. ACE researchers have identified potential subtypes of autism and sex differences in brain structure of children with ASD,^{40,41,42} and found that early brain changes may help predict ASD among high risk infants.^{43,44} To build on past discoveries of the ACE Program, in 2017, NIH awarded nine ACE research grants totaling nearly \$100 million over the next five years.⁴⁵ Two ACE projects aimed at improving ASD diagnosis are studying the development of functional brain connections and infant social interactions to identify early signs of ASD, while a third is evaluating if early developmental screening lowers the average age of ASD diagnosis and leads to earlier interventions and improved outcomes. ACE researchers are also developing interventions appropriate for different subtypes of ASD, examining how attention-deficit/hyperactivity disorder may influence the diagnosis and treatment of ASD, and investigating how ASD differs among girls and boys, particularly during the transition from adolescence into adulthood.

NIMH also supports research through the Services Research for ASD across the Lifespan (ServASD) initiative.⁴⁶ ServASD supports research to develop and test the effectiveness of systems-level interventions to improve functional and health outcomes of individuals with ASD at important developmental points across the lifespan. Following the first successful round of

⁴⁰ <https://www.ncbi.nlm.nih.gov/pubmed/22123952>

⁴¹ <https://www.ncbi.nlm.nih.gov/pubmed/27343889>

⁴² <https://www.ncbi.nlm.nih.gov/pubmed/27566123>

⁴³ <https://www.ncbi.nlm.nih.gov/pubmed/28202961>

⁴⁴ <https://www.ncbi.nlm.nih.gov/pubmed/28592562>

⁴⁵ <https://www.nih.gov/news-events/news-releases/nih-awards-nearly-100-million-autism-centers-excellence-program>

⁴⁶ <https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-100.html>

ServASD grants,⁴⁷ NIMH issued two new funding opportunity announcements aimed at services for transition-age youth⁴⁸ and for adults with ASD.⁴⁹ In 2017, NIMH awarded five new grants that aim to develop an intervention to improve executive functioning and social skills,⁵⁰ test a virtual reality job interview training program,⁵¹ refine a community-based vocational intervention program,⁵² develop and test the effectiveness of an online healthcare toolkit,⁵³ and create a program to facilitate adult sibling engagement in family future planning.⁵⁴ The ultimate goal of these project is to improve independence and functioning of adults with ASD.

Several states have passed Medicaid Home and Community-based Services (HCBS) waivers that expand eligibility criteria and available services for children with ASD. Using HCBS data from 35 states, a recent NIMH-funded study found that Medicaid HCBS waivers significantly decreased the unmet need for health care among children with ASD, particularly among those who would not otherwise qualify for Medicaid.

These established programs, recent initiatives, and studies exemplify NIH's continued commitment to biomedical, intervention, and services research for children and adults with ASD.

⁴⁷ <https://www.nimh.nih.gov/news/science-news/2014/new-grants-fund-cross-lifespan-services-research-for-autism-spectrum-disorder.shtml>

⁴⁸ <https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-17-200.html>

⁴⁹ <https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-17-205.html>

⁵⁰ https://projectreporter.nih.gov/project_info_description.cfm?aid=9213331&icde=36595888

⁵¹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9214114&icde=36595888

⁵² https://projectreporter.nih.gov/project_info_description.cfm?aid=9214860&icde=36595870

⁵³ https://projectreporter.nih.gov/project_info_description.cfm?aid=9214259&icde=36595852

⁵⁴ https://projectreporter.nih.gov/project_info_description.cfm?aid=9213200&icde=36595870

Autism Spectrum Disorder (ASD)

The Committee commends NIH for its commitment to the study of ASD recognizing that there are many different subtypes of autism and that the full range of potential treatments, appropriate to each subtype, have not yet been developed. The Committee encourages NIH to explore a collaborative approach to gain a systematic and comprehensive understanding of each subtype, and to translate this understanding to develop individualized treatments. Such an approach would harness information from academia and industry, as well as individuals and families impacted by ASD. The European Union has a similar integrated research effort underway to focus on this issue, the European Autism Interventions-A Multicentre Study for Developing New Medications. The Committee encourages the NIH to explore this approach and provide an update in the fiscal year 2019 CJ.

Action taken or to be taken:

NIH continues to actively fund research on autism spectrum disorder (ASD). The sampling of activities below demonstrates NIH's commitment to ASD research, and highlights collaborative approaches that aim to understand autism subtypes and potential individualized treatments.

The Autism Biomarkers Consortium for Clinical Trials (ABC-CT) is a \$28 million, multi-year, public-private partnership project to test and refine clinical measures of social impairment in ASD to better evaluate potential behavioral and drug therapies.⁵⁵ Project partners include the NIH Biomarkers Consortium,⁵⁶ the National Institute of Mental Health (NIMH), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute of Neurological Disorders and Stroke (NINDS), the Food and Drug Administration (FDA), industry, academia, advocacy groups, and individuals with ASD. The goal of the ABC-CT is to facilitate the identification and validation of biomarkers to identify biological subtypes of ASD, predict the best treatment option for individuals with ASD, and accelerate the development of individualized therapies. ABC-CT researchers are currently conducting a large multi-site study that will test several eye tracking, brain activity recording, and lab-based measures to determine if these tools can be used to identify subtypes of ASD, or serve as early indicators of treatment response.

In December 2017, NINDS, NICHD, NIMH, the National Center for Advancing Translational Sciences (NCATS), and several non-profit organizations co-sponsored a workshop on biomarkers to enable therapeutics development for neurodevelopmental disorders, such as ASD. This workshop focused on physiological and functional biomarkers that can enable clinical trial readiness and success.

Since 2007, NIMH, NICHD, NINDS, the National Institute on Deafness and Other Communication Disorders (NIDCD), and the National Institute of Environmental Health Sciences (NIEHS) have supported the NIH Autism Centers of Excellence (ACE) Program. The ACE Program is an integrative multidisciplinary, coordinated research effort focused on ASD causes, trajectories, and interventions. ACE researchers have identified potential subtypes of

⁵⁵ https://projectreporter.nih.gov/project_info_description.cfm?aid=9331734&icde=36603366

⁵⁶ <https://fnih.org/what-we-do/biomarkers-consortium>

autism and sex differences in brain structure of children with ASD,^{57,58,59} and found that early brain changes may help predict ASD among high risk infants.^{60,61} To build on past discoveries of the ACE Program, in 2017, NIH awarded nine ACE research grants totaling nearly \$100 million over the next five years.⁶² This round of ACE researchers aim to: develop methods that allowed for earlier screening; improve treatments based on specific symptoms; and, understand how autism may differ in boys and girls. For example, one ACE project is examining brain activity and connectivity during the first year of life as potential ASD predictors of risk in infants from three genetic groups. Data from ACE projects, along with all new NIH-funded ASD research involving human subjects, will be submitted to the NIH National Database for Autism Research (NDAR).⁶³ NDAR's mission is to facilitate data sharing and scientific collaboration on a broad scale, providing a shared common platform for autism researchers to accelerate scientific discovery.

⁵⁷ <https://www.ncbi.nlm.nih.gov/pubmed/22123952>

⁵⁸ <https://www.ncbi.nlm.nih.gov/pubmed/27343889>

⁵⁹ <https://www.ncbi.nlm.nih.gov/pubmed/27566123>

⁶⁰ <https://www.ncbi.nlm.nih.gov/pubmed/28202961>

⁶¹ <https://www.ncbi.nlm.nih.gov/pubmed/28592562>

⁶² <https://www.nih.gov/news-events/news-releases/nih-awards-nearly-100-million-autism-centers-excellence-program>

⁶³ <https://ndar.nih.gov/>

Autoimmune Neuropathies

The Committee encourages NIAID to work with NINDS and other Institutes and Centers to support efforts to gauge the state-of-the-science of autoimmune neuropathies research into conditions like Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy, and to establish a cross-cutting research plan for this portfolio.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) continues to support a robust and cross-cutting basic, preclinical, and clinical research portfolio on autoimmune diseases, including autoimmune neuropathies. NIAID supports research to uncover underlying mechanisms shared by many autoimmune diseases as well as to target specific diseases such as multiple sclerosis (MS), lupus, Guillain-Barré Syndrome (GBS), and chronic inflammatory demyelinating polyneuropathy (CIDP). For example, NIAID scientists are collaborating with health officials in Mexico to characterize the risk of developing GBS after infection with the Zika virus. NINDS also funds research to understand the molecular mechanisms of GBS and CIDP and to improve treatments for these diseases. In these efforts, NIAID works to engage stakeholder perspectives from the autoimmune disease patient advocacy and research communities.

NIAID engages with Federal and non-Federal partners through several consortia that support research on autoimmune diseases. NIAID chairs the Autoimmune Diseases Coordinating Committee, which works to increase collaboration and facilitate coordination of autoimmune disease research among NIH Institutes and Centers, other Federal agencies, professional societies, and patient and advocacy organizations. Along with NINDS, NIAID sponsors the HLA and KIR Region Genomics in Immune Mediated Diseases Consortium, which seeks to understand genetic links to factors including disease progression and response to therapy in immune-mediated diseases including autoimmune disorders such as MS and other neuropathies.

NIAID efforts to investigate genetic and environmental factors in autoimmune disease in partnership with other NIH Institutes and Centers have uncovered clues to potential new therapies for these diseases. NIAID and NINDS scientists have initiated a project to understand the pathogenesis and genomics of MS in families with either multiple affected members or cases of onset in young children. A collaboration between NIAID, NINDS, and NHGRI researchers, as well as additional domestic and international partners, identified a potential autoimmune mechanism for the epileptic disorder Nodding Syndrome (NS) triggered by exposure to the parasite that causes river blindness. This finding suggests that researchers should explore the use of immunotherapies in NS patients.

NIAID will continue to collaborate with NINDS and other NIH Institutes and Centers, as well as other Federal and non-Federal partners to support cross-cutting research into autoimmune diseases including GBS and CIDP. At this time, NIAID does not have plans to establish a separate research plan targeted to autoimmune neuropathies, but NIAID remains committed to supporting GBS and CIDP-related research, and welcomes future grant applications for these and other autoimmune neuropathies.

Barriers to Research

The Committee is concerned that restrictions associated with Schedule 1 of the Controlled Substance Act effectively limit the amount and type of research that can be conducted on certain schedule 1 drugs, especially marijuana or its component chemicals and certain synthetic drugs. At a time when we need as much information as possible about these drugs, we should be lowering regulatory and other barriers to conducting this research. The Committee directs NIDA to provide a short report on the barriers to research that result from the classification of drugs and compounds as Schedule 1 substances.

Action taken or to be taken:

As public perceptions and state policies related to marijuana have changed so have patterns of use. Recreational use of marijuana has been evolving, with the average potency of cannabis seized by the DEA rising and increasing use of high potency extracts such as shatter, budder, and hash oil. Much of the past research applies to lower potency forms of marijuana and very little research has focused on high-potency extracts, edible products, or new modes of administration such as electronic vaporizers. In addition, while there is a growing body of research suggesting the potential therapeutic value of cannabinoids for certain health conditions like epilepsy, seemingly promising early findings do not always translate to effective treatments⁶⁴ and in general, adequate and well-controlled trials are lacking.

NIH shares the Committee's concerns and believes that more research is needed on both the harms associated with marijuana use and the therapeutic potential of marijuana and its constituent compounds. NIH welcomes investigator-initiated research proposals for pre-clinical and clinical research evaluating marijuana and its constituent cannabinoids for treating disease. In addition, to facilitate more research on the therapeutic potential as well as the potential harm of cannabinoids, NIH has released funding opportunity announcements (FOAs) on:

- Public Policy Effects on Alcohol-, Marijuana-, and Other Substance-Related Behaviors and Outcomes
- Marijuana, Prescription Opioid, or Prescription Benzodiazepine Drug Use Among Older Adults
- Fast-Track Development of Medications to Treat Cannabis Use Disorders
- Effects of Cannabis Use and Cannabinoids on the Developing Brain
- Developing the Therapeutic Potential of the Endocannabinoid System for Pain Treatment⁶⁵
- Blueprint Neurotherapeutics Network Small Molecule Drug Discovery and Development for Disorders of the Nervous System⁶⁶
- Clinical Evaluation of Adjuncts to Opioid Therapies for the Treatment of Chronic Pain⁶⁷

NIH supports a broad portfolio of research on cannabinoids and the endocannabinoid system. In FY 2016, NIH supported 292 projects totaling over \$115 million on cannabinoid research.

⁶⁴Gloss, D. and B. Vickrey (2014). Cannabinoids for epilepsy. Cochrane Database of Systematic Reviews. C. The Cochrane. Chichester, UK, John Wiley & Sons, Ltd.

⁶⁵ <https://grants.nih.gov/grants/guide/pa-files/pa-15-188.html>

⁶⁶ <https://grants.nih.gov/grants/guide/pa-files/PAR-17-205.html>

⁶⁷ <https://grants.nih.gov/grants/guide/pa-files/PAR-14-225.html>

Despite efforts to stimulate research on marijuana, the progress of therapeutics development and clinical trials has been slow, in part due to the increased time, costs, and administrative efforts associated with the regulatory framework for conducting research on these and other Schedule I compounds. Specifically:

The Schedule I registration process: Researchers have indicated that this process creates administrative burdens that can act as significant disincentives to conducting research. Separate registrations are required for each Schedule I substance, state registrations are often required before obtaining the federal license, and they can take a year or more to obtain.

Administrative Processes: Researchers with Schedule I registrations have also reported roadblocks associated with changing administrative procedures – such as changes in DEA drug codes – that lead to delays in obtaining the Schedule I substances to be used in their research.

Single source of marijuana for research purposes: Currently, there is one registration for marijuana cultivation in the US--the University of Mississippi, which, through a contract with NIDA, supports the cultivation and distribution of research grade marijuana for the country. While the NIDA supply of marijuana has diversified to include different strains of interest to researchers, it is not possible to provide access to the diversity of strains and products currently available through state dispensaries.

Widespread perceptions of the difficulty of doing research on Schedule I drugs: The perception throughout the scientific community of barriers to Schedule I research can dis-incentivize scientists from engaging in this type of research. The majority of biomedical research in the country is conducted by graduate students and postdoctoral fellows, who are under significant pressure to complete their research projects in a few years. Many avoid any barriers that may pose significant or unpredictable delays in the initiation of their research.

Discrepancies between federal and state laws: NIH is unable to fund researchers to analyze marijuana products available in state dispensaries, since obtaining these samples violate federal law. Understanding the characteristics of the marijuana that is being dispensed, including the potency (i.e., amount of THC) and concentration of other components (e.g., CBD), is important for studying the impact of medical and recreational marijuana on individual and public health. In addition, there are open questions about the legality of state funded research using marijuana from state dispensaries. Universities and researchers are concerned about the potential impact of this type of research on their ability to obtain DEA licenses or federal funding, even if they are not using federal funds.

Path from use of NIDA-supplied marijuana to market: The University of Mississippi, under the contract with NIDA, currently produces a limited supply of marijuana extracts for researchers to use in drug development. Drug developers would need to transition from using NIDA-supplied marijuana products to other sources before FDA approval and market entry. It may be challenging for a pharmaceutical company to demonstrate equivalency between the marijuana used in the clinical trials and the drug product that will be marketed. While FDA has provided

guidance on how this should occur,⁶⁸ the process requires additional time and resources of the developer.

NIH is committed to working with Congress and our federal partners to facilitate more research on both the harms and therapeutic potential of marijuana and cannabinoids and to reduce barriers to research. NIH will continue working closely with the ONDCP, DEA, and FDA to explore ways to streamline these processes to facilitate research.

⁶⁸ <https://www.fda.gov/OHRMS/DOCKETS/98fr/2000d-1392-gdl0002.pdf>

Basic Biomedical Research

The purpose of basic research is to discover the nature and mechanics of disease and identify potential therapeutic avenues likely to lead to the prevention and treatment of human disease. Without this early scientific investigation, future development of treatments and cures would be impossible. Basic biomedical research must remain a key component of both the intramural and extramural research portfolio at the NIH. The Committee encourages NIH to take actions to ensure the percentage of funding in the extramural research program on basic research does not fall below 55 percent of NIH resources.

Action taken or to be taken:

NIH remains committed to funding basic biomedical research and appreciates the Committee's acknowledgement of the importance of this investment for the health and well-being of Americans. By funding rigorous science, NIH expands our fundamental knowledge of the mechanisms of biology and behavior of living systems, with the goal of applying this knowledge to enhance health. Over half of NIH's research budget has been allocated to basic research. NIH continues to invest in basic research that provides a better understanding of disease mechanisms and progression, risk factors and biological markers that can be used as diagnostic tools, or to develop new cures.

NIH strives to maintain a carefully balanced portfolio in a variety of ways, including balancing basic, translational and clinical research. NIH funding for basic biomedical research must also balance supporting research directly, with supporting the infrastructure that makes research possible, as well as supporting training programs for the highly-skilled scientists that are integral for being able to solve tomorrow's problems. In addition, because medical advancements may arise from unexpected discovery, it is critical that our investment spans a broad range of scientific and health-related areas. By funding a broad, well-balanced, and sufficiently diverse basic research portfolio, NIH continues to provide these opportunities and ensures the vitality and productivity that is necessary for tomorrow's breakthroughs.

Basic Molecular Science

The Committee understands basic science is the foundation of the research pyramid that support biomedical and translational research efforts. The Committee is concerned with the recent decrease in the proportion of basic research. The Committee encourages NIH to expand its basic science efforts, with a specific focus on basic molecular research to increase scientific understanding at the molecular level in an effort to support translational molecular medicine research of tomorrow. The Committee requests an update in the fiscal year 2019 CJ on the percentage of spending on basic science for the past 10 years and specific efforts to promote basic research that supports molecular medicine and regenerative medicine using induced pluripotent stem cells.

Action taken or to be taken:

NIH remains committed to funding basic molecular research and appreciates the Committee's acknowledgement of the importance of this investment for the health and well-being of Americans. By funding rigorous science, NIH expands our fundamental knowledge of the mechanisms of biology and behavior of living systems, with the goal of applying this knowledge to enhance health. Over half of NIH's research budget has been allocated to basic research. NIH continues to invest in basic research that provides a better understanding of disease mechanisms and progression, risk factors and biological markers that can be used as diagnostic tools, or to develop new cures.

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NIH will continue to carefully balance our portfolio as outlined in the NIH-Wide Strategic Plan for Fiscal Years 2016-2020,⁶⁹ including substantial support for molecular medicine initiatives. For example, Cryo-Electron Microscopy (Cryo-EM) is an innovative technology that allows scientists to visualize biological structures at a molecular level, in order to reveal potential therapeutic targets for diseases like cystic fibrosis.⁷⁰ NIH is also investing in regenerative medicine efforts, including the Common Fund's Regenerative Medicine Program, which is aimed at addressing challenges in translating the use of induced pluripotent stem cell (iPSC)-based therapies from the lab to the clinic, including basic research on the factors that can induce stem cells to mature into key cell types like neurons.⁷¹ Collectively, these investments will lay the foundation for breakthroughs that could lead to new possibilities for patients.

⁶⁹ <https://www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf>

⁷⁰ <https://directorsblog.nih.gov/2017/07/20/another-milestone-in-the-cystic-fibrosis-journey/>

⁷¹ <https://commonfund.nih.gov/Stemcells/>

Big Data Infrastructure

In 2012, NIH began an extramural program to provide a framework of pilot programs, centers of excellence, and grant opportunities to advance thinking in how to organize, share, and use big data. NIH is using the results from these programs to inform the next phase of development of big data infrastructure, including the ongoing Data Commons Pilot. The second phase is expected to also build off of several other major initiatives including those in cancer, Alzheimer's disease, the human brain, and the All of Us research program. The Committee wants to ensure that these efforts are coordinated and overseen to ensure all of NIH benefits from them. In the interim, the Committee directs NIH to provide a status report in the fiscal year 2019 CJ describing the current status of the strategic plan and its progress in finding a suitable candidate to fill the Associate Director for Data Science [ADDS] vacancy. The Committee recognizes the importance of the ADDS to provide strategic vision and coordinate as an honest broker across NIH on data science issues, and encourages NIH to locate this position within the Office of the Director.

Action taken or to be taken:

We thank the Committee for its continuing interest in this important area. The NIH Scientific Data Council (SDC) is developing the NIH-wide Strategic Plan for Data Science, as directed by the Committee. The SDC is the trans-NIH body that represents Institute and Center (IC) leadership and key components of the Office of the Director on matters pertaining to data science and scientific computing. The SDC, a sub-committee of the NIH Steering Committee, is made up of IC directors and deputy directors, and key subject matter experts. It develops recommendations for the NIH Director and IC leaders on strategic objectives to address critical long-term needs for data science and plan to attain these objectives. The SDC is responsible for overseeing the execution of the plan once they are approved by the NIH Director. The group has developed a framework for the Strategic Plan for Data Science that it will present to the IC directors and other NIH leaders at the NIH Leadership Forum in November 2017. Based on input received from NIH senior leadership, the SDC will refine the framework and develop a draft strategic plan. Stakeholder feedback on the strategic plan will be solicited in early 2018. The final plan will include overall goals, strategic objectives to support each goal, implementation tactics to achieve each objective, and performance measures and milestones to track progress and allow mid-course corrections. The Strategic Plan for Data Science will be aligned with the NIH-wide Strategic Plan to ensure that the former optimally supports the latter. As part of the Strategic Plan for Data Science, the SDC will delineate short, medium, and long-term priorities under each overall goal so that resources can be deployed effectively and future needs can be determined.

To help inform its strategic planning process, the SDC has received regular updates on the status of the NIH Data Commons Pilots. Additionally, as part of its oversight responsibilities, the SDC reviews the funding plans for the Data Commons Pilot activities. A primary focus of the SDC is to ensure that the data science infrastructure needs of NIH as a whole, in addition to the needs of individual ICs, are considered.

The Associate Director for Data Science (ADDS) position is important for developing and coordinating trans-NIH initiatives in conjunction with the SDC; serving as an interface with stakeholders and other agencies; identifying and disseminating best practices; and advising the NIH Director, senior leadership, and the SDC on issues related to data science. Currently, the principal deputy of NIH, Dr. Lawrence A. Tabak, is serving as the interim ADDS. Dr. Tabak, with other members of the NIH Office of the Director is currently developing an updated position description for the ADDS and an optimized organizational plan for the ADDS Office. The NIH hopes to be in a position to recruit a senior-level candidate for this role in the near-future.

Bilateral Renal Agenesis

The Committee requests NIH conduct a state of the science report on bilateral renal agenesis research, possible treatments, and related dialysis for preemies and newborns, and provide an update in the fiscal year 2019 Congressional Justification.

Action taken or to be taken:

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports research to understand the mechanisms underlying bilateral renal agenesis (the absence of both kidneys at birth). Current research efforts in animal models (primarily mice) are investigating normal and abnormal kidney development. Multiple developmental processes have already been identified in which absence of specific molecules or receptors result in limited or completely absent kidney formation. NIDDK also supports a significant body of research aimed at understanding the biology of human kidney development. For example, the NIDDK-supported human GenitoUrinary Development Anatomy Project (hGUDMAP) consortium was initiated to establish a comprehensive understanding of human kidney and urinary tract tissue development to inform the study of defective organ development, tissue maturation and aging, and changes that occur in disease.

In addition, NIDDK supports research to improve the two current treatment options for bilateral renal agenesis: dialysis and kidney transplantation. NIDDK supports a range of research to improve the quality of life for people undergoing dialysis, in areas such as vascular access, nutritional treatments, and technological advancements. The Chronic Kidney Disease in Children study follows children age 1-16 years with mild – moderate kidney disease, and continues to follow them if they proceed to dialysis and/or transplantation. Research to increase access to and health benefit from kidney transplantation for patients with kidney failure also remains a priority for NIDDK.

Bilateral renal agenesis causes a reduction or deficiency in amniotic fluid (oligo/anhydramnios), which can lead to additional malformations in the developing baby. Therefore, renal agenesis was one of the topics discussed at a conference on oligo/anhydramnios, sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), entitled “Workshop on Developmental Renal Malformations, Oligo/Anhydramnios: Pathophysiology and Clinical Aspects,” which was held on August 8, 2016.⁷² NIDDK cosponsored the conference. The epidemiology and genetic basis of renal agenesis were among the topics of discussion. A summary of the workshop and its outcomes is in preparation.

⁷² <https://www.nichd.nih.gov/about/meetings/2016/Pages/080816.aspx>

Biomarkers

Committee encourages NIDDK to accelerate the discovery and validation of biomarkers to aid in designing and conducting clinical trials to prevent, treat, and cure type 1 diabetes. The Committee also encourages NIDDK to work with NIAID to develop biomarkers specifically related to immune interventions for multiple autoimmune diseases, including type 1 diabetes.

Action taken or to be taken:

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) continues to support biomarker research with several efforts. In addition to conducting clinical trials to prevent or reverse type 1 diabetes, NIDDK's Type 1 Diabetes TrialNet conducts mechanistic studies alongside these trials to identify and validate new biomarkers with additional support from the National Institute of Allergy and Infectious Diseases (NIAID). NIDDK also collaborates with NIAID's Immune Tolerance Network (ITN), a clinical research network to evaluate novel tolerance-inducing therapies and identify biomarkers of disease activity and response to treatment for immune-mediated diseases, including type 1 diabetes. For example, biosamples collected from some TrialNet trial participants with newly diagnosed diabetes are currently being tested and analyzed with ITN. TrialNet scientists are also collaborating with JDRF-funded scientists on a new project to investigate gene expression in immune cells in a study of type 1 diabetes progression. Discovery of biomarkers is also a goal of NIDDK's The Environmental Determinants of Diabetes in the Young (TEDDY) study, which aims to identify environmental triggers of type 1 diabetes by following over 6,000 children at high genetic risk. The over 3.5 million biosamples collected to date are currently being analyzed by leading bioinformaticians taking advantage of state-of-the-art technologies; efforts to identify immune biomarkers from TEDDY is also supported by NIAID. Results from TrialNet and TEDDY studies are further refining type 1 diabetes risk, and identifying intermediate endpoints for clinical trials, which could facilitate smaller, shorter, and simpler clinical trials.

Investigators in the Human Islet Research Network's (HIRN) Consortium on Beta Cell Death and Survival are developing technologies and approaches to interrogate human pancreatic tissues, islets, and blood to discover highly specific biomarkers of beta cell injury in asymptomatic type 1 diabetes and developing strategies to step beta cell destruction early in the disease process. HIRN researchers have made exciting progress, developing novel assays that can detect uniquely marked, fragmented DNA released by dying beta cells. To accelerate this research, HIRN collaborates with TrialNet, capitalizing on biosamples collected in TrialNet for validation of newly discovered biomarkers. Another new NIDDK effort in biomarker research is an award to researchers conducting the Glycemic Reduction Approaches in Diabetes: A Comparative Effectiveness Study to address racial differences in the HbA1c test, a measure of long-term blood glucose control. Knowledge stemming from this effort would provide benefit to people with either type 1 or type 2 diabetes. NIDDK also encourages research to identify biomarkers of diabetic complications: in FY17, the Diabetic Complications Consortium announced a funding opportunity for discovery of biomarkers in foot ulcer development/progression.

In addition, NIAID intramural scientists conduct basic research on biological pathways that may be common to multiple autoimmune diseases. For example, NIAID researchers investigating the autoimmune disease psoriasis are studying a biomarker that may play a role in other immune-mediated diseases such as Crohn's disease. Recent discoveries in NIAID's animal model studies

have led to new insights into the psoriasis biomarker and related immune mechanisms of the disease that may inform research on other autoimmune diseases with similar underlying mechanisms.

Biomaterials

The Committee is pleased that NIDCR is exploring approaches to prevent dental caries with probiotic therapy, and in the development of biomaterials. The Committee encourages NIDCR to increase its investment in the development of new and improved biomaterials for use in clinical settings to enhance the prevention and treatment of caries.

Action taken or to be taken:

The National Institute of Dental and Craniofacial Research (NIDCR) supports research to increase the longevity and durability of dental materials for use in clinical settings to enhance the prevention and treatment of caries. Standard treatment for caries involves the application of dental restoratives to replace damaged tooth tissue (a filling) or using a tooth-shaped “cap” to cover the damaged tooth (a crown). However, exposure to the stresses of the mouth, such as chewing and oral bacteria, can lead to damage of the restoration or recurrent dental decay. As a result, fillings or crowns often need to be replaced within 8-10 years. NIDCR-funded research includes a broad range of studies designed to improve restorative materials and dental crowns, enhance the adhesives used to attach them to the tooth, and uncover novel approaches for strengthening and regenerating damaged teeth.

NIDCR-supported investigators are designing potent antibacterial resins with re-mineralizing properties for use in dental composites and adhesives. Researchers are also creating a new form of high-strength ceramics – strong, yet translucent, these dental materials are designed to preserve tooth appearance and structure while extending service life. To reduce the incidence of dental crowns cracking, another group of researchers has developed a computational modeling tool that enables scientists to speed up the discovery process and streamline the development of novel dental materials.

At the center of each tooth lies the dental pulp – a living tissue that contains nerves and blood vessels, as well as stem cells that can form new tooth tissue. Normally dental pulp is covered by a hard layer of enamel. If dental pulp becomes exposed, the result is painful inflammation of the tooth. NIDCR-supported researchers have identified a compound called phenamil that activates dental pulp stem cells to produce new tooth tissue. In the future, researchers hope to integrate phenamil into the protective materials used to cover exposed dental pulp – to stimulate natural tooth repair and help avoid the need for a root canal. Looking to the future, NIDCR is supporting research to ensure new and improved biomaterials are durable and suitable for clinical use to improve the prevention and treatment of caries.

Blepharospasm

The Committee encourages NEI to expand research on blepharospasm, a form of dystonia.

Action taken or to be taken:

Blepharospasm is a condition characterized by sustained and involuntary eye twitching and blinking. Although the direct cause of the disease is not known, the symptoms are associated with abnormal function of a region in the brain that controls movement, called the basal ganglion. In rare cases, having a family history of the disease may be associated with developing blepharospasm, but most people develop blepharospasm without any warning symptoms. The onset may begin with a gradual increase in blinking or eye irritation. Some people may also experience fatigue, emotional tension, or sensitivity to bright light. As the condition progresses, the symptoms become more frequent, and patients may develop facial spasms. Interestingly, blepharospasm may decrease or cease while a person is sleeping or concentrating on a specific task.

To date, there is no successful cure for blepharospasm, although several treatment options can reduce its severity. For example, in the United States, the injection of Oculinum (Botox) into the muscles of the eyelids is an approved treatment for blepharospasm since the botulinum toxin, produced by the bacterium *Clostridium botulinum*, paralyzes the muscles of the eyelids. Although medications for blepharospasm that can be taken by mouth are available, they usually produce unpredictable results, and any symptom relief is usually short-lived and tends to be helpful in only 15 percent of the cases. Another treatment option is myectomy, a surgical procedure to remove some of the muscles and nerves of the eyelids. This surgery has been shown to improve symptoms in 75 to 85 percent of people with blepharospasm. At the National Eye Institute (NEI), blepharospasm research is funded within the Oculomotor Systems Program. Furthermore, the NEI Corneal Diseases Program, which covers ocular surface conditions, includes research on the causes and treatments of blepharitis, an inflammation of the eye lids, which can cause some eye twitching. NEI research is applying new tools in genetics, immunology and neuroscience to expand understanding of various causes and develop treatments for blepharospasm. For example, recent research has explored whether transcranial magnetic stimulation can be used as a safer, non-invasive treatment for patients who don't respond to medications by reducing neuron excitability in specific regions of the brain that control the involuntary eyelid twitching. NEI remains committed to continuing research on and finding effective treatment options for blepharospasm.

Botanical Products and Opioid Addiction

The Committee commends the FDA for establishing guidelines and opening pathways for Investigational New Drug [IND] applications for botanical drugs. Over the past two decades, the dramatic increase in abuse of prescription opioids, non-synthetic opioids, and illicit synthetic opioids has grown to epidemic proportions. Scientific rationale and laboratory studies suggest a decrease in addictive potential when botanical derivatives, including cannabidiol extracts, are used with an opioid in treating patients. The Committee supports study of this integrative approach to treatment and urges NIH, including NIDA, NCCIH, and OCCAM, to support and facilitate trials aimed at reducing addiction under appropriate IND applications.

Action taken or to be taken:

Opioid dependence is a major problem throughout the United States and chronic pain is one of the major factors driving the current crisis. There is research suggesting potential therapeutic value of cannabinoids in certain health conditions. The FDA has approved the cannabinoid medications Marinol (dronabinol), Syndros (dronabinol), and Cesamet (nabilone), for severe nausea and wasting in patients with HIV and cancer. These medications contain synthetic cannabinoids similar to delta-9-tetrahydrocannabinol (THC), which is the main active ingredient found in the marijuana plant. However, patients throughout the country are using marijuana strains and extracts that have not undergone rigorous clinical trials, are not regulated for consistency or quality, and have an insufficient evidence base to support their effectiveness.

There is a pressing need for more research on the potential therapeutic benefits and potential harms of cannabinoids. The progress of therapeutics development and clinical trials has been slow, in part due to increased time, costs, and administrative efforts associated with the regulatory framework for conducting research on these and other Schedule I compounds. NIH is committed to working with our Federal partners to facilitate more research on the therapeutic potential and potential harms of cannabinoids and other botanicals, and to reduce barriers to research.

NIH welcomes investigator-initiated research proposals for pre-clinical and clinical research evaluating cannabinoids and other botanicals for treating pain and other conditions. In addition, to facilitate research on the therapeutic potential of cannabinoids, NIH has released funding opportunity announcements to develop the therapeutic potential of the endocannabinoid system for pain treatment and to promote clinical evaluation of adjuncts to opioid therapies for the treatment of chronic pain.

Another area of interest to NIH is the use of kratom for the treatment of chronic pain and addiction. Kratom is a plant native to Southeast Asia that contains the opioid-like compounds mitragynine and 7-hydroxymitragynine, and is widely used to self-treat for chronic pain, as well as for opioid and alcohol withdrawal symptoms. NIH-supported research has demonstrated that the active ingredients in kratom show some promise as analgesics, with limited physical dependence and respiratory depression. As of November 14, 2017, the FDA has issued a public health advisory⁷³ relating to the Agency's mounting concerns regarding risks associated with the use of kratom.

⁷³ <https://www.fda.gov/newsevents/publichealthfocus/ucm584952.htm>

The National Center for Complementary and Integrative Health (NCCIH) seeks to support research to understand the biology of pain and to evaluate non-pharmacologic pain management approaches and reduce addiction by decreasing opioid exposure. Research on botanicals and other natural products as potential pain relievers is a major area of interest to the NCCIH. The Center seeks to streamline clinical research on natural products through a phased research pipeline starting with early phase studies exploring the mechanism of action of natural products to demonstrate the products are reproducibly biologically active. The most promising compounds will advance to the later research phases that support investigations evaluating clinical outcomes and biological effects through randomized controlled efficacy trials.

NCCIH has issued four funding opportunity announcements for clinical trials of natural products, and pain is listed as a high priority topic. Investigators supported by NCCIH are conducting a study that may provide critical data on the effects of edible marijuana, including impact, dosing, routes of administration, or negative side effects, in individuals with chronic low back pain. The NIH Office of Dietary Supplements, in partnership with NCCIH, supports the Centers for Advancing Research on Botanical and Other Natural Products (CARBON) which are developing new technologies to characterize and determine the biological activity of natural products. The NCCIH botanical-drug interaction program is planning to test potential interactions between marijuana and other drugs.

The National Cancer Institute and the National Institute on Drug Abuse are currently supporting an investigator-initiated research project to evaluate synthetic cannabinoids designed to suppress chronic inflammatory and neuropathic pain symptoms, while avoiding central nervous system side effects. The project will evaluate the cannabinoids in mouse models of oral cancer to determine their effectiveness against cancer pain and chemotherapy-induced neuropathic pain, as well as their antitumor potential.

Brain Aneurysm Research Funding Levels

The Committee is concerned that an estimated one out of every 50 individuals in the U.S. has a brain aneurysm and an estimated 30,000 Americans suffer a brain aneurysm rupture each year, with little to no warning. Ruptured brain aneurysms are fatal in about 40 percent of cases. The Committee requests a report from NINDS regarding its annual funding level for brain aneurysm research funding over the past five years, including the types of grants supported.

Action taken or to be taken:

The NIH reports categorical spending on hundreds of topics through the Research, Condition, and Disease Categorization (RCDC) system. The RCDC system does not have a separate category for brain aneurysm research, which, like the other subtypes of cerebrovascular accidents, is captured in research categories such as “stroke” and “cerebrovascular”. However, approximate, unofficial numbers can be obtained by conducting a text-search in the NIH RePORTER⁷⁴ public search tool, which draws upon a database of NIH-funded grants. Using this approach, we estimate that NIH spent an average of \$24 million per year over the last five years on brain aneurysm research. This unofficial spending total includes projects funded through traditional R01 grants; specialized translational research initiatives (including the Small Business Innovation and Technology Transfer Research (SBIR/STTR) programs; and large, multi-disciplinary team science.

The research portfolio on brain aneurysms is diverse and includes projects exploring basic vessel biology, identifying molecular and genetic pathways that underlie aneurysm development and rupture, and the development of effective prevention and treatment strategies.

For example, NIH supports work to understand how changes in vessel wall molecular and cellular constituents may influence functional properties of the vessels and blood flow. NIH-funded investigators are also exploring changes in the brain’s blood vessels that trigger or exacerbate aneurysm development; and genetic, lifestyle, and other risk factors and associated molecular pathways related to aneurysms and hemorrhagic stroke. Further, NIH-funded research seeks to better understand injury mechanisms that occur when blood ruptures into the brain tissue and cerebrospinal fluid. Clinical trials are underway to test therapies that may improve patient outcomes after brain hemorrhage and hemorrhage into the brain’s fluid-filled ventricles. Initial survivors of aneurysm rupture are at high short-term risk of ischemic stroke due to vasospasm, and understanding how to protect the brain from ischemia is a major emphasis of NIH-funded research. NIH-supported research data informs patients and doctors about the risk of rupture in asymptomatic individuals found to have an aneurysm. This data is critical in determining the risks and benefits of neurosurgical or neurovascular aneurysm treatment.

Pre-clinical and early phase clinical research supported by the NIH are developing new approaches to medical or surgical management of brain aneurysms. Investigators have developed a nanomatrix coating for platinum coils that are commonly placed in aneurysms to prevent rupture in order to determine whether the coating improves the coil’s effectiveness by mimicking properties of the body’s own tissue. Another innovative project is developing and testing an expandable, space-filling polymer device to improve aneurysm healing and reduce risk of recurrence. Another approach being tested by NIH-funded investigators is the use of a non-toxic, liquid protein polymer that could be used to deliver therapeutics directly into the aneurysm to reinforce the weakened vessel walls and stimulate healing. Recent animal studies by NINDS-

⁷⁴ <https://projectreporter.nih.gov/reporter.cfm>

supported investigators indicate the potential for aspirin to stabilize aneurysms and reduce the rate of rupture-related hemorrhage, pointing to another potential medical strategy for further investigation. In early human studies, NIH-funded investigators are testing computer-based simulation of blood flow through the full cerebral arterial vasculature with the ultimate goal of improving effectiveness and safety of current aneurysm treatment devices and to potentially predict recurrence of already treated aneurysms. In another early phase clinical evaluation, NIH-funded investigators are testing a drug that may prevent delayed cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage who undergo clipping of the culprit cerebral aneurysm.

Brain Aneurysm Research

The Committee is concerned that an estimated 1 out of every 50 individuals in the United States has a brain aneurysm and an estimated 30,000 Americans suffer a brain aneurysm rupture each year, with little to no warning. Ruptured brain aneurysms are fatal in about 40 percent of cases. Despite the widespread prevalence of this condition and the high societal cost it imposes on our Nation, the Federal Government only spends approximately \$0.83 per year on brain aneurysm research for each person afflicted with a brain aneurysm. The Committee is concerned that not enough research is focused on prevention and requests a report regarding the annual support level for brain aneurysm research funding over the past 5 years, including the types of grants supported in the fiscal year 2019 CJ.

Action taken or to be taken:

The NIH reports categorical spending on hundreds of topics through the Research, Condition, and Disease Categorization (RCDC) system. The RCDC system does not have a separate category for brain aneurysm research, which, like the other subtypes of cerebrovascular accidents, is captured in research categories such as “stroke” and “cerebrovascular”. However, approximate, unofficial numbers can be obtained by conducting a text-search in the NIH RePORTER⁷⁵ public search tool, which draws upon a database of NIH-funded grants. Using this approach, NIH spent an average of \$24.4 million per year over the last five years on brain aneurysm research. This unofficial spending total includes projects funded through traditional R01 grants; specialized translational research initiatives (including the Small Business Innovation and Technology Transfer Research (SBIR/STTR) programs; and large, multi-disciplinary team science.

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⁷⁵ <https://projectreporter.nih.gov/reporter.cfm>

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Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative

The Committee continues its strong support for the BRAIN Initiative and provides \$400,000,000 in fiscal year 2018. The Committee commends the NIH for its leadership to date on the BRAIN Initiative and the progress made in several areas. The BRAIN Initiative is developing a more complete understanding of brain function and has the possibility of helping millions of people who suffer from a wide variety of neurological and psychiatric disorders such as Parkinson's disease, schizophrenia, Alzheimer's disease, depression, and traumatic brain injury. Powerful new technologies and tools are allowing for the study of anatomical and functional abnormalities in neuro-psychiatric diseases, which is the key to understanding these diseases and developing therapies and cures.

Action taken or to be taken:

NIH utilizes the external scientific community's expert recommendations for achieving the goals of the Brain Research through Brain Research through Advancing Innovative Neurotechnologies® (BRAIN)⁷⁶, articulated in *BRAIN 2025: A Scientific Vision*. Outstanding scientists assist the NIH in ensuring a coordinated and focused effort across the agency through the BRAIN Multi-Council Working Group,⁷⁷ which also facilitates communication among federal BRAIN agencies by including representatives from NSF, DARPA, IARPA and FDA. Along with private partners, these groups coordinate activities and enhance collaboration as members of the public-private BRAIN Initiative Alliance⁷⁷. In October 2017, NIH announced 110 new awards addressing the seven scientific priorities outlined in *BRAIN 2025*, ranging from an unprecedented team project to generate a census of brain cells, to creating new neuroimaging technologies. NIH BRAIN-funded investigators are encouraged to collaborate across all BRAIN funding agencies, in part, through annual BRAIN Initiative Investigators' meetings, the fourth of which will occur in April 2018.

NIH continues to explore ways to broaden the impact of the BRAIN Initiative, and funded projects are on course to increase the yield of data and research tools for the research community. One FY2018 priority is the BRAIN Initiative Cell Census Network (BICCN), a major effort to create a comprehensive reference of the diverse brain cell types across species. Therefore, new BRAIN funding opportunities include development of tools for facilitating detailed brain micro-connectivity analysis and methods to characterize non-neuronal cells in the brain. Other NIH funding opportunities call for research on ethical issues associated with BRAIN Initiative advancements, human brain imaging, neural circuits, and invasive human neuroscience, as well as supporting technology integration and dissemination. With over 260 scientific articles published through October 2017, BRAIN Initiative grants are delivering numerous technologic and scientific breakthroughs, with the potential for advances in a wide variety of neurological and psychiatric disorders.

Through the BRAIN Initiative, new technologies will amplify our ability to precisely monitor and therapeutically change brain circuit activity, elucidating how individual cells and complex neural circuits interact in normal and disordered conditions. Novel tools enable scientists to study the brain in animal models, uncovering secrets of how the brain processes information. As these powerful technologies advance toward future human use, BRAIN researchers are creating

⁷⁶ NIH BRAIN Initiative website: <http://braininitiative.nih.gov/>

⁷⁷ BRAIN Initiative Alliance website: <http://www.braininitiative.org/>

tools to improve brain health in the short-term. For example, machine learning algorithms and image analysis techniques help researchers identify precursors of Alzheimer's disease. Investigators are using advanced deep brain stimulation (DBS) electrodes to understand better the disordered neural circuit activity that underlies Parkinson's disease, obsessive-compulsive disorder, and depression, which enables improved therapeutic use of DBS for these conditions. Other researchers are studying how DBS might activate brain circuits important in recovery after stroke. NIH will continue to submit budget requests at levels appropriate to achieving all goals of the BRAIN Initiative.

Building and Facilities

The Committee notes NIH has a significant backlog of maintenance and repairs. The Committee requests NIH and HHS develop a coordinated plan to address the backlog with the Office of Management and Budget in the fiscal year 2019 Congressional Justification.

Actions taken or to be taken:

NIH shares the concerns expressed by Congress regarding the Backlog of Maintenance and Repair (BMAR). As directed by Congress, NIH has awarded a contract to the National Research Council to “*prepare a report that assesses the capital needs of NIH’s main campus. The report should identify facilities in greatest need of repair, describe the work needed to bring them up to current standards, and include cost estimates for each project.*” Additionally, NIH has developed a multi-faceted plan to address the BMAR over the next five years (2019– 2023). Under each strategy below, we have added the associated projects in italics.

Strategy 1: The first focus area is to conduct targeted improvements to our highest risk facilities. *Replace Surgery, Radiology and Laboratory Medicine (SRLM) with a New Surgery & Radiology Wing for the Clinical Research Center (\$486M).*

Strategy 2: A second strategy is disposing of facilities that are beyond economical repair. *Replace Building 14 Group Animal facility with a new Center for Disease Research (CDR) Building adjacent to Building 10 (\$412M).*

Strategy 3: A third leg of our approach is increasing the authority at the National Cancer Institute’s Frederick facility to use operating funds for Repairs and Improvements. *Increase this authority to \$50M for NCI-Frederick.*

Strategy 4: A fourth prong of our approach is to leverage the Nonrecurring Expenses Fund (NEF). *As suggested by the Committee, NIH and HHS are exploring the potential of increasing the use of the NEF to reduce the backlog (\$150M per year).*

Strategy 5: A fifth facet of our strategy regards a five-year surge in the Buildings & Facilities appropriation, subject to HHS, OMB and Congressional support. *Specifically, NIH will request an increase in the B&F appropriation from \$128 million to \$525 million for Fiscal Years 2019 through 2023. This is additive to Strategies 1 through 4. If these funds are provided, NIH estimates that all clinical and laboratory buildings will have a Condition Index of 90 or above and all office buildings will have a Condition Index of 60 or above.*

In summary, given the magnitude of the BMAR and its impact upon the NIH mission, NIH proposes the use of the above-described strategies to support the NIH mission, achieve scientific discoveries, and assure the safety of our patients, visitors and staff.

Cancer and Mitochondria

The Committee commends the NCI for its work in establishing a Mitochondrial Model Organisms and Cellular Systems Working Group and for its work to identify needs, barriers, and opportunities pertaining to mitochondrial biology relevant to addressing mechanistic questions in cancer. The Committee encourages the NCI to continue to support qualified research studies that examine the mechanisms by which cancer cells utilize oxidative stress in stromal cells to fuel their growth.

Action taken or to be taken:

The National Cancer Institute (NCI) conducts and supports basic science related to mitochondrial biology through both its extramural and intramural research portfolios. For example, NCI intramural researchers examine the mitochondrial stress response to the protein ubiquitin system. Using state-of-the-art imaging technologies, NCI researchers, in collaboration with the National Heart, Lung, and Blood Institute (NHLBI), reported the first clear evidence that muscle cells distribute energy primarily by the rapid conduction of electrical charges through a vast, interconnected network of mitochondria in a way that resembles the wire grid that distributes power throughout a city.⁷⁸ This new information may lead to a better understanding of many diseases linked to energy utilization in the heart and skeletal muscle, such as heart disease, mitochondrial diseases, and muscular dystrophy.

NCI also supports numerous extramural research projects seeking to better elucidate the biology of mitochondria and their role in oncogenesis and cancer cell biology.⁷⁹ NCI-supported scientists also aim to describe mechanisms that are shared between diseases with either germline (inherited) or somatic (acquired) mutations that affect mitochondria function.⁸⁰ NCI seeks to further enhance scientific understanding across the mitochondrial research community through supporting the development of common pre-clinical tools and model systems.

As part of the Cancer MoonshotSM, NCI supports research seeking to understand the evolution of human tumors by documenting the genetic lesions, molecular pathways, and cellular interactions that guide tumor development from pre-cancerous tissue to primary cancer to metastatic disease.⁸¹ The role of mitochondrial dysfunction in these processes is acknowledged but not fully understood, and therefore it will be an important complementary area of investigation. Included in this area, the role of mitochondria in the development of drug resistant tumors will be examined, with the hope of developing new therapeutic agents which may target mitochondria. Researchers have also begun to uncover a role for mitochondria in the immune response, which could play a role in immunotherapy for both children and adults. This is particularly important for treating children, because pediatric cancers often harbor fewer mutations than adult tumors and this can make them less responsive to current immunotherapies that were developed for adult cancers.

⁷⁸ <https://www.nih.gov/news-events/news-releases/high-resolution-3d-images-reveal-muscle-mitochondrial-power-grid>

⁷⁹ <https://www.cancer.gov/about-nci/organization/dcb/research-portfolio/ccbr>

⁸⁰ <https://www.cancer.gov/about-nci/organization/dcb/research-portfolio/dcar>

⁸¹ <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/funding>

NCI also supports research on scientific questions focused on determining whether mitochondrial markers may help to identify new cancer risk factors, specifically in racial and ethnic groups, and how scientists can use mitochondrial proteomic information to understand gene-environment, gene-gene, and cancer development interactions. Other research is dedicated to characterizing mitochondrial involvement in gliomas and ovarian, breast, and colorectal cancer.

NCI has asked the research community, as part of its Provocative Questions (PQ) initiative, to submit grant applications in response to the question, “How does mitochondrial heterogeneity influence tumorigenesis or progression?” This PQ, developed in response to suggestions from the cancer research community, draws attention to the lack of a mechanistic framework to describe how mitochondrial variation is expressed in cancer cell subtypes, or how these differences in mitochondria impact tumorigenesis and cancer progression. Fourteen grants were awarded through this PQ funding opportunity.⁸² NCI is supporting research to develop insights into how mitochondrial processes and function are altered in cancer, which may help researchers better understand cancer cell plasticity and survival advantages, thus, leading to more effective treatment and prevention strategies. In 2017, NCI issued a new funding opportunity⁸³ seeking research projects that examine how inter-organelle communication in cancer cells and/or tumor-associated cells affects cellular function, adaptation, and phenotypic plasticity. NCI also supports five Outstanding Investigator Awards (OIA)⁸⁴ focused on mitochondrial biology. The OIA awards support investigators with outstanding records of productivity in cancer research by providing extended funding stability and encouraging investigators to continue or embark on projects of unusual potential in cancer research.

NCI also participates in several NIH-wide collaborative efforts aimed at better understanding mitochondrial disease. The Trans-NIH Working Group on Mitochondrial Disorders⁸⁵ is co-chaired by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of General Medical Sciences (NIGMS) and has developed working groups to identify areas for collaboration across Institutes that will strengthen research activities related to mitochondrial disorders. In addition, working group members participate on Common Fund Initiatives that relate to mitochondrial function, including the Molecular Transducers of Physical Activity.

Finally, the Mitochondrial Model Organisms and Cellular Systems Working Group, established by the NCI in partnership with the Office of Dietary Supplements, has produced a manuscript entitled, “Nutritional Interventions for Mitochondrial OXPHOS Deficiencies: Mechanisms and Model Systems,” that will be published in the *Annual Review of Pathology: Mechanisms of Disease* in early 2018. This publication will bring further awareness to this important area of scientific research.

⁸² <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-017.html>, <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-018.html>

⁸³ <https://grants.nih.gov/grants/guide/pa-files/PA-17-203.html>, <https://grants.nih.gov/grants/guide/pa-files/PA-17-204.html>

⁸⁴ <https://www.cancer.gov/research/nci-role/spotlight/oia>

⁸⁵ <https://dpcpsi.nih.gov/collaborations/committees.aspx?TID=2#100>

Cancer Kinome

The Committee is aware that research into the role of kinases-enzymes in the human genome that regulate an immense variety of cellular function-holds the promise to drive the development of new treatments and cures for a variety of cancers, including ovarian cancer. The challenge today is to collectively investigate the role of the kinome in triggering cancer and gaining a better understanding of which kinases play a role in cancer development in particular patients, and how kinome "reprogramming" contributes to resistance to anti-cancer drugs. NCI is asked to support this type of promising personalized medicine research.

Action taken or to be taken:

The National Cancer Institute (NCI) continues to conduct and support research to describe the basic science of kinases, their role in oncogenesis, and the ways in which these findings may be leveraged to develop novel cancer therapies. Many cancers exhibit changes in genes that code for kinases – enzymes that regulate numerous cellular activities such as proliferation, survival, movement, and programmed cell death. Thus, kinases are the focus of intense basic and drug discovery research, and the U.S. Food and Drug Administration (FDA) has approved more than 30 small-molecule kinase inhibitors.

Kinases are crucial players in many critical signaling pathways, which are themselves controlled by complex negative feedback loops that keep cell proliferation in check. Upon cancer treatment by kinase inhibitors, these feedback loops may be silenced, resulting in re-activation or activation of other pathway components, rendering the cancer therapy ineffective. This resistance mechanism to treatment, called adaptive kinome reprogramming, is the subject of robust scientific interest.

In addition to basic research into the mechanisms of adaptive kinome reprogramming, the NCI funds research on this topic as it relates to a variety of cancer types. With the goal of identifying new therapeutic targets, NCI-supported scientists are seeking to elucidate specific cellular signaling pathways, including pathways related to pancreatic cancer,⁸⁶ neurofibromatosis,⁸⁷ renal cell carcinoma,⁸⁸ and other cancer types.⁸⁹ Ongoing studies focused on describing how cancer

⁸⁶https://projectreporter.nih.gov/project_info_description.cfm?aid=9212790&icde=36563875&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball

⁸⁷https://projectreporter.nih.gov/project_info_description.cfm?aid=9264991&icde=36563834&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball

⁸⁸https://projectreporter.nih.gov/project_info_description.cfm?aid=9344561&icde=36563944&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball

⁸⁹https://projectreporter.nih.gov/project_info_description.cfm?aid=9214322&icde=36563546&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball

cells become resistant to kinase inhibitors and how to overcome this resistance include projects focused on neuroblastoma,^{90,91,92} chronic myeloid leukemia,⁹³ and pancreatic cancer.⁹⁴

Clinical trials incorporating adaptive kinome reprogramming bring the knowledge gained through basic and translational research to patients. The NCI's Alliance for Nanotechnology supports a team at M.D. Anderson Cancer Center conducting a phase I trial of a therapy targeting the activity of the kinase EphA2 in advanced ovarian, breast, prostate, lung, endometrial, and pancreatic cancers.⁹⁵ In addition, NCI is supporting clinical trials on adaptive kinome reprogramming to melanoma,⁹⁶ squamous cell carcinoma of the head and neck,⁹⁷ and tumors of the pediatric nervous system.⁹⁸

⁹⁰https://projectreporter.nih.gov/project_info_description.cfm?aid=9271153&icde=36563744&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

⁹¹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9359221&icde=36563674

⁹²https://projectreporter.nih.gov/project_info_description.cfm?aid=9390172&icde=36563629&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

⁹³https://projectreporter.nih.gov/project_info_description.cfm?aid=9221976&icde=36563897&ddparam=&ddvalue=&ddsub=&cr=3&csb=default&cs=ASC&pball=

⁹⁴https://projectreporter.nih.gov/project_info_description.cfm?aid=9335810&icde=36563928&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

⁹⁵ <https://clinicaltrials.gov/ct2/show/NCT01591356>

⁹⁶ <https://clinicaltrials.gov/ct2/show/NCT02130466>

⁹⁷ <https://clinicaltrials.gov/ct2/show/NCT02508246>

⁹⁸ <https://clinicaltrials.gov/show/NCT01362803>

Cerebral Cavernous Angioma Research

The Committee urges NIH to expand and strengthen NINDS programs regarding research and related activities for cavernous angioma by including basic, clinical, and translational research as well as promoting training programs for medical and allied health clinicians and scientists, increasing outreach and awareness, and sharing clinical and other surveillance information. The Committee also encourages NIH and FDA to work with patient advocacy organizations to research and promote effective treatments. The Committee is aware of patient advocacy groups asking NIH to conduct clinical trials. The Committee urges NIH to continue to work with these organizations on this request.

Action taken or to be taken:

The National Institute of Neurological Diseases and Stroke (NINDS) supports basic, translational, and clinical research on cerebral cavernous angioma (CCA) to better understand the basic disease processes and to facilitate development of new interventions. NINDS-funded studies are exploring the inherited and spontaneous genetic mutations and downstream molecular signaling pathways that underlie development and progression of CCA lesions. NINDS-funded investigators also recently discovered a surprising role of inflammatory signaling linked to the microbiome in the gut to CCM bleeding which could lead to new preventative strategies. The goal of this work is to lead to a clearer understanding of the genetic basis for CCA, and to identify key signaling abnormalities and susceptibility factors that lead to hemorrhage and could be targeted with new treatments.

NINDS also supports ongoing translational research through the Small Business Innovation Research (SBIR) program to test whether disruption of one molecule shown to be involved in the disease pathway, Rho kinase, shows promise in safety and efficacy studies using cell culture and animal models of CCA disease. The investigators are working closely with the FDA so that if the project is successful, it can lead to Investigational New Drug (IND) filing and subsequent clinical testing in humans.

NINDS investigators are also exploring disease pathways that are independent of Rho kinase, and recently reported promising results in animals where replacement of a factor that normally limits blood vessel growth, but that is lost due to CCA genetic mutation, could prevent formation of cerebrovascular malformations. NINDS also supports the Brain Vascular Malformations Consortium (BVMC) as part of the NIH Rare Disease Clinical Research Network. This program includes natural history and genome-wide association studies on genetic, physiological, and lifestyle factors that influence variability in clinical expression of CCA in patients. The consortium collaborates actively with several foundations focused on different vascular malformation disorders, including, for example, the Angioma Alliance, which sponsors a patient registry that is open to volunteers through its website. The BVMC also includes a robust training program to develop junior clinical and translational investigators who can lead multidisciplinary research teams focused on rare diseases, including CCA.

Cerebral Palsy (CP)

The Committee commends NINDS for developing the CP 5-year Strategic Plan and urges NINDS to implement Funding Opportunity Announcements in support of the top priorities and increase its CP research efforts for prevention, treatment, and cure through the lifespan. The Committee encourages funding for basic and translational research (including regenerative medicine) for improved outcomes for patients with CP, and recommends collaboration with the research and advocacy community. Furthermore, the Committee recommends that NIH form a trans-NIH working group of program officers who manage their Institute's CP portfolio and that this group regularly interact with CP patient advocacy groups.

Action taken or to be taken:

In response to Congressional and community interest and to highlight scientific opportunities, The National Institute of Neurological Disorders and Stroke (NINDS) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) developed the 2017 NINDS/NICHD Strategic Plan for Cerebral Palsy Research. The plan's recommendations for basic and translational research, clinical research, and workforce development emerged through two workshops held by NINDS and NICHD that were attended by scientists, clinicians, and advocates for individuals with CP. NINDS and NICHD program staff with portfolios across the breadth of CP research worked together to finalize the plan, and as a working group, they will determine ways to promote research in the plan's priority areas. These may include new funding opportunities and leveraging existing NIH programs such as the Human Placenta Project and the NIH Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative. To bring a wide range of disciplines to CP research, this group will engage other NIH institutes with expertise relevant to specific goals.

Ongoing extramural and intramural NIH research will also advance the prevention and treatment of CP. NINDS supports research on disease mechanisms and protecting the brain from damage that can lead to CP. Two clinical trials are testing whether erythropoietin, a commercially available hormone, can prevent death or neurodevelopmental disability in very premature infants and infants with hypoxic-ischemic encephalopathy (HIE) due to blocked oxygen or blood supply to the brain. Therapeutic hypothermia is standard care for HIE, but some babies do not respond to this treatment. A study in CP animal models aims to find new therapeutic targets by defining biological signatures of hypothermia responders and non-responders. Other studies funded by NINDS and NICHD on mechanisms at play in intrauterine infection, inflammation, and HIE may also point to new protective or regenerative therapies. Besides brain-focused mechanisms and treatment, NINDS supports studies in children with CP and a new rabbit model on how enhanced spinal cord excitability and deficits at spinal synapses contribute to hypertonia and spasticity.

NICHD funds research on the prevention of preterm birth and fetal brain injury, both of which are associated with CP. This research includes efforts to identify brain imaging and other biomarkers that could inform early intervention. In addition, the National Center for Medical Rehabilitation Research (NCMRR) in NICHD funds clinical trials to assess specific therapies in children with CP, which will provide evidence for more informed treatment decisions. One trial showed significantly improved hand function in children with unilateral spastic CP (motor difficulties affecting mainly one side of the body) after three weeks of intense therapy using both

limbs to practice. Other NCMRR studies aim to provide assistive devices such as exoskeletons or orthoses to assist with walking. The NIH Clinical Center also conducts research on rehabilitative therapies and orthoses for CP. Finally, NINDS and NICHD support studies to understand and measure CP's effects on motor and other functions, which may also aid diagnosis and rehabilitation.

NINDS and NICHD look forward to joining with CP researchers and patient groups to address priorities in the new strategic plan. Such collaboration led to the development of Common Data Elements for CP research – a set of standards to facilitate data collection, comparison, and synthesis in CP clinical research. Outside NIH, researchers and non-profit organizations have partnered to establish a national registry for CP and infrastructure for patient-oriented research. NIH will continue to interact with the CP community, through the NINDS and NICHD working group and other opportunities, such as the annual NINDS Nonprofit Forum and meetings and conferences held by CP patient and professional organizations. NCMRR also interacts with CP researchers and organizations, and CP experts are members of NCMRR's National Advisory Board, allowing input into scientific discussions in this area.

Children in NIH Research

The inclusion of children in clinical research is essential to ensure that children benefit from important scientific advances. The Committee appreciates provisions of the 21st Century Cures Act that will now require NIH to track systematically enrollment data to determine if children are actually being enrolled appropriately in clinical research. The Committee recognizes that without better data collection, the Committee is unable to fully exercise its oversight role and researchers are unable to determine whether children as a whole, or particular pediatric sub- populations, are underrepresented in Federally-funded biomedical research. The Committee directs NIH to implement these new requirements expeditiously.

Action taken or to be taken:

NIH remains committed to ensuring the appropriate inclusion of children in clinical research. The agency's efforts to implement the requirements of the 21st Century Cures Act to provide data on the age of participants in clinical research include the following:

- In June 2017, NIH held the Inclusion Across the Lifespan Workshop. This workshop brought together experts in the field, including clinicians, scientists, government officials, and advocates, to discuss the appropriate inclusion of pediatric and older populations in research studies involving human subjects and approaches to data collection. Results of the workshop are publicly available on the NIH website⁹⁹.
- In April 2017, NIH announced a new FORMS-E grant application package, required for applications submitted for due dates January 25, 2018 or later. The FORMS-E application package includes new fields to capture the age range of participants in studies involving human subjects.
- In December 2017, NIH issued a notice in the NIH Guide for Grants and Contracts to announce a revision to the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects. This policy revision includes an expectation that NIH funding recipients conducting clinical research studies report individual-level participant data on sex/gender, race, ethnicity, and age in annual progress reports. The revised policy applies to grants, contracts, and intramural studies submitted or issued on or after January 25, 2019.

NIH is enhancing its electronic research administration systems to facilitate the upload of individual-level participant data on sex/gender, race, ethnicity, and age. Expected by summer 2018, investigators will be able to provide data on the age of participants in units ranging from hours to years, as well as analyze the intersection of age with other variables, including sex/gender, race, ethnicity, and research condition or disease category.

⁹⁹ https://report.nih.gov/special_reports_and_current_issues/index.aspx

Chronic Fatigue Syndrome (ME/CFS)

The Committee is pleased that NIH has begun to expedite research into ME/CFS, including its intramural study and the RFAs for the collaborative research centers. However, the Committee is concerned that the level of funding is still very low considering the burden of disease and the current plan to expand research will take too long to produce FDA-approved treatments and diagnostic tests. The Committee urges NIH to collaborate with disease experts and the patient community to identify additional opportunities to expedite progress on this understudied disease. Specifically, the Committee recommends that NIH consider increasing research funding to be commensurate with disease burden and use that funding to further accelerate the research field through a set of intramural and extramural investments such as: (1) RFAs for biomarkers and treatment trials, (2) additional funding for investigator initiated studies and early stage investigator awards, (3) an initiative to reach consensus on the case definition, and (4) mechanisms to incentivize researchers to enter the field.

Action taken or to be taken:

Twenty-four NIH Institutes, Centers, and Offices, led by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Allergy and Infectious Diseases (NIAID), contribute to the effort to advance ME/CFS research, and coordinate their activities through the Trans-NIH ME/CFS Working Group.

In September 2017, NIH announced awards to establish three ME/CFS Collaborative Research Centers (CRCs) and a Data Management and Coordinating Center (DMCC). The CRCs will each conduct independent research but will also collaborate on projects, forming a network to advance interdisciplinary research programs while serving as local resources and national leaders in ME/CFS research. Studies being carried out in the CRCs will use a wide range of tools and technologies to search for an infectious disease etiology in ME/CFS and to understand the role of genes, inflammation, and the immune system in the disease. The CRCs will work to develop new diagnostics and identify novel biomarkers of the disease and will also develop ways to stratify patients into subgroups based on clinical presentation. Developing better diagnostics and ways to characterize patients are necessary before reaching consensus on a case definition and in order to target treatments to individual patients. Additional goals of the CRCs are to build the infrastructure in academic institutions to carry out future clinical trials and to partner with stakeholders by fostering community engagement in the CRCs.

While the CRCs are an important component of the NIH ME/CFS research portfolio, the NIH also supports investigator-initiated research grants in this area. For example, NINDS currently funds research to understand the mechanisms underlying exertional exhaustion, muscle pain and fatigue, and to identify metabolic pathways and mediators of these pathways in individuals with ME/CFS. Ongoing NIAID-funded projects are establishing a clinical study to help identify ME/CFS biomarkers and investigating whether there is a link between development of ME/CFS and prior Epstein-Barr virus infection.

NIH continues to encourage new applications for ME/CFS research projects, especially from trainees and early-stage investigators. NINDS recently funded a predoctoral training fellowship award to understand the neural correlates of fatigue and post-exertional malaise in ME/CFS. NIH also expects that the CRCs will provide the necessary leadership to attract an increasing

number of researchers to this field. In addition, NIH program staff regularly present at scientific meetings and have held grant-writing workshops for existing and potential ME/CFS scientists.

The NIH's intramural study on ME/CFS is underway at the NIH Clinical Center. This study is evaluating individuals with ME/CFS with the goal of learning more about the clinical and biological markers and mechanisms of the disease.

ME/CFS funding for FY 2016 was approximately \$8 million, an increase of \$2 million from FY 2015. We expect that funding levels will continue to increase for FY 2017, reflecting support for the CRCs and DMCC, as well as new and ongoing investigator-initiated projects. NIH will continue to look for ways to encourage rapid scientific progress that can lead to the development of new ways to diagnose and treat ME/CFS.

Chronic Overlapping Pain Conditions

The Committee notes the strong evidence base demonstrating deleterious outcomes for patients with Chronic Overlapping Pain Conditions, which include hit-or-miss, ineffective, or even harmful treatments, poor health and quality of life outcomes, markedly increased disability rates and personal and societal financial burdens. The Committee is pleased with NIH's efforts to develop a chronic overlapping pain conditions screening tool. However, an expanded, coordinated, and collaborative initiative is needed to maximize the Federal research investment, reduce spending, and improve clinical practice. There is an urgent need to analyze the state of science on Chronic Overlapping Conditions, which will identify both research gaps and future research directions and collaborations. As such, the Committee urges the Director to consider the relevant recommendations of the Federal Pain Research Strategy to guide the development of a comprehensive effort that spans the basic, translational, and clinical research continuum to advance scientific understanding of chronic overlapping pain conditions, as well as the development and discovery of safe and effective treatments.

Action taken or to be taken:

The NIH continues to work within the trans-NIH Pain Consortium and trans-agency Interagency Pain Research Coordinating Committee (IPRCC) to enhance the understanding of co-occurring pain conditions.

The NIH Pain Consortium addressed the objectives of a 2015 workshop, sponsored by the Office of Research on Women's Health, to develop a case definition and common data elements for overlapping chronic pain conditions -- co-occurrence of at least two chronic pain conditions (vulvodynia, fibromyalgia, irritable bowel disorder, temporomandibular disorders, chronic fatigue syndrome, chronic pelvic pain, interstitial cystitis, chronic low back pain, and migraine). To achieve the objectives of the workshop, the experts agreed that expansion of an existing clinical research tool would serve to facilitate harmonization of data collection and analysis across clinical studies on chronic overlapping pain conditions (COPCs) better than a case definition and common data elements. Based on their recommendations, NIH awarded supplements to ongoing studies to expand an existing standardized research tool, the Complex Medical Symptoms Inventory (CMSI). This tool had been used to define six of the ten overlapping pain conditions, and the supplements supported expansion of the CMSI to include diagnostic criteria for all ten COPCs. The expanded tool is completed, and NIH is discussing plans to validate the criteria in a clinical population and host them on a publicly available website.

The NIH Pain Consortium sponsors two current Funding Opportunity Announcements (FOAs) to solicit applications on *Research on Overlapping Pain Conditions*. To date, three projects were funded through these FOAs, which aim to elucidate potential shared pathways across conditions and are looking for circulating and tissue markers that occur in more than one COPC. These markers will provide clues to common biological mechanisms that underlie COPCs.

The NIH Office of Pain Policy, with oversight by the IPRCC, led the development of the Federal Pain Research Strategy (FPRS), which was completed and released in October 2017, and which will guide research efforts across NIH and other agencies going forward. The FPRS includes research recommendations relevant to COPCs including expanding our understanding of chronic pain mechanisms and variability of chronic pain in specific

populations and individuals, and standardizing pain measures to study multiple chronic pain conditions. One research priority of the FPRS relates to research networks, which could catalyze the development of protocols to standardize data collection, data analysis, and outcome measures for research on multiple chronic pain conditions. Such protocols would facilitate exploration of both shared and unique mechanisms of overlapping pain conditions. Another priority of the FPRS is to address nervous system changes that contribute to or prevent the development of chronic pain and the predisposition for developing multiple pain conditions. The Strategy also calls for research on the epidemiology of single and overlapping pain conditions in disparate populations to identify societal consequences of pain in understudied groups, document effectiveness of specific treatments, and guide intervention efforts.

The NIH hosted three cross cutting science meetings in 2017 to discuss approaches to address the opioid crisis, including development of safer, non-addictive analgesics. Several recommended action items emerged from the meetings, including exploration of the mechanisms that cause acute pain to become chronic, approaches to prevent this transition, and strategies to accelerate better analgesic treatments for chronic pain. These recommendations are relevant to not only single chronic pain disorders, but to COPCs as well.

Clinical and Translational Science Awards (Senate)

The Committee includes \$533,076,000, an increase of \$16,956,000, for the CTSA Program. The Committee is deeply concerned about NCATS' management of the CTSA program. The Committee has provided robust support for the CTSA program over the past several years and NCATS appears to be both ignoring congressional intent regarding the number of CTSA hubs as well as attempting to erode financial support for the hubs. Specifically, the Committee rejects the recent move to reduce some CTSA awards from a 5 year grant cycle to 4 years. Prior notification or justification of this significant change was not provided to the Committee, the CTSA community, or in any written document. The Committee expects NCATS to rectify this change immediately and directs all awards made in fiscal year 2017 and moving forward to be for 5 years. In addition, the Committee strongly supports efforts by NIH to train the next generation of biomedical researchers by supporting key training programs like the "K" and "T" awards. As stated in the National Academies of Sciences, Engineering, Medicine report in 2013, the CTSA program should build on these and other innovative training and education programs that are helping to bridge the gap between the basic and clinical sciences. Further, the Committee is concerned NCATS is considering changing CTSA's configuration and funding structure without adequate congressional notification or stakeholder input. Therefore, the Committee directs NCATS to maintain the existing support structure, including maintaining the number of CTSA hub awards at no less than the fiscal year 2016 level, and to continue funding CTSA hub awards for 5 years. NCATS is directed to provide an update to the Committee no later than 120 days after enactment of this act on any proposed changes to the program and prior to any changes being implemented. In addition, the Committee expects the Director to provide quarterly updates to the principal investigators of CTSA hubs and the Committee, jointly, beginning within 30 days of enactment of this act. Finally, the Committee shall be provided written notification at least 3 days in advance of any public release of CTSA grant awards.

Clinical and Translational Science Awards (House)

The Committee remains deeply concerned over the broad utilization of resources it specifically allocated for the Clinical and Translational Science Awards (CTSA) hubs and has provided NCATS with direct instructions regarding the number of awards. As investment in the CTSA program continues, NCATS is directed to ensure the level of support for CTSA institutions is maintained to appropriately reflect the additional resources provided by the Committee. Further, NCATS is directed to maintain the number of CTSA hubs at no fewer than 64 institutions.

Action taken or to be taken:

The National Center for Advancing Translational Sciences (NCATS) appreciates the Committee's continued support of the Clinical and Translational Science Awards (CTSA) Program and is most appreciative of the proposed increase. NCATS has taken several steps to improve the management of the CTSA Program and make transparent the Center's financial support for the hubs.

First, in late September 2017, NCATS Director Dr. Christopher Austin announced that NCATS would seek a new director to manage the CTSA Program. Until then, NCATS Deputy Director Dr. Pamela McInnes would serve as acting Director over the CTSA Program. On December 10, 2017, Dr. Michael Kurilla joined NCATS as the new Director of NCATS Division of Clinical Innovation, which oversees the CTSA Program. Dr. Kurilla previously served as the Director of the Office of Biodefense, Research Resources and Translational Research at the National Institute of Allergy and Infectious Diseases, NIH.

Additionally, Dr. Austin has reasserted his ongoing commitment to provide the overarching direction and oversight of the program. In October 2017, with the support of the CTSA Program Steering Committee, he assumed the position of co-chair of the CTSA Program Steering Committee.

Finally, to increase transparency concerning the stewardship of CTSA funds, on July 23, 2017, the Center sent to the Committee a table¹⁰⁰ summarizing all the awards and activities supported through the CTSA Program by fiscal year, since FY 2014. The table is posted on NCATS' website and was revised on December 29, 2017, to reflect final data for FY 2017. It will be updated regularly to reflect the future funding actions within the CTSA program.

This table (see below) provides specific funding information on all program activities and initiatives as underlined dollar amounts which are hyperlinks that open initiative-specific award information available in the NIH RePORTER database:

¹⁰⁰ <https://ncats.nih.gov/files/ctsa-funding-information.pdf>

Funded activities under the NCATS Clinical and Translational Science Awards (CTSA) Program

| Row | NCATS Clinical and Translational Science Awards Program ¹ | Fiscal Year 2014 Actual | Fiscal Year 2015 Actual | Fiscal Year 2016 Actual | Fiscal Year 2017 Actual |
|-----|--|----------------------------|----------------------------|----------------------------|----------------------------|
| 1 | CTSA Program Hubs² | | | | |
| 2 | Number of Hub awards ³ | 58 | 58 | 57 | 57 |
| 3 | Hub Awards (A UL1 award with a linked KL2 award and an optional TL1 award) ⁴ | <u>\$404,954,499</u> | <u>\$441,922,552</u> | <u>\$449,584,228</u> | <u>\$447,800,122</u> |
| 4 | Administrative Supplements to Hub Awards ⁵ | <u>\$44,204,713</u> | <u>\$18,534,775</u> | <u>\$9,851,866</u> | <u>\$6,367,377</u> |
| 5 | Bridge Awards (U54) | <u>\$16,798,746</u> | <u>\$3,528,613</u> | <u>\$3,560,718</u> | <u>\$3,497,558</u> |
| 6 | CTSA Program Collaboration Initiatives (per IOM Recommendations) - all awards to CTSA | | | | |
| 7 | CTSA Program Collaborative Innovation Awards (U01/R21) | | | <u>\$8,602,736</u> | <u>\$14,402,042</u> |
| 8 | Consortium Centers (U24/U54) RIC/TIC/CD2H/Coordination | <u>\$2,420,706</u> | <u>\$2,741,255</u> | <u>\$16,354,755</u> | <u>\$29,878,310</u> |
| 9 | Subtotal of Funding to CTSA Program Institutions | \$468,378,664 | \$466,727,195 | \$487,954,303 | \$501,945,409 |
| 10 | Other CTSA Program Activities⁶ | | | | |
| 11 | Other (K23/R13/U13/U19/T15/U2C/U24) | <u>\$1,402,448</u> | <u>\$1,277,800</u> | <u>\$265,000</u> | <u>\$600,000</u> |
| 12 | Loan Repayment Program | <u>\$2,006,148</u> | <u>\$1,986,781</u> | <u>\$2,001,190</u> | <u>\$2,009,444</u> |
| 13 | Program Management (Includes NIH and DHHS assessments and transfers) | <u>\$5,432,517</u> | <u>\$7,399,063</u> | <u>\$9,779,507</u> | <u>\$11,569,957</u> |
| 14 | Grand Total | \$477,219,777 | \$477,390,839 | \$500,000,000 | \$516,124,810 |

Notes:

To view a list of awards from NIH RePORTER, please click on underlined dollar amounts. RePORTER provides the most up-to-date information available on funded projects, so the data are not frozen and changes in the administrative details of prior awards can occur.

¹ NCATS received CTSA Program-specific appropriations language beginning in FY2014. CTSA Program-specific appropriations language in FY2012 and FY2013 was directed to the NIH Office of the Director.

² A CTSA Program Hub is defined as a UL1 award with a linked KL2 award and an optional TL1 award. No Cost Extensions (NCE) to Hub awards do not receive funding from NCATS in a particular fiscal year. NCEs do not count as funded Hubs in that fiscal year and are therefore not reflected in the table.

³ In FY2014 NCATS did not issue a CTSA Program Hub funding announcement as the program was being re-structured in response to the 2013 IOM recommendations. Eight CTSA Program Hubs that were positioned to re-compete for hub awards in FY2014 were issued orderly close-out supplements to enable them to remain active until a FY2015 funding announcement was available and posted.

⁴ The totals reported in this table reflect only NCATS' investment in the CTSA Program. For FY2017, NIH RePORTER data shows an additional \$407,214 due to cofunding provided by DHHS.

⁵ NCATS investment in Administrative Supplements for FY2014 was \$93,000 less than what is shown in NIH RePORTER. NCATS investment in Administrative Supplements for FY2016 was \$23,389 more than what is shown in NIH RePORTER. Grand total amounts for the fiscal years are accurate.

⁶ For a glossary of NIH award codes, please go to https://grants.nih.gov/grants/funding/funding_program.htm

Updated December 29, 2017

- Rows 1-9 provide information regarding awards made to CTSA Program funded institutions or hubs:
 - Rows 1-5 under *CTSA Program Hubs* reflect funds that directly support the funded CTSA Program hub activities, including bridge funding to provide support to CTSA Program hub institutions that did not compete successfully for renewal.
 - *Number of Hub awards* (row 2) provides the number of CTSA Program hub awards funded with appropriated dollars in a fiscal year. For clarity, NCATS defines a CTSA Program hub award as a UL1 award (for the center) with a linked KL2 award (career development) and an optional TL1 award (training grant).
 - Rows 6-8, *CTSA Program Collaboration Initiatives*, provide funding information on activities in response to the National Academies of Sciences, Engineering, Medicine report in 2013 (NAS) report. These funds are directed to existing CTSA Program-funded hub institutions and are addressing issues of importance to the hubs as a national network (e.g., CD2H – an award to address network-wide harmonization of data for data sharing) and collaborative innovation efforts.
- Rows 10-13 provide information on other activities utilizing CTSA Program-directed funds:
 - Rows 11 and 12 are CTSA Program-related activities, and include funding for activities such as the NIH Loan Repayment Program.
 - Row 13, *Program Management*, includes funds needed for management of the CTSA Program and a portion of NCATS' contribution towards NIH and DHHS assessments and transfers. Based on the NAS report recommendation for greater program leadership and oversight, NCATS increased CTSA Program staff levels. Since FY 2014, NCATS has been incrementally implementing the agency-wide assessments.

As the table illustrates, since 2014 when NCATS began receiving CTSA Program-specific appropriations language, the Center has maintained steady support for the number of hubs (table, row 2) and increased the financial support for the hub institutions (table, row 9).

Specifically, the Committee rejects the recent move to reduce some CTSA awards from a 5 year grant cycle to 4 years. Prior notification or justification of this significant change was not provided to the Committee, the CTSA community, or in any written document. The Committee expects NCATS to rectify this change immediately and directs all awards made in fiscal year 2017 and moving forward to be for 5 years.

In FY 2014, NCATS did not issue a CTSA Program hub funding announcement as the program was being re-structured in response to the NAS report recommendations. Therefore, there were no applications for renewal in FY 2014 and, subsequently, two cohorts of hub applicants (2014 and 2015) that applied to the hub funding announcement in FY 2015.

This cycle of a year (FY 2019) with no anticipated renewal applications, followed by a year with a large number of new and renewing applications (including the combined FY 2014 and 2015 cohorts) was forecast to repeat every five years. One solution was to make 4-year awards to a portion of the FY 2015 awards, thereby creating a competing cohort in FY 2019. The applications which were selected for the 4-year awards were those which had weaknesses identified through the peer review process and would potentially benefit from closer oversight. The same philosophy governed NCATS' approach in FY 2016, and yielded a more even distribution of applications projected for the future. Ultimately, NCATS decided to issue all new FY 2017 CTSA Program hub awards for 5 years in duration.

In addition, the Committee strongly supports efforts by NIH to train the next generation of biomedical researchers by supporting key training programs like the “K” and “T” awards. As stated in the National Academies of Sciences, Engineering, Medicine report in 2013, the CTSA program should build on these and other innovative training and education programs that are helping to bridge the gap between the basic and clinical sciences.

NCATS agrees that training the next generation of clinical and translational scientists is important and is committed to providing the support to do so. The CTSA Program supports two types of formal clinical research training awards at CTSA Program hubs. Both programs combine formal course work with direct research experience, and many institutions’ programs offer opportunities to pursue additional advanced degrees. All CTSA Program hubs have a KL2 program, which offers formal research training experience to scholars who already have an M.D., Ph.D. or equivalent doctoral degree. Many CTSA Program hubs also include programs that provide trainees with an introduction to clinical and translational research through the TL1 program.

Building on these efforts, the CTSA Program has additional innovative training resources to facilitate clinical scientists’ efforts to move their advances towards industry and commercialization to advance promising therapeutics towards clinical practice.

Further, the Committee is concerned NCATS is considering changing CTSA’s configuration and funding structure without adequate congressional notification or stakeholder input. Therefore, the Committee directs NCATS to maintain the existing support structure, including maintaining the number of CTSA hub awards at no less than the fiscal year 2016 level, and to continue funding CTSA hub awards for 5 years. NCATS is directed to provide an update to the Committee no later than 120 days after enactment of this act on any proposed changes to the program and prior to any changes being implemented.

NCATS is directed to ensure the level of support for CTSA institutions is maintained to appropriately reflect the additional resources provided by the Committee. Further, NCATS is directed to maintain the number of CTSA hubs at no fewer than 64 institutions.

Per the funding information table, NCATS funded 57 CTSA Program hubs in FY 2016 and 57 hubs in FY 2017. The table utilizes NCATS definition of a hub award and reports the number of hubs funded with fiscal year dollars. Since the establishment of NCATS in FY 2012, the center has never funded 64 CTSA Program hubs in a single fiscal year. Some hub institutions, at the end of their award, request an extension in time at no additional cost to NCATS, termed a no-cost extension (NCE). These institutions that request NCEs are not included in the hub count for the fiscal year of the extension, as no appropriated dollars are awarded to them.

NCATS issued 11 new FY 2017 hub awards for 5 years in duration, thereby maintaining the number of CTSA hub awards at the FY 2016 level (N=57). As described in the table above, only hubs that have received funding in a particular fiscal year are included in the count of hubs. NCATS plans to continue funding scientifically meritorious new and renewed hub awards for 5 years.

NCATS looks forward to providing regular updates to the Committee as the CTSA Program continues its focus on innovative science.

In addition, the Committee expects the Director to provide quarterly updates to the principal investigators of CTSA hubs and the Committee, jointly, beginning within 30 days of enactment of this act.

NCATS has provided regular updates to the Committee since this language was released and will continue to do so. In order to ensure timely and consistent communications regarding resources and the number of awards, both with the Committee and the CTSA investigator community, NCATS has taken several steps:

- Posting of all funded activities under the NCATS CTSA Program, on July 23, 2017, with updates on October 24, 2017, and December 29, 2017.
- A special teleconference between the NCATS Director, the CTSA Program Steering Committee, and all program investigators on July 24, 2017, with posting of follow-up questions and answers on the CTSA Program Data Coordinating Center website.
- Teleconferences with Hill staff and NCATS leadership.
- Enhanced communication efforts through teleconferences with individual CTSA-funded investigators, research administrators, business officials, and NCATS Program and Grants Management staff.
- NCATS Director's and Deputy Director's participation on CTSA Program Steering Committee and Principal Investigator calls.
- NCATS Director's and Deputy Director's participation at the October 2017 CTSA Investigators meeting in Washington, DC.
- At the October 2017 CTSA Investigators meeting, the NCATS Director assumed a permanent position as co-chair of the CTSA Program Steering Committee. As such he will provide the CTSA Program hubs with updates on a regular basis.

Finally, the Committee shall be provided written notification at least 3 days in advance of any public release of CTSA grant awards.

At the request of the Committee, NCATS began sending e-mail notifications to the Committee at least three days prior to the release of all CTSA Program grant awards and will continue to do so.

Combating Antibiotic Resistant Bacteria (CARB)

The Committee remains deeply concerned about the threat posed by the increasing prevalence of antibiotic resistant bacteria. In fiscal years 2016 and 2017, NIAID used funding appropriated by the Committee to expand its support for basic, translational, and applied research on antibiotic-resistant pathogens and the molecular mechanisms of antimicrobial resistance. The Committee strongly supports NIAID's efforts to continue these efforts, and includes \$513,000,000, an increase of \$50,000,000, to fund clinical trials of new antibiotics and novel uses of licensed antibiotics meant to limit the development of antibiotic resistance, as well as the development of diagnostics to quickly identify bacterial pathogens to inform antibacterial stewardship. These funds will also make it possible for NIAID to partner with Federal, academic, and industry researchers to develop diagnostics, immunoprophylactic, therapeutics, and vaccines that target multiple antibiotic-resistant bacteria. The Committee encourages NIH to continue to expand its collaboration with USDA and CDC to increase our understanding of antibiotic resistance and improve the responsible use of antibiotics in agriculture. The Committee requests an update on these activities in the fiscal year 2019 CJ.

Action taken or to be taken:

NIAID continues to make combating antibiotic resistance a key priority. NIAID supports basic and applied research to understand bacterial pathogenesis and the emergence of drug resistance, and to develop vaccines, diagnostics, and therapeutics to address drug-resistant infections.

NIAID is advancing the discovery, development, and clinical testing of novel antibiotics and new formulations of existing antibiotics, including for carbapenem-resistant Enterobacteriaceae (CRE), *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus* (MRSA). NIAID supports clinical trials to identify strategies to optimize and preserve the use of existing antibiotics for community-acquired pneumonia in pediatric patients, urinary tract infections, and multidrug-resistant Gram-negative infections, such as *A. baumannii*, CRE, and *Pseudomonas aeruginosa*. NIAID also supports research to develop vaccines to prevent infections with *S. aureus*, *Neisseria gonorrhoeae*, *Clostridium difficile*, and Group A *Streptococcus*.

NIAID actively engages in cross-agency partnerships to address the issue of antimicrobial resistance, including efforts to improve the responsible use of antibiotics in agriculture. NIAID collaborated with USDA and international partners to plan and participate in a global symposium focused on alternative strategies for preventing and treating animal diseases that reduce the use of medically important antibiotics in agriculture. NIAID also participates in an NIH collaboration with CDC, FDA, and other partners to establish the National Database of Resistant Pathogens to increase understanding of mechanisms of antibiotic resistance. In addition, NIAID scientists are collaborating with NIH and CDC colleagues to identify factors affecting mortality from these Gram-negative bloodstream infections.

NIAID and other Federal agency partners also are engaging with private industry to generate effective tools to combat antimicrobial resistance. NIAID provides preclinical services to the research community and partners with biotechnology and pharmaceutical companies to help advance promising antimicrobial products or platform technologies. NIAID currently is supporting the advancement of candidate broad-spectrum antibacterial therapeutics in collaboration with industry, including a novel tetracycline and a beta-lactamase inhibitor.

NIAID continues to support the development of diagnostics to address antibiotic resistance. For example, NIAID's Antibacterial Resistance Leadership Group is developing a blood test that analyzes gene expression patterns to determine if a patient's respiratory symptoms stem from a bacterial infection, viral infection, or no infection at all. NIAID also supported small business partners who developed a rapid molecular diagnostic panel cleared by FDA to detect multiple pathogens simultaneously. In approximately one hour, the panel can detect 24 microbes that cause bloodstream infections, including fungi and bacteria. In addition, NIH has partnered with BARDA, with technical and regulatory expertise from CDC and FDA, to launch the Antimicrobial Resistance Diagnostic Challenge that may award up to \$20 million in prizes by 2020 for innovative, rapid, point-of-need *in vitro* diagnostic tests to combat the emergence and spread of drug-resistant pathogens.

NIAID continues to place a high priority on antibiotic resistance research and will continue to support robust efforts in this area. This includes ongoing support for NIAID partnerships with other Federal agencies to advance critical research on the identification, characterization, and treatment of antibiotic-resistant pathogens. NIAID will continue to leverage the knowledge gained through this research to develop new rapid diagnostics, therapeutics, and vaccines to address the challenge of antimicrobial resistance.

Congenital Heart Disease

The Committee commends NHLBI for its continued work to better understand causation and appropriate treatments for those with the most life threatening congenital heart defects through its biomedical research program 'Bench to Bassinet' and the critical multi-centered infrastructure of the Pediatric Heart Network. NHLBI should also explore how the new adult CHD accreditation program, that advances and sets quality standards for care, can inform its work in this area. The Committee urges NHLBI to continue its work with other Federal agencies and professional and patient organizations to expand collaborative activities targeted toward prevention and treatment of the diverse lifelong needs of children and adults living with CHD. The Committee requests a report on these efforts in the fiscal year 2019 CJ.

Action taken or to be taken:

Congenital heart disease (CHD) is one of the most prevalent birth defects in the United States and a leading cause of infant mortality associated with birth defects. The National Heart, Lung, and Blood Institute (NHLBI) Bench to Bassinet Program (B2B) focuses on understanding the causes of CHD, its natural history, and its comorbidities across the lifespan. A recent study from the B2B Pediatric Cardiac Genomics Consortium analyzed clinical and genetic data from more than 2800 patients with CHD and their parents, and found that some genetic mutations were passed from parents to offspring, whereas other mutations had appeared spontaneously in the child's genome.¹⁰¹ These new findings could be used to expand current genetic testing panels for CHD, to improve information for parents about risks to their future children, and to guide the long-term care of individuals with CHD.

NHLBI continues to work with other Federal agencies and organizations to improve health outcomes in adults and children with CHD. Recently, the B2B Pediatric Heart Network (PHN) worked closely with advocacy groups to conduct a phase I/II clinical trial exploring whether the medication Udenafil could safely improve blood flow to the lungs in adolescents with single ventricle heart disease. The PHN has recruited almost 300 participants into a larger industry-sponsored trial to establish whether this treatment is effective.¹⁰² The PHN also is collaborating to support a randomized trial evaluating the safety of Apixaban, a new type of anticoagulant, versus more traditionally used anticoagulants in children with congenital or acquired heart disease.¹⁰³

In 2015, NHLBI partnered with the Centers for Disease Control and Prevention and the National Institute of Neurological Disorders and Stroke to launch a surveillance system and registry for sudden death in children up to 19 years of age. The registry has collected information on more than 1000 cases of sudden death in youth in 10 states over the past two years. NHLBI-funded researchers are using registry data to explore the genetic causes and characteristics of sudden cardiac death in the young and the evaluation of surviving family members; this research may ultimately lead to strategies for preventing sudden death from CHD and other causes. NHLBI also is working to bring new heart pumps into clinical practice for children awaiting a heart transplant. In 2017, researchers began a clinical trial of a ventricular assist device for children as part of NHLBI's Pumps for Kids, Infants and Neonates Program.¹⁰⁴

¹⁰¹ <https://www.ncbi.nlm.nih.gov/pubmed/28991257>

¹⁰² <https://www.clinicaltrials.gov/ct2/show/NCT02741115>

¹⁰³ <https://www.clinicaltrials.gov/ct2/show/NCT02981472>

¹⁰⁴ <https://clinicaltrials.gov/ct2/show/NCT02954497>

In line with the new adult CHD accreditation program, NHLBI is committed to improving the quality of care for adults with CHD. NHLBI-supported research has led to improved diagnosis and treatment, and improved the lifespan of people with CHD. Current and future research will be aimed at addressing the growing need to understand how to treat people living longer with CHD, as well as many age-related conditions. The PHN is working with the Alliance for Adult Research in Congenital Cardiology to support research on cognitive function in adults with CHD. NHLBI also works with many centers that have earned national accreditation from the Adult Congenital Heart Association. These efforts are building a community of expertise and resources, and helping to stimulate further research on adult CHD.

Congenital Syphilis

The Committee urges the NICHD to coordinate efforts with NIAID and CDC to identify potential risk factors, increase prevention, improve newborn screening techniques, and provide treatment to improve outcomes in women and infants infected with Syphilis, with special focus on infants infected with HIV and Congenital Syphilis.

Action taken or to be taken:

Congenital syphilis develops when a pregnant woman infected with *Treponema pallidum*, the bacterium that causes syphilis transmits the infection *in utero*. Pregnancies complicated by syphilis can result in miscarriage, stillbirth, and early infant death. Children infected with syphilis can have severe illness, such as deafness, blindness, and neurologic problems. While treatment of women with penicillin is highly effective in preventing congenital syphilis, recently the Centers for Disease Control and Prevention reported a disturbing increase in the number of congenital syphilis cases between 2012-2014.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports a large portfolio of research related to prevention of mother-to-child transmission of infectious diseases, such as HIV. Prevention of perinatal transmission of HIV is an example of how research informed clinical implementation to improve the public's health, resulting in reduction of HIV infection in newborns from 40% to less than 0.5% in the U.S. Similarly, most cases of congenital syphilis could be prevented if infections in pregnant women are identified before the last trimester and treated at least 30 days before delivery. Lack of treatment could lead to additional health consequences; a NICHD-supported study found that untreated syphilis in pregnant women living with HIV could facilitate transmission of *in utero* HIV.

Addressing congenital syphilis involves primary prevention of infection in reproductive age women and their partners, as well as prevention of transmission to the infant in women that have been infected in pregnancy. Innovative screening, prevention, and treatment regimens may need to be explored to help drive the rate of congenital syphilis downward. The NICHD has published a funding opportunity, "Advancing the Understanding, Prevention, and Management of Infections Transmitted from Women to their Infants"¹⁰⁵ to stimulate research that would lead to improved health and well-being of pregnant women and their offspring.

The National Institute of Allergy and Infectious Diseases (NIAID) is supporting research on how the immune response to syphilis in pregnant women may affect pregnancy outcomes, and whether specific *Treponema pallidum* antigens could be used to develop an effective vaccine to prevent primary syphilis infection. NIAID is also supporting research on congenital syphilis to determine how *Treponema pallidum* interacts with placental tissue, as well as research on diagnostics for syphilis that could lead to earlier treatment and potentially a reduction in congenital syphilis.

Looking forward, the NICHD also is exploring the possibility of conducting a scientific workshop with other NIH Institutes and Centers and federal health agencies to identify the gaps in our research knowledge and to inform next steps.

¹⁰⁵ <https://grants.nih.gov/grants/guide/pa-files/PA-16-031.html>, <https://grants.nih.gov/grants/guide/pa-files/PA-16-032.html>

Coordination with the Department of Energy (DOE) and National Laboratories to Implement 21st Century Cures Act

NIH is encouraged enter into collaborative research programs, as appropriate, with DOE, the National Laboratories, and others determined to be appropriate, to utilize the broader scientific and technological capabilities of DOE and the National Laboratories relevant to the successful implementation of the 21st Century Cures Act (P.L. 114– 255).

Action taken or to be taken:

NIH and the Department of Energy (DOE) have a history of collaboration and continue to work together in several significant ways, including utilizing DOE's National Laboratories, to further the research missions of both agencies.

The unique scientific instruments and infrastructure available at the National Laboratories provide NIH grantees with access to vital research resources such as high-performance computing, microfabrication, and high-throughput electron microscopy facilities. In addition to supporting grantees that use the National Laboratories for part of their research, NIH also supports grantees and collaborators that work at the National Laboratories themselves, conducting research on data science, materials science, modeling and simulation, and biomedical imaging, among others. This type of cooperation between NIH and DOE has led to increased understanding of the fundamental composition of molecules, cells, and tissues, as well as the mechanisms of how they work, with implications for a range of diseases such as cancer, heart disease, and diabetes, among others.

As another example of collaborative research, the National Cancer Institute (NCI) and DOE are working together on the Joint Design of Advanced Computing Solutions for Cancer (JDACS4C).¹⁰⁶ This interagency collaboration aligns with the Precision Medicine Initiative, the Cancer Moonshot, and the National Strategic Computing Initiative. It aims to advance cancer research through the application of exascale computing capabilities. The project involves four DOE National Laboratories and multiple NCI components. In FY 2017, the JDACS4C collaboration has initiated three pilots: 1) Cellular Level Pilot for Predictive Modeling for Pre-Clinical Screening; 2) Molecular Level Pilot for RAS Structure and Dynamics in Cellular Membranes; and 3) Population Level Pilot for Population Information Integration, Analysis and Modeling. These pilots will develop machine learning, large-scale data and predictive models based on experimental biological data and a scalable framework for efficient abstraction, curation, integration, and structuring of medical record information. A workshop was held in April 2017 where researchers identified specific new capabilities that would enable scientific insight including new advanced machine learning to account for data uncertainty, cutting edge tools for predictive models for cancer and scalable platforms to enhance open science in precision oncology. Future activities include evaluating the pilots on currently available high-performance computers at Argonne, Oak Ridge, and Lawrence Livermore National Laboratories.

NIH also supports a large network of Biomedical Technology Resource Centers (BTRCs), which bring together technical and biomedical expertise to create cutting-edge methods and technologies that can be applied to basic, translational, and clinical research. Through one such BTRC, NIH supported the development of an advanced x-ray laser synchrotron facility for biomedical research

¹⁰⁶ <https://cbiit.cancer.gov/ncip/hpc/jdacs4c>

at the DOE National Accelerator Laboratory. This experimental facility has the capability to reveal the intimate details of atoms and chemical reactions in protein structures.¹⁰⁷

Finally, the NIH works in conjunction with the DOE Nuclear Medicine Working Group to estimate and prioritize the anticipated annual usage of radioisotopes for biomedical research. This critical service guarantees that NIH researchers have access to rare and time-sensitive radiochemicals, as some isotopes have very short half-lives and need to be created on-demand. It is necessary to coordinate the availability of these radioisotopes to enable intramural and extramural researchers to perform high-impact clinical trials to study the efficacy of new therapies.

¹⁰⁷ <https://publications.nigms.nih.gov/btrrs/searchresults.asp>

Cystic Fibrosis

The Committee applauds the work of NIH to support translational research tools that spur the development of new therapies for rare diseases like cystic fibrosis. Animal models are critical tools for understanding disease progression and identifying potential new treatments. The National Swine Resource and Research Center [NSRRC], funded by the NIH and hosted at the University of Missouri, provides services to develop swine models of many genetic conditions, like cystic fibrosis, to facilitate research and drug development for these diseases. The Committee encourages the continuation of jointly funded clinical research programs occurring at CF care centers in Missouri and across the country. One such project, the OPTIMIZE study, has brought together hospital systems in nearly 30 States to compare treatments for lung infections in those with CF to determine if a commonly used combination of antibiotics is safe and effective. Real world clinical trials such as this one are often only supported by NIH and non-profit organizations, and they may significantly improve care and treatment for people with serious, life-threatening diseases such as cystic fibrosis.

Action taken or to be taken:

The National Heart, Lung, and Blood Institute (NHLBI) continues to support a robust basic and clinical research portfolio for many lung diseases, including cystic fibrosis (CF). This includes efforts toward understanding its fundamental pathobiology, improvement of animal models, earlier detection of lung abnormalities, development of novel therapeutic approaches that target the faulty gene known to cause CF, and translation of these findings into clinical practice.

Animal models of CF are critical for better understanding the disease process and developing new therapies. The CF transmembrane conductance regulator (CFTR) protein regulates the movement of electrolytes and water across tissue surfaces. In lungs, this water flow is necessary for producing mucus that helps the lungs remove inhaled particles and forms a barrier against infection. In one study, researchers used a zebrafish model to examine how genetic changes to the CFTR protein's structure affects its function, which will help to identify sites within the protein that could be targeted with new therapies.¹⁰⁸ Current therapies targeted to the CFTR include small molecule-based drugs, gene repair, and gene replacement.

In addition to mouse models, other animal models are also shedding new light on the disease processes in CF. Swine are well suited as models of many human diseases, including CF. They are closely related to humans in terms of anatomy, genetics, physiology, with organs of similar size and tissue organization. The National Swine Resource and Research Center housed at the University of Missouri has been instrumental since 2003 in helping biomedical researchers across the country gain access to various swine breeds, reagents, and scientific training.

Lung infections are a major contributor to the pathogenesis of CF, are challenging to treat, and often become chronic. NHLBI supports many trials that are currently active in testing treatments for infections in CF. The Optimizing Treatment for Early *Pseudomonas aeruginosa* Infections in CF (OPTIMIZE) trial is investigating whether a combination of antibiotics is beneficial to patients with *P. aeruginosa* bacterial infections.¹⁰⁹ Results are expected in early 2018. NHLBI also funds the IGNITE trial, which has brought together hospital systems in 21 states to determine if gallium nitrate can improve breathing and reduce *P. aeruginosa* burden in the lungs of CF patients.¹¹⁰

¹⁰⁸ <https://www.ncbi.nlm.nih.gov/pubmed/27912062>

¹⁰⁹ <https://clinicaltrials.gov/ct2/show/NCT02054156>

¹¹⁰ <https://clinicaltrials.gov/ct2/show/NCT02354859>

Another NHBLI-funded trial is designed to address reduced airway acidity in CF, which may increase susceptibility to lung infections.¹¹¹

¹¹¹ <https://clinicaltrials.gov/ct2/show/NCT03078088>

Deadliest Cancers

The Committee remains concerned that while more effective screening methods and treatments have lowered overall cancer incidence and death rates, some forms of cancer remain extremely difficult to diagnose and treat. Defined in statute as "recalcitrant cancers"-those whose 5-year survival rate is below 50 percent-they account for nearly half of all cancer deaths in the U.S. and include cancers of the pancreas, liver, ovary, brain, stomach, esophagus, and lung. Given the toll these types of cancer exact on society, the Committee urges NIH and NCI to continue to support research with an emphasis on developing improved screening and early detection tools and more effective treatments. The Committee expects to receive an update in the fiscal year 2019 CJ of how NCI is advancing these goals.

Action taken or to be taken:

The National Cancer Institute (NCI) dedicates its efforts to advancing science for all cancer patients and their families, and to supporting cancer control interventions that will not only prevent thousands of deaths from cancer, but have the potential to save even more people from ever experiencing a cancer diagnosis. Through all of these efforts, NCI is committed to continuing to advance research to address cancers with high mortality and low five-year survival. In addition to cancers of the pancreas, liver, ovary, brain, stomach, esophagus, and lung, there are several subtypes of cancers with similarly poor prognoses, including certain types and subtypes of pediatric cancers.

Early detection is vital to preventing cancer mortality; in general, patients whose cancers are diagnosed in early stages have more treatment options available to them. Rapid progress has been made in developing liquid biopsy approaches – which utilize non-invasive blood samples instead of invasive tissue sampling –for the early detection of biomarkers that can potentially diagnose pancreatic cancer,^{112,113, 114} The liquid biopsy Percepta – which can diagnose lung cancer in people with lung nodules – was approved by the Centers for Medicare and Medicaid Services in 2017.¹¹⁵ Percepta was developed with NCI support, including Small Business Innovation Research (SBIR) program funding. Researchers have continued to explore other ways in which liquid biopsies can be used to target treatments to patients based on detection and identification of tumor DNA circulating within a patient, in the hope of finding the most effective therapy for each patient when he or she is first diagnosed.^{116,117}

To encourage additional research to advance the early detection and treatment of high-mortality cancers, the NCI has issued funding announcements for the creation of the Consortium on Translational Research in Early Detection of Liver Cancer¹¹⁸ and the Small-Cell Lung Cancer Consortium.¹¹⁹ These consortia join existing programs like the Pancreatic Cancer Detection Consortium, which develops and tests new molecular and imaging biomarkers to detect early stage

¹¹² <https://www.ncbi.nlm.nih.gov/pubmed/28701476>

¹¹³ <https://www.ncbi.nlm.nih.gov/pubmed/28874546>

¹¹⁴ <https://www.ncbi.nlm.nih.gov/pubmed/28232049>

¹¹⁵ <https://www.ncbi.nlm.nih.gov/pubmed/26896702>

¹¹⁶ <https://www.ncbi.nlm.nih.gov/pubmed/28899864>

¹¹⁷ <https://www.ncbi.nlm.nih.gov/pubmed/27555497>

¹¹⁸ <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-025.html>, <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-028.html>

¹¹⁹ <https://grants.nih.gov/grants/guide/pa-files/PA-16-051.html>, <https://grants.nih.gov/grants/guide/pa-files/PA-16-049.html>

pancreatic cancer and its precursor lesions,¹²⁰ and the Comparative Brain Tumor Consortium¹²¹ and Pediatric Brain Tumor Consortium,¹²² which serve as resources for scientists engaged in research on brain cancers.

While the NCI hopes to expand the use of early detection methodologies, the NCI supports a robust array of clinical trials for aggressive, late stage cancers. For example, a therapy granted “breakthrough status” (accelerated review) by the FDA in 2016 is now being evaluated for treatment of certain brain cancers in a phase II trial for adults¹²³ and a phase I trial for children.¹²⁴ Through the Pediatric Brain Tumor Consortium, researchers are conducting a phase I trial of a drug to treat a type of pediatric brainstem tumor.¹²⁵ Investigators at NCI’s Center for Cancer Research (CCR) are conducting several clinical trials focused on ovarian and other gynecologic cancers, including a phase I trial of a combination of immunotherapy and chemotherapy.¹²⁶ Other CCR investigators seek to use immune cells taken from patients and genetically modified to fight cancer in the treatment of metastatic cancers, including pancreatic, gastric, and liver cancers.¹²⁷

Advances in discovery and elucidation of genetic signatures and biomarkers associated with cancers and their subtypes are the first step towards developing new targeted therapies. One particularly vital resource for scientists engaged in these efforts is The Cancer Genome Atlas (TCGA), an NCI-supported database containing genomic data from 33 different tumor types, including cancers of the pancreas, liver, ovary, brain, stomach, esophagus, and lung. Recent advances using TCGA data include 1) the identification of a potentially druggable target for the cancer sub-type most often implicated in lung and pancreatic cancers,¹²⁸ 2) the discovery of distinct molecular subtypes of pancreatic cancer,¹²⁹ 3) the identification of three subtypes of liver cancer,¹³⁰ 4) the characterization of different types of esophageal cancer.¹³¹ NCI also supports TARGET (Therapeutically Applicable Research to Generate Effective Treatments), a complementary cancer genomics research resource for the study of several high-risk pediatric cancers.¹³² Several of the pediatric cancer subtypes selected for study through TARGET also have five-year survival rates that fall below fifty percent.¹³³

Additionally, to ensure the coordination of research efforts – including for cancers with low five-year survival rates – the NCI also supports research consortia like those previously mentioned, and Specialized Programs of Research Excellence (SPORes) focused on specific cancer types. The NCI supports SPORes to promote collaborative, interdisciplinary translational cancer research on pancreatic cancer (3 sites), ovarian cancer (3 sites), brain cancer (6 sites), lung cancer (3 sites), and

¹²⁰ <https://prevention.cancer.gov/major-programs/pancreatic-cancer-detection>

¹²¹ <https://ccr.cancer.gov/comparative-oncology-program/research/cbtc>

¹²² <https://www.pbtc.org/>

¹²³ <https://clinicaltrials.gov/ct2/show/NCT02986178>

¹²⁴ <https://clinicaltrials.gov/ct2/show/NCT03043391>

¹²⁵ <https://clinicaltrials.gov/ct2/show/NCT02717455>

¹²⁶ <https://clinicaltrials.gov/ct2/show/NCT02948426>

¹²⁷ <https://clinicaltrials.gov/ct2/show/NCT01174121>

¹²⁸ <https://www.ncbi.nlm.nih.gov/pubmed/28893801>

¹²⁹ <https://www.ncbi.nlm.nih.gov/pubmed/28810144>

¹³⁰ <https://www.ncbi.nlm.nih.gov/pubmed/28622513>

¹³¹ <https://www.ncbi.nlm.nih.gov/pubmed/28052061>

¹³² <https://ocg.cancer.gov/programs/target>

¹³³ These include high-risk pediatric AML, high-risk neuroblastoma, metastatic osteosarcoma, and rhabdomyosarcoma diagnosed among patients ages 15-19 years of age, which has a poorer prognosis in comparison to diagnoses of rhabdomyosarcoma in younger children.

gastrointestinal cancers, which includes cancers of the colon, rectum, stomach, esophagus, small intestine, liver, gallbladder and other digestive organs (4 sites).¹³⁴

NCI remains committed to supporting and advancing cancer research progress for all cancer types, including those with high mortality and low five-year survival. The Institute will continue to support research focused on prevention and early detection, as well as preclinical and clinical research to develop new treatments, with long-term goals of reducing mortality, increasing survival, and improving quality of life for all cancer patients.

¹³⁴ <https://trp.cancer.gov/>

Diabetes

The Committee recognizes the important work of NIDDK, the lead Federal agency conducting research to find a cure for diabetes and improve diabetes care. Individuals with and at risk for diabetes benefit from life-sustaining advancements in preventing and treating diabetes that result from NIDDK studies. The Committee also recognizes the success of the NIDDK-supported research in the development of essential tools to manage diabetes, including insulin pumps and blood glucose monitors, ongoing development of artificial pancreas technologies, and new and better medications to treat diabetes. The Committee urges NIDDK to commit resources commensurate with the severity and escalating costs of the epidemic to further diabetes research that will build upon these past successes, improve prevention and treatment, and bring the Nation closer to a cure.

Action taken or to be taken:

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is building on recent scientific progress and continuing its vigorous support of research toward the prevention, treatment, and cure of diabetes. For example, building on significant advances in the development of artificial pancreas (AP) technologies, which link glucose sensing and insulin delivery, NIDDK is supporting four advanced clinical trials testing novel AP technology. In one of these, researchers will be testing their algorithm, which calculates the amount of insulin to administer based on glucose levels, with different insulin pumps and glucose sensors. This research could advance the goal of having interoperable AP components so that newly developed insulin pumps and glucose sensors could be paired with existing algorithms, making it easier and faster to develop next-generation AP devices.

NIDDK also supports research conducted by small businesses to improve AP device components. For example, one such small business has developed a new soluble, stable formulation of the hormone glucagon, which raises blood sugar levels, that is being used in several products, including a “bihormonal” AP device that delivers both insulin and glucagon. Other small businesses are developing implantable glucose sensors, which can give people with diabetes freedom from having sensors attached to their bodies and having to manage them. NIDDK recognizes that new tools and technologies for diabetes management will only benefit people if they can use them. Thus, research developing AP technologies and other new diabetes management tools is being done in conjunction with research developing behavioral interventions. For example, behavioral researchers are developing a social media resource for parents of very young children with type 1 diabetes that is intended to provide them with support for managing their child’s disease.

NIDDK’s Glycemia Reduction Approaches in Diabetes: An Effectiveness Study recently completed recruitment of over 5,000 people to compare the long-term benefits and risks of four widely used type 2 diabetes drugs in combination with metformin. Results from this study could lead to personalized approaches for type 2 diabetes therapy. NIDDK also continues its leadership of the Accelerating Medicines Partnership Type 2 Diabetes Project to identify and validate promising biological targets for new diagnostic and drug development.

Recent results from an NIDDK-supported study found that Roux-en-Y gastric bypass surgery in adults with severe obesity was associated with significant reduction—by more than 90 percent—of new-onset type 2 diabetes and a remission rate of type 2 diabetes of 51 percent 12 years after surgery.

Research is also progressing toward curing diabetes. Researchers in the Human Islet Research Network (HIRN) are engineering strategies for replacing beta cells destroyed in diabetes, such as replication of the remaining beta cells or regeneration of beta cells from related cells in the body. For example, HIRN is studying the ability of small molecules—which can be developed into drugs—to induce beta cell replication or regeneration.

Regarding diabetes prevention, in January 2018, the Centers for Medicare and Medicaid Services began coverage of a group-based adaptation of an intensive lifestyle intervention for beneficiaries with prediabetes; this type 2 diabetes prevention approach was first pioneered in NIDDK's Diabetes Prevention Program clinical trial. An ongoing NIDDK-led trial testing whether vitamin D supplementation can delay the onset of type 2 diabetes in people at risk recently met its enrollment target. NIDDK's Type 1 Diabetes TrialNet is conducting two clinical trials testing the ability of drugs to prevent type 1 diabetes in relatives of people with the disease.

Drug Treatment in the Justice System

The Committee understands that providing evidence-based treatment for substance use disorders offers a valuable opportunity to interrupt the substance use/criminal justice system cycle for people struggling with substance use disorders. Untreated substance use disorder renders prior criminal offenders particularly vulnerable to recidivism and continued health problems, preventing them from being able to find stable employment, jeopardizing public health and safety, and taxing justice and health system resources. When combined with therapy, medication assisted treatment (MAT) has consistently been shown to be more effective in treating substance use disorder than abstinence. The Committee applauds NIDA's focus on adult and juvenile justice populations in its research around substance use disorder treatment. The Committee supports this important work and asks for a progress report on those efforts, including information on the use and success of MAT in the juvenile justice system.

Action taken or to be taken:

Studies have shown that approximately 70 percent of juveniles involved in the criminal justice system have used drugs and 37 percent meet criteria for a substance use disorder.²³ NIDA's Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS) is guided by the philosophy that all juvenile offenders can benefit from substance use and HIV-related prevention, screening, and treatment interventions. The JJ-TRIALS cooperative was established in 2013 and is composed of six research centers and one coordinating center. The main study is a randomized trial that involves 36 sites in seven states and aims to test the effectiveness of two implementation strategies for promoting system-wide change to improve the continuum of substance use services for juvenile offenders under community supervision.¹³⁵ JJ-TRIALS has led to the development of the Juvenile Justice Behavioral Health Services Cascade, a framework for measurement of unmet substance use treatment needs that can be used to identify services delivery needs and develop strategies to address them.¹³⁶

Beyond juvenile populations, NIDA is currently funding research to test the feasibility and utility of medication assisted treatment, including depot formulations of buprenorphine and naltrexone to prevent relapse to opioid use and recidivism in incarcerated opioid-dependent individuals. Barriers to care are also being investigated; specifically, research on the difficulties that justice-involved veterans have in accessing medications for Opioid Use Disorder and research on the development of eLearning tools to improve attitudes toward medications in drug and felony courts.

The period of transition from incarceration to community living can cause disruption in care for substance use disorders and for associated health conditions such as HIV and HCV. NIDA funds research to identify barriers and facilitators of linkage to care following incarceration, along with research to develop interventions to improve care continuity, reduce overdose risk, and identify factors specific to vulnerable sub-populations. This research includes:

¹³⁵ Knight DK, Belenko S, Wiley T, et al. Juvenile Justice—Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS): a cluster randomized trial targeting system-wide improvement in substance use services. *Implementation Science* : IS 2016;11:57.

¹³⁶ Belenko S, Knight D, Wasserman GA, et al. The Juvenile Justice Behavioral Health Services Cascade: A new framework for measuring unmet substance use treatment services needs among adolescent offenders. *Journal of Substance Abuse Treatment*;74:80-91.

- development of an interventions to support initiation of buprenorphine or methadone treatment following release from incarceration^{137,138}
- Evaluation of pre-release initiation of extended-release naltrexone (XR-NTX) followed by post-release home visits for XR-NTX injection delivery¹³⁹
- development of a program to optimize HIV treatment outcomes for women under community correctional supervision¹⁴⁰
- development and testing of behavioral interventions to reduce risky behaviors and improve treatment adherence post-release^{141,142}

¹³⁷https://projectreporter.nih.gov/project_info_description.cfm?aid=9095289&icde=36721801&ddparam=&ddvalue=&ddsub=&cr=1&cbsb=default&cs=ASC&pball=

¹³⁸https://projectreporter.nih.gov/project_info_description.cfm?aid=9271946&icde=36721822&ddparam=&ddvalue=&ddsub=&cr=1&cbsb=default&cs=ASC&pball=

¹³⁹https://projectreporter.nih.gov/project_info_description.cfm?aid=9325491&icde=36721607&ddparam=&ddvalue=&ddsub=&cr=1&cbsb=default&cs=ASC&pball=

¹⁴⁰https://projectreporter.nih.gov/project_info_description.cfm?aid=9086300&icde=36721724&ddparam=&ddvalue=&ddsub=&cr=1&cbsb=default&cs=ASC&pball=

¹⁴¹https://projectreporter.nih.gov/project_info_description.cfm?aid=9242609&icde=36721632&ddparam=&ddvalue=&ddsub=&cr=1&cbsb=default&cs=ASC&pball=

¹⁴²https://projectreporter.nih.gov/project_info_description.cfm?aid=9349087&icde=36721782&ddparam=&ddvalue=&ddsub=&cr=1&cbsb=default&cs=ASC&pball=

Drug-Induced Liver Injury Network (DILIN)

The Committee commends NIDDK for including analyses of liver injury caused by alternative medicines, such as herbal products and supplements, within its DILIN. However, the Committee is concerned with the limited scope of the current work. Therefore, the Committee directs NIDDK to work to expand to a broader sample of herbal products and supplements associated with liver injury cases to ascertain with greater certainty the causal agents and their prevalence. These samples exist within the DILIN Repository and afford an opportunity to analyze products for unlabeled ingredients, along with current analyses. This work can help generate a database to help identify signals to prevent future liver injury. The Committee requests that NIDDK provide an update to the Committee in the fiscal year 2019 CJ.

Action taken or to be taken:

Since 2003, the NIDDK's Drug-Induced Liver Injury Network (DILIN) has collected and analyzed data from people with severe liver injury caused by over-the-counter and prescription drugs or by alternative medicines such as herbal products and dietary supplements. The purpose of this Network is to advance understanding of this relatively rare, but potentially life-threatening, form of liver injury, as well as improve its diagnosis and management. The Network includes multiple clinical sites across the country, a data coordinating center, and a sample repository. The NIDDK also collaborates with the National Library of Medicine on the "LiverTox" website, a resource designed for use by health care providers, researchers, and the public featuring sample cases from DILIN of people with liver injury from drugs, herbal or dietary supplements. LiverTox also includes a database summarizing liver injuries caused by these agents.¹

Past studies by the Network have shown that cases of confirmed liver injury due to herbal and dietary supplements have increased since DILIN's establishment, with these products now accounting for more than 20 percent of cases reported in the Network.¹⁴³ Liver injury from these products can be severe, leading to a need for a life-saving liver transplantation in some cases. However, unique challenges exist in definitively attributing liver injury to these products, including the variety of ingredients contained in some supplements; the multi-supplement consumption patterns of many consumers; and inaccurate labeling, with some products containing low amounts of stated ingredients but containing undisclosed pharmaceuticals or harmful contaminants.

Network investigators have been conducting chemical analyses of herbal and dietary supplements associated with cases of liver injury. Recent preliminary findings from these analyses were presented at the annual meeting of the American Association for the Study of Liver Diseases in October 2017, summarizing findings made on cases from the Network's start in 2003 until March 2016. During this time period, DILIN collected information on cases of suspected liver injury due to herbal or dietary supplements, the majority of which had undergone chemical analysis at that time. The researchers observed that mislabeling of these supplements was common, particularly for products used for bodybuilding or weight loss. These analyses will be expanded to the remaining cases collected to date, with a goal of attaining "real-time" chemical analysis of these herbal and dietary supplements in the future.

As part of two initiatives to renew the Network in 2017¹⁴⁴, emphasis has been placed on continuing its repository of herbal and dietary supplement products and expanding on an existing collaboration

¹ <https://livertox.nih.gov/>

² <https://www.ncbi.nlm.nih.gov/pubmed/25043597>

¹⁴⁴ <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-17-509.html> and <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-17-510.html>

to analyze the chemical components in these products between the DILIN data coordinating center and a laboratory with expertise in comprehensive analysis of herbal and dietary supplements. These efforts are aimed at better characterizing chemical components in herbal and dietary supplements implicated as the cause of liver injury, which may provide new insights into the nature of this injury, suggest innovative approaches to mechanistic studies, and ultimately lead to better means of prevention or treatment.

Duchenne Muscular Dystrophy

Committee is aware of stakeholder efforts to achieve validated and qualified biomarkers for Duchenne Muscular Dystrophy. The Committee supports these activities and urges NINDS to work with other Institutes and with the FDA to provide the necessary guidance and to assemble a workshop of all stakeholders to advance this work. The Committee is also concerned about a lack of access to federally funded data, such as imaging and biomarker data, that could support qualification of an MRI imaging biomarker and directs NIH to ensure all federally funded investigators, including Duchenne investigators, are in full compliance with the data sharing requirements included in the 21st Century Cures Act.

Action taken or to be taken:

NIH currently funds several projects focused on evaluating and validating biomarkers for the muscular dystrophies. NIH-funded investigators demonstrated that in Duchenne Muscular Dystrophy (DMD) a protein called dystrophin is much reduced or absent at the muscle membrane, and some promising therapeutic development programs have been built around increasing dystrophin levels in muscle biopsies in DMD boys. In addition, NIH-funded work at the University of Florida Paul D. Wellstone Muscular Dystrophy Cooperative Research Center has established standardized methods to assess skeletal muscle health in patients with muscular dystrophies, using magnetic resonance imaging and spectroscopy. These muscle biomarkers are already in use in clinical trials in patients with DMD. NIH-funded projects are also studying biomarkers in patient blood and urine, and using other non-invasive techniques, including electrical impedance myography and ultrasound, to develop biomarkers of muscle composition, structure, and function. National Heart, Lung, and Blood Institute (NHLBI) funds several projects on defining cardiac function biomarkers in DMD and on evaluating serum and imaging biomarkers to detect cardiac dysfunction with the goal of earlier therapeutic intervention. In 2016, National Institute of Neurological Disorders and Stroke (NINDS) released a funding opportunity announcement (FOA) to support clinical trial readiness (including biomarker and outcome qualification) for rare neurological and neuromuscular diseases, including the muscular dystrophies. In the first project funded through this FOA, researchers at the University of Rochester Wellstone Center are working to develop clinical outcome measures and a skeletal muscle biomarker for one form of muscular dystrophy. These tools are needed for the conduct of upcoming clinical trials. The FDA also released funding opportunity for biomarker validation/qualification in rare diseases, and recently funded a grant to develop molecular biomarkers and outcome assessment measures for one form of muscular dystrophy through this initiative.

The topic of biomarkers has been discussed at several Muscular Dystrophy Coordinating Committee (MDCC) meetings and is regularly an agenda item at scientific meetings. At the MDCC meeting in late 2015, following presentations on the FDA Biomarker Qualification Program and ongoing research on imaging and biochemical biomarkers for DMD, MDCC members, invited presenters, and FDA representatives discussed how to advance biomarker development for all the muscular dystrophies.

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public. In addition, NINDS has developed Common Data Elements (CDEs) for many diseases, including DMD. CDEs are data standards for clinical research that can improve data quality and facilitate data sharing. The NIH-funded Wellstone Centers also encourage data sharing and collaboration across the Centers and with the larger muscular dystrophy research community. Finally, one of the MDCC's 2016 meetings included a discussion of ways to facilitate data sharing for muscular dystrophy studies.

Dystonia

Committee encourages NINDS to continue to expand the dystonia research portfolio. NINDS is encouraged to work with stakeholders in support of a conference to examine evolving scientific opportunities in dystonia research and to foster sharing of resources and collaboration among investigators.

Action taken or to be taken:

NIH supports a broad range of research to advance the understanding of dystonia and to improve diagnosis, prevention, and treatment. As befits the rapid changes in the scientific landscape, the NIH dystonia grant portfolio has been especially dynamic. Grants newly funded within the last two years reflect opportunities emerging from diverse areas of biology to advance dystonia research. Recent grants, for example, are exploring how mutations in the THAP1 gene cause dystonia and developing a novel mouse model to study the disease, using brain imaging and noninvasive stimulation to examine which connections in the brain are faulty in focal dystonia, studying which types of dystonia respond well to deep brain stimulation therapy, identifying additional genes that contribute to dystonia, and examining metabolomic profiles in blood, which reflect environmental as well as genetic influences, together with genetics to identify the causes of unexplained dystonia.

Dystonia, whatever its causes, disrupts the proper functioning of brain circuits. In the vast majority of dystonias there is no pathologic change visible on brain examination and with current technologies the brain circuit dysfunction is invisible. Thus dystonia, in the long run, will benefit from the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, which is developing new technologies to understand and measure the activity in brain circuits and, ultimately, to modulate them more precisely. BRAIN engages the expertise from many parts of the NIH, multiple federal agencies, and several private organizations, and researchers are already applying these tools to understand brain circuits in animal models of dystonia.

The National Institute on Neurological Diseases and Stroke agrees that this may be an opportune time for a conference to explore emerging opportunities to accelerate dystonia research, and discussions are underway with stakeholders on such a meeting.

Epidermolysis Bullosa

The Committee recognizes the promising scientific gains and applauds private partners advancing research in pursuit of treatments for Epidermolysis Bullosa. The Committee encourages NIH to continue to support the intensification of such research at NIAMS. The Committee further encourages NIAMS to leverage Federal funds with public-private partnerships in the areas of Epidermolysis Bullosa and related disorders.

Action taken or to be taken:

Epidermolysis bullosa (EB) is a family of inherited disorders of the skin and internal mucosal membranes. For people with EB, the skin and mucosal surfaces are so fragile that even minor rubbing can cause blistering. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports a wide range of research to identify the causes of EB and determine new treatments. Several of these projects address the needs of individuals with a severe form of EB who carry mutations in the gene that encodes type VII collagen, leading to a nonfunctional protein. In a recently completed Phase I clinical trial, NIAMS-funded researchers inserted a normal type VII collagen gene into cells taken from EB patients' own skin. Researchers then expanded these corrected cells into flat sheets, which were well tolerated and expressed the correct type VII collagen when grafted onto EB patients' skin. Other investigators conducting basic research made the promising discovery that amlexanox, a drug approved by the FDA for the treatment of mouth ulcers, increased the level of functional type VII collagen in EB patient cells that were grown in laboratory dishes. In addition, a clinical study co-funded by NIAMS, non-profit organizations, and the Department of Veterans Affairs found that gentamicin therapy might be a readily available treatment for a subset of patients with severe EB. In this pilot study, both topical application and under-the-skin injection with gentamicin successfully induced production of functional type VII collagen that persisted for three months. Further, topical gentamicin reduced skin blistering and improved wound healing. This work represents another promising step towards safe and effective therapy for EB and related disorders.

NIAMS is also utilizing new programs authorized by the 21st Century Cures Act to further the translation of research findings into new treatments for EB. The Regenerative Medicine Innovation Projects funding opportunities made possible by the Act require that recipients match the federal award in at least an equal amount with non-federal funds, thereby amplifying the federal investment and stimulating collaboration across public and private sectors. In FY 2017, a supplemental award issued through this program to a consortium of three NIAMS grantees will allow them to build upon their existing research to correct the EB disease-causing mutations in induced pluripotent stem cells (iPSCs) derived from the patients' own skin, support production of clinical-grade reagents, and facilitate clinical data collection and analysis in preparation for the submission of an Investigational New Drug application to the FDA. If successful, the approach could be expanded to employ iPSCs for the treatment of other diseases that are the result of a single defective gene.

Experimental Program to Stimulate Competitive Research (EPSCoR)

The National Institutes of Health and the National Institute of General Medical Sciences as an agency that administers an Experimental Program to Stimulate Competitive Research program (EPSCoR), will submit a report in response to the following language specified in American Innovation and Competitiveness Act.

FEDERAL AGENCY REPORTS.—Each Federal agency that administers an EPSCoR shall submit to Congress, as part of its Federal budget submission—“(1) a description of the program strategy and objectives; (2) a description of the awards made in the previous fiscal year, including— “(A) the total amount made available, by State, under EPSCoR; “(B) the total amount of agency funding made available to all institutions and entities within each EPSCoR State; “(C) the efforts and accomplishments to more fully integrate the EPSCoR States in major agency activities and initiatives; “(D) the percentage of EPSCoR reviewers from EPSCoR States; and “(E) the number of programs or large collaborator awards involving a partnership of organizations and institutions from EPSCoR and non-EPSCoR States; and “(3) an analysis of the gains in academic research quality and competitiveness, and in science and technology human resource development, achieved by the program over the last 5 fiscal years.”; and (E) in subsection (e)(1), as redesignated, by striking “Experimental Program to Stimulate Competitive Research or a program similar to the Experimental Program to Stimulate Competitive Research” and inserting “EPSCoR”.

Action taken or to be taken

This response summarizes the National Institutes of Health (NIH) funding to institutions and entities in the Institutional Development Award (IDeA) Program States/Jurisdictions in Fiscal Year 2017 (FY 2017), as required by the American Innovation and Competitiveness Act Sec. 103(d)(1-3). Within this report, the term “IDeA-eligible states” refers to the 23 states and territory (Puerto Rico) that are eligible for IDeA funding. Specifically, the report provides details on the following: (1) a description of strategy and objectives of the IDeA Program; (2) a description of the awards made in the previous fiscal year including: [A] the total amount made available by state under the IDeA program; [B] the total amount of agency funding made available to all institutions and entities within each IDeA-eligible states [C] the efforts and accomplishments to more fully integrate the IDeA-eligible states in major agency activities and initiatives; [D] the percentage of IDeA reviewers from IDeA-eligible states; [E] the number of programs or large collaborator awards involving a partnership of organizations and institutions from IDeA and non-IDeA-eligible states; and (3) an analysis of the gains in academic research quality and competitiveness, and in science and technology human resource development, achieved by the program over the last 5 years.

The IDeA Program, administered by the National Institute of General Medical Sciences (NIGMS) at NIH, has 4 major ongoing initiatives in pursuit of its goal of strengthening biomedical research capacity and competitiveness in eligible states. In FY 2017, the IDeA Program received \$333 million in appropriations. The interventional initiatives and the awards made in FY 2017 included the following:

- (1) *IDeA Networks of Biomedical Research Excellence (INBRE)*. The INBRE initiative enhances, extends, and strengthens the research capabilities of biomedical research faculty in IDeA states through a statewide program that links a research-intensive institution with primarily undergraduate institutions. INBRE supports institutional research and infrastructure development; research by faculty, postdoctoral scientists, and students at participating institutions; and outreach to build science and technology knowledge in the states’ workforces.

Only one award is made per IDeA-eligible state. In FY 2017, NIH/NIGMS supported 24 INBRE awards [FY 2017 Budget allocation: \$84.9 million].

- (2) *Centers of Biomedical Research Excellence (COBRE – Phases I, II, and III)*. The COBRE initiative develops and strengthens institutional biomedical research capabilities in IDeA states through three 5-year phases of infrastructure and faculty development of multidisciplinary research centers around a specific biomedical science theme. A major focus of the COBRE initiative is the professional development of early career investigators. In FY 2017, NIH/NIGMS had 122 active COBRE awards (104 awards had FY 2017 budget, 18 were in no-cost extension) [FY 2017 Budget allocation: \$189.5 million].
- (3) *IDeA Program Infrastructure for Clinical and Translational Research (IDeA-CTR)*. The IDeA-CTR initiative develops network infrastructure and capacity in IDeA-eligible states to conduct clinical and translational research focused on health concerns that affect medically underserved populations and/or that are prevalent in IDeA states. IDeA-CTR awards support mentoring and career development activities in clinical and translational research. In FY 2017, NIH/NIGMS supported 10 IDeA-CTR awards [FY 2017 Budget allocation: \$39.7 million].
- (4) the *IDeA Co-funding* initiative provides funding to eligible applications that have already been judged meritorious by NIH peer-review committees and national advisory councils, but are outside the range of applications under consideration for funding by the other NIH Institutes or Centers (ICs). Co-funding priority is given to investigators in their early careers. In FY 2017, IDeA co-funded 63 R01/R15 awards at 17 NIH ICs [FY 2017 Budget allocation: \$19.3 million].

IDeA Program Strategies and Objectives (Sec. 103(d)(1))

The overarching mission of the IDeA Program is inclusive *Biomedical Research Capacity-building* – to develop and strengthen biomedical science research in States/Jurisdictions of the country that are underrepresented in the NIH portfolio, to enable increased engagement and participation of these states in scientific areas that are supported by NIH, and to promote biomedical research capacity and capabilities in these states that are competitive and sustainable. Consequently, the goals of the IDeA program (**Figure 1**) are as follows:

- To grow the next generation of scientific leaders and innovators through targeted professional development efforts.
- To enhance research facilities and resources in eligible States/Jurisdictions that will enable investigators to expand their contributions to scientific discovery, innovation, and learning.
- To establish inclusive and sustainable biomedical workforce development pathways that will equip human resources with the appropriate intellectual and technical scientific skills.
- To effect meaningful engagement of both the research and the at-large communities to address vital and urgent scientific questions and societal priorities including those of the medically underserved and/or the health concerns that are prevalent in eligible states.

Figure 1. Goals of the NIH IDeA Program



NIH funding made available by state under the IDeA Program (Sec. 103(d)(2)(A))

In FY 2017, the NIH IDeA Program invested its entire \$333 million appropriation in support of its programmatic activities. Of this, \$85 million (25.4 percent) was directed to INBRE, \$190 million (56.9 percent) to COBRE, \$40 million (11.9 percent) to IDeA-CTR, and 19 million (5.7 percent) to Co-funding. **Table 1** below details the IDeA Program investments in each of the eligible states.

Table 1. FY 2017 IDeA Program Investments in Eligible States
(US\$, in millions)

| STATE | INBRE | COBRE | IDeA-CTR | Co-funding | TOTAL IDeA |
|--------------|----------------|-----------------|-----------------|-------------------|-------------------|
| AK | 3.72 | - | - | 1.28 | 5.00 |
| AR | 3.68 | 9.55 | - | 0.64 | 13.87 |
| DE | 3.64 | 10.31 | 3.94 | 0.26 | 18.15 |
| HI | 3.72 | 5.64 | - | 0.32 | 9.68 |
| ID | 3.22 | 6.92 | - | - | 10.14 |
| KS | 3.74 | 10.07 | - | 1.28 | 15.09 |
| KY | 3.59 | 12.57 | - | 0.96 | 17.12 |
| LA | 3.64 | 11.84 | 4.00 | 0.96 | 20.44 |
| ME | 3.63 | 7.08 | 4.00 | 0.64 | 15.35 |
| MS | 3.59 | 7.75 | 3.98 | - | 15.32 |
| MT | 3.58 | 6.30 | 4.00 | 0.46 | 14.34 |
| ND | 3.38 | 7.02 | - | 0.54 | 10.94 |
| NE | 3.44 | 12.90 | 3.98 | 1.22 | 21.54 |
| NH | 3.51 | 7.88 | - | 2.02 | 13.41 |
| NM | 3.60 | 8.12 | - | 0.96 | 12.68 |
| NV | 3.47 | 5.41 | 3.83 | 0.31 | 13.02 |
| OK | 3.66 | 15.61 | 4.00 | 1.24 | 24.51 |
| PR | 3.26 | 2.03 | - | 0.32 | 5.61 |
| RI | 3.72 | 15.95 | 3.97 | 1.25 | 24.89 |
| SC | 3.59 | 12.36 | - | 1.27 | 17.22 |
| SD | 3.16 | 7.07 | - | 0.32 | 10.55 |
| VT | 3.49 | 3.02 | - | 1.54 | 8.05 |
| WV | 3.42 | 2.13 | 4.00 | 0.96 | 10.51 |
| WY | 3.46 | 1.94 | - | 0.53 | 5.93 |
| TOTAL | \$84.91 | \$189.47 | \$39.7 | \$19.28 | \$ 333.36 |

Total NIH funding made available in all IDeA-eligible states (Sec. 103(d)(2)(B)).

In FY 2017, NIH invested a total of \$1.718 billion in support of IDeA-eligible states. **Table 2** below details the breakdown of NIH investments in IDeA-eligible states.

Table 2. FY 2017 NIH Investments in IDeA-eligible States
(US\$, in millions)

| Jurisdiction | NIH Funding |
|--------------|-------------|
| AK | 16.81 |
| AR | 55.27 |
| DE | 43.48 |
| HI | 48.09 |
| ID | 14.11 |
| KS | 99.95 |
| KY | 183.92 |
| LA | 134.03 |
| ME | 88.71 |
| MS | 42.40 |
| MT | 33.19 |
| ND | 18.39 |
| NE | 108.03 |
| NH | 108.28 |
| NM | 96.35 |
| NV | 31.51 |
| OK | 90.91 |
| PR | 43.23 |
| RI | 170.82 |
| SC | 178.79 |
| SD | 23.55 |
| VT | 49.30 |
| WV | 26.28 |
| WY | 12.44 |
| Total | \$1,717.84 |

Integration of IDeA-Eligible States in Major Activities and Initiatives of NIH (Sec. 103(d)(2)(C)).

All IDeA programmatic activities are intended to fully engage and integrate IDeA-eligible states into the NIH mission which is *‘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.’ All IDeA Program awards are investigator-initiated projects that fall within the purview of the NIH mission. As a capacity-building program, an implicit goal of the IDeA Program is for grantees to become successful in obtaining mainstream NIH awards such as Research Project Grants (RPGs) (*e.g.*, R01, R21) or Program Project Grants (PPGs) (*e.g.*, P01, U01) from other NIH ICs. IDeA Program staff regularly provide information regarding these opportunities to IDeA-supported investigators through various outlets (*i.e.* e-mail listservs, National and Regional IDeA Meetings, conference calls, Program Staff visits).

NIH relies on a broad spectrum of scientific leaders to serve as subject-matter experts in Scientific Review Groups (SRGs) that review applications submitted to NIH for scientific merit and on IC Advisory Panels that provide valuable input on IC priorities and objectives. Investigators from IDeA-eligible states are actively involved in these efforts. Information is provided in Section V below regarding the service as reviewers from IDeA states. Similarly, in recognition of their scientific excellence and leadership, a number of IDeA Program awardees currently serve on the Advisory Panels of various ICs:

- Judith James M.D. Ph.D. [OK] (IDeA-CTR Principal Investigator), National Institute of Arthritis, Musculoskeletal, and Skin Diseases (NIAMS) Advisory Panel
- Sally Hodder M.D. [WV] (IDeA-CTR Principal Investigator), National Institute of Allergy and Infectious Disease (NIAID) Advisory Panel
- Daniel McNeil Ph.D. [WV] (IDeA-CTR Pilot Project Leader), National Institute of Dental and Craniofacial Research (NIDCR) Advisory Panel
- Cathy Wu Ph.D. [DE] (INBRE Program Coordinator), National Institute of General Medical Sciences (NIGMS) Advisory Council
- William Gern Ph.D. [WY] (INBRE Internal Advisory Committee Member), National Institute of General Medical Sciences (NIGMS) Advisory Council

Information on some key NIH initiatives has been shared with investigators in IDeA states/ jurisdictions to encourage awareness of and participation in these programs, as appropriate. Interactions with IDeA Program awardees include:

- William Gahl M.D., Clinical Director of the National Human Genome Research Institute (NHGRI) made a presentation about the NIH Undiagnosed Diseases Network (UDN) to the IDeA-CTR Principal Investigators group on February 27, 2017.
- Robert Tamburro M.D., M.Sc., from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) made a presentation about the Pediatric Critical Care and Trauma Scientist Development Program to the IDeA-CTR Principal Investigators group on June 20, 2017.
- Christopher Austin M.D., Director of the National Center for Advancing Translational Science (NCATS) spoke about how that IC works to catalyze translational research as the Plenary Speaker at the Great Plains IDeA-CTR Network First Annual Scientific Meeting held in Omaha, NE on October 23, 2017.

IDeA Program Staff are working across NIH on ideas to increase engagement with and of IDeA investigators. These include:

- Potential collaborations on aging-related research with the National Institute of Aging (NIA). NIA Director Richard Hodes M.D., is scheduled to give a presentation at the June 2018 National IDeA Symposium on Biomedical Research Excellence (NISBRE)

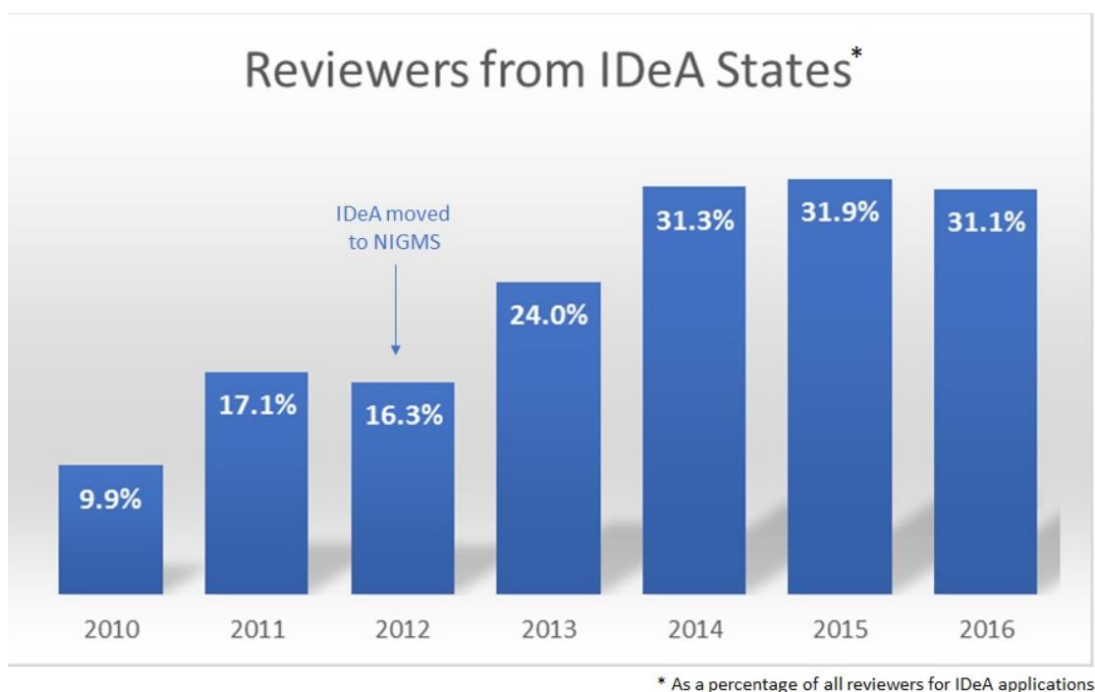
- Encouraging collaborations between IDeA-CTR awardees and the Clinical and Translational Science Award (CTSA) recipients managed by NCATS to leverage resources.
- Synergistic initiatives to address the opioid crisis with the National Institute of Drug Abuse (NIDA)
- Co-funding of shared instrumentation grant applications from IDeA-eligible states with the Office of Research Infrastructure Programs (ORIP) in the NIH Office of the Director (OD)

Recently, NIH published a Funding Opportunity Announcement (FOA) for the development of Regional Technology Transfer Accelerator Hubs for IDeA-eligible states. This FOA was developed in response to a Senate-HHS Committee Report in FY 2016 that asked NIH/ NIGMS ‘to consider allocating funding for one shared innovation incubator in each of the four IDeA regions that would be competitively bid among IDeA States and would serve IDeA States.’ The report further indicated that ‘NIH shall not use funding from its IDeA allocation for these grants.’ The FOA is soliciting applications that will develop, implement, and test a comprehensive program for promoting entrepreneurship, technology transfer, management, small business finance, and other business skills needed to move discoveries and technologies out of the lab and into commercial products. These regional consortia/hubs are anticipated to provide the necessary infrastructure to foster and build an entrepreneurial culture in IDeA states/ jurisdictions.

Reviewers from IDeA-Eligible States (Sec. 103(d)(2)(D)).

Of all reviewers who evaluated IDeA proposals in FY 2017, 31 percent were from IDeA states (Figure 2).

Figure 2. Reviewers from IDeA States/Jurisdictions



I. Programs or Large Collaborator Awards Involving Partnerships of Organizations and Institutions from IDeA and non-IDEA-Eligible States (Sec. 103(d)(2)(E)).

All the IDeA Program FOAs have restrictions indicating that IDeA funds can only be used in IDeA-eligible states. Funds going to non-IDEA-eligible states are allowed only for fee-for-service activities. Because of these restrictions, all IDeA awards that involve collaborations almost exclusively involve partnerships of organizations and institutions within and/or among IDeA-eligible states. All 24 INBREs, all 10 IDeA-CTRs, and a few COBREs involve partnerships and collaborations of organizations/institutions within an IDeA state (intra-state). INBREs are intra-state partnerships that link research-intensive institution(s) with primarily undergraduate institutions. Of the 10 IDeA-CTR awards, one is an exclusively intra-state network, one is an intra- and inter-state (non-IDEA) network, and 8 are intra- and inter-state (IDEA) networks. All IDeA Center awards – INBREs, COBREs, and IDeA-CTRs – require the establishment of External Advisory Boards (EABs) that, invariably, have members from non-IDEA states.

The FOA for the Regional Technology Transfer Accelerator Hubs for IDeA-eligible states mentioned above does not have a restriction as to where the lead applicant is located. It is possible that an award to this initiative could be located in a non-IDEA-eligible state partnering with organizations/institutions in IDeA-eligible states.

II. An analysis of the gains in academic research quality and competitiveness, and in science and technology human resource development, achieved by the program over the last 5 fiscal years (Sec. 103(d)(3)).

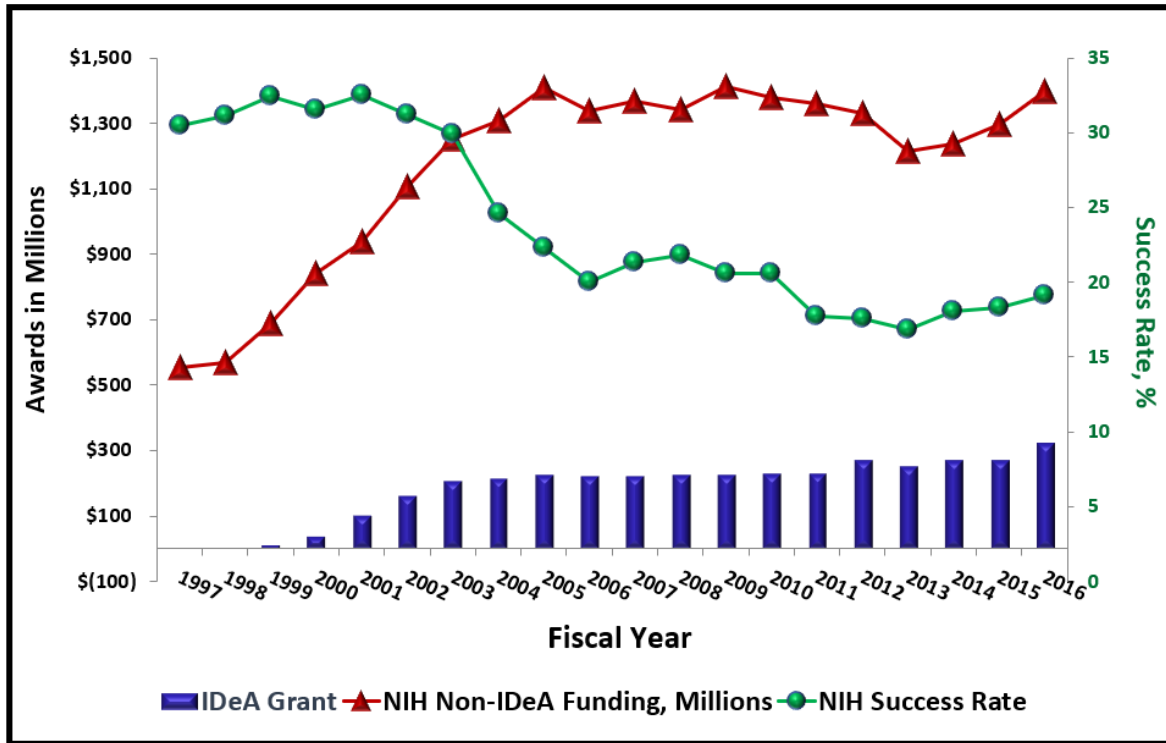
Within the overarching mission of the IDeA Program of inclusive *Biomedical Research Capacity-building* is the objective of promoting competitive and sustainable biomedical research capacity and capabilities in eligible states. Outcome measures that serve as proxies for gains in biomedical research competitiveness include the following:

- (1) Increases in total NIH funding
- (2) Increases in the ability to capture new competitive NIH Research Project Grants (RO1s)
- (3) Increases in scientific publications

A. TOTAL NIH FUNDING

Figure 3 below shows the correlations between IDeA Program appropriation, total NIH funding in the eligible states and the general success rates in obtaining all NIH grants. Data from FY 2013-16 show that while the success rates for obtaining NIH grants in general have declined over the years, investigators in IDeA-eligible states have obtained either the same amount of funding or more, even with only modest increases in IDeA Program appropriations per year. Overall, data from when the first IDeA Program awards were made in 2000 to the present indicate that IDeA-supported scientists have made gains in obtaining more NIH funding compared to non-IDEA-eligible state funding rates.

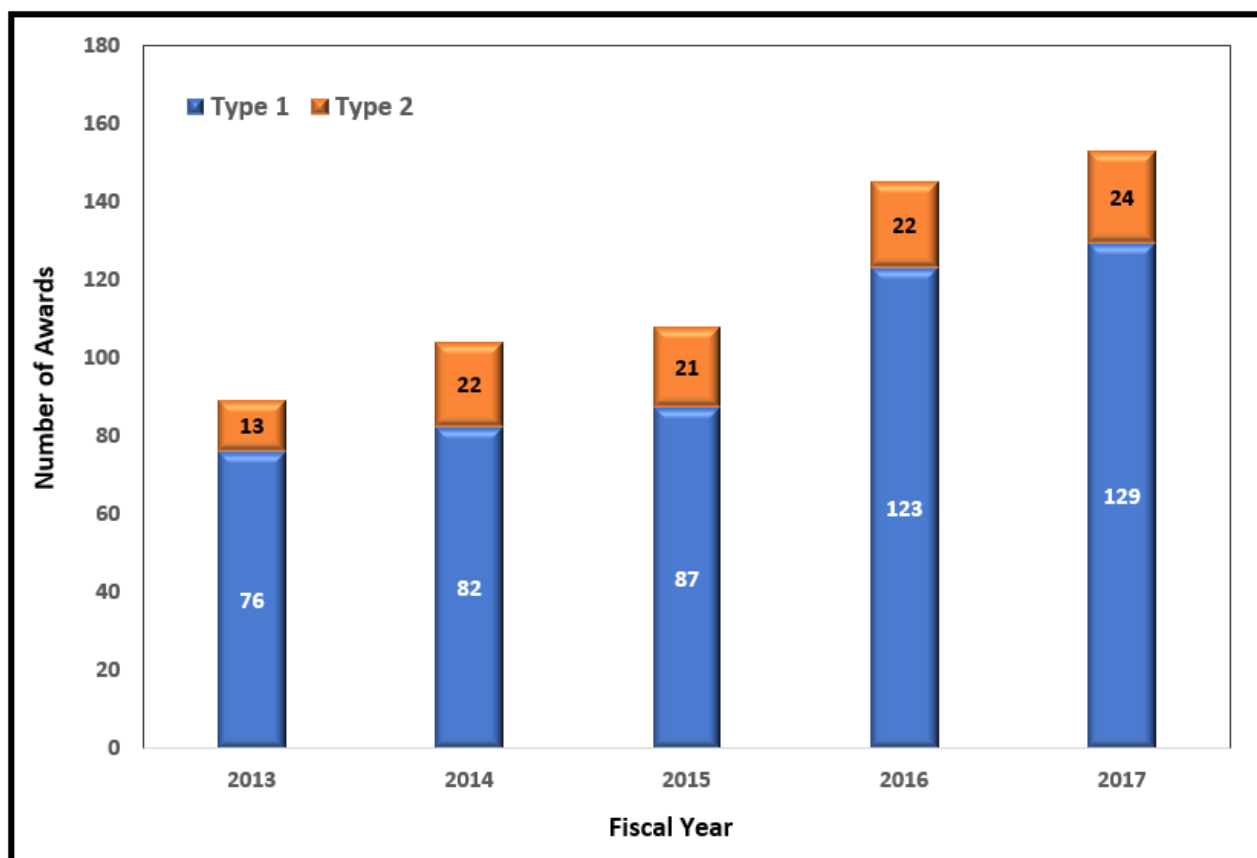
Figure 3. Total NIH Funding, NIH Success Rates, and Total IDeA Program Appropriation in Eligible States.



B. NEW COMPETITIVE NIH RESEARCH PROJECT GRANTS

Data in the last 5 years indicate an increasing trend in the number of NIH R01 research project grants (RPGs) being obtained by investigators who have previously been supported by any of the IDeA Program awards (INBRE, COBRE, IDeA-CTR) (**Figure 4**). Among the various funding mechanisms at NIH, the R01 grant mechanism is the oldest and most utilized research funding mechanism for investigator-initiated research. The R01 grant mechanism supports a discrete, specified, circumscribed project to be performed by the named investigator(s) in an area representing his/her/their specific interests and competencies. It provides monies for research, salary support, equipment, and indirect costs to the institution. It is the most competitive of the NIH RPGs and is often viewed as a prerequisite for tenure and promotion in many universities and academic medical centers. **Figure 4** shows an increasing number of new (Type 1) and renewal (Type 2) R01 awards in the last 5 years by IDeA program supported investigators.

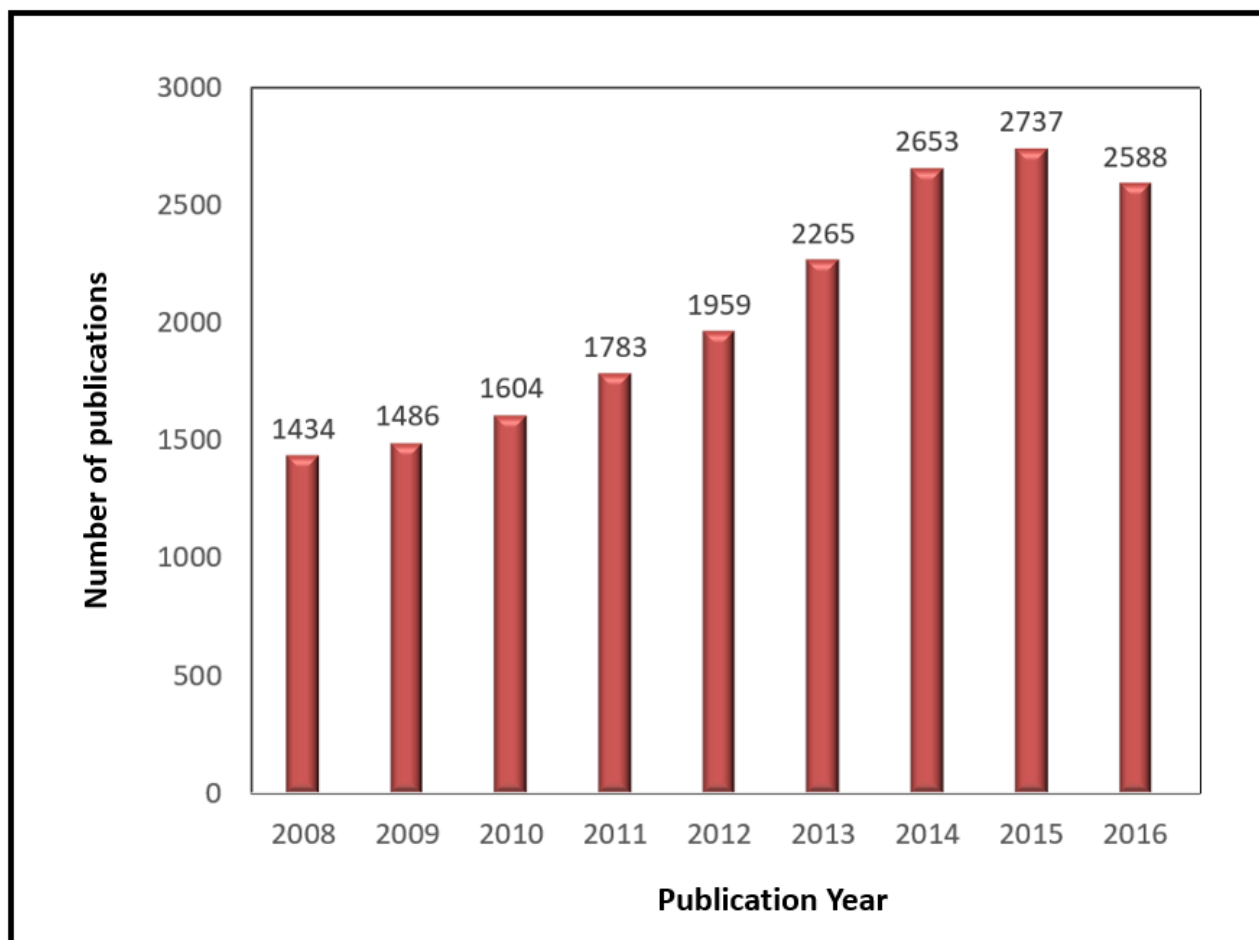
**Figure 4. New NIH Research Projects Grants (R01)
Obtained by IDeA-supported Investigators (FY 2013-2017)**



C. PUBLICATIONS

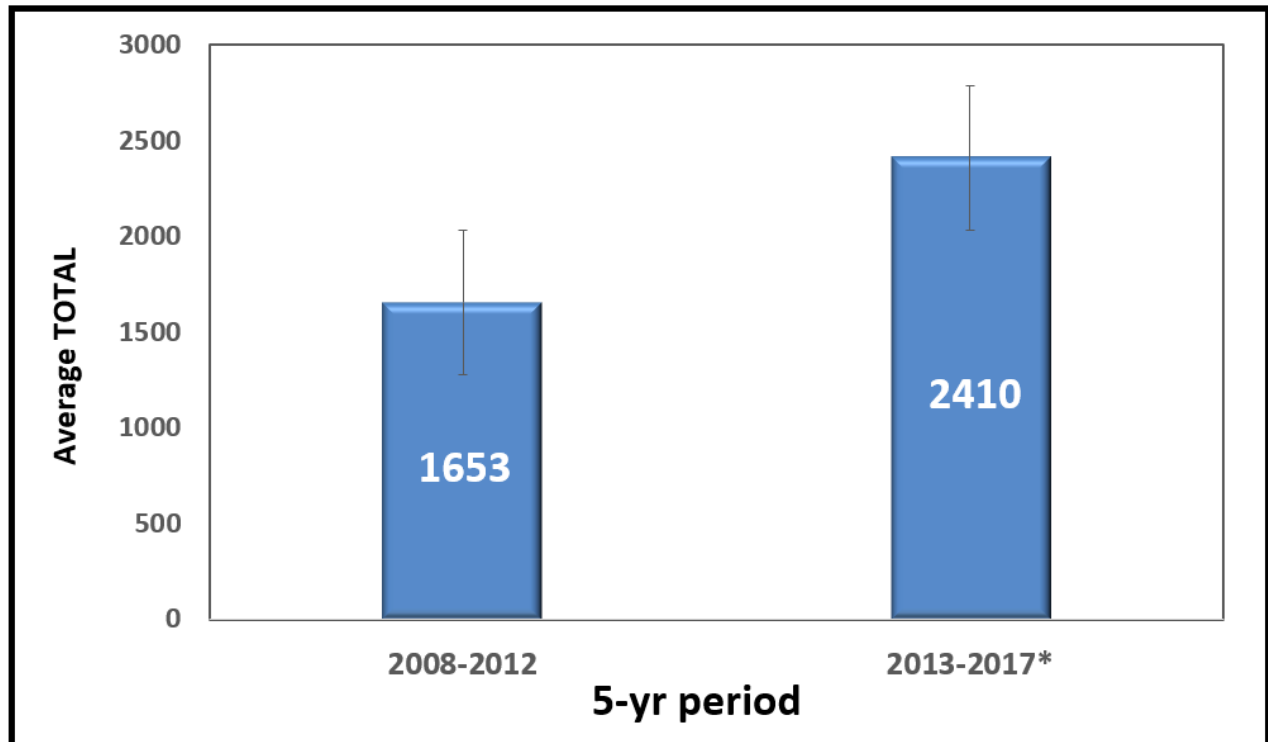
Figure 5 shows the productivity of IDeA-supported investigators in terms of total annual number of publications in scientific journals in the last 10 years (final data for 2017 is not yet available as of this writing [12/07/17]). When the last two 5-year periods are compared (**Figure 6**), the last 5-year period (2013-2016) yearly total publication count average has so far seen a 46% increase in the average total annual publication output compared to the previous 5-year period (2008-2012, yearly total publication count average is 1,653).

Figure 5. Annual Scientific Publication Output by IDeA-supported Investigators (2008-2017).



*Final data for 2017 is not yet available as of this writing.

**Figure 6. Five-year Averages of Scientific Publication Output
by IDeA-supported Investigators (2008-2017).**



*Final data for 2017 is not yet available as of this writing.

Overall, the IDeA program has been successful in its mission to increase NIH funding in IDeA-eligible states and suggests that this program has helped those states build the capacity to obtain and productively use NIH funding for biomedical research.

Fetal Tissue Donation Trial

The Committee acknowledges the many differing views on the merits of human fetal tissue research. New bill language is included to direct NIH to begin a pilot to determine the adequacy of a fetal tissue donor network for supporting all related clinical research from human fetal tissue donated solely from stillbirths and spontaneous abortion.

Action taken or to be taken:

NIH is planning to issue a Funding Opportunity Announcement by the summer of 2018 for a pilot project to determine the adequacy of a human fetal tissue donor network for supporting all related clinical research from human fetal tissue donated solely from stillbirths and spontaneous abortions.

Fibrotic Diseases

The Committee encourages NIH to continue to vigorously support research into fibrotic diseases affecting different organs, including the lungs, liver, kidneys, heart, skin, and bones and to ensure enhanced coordination among its Institutes as they conduct necessary, expanded single organ or cross-organ fibrotic disease research to save lives and reduce healthcare expenses in future years. The Committee also encourages NIH to explore naturally occurring fibrotic disease in domestic animals to investigate opportunities to improve human and animal lives. Since many fibrotic diseases are individually rare diseases, a strategy that provides collaboration across disease and organ areas is recommended. Furthermore, the Committee encourages NIH to continue to provide oversight and direction through coordinated multi-institute activities to improve research efforts and avoid redundancy. The Committee requests a report on the current NIH Fibrosis Interest Group and its progress, which brings together key stakeholders at the NIH and elsewhere, to evaluate current research efforts and develop strategic paths forward to maximize efforts in fibrotic disease research. The Committee also directs NIH to include an update in its fiscal year 2019 CJ on its work relating to idiopathic pulmonary fibrosis following the November 2012 NHLBI workshop, “Strategic Planning for Idiopathic Pulmonary Fibrosis.”

Action taken or to be taken:

NIH remains highly committed to cross-cutting research on fibrotic diseases including pulmonary fibrosis, in part through recommendations put forth by the 2012 "Strategic Planning for Idiopathic Pulmonary Fibrosis (IPF)" workshop and the activities of the NIH Fibrosis Interest Group. This group comprises more than 50 NIH staff and trainees representing multiple Institutes, and serves as a platform that brings together multi-disciplinary fibrosis experts to discuss the state of the science. The group will continue its efforts to enhance coordination and communication across federal and non-federal fibrosis research entities.

As an example of further collaboration across Institutes, the National Heart, Lung, and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases recently joined in an initiative to support Collaborative Projects to Accelerate Research in Organ Fibrosis¹⁴⁵. This initiative aims to characterize mechanisms of aberrant fibrosis in different organ systems, develop novel therapeutic strategies to lessen organ fibrosis, and improve technologies to study fibrosis. Six awarded grants include projects focused on fibrotic diseases of the lung, heart, liver, kidney, and skin. Given that fibrosis shows remarkable similarities across different organ systems and may occur simultaneously in multiple organ systems, this initiative should serve to accelerate and enhance fibrotic disease research.

NHLBI recognizes that aging has a significant impact on disease progression in patients with fibrotic disease, and that there is a need for improved methods and tools to account for the interplay between aging and fibrosis. To this end, NHLBI convened a workshop in September 2015 on the “Intersection Between Aging Biology and Pathobiology of Lung Diseases,” which led to a recommendation that investigators increase their utilization of aged animals for the study of diseases such as pulmonary fibrosis. NHLBI will continue to promote the study of naturally occurring age-related fibrosis in large domestic animals. Further study of these large animal

¹⁴⁵ <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-16-003.html>

models may better recapitulate human disease characteristics and allow for interventions that selectively target age-related biological processes implicated in fibrosis.

Other high-priority areas include basic research grants focused on the importance of a variety of lung cell types in disease development, progression, and mitigation, as well as grants focused on specific molecular and genetic determinants of fibrotic disease. In FY 2017, NHLBI also funded a new multi-site clinical trial to determine if using a combination of therapies that target and reduce autoantibodies known to cause acute exacerbations or serious breathing attacks in patients with IPF will successfully help treat this disease.¹⁴⁶ There are also ongoing trials of autoantibody reduction therapy, as well as antimicrobial therapy, for IPF through NHLBI's Pulmonary Trials Cooperative. These basic research studies and clinical trials constitute a multi-pronged approach to identify and enhance treatments for this devastating condition.

¹⁴⁶ <https://clinicaltrials.gov/ct2/show/NCT03286556>

Focal Segmental Glomerulosclerosis (FSGS)

The Committee encourages NIMHD to continue research collaboration with NIDDK to address the connection between the *APOL1* gene and the onset of FSGS.

Action taken or to be taken:

Recently, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supported 13 grants, with co-funding by the National Institute on Minority Health and Health Disparities (NIMHD), through the *APOL1* Long-term Kidney Transplantation Outcomes Network (APOLLO) Clinical Centers program. APOLLO will establish a multi-center, multidisciplinary network of investigators to examine the association between *APOL1* genes and transplant outcomes for recipients who receive kidneys from African American donors. Studies will also help to determine whether living donors of African American heritage with the *APOL1* genes are at increased risk of developing kidney disease after transplant donation. Continued focus on the *APOL1* gene in African Americans can help to inform clinical practice and policies related to the development, progression, and management of various forms of kidney disease in African Americans, including Focal Segmental Glomerulosclerosis (FSGS).

NIDDK supports a range of research to understand the causes of FSGS and to develop and improve treatments. NIDDK, the National Center for Advancing Translational Sciences (NCATS), and the NIH Office of Rare Diseases Research collaborate to support research on glomerular diseases through the Nephrotic Syndrome Rare Diseases Clinical Research Network (NEPTUNE), a component of NIH's Rare Diseases Clinical Research Network that is focused on nephrotic diseases. NEPTUNE is a multi-site, multidisciplinary collaborative research and education network designed to foster innovative approaches to the understanding of four glomerular disease areas, including FSGS. In addition, NIDDK continues to support the ongoing Human Heredity and Health in Africa (H3Africa) Kidney Disease Research Network, which was established to study prevalent forms of kidney disease, including FSGS, in sub-Saharan Africa and increase the capacity for genetic and genomic research.

In people of African descent, two common variants in the *APOL1* gene have been associated with FSGS. Recent reports have shed light on the proteins and pathways that mediate *APOL1* function in the kidney. One NIDDK-funded study, in mice, provided evidence that *APOL1* gene variants cause kidney disease. Previous research had found associations between *APOL1* and disease risk, but it was not clear if these variants cause disease. The recent study showed that mice engineered to have the low-risk *APOL1* gene variant appeared normal, but mice with a high-risk variant exhibited hallmarks of human kidney disease. Another NIDDK-supported study found that levels of the protein suPAR in the blood can help predict whether kidney function will deteriorate in people with high-risk variants of *APOL1*. These and other studies investigating the mechanisms of *APOL1* protein function that underlie risk of FSGS could inform clinical decisions and the development of new therapeutic strategies for people with high-risk *APOL1* variants.

Fogarty International Center (FIC) Research Training

The Committee recommendation maintains support for FIC, which coordinates global health research and training conducted by U.S. and international investigators, and helps build relationships between health research institutions here and abroad. During the Ebola outbreak in West Africa in 2014, Fogarty graduates played an important role in efforts to contain the spread of virus in Nigeria and Mali, where Fogarty has invested for decades in research training. FIC is now focused on strengthening institutions in Guinea, Liberia, and Sierra Leone, countries that possessed little scientific expertise before the pandemic and consequently suffered the most. The Committee directs NIH to provide an update on these efforts in its fiscal year 2019 CJ.

Action taken or to be taken:

In 2016, recognizing the need to invest in research training in Ebola-infected countries, the Fogarty International Center (FIC) initiated the Emerging Epidemic Virus Research Training for West African Countries with Widespread Transmission of Ebola program. These grants fund collaborations between U.S. and African research institutions in Guinea, Liberia, and/or Sierra Leone to plan research training and capacity building programs, with a focus on emerging viral epidemics. This support enables scientists on the front lines in these countries, which were ground zero for Ebola, to design training programs that increase expertise in Ebola, Lassa fever, and other emerging viral diseases.

For example, Yale University, in partnership with the University of Liberia, are developing the organizational structure, curriculum, and research mentorship opportunities for a public health training program with a specific focus on predictive transmission modeling and epidemiological research. In addition, Fogarty has awarded a planning grant to Tulane University, the Vanderbilt Institute for Global Health, and the University of Sierra Leone. Together, these institutions will advance clinical and translational health services research focused on efficacy studies of novel and existing therapeutics for endemic viral hemorrhagic fevers like Lassa fever, while simultaneously building capacity on how to conduct higher-level clinical trial research during an epidemic like Ebola.

Another grant was awarded to a collaboration with the University of Conakry in Guinea and Mali's University of Science, Technique, and Technologies of Bamako to advance academic programs and strengthen clinical and health services research. This partnership builds on the experience of several researchers who were on the frontlines of the Ebola epidemic and draws on expertise from NIH's National Institute of Allergy and Infectious Diseases (NIAID), Johns Hopkins University, and Northwestern University.

Fragile X

The Committee commends NIH for the NICHD-led effort that has resulted in significant progress in mapping the molecular, physiological, biological and genetic connections among Fragile X (FX), the FX protein, and autism. Increased focus on basic science is needed to identify additional targetable mechanisms of the disease. The Committee acknowledges that recently concluded drug trials were unable to demonstrate and measure positive clinical outcomes when compared to a placebo. The Committee urges the Director to support expanded natural history studies to supplement the CDC's efforts, and to focus on validating outcome measures and biomarkers that bridge the mouse model and humans with the disease across the full spectrum of CGG repeat expansion in males and females. The Committee endorses the creation of a Clinical Trial Network that builds upon the already established consortium of FX clinics to accelerate the development of specialized outcome measures. This will ensure that, as additional targetable mechanisms of the disease are identified, clinical trials can promptly follow. Given the inextricable connection between the FX protein and autism, the Committee urges the Director and his counterparts at each institute with Fragile X and autism portfolios to explore ways to create greater efficiency and synergy among these two research tracks to accelerate translational research toward a better understanding of both conditions and to shorten the time to bring effective treatments for both conditions to market. The Committee commends the NIH for its previous work to create and update the NIH Research Plan on Fragile X Syndrome and Associated Disorders.

Action taken or to be taken:

Fragile X syndrome (FXS) is the most common hereditary cause of intellectual disabilities (ID). The condition is caused by expansions in the *FMR1* gene on the X chromosome. NIH recognizes the need for basic science research to elucidate the genetic, molecular, and cellular mechanisms that underlie Fragile X Syndrome and the Fragile X-associated disorders. All three of the NIH-funded Fragile X Research Centers are examining a different aspect of Fragile X biology, which is fundamental to the eventual identification of targets for future therapies. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) is supporting two research projects that are utilizing unique cohorts of individuals with Fragile X premutation to better understand the natural history of FXS. In one project, researchers are following a cohort of older adults to quantify the development and progression of Fragile X-associated tremor/ataxia syndrome (FXTAS). In another, investigators are exploring whether individuals with less than the full Fragile X mutation experience compromised health and/or an increased risk of having a child with a disability. In research funded by the National Institute on Mental Health (NIMH), imaging and key behavioral and physiological indices are being used to examine the developmental trajectory of anxiety, avoidance, and arousal in girls with FXS. These symptoms are cited as the primary clinical concern of parents of children with FXS; the symptoms persist into adulthood, leading to reduced long-term functional outcomes and quality of life. These studies complement, without duplicating, the CDC's natural history studies.

NICHD encourages researchers to propose the development and validation of outcome measures both for animal models and humans with ID. One recently funded researcher has developed a measure for expressive language, designed for children and adults with low language abilities, which is now being used as the primary outcome measure in a large NINDS-funded multicenter clinical trial of an mGluR5 antagonist on language learning in FXS. In another study, researchers are comparing different approaches to measuring eye tracking in a study in which

they are training children with Fragile X to improve their ability to make eye contact during social interactions. This effort has the potential to increase the usefulness of eye tracking as an outcome measure, and could be applied to studies of individuals with autism spectrum disorder.

Despite strong preclinical evidence, recent clinical trials of mGluR5 antagonists failed as a treatment for FXS. Researchers believe this approach still holds promise and that treatment should begin at earlier ages to prove effective. The National Institute of Neurological Disorders and Stroke (NINDS), along with NICHD, is supporting a new trial through the NINDS NeuroNEXT clinical trials network to assess whether a mGluR5 antagonist will improve language learning in young children with FXS, as compared to speech and language therapy alone. The NeuroNEXT network includes 14 sites across the country. NINDS also is collaborating with NICHD, NIMH, and several non-profit organizations to hold a workshop in December 2017 on biomarker development for neurodevelopmental disorders associated with autism and ID, including FXS. The workshop will focus on physiological and functional biomarkers that can enable clinical trial readiness and success, with participants from basic, translational, and clinical research; industry; the FDA; and funding organizations.

Led by NICHD, the Trans-NIH Fragile X Research Group coordinates NIH's efforts to implement the research objectives described in the NIH Research Plan for Fragile X Syndrome and Associated Disorders. This group is updating the research plan, seeking input from a wide variety of stakeholders, with the goal of publishing an updated plan by summer 2018.

Fragile X (FX)

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Gabriella Miller Kids First Research Act

The Committee provides the full budget request of \$12,600,000. The Committee requests that NIH provide information on how it has disbursed funding, including any personnel that are responsible for overseeing the allocation of designated research dollars, the criteria that NIH employed to ensure awards will advance the objectives of the act, and a description of the research projects that were funded in the fiscal year 2019 CJ.

Action taken or to be taken:

The NIH Common Fund's Gabriella Miller Kids First Research program (Kids First)¹⁴⁷ aims to catalyze pediatric research by making large amounts of high-quality genetic and clinical data from childhood cancer and structural birth defects patient cohorts widely available and easy to use for scientists and clinicians. There is considerable scientific evidence that examining childhood cancer and structural birth defects data together will uncover new connections between them that would not have been discovered if they were examined independently. The Kids First data resource will aggregate Kids First-generated data together with additional existing data sets, increasing researchers' ability to detect rare genetic changes.

Consistent with the requirements of the Kids First Research Act, all funds have been disbursed as grants to support pediatric research. In FYs 2015 and 2016, Kids First provided the entire \$12.6 million to two DNA sequencing centers (\$6.3 million per center). In FY 2017, Kids First provided \$4.8 million each to two sequencing centers, and launched the Kids First Data Resource Center with a \$3.1 million award.¹⁴⁸ The criteria for selection of the sequencing centers was expertise and available sequencing capacity, and the criteria for selection of the Data Resource Center was experience handling large amounts of data, ability to organize data so other researchers can use it, and expertise in pediatrics.

In addition, in FYs 2015, 2016, and 2017, Kids First solicited applications from researchers with childhood cancer or structural birth defects patient cohorts. Successful applicants do not receive funds from Kids First, but do gain access to the sequencing capabilities of the Kids First-supported centers, and the genome sequence data and associated clinical data will form the basis for the Kids First data resource. These cohorts address conditions such as Ewing sarcoma, lymphoma, neuroblastoma, congenital heart defects, hearing loss, and cleft lip/palate. Selection criteria included, but were not limited to, the robustness of the cohort, evidence for a genetic component, and significance to human health and/or understanding of biology.

In FY 2018 and beyond, pending availability of funds, the Kids First program plans to support sequencing of additional pediatric cohorts, build the Data Resource and make data widely available, support Kids First data analysis, and support development of new computational tools to help researchers access and interpret large-scale data sets. As with the current awards, selection of future awards will rely on peer review by experts in pediatric research, and specific criteria for each initiative will be developed through discussion with leading experts in pediatric research across NIH. Additionally, Kids First staff and Data Resource Center awardees are engaged in ongoing conversations with pediatric researchers and patient advocates to share information about the program and gather feedback about the needs and opportunities within

¹⁴⁷ <https://commonfund.nih.gov/KidsFirst>

¹⁴⁸ <https://commonfund.nih.gov/kidsfirst/fundedresearch>

pediatric research that can best be addressed by the Kids First program. Patient advocacy groups participated in the first annual Kids First investigators' meeting, and additional workshops to solicit input are in development. Collectively, rigorous scientific criteria, peer review by experts, and robust discussions with stakeholder ensures that the program initiatives and awards will advance pediatric research and the objectives of the Kids First Act.

Because all appropriated Kids First funds were used to support pediatric research, no appropriated Kids First funds were used to support personnel. Research Management Support (RMS) was provided from the Common Fund budget and totaled \$444,000 in FY 2017, of which \$296,000 was used for personnel support. Kids First is managed by a trans-NIH working group consisting of members from approximately 12 NIH Institutes and Centers (ICs) and the Office of the Director. This representation ensures that appropriately broad expertise is brought to bear on program management and that resources developed through Kids First will enable and promote IC-supported research across the NIH. The ICs providing primary leadership of Kids First are the National Cancer Institute, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Human Genome Research Institute, and the National Heart, Lung, and Blood Institute.

Gastric Cancer

The Committee continues to be concerned about the deadly outcomes of gastric cancer, particularly among young adults. The five-year survival rate for stomach cancer is 30 percent. The Committee encourages NCI to consider developing a scientific framework, as specified by the Recalcitrant Cancer Research Act of 2012, for advancing stomach cancer research.

Action taken or to be taken:

The National Cancer Institute (NCI) is committed to improving outcomes for gastric cancer patients and supporting research to improve the prevention, diagnosis, and treatment of gastric cancer. NCI supports a comprehensive gastric cancer research portfolio that spans from understanding the basic biological mechanisms that lead to the disease through successful treatment. Research highlights include studies to understand how interactions between *H. pylori* bacterium, the gastric environment, and molecular signaling lead to gastric cancers; a genome-wide association study across low- and high-risk populations; studies to test early detection methods; and treatment research evaluating targeted therapies and combination therapies for gastric cancer.

In 2017, an NCI-supported study using data from The Cancer Genome Atlas (TCGA) uncovered four molecular subtypes of gastric cancer: Epstein-Barr virus (EBV), microsatellite instability (MSI), genomically stable (GS), and chromosomal instability (CIN). Researchers will now work to describe the clinical significance of these subtypes, determine prediction models that can reliably stratify patients with gastric cancer to identify optimal treatment protocols, and eventually develop further therapies that best address each form of the disease. These efforts complement an NCI-sponsored clinical study that seeks to provide and evaluate molecular profiles in people with gastric tumors.¹⁴⁹

Two primary drivers of gastric cancer development are infection with the bacterium *Helicobacter pylori* (*H. pylori*) and infection with the Epstein-Barr virus (EBV). Examples of projects examining the role of *H. pylori* include 1) basic research on cellular mechanisms by which *H. pylori* activity gives rise to gastric cancer,¹⁵⁰ and 2) a prevention clinical trial aimed at limiting *H. pylori* activity in high-risk patients.¹⁵¹ The NCI International EBV-Gastric Cancer Consortium, a collaboration among NCI and extramural investigators, is utilizing data and biospecimens from completed and ongoing case series and observational studies of gastric cancer conducted in low- and high-risk populations to understand the role of EBV infection. Analyses from the consortium to date have focused on the epidemiologic and clinicopathologic characterization of EBV-positive gastric cancers. Laboratory studies comparing EBV-positive and -negative cancer cases are currently underway.

Additionally, NCI is sponsoring several clinical trials of immunotherapy and targeted therapy for gastric cancer. Examples include 1) a trial at Rutgers University combining immunotherapy,

¹⁴⁹ <https://clinicaltrials.gov/ct2/show/NCT03027427>

¹⁵⁰

https://projectreporter.nih.gov/project_info_description.cfm?aid=9245560&icde=36594098&ddparam=&ddvalue=&ddsub=&cr=7&csb=default&cs=ASC&pball=

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https://projectreporter.nih.gov/project_info_description.cfm?aid=9321431&icde=36593859&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

chemotherapy, and radiation in the treatment of EBV positive gastric cancer;¹⁵² 2) a targeted cell therapy in which a patient's white blood cells are genetically modified to fight cancer, for patients with a specific genetic mutation¹⁵³; and 3) a cell therapy, also involving white blood cells, for patients with metastatic cancers.¹⁵⁴

NCI also continues to support new and ongoing research efforts focused specifically on opportunities in gastric cancer research, such as five Specialized Programs of Research Excellence focused on gastrointestinal cancers, as well as cross-cutting research that stands to benefit patients with gastric cancer and many other cancer types. NCI's MATCH precision medicine clinical trial is one example of such cross-cutting efforts. This program is designed to match mutations found in any tumor type, including gastric cancer, to drugs that were developed to target specific genetic changes. More than 100 patients with gastroesophageal cancers have enrolled in the MATCH trial.

In accordance with the Recalcitrant Cancer Research Act, in 2014 NCI developed scientific frameworks for pancreatic ductal adenocarcinoma and for small cell lung cancer. However, it is important to understand that formalized horizon-scanning efforts are most fruitful when convened at times of ripe scientific opportunity in order to draw on the collective expertise of the cancer research community to identify specific research areas for exploration. NCI conducts such scientific horizon scanning efforts on an ongoing basis to help advance cancer research in all areas, drawing upon the expertise of our external advisory groups and steering committees. NCI must also consider the significant administrative costs of convening large groups of researchers outside of the regular scientific consultation with our advisory boards and extramural research partners.

The workshops focused on pancreatic cancer and small cell lung cancer are two examples of such efforts, but they do not stand alone. Nor is a formal framework required for NCI to initiate new research efforts. In recent years NCI has also convened horizon scanning efforts and scientific meetings focusing on the following research areas, among others:

- the prevention, diagnosis, and treatment of gastric, liver, and pancreatic cancer in high-risk populations;
- pediatric cancer genomics;
- cancer immunology and immunotherapy;
- hereditary cancer syndromes;
- cancer health disparities; and
- a trans-NIH meeting focused on pancreatitis, pancreatic cancer, and diabetes.

In addition, over the past year, NCI continues to lead implementation of the Cancer Moonshot™, a large-scale effort to accelerate progress in cancer research. To inform the scientific direction for the Cancer Moonshot, a Blue Ribbon Panel (BRP) of many of the nation's top cancer experts—cancer researchers, oncologists, patient advocates, and private-sector leaders—gave careful thought to what could be done to expedite progress against cancer, and issued a set of ten recommendations.¹⁵⁵ The BRP recommendations include several key areas that are likely to

¹⁵² <https://clinicaltrials.gov/ct2/show/NCT03257163>

¹⁵³ <https://clinicaltrials.gov/ct2/show/NCT03190941>

¹⁵⁴ <https://clinicaltrials.gov/ct2/show/NCT01174121>

¹⁵⁵ <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel>

yield benefit for many cancer types, including gastric cancers. Recommendations include a focus on creating a translational network devoted to immunotherapy, developing ways to overcome drug resistance, improving data sharing and patient access to clinical trials, developing new cancer technologies for diagnosis and drug delivery, and expanding prevention and early detection strategies.

Gestational Diabetes

The Committee recognizes the importance of research funded by NIH related to gestational diabetes, a disease affecting up to 9.2 percent of all pregnant women. Given that both women with gestational diabetes and their babies face long-term health consequences as a result of the disease, such as increased risk of developing type 2 diabetes, the Committee urges NIH to explore additional opportunities for research on gestational diabetes.

Action taken or to be taken:

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the NIH Office of Research on Women's Health (ORWH) lead NIH support for research on gestational diabetes mellitus (GDM) and its health impacts on women and their babies. These efforts build upon the knowledge emerging from this research to help identify research gaps and new opportunities.

For example, NICHD established the multi-site Maternal-Fetal Medicine Unit Network in 1986 to design and evaluate programs and treatments for the prevention of preterm birth and for the improvement of maternal and infant outcomes to inform evidence-based medical practices. One of the Network's studies found that treatment for mild GDM was associated with immediate benefits to the baby including a reduction in too-high birth weight (macrosomia); a follow-up study conducted recently with children born during the initial trial determined that female offspring of women treated for mild GDM had lower fasting blood glucose (sugar) levels. NICHD is supporting a new study to compare the two predominant GDM screening approaches to learn whether women diagnosed at lower glucose levels using one of the two sets of criteria can be treated more quickly and lower the risk of adverse perinatal outcomes. Similarly, the NICHD- and NIDDK-supported Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study demonstrated in 2008 a strong linear relationship between increasing maternal glucose concentrations (below those currently used to diagnose GDM) and adverse neonatal outcomes, although without any clear glucose level threshold. In 2017, the HAPO Follow-Up Study, sponsored by NIDDK with additional support from NICHD, reported long term follow-up results at a national diabetes scientific conference: *in utero* exposure to glucose levels found harmful at the time of childbirth in HAPO yield continued harm a decade later. They found a strong relationship between those glucose levels during pregnancy and subsequent type 2 diabetes in the mothers and obesity in the offspring. In another investigative avenue, NIDDK- and ORWH-supported research has led to identification of a molecule detectable in blood, called pGCD59, as a promising new biomarker for diagnosis of GDM in humans and possibly a predictor of risk for adverse perinatal outcomes.

Equipped with findings such as these and looking to the future, NIDDK, together with ORWH, convened an international workshop in August 2017 involving obstetricians, maternal-fetal medicine specialists, internists, and endocrinologists with expertise in GDM to address current research gaps. Areas of particular focus included lack of knowledge on when abnormal blood glucose levels (dysglycemia) manifest during pregnancy, the potential importance of early diagnosis of GDM, and evidence for and against different treatment strategies and therapeutic goals in the management of GDM. A definitive conclusion from the workshop was the need to better understand whether early diagnosis and treatment of maternal dysglycemia would improve the health of the mother and her offspring. The gaps and opportunities in research identified at

the GDM workshop are informing current NIH planning efforts in this area that could pave the way to improved health for women and their children.

Glaucoma

The Committee recognizes the identification of three new genes by the NEI Glaucoma Human Genetics Collaboration Heritable Overall Operational Database [NEIGHBORHOOD] Consortium that are strongly associated with primary open-angle glaucoma [POAG], the most common form of the disease. The finding that variants of these genes may alter the protection of the optic nerve from degeneration due to oxidative stress increases the total number of genes associated with POAG to 15, demonstrating that the underlying mechanisms of the disease may involve the interaction of many genes with environmental influences.

Action taken or to be taken:

Glaucoma is a group of diseases associated with damage to the optic nerve that leads to irreversible vision loss. Over the last decade, scientists from the National Eye Institute (NEI) have made great progress in discovering genes associated with the risk for developing primary open-angle glaucoma (POAG), the most common form of glaucoma. To find the genes that are mutated in POAG, geneticists had to study the genomes of many different individuals to determine if a particular gene variant is associated with developing POAG. To achieve this, NEI led an international collaborative effort called the NEI Glaucoma Human genetics collaboration Heritable Overall Operational Database, or NEIGHBORHOOD. This study compared the genomes of 3,853 POAG patients and 33,480 healthy individuals, making it the largest such genomic study of glaucoma. NEIGHBORHOOD identified 21 genetic variants associated with POAG.¹⁵⁶ However, having these genetic variants alone does not lead to POAG. POAG results from the interactions of many genes and environmental factors, each contributing a small, but significant effect. Furthermore, there are clinical markers of glaucoma such as elevated intraocular pressure (IOP), central corneal thickness, and size of the optic cup and disc. The optic disc is the point where the optic nerve exits the eye to send messages to the brain; the optic cup is at the center of this disc. A large ratio of cup to disc size is used to diagnose glaucoma. In 2017, NEIGHBORHOOD investigators identified nine new regions of the genome associated with optic cup to disc ratio.¹⁵⁷ Furthermore, they identified five new regions associated with optic nerve cup area, and six for disc area. They also announced a new region associated with IOP. Interestingly, the POAG patients were found to often have smaller optic discs. Contrary to prior belief, they also showed evidence that some genetic regions simultaneously impact IOP and disc size.

The consortium also explored possible variants of microRNAs that are associated with POAG. Whereas many genes generate messenger RNAs that contain the codes to make proteins, microRNAs are genetically encoded, inhibitory molecules that prevent the production of particular proteins by attaching to and destroying the messenger RNA. In recent years, the importance of microRNAs in regulating cell behavior, function and disease development has become clear. The NEIGHBORHOOD dataset assessed 76 microRNA genes in two different forms of POAG: patients with elevated IOP and patients with normal IOP.¹⁵⁸ They also looked

¹⁵⁶ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4691082>

¹⁵⁷ <https://www.ncbi.nlm.nih.gov/pubmed/28073927>

¹⁵⁸ <https://www.ncbi.nlm.nih.gov/pubmed/27537254>

at microRNA expression in fluids from glaucoma patients, or in the eye tissue from postmortem glaucoma patients. One microRNA, MIR182, had a common variant associated with glaucoma in patients with elevated IOP. This result and the ones discussed above not only provide new genetic markers for glaucoma, but also expand our understanding of the disease.

Glomerular Diseases

The Committee encourages continued support for the Cure Glomeruloneuropathy initiative which has enrolled over 1,500 clinical research participants to further the understanding of rare forms of kidney diseases.

Action taken or to be taken:

NIH-supported research in the area of glomerular diseases—diseases that affect kidney function by attacking the glomeruli, which are tiny clusters of looping blood vessels within the kidney where blood is cleaned—is leading to a host of scientific advances. Complementing the Nephrotic Syndrome Study Network (NEPTUNE, below), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) continues to support the Cure Glomerulopathy Network (CureGN) consortium. The consortium will conduct translational and clinical research that promotes therapeutic development for primary glomerular diseases, such as Minimal Change Disease (MCD), focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN) and Membranous Nephropathy (MN). CureGN has recruited over 1,900 patients, including children, of a target of 2,400 patients; at least 25 percent of the total recruited will be children. CureGN reached a critical milestone this year in that recruitment was completed for the IgAN cohort. Recruitment is anticipated to be completed later this year for the FSGS cohort, and in the next 1-2 years for the other conditions. The leading priorities for investigation in this study include detailed genetic and biochemical analyses; an assessment of infectious complications among patients with glomerular diseases, who are commonly treated with immunosuppressants; analysis of the clinical characteristics of a national population of American patients with IgAN; and a first ever comparison of adult and pediatric patients with MN. Key innovations of the consortium include a standardized disease activity index and a digital pathology repository. This repository will allow consolidated review of kidney biopsy specimens from multiple clinical centers and afford the opportunity to apply innovative technologies to the criteria for diagnostic and treatment approaches. An external expert panel will be convened in early 2018 to review the scientific progress of the consortium and to advise NIDDK on potential priorities and future paths at the time of re-competition.

NEPTUNE, supported by NIDDK and the National Center for Advancing Translational Sciences (NCATS), is a multi-site, multidisciplinary collaborative research network which complements CureGN, designed to foster innovative approaches to the understanding of MCD, FSGS, and MN. Several recent reports of research progress in glomerular disease have resulted from cohort analyses of NEPTUNE. For example, researchers recently described unique molecular programs that are turned on in the glomerulus of people of African ancestry carrying the high-risk variant of the *APOL1* gene, regardless of their formal clinical diagnosis. In another study, NEPTUNE investigators and other scientists demonstrated two proteins that help regulate cholesterol transport from cells are associated with kidney injury in both FSGS and diabetic kidney disease. Finally, in a national and international collaboration, the group demonstrated that urine epidermal growth factor may be a useful marker with wide applicability for chronic kidney disease of various types. The NEPTUNE study is ongoing.

Government-Wide Collaborations

NIH, VA, and DOD collaborate frequently and successfully on various research activities. The Committee looks forward to the report in the fiscal year 2019 CJ focusing on the cooperative and strategic approach the agencies take in areas of biomedical research that overlap to maximize the potential of the research.

Action taken or to be taken:

NIH has long-standing collaborations with the U.S. Department of Veterans Affairs (VA) and the Department of Defense (DOD), focused on research areas of mutual interest. As highlighted in Objective 1 of the NIH-wide Strategic Plan, capitalizing on cross-cutting opportunities to advance biomedical research is a key NIH strategy.¹⁵⁹

In 2016, NIH participated in at least 126 collaborations with DOD and at least 80 collaborations with the VA, including 47 collaborations that included both DOD and VA. In addition, NIH worked with DOD and/or VA on at least two initiatives undertaken by the National Academies of Sciences, and participated with DOD and/or VA along with other federal agencies in 14 activities of the National Science and Technology Council in the White House Office of Science and Technology Policy. Key areas of shared interest include mental health, suicide, substance use disorders, injury and wound-healing, chronic pain, and biodefense-related diagnostics, drugs, and vaccine research. Highlighted below are two areas in which NIH has collaborated, and continues to collaborate, with our DOD and VA partners to conduct biomedical research aimed towards improving the health of all Americans.

The NIH, DOD, and VA have several collaborations to address the issue of chronic pain. Beginning in 2014, the NIH and VA co-funded 13 grants to study military and veteran health, with a focus on nonpharmacological approaches to pain and related conditions. In 2017, this project was expanded to include the DOD, forming the NIH-DOD-VA Pain Management Collaboratory. The Collaboratory recently issued funding opportunity announcements to develop the capacity to implement cost-effective, large-scale clinical research in military and veteran health care delivery organizations focusing on nonpharmacological approaches to the management of pain.^{160,161} The NIH, DOD, and VA also participate on the Clinical Rehabilitation Medicine Research Program Pain Management Government Steering Committee. This group focuses on improving management of acute and chronic pain, establishing safety margins for individual prescriptions, identifying and treating pain generators, and developing strategies to empower patients in managing their pain. Finally, NIH, DOD, and VA are members of the Interagency Pain Research Coordination Committee to coordinate pain research across the government.¹⁶²

Under a Cross Agency Priority Goal released in 2014, NIH, VA, and DoD are supporting research that will standardize and integrate measurements for traumatic brain injury, post-traumatic stress disorder (PTSD), and suicide prevention research funded by the agencies. Building on the foundation of common data elements for PTSD and suicide prevention research,

¹⁵⁹ <https://www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf>

¹⁶⁰ <https://grants.nih.gov/grants/guide/rfa-files/RFA-AT-17-002.html>

¹⁶¹ <https://grants.nih.gov/grants/guide/rfa-files/RFA-AT-17-001.html>

¹⁶² <https://iprcc.nih.gov/>

efforts are underway to accelerate progress through data sharing, data harmonization, and the reporting of research results.

NIH is also partnering with the DoD and VA on some of its major initiatives. For example, the three agencies, along with other federal partners, are working together on the *All of Us* Research Program, part of the Precision Medicine Initiative launched in FY 2016. The *All of Us* Research Program seeks to extend precision medicine to all diseases by building a national research cohort of one million or more U.S. participants. The DoD is also a key partner in the Cancer Moonshot initiative; a representative from DoD participated in the Blue Ribbon Panel that provided advice on the vision, scientific goals, and implementation of the initiative.

Gut Microbiome

The Committee commends the Office of the Director's partnership with NIDDK on the Human Microbiome project and urges expanded investigation into the manipulation of the microbiome to improve scientific understanding of functional gastrointestinal disorders, including Irritable Bowel Syndrome.

Action taken or to be taken:

NIH appreciates the Committee's recognition of the partnership between the Office of the Director and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) on the Human Microbiome Project, which continues to support research on the gut microbiome's role in the development of gastrointestinal disorders.

In addition to its participation in the Human Microbiome Project, the NIDDK is supporting studies that are exploring the role of the microbiome in irritable bowel syndrome (IBS), a functional gastrointestinal disorder that in many cases is believed to be the result of problems with the signals between the brain and the gut. The Brain Gut Microbiome Research Program, based at the University of California, Los Angeles, is examining the role of the microbiome in IBS by characterizing the complicated interactions among the gut, its microbiome, and the brain. A recent study by this group compared the microbiomes of healthy people and people with IBS. The researchers found that there was a significant portion of people with IBS who had alterations in their microbiomes compared to healthy people. These alterations correlated with prolonged IBS symptoms and structural differences in the brain, pointing to a potential link between the gut microbiome, the brain, and IBS symptoms. Another study is examining the role of the gut microbiome in diet-induced symptoms in children with IBS. The goal of this project is to understand how certain foods interact with the gut microbiome to produce IBS symptoms. Results from these studies could lead to better diet- or probiotic-based IBS therapies and enhance overall understanding of the role the gut microbiome plays in this disorder.

Gynecologic Cancer Clinical Trials

Clinical trials have significantly improved survival for women with gynecologic cancers, including ovarian, endometrial, cervical, and vulvar cancers. The Committee urges the NCI to continue to work with stakeholders through the NCI National Clinical Trials Network Gynecologic Cancers Steering Committee to address priorities for the gynecologic oncology clinical trials scientific agenda, including increasing the availability of trials for these patients. The Committee requests that NCI provide an update to the Committee in the fiscal year 2019 CJ.

Action taken or to be taken

The National Cancer Institute (NCI) is a leader in developing and supporting clinical trials of promising cancer treatments, including treatments for gynecologic cancers. NCI's Coordinating Center for Clinical Trials (CCCT) manages the evaluation of proposed cancer clinical trials to be conducted by the NCI-supported National Clinical Trials Network (NCTN). The CCCT houses the Gynecologic Cancer Steering Committee (GCSC), which holds monthly meetings to evaluate and prioritize proposed NCTN randomized phase 2 and phase 3 clinical trials in adult gynecologic cancers.

In 2015, the GCSC identified strategic priorities for NCTN cervical, uterine corpus, and ovary/fallopian tube cancer clinical trials, including identifying molecular and/or clinico-pathologic cancer subsets from which to drive treatment recommendations, developing combination interventions, and investigating immunotherapy treatments and predictive biomarkers for these diseases, and others.¹⁶³ The GCSC updated these priorities in 2017 and continues to work with NCI, the NCTN, and stakeholders to assure that NCTN gynecologic cancer clinical trials align with their mission.

Currently, the NCTN supports 15 clinical trials evaluating various treatment approaches for gynecologic cancers that are or will be open to accrual in the near future. Examples of trials include a phase 2 trial evaluating whether combining two immunotherapies (nivolumab and ipilimumab) is more effective than nivolumab alone in treating epithelial ovarian, primary peritoneal, or fallopian tube cancer¹⁶⁴; a phase 3 trial assessing whether a single agent inhibitor (olaparib) or the combination of two inhibitors (olaparib and cediranib) is more effective than standard platinum-based chemotherapy in treating patients with platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer¹⁶⁵; and a phase 2 trial studying the ability of the novel agent, triapine, to improve the activity of radiation therapy and cisplatin in treating patients with newly diagnosed locally advanced cervical cancer.¹⁶⁶

Another important effort within the NCTN is the NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) Trial, wherein patients are assigned to receive treatment based on the genetic changes found in their tumors through genomic sequencing. More than 18% of the enrolled

¹⁶³ <https://www.cancer.gov/about-nci/organization/ccct/steering-committees/nctn/gynecologic/gcsc-2015-strategic-priorities.pdf>

¹⁶⁴ <https://www.cancer.gov/about-cancer/treatment/clinical-trials/search/v?t=C4908&loc=0&lo=NRG&rl=2&id=NCI-2014-02424&pn=1&ni=10>

¹⁶⁵ <https://www.cancer.gov/about-cancer/treatment/clinical-trials/search/v?t=C4908&loc=0&lo=NRG&rl=2&id=NCI-2015-00606&pn=1&ni=10>

¹⁶⁶ https://www.cancer.gov/about-cancer/treatment/clinical-trials/search/v?t=C7558&loc=0&tt=treatment,basic_science,screening&lo=NRG&rl=2&id=NCI-2009-00603&pn=1&ni=10

MATCH patients have had gynecologic cancers, which is an over-representation compared to the proportion of gynecologic cancer patients as a share of all cancer patients in the U.S.

In addition to these extramural trials, NCI's Center for Cancer Research is conducting a number of trials with gynecologic cancer patients, including: a trial testing the effectiveness of a cell cycle checkpoint inhibitor in treating BRCA1/2 mutation-associated or high-grade serous ovarian cancer¹⁶⁷; a trial testing whether an experimental drug that has been shown to work against some estrogen-linked cancers works on gynecologic cancers¹⁶⁸; and a pilot study examining internal brachytherapy treatments, which deliver short-range radiation directly to the tumor, in patients with cervical or endometrial cancer.

Lastly, recent developments in NCI-supported gynecologic cancer basic research set the stage for future trials. For instance, investigators with The Cancer Genome Atlas (TCGA) Research Network, including NCI researchers, recently identified novel genomic and molecular characteristics of cervical cancer that will aid in the subclassification of the disease and may help target therapies that are most appropriate for each patient.¹⁶⁹

¹⁶⁷ <https://clinicaltrials.gov/ct2/show/NCT02203513>

¹⁶⁸ <https://clinicaltrials.gov/ct2/show/NCT01273168>

¹⁶⁹ <https://www.cancer.gov/news-events/press-releases/2017/tcga-cervical-cancer>

Headache Disorders

The Committee encourages NIH to prioritize fundamental, translational, and clinical research on headache disorders over the next decade. The World Health Organization has found that migraines are the third most prevalent global disorder and the seventh leading cause of global disability.

Action taken or to be taken:

NIH recognizes the burden of headache and migraine in adults and children and supports a broad portfolio of research to better understand and treat these disorders. NIH research into the mechanisms and causes of migraine pain includes the role of genetics, gender, and hormones in migraine. National Institute of Neurological Disorders and Stroke (NINDS) is supporting researchers who use modern brain imaging techniques to identify biomarkers for pain and to study the progression of brain changes in migraine sufferers as patient's age as well as the differences in these changes between male and female migraineurs. NIH-funded researchers are investigating the impact of other conditions, such as obesity and sleep disturbance on migraine onset and severity. Research supported by NIH also is focused on understanding mechanisms of posttraumatic headache, following head trauma.

Recent results from the NINDS-supported Childhood and Adolescent Migraine Prevention Study (CHAMP) have important implications for the treatment of pediatric migraine. The study showed that two commonly prescribed medications for pediatric migraine were no better than placebo in reducing the number of headache days in children and adolescents. The findings suggest that migraine treatments regularly used for adults may not work in adolescents and children.

To support advancements in headache research, NINDS encourages applications from investigators pursuing basic, translational, and clinical research in headache and migraine. In addition, NINDS recently completed an updated version of the Common Data Elements (CDEs) for headache. CDEs are data standards for clinical research that facilitate comparison of results across studies. As potential new therapies enter clinical trial testing, CDEs are used by scientists in academia and industry to improve data quality, facilitate data sharing, and reduce the time and cost needed to develop data collection tools.

Many of NIH's activities in pain research are also relevant to headache. NIH-funded research to better understand mechanisms of pain, develop novel drugs and non-pharmacological treatments, and develop screening tools and outcome measures for pain can all help inform and advance headache research. Efforts to coordinate pain research across NIH and with other stakeholders are also important. The NINDS Office of Pain Policy manages these activities, including the NIH Pain Consortium, a collaboration of 25 NIH institutes and centers, and the Interagency Pain Research Coordinating Committee (IPRCC), a Federal advisory committee created by HHS. In addition, two other efforts are helping to guide future research directions in pain. The *National Pain Strategy*, released in March 2016, is being implemented under the leadership of the HHS Office of the Assistant Secretary of Health and NIH. It recommends approaches to improve the understanding, prevention, and evidence-based treatments of pain. The *Federal Pain Research Strategy (FPRS)*, developed by the IPRCC and the NIH, includes a number of important research priorities from basic to clinical research across the continuum of pain, as well as priorities on

understanding disparities in pain. Many priorities in the FPRS are directly relevant to headache research, and will help guide the efforts of NIH and other federal agencies going forward.

Health Disparities and Pediatric Kidney Disease

The Committee recognizes that health disparities play a significant role in kidney disease in children, from the incidence and progression of kidney disease in children, to the long-term health outcomes, such as access to kidney transplant, access to living donors and disparate transplant survival. Children of minority populations are disproportionately impacted by kidney disease, and NIMHD's work in this area is critical to defining the basis for these health disparities and developing mechanisms to address them. The Committee requests that NIMHD catalog the research being conducted in this area and report back on the research currently underway and re- search gaps in this area of study in the fiscal year 2019 Congressional Justification.

Action taken or to be taken:

Glomerular diseases are the third leading cause of kidney failure in the U.S., and includes diseases such as IgA nephropathy (IgAN), membranous nephropathy (MN), and lupus nephritis (SLE-N). Racial and ethnic minority populations are more susceptible to chronic kidney disease (CKD), although CKD among both populations is not well understood. Pediatric kidney diseases among racial and ethnic minorities persist due in part to a lack of access to kidney transplants and inadequate numbers of living donors. African American pediatric kidney disease patients maintain the lowest rate of survival from kidney disease compared to other populations. An increased focus on the interaction of biological, genetic, and environmental influences, as well as access to health services, is necessary to reduce the prevalence and death rate from pediatric kidney disease experienced by racial and ethnic minorities.

The National Institute of Minority Health and Health Disparities (NIMHD) supports research to understand the underlying factors that contribute to disparities in pediatric kidney disease. For example, researchers funded by NIMHD are seeking to understand the biological basis of health disparities in childhood onset nephrotic syndrome. Most children on treatment for childhood nephrotic syndrome respond well to corticosteroids, also known as steroid sensitive nephrotic syndrome (SSNS), while about 20 percent do not respond. The study includes children from African American, South Asian, and White backgrounds, and aims to identify genetic risk factors for SSNS to gain insights into the basis for varying response to therapy. Another NIMHD-funded study is examining the degree to which genetic risk factors contribute to the ethnicity-specific variation in the prevalence, disease course, and overall outcomes related to biological processes such as IgAN, MN, and SLE-N in Hispanic or Latino and American Indian communities. Results from these studies can have implications for treating pediatric kidney disease among racial and ethnic minority populations, and developing innovative interventions. NIMHD will continue to support research to understand the genetic and environmental factors that impact pediatric kidney disease to enable the development of tailored interventions and effective treatments.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) multi-center Chronic Kidney Disease in Children (CKiD) study, also supported by NICHD and NHLBI, is examining children with mild to moderately decreased kidney function to investigate risk factors for further kidney decline, as well as closely monitoring neurocognitive development, examining risk factors for heart disease, and following long-term effects of poor growth in this group. To enhance understanding of the health disparities associated with kidney disease in children, the CKiD study cohort included 23 percent African American and 15 percent Hispanic or Latino

participants. CKiD is already providing valuable insights. For example, the study has found that growth is more stunted in lower-income youth with kidney disease compared to their higher-income counterparts. NIDDK has renewed the CKiD study, which will continue to follow current study participants, and is recruiting new participants. In addition, the NIDDK supports a robust portfolio of grants in which investigators are using a variety of approaches to understand disparities in kidney disease, including in pediatric populations. Results from these NIMHD and NIDDK studies can have implications for treating pediatric kidney disease among racial and ethnic minority populations, and developing innovative interventions. NIH will continue to support research to understand the genetic and environmental factors that contribute to health disparities in children with kidney disease, and risk factors for pediatric kidney disease, to enable the development of tailored interventions and effective treatments.

Heart Disease

The Committee is concerned that heart disease continues to impose an enormous burden on our Nation's long-term health and economic stability and directs an NIH-wide prioritization of heart research to significantly increase, expand, intensify, and stimulate its investment commensurate with the impact on public health, the economy, and innovative scientific opportunities. The Committee commends NHLBI for its leadership in launching a Strategic Vision and directs the Institute to accelerate the implementation of the heart research recommendations and priorities, including heart failure and cardiac rehabilitation.

Action taken or to be taken:

Heart disease is the leading cause of death in the United States and a serious public health concern. As such, heart disease research has been a high priority of the National Heart, Lung, and Blood Institute (NHLBI) since its establishment as the National Heart Institute 70 years ago. NHLBI's Strategic Vision, released in 2016, identified priorities that stand to significantly advance our understanding and treatment of heart disease. Among them is the need to ensure that new scientific knowledge is successfully incorporated into clinical practice.

NHLBI supports many diverse funding announcements and investigator initiated research projects to ensure that advances in cardiovascular research lead to more successful prevention and treatment of heart disease. For example, following the landmark NIH SPRINT trial,¹⁷⁰ which found that intensive blood pressure control can reduce heart attacks and strokes in at-risk patients, one study is applying this aggressive treatment approach to a high-risk population in Louisiana.¹⁷¹ NHLBI continues to encourage similar research projects under the "Strategies to Increase Delivery of Guideline-Based Care to Populations with Health Disparities" grant program.¹⁷² A new NHLBI funding opportunity calls for the development of multidisciplinary research teams to study the effectiveness and implementation of new evidence-based practices for managing heart disease in inpatient settings.¹⁷³ NHLBI also is supporting Phase 2 clinical trials of strategies to increase use of cardiovascular rehabilitation by eligible patients.¹⁷⁴

NHLBI also recognizes the need to address the public health burden of heart failure (HF), which affects more than 6 million Americans. While commonly prescribed HF medications provide some symptom relief and contribute to improved survival, they often do not fully address the underlying causes of HF. NHLBI supports a broad portfolio of HF research across the entire basic, clinical, and translational spectrum. A newly funded trial involving 6,000 patients will define the optimal balance between the efficacy and safety profiles of two diuretics to treat fluid retention in HF.¹⁷⁵ Other clinical trials through the Heart Failure Clinical Research Network continue to provide data on new treatment options.¹⁷⁶ The NHLBI Strategic Vision identified the need to define HF pathophysiology and how this condition can be better diagnosed and treated. Toward this end, NHLBI supports research through the Trans-Omics for Precision

¹⁷⁰ <https://www.ncbi.nlm.nih.gov/pubmed/26551272>

¹⁷¹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9376903

¹⁷² <https://grants.nih.gov/grants/guide/pa-files/PA-15-279.html>

¹⁷³ <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-18-018.html>

¹⁷⁴ <https://grants.nih.gov/grants/guide/notice-files/NOT-HL-17-493.html>

¹⁷⁵ https://projectreporter.nih.gov/project_info_description.cfm?aid=9309940

¹⁷⁶ <https://www.hfnetwork.org>

Medicine (TOPMed) program to identify key clinical features and biomarkers that could be used to more accurately predict an individual's risk of HF.¹⁷⁷

While there are partially effective therapies for reduced ejection fraction (where the percentage of blood that leaves the heart as it contracts is less than 50%), there are none for preserved ejection fraction (HFpEF). NHLBI is supporting research and innovation to address this critical need. For example, a recently awarded study will use registry data to evaluate the clinical effectiveness of the diuretic drug spironolactone versus usual care in reducing cardiovascular mortality in 3,200 U.S. and Swedish HFpEF patients who have HF with preserved ejection fraction.¹⁷⁸ To spur innovation, NHLBI held a workshop in September 2017 on “Research Priorities in HFpEF,” enabling experts to discuss opportunities, challenges, and potential new solutions to reduce the burden of this condition.

¹⁷⁷ https://projectreporter.nih.gov/project_info_description.cfm?aid=9313715

¹⁷⁸ https://projectreporter.nih.gov/project_info_description.cfm?aid=9216714

Heavy Ion Cancer Therapy and Research

The Committee supports NIH's continued exploration of advanced therapeutic cancer research, specifically heavy ion irradiation technology. Heavy ion technology will introduce a novel treatment option to cancer patients that is currently not available in the U.S. The Committee notes that the U.S. stands to be a world leader in this advanced research. The Committee encourages NIH to explore further the development of a state of the art heavy ion research facility in the U.S. Furthermore, the Committee encourages NIH to work with the Departments of Defense and Energy, and other applicable Federal agencies to equip the first U.S. heavy ion research center. The Committee urges NIH to capitalize on the expertise and potential of recently awarded heavy ion facility planning grant recipients in order to foster a multidisciplinary approach and advance heavy ion research that would produce novel, cutting edge treatments for cancer patients.

Action taken or to be taken:

A considerable body of experimental and clinical, treatment-based evidence indicates that in certain settings particle beams (including carbon – a heavy ion) might be equally, or more, effective in treating cancer as the most sophisticated photon-based therapies while significantly reducing the exposure of normal tissue. However, since a typical facility may cost well over \$100 million to design and construct, and millions each year in operating costs, there is still a pressing need for an extensive research and development program and more extensive clinical trials to determine appropriate and optimal use of particle beam therapy and to maximize its healthcare benefits. To address this need, the National Cancer Institute (NCI) awarded a contract to the Albert Einstein College of Medicine through the solicitation *Carbon Ion Versus Conventional Radiation Therapy for Locally Advanced, Unresectable Pancreatic Cancer*¹⁷⁹ to conduct a clinical trial, which is a critical next step in validating the benefits of carbon ion therapy. The first manuscript resulting from this trial has been submitted for publication and is currently undergoing peer-review.

To encourage and support planning efforts for the establishment of an independently created and separately funded particle beam radiation therapy facility, the NCI awarded two exploratory planning grants in 2015 through the Funding Opportunity Announcement entitled, *Planning for a National Center for Particle Beam Radiation Therapy Research*.¹⁸⁰ These awards were made to the University of Texas Southwestern Medical Center and the University of California, San Francisco. It is expected that these efforts will eventually lead to a national research resource capable of successfully competing for and securing the funding required to operate a specialized center for clinical proton and heavier ion beam radiation therapy. The NCI is following developments at these centers and others across the country that are considering or have begun the construction of a particle beam therapy facility. Depending upon their progress, the NCI will consider a U54 cooperative agreement when appropriate, to provide funding for a center to serve as a national research resource, specifically supporting the research activities of the center, and not construction or other non-research activities.

¹⁷⁹https://www.fbo.gov/index/index?s=opportunity&mode=form&tab=core&id=5cbab00c50c3a724a36e3a9fb1f6e24a&_cview=1

¹⁸⁰<http://grants.nih.gov/grants/guide/pa-files/PAR-13-371.html>

The NCI also continues to collaborate with other federal agencies, including the Department of Energy (DOE) to advance particle beam therapy for the treatment of cancer. In 2015, the DOE launched the Accelerator Stewardship Program to solicit grant proposals that could improve the technology of particle beam accelerators to make them more efficient, smaller, and potentially less expensive.¹⁸¹ The NCI supports this program by participating on the Scientific Review Panel to provide feedback on the scientific merits of proposals submitted in response to the program and their overall potential impact on cancer therapy. This program has funded multiple awards annually since its inception, including eight new awards in 2017. Furthermore, the NCI recently prepared a report entitled “Characterization of the Physical Parameters of Particle Beams for Biological Research” for use by NIH-funded researchers and aspiring investigators as well as the DOE labs where these researchers may seek to conduct their experiments. This report was shared with DOE and NASA colleagues for feedback and is currently undergoing peer-review prior to publication. Continued collaboration across Federal agencies with related but distinct missions and expertise will contribute greatly to researching the potential benefits and advancing the practicality of particle beam approaches to cancer treatment.

¹⁸¹ <https://science.energy.gov/hep/research/accelerator-stewardship/>

Hemophilia

The Committee encourages NHLBI to bring together leading hemophilia researchers and clinicians, as well as its Federal partners from CDC, FDA, and HRSA to create a national scientific agenda for clinical and translational research for the prevention and eradication of inhibitors, a costly complication affecting people with hemophilia.

Action taken or to be taken:

Hemophilia is a rare bleeding disorder that results from inadequate levels of blood clotting factor in the bloodstream. Without treatment, excessive internal bleeding can cause joint and organ damage. Patients are often treated by replacing the missing clotting factor through infusions. However, about 25-30% of people with hemophilia A and about 2-5% of people with hemophilia B develop antibodies (inhibitors) to the clotting factor concentrate—Factor VIII for hemophilia A and Factor IX for hemophilia B—used for treatment. These FVIII and FIX antibodies can greatly reduce the effectiveness of therapy and represent a major obstacle in treating hemophilia patients. Alternative therapies for patients with FVIII or FIX inhibitors can cost up to \$1 million each year per patient.

New treatment options are needed for patients with hemophilia to prevent the development of inhibitors. To address this need, the National Heart, Lung, and Blood Institute (NHLBI) funds research on new immunologic approaches, including new gene and cell therapies that aim to block the immune response that causes inhibitors.

In March 2017, NHLBI released a funding opportunity announcement to provide more than \$29 million for establishing up to four centers to investigate the mechanisms of FVIII inhibitor formation in patients with hemophilia A.¹⁸² The goal is to encourage bold, innovative applications that incorporate novel approaches and cutting-edge technologies to prevent or eliminate this long-standing obstacle to an improved quality of life among hemophilia patients. These centers will also provide skills development training for the next generation of clinicians and researchers in blood sciences.

Additionally, NHLBI's Trans-Omics for Precision Medicine (TOPMed) program is collecting whole genome sequence data from more than 5000 patients with hemophilia.¹⁸³ These data will provide an unprecedented look into the complex interaction of gene variations that may influence the severity of the disease, as well as the risk of inhibitor formation. High-quality whole genome sequences will be released to the research community through the NIH database of Genotypes and Phenotypes (dbGaP).¹⁸⁴

NHLBI also is sponsoring a state of the science workshop on hemophilia inhibitors in May 2018. The goal of this workshop will be to bring together hemophilia experts from many Federal agencies and partners to develop a national blueprint for basic, translational, and clinical research focused on the prevention or elimination of FVIII inhibitors in hemophilia patients.

¹⁸² <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-18-014.html>

¹⁸³ <https://www.nhlbi.nih.gov/research/resources/nhlbi-precision-medicine-initiative/topmed>

¹⁸⁴ <https://www.ncbi.nlm.nih.gov/gap>

Hepatitis B (HBV)

The Committee recognizes that HBV infection is a serious public health threat. Though infection rates are less than one percent in the United States, Asian Americans and Pacific Islanders experience about 60 percent of the chronic HBV burden. Left undiagnosed and untreated, one in four of those with chronic HBV infection will die prematurely from cirrhosis, liver failure, and/or liver cancer. The Committee also notes that the link between HBV infection and primary liver cancer is well established, with up to 60 percent of global liver cancer cases caused by HBV. The Committee requests that OD ensure that NCI, NIAID, NIMHD, and NIDDK coordinate their strategic research agendas to work toward finding a cure for HBV. The Committee further requests an update on these efforts be included in the fiscal year 2019 CJ.

Action taken or to be taken:

NIH remains committed to addressing hepatitis B virus (HBV) infection and HBV-related diseases such as liver cancer. In pursuit of this goal, several NIH Institutes and Centers (ICs) maintain robust, complementary HBV research portfolios that span a broad array of research areas.

The National Institute of Allergy and Infectious Diseases (NIAID) supports basic, translational, and clinical research on HBV to better understand the disease and to develop novel therapeutics with the potential to serve as a functional cure. NIAID coordinates these activities with other NIH ICs by collaborating to share scientific expertise and soliciting critical research as relevant. NIAID supports the HBV research community by screening candidate therapeutics and providing animal models for the testing of advanced candidates. NIAID-supported researchers have identified or are supporting the development of novel HBV therapeutic candidates, including those that target HBV surface proteins, the viral genome, viral assembly, and the host immune response.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a variety of HBV research programs, including investigator-initiated research, and participates along with other ICs in the Trans-NIH Committee on Viral Hepatitis and the HHS National Viral Hepatitis Action Plan to coordinate efforts on HBV and related liver cancer. NIDDK also supports large research initiatives such as the Hepatitis B Research Network that aims to advance understanding of disease processes and progression and identify effective treatment approaches. Research supported through this Network has shown that HBV genotypes in participants, most of whom are of Asian descent, reflect their international origins, which may lead to new treatment strategies. The Network also is completing a study of long-term outcomes of HBV therapy to see if HBV infection can be cleared and antiviral therapy can be discontinued.

Prevention, screening, and early detection of HBV and liver disease are key focus areas of the National Institute of Minority Health and Health Disparities' (NIMHD) research efforts to address health disparities among Asian American and Pacific Islander populations. Recently, NIMHD partnered with the National Cancer Institute (NCI) to release two funding opportunities to increase understanding of the factors that lead to increases in chronic liver diseases and the mechanisms of liver cancer disparities. NIMHD funds research to examine various lifestyle features of HBV-positive patients to better inform the translation of research to practice and to

reduce the risk of cancer in the Asian American community. NIMHD also supports research on affordable, advanced diagnostics that will increase health awareness in patients and facilitate behavior modification for prevention of HBV and related diseases.

NCI collaborates with NIDDK, NIAID, and the NIH Clinical Center on research about the molecular mechanisms of liver disease processes, to better understand the role of hepatitis viruses in liver carcinogenesis. As HIV infection increases rates of HBV progression to liver cancer, NCI is collaborating with NIAID and the National Institute of Alcohol Abuse and Alcoholism (NIAAA) to support research to better understand the unique challenges of HBV/HIV co-infected individuals and to advance the discovery and development of novel HBV interventions that achieve a functional cure in co-infected individuals. NCI also is supporting research aimed at creating non-invasive blood and urine tests for liver cancer in high-risk populations, including those infected with HBV.

NIAID, NIDDK, NIMHD, and NCI will continue to support collaborative efforts to advance research to develop novel HBV therapeutics that could serve as a functional cure.

Hepatitis B

The Committee notes that infection with hepatitis B virus (HBV) is a serious public health threat and is associated with approximately 887,000 deaths each year worldwide, making it a leading cause of death in the world. In the U.S., one in 20 Americans has been infected with HBV and up to 2.2 million are chronically infected. Left undiagnosed and untreated, one in four of those with chronic HBV infection will die prematurely from cirrhosis, liver failure, and/or liver cancer. With hepatitis C now curable and study of the entire HBV lifecycle now possible, NIAID is urged to intensify its current efforts to find a cure for HBV. To meet this goal, the Committee urges NIAID to issue targeted calls for HBV research proposals in fiscal year 2018, focused on therapeutic development and the many critical research opportunities identified by the scientific community.

Action taken or to be taken:

The National Institute of Allergy and Infectious Disease (NIAID) supports a broad portfolio of basic, translational, and clinical research on hepatitis B virus (HBV), and its contribution to cirrhosis and liver cancer, to identify novel therapies to treat and potentially cure HBV infection. NIAID is expanding these efforts through targeted calls for HBV research applications to advance the discovery and development of novel interventions and cure strategies, with a particular focus on HBV/HIV co-infected individuals.

NIAID is building on basic research advances in HBV to identify new targets for HBV drug development. Recent NIAID-supported projects to uncover the structure of the HBV core protein and its role in viral replication have led to the development of candidate drugs to inhibit assembly of new copies of the virus. NIAID-supported researchers also are exploring immunotherapeutic strategies that are still in the early stages of development. Additional efforts by NIAID grantees are underway to develop new drugs that target HBV surface proteins as well as the HBV genome and its replication.

In addition to basic and translational research on HBV, NIAID provides a comprehensive set of services and tools to the HBV research community to help bridge gaps in the product development pipeline. NIAID offers *in vitro* screening (screening in a dish rather than in an animal or human) of candidate therapeutics for efficacy against HBV to product developers in academia and industry. In FY 2017, NIAID screened 176 such compounds, 20 of which underwent secondary screening, with 2 exhibiting high activity. NIAID also evaluates promising therapeutic candidates in animal models of HBV infection, including a humanized-liver mouse model.

NIAID researchers also are exploring ways to help prevent the spread of HBV. NIAID scientists are investigating the use of nanoparticle technology to design recombinant vaccines that could be used to prime the immune system against multiple HBV viral proteins, enabling a wide variety of new vaccine designs to be explored. NIAID scientists also are performing clinical studies of HIV/HBV co-infection. Recent data suggest that the use of HIV antiretroviral therapy in HIV-positive adults may provide additional protection against HBV infection in conjunction with widespread HBV vaccination.

NIAID is committed to supporting basic, translational, and clinical research to address the problem of chronic HBV infection. NIAID will continue to partner with the HBV research

community to further the development of novel therapeutics to reduce the burden of HBV-related disease and work toward a cure.

Hereditary Angioedema

The Committee applauds the Office of Rare Diseases Research for their efforts to facilitate research into Hereditary Angioedema (HAE) and encourages continued collaboration with other Institutes and Centers (ICs) to advance our scientific understanding and spur the further development of innovative treatment options for patients.

Action taken or to be taken:

Hereditary angioedema (HAE) is a rare inherited disorder associated with highly variable and often unpredictable clinical manifestations. Attacks are associated with significant morbidity and patients have decreased quality of life both during and between attacks. Overall, HAE is associated with chronic and significant functional impairment and occasional fatalities. While therapies are currently available, the complexity and unpredictability of attacks make caring for and treating affected individuals challenging.

The National Institute of Allergy and Infectious Diseases (NIAID) is currently funding a research project testing whether a one-time administration of an adeno-associated virus gene transfer in a mouse model of HAE will protect against angioedema attacks.

NCATS, in collaboration with several other NIH Institutes and Centers, supports a number of research consortia that constitute the Rare Disease Clinical Research Network (RDCRN). Each consortium focuses on at least three related rare diseases. Investigators will have an opportunity to apply for an RDCRN collaborative award in 2018, and the HAE community is encouraged to submit research proposals for this upcoming award cycle.

Hydrocephalus Research

The Committee encourages NIH, under the direction of NINDS, to conduct a scientific workshop on hydrocephalus research. The Committee requests that a key agenda item of the workshop be a discussion of future needs for hydrocephalus research, and that NIH report back to the Committee in the fiscal year 2019 Congressional Justification on this and other findings and recommendations of the workshop.

Action taken or to be taken:

The National Institute of Neurological Diseases and Stroke (NINDS) supports basic, translational, and clinical research to better understand hydrocephalus and to develop and improve diagnostic methods, treatments, and preventive interventions. Surgically implanted shunts to divert excess cerebrospinal fluid (CSF) from the brain are the most common treatment for hydrocephalus, but they are prone to malfunction, obstruction, and infection. NINDS-funded investigators aim to understand and prevent such complications, to devise new and less invasive ways to monitor hydrocephalus and shunt function, and to prevent shunt dependence. The National Institute of Neurological Disorders and Stroke (NINDS), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and the Fogarty International Center (FIC) jointly fund research in Uganda to assess the effectiveness of endoscopic third ventriculostomy (ETV) as a surgical alternative to shunts in children with post-infectious hydrocephalus. This study could have implications for reducing shunt dependence in areas with limited access to care for shunt placement and maintenance, including areas of the U.S. The NIH-funded Management of Myelomeningocele Study (MOMS) found that prenatal surgery to repair spina bifida improved outcomes compared to standard postnatal surgery, including a reduced rate of shunt placement. Results from this clinical trial may also inform decisions about which individuals could benefit most from intrauterine surgery. NICHD and NINDS are supporting an extension of the trial (MOMS 2) to determine the effects of prenatal repair on adaptive behavior, cognitive and motor function, brain morphology and microstructure, urologic health, and other aspects at school age. NINDS-funded investigators have also helped to identify factors that predict the need for chronic CSF shunts after intraventricular hemorrhage (IVH) in adults.

NINDS-funded studies on disease mechanisms in hydrocephalus reflect new directions for the field and may inform novel strategies for treatment and prevention. Researchers are exploring genetic variations and gene-environment interactions in brain malformations associated with congenital hydrocephalus. Several more studies focus on a role for abnormal development and organization of the ependyma, the lining of the brain's ventricles that produces CSF and directs its flow. These changes were first observed in animal models of hydrocephalus due to genetic causes, but shared mechanisms, such as abnormal ependymal development, may mean that they are relevant to understanding other types of hydrocephalus as well. Other research on post-hemorrhagic hydrocephalus includes a study of novel molecular signaling pathways recently implicated in the disease, and clinical studies to identify biomarkers associated with hydrocephalus outcomes. In addition, NINDS funds research on normal pressure hydrocephalus (NPH), a poorly understood condition affecting older populations. One study on genetic and age-related factors in NPH suggests a role for declining function in ciliated ependymal cells, the same cell type researchers are studying in congenital hydrocephalus.

Along with the Hydrocephalus Association, Chiari & Syringomyelia Foundation, and Dandy Walker Alliance, NINDS held a workshop in 2014, on classification and diagnosis, genetics, and animal models for midbrain and hindbrain malformations and hydrocephalus. NINDS will hold a second workshop on hydrocephalus in spring 2018, with emphasis on etiology, research resources such as animal models and cell lines, and potential therapies. Together, the two workshops will inform NINDS and the research community on the state of hydrocephalus research and priorities for moving forward.

IDeA States and Cancer Clinical Trials

The Committee recognizes that NCI supports clinical trials across the country through its National Clinical Trials Network [NCTN] and the NCI Community Oncology Research Program [NCORP]. The Committee understands that there are more than 270 NCORP component sites and 14 NCORP awardees across the country located in IDeA States, and that NCI supports several NCI-designated cancer centers in IDeA States. At the same time, the Committee recognizes that there are still opportunities for academic medical centers in IDeA States to become more engaged in these networks. Therefore, the Committee encourages NCI to coordinate with NIGMS in helping Clinical and Translational Research award sites in IDeA States that do not currently have NCORP or NCTN awards build capacity in these regions to conduct cancer clinical trials. The Committee also encourages NCI to continue to support NCORP in its mission to increase diversity among patients participating in NCI clinical trials, especially with regard to rural and minority populations. Finally, the Committee urges NCI, in consultation with NIGMS, to encourage collaboration between IDeA awardees and existing NCI designated cancer centers, NCTN lead sites, and NCORP sites.

Action taken or to be taken:

The National Cancer Institute (NCI) is committed to providing cancer patients with access to NCI-supported clinical trials across the country. Several NCI-supported networks and programs collaborate and complement one another's efforts to achieve this goal. NCI supports 69 designated cancer centers in 35 states and the District of Columbia. NCI's National Clinical Trials Network (NCTN) includes 30 Lead Academic Participating Sites (LAPS), and the NCI Community Oncology Research Program (NCORP) supports 34 Community Sites, 12 Minority/Underserved Community Sites, and seven research bases. Since 2014, when the program was launched, 600 investigators have been added to the NCORP ranks, bringing the total to 4,025. The number of component and subcomponent sites reached 938. NCORP component and subcomponent sites are affiliated with NCORP awardees, and greatly extend the reach of the NCORP network, ensuring the program can carry out its mission of bringing cancer clinical trials and cancer care delivery research to people in their communities, including rural communities. Notably, NCORP Minority/Underserved Community Sites have a patient population comprised of at least 30 percent racial/ethnic minorities or rural residents.

IDeA states continue to participate in each of these programs, some as awardees, and others as participating sites and valued partners. For example, as the Committee recognizes, 14 NCORP awardees across the country are located in IDeA States. Several IDeA states that are not home to NCORP awardees are well represented within the NCORP network – for example, as of November 2017, Idaho is home to 13 NCORP component and subcomponent sites; Mississippi, 11; Alaska and Nebraska, 10; Kentucky eight, North Dakota, four; and Arkansas and Wyoming, three. Universities, medical centers, community hospitals, and clinics can also continue to participate in NCI-supported clinical trials, even if they are not formally part of the NCORP or NCTN networks. For example, West Virginia, Maine, Rhode Island, and Vermont all participate in NCI's Molecular Analysis for Therapy Choice (MATCH) precision medicine clinical trial, with four to seven sites per state enrolling patients.¹⁸⁵ In addition to NCI MATCH, dozens of

¹⁸⁵ <https://www.cancer.gov/about-cancer/treatment/clinical-trials/search/v?id=NCT02465060&r=1>

NCI-supported clinical trials are available for patients in each of these states: 114 in West Virginia, 73 in Rhode Island, 83 in Vermont, and 100 in Maine.¹⁸⁶

Additionally, several IDeA grantees are working within or in collaboration with an NCI-designated Center in their state. Examples include the University of Kansas Center for Cancer Experimental Therapeutics, which contributes to the efforts of the University of Kansas Cancer Center and the Center for Evolutionary and Theoretical Immunology at the University of New Mexico, which supports research efforts that contribute to the activities of the university's NCI-designated comprehensive cancer center. In West Virginia, NIGMS supports an IDeA Center for Biomedical Research Excellence at West Virginia University's Mary Babb Randolph Cancer Center. This IDeA award will strengthen West Virginia University's core facilities and faculty to make it more competitive if the University chooses to pursue NCI-designated center status. NCI continues to advise emerging cancer centers as they navigate the application process to become an NCI-designated center. The University of Oklahoma Health Sciences Center is currently pursuing NCI designation, and discussions continue between NCI and representatives of cancer centers in Arkansas and other rural communities. NCI encourages interested centers to reach out to the Office of Cancer Centers to learn more about the application and designation process.¹⁸⁷

At the same time, NCI recognizes that despite these programs and resources, individuals from areas with limited access to healthcare, particularly in rural communities, continue to experience higher than expected cancer morbidity and mortality rates. The Institute regularly participates in nationwide meetings to discuss research priorities and evidence-based intervention implementation for rural populations, including two events in FY 2017. Rural health, including advancing access to cancer clinical trials and furthering cancer control and prevention efforts in rural communities, will continue to remain a priority for NCI, both within NCORP and through other NCI-funded efforts. For example, NCI-supported researchers in Kentucky, Ohio, and West Virginia, among others states, have continued a long tradition of attention to cancer control in Appalachia, with signature efforts in cancer surveillance, colorectal cancer screening, and more recently, HPV vaccination. NCI is also supporting two upcoming meetings to continue to advance cancer research in rural areas: "Improving Health Research on Small Populations: A Workshop", in partnership with the National Academy of Sciences, in January 2018; and "Accelerating Rural Cancer Control Research", a conference at the National Institutes of Health in May 2018.¹⁸⁸ Additionally, the Cancer MoonshotSM Blue Ribbon Panel recommended that NCI develop a large-scale patient participation network for tumor profiling, including patients who usually do not participate in clinical trials such as racial and ethnic minorities and other underserved populations. NCI is planning to begin soliciting requests for applications on this topic in FY 2019.

Regardless of whether an institution has achieved NCI-designation, or an NCTN LAPS or NCORP award, researchers at all institutions can also apply for funding for individual research projects through the NIH NCI competitive application and peer review process. More

¹⁸⁶ Current as of October 30, 2017: <https://www.cancer.gov/about-cancer/treatment/clinical-trials/advanced-search>

¹⁸⁷ <https://cancercenters.cancer.gov/Home/Contact>

¹⁸⁸ <https://cancercontrol.cancer.gov/research-emphasis/rural.html>

information about active NCI funding opportunities across the cancer research portfolio are available on NCI's website.¹⁸⁹

¹⁸⁹ <https://www.cancer.gov/grants-training/grants/funding-opportunities>

Imaging

Committee notes that imaging research occurs in multiple Institutes throughout the NIH and is an integral component of the Cancer Moon Shot, the Precision Medicine Initiative, and the BRAIN Initiative. The Committee requests that the Director produce an overview of imaging research across the NIH, including in the focused research fields mentioned above, and assess the quality of interactions in imaging research within NIH, and report the results in the fiscal year 2019 CJ.

Action taken or to be taken:

NIH has long supported research on developing novel imaging technologies that are transforming our understanding of biological and disease processes, enabling patient-centered healthcare, and increasing access through portable and affordable technologies. A key component of the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative¹⁹⁰ is research to develop new technologies that can reveal the structure and inner workings of the brain. This initiative is a partnership of ten NIH Institutes and Centers, other federal agencies, foundations, universities, and industry. The BRAIN Initiative also has a specific public-private partnership component that facilitates partnerships between clinical investigators and manufacturers to conduct clinical research specifically on the central nervous system. This partnership allows for greater efficiency by reducing barriers to information-sharing between manufacturers and researchers. Research supported through BRAIN is leading to new insights. For example, researchers recently developed a method to better understand resting state functional brain networks and connectivity between brain regions. This could have implications for identifying biomarkers of diseases such as Alzheimer's and mild cognitive impairment.

Imaging research is also a part of the Cancer Moonshot InitiativeSM and two specific funding opportunities were recently made available. One opportunity will support development of diagnostic imaging technologies to help identify patients likely to respond to cancer immunotherapies.¹⁹¹ Another opportunity will support development of imaging-based platforms to mapping tumors at the molecular and cellular level.¹⁹² The All of Us Research Program, formerly the Precision Medicine Initiative, is continuing to work towards a full national launch. As implementation proceeds, this program will be considering technologies for participants to share biomedical images in the future.

Other imaging research supported across NIH is developing techniques for diagnosing a range of illnesses and disorders including bacterial infections, creating methods to distinguish aggressive from slow growing tumors, and developing ultrasound interventions for clearing blood clots. Not only are new technologies and methods being developed, but advances utilizing these new methods have led to profound discoveries that require medical textbooks to be re-written. In one example, researchers discovered that the brain does in fact have a lymphatic system for removing waste. This could have implications for many brain disorders including Alzheimer's disease, multiple sclerosis, and Parkinson's disease, among others. Another recent insight used a big data approach to analyze thousands of diffusion tensor imaging (a type of MRI) samples and found

¹⁹⁰ <https://www.braininitiative.nih.gov/index.htm>

¹⁹¹ <https://sbir.cancer.gov/funding/contracts/375>

¹⁹² <https://sbir.cancer.gov/funding/contracts/376>

that schizophrenia is a result of widespread disruptions in the brain's connections and is not limited to specific areas of the brain as previously thought.

Multiple NIH institutes collaborate within NIH and with agencies across the government to advance imaging research, from co-funding specific projects to the broad initiatives described above. Other examples of ongoing programs include the Human Connectome Project,¹⁹³ Human Placenta Project, Quantitative Imaging Biomarkers Alliance,¹⁹⁴ National Biomedical Imaging Archive,¹⁹⁵ and Imaging Tools for Cancer Research.¹⁹⁶ These projects are developing methods for gathering, storing, and analyzing large medical imaging data sets and extracting useful information from these datasets.

NIH institutes and other federal agencies also coordinate and share information through the Interagency Working Group on Medical Imaging, a subcommittee of the Committee on Science in the Office of Science and Technology Policy that is co-chaired by NIH and the National Institute of Standards and Technology. This group has worked to identify gaps and develop a roadmap to accelerate technology development that is more effective, improves patient care, and has the potential to lower cost. A draft report of recommendations is in development.

¹⁹³ <http://www.humanconnectomeproject.org/>

¹⁹⁴ <http://www.rsna.org/qiba/>

¹⁹⁵ <http://ncia.nci.nih.gov/ncia/>

¹⁹⁶ <http://lhncbc.nlm.nih.gov/project/imaging-tools-cancer-research>

Immunotherapy for Childhood Cancers

Recent NIH studies demonstrate that a new cancer immunotherapy method to specifically attack tumor cells that have mutations unique to a patient's cancer could be effective against a wide range of cancers. The Committee encourages NCI to continue to explore further new interventions, such as immunotherapy, as a promising new treatment strategy for children with cancer.

Action taken or to be taken:

Decades of investment by the National Cancer Institute (NCI) has contributed to many recent advances in immunotherapy, a treatment approach that is showing promise for both adult and childhood cancers. For example, chimeric antigen receptor (CAR) T-cells have been successfully engineered to treat patients with acute lymphoblastic leukemia (ALL) who no longer respond to traditional treatments. The Food and Drug Administration (FDA) approved the first therapy of this kind, Kymriah™ (also known as CTL019), on August 30, 2017. NCI was also instrumental in developing, from basic immunology research through a phase III clinical trial, Unituxin® (also known as dinutuximab), which was approved in early 2015 for use in the first-line treatment of children with high-risk neuroblastoma.¹⁹⁷ NCI partnered with United Therapeutics through a Cooperative Research and Development Agreement (CRADA) to bring the drug to market.

While immunotherapies have been successful in treating some childhood cancers, particularly acute lymphoblastic leukemia (ALL), they do not work for every type of pediatric cancer nor for all patients. In recognition of the unique challenges posed by pediatric cancer for immunotherapy development, the 2016 report from the Cancer Moonshot Blue Ribbon Panel (BRP) recommended NCI create a translational science network devoted to pediatric immunotherapy research.

To implement the BRP recommendation, NCI formed the Pediatric Immunotherapy Translational Science Network implementation team, which developed two recently announced NCI funding opportunities for the Pediatric Immunotherapy Discovery and Development Network (PI-DDN).¹⁹⁸ The collaborative research network, set to launch in 2018, will work to identify and advance research opportunities for translating immunotherapy concepts for children and adolescents with cancer toward clinical applications. Primary goals of the PI-DDN will include the discovery and characterization of immunotherapy targets for children and adolescent cancers, the development of new immunotherapy treatment approaches, and an improved understanding of the biological mechanisms by which pediatric tumors evade the immune system.

The recommendations of the BRP have further guided NCI in leveraging existing programs in immunotherapy to better address issues related to pediatric cancer. For example, in January 2017, NCI posted a Notice of Change to announce the expansion of the existing Cancer Immunotherapy Trials Networks (CITN) to include up to five additional sites devoted exclusively to enrolling pediatric patients.¹⁹⁹

¹⁹⁷ <https://www.cancer.gov/news-events/cancer-currents-blog/2015/dinutuximab-neuroblastoma>

¹⁹⁸ <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-050.html>, <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-051.html>

¹⁹⁹ <https://grants.nih.gov/grants/guide/notice-files/NOT-CA-17-021.html>

Additionally, NCI-supported scientists at the Children's Hospital of Philadelphia, together with NCI Center for Cancer Research (CCR) investigators, recently identified and validated a protein that appears to be a strong candidate for immunotherapeutic targeting in high-risk neuroblastoma (NBL).²⁰⁰ Their findings could pave the way for the development of less toxic, more effective immunotherapy drugs for NBL.

Cell-based immunotherapy approaches, including CAR T-cell therapies, continue to be an important research area of focus within NCI's CCR and its Pediatric Oncology Branch (POB). NCI investigators have led a first-in-human clinical trial of CAR T-cells engineered to target the CD22 protein, which is often expressed on the cell surface of B-cell malignancies, including certain types of pediatric ALL and certain pediatric lymphomas. This NCI research team recently published results from the trial, showing that CD22-targeted CAR T-cells can induce remission for some patients. It is the first study to establish the clinical activity of CD22-targeted T-cell immunotherapy for pediatric B-cell ALL.²⁰¹ In addition to CAR T-cell therapy targeting CD22, the POB has also evaluated CAR T-cell therapy targeting CD19, the protein targeted by the recently approved KymriahTM/CTL019 therapy. NCI investigators are now preparing to launch a combination CAR T-cell clinical trial, which will treat children and young adults with pediatric leukemias and lymphomas that express both CD22 and CD19, with CAR T-cells engineered to target both proteins. The trial aims to evaluate whether this combination approach is more effective in inducing long-term remission and cure than targeting CD19 or CD22 alone, including whether a combination approach is effective in preventing these cancers from developing resistance to therapy.

²⁰⁰ <https://www.ncbi.nlm.nih.gov/pubmed/28898695>

²⁰¹ <https://www.ncbi.nlm.nih.gov/pubmed/29155426>

Immunotherapy

NCI-funded research on the immune system's ability to find and destroy tumors has led to a new wave of promising treatments for many forms of cancer. Yet much remains unknown about how immunotherapy works on a cellular level, and especially why such treatments are successful for some patients but not for others. Without a better understanding of the immune system's response to cancer and knowing how cancer escapes immune based therapy, further advances in this field will be slowed. Therefore, the Committee urges NCI to continue to prioritize basic research on the mechanisms of action involved in immunotherapy, including a focus on tumor resistance to immunotherapy.

Action taken or to be taken:

Immunotherapy, treatment that uses a patient's own immune system to help fight diseases including cancer, is a major focus of National Cancer Institute (NCI)-supported research that spans basic science to clinical applications. While new immunotherapy treatments have been successful in many cases, they do not yet work for all cancer types or all cancer patients. NCI recognizes the need to advance research on the mechanisms of immunotherapy response to guide the development of additional treatments, including combination therapies, designed to overcome or prevent the development of immunotherapy resistance. Cancer immunotherapies include, among others, immune checkpoint inhibitors, adoptive cell transfer, and therapeutic vaccines, described below.

Immune checkpoint inhibitors work by taking the “brakes” off the immune system so it can better kill cancer cells. Recent clinical advances in checkpoint inhibitors include the FDA approval of Keytruda® (pembrolizumab) for a variety of cancers, and Bavencio® (avelumab) for metastatic Merkel cell carcinoma. The approval of Keytruda® for cancers with specific molecular characteristics (known as DNA mismatch repair, dMMR, and high microsatellite instability, MSI-H) is particularly notable, given it is the first FDA approval for any solid tumor with a specific genetic marker, regardless of where in the body the cancer originated. These and other checkpoint inhibitors are the result of several decades of basic research, much of it supported by NCI and the National Institute of Allergy and Infectious Diseases, on the function of the immune system, and how it can be used for the treatment of cancer.

Currently, NCI-supported researchers are focused on understanding why these therapies work for some patients and not others. At the level of the cancer cell, NCI-supported researchers published findings in 2017 identifying mutations in cancer cells that are responsible for resistance to checkpoint inhibitors in melanoma patients that enabled the tumors to avoid recognition and attack by immune cells.²⁰² Results from another NCI-supported study of tumors from patients with lung cancer suggest that acquired resistance to immune checkpoint inhibitors may be due to cancer cells eliminating the genetic mutations that the immune system uses to recognize and attack malignant cells.²⁰³

Studies of the tumor microenvironment, the various types of cells and structures surrounding the tumor (blood vessels and immune cells, for example) have also led to the identification of mechanisms of response and resistance. NCI-supported researchers recently showed that

²⁰² <http://cancerdiscovery.aacrjournals.org/content/7/2/188.long>

²⁰³ <http://cancerdiscovery.aacrjournals.org/content/early/2017/01/04/2159-8290.CD-16-0828> (from BRAIN brief)

blocking a molecule called TGF-beta may have promise in reversing immunosuppression.²⁰⁴ Increased expression of other immune checkpoints in the tumor microenvironment can also be associated with resistance to therapy. For example, NCI-supported researchers recently showed that the inhibitor molecule VISTA is increased in tumor samples from patients with prostate cancer that did not benefit from the immune checkpoint inhibitor Yervoy ® (ipilimumab).²⁰⁵

Combining two or more therapies may benefit patients with resistance to a single immunotherapy. NCI-supported researchers are pursuing the promising approach of combining radiation therapy with checkpoint inhibitors.²⁰⁶ Researchers are also using oncolytic viruses,²⁰⁷ vaccines, and molecularly targeted therapies. Understanding the biological underpinnings of how these therapies work together can inform the selection of agents for clinical trials.

Adoptive cell transfer therapy is another type of immunotherapy, in which the patient's own immune cells are extracted, altered in the lab, and reinfused back into the patient. In 2017, the FDA approved the first two of these therapies: Kymriah ® (tisagenlecleucel) and Yescarta® (axicabtagene ciloleucel). This approach was pioneered by NCI-supported investigators.

NCI will soon be launching a Center for Cell-based Therapy (CCT) within its intramural research program. The CCT builds on the NCI's decades-long efforts to understand the principles of cell-based therapies and to bring early stage research to the clinic. The CCT will also train NCI staff and strive to educate visiting investigators. This effort will spearhead the development of advanced treatment technologies with cell-based immunotherapy.

In addition to supporting individual labs, NCI supports collaboration and data sharing among labs to discover and validate immunotherapy markers. Efforts include:

- The **Cancer Immunotherapy Trials Network (CITN)**, which was established in 2010 to design, facilitate, and conduct early-phase immunotherapy clinical trials and support research on patient tumor specimens.²⁰⁸
- **The Partnership to Accelerate Cancer Therapies (PACT)**, a new public-private partnership focused on research identifying and validating biomarkers of response and resistance to cancer therapies, with an emphasis on immunotherapies.²⁰⁹
- **The Cancer Immune Monitoring and Analysis Centers (CIMACs)**, formed by NCI in 2017, that will conduct correlative studies and profiling of tumors and immune cells for NCI-funded early trials of immunotherapy.²¹⁰
- As part of the Cancer MoonshotSM, NCI is establishing two networks to accelerate the translation of immunotherapy research discoveries to clinical applications for adult and pediatric cancers: the **Immuno-Oncology Translational Network** for adult cancers and the **Pediatric Immunotherapy Discovery and Development Network** for pediatric tumors. The goal is to develop and implement a national strategy to discover new immune targets and evaluate novel immune-based approaches, with the goal of increasing

²⁰⁴ <https://www.ncbi.nlm.nih.gov/pubmed/28851824>

²⁰⁵ <https://www.nature.com/nm/journal/v23/n5/full/nm.4308.html>

²⁰⁶ <https://www.cancer.gov/about-nci/budget/plan/treating/combining-therapies/radiation-checkpoint-inhibitors>

²⁰⁷ <https://www.ncbi.nlm.nih.gov/pubmed/28886381>

²⁰⁸ <https://www.cancer.gov/about-nci/budget/plan/2019-annual-plan-budget-proposal.pdf> page 48

²⁰⁹ <https://www.reuters.com/article/us-usa-healthcare-cancer/u-s-nih-11-drugmakers-partner-to-accelerate-cancer-therapy-research-idUSKBN1CH22E>

²¹⁰ <https://www.cancer.gov/about-nci/budget/plan/2019-annual-plan-budget-proposal.pdf> page 49

the cure rate in cancer patients, and eventually to develop vaccines to prevent cancers of all types.²¹¹

NCI shares the Committee's enthusiasm for encouraging early and mid-career researchers. In June 2017, the National Institutes of Health (NIH) announced the Next Generation Researchers Initiative to provide opportunities for earlier research independence while enhancing workforce diversity. The NIH NGRI policy was released on August 31, 2017. In FY17, the NCI funded approximately ten percent more Early Stage Investigator applications than it did in FY16. The NCI is examining the characteristics of its grant-funded workforce to inform a science-based and data-driven approach to develop and implement policies for funding early career investigators for FY 18 and beyond. Supporting and retaining early career investigators in cancer research is critical for advancing NCI's mission.

²¹¹ <https://www.cancer.gov/about-nci/budget/plan/2019-annual-plan-budget-proposal.pdf> page 49

Improving the Treatment of Mental Illness

The Committee shares the concern of the NIMH National Advisory Mental Health Council that over the past decade the NIMH research portfolio has increasingly become focused on basic neuroscience research at the expense of research focused on finding ways to ease the burden of those currently suffering from devastating mental conditions. Therefore, the Committee urges NIMH to diversify its research portfolio to better balance basic neuroscience and applied research to increase the development of more effective treatments for people suffering from mental conditions now.

Action taken or to be taken:

NIMH is committed to maintaining a research portfolio that prioritizes excellent science, with a secondary imperative to balance research with short-, medium-, and long-term timeframes. Basic science is foundational to the development of future treatments, and excellent applied research aims to benefit those who are suffering from mental illnesses now. Indeed, NIMH supports efforts to translate basic science findings into clinical practice, and invests in research to improve delivery of currently available, efficacious treatments to individuals who need them. Examples of high impact NIMH investments in applied research focus on service delivery, such as coordinated specialty care for first episode psychosis, collaborative care models to expand the reach of mental health services delivery, and learning healthcare systems to enhance treatment efficiency and uptake.

Findings from the NIMH-funded Recovery After an Initial Schizophrenia Episode (RAISE) project demonstrate that coordinated specialty care – a team-based, multi-component treatment program for individuals experiencing first episode psychosis – results in superior clinical and functional improvements as compared to typical care.²¹² These improvements are especially pronounced among patients with shorter duration of untreated psychosis, underscoring the critical importance of early intervention. Accordingly, NIMH currently invests in research aimed at intervening early to reduce the duration of untreated psychosis.^{213,214} By focusing on specific aspects of early intervention such as early identification of first episode psychosis, rapid referral to evidence-based services, and effective engagement in coordinated specialty care, NIMH-funded research aims to support an evidence base that captures a wide spectrum of care.^{215,216,217,218}

NIMH also invests in research on collaborative care – support systems that integrate mental and physical health care. Collaborative care models improve the treatment of mental illnesses among people with co-occurring medical problems treated in primary care settings.²¹⁹ This is critically important because individuals experiencing untreated mental illnesses commonly present for care in primary care settings. Research demonstrates that collaborative care is essential to delivering

²¹² <https://www.ncbi.nlm.nih.gov/pubmed/26481174>

²¹³ <https://grants.nih.gov/grants/guide/pa-files/PA-16-265.html>

²¹⁴ <https://grants.nih.gov/grants/guide/pa-files/PA-16-264.html>

²¹⁵ <https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-210.html>

²¹⁶ <https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-211.html>

²¹⁷ <https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-212.html>

²¹⁸ <https://grants.nih.gov/grants/guide/pa-files/PA-16-354.html>

²¹⁹ <https://www.ncbi.nlm.nih.gov/pubmed/16675360>

care to people who need it, and to improving care for individuals with depression, anxiety, post-traumatic stress disorder, and other mental illnesses and co-morbid conditions, across the lifespan.²²⁰

To improve the speed, efficiency, generalizability, and uptake of mental health research and treatment, NIMH also supports the Mental Health Research Network (MHRN).²²¹ MHRN comprises 13 health care systems, reaching approximately 13 million beneficiaries across the country. MHRN serves as NIMH's prototype of a learning healthcare system, and includes large-scale pragmatic trials and services research.

These NIMH-supported efforts seek to identify and treat people who currently suffer from mental illnesses. In the context of a balanced portfolio based on excellent science and diverse timeframes, such efforts support the NIMH mission to transform the understanding and treatment of mental illnesses.

²²⁰ <https://www.ncbi.nlm.nih.gov/pubmed/23076925>

²²¹ <http://hcsrn.org/mhrn/en/>

In Silico Clinical Trials

The Committee appreciates the work of NIBIB in facilitating technology to move the science of in silico clinical trials forward. The Committee directs NIBIB to continue and expand this work and to involve other relevant Institutes in furthering this effort.

Action taken or to be taken:

The National Institute of Biomedical Imaging and Bioengineering (NIBIB) chairs a trans-NIH, and multi-government agency effort to develop the modeling technologies needed to advance the science of in silico experimentation and in silico clinical trials. The Interagency Modeling and Analysis Group²²² (IMAG) members include 22 NIH Institutes/Centers/Offices and representatives from multiple entities within the Department of Defense, the Department of Energy, Food and Drug Administration, National Science Foundation, National Aeronautics and Space Administration, Veterans Affairs, Department of Agriculture, Agency for Healthcare Research and Quality, and Intelligence Advanced Research Projects Activity. The purpose of the interagency group is to support the development of multiscale models to accelerate biological, biomedical, behavioral, environmental and clinical research. To efficiently and effectively address the challenges of understanding multiscale biological and behavioral systems, researchers will need predictive computational models that encompass multiple biological and behavioral scales. IMAG also coordinates the Multiscale Modeling Consortium which is comprised of modeling grantees who come together virtually and at an annual scientific meeting to share developments and ideas for furthering research in this area.

NIH-supported research in this area spans a wide range of human biology. For example, many Americans suffer from injuries of joints, tendons and ligaments and undergo surgical repairs that are not always optimal. To address this problem, researchers are focusing on tendon-to-bone attachment, which is required for successful rotator cuff repair and anterior cruciate ligament reconstruction but is rarely successfully achieved in clinical practice. At the root of these difficulties is the challenge of attaching two vastly different materials: stiff bone and flexible tendon. This research will create multi-scale models of the natural tendon-to-bone area where the two types of tissue connect to guide clinical care decisions and tissue engineering efforts to replicate healing in joints.

Another example is addressing the difficulty of successfully using cardiac pacemakers in patients that have had heart attacks. This project is developing computer models that predict long-term growth and remodeling of damaged and undamaged heart muscle in response to therapy with pacemakers to understand when and why this therapy fails and design better alternatives.

Another project aims to improve treatment for breast cancer to identify early on patients that are not responding to a therapy regimen, providing the opportunity to switch to a potentially more beneficial treatment. Existing methods of determining early response are inadequate and rely primarily on trial and error. Researchers are developing tumor-forecasting methods for predicting response in individual breast cancer patients after a single cycle of therapy.

²²² <https://www.nibib.nih.gov/research-funding/interagency-modeling-and-analysis-group-imag>

Induced Pluripotent Stem Cell Technology

The Committee understands that unlike the controversy linked with embryonic stem cells, iPSCs are derived from adult skin cells making them an acceptable alternative therapeutic. iPSCs have many of the therapeutic properties of embryonic stem cells, but with the additional advantage that they can be derived from patient skin cells for personalized medicine. This establishes iPSCs as a source of cells with great value and potential for curing human disease and injury. iPSCs could potentially be used to treat a wide range of human disease, repair damaged tissue (regenerative medicine), and serve as a platform to develop new therapeutics (small molecule drugs). However, the Committee notes that additional basic research is essential to realize the full biomedical potential of this technology. The Committee encourages NIH to support basic research in this area that leads to pre-clinical trials, cures, diagnostics, and treatments. The Committee requests an update in the fiscal year 2019 CJ on expansion opportunities being considered related to iPSC technology.

Action taken or to be taken:

In recognition of the potential for the development of new treatments for a wide range of disorders, NIH supports a broad portfolio of basic and preclinical research that involves human induced pluripotent stem cells (iPSCs) and other types of adult stem cells. This research spans the translational pipeline, from investigating disease mechanisms using specific cell types generated from patient iPSCs; to identifying high confidence targets for intervention; to predicting individual differences in therapeutic response using cells and organoids generated from normal donors and patient iPSCs; to repairing cells derived from patient iPSCs and using them for potential cell replacement therapies. For example, researchers in the NEI intramural program have developed retinal pigment epithelial cells from iPSCs to treat age-related macular degeneration, tested them in an animal model, and plan to file an IND with FDA next year. NIH-funded researchers at Harvard University have also generated pancreatic β -cells from iPSCs for the first time to treat type 1 diabetes.

Many biological and technological knowledge gaps, including safety and quality control issues, must be addressed before safe and effective iPSC-based therapies are broadly and routinely available. For instance, most protocols for producing specialized cells from iPSCs generate functionally immature cells, which are generally not optimal for regenerative medicine applications or for developing robust *in vitro* platforms. Some progress has been made: for example, the NCATS Stem Cell Translation Laboratory is generating specific human cell types from iPSCs and has automated the differentiation of hepatocyte (liver cells) from iPSCs. However, additional research is needed to determine how to generate functional mature cell types in a reproducible and scalable fashion. Another technical challenge is variability between different iPSC lines, which often compromises reproducibility of experimental protocols and complicates comparisons across different iPSC lines and platforms. An additional critical barrier to potential therapeutic transplantation of tissues or organs is achieving vascularization of regenerated tissues so that the new tissues can survive long-term in the host.

NIH-funded investigators are addressing these and other challenges in regenerative medicine research. This work is capitalizing on recent advances in genome editing and gene targeting

technology, bioengineering, tissue chip and “omics” technologies, systems biology and bioinformatics, among other areas.

NIH is pursuing many scientific opportunities involving iPSCs and other adult stem cells. Examples include the following: (1) Rigorous, scalable protocols that produce most or all specialized cell types at high purity, and have the ability to accurately identify markers of iPSC maturity to pave the way for streamlined cell replacement therapies for a wide variety of diseases. Such methods should significantly improve reproducibility across different iPSC lines, help to implement efficient cell manufacturing standards, and facilitate the definition of clinically acceptable safety criteria. (2) Research with iPSCs can unravel the functional contribution of risk genes and cross-patient differences in complex disorders such as schizophrenia. However, such research requires investment in production and analysis of much larger numbers of patient cell lines to obtain statistically meaningful results, as well as in robotics and automation at each stage of iPSC processing. (3) In 2017, for the first time, NIH-funded investigators produced engraftable blood stem cells that were fully functional in a preclinical model. Additional NIH investment will enable transformation of iPSCs into the full diversity of blood cells with the potential to treat genetic diseases, such as sickle cell disease; to generate platelets for treating trauma; and to deliver therapeutic molecules. (4) Further development of CRISPR-CAS genome editing and gene targeting technologies is underway, which will improve our ability to introduce specific genetic changes into iPSC lines to study disease mechanisms and to engineer cell lines customized for precise treatments of individual patients.

Infectious Diseases (FIC)

Recent disease outbreaks such as Ebola, Zika, and Dengue have shown the importance of the Center's essential role in global infectious disease health research training and health system strengthening to help developing countries to eventually advance their own research and health solutions and tools. FIC has developed important partnerships in countries, including countries unfriendly to the U.S., to not only fight malaria, neglected tropical diseases, and other infectious diseases, but also to have the capabilities to help the U.S. detect and treat infectious diseases that are not endemic to the U.S. before they travel to the U.S., thus protecting Americans here at home. The Committee urges FIC to continue this important work building relationships with scientists abroad to foster a stronger and more effective science workforce and health capacity on the ground, helping to detect infectious diseases and building the capacity to confront those diseases while improving the image of the U.S. through health diplomacy in their countries.

Action taken or to be taken:

The Fogarty International Center (FIC) invests in building leaders in global health research and strengthening the capacity of research institutions in low-and middle-income countries (LMICs) to be sustainable platforms for cutting-edge science, and catalyzing meaningful collaborations between U.S. and foreign institutions. This commitment is articulated in the most current Fogarty International Center Strategic Plan.²²³

FIC's investments comprise a range of capacity-strengthening programs which include, for example, the longstanding HIV Research Training Program (HIVRT) and the Global Infectious Disease Research Training Program (GID). The recent epidemics of Ebola and Zika have highlighted the need for better global preparedness and response to disease epidemics. FIC is funding collaborations between U.S. and West African academic institutions, through the Emerging Epidemic Virus Research Training Program for West African Countries with Widespread Transmission of Ebola, to develop programs that would strengthen the skills required to evaluate vaccines, develop new diagnostic tests and treatments, and identify the most effective intervention strategies for disease outbreaks.

FIC efforts also include programs that strengthen the global health research workforce generally and are designed to foster partnerships among LMIC institutions and between U.S. and LMIC institutions. Programs like the Medical Education Partnership Initiative (MEPI), the Emerging Global Leader Award, and the Global Health Program for Fellows and Scholars Training provide research training support for both US and LMIC scientists across the career development pipeline.

²²³ Fogarty International Center. 2013. *Strategic Plan*. <https://www.fic.nih.gov/About/Documents/fogarty-international-center-nih-strategic-plan.pdf>

Inflammatory Bowel Diseases

The Committee is pleased by NIDDK's support of research into inflammatory bowel diseases. The Committee urges NIDDK to respond to these findings by providing additional support for research on IBD. Research should include a focus on the environmental triggers and epigenetics of IBD as well as interventions for the rising prevalence of IBD. The research should also be targeted at both pediatric and adult patients.

Action taken or to be taken:

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a robust portfolio of projects that are investigating potential causes of Inflammatory Bowel Diseases (IBD). Several studies are exploring environmental causes, such as diet and the composition of the gut microbiome (which is affected by diet, antibiotics, and other environmental factors). For example, the NIDDK is supporting a study that aims to determine whether a diet with low levels of red and processed meat consumption is associated with a lower rate of relapse of Crohn's disease. The NIDDK also continues to actively participate in the NIH's Human Microbiome Project (HMP), which is characterizing the community of microbes present in humans using DNA sequencing technology. Through the HMP, the NIDDK is actively co-funding and managing research to understand how the gut microbiome is altered in IBD. One HMP project, called the IBD Multi'omics Database (IBDMDB), is integrating many different types of measurements of gut microbes as they change within IBD patients, including both children and adults, over time. The goal of the IBDMDB is to provide a resource for analyzing the gut microbiome and its relationship to IBD, improving the ability to understand, diagnose, and treat IBD.

The NIDDK is also supporting research into epigenetic causes (such as environmentally induced changes in expression of genes that do not involve changes to the DNA sequence) of IBD. In addition to characterizing the gut microbiome, a goal of the IBDMDB project is to profile epigenetic changes in people with IBD to gain a better understanding of how the gut microbes are interacting with their hosts. Another study supported by the NIDDK aims to identify genetic variations and epigenetic changes that significantly contribute to IBD. Also, a goal of one of the studies in the recently renewed IBD Genetics Consortium is to identify epigenetic changes that may play a role in the onset of inflammation in people with ulcerative colitis. These projects will help to enhance understanding of how IBD develops and ultimately may be useful for helping detect, prevent, and treat IBD.

The NIDDK also supports clinical trials to test the safety and effectiveness of IBD therapies. The Methotrexate Response in Treatment of Ulcerative Colitis study is investigating the safety and therapeutic value of methotrexate, an inexpensive generic drug, in adult ulcerative colitis patients in whom established therapies have failed. Enrollment for this study was recently completed. The Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) study is evaluating whether a combination of clinical, genetic, and immunologic tests can be used to predict response to standard medical therapy for children newly diagnosed with ulcerative colitis. Recent results from the PROTECT study found that certain diagnostic criteria, such as standardized measurements of disease severity or the amount of albumin in the blood, can be applied to determine the best course of treatment for ulcerative colitis in children.

Institutional Development Award (IDeA)

The Committee provides \$344,313,000 for the IDeA program, an increase of \$10,952,000. The Committee believes the IDeA program has made significant contributions to biomedical research and has led to the creation of a skilled workforce and made the program an essential component of NIH's research portfolio. The Committee supports this important investment, which extends NIH's reach nationwide. Further, the Committee recognizes the importance of the Centers of Biomedical Research Excellence and the IDeA Networks of Biomedical Research Excellence programs and expects funding to be maintained for both. These programs are essential to the overall success of the program.

Action taken or to be taken:

The National Institute of General Medical Sciences (NIGMS) appreciates the Senate's continued support for the Institutional Development Award (IDeA) program. The IDeA Program is designed to enhance the research infrastructure and increase the research capability and competitiveness of investigators in institutions located in states with historically low aggregate grant awards from the NIH. Grant awards are made to independent biomedical research institutes and/or biomedical research institutions that award doctoral degrees in the health sciences or sciences related to health within IDeA-eligible states.

Currently, institutions in 23 states²²⁴ and Puerto Rico are eligible for funding from the IDeA Program. For FY 2018 and in the foreseeable future, the IDeA program will continue to support investigators in eligible states through the following initiatives:

- (1) *IDeA Networks of Biomedical Research Excellence (INBRE)*. The INBRE initiative enhances, extends, and strengthens the research capabilities of biomedical research faculty in IDeA states through a statewide program that links a research-intensive institution with primarily undergraduate institutions. INBRE supports institutional research and infrastructure development; research by faculty, postdoctoral scientists, and students at participating institutions; and outreach to build science and technology knowledge in the states' workforces. Only one award is made per eligible state.
- (2) *Centers of Biomedical Research Excellence (COBRE – Phases I, II, and III)*. The goal of the COBRE initiative is to strengthen institutional biomedical research capabilities in IDeA states through three 5-year phases of infrastructure and faculty development of thematic and multidisciplinary research centers.
- (3) *IDeA Program Infrastructure for Clinical and Translational Research (IDeA-CTR)*. The IDeA-CTR initiative develops network infrastructure and capacity in eligible states to conduct clinical and translational research focused on health concerns that affect medically underserved populations and/or that are prevalent in IDeA states. IDeA-CTR awards support mentoring and career development activities in clinical and translational research.
- (4) *Research co-funding*. IDeA co-funding is provided to eligible applications that have already been judged meritorious by NIH peer-review committees and national advisory

²²⁴ Alaska, Arkansas, Delaware, Hawaii, Idaho, Kansas, Kentucky, Louisiana, Maine, Mississippi, Montana, Nebraska, Nevada, New Hampshire, New Mexico, North Dakota, Oklahoma, Rhode Island, South Carolina, South Dakota, Vermont, West Virginia, Wyoming.

councils but are outside the range of applications under consideration for funding by the other NIH Institutes and Centers (ICs).

For FY 2018, the IDeA program will provide continuing support for the non-competing INBRE, COBRE, and IDeA-CTR awards; these awards constitute the IDeA program budget base. The rest of the IDeA program budget will support new competing COBRE and IDeA-CTR awards, re-competing INBRE awards, and co-funding of meritorious applications from IDeA applicants to other NIH ICs.

The approximately \$11 million increase for the IDeA program that the Senate proposes would allow NIGMS to fund additional meritorious new and competing renewal applications to our program initiatives (COBRE, INBRE, IDeA-CTR, and Co-funding). We also anticipate co-funding S10 applications (Shared Instrumentation Grants) to provide major instrumentation to enhance the research of NIH-funded investigators from IDeA states.

Additionally, the increase presents opportunities for addressing unmet and/or emerging areas for development or enhancement. NIGMS is constantly evaluating the IDeA program to identify such areas. As they are identified, NIGMS can publish one or more administrative supplement solicitations to allow IDeA investigators to address the challenges. Ideas under consideration for possible administrative supplement awards include: (1) consolidation of core facilities, (2) enhancing networking among IDeA scientists, and (3) an initiative for addressing drug addiction, i.e., the opioid crisis.

Institutional Development Awards

The Committee has provided \$373,641,000 for the IDeA program, \$40,000,000 above the fiscal year 2017 enacted level. IDeA supports high-quality research and investigators throughout the country in States in which the success rate for NIH grants has been historically low.

Action taken or to be taken:

The National Institute of General Medical Sciences (NIGMS) appreciates the House's continued support for the Institutional Development Award (IDeA) program. The IDeA Program is designed to enhance the research infrastructure and increase the research capability and competitiveness of investigators in institutions located in states with historically low aggregate grant awards from the NIH. Grant awards are made to independent biomedical research institutes and/or biomedical research institutions that award doctoral degrees in the health sciences or sciences related to health within IDeA-eligible states.

Currently, institutions in 23 states²²⁵ and Puerto Rico are eligible for funding from the IDeA Program. For FY 2018 and in the foreseeable future, the IDeA program will continue to support investigators in eligible states through the following initiatives:

- (1) *IDeA Networks of Biomedical Research Excellence (INBRE)*. The INBRE initiative enhances, extends, and strengthens the research capabilities of biomedical research faculty in IDeA states through a statewide program that links a research-intensive institution with primarily undergraduate institutions. INBRE supports institutional research and infrastructure development; research by faculty, postdoctoral scientists, and students at participating institutions; and outreach to build science and technology knowledge in the states' workforces. Only one award is made per eligible state.
- (2) *Centers of Biomedical Research Excellence (COBRE – Phases I, II, and III)*. The goal of the COBRE initiative is to strengthen institutional biomedical research capabilities in IDeA states through three 5-year phases of infrastructure and faculty development of thematic and multidisciplinary research centers.
- (3) *IDeA Program Infrastructure for Clinical and Translational Research (IDeA-CTR)*. The IDeA-CTR initiative develops network infrastructure and capacity in eligible states to conduct clinical and translational research focused on health concerns that affect medically underserved populations and/or that are prevalent in IDeA states. IDeA-CTR awards support mentoring and career development activities in clinical and translational research.
- (4) *Research co-funding*. IDeA co-funding is provided to eligible applications that have already been judged meritorious by NIH peer-review committees and national advisory councils but are outside the range of applications under consideration for funding by the other NIH Institutes and Centers (ICs).

For FY 2018, the IDeA program will provide continuing support for the non-competing INBRE, COBRE, and IDeA-CTR awards; these awards constitute the IDeA program budget base. The rest of the IDeA program budget will support new competing COBRE and IDeA-CTR awards, re-competing INBRE awards, and co-funding of meritorious applications from IDeA applicants to other NIH ICs.

²²⁵ Alaska, Arkansas, Delaware, Hawaii, Idaho, Kansas, Kentucky, Louisiana, Maine, Mississippi, Montana, Nebraska, Nevada, New Hampshire, New Mexico, North Dakota, Oklahoma, Rhode Island, South Carolina, South Dakota, Vermont, West Virginia, Wyoming.

The \$40 million increase for the IDeA program that the House proposes would allow NIGMS to fund additional meritorious new and competing renewal applications to our program initiatives (COBRE, INBRE, IDeA-CTR, and Co-funding). We also anticipate co-funding S10 applications (Shared Instrumentation Grants) to provide major instrumentation to enhance the research of NIH-funded investigators from IDeA states.

Additionally, the increase presents opportunities for addressing unmet and/or emerging areas for development or enhancement. NIGMS is constantly evaluating the IDeA program to identify such areas. As they are identified, NIGMS can publish one or more administrative supplement solicitations to allow IDeA investigators to address the challenges. Ideas under consideration for possible administrative supplement awards include: (1) consolidation of core facilities, (2) enhancing networking among IDeA scientists, and (3) an initiative for addressing drug addiction, i.e., the opioid crisis.

Interagency Pain Research

Consistent with the Comprehensive Addiction and Recovery Act (Public Law 114–198), the Committee encourages the Director to intensify and coordinate fundamental, translational, and clinical research of the NIH with respect to the understanding of pain, the discovery and development of therapies for chronic pain, and the development of alternatives to opioids for effective pain treatments. In doing so, the Committee urges the NIH to consider recommendations of the Federal Pain Research Strategy. The Committee requests an update in the fiscal year 2019 CJ on this initiative.

Action taken or to be taken:

The NIH is committed to promoting research to understand the biological mechanisms of pain as well as the development of novel and effective therapies for pain. The NIH Pain Consortium supports collaborative activities and initiatives across NIH Institutes and Centers, and the Interagency Pain Research Coordinating Committee (IPRCC) facilitates collaboration and coordinates pain research across federal agencies and departments.

A major undertaking of the IPRCC was the Federal Pain Research Strategy²²⁶ (FPRS), which was released in October 2017. The strategy is an effort of the National Institutes of Health, Office of Pain Policy, with oversight from the IPRCC. The strategy is a set of high priority research recommendations that collectively are relevant to the missions of federal agencies and departments that support pain research. The FPRS was developed within the framework of the themes of prevention of acute and chronic pain, acute pain and acute pain management, transition from acute to chronic pain, chronic pain and chronic pain management, and disparities. It is intended to advance the federal pain research agenda by guiding strategic research planning, and supporting funding decisions that will fill crucial gaps in the research portfolio.

The research recommendations that were developed as part of the FPRS address many areas of pain research from basic mechanisms underlying pain to models of pain care. Several of the top priorities of the FPRS focus on the development of safer opioid analgesics, non-opioid analgesics, and disease modifying agents, and on discovering, validating, and disseminating novel treatment strategies for acute and chronic pain.

In addition to the FPRS, the NIH is working in partnership with the HHS Office of the Assistant Secretary for Health, to engage federal agencies and other departments to implement recommendations of the National Pain Strategy (NPS). The NPS is the federal government's first broad-ranging effort to improve how pain is perceived, assessed, and treated through achievement of a set of discrete steps to improve pain management.

The Director of NIH hosted three cross cutting science meetings in 2017 to inform the development of public-private-partnerships to address the opioid crisis, including the National Institute of Neurological Disorders and Stroke-led component focused on development of safer, non-addictive analgesics. NIH and industry leads are discussing action items from the meetings, including exploration of the mechanisms that result in the transition from acute to chronic pain and strategies to prevent the transition. In addition, NIH is exploring the best approaches to accelerate development of effective and safe analgesic treatments for chronic pain conditions.

²²⁶ https://iprcc.nih.gov/sites/default/files/FPRS_Research_Recommendations_Final_508C.pdf

Interstitial Cystitis

The Committee is pleased with the evolving research on interstitial cystitis and encourages NIDDK to work with stakeholders on a comprehensive scientific conference to examine mechanisms for scientific opportunity.

Action taken or to be taken:

Interstitial cystitis/ bladder pain syndrome (IC/BPS) affects millions of Americans and has traditionally been characterized by pelvic pain strongly associated with the bladder and with urinary symptoms of frequency and urgency. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) efforts in IC/BPS are focused on understanding the cause(s) of this condition, improving diagnosis, finding more effective treatments, 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 NIH Office of Research on Women's Health, is spearheading the evolution in our understanding of IC/BPS and another urologic chronic pelvic pain syndrome, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Network studies have yielded new insights into brain changes, whole body pain patterns, symptom flares, and relationships between IC/BPS and other chronic pain disorders, such as irritable bowel syndrome and fibromyalgia, that exist in people with this syndrome and may help lead to new clinical categories and personalized treatment approaches. Planning is now under way for an NIDDK-sponsored multi-day scientific conference, tentatively titled "Research Advances for Urologic Chronic Pelvic Pain Syndrome: Informing the Next Generation of Clinical Studies," anticipated to be held in late 2018 or early 2019. Initial goals for this meeting include:

- Providing a forum for the exchange of current, key scientific insights from both MAPP Research Network and non-Network investigators, as well as from non-urologic chronic pain studies that may inform the urologic pain field
- Developing recommendations for effective translation of these insights into an improved evidence base for future clinical studies and ultimately improved patient care
- Developing improved strategies for disseminating MAPP Network findings
- Initiating development of new research definitions for urologic pain conditions, based upon the evolving insights into patient characteristics emerging from Network and other studies.

Research opportunities important for IC/BPS should be identified through this effort. At this very early stage, meeting planning is being led by NIDDK scientific staff and MAPP Research Network leadership, and will later 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.

Liver Cancer

The Committee notes that in the U.S. liver cancer is the second deadliest cancer, with a 5-year survival rate of less than 15 percent, and according to the CDC, unlike many other cancers, the rates of liver cancer deaths and incidence are rising. In spite of its growing mortality, research spending focused on liver cancer is not even among the 20 largest NCI cancers research programs; NCI has few liver cancer-oriented grants in its portfolio, and it does not have a Specialized Program of Research Excellence [SPORE] for liver cancer. To increase the 5-year survivability of liver cancer, the Committee urges that NCI support liver cancer research across its portfolio using a variety of methods to stimulate research proposals. The Committee also notes that the link between hepatitis B infection and primary liver cancer is well established with up to 60 percent of global liver cancer cases caused by the hepatitis B virus [HBV] and, therefore, urges close collaboration with NIAID and NIDDK on issues related to HBV research.

Action taken or to be taken:

The National Cancer Institute (NCI) conducts and supports research to improve the prevention, diagnosis, and treatment of liver cancer, or hepatocellular carcinoma (HCC), including research on viral hepatitis and its link to liver cancer.

Early detection is key to preventing deaths from HCC. Unfortunately, conventional diagnostic methods are often either expensive or relatively insensitive. NCI is supporting research to identify better diagnostic tools. NCI's Small Business Innovation Research (SBIR) program is funding the development of a noninvasive, urine-based diagnostic test for the early detection of liver cancer.^{227,228} NCI-supported researchers are also examining DNA markers to develop noninvasive tests for HCC screening of high-risk populations (including patients with cirrhosis or hepatitis)²²⁹, as well as developing a blood-based, smartphone-enabled, point-of-care test for the diagnosis of clinical cancer that will be deployable in low and middle income countries.²³⁰ Next year, NCI plans to establish a liver cancer consortium that will focus on studies to improve the surveillance of liver cancer in high-risk populations, increase the fraction of liver cancer detected at an early stage, and better stratify patients at risk of developing liver cancer.^{231, 232} Additional NCI-supported research aimed at preventing HCC includes a clinical trial of whether the cancer drug erlotinib may prevent liver cancer in patients with cirrhosis undergoing surgery and a study of whether the diabetes drug metformin may prevent hepatitis in cirrhotic livers.^{233, 234}

NCI-supported scientists are also conducting basic research on HCC to identify treatment targets and prognostic biomarkers. In 2017, researchers with The Cancer Genome Atlas (TCGA), a collaboration between NCI and the National Human Genome Research Institute, published the comprehensive genomic characterization of primary HCC.²³⁵ They identified three molecular subtypes and potential targets for therapy. The NCI intramural program is studying the

²²⁷ <https://www.sbir.gov/sbirsearch/detail/1046035>

²²⁸ <https://meetinglibrary.asco.org/record/127866/abstract>

²²⁹ <https://prevention.cancer.gov/research-groups/cancer-biomarkers/grants/R01CA202769>

²³⁰ <http://grantome.com/grant/NIH/UG3-CA211232-01>

²³¹ <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-025.html>

²³² <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-028.html>

²³³ <https://clinicaltrials.gov/ct2/show/NCT02273362>

²³⁴ <https://www.ncbi.nlm.nih.gov/pubmed/26914713>

²³⁵ <https://www.ncbi.nlm.nih.gov/pubmed/28622513>

molecular mechanisms of HCC,²³⁶ and recent studies include the identification of an alteration of a particular protein in patient tumor samples that enhanced HCC progression. Targeting this mechanism may represent a potential therapeutic strategy.²³⁷

NCI is also supporting clinical trials testing potential new therapies, including immunotherapies, for liver cancer. Current trials include: a phase I/II studying whether immune checkpoint inhibition can be enhanced by ablative therapies in patients with advanced HCC;²³⁸ a phase II trial testing adoptive cell transfer therapy plus an immune checkpoint inhibitor for patients with certain metastatic cancers including HCC;²³⁹ and a phase II trial testing the combination of approved drug sorafenib plus investigational agent TRC105, which builds upon encouraging results from the Phase I NCI-supported trial, published in 2017.²⁴⁰

NCI's Center for Cancer Research (CCR) is establishing the NCI Liver Cancer Program (NCI-LCP), a multidisciplinary translational research environment that encompasses several intramural laboratories with a special focus on liver cancer research. NCI-LCP will collaborate with extramural investigators to develop new and diverse approaches to the prevention, early detection, diagnosis and treatment of liver cancer.

Additionally, many NIH research efforts specifically investigate the connection between HCC and the hepatitis B virus (HBV). The National Institute of Allergy and Infectious Diseases (NIAID) works with diverse partners including NCI and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to advance research to understand HBV, including how the virus contributes to the development of liver cancer, and to investigate novel therapies that target HBV. Recently, NIAID researchers investigating HCC associated with hepatitis viruses found that the expression of certain genetic regulatory molecules differs in HCC patients depending on whether their cancer is related to HBV or another hepatitis virus. This discovery may provide new tools for improving the diagnosis of HCC and open new avenues for disease-specific therapeutic interventions. NCI is also partnering with NIAID and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to support research elucidating the role of the human immunodeficiency virus (HIV) in the development of HCC in persons co-infected with HIV plus HBV.²⁴¹ NIAID will continue to coordinate with NCI and NIDDK to support research on HBV and associated liver cancer.

In addition to these collaborative efforts, NIDDK also supports a wide range of research programs related to hepatitis B, including investigator-initiated extramural research, intramural research, and research supported through initiatives, such as large, multi-site studies and ancillary studies to clinical trials. For example, the NIDDK-supported Hepatitis B Research Network aims to advance understanding of disease processes and progression over time, as well as to identify effective approaches to treatment with available and emerging therapies. The Network is currently completing a 5-year study of long-term outcomes of hepatitis B therapy to investigate whether it is possible to clear HBV infection and stop antiviral therapy, as part of efforts toward developing a “cure.” Lastly, the NIDDK participates, along with other NIH ICs,

²³⁶ <https://ccr.cancer.gov/Laboratory-of-Human-Carcinogenesis/xin-wei-wang>

²³⁷ <https://www.ncbi.nlm.nih.gov/pubmed/28697339>

²³⁸ <https://clinicaltrials.gov/ct2/show/NCT02821754>

²³⁹ <https://clinicaltrials.gov/ct2/show/NCT01174121>

²⁴⁰ <https://www.ncbi.nlm.nih.gov/pubmed/28465443>

²⁴¹ <https://grants.nih.gov/grants/guide/pa-files/PA-17-279.html>

in the Trans-NIH Committee on Viral Hepatitis and the HHS National Viral Hepatitis Action Plan to coordinate efforts on hepatitis B and related liver cancer across the NIH and HHS.

Longitudinal Study of Cardiovascular Health in African Americans

The Committee commends NHLBI for accomplishments made by its longitudinal study of cardiovascular health in African Americans. This 16-year study has provided new insights into and better understanding of the burden of cardiovascular disease among African Americans in the United States. With this increased understanding comes knowledge of the gaps in a number of other health conditions that affect African Americans disproportionately, such as obesity, diabetes, hypertension, chronic kidney disease, and heart failure. Additionally, research has revealed that some of these chronic conditions may have an impact on healthy aging, including cognition and risk of dementia and may have transgenerational effects. Therefore, the Committee encourages NHLBI to continue to follow-up with all current study participants, conduct broader examinations for these participants, and explore enrollment of a new group of participants, including children and grandchildren of current study participants. An expanded study will provide researchers more information about the roles of familial factors and shared environments in the development and progression of cardiovascular disease and other conditions. The new round of examinations should include measurements that utilize the latest technology, such as Magnetic Resonance Imaging, to assess the status of the heart, muscles, and adiposity and to evaluate structural brain changes that may be related to hypertension, diabetes, and other chronic disorders.

Action taken or to be taken:

The Jackson Heart Study (JHS) in Jackson, Miss. is the largest community-based cohort study focused on cardiovascular disease (CVD) in African Americans. Since its launch in 1998, the study has produced extensive data on physiological, behavioral, socioeconomic, and sociocultural risk factors for CVD in African Americans, and has used this information to improve cardiovascular health in this population. With advances in genetics research, the study also has incorporated state-of-the-art methods to identify genetic factors that contribute to CVD in African Americans.

In its next phase, the study will examine factors that influence the risk of cognitive decline, as well as the risk of specific outcomes of CVD, such as heart failure. Over a span of nearly 20 years, researchers will examine changes in cardiac structure and function, as well as changes in cognitive function and signs of microvascular pathology on brain magnetic resonance imaging. Additionally, JHS researchers will expand their research to examine the burden of CVD across generations. The JHS Kids Study, funded through the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, has recruited 200 children and grandchildren (ages 12–19) of JHS participants to identify early life risk factors for CVD.²⁴² This pilot study may form the basis for a larger, long-term study of this generation. The next phase of JHS will have a stronger focus on community engagement to ensure that the people of Jackson are seeing benefits from the study, and in turn, that their participation is supporting science that will continue to benefit other communities across the U.S.

²⁴² <https://www.ncbi.nlm.nih.gov/pubmed/27129858>

Lung Cancer

The Committee encourages NCI to continue to prioritize support for meritorious research for lung cancer generally and specifically related to early detection of lung cancer and continued advances in treating lung cancer with personalized medicine, immunotherapy, and other innovative treatments. The Committee requests an update in the fiscal year 2019 budget request on these efforts.

Action taken or to be taken:

The National Cancer Institute (NCI) remains committed to conducting and supporting research on lung and bronchus cancer, which is expected to account for nearly 26 percent of cancer deaths in 2017. Lung cancer research has been at the forefront of recent advances in early cancer detection, personalized medicine, and immunotherapy development.

Early detection is a key factor in preventing lung cancer deaths. NCI's Early Detection Research Network (EDRN) identifies cancer biomarkers and supports the development of diagnostic tools by promoting collaboration among academic and industry partners. The Lung and Aerodigestive Cancers Research Group has supported over thirty projects and protocols, including a nationwide protocol focused on the identification of biomarkers for lung cancer in individuals who have never smoked.²⁴³ The EDRN is making progress toward discovering better diagnostic markers and tools. For instance, in 2016, NCI-supported researchers determined that a biomarker in the lung indicating lung cancer is also detectable in the nasal cavity, opening the door for less invasive lung cancer detection tools in the future.²⁴⁴ NCI was also instrumental in the development of Percepta, a diagnostic test that genetically classifies a patient's cells to improve the accuracy of bronchoscopy, potentially reducing the need for invasive biopsies. In 2017, Percepta was approved by the Centers for Medicaid and Medicare Services.

NCI also sponsored the landmark National Lung Cancer Screening Trial (NLST), which showed that screening people at high risk of lung cancer with low-dose, helical computed tomography (LHCT) scans reduced their risk of dying from lung cancer by 20 percent when compared with patients screened with traditional chest x-rays.²⁴⁵ Researchers have since created a user-friendly online lung-cancer screening risk-tool to provide individualized risk information for patients considering entering lung screening.²⁴⁶ In addition, NCI's Cancer Intervention and Surveillance Modeling Network (CISNET) Lung Working Group continues to develop and apply population models for lung cancer, quantifying the impact of tobacco control and LHCT screening on lung cancer incidence and mortality.

Research has shown that precision medicine holds promise for effectively treating lung cancer, and NCI is at the forefront of elucidating the molecular causes of cancer as a means to identifying the most effective targeted treatments. For instance, NCI, together with the Department of Defense (DoD) and the Department of Veterans Affairs (VA), launched the

²⁴³ <https://edrn.nci.nih.gov/collaborative-groups/lung-and-upper-aerodigestive-cancers-research>

²⁴⁴ <https://www.ncbi.nlm.nih.gov/pubmed/28376173>

²⁴⁵ <https://www.cancer.gov/research/areas/screening>

²⁴⁶ <https://analysistools.nci.nih.gov/lungCancerScreening/#/>

Applied Proteogenomics Organizational Learning and Outcomes Network (APOLLO) in 2016 through the Cancer Moonshot initiative. APOLLO brings together the NCI with the nation's two largest health care systems, the DoD and VA, to screen patients with lung cancer for genomic abnormalities and proteomic information that can be used to match their tumor types to targeted cancer therapies.²⁴⁷ In addition, scientists associated with NCI's Cancer Driver Discovery Program report that a receptor expressed on the surface of some cancer cells, known as GARP, could be a novel diagnostic marker for breast, colon, and lung cancer. Investigators are now studying whether targeting GARP with an antibody could represent a new addition to established therapies for cancer.²⁴⁸ NCI supports several precision medicine clinical trials for lung cancer, including the "Lung Cancer Master Protocol" (Lung-MAP), a multi-drug, biomarker-driven squamous cell lung cancer precision clinical trial that has enrolled more than 1,000 patients in 700 locations since its 2014 launch.²⁴⁹ Similarly, NCI supports the "Adjuvant Lung Cancer Enrichment Market Identification and Sequencing Trials" (ALCHEMIST) precision medicine program, a group of four clinical trials, including an immunotherapy clinical trial, testing whether adding targeted therapy will help prevent a patient's cancer from returning, thus improving patient outcomes.

As with many cancers, immunotherapy has the potential to revolutionize how lung cancer is treated. Recent advances in cancer immunotherapy are the result of several decades of basic research, in large part supported by NCI, on the function of the immune system and how it can be used for the treatment of cancer. To date, three immune checkpoint inhibitors have been approved to treat lung cancer, including two (atezolizumab [Tecentriq®] and pembrolizumab [Keytruda®]) that were approved since October 2016. Progress in this area continues, with NCI-supported researchers recently identifying a number of new driver mutations in the two major types of lung cancer that may be responsive to immunotherapy.²⁵⁰ Despite these advances, the need for better tolerated therapies is clear. NCI continues to support immunotherapy research, including research at three lung-specific Specialized Programs of Research Excellence (SPOREs), in order to find the most effective therapies with the fewest negative side effects.²⁵¹

An emerging area of opportunity is the development of vaccines to prevent cancer. Recently, NCI-supported scientists demonstrated in mice the effectiveness of a vaccine in preventing lung adenocarcinoma driven by a mutated KRAS protein, detected in up to 30 percent of lung cancers.²⁵²

²⁴⁷ <https://proteomics.cancer.gov/programs/apollo-network>

²⁴⁸ https://projectreporter.nih.gov/project_info_description.cfm?aid=9321014&icde=36683691&ddparam=&ddvalue=&ddsub=&cr=5&csb=default&cs=ASC&pball=

²⁴⁹ <http://www.lung-map.org/media/press/lung-map-infographics-illustrate-how-trial-helping-patients>

²⁵⁰ https://www.eurekalert.org/pub_releases/2016-05/iu-dol050616.php

²⁵¹ See: https://projectreporter.nih.gov/project_info_description.cfm?aid=9325321&icde=36281585

²⁵² <http://www.impactjournals.com/oncotarget/index.php?journal=oncotarget&page=article&op=view&path%5B%5D=19831>

Lung Disease

Lung disease is the third leading cause of death in the U.S., with a rising morbidity and mortality burden among all Americans, including older Americans. The Committee urges the institute to collaborate with the National Institute on Aging to study the impact of the lungs vulnerability to systemic disease and aging.

Action taken or to be taken:

The term “lung disease” covers a wide range of disorders that impact the functionality of the lungs and cause breathing problems. The National Heart, Lung, and Blood Institute (NHLBI) is committed to supporting basic, clinical, and translational research to ease the burden of lung disease, which is a major cause of death and disability in older Americans.

Chronic obstructive pulmonary disease (COPD) is the most common age-related lung disease and the third leading cause of death in the United States. Researchers are developing functional, structural, and molecular imaging techniques to detect COPD and other lung diseases at earlier stages. They are also using these techniques to differentiate normal aging from disease. For example, researchers with the Subpopulations and Intermediate Markers in COPD Study (SPIROMICS) used CT scans to determine that functional small airway abnormalities increase with age – about 2% per decade after the age of 50, even in never-smokers.²⁵³

Recent NHLBI-supported research reveals that lung diseases such as idiopathic pulmonary fibrosis (IPF) and emphysema are associated with signs of accelerated aging in lung tissue. This includes evidence for damage to the caps on the ends of chromosomes, a process that is known as telomere shortening and is a hallmark of aged cells. A recent NHLBI-supported study showed that aging cells, without the capacity to produce new lung tissue, are increased in the lungs of patients with IPF and contribute to disease progression in a mouse model of IPF.²⁵⁴

The National Institute on Aging (NIA) also supports research on lung diseases common among older people, including basic research investigating the susceptibility of the lungs to age, and how to prevent, reverse and/or slow the aging process in the lungs. Distinguishing between age-related changes and disease and/or environmental changes in lung function is another focus of investigation. NIA-funded investigators also have worked to develop novel technologies, techniques, imaging methods, and treatments to better the quality of life in the elderly with lung conditions. This includes research to inform the increasing use of lung transplantation in older adults, with a focus on addressing issues such as organ allocation and matching, and immunosuppression in transplant recipients. Clinical research on improving optimal strategies for pulmonary rehabilitation in older patients is another area of interest to both NIA and NHLBI.

In 2017, NHLBI and NIA published a report from a workshop on "The Intersection between Aging Biology and Pathobiology of Lung Diseases," where scientists discussed gaps in current knowledge and opportunities to collaborate.²⁵⁵ The report recommends promoting study of the normal biological aging of human lung, using both aged animal models and human lung tissue samples. NIA supports aged rodent colonies and NHLBI supports the Lung Tissue Research Consortium, which has collected human lung tissue samples from middle-aged to elderly

²⁵³ <https://www.ncbi.nlm.nih.gov/pubmed/27564413>

²⁵⁴ <https://www.ncbi.nlm.nih.gov/pubmed/28230051>

²⁵⁵ <https://www.ncbi.nlm.nih.gov/pubmed/28498894>

subjects with chronic lung conditions such as interstitial fibrotic lung disease and COPD. Both resources could be used to support studies of aging in the lung to understand age-related lung disease. Along those lines, NHLBI is planning an initiative to characterize dynamic changes that occur at a molecular level during the lung aging process.

Advances in novel technologies for genomic analysis and the availability of NHLBI and NIA resources will provide excellent opportunities for further research on aging in the lung, which could yield significant health benefits for the aging U.S. population.

Lyme Disease

With more than 300,000 Americans suffering from Lyme disease, especially in rural States across the United States, an improved understanding and treatment of the disease is essential for the health and well-being of Americans. The Committee encourages NIH to issue requests for grant applications for research to investigate causes of all forms and manifestations of Lyme disease, including post-treatment symptoms, as well as research to develop diagnostics, preventions, and treatments for those conditions and for complications caused by co-infection by other tick-transmitted bacteria, viruses, and parasites. The Committee notes that in patients who suffer from long-term complications associated with Lyme disease, clear treatment pathways are often missed as a result of inaccurate and incomplete testing. The Committee urges NIAID, in coordination with CDC, to study the long-term effects on patients suffering from post-treatment Lyme disease syndrome, or “chronic Lyme disease.” Specifically, the Committee urges NIAID to evaluate the effectiveness of laboratory tests associated with the detection of *Borrelia burgdorferi* to diagnose the disease early, which can improve the treatment of patients suffering from chronic Lyme disease. The Committee also encourages the National Library of Medicine, in coordination with NIAID, to update its terminology in line with new research to more accurately reflect the long-term effects of chronic Lyme disease.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) maintains a diverse research portfolio in Lyme disease and other tick-borne diseases. In fiscal year 2016, NIAID released funding announcements to encourage research on tick-borne pathogens, including the study of diagnostics, therapeutics, and vaccines to combat these infections, as well as factors that may contribute to post-treatment Lyme disease syndrome.

NIAID engages in important collaborations with Federal partners, Lyme disease experts, patients, and others as a member of the HHS Tick-Borne Diseases Working Group. NIAID is participating in an all-inclusive review of Federal activities and research related to tick-borne diseases led by the Working Group. In addition, NIAID published on its website a comprehensive report titled “Current Efforts in Lyme Disease Research, 2017.” This report describes current research toward improved prevention, diagnosis, treatment, and understanding of why symptoms persist in some patients following recommended treatment. Highlights of NIAID Lyme and tick-borne diseases research are described below.

NIAID supports basic research on how *Borrelia* species, including *B. burgdorferi*, *B. miyamotoi*, and *B. mayonii*, infect the host, multiply, and ultimately cause Lyme disease and related conditions. NIAID grantees are using real-time imaging to track *B. burgdorferi* infection in mice and investigating how *B. burgdorferi* evades the immune system. NIAID scientists have developed a novel tick infection model for flaviviruses that could be used to evaluate tools to combat the deadly Powassan and tick-borne encephalitis viruses. NIAID also supports Lyme disease prevention research, including efforts to target proteins in tick saliva that are critical for effective transmission of *B. burgdorferi*, develop oral-bait vaccines targeting mice and other animal hosts for *B. burgdorferi*, and adapt a successful canine Lyme disease vaccine for potential use in humans.

NIAID is collaborating with CDC and others to develop improved Lyme disease diagnostics including next generation molecular tests. NIAID-supported scientists are working to identify

biomarkers that could allow for earlier and more rapid diagnosis; accurate indication of disease stage and progression; indications of successful treatment; and ability to distinguish between Lyme and other tick-borne infections. NIAID researchers and colleagues also are using a process known as xenodiagnosis, which uses disease-free, laboratory-bred ticks to detect *B. burgdorferi* in people that have completed antibiotic therapy. In addition, NIAID is conducting a clinical trial assessing whether continued *B. burgdorferi* infection could contribute to persistent symptoms in patients following antibiotic treatment. The findings of this study may inform Lyme disease diagnostic criteria and future treatment trials.

NIAID remains committed to participating in partnerships and outreach efforts on Lyme and other tick-borne diseases, including public webinars organized along with Federal colleagues. NIAID will continue to work with NLM to ensure that terminology accurately reflects the current state of scientific knowledge about Lyme disease and its effects. NIAID will continue to foster these collaborations and encourage tick-borne disease research to advance the development of vaccines, therapeutics, and diagnostics.

Lymphangioleiomyomatosis (LAM)

The Committee remains very interested in efforts to find a cure for LAM, a progressive and often fatal lung disease in women. The Committee supports both intramural and extramural research on LAM and urges NHLBI to use all available mechanisms as appropriate, including Translational Program Project Grants, to stimulate a broad range of clinical and basic research. The Committee commends NIH for supporting multicenter LAM trials and encourages additional support of such trials.

Action taken or to be taken:

Lymphangioleiomyomatosis (LAM) is a rare, slowly progressive, disease that affects women almost exclusively and gradually destroys the lungs, often leading to respiratory failure. It is characterized by the proliferation of smooth muscle-like cells and cystic lesions in the lung. While lung transplant is a treatment option for patients with advanced LAM, there is a need for treatments that slow or stop the disease earlier in its course. The National Heart, Lung, and Blood Institute (NHLBI) remains committed to identifying the causes of LAM and improving treatment for patients. NHLBI research is supported through the extramural program as well as through the intramural program on the NIH campus. The programs are collaborating to determine if LAM biomarkers can be used to develop personalized strategies for improved treatment.

NHLBI-funded research has played a critical role in the development of effective drug treatments for LAM. For example, the MILES study showed that the drug Sirolimus stabilized lung function, reduced symptoms, and improved quality of life for women with advanced LAM. Sirolimus became the first FDA-approved treatment for LAM in 2015. NHLBI's Multicenter Interventional LAM Early Disease (MILED) trial is investigating whether Sirolimus can be used earlier and in lower doses to improve lung function in patients with milder forms of LAM.²⁵⁶

In partnership with the National Center for Advancing Translational Sciences through the Rare Lung Diseases Consortium (RLDC), NHLBI co-funds the Multicenter International Durability and Safety of Sirolimus (MIDAS) study to examine long-term treatment outcomes of Sirolimus among LAM patients.²⁵⁷ The study is currently recruiting 300 LAM patients. In addition to conducting clinical research in rare lung diseases, the RLDC provides clinical research training, conducts pilot and demonstration projects, and supports professional and public education about rare lung diseases.²⁵⁸

Preclinical studies have suggested that Sirolimus might have the undesired effect of stimulating autophagy, a cellular process that can help tumor cells survive and proliferate. To address this issue, NHLBI supported a small trial to investigate the use of Sirolimus and the autophagy inhibitor hydroxychloroquine for LAM. Although additional research is needed to explore long-term efficacy of this drug combination, the trial found that it was safe and well-tolerated among 13 LAM patients.²⁵⁹ Following other compelling preclinical findings, a current NHLBI-funded trial is seeking to determine the benefit of adding resveratrol to Sirolimus therapy.

²⁵⁶ <https://clinicaltrials.gov/ct2/show/NCT03150914>

²⁵⁷ <https://clinicaltrials.gov/ct2/show/NCT02432560>

²⁵⁸ <https://www.rarediseasesnetwork.org/cms/rld>

²⁵⁹ <https://www.ncbi.nlm.nih.gov/pubmed/28192114>

NHLBI is also committed to supporting basic research on mechanisms of LAM that may lead to novel and potentially curative therapies. In addition to supporting investigator-initiated basic research on LAM, NHLBI co-funds the National Disease Research Interchange, which provides tissue and specimen collection, storage, and distribution for heart, lung, blood, and sleep research, with a particular emphasis on LAM research.²⁶⁰ This program has distributed more than 720 LAM tissue specimens to the LAM research community in the past five years.

²⁶⁰ https://projectreporter.nih.gov/project_info_description.cfm?aid=9306966

Lymphatic System

The Committee supports building on the momentum of the 2015 NIH Lymphatic Symposium by growing the cadre of lymphatic researchers through the establishment of extramural interdisciplinary research training programs relevant to the lymphatic system in health and disease and by incorporating more reviewer expertise in lymphatic biology/disease in the pertinent standing study sections within the Center for Scientific Review. This research will be instrumental in understanding the pivotal role of the lymphatic system in the pathogenesis and/or treatment of cancer metastasis, AIDS, auto-immune diseases, obesity, cardiovascular disease, and organ transplantation as well as those affected by lymphatic conditions after cancer or those with congenital conditions.

Action taken or to be taken:

The goal of the 2015 NIH Lymphatic symposium was to stimulate research into how the lymphatic system interacts with other organ systems in the body, how lymphatic function affects health and diseases of other organs, and how diseases of other organ systems affect lymphatic function. A survey of research funded by NIH training and loan repayment awards indicates that this goal is being met in some areas such as the pulmonary system, obesity, cancer metastasis, and lymphedema. NIH will continue to encourage training in these and additional areas as set forth by the 2015 symposium.

NIH supports the training of next-generation lymphatic researchers by funding a spectrum of awards for various stages of scientific research careers and by providing loan repayment awards. The training awards funded in lymphatic research include pre- and postdoctoral awards, mentored career development awards, and pathway-to-independence awards that bridge mentored postdoctoral training to independent scientist positions. Over the last ten years, several career development and pathway-to-independence awardees have gone on to receive independent scientist awards including R01 grants and the NIH Director's New Innovator Award. During the same period, the overall success rate of training applications in lymphatic research has been similar to the overall success rates across all fields, indicating that NIH scientific review panels are receptive to applications in lymphatic research.

In FY 2015 and 2016, the NIH Center for Scientific Review (CSR) organized peer review of 367 R01 applications focused on lymphatic research and enlisted 353 reviewers with expertise in the field. Of note, most applications in lymphatic research typically require expertise in other scientific areas. In addition, even for pure lymphatic research applications, CSR's practice is to cross-assign applications so that at least one reviewer (out of three) has arm's length expertise from a related area to ensure a broad perspective and to minimize tendencies to favorably scoring one's own scientific area. CSR is mindful of scientific developments—such as the recent discovery of a lymphatic system in the brain²⁶¹—and will recruit or shift reviewers as needed to leverage new research opportunities.

²⁶¹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3551275>

Malaria

The Committee urges NIH to continue its efforts to understand the biology of the malaria parasite, and to continue its role in developing tools needed for effective and sustainable malaria prevention, treatment, and control, including vaccines.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) supports a comprehensive malaria research portfolio that includes basic, translational, and clinical research to support the goal of controlling and ultimately eradicating malaria worldwide. NIAID research aims to uncover the biology of malaria parasites and their mosquito vectors as well as the mechanisms of antimalarial drug resistance and mosquito insecticide resistance. This knowledge informs the development of new tools to diagnose, treat, and prevent malaria. NIAID also builds local malaria research capacity in endemic regions by supporting a global network of malaria research centers.

NIAID is addressing the spread of drug-resistant malaria in key regions of the world by supporting the development of novel therapeutics. For example, the therapeutic, DSM265, developed with NIAID support, has been shown to cure infection with the malaria parasite *Plasmodium falciparum* in a Phase II clinical trial. NIAID also is supporting preclinical development of DSM421, a similar compound that targets *P. falciparum* as well as another malaria parasite, *P. vivax*. In addition, NIAID is evaluating novel biomarkers that may be used to detect malaria infection or response to treatment, as well as pursuing improved malaria diagnostic tools, including an FDA-approved fluorescence-based test to diagnose *P. falciparum* and *P. vivax* infection.

The development of a safe, effective vaccine to prevent malaria continues to be an NIAID priority. NIAID has supported multiple malaria vaccine candidates in various stages of development, including ten candidates currently in clinical trials. One such candidate, PfSPZ, has shown promising results in several clinical trials. NIAID researchers evaluating PfSPZ have demonstrated that the vaccine protects a significant proportion of adults in malaria-endemic areas in Mali. NIAID scientists also are developing AMA1-RON2L, a novel vaccine candidate designed to block malaria parasites from entering red blood cells and causing the disease. This candidate, which was shown to protect against malaria infection in a monkey model, will be further evaluated for potential testing in humans.

In addition to malaria vaccines, NIAID is investigating multiple strategies to prevent malaria transmission, including novel approaches to control mosquitos by manipulating the mosquito's sense of smell. NIAID scientists also are using advanced genetic analysis to identify proteins in mosquito saliva that could be targeted to develop novel insecticides or vector control tools.

NIAID will continue to support a robust research portfolio on malaria, including vaccine, drug, and diagnostics research, development, and clinical evaluation; collaborative studies between U.S. and foreign scientists working in malaria-endemic areas; and research on innovative malaria vector control measures, drug resistance surveillance, and the treatment of malaria.

Marijuana Research

The Committee is concerned that States are changing public policies related to marijuana without the benefit of scientific research to help guide those decisions. NIDA is encouraged to continue supporting a full range of research on the effects of marijuana and its components, including research focused on policy change and implementation across the country.

Action taken or to be taken:

While marijuana use remains illegal at the federal level, to date, eight states and Washington, D.C. have passed laws permitting recreational marijuana use and 29 states and Washington, D.C. have passed laws allowing marijuana to be used for a variety of medical conditions. As public perceptions and state policies related to marijuana have changed so have patterns of use. Recreational use of marijuana has been evolving, with the average potency of cannabis seized by the DEA rising and the use of high potency extracts increasing. Much of the past research applies to lower potency forms of marijuana and little research has focused on high-potency extracts, edible products, or new modes of administration – such as vaporizers. In addition, while there is a growing body of research suggesting the potential therapeutic value of cannabinoids for certain health conditions like epilepsy, seemingly promising early findings do not always translate to effective treatments²⁴ and in general, adequate and well-controlled trials are lacking.

There is a pressing need for more research on the both the harms associated with marijuana use and its therapeutic potential. The progress of this research has been slow, in part due to the increased time, cost, and administrative efforts associated with the regulatory framework for conducting research on these and other Schedule I compounds. NIH is committed to working with Congress and our federal partners to facilitate more research in this area.

There are also many open questions related to the impact of changing marijuana-related policies on public health outcomes. Regular use of marijuana among adolescents is correlated with changes in the developing brain and negative social and behavioral outcomes²⁶² however it is currently unclear how changes in local, state, and national policies will impact adolescent use and related outcomes. Over the last few years the NIH has issued multiple funding opportunity announcements to explore the impact of changes in state marijuana policies on health outcomes:

- PAS-14-020: Public Health Impact of the Changing Policy/Legal Environment for Marijuana
- PA-13-138: Research on Marijuana Legalization in the US
- RFA-DA-11-008: Medical Marijuana Policy Research: Exploring Trends and Impacts
- PA-15-003: Epidemiology of Drug Abuse
- PA-17-135: Public Policy Effects on Alcohol-, Marijuana-, and Other Substance-Related Behaviors and Outcomes

The National Institute on Drug Abuse (NIDA) has funded 23 grants resulting in over 160 publications so far that have examined how state policy changes have affected:

²⁶² N.D. Volkow, R.D. Baler, W.M. Compton, and S.R. Weiss. Adverse Health Effects of Marijuana Use. *N Engl J Med* 2014; 370:2219-2227.

- Use of marijuana and related health outcomes, including mental illness
- Usage patterns of other drugs, alcohol, and tobacco
- Public-safety outcomes related to drugged driving, crime, etc.
- Potency and cannabinoid content of commonly consumed strains
- Use of newer routes of administration (e.g., vaping, dabbing, edibles)
- Societal norms and perceptions

One of the most important lessons learned so far is that no two states are alike in their marijuana policies and the details of these policies and their implementations make a big difference for the impact on society. Factors such as registration requirements, the breadth of conditions permitted to be treated with medical marijuana, the density of dispensaries, the allowance of home cultivation, price, marketing, etc., are important variables to consider in analyzing the effect of marijuana laws. For example, studies exploring the general impact of medical marijuana laws do not find an increase in recreational use in states that have enacted such laws. However, in states that allow medical marijuana dispensaries, an increase in recreational use has been shown for adults, but not adolescents. Research is ongoing that will provide more detailed analyses to inform public health efforts.

Research is also needed to develop prevention interventions that target marijuana use among youth, to understand the health consequences related to the increasing potency of marijuana, to characterize the consequences of marijuana use on the developing brain, and to develop new treatment strategies for cannabis use disorders. NIDA-supported science aims to address these gaps and to help inform decision making related to state and federal marijuana policies. NIDA's Advisory Council currently has a working group charged with providing recommendations to NIDA and NIH on the priorities for research related to the impact of changing policies related to marijuana. Their report is expected to be completed by early 2018. In addition, and in line with NIDA's mission of reducing the burden of drug use and substance use disorders, ongoing research will continue to explore the claimed therapeutic potential of marijuana-derived compounds for pain and addiction.

Melanoma

Given the significant advances in melanoma research, in biology, molecular profiling, targeted therapies, immunology, vaccines, and other areas, and with added Congressional support to achieve Cancer Moonshot goals in five years, the Committee requests that NCI update the Committee on advances in melanoma research in the fiscal year 2019 Congressional Justification.

Action taken or to be taken:

Decades of strong National Cancer Institute (NCI) support for melanoma research has provided the foundation for significant advances over the past several years. Progress in melanoma research has helped accelerate the approval of six new U.S. Food and Drug Administration (FDA)-approved drugs for melanoma patients between 2011 and 2015, as compared to no new drug approvals during the previous 13 years.²⁶³ Recently, NCI-funded research identified several new mechanisms underlying melanoma development and progression, including mutations that facilitate the transformation of normal melanocytes to melanoma²⁶⁴, factors that contribute to melanoma progression²⁶⁵, and genes that play a role in melanoma risk.²⁶⁶

NCI's investments in understanding the immune system's interaction with cancer has also led to clinical breakthroughs with the FDA approval of immune checkpoint inhibitors beginning in 2011. These agents do not benefit all patients, but patients who do benefit can have durable responses lasting years. NCI is supporting ongoing immunotherapy trials within Center for Cancer Research (CCR) to treat melanoma.²⁶⁷ Nevertheless, most patients relapse after responding or have up-front resistance. Identifying mechanisms of response, resistance, and toxicity is a major priority to enable new drug development and inform therapy choice. Numerous NCI-supported extramural studies are focused on this issue. For example, NCI-funded investigators recently identified mechanisms of up-front²⁶⁸ and acquired resistance²⁶⁹ to anti-PD-1 in melanoma patients.

With these new therapeutic approaches, understanding how to combine and sequence treatments is critical. For patients whose melanomas have BRAF mutations, for instance, both molecularly targeted therapies (BRAF and MEK inhibitors) and immunotherapies are options. NCI is supporting several trials aimed at identifying the most effective combinations of these therapies.

²⁷⁰, ²⁷¹

While many new treatments can extend survival for patients, many patients relapse due to drug resistance. Understanding how tumors circumvent these therapies is a major priority for cancer

²⁶³ The following treatment approaches (single agent and combinations have been FDA approved since 2011: 1) Ipilimumab, 2) pembrolizumab, 3) nivolumab, 4) TVEC, 5) nivo + ipi combination, 6) vemurafenib, 7) dabrafenib, 8) trametinib, 9) dabrafenib + trametinib combo, 10) vemurafenib + cobimetinib combo, 11) peginterferon alfa-2b

²⁶⁴ <https://www.ncbi.nlm.nih.gov/pubmed/28818973>

²⁶⁵ <https://www.ncbi.nlm.nih.gov/pubmed/28927893>

²⁶⁶ <https://www.ncbi.nlm.nih.gov/pubmed/28759004>

²⁶⁷ See: <https://clinicaltrials.gov/ct2/show/NCT01993719>

²⁶⁸ <https://www.ncbi.nlm.nih.gov/pubmed/27903500>

²⁶⁹ <https://www.ncbi.nlm.nih.gov/pubmed/27433843>

²⁷⁰ <https://clinicaltrials.gov/ct2/show/NCT01940809>

²⁷¹ <https://clinicaltrials.gov/ct2/show/NCT02224781>

research. Multiple resistance mechanisms have been described with the support of NCI funding, identifying new areas for intervention.

NCI also supports the Multicenter Selective Lymphadenectomy Trial (MSLT-II), which recently found that for patients with melanoma that has spread from the skin to one or a small number of lymph nodes, a conservative approach to lymph node removal surgery may be best. The trial showed no difference in survival with more extensive lymph node removal, yet patients who underwent the more aggressive surgery also had far more post-surgical complications.

NCI will continue to support a diverse and productive portfolio of research to advance progress for patients with melanoma and their families, and to continue to extend the benefits of the knowledge gained from research on immunotherapy approaches for melanoma to many other cancer types.

Metastatic Brain Tumor Research

Metastatic brain tumors are the most common brain tumor in adults. While the exact incidence of metastatic brain tumors is not known, it is estimated at between 200,000 and 300,000 people per year. The Cancer Moonshot Initiative has helped to raise awareness of this often neglected form of cancer, and the Committee urges NCI to continue working with stakeholder organizations to advance research into improving brain imaging technologies and developing treatments to increase survivorship.

Action taken or to be taken:

As more Americans survive and live longer after primary cancer treatments, the incidence of metastatic brain cancer, also called secondary brain cancer, has been increasing. The National Cancer Institute (NCI) supports a broad portfolio of research aimed at determining the mechanisms of metastasis as well as detecting and treating metastatic brain tumors.

NCI provides support for six Specialized Programs of Research Excellence (SPOREs) specifically focused on brain cancer, as well as other SPOREs with a focus on researching cancers (e.g., lung cancer and melanoma) that preferentially metastasize to the brain. In 2016, scientists at the NCI-supported Lung Cancer and Skin Cancer SPOREs at Yale Cancer Center published an early analysis of a trial measuring the activity and safety of the PD-1 inhibitor pembrolizumab in patients with untreated or progressive brain metastases. Results suggest there may be a role for systematic immunotherapy in these patients.²⁷²

Attempting to answer the question of why certain cancers preferentially metastasize to the brain is also the subject of NCI-supported research. Scientists at Memorial Sloan Kettering Cancer Center made a discovery that sheds light on the role of exosomes— sac-like structures secreted by tumor cells— in metastasis, igniting a new field of research. The number of scientists studying tumor exosomes has swelled from several dozen in 2012 to more than a thousand in 2017.²⁷³ Their research could lead to new ways to treat metastatic brain cancer.

NCI's Provocative Questions Initiative, which supports projects design to solve specific problems and paradoxes in cancer research, included two questions on metastasis: one aimed at developing new approaches to study metastasis (e.g., engineered tissue grafts) and one aimed at identifying properties of non-malignant lesions that predict the likelihood of progression to metastatic disease. NCI has funded seven research projects under this initiative.

Improving brain imaging methods, which often have broad applicability for both primary and secondary brain tumors, is also an area of focus for NCI. NCI-supported researchers are currently harnessing the potential of nanoparticulate materials to penetrate the blood-brain barrier to enable better diagnosis and treatment of brain metastasis using magnetic resonance imaging (MRI).²⁷⁴ As part of the Cancer Moonshot, NCI-supported researchers are also developing and validating a new MRI test for assessing early response to therapy in patients with brain tumors. This could help doctors prolong survival by helping them quickly identify if a

²⁷² <https://www.ncbi.nlm.nih.gov/pubmed/27267608>

²⁷³ <https://www.cancer.gov/about-nci/budget/plan/2019-annual-plan-budget-proposal.pdf> page 20

²⁷⁴ https://projectreporter.nih.gov/project_info_description.cfm?aid=9248262&icde=36651819&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

therapy is working and change the treatment plan if it is not.²⁷⁵ The increasing number of clinical trials using immunotherapy to treat brain metastases has also created a demand for improved brain imaging techniques. NCI is supporting a study incorporating longitudinal MRI into a clinical trial of pembrolizumab, a type of immunotherapy, to characterize tumor response to the treatment.²⁷⁶ Additionally, NCI has championed the standardization of brain imaging protocols across clinical trials by participating in a consensus effort to craft recommendations for a standard protocol. Standardization will allow for a better understanding of tumor response to novel therapeutics, as well as allow a combination of scans from many patients so that advanced machine learning and artificial intelligence methods can be applied.²⁷⁷

In addition to these extramural research efforts, NCI's intramural research program is also enrolling patients into clinical trials on brain metastasis at the NIH Clinical Center. One trial is studying whether combining the brain tumor drug temozolomide with the drug T-DM1 prevents the formation of new metastases in the brain.²⁷⁸ Another trial is studying whether there is a change in patients' neuropsychological functioning after radiation treatment for metastatic brain cancer.²⁷⁹

The 2016 report from the Cancer Moonshot Blue Ribbon Panel set a roadmap for future metastases research when recommending that NCI develop a high-resolution map that documents the genetic lesions, molecular pathways, and cellular interactions that guide tumor progression to metastasis.²⁸⁰ NCI anticipates releasing funding opportunity announcements related to this recommendation in late FY 2018.

²⁷⁵https://projectreporter.nih.gov/project_info_description.cfm?aid=9483217&icde=36652172&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pbll=

²⁷⁶ https://projectreporter.nih.gov/project_info_description.cfm?aid=9220872&icde=36552822

²⁷⁷ https://imaging.cancer.gov/clinical_trials/docs/Consensus%20Recommendations%20for%20Brain%20Tumor%20Imaging%20-%20Ellingson.pdf

²⁷⁸ <https://clinicaltrials.gov/ct2/show/NCT03190967>

²⁷⁹ <https://clinicaltrials.gov/ct2/show/NCT01445483>

²⁸⁰ See: Blue Ribbon Panel Report, page 46-49: <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel/blue-ribbon-panel-report-2016.pdf>

Microbicides

The Committee recognizes that with NIH and United States Agency for International Development (USAID) leadership, research has shown the potential for antiretroviral (ARV) drugs to prevent HIV infection in women. The Committee encourages NIAID to continue coordination with USAID, the State Department, and others to advance ARV-based microbicide development efforts with the goal of enabling regulatory approval of the first safe and effective microbicide for women and supporting an active ARV-based microbicide pipeline to produce additional solutions to prevent HIV and to help end the epidemic.

Action taken or to be taken:

The National Institute of Allergies and Infectious Diseases (NIAID) supports a robust research program to develop effective prevention and treatment approaches to control HIV. NIAID supports microbicide research, from early-stage research to assess drug targets and delivery methods to clinical research to evaluate safety and efficacy as well as factors affecting the use of candidate products. Partnerships with product developers and implementers including USAID and the State Department are critical to advancing progress toward eventual deployment of microbicides to prevent HIV.

NIAID-supported basic and preclinical research is helping to identify candidate drugs and formulations for prevention products, including microbicides. NIAID grantees are investigating the use of nanoparticles responsive to pH and temperature, and using nanoengineering techniques to improve the duration of effect, efficacy, and safety of delivery of HIV prevention products. NIAID researchers also have identified novel signaling molecules, CXCL4 and XCL1, that suppress HIV and show broad-spectrum antiviral activity. This discovery may lead to the development of novel anti-HIV compounds, including microbicides.

NIAID is advancing the clinical development of promising microbicides to reduce the sexual transmission of HIV through its Microbicide Trials Network (MTN). Recent MTN studies have evaluated an intravaginal microbicide ring developed by the International Partnership for Microbicides that contains the experimental antiviral drug dapivirine. Initial NIAID, National Institute on Mental Health (NIMH), and National Institute for Child Health and Human Development (NICHD)-supported studies showed that use of the dapivirine ring reduced the risk of HIV infection by 27 percent among all women, and 61 percent in women 25 and older, who had the highest levels of adherence to use of the ring as directed. Follow-up studies supported by NIAID and NICHD are further assessing safety, acceptability, and adherence to use of the ring in additional populations including adolescent girls and breastfeeding women. The ring also is being evaluated for safety and user adherence in a study of post-menopausal women. NIAID also coordinates with partners such as NIMH and USAID to understand the needs of potential end-users to ensure that microbicide products are designed for optimal use and effectiveness.

NIAID is exploring the development of microbicide products that use combinations of drugs to prevent more than one sexually transmitted infection (STI) or to include contraceptives along with STI prevention. NIAID also is investigating SR-SP, a novel microbicide gel for prevention containing the antiviral drugs acyclovir (used to treat herpes virus) and tenofovir (used to treat hepatitis B virus and HIV). A recent mouse model study showed SR-2P was effective in treating herpes simplex virus 2, and additional animal model studies are planned to further assess the gel.

NIAID is committed to basic, translational, and clinical research focusing on the development of products to prevent HIV that facilitate regular use and are safe, effective, and long-acting. NIAID will continue to support the preclinical discovery of new, innovative, and highly effective microbicide products in collaboration with USAID, State Department, and other longstanding partners.

Mitochondrial Disease Research

The Committee understands that no less than 17 Institutes and offices are involved in a variety of research efforts related to mitochondrial disease and dysfunction. The Committee appreciates the NIH's support of the trans-NIH Mitochondrial Disorders Working Group, the North American Mitochondrial Disease Consortium, the Mitochondrial Disease Sequence Data Resource Consortium, and its support for investigator initiated intramural and extramural studies, and urges the NIH to expand upon its November 2016 research agenda on nutritional interventions in primary mitochondrial disorders. The Committee understands that the NIH has established the Environmental influences on Child Health Outcomes program, which supports longitudinal studies to investigate the effects of environmental exposures- in conjunction with genetic influences-on children's health and development. The Committee encourages the Director to explore whether the longitudinal cohort studies included within ECHO can shed light on any of the mitochondrial diseases occurring in children. The Committee further encourages the Director to competitively fund basic and clinical research on mitochondrial disease.

Action taken or to be taken:

The National Institutes of Health (NIH) continues to actively support research on mitochondrial function and disorders. Led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute on Neurological Disorders and Stroke (NINDS), and the National Institute on General Medical Sciences (NIGMS), the trans-NIH Mitochondrial Disorders Working Group coordinates efforts on mitochondrial disorder research across the NIH, including planning and support for trans-NIH scientific workshops and proposals for new funding opportunities. Along with NINDS, the Office of Dietary Supplements, and the National Center for Advancing Translational Sciences, NICHD supports the North American Mitochondrial Disease Consortium, a member of the NIH Rare Diseases Clinical Research Network. The consortium conducts research on primary mitochondrial diseases and has established a network of 18 clinical centers, a patient registry, a biorepository, and consensus criteria for diagnosis, as well as a clinical fellowship program to train future clinician scientists in mitochondrial disease research. Current consortium studies include three natural history studies, and investigations of nutritional supplementation for mitochondrial diseases.

Multiple NIH institutes support a wide array of research in both their extramural and intramural programs on basic and clinical aspects of mitochondrial function. NICHD supports the activities of the Mitochondrial Disease Sequence Data Resource Consortium (MSeqDR), in which expert panels select genes and genomic variants associated with pediatric mitochondrial diseases and determine their clinical significance and utility for diagnosis and treatment. Research funded by NINDS focuses on normal mitochondrial function in the nervous system, disease mechanisms, and potential interventions for primary mitochondrial diseases. Using state-of-the-art imaging technologies, National Cancer Institute researchers, in collaboration with the National Heart, Lung, and Blood Institute (NHLBI), reported the first clear evidence that muscle cells distribute energy primarily by the rapid conduction of electrical charges through a vast, interconnected network of mitochondria in a way that resembles the wire grid that distributes power throughout a city.²⁸¹ This new information may lead to a better understanding of many diseases linked to

²⁸¹ <https://www.nih.gov/news-events/news-releases/high-resolution-3d-images-reveal-muscle-mitochondrial-power-grid>

energy utilization in the heart and skeletal muscle, such as heart disease, mitochondrial diseases, and muscular dystrophy.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports research to explore the role of brain, liver, skeletal muscle, and fat mitochondria in maintaining glucose and energy homeostasis. NIDDK also funds research on mitochondrial dysfunction that may predispose people to diabetes and obesity, and the impact of drugs that treat these diseases on mitochondrial functions. The National Institute of Nursing Research funds research on the role of mitochondria in symptoms following traumatic brain injury and in metabolic dysfunction in HIV infected individuals. NIGMS supports research on whether nutritional supplements can mitigate mitochondrial dysfunction in animal models of mitochondrial disease. The goals are to validate nutrition as an environmental cause of disease, to provide insight into optimal combinations, and to identify mechanisms that alleviate dysfunction. National Eye Institute (NEI) grantees are studying the role of mitochondria and its mutations in inherited ocular diseases, leading in one case to a clinical trial for the treatment of individuals with Leber hereditary optic neuropathy. NEI also is studying whether vitamin B3 supplementation modulates mitochondrial vulnerability and prevents glaucoma in mice. At the largest dose tested, 93% of the mice did not develop glaucoma. The Environmental influences on Child Health Outcomes (ECHO) program leverages existing cohorts to advance knowledge about the impact of early life exposures on common child health outcomes, including pre-, peri-, and postnatal outcomes, upper and lower airway disorders, neurodevelopment, obesity, and positive child health. These cohorts may be useful for the study of mitochondrial diseases occurring in children. NHLBI's Trans-Omics for Precision Medicine Program is sequencing thousands of patient samples; results obtained from patients with heart, lung and blood diseases will be applied to ECHO and other cohort studies.

Mucopolysaccharide (MPS)

MPS diseases are inherited, with death occurring for many in early childhood. This systemic disease causes progressive damage to the bones, heart, respiratory system, and brain. The Committee continues to urge NIH to put a high priority on better understanding and treating MPS and mucopolipidosis diseases. The Committee commends NIH for allocating funds to discover, develop, define, and make available for research animal models of human genetic disease. The Committee encourages expanded research of treatments for neurological, chronic inflammation, cardiovascular and skeletal manifestations of MPS, with an emphasis on gene therapy. The Committee thanks NINDS, NIDDK, and ORDR for funding the Lysosomal Disease Network through the Rare Disease Clinical Network and for funding lysosomal research meetings. The Committee encourages the NIH

to increase funding to grantees to incentivize MPS research, particularly given the aging and small population of current researchers. Understanding the manifestations and treatments of both the skeletal and neurological disease continues to be the greatest areas of unmet need.

Action taken or to be taken:

NIH supports research on mucopolysaccharidoses (MPS), mucopolipidoses, and other lysosomal storage disorders. These diseases have become a test bed for innovative experimental treatments, and because similar approaches are being pursued for a range of lysosomal storage disorders, advances to overcome challenges in one disease are likely to be relevant to others.

The National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Center for Advancing Translational Sciences (NCATS) jointly support the Lysosomal Disease Network (LDN), a member of the NIH Rare Disease Clinical Research Network program. Because lysosomal storage diseases are rare, no single medical research center sees enough patients to study the full spectrum of disease or adequately test new therapies. The LDN focuses on creating a collaborative network of centers with expertise in one or more of these diseases. Research on MPS within the LDN includes longitudinal studies of brain structure and function and of bone and endocrine disease in children with different MPS types, to understand disease progression and inform strategies for diagnosis, monitoring, and treatment. Network investigators are also conducting an open label clinical trial in MPS I patients to determine if delivering enzyme replacement therapy (ERT) directly to the spinal fluid (intrathecal delivery) will safely treat symptoms of cognitive decline, such as memory loss and language and learning difficulties. Intravenous ERT for MPS I does not address these neurological symptoms because it does not cross the blood-brain barrier, an issue that intrathecal delivery bypasses. In a recent success enabled by NIH support, the FDA approved direct central nervous system delivery of ERT for CLN2 disease, a different lysosomal storage disorder. The LDN study will provide long term safety and efficacy data to support further development of a similar approach for MPS I. Another pilot study within the network will examine the roles of oxidative stress and inflammation in brain abnormalities that continue in MPS I patients after treatment with ERT or hematopoietic cell transplants.

NINDS supports additional research on gene therapy and ERT for MPS, including efforts by academic and small business investigators to optimize gene therapy vectors and to bioengineer novel fusion proteins for improved ERT access to the brain and other organ systems. Other studies focus on alternative treatment approaches, including the first small molecule drugs for MPS and genetic modification of patient-derived blood and neural stem cells to produce missing enzymes and re-injection of those cells back into patients. Finally, NINDS supports research to better understand how neuropathology results from enzyme deficiencies in MPS and other storage disorders, which may point to new therapeutic strategies. NIDDK also funds research on gene therapy for treating MPS. In addition, a test for simultaneous screening of six lysosomal storage diseases (MPS I, Pompe, Fabry, Niemann-Pick A/B, Gaucher, and Krabbe) was recently developed with grant support from NIDDK, and is now available worldwide.

To bring new investigators to lysosomal storage disease research, the LDN includes training opportunities, and NIH-wide and Institute-specific programs for research training and career development are also available. Moreover, NINDS is committed to supporting early stage investigators, consistent with or exceeding NIH-wide policies, which could foster growth in the lysosomal storage disease research workforce. Scientific conferences are another way to stimulate growth and new research directions. LDN leaders organize an annual international research conference that convenes researchers, clinicians, patient organizations, and others to discuss research priorities and promote collaboration. NIH also supports a variety of other scientific meetings and conferences focused on lysosomal storage diseases.

Multidisciplinary Approach to the Study of Chronic Pelvic Pain

The Committee is pleased with the progress of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network and encourages collaborations with stakeholders to ensure proper dissemination of information.

Action taken or to be taken:

The urologic chronic pelvic pain syndrome (UCPPS), interstitial cystitis/ bladder pain syndrome (IC/PBS), and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) affect millions of Americans, yet understanding and treatment of these syndromes have remained elusive. The innovative multi-site Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, now in its second phase and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the NIH Office of Research on Women's Health, is spearheading the evolution in our understanding of UCPPS. MAPP Network studies have yielded new insights into, among other things, brain changes, whole body pain patterns, and symptom flares. The Network has also found relationships between UCPPS and other chronic pain disorders that are also found in IC/PBS and CP/CPPS patients, such as irritable bowel syndrome and fibromyalgia, that may help lead to new clinical categories and personalized treatment approaches to these syndromes.

At the same time, Network leadership and NIDDK have and continue to work through multiple avenues to quickly disseminate findings to participants, patient advocacy groups, and scientific communities. For example, the Network maintains regular outreach to patient advocacy groups such as the Interstitial Cystitis Association and Prostatitis Foundation, including inviting representatives to regularly held Network meetings; provides periodic presentations to leadership of the American Urological Association (AUA) on Network activities; and develops and distributes a newsletter for Network participants on average twice a year. Collaborations with patient advocacy groups in particular have helped highlight Network activities and findings to appropriate patient communities and helped achieve target recruitment goals for Network studies. The Network is also publishing study findings at a robust pace, with approximately 100 manuscripts either published, in press, under review, or in development to date, including invited reviews of findings and their clinical implications by such journals. The Network also continues to provide urologic, urogynecologic, pain research, and clinical communities with “early alerts” to emerging findings through plenary and other presentations and abstracts at diverse scientific meetings, such as those of the AUA, the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction, the American Urogynecologic Society, and of various pain societies. Complementing these efforts, NIDDK scientific staff working with the Network have also been working collaboratively in Trans-NIH Committees with oversight of conditions of high relevance to urologic chronic pelvic pain, and have continued close interaction/integration between the Network and other relevant NIDDK-supported clinical studies, such as the Symptoms of Lower Urinary Tract Dysfunction Research Network and the Prevention of Lower Urinary Symptoms in Women Consortium. There have also been robust efforts to incorporate new collaborative investigators and studies into the Network to expand the scope of its integrated, complementary scientific studies—for example, through inviting investigator-initiated ancillary studies—thereby also potentially expanding the reach of Network findings and activities into new scientific communities. Finally, recognizing that there could be additional avenues and opportunities along these lines, developing improved strategies for disseminating Network findings is among the initial goals for a multi-day scientific meeting on urologic

chronic pelvic pain syndromes that is being planned for late 2018 or early 2019 and that will include stakeholders from patient advocacy and scientific communities.

Myotonic Dystrophy

The Committee recognized there are significant gaps in our scientific understanding of the causes of myotonic dystrophy and there are still no FDA approved treatments for this inherited genetic disorder that can cause multiple organ systems to fail or severely disrupt their function that affects approximately 100,000 Americans. The Committee encourages the NIH to fund efforts to recruit young researchers to this field and stimulate more high quality research proposals to advance this critical scientific field. Myotonic dystrophy research holds significant promise for major advances across many neurodegenerative diseases, particularly other triplet repeat expansion diseases.

Action taken or to be taken:

Research on myotonic dystrophy (a type of muscular dystrophy characterized by the inability to relax muscles and progressive muscle weakness) including efforts to understand and treat the multi-systemic nature of the disease, makes up a robust component of the NIH-funded muscular dystrophy portfolio. For example, researchers at the NIH-funded Paul D. Wellstone Muscular Dystrophy Research Center at the University of Rochester are examining cellular and molecular factors that contribute to myotonic dystrophy's effects on multiple organ systems, including the heart and brain. NIH also funds studies to understand the underlying genetic mechanisms of myotonic dystrophy, to identify small molecules capable of reversing the causes of disease in patient-derived muscle cells and in animal models, and a multi-project grant to understand neurological features of the disease, such as changes in brain development and cognitive deficits.

The National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) currently fund awards to support the career development of clinician-scientists working in myotonic dystrophy. One NINDS awardee is working to understand how triplet repeat expansions cause some forms of muscular dystrophy, including myotonic dystrophy, and to correlate biomarkers and clinical endpoints with these underlying mechanisms. An NIAMS grantee is studying approaches to correct the mutant gene defect in myotonic dystrophy using induced pluripotent stem cells. In addition, one goal of the Wellstone Centers is to provide an outstanding training environment for new scientists pursuing research careers in muscular dystrophy. The Centers each include a training core, which sponsors activities such as seminars, grantsmanship training, and journal clubs to help support trainees and junior investigators, many of whom continue their careers in muscular dystrophy research. The University of Rochester Wellstone Center – which has been continuously funded since the inception of the Wellstone program – is focused on research, education, and training specifically in myotonic dystrophy and facioscapulohumeral muscular dystrophy. NIH continues to encourage applications from trainees and early-stage investigators working in all forms of muscular dystrophy. In addition, recent meetings of the interagency Muscular Dystrophy Coordinating Committee (MDCC) have included discussions about the robustness of the muscular dystrophy workforce and ways that all partners – federal, academic, and private – can encourage and promote the success of new investigators in the muscular dystrophies.

In addition to the NINDS-funded career development award described above, NIH funds research on understanding the role of triplet repeat expansions in other diseases, such as Huntington's disease. For example, one project is studying the molecular structure of triplet

repeat expansions and how a critical threshold length in the number of repeats leads to toxicity. Another study is investigating how triplet repeat expansions result in the production of abnormal proteins and ways to inhibit their production. Studies such as these have broader applicability to understanding the mechanisms of other repeat expansion diseases such as myotonic dystrophy.

National Breastfeeding Research Consortium

The Committee is aware of the substantial amount of research showing that breastfeeding can contribute significantly to health and the prevention of childhood obesity and chronic conditions. The Committee supports the Surgeon General's Call to Action to Support Breastfeeding and its recommendations for the development of a national consortium on breastfeeding research. The Committee urges NICHD to convene the national consortium on breastfeeding research called for by the Surgeon General.

Action taken or to be taken:

In response to the 2011 *Surgeon General's Call to Action to Support Breastfeeding*,²⁸² representatives of several federal agencies, including NIH, convened to form the Federal Breastfeeding Working Group in 2011 to discuss implementing steps outlined in the Call to Action document. Among the goals set forth by the Call to Action was that the government should strengthen and increase capacity for conducting research on breastfeeding.

To address this goal, the Working Group formed a Breastfeeding Research Scientific Interest Group, led by NIH and including the Food and Drug Administration and the Centers for Disease Control and Prevention. Working with the NIH Library, this group reviews newly published scientific literature on breastfeeding, and shares them with scientists inside and outside the government so that researchers working in this area have the most updated information on which to base further studies.

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) also supports a wide range of investigator-initiated research related to breastfeeding and infant and child nutrition. In partnership with the U.S. Department of Agriculture's Center for Nutrition, a systematic review of the scientific literature helped to identify priority research needs that includes a better understanding of human milk composition and further knowledge about infant feeding practices. In addition, NICHD is leading the new Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC). PRGLAC is charged with providing recommendations to the HHS Secretary and Congress on the safety and efficacy of therapeutics used by these populations. Preliminary analysis of the landscape of clinical research performed to date has demonstrated a significant gap in knowledge with regard to the effects of drugs on lactating women and their infants.

The Federal Breastfeeding Working Group has discussed a national consortium on breastfeeding research, which would extend the Working Group's membership and foster collaboration among scientific disciplines and across economic and legal sectors. As envisioned, the consortium could help to identify gaps and priority research areas, and discuss strategies for translation of new research findings into evidence-based care to promote infant and young child nutrition, as well as facilitate standardized usage of specific terms related to breastfeeding. However, waiting until the PRGLAC report has been submitted to the HHS Secretary and Congress (September 2018) prior to determining whether a National Breastfeeding Consortium is warranted would ensure that federal research activities in this area are not duplicated.

²⁸² <http://www.surgeongeneral.gov/library/calls/breastfeeding/calltoactiontosupportbreastfeeding.pdf>

National Center on Sleep Disorders Research [NCSDR]

The Committee commends NHLBI and NSCDR for recent efforts to reinvigorate collaborations on important research in sleep, sleep disorders, and circadian rhythms. NHLBI and NSCDR are encouraged to continue to show leadership in this area and further incorporate sleep into relevant research activities across NIH Institutes and Centers.

Action taken or to be taken:

The National Center on Sleep Disorders Research (NCSDR), located within the National Heart, Lung, and Blood Institute (NHLBI), provides global leadership and support for research to understand how sleep disorders, sleep deficiency, and circadian biology impact health, safety, and society. To accomplish this, NCSDR coordinates research, training, and education efforts across NIH Institutes and Centers, and with other federal agencies.

Some examples of recent NIH collaborative efforts include several initiatives designed to advance the sleep phenotype and biomarker research. NHLBI and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) announced a funding opportunity to look at the “Circadian Mechanisms Contributing to Obesity, Diabetes Metabolism, and Underlying Heart, Lung, and Blood Disorders.”²⁸³ Another funding opportunity led by NIDDK and the Office of Research on Women’s Health will support research to look at the interactions between sleep and diabetes.²⁸⁴

NHLBI is working with other Institutes to support research focused on a better understanding of sleep phenotypes and breathing problems in newborns. A new NHLBI-led initiative in FY 2018 aims to stimulate studies of sleep and circadian phenotypes contributing to HIV-related comorbidities.²⁸⁵ NHLBI also has joined with the National Institute on Minority Health and Health Disparities (NIMHD) and seven other Institutes in a new three-year initiative to better understand the underlying mechanisms contributing to sleep deficiencies among racial and ethnic minorities and other vulnerable populations, and how sleep deficiencies may lead to disparities in health outcomes.²⁸⁶

²⁸³ <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-17-020.html>

²⁸⁴ <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-16-005.html>

²⁸⁵ <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-18-005.html>

²⁸⁶ <https://grants.nih.gov/grants/guide/pa-files/PA-17-234.html>

National Children's Study (NSC) Follow-On

The Committee continues to recognize the importance of investigating the effects of environmental exposures on child health and development. The National Children's Study (NCS)/Environmental Influences on Child Health Outcomes (ECHO) Project has the potential to increase greatly understanding of this critical determinate of health across the lifespan. The Committee is pleased that NIH has established an External Scientific Board for NCS/ECHO that reports directly to the NIH Director, and encourages greater communication about to the program's progress toward goals, milestones, and projected funding estimates with both external stakeholders and Congress. The Committee directs NIH to provide an update in the fiscal year 2019 Congressional Justification including a summary of progress made to date, an analysis of the composition of the funded cohort studies, and the short and long-term goals of the study.

Action taken or to be taken:

Launched in FY 2016, the NIH Environmental Influences on Child Health Outcomes (ECHO) program supports multiple synergistic, longitudinal studies by leveraging, harmonizing, and combining existing and new data from 83 maternal/pediatric cohorts to create one ECHO-wide cohort with 50,000 participants. Integrating standardized data from these cohorts of mothers and children, researchers will investigate the effects of a broad range of early life environmental exposures (e.g., physical/chemical, societal, psychosocial, behavioral, biological) on four key pediatric outcomes with high public health impact: pre-, peri-, and postnatal outcomes; upper and lower airway conditions; obesity; and neurodevelopment. Another innovative fifth outcome, positive health, examines child well-being and healthy development. Characterized by racial, ethnic, socioeconomic, and geographic diversity, the ECHO-wide cohort offers the opportunity to address solution-oriented research questions that no single cohort, or even several cohorts, could answer alone.

After one year, ECHO has: created a harmonized ECHO-wide cohort data collection protocol; developed ECHO-wide Cohort organizational functions and policies regarding consortium publications and data sharing; begun collective analyses that address determinants of preterm birth and childhood obesity; and published data from individual cohorts on maternal diet during pregnancy and epigenetics, sophisticated study designs to address both genes and environment, and aspects of development of the placenta.

An equally important component of ECHO is the IDeA States Pediatric Clinical Trials Network (ISPCTN), whose goal is to provide rural and medically underserved children access to state-of-the-art clinical trials. The network also builds institutional capacity, provides professional development to researchers, and leverages partnerships with outside academic institutions. After one year, the Network is participating in several trials:

- 1.) The ISPCTN is participating in the Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care (POPS) study. The POPS study allows ECHO to leverage partnerships between ISPCTN community-based investigators and a well-established NIH-trials network to fill gaps in information about pediatric drug dosing, safety, and efficacy.
- 2.) Developing its own in-Network trials. The ISPCTN is developing protocols for two trials in the areas of childhood obesity and asthma.

3.) Working with other NIH institutes to develop new solutions to important public health issues. The ISPCTN is focusing efforts on the youngest victims of the opioid epidemic by partnering with the Eunice Shriver Kennedy National Institute on Child Health and Human Development (NICHD) to conduct the Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome study (ACT NOW). After surveying sites to assess capacity and current approaches to treatment, ISPCTN and NICHD will then develop a joint protocol for a clinical trial to lessen the burden of NOWS. Moreover, the ECHO Cohorts are collecting and analyzing existing data to understand more about how both mothers and infants are affected, to refine measures of opioid exposure, and to address the extent to which both prenatal exposure to opioids and NOWS affect longer-term brain development and other child health outcomes.

National Commission on Digestive Disease Research

The Committee continues to value and support the implementation of the 2009 National Commission on Digestive Disease Research report entitled "Opportunities & Challenges in Digestive Diseases." The Committee requests an update on the implementation of the recommendations of the National Commission.

Action taken or to be taken:

The National Commission on Digestive Disease Research's 2009 digestive diseases research plan represented a large, trans-NIH effort that identified research goals to be pursued by the NIH and the digestive diseases research community over the next decade. The plan is being actively implemented by a number of NIH Institutes, Centers, and Offices (ICOs), as well as other federal and non-federal partners involved in digestive diseases research. NIH-wide funding for digestive disease research was \$1.745 billion in FY 2016, the most recent fiscal year with final data available.²⁸⁷

Within the NIH, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has contributed to implementing recommendations in the Commission's research plan. Recent implementation activities include the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer, established in 2015. This collaboration with the National Cancer Institute (NCI) conducts studies of people with chronic pancreatitis to improve understanding of disease processes and related outcomes, such as diabetes and pancreatic cancer. The NIDDK plans to expand support for the Consortium in FY 2018 and FY 2019, and the NCI also plans to add significant funding for a study of new-onset diabetes, which will identify predictors for early diagnosis of pancreatic cancer in people with diabetes. Another example of the research plan implementation is the NIDDK's continuing support for the Inflammatory Bowel Disease (IBD) Genetics Consortium and its ongoing search for genetic factors that contribute to increased susceptibility for developing IBD. In collaboration with the International IBD Genetics Consortium, of which it is a member, the IBD Genetics Consortium has enrolled thousands of participants and identified about 200 regions of the human genome associated with IBD risk. The NIDDK-supported Hepatitis B Research Network has initiated multiple clinical trials and ancillary studies in both adults and children with hepatitis B virus (HBV) to advance understanding of disease processes and progression over time, as well as to identify effective approaches to treatment with available and emerging therapies. The Network is currently completing a 5-year study of long-term outcomes of hepatitis B therapy to investigate whether it is possible to clear HBV infection and stop antiviral therapy as part of efforts toward developing a cure. The Drug-Induced Liver Injury Network, supported by NIDDK since 2003 and recently expanded in 2017, collects and analyzes data from people with severe liver injury caused by over-the-counter and prescription drugs, or by herbal products and dietary supplements, to aid in improving understanding of this liver injury and its diagnosis. The NIDDK's Nonalcoholic Steatohepatitis (NASH) Clinical Research Network has conducted studies into therapies for adults and children with NASH, including a clinical trial with a synthetic bile acid that showed promise for reducing severe disease and also spurred industry interest in developing new NASH treatments.

²⁸⁷ https://report.nih.gov/categorical_spending.aspx

The NIDDK also participates in NIH Common Fund programs that advance cross-cutting digestive diseases research across the agency. For example, the Human Microbiome Project, now in its next phase as the Integrative Human Microbiome Project, includes IBD as one of three, disease-specific cohort studies using multiple ‘omics technologies to study microbiome-associated conditions. Another Common Fund program, called Stimulating Peripheral Activity to Relieve Conditions, has projects that include mapping the GI nervous system and developing intestinal organoids with functional nervous systems for the study of gut motility disorders.

National Laboratories

NIH is encouraged to enter into collaborative research programs with the Secretary of Energy, National Laboratories, and others determined to be appropriate by the Director, to utilize the broader scientific and technological capabilities of the Department of Energy [DOE] and National Laboratories. In particular, DOE and NIH should work together to support access for biomedical researchers to cutting-edge technology resources.

Action taken or to be taken:

The National Institutes of Health (NIH) and Department of Energy (DOE) have a history of collaboration and continue to work together in several significant ways, including utilizing DOE's National Laboratories, to further the research missions of both agencies. When expertise at both agencies is brought together scientific discovery can be obtained more efficiently and for the greater benefit of biomedical breakthroughs.

NIH supports grantees at DOE's National Labs to conduct research on data science, materials science, modeling and simulation, and biomedical imaging, among others. Many individual research projects are supported by NIH to grantees at National Labs and to grantees utilizing National Labs for research, or serving in collaborative roles. This includes support from the National Institute of General Medical Sciences at a number of Biomedical Technology Research Centers (BTRC) and mature synchrotron resource facilities at multiple DOE National Labs. Through one BTRC, for example, NIH supported the development of an advanced x-ray laser synchrotron facility for biomedical research at the DOE National Accelerator Laboratory. This experimental facility has the capability to reveal the intimate details of atoms and chemical reactions in protein structures.²⁸⁸

In addition, the National Cancer Institute and DOE are working together on the Joint Design of Advanced Computing Solutions for Cancer (JDACS4C).²⁸⁹ This interagency collaboration aligns with the Precision Medicine Initiative, the Cancer Moonshot, and the National Strategic Computing Initiative. It aims to advance cancer research through the application of exascale computing capabilities. The collaboration involves four National Laboratories and multiple NCI components. In FY 2017 the JDACS4C collaboration has initiated three pilots: Cellular Level Pilot for Predictive Modeling for Pre-Clinical Screening, Molecular Level Pilot for RAS Structure and Dynamics in Cellular Membranes, and Population Level Pilot for Population Information Integration, Analysis and Modeling. These pilots will develop machine learning, large-scale data and predictive models based on experimental biological data and a scalable framework for efficient abstraction, curation, integration, and structuring of medical record information. A workshop was held in April 2017 where researchers identified specific new capabilities that would enable scientific insight including new advanced machine learning to account for data uncertainty, cutting edge tools for predictive models for cancer and scalable platforms to enhance open science in precision oncology. Future activities include evaluating the pilots on currently available high-performance computers at Argonne, Oak Ridge, and Lawrence Livermore National Laboratories.

²⁸⁸ <https://publications.nigms.nih.gov/btrrs/searchresults.asp>

²⁸⁹ <https://cbiit.cancer.gov/ncip/hpc/jdacs4c>

Also, the NIH and DOE Nuclear Medicine Working Group continues to work together to estimate and prioritize the radioisotopes needed for biomedical research on an annual basis. This valuable service guarantees the NIH Clinical Center and grantees with access to rare radiochemical research opportunities in clinical settings. Coordination is a critical component of this partnership as these clinical trials often use isotopes with very short half-lives.

This type of cooperation between NIH and DOE has led to increased understanding of the fundamental make-up of molecules, cells, and tissues and the mechanisms of how they work, with implications for a range of diseases such as cancer, heart disease, and diabetes, among others. DOE National Labs also provide NIH grantees with access to their unique infrastructure, such as high-performance computing, microfabrication, and high-throughput electron microscopy facilities.

National Testing Program for Schedule I Marijuana-Derived Products in U.S. Distribution

The Committee appreciates NIDA's work in marijuana research, but is concerned that NIDA ceased funding for analysis of marijuana samples seized by law enforcement in 2014. Without dedicated funding for this activity, the number of analyzed seized samples has plummeted, meaning that available data is no longer current or robust. The Committee believes that such research, along with analysis of marijuana and marijuana-derived products sold commercially in dispensaries or online, is essential for informing substance abuse prevention efforts, public health policy, and law enforcement tactics across the Federal Government. Therefore, the Committee directs NIDA to work with law enforcement, including the Drug Enforcement Agency, to facilitate and ultimately fund a National Testing Program for Schedule I Marijuana-Derived Products in U.S. distribution to conduct such analysis of both samples seized by law enforcement and of samples collected from non-DEA approved sources to provide robust reliable data that can inform policy.

Action taken or to be taken:

Understanding the characteristics of marijuana (i.e., amount of THC, CBD, and other components) that is used across the country, including the products available in state dispensaries, is important for understanding the impact of medical and recreational marijuana use on individual and public health. According to the April 2017 Quarterly Report, there were a total of 4,304 samples waiting to be analyzed and we continue to receive and accept DEA-seized samples into the program. While the National Institute on Drug Abuse (NIDA) has a contract with the University of Mississippi that includes an option for these analyses, NIDA does not currently exercise that option. This is in part due to limited resources and in part because we consider them to be of limited value for determining trends in the potency of the marijuana currently being used across the country because these samples do not contain products obtained from state dispensaries. Neither NIDA nor the University of Mississippi can legally obtain samples from state dispensaries, since obtaining these samples would violate federal law.

The existing samples are being stored and could be retroactively analyzed if resources become available; however, we would recommend that additional sources of marijuana be added to improve the validity of the program.

Neglected Tropical Diseases

One-sixth of the world's population suffers from one or more neglected tropical diseases (NTDs). In the U.S., we have seen Chikungunya, Dengue, and Chagas disease emerge. Research conducted by NIH is a key component to ensuring there are tools to treat, control, and eventually eradicate many neglected diseases. The Committee urges NIH to continue its investment in malaria and NTD research, including work in late-stage and translational research for NTDs, and to work with other agencies to foster research and ensure that basic discoveries are translated into solutions.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) supports a longstanding research program devoted to better understanding, preventing, and treating neglected tropical diseases (NTDs). This program includes basic research to better understand these diseases, as well as translational and clinical research to advance novel NTD diagnostics, therapeutics, and vaccines. NIAID engages in key partnerships with academia, industry, and other Federal agencies to address the global public health threat of NTDs. NIAID also supports a robust malaria research portfolio as described in detail elsewhere in this volume.

NIAID provides data, tools, and services to the NTD research community to advance promising discoveries toward the development of countermeasures to combat NTDs. NIAID also invests in establishing and strengthening sustainable local research capacity in NTD-endemic countries by providing scientists with access to critical research resources and training new investigators in the field. NIAID has long supported the Tropical Medicine Research Centers (TMRC), which conduct a variety of in-country clinical and field-oriented research on NTDs. TMRC research includes efforts to characterize immune responses in *Leishmania* infections, assess deworming programs, and investigate issues related to NTD co-infections.

NIAID also supports the development of novel NTD diagnostics, especially point-of-care tests that could be utilized in resource-poor settings. For example, NIAID scientists and academic collaborators developed CellScope Loa, a video microscope attachment for smartphones that can be used to identify individuals infected with the parasitic worm *Loa*. NIAID is currently supporting the development of diagnostic tests for filariasis, leishmaniasis, and Chagas disease.

Furthermore, NIAID is advancing the development of several NTD vaccine candidates that are the culmination of longstanding basic and preclinical research efforts and partnerships. These candidates include an investigational chikungunya vaccine candidate developed by NIAID scientists that is currently in a Phase II clinical trial. This vaccine candidate uses non-infectious virus-like particles to simulate an infection, thereby stimulating a protective immune response. NIAID, through its Vaccine and Treatment Evaluation Units, also is partnering with industry to support a Phase I/II clinical trial of another experimental chikungunya vaccine. In addition, NIAID researchers have developed an investigational vaccine designed to protect against all four commonly circulating strains of dengue that is currently in a Phase III clinical trial. A version of this vaccine that also protects against Zika virus will enter clinical testing in early 2018. NIAID also recognizes the need to address the vectors that transmit NTDs and supports the development of novel vector control methods.

NIAID remains committed to the development of diagnostics, therapeutics, vaccines, and vector control strategies to aid in the eradication of NTDs. NIAID will continue critical scientific

partnerships and sustain support for a robust research portfolio that includes late-stage and translational research to address NTDs worldwide.

Neonatal Abstinence Syndrome

The Committee recognizes the importance of research on prevention, identification, and treatment of prenatal opioid exposure and Neonatal Abstinence Syndrome. The Committee encourages NIDA to ensure that the review process includes appropriate focus on geographic locations where the problem is particularly acute. The Committee encourages NIH, based on appropriate scientific review, to support meritorious research opportunities in Appalachia and at institutions that have unique opportunities to study innovative care models.

Action taken or to be taken:

The emergent public health opioid epidemic is affecting individuals across the country, including infants who were exposed prenatally to opioids. To address the gaps in knowledge for prenatal opioid exposure and neonatal abstinence syndrome (NAS) (which scientists also refer to as neonatal opioid withdrawal syndrome, or NOWS), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) held a scientific workshop in 2016, *Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes*. The workshop identified a range of research needs, including better methods to screen for NAS, research on non-drug treatments, and studies on long-term outcomes of infants who were exposed to opioids *in utero*. NICHD also supported two recent investigator-initiated grants focused on NAS. One, on the prevention of NAS, is a multi-center, randomized clinical trial to determine whether treatment with an anti-emetic drug will reduce the incidence or severity of NAS. It found that administering it to pregnant opioid-using women just prior to delivery, followed by a 3-day period of giving to the newborn, could reduce the incidence or severity of NAS symptoms. Another study is determining whether more accurate prescribing of buprenorphine is possible based on how pregnant women metabolize the drug.

In addition to supporting investigator-initiated grants, NICHD has two new research efforts specifically aimed at addressing NAS. A new funding opportunity on opioid use disorder in pregnancy, with the National Institute on Drug Abuse (NIDA), will support clinical studies of medically supervised withdrawal, research on how pregnant and postpartum women metabolize medications used to treat opioid use disorder, and studies on how genetic factors may interact with the effects of opioid use during pregnancy. Other recently funded studies include evaluating antenatal prescribing patterns for risk of developing NAS, determining whether epigenetic and neurobehavioral factors correlate with the onset and severity of NAS, evaluation of preventive interventions or therapies on reducing the incidence and/or severity of NAS, and reexamining existing substance use screening tools in pregnant women. NIDA also is partnering with the Appalachian Regional Commission on a toolbox for use by local health departments in rural areas to implement service delivery plans that address the opioid epidemic.

Announced in 2017, a new study called the Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW) will evaluate treatment options and improve clinical care of infants with NAS/NOWS. The study is a collaboration between NICHD's Neonatal Research Network (which has 30 years of experience in conducting clinical trials with newborns) and the new IDeA States Pediatric Clinical Trials Network (within the NIH Office of the Director's Environmental Influences on Child Health Outcomes (ECHO) Program), with sites located in rural and medically underserved communities. This joint research effort will use the reach of both networks to assess the prevalence of NAS, understand current approaches to managing

NOWS cases (including non-pharmacological approaches), and develop common protocols for conducting large scale comparative effectiveness studies across the country to inform clinical care for affected infants.

Neuroblastoma

Committee encourages NCI to expand its support for research on high-risk neuroblastoma, including the detection and treatment of central nervous system metastases. The Committee requests an update on these activities in the fiscal year 2019 CJ.

Action taken or to be taken:

Neuroblastoma, the second most common solid tumor in childhood (after brain and central nervous system tumors), is a disease in which cancer cells form in certain types of nerve tissue. Neuroblastoma (NBL) most often occurs in children younger than 5 years of age. Sometimes it forms before birth and is found during a routine pregnancy ultrasound. Neuroblastoma is usually found when the tumor begins to grow and cause signs or symptoms. By the time it is diagnosed, the cancer has usually metastasized. More than 650 cases are diagnosed each year in North America^{290,291}.

The National Cancer Institute (NCI) has long invested in basic research to better understand the abnormal cell signaling pathways that lead to NBL. NCI's Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative, which uses comprehensive molecular characterization to determine the genetic changes that drive the initiation and progression of hard-to-treat childhood cancers, houses a NBL project that has produced comprehensive genomic profiles of more than 200 high-risk patients. The TARGET data is made available to the greater research community for further investigation, with a goal of accelerating molecular discoveries and facilitating rapid translation of those findings into the clinic.

Advances in scientific understanding of the anaplastic lymphoma kinase (ALK) cellular signaling pathway, important in embryonic nervous system development, facilitated the development of crizotinib, an agent that is currently being tested in Children's Oncology Group (COG)-supported clinical trials to treat NBL. In addition, NCI's Small Business Innovation Research program, a major source of early stage technology financing for small businesses engaged in research and development that has the potential for public benefit, is supporting a company, HaRo Pharmaceuticals, that is developing a promising agent that affects cellular pathways which have been shown to be important for the treatment of NBL.²⁹²

Furthermore, decades of investment in immunology research have also led to many recent advances in immunotherapy, a promising new field of cancer treatment. NCI was instrumental in developing, from basic immunology research through a phase III clinical trial, Unituxin® (also known as dinutuximab), which was approved in early 2015 for use in the first-line treatment of children with high-risk NBL. More recently, NCI-supported scientists at the Children's Hospital of Philadelphia, together with NCI Center for Cancer Research (CCR) investigators, who identified and validated a protein that appears to be a strong candidate for

²⁹⁰ Howlader N, Noone AM, Krapcho M, et al., eds.: SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations). Bethesda, Md: National Cancer Institute, 2012. Also available online.

²⁹¹ Gurney JG, Ross JA, Wall DA, et al.: Infant cancer in the U.S.: histology-specific incidence and trends, 1973 to 1992. *J Pediatr Hematol Oncol* 19 (5): 428-32, 1997 Sep-Oct. [PUBMED Abstract]

²⁹² <https://sbirsource.com/sbir/awards/150654-optimization-of-bifunctional-pharmacophores-for-the-treatment-of-neuroblastoma>

immunotherapeutic targeting in high-risk NBL.²⁹³ Their findings could pave the way for the development of less toxic, more effective immunotherapy drugs for NBL.

Additionally, in 2016, an NCI-supported clinical trial demonstrated encouraging improvements in survivorship using dual stem cell transplants to treat high-risk neuroblastoma. The results were practice-changing, and dual transplants have now become the standard of care for high-risk NBL.²⁹⁴ NCI continues to support intramural and extramural clinical trials of therapies that hold similar promise for improving NBL treatment. These include the trials in the newly launched nationwide NCI-COG Pediatric MATCH²⁹⁵ precision medicine trial, as well as a trial of lorvotuzumab mertansine, a therapy combining an antibody (a protein used by the body's immune system to fight foreign or diseased cells) with an anti-cancer drug.

Recognizing that cancer treatments can have long-term negative side effects, NCI is also engaged in researching NBL survivorship. The Childhood Cancer Survivor Study, which originally launched in 1994 with funding from NCI and other organizations, continues to collect and analyze data on childhood cancer survivors to identify late effects of cancer treatments and develop strategies for preventing or better managing these effects.

²⁹³ “Identification of GPC2 as an Oncoprotein and Candidate Immunotherapeutic Target in High-Risk Neuroblastoma,” Bosse, Kristopher R. et al. *Cancer Cell*, Volume 32 , Issue 3 , 295 - 309.e12

²⁹⁴ <https://www.cancer.gov/about-nci/budget/plan/treating/children/tandem-transplants-treat-neuroblastoma>

²⁹⁵ <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match>

Neurofibromatosis (NF)

The Committee supports efforts to increase funding and resources for NF research and treatment at multiple Institutes, including NCI, NINDS, NIDCD, NHLBI, NICHD, NIMH, NCATS, and NEI. Children and adults with NF are at significant risk for the development of many forms of cancer; the Committee encourages NCI to increase its NF research portfolio in fundamental basic science, translational research, and clinical trials focused on NF. The Committee also encourages NCI to support NF centers, clinical trials consortia, preclinical mouse models consortia, and associated tumor sequencing efforts. Because NF causes brain and nerve tumors and is associated with cognitive and behavioral problems, the Committee urges NINDS to continue to aggressively fund fundamental basic science research on NF relevant to nerve damage and repair. Based on emerging findings from numerous researchers worldwide demonstrating that children with NF are at significant risk for autism, learning disabilities, motor delays, and attention deficits, the Committee encourages NINDS, NIMH, and NICHD to expand their investments in laboratory-based and clinical investigations in these areas. Since NF2 accounts for approximately 5 percent of genetic forms of deafness, the Committee encourages NIDCD to expand its investment in NF2 basic and clinical research. NF1 can cause vision loss due to optic gliomas. The Committee encourages NEI to expand its investment in NF1 basic and clinical research.

Action taken or to be taken:

The NIH supports a wide range of research focused on neurofibromatoses (NF), a group of genetically distinct disorders that cause tumors to grow in the nervous system, affecting an estimated 100,000 Americans.

The National Cancer Institute's (NCI's) Translational Research Program supports a Developmental and HyperActive Ras Tumor (DHART) Specialized Program of Research Excellence (SPORE) that focuses on cancers caused by NF1 mutations which lead to the aberrant behavior of Ras proteins or proteins that are activated by Ras. This work, conducted across nine research institutions including the NCI Pediatric Oncology Branch (POB), seeks to implement effective new targeted therapies for NF1 tumors.²⁹⁶ In addition to these genetic studies, NCI's POB conducts a large clinical trial program for children and adults with NF1. In December 2016, results of a multicenter Phase I clinical trial led by investigators in the POB were published, showing that selumetinib, a new oral drug, shrunk tumors in children with NF1 and plexiform neurofibromas.²⁹⁷ Given the lack of therapies considered effective for NF1-related large plexiform neurofibromas, the tumor shrinkage observed in this trial is especially encouraging. As a result of these findings, NCI investigators in collaboration with the drug company manufacturing selumetinib and with guidance from the FDA, developed a phase II registration study of selumetinib for children with inoperable plexiform neurofibromas. This study has completed enrollment and data are being prepared for submission to the FDA.

NCI also supports several other clinical trials underway for NF and related conditions.²⁹⁸ With increasing numbers of clinical trials conducted in NF, there is a need for meaningful and

²⁹⁶ https://trp.cancer.gov/spores/abstracts/indiana_hyperactive.htm

²⁹⁷ <https://www.ncbi.nlm.nih.gov/pubmed/28029918>

²⁹⁸ <https://clinicaltrials.gov/ct2/show/NCT02407405>, <https://clinicaltrials.gov/ct2/show/NCT03109301>, <https://clinicaltrials.gov/ct2/show/NCT01362803>, <https://clinicaltrials.gov/ct2/show/NCT01362803>

standardized clinical trial designs and endpoints across trials. The NCI co-chairs the international collaboration Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) to help build consensus about the design of future clinical trials. REiNS working groups focus on imaging of tumor response; functional, visual, patient-reported, and neurocognitive outcomes; whole-body MRI; disease biomarkers; and cutaneous neurofibromas. NCI leads the imaging and patient reported outcomes REiNS working groups and conducts central response evaluation on most national trials directed at NF1 plexiform neurofibromas.²⁹⁹

Malignant peripheral nerve sheath tumors (MPNST) are aggressive sarcomas, which develop in up to 15% of people with NF1. These tumors require aggressive surgery for cure and have a very poor prognosis if complete surgery is not feasible. Investigators at the NCI and several other institutions identified that tumors called atypical neurofibromas are precursor lesions to MPNST. NCI and the Children's Tumor Foundation recently convened a conference directed at translating advances in the basic understanding of MPNST to improvement in clinical outcomes. Through this effort, a group of international researchers developed research and clinical priorities for MPNST research.^{300,301,302}

The National Institute of Neurological Disorders and Stroke (NINDS) supports basic research focused on characterizing the roles of NF1 and NF2 in relevant signaling pathways. For example, a variety of NINDS-funded projects are examining several cell signaling pathways as potential mechanisms by which NF1 loss promotes tumor formation and impacts brain cell function. NINDS also supports studies focused on characterizing the role of NF2 in cell proliferation and neural circuit formation, and intramural researchers at NINDS are conducting a natural history study of patients with NF2 mutations to identify factors that influence tumor formation. Other NINDS-funded projects are introducing patient-derived NF1 and NF2 mutations into animal models to study the effects of individual mutations on signaling pathways, the effectiveness of anti-tumor drugs, and clinical outcomes strongly associated with NF such as cognitive and behavioral impairments.

In addition, NINDS, along with the National Center to Advance Translational Sciences (NCATS) provided funding for the Children's Tumor Foundation's NF meeting in 2017, which brought together hundreds of researchers and clinicians to collectively advance the NF field. The conference is designed to provide information about best clinical practices for these rare genetic tumor syndromes, opportunities to share major advances in research, and to aid in the development of new collaborations. NCATS also funded with NINDS, NCI, The *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development (NICHD), and the National Institute of Arthritis and Musculoskeletal and Skin Diseases an international symposium on RASopathies of which NF1 was the first identified RASopathy. This symposium brought together affected families, clinicians, industry representatives, and other stakeholders to discuss the manifestations of RAS-signaling imbalance, the impact of the syndromes on quality of life, and potential therapeutic interventions.

²⁹⁹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3908340/>

³⁰⁰ <https://www.hindawi.com/journals/sarcoma/2017/7429697/>

³⁰¹ <https://www.ncbi.nlm.nih.gov/pubmed/28551330>

³⁰² <https://academic.oup.com/jnci/article/109/8/djx124/4004723/Neurofibromatosis-Type-1-Associated-MPNST-State-of>

Scientists supported by the National Institute on Deafness and Other Communications Disorders (NIDCD) hope to prevent and treat hearing loss caused by inner ear tumors that develop in individuals who inherit gene mutations that cause NF2. They determined that hearing loss severity is correlated with a protein called TNF-alpha, secreted by the inner ear tumors. In animal models of NF2, they are currently testing a molecule to block TNF-alpha in the hope of preventing the correlated hearing loss. Next, they plan to translate this research to human clinical trials to prevent hearing loss in individuals who have NF2.

The National Eye Institute (NEI) has supported NF basic research, such as developing genetically engineered NF1 and NF2 disease models in fish and rodents and testing their visual performance. Mouse models with NF1 deletions help researchers dissect molecular mechanisms of cell signaling, tumor formation, and metabolic diseases in optic nerve dysfunction and regeneration. To expand clinical NF research capabilities, NEI is presenting in NEI's Ophthalmic Genetics Fellowship, which trains early stage clinicians to pursue research careers. An NEI funded NF1 surveillance study reviewed biomarkers, risk and treatment decisions in children with NF1, of which nearly 20 percent develop optic pathway tumors.³⁰³ NEI and NCI scientists collaborate at the NIH Clinical Center in drug trials to prevent or slow growth of neurofibromas in patients with inherited mutations of NF1.

NICHHD continues to support research pertaining to Neurofibromatosis Type 1 (NF1). Those who have the NF1 mutation are four times more likely to experience learning disabilities compared to the 15% of the general population who have such disabilities. An on-going NICHHD-funded clinical study is examining the synergistic effects of a pharmaceutical intervention plus tutoring in reading to counteract the effects of the defective protein, and thereby reduce learning disabilities in NF1 individuals. This work also may have broader applicability for understanding better human learning mechanisms in developmental disorders.

³⁰³ De Blank *et al.* J of Neuro-Ophthalmology 37:S23-S32 (2017)

Neurogenic Bladder and Kidney Disease

The Committee encourages NIA, NIDDK, NICHD, and NINDS to study the causes and care of the neurogenic bladder and kidney disease in order to improve the quality of life of children and adults with Spina Bifida; to support research to address issues related to the treatment and management of Spina Bifida and associated secondary conditions, such as hydrocephalus; and to invest in understanding the myriad co-morbid conditions experienced by individuals with Spina Bifida, including those associated with both paralysis and developmental delay.

Action taken or to be taken:

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) continues to actively support research on Spina Bifida (SB). Research has contributed to the decline in prevalence rate of SB by 31% from 1995 to 2006; this translates into 1,000 fewer babies born with a neural tube defect each year. The NICHD supports scientific research on the genetic, neurological and environmental variables that influence neurobehavioral outcomes for children with SB, the assessment of SB's effects on physical and cognitive development in early childhood, and the development of new diagnostic and ultrasound techniques. Research conducted by NICHD intramural scientists focuses on how nutritional and other interventions might prevent neural tube defects such as SB. NICHD's original Management of Myelomeningocele ("MOMS") study showed that infants who had been diagnosed *in utero* with SB had better health and functional outcomes with prenatal surgery compared to the standard postnatal surgery. MOMS 2, co-funded by the NICHD and the National Institute of Neurological Disorders and Stroke (NINDS), followed the children who had participated in the original MOMS study to school age to assess health outcomes, as well as their capacity to live more independently and function more safely in daily life. This follow-up study is determining the effects of prenatal repair on adaptive behavior, cognitive and motor function, brain morphology and microstructure, urologic health, and other health aspects at school age. Initial results suggest that fetal surgery also improves long-term functional outcomes and ambulatory status, with the majority of children being able to successfully complete daily tasks.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports basic and clinical research efforts to address the causes and care of bladder and kidney complications of SB. The GenitoUrinary Development Molecular Anatomy Project (GUDMAP) Consortium is expanding our knowledge about the developing kidney and lower urinary tract, which could lead to new research models of congenital conditions, and ultimately, organ repair and regeneration. Newly funded basic research studies are examining the role of brain pathways in control of urine retention and release from the bladder, while ongoing research in an animal model is examining how targeted spinal stimulation modulates a specific component of voiding activity in a condition known as neurogenic bladder. Research recommendations identified from the 2015 NIDDK-hosted meeting, "Research Needs for Effective Transition in Lifelong Care of Congenital Genitourinary Conditions," were published in 2017. Additionally, NIDDK hosted a scientific meeting entitled "Individualizing Treatment—Broadening the Framework for Urinary Incontinence Research," which will set the foundation for a 2018 meeting, entitled "Individualizing Treatment for Urinary Incontinence—Evolving Research Questions into Research Plans," including neurogenic bladder.

NINDS supports research on the normal process of neural tube closure as well as neural tube defects, which together, may inform new strategies for prevention and treatment. For example,

one NINDS-funded project is developing a novel approach to *in utero* repair for SB using placenta-derived regenerative cells and a bioengineered tissue scaffold. Other NINDS-funded projects focus on understanding and improving treatments for hydrocephalus, a condition where fluid builds up within the brain, which often affects people with SB. Investigators are also working on developing less invasive tools to monitor conditions such as hydrocephalus and the function of a medical device, called a shunt, that prevents fluid accumulation in the brain. Lastly, NINDS also supports research relevant to understanding and treating neurogenic bladder in SB, including efforts to develop a drug to induce urine voiding as an alternative to catheterization, a low oxygen breathing therapy to improve urinary tract function, and a surgical method to restore neural connectivity to the bladder and urethral sphincter.

New Investigators

The Committee expects NIH to report on actions it has taken to lower the median age at which investigators receive their first R01 awards annually in the fiscal year 2019 Congressional Justification. In addition, the NIH shall provide an update on the concrete steps it is taking to lower the median age at which individuals receive their first R01 award within 60 days of enactment of this Act.

Action taken or to be taken:

NIH continues to take new steps to foster the stability of the biomedical research workforce, and ensure that emerging early-stage investigators have opportunities to receive R01 research grants at an early age and without undue delay.

In August 2017, NIH announced new steps³⁰⁴ to invest in the next generation of researchers.³⁰⁵ This included a goal of funding approximately 200 more early-stage investigators in 2017 than in 2016. As part of this initiative, NIH Institutes and Centers are expected to develop new evidence-based strategies to identify, recruit, and retain early-stage investigators. The NIH Office of the Director will centrally track and maintain an updated census of early-stage investigators and monitor the median age at which individuals receive their first R01 award.

In addition to these steps, applications from New Researchers will be clustered in peer review. These reviewers will be instructed to focus more on the proposed research question, significance, innovation, and approach and less on preliminary data and the investigator's 'track record'.

NIH also continues to support specialized programs that focus on Early Stage Investigators that lead to research awards at a lower age. Examples include the Pathway to Independence Award (K99-R00), Early Independence Award (DP5), and NIH Director's New Innovator Award (DP2). Some NIH Institutes and Centers are also making R35 "outstanding investigator" awards to early-stage investigators as a means of providing them with longer term and more stable research support.

The NIH Director has charged a working group of the Advisory Committee to the (NIH) Director (ACD)³⁰⁶ to examine all dimensions of this issue with an initial recommendations due in June of 2018. NIH is also looking forward to the recommendations of a National Academies committee, convened in early 2017, to study and recommend solutions to any barriers that may extend periods of training and time to independence or impede sustained success in research. A final report and recommendations are expected in the spring of 2018.

³⁰⁴ *NIH Guide for Grants and Contracts*, Policy Supporting the Next Generation Researchers Initiative, Notice NOT-OD-17-101, August 31, 2017.

³⁰⁵ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-101.html>

³⁰⁶ <https://acd.od.nih.gov/working-groups/nextgen.html>

Next Generation Researchers Initiative

Committee supports robust implementation of the Next Generation Researchers Initiative within the Office, as established in the 21st Century Cures Act, and is encouraged by NIH's continued work in this space. The Committee directs NIH to prioritize improving opportunities for our next generation of researchers by working through the Initiative to coordinate all current and new NIH policies to promote opportunities for new scientists and earlier research independence, including enhancing training and mentorship programs for researchers, and enhancing workforce diversity. As required by the 21st Century Cures Act, the Committee directs NIH to consider the recommendations made by the National Academies of Science study under Public Law 114-113 in carrying out the activities of the Initiative.

Action taken or to be taken:

For more than 40 years, NIH and its stakeholder community have been concerned about the ability of recently trained biomedical researchers to establish and sustain an independent research career. Hypercompetition for NIH research grants leaves many highly meritorious research projects unfunded. In some cases, promising investigators are unable to establish stable research careers.

NIH has implemented a variety of programs to help stabilize the biomedical research workforce, especially for new researchers.³⁰⁷ While the percentage of NIH awards that support early-career investigators has stabilized over time, these gains have been offset by a decline in the percentage of NIH awards that support early established investigators. NIH analyses suggest that investigators who benefit from policies and programs aimed at early-career investigators sometimes face difficulty sustaining continued funding as they become more established and are no longer eligible for early investigator programs, preventing them from maintaining stable research careers.

In response to the 21st Century Cures Act, NIH launched the Next Generation Researchers Initiative (NGRI) in September 2017 to bolster opportunities for early-stage investigators (ESIs) and early-established investigators (EEIs).³⁰⁸ ESIs are defined as those within ten years of completing postgraduate clinical training or their most recent advanced research degree, while EEIs are individuals within 10 years of their first substantive research award earned as an ESI applying for subsequent NIH support.³⁰⁹ Through this initiative, NIH Institutes and Centers (ICs) are requested to prioritize funding for additional ESIs and EEIs. Further, NIH will track the impact of funding decisions for ESIs and EEIs to ensure this new strategy is effectively implemented. An NGRI working group will operate under the NIH Advisory Committee to the Director to assess the success of the new programs as well as offer additional suggestions to promote and sustain successful research careers. Such suggestions include activities related to enhancing training and mentorship as well as enhancing diversity of the biomedical workforce.

³⁰⁷ <https://grants.nih.gov/policy/early-investigators/index.htm>

³⁰⁸ <https://grants.nih.gov/ngri.htm>

³⁰⁹ <https://grants.nih.gov/policy/early-investigators/index.htm>

The NIH Director has charged a working group of the Advisory Committee to the (NIH) Director (ACD)³¹⁰ to examine all dimensions of this issue with an initial recommendations due in June of 2018. In addition, as required by Section 404M of P.L 114-113, NIH funded a study via the National Academies of Sciences, Engineering, and Medicine, who convened a high-level committee with broad input for the research community. Thus far, five public meetings have been held, with the most recent in October 2017. A final report and recommendations is expected in spring 2018.

NIH will continue to focus attention on efforts to strengthen and enhance diversity in the biomedical research workforce as well. Programs will promote and accelerate the transition to independence and retain outstanding early career investigators in the NIH funded workforce.

In addition to these steps, applications from New Researchers will be clustered in peer review, so that they are compared to their peers, rather than to established researchers. When evaluating these applications, reviewers will be instructed to focus more on the proposed research question, significance, innovation, and approach and less on preliminary data and the investigator's track record, in order to emphasize proposals from new researchers with novel, feasible, high-impact research ideas.

³¹⁰ <https://acd.od.nih.gov/working-groups/nextgen.html>

Non-Pharmacological Approaches to Pain Management

The Committee is encouraged by the ongoing collaboration between NCCIH, VA, DOD, and other Institutes across the NIH to develop and test efficacious non-pharmacological approaches to pain management and comorbidities-including opioid misuse, abuse, and disorder-in military personnel, veterans, and their families. As opioid prescribing rates have increased at the VA in recent years, and opioid abuse has risen among young veterans, the Committee believes it is critical that we support research on non-pharmacological treatments to ensure the best quality of care for our Nation's veterans and servicemembers, and urges the NIH, VA, and DOD to continue this vital research. The Comprehensive Addiction and Recovery Act (Public Law 114-198) calls for an expansion of research and education on and delivery of complementary and integrative health to veterans, and the NCCIH can play an important role in coordinating efforts with the VA, DOD, and other relevant Federal agencies.

Action taken or to be taken:

Pain is the most common medical condition requiring treatment for military personnel. Studies report nearly 45 percent of service members and 50 percent of veteran's experience pain on a regular basis, and there is significant overlap among chronic pain, post-traumatic stress syndrome, and persistent post-concussive symptoms. Data from the 2010-2014 National Health Interview Survey shows that American veterans experience a higher prevalence of pain and more severe pain than non-veterans. Although opioids are often prescribed to treat chronic pain, there is limited evidence to suggest that they are effective for chronic pain. In addition, opioid use is often associated with severe adverse effects and may lead to addiction, overdose, and death. Therefore, there is a need for non-drug approaches to complement current strategies for pain management and to reduce the need for, and hazards of, excessive reliance on opioids.

Building on previously funded research in a partnership with the National Institute of Drug Abuse (NIDA) and the U.S. Department of Veterans Affairs (VA), the National Center for Complementary and Integrative Health (NCCIH) is leading a new interagency partnership involving the U.S. Department of Health and Human Services, with participation by NIAAA, NICHD, NIDA, NINDS, NINR, OBSSR, and the NIH ORWH; the U.S. Department of Defense (DoD); and the VA to fund a multi-project research program focusing on non-drug approaches for pain management. This initiative, called the HHS-DoD-VA Pain Management Collaboratory, will focus on developing, implementing, and testing cost-effective, large-scale, real-world research on non-drug approaches for pain management and related conditions in military and veteran health care delivery organizations. The Pain Management Collaboratory plans to fund twelve research projects, totaling approximately \$81 million over 6 years, with the NCCIH contributing more than half of these funds. The research projects will provide valuable information about the feasibility, acceptability, safety, and effectiveness of non-drug approaches in treating pain within health care systems that serve the military or veterans. The types of approaches being studied include mindfulness/meditative interventions, movement interventions (e.g., structured exercise, tai chi, yoga), manual therapies (e.g., spinal manipulation, massage, acupuncture), psychological and behavioral interventions (e.g., cognitive behavioral therapy), integrative approaches that involve more than one intervention, and integrated models of multi-modal care. The results of these studies may inform new pain management practices within the DoD and VA and support the use of non-drug approaches for pain management in the general population. In addition to the trials, NCCIH funded a central resource coordinating center to provide technical assistance to the projects, coordination of the steering committee and program

workgroups, as well as developing guidelines and best practices for the scientific community to make it easier for future researchers to conduct of pragmatic trials within military and veteran health care systems. Coordination of the program will continue to engage senior leadership and program staff from NIH, DoD, and VA.

Office of Disease Prevention

The Office of Disease Prevention (ODP) assesses, facilitates, stimulates research into disease prevention and health promotion in collaboration with NIH and other public and private partners, and disseminates the results of this research to improve public health. ODP produces evidence-based consensus statements addressing controversial medical issues. The Committee expects ODP to disseminate consensus statements and disease prevention and health promotion information through appropriate HHS outreach programs.

Action taken or to be taken:

Today, the ODP coordinates the Pathways to Prevention (P2P) program, which was modeled after many of the elements of the CDP. However, while the CDP focused on clinical practice, the P2P identifies research gaps in a selected scientific area, identifies methodological and scientific weaknesses in that scientific area, and suggests future research directions to move the field forward. Each P2P workshop results in a systematic evidence review and a final report on the workshop's findings. P2P workshop reports are disseminated through numerous channels, including online postings, publication in a peer-reviewed journal, and a variety of NIH and HHS outreach programs. In 2016, ODP partnered with NIMH, NIDA, and NCCIH to host a P2P workshop on Advancing Research to Prevent Youth Suicide.³¹¹ The final report provided a roadmap for optimizing youth suicide prevention efforts by highlighting strategies for guiding the next decade of research on youth suicide. The workshop has also stimulated the development of two new Requests for Applications on Addressing Suicide Research Gaps: Aggregating and Mining Existing Data Sets for Secondary Analyses³¹² and Understanding Mortality Outcomes.³¹³

The ODP is committed to widely disseminating P2P results, as well as other information that will increase the visibility of prevention research at the NIH and across the country. For example, the ODP website³¹⁴, in addition to the P2P workshop pages³¹⁵, includes extensive resources for researchers³¹⁶ including a listing of prevention research needs and gaps as well as a comprehensive list of NIH training opportunities in prevention research methods. The ODP also disseminates its resources via various listservs and by reaching out to relevant professional societies and associations, by sharing information with NIH and HHS partners, and on Twitter.³¹⁷

In addition, over 160 consensus statements are available in an online archive of the Consensus Development Program³¹⁸ (that was retired in 2013).

³¹¹ <https://prevention.nih.gov/p2psp>

³¹² <https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-18-400.html>

³¹³ <https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-18-410.html>

⁵ <https://prevention.nih.gov/>

⁶ <https://prevention.nih.gov/programs-events/pathways-to-prevention>

⁷ <https://prevention.nih.gov/resources-for-researchers>

³¹⁷ @NIHprevents

³¹⁸ <https://consensus.nih.gov>

Opioid Misuse and Addiction

The Committee continues to be extremely concerned about the epidemic of prescription opioids, heroin, and synthetic opioid use, addiction, and overdose in the United States. Approximately 144 people die each day in this country from opioid overdose, making it one of the most common causes of non-disease-related deaths for adolescents and young adults. This crisis has been exacerbated by the availability of fentanyl and its analogs in many communities. The Committee appreciates the important role that research can and should play in the various Federal initiatives aimed at this crisis. Although NIDA has studied the effectiveness and risks associated with long-term opioid use for chronic pain, little research has been done to investigate new and alternative treatment options. The Committee urges NIDA to expand scientific activities related to research on medications used to treat and reduce chronic pain. The Committee encourages NIDA to coordinate with the agencies of the NIH Pain Consortium, the pharmaceutical industry, experts in the field of pain research and addiction, and the medical research community at large to identify gaps in scientific research related to opioid abuse and addiction, and the treatment of chronic pain, especially the development of medications with reduced abuse liability. NIDA is encouraged, as appropriate, to work with private companies to fund innovative research into such medications and to sponsor research to better understand the effects of long-term prescription opioid use, especially as it relates to the prevention and treatment of opioid abuse and addiction. Finally, the Committee also requests an update for the NIH's plan of action to implement Section 108 of the Comprehensive Addiction and Recovery Act, directing the NIH to consider recommendations made by the Interagency Pain Research Coordinating Committee in concert with the Pain Management Best Practices Inter-Agency Task Force, and in accordance with the National Pain Strategy, the Federal Pain Research Strategy, and the NIH- Wide Strategic Plan for Fiscal Years 2016–2020, the latter of which calls for the relative burdens of individual diseases and medical disorders to be regarded as crucial considerations in balancing the priorities of the Federal research portfolio.

Action taken or to be taken:

The National Institute of Drug Abuse (NIDA) is one of multiple institutes of the NIH supporting research on pain. Research is a key element in the Department of Health and Human Service's 5-point strategy to fight the opioid crisis.

NIH's current research efforts include basic research to understand pain mechanisms, why acute pain becomes chronic, and how to prevent and treat chronic pain based on biological mechanisms. NIH also funds translational research to develop non-opioid analgesics and safer opioids from early stage drug discovery focused on targeting pain signaling pathways, screening novel and existing compounds to determine their potential as analgesics, optimizing the structure of promising molecules for drug formulations, and safety and toxicity testing of drugs. NIH supports research on a number of novel analgesic drug targets, in part through the Blueprint Neurotherapeutics Program for small molecule drug discovery and development.

Some of the most promising potential therapies include:

- *Abuse Resistant Opioid Analgesics*: Efforts are underway to identify new opioid pain medicines with reduced misuse, tolerance, and dependence risk, as well as alternative delivery systems and formulations for existing medications that minimize diversion and misuse (e.g., by preventing tampering) and reduce the risk of overdose deaths.

- ***Non-Opioid Medications:*** Some non-opioid targets with promising preliminary data include fatty acid binding proteins, the G-protein receptor 55, cannabinoids, and transient receptor potential cation channel A1.
- ***Brain Stimulation Therapies:*** Several non-invasive brain stimulation therapies – including transcranial magnetic stimulation and transcranial direct current stimulation, as well as electrical deep brain stimulation and peripheral nerves/tissues stimulation – have shown promise for the treatment of chronic pain. These devices have been approved by the FDA for treatment of other conditions but more research is needed on their effectiveness for pain.
- ***Neurofeedback:*** Neurofeedback is a novel treatment modality in which patients learn to regulate the activity of specific brain regions by getting feedback from real-time brain imaging. This technique shows promise for altering the perception of pain in healthy adults and chronic pain patients and may also be effective for the treatment of addiction.

In addition, as part of a government-wide effort to address the current opioid crisis and implement the Department's Opioid Strategy, the NIH is launching a public-private collaborative research initiative to develop new, safe, and effective strategies to prevent and treat pain, opioid addiction, and overdose reversal and prevention.

To identify the scientific strategies with the greatest potential, NIH brought together innovative experts from government, industry, and academia for a series of three cutting-edge science meetings.³¹⁹ Plans are underway to develop a draft strategy for collaborative activities including major goals of the initiative, action steps, key partners, deliverables, timeline, and resources (in-kind and financial costs) to fully carry out the proposed action steps. The Foundation for the National Institutes of Health will solicit input on the final draft will be solicited from participants including federal partners as well as other relevant stakeholders. Upon final approval of the plan, it will be posted on the NIH website at: <https://www.nih.gov/opioid-crisis>.

Promising potential action steps related to pain include:

1. **Accelerate development of new non-addictive pain therapies** through:
 - a. Enhanced data and information sharing collaborative between industry partners and with academic scientists
 - b. Development and testing of a standardized platform for drug-target validation
 - c. Identifying and validating biomarkers for pain and treatment response
 - d. Nocimeter/Pain-meter development and testing
 - e. Rapidly bring to market novel non addictive drugs and devices to treat pain
2. **Pilot clinical research networks** to:
 - a. Measure strategies to improve treatment effectiveness for pain, opioid addiction, and overdose prevention/reversal in real-world settings.
 - b. Test new therapies for pain management, especially in high-impact, well defined pain populations
 - c. Understand the transition from acute to chronic pain

³¹⁹ For more information, see: <https://www.nih.gov/opioid-crisis>

NIH is working to implement Section 108 of the Comprehensive Addiction and Recovery Act. The Federal Pain Research Strategy is an effort of the Interagency Pain Research Coordinating Committee and the Office of Pain Policy of the National Institutes of Health to oversee development of a long-term strategic plan for those federal agencies and departments that support pain research. It was completed in 2017 and identifies high priority research recommendations in the key areas of pain prevention, mechanisms of acute and chronic pain, the transition from acute to chronic pain, and pain management. The research strategy also supports development of safer alternatives to prescription medicines for pain care.³²⁰ Specific areas of focus include:

- Development of non-opioid analgesics that target the molecular pathways of pain signaling
- Development of novel opioid analgesics with reduced potential for addiction and overdose
- Comparative effectiveness and precision medicine research to identify which treatments will be most effective for a specific patient
- Nonpharmacological treatments for pain, including the use of stimulation devices, biofeedback, genetic manipulation, nanotechnology, and behavioral and psychosocial treatments
- Basic research on the mechanisms of pain

Finally, the NIH is collaborating with the Office of the Assistant Secretary for Health to coordinate the implementation of the National Pain Strategy (NPS). Implementation work groups are developing work plans to achieve the deliverables of the NPS, many of which are related to research.

³²⁰ NIH's Interagency Pain Research Coordinating Committee: Federal Pain Research Strategy. Available at: <https://iprcc.nih.gov/FPRS/FPRS.htm>

Pancreatic Cancer

In 2016, pancreatic cancer rose to become the third-leading cause of cancer-related death in the U.S., claiming the lives of nearly 42,000 Americans. Despite progress in combating other forms of cancer, pancreatic cancer remains the only major cancer with a 5-year survival rate in the single digits, at nine percent, in large part because there are no reliable early detection methods nor effective treatment options. To help turn the tide against this deadly cancer, Congress in 2012 passed the Recalcitrant Cancer Research Act (Public Law 112-239), calling for the development of scientific frameworks for certain cancers. The Committee requests an update on pancreatic cancer in the fiscal year 2019 CJ.

Action taken or to be taken:

Pancreatic cancer accounts for only three percent of new cancer cases, but is the third leading cause of cancer-related death in the United States.^{321,322} In response to the Recalcitrant Cancer Research Act, and in collaboration with the extramural research community and advocacy groups, the National Cancer Institute (NCI) released a Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC) in 2014. The framework identified four priority areas to guide future research efforts: (1) development of an in-depth understanding of the biological and clinical relationship between PDAC and diabetes; (2) evaluation of longitudinal screening protocols, associated with the development of new molecular and imaging biomarkers, for patients at high risk for PDAC; (3) implementation of new immunotherapy approaches; and (4) development of new treatment strategies that interfere with RAS oncogene-dependent signaling pathways.

NCI is working to improve detection and diagnosis of pancreatic cancer in several ways, including funding the Pancreatic Cancer Detection Consortium (PCDC) and supporting seven multi-disciplinary research teams focused on developing and testing new molecular and imaging biomarkers to improve the detection of early stage PDAC and its precursor lesions in order to identify individuals who are at high risk and who may be candidates for early intervention. In August 2017, a research team from the University of Pennsylvania and the Mayo Clinic (one of the PCDC teams) published its findings indicating that a new blood test may be able to accurately detect pancreatic cancer at its earliest stages.³²³

Through the Early Detection Research Network (EDRN), NCI is supporting research to validate biomarkers in blood, cystic fluids, and tissues that may be useful in the early detection and treatment of pancreatic cancer.³²⁴ Researchers have made rapid progress in developing noninvasive liquid biopsy approaches that can detect biomarkers indicating certain types of pancreatic cancer earlier than current methods³²⁵. NCI-supported researchers have also made progress in developing a blood plasma test that can distinguish between pancreatic cancer and the less serious chronic pancreatitis, helping to ensure patients with cancer receive the correct treatment faster while avoiding unwarranted surgery for patients with pancreatitis.³²⁶ In addition,

³²¹ <https://www.cancer.org/cancer/pancreatic-cancer/about/key-statistics.html>

³²² <https://www.pancan.org/wp-content/uploads/2016/02/2016-GAA-PC-Facts.pdf>

³²³ <https://www.cancer.gov/news-events/cancer-currents-blog/2017/blood-test-pancreatic-cancer>

³²⁴ https://projectreporter.nih.gov/project_info_description.cfm?aid=9463066&icde=36683935&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

³²⁵ <https://www.ncbi.nlm.nih.gov/pubmed/28874546>

³²⁶ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5386003/>

NCI established the RAS initiative at the Frederick National Lab for Cancer Research to better understand the role of RAS (a mutation found in 95% of pancreatic cancers) in the development of cancer and to explore new treatments to neutralize RAS. Researchers recently identified a new druggable vulnerability for KRAS (one of the main members of the RAS gene family and the one most commonly found in pancreatic cancer) oncogenes, revealing a potential target for future treatments.³²⁷

To further our understanding of PDAC and diabetes, NCI has partnered with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to establish and co-fund a consortium to examine chronic pancreatitis (CP) and factors that increase the risk of pancreatic cancer in patients with newly diagnosed diabetes. Through the acquisition of a cohort of well-characterized patients and associated biospecimens, this clinical research network will provide important resources and collaborative opportunities.

NCI-supported investigators are also pursuing a cancer vaccine which aims to prevent pancreatic cancer. Precursor lesions of pancreatic cancer produce an abnormal protein called MUC1, which can be recognized by a type of immune cell that can kill cancer cells. A MUC1 vaccine has already been shown to produce a strong immune response in patients with advanced colorectal polyps³²⁸, and research is underway to evaluate its potential for prevention of pancreatic cancer.

In addition to funding research related to pancreatic cancer detection and prevention, NCI also coordinates and supports clinical trials to identify more effective treatments. The NCI is recruiting pancreatic cancer patients for a trial at the NIH Clinical Center to determine whether a combination of chemotherapy and stereotactic body radiation therapy (which uses advanced imaging techniques to deliver a high dose of radiation to a precisely targeted area) is more effective than chemotherapy alone.³²⁹ The NCI-sponsored National Clinical Trial Network (NCTN) is conducting a 950-patient international Phase III trial to assess the value of adding radiation to chemotherapy to treat pancreatic cancer, and as of October 2017, a total of 527 patients have been enrolled. Additionally, as part of the NCI-supported Cancer Genome Atlas Research Network, researchers conducted genetic profiling of 150 pancreatic cancer specimens. Their analysis provides a roadmap for future precision medicine trials.³³⁰

NCI will continue to pursue the research opportunities identified through the PDAC framework, fund meritorious grant proposals in other areas of pancreatic cancer research, and support cross-cutting research that stands to benefit pancreatic cancer patients and their families – from basic research, to precision medicine clinical trials, to immunotherapy research.

³²⁷ <https://www.ncbi.nlm.nih.gov/pubmed/28893801>

³²⁸ <https://www.cancer.gov/about-nci/budget/plan/2019-annual-plan-budget-proposal.pdf> page 26

³²⁹ <https://clinicaltrials.gov/ct2/show/NCT02311361?recrs=abdf&type=Intr&cond=Pancreatic+Cancer&spons=national+cancer+institute&draw=1&rank=7>

³³⁰ <https://www.ncbi.nlm.nih.gov/pubmed/28810144>

Pediatric Cancer

The Committee remains concerned about the lack of child-specific solutions for pediatric cancer patients and the consistent overall rise in rate of incidence (35 percent increase since 1975). The Committee acknowledges that the needs of pediatric cancer patients are unique and different from the needs of adults with cancer. The majority of cancers in children are not seen in the adult population, but the vast majority of solutions continue to be adopted and adapted from adult cancer drugs for use in children, despite the toxicity of the drugs for their small developing bodies. The consequences continue to leave two-thirds of childhood cancer survivors with serious lifelong complications and one-third of childhood cancer survivors dead by the age of 36. As a result, cancer continues to kill more children than all other diseases combined. The Committee notes that childhood cancer is unique from adult cancer and should be approached from a child-specific perspective. Accordingly, the Committee urges the NCI to continue to support research that addresses the unique characteristics of childhood cancers and the unique needs of childhood survivors. There are some encouraging efforts currently focusing on child-specific solutions, and there should continue to be parallel efforts to determine the efficacy of adult research and treatments for childhood cancer; however, they should not be the primary focus. Just as adult research hopes to benefit children, it is more likely childhood cancer research may benefit adults. Therefore, the Committee encourages the continuation of important pediatric oncology research, including clinical trials for children with brain tumors and preclinical testing program evaluating new agents for treating pediatric malignancies. Within the additional resources provided for cancer research, the Committee requests a report within 120 days after enactment of this act on how the NCI is focusing on the unique needs of children. The Committee also encourages NCI to continue its investments in the novel pediatric Molecular Analysis for Therapy Choice [MATCH] study. The Committee requests an update on the progress of MATCH implementation for children with cancer, with specific information on issues such as accrual, participating institutions, and the scope and progress of the trials in the fiscal year 2019 CJ.

Action taken or to be taken:

Recognizing that cancers diagnosed during childhood are most often biologically unique from cancers diagnosed during adulthood, the National Cancer Institute (NCI) is committed to addressing the unique scientific challenges and opportunities that pediatric cancers pose. Although the survival rates for most childhood cancers have improved greatly over the last half-century, survival rates remain low for some cancer types, including some types of brain cancer.³³¹ NCI formed the Pediatric Brain Tumor Consortium (PBTC) in 1999 to address this disparity and improve the treatment of primary brain tumors in children. The PBTC is comprised of 11 academic centers and children's hospitals located across the United States and aims to rapidly conduct novel phase I and II clinical trials, identify potential biomarkers to predict treatment response, and conduct research on brain tumors in the laboratory to further understand the biology of pediatric brain tumors. To date, the PBTC has enrolled more than 1,700 patients, completed 34 therapeutic studies (seven are currently active), and activated 10 non-therapeutic studies.³³²

³³¹ <https://www.cancer.gov/types/childhood-cancers/child-adolescent-cancers-fact-sheet>

³³² <https://www.pbtc.org/>

Addressing key challenges with the development of new therapies for children with cancer remains a focus of NCI's pediatric oncology work. NCI's Preclinical Testing Consortium (PPTC) develops reliable preclinical testing data for pediatric drug candidates that can be used to inform new agent prioritization decisions. The PPTC consists of a Coordinating Center and five Research Programs that perform *in vivo* testing of pediatric anticancer drug candidates for a particular cancer (sarcoma and renal, neuroblastoma, osteosarcoma, leukemia, and brain tumors). The PPTC collaborates with pharmaceutical companies and academic drug developers to systematically test candidate agents against childhood cancer models in order to identify those investigational agents most likely to have clinical activity against childhood cancers. For example, in 2011, the PPTC developed a model for a subtype of pediatric low-grade astrocytoma (PLGA, a type of brain tumor) with a mutation in a gene called *BRAF* and identified a targeted therapy, selumetinib, for additional research. Building upon these findings, the PBTC conducted a Phase 1 trial of selumetinib.³³³ In this trial, children with *BRAF*-mutated PLGAs responded to treatment by showing tumor shrinkage. Based on these promising findings, the trial is now in a Phase 2 expansion with results from several cohorts reported in 2017 showing that selumetinib is a possible treatment for patients with two subtypes of *BRAF*-mutated PLGAs.³³⁴

NCI is also a leader in advancing precision medicine. In July 2017, investigators at NCI and the NCI-supported Children's Oncology Group (COG) launched the Pediatric Molecular Analysis for Therapy Choice (Pediatric MATCH) Trial.³³⁵ Pediatric MATCH is a nationwide trial to explore whether targeted therapies can be effective for children and adolescents with solid tumors that harbor specific genetic mutations and have progressed during or after standard therapy. The trial is accessible at about 200 COG sites nationwide.³³⁶ The trial is currently enrolling patients in eight arms, and as of November 2017, 35 patients have enrolled for screening. As the trial continues, new treatment arms will open as drugs become available and others will close as they reach enrollment. Three more arms have been approved for development as of November 2017, and these arms are expected to open for screening enrollment in 2018. This structure is possible through a collaboration between NCI, COG, and several pharmaceutical partners who are providing targeted agents for this trial, as well as close consultation with the Food and Drug Administration. The genomic data captured in the trial will also produce an invaluable resource for studying the genetic basis of why some pediatric cancers progress or recur while others do not. Some of the agents have not previously been tested in children, so this trial will provide broader access to targeted agents for children and adolescents. Patients found not to have a matched drug may, with the help of their oncologists, be able to enroll in other studies available through the NCI-supported COG Developmental Therapeutics Program, the PBTC, the New Approaches to Neuroblastoma Therapy Consortium, and pharmaceutical trials.

NCI's support of pediatric cancer research does not stop when a patient is deemed "cured." In recognition of the severe late effects that often arise from cancer treatments, NCI supports several childhood cancer survivorship research efforts. The Childhood Cancer Survivor Study (CCSS), which NCI launched in 1994, is a multi-institutional, multidisciplinary collaborative

³³³ <https://clinicaltrials.gov/ct2/show/NCT01089101>

³³⁴ http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.10504

³³⁵ <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match>

³³⁶ <https://www.childrensoncologygroup.org/index.php/locations/>

research resource. Through CCSS, 31 institutions across the United States work with a cohort of 34,000 pediatric cancer survivors and their families to gather biospecimens and information on cancer diagnosis, treatment-related exposures, and outcomes. In addition, CCSS collects data on virtually every aspect of cancer survivorship, including late effects of treatment, health-related quality of life, health-related behaviors, and patterns of medical care use. These data are made available to the research community and have become an indispensable resource. To date, more than 250 publications have used CCSS data and approximately \$37 million in investigator-initiated grants have been awarded based on applications that used CCSS data. CCSS accomplishments include developing a heart failure prediction model for childhood cancer survivors, investigating the likelihood of developing breast cancer after chest radiation therapy, and identifying genetic risk factors for radiation-associated second cancers.

NCI also supports the St. Jude Lifetime survivorship cohort study, that is smaller (approximately 4,000 participants), but highly complementary to the CCSS. The St. Jude Lifetime cohort is designed to capture longitudinal, detailed, in-person clinical assessment and functional performance information on children treated at St. Jude. Additionally, NCI continues to support childhood cancer survivorship research through investigator-initiated research efforts, including the Pediatric Provocative Questions (PQ) initiative, which invites applications for research projects designed to use sound and innovative strategies to solve specific problems and paradoxes in childhood cancer research. The first round of awards were made in spring 2017, and two projects are studying late effects of treatment.

Pediatric Clinical Trials

The Committee supports the pediatric clinical trials conducted under the Best Pharmaceutical Practices for Children Act [BPCA], and strongly encourages the NIH to continue to support this program. BPCA has made significant steps in closing the knowledge gap on the efficacy of drugs being used on children and encourages enhanced coordination of BPCA activities with other NIH pediatric research and initiatives, including, but not limited to, pediatric cancer, the pediatric MATCH study, muscular dystrophy, the IDeA States Pediatric Clinical Trials Network Program, and the All of Us Precision Medicine Initiative. The Committee requests an update in the fiscal year 2019 CJ on the status of research related to this topic.

Action taken or to be taken:

Pediatric clinical trials are supported across NIH. The Pediatric Trials Network (PTN)³³⁷ is conducted under the auspices of the Best Pharmaceuticals for Children (BPCA) program, overseen by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Despite the increase in knowledge about drugs prescribed for children, in most therapeutic areas, there is still a high rate of off-label use of medications in pediatrics due to limited data; these limitations in information can increase a child's risk for poor health outcomes. The PTN was established in 2010 to create an infrastructure for investigators to conduct clinical trials that improve pediatric drug labeling by testing drugs prescribed for children, however there is still a lack of dosing, safety or efficacy data. Data from the PTN's clinical studies are submitted to the Food and Drug Administration for potential label modification, and will be made available to investigators and clinicians by posting on NICHD's public website. To date, over 7000 children have been enrolled in studies conducted by the PTN in over 160 pediatric sites, with 74 drugs studied. Ten completed Clinical Study Reports have been submitted to the FDA for label changes, with 20 more planned submissions by FY 2018. NICHD also supports several other pediatric trials networks, including the Collaborative Pediatric Critical Care Research Network (CPCCRN), which is committed to improving outcomes of critically ill, non-neonatal pediatric patients through research. Such research is vital as there is little evidence-based data to inform care for these children, and treatments are often based on adult studies. The CPCCRN consists of a Data Coordinating Center and seven large children's hospitals from across the U.S., and is currently conducting eleven projects, including testing an intervention to reverse the immunoparalysis commonly encountered in children with severe traumatic brain injury, and a clinical trial of therapeutic hypothermia attempting to inform the best approach to resuscitating children following cardiac arrest.

Announced in 2017, a new study called the Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW) will evaluate treatment options and improve clinical care of infants with neonatal abstinence syndrome (NAS), or NOWS. The study is a collaboration between NICHD's Neonatal Research Network (which has 30 years of experience in conducting clinical trials with newborns) and the new IDeA States Pediatric Clinical Trials Network (within the NIH Office of the Director's Environmental Influences on Child Health Outcomes (ECHO) Program), with sites located in rural and medically underserved communities. This joint research effort will use the reach of both networks to assess the prevalence of NAS, understand current approaches to managing NOWS cases (including non-pharmacological approaches), and

³³⁷ <https://pediatrictrials.org/>

develop common protocols for conducting large scale comparative effectiveness studies across the country to inform clinical care for affected infants.

In July 2017, investigators at the National Cancer Institute (NCI) and the NCI-supported Children's Oncology Group (COG) launched the Pediatric Molecular Analysis for Therapy Choice (Pediatric MATCH) Trial.³³⁸ Pediatric MATCH is a nationwide trial, accessible at about 200 COG sites, to explore whether targeted therapies can be effective for children and adolescents with solid tumors that harbor specific genetic mutations and have progressed during or after standard therapy.

³³⁸ <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match>

Pediatric Kidney Disease

The Committee is encouraged by the current multicenter pediatric kidney disease research funded by NIDDK. While important strides have been made, further research is critical to the validation of new prognostic indicators, novel diagnostic biomarkers, and therapeutics necessary to better understand and treat kidney disease as children mature from newborns and ultimately transition to adulthood. The Committee urges the NIDDK to work collaboratively with other NIH institutes, including the NICHD, NHLBI, and NIMHD, to advance further multidisciplinary research for children and young adults with kidney disease and its complex co-morbidities. The Committee requests that NIDDK report back in the fiscal year 2019 Congressional Justification on the steps taken to advance this type of collaborative research.

Action taken or to be taken:

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a multi-faceted program of research to 1) identify the causes, 2) understand and halt disease progression, 3) develop and improve treatments, and 4) ultimately prevent kidney diseases and kidney failure in children. In FY 2018, NIDDK plans to focus one meeting of the Kidney Interagency Coordinating Committee (KICC) on pediatric kidney disease, with the goal of encouraging cooperation, communication, and collaboration among all NIH Institutes and federal agencies involved in kidney research.

NIDDK continues to support the multi-center Chronic Kidney Disease in Children (CKiD) study, in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). CKiD is investigating risk factors for further kidney function decline in children with mild to moderately decreased kidney function, as well as closely monitoring neurocognitive development, examining risk factors for heart disease, and following long-term effects of poor growth. In 2017, CKiD held a data workshop and an Observational Study Monitoring Board meeting. NHLBI supports CKiD cardiovascular efforts, which have identified a high prevalence of cardiovascular risk factors among children with chronic kidney disease (CKD) and an association between hypertension (high blood pressure) and left ventricular hypertrophy (the thickening of the muscle in the left heart chamber). The latter finding led to a practice-changing recommendation to use early echocardiography to screen for left ventricular hypertrophy in children with CKD.

NHLBI is working with NIDDK and others to evaluate long-term renal outcomes after cardiac surgery in children. Researchers found CKD and hypertension are common 5 years after pediatric cardiac surgery, but that these complications were not associated with acute kidney injury (AKI). The researchers are now working together to identify and evaluate novel urinary and blood biomarkers that provide valuable information regarding the relationship of AKI to long term complications such as hypertension and recurrent cardiovascular events and death.

NICHD continues to fund research projects on pediatric kidney disease. One ongoing study is exploring the impact of steroid hormones, glucocorticoids, provided prenatally on renal damage in adulthood. The Validating Injury to the Renal Transplant Using Urinary Signatures in Children (VIRTUUS) study is a multi-center study designed to improve approaches for identifying early allograft injury in children with kidney transplants. The NICHD also is funding mentored research projects that will allow new investigators to obtain the research training to lead clinical projects on pediatric kidney disease in the future, including one study on whether a

pharmaceutical therapy is safe and efficacious as a treatment for acute kidney injury in newborns.

NIMHD supports research to understand the underlying factors that contribute to the disparities in pediatric kidney disease. Most children receiving treatment for childhood nephrotic syndrome respond well to steroids, also known as steroid-sensitive nephrotic syndrome (SSNS), while about 20 percent do not. An NIMHD-funded study that includes children from African American, South Asian, and White backgrounds aims to identify genetic risk factors for SSNS to gain insights into the basis for varying response to therapy. Another NIMHD-funded study is examining the degree to which genetic risk factors contribute to the ethnicity-specific variation in the prevalence, disease course, and overall outcomes related to biological processes such as IgA Nephropathy, Membranous Nephropathy, and Systemic Lupus Erythematosus Nephropathy in Hispanic and American Indian communities.

Pediatric Rare Diseases

The Committee is encouraged by the work of the Rare Diseases Clinical Research Network (RDCRN) across a range of rare diseases. The burden of pediatric rare diseases is especially difficult for families navigating multiple research opportunities and clinical service needs. The Committee encourages NCATS to work with RDCRN members to create a pediatric rare disease center of excellence model.

Action taken or to be taken:

The Rare Diseases Clinical Research Network (RDCRN) program, led by the National Center for Advancing Translational Sciences (NCATS) in collaboration with other NIH Institutes, is a model designed to advance medical research on rare diseases. It does this by supporting clinical studies and facilitating collaboration and data sharing within and across consortia, patient enrollment through a central contact registry for all consortia studies, and the network's mandatory inclusion of patient support organizations in each consortium. Through the RDCRN, clinicians and scientists from multiple disciplines at more than 250 clinical sites across the nation and around the world work together with patient advocacy groups to study more than 200 rare diseases. The individual RDCRN research consortia are organized around a cluster of three or more diseases or a therapeutic concept (such as an organ system or related genetic mutations) so that the expert community for this disease area are able to come together to advance research in this specific rare disease area.

Several of the Rare Diseases Clinical Research Consortia (RDCRC) focus on or include rare diseases that affect children, including brittle bone diseases, mitochondrial diseases, immune deficiencies, Rett syndrome and Rett-related disorders, sterol and isoprenoid conditions, urea cycle disorders, genetic disorders of mucociliary clearance, developmental synaptopathies, and lysosomal storage diseases, among others. One illustrative example is the Lysosomal Disease Network Consortium. In lysosomal diseases, there is a deficiency in or absence of an enzyme that breaks down cellular materials, such as a protein, as part of normal cellular recycling processes. This results in the inappropriate buildup of materials in the body's cells, which leads to cellular, tissue, and organ damage, resulting in chronic illness, progressive disability (typically in multiple organ systems), and often early death. The Lysosomal Disease Network brings together doctors, researchers, and patient advocacy groups for many lysosomal diseases, such as Batten disease, Fabry disease, Gaucher disease, Krabbe disease, mucopolysaccharidoses, Niemann–Pick diseases, Pompe disease, Tay-Sachs disease and Wolman disease, to address major challenges in diagnosis and disease management and treatment. All of the lysosomal storage diseases are genetic and affect children and young adults. In some cases the diseases are fatal in children; in others, patients live to adulthood but usually with significant disabilities. NCATS supports each of the RDCRCs in collaboration with other NIH Institutes and Centers.

NIH funds over 100 pediatric research centers and networks, most of which are working on rare conditions, so an additional pediatric rare disease center of excellence might be duplicative of current efforts.

Peripheral Neuropathies

The Committee is pleased at the progress of ongoing research into Guillain-Barre syndrome [GBS], chronic inflammatory demyelinating polyneuropathy, and related conditions, and notes the important connection between Zika and GBS. The Committee encourages NINDS to continue work to advance emerging research in a meaningful way.

Action taken or to be taken:

NINDS funds research to understand the molecular mechanisms of Guillain-Barre' syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) and to improve treatments for these diseases.

In GBS and CIDP, a person's own immune system attacks their peripheral nerves, damaging the nerve cells or the fatty covering (myelin) that insulates and protects them. The nerve's ability to conduct electrical signals is diminished, resulting in pain, weakness, numbness, tingling sensations or even paralysis. Anti-ganglioside antibodies are frequently found in people with GBS, and studies indicate that these antibodies inhibit nerve repair. NINDS currently funds research to examine immune mechanisms and cells involved in antibody-mediated inhibition of nerve repair, which may lead to new strategies for aiding nerve repair in people with GBS, and NINDS-funded researchers are examining the mechanisms by which intravenous immunoglobulin (IVIg), a current treatment for GBS, reduces anti-ganglioside mediated-inflammation. In genetic mouse models of CIDP, NINDS-funded researchers are trying to identify potential therapeutic targets by examining nerve proteins that are attacked by the immune system and how different components of the immune system contribute to the autoimmune response. NINDS-funded researchers recently showed that certain cell adhesion proteins may play a role in allowing immune cells to cross the blood nerve barrier in CIDP, suggesting that treatments that target these cell adhesion molecules may reduce inflammatory demyelination in people with CIDP.

Certain viral and bacterial infections, including Zika, increase the risk of developing GBS, but the molecular and cellular mechanisms by which Zika might cause GBS are not clear. NINDS researchers are developing animal and cell models of Zika infection that will allow a deeper understanding of the pathophysiology of Zika-associated GBS. In a recent study, NINDS-funded researchers showed that Zika virus can directly infect peripheral nerves in mouse models and that these infected nerves have altered expression of genes involved in cell growth and programmed cell death. A deeper understanding of how Zika virus affects peripheral nerves may lead to new insights into how different kinds of infections cause GBS.

Phelan-McDermid Syndrome

Phelan-McDermid Syndrome is a genetic disorder caused by a partial deletion of chromosome 22 and loss of the SHANK3 gene. The Committee continues to support a multi-Institute approach to support research into Phelan-McDermid Syndrome, examining in particular the disorder's correlation with autism, epilepsy and other developmental disabilities. The Committee requests an update in the fiscal year 2019 CJ on the status of research related to this topic.

Action taken or to be taken:

The National Institute of Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke (NINDS), the *Eunice Kennedy Shriver* National Institute of Child Health and Development (NICHD), and the National Center for Advancing Translational Sciences (NCATS) collaborate in supporting the NIH Rare Disease Clinical Research Network. This network focuses on genetic mutations – including the SHANK 3 loss – associated with Phelan-McDermid Syndrome, autism spectrum disorder (ASD), and other neurodevelopmental disorders. This consortium is conducting a longitudinal observational study of individuals with Phelan-McDermid Syndrome to assess natural history, neuroimaging data, and genetic factors to fully characterize the disorder, and to uncover biomarkers that may predict the severity of cognitive, language, motor, and social interaction impairment.

One of the consortium sites is co-located at, and uses resources from, an NICHD-funded Intellectual and Developmental Disabilities Research Center designed to advance the diagnosis, prevention, treatment, and amelioration of intellectual and developmental disabilities. Additionally, NICHD funds a small business grant to explore development of anti-oxidant compounds to treat some symptoms of Phelan-McDermid Syndrome.

NIMH is also supporting basic and applied research on shared mechanisms and symptoms of Phelan-McDermid Syndrome and ASD. For example, NIMH-funded studies are focusing on loss of the SHANK3 gene in experimental systems (e.g., mouse models) to uncover molecular, synaptic, and neural circuit properties associated with this genetic mutation.^{339,340} Other NIMH-funded researchers are applying induced pluripotent stem cell technology – a method by which patients' skin cells are isolated and differentiated into neurons in a laboratory setting – to understand electrical properties of neural networks in people with Phelan-McDermid Syndrome and ASD.³⁴¹ NIMH also supports research to unveil brain-based and behavioral mechanisms that underlie sensory processing deficits in these individuals; this research is aimed at informing objective, reliable methods that accurately measure outcomes in treatment studies.³⁴²

NINDS is also funding basic research to understand mechanisms associated with the loss of SHANK3. For example, one NINDS-funded study is using a mouse model to determine how loss of SHANK3 gives rise to disturbed sleep, including mechanisms that might serve as drug targets for treating sleep disturbances associated with Phelan-McDermid Syndrome, ASD, and related disorders. Other NINDS-funded researchers are investigating how SHANK3 function

³³⁹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9050706

³⁴⁰ https://projectreporter.nih.gov/project_info_description.cfm?aid=9264590

³⁴¹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9353469

³⁴² https://projectreporter.nih.gov/project_info_description.cfm?aid=9357290

affects specific brain areas that may give rise to the motor deficits observed in Phelan-McDermid syndrome.

Population Health Training

The Committee acknowledges the growing understanding that the living systems that produce health and disease encompass health determinants "from cells to society." The Office of Behavioral and Social Science Research should continue to work with NIH Institutes and Centers to encourage interdisciplinary population health science training to enhance our understanding of how social, cultural, genetic, biological, and environmental factors combine to influence outcomes in health and human development.

Action taken or to be taken:

It is widely recognized that social, environmental, and behavioral influences are strong predictors of health and disease. Understanding how these variables interact to impact health outcomes is important to transform the health of individuals and communities. The Office of Behavioral and Social Sciences Research (OBSSR) actively encourages funding for interdisciplinary population health training to nurture a community of scholars and clinicians interested in behavioral and social science research. OBSSR recognizes comprehensive training in population health science requires increased proficiency in methods, metrics and research design to advance research on population health and health disparities. To promote a diverse interdisciplinary environment and rapidly advance population health research, OBSSR coordinates behavioral and social sciences research activities across the NIH and facilitates networking opportunities for the larger community of stakeholders.

In FY2017, 13 percent of co-funding from OBSSR to NIH Institutes, Centers and Offices, was dedicated to population-health based training, including four pre-doctoral research grants awarded to individuals integrating social science into training. Additionally, support was provided for meetings and workshops addressing multiple components of health, such as biology, behavior, and social environments. Topics covered included the development of precision medicine approaches to the treatment of obesity, and exploring telomere length to better understand environmental exposure and stress.

Educational training research supported by NIH capitalizes on opportunities afforded by new technologies, including digital platforms. The Big Data to Knowledge (BD2K) Common Fund program, to which OBSSR contributes, was developed to facilitate broad use of biomedical big data and to support training courses for researchers to learn foundational principles and best practices related to collecting, storing, analyzing, and utilizing behavior-based sensor data. This information can be used to provide quality health care sensitive to individual lifestyle and health needs. The skills obtained from these BD2K training efforts are applicable to a broad range of big data population health questions.

Complementing BD2K, trans-NIH support for research using sensing technologies examining the causal inference of genetic, behavioral, and social variables has made it easier to gain high resolution and individualized health data at scale. Given the promise of mobile technology in facilitating health-behavior change, the National Institute on Drug Abuse in collaboration with the National Institute on Alcohol Abuse and Alcoholism and OBSSR provided support for a training course in mobile health (mHealth) methodologies. This immersion program, followed by ongoing mentoring and facilitated collaboration, allows participants from disparate disciplines to learn necessary fundamentals and methodologies to adequately address specific health problems.

OBSSR is committed to advancing scientific population health training opportunities through co-funding opportunities, funding announcements, and meeting and workshops. Increasing efficiency in methodological approaches, such as data visualization, modeling, innovative study design, and data collection, will improve research analysis and help us better address the multifactorial origins of health outcomes. In the coming year, OBSSR plans to augment these training opportunities to advance future population health research.

Population Research (NIA)

The Committee recognizes the Institute's leadership in making data, especially longitudinal data, available to the broader research community. NIA's investments in data infrastructure, such as the ground-breaking Health and Retirement Study [HRS], have spurred significant scientific research findings as well as important interagency and international collaborations. In fiscal year 2018, the Committee urges NIA and SSA to continue working jointly to support the HRS. The Committee also encourages the Institute to consider recommendations recently issued by an outside expert Committee regarding NIA's major surveys and to adopt innovations that will enhance data quality and accessibility. The Committee also urges NIA to pursue data collection and dissemination and research activities via its support of the prestigious Centers of Demography and Economics of Aging.

Action taken or to be taken:

The National Institute on Aging (NIA)-supported demographic, epidemiologic, and longitudinal studies provide the critical data we need to understand trends, track incidence and prevalence of disease, and identify potential risk and protective factors for Alzheimer's and related dementias.

For example, the Health and Retirement Study, the ground-breaking population-based study that follows over 20,000 Americans from age 50 until death, will be renewed in FY 2019. During the next phase of the study, NIA anticipates continuing to collect the comprehensive and high-quality data for which the HRS is recognized while reducing administrative burden on our respondents. We also plan to establish a repository of blood samples for future study; strengthen our collaborations with genetics consortia, which will enable us to link genetic information to social, behavioral, and economic outcomes; and conduct follow-up dementia assessment using the innovative Harmonized Cognitive Assessment Protocol to update data on the national prevalence of Alzheimer's disease and related forms of dementia. Importantly, the first Generation X respondents will be added to the study in 2022, and the study will continue the same expanded minority oversample design for the Gen-X cohort as was implemented in 2010 and 2016 for the baby boom cohorts. NIA looks forward to continuing its fruitful collaboration with the Social Security Administration on this important initiative.

In 2016, NIA's Division of Behavioral and Social Research (DBSR) commissioned an independent assessment of the NIA data infrastructure by a panel of nationally-recognized experts representing the range of fields for which data infrastructure is an abiding concern, including population studies, public health and epidemiology, psychology, economics, sociology, and demography. NIA is using the principles recommended in the report to evaluate proposals for large new data resource projects that emerge either in inquiries from investigators or discussions with staff from other institutes. In addition, DBSR has revived an Office of Research Resources to help coordinate data infrastructure activities, and has asked the National Academy of Sciences to organize a workshop on methodological research for longitudinal studies to find ways make these investments more cost-effective.

Finally, NIA anticipates renewing funding for the Centers on the Demography and Economics of Aging is anticipated to be renewed FY 2019. These prestigious Centers have provided support to over 35 U.S.-based and international data-resources relevant to aging, including the Health and Retirement Study, the National Health and Aging Trends Study, the National Long-Term Care

Survey, the Panel Study of Income Dynamics, and longitudinal and/or population studies in China, India, Latin America, Europe, and Africa.

Population Research (NICHD)

The NICHD Population Dynamics Branch fosters scientific understanding of changes in human health and development at the population level by supporting research and research training in demography, especially through the Population Dynamics Centers Research Infrastructure Program, which promotes efficient use of research funding, innovative research, data sharing, and the development of young scientists. The Branch also spurs scientific innovation in demographic, or population, research by wisely investing in large-scale longitudinal studies, including the Fragile Families and Child Well Being study and the National Survey of Family Growth, the latter which revealed the decline of unintended pregnancies in the United States. The Committee urges NICHD to sustain its investment in the full spectrum of population research activities to advance our understanding of how the demography and health of our Nation are fundamentally intertwined.

Action taken or to be taken:

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), continues to support a wide range of research in demography and population health. In addition to funding investigator-initiated research, NICHD supports large-scale longitudinal research studies including the Fragile Families and Child Wellbeing Study, the National Survey of Family Growth, the National Longitudinal Study of Adolescent to Adult Health (Add Health), and the Panel Study of Income Dynamics Child Development Supplement. These studies provide data to researchers, services programs, and the public. Among the many new projects funded over the last year, NICHD awarded a grant for the continuation of the *National Longitudinal Survey of Youth: Older Children*, comprising large-scale, diverse, multi-generational studies that are collecting data on issues central to the lives of families. NICHD also continues its commitment to curating, archiving, and disseminating data in order to foster research within the scope of the Institute, such as the Data Sharing for Demographic Research archive at the University of Michigan, and the Demographic and Health Surveys project, which provides international harmonized data on maternal and child health, expanding its scope from sub-Saharan African, Egypt, India, to include North Africa, the Middle East, and South Asia. A new program will allow grantees to archive and document existing data sets.

Demography and health research is central to NICHD's mission. In 2017, a long-time grantee received a major award from the Irish government for developing statistical methods that account for uncertainty when forecasting population changes.³⁴³ Recently, a new project was funded to harmonize current and historical international data on under-five mortality, which will allow a most comprehensive examination of factors affecting early-life mortality to date. Another new grant is supporting the development of new methodologies to improve measurement of adolescent and adult mortality in low-income countries. NICHD also recently awarded two new research projects to examine how early life experiences of children affect short- and long-term health. One research team will study the effects of family resources on children's cognitive and behavioral development in the first three years, while the other will examine how educational experiences and adversity in early life affect health during adulthood.

³⁴³ <https://www.nichd.nih.gov/news/releases/Pages/031517-raftery.aspx>

The Population Dynamics Centers Research Infrastructure Program remains a central feature of NICHD's support for scientific research on population. The program provides funding for research infrastructure cores at productive institutions that produce high-impact research and publish innovative work. About a fifth of the 19 center infrastructure grants are re-competed each year. In FY 2017, NICHD funded three center research infrastructure grants and one coordinating and translation center grant.

To foster young investigators in population and demographic research, NICHD also supports the training and development of new and early career population scientists through a wide range of programs, including regular re-competition of its 11 institutional training awards, individual pre-doctoral fellowships, and individual post-doctoral fellows. For career development for investigators at the beginning of their careers, NICHD supports 26 individual career development awards, and two awards to support mentorship by mid-career scientists.

Postural Orthostatic Tachycardia Syndrome [POTS]

With an estimated 1,000,000 to 3,000,000 Americans suffering from POTS, a neurological disorder that affects mostly adolescent and adult women, there are no effective treatments to address this often misdiagnosed and debilitating condition. The level of disability resulting from POTS can be similar to that occurring in multiple sclerosis and congestive heart failure, but little research funding has been dedicated to date to improving understanding of POTS. Due to the lack of effective treatments, many patients are unable to attend school or work, resulting in significant impacts to the U.S. economy. The World Health Organization recently approved the first unique ICD code for POTS, which when implemented, will hopefully enable more precise epidemiological research on the disease. The Committee expects NHLBI and NINDS to work with stakeholders to stimulate the field and develop strategies that will increase our understanding of POTS and lead to effective treatments.

Action taken or to be taken:

The National Heart, Lung, and Blood Institute (NHLBI) and the National Institute on Neurological Disorders and Stroke (NINDS) support research to identify the causes of and discover effective treatments for postural orthostatic tachycardia syndrome (POTS). POTS is characterized by lightheadedness, fatigue, confusion, or memory loss upon standing from a supine or sitting position (called orthostatic intolerance), as well as by a rapid increase in heart rate. It frequently occurs with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

NINDS funds basic research on the control of heart rate by the autonomic (fight-or-flight) nervous system. Although this autonomic control is impaired in POTS, the exact mechanisms are not clear. At the clinical research end of the spectrum, NINDS is supporting a trial to determine whether oral rehydration solution can reduce orthostatic intolerance among patients with POTS and ME/CFS.³⁴⁴ NINDS also supports the multi-center Autonomic Disorders Consortium, a part of the Rare Diseases Clinical Research Network.³⁴⁵ The consortium is currently investigating whether patients benefit from vagal nerve stimulation, in which mild electrical shocks are applied to the earlobe to stimulate the vagus nerve, which regulates heart rate and blood pressure.

NHLBI supports comprehensive research on POTS, with many projects seeking to connect the latest theories about the mechanisms of the disorder to potential new therapies. For example, one theory is that nitric oxide within the body's tissues may contribute to the cardiovascular symptoms of POTS. Nitric oxide plays a normal role in regulating blood pressure. In individuals with POTS, abnormal production of nitric oxide may lead to rapid changes in blood pressure that commonly occur with orthostatic intolerance. An NHLBI-funded study is testing this idea by using very precise methods to simultaneously measure blood flow and nitric oxide levels in small patches of skin in POTS patients.³⁴⁶ A clinical trial is investigating how abnormal fluctuations in blood pressure may affect cerebral blood flow, contributing to the cognitive symptoms of POTS. The trial will also test a drug combination that may improve these symptoms – digoxin, a drug commonly prescribed for heart failure; and pyridostigmine, which may help correct autonomic control of the heart.³⁴⁷ Other projects are investigating the risk

³⁴⁴ <https://www.clinicaltrials.gov/ct2/show/NCT02854683>

³⁴⁵ <https://www.rarediseasesnetwork.org/cms/autonomic>

³⁴⁶ <https://www.clinicaltrials.gov/ct2/show/NCT01791816>

³⁴⁷ <https://www.clinicaltrials.gov/ct2/show/NCT03261570>

factors and causes behind POTS pathology, including a potential autoimmune basis for POTS. NHLBI-funded investigators have discovered that some patients have auto-antibodies directed against their own cellular adrenalin receptors. These antibodies may be responsible for the rapid heart rate associated with POTS, and may hold keys to new, more effective therapies.³⁴⁸

³⁴⁸ https://projectreporter.nih.gov/project_info_description.cfm?aid=9237533

Precision Medicine Initiative [PMI]

The Committee continues its strong support of NCI PMI and provides no less than

\$80,000,000 to continue its efforts to develop individualized treatments for cancer patients. The Committee recognizes the potential for significant advancements in cancer treatments from the NCI MATCH trial. It remains the central pillar of the precision medicine research focused on oncology for cancers that are unresponsive to standard interventions. The Committee urges NCI to continue to expand precision oncology trials. NCI should also continue to focus on launching the important pediatric MATCH trial as pediatric oncology mechanisms are very different from mutations seen in adults. Further, the Committee continues to believe in the necessity of NCI-funded clinical trials in the area of immuno-oncology, where a patient's engineered T-cells are used in combination with the immune system to fight late stage disease and commends NCI for its continued leadership in this area. Of particular interest is the use of precision medicine to develop therapies for late stage cancers and for those forms of the disease for which meaningful conventional treatments have proved largely ineffective for long term survival of the patients. NCI shall provide an update on these activities in the fiscal year 2019 CJ.

Action taken or to be taken:

The National Cancer Institute (NCI) remains optimistic about recent, rapid advances in precision oncology, which continue to propel medicine towards the goal of treating patients with therapies targeted to the unique genetic and molecular changes of their cancers. While the NCI supports a diverse portfolio of research on precision oncology, the NCI Molecular Analysis for Therapy Choice (MATCH) Trial³⁴⁹ and the Pediatric MATCH Trial³⁵⁰ remain the cornerstones of NCI's Precision Medicine Initiative. In 2017, the MATCH Trial exceeded its screening enrollment goal nearly two years ahead of schedule, and the Pediatric MATCH Trial opened for enrollment. Both MATCH and Pediatric MATCH are open to patients for whom conventional treatments have proven ineffective.

Rather than choosing therapies based on where the tumor originated in the body, the NCI MATCH Trial seeks to determine whether treating cancer based on specific genetic changes is effective. The trial is open to patients with solid tumors, lymphomas, or myeloma who have found standard treatments to be ineffective or who have a rare cancer for which no standard treatment exists. Patients enter the trial by first receiving genomic sequencing of their tumors; following sequencing, patients who have a genetic change that matches one of the therapeutic agents available through the trial are enrolled in a treatment arm. Currently, 18 arms are enrolling patients, but due to the novel design of the MATCH Trial, new agents may be added at any time. Eight of the 30 treatment arms have already reached their enrollment goal of at least 35 patients.

As of October 2017, more than 6,400 patients had been screened for the MATCH Trial, and 723 patients have been enrolled in a treatment arm. The original target of 6,000 screened patients was met nearly two years ahead of schedule, with an uncharacteristically large number of patients receiving screening through community cancer centers; more than 1,000 institutions

³⁴⁹ <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match>

³⁵⁰ <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match>

across the United States enrolled a patient for screening, representing all 50 states. Efforts are continuing to enroll patients whose tumors have rare genetic mutations.

In recognition that childhood cancers are genetically distinct from adult cancers, the NCI, through the Children's Oncology Group (COG), launched the Pediatric MATCH Trial in July 2017. The structure of the Pediatric MATCH Trial is similar to its adult counterpart, with the goal of screening 1,000 patients for genetic changes. Researchers expect to screen 200-300 patients per year and will enroll at least 20 patients per treatment arm. As of October 2017, seven treatment arms are open, and three additional arms are expected to open in the coming months. The Pediatric MATCH Trial is accessible at the approximately 200 COG sites across the country, where the vast majority of pediatric cancer patients receive treatment.

While the MATCH Trials will provide extensive data for the analysis of whether matching drugs to molecular targets results in meaningful response rates and improved patient outcomes, the Institute also looks forward to the results of other precision medicine trials, including the Lung Cancer Master Protocol (Lung-MAP) Trial,³⁵¹ the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST),³⁵² and Molecular Profiling-Based Assignment of Cancer Therapy (NCI-MPACT) Trial.³⁵³

In addition to these clinical trials, NCI has continued to expand its efforts in precision oncology. The NCI plans to support new immunotherapy clinical trials, testing new combinations of cell, antibody, small molecule, and radiation therapy studies that include sequencing of tumor specimens. Plans are also underway to develop a consortium of research institutions to conduct deep immunological characterizations of patients enrolled in immunotherapy trials. The Institute also plans to develop new laboratory models that will help researchers gain new insights into tumor biology and better predict patients' responses to cancer treatment, including the Patient-Derived Models Repository,³⁵⁴ the Canine Immunotherapy Models Consortium,³⁵⁵ a piloting consortium of preclinical models, and the Human Cancer Models Initiative.³⁵⁶

The Institute continues to cultivate a national cancer knowledge system to share data among researchers across the country, in the hope of identifying new treatment directions. These efforts include the Genomic Data Commons,³⁵⁷ the NCI Cloud Resources,³⁵⁸ and the Genomics Application Programming Interface.³⁵⁹

The NCI will continue to conduct and support research in precision oncology, which holds the promise of treating patients with maximum efficacy and minimal side effects.

³⁵¹ <http://www.lung-map.org/>

³⁵² <https://www.cancer.gov/types/lung/research/alchemist>

³⁵³ https://dctd.cancer.gov/majorinitiatives/NCI-sponsored_trials_in_precision_medicine.htm#h05

³⁵⁴ <https://pdmr.cancer.gov/>

³⁵⁵ <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-001.html>

³⁵⁶ <https://ocg.cancer.gov/programs/HCFI>

³⁵⁷ <https://gdc.cancer.gov/>

³⁵⁸ <https://cbiit.cancer.gov/ncip/cloudresources>

³⁵⁹ <https://gdc.cancer.gov/developers/gdc-application-programming-interface-api>

Pregnancy-Related Research

Each year, approximately four million women give birth in the U.S. Pregnancy research is essential to learning more about the health and development of both mother and baby, yet this research lags behind disease or organ-specific research. The U.S. is ranked 47th globally for its maternal mortality rate, and unlike any other industrialized country, its rates are on the rise. As maternal mortality and maternal morbidity increases, health care costs rise, and pregnancy presents a greater need for improved research and clinical guidance, the need to understand how to manage pregnancy better to prevent poor outcomes and to have evidence-based guidelines for management of high-risk pregnancies is imperative. The Committee requests that NIH conduct a state of the science report on pregnancy research and provide an update in the fiscal year 2019 Congressional Justification. The Committee requests the following additional information from the NIH as it relates to research in pregnancy, for each of the last three years: the number of clinical research awards, including all Institutes and Centers, addressing questions related to pregnancy; within NICHD, what is the proportion of the total NICHD budget spent on clinical research involving pregnancy; and how might NIH better address questions related to pregnancy across the ICs.

Action taken or to be taken:

Pregnancy-related health outcomes are influenced by a woman's health and other factors such as age, income, race/ethnicity, and potential complications of co-existing conditions. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports a large portfolio of research on the diverse aspects of pregnancy and maternal health. The NICHD-supported Maternal-Fetal Medicine Unit (MFMU) Network designs programs and treatments for the prevention of preterm birth and for the improvement of maternal and infant outcomes using evidence-based medical practices. NICHD also partners with other NIH Institutes and Centers (ICs) on research related to aspects of pregnancy. NICHD joined with the National Heart, Lung, and Blood Institute (NHLBI) to support a sleep study to estimate the prevalence of sleep apnea among 3,700 women in their first pregnancies; initial analysis showed that sleep apnea during pregnancy was associated with the development of hypertensive disorders of pregnancy and gestational diabetes.

Medication use during pregnancy remains a critically needed area of research. Recently, NICHD-funded researchers reported that pregnant women being treated with buprenorphine for opioid dependence need more frequent daily doses of the medication than the currently recommended dosing for non-pregnant women. NICHD's Obstetric-Fetal Pharmacology Research Network provides the expert infrastructure needed to test therapeutic drugs during pregnancy. A recent clinical study showed that women who were known to be at high risk of preeclampsia who had been given the cardiovascular drug Pravastatin did not develop preeclampsia. NICHD is leading the new, trans-agency, congressionally mandated Task Force on Research Specific to Pregnant Women and Lactating Women, which will provide recommendations to the HHS Secretary and Congress on how to address research gaps on prescription medications commonly used by, but not tested or labeled for, these populations. Another large, collaborative research endeavor, the Human Placenta Project, will continue advancing research on the least understood human organ, the placenta, and one of the most important for the health of both woman and fetus during pregnancy and thereafter. Working with the National Institute of Biomedical Imaging and Bioengineering (NIBIB), industry, and others, this project is aimed at assessing placental development in real time and developing

interventions to prevent abnormal placental development and improve pregnancy outcomes. Another NICHD project, known as PregSource™, is using a crowd-sourcing approach, asking pregnant women who wish to participate, to enter information regularly and directly about their pregnancies into online surveys and trackers via a website. This project will help researchers better understand the range of physical and emotional alterations that women experience during pregnancy and after giving birth, the impact of these experiences on their lives, and the challenges encountered by special sub-populations of women before and after childbirth.

In mid-2017, NIH completed a multi-year effort to improve the agency's reporting on research related to pregnancy, maternal health, and infancy. Three new reporting categories were developed – pregnancy; maternal health; and breastfeeding, lactation, and breast milk. With the release of these new trans-NIH reporting categories and re-alignment of existing categories in infant mortality and preterm birth for FY 2017, NIH will be able to provide detailed and accurate reporting on these topics in the years to come. Preliminary data indicate that at least 21 NIH ICs support research related to pregnancy, and that the bulk of the portfolio focuses on clinical research. Areas of emphasis coordinated across multiple NIH ICs include gestational diabetes, preeclampsia, nutrition, obstetric pharmacology, the effects of environmental exposures during pregnancy, infectious diseases during pregnancy, and postpartum depression.

Preterm Birth Research

The Committee applauds NICHD's work with leading global health organizations to develop a research agenda aimed at reducing preterm birth. Public and privately funded research that spans the range of discovery, development, and delivery science is needed to identify the causes of premature birth. The Committee urges NICHD to enhance investments in biomedical and clinical research related to the prevention of preterm birth and the care and treatment of preterm infants.

Action taken or to be taken:

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) continues to support a diverse research portfolio related to the causes and prevention of prematurity as well as decreasing the potential complications of preterm delivery. New research shows that the smallest preterm infants may be at increased risk of additional chronic health problems later in life, such as asthma and obesity. The NICHD-supported Maternal Fetal Medicine Units (MFMU) Network has a long history of conducting clinical research on the prevention of preterm birth and improved treatments for associated medical problems. One ongoing MFMU study is focused on preterm delivery prevention in twins, which account for only 3% of all live births but are responsible for 15% of all infant deaths due to the higher rate of preterm birth. To date, no screening or intervention strategy has proven effective in reducing the risk of preterm birth in twins. However, promising but limited data shows that pessary therapy and treatment with the hormone progesterone may decrease preterm birth in women with a twin gestation and short cervix. To test these approaches, the MFMU Network is currently conducting a randomized clinical trial to assess whether hormone progesterone pessary therapy and treatment reduce the risk of preterm delivery prior to 35 weeks in women who are carrying twins, or in women with a singleton pregnancy and short cervix.

The NICHD also is supporting research on the impact that various exposures may have on the likelihood of delivering a baby preterm. Infections during pregnancy account for 25-40% of preterm births in the U.S. and are the primary cause of preterm birth in low resource settings. Recently, a NICHD-funded study showed that pregnant women with asthma may experience a higher risk for preterm birth when exposed to high levels of traffic-related air pollutants such as carbon monoxide. The study found that when women are exposed just before conception and in the early weeks of pregnancy, they faced an even greater risk of preterm birth. Babies infected with cytomegalovirus *in utero* (cCMV) may develop severe health consequences such as hearing loss and even death. A study being conducted by the MFMU is designed to determine whether treating pregnant women who are infected with cCMV with antibodies prior to 6 months of pregnancy could reduce the number of babies infected, thus preventing morbidity and mortality in these infants. In a study of over 100,000 women, NICHD intramural researchers found that maternal overweight and obesity increase the chances of giving birth prematurely. Another NICHD-funded study is exploring whether treating pregnant women who are living with HIV with progesterone could reduce the number of infants born prematurely. The NICHD further leverages its research networks to facilitate collaborations with other NIH institutes to study preterm birth. For example, the National Institute on Neurological Disorders and Stroke (NINDS) provided co-funding for the Beneficial Effects of Antenatal Magnesium Sulfate study, which helped to establish that providing magnesium sulfate therapy to pregnant women at risk of preterm birth helped to reduce the incidence of cerebral palsy in their infants.

NICHHD also supports research to improve the care of infants born preterm. Based on earlier research, administration of antenatal corticosteroids to women at risk of delivering prematurely was shown to reduce neonatal morbidity and mortality in the U.S. Steroids are now a standard treatment for women likely to deliver before 34 weeks of pregnancy to reduce respiratory and other complications, as well as death, among infants born early preterm. However, not all neonates respond similarly to this therapy. To refine these findings, the NICHHD recently supported a study that showed that steroids reduce the occurrence of serious respiratory complications in late preterm infants (34-36 weeks). These children now will be followed until age 6 to determine the effect of steroids on cognitive and lung function. This study has significant implications for over 300,000 pregnancies that are delivered in the late preterm period in the U.S every year.

Prostate Cancer

The Committee is aware of NCI's ongoing investment in prostate cancer research and is concerned that prostate cancer lacks treatments for men with advancing disease as well as adequate diagnostic and imaging methodologies common in other hormone-driven cancers with similar disease burden. To ensure Federal resources are leveraged to the greatest extent possible, the Committee encourages NCI to continue to coordinate its response to these needs with other Federal agencies, including DOD, as well as private research foundations and advocacy groups.

Action taken or to be taken:

Research on the prevention, diagnosis, and treatment of prostate cancer remains a priority for the National Cancer Institute (NCI).

NCI supports a robust research portfolio on diagnostic and imaging methodologies. Continuing the work of the interdisciplinary team of scientists in NCI's Center for Cancer Research (CCR) who developed the UroNav, a system that combines MRI and ultrasound images to biopsy the prostate, researchers in CCR analyzed biopsies from more than 1,000 men who received both standard and targeted biopsies as part of a clinical trial. Both biopsy methods detected a similar number of cancer cases in the group, but targeted fusion biopsies detected more high-grade cancers than the standard procedure.³⁶⁰ In addition, the team determined that fusion imaging improves clinicians' ability to monitor existing prostate tumors and determine whether they have progressed.³⁶¹ The NCI also supports extramural diagnostic and imaging research across the country through the Cancer Imaging Program in NCI's Division of Cancer Treatment and Diagnosis.

In addition to imaging studies, the NCI recently supported a multi-site project that found that a urine sample test for certain biomarkers provided higher specificity over the currently available prostate-specific antigen (PSA) screening for detecting aggressive, early stage prostate cancer. The use of this test, which combines two biomarkers (PCA3 and TMPRSS2: ERG RNA), has the potential to safely exclude men from unnecessary prostate biopsy while retaining high sensitivity for aggressive cancer.³⁶² Data collected through the Prostate, Lung, Colorectal, and Ovarian Screening Trial (PLCO) also continues to answer questions surrounding prostate cancer screening at a population level; this large cohort study of etiologic determinants of cancer spans 10 U.S. screening centers and examines the effects of screening on cancer-related mortality and secondary endpoints in individuals aged 55-74 years. While the screening component of the trial is complete, numerous epidemiologic and ancillary studies are underway to answer related crucial questions.³⁶³

To guide the development of future directions in research on improving diagnostic techniques and prevention strategies, NCI supports research on genetic risk factors and cellular mechanisms that increase prostate cancer risk. One example is the Prostate Tissue Study, conducted by NCI's Division of Cancer Epidemiology and Genetics, which investigates the extent to which

³⁶⁰ <https://www.ncbi.nlm.nih.gov/pubmed/?term=PMID%3A+27130933>

³⁶¹ <https://www.ncbi.nlm.nih.gov/pubmed/27613356>

³⁶² <https://www.ncbi.nlm.nih.gov/pubmed/28520829>

³⁶³ <https://prevention.cancer.gov/major-programs/prostate-lung-colorectal>

concentrations of sex hormones in the blood represent concentrations of these hormones in the prostate.³⁶⁴

The NCI also supports a variety of clinical trials that leverage the latest advances in targeted and immunotherapy to treat advanced prostate cancer. Examples include 1) trials combining immunotherapy and hormone therapy,^{365,366} 2) a trial for patients whose cancer is at intermediate or high risk of spreading that combines a targeted therapy with radiation and antihormone therapy,³⁶⁷ and 3) a targeted therapy for patients with metastatic cancer with an abnormality in a protein called mechanistic target of rapamycin (mTOR), which is identified through genetic testing.³⁶⁸

Many of the projects discussed are conducted through nine prostate cancer Specialized Programs of Research Excellence (SPORes), located across the country.³⁶⁹ The goal of SPORes is to synthesize research across institutions, and to rapidly translate basic research on prostate cancer to prevention and therapeutic clinical trials.

The partnership between NCI and the Center for Prostate Disease Research (CPDR) at the Walter Reed National Military Medical Center, a Department of Defense (DoD) research center, remains vital to advancing prostate cancer research.³⁷⁰ The CCR considers the ability to leverage the unique resources of the intramural program to facilitate cancer research in the extramural community an increasingly important priority. An example is an emerging joint project between the Rutgers Cancer Institute of New Jersey (CINJ) and the CCR. The focus of the program is to jointly study DNA damage and repair as a target for the development of novel cancer therapies. CINJ was awarded a \$2 million grant by the Robert Wood Johnson Foundation specifically to fund CINJ work in collaboration with the CCR investigators. Equivalent intramural resources are allocated to CCR intramural investigators in these areas of research as part of the joint effort between these institutions. This type of intra-extramural mechanism increases the ability to conduct synergistic research between multiple institutions in the future. NCI encourages additional research collaborations in several ways, including supporting academic-industrial partnerships to translate and validate in vivo cancer imaging systems.³⁷¹

Experts from the NCI coordinate and collaborate with their DoD scientific colleagues by serving as DoD Congressionally Directed Medical Research Program (CDMRP) Prostate Cancer Research Program peer reviewers, and on the CDMRP Prostate Cancer Programmatic Panel.

³⁶⁴ <https://dceg.cancer.gov/research/what-we-study/prostate-tissue-study>

³⁶⁵ <https://www.clinicaltrials.gov/ct2/show/NCT01120236?recrs=abdf&type=Intr&cond=Prostate+Cancer&spons=National+Cancer+Institute&draw=1&rank=3>

³⁶⁶ <https://www.clinicaltrials.gov/ct2/show/NCT01867333?recrs=abdf&type=Intr&cond=Prostate+Cancer&spons=National+Cancer+Institute&draw=2&rank=11>

³⁶⁷ <https://www.clinicaltrials.gov/ct2/show/NCT02472275?term=targeted+therapy&recrs=abdf&type=Intr&cond=Prostate+Cancer&spons=National+Cancer+Institute&draw=2&rank=3>

³⁶⁸ <https://www.clinicaltrials.gov/ct2/show/NCT02646319?term=targeted+therapy&recrs=abdf&type=Intr&cond=Prostate+Cancer&spons=National+Cancer+Institute&draw=3&rank=14>

³⁶⁹ <https://trp.cancer.gov/spores/prostate.htm>

³⁷⁰ <https://www.wrnmcc.capmed.mil/Health%20Services/Surgery/Surgery/Urology/SitePages/CPDR.aspx>

³⁷¹ <https://grants.nih.gov/grants/guide/pa-files/PA-17-093.html>

Similarly, DoD colleagues serve as peer reviewers for NCI research proposals. Patient advocates also participate in reviews of research proposals and serve on advisory committees such as the NCI's Council of Research Advocates, the NCI National Clinical Trials Network's Genitourinary (GU) Cancers Steering Committee, and the GU Steering Committee's Prostate Task Force. These collaborative efforts provide important opportunities for colleagues from sister research agencies and programs, and from the cancer research advocacy community, to share their expertise and experience for the benefit of NCI's cancer research portfolio.

The NCI will continue to support and conduct prostate cancer research to increase the rate of early detection and successfully treat the disease, and to minimize negative effects of treatment and improve patients' quality of life.

Psycho-Social Distress Complications

According to the Institute of Medicine, nearly 50 percent of all cancer patients experience distress. Further, studies suggest that distress in cancer patients leads to higher healthcare costs, less compliance with treatment pathways, and poorer health outcomes. While significant advancements have been made in biomedical treatments in cancer care, the Committee is concerned that the unaddressed psycho-social needs of patients are adversely impacting the effectiveness and cost of care, as well as the individuals' overall well-being. The Committee encourages NCI to continue to implement distress screenings in the

NIH Clinical Center and in NCI-funded clinical trials as appropriate, coordinate and share information on this effort with the FDA, and provide an update on such activities in the fiscal year 2019 CJ.

Action taken or to be taken:

The National Cancer Institute (NCI) recognizes the need for psychosocial support for cancer patients and their families during and after treatment, as the effects of therapy extend beyond the physical to distress symptoms such as insomnia, anxiety, fatigue, and depression. The Institute is committed to encouraging the use of distress screenings in clinical trials, supporting research to identify the best methods of providing support to individuals affected by cancer, and promoting known best practices among cancer care providers.

The NCI Community Oncology Research Program (NCORP), one of the key components of NCI's national clinical research infrastructure, conducts health-related quality of life studies for patients on treatment trials and delivers cancer prevention, supportive care and symptom management, screening, and surveillance clinical trials to communities throughout the country. To be eligible to become an NCORP site, institutions must demonstrate that they are able to provide distress screening to patients. Several NCORP sites are also affiliated with NCI-Designated Cancer Centers, another key element of NCI's clinical research infrastructure focused on treatment clinical trials.

Patients who receive treatment through NCI's Center for Cancer Research (CCR) on the main NIH campus may be recommended for distress screening through the Pain and Palliative Care Consultation Service, an NIH-wide program that provides skilled management of symptoms from the burden of disease and treatments. In addition, NCI's Psychosocial Support and Research Program provides comprehensive care and support services to pediatric patients on clinical trials.

The Psychosocial Support and Research Program also conducts research designed to describe how to best support pediatric patients and their families. Current projects include the development and validation of an electronic psychosocial distress screening measure.³⁷² NCI provides support for similar projects focused on adult and pediatric patients around the country. Examples include a tele-healthcare protocol to treat distress in rural cancer survivors³⁷³, an

³⁷² <https://clinicaltrials.gov/ct2/show/NCT02423031>

³⁷³ https://projectreporter.nih.gov/project_info_description.cfm?aid=9262174&icde=36303562&ddparam=&ddvalue=&ddsub=&cr=6&csb=default&cs=ASC&pball=

intervention for mothers of childhood cancer patients to reduce distress,³⁷⁴ and the development of novel programs to identify and treat distress.^{375,376}

NCI's research on psychosocial care is informed by the Symptom Management and Health-Related Quality of Life Steering Committee, established in 2006.³⁷⁷ At monthly meetings, the steering committee addresses the design, prioritization, and evaluation of clinical trials to control cancer symptoms and cancer treatment side effects. The committee's most recent set of strategic priorities, released in 2015, identifies psychosocial distress as a priority area for research.

The NCI recently released two funding opportunity announcements (FOAs) associated with the Cancer MoonshotSM that will lead to the creation of a research consortium on symptom management during and following cancer treatment.^{378,379} The purpose of these FOAs is to promote research on the implementation and evaluation of comprehensive symptom management systems for use in cancer care delivery. This research will provide new insights and valuable evidence that can be used to guide efforts to improve symptom control for cancer patients during treatment and survivorship.

³⁷⁴https://projectreporter.nih.gov/project_info_description.cfm?aid=9272365&icde=36303562&ddparam=&ddvalue=&ddsub=&cr=31&csb=default&cs=ASC&pball=

³⁷⁵https://projectreporter.nih.gov/project_info_description.cfm?aid=9283237&icde=36303562&ddparam=&ddvalue=&ddsub=&cr=21&csb=default&cs=ASC&pball=

³⁷⁶https://projectreporter.nih.gov/project_info_description.cfm?aid=9272369&icde=36303562&ddparam=&ddvalue=&ddsub=&cr=39&csb=default&cs=ASC&pball=

³⁷⁷ <https://www.cancer.gov/about-nci/organization/ccct/steering-committees/ncorp/symptom-management>

³⁷⁸ <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-042.html>

³⁷⁹ <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-043.html>

Pulmonary Hypertension

The Committee applauds NHLBI for identifying the study of underlying mechanisms of disease of PH as one of its areas of focus within its recent strategic vision plan for research. The Committee encourages NHLBI to continue its focus in this area, particularly on idiopathic pulmonary arterial hypertension, so that additional gains can be made that benefit patient outcomes and further improve survivability for affected individuals.

Action taken or to be taken:

The National Heart, Lung, and Blood Institute is dedicated to discovering underlying causes of Pulmonary Hypertension (PH) and effective treatments for patients with PH. NHLBI funding supports research at every level from basic biology to new methods of diagnosis and treatment with the unifying goal to improve patient outcomes.

NHLBI intramural scientists are studying genes and molecular pathways that contribute to inflammation in the pulmonary arteries, which may lead to the development of idiopathic pulmonary arterial hypertension (PAH). Researchers in extramural labs funded by NHLBI are also studying the pathogenesis of PAH, including the role that hypoxia (oxygen deprivation) plays in abnormal pulmonary artery remodeling.

To improve diagnosis of PH and prediction of disease outcomes, NHLBI has partnered with the Pulmonary Hypertension Association to support the Pulmonary Vascular Disease Phenomics (PVDOMICS) program. This multi-center program is gathering in-depth data on the cellular, molecular, and clinical features associated with different types of PH to develop more sensitive diagnostic and prognostic tools for PH subtypes, including idiopathic PAH. Other program goals include identification of biomarkers and clinical characteristics that could be used as surrogate outcome measures in clinical trials, and development of a refined PH classification system to better inform precision medicine. Currently, nearly 400 patients with PH have been enrolled in the program.³⁸⁰ The study is expected to be completed in fall 2021.

Other NHLBI programs, such as the Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Diseases II (CADET II) and the Vascular Interventions/Innovations and Therapeutic Advances (VITA) program have led to several new PH clinical trials. For example, the Pulmonary Hypertension and Anastrozole (PHANTOM) trial will test whether a generic aromatase inhibitor, anastrozole, improves symptoms and quality of life in patients with PH.³⁸¹ Another early phase clinical trial will test the toxicity, pharmacokinetics, and efficacy of the elastase inhibitor Elafin as a novel treatment for PAH.³⁸²

The NHLBI VITA program supports early-stage translational research and development of clinical technologies and therapeutic products that can improve the lives of PAH patients. Thus far, VITA funding has led to a Phase 1 trial for a bioengineered vascular graft substitute, and the successful completion of a Phase II trial for a new PAH monitoring system. Recently, NHLBI has funded projects through the VITA II program that have the potential to improve the health of patients with PAH. One study seeks to develop a novel non-invasive diagnostic technology using polarized xenon and magnetic resonance imaging to measure the transport of oxygen and

³⁸⁰ <https://clinicaltrials.gov/ct2/show/NCT02980887>

³⁸¹ <https://clinicaltrials.gov/ct2/show/NCT03229499>

³⁸² https://projectreporter.nih.gov/project_info_description.cfm?aid=9147499

carbon dioxide between the lungs and blood, and precisely identify abnormalities that are characteristic of PAH. Another study is testing drugs that could reverse the pathological remodeling of blood vessels in the lung that occurs during progression of PAH.

Raising Awareness and Engaging the Medical Community in Drug Abuse and Addiction Prevention and Treatment

Education is a critical component of any effort to curb drug use and addiction, and it must target every segment of society, including healthcare providers (doctors, nurses, dentists, and pharmacists), patients, and families. Medical professionals must be in the forefront of efforts to curb the opioid crisis. The Committee continues to be pleased with the NIDAMeD initiative, targeting physicians-in-training, including medical students and resident physicians in primary care specialties (e.g., internal medicine, family practice, and pediatrics). NIDA should continue its efforts in this space, providing physicians and other medical professionals with the tools and skills needed to incorporate drug abuse screening and treatment into their clinical practices.

Action taken or to be taken

NIDAMeD's mission is to develop and disseminate science-based resources on substance use disorders (SUD) to educate health professionals and those in training about prevention and treatment of SUDs; and enhancing awareness of addiction as a treatable brain disorder. Among other things, the NIDAMeD initiative brings the latest science to clinicians by hosting a centralized Web Portal where relevant resources can be accessed, including continuing medical education (CME) relevant to primary care and treatment providers. In 2012, NIDAMED created two CME courses entitled Safe Prescribing for Pain and Managing Pain Patients Who Abuse Prescription Drugs, to train providers on safe opioid prescribing practices. More than 100,000 clinicians completed these modules and were certified while they were available.

The current phase of the NIDAMED initiative was developed with a Coalition of Health Professions Organizations, and resulted in the latest CME, *the Adolescent Substance Use and Rx Medication Misuse CME/CE*, launched in June 2017 on the NIDAMED Web Portal. As of October 2017, over 1,000 primary care clinicians have completed the course.

Through this project, the National Institute on Drug Abuse (NIDA) has created multiple online modules that focus on: 1) prescription opioids; 2) marijuana; 3) screening for substance use; 4) key messaging to communicate to adolescents and their caregivers about drugs; 5) successful ways for clinicians to engage in conversations with adolescents (ages 13-18), and their parents; and 6) how best to address issues such as privacy and confidentiality. This CME also provides clinician/patient communication tools which include brochures/handouts and an in-office, mobile ready game or app that clinicians can use with adolescents to help initiate a conversation about substance use and provide information about the consequences of use.

In addition to the NIDAMED CME's for health care providers, curriculum resources were developed for current medical students and resident physicians. In partnership with eight medical schools and the American Medical Association's medical education research collaborative, Innovative Strategies for Transforming the Education of Physicians (ISTEP) Associations, NIDA established the Centers of Excellence for Physician Information (NIDA CoEs) in 2004. These curriculum resources can help prepare physicians and clinicians for the challenge of addressing substance use disorders in their patients. Today, almost all schools are using the curriculum developed as required coursework.

Regional Clinical Trial Networks

The Committee encourages NCI to coordinate with other ICs to leverage existing platforms and consider new approaches in conjunction with communities to identify clinical research and fosters enhanced participation in clinical trials by community members. The Committee encourages that the resulting model include robust collaboration with industry partners, the identification of best practices, and methods to efficiently implement clinical studies in the regional networks.

Action taken or to be taken:

The National Cancer Institute (NCI) recognizes the benefits of bringing cancer research and clinical trials to larger and more diverse patient populations, not only for the betterment of the patients, but also for the scientific validity of the trial results as well.

In 2014, after several years of extensive consultation and coordination with many stakeholders, NCI transformed its longstanding Cooperative Group program into the National Clinical Trials Network (NCTN), to ensure NCI and its clinical trials infrastructure best serves patients while keeping pace with the latest advances in cancer research. The NCTN structure includes five U.S. network groups and the Canadian Collaborating Clinical Trials Network. Sites can belong to more than one group, and membership in at least one group allows a site to participate in the trials led by any NCTN group for which their investigators are qualified. Consequently, researchers from a wide variety of academic centers, community practices, and international members associated with the network groups may all enroll patients into NCTN trials.

An important aspect of NCI's efforts to support clinical trial participation in underserved communities is the NCI Community Oncology Research Program (NCORP). Also formed in 2014, NCORP brings cancer prevention and cancer care delivery research to community settings around the country, and complements NCTN. NCORP is comprised of seven research bases, 12 minority/underserved community sites, and 34 community sites. The network also includes more than 900 component sites, affiliates to the minority/underserved and community sites. NCORP is currently engaged in 52 active trials integrating all age levels from pediatrics to the elderly, and its network aims to accelerate accrual to clinical trials, including NCTN trials. For example, NCORP was critical in enrolling patients on the NCI MATCH (Molecular Analysis for Therapy Choice) precision medicine trial. NCORP sites and component sites accounted for 44 percent of all enrollment (approximately 2,640 patients) for NCI MATCH, and played an important role in demonstrating the feasibility of implementing a multi-arm precision medicine cancer clinical trial in the community setting.

Sharing information and resources about NCI's extensive efforts to develop community based clinical trials may aid other NIH Institutes and Centers or extramural research institutions interested in strengthening their clinical trials model. Therefore, NCI program leaders and NCI-supported investigators regularly publish articles about these activities in academic journals and participate in events that are open to the NIH and broader research community. For instance, NCI investigators have published articles identifying messages that may raise awareness, increase interest, and increase accrual in clinical trials.³⁸³ Additionally, NCORP's most recent

³⁸³ See: Massett, H., et al. Raising Public Awareness of Clinical Trials: Development of Messages for a National Health Communication Campaign. *Journal of Health Communication*. 2017; 22 (5): 373-385. Available: <http://www.tandfonline.com/doi/abs/10.1080/10810730.2017.1290715>

annual meeting, held at the NIH, included a progress update on improving the accrual of elderly patients in trials, a discussion of diversity considerations in addressing minority health disparities, and a “blue ribbon panel” featuring experts in community healthcare.³⁸⁴ NCI will continue to share best practices and research results as the Institute continues to support research to evaluate and enhance the implementation of clinical studies in community settings.

³⁸⁴ NCORP Meeting agenda is available here: <https://www.scgcorp.com/ncorp2017/Agenda>

Rehabilitation Research

The Committee encourages NIH to fully implement Section 2040 of the 21st Century Cures Act to enhance the stature, visibility, and coordination of medical rehabilitation research conducted at NIH. The Committee is encouraged by the release of NIH's new Rehabilitation Research Plan, looks forward to reviewing its first annual progress report, and is encouraged by its ongoing efforts to ensure that reporting of rehabilitation research is consistent with the definition of "rehabilitation research" included in the legislation.

Action taken or to be taken:

The National Center for Medical Rehabilitation Research (NCMRR) in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development was established to promote rehabilitation research within the National Institutes of Health, coordinate NIH's research efforts across Institutes and Centers, and foster collaboration with other federal agencies. Together, they provide funding for research projects, career development, small business efforts, and research infrastructure. NCMRR oversees implementation of the updated provisions of Section 2040 of the 21st Century Cures Act; implementation is well underway.

A scientific workshop on the state of rehabilitation research was held in the spring of 2016. This widely attended workshop informed the development of the NIH Research Plan on Rehabilitation, which was published in late 2016. The Plan, which will be next updated in 2021, sets forth NIH's research priorities in five major areas: Rehabilitation Across the Lifespan, Community and Family, Technology Use and Development, Research Design and Methodology, Translational Science, and Building Research Capacity and Infrastructure. The NIH Rehabilitation Research Coordinating Committee, led by NCMRR, coordinates the NIH's efforts in carrying out the Plan's priorities. For example, NCMRR has worked with other NIH Institutes and Centers, and other federal agencies to sponsor research workshops on Clinical Trials in Rehabilitation (2016) and Optimizing the Investment in Medical Devices for Rehabilitation (2017). In addition, NICHD recently awarded new grants to support research infrastructure in rehabilitation, including biomechanics and modeling of movement, and regenerative medicine. Working with other NIH Institutes, multiple funding opportunities on aspects of rehabilitation research have been published, seeking grant applications on sleep disorders in the context of medical rehabilitation, and tailoring cardiac rehabilitation to enhance participation of older adults, among others.

The first analysis of the rehabilitation research portfolio at NIH is complete and will be presented as part of NCMRR's annual report at the December 2017 meeting of the National Advisory Board for Medical Rehabilitation Research. Additional data tracking the first two years of changes in the portfolio following the publication of the research plan will be provided to the Board at its May meeting, 2018. The reporting of rehabilitation research is consistent with the definition in Section 2040 and, as required, the Director of NIH's Division of Program Coordination, Planning, and Strategic Initiatives is now a member of the Advisory Board.

Rehabilitation Research

The Committee recognizes the significant challenges faced by patients with neurological impairments who live in rural areas, where access to assistive devices, medical advice, and community resources can be limited. Proper rehabilitation, with the help of patient “navigators,” is critical to improving patients’ quality of life and preventing further, and more costly, health problems. Therefore, the Committee urges the NIH, acting through the trans-NIH Rehabilitation Coordinating Committee that is chaired by the National Center for Medical Rehabilitation Research at NICHD, to provide greater support for research efforts that involve the combination of patient navigators and assistive health technology, particularly in underserved rural settings.

Action taken or to be taken:

The National Center for Medical Rehabilitation Research (NCMRR), within the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and other Institutes and Centers at the National Institutes of Health (NIH) that support rehabilitation research, actively support the development of assistive health technologies for tele-rehabilitation purposes. The NCMRR is supporting multiple research projects that involve patient navigators and assistive health technologies for individuals with neurological impairments. In addition, the NCMRR provides funds for a number of treatment trials testing rehabilitation therapies remotely or in the home, which would greatly increase the reach of treatments for this population. For example, one currently funded project will build a post-physical therapy, in-home physical activity program for people with Parkinson’s Disease. The device, known as a “dynamic standing table,” consists of a tabletop that oscillates horizontally, signaling to users to shift their body weight. The study will measure whether physical activity can be improved in this often-sedentary population by using this device. Another, ongoing, project funded by the NCMRR is assessing the value of a collaborative care model for children with persistent symptoms after concussion, including a patient navigator to facilitate follow-up treatment. This model of care, once validated, could be extended to underserved populations in rural and remote areas.

NCMRR also provides funding to researchers using the Small Business Innovation Research (SBIR) awards mechanism. One recent award was made to develop automatic positioning capabilities for communication and other equipment for people with severe impairments, helping individuals with disabilities achieve more independence. Another SBIR award is being used to encourage movement by the weak or paralyzed limb following a stroke in the home environment, reducing socioeconomic and geographic disparities in rehabilitation outcomes by facilitating cost-effective in-home training.

The NCMRR supports research on therapies and rehabilitative approaches for Cerebral Palsy (CP), including approaches that could be home-based. For example, sensory feedback can modify how a person uses their muscles; a new partnership between three institutions in the U.S. and one in Italy is examining the effectiveness of small, wearable sensory devices to improve arm function in children with dyskinetic cerebral palsy. Other multi-site trials aimed at improving upper extremity function, walking, and treatment delivery of rehabilitation for children with cerebral palsy are underway, as are studies aimed at providing assistive devices such as exoskeletons or orthoses to assist with gait, toy-based or game-based interventions to

help with rehabilitation in children with CP, and new neuromodulation techniques to help with weakness and paresis (slight paralysis).

Research Centers in Minority Institutions

The Committee continues to recognize the critical role played by minority institutions, especially at the graduate level, in addressing the health research and training needs of minority populations. In particular, the RCMI program fosters the development of new generations of minority scientists for the Nation and provides support for crucial gaps in the biomedical workforce pipeline, with each dollar invested being leveraged to generate an additional five to six dollars in competitive research funding. The RCMI program has the capability to promote solutions to the significant gap in RO1 grant funding among black and other minority researchers when compared to non-minority researchers. The Committee expects NIMHD to engage stakeholders and the Committee if any changes to the RCMI program are being considered, and prior to any Funding Opportunity Announcement release.

Action taken or to be taken:

The Research Centers in Minority Institutions (RCMI) Program aims to expand the national capacity for research in the health sciences by providing support to institutions that offer doctorate degrees in the health professions or in a health-related science, and that have a historical and current commitment to educating underrepresented students. The RCMI program has been enhanced to align better with the National Institute on Minority Health and Health Disparities's (NIMHD's) vision to advance the science of minority health and health disparities. During 2016, NIMHD leadership engaged in a year-long dialogue with key stakeholders regarding the RCMI Program, including several members of Congress, current principal investigators and RCMI scientists, presidents and leadership from RCMI institutions, the advocacy community, and diverse academic and scientific leaders in minority health and health disparities. NIMHD incorporated feedback from these discussions into the proposed plans for the RCMI Program.

Based on this feedback, NIH published a new RCMI Funding Opportunity Announcement (FOA) on Friday, December 9, 2016. NIMHD staff notified key stakeholders, including several members of Congress, current principal investigators, RCMI scientists, and institutional leaders, as well as the advocacy community and diverse academic and scientific leaders. On January 10, 2017, NIMHD held a technical assistance webinar on the RCMI FOA to provide more information about applying for this funding opportunity and responded to a letter requesting clarification from the organization of RCMI institutional principal investigators. There were 107 participants in this webinar. The FOA closed on March 8, 2017. Grant applications were peer reviewed when the Scientific Review Group met June 21-23, 2017. The National Advisory Council on Minority Health and Health Disparities provided the secondary level of review when the Council met on September 8, 2017 and NIMHD issued seven awards by the end of the fiscal year. NIMHD continues to support ongoing RCMI programs at an additional 12 institutions.

The RCMI programmatic content requirements remained essentially the same, with continued support to strengthen research infrastructure and capacity, recruitment of new faculty, professional development activities for faculty, and funding scientific pilot projects. The main changes were the addition of scientific research projects as a programmatic requirement and the required minimum allocation of resources for pilot studies. The RCMI program has been modified to align better with the Institute's vision to advance the science of minority health and health disparities. The RCMI FOA issued in December 2016 is more flexible with options for one to three types of research studies for basic, clinical, and/or behavioral research. The most

recent FOA for RCMI applications was published in September 2017 and closed in December 2017.

NIMHD continues to seek innovative ways to strengthen the alignment of RCMI with the core mission of NIMHD so that the program contributes to both the enhancement of the biomedical research workforce's diversity and research that improves the health of minority communities as well as advances knowledge in health disparities science. NIMHD will continue to engage the stakeholders and the Committee if any changes to the RCMI program are being considered, and prior to any Funding Opportunity Announcement release.

Research Facilities

Much of the Nation's biomedical research infrastructure, including laboratories and research facilities at academic institutions and nonprofit research organizations, is outdated or insufficient. For taxpayers to receive full value from their considerable investments in biomedical research, researchers must have access to appropriate research facilities. \$50,000,000 is provided for grants or contracts to public, nonprofit, and not-for-profit entities to expand, remodel, renovate, or alter existing research facilities or construct new research facilities as authorized under 42 U.S.C. section 283k. The Committee urges NIH to consider recommendations made by the NIH Working Group on Construction of Research Facilities, including making awards that are large enough to underwrite the cost of a significant portion of newly constructed or renovated facilities.

Action taken or to be taken:

The Office of Research Infrastructure Programs (ORIP), located in the Division of Program Coordination Planning and Strategic Initiatives (DPCPSI) within the NIH Office of the Director, is authorized to issue and manage construction awards to biomedical extramural research institutions, when funds for such awards are appropriated by Congress pursuant to authorities in 42 U.S.C. Section 283k.

Consistent with Federal regulations, NIH submits all construction grant applications to a two-level peer review process. The first level of review is for scientific merit and is conducted by the Scientific Technical Review Board (STOD) authorized by 42 U.S.C. Section 283k; the second level is overseen by the DPCPSI's Council of Councils. Following funding decisions and issuing of the Notice of Award, applicants are required to submit design construction documents; these documents are reviewed by the NIH Office of Research Facilities (ORF) Division of Technical Resources (DTR) to ensure compliance with the NIH Design Requirement Manual. Grant recipients are allowed to proceed with construction only after the design documents have been accepted by DTR. This formal review process ensures that taxpayers receive the full value of investments in biomedical research.

In addition, in accordance with Federal regulations, NIH provides construction surveillance to ensure that construction is compliant with the approved design documents. Lastly, NIH monitors the long-term use of the facility for its intended functions under the Notice of Federal Interest.

Research Initiative on Ethnic and Racial Diversity in Cancer

The Committee recognizes that the NIH's Cancer Moonshot initiative aims to accelerate the discovery of new ways to cure cancers, including through an understanding and application of cancer genetic information to the prevention and treatment of cancer. The Committee urges the NIH, through the NIMHD and NCI, to continue to support research on the cause, prevention, and treatment of cancer in populations with diverse cultural, racial, and ethnic composition. To further support such collaborations, the NCI is encouraged to consider research expertise in ethnic and racial diversity and its impact on cancer development and outcomes in evaluating applications for NCI-designated cancer centers.

Action taken or to be taken:

The National Institutes of Health (NIH), particularly through the National Cancer Institute (NCI) and the National Institute on Minority Health and Health Disparities (NIMHD), support a wide range of research projects that study the cause, prevention, and treatment of various forms of cancer that affect racial, ethnic, and culturally diverse populations. Reducing cancer disparities is a cross-cutting theme of the Blue Ribbon Panel (BRP) report and recommendations guiding the Cancer MoonshotSM to accelerate cancer research progress.³⁸⁵ As part of the BRP recommendations, NCI and NIMHD established four working groups to facilitate the implementation of the report's recommendations to address cancer disparities among racial and ethnically diverse communities and health disparity populations. NCI and NIMHD have partnered on the development of new initiatives related to symptom management research, retrospective analysis of biospecimens from patients treated with standard care, evidence-based approaches to prevention and screening, direct patient engagement, and the creation of a cancer immunotherapy network.

In recognition that racially and ethnically diverse populations and those from urban and rural areas who are poor and medically underserved continue to suffer disproportionately from certain cancers, Cancer MoonshotSM funding opportunity announcements (FOAs) include language highlighting the need for research in health disparities. Where applicable, the research strategies of proposed work for the Cancer MoonshotSM FOAs must address how data from racially and ethnically diverse populations will be integrated into the proposed studies. Cancer Moonshot FOAs that emphasize disparities research include 1) approaches to identify and care for individuals with inherited cancer syndromes,³⁸⁶ 2) improving smoking cessation in socioeconomically disadvantaged populations via scalable interventions,³⁸⁷ and 4) fusion oncoproteins in childhood cancer (FusOnC2) consortium.³⁸⁸

In addition to the work supported by the Cancer Moonshot, the NCI has recently funded several major research initiatives aimed at describing and understanding health disparities. In FY2017, NCI awarded funding to the University of Southern California and Boston University to lead the Breast Cancer Study in African-Ancestry Populations, the largest study to date on how genetic and biological factors contribute to breast cancer risk among African-American women.³⁸⁹ The

³⁸⁵ <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/blue-ribbon-panel>

³⁸⁶ <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-041.html>

³⁸⁷ <https://grants.nih.gov/grants/guide/pa-files/PA-16-202.html>

³⁸⁸ <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-049.html>

³⁸⁹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9297261&icde=36467620

NCI-supported Detroit Research on Cancer Survivors (Detroit ROCS) Study was launched by Wayne State University School of Medicine and the Karmanos Cancer Institute; this cohort study will support a broad research agenda looking at the major factors affecting cancer progression, recurrence, mortality, and quality of life among African-American cancer survivors.³⁹⁰ The NCI awarded funding to the University of New Mexico Comprehensive Cancer Center, the Albuquerque Area Indian Health Board, and six Pueblo tribes in the rural Southwest to conduct a study on the efficacy of interventions designed to enhance annual colorectal screening among American Indian populations.³⁹¹ The NCI also helped to ensure the future of cancer disparities research by supporting the Southeast Partnership for Improving Research and Training in Cancer Health Disparities, run by the Louisiana State University Health Sciences Center and the Moffitt Comprehensive Cancer Center, and focused on advancing translational research on the biological mechanisms of cancer health disparities by focusing on biospecimen-based research and precision medicine.³⁹²

Individuals from areas with limited access to healthcare, particularly in rural communities, continue to experience higher than expected morbidity and mortality rates. The NCI regularly participates in nationwide meetings to discuss research priorities and evidence-based intervention implementation for rural populations, including two events in FY2017. The Institute also issued an FOA on the integration of individual residential histories into cancer research.³⁹³

NCI and NIMHD encourage further research on disparities through a variety of FOAs, on topics that include 1) mechanisms of disparities in chronic liver diseases and cancer,³⁹⁴ 2) collaborative minority health and health disparities research with tribal epidemiology centers,³⁹⁵ 3) surgical disparities research,³⁹⁶ 4) social epigenomics research focused on minority health and health disparities,³⁹⁷ and 5) addressing the causes of health disparities and health advantages among immigrant populations.³⁹⁸ Additionally, NCI has recently issued FOAs on basic cancer research in cancer health disparities³⁹⁹ and leveraging population-based cancer registry data to study health disparities.⁴⁰⁰ The NIH remains committed to reducing the burden of cancer for all populations within the United States.

³⁹⁰ https://projectreporter.nih.gov/project_info_description.cfm?aid=9107577&icde=36467790

³⁹¹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9247763&icde=36506948&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball

³⁹² https://projectreporter.nih.gov/project_info_description.cfm?aid=9418806&icde=36450382

³⁹³ <https://grants.nih.gov/grants/guide/pa-files/PA-17-298.html>

³⁹⁴ <https://grants.nih.gov/grants/guide/pa-files/PA-17-150.html>

³⁹⁵ <https://grants.nih.gov/grants/guide/pa-files/PA-17-484.html>

³⁹⁶ <https://grants.nih.gov/grants/guide/pa-files/PA-16-391.html>

³⁹⁷ <https://grants.nih.gov/grants/guide/pa-files/PA-16-355.html>

³⁹⁸ <https://grants.nih.gov/grants/guide/pa-files/PA-17-041.html>

³⁹⁹ <https://grants.nih.gov/grants/guide/pa-files/PA-15-093.html>

⁴⁰⁰ <https://grants.nih.gov/grants/guide/pa-files/PA-17-289.html>

Research on the Long-Term and Developmental Health Effects of Zika

The Committee recognizes the unique nature of NICHD research into how the Zika virus infection affects pregnancy and the long-term and developmental health effects on children exposed to the Zika virus. The Committee urges NICHD to prioritize investment into long-term and developmental health effects of the Zika virus as the fight against the virus continues.

Action taken or to be taken:

Zika virus (ZIKV) is primarily a mosquito-borne flavivirus. In 2015, Zika virus began spreading rapidly in South and Central America, and also appearing in U.S. territories and the continental U.S. Zika was originally considered to be a mild infection. However, in the more recent outbreaks, Zika was noted to be transmitted sexually and, most important, transmitted vertically from mother to child during pregnancy, causing far more serious health outcomes, including microcephaly and other birth defects. In 2016, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) sponsored a scientific workshop to identify the range of effects of Zika virus on child development.⁴⁰¹

NICHD, in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Environment Health Sciences (NIEHS), and Fundacao Oswaldo Cruz-Fiocruz, the national scientific organization linked to the Brazilian Ministry of Health, launched the Zika in Infants and Pregnancy (ZIP) Cohort study in 2016, a multi-country study aimed at evaluating the magnitude of health risks that Zika virus infection poses to pregnant women and their pregnancy outcomes. Over 5,300 participants have been enrolled to date at sites in Brazil, Colombia, Guatemala, Nicaragua, Peru, and U.S. Puerto Rico. Women participating in the study will be followed throughout their pregnancies to determine if they become infected with Zika virus and, if so, what are the health outcomes of the mothers and their children. Participating infants also will be followed for at least one year after birth. The next phase of the ZIP Cohort Study will focus on understanding the longer-term health effects of Zika infection by extending the follow-up of infants to at least 4-5 years of age, tracking the full spectrum of adverse cognitive and health outcomes in these children. In addition, recent data (in mice) indicate that Zika infection affects the testis and sperm quality, so the ZIP study is being leveraged to evaluate male partners and symptomatic men in Zika endemic areas.

Scientific questions remain concerning the impact of Zika co-infection with other viral infections. To address some of these questions, the NICHD has also launched the Prospective Cohort Study of HIV in Zika in Infants and Pregnancy (ZIP-HIV Cohort study) with a focus on HIV/ZIKV co-infected individuals. This is a two-phase, prospective international cohort study of pregnant women and their infants; its goal is to compare the incidence of ZIKV infection among pregnant women with and without HIV infection and to determine the risk of adverse maternal and child outcomes associated with Zika and HIV co-infection across clinical sites in the continental U.S., Puerto Rico, and Brazil. Other concerns include whether infection with the Zika virus and HIV might increase the risk of damage to the fetal brain seen with Zika virus. The infants enrolled in the study will be followed for at least one year.

⁴⁰¹ Kapogiannis BG, Chakhtoura N, Hazra R, Spong CY. Bridging Knowledge Gaps to Understand How Zika Virus Exposure and Infection Affect Child Development. *JAMA Pediatric*. Feb 20, 2017

NIH welcomes investigator-initiated applications to further explore the impact of the Zika virus on human health and development. In 2017, NICHD, along with other NIH institutes, published a funding opportunity⁴⁰² to investigate Zika virus complications with specific focus on infant and child outcomes such as vision, hearing, neurological, and neurodevelopmental complications.

⁴⁰² <https://grants.nih.gov/grants/guide/pa-files/PA-17-085.html>

Science Education Partnership Awards (SEPA)

SEPA fosters important connections between biomedical researchers and K-12 teachers and their students. These connections establish an education pipeline to careers in biomedical sciences, which is one of the most important areas of workforce development for the U.S. economy. SEPA has been level funded for a number of years and the Committee encourages NIGMS to provide additional resources for the program within their general increase for fiscal year 2018. Additional funding should be used to award additional innovative K-12 science, technology, engineering and mathematics educational projects.

Action taken or to be taken:

The SEPA program encourages the development of innovative educational activities for pre-kindergarten to grade 12 (P-12), pre-service and in-service teachers, and students from underserved communities with a focus on Courses for Skills Development, Research Experiences, Mentoring Activities, Curriculum or Methods Development, and Outreach.

Currently, NIGMS SEPA staff have been involved in the following activities:

- Supporting collaborations between SEPA and NIGMS capacity building, and research infrastructure programs within the Center for Research Capacity Building, e.g., Institutional Development Awards (IDeA), Native American Research Centers for Health (NARCH) and workforce diversity in the Division of Training, Workforce Development, and Diversity, e.g., MARC Undergraduate Student Training in Academic Research (U-STAR), Research Initiative for Scientific Enhancement (RISE) or Bridges to the Baccalaureate.
- Collaborations with the Clinical and Translational Science Awards and Research Centers in Minority Institutions programs.
- Using the U13 Conference--Cooperative Agreement funding mechanism organizes and participates in 2 ½ day Annual SEPA Principal Investigator Conference in Washington, DC. A number of program staff from other federal agencies with P-12 science, technology, engineering, and mathematics (STEM) and informal science education (ISE) also participate.
- Program staff conducts workshops and makes presentations at national, professional society meetings such as the 2017 S.E. Regional IDeA, National Association of Science Teachers (NSTA), Association of Science-Technology Centers (ASTC), NSF-funded Association of Informal Science Learning (AISL), as well as more focused conferences targeting citizen science, state teacher association, and the use of interactive digital media for learning. Workshops at these conferences focus on grant application writing and P-12 STEM and ISE resources for teachers, students and the community. The SEPA Exhibit Booth provides greater dissemination outcomes at the larger conferences.
- Market and distribute (over 500,000 shipped to teachers since 2000) the NIH Curriculum Supplement Series resources to P-12 teachers, schools and other education-based organizations.
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To ensure the success of these programs, NIGMS plans to continue to:

- Promote collaborations between SEPA and the NIGMS Center for Research Capacity Building (CRCB) and Training and Workforce Development (TWD) programs.
- Play an active role in trans-NIH P-12 activities, e.g., citizen science and pre-college STEM resources.
- Participate in the P-12 CoSTEM Interagency Working Group activities.
- Partner with the other federal agencies to pool P-12 STEM and ISE resources and market these to teachers.

Scleroderma

The Committee applauds NIAMS for its support of research into diseases that cause fibrosis in various organ systems, such as scleroderma. The Committee encourages NIAMS to prioritize research in this area and pursue collaborative opportunities with other ICs investigating fibrotic diseases.

Action taken or to be taken:

Scleroderma is a complex disease resulting from inflammation and causing soft tissue scarring and hardening in the skin, blood vessels, gastrointestinal tract, lung, heart, kidney, muscles, and joints. It is an autoimmune disease in which much of the tissue damage is thought to be caused by the patient's own immune system. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) continues our strong commitment to scleroderma research through investigator-initiated grants, Institute initiatives, as well as other collaborative efforts. In FY 2017, NIAMS funded projects to improve clinical trial design for a type of severe scleroderma and to better define outcome variables in scleroderma-associated interstitial lung disease clinical studies. Further, NIAMS funded a Core Center for Clinical Research focused on translational, clinical, and outcomes research on scleroderma and lupus in a minority patient population. Several Small Business Innovation Research grantees are also pursuing projects related to scleroderma, such as the development of a cellular immunotherapy for scleroderma and a 3-D bioengineered skin-like tissue model that mimics scleroderma and could aid in preclinical drug testing.

Since scleroderma can cause fibrosis in a number of organs, multiple NIH Institutes and Centers share a strong interest in fibrosis research. In 2016, the Fibrosis Scientific Interest Group was formed to facilitate trans-NIH collaborations, create synergy between research programs, and offer opportunities to mentor trainees. The group provides a forum for individuals from NIH and the extramural community to discuss basic, translational, and clinical research related to fibrosis. Since its inception, the group has held several trans-NIH seminars on fibrotic diseases. These efforts represent the NIH's and NIAMS' commitment to supporting scleroderma research to identify new therapeutic targets and advancing promising treatments into clinical trials and, eventually, patient care.

Sexually Transmitted Diseases (STDs)

The Committee is aware of the most recent STD Surveillance Report that found that the total combined reported cases of chlamydia, gonorrhea, and syphilis reached a record high and that the CDC estimates 20,000,000 new STDs occur every year. The Committee encourages NIAID to work in collaboration with CDC to develop effective strategies for prevention and treatment approaches, including vaccine development, to combat STDs, and to increase research to understand the evolution and structure of STDs and the inter-relationship with HIV/AIDS to better control for these diseases.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) supports basic, translational, and clinical research on sexually transmitted infections (STIs) such as HIV/AIDS, chlamydia, gonorrhea, and syphilis, with the goal of advancing improved tools for STI prevention and treatment. This includes the development of new diagnostics, therapeutics, and vaccines, especially for drug-resistant STIs. NIAID also is addressing co-infections with HIV and other STIs, including soliciting research to advance novel interventions and cure strategies in individuals infected with hepatitis B virus and HIV. NIAID collaborations with CDC and other partners are essential to the advancement of STI research.

NIAID supports the development of new strategies to address STIs, including novel therapeutics to treat antibiotic-resistant bacterial infections. NIAID, in collaboration with Entasis Therapeutics, supported a Phase II clinical trial of zoliflodacin, a new antibiotic to treat drug-resistant gonorrhea. Based on promising results from this trial, NIAID is supporting further pharmacological studies of zoliflodacin in conjunction with a global Phase III clinical trial of the drug conducted by Entasis and the Global Antibiotic Research and Development Partnership. NIAID scientists also are performing basic and clinical research on *Chlamydia trachomatis*, bacteria that cause chlamydia and blinding trachoma. NIAID scientists are evaluating the mass administration of an antibiotic used to treat bacterial infections, azithromycin, as a method of controlling *C. trachomatis*-related disease. Additionally, NIAID scientists discovered that a small, circular piece of DNA known as a plasmid plays a major role in *C. trachomatis* virulence. This finding has prompted the scientists to develop an experimental vaccine containing *Chlamydia* that lack this plasmid.

NIAID also tests interventions to prevent and control STIs and assesses the feasibility and accuracy of diagnostic and screening tests via its Sexually Transmitted Infections Clinical Trials Group (STICTG). STICTG is evaluating a point-of-care molecular test for ciprofloxacin-susceptibility to facilitate more prudent use of ciprofloxacin in patients infected with gonorrhea, as well as a rapid STI diagnostic to detect gonorrhea, trichomoniasis, and chlamydia. An STICTG-supported Phase IIB trial is investigating an intravaginal live biotherapeutic gel to prevent bacterial vaginosis, an imbalance of bacteria in the vagina that can increase the risk of other STIs.

NIAID encourages collaboration among experts to advance the development of vaccines for STI prevention. NIAID has convened scientists for vaccine development workshops focused on herpes simplex virus, chlamydia, and gonorrhea. NIAID also supported a review of ongoing STI vaccine research. NIAID also has a robust collaboration with CDC to address public health

issues related to syphilis, and recently partnered with CDC to convene a workshop on “Development of Vaccines to Prevent Syphilis.”

NIAID will continue to support research on STIs, including research on prevention and treatment strategies. NIAID is committed to furthering the development of new diagnostics, therapeutics, and vaccines, as well as continued collaboration with CDC and other partners to strengthen these efforts.

Sickle Cell Disease Research

The Committee understands the burden sickle cell disease places on more than 100,000 Americans. Additionally, Federal research spending on sickle cell disease has historically been eclipsed by other medical conditions that affect fewer Americans. The Committee encourages NHLBI to consider an increased focus on innovation in treatment of sickle cell disease and continue support for highly meritorious research on sickle cell disease.

Action taken or to be taken:

The National Heart, Lung, Blood Institute (NHLBI) has a long history of supporting research that has improved health outcomes for people with sickle cell disease (SCD). Years of study funded by NHLBI and others at NIH led to the discovery of a single genetic mutation that causes SCD, and have generated new treatments, interventions, and screening programs that have improved life expectancy and quality of life for the approximately 100,000 people with SCD in the United States. NHLBI will continue to build on this foundation of knowledge through funding basic and translational research and facilitating cooperation of scientists from different sectors to support innovative SCD treatments.

An NIH-sponsored workshop, “Accelerating Cures in Hemoglobinopathies,” held March 10, 2017, brought together thought leaders in genetic therapies and gene editing, including representatives from academia and the pharmaceutical industry, to accelerate the development of potentially curative therapies for SCD. Workshop participants endorsed the concept of a collaborative consortium of academia and industry partners advancing multiple genetic and cellular strategies simultaneously to optimize and accelerate progress toward a cure.

The Sickle Cell Cures Initiative, currently in development, will engage investigators in academia and industry to conceive and study innovative strategies to cure SCD. Through this initiative, NIH will provide access to scientific expertise and resources that will catalyze the production of genetic therapies for SCD. Additionally, NHLBI’s Excellence in Hemoglobinopathies Research Award program supports eight multidisciplinary research centers to understand mechanisms of SCD and other blood disorders and translate these insights into new therapies.⁴⁰³

NHLBI also is leveraging data science tools to define the burden of SCD and the impact of approved treatments. For example, the Trans-Omics for Precision Medicine (TOPMed) program includes thousands of participants with SCD, which may shed light on genetic and environmental factors that modify disease severity and responses to treatment.⁴⁰⁴ Additionally, NIH is funding development of the PhenX Toolkit, a catalog of measures used in clinical studies (e.g., tests of heart and lung function) that enables researchers studying a particular disease to standardize measures and share data across separate studies. NHLBI is funding a supplement to the PhenX project to develop a set of high-quality standard measures related to SCD and a framework for data sharing across different SCD research projects.⁴⁰⁵

⁴⁰³ <https://www.nhlbi.nih.gov/news/spotlight/fact-sheet/nhlbi-funded-research-centers-target-hemoglobinopathies>

⁴⁰⁴ <http://www.nhlbi.nih.gov/research/resources/nhlbi-precision-medicine-initiative/topmed>

⁴⁰⁵ <https://www.phenxtoolkit.org/index.php?pageLink=about.scd>

NHLBI also supports research to improve patient care. The SCD Implementation Consortium includes eight regional centers working together to identify barriers and close gaps that limit the delivery of consistent, quality care.⁴⁰⁶ This consortium also is developing a new SCD registry.

⁴⁰⁶ <https://www.nhlbi.nih.gov/news/press-releases/2016/media-availability-nhlbi-awards-grants-help-improve-health-outcomes-teens>

Sickle Cell Disease

The Committee encourages NHLBI to prioritize the study of sickle cell disease. Academic medical centers located in States with significant populations of sickle cell patients have made progress in treating the disease through NIH sponsored clinical trials and through blood and marrow transplantation for sickle cell disease, which is currently the only therapy that can cure the disease. However, more research dollars are needed to augment the limited treatment options available if we are to have a real impact on sickle cell disease.

Action taken or to be taken:

Sickle cell disease (SCD) is a genetic blood disorder caused by a variation in one of the genes that encodes hemoglobin, the protein that carries oxygen in red blood cells. The sickle-cell gene variant can cause hemoglobin to aggregate and distort red blood cells into a sickle shape, blocking small blood vessels and causing extreme pain, serious infections, organ damage, and, often, life-threatening complications such as strokes. SCD affects approximately 100,000 people in the United States, among them, one in 365 African Americans.

Although there is no widely available cure for SCD at this time, several therapies supported by the National Heart, Lung, and Blood Institute (NHLBI) have improved the longevity and well-being of people living with the disease. Drugs developed through NHLBI-supported research, such as hydroxyurea, can reduce pain and are effective at reducing blood flow velocities in the brain, a key predictor of stroke in pediatric patients. Additionally, clinical trials have established that bone marrow transplantation can cure SCD when a genetically well-matched, unaffected sibling serves as the donor. However, few patients (less than 25%) have a genetically well-matched related sibling who could provide bone marrow with the immunological compatibility necessary for a successful transplant. NHLBI is now funding trials to test the efficacy and safety of bone marrow transplants from unrelated, but fully matched donors, and related partially matched donors. Treatments used before and after transplant are adjusted to increase the chances of success to overcome the immunological differences between patients and their donors in case of partial matching. If successful, these new transplant strategies could allow almost all patients to benefit from a transplant, regardless of whether they have a fully matched sibling.

An NIH-sponsored workshop, “Accelerating Cures in Hemoglobinopathies,” held March 10, 2017, brought together thought leaders in genetic therapies and gene editing, including representatives from academia and the pharmaceutical industry, to accelerate the development of potentially curative therapies for SCD. Workshop participants endorsed the concept of a collaborative consortium of academia and industry partners advancing multiple genetic and cellular strategies simultaneously to optimize and accelerate progress toward a cure. The Sickle Cell Cures Initiative, currently in development, will engage investigators in academia and industry to conceive and study innovative strategies to cure SCD. Through this Initiative, NIH will provide access to scientific expertise and resources that will catalyze the production of genetic therapies to improve lifespan and quality of life for people with SCD. Additionally, researchers funded through NHLBI’s Excellence in Hemoglobinopathies Research Award program are working to understand mechanisms of SCD and other blood disorders and translate these insights into new therapies.⁴⁰⁷ For example, one group is exploring regulation of a form of hemoglobin that is active during fetal life but is silenced in adulthood by a gene regulator known

⁴⁰⁷ <https://www.nhlbi.nih.gov/news/spotlight/fact-sheet/nhlbi-funded-research-centers-target-hemoglobinopathies>

as BCL11A. The researchers are working to identify key molecular switches within BCL11A. They also are engineering new animal models to test potential small-molecule BCL11A inhibitors that could be used to reactivate fetal hemoglobin in patients with SCD.⁴⁰⁸

⁴⁰⁸ https://projectreporter.nih.gov/project_info_description.cfm?aid=9267496&icde=36898893

Sleep Disorders

The Committee recognizes sleep disorders as a serious public health concern. Sleep disorders affects approximately 70,000,000 Americans and contribute to lost productivity, increase the risk for accidents, and are associated with other chronic illnesses, such as hypertension and mental health conditions. The Committee encourages the NIH to advance the work of the National Center on Sleep Disorders Research, which coordinates research activities across Institutes and Centers. The Committee also encourages NIH to facilitate implementation of the ongoing NIH Sleep Disorders Research Plan.

Action taken or to be taken:

The National Center on Sleep Disorders Research (NCSDR), located within the National Heart, Lung, and Blood Institute (NHLBI), works across NIH to address the biomedical opportunities outlined in the NIH Sleep Disorders Research Plan, which is currently under revision. The NIH Sleep Disorders Research Advisory Board meets twice annually for briefings on NIH sleep-related research, coordination activities, and to discuss research needs and opportunities. In 2017, the Board identified the development of sleep and circadian biomarkers as an urgent research objective, which will be highlighted in the revised Sleep Disorders Research Plan. With guidance from the advisory board and the NIH-Wide Strategic Plan,⁴⁰⁹ NCSDR has led the development of several new funding opportunities to support sleep disorders research, across the spectrum from basic to clinical studies. For example, new initiatives aim to stimulate basic research linking sleep and circadian rhythms to obesity,⁴¹⁰ diabetes,⁴¹¹ and HIV-related co-morbidities.⁴¹² Other initiatives and projects focus on clinical studies to develop and test treatments for sleep disorders. For example, a recent NHLBI-funded multi-site study found that pregnant women with sleep apnea are at higher risk for both gestational hypertension and diabetes. Based on these findings, NHLBI and the National Institute on Child Health and Human Development are jointly funding a clinical trial to examine the benefits of treating sleep apnea among pregnant women. A long-term observational study is also underway to determine whether sleep apnea during pregnancy contributes to the maternal risk of cardiometabolic disease 2-3 years after pregnancy. Other clinical studies are investigating the benefits of adenotonsillectomy in children with obstructive sleep apnea, and working to improve patient adherence to sleep apnea treatment. Another NHLBI-funded network, Prematurity-Related Ventilatory Control: Role in Respiratory Outcomes Clinical Research Centers,⁴¹³ focuses on improving treatment outcomes for premature infants, includes research to understand sleep phenotypes and breathing problems in newborns.

Also in line with the NIH-Wide Strategic Plan, NCSDR is supporting programs to reduce disparities in sleep health and to leverage data science in sleep research. A new three-year program supported by NHLBI and eight other Institutes calls for new studies to elucidate the role of sleep deficiency in health and socioeconomic disparities.⁴¹⁴ The NHLBI-funded National

⁴⁰⁹ <https://www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf>

⁴¹⁰ <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-17-020.html>

⁴¹¹ <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-16-005.html>

⁴¹² <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-18-005.html>

⁴¹³ <https://clinicaltrials.gov/ct2/show/NCT03174301>

⁴¹⁴ <https://grants.nih.gov/grants/guide/pa-files/PA-17-234.html>

Sleep Research Resource allows for big-data sharing, pooling of datasets, and novel analyses of bioinformatically-defined clinical sleep data online by >1000 researchers worldwide.

Sleep Health and Alzheimer's

The Committee recognizes that poor sleep health and sleep disorders promote or influence the development of diseases that impair cognitive functioning, such as Alzheimer's. The Committee encourages research to explore the linkages between the sleep cycle, cardiovascular system, and Alzheimer's in an effort to inform prevention.

Action taken or to be taken:

An estimated 70 million Americans suffer from a sleep disorder, and 50 percent or more older Americans report chronic sleep problems. Disordered sleep has been associated with Alzheimer's disease (AD), both as a potential contributing factor and a likely consequence of the disease. At the same time, cardiovascular diseases and conditions such as high blood pressure and sleep apnea have also been linked with both sleep disorders and dementia. NIH-supported scientists are exploring with increasing interest the complex interrelationships among sleep disorders, cardiovascular diseases, and Alzheimer's and related forms of dementia.

For example, data from the National Heart, Lung, and Blood Institute's (NHLBI) Framingham Heart Study have revealed a parallel decline in the incidence of both cardiovascular disease and dementia over three decades. In a recent study, researchers found an increase in the use of blood pressure medications and in blood pressure control during that time period, suggesting that earlier diagnosis and more effective treatment of stroke and heart disease might be reducing the incidence of dementia.⁴¹⁵ NHLBI and the National Institute of Diabetes and Digestive and Kidney Diseases are also supporting a new initiative aimed to stimulate research linking sleep and circadian rhythms to cardiometabolic diseases such as obesity⁴¹⁶ and diabetes.⁴¹⁷

The National Institute on Aging (NIA) supports research on the relationships among sleep, the cardiovascular system, and AD. Representative ongoing research includes:

- An ongoing study exploring how sleep, circadian rhythms, and cardiometabolic risk are affected by night shift work.
- A study investigating possible links between sleep apnea and early neurocognitive decline, mild cognitive impairment (MCI), and AD among middle-aged and older Latinos, an at-risk population with a large burden of vascular disease.
- A trial to determine whether positive airway pressure therapy can delay the progression of amnesic MCI, the subtype of MCI most closely linked with progression to AD.

NIA-supported investigators are also studying whether accumulation of tau tangles, a pathological hallmark of AD, in the brain's medial temporal lobe contributes to sleep dysfunction and memory loss, as well determining how aging and defective circadian clocks impact blood vessel function and to identify the molecular signals involved. In September 2017, the National Advisory Council on Aging approved in concept a Funding Opportunity Announcement (FOA) soliciting research on the molecular and cellular mechanisms linking disordered sleep and circadian rhythms with Alzheimer's and related dementias. Projects funded under this FOA will be active in FY 2019.

⁴¹⁵ Satizabal C, Incidence of Dementia over Three Decades in the Framingham Heart Study, *N Engl J Med* 2016; 374:523-532, 2016; <http://www.nejm.org/doi/full/10.1056/NEJMoa1504327#t=article>

⁴¹⁶ <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-17-020.html>

⁴¹⁷ <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-16-005.html>

Sleep Health and Cancer

The Committee understands the complex intersection between sleep health and cancer development, cancer progression, and remission. The Committee encourages NCI to continue to explore the role of sleep health in cancer development and progression.

Action taken or to be taken:

The National Cancer Institute (NCI) recognizes the vital role sleep plays in human health, and supports research aimed at bettering the understanding of interactions between sleep and cancer. While insomnia can strike anyone, people living with cancer- who often face immense stress, frequent hospitalizations, and treatments that alter sleep patterns- are particularly susceptible. Sometimes even tumors themselves can cause sleep problems if they itch, put pressure on nearby parts of the body, or cause fever, cough, or trouble breathing. Unfortunately, sleep problems do not always subside once treatment ends. Researchers at Johns Hopkins Medicine found that nearly one in four survivors of childhood cancer had difficulty falling asleep and staying asleep.⁴¹⁸ More than merely an annoyance, increasing evidence suggests sleep disturbance may be a risk factor for depression amongst cancer patients and survivors.⁴¹⁹

At NCI designated cancer centers like the University of Pittsburgh Cancer Institute and the MD Anderson Cancer Center, sleep clinics help cancer patients, who are three times more likely to have trouble sleeping than those who do not have cancer, improve their sleep. Clinics address sleep problems by using behavioral treatments, which may be more effective and cause fewer side effects with longer-lasting benefits than taking medication alone.

In addition, NCI supports several additional research projects focused on cancer and sleep health, including:

- A pilot study using cognitive behavioral therapy (CBT) to reduce emotional distress (including sleep disturbance) on cancer survivors living in rural areas.⁴²⁰
- A project to develop a mobile health (mHealth) treatment for cancer-related sleep disturbance that is culturally targeted to African American breast cancer survivors.⁴²¹
- A study investigating circadian disruption (i.e. sleep disorders) as a risk factor for prostate cancer.⁴²²
- A study that aims to characterize the ways in which obstructive sleep apnea (OSA) relates to cancer incidence and survivorship.⁴²³

⁴¹⁸ <http://www.hopkinsmedicine.org/health/healthy-sleep/health-risks/lack-of-sleep-and-cancer-is-there-a-connection>

⁴¹⁹ <https://cancercontrol.cancer.gov/brp/bbpsb/docs/11-1936.pdf>

⁴²⁰ https://projectreporter.nih.gov/project_info_description.cfm?aid=9262174&icde=36727299&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

⁴²¹ https://projectreporter.nih.gov/project_info_description.cfm?aid=9353357&icde=36727310&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

⁴²² https://projectreporter.nih.gov/project_info_description.cfm?aid=9207451&icde=36727369&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

⁴²³ https://projectreporter.nih.gov/project_info_description.cfm?aid=9305919&icde=36727386&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

- A phase III randomized clinical trial to test the impact of two promising interventions (survivorship education or mindful awareness practices) on sleep disturbance, depression, and fatigue in younger breast cancer survivors.⁴²⁴
- A study examining a potential connection between thoracic radiation and OSA in childhood cancer survivors.⁴²⁵

NCI will continue to support promising research that elucidates the connection between sleep health and cancer development, progression, and remission in order to help cancer patients and survivors live healthier lives.

⁴²⁴https://projectreporter.nih.gov/project_info_description.cfm?aid=9315784&icde=36727414&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

⁴²⁵https://projectreporter.nih.gov/project_info_description.cfm?aid=9402254&icde=36727431&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=

Sleep Phenotypes

The health consequences of sleep disorders such as obstructive sleep apnea and insomnia include increased risk of hypertension, cardiovascular disease and obesity. The Committee is encouraged by the Institute's efforts to improve our understanding of sleep disorders and urges the Institute to partner with other NIH Institutes to continue advancing research for sleep phenotypes and biomarkers that further explore health disparities and the intersection between chronic diseases and sleep.

Action taken or to be taken:

The National Center on Sleep Disorders Research (NCSDR), located within the National Heart, Lung, and Blood Institute (NHLBI), supports research to understand how sleep disorders, sleep deficiency, and circadian rhythm impact health, safety, and society. NCSDR helps to coordinate research across NIH and with other Federal entities including the Centers for Disease Control and Prevention, the Department of Transportation, and the Department of Defense. This coordinating function has enabled an array of NIH initiatives to advance research on sleep biomarkers and sleep phenotypes, such as insomnia and sleep apnea. For example, in FY 2017, NIH launched initiatives to examine associations of sleep and circadian biology with obesity⁴²⁶ and diabetes.⁴²⁷ Because recent NIH-research shows that pregnant women with a sleep apnea phenotype have an increased risk of hypertensive disorders and diabetes during pregnancy, NHLBI and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development are jointly funding a clinical trial in FY 2018 to examine the benefits of treating sleep apnea among pregnant women. NHLBI supports a range of other clinical trials to assess the benefit of treating abnormal sleep phenotypes, including a trial of adenotonsillectomy in children with obstructive sleep apnea.⁴²⁸

An NHLBI-funded network focused on improving treatment outcomes for premature infants includes research to increase understanding of sleep phenotypes and breathing problems in newborns. New investigations are also underway to study sleep phenotypes in people living with HIV, including the impact of sleep disorders on health and quality of life. A new NHLBI initiative aims to stimulate studies of sleep and circadian phenotypes contributing to HIV-associated co-morbidities. NHLBI also has joined with the National Institute on Minority Health and Health Disparities and seven other Institutes in a new three-year initiative to study sleep phenotypes contributing to health and social disparities.⁴²⁹

In 2017, the NIH Sleep Disorders Research Advisory Board identified the development of sleep and circadian biomarkers as one approach to identify sleep phenotypes and facilitate the screening, diagnosis, and treatment of sleep disorders. This objective will be highlighted in a revision of the NIH sleep research plan currently underway.

⁴²⁶ <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-17-020.html>

⁴²⁷ <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-16-005.html>

⁴²⁸ https://projectreporter.nih.gov/project_info_description.cfm?aid=7918056

⁴²⁹ <https://grants.nih.gov/grants/guide/pa-files/PA-17-234.html>

Spasmodic Dysphonia

The Committee encourages NIDCD to expand research on spasmodic dysphonia, a form of dystonia.

Action taken or to be taken:

Spasmodic dysphonia (SD), also referred to as laryngeal dystonia, is a voice disorder that belongs to a family of neurological disorders called focal dystonias. As voice disorders are under-recognized, NIDCD supports basic and clinical research studies that focus on normal voice production and the prevention and treatment of voice disorders.

SD can affect anyone. When a person with SD 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, occurring in roughly one to six of every 100,000 people. The first signs of this disorder start to appear in individuals aged 30 to 50 years. More women than men are affected. Currently, there is no cure for SD, and the most common treatment is the injection of very small amounts of botulinum toxin directly into the affected muscles of the larynx. Repeat injections are necessary as the effects last only a few months. In addition, 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.

NIDCD currently funds research to determine the causes and pathophysiology of SD in order to develop new diagnostics and better treatment options. NIDCD-supported scientists are using multi-modal imaging and next-generation DNA sequencing to identify brain abnormalities and genetic risk factors for SD. By identifying genes responsible for this voice disorder, the Institute is directly addressing the need for better, more accurate detection and diagnosis in this clinical population. NIDCD-supported scientists are now pursuing two new areas for therapies and surgical interventions: locating specific brain areas involved in regulating laryngeal muscles and understanding the neural mechanisms by which they exert their control. In addition, research is also focused on determining if there are deficits in auditory and sensory feedback processing.

NIDCD will continue to support voice disorders research, guided by recommendations from a 2013 NIDCD-sponsored workshop on voice sciences and disorders. Leading experts in the field agreed that it is essential to strengthen the pipeline of future voice scientists by creating collaborative teams to address lingering research questions. Accordingly, NIDCD funds various projects to advance research in voice disorders. This portfolio includes projects to develop biomaterials for engineering vocal fold tissue and ambulatory biofeedback approaches for management of patients with voice disorders. It also aims to improve patient outcomes, health services, and community-based research with special attention to the needs of individuals with low socio-economic status, disparities, rural, second language populations, and women's health.

Spina Bifida

The Committee encourages NIA, NIDDK, NICHD, and NINDS to study the causes and care of the neurogenic bladder and kidney disease to improve the quality of life of children and adults with Spina Bifida; to support research to address issues related to the treatment of Spina Bifida and associated secondary conditions, such as hydrocephalus; and to invest in understanding the myriad co-morbid conditions experienced by individuals with Spina Bifida.

Action taken or to be taken:

The *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development (NICHD) continues to actively support research on Spina Bifida (SB). Research has contributed to the decline in prevalence rate of SB by 31% from 1995 to 2006; this translates into 1,000 fewer babies born with a neural tube defect each year. The NICHD supports scientific research on the genetic, neurological and environmental variables that influence neurobehavioral outcomes for children with SB, the assessment of SB's effects on physical and cognitive development in early childhood, and the development of new diagnostic and ultrasound techniques. Research conducted by NICHD intramural scientists focuses on how nutritional and other interventions might prevent neural tube defects such as SB. NICHD's original Management of Myelomeningocele ("MOMS") study showed that infants who had been diagnosed *in utero* with spina bifida had better health and functional outcomes with prenatal surgery compared to the standard postnatal surgery. MOMS 2, co-funded by the NICHD and the National Institute of Neurological Disorders and Stroke (NINDS), followed the children who had participated in the original MOMS study to school age to assess health outcomes, as well as capacity to live more independently and function more safely in daily life. This follow-up study is determining the effects of prenatal repair on adaptive behavior, cognitive and motor function, brain morphology and microstructure, urologic health, and other aspects at school age. Initial results suggest that fetal surgery also improves long-term functional outcome and ambulatory status, with the majority of children able to successfully complete daily tasks.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports basic and clinical research efforts to address causes and care of bladder and kidney complications of spina bifida. The GenitoUrinary Development Molecular Anatomy Project (GUDMAP) Consortium is expanding knowledge about the developing kidney and lower urinary tract that could lead to new research models of congenital conditions and ultimately organ repair and regeneration. Newly funded basic research studies are examining the role of brain pathways in control of urine retention and release from the bladder, while ongoing research in an animal model is examining how targeted spinal stimulation modulates a specific component of voiding activity in neurogenic bladder. Research recommendations identified from the 2015 NIDDK-hosted meeting, "Research Needs for Effective Transition in Lifelong Care of Congenital Genitourinary Conditions," were published in 2017, and NIDDK hosted a scientific meeting entitled "Individualizing Treatment—Broadening the Framework for Urinary Incontinence Research," which will set the foundation for a 2018 meeting, entitled "Individualizing Treatment for Urinary Incontinence—Evolving Research Questions into Research Plans," including neurogenic bladder.

NINDS supports research on the normal process of neural tube closure as well as neural tube defects, which together may inform new strategies for prevention and treatment. One NINDS-funded project is developing a novel approach to *in utero* repair for SB using placenta-derived

regenerative cells and a bioengineered tissue scaffold. Other NINDS-funded projects focus on understanding and improving treatments for hydrocephalus, which often affects people with SB. Investigators are working to develop less invasive ways to monitor hydrocephalus and shunt function. NINDS also supports research relevant to understanding and treating neurogenic bladder in SB, including efforts to develop a drug to induce urine voiding as an alternative to catheterization, a low oxygen breathing therapy to improve urinary tract function, and a surgical method to restore neural connectivity to the bladder and urethral sphincter.

Sports Related Head Impact Research

The Committee is concerned about the growing prevalence of head impacts, concussion, and the associated risk of concussive morbidities among participants in youth sports. The Committee strongly encourages NICHD to bolster pediatric sports-related concussion research, including investing in research focused on behavioral interventions and other preventative strategies that can reduce head impacts and concussion among young athletes.

Action taken or to be taken:

Prevention, diagnosis, and management of pediatric concussions and their consequences is important to the National Institutes of Health (NIH). In late 2016, NIH convened researchers with expertise on traumatic brain injury, experts on brain development, clinicians who treat youth concussion, and patient advocates to discuss the state of knowledge, the adequacy of current diagnostic tools and treatments, ongoing research, and feasible study designs to address the gaps in knowledge. The critical need for biomarkers (measurable indicators) to prevent and improve treatment for concussion in children arose as a consensus priority from this meeting. Because concussion monitoring currently relies on self-reporting of symptoms, younger patients may present challenges, and objective biological measures are essential. In 2017, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) issued a Small Business Innovation Research award for the development of biomarkers to track the neurocognitive deficits of children and adults with sports-related concussion. This is the first step in creating a point of care diagnostic device using saliva to predict the long-term prognosis of mild head injury patients. In addition, a FY 2019 NIH initiative will develop biomarkers to predict and monitor recovery from persistent symptoms of concussion in youth. These biomarkers will be integrated with patient-reported measures into a risk stratification algorithm to help clinicians diagnose and treat concussions.

Understanding the range of medical and behavioral consequences of pediatric concussions is critical to improve treatment. In 2017, NICHD funded a study of children with brain injury that will relate behavioral outcomes with a type of brain imaging called magnetoencephalography (MEG) to show the mechanisms of injury in mild cases of head injury which are undetectable by current imaging methods. The amount of physical and cognitive rest required by an individual child after a sports-related concussion is being examined in a NIH Exploratory/Developmental Research Grant, which will collect real-time data on the type, duration, and intensity of physical and cognitive rest/activity. The results of this study may shape standards of care and inform treatment decisions about optimal rest or activity following sports-related concussions among youth. Another NICHD-funded study is exploring the utility of commonly used diagnostic methods for predicting persistent post-concussive symptoms and functional impairments in children with mild traumatic brain injury; results are expected next year.

To fill the knowledge gap about the longer-term health consequences of concussions, the National Center for Medical Rehabilitation Research (NCMRR) is currently funding a novel collaborative care trial for athletes and their families who have significant post-concussive syndrome. This multi-site clinical trial will examine the difference between a team-based treatments approaches compared to normal care for athletes who experience symptoms from their concussion outside of the typical recovery period. Another recent grant is testing a web-based self-management program for youth athletes who experience concussion. The Self-

Management Activity-regulation and Relaxation Training (SMART) integrates self-monitoring system with modules to help children cope with symptoms and improve psychological function.

NCMRR invested in the development of one of the first in-helmet force detection system (HIT Tracker) and the InSite Impact Response System that is used on the sidelines to measure head impacts in athletes during practice and competition. This technology was acquired by Riddell, the helmet manufacturer, and its use is becoming more widespread at the high school and college level.

Strategic Focus of Resources (OAR)

The Director of OAR and the Director of NIH jointly determine the total for AIDS research within the NIH appropriation based on scientific need and meritorious scientific opportunity relative to NIH's overall plan. The Committee encourages the Office to use a strategic focus of resources allocated to AIDS towards the highest quality peer reviewed projects aimed at finding cures, creating a vaccine, and developing better treatments for the disease.

Action taken or to be taken:

The NIH Office of AIDS Research (OAR) is responsible for allocating the total HIV/AIDS research budget across the 27 Institutes, Centers, and Offices of the NIH. The OAR has established rigorous processes to ensure that projects funded with the HIV/AIDS budget allocation are aligned with the highest priority research areas, as defined in the Notice (NOT-OD-15-137)⁴³⁰ released by the NIH Director in August 2015, titled NIH HIV/AIDS Research Priorities and Guidelines for Determining AIDS Funding. These priority areas encompass research: to reduce the incidence of HIV; to develop next generation therapies towards a cure for people living with HIV; and, to mitigate HIV-associated comorbidities, coinfections, and complications. Crosscutting scientific disciplines are also highlighted in the Notice, including basic research, health disparities, and training of the next generation of HIV researchers. In addition, the OAR includes behavioral and social sciences research, information dissemination, and epidemiologic research as important cross cutting themes.

The OAR conducts an annual portfolio review of all projects supported with HIV/AIDS research funds to assess alignment with the current HIV/AIDS high priority areas. Projects previously supported with the HIV/AIDS allocation that no longer meet the high priority designation are no longer funded with HIV/AIDS dollars. All funds from projects not aligned with the priority research areas are reinvested by the OAR through the strategic initiative funding process. New high priority, peer reviewed, and scientifically meritorious projects that have the potential for significant impact, as determined by both the Institute/Center and OAR leadership, can compete for and receive support from these funds.

In addition to the portfolio review, the OAR conducts an evaluation of the entire HIV/AIDS portfolio of projects to identify research gaps and opportunities. These analyses allow the OAR to target funding to specific high priority areas of HIV research and emerging scientific opportunities.

In coordination with the OAR, the Center for Scientific Review (CSR) has recently completed an assessment of the cluster of study sections that manage AIDS applications and is making adjustments to optimize the review process. After input from the external community and from the ICs, CSR plans to reduce the number of study sections from 9 to 6. This will improve the review of applications per study section, incorporate emerging areas ranging from basic foundational to population health research, and ensure that the highest priority areas and best scientific ideas are funded.

⁴³⁰ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-137.html>

Stroke

The Committee is concerned that stroke continues to enact a massive burden on our Nation's long-term health and economic stability, and encourages NIH to expand its investment commensurate with the impact on public health, the economy, and innovative scientific opportunities. NINDS shall continue to implement top priorities identified in the 2012 planning initiative for stroke prevention, treatment, and recovery research, particularly augmentation of the Stroke Clinical Trials Network, including early stroke recovery. The Committee lauds the NINDS for its leadership in convening a workshop on "Translational Stroke Research: Vision and Opportunities" and directs the Institute to accelerate implementation of key recommendations and other findings.

Action taken or to be taken:

NINDS continues its substantial investment across the full spectrum of stroke research, with an emphasis on supporting activities that address the priorities identified in the 2012 planning effort. The NIH StrokeNet initiative, one of the major outcomes of the 2012 planning effort, is currently finishing its fifth year of funding, and is supporting eight clinical trials. The trials span stroke prevention (three trials), treatment (four trials), and recovery (one trial), and the NINDS continues to work with the stroke research community to maximize use and impact of the network. The most recent trial (ARCADIA) initiated in the network will determine whether apixaban (a powerful anti-clotting agent) can prevent recurrent stroke in patients who have evidence of atrial cardiomyopathy (a disorder affecting the heart muscle) and a stroke of unknown cause. Recently, the DEFUSE3 trial, which used neuroimaging to safely identify ischemic stroke patients who could be treated with endovascular treatment in an extended time window, became the first StrokeNet trial to be completed when it was stopped early after interim analyses showed a high likelihood of benefit. The first stroke recovery trial (Telerehab) in the network is also nearing completion. This trial is testing whether a therapy via an in-home computer can improve arm recovery after stroke compared to therapy in a clinic. All trials conducted through the network have met or exceeded patient recruitment targets, and NINDS is currently planning for the renewal of the StrokeNet infrastructure grants so that it can continue to serve as a national clinical research network for the stroke community. NINDS is also working with NCMRR to hold a workshop to identify optimal strategies that could be leveraged in StrokeNet to better facilitate translation of recovery and rehabilitation science into clinically proven stroke rehabilitation approaches.

The NINDS also held a stroke translational workshop in November 2016 which led to recommendations for stimulating and enhancing preclinical stroke research⁴³¹. Major topics addressed include creating and validating preclinical outcome measures, validation of experimental animal models, and work to facilitate preclinical data standards, team science, and replication studies. NINDS is committed to working with the community to advance research that addresses the priorities identified from the workshop discussions.

To address basic research priorities identified in the planning effort, NINDS led a trans-NIH small vessel biology working group to encourage multidisciplinary communication on research advances and challenges related to small vessels in both healthy and diseased conditions. As a result of this collaboration, NIH Neuroscience Blueprint funding opportunity announcements are

⁴³¹ PMID: 28751554

soliciting research to map the small blood and lymphatic vessels in the central nervous system, and to explore mechanisms underlying differences between vessels, differences in susceptibility to stroke, role in disease and repair processes, and response to therapies. In addition, with support from National Action Plan for Alzheimer's funding to NIA, NINDS has launched research programs to elucidate mechanisms by which cerebrovascular pathology contributes to dementia, and to develop biomarkers that could be tracked for therapeutic efficacy in phase 2 trials.

Finally, the NINDS is in the early planning stages for an effort to update the 2012 stroke research priorities to build on progress and major advances in the field over the past five years. This will ensure that NINDS investments continue to be guided by community-identified needs and priorities in ways that effectively leverage the current state of the science.

Study of Overrepresented and Medically Underserved Populations with Diabetes

The Committee is concerned about specific diabetic populations that are more likely to be overrepresented and medically underserved. The Committee encourages NIDDK to support research on these specific populations. The Committee also encourages NIDDK to work with Hispanic-Serving Institutions and Historically Black Colleges and Universities in this effort.

Action taken or to be taken:

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is committed to addressing the substantial prevalence and outcomes disparities that exist in type 2 diabetes. For this reason, clinical trials testing type 2 diabetes treatment or prevention strategies as well as studies of the epidemiology of the disease, conducted jointly with Centers for Disease Control and Prevention (CDC), over-recruit from minority populations. This will ensure that results from major NIDDK-supported studies are generalizable to the populations that are disproportionately affected. For example, individuals from underserved populations represented at least 40 percent of participants in several NIDDK-supported studies, including the Diabetes Prevention Program clinical trial and its Outcomes Study, the Glycemia Reduction Approaches in Diabetes: a Comparative Effectiveness Study clinical trial and the Vitamin D and Type 2 Diabetes study. In the Treatment Options for Type 2 Diabetes in Adolescents and Youth clinical trial, 32% percent of participants were African American, 41 percent were Hispanic, and 6 percent were American Indian). NIDDK also supports smaller, focused studies to address diabetes health disparities, such as a project titled “Encouraging Mail Order Pharmacy Use to Improve Outcomes and Reduce Disparities”: cardiovascular (CVD) complications of diabetes are the number one killer of people with diabetes, and although adherence to CVD medication regimens is known to be extremely helpful for lowering CVD risk in people with diabetes, there are substantial racial/ethnic disparities in adherence rates, which this study seeks to address. NIDDK also supplies funding to explore diabetes research questions in the National Heart, Lung, and Blood Institute (NHLBI)-led Hispanic Community Health Study/Study of Latinos. NIDDK recently held a workshop in which experts sought to identify and discuss research opportunities for reducing diabetes and obesity-related health disparities.

While not specifically tailored to minority-serving institutions (MSI), NIDDK’s funding solicitations, like other NIH funding announcements, specifically encourage applications from Hispanic-serving Institutions, Historically Black Colleges and Universities (HBCUs), Tribally Controlled Colleges and Universities, Alaska Native and Native Hawaiian Serving Institutions, and Asian American Native American Pacific Islander Serving Institutions. Furthermore, a grant received by an institution that is not an MSI may enable a partnership with such an institution. For example, the NIDDK-supported Vanderbilt Center for Diabetes Translation Research partners with Meharry Medical College, a nearby HBCU. Initiatives like the NIH Research Supplements to Promote Diversity in Health-Related Research seek to improve the diversity of the research workforce by recruiting researchers from groups that have been shown to be underrepresented in health-related research. NIDDK participates in this program to support researchers that are interested in pursuing research on type 2 diabetes as well as other conditions of importance to NIDDK’s mission. Other programs include NIDDK Travel Awards for the National Medical Association's Annual Convention and Scientific Assembly and NIDDK/National Hispanic Medical Association (NHMA) Travel Awards for Residents and Fellows Attending NHMA’s Annual Conference.

Task Force on Research in Pregnant Women and Lactating Women

The Committee looks forward to an update on the work of the Task Force on Research in Pregnant Women and Lactating Women, and continues to encourage and support the important work of the Task Force to ensure that consumers and health care professionals have up-to-date and accurate information on the safety and efficacy of drugs that women are taking while pregnant or breastfeeding.

Action taken or to be taken:

Implementation of the Task Force on Research Relevant to Pregnant Women and Lactating Women, mandated by the 21st Century Cures Act (P.L. 114-255) is a priority for the National Institutes of Health (NIH). In January 2017, the Secretary of HHS delegated authority for its establishment to the NIH, but retained authority to approve the slate of nominees. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is leading implementation efforts.

Operating as an advisory body under the Federal Advisory Committee Act, a Charter was filed at HHS on March 13, 2017, formally establishing the Task Force and meeting the 90-day timeframe required by the 21st Century Cures Act. The slate includes representatives of the Federal agencies required by the 21st Century Cures Act, representatives of professional societies that serve pregnant and lactating women, patient advocates, and industry delegates. The report on the Task Force's findings and recommendations is due to the HHS Secretary and Congress by September 2018.

The first of four Task Force meetings was held in August 2017, and the second in November 2017. An analysis of currently supported Federal research in this area was presented at the first meeting, and each federal member of the Task Force provided an overview of their efforts in this area. A summary of these efforts will be part of the final report. The November meeting included further information on federal activities related to herbals, vitamins and other dietary supplements for pregnant and lactating women, and a discussion of the ethical issues surrounding the inclusion of pregnant and lactating women in clinical research.

Notices of all Task Force meetings are published in the *Federal Register*. All meetings are open to the public, include a period for public comments, and are videotaped for concurrent or future viewing. In addition, a web page was created on NICHD's website to ensure that any interested parties can access information about the Task Force's deliberations, including information about how to submit comments:

<https://www.nichd.nih.gov/about/advisory/PRGLAC/Pages/index.aspx>. Public comments submitted before or after each meeting also are posted.

Teacher Stress

The Committee is aware that high levels of stress are adversely affecting the health of teachers. Elementary school teachers who have greater stress and show more symptoms of depression create classroom environments that are less conducive to learning. Stress is contributing to the high turnover rate among teachers. The Committee encourages NIH to support research on reducing teacher stress and promoting wellbeing by implementing and analyzing evidence-based stress management programs that will help reduce the stress of teachers.

Action taken or to be taken:

The adverse effects of high levels of stress on health are well documented.⁴³² To address the impact that stress may have on an individual's work, family, and relationships, the National Institute of Mental Health (NIMH) portfolio includes services and intervention research aimed at identifying and supporting mental health needs across a variety of settings, including the workplace.^{433,434,435} In addition, NIMH supports basic and clinical research aimed at elucidating the biological mechanisms that modulate stress, and its relationship to illnesses like depression.^{436,437,438}

To advance intervention efforts that positively impact the mental health and working conditions of teachers, NIMH-funded researchers investigated teacher stress and job satisfaction in high-poverty urban schools.⁴³⁹ The researchers concluded that teacher efficacy, stress, and job satisfaction were associated with the presence or absence of a positive learning environment. The findings also highlighted teachers' relations with their peers, school leadership, and students as important to mitigating a stressful work environment. Another NIMH-funded study investigated a teacher consultation and coaching model in urban elementary schools that was designed to provide personal and professional support in classrooms.⁴⁴⁰ The findings showed there was a need for more implementation research efforts to address the complexities and variations that exist within school organizations and classroom contexts. A third NIMH-funded study sought to measure critical issues for teachers of children with autism spectrum disorder in the classroom;⁴⁴¹ the findings highlighted the importance of providing teachers opportunities for increased collaboration and communication.

To measure the impact that high levels of teacher stress can have on students' classroom experience and achievement, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development recently funded a study showing that in classrooms with teachers reporting more depressive symptoms, struggling learners demonstrated poorer outcomes in math than in

⁴³² <https://www.nimh.nih.gov/health/publications/stress/index.shtml>

⁴³³ https://projectreporter.nih.gov/project_info_description.cfm?aid=9381230&icde=36596196

⁴³⁴ https://projectreporter.nih.gov/project_info_description.cfm?aid=9317064&icde=36596271

⁴³⁵ https://projectreporter.nih.gov/project_info_description.cfm?aid=9214860&icde=36596271

⁴³⁶ https://projectreporter.nih.gov/project_info_description.cfm?aid=9260946&icde=36595073

⁴³⁷ https://projectreporter.nih.gov/project_info_description.cfm?aid=9242073&icde=36596001

⁴³⁸ https://projectreporter.nih.gov/project_info_description.cfm?aid=9424790&icde=36595073

⁴³⁹ <https://www.ncbi.nlm.nih.gov/pubmed/23935763?dopt=AbstractPlus>

⁴⁴⁰ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4896075/>

⁴⁴¹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4676744/>

classrooms with teachers reporting fewer depressive symptoms. Furthermore, the researchers found that teachers experiencing more depressive symptoms were less likely to provide positive feedback to low-achieving students. Based on these results, the researchers concluded that evidence-based programs could provide support for teachers' mental health needs.⁴⁴²

⁴⁴² <http://onlinelibrary.wiley.com/doi/10.1111/cdev.12344/full>

Temporomandibular Disorder Trans-NIH

The Committee recognizes NIDCR's leadership in TMD pain research, which has led to establishing TMD as a multisystem disorder with overlapping pain and non-pain conditions. The Committee encourages NIDCR to continue its leadership as a critical member of the Trans-NIH Working Group on Chronic Overlapping Pain Conditions by promoting and advancing integrated research on these conditions. In addition, as the oral disability associated with TMD affects a patient's nutritional health status, the Committee encourages NIDCR to improve research on orofacial function relevant to the nutritional implications of TMD. Finally, the Committee is aware of the scientific meetings on an integrated systems approach of precision medicine related to cellular-molecular-genetic-epigenetic mechanisms related to diagnosis and treatment of TMD and its comorbid conditions. In 2013, several Institutes co-sponsored a workshop on the topic of the temporomandibular joint. The Committee requests an update on initiatives that resulted from the recommendations that came forth from these meetings in the fiscal year 2019 CJ.

Action taken or to be taken:

NIDCR maintains a leadership role on the NIH Pain Consortium and the Trans-NIH Working Group on Chronic Overlapping Pain Conditions, promoting and advancing integrated research on TMD, orofacial pain, and overlapping chronic pain conditions. Over a decade ago, NIDCR launched the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study to accelerate research to improve TMD and orofacial pain treatments. OPPERA is the first-ever large, prospective clinical study to identify risk factors that contribute to someone developing TMD. In FY 2016 NIDCR began partnering with NIDDK to add investigations of chronic overlapping pain conditions (COPCs) to existing pain cohorts, like OPPERA. As a result, OPPERA has received additional funding to expand the research scope beyond TMD and to develop an easy-to-use online research tool to help identify individuals with COPCs and understand common risk factors across COPCs.

NIDCR also supports research to develop patient-centered non-pharmacological strategies to prevent and treat chronic TMD. Scientists are testing a web-based tool designed to improve diet, sleep, and oral health behaviors, tailored for each individual. This program will help develop the evidence base to empower patients to optimally manage their own health.

As a result of the 2013 trans-NIH Temporomandibular Joint in Health and Disease Roundtable, NIDCR is funding a project that is providing longer-lasting TMD pain relief using a state-of-the-art technology called high-definition transcranial direct current stimulation. This non-invasive procedure stimulates the brain to release naturally occurring opioid-like molecules, a part of the body's pain relief system. The researchers are testing the stimulation method to turn on a receptor protein – called the μ -opioid receptor – that receives a signal from endorphins or opioids to relieve pain. Additional studies in this area could lead to new non-opioid pain management therapies to treat TMD and other pain conditions.

Temporomandibular Disorders (TMD)

The Committee understands that NIH-funded research has demonstrated that temporomandibular disorders [TMD] are primarily a multisystem disorder with overlapping conditions influenced by multiple biological and environmental factors rather than solely an orofacial pain condition.

However, diagnosis and care of patients have not changed to reflect this major paradigm shift, with many patients continuing to receive treatments solely focused on teeth and jaws. Moreover, the medical community lacks education regarding the complexity and systemic aspects of TMD as well as its many comorbid medical conditions. Patients are treated by a multitude of practitioners across numerous disciplines with treatments that have the potential to cause harm. To address these issues, the Committee requests that NIH provide an update on the state of TMD research, activities related to TMD education, and clinical studies of TMD in the fiscal year 2019 CJ.

Action taken or to be taken:

To provide the evidence base needed to improve Temporomandibular Disorders (TMD) diagnosis and patient care, the National Institute of Dental and Craniofacial Research (NIDCR) funds a diverse research portfolio focused on the development, structure, function, regeneration, and replacement of the temporomandibular joint (TMJ), as well as studies on chronic orofacial pain and comorbid conditions associated with TMD. NIDCR also supports Centers of Excellence in Pain Education (CoEPEs), key hubs for developing and distributing pain management curriculum resources to enhance and improve how health care professionals are taught about pain and its treatment. Through CoEPEs, a number of online training modules have been developed for comorbid conditions associated with TMD, including a tutorial on Burning Mouth Syndrome and related orofacial pain.⁴⁴³

NIDCR supports basic research to understand TMJ biology and function to improve long-term health. Scientists are investigating how the TMJ develops, including formation of the disc and joint cavities, maturation of joint lubricant-producing cells, and the long-term maintenance and renewal of TMJ cells and structures that are essential for joint health. Foundational knowledge on TMJ biology is critical for the advancement of joint repair and regeneration.

Another NIDCR-funded project is developing tools to measure the structural changes to temporomandibular bones to improve the ability to evaluate clinical changes in TMD diagnosis, assessment, and treatment. Clinicians, computer scientists, and engineers are collaborating to investigate the use of imaging markers to analyze bones, making much of their data and tools freely available to the scientific community to accelerate TMD research and the development of new therapies.

NIDCR's Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) clinical research study is generating the evidence base to inform the development of novel approaches to treat TMD, orofacial pain, and other overlapping pain conditions. The researchers investigated the role of genetics in pain sensation, and have demonstrated an important function for a signaling protein called epiregulin and its corresponding receptor, epidermal growth factor receptor (EGFR). When the epiregulin-EGFR pathway is activated in mice, the perception of pain was increased, while using drugs that inhibit the EGFR pathway reduced the pain sensation.

⁴⁴³ <http://painmeded.com/>

Additional research on these therapeutic drugs may open new avenues to treat TMD and other pain conditions.

Thoracic Aortic Disease

The Committee is concerned about sudden, preventable death caused by thoracic aortic aneurysm and dissection attributed to structural cardiovascular disorders, such as Marfan syndrome, and encourages NHLBI to further study the mechanisms of disease and opportunities to improve patient health.

Action taken or to be taken:

The National Heart, Lung, and Blood Institute (NHLBI) continues to fund investigator-initiated basic and translational research on thoracic aortic disease to better understand its pathology and to identify strategies to prevent dissection and progression of thoracic aortic aneurysms. NHLBI has a program that focuses on calcific aortic valve disease (CAVD), which is already yielding results that are applicable to thoracic aortic disease. For example, researchers funded through this program are developing a non-invasive molecular imaging approach that could be used to assess the risk of CAVD and other aortic diseases.⁴⁴⁴ NHLBI has renewed this program to stimulate further research into disease mechanisms and the development of novel diagnostic tools and treatments for a variety of aortic diseases.⁴⁴⁵ Funding also includes training support to nurture the next generation of researchers in this field.

NHLBI's National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) was established in 2006 to collect information from patients with genetic conditions that predispose them to thoracic aortic aneurysms. The registry includes de-identified data and biological samples from nearly 4,000 individuals, representing 13 conditions including Marfan, Ehlers-Danlos, Loeys-Dietz and Turner syndromes. NHLBI funding for GenTAC concluded at the end of FY 2016, and its data and biospecimens were transferred to the NHLBI's larger BioLINCC repository, where they remain available at no cost to investigators for research on thoracic aortic disease.⁴⁴⁶ In addition, the GenTAC registry built a lasting infrastructure and patient cohort enabling several foundations and universities to establish new registries that focus on specific conditions included in the GenTAC cohort. These registries will extend the longitudinal data collection initiated by GenTAC and expand the original GenTAC cohort by enrolling new participants.

GenTAC demonstrated the value of studying cohorts of different genetic syndromes with shared cardiovascular outcomes. NHLBI is continuing to engage with investigators and stakeholders in the field to capitalize on the progress made to date.

⁴⁴⁴ https://projectreporter.nih.gov/project_info_description.cfm?aid=9086412

⁴⁴⁵ <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-18-010.html>

⁴⁴⁶ <https://biolincc.nhlbi.nih.gov/home>

Tick-Borne Diseases (NIMH)

Lyme disease and other tick-borne diseases are known to cause a wide range of psychiatric manifestations. Published research has shown a higher prevalence of antibodies to *Borrelia burgdorferi* in psychiatric patients than in healthy subjects. Other tick-borne diseases, such as *Bartonella* have also been reported to cause neurological and neurocognitive dysfunction, as well as causing agitation, panic disorder, and treatment resistant depression. It is therefore plausible that a certain number of cases of severe psychiatric presentations are due to underlying infections, especially since Lyme disease is the number one spreading vector-borne disease in the world. To further investigate this hypothesis, the Committee urges NIMH to review the published literature on links between tick-borne diseases and psychiatric illnesses, and provide an update in the fiscal year 2019 CJ.

Action taken or to be taken:

The mission of the National Institute of Mental Health (NIMH) is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure. NIMH has funded efforts related to understanding the links between tick-borne diseases and mental illnesses. A past NIMH-funded study suggests that Lyme disease may disrupt dopamine function in the central nervous system, but this study did not directly examine symptoms associated with Lyme disease.⁴⁴⁷ A review article summarizing neuropsychiatric manifestations of infectious diseases indicates that no large-scale well-controlled studies suggest that patients with Lyme disease have a higher prevalence of psychiatric symptoms than the general population.⁴⁴⁸ Psychiatric symptoms may develop in patients with Lyme disease, but research is unclear regarding a biological mechanism that might explain a relationship between Lyme disease and mental illnesses.⁴⁴⁹

⁴⁴⁷ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5521197/>

⁴⁴⁸ <http://www.sciencedirect.com/science/article/pii/S0749070417300192?via%3Dihub>

⁴⁴⁹ <http://www.sciencedirect.com/science/article/pii/S0002934312008753>

Tick-Borne Diseases

The Committee encourages NIH to intensify research on Lyme and tick-borne diseases, including research that will increase understanding of the full range of Lyme disease processes and the physiology of *Borrelia burgdorferi* and *Borrelia mayonii*, including the mechanisms of persistent infection such as persisters and potential treatment protocols for identified mechanisms of persistence. The Committee also encourages NIH to intensify research efforts focused on the development of more sensitive and accurate diagnostic tests for Lyme and tick-borne diseases, including next generation polymerase chain reaction and new testing methodologies such as proteomics and metabolomics.

Action taken or to be taken:

The National Institute of Allergy and Infectious Disease (NIAID) maintains a diverse research portfolio in Lyme disease and other tick-borne diseases. In fiscal year 2016, NIAID released funding announcements to encourage research on tick-borne pathogens, including the study of diagnostics, therapeutics, and vaccines to combat these infections, as well as factors that may contribute to post-treatment Lyme disease syndrome.

NIAID engages in important collaborations with Federal partners, Lyme disease experts, patients, and others as a member of the HHS Tick-Borne Diseases Working Group. NIAID is participating in an all-inclusive review of Federal activities and research related to tick-borne diseases led by the Working Group. In addition, NIAID published on its website a comprehensive report titled “Current Efforts in Lyme Disease Research, 2017.” This report describes current research toward improved prevention, diagnosis, treatment, and understanding of why symptoms persist in some patients following recommended treatment. Highlights of NIAID Lyme and tick-borne diseases research are described below.

NIAID supports basic research on how *Borrelia* species, including *B. burgdorferi*, *B. miyamotoi*, and *B. mayonii*, infect the host, multiply, and ultimately cause Lyme disease and related conditions. NIAID grantees are using real-time imaging to track *B. burgdorferi* infection in mice and investigating how *B. burgdorferi* evades the immune system. NIAID scientists have developed a novel tick infection model for flaviviruses that could be used to evaluate tools to combat the deadly Powassan and tick-borne encephalitis viruses. NIAID also supports Lyme disease prevention research, including efforts to target proteins in tick saliva that are critical for effective transmission of *B. burgdorferi*, develop oral-bait vaccines targeting mice and other animal hosts for *B. burgdorferi*, and adapt a successful canine Lyme disease vaccine for potential use in humans.

NIAID is collaborating with CDC and others to develop improved Lyme disease diagnostics including next generation molecular tests. NIAID-supported scientists are working to identify biomarkers that could allow for earlier and more rapid diagnosis; accurate indication of disease stage and progression; indications of successful treatment; and ability to distinguish between Lyme and other tick-borne infections. NIAID researchers and colleagues also are using a process known as xenodiagnosis, which uses disease-free, laboratory-bred ticks to detect *B. burgdorferi* in people that have completed antibiotic therapy. In addition, NIAID is conducting a clinical trial assessing whether continued *B. burgdorferi* infection could contribute to persistent symptoms in patients following antibiotic treatment. The findings of this study may inform Lyme disease diagnostic criteria and future treatment trials.

NIAID remains committed to participating in partnerships and outreach efforts on Lyme and other tick-borne diseases, including public webinars organized along with Federal colleagues. NIAID will continue to work with NLM to ensure that terminology accurately reflects the current state of scientific knowledge about Lyme disease and its effects. NIAID will continue to foster these collaborations and encourage tick-borne disease research to advance the development of vaccines, therapeutics, and diagnostics.

Translational Research Program

The Committee notes the SPORE program is NCI's cornerstone effort to promote collaborative, interdisciplinary translational cancer research. The Committee continues robust support for the SPORE grant program as it works to bring basic research into practical treatments. The Committee requests an update in the fiscal year 2019 CJ on the SPORE program.

Action taken or to be taken:

Established in 1992, the Specialized Programs of Research Excellence (SPOREs) are a key component of the National Cancer Institute's (NCI) Translational Research Program. SPORE grants involve both basic and applied/clinical science, and support projects that will result in new and diverse approaches to the prevention, early detection, diagnosis and treatment of human cancers. There are currently 50 fully funded SPOREs focusing on 18 organ sites, groups of related cancers, or diseases that share a common pathway or cross-cutting theme. Specifically, these are brain, breast, cervical, endometrial, gastrointestinal, head and neck, kidney, leukemia, lung, lymphoma, myeloma, neuroendocrine, ovarian, pancreatic, prostate, skin, and thyroid cancers, as well as hyperactive RAS tumors. SPOREs are currently awarded in 22 states and at 32 institutions.

The original SPOREs were focused on high incidence solid malignancies including breast, prostate, lung, and gastrointestinal cancers. In recent years, additional SPOREs were included that focus on a common pathway or different cancers that are tied together thematically. For instance, the Developmental and HyperActive Ras Tumor (DHART) SPORE focuses on devising better treatment for cancers and pre-malignant conditions associated with Neurofibromatosis 1 (NF1) mutations. Persons with NF1 have a markedly increased incidence of developing specific tumors, which are frequently diagnosed in children, adolescents, and young adults. Furthermore, research on patients with NF1 has broad relevance for improving the treatment of a large number of cancers arising in patients without NF1 that carry mutations in NF1 or RAS genes, including glioblastoma, lung cancer, melanoma, and leukemia.

Precision medicine, an emerging approach for disease treatment that considers individual variability in genes, environment and lifestyle, and immunotherapy, a treatment that uses the body's own immune system to fight cancer, are rapidly changing the way cancer is studied and treated. In May 2017, the Food and Drug Administration (FDA) issued the first ever approval of a "tumor-agnostic" cancer treatment, basing the approval on the tumor's specific genetic features rather than the location in the body where the tumor originated. Researchers supported by NCI SPORE grants have studied whether the immunotherapy drug, pembrolizumab, could be used to treat patients with tumors with mismatch repair deficiency (dMMR), an inheritable DNA repair defect. The positive trial results and other data led FDA to grant pembrolizumab accelerated approval for the treatment of dMMR cancers, creating a new option for patients who might not otherwise be candidates for this therapy.⁴⁵⁰

Recently, five-year SPORE awards made in FY2017 include four new SPORE sites and three competitive renewals:

⁴⁵⁰ <https://www.cancer.gov/about-nci/budget/plan/2019-annual-plan-budget-proposal.pdf> page 52-53

- A new grant to Brigham and Women's Hospital to develop novel, effective therapeutic strategies for patients with treatment-resistant myeloid malignancies.⁴⁵¹
- A new grant to MD Anderson Cancer Center which aims to improve outcomes for ovarian cancer by combining targeted agents based on the molecular, cellular, and clinical biology of the disease.⁴⁵²
- A new grant to the University of California Los Angeles to contribute to the progress in the diagnosis, prognosis, and treatment of brain cancer.⁴⁵³
- A new grant to Weill Cornell Medicine to improve the detection, diagnosis, and treatment of prostate cancer including a neuroendocrine subset that has been understudied in the past.⁴⁵⁴
- A renewal grant to the Center for Cell and Gene Therapy at Baylor College of Medicine, Houston Methodist Hospital, and Texas Children's Hospital to continue developing and testing new forms of T-cell immunotherapies to fight lymphoma.⁴⁵⁵
- A renewal grant to the University of Iowa and the Mayo Clinic to continue developing new lymphoma prevention, detection, and treatment methods.⁴⁵⁶
- A renewal grant to Case Western University to continue to investigate gastrointestinal malignancies with emphasis on colorectal cancers and adenocarcinoma of the esophagus, with the aim to make important and significant translational advances to reduce mortality from these two malignancies.⁴⁵⁷

Additionally, NCI issued a Funding Opportunity Announcement (FOA)⁴⁵⁸ in October 2017 to invite applications for P20 planning grants to develop translational research programs that are focused on investigating cancer health disparities. The P20 grants will support feasibility and planning activities to build cancer health disparities research programs. It is the expectation that the research programs developed by the P20 awards should be competitive with other SPORC applications, addressing cancer health disparities as a cross-cutting research theme. All applications must propose translational research that will contribute to improved prevention, early detection, diagnosis, and/or treatment of cancers found to disproportionately affect specific racial/ethnic minority populations.

NCI remains committed to supporting a diverse portfolio of translational cancer research to advance progress across cancer types and across populations, and to better understand key molecular pathways known to drive cancer progression. Additional information about individual

⁴⁵¹https://projectreporter.nih.gov/project_info_description.cfm?aid=9356666&icde=36654769&ddparam=&ddvalue=&ddsub=&cr=7&csb=default&cs=ASC&pball=

⁴⁵²https://projectreporter.nih.gov/project_info_description.cfm?aid=9356787&icde=36654794&ddparam=&ddvalue=&ddsub=&cr=3&csb=default&cs=ASC&pball=

⁴⁵³https://projectreporter.nih.gov/project_info_description.cfm?aid=9357412&icde=36655041&ddparam=&ddvalue=&ddsub=&cr=6&csb=default&cs=ASC&pball=

⁴⁵⁴ https://projectreporter.nih.gov/project_info_description.cfm?aid=9357034&icde=36654347

⁴⁵⁵https://projectreporter.nih.gov/project_info_description.cfm?aid=9354046&icde=36654901&ddparam=&ddvalue=&ddsub=&cr=25&csb=default&cs=ASC&pball=

⁴⁵⁶https://projectreporter.nih.gov/project_info_description.cfm?aid=9356976&icde=36655015&ddparam=&ddvalue=&ddsub=&cr=8&csb=default&cs=ASC&pball=

⁴⁵⁷https://projectreporter.nih.gov/project_info_description.cfm?aid=9353956&icde=36655081&ddparam=&ddvalue=&ddsub=&cr=3&csb=default&cs=ASC&pball=

⁴⁵⁸ https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-033.html?utm_medium=email&utm_source=govdelivery

SPORE sites, as well as recent scientific advances achieved through the SPOREs is available on the NCI Translation Research Program webpage.⁴⁵⁹

⁴⁵⁹ <https://trp.cancer.gov/>, https://trp.cancer.gov/spore_advances/default.htm

Translational Science of Natural Products for Cancer

The Committee has recognized the importance of moving natural products and their derivatives through development and testing, with the goal of accelerating the designation of Investigational New Drug to promising natural products that can treat cancer. The Committee directs NCI to continue to support this work.

Action taken or to be taken:

NCI's Natural Products Branch (NPB) launched the Natural Products Repository in 1986. Today, this collection contains approximately 230,000 extracts from plant, marine, and microbial sources from over 25 tropical and subtropical countries worldwide. NCI considers the Natural Products Repository to be a national resource, and thus makes these extracts available to NIH-supported and other researchers. This past year the NPB also created a set of extracts from plants described in Traditional Chinese Medicine (TCM) and made it accessible to drug discovery researchers worldwide to investigate TCM plants as potential sources of agents for the treatment of human disease.

The medicinal properties of natural products, including plants and marine organisms, have long provided “leads” and identified promising molecules for researchers developing cancer drugs. In fact, many cancer drugs are based on natural products, including paclitaxel (Taxol®) from the Pacific yew tree for breast and ovarian cancers and vinblastine (Velban®) and vincristine (Marqibo®) from another plant, the rosy periwinkle, for childhood leukemias and other cancers⁴⁶⁰. In fact, a recent review of drug approvals has shown that 49% of all cancer drugs approved by FDA from around the 1940s to the end of 2014 were derived from natural products⁴⁶¹.

One notable example of a natural product leading to a new therapy is that of research on compounds found in a type of sea sponge that led to the development of a new cancer drug. In 1986, Japanese researchers reported on a group of compounds called halichondrins, isolated from the sea sponge *Halichondria okadai*, that had promising anticancer activity. Subsequently, a team of NCI intramural and extramural investigators discovered that one of the halichondrins from this sponge and other sponge types from the Pacific blocked cell growth by inhibiting the protein tubulin, confirming its anticancer potential and demonstrating its mechanism of action. NCI worked with institutions in New Zealand to obtain a supply of this halichondrin for testing. Because it was present in such small amounts in the sponges, NCI-funded researchers, led by Yoshito Kishi, Ph.D., of Harvard University, developed a way to generate the halichondrin in the laboratory. Recognizing halichondrin's potential against cancer, a pharmaceutical company licensed the compound and made a series of modified versions, or analogs, for testing. Positive results from the tests led to the development of one of the analogs, which became known as eribulin (Havalan).⁴⁶² NCI supported the preclinical studies and early clinical trials of eribulin, and the company subsequently tested the drug in large phase III clinical trials. Eribulin was approved by the Food and Drug Administration in 2010 for certain patients with breast cancer⁴⁶³

⁴⁶⁰ <https://www.cancer.gov/about-nci/budget/plan/research-enterprise/eribulin-from-sea-sponge>

⁴⁶¹ Newman D, Cragg G: Natural Products as Sources of New Drugs from 1981 to 2014. *Journal of Natural Products* 79 (3): 629–661, 2016. Also available online.

⁴⁶² https://dtp.cancer.gov/discovery_development/scientific_Eribulin.htm

⁴⁶³ <https://www.cancer.gov/about-cancer/treatment/drugs/fda-eribulinmesylate>

and in 2016 as the first drug to improve survival for patients with liposarcoma⁴⁶⁴ The NCI played a major role in the development of this natural product as a treatment for cancer patients.

NCI's extensive work and investment, as well as the interplay of academia, industry, and government, played important roles in developing and bringing eribulin to market over the course of two decades. The Natural Products Repository is an indispensable tool for researchers exploring ways to use natural products that show anticancer effects. Going forward, NCI plans to expand its support of natural products research by establishing the NCI Program for Natural Products Discovery. This effort is possible through a collaboration between NCI's intramural Center for Cancer Research and the Natural Products Repository, an extramural program within NCI's Division of Cancer Treatment and Diagnosis. This unique intramural-extramural partnership aims to greatly accelerate the discovery of new molecules that impact biological processes central to cancer. This library will be made freely available to the entire research community—including National Institutes of Health (NIH) Institutes, the Department of Defense (DOD), and academic institutions, and industry partners-- enabling rapid active compound identification and empowering both intramural and extramural researchers to develop anti-cancer drugs (also potentially drugs for other diseases) and make a positive impact on human health.

⁴⁶⁴ <https://www.cancer.gov/news-events/cancer-currents-blog/2016/fda-eribulin-mesylate>

Translational Science of Natural Products

The FDA has opened new pathways for development and testing of botanical compounds for medical applications, advancing complementary and integrative health through the use of natural products and their derivatives in treating disease. The Committee directs the NCCIH to consider the use of natural products in its research portfolio with the goal of speeding the development and testing of natural products and their derivatives.

Action taken or to be taken:

Although many natural products are widely marketed and readily available to consumers as dietary supplements, evidence regarding usefulness and safety does not uniformly exist. The National Center for Complementary and Integrative Health (NCCIH) continues to support rigorous research on the risks, mechanisms of action, and potential clinical benefits of natural products. The Center seeks to streamline clinical research on natural products through a phased research pipeline starting with early phase studies exploring the mechanism of action. The most promising natural products will advance to later research phases that support investigations comparing clinical outcomes and biological effects through randomized controlled efficacy trials. In FY 2017, NCCIH released two funding opportunity announcements to solicit grant applications in these areas.

NCCIH and the NIH Office of Dietary Supplements, through the Centers for Advancing Research on Botanical and Other Natural Products (CARBON) Program are funding three Botanical Dietary Supplements Research Centers and two Centers for Advancing Natural Products Innovation and Technology to develop pioneering methods and techniques to catalyze new research approaches and technologies that may have significant impact on the chemical and biological investigation of natural products.

NCCIH currently supports research on **cytisine**, a natural product for smoking cessation. Cytisine, isolated more than 50 years ago from the plant *Laburnum anagyroides*, binds to the same receptors as nicotine and has been used as a smoking cessation aid, primarily in several eastern European countries, for several decades. Despite promising results from clinical trials conducted outside the United States, cytisine has not yet been approved for use in the United States. NCCIH supported a series of pre-clinical studies on cytisine through a strategic collaboration with Achieve Life Sciences, Inc., OncoGenex Pharmaceutical, Inc., other NIH Institutes and Centers (ICs), and private research organizations. Recently, the FDA allowed an Investigational New Drug application to go into effect that permits phase 2 clinical studies to further assess cytisine as a smoking cessation treatment. This continuing public-private partnership may lead to the wide availability of a new smoking cessation option to address the major public health issues associated with tobacco use.

Translational Vaccinology

The Committee notes a very promising area in the field of vaccine and immunology is translational vaccinology, in which researchers are able to translate the science of vaccine design and development into the assessment of current and novel, experimental vaccines through pre-clinical and clinical trials. The Committee strongly encourages NIAID to support a robust portfolio of extramural, highly meritorious translational vaccine research that focus on an interdisciplinary approach to this research. The Committee requests NIAID provide an update in the fiscal year 2019 Congressional Justification on expansion opportunities for interdisciplinary translational vaccinology research.

Action taken or to be taken:

The National Institute of Allergy and Infectious Disease (NIAID) has implemented several programs that enable a translational vaccinology approach to generate and advance vaccine candidates, platforms, and technologies, including those that can be quickly adapted to address emerging and re-emerging pathogens. These efforts include extramural research programs such as the NIAID Partnerships Program for Translational Research that fosters collaborations among diverse scientists to advance development of vaccines and other products to address biological threats. NIAID also expedites preclinical assessment of vaccine candidates by providing researchers with access to animal models, safety and toxicity testing, and preparation of pilot lots for testing. These services provide critical information to advance promising basic research findings and direct candidate vaccines along the critical path toward licensure. In addition, the NIAID Vaccine Research Center (VRC) brings together a team of experts in a variety of fields to accelerate the development of innovative vaccines.

NIAID uses advances in genomics, structural biology, immunology, and platforms such as viral vectors to improve the design of vaccine technologies, especially for viruses with pandemic potential such as influenza. In 2017, NIAID convened a workshop “Pathway to a Universal Influenza Vaccine” that brought together global scientific experts to inform the strategic development of an improved influenza vaccine. NIAID is building on this collaboration by supporting researchers exploring diverse approaches toward a vaccine that could broadly protect against a variety of seasonal and pandemic influenza strains. These efforts include ongoing structure-based vaccine design at the NIAID VRC to target a specific region of the influenza virus that is highly conserved from strain to strain.

NIAID supports additional innovative vaccine approaches that build on basic research advances. One strategy utilizes non-infectious virus-like particles to generate an immune response by mimicking a viral infection. NIAID scientists used virus-like particles to develop a universal influenza vaccine candidate that protects mice against a variety of influenza strains as well as a chikungunya vaccine candidate currently in Phase II clinical trials. Another promising new approach uses engineered nanoparticles to generate immune responses to diverse viruses. NIAID is supporting the development of nanoparticle vaccine candidates for influenza, herpes simplex virus, and Epstein-Barr virus. NIAID researchers used advances in structural engineering to stabilize a key protein from Respiratory Syncytial Virus, the leading cause of severe pediatric respiratory illness, to develop a candidate vaccine that is currently in a Phase I clinical trial. NIAID also supports efforts to rapidly develop novel, DNA-based vaccines that target proteins from a variety of pathogens. The NIAID VRC used this approach to develop a

Zika vaccine candidate that went from initial design to a Phase I clinical trial in only four months. This candidate is now being evaluated for safety and efficacy in a Phase II clinical trial at targeted sites in the Americas.

NIAID remains committed to advancing the field of translational vaccinology to facilitate the development of innovative vaccines against a variety of infectious disease threats. NIAID will continue to support robust extra- and intramural research to further advance interdisciplinary vaccine development.

Trans-NIH Strategic Approach

The Committee directs the Director of DPCPSI to develop a trans-NIH strategic approach to improve coordination and facilitation of trans-NIH research with measurable objectives. The Director should also take specific steps with the ICs to strengthen to reduce duplication and increase effectiveness and efficiency of research.

Action taken or to be taken

The Division of Program Coordination Planning and Strategic Initiatives (DPCPSI) in the Office of the Director, NIH continues to provide scientific leadership, coordination, and facilitation across a range of trans-NIH research areas. These efforts are implemented across the programmatic offices in the division, and a few examples are highlighted below.

The Office of Portfolio Analysis (OPA) provide leadership and facilitates individual Institute and Center as well as trans-NIH portfolio analysis efforts. The OPA developed a standardized metric of scientific influence, the Relative Citation Ratio^{465, 466, 467} and a website, *iCite*,⁴⁶⁸ which provides open access to this metric. Training in the use of the *iCite* tool is provided to NIH staff along with user manuals, FAQs, and instructional videos. OPA also develops computational tools to retrieve and clean data used to analyze information about NIH investments, funded collaborations, publication records, and bench-to-bedside translation, to leverage advanced data mining and knowledge discovery techniques to link people, funding, and research outputs across data sets, and to analyze the content of grant applications, awards, publications, and patents. Newer OPA analytics are designed to identify duplication and improve strategic planning, including *iSearch*, the OPA NextGen portfolio analysis platform. *iSearch* provides NIH scientific staff comprehensive, easy-to-use access to carefully curated, extensively linked datasets encompassing publications, clinical trials, patents, approved drugs, investigators, and awards made by other funders, both domestic and international. These tools can help identify overlapping investments, emerging areas of science, and research gaps to help ensure that the NIH research portfolio is balanced, free of unnecessary duplication, and takes advantage of collaborative, cross-cutting research.

In the past year, several trans-NIH program offices, located in DPCPSI, updated or are developing new or updated Strategic Plans. Development of these plans involves extensive public input and internal coordination which helps to reduce duplication and promote coordination and collaboration.

- The Office of Behavioral and Social Sciences Research (OBSSR) published its FY 2017-2021 strategic plan in 2017 <https://obssr.od.nih.gov/about-us/strategic-plan/>. The plan focuses on three scientific priorities reflecting key research challenges OBSSR is uniquely positioned to address, along with four foundational processes to enhance and support these scientific priorities as well as the OBSSR's broader mission.

⁴⁶⁵ Hutchins, B.I., Yuan, X., Anderson, J.M., and Santangelo, G.M. (2016). Relative Citation Ratio (RCR): A New Metric That Uses Citation Rates to Measure Influence at the Article Level. *PLoS biology* 14, e1002541.

⁴⁶⁶ Naik, G. (2016). The quiet rise of the NIH's hot new metric. *Nature* 539, 150.

⁴⁶⁷ Santangelo, G.M. (2017) Article-level assessment of influence and translation in biomedical research. *Mol. Biol. Cell* 28, 11 1401-1408

⁴⁶⁸ <https://icite.od.nih.gov/>

- Strategic planning for new Common Fund programs is underway. Since Common Fund programs are time-limited (5-10 years), the churn of funds as programs end means that new programs are launched on a regular basis. The DPCPSI Office of Strategic Coordination (OSC), which manages the Common Fund, is planning for potential new Common Fund programs to be launched over the next several years. On September 1, 2017, the NIH Council of Councils cleared two concepts being considered for fiscal year 2018: [Acute-to-Chronic Transition Signatures \(ACTS\) for Pain](#) and [Accelerating Therapeutic Somatic Cell Gene Editing Approaches](#). Trans-NIH Working Groups are now developing detailed proposals to be considered by the NIH Director for final program approval. Additionally, OSC is soliciting ideas from NIH ICs for potential programs in fiscal years 2019 or 2020. These ideas were due October 2, 2017, and will be prioritized by IC Directors and NIH Leadership to select the most compelling concepts to send for Council of Councils clearance in January 2018.
- The Tribal Health Research Office (THRO) initiated a strategic planning process, involving consultation within and external to the NIH. This included a June 2017 THRO Strategic Plan Consultation <https://dpcpsi.nih.gov/thro/consultationJun2017>, held in conjunction with the National Indian Health Board's Tribal Public Health Summit and involved soliciting ideas from the NIH Tribal Advisory Committee. A Request for Information seeking additional input to the development of the Plan will be published in October-November 2017.
- The Office of Research on Women's Health (ORWH) published a Request for Information (RFI) <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-108.html> on the next Trans-NIH Strategic Plan for Research on Women's Health. ORWH seeks feedback on three cross-cutting themes and goals under consideration: Theme 1: Expand the Exploration of Sex as a Biological Variable (SABV) in NIH Research; Theme 2: A Multi-Dimensional Approach to the Science of Women's Health; Theme 3: Quality of Life and Disease Burden over the Life-Course. These themes will stimulate new research areas, priorities, and approaches to help put science to work for the health of women.

In addition to the efforts summarized above, most of the DPCPSI program offices convene Trans-NIH Research Coordinating Committees in their respective areas. These committees, composed of representatives of the NIH Institutes and Centers (IC), promote coordination, facilitate collaboration, and ensure continuing communication among the ICs in programmatic and scientific activities. The recently established Tribal Health Research Coordinating Committee joins existing committees (the Office of AIDS Research Executive Committee, the Behavioral and Social Sciences Research Coordinating Committee, the Prevention Research Coordinating Committee, the Coordinating Committee on Research on Women's Health, and the Sexual and Gender Minority Research Coordinating Committee) in improving research coordination across the NIH.

Trans-NIH Working Group of Fibrosis

The Committee recognizes that fibrosis can occur across body systems and applauds NIH for establishing a trans-NIH working group on fibrosis. The Committee encourages NIH to continue the cross-cutting coordination of research between ICs in this area.

Action taken or to be taken:

Fibrosis is the formation and abnormal accumulation of excessive fibrous connective tissue that may stem from a variety of causes. It is a progressive and complex process that affects multiple organs, leads to organ dysfunction, and causes substantial economic burden. Patients with fibrotic diseases have large unmet medical needs and limited treatment options. In recognition of the vast impact that fibrosis has on U.S. and global populations, the Fibrosis Scientific Interest Group was formed in September 2016 to provide a forum for individuals from NIH and the greater scientific community to discuss basic, translational and clinical research related to fibrosis. Trainees, basic laboratory researchers and clinicians from academic institutions or medical centers are part of this interdisciplinary group. Discussion among multidisciplinary experts on fibrosis will drive scientific discovery and potentially generate innovative concepts to improve the understanding of fibrotic diseases and enhance the therapeutic approach for these devastating disorders.

The Fibrosis Scientific Interest Group meets monthly to engage in interactive discussions focusing on our membership's interests related to fibrosis and to organize seminars. The group's membership has grown to 52 individuals, primarily NIH staff and trainees, from a wide variety of Institutes and Centers including the National Human Genome Research Institute, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Allergy and Infectious Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, the National Cancer Institute, the National Center for Advancing Translational Sciences, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Heart, Lung, and Blood Institute. Invited speakers who present their projects related to fibrosis may include researchers internal or external to NIH. To date, seven different scientists or physicians, including a prominent academic expert in pulmonary (relating to the lungs) fibrosis, have presented at monthly seminars. These monthly meetings facilitate trans-NIH collaborations, potentially create synergy between research programs, stimulate productive and insightful feedback on research findings, and provide opportunities to offer mentoring to trainees.

In the future, the Fibrosis Scientific Interest Group aims to broaden membership to include a greater representation from academic centers and other federal institutions, including the Food and Drug Administration as well as Walter Reed National Military Medical Center. This expanded membership will be facilitated by WebEx in order to offer remote meeting attendance. The Group will also continue to invite distinguished speakers from the academic community to present at meetings, interact with NIH investigators, and facilitate collaborations. The Group would also like to host a biennial mini-symposium highlighting strategic areas of fibrosis research. Finally, the Group has established a new relationship to explore potential collaborations with a biotechnology company, which has an interest in fibrosis.

Trauma Research

To ensure that our Nation's trauma response network and workforce remain adequately prepared, the Committee recommends an increased focus by NIH on trauma research, including to establish a NIH-led trauma research agenda coordinated with the extensive, and often groundbreaking, DOD activities on trauma. This research is critical to minimize the loss of human life, disability, and injury by ensuring that patient-specific trauma care is based on scientifically validated findings.

Action taken or to be taken:

NIH supports research on all aspects related to the physiological response to injury, including resuscitation, shock, coagulopathy (impaired ability of blood to form clots), organ failure, ensuing complications like sepsis or acute respiratory distress syndrome, tissue repair and wound healing, rehabilitation, and long-term physiological and psychological complications and consequences of trauma. NIH also funds research training in topics related to trauma at the postdoctoral and junior faculty levels.

Several NIH Institutes and the NIH Office of Emergency Care Research (OECR) collaborate on the Strategies to Innovate EmeRgENcy Care Clinical Trials Network (SIREN) initiative, which enables researchers to conduct high-quality, multi-site clinical trials in the pre-hospital and emergency department in order to improve outcomes for patients with neurologic, cardiac, respiratory, hematologic, and trauma emergency events. The first study in the network examines a new therapy for acute severe traumatic brain injury (TBI). Other potential topics to be studied include traumatic spinal cord injury, acute management of severe migraine or other primary headache disorders, cardiopulmonary resuscitation, acute congestive heart failure, asthma, new onset atrial fibrillation, and chest pain.

There is also close inter-agency cooperation between NIH and the Department of Defense (DoD) on trauma research. For example, the director of NIH's OECR is a member of the steering committee of the DoD's trauma research network; likewise, the DoD is represented on the federal committee for SIREN. In addition, the NIH is partnering with the DoD in the Trans-Agency Research Consortium for Trauma-Induced Coagulopathy (TACTIC) to address multiple research aspects of trauma-induced coagulopathy (TIC). In this partnership, clinical investigators involved with DoD-funded clinical trials at Level I trauma centers are linked to scientists conducting basic research on TIC to analyze patient samples and better understand TIC pathophysiology. TACTIC represents an integrated program to define the cell and molecular pathways of TIC and to provide insight into the diagnosis and interventions for post-traumatic hemorrhage. The NIH and DoD also coordinate neurotrauma activities extensively, especially on TBI.

In March 2017, the NIH hosted a conference on achieving zero preventable deaths from trauma. It was sponsored by the OECR, the American College of Surgeons, and the DoD's Combat Casualty Care Research Program.

Traumatic Brain Injuries (NIBIB)

Neurotrauma is the umbrella term for two primary pathologies, spinal cord injuries and traumatic brain injuries. These injuries are unique in that they affect how we are and who we are, with incredible variation between patients. The sizable incidence of injury and prevalence of disability resulting from neurotrauma results in significant human and economic burden. As befits the complexity of the challenges from neurotrauma, multiple NIH Institutes and Centers coordinate research, which ranges across a wide spectrum, from understanding the cellular mechanisms of immediate and delayed damage, though development of better prevention, treatment, and rehabilitation, and engages scientists, engineers, and clinicians from a broad range of disciplines.

The Committee recognizes the need for cross-disciplinary collaboration to meet these challenges and strongly encourages NIH to support such research through all appropriate support mechanisms.

Action taken or to be taken:

Neurotrauma presents challenges to patients and medical science. To address these challenges, NIH supports a range of research from basic science to better understand the molecular biology of traumatic brain injury (TBI), to translational and clinical research aimed at improving the quality of life for people living with TBI. NIH's broad portfolio is supported by various research mechanisms including investigator-initiated research, support for early career investigators, and targeted support mechanisms tailored for the needs of basic, translational, and clinical research. Projects range from small pilot investigations to large, multi-site clinical studies and consortia.

NIH-supported neurotrauma research includes collaboration among NIH institutes and other federal agencies and is also multi-disciplinary, bringing together researchers with an array of expertise. One example of this type of collaboration is the Alliance for Regenerative Rehabilitation Research and Training (AR3T). AR3T promotes the use of regenerative medicine and is led by the National Center for Medical Rehabilitation Research (NCMRR) in the *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development (NICHD), with support from the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Biomedical Imaging and Bioengineering (NIBIB). NCMRR's work includes the use of neural stem cell therapy and integration of sensory input and motor activity to improve outcomes after the use of these regenerative approaches. Another collaborative project includes the TBI Endpoints Development (TED) project led by the Department of Defense.

Also, in 2017, NINDS solicited applications for the Translational Outcomes Project in Neurotrauma (TOP-NT). This project will engage experts from multiple disciplines to develop and validate a reproducible battery of preclinical functional outcomes that address injury heterogeneity and are closely aligned with feasible and sensitive clinical assessments in traumatic brain and/or spinal cord injury.

Other types of research include a NIH New Innovator award to conduct translational research in a mouse model, using a new tissue engineering approach to allow easier transportation of reparative stem cells to the brain. In addition, NIBIB is supporting the Center for Adaptive Neurotechnologies, which is building a unique technical infrastructure that supports real-time interactions with the central nervous system (CNS). Examples of technologies include

approaches to help train damaged neural pathways in the brain and spinal cord to relearn how to function; and brain-computer interface systems to improve motor control in people with severe neuromuscular disabilities due to TBI. Another NIBIB-funded project focuses on the loss of arm function following neurological trauma by developing a rehabilitation therapy that uses advanced robotics. In this project, researchers are designing a comfortable, lightweight, and portable device that facilitates active limb use in everyday tasks. The exoskeleton and is an example of a new class of wearable robotic devices that could improve the quality of life for millions with arm dysfunction due to neurological trauma.

NIH is committed to using the full spectrum of research approaches and expertise to address the scientific challenges posed by TBI.

Traumatic Brain Injury (NINDS)

The Committee understands regenerative medicine research and the use of adult stem cells may play an important role in the treatment of Traumatic Brain Injury (TBI). The Committee strongly encourages NINDS to work with the National Institute of Aging to support a robust and coordinated portfolio of TBI research with a focus on how to leverage regenerative medicine research and the use of adult stem cells in the treatment of TBI. The Committee requests an update in the fiscal year 2019 Congressional Justification on efforts in these specific areas of TBI research.

Action taken or to be taken:

Traumatic Brain Injury (TBI) often causes loss of brain cells, interrupts nerve fiber pathways, and impairs blood circulation, which can exacerbate brain damage. Repairing damage after TBI is a fundamental unsolved challenge. TBI is a particularly important area of study among older adults because of the connection between TBI and cognitive decline in aging. Multiple NIH Institutes, including NINDS, *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development (NICHD), and NIA, support a robust portfolio of research that aims to leverage the brain's intrinsic regenerative capacity and/or the use of transplanted adult-derived cells to restore brain function after TBI. NINDS coordinates TBI research closely with the Department of Defense and directs the Federal Interagency TBI Research Informatics project to make data from all major TBI studies accessible for analysis.

Ongoing projects in animal models that focus on the adult brain's inherent capacity to generate new cells include, for example, exploring of chemical strategies to reprogram glial (supporting) cells to generate new neurons, combining hypothermia to protect the brain with drugs that promote regenerative mechanisms, using tissue plasminogen activator (tPA) to promote repair processes in white matter (nerve fibers), and using ultrasound-mediated gene transfer to deliver regulatory proteins that simulate the brain's stem cells to generate new nerve cells. Other projects are designing engineered tissue matrixes that support stem cells and using biomaterial-assisted transplantation of induced pluripotent stem cells. Other crucial issues for regenerative therapies are also under study, including blood vessel remodeling in the brain following TBI and chemical control signals for TBI repair processes in aging. An early phase clinical trial using cells from patients' own bone marrow to treat severe pediatric TBI is underway.

Among the larger collaborative programs, the National Center for Medical Rehabilitation Research (NCMRR) in the NICHD is co-funding the Alliance for Regenerative Rehabilitation Research and Training (AR3T) with NIBIB and NINDS to promote the use of regenerative medicine. The Center's work includes the use of neural stem cell therapy and integration of sensory input and motor activity to improve outcomes after the use of these regenerative approaches. The joint NIH Intramural Research Program - Department of Defense Center for Neuroscience and Regenerative Medicine (CNRN) is also focused on TBI.

More broadly, NIH supports extensive research on stem cell and regenerative biology that is not focused on TBI, but provides the foundation for developing regenerative medicine therapies. Notably, the regenerative medicine provisions of the 21st Century Cures Act have enabled NIH to increase research in this area. As part of the Act's implementation, for example, in 2017 NIH and FDA held a joint Regenerative Medicine Innovation Workshop, which focused on adult stem cells and explored critical gaps that must be addressed to move regenerative medicine therapies

to the clinic. NINDS, NIA, NICHD, and other components of NIH continue to work closely together in all matters on which their missions intersect, such as TBI and regenerative medicine.

Trisomy 21

The Committee continues to recognize that the presence of a third copy of human chromosome 21, which causes Down syndrome, predisposes individuals to significant immune system dysregulation. This dysregulation is associated with the occurrence of Alzheimer's disease as individuals with Down syndrome age and the high incidence of autoimmune disease as well as protections against most solid tumor cancers and cardiovascular disease. These findings present a rich research opportunity and, based on the NIH's recently released report on the Feasibility of a Multi-Year Study on Trisomy 21 in Humans, the Committee encourages NIH to pursue a multi-year, trans-NIH research initiative examining immune system dysregulation and trisomy 21, with the aim of yielding scientific learnings that could significantly improve the health of individuals with Down syndrome as well as millions of typical individuals.

Action taken or to be taken:

Down syndrome (DS) is a set of cognitive and physical symptoms that result from having a whole or partial extra copy of chromosome 21, which changes the body's and the brain's typical development. The life expectancy for those with DS has increased dramatically from 25 years in 1983 to 60 years today. Common co-occurring conditions include congenital heart disease; problems with hearing, vision, intestinal, immune, thyroid, skeletal function; and, in adults, dementia akin to Alzheimer's dementia.

The National Institutes of Health funds a wide-range of research projects and other efforts to improve the health of people with DS, including activities related to the high prevalence of Alzheimer's Disease (AD) in DS. The National Institute on Aging (NIA) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) have launched a new project to identify biomarkers and track the progression of AD in people with DS.⁴⁶⁹ The NIH Alzheimer's Biomarker Consortium – Down Syndrome (ABC-DS) supports two teams of researchers using brain imaging, as well as fluid and tissue biomarkers, in research to help understand the progression of disease, and may one day lead to improved testing of interventions. NIA is supporting a clinical trial of an immunotherapy for cognitive impairment in adults with Down syndrome. This is designed to study the safety, tolerability, and immunogenicity of a vaccine in a Phase I clinical trial in adults with DS age 35-55 years. NIA also funds a project investigating the natural history of plaque deposits using brain imaging at 24-month intervals; study participants' cognitive function also is assessed to determine if there is a predictable trajectory toward clinical Alzheimer's.

NICHD, NIA, the National Institute on Neurological Disorders and Stroke (NINDS), and several nonprofit organizations cosponsored a workshop in 2013, "Advancing Treatments for Alzheimer's Disease in Individuals with Down Syndrome." A 2015 follow-up effort led to the development of funding opportunities. NICHD and NIA partner on a Funding Opportunity Announcement to evaluate aging in the DS population, "Factors Affecting Cognitive Function in Adults with Down Syndrome (R01)." One of the productive projects funded under this RFA has been renewed for another 5 years.

⁴⁶⁹ <https://www.nih.gov/news-events/news-releases/nih-supports-new-studies-find-alzheimers-biomarkers-down-syndrome>

NINDS supports research on disease mechanisms leading to intellectual disability and other impairments in DS, which may suggest new targets for future treatments. For example, one project hypothesizes that targeting a single signaling pathway altered in DS may restore cognitive function through effects on synaptic plasticity mechanisms and inhibitory communication between neurons. Other researchers are examining how an extra copy of the chromosome 21 gene *DSCAM* leads to defects in the migration of neurons during early brain development, and how non-protein coding regions of chromosome 21 regulate gene expression during the formation of neurons and the junctions between them (synapses). NINDS also supports research to understand the development of early-onset AD in DS, including studies on structural and functional defects in neurons and synapses induced by amyloid beta, a protein encoded by a gene on chromosome 21 and the main component of characteristic plaques in the brains of AD patients.

The National Human Genome Research Institute is supporting research that is focused on developing safe and efficacious treatments that a pregnant woman could take to improve brain development and function following a prenatal diagnosis of trisomy 21. Investigators are using three different untreated mouse models of DS to compare brain anatomy, gene expression and behavioral performance at three different stages of the life cycle as endpoints from which to test the effects of different medical therapies. In independent experiments, cells from individuals with and without trisomy 21 are being analyzed, looking for improved cellular proliferation and mitochondrial function, and reduction of oxidative stress as markers for a therapeutic response.

Tuberculosis

According to the World Health Organization (WHO), Tuberculosis (TB) is the leading global infectious disease killer, accounting for the deaths of 1.8 million people annually and the continued spread of drug resistant TB is a serious global health problem. There is an urgent need to develop faster point-of-care diagnostics; shorter, safer, and more tolerable treatments; and effective vaccines for all populations, including for drug resistant TB. The Committee urges the Institute to prioritize the development of new TB diagnostic, treatment, and prevention tools.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) supports a comprehensive portfolio of tuberculosis (TB) research covering basic, translational, and clinical studies to better understand the natural history of TB and increasing drug resistance, and to facilitate the development of new TB diagnostic, treatment, and prevention tools. In collaboration with USAID and CDC, NIAID also continues to play a key role in implementing the research component of the National Action Plan for Combating Multidrug-Resistant Tuberculosis (MDR-TB).

NIAID supports the development of rapid, point-of care TB diagnostics, including the GeneXpert® MTB/RIF test that rapidly detects the bacteria that cause TB and the mutations associated with resistance to the drug rifampin. NIAID scientists collaborated with colleagues in the United States, China, South Korea, and South Africa to evaluate a new test using the GeneXpert® technology that can identify resistance to several additional TB drugs. NIAID scientists also are launching a new clinical trial to assess whether diagnostic biomarkers can identify individuals with less severe TB who could be treated with a shorter, safer, and more tolerable treatment regimen than the standard six-month therapy.

NIAID employs a multifaceted approach to the development of novel TB therapeutics and has supported two-thirds of the TB drug candidates currently in clinical studies worldwide. NIAID supports basic research to understand how TB responds to different drugs, translational studies to identify host immune responses, and clinical trials to evaluate new TB drugs. NIAID researchers are exploring potential targets for novel host-directed TB therapies by investigating the host immune response in a mouse model of TB infection. For example, NIAID recently launched a clinical trial to determine whether adding bedaquiline to TB treatment regimens is safe and tolerable in young MDR-TB patients. Also, NIAID is collaborating with the CDC to evaluate whether treatment with two newer TB drugs, rifapentine and moxifloxacin, can be used to shorten the standard six-month treatment regimen in adults.

Furthermore, NIAID is pursuing the development of improved TB prevention strategies. A Phase III clinical trial to evaluate whether shortened treatment regimens are able to prevent the development of active TB in HIV-infected individuals is currently underway. NIAID also is planning to launch a clinical study comparing two therapies in household contacts of MDR-TB patients that may inform TB prevention for this at-risk population. In addition, NIAID has supported targeted research and provided preclinical services to advance the development of new vaccines to prevent TB, contributing to approximately 10 candidates that are currently in clinical trials.

NIAID will continue to support basic and translational research in order to develop new and more effective TB diagnostics, therapeutics, and vaccines. This includes ongoing support for NIAID partnerships with other Federal agencies to implement the National Action Plan for Combating MDR-TB.

Undiagnosed Illnesses

The Committee urges the Undiagnosed Disease Network (UDN) to continue efforts to enhance access to patients, caregivers, and other stakeholders as well as make information obtained through the UDN available to Federal agencies and health-related agencies.

Action taken or to be taken:

The NIH Undiagnosed Diseases Program (UDP) was established in 2008 by the National Human Genome Research Institute, the NIH Office of Rare Diseases Research, and the NIH Clinical Center to help provide diagnosis and treatment for patients with unknown disorders. Recognizing the unmet need the UDP could only begin to address, the NIH Common Fund funded phase I from 2013 to 2017, extending the program into a network of seven Clinical Sites, a Coordinating Center, and five Core Laboratories. These components comprise the Undiagnosed Diseases Network or UDN. In 2018 the UDN begins its second phase and is now funded through 2022 with an anticipated two to four new Clinical Sites and one to two new Core Laboratories. NIH's initiation and continued support of the UDN is aimed at improving the level of diagnosis and care for patients with undiagnosed diseases, facilitating research into the causes of undiagnosed diseases, and creating an integrated and collaborative research community to identify improved options for patient care and treatments of these new and rare diseases.

The UDN is committed to ensuring as many researchers, clinicians, and patients as possible have access to this network. To this end, the UDN's expertise and resources are disseminated through 13 geographically diverse clinical and research centers. In continued efforts to expand opportunities for patients to participate in the UDN, the National Organization for Rare Disorders⁴⁷⁰ runs a patient assistance fund for the network, providing financial assistance for costs associated with participation in the program to UDN participants. Co-pays, deductibles, or travel expenses for additional family members are all eligible for assistance.

Ensuring unfettered access to data is critical to supporting the mission of the UDN. To carry this out, the UDN has created a Participant Pages project⁴⁷¹ with 37 participants to date. These pages allow UDN participants to share information about their condition and genetic variants found through the UDN⁴⁷² with the aim of identifying additional cases. To date, the UDN Coordinating Center has received 107 inquiries based on the participant pages. All case information has also been deposited in the database of genotypes and phenotypes (dbGaP⁴⁷³), a resource developed and operated by the National Library of Medicine's National Center for Biotechnology Information. dbGaP staff are conducting final review to grant researchers access to 134 participants' data. The UDN also has Twitter and Facebook accounts. Research findings from the network and information of interest to the undiagnosed and rare disease community are posted in further efforts to make the UDN's findings as broadly accessible as possible. The

⁴⁷⁰ rarediseases.org

⁴⁷¹ <https://undiagnosed.hms.harvard.edu/our-participants/>

⁴⁷² <https://undiagnosed.hms.harvard.edu/genes/>

⁴⁷³ https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001232.v1.p1

Twitter account⁴⁷⁴ has over 2,000 followers and the Facebook account⁴⁷⁵ has over 2,400 followers.

Additionally, the UDN makes information available to Federal agencies and other health-related agencies. All protocols are shared online in the UDN Manual of Operations⁴⁷⁶. The UDN has also started major initiatives involving data sharing with international partners. At the Fifth International Rare and Undiagnosed Diseases Conference held in August 2017, a Charter for the Undiagnosed Diseases Network International (UDNI) was approved, including policies and practices for data sharing. A Data Sharing Working Group was also established to continue working on implementation strategies for sharing data globally across the UDNI.

⁴⁷⁴ <https://twitter.com/udnconnect>

⁴⁷⁵ <https://www.facebook.com/udnconnect/>

⁴⁷⁶ <https://undiagnosed.hms.harvard.edu/udn-manual-of-operations/>

Usher Syndrome

The Committee continues to urge the NIH to prioritize Usher syndrome research at NEI and NIDCD. The Committee requests an update in the fiscal year 2019 Congressional Justification. The update should include efforts to stimulate the field and to accelerate viable human treatment options for those with Usher syndrome.

Action taken or to be taken:

Usher syndrome (USH) is a set of rare genetic disorders that affect hearing, balance, and vision. USH affects between 4 to 17 per 100,000 people.^{477,478} NIH is committed to funding all investigator-initiated USH research that scores well in peer review. The National Eye Institute (NEI) and the National Institute on Deafness and Other Communication Disorders (NIDCD) lead the NIH in supporting USH research. To prioritize USH research, both NEI and NIDCD include objectives in their strategic plans that could help stimulate meritorious research for USH. For example, one NEI strategic plan⁴⁷⁹ aim is to develop animal models for pathological features of vision disorders “including syndromic disorders such as Usher’s disease.” The NIDCD strategic plan⁴⁸⁰ objectives include “genetic causes of hearing loss.” NIDCD and NEI have research priorities focused on developing new gene therapy and gene delivery methods, which includes USH genes. Further, the NIDCD strategic plan places emphasis on research to develop and improve assistive device technology--including hearing aids, cochlear implants, and vestibular prosthesis--and treatment outcomes for individuals that use them. In July 2018, an International USH Conference, co-funded by NIDCD and NEI, will convene scientists, people with USH, and their families. The conference will foster research collaborations between scientists and educate individuals and families affected by USH on current research. It will also serve to make researchers aware of the needs of people with USH and their families to direct new research priorities in diagnosis, prevention, and treatment.

Further, NEI and NIDCD intramural scientists collaborate to identify and characterize new USH genes and collaborate on clinical research projects with individuals with USH, focusing on neural mechanism underlying hearing, balance, and vision. NIH funded teams are currently testing gene therapy tools in cell-based and animal models of multiple USH genes. New gene editing technology called CRISPR/Cas9 allows scientists to edit single mutations within a cell. NEI-funded scientists are using this technology in stem cells taken from an individual with USH type 2 (USH2). This research may lead to a stem cell-based therapy in which an individual is treated with his/her own cells, with the gene mutation corrected.

NIDCD intramural scientists are also using gene therapy to restore hearing and balance in an USH2 animal model⁴⁸¹, and look to move from animals to gene delivery to the human inner ear. The researchers are working on methods to minimize trauma to the inner ear during gene delivery surgery and investigating the consequences of surgical manipulation to the inner ear in pre-clinical animal studies. In another study, NEI- and NIDCD-supported scientists developed a

⁴⁷⁷ <https://www.ncbi.nlm.nih.gov/pubmed/6885960>

⁴⁷⁸ <https://www.ncbi.nlm.nih.gov/pubmed/20613545>

⁴⁷⁹ <https://www.nei.nih.gov/sites/default/files/nei-pdfs/VisionResearch2012.pdf>

⁴⁸⁰ <https://www.nidcd.nih.gov/about/strategic-plans>

⁴⁸¹ <https://www.ncbi.nlm.nih.gov/pubmed/28254438>

synthetic viral vector that resulted in more efficient transduction of auditory and vestibular sensory hair cells in the mouse inner ear.⁴⁸² Then, researchers funded in part by NIDCD used that delivery method for gene therapy to restore USH type 1 gene function in a mouse model. Treatment restored gene and protein expression to near normal levels and significantly rescued hearing and balance behavior in those animals.⁴⁸³ While challenges remain before inner ear gene therapy can become a reality in humans, these studies lay the foundation for future treatment options for hearing and balance impairment in individuals with USH. Furthermore, in 2017, the FDA granted orphan drug designation to an RNA-based therapy for USH2A under development by the company ProQR. NIH is also funding rehabilitation research, including a new NEI grant in 2017, to study and enhance peripheral vision in the context of disease progression. The goal is to modify vision rehabilitation to improve locomotive abilities and other activities of daily living.

⁴⁸² <https://www.ncbi.nlm.nih.gov/pubmed/28165475>

⁴⁸³ <https://www.ncbi.nlm.nih.gov/pubmed/28165476>

Valley Fever

The Committee commends NIH and CDC on launching a Randomized Control Trial (RCT) to identify an effective treatment for Valley Fever. The Committee requests an update on the status of the RCT, and continues to support efforts to develop early diagnostic tests, increase awareness of this disease among medical professionals and the public, and develop a vaccine.

Action taken or to be taken:

Coccidioidomycosis, or Valley Fever, is a fungal infection that results from inhalation of *Coccidioides* species spores and is endemic to the southwestern United States, with the highest number of cases occurring in Arizona and California. Although most people with Valley Fever have mild flu-like symptoms, severe cases may require hospitalization, and infection can result in weeks to months of significant symptoms. *Coccidioides* species also have been found to be the cause of an estimated 15 to 30 percent of community-acquired pneumonia (CAP) in highly endemic areas, emphasizing the importance of research addressing this disease.

The National Institute of Allergy and Infectious Diseases (NIAID), with technical assistance from CDC, is funding a randomized controlled trial (RCT) that seeks to evaluate the treatment of individuals with CAP in areas where *Coccidioides* infection is prevalent. Since CAP may be caused by different pathogens, including fungi like *Coccidioides*, the RCT will compare outcomes in patients receiving the standard-of-care antibacterial drug, azithromycin, with or without the antifungal drug fluconazole. CDC identified potential RCT study sites in areas with many Valley Fever and CAP cases, while NIAID worked with subject matter experts from Valley Fever-endemic regions to finalize the clinical trial protocol. The trial is managed by an NIAID-supported Vaccine and Treatment Evaluation Unit and enrollment has been initiated at four sites in Arizona and California. To date, enrollment in the study has been slower than expected. To address this issue, NIAID is expanding the number of trial sites and pursuing other activities to encourage study participation.

NIAID anticipates that this RCT will also increase awareness of Valley Fever in the endemic area and may prompt those experiencing symptoms to seek medical care earlier in the course of the disease. Additional public awareness may be generated via NIAID support for the development of a web-based K-12 curriculum on infection and immunity that will contain information on Valley Fever infection and related health outcomes.

NIAID is also supporting basic research to understand molecular mechanisms of Valley Fever and provides insight into novel ways to prevent and treat the disease. For example, NIAID scientists have identified defects in an immune signaling pathway that may predispose an individual to develop chronic Valley Fever. NIAID researchers are building on this observation via clinical studies to identify underlying factors, including specific strains of *Coccidioides*, that may contribute to the development of more severe forms of Valley Fever. In addition to these efforts, NIAID supports the development and evaluation of novel *Coccidioides* diagnostics and therapeutics, as well as several experimental vaccines including a plant-based, oral vaccine.

NIAID remains committed to supporting a dynamic research portfolio on Valley Fever to aid in the development of new diagnostics, therapeutics, and vaccines. NIAID will continue to engage with Federal partners, scientists, public health officials, and affected communities to address disease resulting from *Coccidioides* infection.

Vector-Borne Disease

The Committee continues to support NIAID's ongoing research on a variety of vector-borne diseases including Zika, chikungunya, and dengue, and the Institute's development of effective countermeasures and strategies. The Committee supports NIAID developing new and expanded research efforts to enhance the array of innovative vector control technologies to counter transmission of Zika and other vector-borne infectious disease threats.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and translational research to help prevent the spread of vector-borne diseases. These efforts include studies to understand vector-host and vector-pathogen interactions, as well as research to further the development of tools to control vector populations and limit the transmission of vector-borne pathogens. NIAID vector biology and vector control research complements a robust portfolio of research on diagnostics, therapeutics, and vaccines for specific vector-borne pathogens. Details of NIAID-supported research on countermeasures for neglected tropical diseases including chikungunya and dengue viruses, tick-borne diseases including Lyme disease, Zika virus, and malaria are summarized elsewhere in this volume.

NIAID has a longstanding program of research dedicated to understanding basic vector biology and vector-pathogen interactions, as well as the development of novel vector research methods. Researchers at NIAID's Rocky Mountain Laboratories have developed a new model to study how flaviviruses infect tick vectors that could be used as a tool to evaluate medical countermeasures against the Powassan and tick-borne encephalitis viruses. NIAID researchers also have identified a key step in a major defense mechanism used by mosquitoes to limit malaria infection that could serve as a target for new tools to reduce the spread of malaria.

NIAID scientists are investigating the saliva of blood-feeding vectors to identify compounds that facilitate blood feeding and parasite transmission that could be targeted in vector control efforts. For example, NIAID scientists have characterized the genetic structure of salivary protein families in 16 species of the malaria-transmitting *Anopheles* mosquito. NIAID researchers also are collaborating with industry partners to conduct a Phase I clinical trial to test a "universal" mosquito saliva vaccine that builds upon basic research in mosquito biology. This vaccine candidate is designed to trigger a protective immune response to mosquito saliva and prevent transmission of a variety of mosquito-borne infections.

In addition, NIAID supports efforts to improve traditional vector population control methods such as traps used in and around homes as well as the development of novel larvicides, insecticides, and repellents. NIAID grantees are evaluating the effectiveness of treating male mosquitoes with larvicide to reduce mosquito populations. NIAID also is supporting the development of an approach where male mosquitoes are infected with *Wolbachia* bacteria to limit their capacity to produce viable offspring.

NIAID will continue to support basic and translational research on a wide range of vectors to better understand vector biology and behavior and to develop products that can help prevent the spread of vector-borne disease, including diagnostics, therapeutics, vaccines, and innovative vector control technologies.

Young Investigators

The Committee expects NIH to report on actions it has taken to lower the median age at which investigators receive their first R01 awards annually in the fiscal year 2019 Congressional Justification. In addition, the NIH shall provide an update on the concrete steps it is taking to lower the median age at which individuals receive their first R01 award within 60 days of enactment of this Act.

Action taken or to be taken:

NIH continues to take new steps to foster the stability of the biomedical research workforce, and ensure that emerging early-stage investigators have opportunities to receive R01 research grants at any early age and without undue delay.

In August 2017, NIH announced new steps⁴⁸⁴ to invest in the next generation of researchers.⁴⁸⁵ This included a goal of funding approximately 200 more early-stage investigators in 2017 than in 2016. As part of this initiative, NIH Institutes and Centers are expected to develop new evidence-based strategies to identify, recruit, and retain early-stage investigators. The NIH Office of the Director will centrally track and maintain an updated census of early-stage investigators and monitor the median age at which individuals receive their first R01 award.

In addition to these steps, applications from New Researchers will be clustered in peer review. These reviewers will be instructed to focus more on the proposed research question, significance, innovation, and approach and less on preliminary data and the investigator's track record'.

NIH also continues to support specialized programs that focus on Early Stage Investigators that lead to research awards at a lower age. Examples include the Pathway to Independence award (K99-R00), Early Independence Award (DP5), and NIH Director's New Innovator Award (DP2). Some NIH Institutes and Centers are also making R35 "outstanding investigator" awards to early-stage investigators as a means of providing them with longer term and more stable research support.

The NIH Director has charged a working group of the Advisory Committee to the (NIH) Director (ACD)⁴⁸⁶ to examine all dimensions of the Next Generation of Scientists issue, with initial recommendations due in June of 2018. Lastly, NIH is looking forward to the recommendations of a National Academies committee, convened in early 2017 to study and recommend solutions to any barriers that may extend periods of training, time to independence, or impede sustained success in research. A final report and recommendations are expected in the spring of 2018.

⁴⁸⁴ *NIH Guide for Grants and Contracts*, Policy Supporting the Next Generation Researchers Initiative, Notice NOT-OD-17-101, August 31, 2017.

⁴⁸⁵ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-101.html>

⁴⁸⁶ <https://acd.od.nih.gov/working-groups/nextgen.html>

Zika-Related Conditions

The Committee encourages NIAID along with other Institutes and Centers to establish cross-cutting research activities to combat Zika-related conditions, including Guillain-Barre' Syndrome.

Action taken or to be taken:

The National Institute of Allergy and Infectious Disease (NIAID) is supporting research to identify and understand the biology of diverse conditions linked to infection with Zika virus, including Guillain-Barré Syndrome (GBS) and other neurological disorders. NIAID also is supporting a portfolio of basic, translational, and clinical research on Zika virus to aid in the development of prevention and treatment strategies.

NIAID supports basic research on Zika virus transmission, pathogenicity, and host immune-response to infection. NIAID also has developed several animal and cell-based models of Zika virus infection to aid researchers studying Zika and Zika-related diseases. These activities aid in understanding the body's response to Zika and provide insight into the development of effective vaccines and therapeutics. For example, NIAID scientists comparing immune responses to African and Asian Zika virus lineages in a mouse model demonstrated that these lineages represent a single viral serotype, a classification of a microbe based on its ability to react to specific antibodies, suggesting that vaccine candidates targeting this serotype should be effective against both lineages. In addition, NIAID researchers and grantees have shown that the Zika virus protein NS5 helps the virus establish infection by overcoming a person's immune defenses, indicating that this protein may be a good therapeutic target.

NIAID also supports clinical research to understand the natural history and pathogenesis of Zika virus infection. NIAID is collaborating with the Mexico Ministry of Health to evaluate individuals diagnosed with GBS in a Zika-endemic area to characterize the risk of developing GBS after Zika virus infection. In separate NIAID-supported studies, researchers are investigating Zika-related conditions in infants and children. The Zika in Infants and Pregnancy study, supported by NIAID, NICHD, NIEHS, and Fiocruz, is evaluating the effect of Zika infection during pregnancy on the development of abnormalities in fetuses and newborns. Another NIAID-supported study underway in Guatemala aims to characterize the clinical and neurological manifestations of postnatally-acquired Zika infection on infants and children.

NIAID also is supporting research to develop a safe and effective Zika vaccine, which would be an invaluable tool to help stop the spread of infection, prevent future outbreaks, and avert Zika-related conditions including GBS. NIAID is supporting development and evaluation of several candidate Zika vaccines, including a DNA-based vaccine that has entered Phase II/IIb clinical testing, to evaluate safety and efficacy in response to natural Zika infection.

NIAID will continue to support research on Zika-related conditions, such as GBS and other neurological disorders, to better characterize and understand these diseases and their relationship to Zika infection. In addition, NIAID will maintain a broad research portfolio to advance the development of Zika vaccines, therapeutics, and diagnostics.