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Academic Partnerships to Support Clinical Development

The Committee understands the importance and partnerships between NIH's intramural research program and academic based entities to transition intramural research ideas into development efforts. As such, the Committee encourages the center to support such partnerships and provide a report on the center's efforts in the fiscal year 2018 budget request.

Action taken or to be taken

The Division of Pre-Clinical Innovation (DPI) serves as the intramural research program of the National Center for Advancing Translational Sciences (NCATS) and advances collaborative research projects across the pre-clinical phase of the translational science spectrum. Pre-clinical research connects the basic science of disease with human medicine. During this stage of translational research, DPI scientists develop model interventions to further understand the basis of a disease or disorder and find ways to treat it. Testing is carried out using cell or animal models of disease; samples of human or animal tissues; or computer-assisted simulations of drug, device or diagnostic interactions within living systems. Based upon the findings from pre-clinical research, promising medical interventions can advance into the clinical phase for efficacy and safety testing in human research participants. However, medical interventions face many challenging roadblocks in the transition from the pre-clinical to clinical stages of development and carry with them significant risk of failure to become a safe and effective drug, vaccine, device or diagnostic. DPI programs overcome these roadblocks by supporting the development of new technologies to "de-risk" therapeutic targets and disease projects so they will attract external partners for further clinical development and dissemination and become available to patients. Through collaborations with academic research institutions, as well as other NIH Institutes and Centers, industry members, patient advocacy and other nonprofit groups, DPI provides:

- New scientific understanding, technologies and approaches that directly address bottlenecks that limit the efficiency of the therapeutic or diagnostic development process;
- Collaborative pre-clinical drug development expertise and resources, including the generation of safety and efficacy data needed for regulatory approval; and
- A variety of mechanisms to streamline partnerships and collaborations.

Importantly, each collaborative project has a dual mission: first, to de-risk and advance a project to the next phase of translation; and second, to understand the scientific and operational underpinnings of successful approaches and apply them to future projects for more efficient translation. Partnerships and collaborations across organizations are essential because the expertise, capabilities, and viewpoints required for successful translation tend to reside in different groups with distinct missions.

The majority of research conducted by NCATS intramural researchers involves a collaborator from an academic research institution. Of the nearly 250 translational research projects currently underway in the NCATS DPI, approximately 70 percent include an academic investigator as a partner in the project. Of those projects, roughly one-third also engage researchers from one or more NIH Institutes or Centers. Academic researchers typically bring deep knowledge of disease biology and chemistry to the collaborative projects, while NCATS researchers provide expertise in pre-clinical development, project management, clinical research, and regulatory science. Taken together, these scientists spanning the government and academic sectors translate biological discovery into therapeutic potential and catalyze the development of novel treatments

and cures. For example, NCATS researchers recently partnered with experts in Zika virus biology from Johns Hopkins University and Florida State University to rapidly screen thousands of existing and experimental drugs to identify compounds that potentially can be used to inhibit Zika virus replication and reduce its ability to kill brain cells. The researchers identified three compounds which can now be studied by the broader research community. Overall, NCATS' screening effort enabled the research team to quickly translate their earlier discoveries toward work to develop treatments for Zika virus infection.

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. In particular, 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 EPSCoR States, but not IDeA States. The Committee encourages NIH to enhance support for the AREA program by holding regional workshops to provide guidance on writing and submitting R15/AREA applications and on developing institutional capacities for undergraduate research. Further, NIH 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. Currently, NIH staff has been involved in the following activities:

- The IDeA Networks of Biomedical Research Excellence (INBRE) program, a component of the IDeA program, has been organizing statewide R15 grant application writing workshops for investigators at the network primarily undergraduate institutions (PUIs). Because of INBRE's impact in building a sustainable research infrastructure and offering regular INBRE-supported R15 application writing workshops, there has been tremendous success for an increase in the R15 awards at PUIs in Kentucky and in other IDeA states including South Carolina, Louisiana, and Arkansas. At many of these PUI institutions, R15 is the first federal grant from NIH.
- The proposed IDeA Program Eligibility Criteria provides for the participation of PUIs in EPSCoR states that are not IDeA eligible to partner with existing INBRE Networks. These eligibility criteria were transmitted as a legislative proposal to Congress by the Department of Health and Human Services this year.
- NIH organizes and participates in 2-day regional meetings twice a year in different parts of the country. The program includes workshops on the preparation of grant applications and on the development of undergraduate research. Among the major grant mechanisms discussed, the AREA program is highlighted with presentations on the preparation of R15 applications and responses to questions on collaborations, budgets, and scope of projects.
- Program staff conducts workshops and makes presentations at national, professional society meetings such as the American Society for Cell Biology (ASCB), the American Society for Biochemistry & Molecular Biology (ASBMB), and the Biophysical Society. Some of these sessions focus on grant application writing while others discuss how faculty members at PUI manage time for teaching and research.
- NIH program staff makes presentations at various meetings held by the Council on Undergraduate Research (CUR). The goals of CUR are to enhance and provide undergraduate research opportunities for faculty and students at all institutions serving undergraduate students by having regional and national workshops.

- Within NIH, the AREA Program Advisory Committee, composed of program staff from each of the NIH institutes, meet to discuss how better to reach out to the AREA-eligible community and to meet their needs. The Director of the NIH AREA Program is extremely responsive to questions from the AREA-eligible investigators.

To ensure the success of these programs, we plan to continue to

- Build active biomedical research environments in IDeA states and improve access to modern, state-of-the-art biomedical research for students, and researchers.
- Continue to promote collaboration between the research intensive institutions and the PUIs to achieve research goals while preserving the goals of the R15/AREA program.
- Encourage collaborations and leveraging among IDeA research resource centers at regional and national IDeA meetings.
- Facilitate the consolidation of core facilities and promote access to this technology through a core laboratory database.
- Support the above NIH-wide activities across the nation to enhance the competitiveness of AREA-eligible investigators for research and also by providing opportunities for talented undergraduate students to participate in research training and research careers in the biomedical sciences.

Accelerate Cures Related to Retina Disease

The Committee requests an update on the new challenge program to advance the speed of basic research to cure retina disease in the fiscal year 2018 budget request.

Action taken or to be taken

Accelerating the development of therapies to treat retinal diseases requires the development of robust disease models and platforms to screen and test potential therapeutics. Thus, the National Eye Institute (NEI) is preparing to launch a tissue-engineering challenge competition to develop 3-D human retina organoids. Organoids are 3-D miniature organs grown in a culture dish from stem cells. In other systems, such as liver, gut, and pancreas, organoids have been used in disease modeling and drug development. To gauge the state of the science and determine appropriate parameters for the challenge, NEI held a planning meeting on April 4, 2016, where scientists and engineers from industry and academia brought together expertise in retinal regenerative medicine and experience with organoids from other systems. Experts discussed various methods for creating organoids from directed self-assembly of cells, to using scaffolds to construct 3-D architecture, to bioprinting cells, to organoids assembled on chips connected by fluid filled channels. In addition to the website <https://nei.nih.gov/3droc>, NEI established an online forum for potential solvers to find and build teams for collaborating toward the end goals <https://forum.nei.nih.gov/>.

The challenge will focus on two goals, disease modeling and drug development, with cash prizes for the most successful submission toward each goal. The challenge will consist of two phases: Phase 1 will assemble interdisciplinary teams and develop concrete, tangible concept proposals to develop retina organoid models; the deadline is projected to be July 2017. Phase 2 focuses on system development and is tentatively planned to conclude in June 2018. Following the planning meeting, NEI established criteria that must be satisfied in the challenge. Retina organoids must be generated from human stem cells. Their 3-D architecture must recapitulate the layers of a retina and exhibit multiple classes of interconnected neurons and a support structure called the retinal pigment epithelium. The mature tissue must display retinal function, such as response to light and cell to cell communication. In addition to these and other basic criteria, submissions will be judged based on additional complexity and recapitulation of normal retinal biology, such as how long the tissue survives, how flexible it is to model various diseases, and how easily the technology can be leveraged by the broader research community. Solvers will retain the intellectual property of their inventions and are encouraged to translate their work into commercially viable products.

Administrative Burden Workgroup

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

In 2015, NIH participated in a National Academy of Sciences (NAS) study to review federal research regulations and reporting requirements, with specific attention to those directed at research universities.¹ The study was initiated amid concerns that federal laws, regulations, rules, policies, and reporting requirements have led to an environment in which a significant percentage of an investigator's time is spent complying with regulations. While essential to a well-functioning, responsible system of research, these requirements take time away from an investigator's research, education, and scholarship.

In 2016, NAS released Part 2 of their report entitled, "Optimizing the Nation's Investment in Academic Research: A New Regulatory Framework for the 21st Century."² The report reviewed the federal regulatory framework for research institutions as it currently exists, considered specific regulations that have placed burdens on the research enterprise, and reassessed the process by which these regulations are created, reviewed, and retired. If implemented, these actions could help reduce regulatory burden. In this update, we focus on the NAS recommendations related to human subjects protections, intellectual property and technology transfer reporting, research with select agents and toxins, and export controls.

Human Subjects Protections

The NAS report includes recommendations related to the protection of research participants (e.g. the Common Rule; 45 CFR 46), suggesting changes to achieve protections that are more finely-calibrated to the nature and risk of research as it is conducted today, and to reduce unnecessary regulatory burdens. Minimal changes had been made to the Common Rule since its promulgation in 1991, and the Administration's decision to move forward with a comprehensive effort to modernize it was welcomed by NIH. A proposed rule was issued in 2015 for public comment,³ with the final rule being published in January 2017.⁴ The final rule reflects a careful consideration of public comments on the proposed rule, and it addresses the NAS call for changes that better align protections with the levels of risk posed by research today. For example, the Final Rule eliminates (1) the requirement for continuing review by an Institutional Review Board (IRB) for studies that were eligible for expedited initial review and for studies that have reached the stage of data analysis as well as (2) duplicative IRB review in multi-site research studies by requiring such studies to rely on a single IRB. The reduction in review burden will allow IRBs to devote more attention to research proposals that pose higher risks to participants. Through these and other changes, the final rule achieves an appropriate balance in the protection of research participants while reducing unnecessary regulatory burden.

¹ <https://www8.nationalacademies.org/cp/projectview.aspx?key=49675>

² http://sites.nationalacademies.org/PGA/stl/researchregs/index.htm?utm_source=CSTL+Mailing+List&utm_campaign=af1df78538-University_Research_Regulations_Announcement&utm_medium=email&utm_term=0_36510203a8-af1df78538-127923941

³ <https://www.gpo.gov/fdsys/pkg/FR-2015-09-08/pdf/2015-21756.pdf>

⁴ <https://www.gpo.gov/fdsys/pkg/FR-2017-01-19/pdf/2017-01058.pdf>

Select Agents and Export Controls

The NAS recommendations on select agent regulations (SAR) were aimed at enhancing biosecurity surrounding biological select agents and toxins, increasing transparency on decision-making, and increasing access to lower-virulent strains of select agents and toxins. Though administered by CDC and USDA, NIH works to assure that NIH-funded research adheres to the requirements of the federal select agent regulations⁵. The regulations divide agents and toxins into two tiers based on the risks associated with the deliberate misuse of the agents. Through this approach, the oversight of select agents is commensurate with the associated potential risks, which helps minimize burden. The list of agents and toxins is also regularly reviewed and amended if needed based on factors including the latest scientific, medical, and public health information. CDC and USDA consult with the public regarding amendments to the SAR through Federal Register notices and more informal communications. Moreover, a list of excluded agents and toxins, including lower-virulent strains not regulated under the SAR, is publicly available to the research community.

The SAR covers the full range of diverse research sponsored by the federal government, involving animal (both human and non-human) and plant pathogens. Efficient oversight requires specialized knowledge of the unique research activities, risks, safety, security practices, as well as engineering and biocontainment needs for these distinct fields of study. Consolidation of oversight within a single agency as recommended in the NAS report may undermine the SAR's ability to safeguard the nation's biosecurity. However, the NAS recommendation to streamline and simplify export control regulations as a means to reduce administrative burden is consistent with continuing federal efforts.

Intellectual Property and Inventions Reporting

The NAS report recommended that responsibility for the operation of Interagency Edison (iEdison), the fed-wide invention reporting system, be transferred from the NIH to the Department of Commerce (DoC). Additional resources were also recommended to update the system, specifically to establish a more user-friendly interface to input data on inventions. The recommendations further specify that the DoC, in consultation with the Research Policy Board, develop uniform, federal-wide invention reporting requirements for agencies, ensuring that the frequency and type of data collected do not exceed what is required by the Bayh-Dole Act.

Regardless of where the iEdison system resides, a shared funding model should be considered to support iEdison (e.g. charging agencies proportionally based on their use). Though transferring iEdison to DoC would localize the system with operating divisions responsible for the overall Bayh-Dole regulatory structure, the funding agencies would continue to manage the research enterprise, including the enforcement of compliance with federal award terms and conditions. This knowledge is pivotal to effectively host a reporting system for federally sponsored inventions resulting from activities covering diverse research programs and science areas. Administrative burden would be reduced if all research funding agencies used the same patent reporting system and adhered to uniform, streamlined reporting requirements. Furthermore, the user interface would benefit from adopting recent web technology advances to make it easier for institutions to access, use, and expedite entry of data.

⁵ <http://www.selectagents.gov/>

NIH regularly redesigns and updates the functionality and compatibility of iEdison, even while the system remains active for users. Many of these updates are in response to changes in the reporting requirements found in U.S. patent law. NIH will continue to focus attention on developing a more robust, modern, streamlined system to allow reporting on inventions as a means to address administrative burden concerns.

Adolescent Behavioral and Cognitive Development (ABCD)

The Committee continues to applaud the collaborative research on addictions and the launch of the ABCD study. Unique in its scope and duration, the study will recruit 10,000 youth before they begin using alcohol, marijuana, nicotine and other drugs, and follow them over 10 years into early adulthood to assess how substance use affects the trajectory of the developing brain. The Committee commends the study design, which will use advanced brain imaging as well as psychological and behavioral research tools to evaluate brain structure and function and track substance use, academic achievement, IQ, cognitive skills, and mental health over time. The Committee requests NIDA provide an update on the comprehensive study.

Action taken or to be taken

Adolescence is a period of intense brain and cognitive growth that gives rise to an unprecedented number of new experiences and provides opportunities for teens to develop expertise and shape their 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), and the CDC Division of Adolescent and School Health, is funding the landmark Adolescent Brain Cognitive Development (ABCD) Study⁶, a multi-site, longitudinal investigation of 10,000 children from ages nine and ten into early adulthood. During this time, roughly 60 percent are likely to initiate alcohol use, about 45 percent are expected to initiate marijuana use, and about 20 percent are likely to try an illicit drug other than marijuana. The ABCD study will explore the impact of these and other experiences on brain development as well as physical and mental health.

In 2016, the ABCD Study finalized its recruitment approach—working with school systems to reach a diverse pool of student participants—and conducted a multi-site pilot study to refine and finalize study procedures. The ABCD Study launched recruitment at 19 research sites across the country in September 2016. To date, 851⁷ 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 – including hair, saliva, and blood – for genetic, epigenetic, hormonal, environmental exposure, and substance use analysis.

To enrich the value of the study, ABCD will release anonymized data annually to the research community in an open science model to allow scientists from all over the world to pool resources

⁶ <http://abcdstudy.org/index.html>

⁷ As of January 19, 2017.

to rapidly analyze the data, expanding the scientific questions that will be answered. The actionable information coming out of this study will be a foundation upon which to develop and refine substance use prevention and other health promotion interventions that are rooted in a deep understanding of the neurobiological and psychosocial factors that influence adolescent health and wellness and are focused on optimizing the wellbeing and success of our Nation's children.

Adolescents and Young Adults Substance Abuse

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 2018 budget requests on actions to further these desires.

Action taken or to be taken

Brain development is ongoing in adolescence and into young adulthood—a time when risk-taking behaviors, including substance use, can emerge. NIH supports a broad research portfolio addressing adolescent substance use ranging from basic research studies in animal models to prospective longitudinal studies in humans that provide critical insight into how substance use affects health outcomes in young people.

The Collaborative Research on Addiction at NIH (CRAN), a partnership between the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), and the National Cancer Institute (NCI), was created to foster research in polysubstance use and support studies aimed at increasing our understanding of factors that underlie vulnerabilities to substance use and addiction. In 2015, CRAN initiated the Adolescent Brain Cognitive Development (ABCD) Study, which will follow 10,000 children from pre-adolescence into adulthood and shed light on cognitive, emotional, and physical development during adolescence (see also Significant Item on ABCD Study).

Additionally, NIH continues to support the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA), a nationally representative, longitudinal study evaluating brain structure and function in more than 800 youth before and after they began alcohol use. NCANDA has provided important information on the adverse effects of alcohol on the adolescent brain and laid the methodological foundation for the ABCD study.

Complementing ABCD and NCANDA, NIAAA and NIDA support research that examines, in animal models, the molecular, cellular, and circuit-level mechanisms by which adolescent drinking affects brain structure and function in the short- and long-term and how the changes observed during this critical period persist into adulthood.

NIDA also leads the Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System (JJ-TRIALS), a 5-year cooperative study designed to identify and test strategies for improving the delivery of evidence-based substance use and HIV prevention and treatment services for justice-involved youth.

In addition, through its NIDAMED initiative, NIDA, in partnership with leading experts and medical associations, created a continuing medical education course (CME) that provides clinicians with research-based information and clinical strategies to help them prevent, identify, and address substance use disorders and prescription medication misuse in their adolescent patients. This web-based CME is expected to launch by January 2017. Similarly, NIAAA released an evidence-based youth alcohol screening guide to help health care providers identify risk for alcohol use, current alcohol use, and alcohol-related problems in youth ages 9-18. The

screening guide was evaluated in primary care, emergency department, juvenile justice, and school settings, and with youth who have a chronic condition.

Alopecia Areata Research

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned

Action taken or to be taken

Alopecia areata (AA) is an autoimmune disease in which the immune system, which normally protects the body from foreign invaders such as viruses and bacteria, mistakenly attacks the hair follicles, the structures from which hairs grow. This can lead to hair loss on the scalp and elsewhere. NIAMS-funded research has improved understanding of the genetic underpinnings of AA and led to marked progress in the search for new treatments. Basic research studies supported by the Institute revealed that some of the disease pathways active in AA also play a role in other autoimmune diseases, such as rheumatoid arthritis (RA). Follow-up studies identified abnormal immune cells and signaling pathways in the disease, and led to the hypothesis that one class of RA drugs, called JAK-STAT inhibitors, might be effective in treating AA. In 2015, NIAMS-funded researchers reported that two JAK-STAT inhibitors, ruxolitinib and tofacitinib, could prevent hair loss when administered systemically and restore hair growth when applied topically in a mouse model of AA. In addition, preliminary clinical results suggested that ruxolitinib could stimulate hair regrowth in patients. A subsequent study of ruxolitinib in 12 patients with moderate to severe disease showed that 3-6 months of treatment with the drug led to hair regrowth and scalp improvement in 75 percent of participants. In a 3 month clinical trial of tofacitinib in 66 patients, about 50 percent of participants taking the drug experienced some hair regrowth. Scientists are planning additional studies to further explore the safety and efficacy of JAK-STAT inhibitors in AA and to understand why some patients fail to respond to the treatment. In FY 2016, to speed the translation of AA basic research discoveries to the clinical setting, NIAMS funded a new Alopecia Areata Center for Research Translation to investigate the role of the microbiome in AA, explore new therapeutic approaches, and lay the foundation for studies to evaluate emerging therapies.

Alzheimer's Disease

The Committee recommends an increase of \$350,000,000 within NIA to support a total of at least \$1,260,000,000 on Alzheimer's disease research. In recognition that Alzheimer's disease poses a serious threat to the Nation's long-term health and economic stability, the Committee expects this increase to be directed to research on Alzheimer's. The 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. The Committee has been encouraged by recent advances in the area of prevention, with respect to using drug therapy to reverse cellular and genetic changes associated with cognitive decline. The Committee understands that similarly exciting research is also underway to prevent cognitive impairment and Alzheimer's disease. A broad approach is critical to future progress, and the NIA is encouraged to continue exploring multiple avenues of prevention research—including both pharmacological and non-pharmacological approaches—and a broad range of potential therapeutic targets. The Committee requests an update on the progress in the fiscal year 2018 budget request that specifically notes how NIH is using population cohort studies within the National Plan. The Committee expects NIA to continue to support Alzheimer's research with meritorious IDeA program researchers in a manner that does not count against any NIHCOBRE policy limit. The Committee is encouraged from the positive feedback of stakeholders on the willingness of NIA and other ICs to work with such groups to develop new mechanisms to supplement and not supplant funding for Alzheimer's research using meritorious research proposals submitted to but not funded by the NIA or NIH to further leverage non-NIH funding. The Committees encourages the further use of this mechanism across NIH.

Action taken or to be taken

NIH's plans for addressing the research goals set forth in the National Plan to Address Alzheimer's Disease (AD) are presented in NIH's professional judgment budget ("Bypass Budget") for Alzheimer's disease and related dementias. The latest Bypass Budget, for FY 2018, was released on August 1, 2016.⁸ This document provides an estimate of the funds in FY 2018 above the NIH's base appropriation that will enable NIH to fully pursue scientific opportunities relative to the milestones established in the National Plan, and work toward the ultimate goal of finding a cure for Alzheimer's and related dementias. Many strategic planning efforts have informed the development of the AD Bypass Budget, including but not limited to the 2012 and 2015 Alzheimer's Disease Research Summits, the 2013 and 2016 Summits on Alzheimer's Disease-Related Dementias, and the 2013 meeting on Advancing Treatment for Alzheimer's Disease in Individuals with Down Syndrome. Upcoming Summits include a third Alzheimer's Disease Summit to assess progress and update and refine milestones, as well as an AD Care and Services Summit. Both are planned for FY 2018.

Recent advances in the prevention of cognitive decline, AD, and related dementias have indeed been promising. For example, initial testing is ongoing of the experimental compound BPN14770, which enhances activity of neurons involved in memory and cognition and was developed under the NIH Blueprint Neurotherapeutics Program. NIH supports clinical trials of

⁸ <https://www.nia.nih.gov/alzheimers/publication/stopping-alzheimers-disease-and-related-dementias/about-fy-2018-bypass-budget>

other compounds, as well as nonpharmaceutical interventions such as exercise, conversational engagement, and cognitive training. NIA also recently issued two Funding Opportunity Announcements for both early- and late-stage clinical trials of promising pharmacological and non-pharmacological interventions in individuals with age-related cognitive decline and across the AD spectrum, from pre-symptomatic to more severe stages of disease.

NIH's IDeA program fosters health-related research and enhances the competitiveness of investigators at institutions located in states in which the success rate for applications to NIH has historically been low. Centers are active at institutions in 23 states and Puerto Rico; many centers have a neuroscience focus. We will continue to welcome meritorious applications on AD and related dementias from researchers at these groundbreaking centers. Notably, Alzheimer's-related awards made using these dedicated funds are not considered COBRE awards and will not be subject to IDeA program policy limits.

Finally, the Online Partnership to Accelerate Research (OnPar) initiative is a collaboration between NIH and Leidos Health Sciences that provides an electronic system matching peer-reviewed, unfunded NIH grant applications with stakeholder organizations looking to fund promising proposals. Any investigator receiving a meritorious score may submit his or her application to OnPar; NIH's role in the collaboration is to alert investigators to the existence of the program. The AD/ADRD stakeholder groups are not yet involved in OnPar, but several have expressed an interest in potentially joining the program.

Alzheimer's Disease

The bill includes approximately \$1,391,000,000, an increase of \$400,000,000 above fiscal year 2016, for high-quality research on Alzheimer's disease, subject to the scientific opportunity presented in the peer review process. NIA is encouraged to continue addressing 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. Further, the Committee recognizes the importance of well-characterized, longitudinal, population-based cohort studies in providing new 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. The Committee directs NIH to support research involving 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. In particular, NIA is encouraged to fund a pilot program to test community-based clinical trials for the prevention of cognitive decline. Such a longitudinal study should include an ethnically representative sample, incorporate genomic and environmental

Alzheimer's disease risk factors and monitor cognitive and motor function, disability, and morbidity over time. The Committee notes that poor sleep health and sleep disorders progress diseases that impair cognitive functioning, such as Alzheimer's disease. The Committee encourages support for research that explores the linkages between sleep cycle, cardiovascular system, and Alzheimer's disease, in an effort to inform prevention. Priority consideration should be given to applicants with a NIA designated Alzheimer's Disease Center, Alzheimer's Disease Accelerating Medicines Partnership award, and at least one Patient-Centered Outcomes Research Institute grant. Finally, the Committee is particularly interested in NIH's plans to place additional emphasis on high-risk, high-reward projects using a DARPA-like approach to goal-oriented and milestone-driven research. The Committee believes such an approach can be particularly valuable in addressing major scientific gaps and encourages NIH to establish clear priorities, including Alzheimer's disease and dementia and other high-cost diseases of aging, particularly given our national goal of preventing and effectively treating Alzheimer's disease by 2025.

Action taken or to be taken

Note: To ensure that we provide a comprehensive and cohesive response, and with the approval of the Committee staff, the NIA has re-ordered the language within and expanded our response to this complex Item.

NIH's plans for addressing the research goals set forth in the National Plan to Address Alzheimer's Disease, along with information about initiatives and advances, are presented in NIH's professional judgment budget ("Bypass Budget") for Alzheimer's disease and related dementias. The latest Bypass Budget, for FY 2018, was released on August 1, 2016.⁹ This document provides an estimate of the funds in FY 2018 above the NIH's base appropriation that will enable NIH to fully pursue scientific opportunities relative to the milestones established in

⁹ <https://www.nia.nih.gov/alzheimers/publication/stopping-alzheimers-disease-and-related-dementias/about-fy-2018-bypass-budget>

the National Plan, and work toward the ultimate goal of finding a cure for Alzheimer's and related dementias. Many strategic planning efforts in AD and related dementias have informed the development of the AD Bypass Budget, including but not limited to the 2012 and 2015 Alzheimer's Disease Research Summits; the 2013 and 2016 Summits on Alzheimer's Disease-Related Dementias, and the 2013 meeting on Advancing Treatment for Alzheimer's Disease in Individuals with Down Syndrome. Upcoming Summits include a third Alzheimer's Disease Summit to assess progress and update and refine milestones, as well as an AD Care and Services Summit. Both are planned for FY 2018.

Guided by the goals and milestones presented in the Bypass Budget and the National Plan, and with the benefit of additional funds targeted at Alzheimer's and related dementias over the past several years, the NIH has supported a number of new initiatives across the spectrum of AD research. In September/October 2015, the National Institute on Aging (NIA) posted a series of 10 Program Announcements (PAs) focused on Alzheimer's disease. These PAs included set-aside funding and offered opportunities for investigators in virtually every aspect of AD research—from basic biological studies to epidemiology to caregiving to clinical trials. The response to these PAs was encouraging, and initial awards were made in late FY 2016.

Early in FY 2017, NIA approved the concepts for 26 new Funding Opportunity Announcements (FOAs) supporting Alzheimer's research, and the Institute is currently in the process of rolling them out. The topics of these solicitations fall into five broad categories, including leveraging existing resources to facilitate discovery and speed progress; enhancing caregiving and clinical care; rapid translation of new research from the laboratory to the clinic; basic research on AD and related dementias; and training for researchers in key scientific disciplines. The FOAs have set-aside funds associated with them, and will be supported according to the availability of funds in FY17 and FY18.

With the NIA, the National Institute of Neurological Disorders and Stroke (NINDS) leads much of the research on Alzheimer's Disease-Related Dementias (ADRD) at NIH, and in collaboration with the NIA hosts Summits that establish clear priorities and milestones for research in frontotemporal, Lewy body, vascular, and mixed dementias, all of which contribute significantly to the burden of illness due to dementia. Updates are informed by scientific progress and solicited input from scientific experts, non-governmental organizations, patients, families, and caregivers. Priorities set in 2013 have led to a number of new funding opportunities, including six launched by the NIH this year. Of note, two are for a new national Small Vessel Vascular Contributions to Cognitive Impairment and Dementia Biomarkers Consortium. The updated 2016 ADRD milestones will inform and guide ADRD research for the next 3-10 years.

NIA supports a number of demographic, epidemiologic, and longitudinal studies that collect vital data on Alzheimer's disease and related dementias, including many that specifically involve members of underrepresented populations. These studies are crucial to understanding trends, tracking incidence and prevalence, and identifying potential risk and protective factors for these diseases.

For example, in September 2015, NIA funded a new extension to the Health and Retirement Study, a population-based study following over 20,000 Americans from age 50 until death, to develop a new harmonized cognitive assessment protocol (HCAP) that will allow the more efficient re-estimation of dementia prevalence in the United States and allow us to investigate racial, ethnic, and gender disparities in dementia.

Also in 2015, NIA released an FOA soliciting projects adding additional measures and information about participants in existing cohorts, along with research on all aspects of epidemiology relevant to AD and cognitive resilience. Eighteen projects have been funded under this FOA to date, including a study of the genetic epidemiology of cerebrovascular factors in AD among members of a large, multi-ethnic cohort in New York; a study of the genetic epidemiology of early-onset disease among Caribbean Hispanics and non-Hispanic whites; addition of cutting-edge brain imaging and combination of this data with existing genetic information to assess dementia risk and identify potential new biomarkers in the long-running Framingham Heart Study; and a study that will explore available health, functional, and lifestyle information, together with repeated cognitive assessments and brain autopsy data, to identify factors that contribute to cognitive resilience among male and female participants in two longitudinal studies.

The Committee directs NIH to support research involving 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. In particular, NIA is encouraged to fund a pilot program to test community-based clinical trials for the prevention of cognitive decline. Priority consideration should be given to applicants with a NIA designated Alzheimer's Disease Center, Alzheimer's Disease Accelerating Medicines Partnership award, and at least one Patient-Centered Outcomes Research Institute grant.

NIA supports several multigenerational cohort studies that are providing important insight into potential risk and protective factors for Alzheimer's and related dementias. For example:

- The Adult Children Study is following a cohort of middle-aged and older individuals, with and without a family history of AD, who longitudinally undergo biological, clinical and cognitive tests to identify the earliest brain changes of AD prior to any clinical symptoms. Investigators are currently focusing on defining the 'trigger(s)' that leads to symptomatic AD.
- The NIA - Late Onset Alzheimer's Disease Family Study (NIA-LOAD), explores the risk and protective factors for late-onset disease and clarifies the ways in which non-genetic risk or protective factors modify the effects of the variants on disease risk.
- A new study based at Columbia University has been established to identify underlying biological and sociocultural mechanisms of racial/ethnic disparities in cognitive function among a middle-aged cohort of 3,000 offspring whose parents do and do not have AD.

Clinical trials for the prevention of cognitive decline, AD, and related dementias – including community-based trials – continue to be a major priority for the NIH. For example, a recent FOA is soliciting proposals for “real-world” studies of interventions to enhance dementia care in long-term care settings. NIA is also supporting a well-established partnership of Area Agencies on Aging (AAAs) and an experienced group of multidisciplinary researchers from the University of Washington as they collaborate to investigate the systematic translation, implementation, and effectiveness of the Reducing Disabilities in Alzheimer's Disease (RDAD) intervention as administered by AAA staff within the community. RDAD is an evidence-based program with demonstrated efficacy in helping older adults with dementia maintain physical function and remain physically and mentally healthy.

With respect to prevention of cognitive decline, mild cognitive impairment, and Alzheimer's dementia, evidence for and against the effectiveness of many specific interventions is often unclear, contradictory, or of insufficient quality. NIA has asked the National Academies of Sciences, Engineering, and Medicine (the National Academies) to convene an expert committee to make recommendations that inform public health strategies and messaging on preventive interventions on this topic, and recommendations for future research. To aid the Committee in its work, the NIA has asked the Agency for Healthcare Research and Quality (AHRQ) to commission and oversee a systematic review—conducted by the Minnesota Evidence-based Practice Center—of the evidence on interventions associated with preventing, slowing, or delaying the onset of clinical Alzheimer's-type dementia and MCI, and delaying or slowing age-related cognitive decline. An expert workshop was held in October 2016, and we anticipate the final report to be released in summer-fall 2017.

Such a longitudinal study should include an ethnically representative sample, incorporate genomic and environmental Alzheimer's disease risk factors and monitor cognitive and motor function, disability, and morbidity over time.

NIA is committed to understanding health disparities related to AD, and the Institute supports studies dedicated to understanding risk factors and implementing preventive and treatment interventions in diverse racial and ethnic groups.

In 2015, NIA released a Funding Opportunity Announcement (FOA) soliciting projects adding additional measures and information about participants in existing cohorts, along with research on all aspects of epidemiology relevant to AD and cognitive resilience. Some of the projects funded under this FOA are described above. NIA also released an FOA in 2015 on health disparities in AD; six projects have been funded exploring the effects of a variety of behavioral and social factors on cognitive health among diverse populations. Notably, Satellite Diagnostic and Treatment Centers, part of the national Alzheimer's Disease Centers (ADC) Program, have successfully recruited African Americans, Hispanics, Native Americans, and American Indian/Alaska Natives to AD prevention and treatment studies.

In addition, the NIA, with the National Heart, Lung, and Blood Institute, the National Institute of Neurological Disorders and Stroke, and the National Institute on Deafness and other Communication Disorders, co-funds the Atherosclerosis Risk in Communities (ARIC) neurocognitive study, a multi-site cohort study that now focuses on AD and dementia. Over the past 20 years, the original ARIC study and the ARIC neurocognitive study have collected data on an initial cohort of 15,792 middle age African-American and white men and women to investigate risk factors for diseases and factors including heart disease, hypertension and cognitive function. Using the data from this study and the wealth of information already collected in ARIC, we expect to find out more about the causes of dementia and less severe symptoms of mild cognitive impairment. The University of Mississippi Medical Center (Jackson, MS) is one of several institutions participating in this groundbreaking study.

The Committee notes that poor sleep health and sleep disorders progress diseases that impair cognitive functioning, such as Alzheimer's disease. The Committee encourages support for research that explores the linkages between sleep cycle, cardiovascular system, and Alzheimer's disease, in an effort to inform prevention.

Previous research has shown that disturbed sleep (e.g., abnormal sleep duration, fragmented sleep, or delayed sleep onset) and sleep-disordered breathing may be important contributors to Alzheimer's disease, and disturbed sleep is known to be associated with cognitive decline more generally.

NIH supports a number of projects that explore the links between sleep and cognition: In one large study, data on sleep quality collected two decades ago from participants in the ARIC study and the Sleep Heart Health Study (SHHS) will be linked with current neuroimaging results to determine the extent to which disturbed sleep and sleep-disordered breathing are associated with beta amyloid deposition – a hallmark of Alzheimer's disease pathology – in the brain.

Other investigators are exploring the associations of sleep disorders with chronic inflammation, which is implicated in cardiovascular disease and, increasingly, in cognitive decline. Still others are identifying the underlying the metabolic, inflammatory, and other molecular pathways through which sleep duration and quality influence the development and progression of Alzheimer's, cardiovascular disease, and other chronic health conditions.

Sleep apnea is associated with risk of cognitive decline and Alzheimer's disease. For example, sleep disordered breathing is associated with the increase of cerebrospinal fluid, phosphorylated-Tau, and total-Tau, decreases in glucose uptake and volume in the medial temporal lobe, and progressive memory decline, all of which have been shown to be useful in predicting future dementia in cognitively normal older adults. NIH supports a study to determine whether these changes cause or result from Alzheimer's disease.

Finally, the Committee is particularly interested in NIH's plans to place additional emphasis on high-risk, high-reward projects using a DARPA-like approach to goal-oriented and milestone-driven research. The Committee believes such an approach can be particularly valuable in addressing major scientific gaps and encourages NIH to establish clear priorities, including Alzheimer's disease and dementia and other high-cost diseases of aging, particularly given our national goal of preventing and effectively treating Alzheimer's disease by 2025.

An important NIH mechanism supporting high-risk, high-reward research is the Cures Acceleration Network (CAN) at the National Center for Advancing Translational Sciences (NCATS). This groundbreaking initiative was created to advance the development of “high need cures” and reduce significant barriers between research discovery and clinical trials. CAN may use up to 20 percent of its funds to support flexible research under an authority that allows projects to be actively and aggressively managed by using mechanisms similar to those used by the Defense Advanced Research Projects Agency. CAN initiatives will advance translational science across many diseases and conditions, and will help bring more treatments to more patients more quickly, including – we anticipate – for Alzheimer's disease.

Amyotrophic Lateral Sclerosis [ALS]

The Committee strongly supports NIH's research in ALS and encourages NIH to continue to support promising ALS research related to IPS cells, whole genome sequencing, biomarkers, precision medicine, natural history studies, and translational research that could help identify new treatments for the disease. NIH is encouraged to partner with ALS organizations and other Federal agencies and programs, including the ALS Research Program at DOD, the VA, and the National ALS Registry at CDC/ATSDR. The Committee further encourages NIH to work with FDA, industry, and other stakeholders to identify opportunities to inform and advance the development of treatments for ALS, particularly how the NIH can support Phase II and Phase III clinical trials in ALS.

Action taken or to be taken

About 10% of ALS is known to be genetic, but it is still largely unknown what causes ALS in most cases. In 2015, scientists at NINDS reported a possible link between ALS and the activation of dormant viral genes that are embedded in the human genome. More recently, scientists funded by NIH and several international ALS organizations performed whole exome sequencing on ALS patient samples to discover a new risk gene called NEK1. Continuing efforts to identify genetic and other risk factors that contribute to ALS will provide clues that should advance and guide treatment strategies, including personalized treatment based on precision medicine.

The National Institute of Neurological Disorders and Stroke (NINDS) supports over 120 projects within a broad spectrum of ALS research from basic to translational to clinical. For instance, NeuroLINCS is an NIH-funded, collaborative effort between various academic research teams that are analyzing molecular signatures of an array of human brain and spinal cord cell types derived from induced pluripotent stem (iPS) cells from patients with motor neuron diseases, including ALS. Their goal is to identify unique molecular signatures found in neurological diseases and discover new therapeutic targets. Other researchers are testing small molecules that inhibit toxic protein aggregates found in ALS and genetically targeted therapies to block or replace defective genes in ALS. In partnership with the National Center for Advancing Translational Science (NCATS), NINDS funds the “Clinical Research in ALS and Related Disorders for Therapeutic Development (CREATe)” consortium, a network of over ten clinical centers that performs natural history studies, whole genome sequencing, and biomarker discovery studies to enable earlier diagnosis and accurate tracking of disease progression in ALS and related disorders. In a complementary effort, researchers at the National Institute on Aging and NINDS are recruiting individuals with a specific gene mutation associated with ALS and frontotemporal degeneration (FTD) to study natural history and discover biomarkers for this genetic subtype of ALS and FTD. In support of a recently-initiated, industry-sponsored clinical trial in another genetic subtype of ALS, NINDS is funding a targeted biomarker study to optimize the trial's design and data analysis.

NIH is actively involved in collaborating with other federal agencies and various stakeholders. NIH staff participate on a programmatic review panel for the DOD ALS Research Program, regularly interact with VA program staff to coordinate ALS research investments, and serve on the advisory committee for the National ALS Registry at ATSDR/CDC. NINDS also meets quarterly with the FDA Center for Biologics Evaluation and Research to expedite development of promising cell-based and gene therapies for ALS. In March 2016, NINDS, NCATS, ALS

organizations, and physician scientists worked together to host an international workshop, “ALS Clinical Trial Guidelines 2016,” which brought together experts from academia, industry, NIH, FDA and multiple ALS organizations to review challenges in current ALS clinical trials, and to update guidelines that provide investigators with recommendations on the design and implementation of clinical studies in ALS.

Amyloidosis

The Committee recommends that NIH continue 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 requests NIH to update the Committee on the steps taken to increase the understanding of the causes of amyloidosis and the efforts to improve the diagnosis and treatment of this devastating group of diseases.

Action taken or to be taken

Research on the causes of and improved diagnosis and treatments for amyloidosis, a rare disease in which a protein called amyloid builds up in the organs, causing organ failure and often death, is supported across the NIH.

Basic Research: The National Institute on Aging (NIA) supports studies to determine the structure of the amyloid protein. NIA-supported researchers are also establishing the prevalence among African Americans of a genetic variant associated with increased risk of amyloid deposits in the heart. Investigators at the National Heart, Lung, and Blood Institute (NHLBI) have identified molecular changes that underlie damage to the heart in light chain amyloidosis, the most common form of systemic amyloidosis in the United States.

Diagnostics: NHLBI also supports research into new imaging methods for amyloidosis, including a combined CT-PET method for quantitative, whole-body visualization of amyloid. Meanwhile, investigators supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) have developed a blood-based diagnostic that distinguishes symptomatic familial amyloid polyneuropathy (FAP) from asymptomatic carriers. This study demonstrated that the molecular “signatures” for FAP differ in men and women; these findings may explain why FAP progresses more rapidly in male patients. Other NIDDK-supported researchers found that the imaging agent p5+14 had a broader tissue range than two other non-invasive imaging agents, supporting its utility in detecting evidence of disease.

Treatment: NIA supports development and preclinical testing of compounds that can inhibit amyloid formation in the organs. In addition, NIDDK-supported scientists screened over 600,000 small molecules for the ability to “turn on” genes needed to boost the cell’s capacity to fold proteins properly, and identified one small molecule that effectively prevented harmful deposits of improperly folded protein from populating the space surrounding cells.

Research on Cerebral Amyloid Angiopathy (CAA): CAA is a form of amyloidosis in which amyloid builds up in the walls of the blood vessels in the brain. CAA is a common cause of spontaneous hemorrhage. It also contributes to cognitive impairment in the elderly and is present in a majority of people with Alzheimer’s disease (AD). Investigators supported by the National Institute of Neurological Disorders and Stroke are investigating mechanisms underlying amyloid accumulation within cerebral blood vessels and the related cerebrovascular injury and dysfunction to better understand how these mechanisms contribute to cognitive impairment and dementia, including AD. In addition, researchers are developing new experimental tools to help investigate CAA in models that reflect the human disease more closely. NIH also supports biomarker projects that may lead to improved ways to detect CAA early in the disease process, thereby facilitating treatment before the onset of clinical symptoms. NIA-supported investigators

are creating a “library” of amyloid structures that form in both AD and CAA, and are developing an imaging agent to facilitate visualization of amyloid in CAA.

Angelman Syndrome

The Committee recognizes the promising scientific gains made in the pursuit of treatments for Angelman Syndrome. The Committee applauds the contributions of the Angelman Syndrome Natural History Study, funded by NIH, and the private partners working to advance the growing body of Angelman Syndrome research towards practical treatments. The Committee encourages NIH to consider research on the roles of the *UBE3A* gene in brain functions and explore innovative new treatments. The Committee urges NIH to explore how public-private partnerships can be leveraged to support translational research in this area.

Action Taken or to be Taken

Angelman syndrome is a genetic disorder associated with intellectual disability, seizures, minimal speech, and often, autism spectrum disorder. It can be caused by chromosomal differences in a portion of chromosome 15—either deletions of the copy of the chromosome inherited from the mother, imprinting defects (deletions on the copy of chromosome 15), or mutations in a gene known as *UBE3A* that falls within this region. The *UBE3A* protein is especially important for optimal function of the nervous system.

Research at NIH includes NIGMS- and NICHD-funded studies to understand the chemical signals that affect synapse development, neuroplasticity, and cell survival, and assessing compounds for their ability to restore normal learning or improve cognitive performance in mouse models. Other studies funded by NIMH and NINDS are trying to identify the specific targets of *UBE3A* to determine if any ultimately might serve as targets for interventions. For example, researchers recently demonstrated that delivery of a particular protein could increase *UBE3A* expression in the brain of an Angelman syndrome mouse model and identified protein kinases (enzymes) that could be useful therapeutic targets. Another researcher is developing a reliable language tool to use as an outcome measure for communication deficits in those with severe disabilities including Angelman syndrome. In addition, to obtain data on individuals' development over time, the NICHD and the NIH's Office of Rare Diseases Research have jointly funded for 10 years a rare diseases consortium to study the natural history in individuals with Angelman syndrome, building a rich trove of information on the evolving features of this relatively rare condition. The investigators involved in the project work in partnership with this group of families to improve outcomes for many of the challenging features of the disorder.

To develop potential therapies for the complex medical and behavioral conditions associated with Angelman syndrome, some investigators are developing cell culture models such as induced pluripotent stem cells (cells derived from skin cells or blood cells that are coaxed to develop into other cell types such as neurons) that might be amenable to high throughput drug screening, allowing rapid preliminary analysis. One of the NICHD-funded Intellectual and Developmental Disabilities Research Centers (IDDRCs) is studying the physiological and behavioral dysfunction associated with Angelman syndrome mice and treating them with a known FDA-approved drug in order to “unsilence” the paternal *UBE3A* gene and restore neurological function. A different IDDRC is conducting an innovative preclinical research project, taking steps toward a paternal gene activation therapy for Angelman syndrome that may evolve into a genetically-based treatment for the condition. Still another study is looking at small molecules that affect the targets of *UBE3A* as potential treatments for learning and memory deficits. All of

these promising efforts to develop therapies require a deep understanding of the mechanism of the condition and the development of model organisms to study possible therapeutics.

The NICHD remains committed to working with constituent organizations to leverage existing resources and expertise.

Angiogenesis

The Committee commends the NIH for posting the Trans-NIH Angiogenesis Workshop findings. The Committee urges NIH to address the needs outlined in the comments including, the establishment of cross-disciplinary collaborations across therapeutic fields by NCI, NHLBI, NIDDK, NEI, and other institutes, and the creation of a trans-NIH Program Project Grant. The Committee further encourages NIH to examine angiogenesis modifying interventions across populations using data to identify differences in response and benefit across age, gender, ethnicity/race/ancestral categories, socioeconomic strata, chronic disease States, and genetic background. Specifically, NIH is encouraged to study: angiogenesis and metabolism; biomarkers that reflect normal and abnormal angiogenesis; epigenetic changes of angiogenesis induced by natural stimuli such as diet, physical activity, and lifestyle, as well as medications; the effect of angiogenesis regulation on health and disease outcomes; the functional connections between angiogenesis and other health defense systems in the body (inflammation, regeneration, anti-aging, and immunity).

Action taken or to be taken

Angiogenesis is the process by which new blood vessels develop from pre-existing vessels. The National Heart, Lung, and Blood Institute (NHLBI) and other Institutes are contributing to basic and translational research in angiogenesis. For example, in the area of basic research, NHLBI-supported investigators recently discovered that the health and metabolism of endothelial cells, the cells that form the blood vessel lining, play a key role in regulating the formation of new blood vessels. In particular, the researchers found that changes in endothelial cell glucose, fatty acid, and protein metabolism may function as a “metabolic switch” for angiogenesis. Researchers are investigating these pathways further in an effort to identify biomarkers of endothelial cell health and disease, and to discover potential ways to alter defective angiogenesis.

The NIH also supports significant clinical research relating to angiogenesis. For example, the NHLBI is supporting a clinical trial testing an anti-angiogenesis drug to treat hereditary hemorrhagic telangiectasia, a genetic disorder that involves abnormal blood vessel formation and can result in significant health problems such as hemorrhage, anemia, brain abscess, and stroke. In addition, the NIH has funded several clinical studies comparing the effectiveness of anti-angiogenesis drugs for treating vision loss. Abnormal angiogenesis in the eye underlies many leading causes of blindness, including age-related macular degeneration (AMD) (progressive damage to the central retina), diabetic retinopathy (damage to the retina associated with diabetes), retinal vein occlusion (blockage of veins in the retina), and retinopathy of prematurity (a risk for premature infants). For each of these conditions, trials funded by the National Eye Institute (NEI) have tested and compared the efficacy of different anti-angiogenesis drugs, some of which have been repurposed from different indications such as cancer. A recent NEI-funded study followed 650 AMD patients treated with anti-angiogenesis drugs, and found that after five years, half of the patients had vision 20/40 or better, good enough to drive or read standard print. Those outcomes were almost unimaginable 10 years ago, when less than 15 percent of patients were expected to retain 20/40 vision after one year.

In another study funded by the NEI and the National Institute of Diabetes and Digestive and Kidney Diseases, researchers compared three anti-angiogenesis drugs for diabetic retinopathy and found that after two years, all three drugs resulted in similar gains in patients with mild to moderate vision loss, but two of the drugs outperformed the third for patients with more severe

vision loss. These results will now allow patients and doctors to personalize treatment based on their condition. As these findings show, anti-angiogenesis drugs are transforming vision care and preventing blindness for people with AMD.

These are just a few of the studies on angiogenesis being funded across the NIH. Though many of them have a specific disease focus, their contribution to our growing knowledge about angiogenesis has the potential to impact many areas of health.

Antimicrobial Resistance

The Committee continues to support the 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 2018 budget request on how NIAID is working with CDC and other Federal partners in this field of research.

Action taken or to be taken

Addressing the growing problem of antimicrobial resistance is a top NIAID 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. This work complements the Administration's National Action Plan for Combating Antibiotic-Resistant Bacteria, which outlines steps for Federal departments and agencies to coordinate and implement to address antibiotic resistance.

NIAID actively engages in cross-agency partnerships to address the issue of antimicrobial resistance. NIAID, along with CDC, FDA, and other NIH partners, is working to establish and maintain the National Database of Resistant Pathogens as part of the National Action Plan. NIAID is supporting the sequencing of high-priority reference strains identified by CDC and FDA for inclusion in the database. These genomic data will be used to help advance the development of new diagnostics and therapeutics, improve surveillance and monitoring methods, and increase our knowledge of the underlying mechanisms of antibiotic resistance. NIAID also collaborates with BARDA and international research partners on the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, or CARB-X, a new global public-private partnership to advance the preclinical development of promising antibacterial products. NIAID also has participated with CDC and FDA in a USDA stakeholder webinar, and convened a roundtable to bring together Federal partners and experts on systems biology and other research tools to combat antibiotic resistance.

NIAID continues to conduct and support basic and applied research focused on the development of novel strategies to address antimicrobial resistance. Current work by NIAID researchers aims to understand the immune system response to infection in order to identify potential targets for novel immunotherapy-based approaches to treat dangerous drug-resistant microbes such as carbapenem-resistant *Klebsiella pneumoniae*. NIAID also supports a broad portfolio of basic research to better understand bacterial pathogenesis and host interactions in order to identify novel drug targets. NIAID is funding research investigating novel antibacterial strategies including anti-virulence, immune-based, host-targeted, and adjunctive therapies; biofilm inhibitors; and non-traditional therapeutics. In addition, NIAID supports the development of vaccines to prevent infections with bacteria that are increasingly resistant to antibiotics, including *Staphylococcus aureus*, *Neisseria gonorrhoeae*, *Clostridium difficile*, and *Salmonella*. Ongoing NIAID-funded clinical trials also aim to optimize the use of licensed drugs for the treatment of drug-resistant infections and evaluate novel broad-spectrum antibiotics.

NIAID remains committed to its ongoing partnerships with CDC and 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 diagnostics, therapeutics, and vaccines to address the challenge of antimicrobial resistance.

Antimicrobial Stewardship

The Committee supports AHRQ's efforts to develop, improve, and disseminate antimicrobial stewardship interventions to combat the ongoing and serious threat of antimicrobial resistance. AHRQ is directed to work closely with CDC, NIH, and other Federal agencies to coordinate efforts to improve the use of antibiotics in humans across hospital and community settings.

Action Taken or to be Taken

AHRQ is conducting a major project to promote the implementation of antibiotic stewardship programs by applying AHRQ's Comprehensive Unit-based Safety Program (CUSP). This 5-year nationwide project will accelerate adoption of antibiotic stewardship programs in all healthcare settings: hospitals, long-term care, and ambulatory care. AHRQ is coordinating its efforts with CMS and CDC in carrying out the project, and the stewardship interventions in the project will be consistent with CDC's Core Elements of Antibiotic Stewardship in the various settings. In addition, AHRQ is collaborating with NIH, CDC, CMS, and other Federal agencies in the HHS Agency Priority Goal for Combating Antibiotic-Resistant Bacteria (CARB), which aims to increase significantly the percent of hospitals that have antibiotic stewardship programs that incorporate all the core elements. AHRQ's CUSP for Antibiotic Stewardship project will make a major contribution to attaining this goal.

Arthritis Disparities

Research from CDC notes that minority groups, including Mexican American and Latino/Hispanic populations, experience higher rates of arthritis-attributable activity and work limitations than other populations. The Committee encourages NIAMS to support research to understand these disparities, in collaboration with NIMHD.

Action taken or to be taken

Arthritis affects roughly 50 million adults in the United States, and remains one of the leading causes of disability. American Indians and Alaska Natives have the highest rate of arthritis, compared with other racial and ethnic groups. Although Hispanics and African Americans have lower rates of arthritis, compared with Whites, the populations are disproportionately impacted by the disabling effects of the disease. For example, African Americans, American Indians, Alaska Natives, and Hispanics report a higher prevalence of activity limitations in work and more severe pain compared with Whites with arthritis.

To improve understanding of the causes of arthritis health disparities, the NIH supports investigations of the potential contribution of genetic, biological, and environmental factors, as well as the effects of behavioral, cultural, and health systems influences. For example, the NIAMS-led Osteoarthritis Initiative, a public-private partnership, seeks to identify biomarkers of severity and progression for osteoarthritis (sometimes called wear-and-tear arthritis) in the general population and members of racial and ethnic groups that are disproportionately affected. NIAMS also funds studies exploring genetic factors that may influence the severity of rheumatoid arthritis (RA), an inflammatory form of the condition, in African Americans. Through the NIAMS Community Health Center, intramural researchers are working to improve understanding of racial and ethnic differences and barriers to care for patients with RA and other rheumatic diseases in underserved minority communities in the Washington, D.C. metropolitan area.

Other research seeks to understand the causes of disparities in access to or use of particular treatments. NIAMS funds research related to reducing racial and ethnic disparities in total joint replacement, including a study to understand why African Americans and other minority groups are less likely than Whites to undergo joint replacement for end-stage osteoarthritis. In FY 2016, NIMHD, NIAMS, NCI, ORWH, and NINR issued a funding opportunity announcement to stimulate research focused on understanding and addressing disparities in minority and health disparity populations in surgical care and outcomes. Grants are expected to be funded in FY 2017.

Grants funded by NIH also address ways to reduce disparities by targeting the mechanisms driving gaps in outcomes. One NIAMS-sponsored study supports research on improving communication between clinicians and RA patients from diverse populations, including those with limited English proficiency. Another is testing whether a patient-centered educational intervention will increase the likelihood that African American patients who are good candidates for joint replacement will receive a recommendation for the procedure. An NIMHD-supported grant addresses disparities in arthritis between older African American and White adults through development of rehabilitation interventions to improve arthritis-related outcomes in older African American adults. Another grant funded by NIMHD focuses on combining individual-

level precision medicine and population-level health disparities perspectives to address arthritis-related disability among American Indians.

Asthma – Precision Medicine Initiative

The Committee applauds NHLBI for its efforts to develop better treatments to manage severe asthma as part of the Precision Medicine Initiative, and urges the NHLBI to expand these efforts.

Action taken or to be taken

Even among patients with similar asthma symptoms, there can be substantial differences in the causes of asthma, pathobiology, other disease manifestations, and therapeutic responsiveness. Patients with severe disease—those whose disease remains poorly controlled despite maximal doses of existing therapeutics—are particularly difficult to treat. Although patients with severe or exacerbation-prone asthma constitute a minority of the asthma population (20 percent), they account for 80 percent of the cost for asthma care in the United States. Patients with severe asthma exhibit significant variability in responses to therapeutics, likely resulting from substantial differences in the underlying disease process among patients. This complicates both clinical management and the design of clinical trials. An underlying goal of the NIH Precision Medicine Initiative is to better understand the differences among patients to personalize treatments in a way that will maximize benefits and minimize adverse effects.

The National Heart, Lung, and Blood Institute (NHLBI) is pursuing precision medicine for asthma through genotyping, deep phenotyping, and clinical trials. Genetic differences likely make a strong contribution to variations in disease mechanism among patients. Numerous genetic variants have already been associated with asthma through genome-wide association studies, many of which involved patient cohorts that were established and characterized with NHLBI support. In addition, the NHLBI Trans-Omics for Precision Medicine (TOPMed) program is sequencing the entire genome of more than 5,000 individuals with asthma.

The NHLBI Severe Asthma Research Program (SARP) has recruited and phenotyped (characterized) thousands of individuals with severe asthma and has identified distinct disease subtypes based on clinical and molecular data. These studies are linking clinical characteristics (such as a propensity to disease exacerbations) to specific molecular abnormalities that may represent novel therapeutic targets. They also are confirming the concept that asthma involves interactions among multiple, diverse pathobiological mechanisms over time, and are providing opportunities to develop more precise, biologically based approaches for asthma management.

Finally, NHLBI recently issued two funding opportunity announcements (RFA-HL-17-009 and RFA-HL-17-010) that will establish a network of clinical centers to conduct precision medicine trials in asthma. By leveraging data from TOPMed and SARP, this network will develop and examine precise, adaptive interventions in subgroups of patients with severe and/or exacerbation-prone asthma. It is hoped that these trials will yield a tailored management strategy for each patient, and will also generate new data to inform future therapeutic development.

Asthma - Update

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned

Action taken or to be taken

Asthma remains one of the most prevalent diseases in the United States, impacting more than 24 million American adults and children in 2014. The National Heart, Lung, and Blood Institute (NHLBI) will continue several important research programs that address the racial and ethnic disparities in asthma, target the difficulties of clinical management in severe and exacerbation-prone asthma, and improve outcomes among patients with asthma by developing more precise approaches for treatment.

A disproportionate burden of asthma is borne by black, non-Hispanic children (13.4 percent affected) and by Puerto Ricans (23.5 percent of children and 13.3 percent of adults, compared to 7.6 percent of white children and adults). Individuals living below the poverty line also experience higher rates of asthma. The NHLBI plays a leadership role in the President's Task Force on Environmental Health Risks and Safety Risks to Children, and in particular, the subcommittee on Asthma Disparities. That group's Federal Action Plan is the basis for a large Asthma Empowerment research program recently initiated by NHLBI¹⁰. This program will fund research to assess and improve asthma care delivery methods in four communities. In an effort to improve the care for all Americans with asthma, NHLBI, with the guidance of the National Asthma Education and Prevention Program (NAEPP), will also continue work to update the Guidelines for the Diagnosis and Management of Asthma, (Expert Panel Report-3, 2007).

While patients with severe asthma account for a relatively small proportion of the entire asthma population, they account for the majority of the costs of asthma care in the United States. To support the development of more effective drugs for treating severe asthma, NHLBI will continue to support the Centers for Advanced Diagnostic and Experimental Therapeutics program (CADET), which funds two investigators developing novel therapies for asthma. Additionally, NHLBI has issued two funding opportunity announcements (RFA-HL-17-009 and RFA-HL-17-010) that will establish a network of clinical centers to conduct precision medicine trials in asthma, with the goal of optimizing therapy, and potentially modifying the underlying disease, at the individual patient level. These trials will leverage the enhanced understanding of complex genotypes and phenotypes in severe and exacerbation-prone asthma generated by NHLBI's Trans-Omics for Precision Medicine program (TOPMed) and Severe Asthma Research Program (SARP).

¹⁰ <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-17-001.html>

Autism and GI Disease

The Committee urges NIDDK to study the relationship between GI diseases and Autism Spectrum Disorders.

Action taken or to be taken

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports research on gastrointestinal (GI) diseases that afflict a subset of individuals with autism spectrum disorder (ASD), including chronic diarrhea, constipation, cramping, bloating, and more serious chronic conditions such as inflammatory bowel disease (IBD). The NIDDK also supports basic research on the impact on digestive diseases of the gut microbial community, which is altered in some individuals with ASD. These avenues of research can help inform studies of GI conditions associated with autism. For example, an NIDDK grantee studying gut microbe-based therapies for IBD has also conducted other research, supported by the National Institute of Mental Health (NIMH) that has utilized a mouse model with some behavioral dysfunction, components of which may resemble some behavioral aspects of ASD, as well as GI dysfunction. In this model system, the researchers showed that the mice had altered gut microbes; giving the mice *Bacteroides fragilis* bacteria improved their GI function and also conferred some behavioral benefits.

Autism - NIEHS

The Committee urges the NIEHS, as the lead agency on environmental health research and a member agency of the Interagency Autism Coordinating Committee [IACC], to ask the IACC to consider research on environmental factors related to autism, including onset patterns, in the upcoming revision to the IACC Strategic Plan for Autism Research. In addition, as the lead NIH Institute on Autism Spectrum Disorders research, the Committee suggests that NIMH work in coordination with NIEHS to assure that research on environmental factors continues to be supported.

Action taken or to be taken

Research conducted in Autism Spectrum Disorder (ASD) has uncovered a strong genetic basis for risk; but recent efforts have further identified environmental contributors that might interact with underlying genetic susceptibility. NIEHS is committed to promoting and pursuing such research as well as actively coordinating interests in environmental health research, across government agencies (such as through the IACC) and in partnership with other institutes of the NIH.

As a member agency, NIEHS co-leads the working group responsible for updating the language of the IACC Strategic Plan for Autism Research Question 3: *What Caused This To Happen, and Can It Be Prevented?* This working group includes representatives from federal agencies, experts in relevant fields of research, and members of the public, such as family advocates who have an interest in better understanding the environmental risk factors for autism. Further research in environmental risk factors is a major component in the response to this question, and objectives address the need for research on gene-environment interactions, epigenetics, and populations that may be vulnerable to environmental exposures, including groups that differ in pattern of onset.

NIEHS partners with other NIH institutes, including NIMH, to discuss ongoing research and plan ASD-related activities across the NIH, including initiatives focused on environmental exposures and gene-environment interactions during pregnancy and early childhood that may influence risk. Furthermore, NIMH and NICHD currently participate in an NIEHS-led initiative on Environmental Contributors to Autism Spectrum Disorder that seeks to understand how environmental factors impact the underlying biological processes implicated in ASD. In fiscal year 2016, there were 19 active awards totaling over \$7.3 million, addressing a broad range of environmental factors and mechanisms using both human and animal studies. The awards under this collaborative initiative are an important component of the overall NIEHS investment in autism, which was approximately \$13 million for FY2016.

NIEHS further prioritizes the goals of identifying and understanding risk and protective factors of ASD through coordination of an international group of autism epidemiologists known as the Epidemiology of Environmental Risks for Autism Network (EEARN). A yearly face-to-face EEARN meeting also provides a forum to help address these goals by sharing information about ongoing studies, facilitating new collaborations, stimulating cross-fertilization of ideas, and discussing possible solutions to common problems. In FY 2016, NIEHS also launched the Children's Health Exposure Analysis Resource (CHEAR), an infrastructure meant to provide the extramural research community with access to laboratory and data analyses that add or expand the inclusion of environmental measurements in children's health research. NIEHS has promoted this opportunity to autism researchers, including all EEARN members, so they can add or expand an environmental component to existing studies in a cost-effective manner.

Autism - Research on Environmental Factors - NIMH

As the lead agency on Autism Spectrum Disorders policy, the Committee urges the NIMH to include research on environmental factors related to autism, especially regressive autism, in the upcoming revision to the Strategic Plan for Autism Research.

Action taken or to be taken

The National Institute of Mental Health (NIMH) is committed to supporting innovative and high-impact biomedical research on genetic and environmental factors relevant to autism spectrum disorder (ASD). NIMH and the National Institute of Child Health and Human Development (NICHD) participate in the National Institute of Environmental Health Sciences (NIEHS)-led initiatives that seek to identify environmental contributors to risk and expression of ASD, and understand how environmental factors impact the underlying biological processes implicated in ASD. NIMH, along with NICHD, the National Institute on Deafness and Other Communication Disorders (NIDCD), NIEHS and the National Institute of Neurological Disorders and Stroke (NINDS), currently supports three initiatives that, in part, call for research related to what causes ASD, including risk and protective processes. These initiatives include research on environmental exposures during pregnancy and early childhood, and environmental factors that interact with genetic risk for ASD. These initiatives also support research on the loss of previously acquired skills in ASD (regressive autism).

On February 19, 2016, NIH sponsored a scientific workshop entitled “Loss of Skills and Onset Patterns in Neurodevelopmental Disorders: Understanding the Neurobiological Mechanisms.” This workshop was a collaborative effort, supported financially by the NIMH Office of Autism Research Coordination, and planned by staff from NIMH, NICHD, NINDS, NIDCD, and NIEHS. The workshop brought together researchers who discussed issues surrounding loss of skills in ASD (regressive autism), including: how symptoms emerge and how they differ from other patterns of ASD symptom onset, the biological processes that could be contributing to these patterns of onset, and how clinical and basic research methods can be used to identify the underlying biological causes of atypical development.

As a member agency, NIMH may suggest priorities for inclusion in the IACC Strategic Plan for Autism Research, which includes a section focused on genetic and environmental risk factors for autism. Further research in environmental risk factors is a priority of the IACC Strategic Plan, and objectives address the need for research on gene-environment interactions, epigenetics, and populations that may be vulnerable to environmental exposures, including groups that differ in pattern of onset. The priorities of the IACC Strategic Plan are determined through deliberation and agreement of the committee.

Autoimmune Neuropathies

The Committee encourages NIAID to work with NINDS and other ICs 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) has long supported a cross-cutting research portfolio on autoimmune diseases, in which the immune system injures the body's own organs, tissues, and cells. This portfolio supports basic, preclinical, and clinical research on the immunologic basis of autoimmunity and the development of improved approaches to diagnose, prevent, and treat autoimmune diseases including autoimmune skin diseases such as alopecia areata, as well as autoimmune neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP) and Guillain-Barré syndrome (GBS).

NIAID is working to increase collaboration and facilitate coordination of autoimmune disease research by chairing the NIH Autoimmune Diseases Coordinating Committee with participation from other NIH institutes and centers (ICs), including the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), other relevant federal agencies, and advocacy groups. NIAID also supports several cross-cutting research networks and consortia that fund basic and clinical research on autoimmune diseases. NIAID's Autoimmunity Centers of Excellence aim to accelerate the translation of scientific advances in autoimmunity research to improve patient care. Through its Immune Tolerance Network, NIAID evaluates novel therapies for these diseases and supports mechanistic studies to understand the biological pathways associated with them.

NIAID, with cosponsor NINDS, supports the Human Leukocyte Antigen (HLA) and Natural Killer Cell Immunoglobulin-like Receptor (KIR) Region Genomics in Immune-Mediated Diseases Consortium, a cooperative research group investigating how the mechanisms behind an autoimmune response determine autoimmune disease susceptibility and progression. NIAID and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) also fund the Cooperative Study Group for Autoimmune Disease Prevention to develop novel approaches for preventing and treating autoimmune disease, emphasizing the common molecular mechanisms of these diseases.

NIAID intramural scientists are working to understand the function of regulatory T cells, or "Tregs," which help regulate the immune system by suppressing auto-reactive cells. Using a new microscopy method to track cells in tissues, NIAID researchers found that Tregs form clusters of cells that are critical in controlling autoimmunity. These observations of autoimmune suppression in healthy tissues may one day provide insight into how to treat or prevent the development of autoimmune disease.

NIAID and NINDS scientists are exploring how infections can trigger GBS and result in neuronal damage. In particular, NIAID researchers are examining the immune and neuronal cell response to Zika virus infection, which is associated with GBS in adults, to identify targets for new therapies against viral-mediated neurological diseases. Complementing these efforts, NINDS researchers are developing animal and cell models that will allow a deeper

understanding of the pathophysiology of Zika-associated GBS. NINDS also organized a discussion between members of the NIH Zika Coordinating Group, including NIAID, and GBS researchers to review the state of the science, identify research priorities, and highlight available NIH funding opportunities.

NIAID will continue to collaborate with NINDS, NIAMS, and other NIH ICs to support cross-cutting research to understand the underlying mechanisms of autoimmune disease and develop tools to prevent and treat diseases like CIDP, GBS, and alopecia areata. At this time, NIAID does not plan to establish a separate research plan targeted to autoimmune neuropathies.

Autoimmune Research

The Committee notes recent research breakthroughs that are leading to the development of potential treatment options for autoimmune conditions, including alopecia areata, and encourages NIAID to support cross-cutting autoimmune research projects. The Committee encourages NIAID to work with NINDS and other ICs on these efforts. Further, the Committee requests an update in the fiscal year 2018 budget request on the latest state-of-the-science for autoimmune neuropathies research into conditions like Guillain-Barre syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP), and the status of a cross-cutting research plan for this portfolio.

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) has long supported a cross-cutting research portfolio on autoimmune diseases, in which the immune system injures the body's own organs, tissues, and cells. This portfolio supports basic, preclinical, and clinical research on the immunologic basis of autoimmunity and the development of improved approaches to diagnose, prevent, and treat autoimmune diseases including autoimmune skin diseases such as alopecia areata, as well as autoimmune neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP), and Guillain-Barré syndrome (GBS).

NIAID is working to increase collaboration and facilitate coordination of autoimmune disease research by chairing the National Institutes of Health (NIH) Autoimmune Diseases Coordinating Committee with participation from other NIH institutes and centers (ICs), including the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), other relevant federal agencies, and advocacy groups. NIAID also supports several cross-cutting research networks and consortia that fund basic and clinical research on autoimmune diseases. NIAID's Autoimmunity Centers of Excellence aim to accelerate the translation of scientific advances in autoimmunity research to improve patient care. Through its Immune Tolerance Network, NIAID evaluates novel therapies for these diseases and supports mechanistic studies to understand the biological pathways associated with them.

NIAID, with cosponsor NINDS, supports the Human Leukocyte Antigen (HLA) and Natural Killer Cell Immunoglobulin-like Receptor (KIR) Region Genomics in Immune-Mediated Diseases Consortium, a cooperative research group investigating how the mechanisms behind an autoimmune response determine autoimmune disease susceptibility and progression. NIAID and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) also fund the Cooperative Study Group for Autoimmune Disease Prevention to develop novel approaches for preventing and treating autoimmune disease, emphasizing the common molecular mechanisms of these diseases.

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NIAID will continue to collaborate with NINDS, NIAMS, and other NIH ICs to support cross-cutting research to understand the underlying mechanisms of autoimmune disease and develop tools to prevent and treat diseases like CIDP, GBS, and alopecia areata. At this time, NIAID does not plan to establish a separate research plan targeted to autoimmune neuropathies.

Basic Biomedical Research

The Committee urges the NIH Director to continue the traditional focus on 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 also requests NIH 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

Between 52 and 56 percent of NIH's research budget, excluding amounts allocated to R&D facilities and training, supported basic research during FYs 2006-2015.¹¹ NIH agrees that answering fundamental questions in biology, behavior, physics, and chemistry results in countless medical and scientific advancements. Basic research provides the foundational knowledge about how living systems work at the molecular, cellular, and organismal level. Such knowledge, often built in small increments, is necessary to understand the causes of disease onset and progression, identify risk factors and biological markers that improve diagnostics, develop new cures, and optimize existing preventive strategies.

NIH-supported research serves as the world's leading source of foundational knowledge of relevance to both the public and private sectors of biomedicine. To emphasize its commitment to basic discoveries, the 5-year NIH-wide Strategic Plan, released in 2016, describes exploration of fundamental science, along with discovery of treatments and cures, and advancement of health promotion and disease prevention, as three interdependent components critical for advancing biomedical research.¹² While the private sector primarily focuses on translational and clinical research, NIH's funding of extramural and intramural basic research is a necessary balancing factor for the health of the overall national research enterprise. As such, continued Federal investment in basic biomedical and behavioral research is critical to improving human health and producing tomorrow's scientific breakthroughs. Current NIH research efforts in basic biomedical research include, but are not limited to: molecular immunology; genomics; epigenetics; gene editing; informatics and big data science; microbiomic exploration and analysis; structural and systems biology; single-cell analysis; imaging; nanotechnology; and basic behavioral and social science research. The current Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, for example, shows how several disciplines can coalesce around a basic research inquiry to ultimately impact human health. With a mission to reveal how individual brain cells and complex neural circuits dynamically interact in time and space, allowing scientists to explore how the brain records, stores, and processes vast quantities of information, BRAIN promises to provide insight towards new therapeutic approaches towards preventing and treating devastating neurological and psychiatric conditions.

¹¹ <https://officeofbudget.od.nih.gov/pdfs/FY16/Basic%20and%20Applied%20FY%202002%20-%20FY%202017%20R2%20-%20V.pdf>

¹² <https://www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf>

NIH will continue to ensure the vitality and productivity of basic biomedical research through its broad basic research portfolio. Moreover, NIH remains dedicated to supporting training and career development opportunities in basic research to cultivate and maintain a diverse, highly-skilled, scientific workforce.

Biomarkers

The 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) supports research to identify and validate biomarkers in type 1 diabetes through several different efforts. The identification of biomarkers has already facilitated the design and conduct of clinical trials: Type 1 Diabetes TrialNet identifies those at risk based on known biomarkers, and enrolls eligible participants in prevention trials. TrialNet also aims to discover or validate biomarkers, which could improve identification of people at risk for the disease and enhance the Network's ability to conduct future trials. Biomarkers could also be used to identify people most likely to benefit from a specific prevention strategy and lead to prevention approaches personalized to each individual.

In FY 2016, funding was made available to TrialNet collaborators to evaluate biomarkers of drug action in the ongoing oral insulin prevention trial. Discovery of biomarkers is also a goal of The Environmental Determinants of Diabetes in the Young (TEDDY) study, which is following over 6,000 infants at high genetic risk to identify environmental triggers of the disease. TEDDY researchers are now analyzing over 60,000 bio samples to identify biomarkers predictive of autoimmunity and type 1 diabetes in these children. New biomarkers of disease progression could also help researchers monitor treatment response in clinical trials for people who have type 1 diabetes. Insights from TrialNet and TEDDY could lead to the discovery of biomarkers and facilitate smaller, shorter, and simpler clinical trials toward preventing, treating, and curing type 1 diabetes.

Biomarkers could also be used in similar ways to prevent, treat, or cure diabetic complications. NIDDK issued a funding opportunity announcement in FY 2016 for studies with participants and/or their bio samples from large clinical trials and observational studies, to identify biomarkers for complications of diabetes; three awards were made. The NIDDK also funded research on the development of biomarkers using minimally or non-invasive measures of blood vessels and nerves in the eye. Researchers supported by this effort reported a noninvasive technique for imaging small nerves in the front of the eye. The technique appeared to be just as effective as a skin biopsy at detecting evidence of diabetic nerve damage. Biomarkers that reveal changes in blood vessels and nerves before clinical signs develop could aid diagnosis and could act to measure early responses to an intervention, improving design and conduct of diabetic complications clinical trials.

NIDDK works closely with the National Institute of Allergy and Infectious Diseases (NIAID) in supporting research to develop biomarkers for type 1 diabetes, including through TEDDY and TrialNet. In addition, NIDDK participates in the type 1 diabetes-related research efforts of NIAID's Immune Tolerance Network (ITN), which evaluates novel tolerance-inducing therapies for immune-mediated diseases such as type 1 diabetes. All ITN clinical trials include a component to identify biomarkers of disease activity and response to treatment. NIAID intramural investigators also conduct basic research to identify new biomarkers for autoimmune

diseases. NIAID scientists recently found in a mouse model of lupus that the presence of a specific type of atypical immune cell may indicate accelerated progression and increased severity of systemic autoimmune disease. NIAID scientists also found that the clinical severity of ulcerative colitis may be linked to the number of T cells, immune cells that facilitate, regulate, and direct the destruction of infected or cancerous cells, which exhibit specific immune markers. The discovery of these biomarkers may help to understand better autoimmune disease processes and monitor the effectiveness of treatments.

Biomaterials

The Committee understands biomaterials are an important section of biomedical research. The Committee encourages NIDCR to consider efforts to encourage an increased focus on the development and innovation of dental materials.

Action taken or to be taken

The National Institute of Dental and Craniofacial Research (NIDCR) has a history of supporting foundational research on the materials that are used to restore damaged and diseased teeth. Dental restorations made with tooth-colored resin composite materials, while esthetically pleasing, can fail after about eight years and need to be replaced. Some of the main reasons for restoration failure are degradation by oral bacteria, inadequate bonding to the tooth, and cracking or breaking. In 2013, NIDCR invested \$2.8 million to develop innovative biomaterials to double the service life of dental restorations. These studies are producing novel types of compounds with superior mechanical properties that resist degradation and cracking.

NIDCR is funding scientists who are creating self-healing dental materials that contain microcapsules. When cracks form in the dental restoration, the microcapsules break open, releasing a liquid that reacts with particles embedded in the dental material to fill and seal the spaces automatically. NIDCR also supports a small business that is tackling the problem from a different angle by creating a novel dental adhesive with long lasting antimicrobial activity against the bacteria that cause tooth decay. Other NIDCR-supported scientists are using plasma technology to improve the bonding of the dental restoration to the tooth. This plasma, a type of ionized gas, has the added effect of killing cavity causing bacteria before placing the dental restoration.

Looking ahead, NIDCR has begun investing in the development of novel restoratives that are effective for a specific type of tooth decay affecting the root, called Class V lesions. These restorations are much more likely to fail and are common in aging individuals due to recession of their gums. This research will help address the growing need for improved Class V restorations as the demographics of the country continues to change.

Biospecimen Resource Locator

The Committee appreciates that the NCI has developed and supports the Specimen Resource Locator, a searchable database of biospecimen collections. The Committee also appreciates that pediatric cancer biospecimens resources are included within the Specimen Resource Locator, and requests and update from NCI on pediatric cancer biospecimen collections in the fiscal year 2018 CJ.

Action taken or to be taken

The Specimen Resource Locator (SRL),¹³ administered by the National Cancer Institute's (NCI's) Division of Cancer Treatment and Diagnosis (DCDT), is a public biospecimen resource database that helps researchers locate samples needed for their investigational use. Investigators can search the database for access to thousands of specimens of various tumor, organ, and preservation methods. Information about biospecimen banks and sample procurement services can also be found through the SRL. Specimens and samples come from non-commercial resources that may be funded by the NCI or other outside (non-NCI) resources.

The SRL includes a number of collections focused exclusively on pediatric biospecimens, such as NCI's Pediatric Cooperative Human Tissue Network (pCHTN) and the National Clinical Trials Network's Children's Oncology Group (COG) Biorepository. The former works prospectively with each investigator to tailor specimen acquisition and processing to meet their project requirements, while the latter stores biospecimens from more than 200 hospitals and cancer research organizations across the U.S. that conduct NCI-supported pediatric cancer clinical trials through the COG. Additionally, the National Institute of Child Health and Human Development's National Children's Study Archive, a repository of data collected from more than 5,000 children and their families between 2009-2014, provides pediatric cancer researchers insight on the role that environment and genetics play in the overall health of children.

Various other collections within the SRL include both adult and pediatric specimens for research use. For example, many collections from NCI-designated cancer centers and other academic collaborators store specimens from cancer patients of various ages. Examples of collections that include pediatric specimens are:

- The Duke Cancer Institute Department of Pathology
- Multiple collections at Baylor College of Medicine's Dan L/ Duncan Cancer Center
- The Gundersen Biobank; the Hollings Cancer Center Biorepository
- The Nervous System Tumor Bank (Medulloblastoma Collection)
- Oregon Health and Science University's Knight Bio Laboratory (includes Rhabdomyosarcoma and neuroblastoma samples)
- Roswell Park Cancer Institute's Data Bank and Biorepository (includes pediatric blood cancer and neuroblastoma samples)
- SARC Sarcoma Biospecimen Bank
- Siteman Cancer Center's Tissue Procurement Core Facility (includes Rhabdomyosarcoma samples)
- University of Iowa's Tissue Procurement Core Facility (includes neuroblastoma samples)

¹³ <https://specimens.cancer.gov/>

- NCI Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (includes Ewing sarcoma and Rhabdomyosarcoma samples)
- Biospecimen Pre-analytic Variables

Additionally, while not specific to the SRL, the NCI supports a number of other childhood cancer research efforts that are dependent on the availability of high quality pediatric cancer biospecimens. Examples of these efforts include the development of pediatric cancer cell lines and models within NCI's Pediatric Preclinical Testing Consortium, as well as the future NCI-Pediatric Molecular Analysis for Therapy Choice (MATCH)¹⁴ precision medicine clinical trial. NCI-Pediatric MATCH will include the collection of pediatric solid tumor samples at relapse, and the study team will conduct extensive molecular analysis of the samples to determine whether each cancer has specific molecular drivers targeted by a therapy available through the trial. This in-depth molecular analysis will provide critical data for researchers to better understand relapsed disease across many types of childhood cancers.

¹⁴ <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match>

Bisphenol A Toxicity

The Committee is aware of the ongoing debate on toxicity exposure from Bisphenol A (BPA) amongst the National Toxicology Program (NTP), NIEHS, and Food and Drug Administration (FDA). The program includes the 2008 Draft Assessment of Bisphenol A for Use in Food Contact Applications, which reviewed the available data on the toxicity of BPA, performed by FDA staff at the Agency's National Center for Toxicological Research. The Committee requests NIEHS coordinate with FDA to publish the results of relevant studies as soon as the data analysis is completed. The Committee requests NIH publish a jointly agreed upon FDA/NIEHS/NTP timeline for publishing the most recent study results from the interagency consortium in the fiscal year 2018 budget request.

Action taken or to be taken

NIEHS and FDA have been engaged collaboratively in a guideline chronic toxicity study of BPA, expanded to include exposures across the lifespan to a wider than usual set of doses, conducted under Good Laboratory Practice (GLP) regulations at an FDA facility (the "core study"), and involving university-based investigators who were given animals and/or biological samples from that study to pursue functional, morphological, and molecular endpoints that are not typically included in guideline-compliant studies. The resulting consortium-based research program, called Consortium Linking Academic and Regulatory Insights on Toxicity of BPA (CLARITY-BPA), integrates FDA guideline-compliant research with 13 NIEHS-funded university-based studies. The comprehensive evaluation of guideline-compliant validated endpoints with additional endpoints in the frame of a common and robust study design is expected to significantly improve the interpretation of the wealth of data that is being generated by all consortium partners, including the characterization of the dose response of the effects observed and their interpretation in an integrated biological context. NTP is currently evaluating the findings from the BPA Clarity Study and anticipates releasing the draft report for public comment and peer review in mid-2018.

All the steps above refer specifically to the data from the core study. Data generated from the university-based consortia are intended to be made publicly available by mid-2018, around the time of the core study final report peer review. The consortium data will also reside in the CEBS database. However, additional publications in the peer-reviewed scientific literature from academic consortium members can be expected to be published up to several years after the public release of the data; the timeline for these reports depends on factors that are outside of government control.

Brain Health

The Committee supports brain health research, education, and care that can be advanced through collaborative and interdisciplinary efforts that seek to study issues of cognition across the age spectrum with a goal to improve overall community health. The Director is strongly encouraged to recognize brain health as a top research priority with a special emphasis for initiatives that cross the age continuum and include autism, PTSD/TBI, and Alzheimer's Disease.

Action taken or to be taken

Brain health is an important research priority at the NIH that is relevant to the missions of many institutes and centers. It is a complex area of research, critical to health across the life span and also affected by many different diseases and disorders. NIH supports many research programs that focus on understanding the determinants of brain health across the age continuum and for maintaining and improving brain health in various disorders. Some NIH-led programs focus on how exposures and experiences shape brain development during childhood. For example, the Environmental influences on Child Health Outcomes (ECHO) is a new nationwide 7-year study to understand effects of early environmental exposures on child health and development. These health outcomes include child and adolescent neurodevelopment across domains of attention, emotion, cognition, and behavior. The Adolescent Brain Cognitive Development (ABCD) study¹⁵ will follow the biological and behavioral development of more than 10,000 children from ages 9-10 through adolescence and early adulthood, and provide insight on how a variety of biological events and environmental exposures affect brain development.

Other research efforts at the NIH are also exploring disorders that affect the brain across the life span. For example, NIMH collaborates with other institutes to support research on cognitive development across the lifespan in individuals with autism spectrum disorder (ASD). NIMH also funds longitudinal studies to assess the effects of trauma on brain development in children, and to examine consequences of exposure to traumatic events - including brain injury - in adults. NIH scientists participated in recent meetings that included Down syndrome (DS) and Alzheimer's disease (AD) researchers to examine the early onset of AD that affects many adults with DS. NIA and NICHD recently funded the AD Biomarkers Study to identify predictive markers of AD in almost 500 adults with DS, with the ultimate goal of developing treatments for anyone experiencing such declines.

In addition to an extensive portfolio of research on AD, NIA supports research on cognition and brain health in older age, including research on structural, cellular, and molecular changes in the aging brain; studies to identify cognitive and behavioral changes that occur with age; epidemiological studies to identify factors related to cognitive decline; and clinical trials to ameliorate age-related cognitive decline. In April 2017, the NIA will convene a third Cognitive Aging Summit, made possible by the McKnight Brain Research Foundation through a generous grant to the Foundation for the NIH. Finally, NIA has partnered with several other NIH institutes, the Administration for Community Living (ACL), and the Centers for Disease Control and Prevention (CDC) to develop the Brain Health Resource¹⁶, a presentation toolkit offering current, evidence-based information and resources to facilitate conversations with older people about brain health.

¹⁵ <http://www.abcdstudy.org/>

¹⁶ <https://www.nia.nih.gov/health/publication/brain-health-resource>

In early 2016, the NINDS, in cooperation with NHLBI, NIA, CDC, and the ACL, launched a public health education campaign called *Mind Your Risks*¹⁷ to highlight emerging evidence that having high blood pressure in midlife can raise the risk for strokes, dementia, and cognitive impairment later in life. This campaign is intended to be the first piece of a larger Brain Health public education strategy which will focus on evidence-based messages related to promotion and preservation of brain health.

¹⁷ <https://mindyourrisks.nih.gov/>

Brain Research through Advancing Innovative Neurotechnologies

The Committee provides a \$45,000,000 increase for a total of \$195,000,000 to NINDS, NICHD, NEI, NIA, NIDCD, NIAAA, NIDA, NIMH, NIBIB, and NCCIH on the same pro-rata basis as provided in the past. The Committee recognizes initiatives of this nature must maintain adequate funding to assure achievement of the goals and plan milestones. The Committee expects NIH to ensure the fiscal year 2018 budget request provides an appropriate level of funding to keep on track toward the plan's milestones. Further, the Committee encourages the distribution of a reasonable portion of BRAIN research resources through co-funded projects in the IDeA program.

Action taken or to be taken

The NIH utilizes the external scientific community's expert recommendations for achieving the goals of the BRAIN Initiative¹⁸, articulated in *BRAIN 2025: A Scientific Vision*. Outside experts assist the NIH in ensuring a coordinated and focused effort across the agency through the BRAIN Multi-Council Working Group, and this group also facilitates communication among the federal BRAIN agencies by including representatives from NSF, DARPA, IARPA and FDA. In October 2016, the NIH announced 108 new awards addressing the seven scientific priorities outlined in the *BRAIN 2025* report, ranging from generating 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 third of which occurred in December 2016 and included public-facing plenary sessions and a session devoted to collaboration with the European Union funded Human Brain Project.

The NIH continues to explore ways to broaden the impact of the BRAIN Initiative. Select applications responsive to BRAIN funding opportunities may be recommended for co-funding through the NIH Institutional Development Awards (IDeA) program. For FY2017, the NIH released three BRAIN funding opportunities for building the informatics infrastructure of the Initiative; two new training opportunities; and support for specialized centers focused on classifying all mouse, non-human primate, and human brain cells. A new public-private BRAIN Initiative Alliance, which recently launched a website¹⁹, will also enhance collaboration among the federal and private programs. Looking ahead, projects from the Initiative are on course to increase the yield of data and research tools for the research community. For this reason, new funding opportunities in FY2017-18 will focus on data infrastructure to support the collaborative research as well as data sharing. Dissemination of new experimental technologies and the skills needed to employ them across the country's neuroscience laboratories are also high priorities for FY 2017-2018.

BRAIN Initiative grants have already resulted in numerous scientific breakthroughs, and more than 145 scientific articles have been published. BRAIN investigators developed a breakthrough method for studying cell lineage in complex, whole organisms, along with a technological leap in designing electrodes that remain stable when chronically implanted in the brain. As an example of the serendipitous outcomes of basic science research, a BRAIN Initiative project on cell types

¹⁸NIH BRAIN Initiative website: <http://braininitiative.nih.gov/>

¹⁹ BRAIN Initiative Alliance website: <http://www.braininitiative.org/>

yielded crucial insights about how the Zika virus affects the developing brain and revealed a potential target for intervention.

Recognizing that development of new tools and technologies to unlock the mystery of how the brain functions will raise important ethical questions, the NIH established the Neuroethics Division of the BRAIN Multi-Council Working Group and released a funding opportunity for research on the ethical implications of BRAIN research. Together, these diverse efforts aim to provide the critical knowledge base for researchers aspiring to treat, cure, and even prevent brain disorders. The NIH will continue to submit budget requests at levels appropriate to achieving all of the goals of the BRAIN initiative.

Breast Cancer

Recent advances in breast cancer screening include the introduction of digital mammography [DM] and magnetic resonance imaging [MRI] for women at high risk for breast cancer. A new technology available for breast cancer screening, tomosynthesis [TM], is FDA-approved and being adopted as the "standard of care" in some markets. Limited trial results to date show a strong reduction in false positives and a trend toward more cancers diagnosed with TM than with DM. The Committee recommends NCI continue its vital research to help provide breast cancer patients and their physicians with a clear, informed picture of the role of breast cancer imaging. The Committee encourages NCI to conduct a 5-year, large cohort study exploring the validity and merits of TM and how it compares to other forms of imaging.

Breast Cancer

The Committee understands a new Food and Drug Administration approved technology is available for breast cancer screening, called tomosynthesis (TM). The Committee encourages NCI to continue their vital research to help provide breast cancer patients and their physicians with a clear, informed picture of how breast cancer imaging should be considered for women's health. The Committee requests an update describing planned and on-going research related to TM technology and if any cohort studies are on-going and planned on TM imaging.

Action taken or to be taken

The National Cancer Institute (NCI) conducts and supports research to enhance current breast cancer screening strategies, to develop new technologies for improved screenings, and to evaluate the efficacy of screenings in reducing breast cancer mortality. Digital mammography (DM) and magnetic resonance imaging (MRI) continue to be an important part of breast cancer screenings and diagnoses, as well as newer technologies like tomosynthesis (TM), also known as 3D mammography, that produces 3-dimensional images of the entire breast.

Most recently, the NCI approved funding for the Tomosynthesis Mammography Imaging Screening Trial (TMIST), the first large-scale breast cancer screening trial in nearly 25 years. The trial will require up to 100 sites and will be conducted through the NCI Community Oncology Research Program (NCORP). TMIST will enroll 165,000 asymptomatic women in the U.S. and Canada, between the ages of 45 and 74, to compare the incidence of advanced cancers in those screened for four years with digital breast tomosynthesis versus standard digital mammography. The study aims to provide a modern basis for the continued use of mammography for breast cancer screening.

In addition, NCI supports a broad portfolio of breast cancer screening research as noted in the examples below:

- NCI's Digital Breast Tomosynthesis Guided Tomographic Optical Breast Imaging (TOBI) clinical trial²⁰ is analyzing whether combined images can be used to diagnose breast cancer with significantly improved sensitivity and specificity compared to digital breast tomosynthesis alone. Data collection and analysis will continue in the coming years and the study is estimated to be completed in 2019.

²⁰ <https://clinicaltrials.gov/ct2/show/NCT02033486>

- In its recently released funding opportunity entitled “Imaging and Biomarkers for Early Detection of Aggressive Cancer,”²¹ NCI encourages researchers to explore ways to harmonize imaging strategies with biomarker methodologies in order to create an integrated system for cancer prevention, screening, diagnosis and care. As part of this effort, the NCI created the Consortium for Imaging and Biomarkers (CIB)²² to drive and facilitate collaborative studies, information exchange, knowledge sharing, and resource dissemination.
- NCI’s Early Detection Research Network (EDRN) is studying new methods to identify the molecular “fingerprints” of screen-detected tumors with little lethal potential, so that more patients can be followed without unnecessary aggressive treatments.
- The Cancer Intervention and Surveillance Modeling Network (CISNET) Breast Working Group is conducting collaborative modeling research to address critical early detection and clinical management issues in breast cancer. They are modeling breast cancer as four separate subtypes to be able to project the impact of the most promising emerging cancer control strategies and technologies.
- The Breast Cancer Surveillance Consortium (BCSC) assesses the delivery and quality of breast cancer screening, allowing investigators to study how mammography screening performance may be improved and how screening relates to changes in disease stage at diagnosis, survival, and mortality.
- The Population-based Research Optimizing Screening through Personalized Regimens (PROSPR) network is studying ways to improve the screening process (recruitment, screening, diagnosis, referral for treatment) for breast, colorectal, and cervical cancers.
- An example of cutting edge investigator-initiated research in this area is a recent grant focusing on the composition of breast lesions and analyzing quantitative imaging approaches for breast cancer diagnosis. The long-term goal of this research project is to reduce unnecessary breast biopsies by creating diagnostic imaging models using the strongest computer-aided algorithm advances available and applying them clinically.

NCI will continue to support these and other promising scientific opportunities in breast cancer screening research to maximize benefit and minimize harm from screening.

²¹ <http://grants.nih.gov/grants/guide/pa-files/PAR-16-089.html>

²² <https://prevention.cancer.gov/news-and-events/news/consortium-imaging-and>

Building and Facilities

The Committee provides bill language to allow for the demolition of buildings 18, 18T, and 32 that NIH has noted are beyond service life and too expensive to maintain. NIH expects the one-year authority to provide long-term maintenance and building savings. The Committee requests an update in the fiscal year 2018 budget request on the projected 10-year savings of these three projects and does not expect this authority to be used beyond these three specific projects. Further, 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 2018 budget request.

Action taken or to be taken

NIH's mission 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. Comprised of 27 Institutes and Centers, NIH conducts its mission in five campuses containing 281 buildings comprising more than 15 million square feet as well as over four million square feet of leased facilities. The five owned campuses are located in Bethesda, MD (main campus), Poolesville, MD (animals), Frederick (NCI), Research Triangle Park NC (NIEHS), New Iberia, LA and Hamilton Mt (NIAID, Rocky Mountain Laboratories, RML). NIH's Backlog of Maintenance & Repair is \$1.8 billion, by far the largest in HHS, and is growing at an accelerating rate. The average Condition Index of NIH buildings is 71 out of 100, among the lowest levels in the entire federal government, and worsening over time. Consequences include: challenges complying with regulations governing patient safety, research animal care and use, occupational health and safety, and environmental protection; delayed science -- cutting edge research can require precise temperature, humidity and vibration level; higher operating costs due to emergencies (e.g., water pipe bursts, utility outages) and energy-inefficient buildings (e.g., single-pane windows); waste of prior taxpayer investments -- the NIH Plant Replacement Value is \$9.8 billion; and adverse impacts on recruiting, retention, employee engagement and staff morale.

NIH has requested the authority to demolish Buildings 18, 18T, and 32 on the Bethesda Campus. The savings associated with the demolition would be negligible at this time because the buildings are small and they are already vacant. NIH is currently not investing in maintaining them or making capital repairs to them. However, demolishing the buildings now will allow NIH to remove the building before their neglected state becomes a safety hazard and a blight to the campus.

The Buildings & Facilities appropriation has been insufficient to address the backlog, forcing NIH to rely heavily upon one-time funding solutions such as ARRA and the HHS Nonrecurring Expenses Fund (NEF). Proposals to rescind or redirect the NEF could block NIH from using the \$162 million designated by HHS in FY 2016 for the Clinical Center E-Wing renovation. This would stop the project and have a devastating long-term impact on NIH, especially regarding cell therapies relative to cancer and eye disease.

Building Infrastructure Leading to Diversity [BUILD]

The Committee supports the NIH Director's efforts to reverse the trend of underrepresentation of researchers from ethnically diverse backgrounds and continues to be pleased with the commitment to increase the number of minority investigators. The Committee encourages NIH to ensure that graduate institutions with a historic mission of educating minorities in the health professions and biomedical sciences can participate in the program.

Action taken or to be taken

An additional trans-NIH diversity training program managed by NIGMS is Building Infrastructure Leading to Diversity (BUILD). BUILD is part of the “Enhancing the Diversity of the NIH-Funded Workforce,” also known as the Diversity Program Consortium. BUILD is intended to support the design and implementation of innovative programs, strategies and approaches to transform undergraduate research training and mentorship. The five-year BUILD awards were issued in Fiscal Year 2014 to 10 institutions throughout the nation. Eight of the BUILD institutions are classified as minority-serving institutions, including: two HBCUs; four HSIs, two of which are also AANAPISIs; and two AIANSIs. The BUILD institutions each have pipeline and research-intensive partnerships, totaling nearly 100 additional institutions, 44 of which are minority-serving institutions.

To ensure the vitality and continued productivity of the research enterprise, National Institute of General Medical Sciences (NIGMS) provides leadership in training the next generation of scientists in basic and general biological and biomedical sciences, enhancing the diversity of the scientific workforce, and developing research capacities throughout the country. To accomplish these objectives, NIGMS supports a variety of training programs with the goal of developing a diverse pool of well-trained scientists available to address the nation’s research needs. NIGMS seeks to increase the number of individuals from groups underrepresented in the biomedical workforce by providing training opportunities during multiple training and career stages at a variety of institutions and educational settings nationwide. Three of these programs are specifically dedicated to providing support for institutions that have a commitment and history of educating students from underrepresented backgrounds. These programs include: Research Initiative for Scientific Enhancement (RISE), Support of Competitive Research (SCORE) program, and the Institutional Research and Academic Career Development Award (IRACDA).

Overall, NIGMS provides funding to 123 minority serving institutions: 41 Historically Black Colleges and Universities (HBCUs), 5 Predominantly Black Institutions (PBIs), 3 Tribal Colleges and Universities (TCUs), 28 Asian American and Native American Pacific Islander-Serving Institutions (AANAPISIs), 12 American Indian Alaska Native Serving Institutions (AIANSIs) and 56 Hispanic-Serving Institutions (HSIs).

These programs illustrate NIGMS’s ongoing commitment to galvanize efforts to diversify the workforce by recruiting talented researchers from all groups and supporting quality educational and training environments in a wide variety of institutional settings.

Burden of Disease

The Committee expects NIH to consider the burden of a disease when setting priorities and developing strategic plans across its Institutes and Centers. Diseases such as Alzheimer's, diabetes, heart disease, and cancer affect a large portion of the population, especially the aging population. The impact of these diseases on patients and their families are substantial and costly. Targeting biomedical research funding toward these diseases is an important strategy to finding better treatments and cures. Further, the Committee commends the NIH on the inclusion of burden of disease as part of its NIH-Wide Strategic Plan for Fiscal Years 2016-2020. The Plan 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. The Committee supports a focus on conditions in need of further funding such as chronic pain, including migraine and other treatment alternatives for chronic pain.

Action taken or to be taken

NIH's mission 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. NIH is committed to recognizing unmet and/or emerging public health needs, and to funding research that addresses those needs.

NIH continues to strengthen its commitment to a transparent, evidence-based process that: enhances the nimbleness needed to meet public health needs and capitalize upon scientific opportunity, using new portfolio analysis tools; incorporates burden of disease as an important, but not sole, factor; takes advantage of opportunities presented by rare diseases to advance research; and considers the value of permanently eradicating a disease. In addition to public health needs, NIH also considers scientific merit as measured by rigorous peer review, scientific opportunities within a field, and the need to maintain a balanced portfolio across a diverse range of scientific endeavors.

The relative burden that various diseases place upon human health and wellbeing serves as a crucial, but not the only, consideration in aligning NIH's research priorities with public health needs. To this end, the Strategic Plan states that NIH will work with its many partners, including CDC, to strengthen the collection of high quality, comparable data on the burden of disease and will continue to integrate analyses of such data into its priority setting process. For example, NIH has made several CDC sources of disease burden data available alongside NIH spending data for a variety of diseases and conditions, so that stakeholders may better understand the portfolio.²³

However, it is important to note that there is no simple metric or single measurement that sufficiently captures the burden of a disease. NIH believes that careful consideration of multiple data types and sources on a case-by-case basis provides the best strategy for understanding disease burden and public health need. Several measurements are useful in this regard, including prevalence and incidence measures, estimating either the number of people diagnosed, mortality rates, or the new cases in a year with certain diseases or conditions. NIH also considers more complex measures such as disability-adjusted life years, or DALYs, which combine death and

²³ https://report.nih.gov/categorical_spending.aspx

disability data into a single life-year measurement. NIH recently published an analysis relating NIH spending to U.S. and global DALY data for a variety of diseases and conditions.²⁴

NIH also strongly supports basic research, which seeks to understand the normal, healthy functioning of living systems and can provide invaluable insights for future therapies. Such research is often not tied to a particular disease, but is essential to identifying new targets for biomedical intervention. Thus, NIH believes that its priority-setting process needs to ensure we fund the best science, maintain a balanced portfolio, capitalize on scientific opportunities as they arise, and address key public health needs. Using these principles allows NIH to make flexible, strategic investments to advance its mission, prioritizing promising, innovative research with the potential to reduce illness and disability.

Recognizing the substantial burden of chronic pain, NIH places great importance to the funding of chronic pain research; NIH is an active federal participant in the Interagency Pain Research Coordinating Committee (IPRCC) which is chaired by NINDS director Walter Koroshetz, and is working in concert with other relevant federal agencies to implement the National Pain Strategy.²⁵ The IPRCC, with NIH's support and leadership, is currently working on a Federal pain research strategy to complement the more care-focused recommendations of the National Pain Strategy, and a final report is expected to be released in 2017. Within NIH, the NIH Pain Consortium, a collaboration of 25 institutes, centers, and offices, helps to identify, coordinate, and support collaborative pain research initiatives and activities at NIH.

NIH funds a broad research portfolio on chronic pain, ranging from basic research into the molecular, genetic, and bio-behavioral basis of chronic pain to large-scale clinical studies of potential treatments. NIH is committed to supporting studies that examine alternative treatments for chronic pain without the risk factors associated with opioid use. This includes studies which have identified compounds that act on opioid and non-opioid brain receptors to reduce pain, but avoid the pathways that cause deleterious side effects, including dependence and addiction. NIH also funds research into non-pharmacological treatments, such as transcranial magnetic stimulation, or using mind-body therapies to reduce the need for opioids. Recognizing that it is important to get new therapeutic innovations to patients, NIH is also a partner in Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations, Opportunities, and Networks (ACTTION), a public-private partnership established to improve analgesic clinical trial design and facilitate evaluation of pain treatments. In 2016, ACTTION was awarded a second 5-year cooperative agreement from the FDA to expedite analgesic testing. The NIH pain research portfolio is exploring a diverse range of approaches to understanding and treating chronic pain, with the goal of developing or improving safe, effective treatments that can reducing the burden chronic pain places on patients and their families .

²⁴ https://report.nih.gov/info_disease_burden.aspx

²⁵ https://iprcc.nih.gov/docs/HHSNational_Pain_Strategy.pdf

Cancer and Hereditary Hemorrhagic Telangiectasia (HHT)

HHT is a genetic disorder of the blood vessels, and one variation of the disorder, HHT, is characterized by deficiency in endoglin, an angiogenic protein. Recent research has indicated improved survival outcomes for cancer patients who also have HHT. The Committee encourages NCI to support research investigating whether reduced systemic endoglin levels, expected in patients diagnosed with HHT, impacts clinical outcomes for cancer. The Committee requests an update in the fiscal year 2018 CJ on the status of research related to this topic.

Action taken or to be taken

The National Cancer Institute (NCI) continues to support research evaluating anti-cancer therapies that aim to restrict angiogenesis (the formation of new blood vessels from existing ones) in cancer cells. Endoglin, an angiogenic cell membrane protein, is an important biomarker in evaluating the growth of tumor blood vessels, as endoglin levels are strongly associated with tumor progression, metastases, and survival.

NCI funds an R01 research project grant²⁶ for a study at the Ohio State University with the goal of elucidating the mechanism of endoglin-targeted anticancer therapy. This project seeks to explain how antiangiogenic drugs function in the body in order to identify new therapeutic targets and describe the best ways in which to use endoglin-targeting drugs to treat cancer.

NCI also invests in research related to angiogenesis broadly, from understanding its basic biological mechanisms to clinical applications. Examples include projects that seek to describe endoglin signaling pathways and interactions with other proteins, pharmacokinetic and pharmacodynamic modeling of anticancer agents that draw upon our knowledge of endoglin, the use of endoglin as part of assays used to provide diagnostic and prognostic information, and clinical trials of an investigational monoclonal antibody (mAb) in glioblastoma multiforme and renal cell cancer patients. NCI scientists recently reported promising results in phase I²⁷ and phase II²⁸ trials that evaluated the use of the anti-endoglin antibody TRC105 in prostate and bladder cancers, and a phase Ib study²⁹ that combined TRC05 and bevacizumab (a chemotherapy drug) in patients with glioblastoma, renal cell carcinoma, hepatocellular carcinoma, and soft tissue carcinoma found that the antibody was well tolerated. Researchers will continue to explore the ways in which knowledge of endoglin can be leveraged to develop new cancer therapies and how widely these treatments could be used.

²⁶https://projectreporter.nih.gov/project_info_description.cfm?aid=9036958&icde=30892644&ddparam=&ddvalue=&ddsub=&cr=5&csb=default&cs=ASC

²⁷ A phase I study of TRC105 anti-endoglin (CD105) antibody in metastatic castration-resistant prostate cancer. *BJU Int.* 2015 Oct;116(4):546-55 PMID: 25407442=

²⁸ A Phase II Clinical Trial of TRC105 (Anti-Endoglin Antibody) in Adults With Advanced/Metastatic Urothelial Carcinoma. *Clin Genitourin Cancer.* 2016 May 27. pii: S1558-7673(16)30136-7. PMID: 27328856

²⁹ An open-label phase Ib dose-escalation study of TRC105 (anti-endoglin antibody) with bevacizumab in patients with advanced cancer. *Clinical Cancer Research*, 20(23). 2014 December 1. doi: 10.1158/1078-0432.CCR-14-1143

Cancer Kinome and Ovarian Cancer

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. NCI is encouraged to support research in this area.

Action taken or to be taken

The study of kinases (enzymes that regulate genes and other proteins) involved in cell signaling, metabolism, division, and survival has led to a better understanding of how cells become cancerous at a molecular level. Based on an understanding of aberrant kinase behavior that triggers cancer development, scientists have developed a number of targeted cancer therapies called kinase inhibitors, which block the action of certain kinases to limit the growth of cancer cells. NCI continues to support genomics research aimed at the continued identification of kinase mutations, basic research into kinase pathways, and clinical testing of treatments built upon this knowledge for a variety of cancers, including ovarian.

The NCI's Center for Cancer Genomics (CCG) aims to advance a modern era of cancer diagnosis, treatment and prevention based on the study of genomes, combining genomic and clinical data and making it available to researchers. In 2016, CCG established the NCI Genomic Data Commons (GDC), an interactive database with enhanced computational abilities that combines data from the Cancer Genome Characterization Initiative (CGCI), the Cancer Genome Atlas (TCGA), Therapeutically Applicable Research to Generate Effective Treatments (TARGET), and the Cancer Cell Line Encyclopedia (CCLE). NCI hopes to speed progress in genomics research by unifying these cancer data resources, which represents 38 disease types and 14,531 cancer cases, widely available to the research community. In addition to the GDC, CCG supports the Cancer Genome Characterization Initiative (CGCI), the Cancer Target Discovery and Development Network (CTD²), and the Cancer Driver Discovery Program (CDDP). As a pilot project, the CDDP has selected samples from lung, colorectal, and ovarian cancer patients for analysis in the hopes of discovering additional driver mutations.

In addition to identifying genetic mutations that give rise to abnormal kinase activity, NCI conducts and supports research aimed at better elucidating kinase pathways themselves. For example, researchers in the Women's Malignancy Branch in NCI's Center for Cancer Research (CCR) are studying the NF- κ B family of gene transcription factors, which have been shown to play a role in the development of epithelial tumors, including ovarian malignancies. This research complements extramural research on similar topics, including kinase pathways that may be targets for ovarian cancer treatments.

The NCI works to translate knowledge of kinase activity into therapies through the support of clinical trials for kinase inhibitors. NCI currently supports a number of kinase inhibitor clinical trials targeting ovarian cancer. These trials encompass trial phases I through III and a variety of therapeutic agents, including trametinib, buparlisib, alpelisib, VX-970, LY2606368, AL3818, and AZD2014. Each of these agents is targeted to control the activity of distinct kinases implicated in specific subtypes of ovarian cancer. NCI also supports research into the long-term effects of these treatments, such as a study examining the long-term effects of tyrosine kinase inhibitors on fertility.

NCI will continue to invest in expanding scientific knowledge of kinases and how kinase pathways can be targets for ovarian cancer therapies.

Capstone Awards

The Committee continues to expect NIH to pursue the establishment of the Capstone awards. The program is expected to promote partnerships between senior and junior investigators, provide opportunities to acquire skills to transition to a new role, and other purposes. The Committee expects the Director of NIH to consult with the IC Directors, patient advocacy groups, and industry leaders. The Committee requests an update and timeline on the development, duration, and amount for capstone awards in the fiscal year 2018 budget request.

Action taken or to be taken

In 2014, NIH convened an internal working group to consider new ideas for decreasing the time required for early career investigators to reach research independence. Among the many proposals discussed by the working group was the concept of a new “Emeritus” award (later renamed the “Capstone” award) that would allow established investigators to complete important research goals and bring their research programs to an orderly conclusion. The expectation would be that an investigator supported by a Capstone award could not have principal investigator status on future NIH grants. The idea was that facilitating the transition of some investigators out of the NIH-funding pool might provide opportunities for early career scientists.

To gauge community interest in such an award program and the community’s perspectives on whether such an award program would further the interests of junior investigators, NIH issued a Request for Information (RFI) in February, 2015 (NOT-OD-15-064³⁰). The RFI described a few potential ideas for how an Emeritus Award could be used, such as enabling senior investigators to complete their projects and help them close out their laboratories; supporting a senior investigator during the transition to a new role, such as full time teaching or executive research administration; or facilitating a senior investigator in forming a partnership with a junior faculty member to hand off his or her line of research inquiry.

Feedback from the RFI was mixed; roughly half of the respondents indicated support for the concept, while the other half expressed skepticism that such an award would be helpful to junior investigators. This skepticism was also voiced over social media^{31,32}. One frequent comment was that NIH did not need a new type of grant to facilitate mentorship between junior and senior investigators, as mentorship is already fostered through existing mechanisms, such as the Ruth L. Kirschstein National Research Service Awards and research career development awards. Moreover, if a senior investigator wishes to transfer his or her research project to a junior investigator, the grantee institution can request a change in the status of the key personnel named on the grant through existing mechanisms. Other RFI respondents advocated for higher priority for additional funding opportunities that directly target early career investigators.

Over the course of numerous internal NIH discussions, while considering the research community’s concerns, it became clear that the Capstone award concept was unlikely to achieve its intended goals. Rather than pursue the Capstone award, NIH senior leadership and their staff are exploring other strategies for sustaining the biomedical workforce. Several NIH Institutes

³⁰ <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-064.html>

³¹ <http://news.sciencemag.org/funding/2015/02/nih-proposal-create-grant-aging-scientists-hits-nerve>

³² <http://www.nature.com/news/nih-plan-to-give-ageing-scientists-cash-draws-scepticism-1.16895>

are currently piloting new mechanisms for providing stable, long-term funding for both early career and established investigators.^{33,34,35,36,37,38,39,40,41}

Furthermore, as requested in the Consolidated Appropriations Act of 2016, NIH is working with the National Academies of Sciences, Engineering, and Medicine to conduct a comprehensive study on policies affecting the next generation of researchers in the United States. It is our hope that by consulting a broad range of stakeholders with varied perspectives, the National Academies study will produce unique insights for NIH and other stakeholders

³³ <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-16-025.html>

³⁴ <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-16-024.html>

³⁵ <https://grants.nih.gov/grants/guide/rfa-files/RFA-GM-17-002.html>

³⁶ <https://grants.nih.gov/grants/guide/rfa-files/RFA-GM-16-003.html>

³⁷ <https://grants.nih.gov/grants/guide/rfa-files/RFA-GM-17-004.html>

³⁸ <https://grants.nih.gov/grants/guide/pa-files/PA-16-411.html>

³⁹ <https://grants.nih.gov/grants/guide/rfa-files/RFA-NS-16-001.html>

⁴⁰ <https://grants.nih.gov/grants/guide/rfa-files/RFA-DE-17-002.html>

⁴¹ <https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-16-008.html>

Cardiovascular Disease [CVD]

The Committee is aware that for certain disease areas, like CVD, rural States and their respective patient populations have disproportionately high incidence. In the case of cardiovascular disease, high rates of obesity, diabetes, and smoking among rural populations create much higher risks for acute cardiovascular disease. While the NHLBI has the primary lead for research in CVD, other Institutes that include emphasis on children or bioengineering have important secondary roles in helping to generate positive research outcomes to combat this disease area. For this reason, the Committee urges the NIH to consider convening a cross disciplinary, multi-Institute effort to identify ways to include rural populations in research and to work with institutions located in heavily rural States.

Action taken or to be taken

The National Heart, Lung, and Blood Institute (NHLBI) is supporting several important multi-Institute-funded clinical trials testing interventions to reduce the incidence of obesity, major cardiovascular risk factors, or cardiovascular disease (CVD) in rural America. A prime example is a clinical trial that involves 2,000 participants in the Stroke Belt in Alabama and North Carolina. This project, funded by the Patient-Centered Outcomes Research Institute, the NHLBI, and the National Institute of Neurological Disorders and Stroke (NINDS), will compare two strategies designed to improve blood pressure control in primary care practices.

Two other multi-Institute efforts focus on the cardiovascular health of ethnic minorities living in primarily rural areas. For example, the Jackson Heart Study (JHS) in the Mississippi delta, funded by the NHLBI and the National Institute on Minority Health and Health Disparities, is the largest study in history to investigate risk factors that affect high blood pressure, heart disease, stroke, diabetes, and other important diseases in African Americans. The Strong Heart Study (SHS) began in 1988 and focuses on cardiovascular health for American Indians, many of whom live on rural reservations. Many ancillary studies to the SHS are funded by multiple Institutes, including the National Institute on Aging (NIA), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Environmental Health Sciences (NIEHS), and NINDS.

The NHLBI is also funding several studies to enhance the use of innovative technologies and to improve children's cardiovascular health in rural communities. For example, a study in rural Minnesota is testing whether family and community-based interventions that promote healthful food changes and physical activity at home can prevent children from gaining excess weight. Another study that the Institute is funding in rural Minnesota is evaluating an electronic health record-linked, web-based clinical decision support system to identify patients with prediabetes and provide treatment recommendations. If the decision tool proves successful, it could be broadly applied across many diseases to improve health care in medically underserved areas. In addition, an NHLBI-supported study in rural counties in Florida is testing whether a group-based telephone intervention can reduce obesity and CVD risk factors in obese adults.

Thus, the NHLBI is involved in several promising studies that are leveraging technology and innovations to improve health care in rural, underserved areas. In addition, the Institute remains open to other multi-Institute research efforts that include rural populations or involve institutions located in heavily rural states.

Celiac Disease and Type 1 Diabetes

The Committee is encouraged by the TEDDY study which has led to discoveries in the risk for pediatric celiac disease and the development of type 1 diabetes. The Committee urges the Institute to explore the intersection of type 1 diabetes with celiac disease prevention.

Action taken or to be taken

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) will continue to support research on celiac disease and type 1 diabetes prevention. Celiac disease and type 1 diabetes are both autoimmune diseases. Celiac disease is caused by an autoimmune attack on the lining of the small intestine in response to gluten exposure, and type 1 diabetes is caused by an autoimmune attack on the insulin-producing pancreatic beta cells. Therefore, identifying factors that cause or contribute to one disease could be relevant to the other, leading to strategies to prevent both.

The Environmental Determinants of Diabetes in the Young (TEDDY) study is following over 6,000 infants at high genetic risk of type 1 diabetes until they are 15 years of age, with the goal of identifying environmental triggers of the disease. Since type 1 diabetes and celiac disease share many risk genes, the TEDDY study provides a great opportunity to explore genetic and environmental risk factors for both diseases. Already TEDDY researchers have made important discoveries about pediatric celiac disease. For example, TEDDY researchers have found that more than one quarter of children with two copies of a specific high-risk genetic variant develop an early sign of celiac disease by age 5. TEDDY researchers have also expanded the understanding of what genetic regions contribute to early markers of celiac disease. Overall, these results may have future implications for celiac disease screening in young children, facilitating testing of prevention strategies and allowing children to benefit from such strategies once they are developed.

The co-occurrence of type 1 diabetes and celiac disease cannot be fully explained by demographics and genetics. Shared environmental or physiological factors also are likely to contribute. Researchers are analyzing the detailed dietary information collected in TEDDY and have found that the timing of first gluten introduction is not associated with increased celiac disease risk, nor is maternal gluten exposure during pregnancy. TEDDY researchers are now examining the possible role of various types of carbohydrates eaten by TEDDY participants in different geographic regions. Additionally, TEDDY investigators are analyzing participants' stool samples to investigate how viruses and bacterial dynamics may affect celiac disease development.

The TEDDY study is ongoing through 2025. As new discoveries are made with the rich information and biosamples from this study, TEDDY investigators are poised to investigate the causes of type 1 diabetes and celiac disease to pave the way to new prevention strategies.

Chronic Obstructive Pulmonary Disease [COPD]

The Committee notes NHLBI's collaboration with the CDC in the development of a COPD action plan and is pleased with the stakeholder town hall meeting held recently on the NIH campus to advance its completion. The Committee expects CDC and NIH to work together to complete the action plan on a timely basis and report bi-annually on the implementation of the plan's recommendations. Further, the Committee remains aware and concerned that Alpha 1 Antitrypsin Deficiency [Alpha 1] is a major genetic risk factor for developing COPD. The Committee, therefore, encourages NHLBI to continue to advance Alpha 1 research as part of the overall plan.

Action taken or to be taken

The National Heart, Lung, and Blood Institute (NHLBI) convened a stakeholder town hall meeting on February 29 and March 1, 2016, to advance the development of a COPD action plan. The meeting drew substantial participation by patients, their families, healthcare providers, researchers, industry representatives, and federal partners, including the Centers for Disease Control and Prevention (CDC), and all contributed to the identification of five goals to serve as the backbone of a national action plan for COPD. These goals are: 1) Empower people with COPD, their families, and caregivers to recognize and reduce the burden of COPD; 2) Improve the prevention, diagnosis, treatment, and management of COPD by promoting and sustaining the education and training of health care professionals; 3) Collect, analyze, disseminate, and report COPD-related public health data that drives change and tracks progress; 4) Increase and sustain research to better understand prevention, pathogenesis, diagnosis, treatment, and management of COPD; and 5) Translate national policy, educational, and program recommendations into legislative, research and public health care actions. NHLBI and partner stakeholders submitted a draft plan for public comment that was published in the Federal Register on September 28, 2016. Once all comments are collected and reviewed, a final document should be ready by early 2017.

An important consideration in the development of the COPD action plan was Alpha-1 Antitrypsin Deficiency (Alpha-1), a strong genetic risk factor for developing COPD. NHLBI has a long-standing commitment to supporting research on Alpha-1-related lung disease, and the institute currently funds several lines of research targeting this disease. Among these is an institute-initiated program entitled Genomic Research in Alpha-1 Antitrypsin Deficiency and Sarcoidosis (GRADS). GRADS researchers are analyzing how microorganisms living in the body (the microbiome) may contribute to the development of Alpha-1-related lung disease and how this could in turn affect individual responses to therapy. Results from GRADS are expected in 2017. Additionally, NHLBI recently funded a program project grant that will test innovative gene therapy approaches to correct the fundamental molecular defect in Alpha-1 deficiency. Finally, because many treatments for Alpha-1-related lung disease are the same as those for COPD, NHLBI-funded trials in COPD often include Alpha-1 participants.

Cerebral Cavernous Angioma

The Committee urges HHS agencies [NIH, FDA, and CDC] to work together with the research and advocacy community to increase the efficiency and effectiveness of the research and clinical drug trials effort.

Action taken or to be taken

The NINDS currently supports a portfolio of basic and translational research to understand the molecular, cellular, and genetic processes involved in cerebral cavernous angiomas (CCA). Active investigations are gaining a better understanding of the normal development of cerebral blood vessels and how genes associated with CCA cause abnormal vessel formation, while other studies are examining the role of specific CCA-related genes that affect blood vessel function, which may give rise to clinical symptoms in patients impacted by CCA. Studies are also identifying molecules related to the hypothesized disease mechanisms that could serve as biomarkers of disease severity. Furthermore, several NINDS-supported studies are identifying small molecule compounds to disrupt development of blood vessel malformations by modifying CCA-related gene action or downstream effects.

NINDS and the National Center for Advancing Translational Research support a Brain Vascular Malformations Consortium (BVMC), as part of the NIH Rare Disease Clinical Research Network, which includes a prospective natural history and genome-wide association study investigating genetic, physiological, and lifestyle factors which affect CCA clinical variability. The BVMC has active collaborations with the Angioma Alliance, the Sturge-Weber Foundation, and the HHT Foundation, groups which represent different types of vascular malformation disorders. NIH program staff interact with these groups and participate in the Angioma Alliance's annual scientific meetings on a regular basis, which also involve other HHS agencies such as the FDA. NINDS frequently provides funds for this conference, including the one planned for November, 2016.

CCA is an important cause of hemorrhagic stroke, a severe type of stroke that occurs when a weakened blood vessel ruptures, for which there is currently no effective treatment. NINDS supports a national Stroke Trials Network, NIH StrokeNet, which has the capacity and expertise to conduct small as well as large, multi-site clinical trials in stroke prevention, treatment, and recovery research. This network is poised to answer clinical questions related to CCA, including testing promising treatments that may emerge from current preclinical work.

Cerebral Palsy (CP)

Over 800,000 Americans are impacted by CP and currently there are no identified best practices at diagnosis or through the lifespan, organized standards of care, CP Registry, or proven therapy protocols. The Committee commends NINDS for working with scientists and stakeholders to develop a 5-year, research-focused strategic plan for CP prevention, treatment, and cure through the lifespan. The Committee urges NINDS, working with other relevant NIH ICs, to strengthen research efforts in support of the strategic plan to advance basic and translational research for CP, as well as clinical efforts to improve outcomes of diverse impairments and health issues on functioning, participation and well-being across the lifespan.

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports a wide spectrum of research on cerebral palsy (CP), from laboratory investigations through clinical trials of interventions. Ongoing laboratory research is investigating causes of prenatal and postnatal brain injury and mechanisms underlying neuroprotection and repair. Clinical studies aim to improve prediction of which infants are at risk for CP and identification of biomarkers of outcomes to inform future interventions. This research includes, for example, quantification of metabolic rate in neonates at risk for brain damage; refinement of brain imaging methods to recognize abnormalities in fetal brain development; and a major, longitudinal study of more than 900 extremely prematurely born infants, from birth to age nine, to identify early biomarkers of neurodevelopmental disorders such as CP. NINDS is advancing new therapies through preclinical studies of potential drug and stem cell treatments for CP – including a recent small business project developing a treatment for spasticity using recombinant botulinum neurotoxin and a study utilizing a novel, nanotechnology-based drug delivery system – and testing whether targeted electrical stimulation can restore normal circuitry between brain and muscle in an animal model. In addition, NINDS supports an ongoing and newly funded clinical trial assessing erythropoietin for neuroprotection in extremely premature infants or infants with brain damage caused by reduced blood flow and oxygen, respectively.

The National Center for Medical Rehabilitation Research (NCMRR) within the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) funds multi-site trials aimed at improving upper extremity function, walking, and treatment delivery of rehabilitation for children with CP. Multiple grants are 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 partial paralysis. NICHD also supports research on treatment for adults with CP including use of new neuromodulation techniques, powered walkers, custom orthotics, and interventions for balance and posture.

To identify gaps in research and identify priorities for CP, NINDS and NICHD convened two scientific workshops: in November 2014 (“The State of the Science and Treatment Decisions in Cerebral Palsy”) and March 2016 (“Basic and Translational Research in Cerebral Palsy”). These workshops brought together scientists, clinicians, advocates, and other stakeholders to discuss topics such as the current gaps in the evidence base for therapeutics and interventions, and the role of non-human basic research in understanding the biology of CP and the development of

new therapies. Publications summarizing the first and second workshops are available⁴² and under production, respectively. Concurrently, NINDS is compiling key recommendations from both workshops to draft a 5-year strategic plan, which will be posted to the NINDS website upon completion. In accordance with the workshop recommendations, NINDS has developed a set of standardized assessment metrics (Common Data Elements; CDEs), and a community of researchers, clinicians, and patient advocates has founded a network with the goal of defining a national CP registry and conducting more comparative effectiveness research.

⁴² Lungu, et al. (2016). Available at <https://www.ncbi.nlm.nih.gov/pubmed/27558377>

Chimpanzees

The Committee supports NIH in its decision to make chimpanzees eligible for retirement from NIH-supported biomedical research and reaffirm its commitment to the care of the federally owned and supported chimpanzee population. Consistent with that policy, the Committee directs NIH to report its estimated timeline for moving chimpanzees to accredited sanctuaries within 30 days after enactment of this act. In addition, the Committee recognizes the need to provide greater financial support for the lifelong care of federally owned and supported chimpanzees, including sanctuary facility capital and care costs.

Action taken or to be taken

In November 2015, NIH announced that it will no longer support biomedical research on chimpanzees, and that NIH-owned and NIH-supported chimpanzees that reside outside of the Federal Sanctuary are eligible for retirement to the sanctuary as required by the Chimpanzee Health Improvement, Maintenance and Protection Act [CHIMP Act, as amended (42 U.S.C. § 283m)]. Efforts are being made to relocate the animals as quickly and safely as possible while allowing for optimal transition of each individual chimpanzee with careful consideration of their welfare, including their health and social grouping. The NIH-supported chimpanzee facilities have decades of experience relocating chimpanzees and ensuring adherence to animal welfare policies as defined by the Animal Welfare Act administered by the Animal Care, Animal and Plant Health Inspection Service; the Health Research Extension Act of 1985; and the Public Health Service Policy on Human Care and Use of Laboratory Animals implemented by the NIH Office of Laboratory Animal Welfare. All institutions housing NIH-owned or -supported chimpanzees are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International, further demonstrating NIH's commitment to responsible animal care and use.

The NIH has developed a plan for the retirement of all NIH-owned and -supported chimpanzees to the Federal Sanctuary operated by Chimp Haven, Inc. (Chimp Haven). This plan is posted on the NIH website.⁴³ The current capacity of Chimp Haven, depending on the animals' social groupings, along with modeling of the natural attrition in this aging population, has been used to develop estimates for the number of chimpanzees that can be transferred to the Federal Sanctuary each year. The prioritization of chimpanzees for relocation in the plan is based on animal health and well-being, including animals' social grouping.

The order of transfer of animals to Chimp Haven is expected to be NIH-owned animals at the Alamogordo Primate Facility (APF) followed by NIH-owned animals at the Keeling Center for Comparative Medicine and Research (KCCMR), and finally the NIH-supported animals at the Southwest National Primate Research Center (SNPRC). The APF animals have already begun relocating, with the last animals expected to be retired at Chimp Haven at the latest in FY 2021. KCCMR will begin transferring animals immediately upon availability of space at Chimp Haven and following completion of the transfer of the APF animals. This is expected to begin in FY 2021 and to be completed at the latest in FY 2025. After all KCCMR animals have been retired at Chimp Haven, NIH will begin retiring the NIH-supported animals remaining at SNPRC. Retirement of all SNPRC NIH-supported animals is expected to be completed at the latest in FY 2026. Each animal will be evaluated on a case-by-case basis with animal welfare being the

⁴³ <https://dpcpsi.nih.gov/orip/cm/chimpanzeeretirement>

driving factor in determining whether the animal can be transferred to Chimp Haven. A subset of animals may never be able to be transferred because their advanced age or medical condition(s) would make them unsuitable for and unlikely to survive the transfer.

Chronic Fatigue Syndrome (CFS)

The Committee is pleased to see the 2015 reports from the Institute of Medicine and the NIH's Pathways to Prevention Workshop, along with the recent advances in science and renewed interests of researchers, relating to CFS. The Committee urges the NIH to collaborate with disease researchers, clinicians, patients, and their advocates to address the historical lack of research and to capitalize on these opportunities to make progress on this poorly understood disease. Specifically, the Committee encourages NIH to use funding to jumpstart the field through a set of intramural and extramural investments that could include Funding Opportunity Announcements for biomarkers and treatment trials; other investigator-initiated studies, including for early-stage research; and support for research to develop consensus on a case definition and research standards.

Action taken or to be taken

The complexity of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) necessitates an inter-disciplinary approach to understand and develop treatments for this disease, and many NIH Institutes and Centers contribute to the effort to expand research on ME/CFS. National Institute of Allergy and Infectious Diseases (NIAID)-supported research under this effort includes projects examining links between Epstein-Barr virus infection and subsequent development of ME/CFS, and establishing a longitudinal immunological and virological study to help discover biomarkers of ME/CFS. NIAID also encourages further research on the disease by announcing when clinical samples resulting from NIAID-supported ME/CFS research are available for further study. The National Institute of Neurological Disorders and Stroke (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 men and women with ME/CFS.

Twenty-four NIH Institutes, Centers, and Offices coordinate their efforts through the Trans-NIH ME/CFS Working Group, which meets regularly to discuss the best approaches to foster ME/CFS research. As a first step toward encouraging ME/CFS research in the extramural community, NIH funded seven supplements to existing awards focused on understanding the causes and mechanisms of ME/CFS. Awarded supplements will enable existing projects to expand the collection and analysis of ME/CFS patient samples to aid in biomarker identification and to help identify potential therapeutic targets. The working group is also preparing two funding opportunity announcements (FOAs) to support ME/CFS Collaborative Research Consortia and a Data Management Coordinating Center. NIH recently released two Notices announcing the intent to publish these FOAs in December 2016.

A clinical research study on ME/CFS at the NIH Clinical Center is underway. This study will explore the clinical and biological characteristics of ME/CFS following a probable infection and aims to improve our understanding of the disease's cause(s) and progression. Healthy volunteers are currently being admitted into the study, and the protocol team will begin to bring individuals with ME/CFS to the NIH campus starting in early 2017.

To make progress in research in ME/CFS, partnerships between clinicians, researchers, patients, advocates, and funding organizations are critical. In May 2016, the Trans-NIH ME/CFS Working Group issued a Request for Information (RFI) to solicit input on strategies and priorities for ME/CFS research. The responses to the RFI are posted on the NIH website, and the

input will help guide future NIH research activities. NIH communicates regularly with ME/CFS stakeholders; the latest tele-briefing with stakeholders occurred on November 2, 2016 and two tele-briefings are scheduled for future dates. Patient advocacy groups will also be important partners in the Collaborative Research Centers, particularly with regard to recruitment for clinical studies. NIH is also fostering collaboration and communication across federal agencies. A Federal Partners meeting was held in April 2016 as a follow-up to the NIH Pathways to Prevention workshop, *Advancing the Research on ME/CFS*. The federal partners identified ways in which new and ongoing activities can be enhanced through collaborations among the federal agencies. Representatives on the Trans-NIH ME/CFS Working Group will work with the appropriate agencies to foster these activities.

Chronic Kidney Disease - Update

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

NIH continues to support a multi-faceted program of research to identify causes of kidney disease, understand and halt disease progression, develop and improve treatments, and ultimately prevent kidney diseases and kidney failure in adults and children. One recent National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-funded study found that the use of a commonly prescribed class of drugs called proton pump inhibitors increases risk for developing chronic kidney disease (CKD). In another study, researchers reported an increase in 8 year survival for people who received immune desensitization then a kidney transplant from an immune system-incompatible live donor compared with either those remaining on the kidney transplant waiting list or those who received a kidney transplant from an immune system-compatible deceased donor. Because there remains a shortage in the number of compatible living kidney donors, these results suggest that HLA-incompatible kidney transplants from living donors could represent a new option available for people with kidney failure.

In 2016, the NIDDK released three funding opportunity announcements to establish the Kidney Precision Medicine Project (KPMP), which aims to obtain ethically and evaluate human kidney biopsies from participants with acute kidney injury (AKI) or CKD, create a kidney tissue atlas, define disease subgroups, and identify critical cells, pathways, and targets for novel therapies. Additional technology development in support of the KPMP will be supported by small business programs.

In July of 2016, NIDDK convened a workshop to discuss clinical studies of treatments for CKD in children, and to explore potential therapeutic target areas for children with CKD. Based on discussion at the workshop, NIDDK announced a funding opportunity to establish a network of clinical centers to conduct pilot and feasibility studies of therapies to slow or reverse the progression of CKD in children. These pilot studies will seek to optimize critical elements for designing a full-scale randomized control trial – the most promising study question, potential therapeutic agent(s) and dosing, the study population, data collection, and appropriate outcomes to assess. The ultimate goal of this initiative is to obtain the necessary information to design and implement one or more full-scale randomized controlled clinical trials of therapies to reduce morbidity in children with CKD.

NIDDK and the National Institute on Minority Health and Health Disparities (NIMHD), as well as the National Institute of Allergy and Infectious Diseases (NIAID), have been collaborating to plan a new effort to advance research on the effects of *APOLI* genetic variants on kidney transplant donors and recipients. In November 2016, the three Institutes released a Funding Opportunity Announcement that calls for applications for Clinical Centers to evaluate outcomes in recipients after transplantation of kidneys donated by African Americans and those with high probability of having variant alleles.

Chronic Overlapping Pain Conditions

The Committee notes the strong scientific evidence substantiating common disease mechanisms underlying Chronic Overlapping Pain Conditions. However, evidence needed to inform practice guidelines is insufficient, sometimes resulting in the misdiagnosis and ineffective and harmful treatment of patients with these disorders. A coordinated effort on chronic overlapping pain conditions is urgently needed to maximize the Federal research investment and inform clinical practice. Research recommendations from the 2012 NIH Workshop on Chronic Overlapping Pain Conditions and September 2014 scientific meeting, co-sponsored by various NIH ICs and the TMJ Association, should continue to guide the relevant ICs in advancing research 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 Pain Consortium, a collaboration of 25 institutes, centers, and offices, continues its collaborative efforts to better understand the underlying neurobiological mechanisms of chronic pain conditions that overlap in an individual and to determine the most effective treatment approaches. The consortium held workshops, supported a funding opportunity announcement (FOA) to promote understanding of chronic overlapping pain conditions research, and funded the development of clinical research tools.

Current efforts to address the research recommendations from the 2012 Workshop on Chronic Overlapping Pain Conditions⁴⁴ and to inform practice guidelines for patients are shared by several NIH institutes and centers. An FOA on Chronic Overlapping Pain Conditions was released in 2014 in response to recommendations from the 2012 workshop. To date, three projects funded through this FOA aim to elucidate potential shared mechanistic pathways across overlapping pain conditions. One study examines the role of proteins, microRNAs, and genes in the development of temporomandibular disorder (TMD) and five overlapping pain conditions (migraine, low back pain, irritable bowel syndrome, pelvic pain, and widespread body pain). The study leverages existing resources by utilizing stored bio-specimens from the National Institute of Dental and Craniofacial Research (NIDCR)-funded Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study. These new data will be combined with existing neurobiological findings and psychosocial characteristics collected from the patient cohort to identify novel underlying mechanisms common to overlapping pain conditions. NIH also continues to fund prospective population-based epidemiological studies on multiple pain conditions that commonly co-occur. These include studies funded by NIDCR to identify risk factors that predict whether TMD will develop as a single condition or in conjunction with other chronic pain conditions, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) which supports the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, a multi-center study of urologic chronic pelvic pain syndromes and other co-occurring pain conditions.

The NIH Pain Consortium hosted the 2014 and 2015 Investigators' Meetings on Chronic Overlapping Pain Conditions. Recommendations from these workshops focused on development of clinical research resources to advance the science, including a common case definition for

⁴⁴ http://www.ninds.nih.gov/news_and_events/events/meeting-summary-chronic-pain.htm

overlapping conditions and a minimal data set to be collected in all relevant clinical studies. Experts on one or more of ten identified overlapping pain conditions recommended that a standardized research tool, developed through the MAPP network, be expanded to other overlapping pain conditions. This tool collects in a standardized way, the symptoms and features of co-morbid chronic pain conditions in individuals participating in clinical research. Based on this recommendation, the NIH funded two supplements to ongoing studies of overlapping pain conditions to expand this tool. This new resource will allow investigators to collect consistent and relevant data across studies to help identify shared mechanisms of these pain conditions and ultimately to inform clinical care of patients with these conditions.

Additional recommendations from the 2015 Investigator's meeting included providing information on available data sharing resources on the NIH Pain Consortium website.⁴⁵ Information on existing pain registries and the process for submitting shared data to the Database of Genotypes and Phenotypes (dbGAP) are now on the NIH Pain Consortium website.

⁴⁵ <https://painconsortium.nih.gov/index.html>

Chronic Pain Conditions

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

NIH supports chronic pain research through investigator-initiated studies, targeted Funding Opportunity Announcements (FOAs), and trans-NIH initiatives. The projects in the portfolio reflect the breadth of pain research from cell and molecular mechanisms of chronic pain to therapy development to large scale clinical trials. Many pain research-focused funding opportunities were released in 2016, and FY 2018 funds will be directed to projects awarded through these solicitations. Topic areas of these funding opportunities include sickle cell disease pain, pharmacogenetics of pain management, translational research on pelvic pain, and therapeutic potential of endocannabinoids. The NIH, along with other federal agencies and departments recognize the pressing need to encourage the development of new pain treatments, especially those with reduced risk for misuse, as well new treatments for opioid addiction and overdose reversal and developed high priority research recommendations to address this need. Some of these research priorities are ongoing through NIH support or planned for the near future.

The NIH Pain Consortium, a collaboration of 25 institutes, centers, and offices, was established to enhance collaboration and coordinate NIH research efforts. Many of the FOAs described above that solicit and support priority areas of pain research are sponsored by multiple NIH Pain Consortium member institutes.

The Interagency Pain Research Coordinating Committee (IPRCC) was established to coordinate all pain research efforts across HHS, as well as relevant federal departments. It includes federal (six agencies and departments), public, clinical, and scientific members. An ongoing IPRCC initiative is the development of the Federal Pain Research Strategy (FPRS) to help guide NIH, as well as other agencies, in funding decisions on future pain research. Its expected completion and delivery to NIH is early 2017. In addition, the National Pain Strategy (NPS), the government's first coordinated plan to reduce the burden of pain, was released in March 2016 and sets forth recommendations for research to identify population-level prevalence, trends, and impact of chronic pain, as well as to provide quality evidence for clinical decision points on pain care. NIH and other federal agencies and departments are collaborating to move implementation of NPS research objectives forward.

Chronic Pain Research

The 2011 Institute of Medicine report, "Relieving Pain in America," revealed the devastating public health crisis of chronic pain, demonstrating that 4-in-10 American adults report chronic pain at a cost of \$1,600,000,000 per day. The Committee strongly urges NIH to intensify and expand its basic, translational, and clinical research effort on chronic pain to elucidate underlying mechanisms of disease, as well as to discover and develop safe, effective, non-habit forming drug and non-drug therapies. The Committee encourages the Director to include chronic pain in ongoing NIH initiatives that have potential for yielding significant advancements in this area, such as the Precision Medicine Initiative, the NIH Common Fund, Advanced Medicines Partnership, BRAIN Initiative, and public-private partnerships within NCATS.

Action taken or to be taken

Many institutes and centers at NIH fund chronic pain research, ranging from fundamental research on the molecular, genetic, and bio-behavioral basis of chronic pain to clinical studies of pharmacological and non-pharmacological pain treatments. NIH supports chronic pain research through investigator-initiated studies, targeted Funding Opportunity Announcements (FOAs), and trans-NIH initiatives. The NIH Pain Consortium, a collaboration of 25 institutes, centers, and offices, was established to enhance collaboration and coordinate NIH research efforts. Many FOAs that solicit and support priority areas of pain research are sponsored by multiple NIH Pain Consortium member institutes.

The NIH Common Fund's Health Care System Research Collaboratory also supports pain research, including through pragmatic trials- large scale trials in a real-world setting.

The **Lumbar Imaging with Reporting of Epidemiology pragmatic trial** is testing how providing doctors with normal spine image reports helps them to diagnose and treat patients with lower back pain. The Collaborative Care for Chronic Pain in Primary Care pragmatic trial is evaluating how integration of psychosocial services into the primary care environment compares to usual management in the primary care setting in reducing pain, disability, and reliance on opioids. It also is assessing the interaction of pain with sleep disorders and will explore population level data on specific pain conditions. Given the current crisis due to opioid overuse and related overdose deaths, the study of alternative approaches to pain care is critically important.

Cutting edge pain research is supported by the NIH Common Fund's "Stimulating Peripheral Activity to Relieve Conditions" (SPARC) initiative, which engages non-traditional partners to drive therapeutic advances through multiple avenues, including novel tools and technologies. Several projects explore novel minimally or non-invasive technology to drive neuro-modulation of peripheral nerves, which has been effective, especially in managing chronic neuropathic pain. Approaches include targeted gene delivery to alter nerve activity for bladder pain and function and implantable, micro-scale devices to deliver local anti-inflammatory agents to reduce neural pain-generating activity in response to injury or disease processes.

Through the trans-NIH Blueprint Therapeutics program, novel analgesics for migraine and neuropathic pain are under development. In addition, the BRAIN Initiative is developing tools and technologies that provide highly relevant opportunities to advance pain research. The Initiative aims to develop innovative technologies to modulate neuronal activity, explore large

scale neuronal interactions, and visualize and understand brain circuitry, which are key to understanding the altered neural activity associated with chronic pain and treating pain by targeting these changes.

The Precision Medicine Initiative will collect data relevant to many chronic diseases, including chronic pain and its co-existing conditions, from over a million people. Collected health records, health survey information, mobile health data on activity, lifestyle, and environmental exposures, medication use and medical history, and bio-samples will provide valuable opportunities to identify risk and preventive factors for chronic pain, medication use, response, and risk, and other pain relevant information across different populations.

The ongoing effort to develop a Federal Pain Research Strategy led by the NINDS Office of Pain Policy for the Interagency Pain Research Coordinating Committee (IPRCC) will provide high priority research recommendations specifically targeted to chronic pain mechanisms, assessment, and management. The strategy creates a long-term pain research agenda for the federal agencies and departments that support pain research.

Clinical and Translational Science Awards (CTSA) Program

The Committee includes \$520,740,000, an increase of \$20,740,000, for the CTSA Program. The Committee applauds the success of the CTSA Program and recognizes recent NCATS efforts to update the program following the recommendations of the Institute of Medicine. NCATS is encouraged to further integrate the CTSA Program into the full spectrum of medical research activities at NIH, including collaboration with other ICs, and greater support for the CTSA hubs and network.

Action taken or to be taken

The Clinical and Translational Science Awards (CTSA) Program is comprised of more than 50 distinct academic medical centers (hubs) across the country, which work to improve the translational research process to get more treatments to more people more quickly. The National Center for Advancing Translational Sciences (NCATS) relies on the individual strengths of the CTSA Program hubs and partners with them to develop and implement innovative, collaborative solutions intended to transform clinical and translational research. Together, they address common areas of need that call for collaborative solutions, including:

- Training and cultivating the translational science workforce;
- Engaging patients and communities in every phase of the translational process;
- Promoting the integration of special and underserved populations in translational research across the human lifespan;
- Innovating methods and processes to increase the quality and efficiency of translational research, particularly of multisite trials; and
- Advancing the use of cutting-edge informatics.

To further its goal of spurring innovation and collaboration in clinical and translational research, NCATS funded in 2016 a set of CTSA Program Collaborative Innovation Awards (CCIA). These projects are designed to stimulate team-based research across the program's network. CCIA projects are intended to foster research collaboration by encouraging teams from three or more CTSA Program hubs to work together to develop, demonstrate, and disseminate innovative, experimental approaches to overcoming translational science roadblocks. This program responds to the Institute of Medicine's report recommendation that the CTSA Program establish an innovation fund to promote collaboration.

The NCATS' Trial Innovation Network is a new collaborative initiative within its CTSA Program composed of three key organizational partners:

- Trial Innovation Centers (TICs) – awarded in FY 2016
- Recruitment Innovation Center (RIC) – awarded in FY 2016
- CTSA Program Hubs

The vision for the Trial Innovation Network is to innovatively address critical roadblocks in clinical trials and to accelerate the translation of novel interventions into treatments and therapies. The network will focus on operational innovation, operational excellence and collaboration, relying on the expertise, diversity, and broad reach of the CTSA Program hubs. The network will apply CTSA Program features such as a single institutional review board system, master contracting agreements, quality-by-design approaches, and a focus on evidence-based strategies to recruitment and patient engagement.

Early plans include building partnerships with other NIH Institutes and Centers. As the network evolves and gains momentum, the goal is to launch network-led clinical trials collaboratively with other partners in 2017.

Clinical Center

The Committee commends the NIH Advisory Committee to the Director (ACD) for recognizing and chartering a review due to the lapses in safety and compliance in the sterile manufacturing components of the NIH pharmacy. The investigation into the event led to an appreciation of broader organizational deficiencies relating to priorities, quality, compliance, and accountability. The public report identifies issues related to a lack of a culture and practice of safety; leadership issues related to clinical care quality, oversight, and compliance; and specific issues with sterile processing. The Committee agrees with the ACD that the implementation of Red Team's recommend-actions should greatly reduce risks, increase assurance of participant safety, and improve research quality. In addition, the Committee supports the steps NIH has started such as starting the process to replace the leadership of the NIH Clinical Center (CC), establish a comprehensive oversight/compliance office, and strengthen the board of the CC. The Committee agrees NIH should issue a policy and begin tangible steps to adopt commonly accepted best practices and rules governing hospitals, clinical research, and laboratory programs, ensure appropriate regulatory requirements are uniformly applied, meeting and exceeding minimum requirements for any research facility or laboratory. The intramural research program (IRP), not limited to the CC, should seek voluntary accreditation associated with quality and safety. The NIH IRP should be an example of excellence and should meet the highest standards in safety, quality, and compliance. The Committee expects quarterly updates on the creation and use of CC patient safety and quality measures, selection and implementation of the voluntary adherence to regulatory requirements. NIH should also provide plans and quarterly progress on steps to improve leadership, culture of patient safety, and research quality throughout the IRP and CC. Finally, the Committee expects NIH to fund the costs of implementing these recommendations from within existing IRP resources and not from shifting extramural resources towards these efforts.

Action taken or to be taken

As described by the internal task force investigating the Pharmaceutical Development Section (PDS) failures and the NIH Advisory Committee to the Director (ACD), weaknesses in the structural organization of the Clinical Center (CC) contributed to problems discovered in the pharmacy and other NIH facilities. Redressing the problems identified required the advice of numerous outside experts, and dedicated time from senior NIH leadership and staff. NIH has made significant progress, but there is still work to be done.

Additionally, more recent FDA inspections identified further concerns. In July and August 2016 the FDA conducted a not-for-cause inspection of the Department of Transfusion Medicine and offered suggestions for process improvements. During September and October 2016, the FDA conducted for-cause inspections of the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) and a clinical trial sponsored by CTEP. The inspections identified serious problems in reporting adverse events and unanticipated problems to the study sponsor, Institutional Review Board (IRB), and the FDA. In March and April 2017, the FDA conducted a not-for-cause inspection of the NIH Radioactive Drug Research Committee, finding certain procedural deficiencies.

In response to these issues, NIH established a series of new centralized approaches to: 1) put in place the highest quality clinical care standards; 2) maintain ongoing monitoring of all operations and facilities related to patient care and quality assurance; and 3) address underlying

organizational issues in the CC. We have in place a plan for much of the infrastructure required to ensure robust oversight of all clinical research operations. The following is a detailed outline of ongoing and planned efforts that NIH is undertaking to rectify safety and monitoring problems and create a CC structure that fosters and supports the highest quality of patient safety and research support:

1. Establishment of a new hospital board: The new NIH Clinical Center Research Hospital Board, chaired by Dr. Laura Forese, Executive Vice President and Chief Operating Officer of New York-Presbyterian, held its first meeting on July 15, 2016, and will guide the CC's continued efforts to build systems integrating patient safety, operationalizing quality measures, and centralizing management. The Board's next meeting was held on April 28, 2017.
2. Realignment of CC leadership structure: In May 2016, NIH announced a restructuring of the CC leadership. In August 2016, NIH successfully recruited Dr. Majid Tanas, a renowned leader in research pharmacy operations, as the new Chief of Pharmacy at the CC. In August 2016, Dr. John Gallin (the previous CC Director) assumed the newly created dual position of Associate Director for Clinical Research and CC Chief Scientific Officer, in which his new responsibilities include overseeing the scientific review process for all clinical protocols conducted within the NIH intramural program, helping set priorities for clinical research performed at the CC across Institutes and Centers (ICs), and leading the strategic planning process for intramural clinical research. Finally, in January 2017, Dr. James Gilman, a retired Army Major General with extensive experience in research hospital management, joined NIH as the new CC Chief Executive Officer (CEO).
3. Hotline for Concerns Regarding Safety Issues: Last summer, a toll-free hotline (1-866-444-8811) was deployed for staff, patients, and visitors to report anonymously any patient safety and other concerns related to care at the CC. It is being monitored by an external service. Details on the nature of the concerns and the way NIH responds to them are reported directly to the Hospital Board for evaluation.
4. Improving reporting relationships: A central theme identified by the NIH ACD was the problems created by the decentralized nature of CC operations, in which many of the staff working at the hospital reported directly to their IC, rather than CC leadership. This lack of centralized CC authority over all staff operating in the CC was identified as a significant impediment to improving patient safety and research quality. To address this, NIH changed the performance plans of all CC staff to include a direct reporting relationship to the CC leadership structure, in addition to their relationship with their home IC. Additionally, all Clinical Directors now report directly to their IC Director, and a new element has been added to the performance plans of all IC Directors to emphasize their responsibility for their IC's clinical program.
5. Establishment of CC Engagement Working Group: Recognizing that CC staff at all levels should be empowered and engaged in the changes taking place, NIH has

established a CC Engagement Working Group to solicit new ideas about how to enhance patient care and optimize the operations of the CC. Multiple town hall-style meetings with NIH staff have been held.

6. A series of focus groups, facilitated by Mr. Stewart Simonson, were conducted to gather input from rank and file staff that work within the CC from across the Intramural Research Program. This information was provided to Dr. Gilman to inform a dialogue on next steps forward to further strengthen the hospital.
7. Creation of the central Office of Research Support and Compliance (ORSC): A key part of NIH's response to the problems at the CC was the establishment of the centralized ORSC. ORSC was formed as an office within the Office of the NIH Director, Office of Intramural Research, to ensure that research conducted across all the ICs, whether in or outside of the CC, adheres to the highest regulatory, professional, and ethical standards. This includes developing policy for current and emerging regulatory requirements in FDA and HHS regulated research, coordinating engineering and administrative controls for GMP and other production facilities, engaging with FDA and other oversight authorities during compliance inspections and monitoring compliance. The office serves as an educator, facilitator, and resource center to help intramural researchers navigate the medical research regulatory landscape. ORSC continues to establish lines of communication among all stakeholders. Centralized systems for tracking clinical protocols, FDA-regulated drug and device research, and implementing other regulatory compliance standards are being developed by ORSC. ORSC is now under the acting leadership of Dr. Andy Griffith, the Scientific Director of the National Institute on Deafness and Other Communication Disorders and the Deputy Director of Intramural Clinical Research in the Office of Intramural Research and Valerie Bonham, JD, ORSC Deputy Director.
8. Review of Facilities: All sterile and non-sterile production facilities at NIH are undergoing an intensive review, involving a deep-dive inspection, consideration of current and future utilization, and development of remediation and monitoring plans. ORSC is responsible for coordinating monitoring of these facilities and related activities. A summary of some of the major facility remediation efforts is below:
 - a. The former PDS was remodeled to serve as the interim-Intravenous Admixture Unit (I-IVAU). The I-IVAU is scheduled to open in April 2017, at which time, construction will begin on a new IVAU.
 - b. A new facility for the Department of Transfusion Medicine will be operational in the second half of 2017, after which time, remodelling construction on the current facility will begin.
 - c. In spring 2017, consideration is underway to employ prefabricated modular components in an existing NIH building to expand the NCI Surgery Branch's cGMP capacity.
 - d. A total of four aseptic, state-of-the-art modules (i.e., trailers) are being purchased to provide supplemental space for sterile product and cell

processing. One trailer is now on-site, one is being constructed, and the other two are being designed.

9. **Audit of Clinical Protocols:** In response to the recent FDA inspections, NIH initiated a self-audit of clinical protocols from all ICs conducting clinical research to assess compliance with reporting requirements for IRBs and FDA. This review confirmed that the issues with late reporting identified by the FDA inspection of the NCI were not isolated. At the same time, the NIH Director reached out directly to IC Directors, Clinical and Scientific Directors, IRB chairs, and principal investigators to underscore these regulatory requirements and the critical importance of timely reporting of serious adverse events and unanticipated problems. Retraining for all investigators and research staff was undertaken to ensure full awareness and compliance with event reporting requirements. Through the central ORSC, NIH also undertook a root cause analysis consultation to identify possible systemic challenges to prompt reporting and is initiating a formal audit this spring to assess compliance across a sample of studies and identify additional improvement strategies. This recent identification of NIH-wide late reporting concerns reinforces NIH's decision to implement a rigorous centralized system to enhance patient safety and oversight across all of the IC research activities in and outside of the NIH CC.

All of the steps outlined above are designed to make NIH's unique hospital and research program even more outstanding. We, at NIH, recognize that establishing a culture of quality, compliance, and accountability is a continuous process. In addition, NIH is working to ensure that the implementation of changes at the CC is carried out in a way that enlists the support of the whole staff, not as a "top down" imposition. NIH is fully committed to focusing on quality and safety as an integral part of all activities at the CC and across the IC research programs, and it is striving to meet and exceed all standards and accreditations. We appreciate your continued support in this effort to enhance our Nation's research hospital.

Clinical Trial Stewardship

The recent GAO report (GAO–16–304) provides recommendations to enhance stewardship of the clinical trials across NIH with additional data. The Committee requests an update in the fiscal year 2018 budget request on the steps taken, planned, and timeline to complete the establishment of the process to collect, analyze, and review the data needed to enhance stewardship of NIH clinical trials as recommended in the GAO report.

Action taken or to be taken

NIH has completed a number of important steps in our multi-pronged program to enhance the quality, relevance, feasibility, efficiency, and transparency of NIH funded clinical trials through stewardship reforms.⁴⁶ These include:

- Issued a policy requiring all applications for NIH funding for the conduct of a clinical trial to be submitted in response to a clinical trial specific funding opportunity announcement (FOA) and to contain specific information about proposed trials and other information necessary for peer review and IC funding decisions. Clinical trial-specific FOAs will also include review criteria that focus on the rationale, design, and operational and analysis plans. Terms and conditions specific to clinical trial research will be incorporated into Notices of Award to notify awardees of their responsibilities, including timely sharing of research results. See <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-147.html>.
- Developed standardized language to be used with all clinical trial FOAs that Institutes and Centers (ICs) develop. The standard language contains the elements necessary to ensure that applicants submit the essential information needed to evaluate the application’s merit and feasibility. This is also the information that will be captured by the new electronic clinical trial management and oversight system (see below).
- Published the Final Rule on Clinical Trials Registration and Results Information Submission (42 CFR Part 11). The final rule furthers the implementation of section 402(j) of the Public Health Service Act. Requires public and private sector sponsors to register and submit results information to ClinicalTrials.gov for applicable clinical trials (phase 2 and above trials of FDA-regulated drug products and trials of FDA-regulated device products, except small feasibility studies of devices). Increases transparency clinical trial results which, among other benefits, will strengthen the design of future clinical trials. See <https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission>.
- Issued the NIH Policy on Dissemination of NIH-Funded Clinical Trial Information which establishes complementary registration and results information submission expectation for all NIH-funded clinical trials (includes all FDA-regulated product trials regardless of phase or stage and trials of non-FDA regulated interventions, e.g., behavioral strategies. Increases transparency clinical trial results which, among other benefits, will strengthen

⁴⁶ These steps are summarized in Hudson KL, Lauer MS, Collins, FS. Toward a New Era of Trust and Transparency in Clinical Trials. *JAMA*. 2016;316(13):1353-1354.

the design of future clinical trials. See <https://www.federalregister.gov/documents/2016/09/21/2016-22379/nih-policy-on-the-dissemination-of-nih-funded-clinical-trial-information>.

- Completed the identification of specific data elements for the new electronic clinical trial management and oversight system. NIH designed the system to increase accountability, support strategic planning and priority setting, and facilitate portfolio analysis and reporting.

NIH has also made significant progress in the design of the new electronic clinical trial management and oversight system to enhance and standardize clinical trial monitoring across the agency and within the individual Institutes and Centers. The new system will include a basic core set of elements for oversight and monitoring of clinical trials such as clinical trial milestones, enrollment, data and safety monitoring, fiscal resource utilization. It will be designed to be integrated with ClinicalTrials.gov standardized definitions to allow for interoperability and leverage information captured in IC systems, when feasible. It will also minimize burdens for applicants, investigators, and NIH staff in terms of acquiring, loading, and updating information. NIH anticipates that the system will be fully operational, i.e., be capable of collecting, storing, and retrieving data on clinical trials funded through extramural grants, contracts, and the intramural program, by FY 2019.

Cohort Studies

The Committee is aware of novel efforts underway to recruit individuals from racially and ethnically diverse backgrounds for participation in the PMI Cohort Program. Information from the cohort will be a broad, powerful resource for researchers working on a variety of important health questions. The Committee applauds NIH's efforts to partner with HRSA to begin partnerships with several Federally Qualified Health Centers to develop, pilot, and refine approaches for bringing underserved individuals, families, and communities into the PMI Cohort Program. The Committee believes that the NIMHD can and should help support these efforts to ensure participation of racially and ethnically diverse individuals.

Action taken or to be taken

The *All of Us* Research Program, formerly the PMI Cohort Program, is grateful for the Committee's support and for its appreciation that achieving diversity is central to the promise of the Cohort and its ability to ensure that the benefits of precision medicine are available to all Americans – especially those historically underrepresented in biomedical research. To that end, the Program implementation is heavily focused on reflecting the diversity of America in all its richness: racial and ethnic identity, health status, sexual orientation, age, geographic region, decisional capacity, socioeconomic status, etc. NIH issued funding opportunities announcements to build partnerships with health care provider organizations (HPOs) – including regional medical centers (RMCs) and Federally Qualified Health Centers (FQHCs) – which have focused intensively on the capacity of these entities to engage, enroll, and retain diverse participants across the continental United States (see RFA-PM-16-002⁴⁷ and OT-PM-16-003⁴⁸). Likewise, the Program's approach to Direct Volunteers enrollment ensures that anyone across the United States can volunteer to be part of the program and includes special attention to ways to reach those not reached by HPOs and those who live with marginal access to traditional health care, such as through mobile outreach.

The *All of Us* Research Program has benefitted greatly from the advice and engagement of NIMHD leadership and its deeply committed staff through the planning and implementation of the Program. NIMHD will continue to support outreach efforts to help ensure participation of minority, rural and economically disadvantaged populations. The NIMHD has already begun the process of reaching out to its stakeholder community in support of the Program, as manifest in its website expressing Why NIMHD Supports the PMI Cohort Program,⁴⁹ and will continue to work with the Program's communications and outreach program to share messaging and engagement opportunities across a variety of communication modalities.

⁴⁷ <http://grants.nih.gov/grants/guide/rfa-files/RFA-PM-16-002.html>

⁴⁸ <https://www.nih.gov/sites/default/files/research-training/initiatives/pmi/20160728-hpo.pdf>

⁴⁹ <http://www.nimhd.nih.gov/programs/collab/pmi/>

Colorectal Cancer

The Committee encourages support of meritorious scientific research on colorectal cancer to better understand the biology of young-onset colorectal cancer. The Committee encourages additional research on the developmental pathway of colorectal cancer among patients with inflammatory bowel diseases.

Colorectal Cancer and Inflammatory Bowel Diseases

The Committee recognizes that left untreated, inflammatory bowel diseases can advance to colorectal cancer. The Committee encourages additional research on the developmental pathway of colorectal cancer among patients with IBD.

Action taken or to be taken

While overall colorectal cancer (CRC) incidence and death rates continue to decline, survival rates for young CRC patients have seen only incremental changes, and the number of new cases of CRC among these age groups continues to rise.⁵⁰ CRC in the adolescent and young adult population tends to be detected later, is more aggressive, and is typically less responsive to standard treatments. Inflammatory bowel diseases (IBDs) like ulcerative colitis or Crohn's disease affect 1.6 million Americans and increase the risk of developing CRC.

Preliminary results have identified several genes that are mutated at much higher frequency in adolescent and young adult patient's tumors compared to those in adults with CRC.

Investigators are currently working to validate the significance of these mutations. In addition, complementary efforts are underway through the NCI Specialized Programs of Research Excellence, where NCI supported a pilot project on the genomic features of young onset CRC.

Recognizing the knowledge gaps about CRC in adolescents and young adults, the NCI works with the LIVESTRONG Young Adult Alliance to identify research opportunities and recommendations for improving cancer care and outcomes. In 2016, the NCI and LIVESTRONG Foundation sponsored a workshop, *Next Steps in Adolescent and Young Adult Oncology*, where participants identified the need for basic biologic, genomic, and model development for adolescent and young adult cancers as well as translation research studies to elucidate any fundamental differences between pediatric, adolescent and young adult, and adult cancers. Also in 2016, the NCI participated in the *8th Biennial Cancer Survivorship Research Conference* where key stakeholders learned about current and emerging pediatric, adolescent, and young adult cancer survivorship innovations. NCI continues to drive basic and translational research to investigate the potential biological basis of age-related differences in outcome for adolescent and young adult cancers.

Additionally, the NCI's Cancer and Inflammation Program (CIP) constitutes a major immunologic component of the Center for Cancer Research's (CCR) inflammation and cancer initiative that connects NCI's expertise in inflammation and immunology with its cancer etiology and carcinogenesis program. Recent studies are shedding new light on how innate and adaptive immunity are integral parts of inflammation and participate in oncogenesis and tumor surveillance. With innate immune response, the body depends on physical barriers like the skin

⁵⁰ Bailey CE, Hu C, You YN, Bednarski BK, Rodriguez-Bigas MA, Skibber JM, Cantor SB, Chang GJ. Increasing Disparities in the Age-Related Incidences of Colon and Rectal Cancers in the United States, 1975-2010. *JAMA Surg.* 2015;150(1):17-22.

or mucosal linings of the GI and respiratory tracts as a first line of defense, while adaptive immune response is acquired in which T- and B-Lymphocyte cells remember past foreign invaders and fight them off effectively. Although IBD-associated CRC accounts for only one to two percent of all cases of CRC, IBD with colon involvement is among the top three high-risk conditions for CRC.⁵¹

Genetic mutations also lead to CRC in young people and is being studied by the NCI to discern any mutation differences between genomes of colon cancers in adolescent and young adult patients compared to those found in adults. NCI-supported investigators are using DNA sequencing methods to analyze the tumor genomes from these two groups of patients and then identify differences between them. The latter is a collaborative effort among scientists at NCI's CCR and Frederick National Laboratory for Cancer Research and two NCI-designated comprehensive cancer centers, the Mayo Clinic and the St. Jude Children's Hospital.

The NCI will continue to support research to better understand and enhance surveillance and treatment for cancer in youth and adolescents, as well as examine the role IBD plays in the development of CRC.

⁵¹ Karanikas, Michail, and Agis Esebidis. "Increasing Incidence of Colon Cancer in Patients <50 Years Old: A New Entity?" *Annals of Translational Medicine* 4.9 (2016): 164. *PMC*. Web. 3 Jan. 2017.

Combating Antibiotic Resistant Bacteria (CARB)

With the identification of the first case of CRE in the United States last month, the Committee remains deeply concerned by the threat posed by the rise of antibiotic resistant bacteria. The Committee continues to strongly support NIAID's work related to CARB and includes approximately \$463,000,000, an increase of \$50,000,000, for NIAID to expand efforts to develop new antibiotics and rapid diagnostic tests, and build a national genome sequence database on all reported resistant human infections. Critical to the success of these efforts is developing a comprehensive understanding of the biological mechanisms that cause or contribute to antibiotic resistance, both in terms of resistance due to human activity or by inherent natural processes. This fundamental knowledge will enhance efforts to responsibly steward existing antibiotics, develop new antibiotics, and repurpose current antibiotics in new ways or combinations. The Committee encourages NIH and FDA to convene industry and other stakeholders to develop strategies to augment and enhance the infrastructure supporting clinical trials of new antibiotics. The Committee also encourages NIH to continue and expand its collaboration with USDA and CDC to develop a research strategy to promote a fundamental understanding of antibiotic resistance and improving the responsible use of antibiotics in agriculture. The Committee requests an update on these activities in the fiscal year 2018 CJ.

Action taken or to be taken

NIAID is a key implementer of the Administration's National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB). NIAID is currently working with CDC, FDA, and other NIH partners to enable the creation of the National Database of Resistant Pathogens, a repository for genomic data on drug-resistant pathogens. These data will inform research about the underlying mechanisms of resistance as well as help advance the development of diagnostics, therapeutics, and vaccines for antibiotic-resistant pathogens. In addition, NIH has partnered with the Biomedical Advance Research Development Authority (BARDA) to launch the Antimicrobial Resistance Diagnostic Challenge. This prize competition aims to develop rapid, point-of-care diagnostic tests to detect drug-resistant bacteria and identify effective treatments for patients.

NIAID is pursuing research to enhance fundamental understanding of antibiotic resistance along with partners in academia, industry, and the Federal government, including USDA, CDC, and FDA. NIAID scientists and collaborators recently identified a critical step in the ability of the immune system to control carbapenem-resistant *Klebsiella pneumoniae* infection. The researchers suggest that this aspect of the immune response could be targeted as a potential immunotherapy-based treatment for this resistant pathogen. NIAID also supports research to understand bacterial mechanisms contributing to antibiotic resistance, such as bacterial cell wall synthesis, beta-lactamase-mediated resistance, and proteomics and structural genomics of drug-resistant bacteria. In addition, NIAID has funded research that investigates the sources of resistance genes in humans, including those in food-producing animals. NIAID has participated in a USDA stakeholder webinar and convened a roundtable to bring together experts and Federal partners to gather input on strategies, including systems biology approaches, to advance research to combat antibiotic resistance. These partnerships will be critical to advance research strategies to develop a fundamental understanding of antibiotic resistance and inform the responsible use of antibiotics.

NIAID also is making research investments to develop new antibiotics and repurpose existing antibiotics to address the challenge of drug resistance. NIAID is exploring novel uses for off-patent antibiotics to treat community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA). Promising approaches and therapeutic targets for drug-resistant microbes can be further explored via NIAID's suite of preclinical and clinical support services. These resources are made available to the antimicrobial resistance research community to foster product development by academic and industry researchers. NIAID also is collaborating with BARDA on the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), an innovative global public-private partnership to advance promising antibacterial products from preclinical development into clinical testing.

NIAID works with international partners to promote collaboration and share best practices for clinical trials related to antimicrobial resistance. In 2016, NIAID co-sponsored meetings with European stakeholders, BARDA, and FDA to discuss strategies to address antibiotic resistance and explore barriers to conducting clinical trials of antibacterial drugs. Recently, together with FDA and BARDA colleagues, NIAID participated in a workshop organized by European counterparts to continue discussions about a clinical trial network for new antibacterial agents.

NIAID remains committed to advancing basic, translational, and clinical research to develop new antibacterial treatments and diagnostics. As part of this effort, NIAID will continue to collaborate with national and international partners, conduct cutting-edge research, and support the antimicrobial resistance research community.

Congenital Heart Disease [CHD]

The Committee commends the NHLBI for its continued work to better understand causation and appropriate treatment needs 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. The Committee urges NHLBI to continue its work with other Federal agencies and professional and patient organizations to expand collaborative research initiatives and other related activities targeted toward prevention and treatment of the diverse lifelong needs of children and adults living with CHD.

Action taken or to be taken

The National Heart, Lung, and Blood Institute (NHLBI) continues to support the Bench to Bassinet Program, comprised of the Pediatric Cardiac Genomics Consortium (PCGC), the Cardiovascular Development Consortium (CvDC), and the Pediatric Heart Network (PHN), to identify genetic and epigenetic causes of congenital heart disease (CHD) and perform clinical research in adults and children with CHD. Using state-of-the-art genomics approaches, PCGC and CvDC researchers are working to increase knowledge about the role of genetics in disease development and outcomes across the lifespan and to facilitate the use of genetic information as an additional tool to personalize treatment. Investigators in the PHN conduct research studies that inform clinical care for CHD and work to improve health outcomes in adults and children with CHD.

The PCGC has recruited more than 10,000 patients with CHD, resulting in the largest collection of genetic and clinical information about individuals with CHD to date. PCGC investigators previously identified a new molecular pathway that potentially links CHD and neurodevelopmental abnormalities, uncovering new causal genes implicated in CHD. In addition, PCGC investigators have found that many of the genes involved in CHD have effects in early development in both the heart and the brain, suggesting that a single mutation can lead to both CHD and abnormal brain development.

In conjunction with the PCGC, CvDC scientists have studied heart tissue from children with CHD to determine how these disorders affect patterns of gene activity in the heart. This is a critical step in discovering not just which genes have caused the heart disease, but how mutations in those genes turn on or off other genes necessary for normal development of the heart. Working with the PCGC, CvDC investigators are also studying the stem cells that form cardiac tissue in children with CHD to learn more about how CHD alters the development of the heart muscle cells.

The PHN continues to gather data on individuals with complex single ventricle heart disease across their lifespan, following them from birth to age eleven in one study, and from ages six to 25 in a group of other studies. These studies provide valuable information about the ongoing morbidities and complications in this patient population and identify opportunities to improve care. The PHN and PCGC investigators are collaborating to link clinical information with analysis of genetic information to understand patient outcomes over time. Working closely with advocacy organizations, the PHN recently launched a study to test whether treatment with the medication Udenafil can improve exercise performance in adolescents with single ventricle heart disease and ultimately delay the development of heart failure.

Collaborating with the Centers for Disease Control and Prevention (CDC) and the National Institute of Neurological Disorders and Stroke (NINDS), in 2015 NHLBI launched a surveillance system and registry for sudden cardiac death, sudden death in epilepsy, and sudden infant death in children up to 18 years of age in 10 states/jurisdictions in the United States. In April 2016, the NHLBI funded three teams of investigators to work together to use data and DNA from the registry to explore the causes and characteristics of sudden cardiac death in the young.

NHLBI will continue to expand collaborative research initiatives to improve prevention and treatment of the diverse lifelong needs of children and adults living with CHD.

Concussive and Subconcussive (Traumatic Brain Injury)

The Committee encourages NINDS to work with the private sector to explore the use of tools to monitor head impacts and help diagnose, treat and prevent concussions in youth sports. In particular, the Committee encourages NINDS to consider meritorious research related to head impact sensor technology, including biomechanical, which may assist diagnosis.

Action taken or to be taken

Head impacts in youth sports raise concerns because of the large numbers of children who participate in youth sports and the vulnerability of the developing brain. Good science is crucial to properly balance concerns about harm against the known benefits of sports participation. Although the NIH supports extensive research on concussions, including research on the long term consequences of head impacts in professional athletes, and the NCAA and DoD are also supporting related research on college athletes, much less is known about the effects of concussive and subconcussive blows on the developing brain in children. A recent publication using helmet monitors and sophisticated brain imaging found detectable changes in the brain over a single season of youth football, reinforcing the importance of research to clarify the risks.

In October 2016, NIH held a two-day scientific workshop that brought together experts in traumatic brain injury (TBI) research and other disciplines to discuss priorities for further research on the consequences of concussion and repetitive sub-concussive head impact in children. These basic and clinical scientists discussed current knowledge, the limitations of existing monitors and assessment tools, and studies that are now underway. Decades of NIH supported research have begun to build a foundation for the development of tools that can monitor head impacts and help diagnose, treat, and prevent concussions in youth sports. The National Institute of Neurological Disorders and Stroke (NINDS), for example, currently funds a study to monitor head impacts and clinical data in youth (6 to 14 year old) football players. However, there are crucial gaps in knowledge that must be. NIH research has shown, for example, that the relationship between physical impact and brain injury is far from simple, that repetitive sub-concussive blows may be as damaging in the long run as concussions, and that individuals differ in susceptibility to the same physical forces.

To fill in the knowledge gaps, ongoing NIH research is investigating the biomechanics of head injury, computer models to better describe how impact affects the brain, the physiological responses to concussion and resulting exercise intolerance, high time resolution ultrasound assessment of the relationship of head acceleration to brain injury, and the effects of soccer heading, among many other topics. In addition to providing the necessary knowledge base, NIH directly supports private sector development of tools through SBIR and other programs. Recent projects include sideline diagnostics, bicycle helmets that reduce rotational acceleration, and low cost head impact alert systems for sports. The workshop participants are preparing a white paper that will inform and guide future NIH investment.

Consumer Assessment of Healthcare Providers and Systems (CAHPS)

The Committee notes that CAHPS surveys are important tools for patients to make more informed decisions about their medical care and for providers and insurers to inform quality improvement initiatives and incentives. Patient experience data in maternity care is currently not regularly and systematically collected. Therefore, the Committee urges AHRQ to expand its current set of surveys and develop a CAHPS survey for maternity care.

Action Taken or to be Taken

AHRQ appreciates the Committee's support of the CAHPS survey. It is important to note that some patient experience of maternity care (i.e., inpatient) is collected by CMS through the HCAHPS (Hospital CAHPS) survey, which identifies maternity, medical, and surgical services lines of care. AHRQ agrees that maternity care is an important issue. If funding were available, the program could pursue initial steps for the development of resources to optimally assess patient experience in maternity care. This might include, for example, a supplemental item set for use with the Clinician and Group CAHPS survey for outpatient care. An advantage of this approach is that the questions focused on maternity care could be appended to an existing survey and administered to patients receiving maternity care. Please note, due to potential overlap with other HHS programs the CAHPS survey is proposed for elimination in NIRSQ's FY 2018 President's Budget to help focus resources on the highest priority research and reorganize federal activities in a more effective manner.

Duplicative Activity

The Committee notes that over time other HHS agencies have expanded into AHRQ's mission area. Therefore, AHRQ's mission and areas of research are duplicated in other HHS agencies. For example, NIH estimates that in fiscal year 2017 it will spend almost \$1,500,000,000 on health services research, about five times AHRQ's total budget request. CDC, like AHRQ, conducts Prevention Research and Care Management activities. The Office of National Coordinator for Health Information Technology (ONC) and CMS are both supporting Health IT activity. The Committee directs the Secretary to work with all other HHS OpDivs to determine where they have activities that overlap with AHRQ in an effort to consolidate, reduce duplication, and reduce overlap of mission areas across the OpDivs. The review should include a plan to streamline all OpDiv mission focus areas to improve the effectiveness, consolidate operations, and reduce duplicative and related overhead costs to taxpayers.

Action Taken or to be Taken

HHS supports the Committee's concern to consolidate, reduce duplication, and reduce overlap of mission among HHS OpDivs. To help focus resources on the highest priority research and reorganize federal activities in a more effective manner, the FY 2018 Budget consolidates AHRQ into NIH as the as the National Institute for Research on Safety and Quality. This new Institute will lead a review of coordination of health services research at NIH. AHRQ and its successor agency in NIH also lead the federal government's work to improve patient safety and prevent medical errors. Additionally, AHRQ and its successor agency coordinate federal efforts to generate evidence to make health care safer, higher quality, and more accessible, equitable and affordable, and making sure that the evidence is understood and used. AHRQ develops the knowledge, tools, innovative delivery models and data monitoring approaches needed to support improvements in health care delivery and make sharing new health care findings possible. These tools also make it possible to learn if and how these improvements are working, and what changes need to be made to gain the most benefit to actually improve health care for patients.

AHRQ and its successor agency also plays an important, complementary role to the biomedical discovery activities at NIH. This important role is recognized in the proposal to consolidate AHRQ into NIH as the National Institute for Research on Safety and Quality in FY 2018 President's Budget. AHRQ invests in research on health care systems that supports the transfer of knowledge on the diagnosis, prevention, and cure of human diseases developed by NIH, other Federal agencies, and public- and private-sector organizations to the frontlines of care. Investments by AHRQ and its successor agency help ensure that NIH investments in medical science are translated into practical tools and knowledge that can be adopted by clinicians to benefit the American people. AHRQ synthesizes the findings from related studies on a clinical topic area to help clinicians, health systems, and policymakers to know what constitutes best practices. For example, AHRQ supported the development of evidence-based guidance issued by the National Institute on Alcohol Abuse and Alcoholism, the Substance Abuse and Mental Health Services Administration, and the Veterans Administration. AHRQ is conducting a systematic review of the role of pharmacotherapy in the treatment of alcohol use disorder. AHRQ is conducting a series of systematic evidence reviews in support of work at NHLBI to create national guidelines on asthma care.

AHRQ meets regularly with NIH and works together with NIH on dissemination and implementation efforts and holds an annual dissemination and implementation meeting together, along with others, every year. AHRQ's investments in training the next generation of health delivery system researchers (or health services researchers) compliments NIH's K-award programs which, alternatively, focus on developing basic science researchers. These coordination efforts will intensify and expand as a result of the consolidation into NIH.

AHRQ also works closely with other HHS Agency's and other government agencies, including CDC, CMS, and the Department of Veteran's affairs to ensure our work is complementary and not duplicative. Those particular Agencies also serve as ex-officio members to our AHRQ National Advisory Council (AHRQ). The NAC meets three times a year to discuss AHRQ's programs and provides advice to the Director of AHRQ and the Secretary HHS. AHRQ also participates in many work groups and meets regularly with other OpDivs to ensure complementary and not duplicative work.

As an example, AHRQ coordinates activities with NIH, CDC, CMS, and OASH in the development and implementation of the National Action Plans for Preventing HAIs and for preventing adverse drug events. We are working together with these Agencies on the HHS coordinating efforts for antibiotic stewardship, and participating on the Task Force for national effort on Combating Antibiotic-Resistant Bacteria (CARB).

Coordination of New Scientific Information

The mission of NIDCR is to improve the Nation's oral, dental and craniofacial health through research and research training. NIDCR accomplishes its mission by performing and supporting basic and clinical research; conducting and funding research training and career development programs to ensure that there is an adequate number of talented, well-prepared, and diverse investigators; and coordinating and assisting relevant research and research-related activities. The Committee expects the Institute to systematically coordinate through other HHS agencies to share new scientific information to ensure it reaches the community and providers through various other HHS outreach programs.

Action taken or to be taken

The National Institute of Dental and Craniofacial Research (NIDCR) recognizes that systematic coordination and dissemination of relevant research and research-related activities is an absolute necessity if we are to ensure that all populations benefit from the Nation's investments in scientific discoveries.

NIDCR collaborates with other HHS agencies to share research results with the community and providers. The Institute strongly supports the efforts of the United States Public Health Service (USPHS) Oral Health Coordinating Committee (OHCC), which promotes the oral health of the American public through coordination of policy efforts, research, and programmatic activities within USPHS, across Federal Agencies, and between public and private sectors. NIDCR played a key role in the development of the 2014-2016 OHCC Oral Health Strategic Framework, a roadmap that provides agency and community stakeholders with actionable goals and strategies to advance oral health. In FY 2016 NIDCR collaborated with members from several agencies in the broad dissemination of information about the Framework through a joint webinar. NIDCR-funded research is aligned with specific goals and strategies throughout the Framework. Notably, studies to help prevent disease and promote oral health, to eliminate disparities, and to increase the dissemination of oral health information and improve health literacy.

Another example of outreach to the oral health community and providers is the Interagency Pain Research Coordinating Committee (IPRCC), a Federal advisory committee created on behalf of HHS by the NIH to enhance pain research efforts and promote collaboration across the government, with the ultimate goals of advancing the fundamental understanding of pain and improving pain-related treatment approaches. The Committee is composed of both Federal members, including the NIDCR Director, and non-Federal members from the scientific and medical communities, members of the public, and stakeholder groups. In 2011, in recognition of the public health problem of pain in America, the Institute of Medicine, now the National Academy of Medicine, called for a coordinated national effort of public and private organizations to transform how the nation understands and approaches pain management and prevention. In response, HHS tasked the IPRCC with creating a National Pain Strategy (NPS) that recognizes access to safe and effective care for people suffering from pain as a public health priority. The NPS was released in the spring of 2016. The IPRCC is now in the process of developing a national pain research strategy, focused on prevention of acute and chronic pain, acute pain and acute pain management, the transition from acute to chronic pain, chronic pain and chronic pain management, and the cross-cutting theme of health disparities.

Cystic Fibrosis [CF]

The Committee encourages advancement of cell-based tools to advance new therapies to patients based on an individual's specific CF -causing mutation. These tools may be used to develop new personalized approaches to CF therapeutics, including new means to identify and characterize the efficacy of multi drug therapies that address the mutant CFTR protein, which is the underlying cause of CF in the majority of those with the disease. In particular, the Committee supports research into nonsense mutations for CF, which truncate the creation of CFTR protein in about 10 percent of the CF population and contribute to thousands of other genetic diseases. In addition, the Committee urges further research into live cell imaging modalities that are able to characterize mucus and monitor mucociliary clearance, the defense mechanisms at the heart of CF, and many other respiratory diseases. The Committee encourages funding for new technologies aimed at the genetic repair of cystic fibrosis. This includes technologies for gene editing, lung stem cell biology and nucleic acid delivery. Such technologies are critical for developing therapies to reach all CF patients, especially those with mutations that are not amenable to protein manipulation with CFTR modulating therapies.

Action taken or to be taken

The National Heart, Lung, and Blood Institute (NHLBI) continues to support a vigorous basic and clinical research program for cystic fibrosis (CF) that includes efforts toward understanding its fundamental pathobiology, improvement of animal models, earlier detection of lung abnormalities, development of novel therapeutic approaches, and translation into clinical practice. For example, one research project is developing real-time non-invasive imaging to examine the microanatomy of the airway surface and mechanisms of abnormal mucus clearance in CF. Another NHLBI-initiated program funds small businesses to develop and validate cell-based systems using cells from individual CF patients. These systems can be used to recapitulate the cellular effects of distinct CFTR mutations, and to screen potential new therapies. This initiative thus supports precision medicine and optimization of treatment based on each patient's unique CFTR gene mutations.

There are other ongoing research efforts toward approaches to repair or overcome CFTR gene mutations. Small molecule “corrector” and “potentiator” drugs that partially reverse the CF genetic defect or improve CFTR function, when used alone or in combination, have been shown to be effective in large clinical trials. Additionally, NHLBI has supported Phase 3 investigation of “production corrector” drugs such as Ataluren that might enable read-through of CFTR nonsense-mutations.

For the many individuals with CF who have rare CFTR mutations, corrective treatments through either gene replacement therapy or cell-based therapy are urgently needed. A lack of suitable gene delivery methods has impeded progress for both gene replacement therapy and genomic editing systems. However, NHLBI-funded studies in a CF mouse model have recently demonstrated that nanoparticles can be used to deliver triplex-forming peptide nucleic acids capable of repairing CFTR mutations in airway epithelium. Such nanoparticles might be used to deliver other *in vivo* gene editing technologies. Other future opportunities include administration of gene-modified cells or healthy stem cells to regenerate the airway epithelium.

Deadliest Cancers

While overall cancer incidence and death rates are declining, the Committee is concerned that there are a group of cancers, defined in statute as recalcitrant cancers, whose five-year survival rates remains below 50 percent. Estimates are that half of cancer deaths are caused by eight site-specific cancers that meet this definition: pancreatic, liver, ovarian, myeloma, brain, stomach, esophagus and lung. The Committee applauds the NCI for launching the Molecular Analysis for Therapy Choice (MATCH), a potentially ground-breaking trial that analyzes patients' tumors to determine whether they contain genetic abnormalities for which a targeted drug exists and assigns treatment based on the abnormality. The goal for MATCH is for at least 25 percent of the patients enrolled in the trial to have rare cancers. Given the growing toll recalcitrant cancers take on society, and the enormous potential MATCH offers for our Nation's deadliest cancers, the Committee strongly urges NCI to increase the set-aside goal and to broaden it to include recalcitrant cancers. (House)

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Action taken or to be taken

We now recognize that cancer is a collection of many diseases that no longer fit neatly into organ-specific categories, and cancer types might share common genetic features that could be susceptible to some targeted therapies that are already on the market for cancers in a different organ site. In other words, seemingly dissimilar cancer types may share a vulnerability for which a drug is already available.

NCI is supporting many new projects to expand on these analyses, including the Molecular Analysis for Therapy Choice (NCI-MATCH) study, a clinical trial based on genetic abnormalities of a patient's tumor, rather than on the organ site of the tumor. MATCH, part of the Precision Medicine Initiative's oncology efforts, is evaluating the effectiveness of treatment tumors by their genetic abnormalities, and is expected to provide new research ideas and opportunities for advances in all cancer types, including those with poor survival rates. Although most trials study cancers arising at a particular anatomic site, the MATCH trial changes this paradigm by emphasizing the molecular abnormality and by testing a large number of chemotherapeutic agents in virtually any tumor type in which appropriate abnormalities are identified. The most common cancers as defined for the purposes of this trial are those of the breast, colon, lung, and prostate. A goal for the MATCH study is for at least 25 percent of the total patients matched to a treatment arm of the trial to have rare cancers.

Rare cancers are those cancers other than the most common sites listed above, but can include cancers at sites in the body where cancer rarely occurs, such as the eye, ureter, and pituitary gland, as well as cancers that are classified as rare because the primary location of the tumor could not be determined at the time of diagnosis. As a point of clarification, the statutory definition of “recalcitrant cancers” encompasses cancers with a 5-year relative survival rate of less than 50 percent. All cancers that fall into this recalcitrant cancer-category-except for lung cancer-would also fall under the MATCH definition of “rare cancers” as noted above.

NCI and the ECOG-ACRIN Cancer Research Group (the National Clinical Trials Network group that is working in partnership with NCI to coordinate the MATCH trial) have completed initial analysis of 795 patients enrolled for screening as of November 2015. As noted, the goal of the trial was for 25 percent of patients matched to a treatment arm to have rare cancers. This goal was exceeded, with approximately 58 percent of patients who were assigned to a treatment arm having a rare cancer. Overall, more than 60 percent of tumor samples screened for mutations were rare cancers. Following the interim analysis, the MATCH study has been expanded from 3,000 to 6,000 patients, and from 10 to 24 treatment arms, with additional arms to be added in the near future. We anticipate a similar proportion of patients with rare cancers to enroll in the study going forward, and much to be learned about all cancer types through precision medicine studies like MATCH.

In the analysis of the first 1700 or so patients who had molecular profiling in NCI-MATCH, we continue to enroll about 60% rare cancers (defined as cancers other than those of lung, breast, prostate or colorectal). As of October, 2016, we were pleased that the following cancers were represented within NCI-MATCH screening: pancreatic (6%), liver/hepatobiliary (4%), ovarian (11%), myeloma (to be included soon), brain (1%), stomach, esophagus (gastroesophageal 3% and lung (10%).

Demographic Research - NIA

The Committee is greatly concerned by the health and financial threats that dementia-related disorders, including Alzheimer's disease, pose as the U.S. population ages. NIA is urged to respond by investing in the full spectrum of scientific research, including population research, to address the complex nature of dementia-related disorders and its devastating effects on patients, families, and caregivers. This effort should include sustained investment in large-scale longitudinal studies, such as the Health and Retirement Study. The Committee encourages NIA to support research and data collection on the causes of widening disparities in health and longevity at older ages, and the role of social factors, such as education and income, in the health and well-being of older people.

Action taken or to be taken

The National Institute on Aging (NIA) supports demographic, epidemiologic, and longitudinal studies to help understand trends, track incidence and prevalence, and identify potential risk and protective factors for Alzheimer's and related dementias.

For example, in September 2015, NIA funded a new extension to the Health and Retirement Study, a population-based study following over 20,000 Americans from age 50 until death, to assess dementia via a new harmonized cognitive assessment protocol in a subset of respondents over age 65. This methodology will allow an efficient estimation of dementia prevalence in the United States and allow us to investigate racial, ethnic, and gender disparities. This study will provide the first national estimates of dementia prevalence since 2002 and the first estimates of dementia prevalence in African Americans ever. The same protocol is being implemented in England, India, Mexico, and China, enabling cross-national studies of disease prevalence and future trends, as well as the potential identification of new risk and protective factors.

Also in 2015, NIA released a Funding Opportunity Announcement (FOA) soliciting projects to add new measures and collect new information about participants in existing cohorts, as well as epidemiologic research relevant to AD and cognitive resilience. Eighteen projects have been funded under this FOA to date, including a study of the genetic epidemiology of cerebrovascular factors in AD among members of a large, multi-ethnic cohort in New York; a study of the genetic epidemiology of early-onset disease among Caribbean Hispanics and non-Hispanic whites; and addition of cutting-edge brain imaging and combination of this data with existing genetic information to assess dementia risk and identify potential new biomarkers in the Framingham Heart Study.

NIA also supports research on the causes of widening disparities in health and longevity at older ages and the role of social factors in the health and well-being of older people. In support of this research, NIA has developed the NIA Health Disparities Research Framework to organize factors examined in health disparities research related to aging. The Framework highlights fundamental factors that determine priority populations for health disparities research and enumerates a range of factors that potentially influence health disparities, which will enhance our ability to delineate causal pathways and link environmental, sociocultural, behavioral, and biological factors to health and disease.

Other NIA-supported initiatives include a 2015 FOA on health disparities in AD; six projects have been funded exploring the effects of a variety of behavioral and social factors on cognitive health among diverse populations. Seven Resource Centers for Minority Aging Research support

and conduct a range of research on health disparities while supporting the development of researchers from traditionally underrepresented communities. Finally, the Healthy Aging in Neighborhoods of Diversity across the Lifespan (HANDLS) study within the NIA Intramural Research Program continues to examine the influences of race and socioeconomic status on the development of age-related health disparities among socioeconomically diverse African Americans and whites in Baltimore, Maryland.

Demographic 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- the scientific study of human populations-and reproductive health. The Committee urges NICHD to sustain this research by making a strong investment in its Population Dynamics Centers Research Infrastructure Program. Further, the Committee supports NICHD's efforts to make wise investments in large-scale longitudinal scientific surveys and prioritize data sharing as a condition of award. Making these survey data widely available efficiently promotes and supports broad-based scientific research activities on health and development.

Action taken or to be taken

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports a diverse portfolio in demographic research. Among many research projects funded over the last year, the NICHD recently awarded two grants involving continuation of large-scale, diverse, multi-generational studies that are collecting data on issues central to the lives of families. One is exploring family dynamics, fertility, and health disparities, while the other is collecting new information on the transition to adulthood, childhood health, and fertility-related behavior and pregnancy intentions. For example, a new analysis funded by the NICHD found that maternal mortality rates in the United States have increased substantially since 2000; this finding suggests the need to redouble efforts to prevent maternal deaths and improve maternity care. Training grants to encourage the next generation of researchers also is a top priority of the program in demographic research; a new investigator recently participated in a large prospective observational study, finding that oral contraceptive exposure around the time of pregnancy does not appear to be associated with an increased risk of major birth defects. The NICHD's investment in the Population Dynamics Centers Research Infrastructure Program remains a central feature of its overall program of research. The interdisciplinary nature of the centers allows for new ideas to be fostered, and for early stage investigators to benefit from exposure to experts in a range of disciplines. Re-competitions for center grants are staggered; in FY 2016, the NICHD funded a new round of grants to four of the twenty research centers, about \$2.5 million in total funding.

The NICHD continues its longstanding support of important longitudinal studies, such as the *Fragile Families and Child Wellbeing Study* and the *National Longitudinal Study of Adolescent to Adult Health (Add Health)*, both of which have been crucial in discovering the influence of early life factors on health across the life span. Earlier this year, for example, Add Health investigators showed that the more social ties people had at a young age, the better their physical health early and late in life. To maximize the value to the research community and the public of these irreplaceable data sets, the NICHD's Population Dynamics Branch has taken a leading role in ensuring that this information is widely disseminated. In FY 2016, the NICHD sponsored a new funding opportunity announcement to support archiving and documenting existing data sets in order to enable secondary analysis of these data by the scientific community. In addition, the Institute continues to support the *Demographic Data Sharing and Archiving* project, which maintains an extensive repository of NIH-supported datasets and widely disseminates them. The project investigators also advise and assist researchers by offering services for data archiving and documentation, particularly in the area of confidentiality and disclosure review, enhance further dissemination of data and documentation by developing innovative protocols and technologies

for data sharing, and promote secondary analysis of data by providing user support, access to data, training on analyzing complex data sets, and consultation.

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. The Committee recognizes the success of 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

Building on past National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-supported research, significant recent progress has been made toward prevention, treatment, and cure of diabetes. For example, in September 2016, the U.S. Food and Drug Administration (FDA) approved the first hybrid artificial pancreas (AP) device, which links glucose sensing and insulin delivery; early NIDDK funding contributed to the development of the approved device. NIDDK continues to support AP research, including phase 3 clinical trials testing novel AP devices, research to develop next-generation components of AP devices, and behavioral research to ensure that people could use and benefit from new devices. At the same time, research is also progressing toward curing diabetes. For example, the Clinical Islet Transplantation Consortium recently published results from a phase 3 clinical trial showing that islet transplantation is an effective treatment for people with type 1 diabetes who have had severe episodes of dangerously low blood sugar despite receiving expert care. Toward overcoming the shortage of cadaveric islets for transplant, researchers discovered how to generate large quantities of insulin-producing cells in the laboratory. The Human Islet Research Network (HIRN) built on this progress by encapsulating those cells to protect them from immune system attack after transplantation in a mouse model. HIRN research could potentially lead to a cure for type 1 diabetes. The NIDDK's Longitudinal Assessment of Bariatric Surgery-2 study recently showed that Roux-en-Y gastric bypass achieves a higher likelihood of type 2 diabetes remission in obese patients with the disease than does laparoscopic gastric banding, even when controlling for weight loss, providing clues as to the mechanism that may lead to improved treatment or even reverse the disease. Ongoing initiatives are vigorously exploring this possibility.

Although a safe, effective, well-tolerated first line drug for type 2 diabetes, metformin alone often proves insufficient to maintain long-term blood glucose control, and it is thus critical to determine what other available drugs can best help patients improve glucose control. Glycemia Reduction Approaches in Diabetes: An Effectiveness Study is comparing the long-term benefits and risks of four widely used type 2 diabetes drugs in combination with metformin. The Accelerating Medicines Partnership T2D Project has developed and is expanding a Knowledge Portal to leverage the dramatic NIH-led progress in type 2 diabetes genetics to identify and validate the most promising biological targets for new diagnostic and drug development.

In March 2016, the Centers for Medicare & Medicaid Services (CMS) Office of the Actuary certified that a lifestyle intervention adapted from one proven effective by the NIDDK-led Diabetes Prevention Program (DPP) saved an estimated \$2,650 per participating Medicare beneficiary over 15 months. The adapted version of the intervention was also developed and

tested with NIDDK research support. Based on the finding of cost saving, CMS determined that the lifestyle intervention will be a covered expense for eligible Medicare recipients starting in 2018, greatly expanding access to this preventive intervention. The DPP also found that the type 2 diabetes drug metformin was useful for preventing diabetes, particularly in younger adults and women with a history of gestational diabetes, and that use of this drug was cost-saving. Recent research, however, shows that metformin is much underutilized for type 2 diabetes prevention, possibly because it is not FDA-approved for this indication. The NIDDK is testing other low-cost approaches for type 2 diabetes prevention, such as vitamin D.

Diabetic Retinopathy Clinical Research Network

The Committee commends NEI for the collaborative efforts of the Diabetic Retinopathy Clinical Research Network. The Committee acknowledges the importance of clinical trial networks and hopes the NEI will maintain the Diabetic Retinopathy Clinical Research Network's commitment to facilitating clinical research on diabetic retinopathy. The Committee strongly encourages the NEI to build on the success of the Diabetic Retinopathy Clinical Research Network to expand and extend the scope of the network to include other retinal diseases.

Action taken or to be taken

The Diabetic Retinopathy Clinical Research Network facilitates multicenter clinical research of diabetic retinopathy, diabetic macular edema, and associated conditions. The Network was formed in 2002 and has participation from over 115 sites, approximately 2/3 of which are community-based practices, across 41 states. It is an open network (all retinal specialists are eligible to participate and propose new protocols) with almost 400 participating physicians. Protocols are reviewed at multiple levels within the network, before being implemented. The Network pursues clinical trials that complement each other in terms of patient eligibility and therapeutic approach, preventing competition between studies for similar patients and expanding the opportunities for patients to participate in these investigations. This infrastructure enables the network to initiate new clinical trials and recruit patients quickly.

In the January 2016 Council meeting, the National Eye Institute (NEI) endorsed a request from the Network to expand its scope beyond diabetic retinopathy. NEI has been working with the Network to implement this change such that it maintains its commitment to high quality, innovative research in the field of diabetic eye disease while also leveraging its infrastructure and experience to extend research to other retinal diseases including non-diabetic vascular disease, age-related macular degeneration, retinitis pigmentosa, retinal inflammatory conditions, and other retinal diseases. Research protocols exploring these other conditions are under development but have not yet been approved by the Network. Given this substantial expansion in scope, the Network Executive Committee created two vice-chair positions. One of the Network vice-chairs will be responsible for overseeing diabetic retinopathy initiatives and the other Network vice-chair will be responsible for overseeing studies for other, non-diabetic retinal conditions. The Network will still have one executive committee, one operations committee, one coordinating center, and one data and safety monitoring committee. The overall impact will enhance NEI's entire clinical retinal research program. The Network has been successful in establishing collaborations with relevant foundations and industry partners and could be expected to do so outside the field of diabetic retinopathy. NEI will continue to fund outstanding scientific opportunities both within and outside the Network.

Duchenne Muscular Dystrophy - Update

The Committee encourages the ICs to consider strategies that could lead to the development of combination therapies. The Committee requests an update on current and planned research across NIH for DMD and timeline for the next state-of-the-science in the fiscal year 2018 budget request.

Action taken or to be taken

Clinical care for muscular dystrophy patients is likely to involve combinations of drugs, biologics, and/or other treatments. Combination therapies may act in different ways on the same target, or may affect multiple targets or pathways. In most cases, prior to testing combination therapies in human clinical trials, single therapies (monotherapies) must first be developed and approved by the FDA. Preclinical studies to test combinations of candidate therapeutics may accelerate the process of selecting strong candidates to test combinations in clinical trials. Preclinical studies can help determine overlapping toxicities as well as the dose ratios, sequences, and timing that contribute to therapeutic effects. NIH funds research to develop animal and cell models that may be used in such research. For example, one study is working to establish the zebrafish DMD model for evaluating DMD drug combination therapies. The drugs that will be tested in this model are already in use in DMD patients or in clinical trials. NIH-funded research is also focused on developing DMD cell models, including DMD patient-derived induced pluripotent stem cells (iPSCs), as a tool for evaluating both mono- and combination drug therapies. In addition, a high-throughput drug screening program funded by NIH has already identified a compound that may have potential for enhancing exon skipping – a way to ‘skip over’ or bypass the faulty part of a gene – when used in combination with another genetic modifying approach.

Current NIH research activities in DMD include: basic research to understand muscle cell differentiation and muscle growth, damage, and repair; translational research to develop therapeutic strategies including exon skipping and gene therapy approaches; the identification of biomarkers, especially non-invasive biomarkers of DMD; and clinical research, including a trial to compare the benefits and side effects of different corticosteroid regimens in children with DMD. Several of these research activities are being carried out at the NIH-supported Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers.

The development of the *2015 Action Plan for the Muscular Dystrophies* included a review of the state-of-the science in the muscular dystrophies. Action Plan working groups examined progress made since the 2005 Plan in the mechanistic understanding of the muscular dystrophies, the development of therapeutic strategies, and improvements in clinical management and quality of life for individuals living with muscular dystrophy. The MDCC’s twice-yearly meetings serve as an ongoing forum to discuss recent research advances, improvements in patient care, access to care and services, and ways to facilitate opportunities in education and workforce integration for those with muscular dystrophy. The Committee regularly discusses progress toward the goals of the Action Plan, and collaborative opportunities to move the science forward. The next MDCC meeting will be held November 26, 2016. NIH also supports workshops and conferences where scientists discuss the state-of-the science in muscle disease, muscle cell biology, and other research topics relevant to the muscular dystrophies.

Drug Treatment in Justice System Settings

The Committee understands that providing evidence-based treatment for substance use disorders offers a strong alternative for interrupting the drug use/criminal justice cycle for offenders with drug problems. NIDA's Juvenile Justice Translational Research on Interventions for Adolescents in the Legal System [JJ-TRIALS] program identifies and tests strategies for improving the delivery of evidence-based substance abuse and HIV prevention and treatment services for justice-involved youth. The JJ-TRIALS initiative will provide insight into the process by which juvenile justice and other service settings can successfully adopt and adapt existing evidence-based programs and strategies to improve treatment for at-risk youth. The Committee requests an update on the JJ-TRIALS in the fiscal year 2018 CJ.

Action taken or to be taken

The National Institute on Drug Abuse's (NIDA) 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. In 2015, the cooperative fielded a national survey of over 200 juvenile justice agencies, juvenile court judges, and behavioral health agencies serving justice-involved youth which showed that over half of justice-involved youth present with substance use problems, but only 64% of agencies screen for these problems. The survey also identified several gaps in the behavioral health service delivery system that serve youth. Services such as residential treatment, detoxification, and medication assisted treatment are not available in more than a third of localities⁵². These and other survey findings are currently being summarized in several publications that will soon be reviewed for publication. In addition, a second wave of this survey will be fielded in 2017 to determine whether and how juvenile justice practices related to evidence-based substance use services changed nationally from 2015-2017.

In 2015, the cooperative also launched a randomized controlled trial (RCT) comparing two different data-driven implementation interventions aimed at improving the uptake of evidence-based substance use screening, assessment, and treatment services in 39 juvenile justice agencies across the country. In 2016, these 39 sites received training and technical assistance to facilitate the development of partnerships with local behavioral health providers across the continuum of care for youth substance use. All sites have established workgroups and set individualized goals for how to improve substance use services in their system. As of October 2017, more than 17,000 youth records have been collected from participating sites and are being analyzed to understand changes in substance use service referral and utilization patterns over time at these locations. Data collection for this study will be complete in late 2017. The RCT will provide insights into which strategies are most effective at helping juvenile justice organizations improve youth substance use service delivery.

In 2016, JJ-TRIALS also launched a third part of the study, which is examining partnerships between justice organizations and public health agencies to improve the delivery of HIV

⁵² Scott, C. K., Dennis, M. L., Funk, L., & Nicholson, L. (2016, October). *Preliminary Findings from the JJ-TRIALS National Survey on Behavioral Health Services for Youth Under Community Supervision*. Presented at the Addiction Health Services Research Conference.

screening and prevention services for justice-involved youth. Six sites participated in this smaller pilot study. While the larger RCT described above targeted a partnership model between juvenile justice agencies and behavioral health providers, this pilot study will help test the robustness of that partnership model and will provide insights into how to improve services that address screening and prevention for HIV and sexually transmitted infections in this population.

Dystonia

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Dystonia refers to a diverse group of disorders in which inappropriate muscle contractions cause abnormal, often repetitive, movements and postures. Dystonias can affect different parts of the body, emerge in children or adults, and appear alone or with other neurological problems. The cause may be inherited, acquired, or a combination of both. Not surprisingly, this heterogeneity often leads to delayed diagnosis and difficulties in treatment, but there has been progress. For more than 30 adolescent and childhood dystonias, disease-related treatments are now available. Although most of these treatable dystonias are rare and many dystonias are still poorly understood and treated, advanced genetic technologies are accelerating identification of gene defects that cause dystonia. Determining how these gene defects cause dystonia is a major thrust of research, and there is increasing recognition of disease mechanisms shared across different dystonias that are potential targets for therapy. For example, several different gene defects perturb the function of the neurotransmitter dopamine. All types of dystonia affect brain movement control circuits, and surgically implanted electrical stimulation (deep brain stimulation, or DBS) can rebalance altered circuits and improve symptoms for some people. In the long term, dystonias may benefit from the BRAIN (Brain Research through Advancing Innovative Neurotechnologies) Initiative which is transforming scientists' ability to determine how circuits of nerve cells in the brain work, and what goes wrong in diseases like dystonia.

NINDS leads dystonia research, and other parts of the NIH support research as appropriate to their expertise and mission. For example, NIDCD supports research on dystonias that affect voice, which seriously affect quality of life, and the Office of Rare Disease Research supports the Dystonia Coalition. The Coalition, which is part of the Rare Diseases Clinical Research Network, brings together several researchers and private dystonia groups to conduct natural history studies, provide a biorepository for biomarker development and gene identification, assess clinical monitoring tools, and encourage new investigators and collaborations. NIH is committed to reducing the burden of dystonia through research to better understand the disease and develop treatments.

Effective Healthcare Program

The Committee is aware of AHRQ's interest in expanding the areas of focus for the Horizon Scanning System. The Committee believes it is equally important for AHRQ to improve the utility of the system by streamlining the processes by which it collects information and improving the manner and timeliness that this information is made available to the public. Therefore, the Committee requests a report from AHRQ within 90 days of enactment regarding how it can better accomplish these objectives.

Action Taken or to be Taken

The Horizon Scanning System was a five year project that is now ended due to finite AHRQ resources. The project tracked new innovations in health care and flagged innovations with potential high impact for helping to improve patient outcomes. The project succeeded in tracking over 500 innovations at any given time and updating the information every two months. Health systems used the outputs of the horizon scanning system to predict issues for coverage of new technologies, establish and price health plans, contract with health care providers, and promote innovation. From this experience, we have the knowledge to streamline the processes for collecting the information and creating an online searchable database. AHRQ would welcome the opportunity to submit a plan to accomplish this should funding become available.

Environmental Influences on Child Health Outcomes Program/National Children's Study Alternative (ECHO)

The Committee continues its support of the ECHO program and the goal to understand the effects of environmental exposures on child health and development. Sufficient funding, level with fiscal year 2016, is provided to the OD to continue this program. In particular, the Committee notes its support for the IDeA States Pediatric Clinical Trials Network in ECHO which will leverage the infrastructure at existing IDeA State centers by embedding clinical trials experts at IDeA State locations. This structure will facilitate their partnership with other academic institutions and help address access gaps for rural and medically underserved children.

Action taken or to be taken

The vision of Environmental Influences on Child Health Outcome Program/National Children's Study Alternative (ECHO) is to become one of the nation's preeminent programs to study children's health. Through a series of FY 2016 funding opportunity announcements,* on September 21, 2016 NIH announced over \$157 million in awards to establish 35 Pediatric Cohort projects, a Coordinating Center, a Data Analysis Center, a Patient/Person Reported Outcomes Core, six Children's Health Exposure Analysis Resource projects, 17 IDeA States Pediatric Clinical Trials Network (ISPCTN) research sites, and the ISPCTN Data Coordination and Operating Center⁵³. In addition, NIH awarded \$7 million to maintain the National Children's Study data and biorepositories.

ECHO focuses on five key high impact pediatric outcomes: perinatal outcomes, airway disorders, obesity, neurodevelopment, and a cross-cutting outcome, positive child health. . By harmonizing the information gathered from existing cohort studies of mothers and children, ECHO will create a new, larger cohort—collectively > 50,000 children—that will enhance scientists' ability to answer critical public health questions about the impact of early life exposures on these four outcomes. ECHO will allow researchers to test new tools for environmental and pediatric monitoring, maximize the use of existing resources such as biological tissues collected during pregnancy and delivery, develop and apply sophisticated statistical models to predict development of high-impact health outcomes, and incorporate the voices of children and their families.

Rural and medically underserved children have been underrepresented in clinical trials. To help address this shortfall, ISPCTN will build state-of-the art pediatric clinical research networks in states with historically low rates of NIH funding, particularly to address the four ECHO key pediatric focus areas. The goals of the Network are to develop a pediatric clinical trial research infrastructure and build capacity at institutions in IDeA states; increase access to clinical trials for children who are unable to travel long distances to participate; and allow researchers to recruit a greater diversity of pediatric participants in a cost-effective manner. Coordination with ECHO Pediatric Cohorts will facilitate their research findings to inform the design and implementation of interventions.

⁵³ <https://www.nih.gov/news-events/news-releases/nih-awards-more-150-million-research-environmental-influences-child-health>

In FY 2016 and FY 2017, the ECHO pediatric cohorts will pilot collaborative research examining how a wide variety of chemical, social, behavioral, biological, and other early life (including maternal prenatal) exposures affect children's health outcomes. ECHO research teams will demonstrate the ability to collect standardized data across five Core Elements: demographics; typical early health and development; genetic influences; environmental factors; and parent/child-reported outcomes. In FY2018 ECHO cohorts that are successful in the 2-year pilot phase will transition to the 5-year phase of longitudinal data collection and sophisticated analyses of influences of early life exposures on child health outcomes, thus informing strategies to improve American children's health.

ECHO Program Director, Dr. Matthew Gillman, has extensive expertise in clinical epidemiology and managing large cohorts and clinical trials. He and outside investigators from the Coordinating Center and Data Analytics Center form the ECHO Leadership Triad, to oversee development of multi-cohort research objectives, protocols for standard core data element collection, and data analyses. As members of the Steering Committee, awardees from all ECHO components will prioritize collaborative research objectives. An External Scientific Board, composed of 7-8 outside experts in epidemiology, toxicology, pediatrics, genetics, and maternal and child health, will advise ECHO leadership on strategic objectives.

Enhanced Reporting on Research Spending

The Committee appreciates the initial steps taken by NIH to make public on an annual basis, enhanced Research, Condition, and Disease Categorization spending data with the number of Americans affected by each category of disease according to CDC or other Federally sourced data. The Committee requests an update on the plan to maintain and provide data for the remaining categories, where such data exists, in the fiscal year 2018 budget request.

Action taken or to be taken

As described in its strategic plan, NIH balances scientific merit, public health needs, research opportunities, portfolio balance, and budgetary constraints when setting its priorities to support biomedical and behavioral research.⁵⁴ Burden of disease can help assess public health needs as measured by prevalence, incidence, mortality, morbidity, extent of disability, and financial cost. NIH believes that examining multiple sources of disease burden data and measures allows for a better understanding of public health needs.

In 2016, NIH enhanced its reporting of research support with the addition of federally sourced health statistics on the NIH RePORT website.⁵⁵ NIH collaborated with the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention to obtain federally-sourced data on the prevalence and mortality of many of the diseases and conditions for which NIH reports Research, Condition, and Disease Categorization (RCDC) spending data. In consultation with NCHS, NIH posted 2014 data from the National Health Interview Study as a measure of prevalence, and 2014 data from the National Vital Statistics System as a measure of mortality. It is important to note, however, that there are diseases for which federally-sourced data do not exist, especially rare diseases, and that even with close consultation with NCHS experts on an annual basis, it is unlikely that appropriately matched CDC data will be available for every RCDC disease category. In addition, many RCDC categories are research-related (e.g., genetics), rather than disease-related and would not be appropriate to match with disease burden metrics measures. With these caveats, NIH plans to update the posted data on an annual basis, using the procedure described below.

In 2017, NIH will prepare a list of the current RCDC spending categories that report on diseases, and indicate which categories currently have no posted prevalence or mortality data. This will include both new categories, as well as categories for which NCHS has not yet identified a suitable data source. Using this list, NIH will consult with NCHS to determine whether data may have become available which could be appropriately matched to any of the remaining categories. NIH will also work with NCHS to identify any data sources that have been updated to include more recent years to ensure that all data are as current as possible.

In addition, NIH will consult with NCHS to evaluate whether the data sources chosen in 2016 are still the most appropriate for understanding the NIH portfolio. If other data sources are available that might provide data for a larger number of RCDC categories, or if existing data sources have altered their breadth or methodology, NIH and NCHS will work together to determine whether NIH should report data from different sources.

⁵⁴ <https://www.nih.gov/about-nih/nih-wide-strategic-plan>

⁵⁵ https://report.nih.gov/categorical_spending.aspx

NIH believes that the procedure described above will best leverage the respective expertise of NIH and NCHS to identify the most appropriate, rigorous, and comparable data sources for reporting information on diseases and conditions included on the NIH RePORT web site.

Environmental Exposures - Update

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Different cell types have distinctive patterns of chemical compounds in addition to their DNA sequence that regulate gene expression. When these chemical compounds attach to DNA, they are referred to as epigenetic regulatory marks. DNA methylation, or the addition of a methyl group to a DNA molecule, can turn a gene on or off. Histone modifications affect the way in which DNA is condensed within a cell and helps direct proteins to regions of DNA that should be used or ignored within that cell. These epigenetic modifications are changes that affect gene function without changing the underlying DNA. Exposure to toxins in the environment can lead to changes in these normal epigenetic patterns that have been associated with the development of environmentally-induced disease. One of the challenges in making direct connections between exposure-induced epigenetic changes and health outcomes in human populations is that it is not always easy to obtain the tissues directly involved in disease pathogenesis (e.g., brain, breast, liver). Researchers are relying increasingly on analyses of 'surrogate' tissues, such as those found in peripheral blood or skin cells that have been indirectly implicated in disease pathogenesis, to gain insight into epigenetic changes. However, more research is needed to establish under which exposures and conditions and in which tissues epigenetic changes associated with the development of disease occur, and are conserved in surrogate tissues.

In 2012, NIEHS established the multi-phased Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription (TaRGET) Program⁵⁶ to further address the role of the environment in disease susceptibility as a function of changes to the epigenome. The first phase of this program, TaRGET I, funded applications that support research objectives aimed at understanding the environmental control of epigenetic mechanisms. These grants consider the impact of environmental toxicants on the following processes: nucleosome positioning, chromatin accessibility, chromatin remodeling, and the role of non-coding RNAs.

In 2016, the second phase of this program, TaRGET II⁵⁷, awarded six cooperative agreements, consisting of five production awards and one Data Coordination Center, to form a consortium to study the conservation of exposure-induced epigenetic perturbations between surrogate and disease-relevant target tissues. The purpose of this program is to characterize the epigenetic changes that are caused by environmental exposures in a variety of tissues and cell types, to investigate the factors that influence whether induced changes are conserved across tissues, and to assess the utility of surrogate cell types for epigenetic analyses in environmental health research.

Early life represents a key window of susceptibility to environmental exposures and is important for development-associated disease. Using mouse models of environmentally relevant diseases, the consortium is currently evaluating the impacts of developmental exposure, specifically exposures occurring from 2 weeks prior to conception and throughout gestation and lactation, at

⁵⁶ <https://www.niehs.nih.gov/research/supported/health/envepi/target/index.cfm>

⁵⁷ <http://targetepigenomics.org>

environmentally-relevant doses. The exposures currently being addressed encompass a broad range of factors, including air pollution, endocrine disrupting chemicals, chemicals involved in weight gain, and metals such as lead and arsenic. Target tissues being assessed include liver, brain, heart, lung, and uterus, and surrogate tissues include blood and skin cells. Epigenomic signatures will be assessed across the life course of animals and include time points at 3 weeks of age (weaning signature, potentially reflecting the short-term effects of developmental exposure), 5 months of age (adult signature, potentially reflecting the lasting effects of developmental exposure) and 12 months of age (aged signature, potentially reflecting the disease state).

The data generated will serve as a resource for the scientific community to enhance understanding of exposure-related disease mechanisms. This research will also lay the groundwork to see if epigenetic changes in surrogate tissues (such as blood and skin cells) can serve as biomarkers of exposure-associated disease processes. Ultimately, the TaRGET II program will provide insights into the design and interpretation of human studies where target tissues are inaccessible.

Epidermolysis Bullosa (EB)

The Committee recognizes the promising scientific gains made in pursuit of treatments for EB and applauds the private partners working to advance research towards practical treatments for EB. Further research in this area holds great promise in terms of treatments for EB and for other skin and connective-tissue disorders. The Committee encourages NIH continue to support such research through expert-led scientific conference awards through NIAMS and NCATS. The Committee further encourages NIH to leverage Federal funds with public-private partnerships in the areas of EB and related disorders.

Action taken or to be taken

Epidermolysis bullosa (EB) is a group of blistering skin conditions. The skin is so fragile in people with EB that even minor rubbing may cause blistering. NIAMS supports a broad spectrum of research to identify gene mutations that cause EB, determine the molecular effects of those mutations, and correct or replace the mutated genes and proteins with functional ones. NIAMS also funds research on healthy skin to gain insights into how EB mutations perturb skin development and function. These efforts have yielded a number of exciting advances. Individuals with the most severe form of EB, recessive dystrophic epidermolysis bullosa (RDEB), have a high risk of developing a form of skin cancer called squamous cell carcinoma that occurs in the wounds of these patients and is often fatal. NIAMS-funded researchers succeeded in healing wounds in a mouse model of RDEB by administering a collagen protein that is missing or deficient in patients with the disease. Other scientists, supported by the NIAMS in collaboration with private organizations and state governments, demonstrated the feasibility of creating so-called induced pluripotent stem (iPS) cells using cells taken from EB patients' own skin. The scientists were then able to correct the disease-causing mutation in the iPS cells and use them to generate skin tissue. When grafted onto mice, the iPS cell-derived tissue formed structurally normal skin. In a phase I clinical study, funded by NIAMS, the Epidermolysis Bullosa Medical Research Foundation, and the Epidermolysis Bullosa Research Partnership, researchers used gene therapy to introduce a functional form of the mutated collagen gene into skin biopsies from RDEB patients. In this small study, skin grafts produced using the corrected cells improved healing when applied to patients' wounds without serious side effects. Based on the results, the researchers have initiated a Phase IIa study. This work represents a promising step towards the goal of a safe and effective therapy for EB and related disorders.

In November 2014, the NIAMS convened a meeting to discuss opportunities and challenges for creating new 3-dimensional models of human tissues. EB was one of the promising research areas discussed. The meeting included academic researchers and subject matter experts from NIAMS, NHLBI, NIBIB, NIDCR, and NCATS, as well as a representative from industry and a participant from the Jackson Gabriel Silver Foundation/EB Research Partnership. The meeting informed the development of an FY 2016 NIAMS Funding Opportunity Announcement titled Building Complex 3-Dimensional in Vitro Human Musculoskeletal and Skin Tissue Models. The new initiative encourages grant applications from small businesses to develop 3-dimensional models that could serve as an alternative to animal models of diseases, enable the study of human tissue physiology and disease pathophysiology in vitro, and ultimately lead to better therapies. For skin diseases such as EB, the initiative could foster the development of more efficient protocols for the creation of skin grafts from patient-specific cells.

The NIAMS also supports scientific conference and meeting grants relevant to EB. In FY 2016, NIAMS provided support for the 2016 Pediatric Dermatology Research Alliance Annual

Conference. The meeting brought together experts in pediatric dermatology to discuss planned studies, hear updates on ongoing research, and share best practices. One session included a presentation on mechanism-based clinical trials in EB. NIAMS also provided support for the 2017 Collagen Gordon Research Conference, which will take place on July 16-21, 2017. The meeting will explore the diverse functions of collagens, which are mutated in some forms of EB, in development and tissue repair. One session will focus on the role of and therapies for collagen dysfunction in inherited and common diseases. The NIAMS and NCATS will continue to support meritorious conference grant applications focused on research within their missions, such as EB research.

Evaluation of the Basic Behavioral and Social Science Opportunity Network

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned:

Action taken or to be taken

The NIH Basic Behavioral and Social Science Opportunity Network (OppNet), initiated in fiscal year 2009, has as its mission to, “pursue opportunities for strengthening basic behavioral and social science research (b-BSSR) at the NIH while innovating beyond existing investments.”

Pursuant to that mission, OppNet has three specific goals:

- Advance basic behavioral and social science research through activities and initiatives that build a body of knowledge about the nature of behavior and social systems.
- Prioritize activities and initiatives that focus on basic mechanisms of behavior and social processes and build upon existing NIH investments without replicating them.
- Expand the b-BSSR portfolio by opening opportunities to investigators who had not applied previously to NIH for b-BSSR funding or had applied previously but were unsuccessful or minimally successful.

In 2013, the Office of Behavioral and Social Sciences Research (OBSSR) led a mid-course progress review of OppNet program data. The results of this review suggested that OppNet had expanded opportunities and brought new researchers into the NIH fold and also solicited unique b-BSSR projects that span the missions of multiple ICs. However, once the program completed a full funding cycle in 2014, OBSSR initiated a formal evaluation of the OppNet program to determine the impact of five years of OppNet funding on the composition of NIH-funded socio-behavioral researchers, the agency’s overall basic socio-behavioral research portfolio, and the broader NIH environment. To conduct the evaluation, OBSSR established a contract with the Institute for Defense Analysis’ Science and Technology Policy Institute (STPI). Specifically, in collaboration with OBSSR, STPI developed and implemented a formative and a summative evaluation of the OppNet program. The formative evaluation (process evaluation) will address three primary study questions: (1) what are OppNet’s program goals and how have they evolved, (2) did OppNet’s policies, procedures, and operations meet the initiative’s goals, and (3) how did participation in OppNet influence NIH Institute and Centers (ICs) and program directors? For the summative evaluation (outcome evaluation), the study will address the following three study questions: (1) to what extent did the OppNet portfolio advance innovative research beyond existing investments, (2) to what extent did OppNet-related training projects innovate beyond existing investments, and (3) how have OppNet grantees fared in productivity, “graduated” mentees or students, receipt of additional NIH or other agency/organizational research grants?

At present, these projects are ongoing. Preliminary results have been presented to the OppNet Evaluation Advisory Committee. Further, on September 1, 2016, STPI provided a detailed briefing on these projects to the NIH’s OppNet Steering Committee. At this point, STPI is in the process of drafting the two reports (Process and Outcome Evaluations). OBSSR expects to receive the final reports on June 30, 2017.

Evidence Based Intervention

The Committee encourages consideration of research that may result in evidence-based intervention on proven theory and tested methodologies to reduce alcohol use and abuse in adolescent students in high school.

Action taken or to be taken

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) considers the development of evidence-based interventions to prevent and reduce alcohol use among adolescents a high priority. Alcohol is the substance of choice among U.S. adolescents, and is associated with a range of negative consequences in youth. These include potential adverse effects on normal brain development and cognitive functioning, as well as risky sexual behavior, physical and sexual assaults, injuries, alcohol use disorder (AUD), blackouts, alcohol overdose, and even death. NIAAA supports a broad research portfolio to elucidate the factors that contribute to underage drinking and to develop evidence-based strategies to detect, prevent, and reduce underage alcohol use in a variety of settings. NIAAA also supports basic and clinical research to identify the effects of alcohol use on the developing adolescent brain, which could pave the way for new prevention and treatment strategies for addressing underage alcohol use. This research includes two important longitudinal studies, the National Consortium on Alcohol and Neurodevelopment in Adolescence and the Adolescent Brain Cognitive Development study, which seek to understand how alcohol and other drugs influence normal brain development and cognitive functioning in adolescents.

Alcohol screening and brief intervention by health care providers is effective in detecting and reducing problem drinking in adults, and a growing body of evidence supports its use with adolescents. To encourage universal screening for youth in health care and other settings, NIAAA developed a very brief, empirically based alcohol screener and guide to help primary care providers identify 9 to 18-year-olds who are at risk for alcohol use, are using alcohol, or have AUD, and intervene as appropriate. Although the tool was developed primarily for use in primary care settings, it may also be useful in other settings. NIAAA has supported six studies (five studies are ongoing) to evaluate the guide's effectiveness in healthcare, academic, and juvenile justice settings. A recently published study showed that NIAAA's youth screening tool is highly efficient for detecting alcohol use among youth with chronic medical conditions. A separate study recently demonstrated its utility in identifying AUD among youth seen in rural primary care practices.

In addition to supporting research, NIAAA collaborates with other NIH institutes as well as a range of other organizations in its efforts to prevent and reduce underage drinking. Collaborative activities include National Drug & Alcohol Facts Week, an annual event co-hosted by NIAAA and the National Institute on Drug Abuse that provides a forum for teenagers to ask scientific experts questions about alcohol and other drug use. NIAAA is a key member of the Interagency Coordinating Committee on the Prevention of Underage Drinking (ICCPUD) established by Congress to coordinate federal efforts towards preventing and reducing underage drinking. NIAAA also partners with various community organizations that focus on preventing and reducing adolescent alcohol use, including the Community Anti-Drug Coalitions of America and the Community of Concern, a national network of parent-school partnerships that strives to increase awareness of the harmful effects of alcohol and other drug use among students.

Evidence Based Programs to Prevent Obesity

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports multiple avenues of research to develop and test intervention approaches to prevent obesity. Studies of interventions across the lifespan include children and adults from diverse populations, including racial/ethnic groups and economically disadvantaged populations disproportionately affected by obesity. For example, because risk for obesity can begin in childhood and during pregnancy, the Lifestyle Interventions for Expectant Moms consortium, supported by NIDDK and other NIH components, has been conducting clinical trials of interventions to improve weight and metabolic outcomes for overweight and obese pregnant women and their children. NIDDK also supports studies testing strategies in the home and childcare settings to promote healthy eating and physical activity in very young children. One study, for example, recently reported promising results of a parenting strategy to reduce infants' risk of becoming overweight by age 1. Other ongoing studies are testing interventions for obesity prevention and health promotion in military personnel and adolescent military dependents. NIDDK and other NIH components also support studies to evaluate efforts implemented by policy makers or others that could affect physical activity or diet, such as new light rail lines and venues for buying healthier foods in communities, to identify potential benefits or unintended consequences; this research can provide an evidence base for future efforts to reduce or prevent obesity. Other studies aim to prevent further weight gain in those already overweight or obese. NIDDK also supports basic, clinical, and translational research to identify factors associated with risk for obesity, which could lead to new prevention strategies. For example, some studies have found that the gut microbiome (microbes in the gut) differs between lean and obese individuals; ongoing research in humans and mice may lead to new approaches to modulate the microbiome to prevent obesity.

The National Heart, Lung, and Blood Institute (NHLBI) continues to support the Childhood Obesity Prevention and Treatment Research Program, which has enabled some of the first long-term obesity prevention and treatment research trials in children. Two randomized clinical trials are underway to test methods to prevent obesity in young people, and two others are testing methods to reduce weight in obese youth. Other NIH components also contribute to this program, which began in 2010 and will be completed in 2017. Results are expected soon from the Healthy Communities Study: How Communities Shape Children's Health (HCS). This observational study was conducted between 2010 and 2016, and was supported by NHLBI and other NIH components. The HCS evaluated existing community efforts to reduce local childhood obesity rates in 130 demographically diverse communities. Investigators examined how effective such efforts were in changing diet and physical activity and in reducing body weight.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) actively supports a wide range of research aimed at reducing pediatric obesity. One current grant is developing and evaluating a family-based behavioral intervention designed to address the unique needs of overweight or obese Hispanic children and their parents. Because physical activity plays a key role in health and childhood obesity prevention, a randomized

controlled NICHD-supported study is evaluating the impact of school-based physical activity programs on moderate-to-vigorous physical activity, cognitive performance, and academic achievement in underserved schoolchildren. In addition to these programs focusing on the pediatric population, a NICHD-supported study recently showed that proper maternal folate (an essential B vitamin) levels during pregnancy may protect children from a future risk of obesity, especially those born to obese mothers

Expansion of Research on Opioid Alternatives

The Committee remains concerned about the growing epidemic of opioid overdoses. The widespread availability of opioid painkillers has contributed to the millions of Americans who suffer from addiction disorders. 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 for treating pain, both acute and chronic. The Committee strongly encourages NIDA to expand scientific activities related to research on medications used to treat and reduce chronic pain. In doing this, NIDA should coordinate with CDC, HHS, VA, FDA, DOD, DEA, 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 acute and chronic pain. In addition, NIDA should continue 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.

Action taken or to be taken

While there are many strategies currently being utilized to address the opioid crisis – including requiring use of prescription drug monitoring programs, improving access to evidence-based treatments for opioid use disorders, improving prescriber education, and expanding access to the overdose reversal drug naloxone – there remains a pressing need to develop safer and more effective treatments for pain while ensuring careful use of opioids when medically necessary.

The National Institute on Drug Abuse (NIDA) worked with the CDC to develop its *Guideline for Prescribing Opioids for Chronic Pain*⁵⁸, published in March of 2016, which provides evidence-based recommendations for opioid prescribing. NIDA also contributes to the Interagency Pain Research Coordinating Committee, which fosters collaboration between NIH, AHRQ, CDC, CMS, DoD, FDA, SAMHSA, and VA as well as a number of HHS staff divisions, including the Office of the Secretary (OS), the Office of the Assistant Secretary for Financial Resources (ASFR), the Office of the Assistant Secretary for Planning and Evaluation (ASPE), and the Office of the Assistant Secretary for Health (OASH). Also in March of 2016, this committee published the National Pain Strategy⁵⁹, the government's first coordinated plan to reduce the burden of chronic pain; this strategy focuses on safer opioid use and research to better optimize pain care.

NIH supports a significant research portfolio to foster the development of better pain therapies. 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 drugs that minimize diversion and misuse (e.g., by preventing tampering) and reduce the risk of overdose deaths. Two recent publications of NIDA-funded research in high-profile journals detail recent progress made in the discovery of opioid analgesics with reduced abuse liability.^{60,61}

⁵⁸ <http://www.cdc.gov/drugoverdose/prescribing/guideline.html>

⁵⁹ https://iprcc.nih.gov/docs/HHSNational_Pain_Strategy.pdf

⁶⁰ Manglik A, Lin H, Aryal DK, et al. Structure-based discovery of opioid analgesics with reduced side effects. *Nature*. 2016;537(7619):185-190. doi:10.1038/nature19112.

⁶¹ Ding H, Czoty PW, Kiguchi N, et al. A novel orvinol analog, BU08028, as a safe opioid analgesic without abuse liability in primates. *Proc Natl Acad Sci*. August 2016;201605295. doi:10.1073/pnas.1605295113.

- *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.

Fibrotic Diseases

The Committee encourages NIH to continue to vigorously support research into fibrotic diseases affecting different organs, including the lung, liver, kidney, heart, and skin, and to ensure enhanced coordination between its Institutes as they conduct necessary, expanded single organ or cross-organ fibrotic disease research to save lives and reduce healthcare expenses in future budget years. Furthermore, the Committee encourages NIH to explore the creation of a trans-NIH fibrotic disease working group, which would bring 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 2018 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

The National Heart, Lung, and Blood Institute (NHLBI) is supporting lung fibrosis research with many new activities that are based on recommendations from the 2012 workshop, “Strategic Planning for Idiopathic Pulmonary Fibrosis.” For example, NHLBI issued a cross-cutting initiative along with the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute on Aging (NIA) called “Collaborative Projects to Accelerate Research in Organ Fibrosis (R01),” which encourages collaborations among researchers studying fibrosis in different organ systems. Three projects were funded through this initiative in Fiscal Year 2016, and will combine studies of lung, heart, liver, and kidney. These diverse collaborations are expected to generate insights that will drive future research directions into common fibrosis pathways across organs. This initiative will accept applications again in Fiscal Year 2017.

Additional trans-NIH collaborations are underway. In particular, NHLBI has begun discussions with the National Center for Advancing Translational Sciences (NCATS) and the National Human Genome Research Institute (NHGRI) concerning (1) a trans-NIH coordinating committee and (2) participation in an NIH Fibrosis Scientific Interest Group to determine the most productive way to jointly make advances in fibrotic disease research. Recognizing the need for improved animal models, the NHLBI convened a workshop in 2016 entitled “Animal Models of Lung Transplant Research,” which enabled discussion of the opportunities to improve translational studies in lung fibrosis. NHLBI also contributed support to the 2016 ASPEN Lung Conference on Lung Transplantation: “Opportunities for Repair and Regeneration.” Reports and research recommendations from these meetings will identify critical gaps and emerging opportunities for research on idiopathic pulmonary fibrosis (IPF).

NHLBI is also addressing the need for rigorously characterized patients and samples. For example, the NHLBI Pulmonary Trials Cooperative will support a new clinical trial called the Study of Clinical Efficacy of Antimicrobial Therapy Strategy Using Pragmatic Design in Idiopathic Pulmonary Fibrosis (CleanUP-IPF). As part of the trial, the investigators will collect patient DNA and cell samples for genetic and molecular biological studies. They will examine how the body’s resident population of microorganisms (the microbiome) affect disease progression and responsiveness to determine whether there is a role for antibiotics as a treatment for IPF. In addition to these activities, NHLBI is funding investigator-initiated grants that will explore the molecular changes in lung cells that cause them to become fibrotic; seek genetic factors in the disease through studies of familial IPF; and complete early studies of novel therapies for IPF.

Focal Segmental Glomerulosclerosis (FSGS)

The Committee understands the *APOL1* gene plays a role in the onset of FSGS and subsequent end stage renal disease in African Americans. The Committee encourages NIMHD to explore collaboration on high quality peer reviewed research with NIDDK.

Action taken or to be taken

Recognizing that glomerular diseases, including focal segmental glomerulosclerosis (FSGS), can lead to end stage renal disease, and that African Americans are at greater risk for progressing to kidney failure from glomerular disease, the NIH supports multiple research efforts on these conditions.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a range of research to understand the causes of FSGS and to develop and improve treatments. NIDDK and the National Center for Advancing Translational Sciences' (NCATS) 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 the Rare Diseases Clinical Research Network. NEPTUNE is a multi-site, multidisciplinary collaborative research and education network designed to foster innovative approaches to the understanding of glomerular diseases, including FSGS.

The National Institute on Minority Health and Health Disparities (NIMHD) funds projects that address health disparities by investigating the causes of disease progression. For example, one NIMHD-funded grant investigates the effect of race and ethnicity-specific genetic risk factors on the prevalence of immune-mediated glomerular disorders. A second NIMHD-funded grant focuses on increasing the understanding of two specific genetic variants of the *ApoL1* gene, present only in individuals with recent African ancestry. This variant may partially explain racial disparities in kidney failure, affecting as many as 3.5 million African Americans who possess one of the two genetic variants.

NIMHD, as well as the National Institute of Allergy and Infectious Diseases (NIAID), are collaborating with NIDDK, to plan a new effort to advance research on the effects of *APOL1* genetic variants on kidney transplant donors and recipients. The cohort will include patients with FSGS.

Fragile X Research

The Committee encourages the ICs 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 NIH for its previous work to create and update the NIH Research Plan on Fragile X Syndrome and Associated Disorders, last updated in 2012, and encourages NICHD to reconvene this group before the end of fiscal year 2017 to update and publish a revised research plan.

Action taken or to be taken

The NIH continues its longstanding support for research on the molecular, physiological, biological and genetic aspects of Fragile X syndrome (FXS) and its connections to autism spectrum disorder (ASD). Working in collaboration with the National Institute of Mental Health (NIMH) and the National Institute of Neurological Disorders and Stroke (NINDS), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) employs multiple strategies to support this work, including funding three multi-site Centers for Collaborative Research in Fragile X, supporting a major biannual research conference on Fragile X and ASD, and awarding grants on a broad array of topics related to FXS and ASD research. These grants, made to academic institutions across the country, range from basic genetic studies, to studies in animal models of FXS, to clinical trials targeting language outcomes.

Among these research efforts are projects directed at validating outcome measures and identifying biomarkers for Fragile X and autism. Without such research tools, scientists have difficulty comparing results across studies, impeding development of effective treatments. The NICHD, NIMH, and NINDS, as well as the Foundation for the NIH (FNIH), are supporting a multicenter study whose primary goal is to develop and validate biomarkers that can be used in clinical trials for individuals with Fragile X and other ASDs. The NICHD and NIMH together published a funding solicitation for the development of outcome measures for individuals with intellectual and developmental disabilities, and NICHD recently funded a project aimed at developing memory measures for clinical trials in Down syndrome and FXS. Another study, funded by NIMH, is designed to examine the early emergence of autism and features FXS and the FX premutation (FXpm) in female carriers. The full disorder is most commonly seen in males, because they only have one copy of the X chromosome. However, the premutation in females may lead to subtle effects on health and development that may provide insight into the natural history of FXS in males with the full mutation. The goal of this new project is to understand biological pathways and timing of symptom emergence to identify patterns of risk across FXS, FXpm, and ASD; clarify the developmental emergence of autism features in FXS; and increase understanding of the natural history of emerging autism features in FX-associated disorders.

The NIMH, along with NICHD, the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute of Environmental Health Sciences (NIEHS), and NINDS, currently supports three funding opportunity announcements that encourage research on the shared neurobiology of ASD and FXS. These studies examine the developmental and functional processes, pathways, and brain mechanisms that may lead to an understanding of shared causes or biological processes associated with ASD and FXS, and identification of specific clinical endpoints to measure improvements in response to treatment interventions. The

NINDS also funds basic research to understand the mechanisms underlying deficits in neuronal development, cell signaling, and synaptic plasticity that contribute to cognitive and behavioral impairment in FXS, and whether those mechanisms also contribute to ASD. An exploratory study is testing whether and how stem cell therapy improves learning in a mouse model of FXS, which could inform therapeutic options. A large, newly funded clinical trial will evaluate whether a drug candidate can improve developmental functioning.

The Trans-NIH Working Group on Fragile X Syndrome, chaired by the NICHD, continues to meet to maximize synergy of efforts across NIH in support of FXS research, and to ensure coordination with research programs on ASDs. Among the activities planned by this group in the coming year is an effort to evaluate progress on the current NIH Research Plan on Fragile X Syndrome and Associated Disorders, review the research portfolio and remaining gaps, and begin working across NIH and with stakeholder groups on updating the plan.

Gabriella Miller Kids First Research Act - Update

The Committee encourages NIH to prioritize research relating to childhood cancer within the Kids First program and requests an update in the fiscal year 2018 budget request on the 10-year program, planned activities, and on-going research.

Action taken or to be taken

The NIH Common Fund's Gabriella Miller Kids First Research program (Kids First)⁶² aims to catalyze pediatric research by making large amounts of high-quality genetic and clinical data from pediatric patient cohorts widely available and easy to use for scientists and clinicians. The Kids First data resource will integrate data from patients with childhood cancer or structural birth defects, conditions which have profound, lifelong effects on patients and their families. 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. Having these data sets together in a single, widely accessible resource is anticipated to facilitate new discoveries and novel ways of thinking about these conditions. Importantly, the Kids First data resource will aggregate Kids First-generated data together with many additional existing data sets, thus increasing researchers' ability to detect rare genetic changes that contribute to these conditions.

In FYs 2015 and 2016, Kids First provided support to DNA sequencing centers based on their expertise and available sequencing capacity. In addition, Kids First solicited applications from researchers with pediatric patient cohorts for childhood cancer or structural birth defects.⁶³ Successful applicants do not receive funds, but do gain access to the sequencing capabilities of the NIH-supported centers, and the genome sequence data and associated clinical data will form the basis for the Kids First data resource. The first cohorts to be sequenced were announced in October 2015, and data from these cohorts are anticipated to be available to the research community on a rolling basis, starting in early to mid-2017.⁶⁴ These cohorts address conditions such as Ewing sarcoma (cancer of the bone or soft tissue), bone cancers that were resistant to drug treatment, congenital heart defects, and cleft lip/palate. Additional cohorts are expected to be announced in fall 2016. Selection criteria included, but were not limited to, the robustness of the cohort, evidence for a genetic component, potential to provide new information and address important questions, and significance to human health and/or understanding of biology.

Childhood cancer cohorts include sequencing four samples per patient (DNA of the patient, the tumor, and the parents), while structural birth defects cohorts include three samples per patient (DNA of the patient and parents). Additionally, the cancer samples require more robust sequencing. We anticipate that approximately half of the Kids First support will be used to sequence childhood cancer samples and half will be used to sequence birth defects samples. Having both types of data together in one resource is expected to be synergistic, providing novel insights into both conditions that would not be appreciated if these conditions were examined independently.

⁶² <https://commonfund.nih.gov/KidsFirst>

⁶³ <http://grants.nih.gov/grants/guide/pa-files/PAR-15-259.html> and <http://grants.nih.gov/grants/guide/pa-files/PAR-16-150.html>

⁶⁴ <https://commonfund.nih.gov/kidsfirst/fundedresearch>

In future years, pending availability of funds, the Kids First program plans to support sequencing of additional pediatric cohorts, build the Kids First data resource and make data widely available, support analyses of data provided through the Kids First data resource, and support development of new computational tools to help researchers access and interpret large-scale data sets.

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 the fiscal year 2016 funding for the Gabriella Miller Kids First Research Act, 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 at the end of fiscal year 2016. This report should also describe the criteria and process for grant awards the NIH intends to use for fiscal year 2017 and subsequent years of funding under the act.

Action taken or to be taken

The NIH Common Fund's Gabriella Miller Kids First Research program (Kids First)⁶⁵ aims to catalyze pediatric research by making large amounts of high-quality genetic and clinical data from pediatric patient cohorts widely available and easy to use for scientists and clinicians. The Kids First data resource will integrate data from patients with childhood cancer or structural birth defects, conditions which have profound, lifelong effects on patients and their families. 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. Having these data sets together in a single, widely accessible resource is anticipated to facilitate new discoveries and novel ways of thinking about these conditions. Importantly, the Kids First data resource will aggregate Kids First-generated data together with many additional existing data sets, thus increasing researchers' ability to detect rare genetic changes that contribute to these conditions.

Consistent with the requirements of the Gabriella Miller Kids First Research Act, all funds have been disbursed as grants to support pediatric research. In FYs 2015 and 2016, Kids First provided \$12.6 million each year (the total amount of the Kids First program) to DNA sequencing centers. In FY 2015, the Kids First-supported sequencing centers were at Baylor College of Medicine and Washington University, each center receiving a \$6.3 million award for the year. In FY 2016, the Kids First-supported sequencing centers were at Broad Institute and Hudson-Alpha Institute for Biotechnology, each center receiving a \$6.3 million award for the year. The criteria for selection of these sequencing centers was their expertise and available sequencing capacity. To jump-start the Kids First program rapidly in FY 2015, the sequencing centers were selected from among institutions currently funded by NIH to conduct large-scale genomic sequencing. FY 2016 centers were selected by peer review by experts in the field of genomic sequencing in an open competition. In addition, Kids First solicited applications from researchers with childhood cancer or structural birth defects patient cohorts.⁶⁶ 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. The first cohorts to be sequenced were announced in October 2015, and data from these cohorts are anticipated to be available to the research community on a rolling basis, starting in early to mid-2017.⁶⁷ These cohorts address conditions such as Ewing sarcoma (cancer of the bone or soft tissue), bone cancers that were

⁶⁵ <https://commonfund.nih.gov/KidsFirst>

⁶⁶ <http://grants.nih.gov/grants/guide/pa-files/PAR-15-259.html> and <http://grants.nih.gov/grants/guide/pa-files/PAR-16-150.html>

⁶⁷ <https://commonfund.nih.gov/kidsfirst/fundedresearch>

resistant to drug treatment, congenital heart defects, and cleft lip/palate. Additional cohorts are expected to be announced in fall 2016. Selection criteria included, but were not limited to, the robustness of the cohort, evidence for a genetic component, potential to provide new information and address important questions, and significance to human health and/or understanding of biology. These cohorts were selected by peer review involving external experts in pediatric research. Collectively, rigorous scientific criteria, peer review by experts, and robust discussions between NIH, pediatric researchers, and patient advocates ensures that the program initiatives and awards will advance pediatric research and the objectives of the Kids First Act.

In FY 2017 and beyond, pending availability of funds, the Kids First program plans to support sequencing of additional pediatric cohorts, build the Kids First 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 to identify meritorious applications with the highest potential to accelerate 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 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 pediatric research that can best be addressed by the Kids First program.

Because all appropriated Kids First funds were used to support the sequencing centers, no appropriated Kids First funds were used to support personnel overseeing allocation of designated research dollars. All Research Management Support (RMS) for the Kids First program came from the NIH Common Fund. This totaled \$528,419 in FY 2016, of which \$396,900 was used for personnel support. The remaining funds supported peer review activities and meetings with scientific experts. 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.

Genomic Research and Alcohol Dependence - Update

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

The National Institute of Alcohol Abuse and Alcoholism (NIAAA) is encouraged by the Committee's interest in the genomics of alcohol use disorder (AUD). Evidence from family, adoption, and twin studies demonstrates that genetic factors account for about half an individual's risk for developing AUD. Like many chronic health conditions, AUD risk is influenced by a complex interplay between multiple genetic and environmental factors, which differ among individuals and contribute to the heterogeneity of AUD. Elucidating the genetic factors that influence AUD risk and the mechanisms through which these factors exert their effects could improve strategies for diagnosing, preventing, and treating the disease.

Thus far, the genes most strongly implicated in AUD and best characterized include those that encode enzymes involved in alcohol metabolism. These genetic factors typically protect against AUD. Other gene variants involved in AUD or alcohol misuse include those associated with impulsivity as well as deficits in reward, stress responses, and cognitive functioning, and the activity of the neurotransmitters associated with them.

Over the past several decades, NIAAA has supported a number of large initiatives to identify genetic variants that influence risk for AUD. For example, in 1989, NIAAA launched the Collaborative Studies on the Genetics of Alcoholism (COGA), a prospective study of more than 2,200 extended families (over 17,700 individuals) in which many members have AUD. This study has yielded an unprecedented amount of information about the genetic determinants of AUD and alcohol-related phenotypes. A current focus of COGA is to understand how genetic risk for alcohol misuse and AUD changes across adolescence and young adulthood, and why some individuals develop alcohol problems while others do not. NIAAA also supports a robust intramural research program that uses cutting-edge genomic technologies, and basic and clinical approaches, to elucidate the genetic factors that confer risk for AUD and the pathways through which genetic, environmental, and neurobiological factors interact to influence vulnerability. This program has made seminal contributions in identifying genetic variants that predict vulnerability to AUD and co-occurring problems, and in understanding the contributions of gene-environment interactions in conferring risk for AUD in American Indian and other diverse populations.

The next generation of research in the genetics of AUD will be facilitated by recent advances in genomic technologies, and large-scale data collection and analysis techniques. For example, NIAAA has established a DNA repository of samples collected as part of its most recent National Epidemiologic Survey of Alcohol Related Conditions, a national survey of more than 36,000 individuals, ages 18 and older that will facilitate future research. Collection and analysis of genetic data are also standard components of NIAAA-sponsored clinical trials and treatment studies, and have been incorporated into two longitudinal studies of adolescent brain development, NIAAA's National Consortium on Alcohol and Neurodevelopment in Adolescence and the NIH Adolescent Brain Cognitive Development Study. In addition, NIAAA is pursuing

efforts to combine data from existing genetics datasets, and utilize appropriate metrics of alcohol misuse and related phenotypes across AUD genetic studies. The goal of these efforts is to increase the statistical power of AUD genetic analyses, thereby enhancing our ability to identify additional common and rare AUD genetic variants.

Gestational Diabetes

The Committee recognizes the importance of research funded by the NIDDK 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 NIDDK 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) is exploring new and emerging opportunities to support research on gestational diabetes, as well as supporting ongoing efforts that could provide important new insights in this area. For example, planning is under way for a 2017 workshop with experts in the field to define the most critical questions in treatment of gestational diabetes and to discuss potential clinical trial designs. The workshop is expected to lay the groundwork for potential new research. In ongoing studies, the LIFE-Moms (Lifestyle Interventions for Expectant Moms) consortium, spearheaded by the NIDDK with co-funding from the National Heart, Lung, and Blood Institute, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Center for Complementary and Integrative Health, the Office of Research on Women's Health, and the Office of Behavioral and Social Sciences Research, has been testing lifestyle interventions for overweight or obese pregnant women to improve weight and metabolic outcomes—including development of gestational diabetes—in both the women and their children. The individual trials have completed their intervention programs through the end of pregnancy (delivery), and it is anticipated that the first results will become available in 2017.

Follow up is continuing through 1 year post-delivery for the women and 1 year of age for the offspring. Also, the NIDDK is supporting continued follow up of participants in the Diabetes Prevention Program Outcomes Study—now in its 15th year—including further examination of differences between women with and without a history of gestational diabetes in their development of diabetes later in life. In related research, NIDDK-supported scientists are studying, in a non-human primate model, how a Western-style diet during pregnancy affects the metabolic health and behavior of offspring, and whether applying dietary interventions in the mother can modify these effects. The results of these studies in an animal model could help inform future clinical research for pregnant women regarding diet, including women who may develop gestational diabetes.

The NICHD is the lead NIH Institute for research on gestational diabetes. Its efforts include pursuit of research opportunities in areas of shared interest with the NIDDK in gestational diabetes, such as the long-term health of offspring. For example, the NICHD-supported Maternal Fetal Medicine Units (MFMU) Network followed up on children who had been enrolled in a treatment trial of mild gestational diabetes. In an earlier study, the MFMU found that treatment of mild gestational diabetes was associated with immediate benefits to the baby, including a reduction in birth weight and macrosomia and neonatal fat mass. In the follow-up study of the children now aged 5 to 10 years, no reduction in childhood obesity or metabolic dysfunction was found, but the daughters of women treated for mild gestational diabetes were found to have a lower fasting glucose level.

Global Health Research

Recent disease outbreaks such as Ebola and the flu have shown the importance of the Center's essential role in global infectious disease health research training and health system strengthening. These efforts help developing countries to eventually advance their own research and health solutions and tools. FIC also has developed partnerships in countries to fight malaria, neglected tropical diseases, and other infectious diseases that disproportionately impact the global poor. The Committee urges FIC to continue this important work of building relationships with scientists abroad to foster a stronger and more effective science workforce and health capacity on the ground, and improving the image of the United States through health diplomacy in their countries.

Action taken or to be taken

The Fogarty International Center (FIC) is committed to continuing to invest in building leaders in global health research, 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 FIC Strategic Plan.

FIC's investments comprise a range of capacity-strengthening programs, which include, for example, the longstanding HIV Research Training Program (HIVRT), the Global Infectious Disease Research Training Program (GID), and the International Research Ethics Education and Curriculum Development Award. The recent epidemics of the Ebola and Zika viruses have highlighted the need for better global preparedness for, and response to, emerging infectious disease threats. FIC is funding collaborations between U.S. and West African academic institutions to develop research training programs aiming to 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 more 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 U.S. and LMIC scientists across the career development pipeline.

Glomerular Diseases - Update

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

NIH-supported research in the area of glomerular diseases, such as Minimal Change Disease (MCD), focal segmental glomerulosclerosis (FSGS), and Membranous Nephropathy (MN), is leading to multiple scientific advances. Several recent advances in glomerular disease have resulted from cohort analyses of the Nephrotic Syndrome Study Network (NEPTUNE), which is a multi-site, multidisciplinary collaborative research network designed to foster innovative approaches to the understanding of MCD, FSGS, and MN. NEPTUNE is supported by the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) and the National Center for Advancing Translational Sciences (NCATS). For example, researchers recently described baseline characteristics of the NEPTUNE cohort of patients undergoing kidney biopsy, and defined factors, such as immunosuppressive therapy, that were associated with short-term remission. In another study, scientists identified molecular, histological, and physiological characteristics associated with variants of the *APOLI* gene in African American participants from the NEPTUNE study, linking these factors to clinical outcomes. A recent report from both NEPTUNE and the Chronic Kidney Disease in Children (CKiD) studies showed that children of African ancestry who have high-risk *APOLI* genetic variants appear to have increased prevalence of premature birth, FSGS, and reduced and rapidly declining kidney function. In another study, researchers found that a commonly used diagnostic technique for predicting kidney function, called random urine protein-to-creatinine ratio (UCPR), only moderately correlates with the 24-hour urine protein excretion test—a gold-standard, albeit much more cumbersome, diagnostic test for patients with glomerular disease. The scientists also developed an algorithm to improve the predictive value of UCPR, but additional studies are needed to define better the links between these metrics and clinical outcomes. Both the NEPTUNE and CKiD studies are ongoing.

Complementing NEPTUNE, the NIDDK continues to support the Cure Glomerulopathy Network (CureGN) consortium, which will conduct translational and clinical research that promotes therapeutic development for primary glomerular diseases. CureGN is in the process of recruiting 2400 patients, of which at least 25 percent will be children.

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 2018 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 had a long-standing relationship working closely with the U.S. Department of Veterans Affairs (VA) and the Department of Defense (DOD) to collaborate in areas of scientific overlap, cultivating many areas of fruitful research and enhancing evidence-based medicine and supportive services. 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.⁶⁸

One example of the value-add that can be achieved through partnership is in the co-occurring areas of post-traumatic stress disorder (PTSD) and traumatic brain injury (TBI). The NIH, DOD, and VA, along with other relevant federal agencies, developed and are now working to implement the National Research Action Plan on PTSD, TBI, and other co-occurring conditions.⁶⁹ Examples of collaborative PTSD and TBI activities include holding joint workshops, NIH participation on DOD and VA program review panels, DOD and VA representation on the NIH's National Advisory Neurological Disorders and Stroke Council, and collaborative research performed in the Center for Neurosciences and Regenerative Medicine of the Uniformed Services University of the Health Sciences (USUHS), which is a major program funded through DOD appropriations to support TBI researchers at USUHS, the NIH Intramural Research Program, and the Walter Reed Medical Center. In addition, the Federal Interagency Traumatic Brain Injury Research (FITBIR) informatics system⁷⁰ – developed to share data across the entire TBI research field – is a critical research resource supported by NIH, DOD, and the VA, among other relevant federal partners.

Another example of strategic coordination between NIH, DOD, and the VA is in the area of pain research, where federal activities are informed by the Interagency Pain Research Coordinating Committee.⁷¹ As an offshoot, NIH and the VA are co-funding an initiative focused on identifying non-drug approaches to improve options for the management of pain and associated problems – such as post-traumatic PTSD, drug abuse, and sleep issues – in military personnel, veterans, and their families.

Other areas of shared interest include broader mental health, suicide, substance use disorders, injury and wound-healing, and biodefense-related diagnostics, drugs, and vaccine research. In summary, NIH, DOD, and the VA collaborate in various ways to support research aimed at improving the health and wellness of American service members and veterans, including understanding risk factors, developing supportive technologies, and delivering evidence-based care and services.

⁶⁸ <https://www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf>

⁶⁹ https://www.whitehouse.gov/sites/default/files/uploads/nrap_for_eo_on_mental_health_august_2013.pdf

⁷⁰ <https://fitbir.nih.gov/>

⁷¹ <https://iprcc.nih.gov/>

Grant Review

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Ensure the Quality of NIH Peer Review: With NIH application success rates still at historic lows, NIH peer reviewers are asked to make fine distinctions among exceptional applications. While researchers from Harvard and Boston universities⁷² have shown that better review scores were associated consistently with better research outcomes, the data are noisy and the NIH Center for Scientific Review (CSR) constantly evaluates how best to identify promise in investigators and their research applications. This includes: (1) work with NIH and extramural scientists to evaluate methods to assess peer review outcomes and quality; (2) evaluate the advantages of increasing the scoring range reviewers can use during their meetings -- a recent pilot test of whole and half point scoring found that increased scoring options reduced ties and spread scores; (3) examine all CSR work units on a regular basis, engaging internal and external experts; and (4) survey applicants, reviewers, and NIH staff to assess and improve CSR peer review services.

Ensure the Fairness of NIH Peer Review: NIH-funded researchers and staff found that Black applicants were 10 percentage points less likely than whites to be awarded NIH research funding. CSR is conducting application anonymization studies and other evaluations to understand and address possible disparities in NIH awards. The current anonymization study is under way, with work associated with making the applications anonymous ongoing. In the meantime, CSR has increased the numbers of underrepresented minority reviewers, and it increased the numbers of emerging researchers who can participate in its Early Career Reviewer Program, which gives them career-boosting experiences.⁷³

Reduce Applicant and Reviewer Burdens: Historically low success rates mean that many promising applications are not funded. Competition has soared with NIH and HHS grant applications rising from 40,000 in 1998 to 92,000 in 2015, while the number of awards has remained constant. The scientific community is spending more and more time submitting and reviewing grant applications. To reduce these burdens, CSR is (1) developing a pilot to see if doing away with deadlines will reduce application submissions as they did when NSF eliminated some deadlines, (2) expanding and evaluating video and internet assisted review meeting formats that enable CSR to recruit reviewers who would not otherwise be able to attend a face-to-face meeting, and (3) reducing the burden of face-to-face meetings by holding review meetings in relatively inexpensive cities near a high concentration of reviewers. While face-to-face meetings remain the gold standard, reviewers and CSR staff give increasingly high marks to video and internet assisted reviews as the technology and usage evolve.

⁷² Big names or big ideas: Do peer-review panels select the best science proposals? Danielle Li and Leila Agha, *Science* 24 April 2015: 348 (6233), 434-438

⁷³ www.csr.nih.gov/ecr

Gut Microbiome

The Committee commends the Office of the Director for its work to partner with NIDDK on the Human Microbiome project, which has led to valuable scientific discoveries in therapeutic and genetic research on inflammatory bowel diseases. The Committee urges expanded research on predictors and modifiable factors that can improve early interventions and treatments, particularly among pediatric and young adult populations.

Action taken or to be taken

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) continues to support projects related to gut microbial effects on inflammatory bowel disease (IBD) and other forms of digestive disease. For example, a recent study identified disease-related changes in the gut microbial community and in genes activated in gut cells in children with IBD, showing that they had a particular microbial and genetic “signature” that could provide targets for improving diagnosis and therapy. Another study in children and teens recently showed that different treatments for Crohn’s disease have varying effects on the gut microbiome—a finding with implications for approaches to monitoring treatment response and for potentially developing microbiome-targeted therapies. As part of the second phase of the NIH Human Microbiome Project, one continuing study is a multi-institutional effort to understand how the human gut microbiome changes over time in adults and children with IBD. The overall goal of this study is to provide targets for developing new approaches to IBD therapy or diagnosis. Additionally, the NIDDK issued two funding opportunity announcements in June 2015 that encouraged research the Institute is currently supporting on the human microbiome and its effects on digestive diseases, in addition to obesity, nutrition, and liver diseases.

The NIDDK also supports a clinical study of new approaches to IBD in children, called the Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT-UC) Study. This 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. One ongoing study within PROTECT-UC is studying the role of viruses in the gut as a possible environmental trigger for pediatric ulcerative colitis. PROTECT-UC has recently completed final patient evaluations and will begin the analysis process. This analysis will inform the next steps that are needed in this research area.

Healthcare-Associated Infections (HAIs)

HAIs are estimated to occur in 5 percent of all hospitalizations in the United States, resulting in more than 1.7 million illnesses and 99,000 deaths annually. While HHS has been leading efforts to develop and encourage hospitals to implement improved infection control strategies, potential solutions are complicated by the difficulty of removing dangerous pathogens, including multidrug-resistant organisms, from the clinical environment by disinfection protocols alone.

The Committee has been encouraged by the progress made in reducing central line-associated bloodstream infections and methicillin-resistant *Staphylococcus aureus bacteremia*, but there has been little or no improvement since 2009 in, for example, the rates of catheter-associated urinary tract infections and colon surgery surgical site infections (SSI). Clearly, more action is needed at every level of health care to eliminate infections that commonly threaten hospital patients. As efforts to develop a systems approach to decontamination increase, one of most promising areas of research is related to technologies that can provide surfaces with self-disinfection capability. Advancements in this area could be greatly beneficial to health outcomes, reduce healthcare expenses, and improve patient life-quality. The Committee encourages NIAID/NIBIB (same language in both sections) to support efforts to accelerate the development of self-disinfecting medical devices, disinfecting strategies to alleviate SSIs, as well as materials engineering approaches to minimize or prevent the transmission of pathogens from surfaces within clinical care environments.

Action taken or to be taken

Antibiotic-resistant pathogens acquired in healthcare settings, such as *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* (MRSA), have become an increasing public health concern. The Administration's National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB), released in March 2015, outlines activities across the Federal government to address antibiotic resistance. In this regard, NIAID supports research that spans multiple goals within the National Action Plan and is working toward reducing antibiotic-resistant infections, including those associated with healthcare settings.

NIAID supports research to develop novel sterilization techniques for medical devices that could help prevent healthcare-associated infections. These efforts include the development of a sterilization tool for endoscopes, photodynamic therapy to kill bacteria from catheter-associated urinary tract infections, and UV-based techniques to reduce surgical site infections (SSIs). In addition, NIAID funds studies evaluating the use of chlorhexidine baths and nasally administered antibiotics for removing *S. aureus* from the skin and nose respectively.

A major emphasis of NIBIB-funded researchers is the disruption of bacterial biofilms, in which bacteria group themselves together and adhere to surfaces in an antibiotic-resistant coating. Biofilms are the leading cause of infections acquired in hospitals. One approach targets the communication between bacteria on surfaces, known as quorum sensing, that triggers biofilm formation. Researchers are coating urinary catheters with an enzyme, aminoacylase that blocks the quorum sensing mechanism and therefore blocks the formation of surface biofilms. The researchers are testing the inhibitory activity of aminoacylase-coated catheters on the formation of biofilms by *Pseudomonas aeruginosa*, which is one of the prevalent bacteria in biofilm infections in catheters. An estimated 51,000 healthcare-associated *P. aeruginosa* infections occur in the United States each year. Another research group is testing the chemistry of compounds with the ability to bind a variety of substances, including antibiotics, which could be

used as an antibiotic coating on medical devices. In initial studies, the coating exhibited the ability to be easily loaded with the antibiotic gentamicin, which successfully killed *S. aureus* on the surface of medical devices. The ease of engineering this coating will enable new applications of coatings for preventing bacterial colonization of treated surfaces.

In another project, NIBIB scientists are employing a computational modeling approach to address the challenge of characterizing, predicting behavior of, and treating complex, self-organized, three-dimensional biofilms. The project aims to develop an experimentally driven model that gives accurate predictions of how biofilms are formed and respond to treatments. The model predictions will be used to generate strategies for treating biofilms such as those found in chronic non-healing wounds and catheter-related infections.

Regarding SSIs, NIBIB-funded researchers are engineering a film that can be applied directly to the surface of a wound to prevent bacteria from growing and causing infection. An initial approach uses nanobeads, which adhere to the wound surface, loaded with silver nanoparticles that have antimicrobial activity. The approach provides a highly innovative strategy to address a major health problem, avoid potential side effects, and limit the development of multidrug-resistant organisms.

Healthcare-Associated Infections

Within the Patient Safety portfolio, the Committee provides \$37,253,000, the same level as in fiscal year 2016, for healthcare-associated infection activities. Within this funding level, the Committee includes \$10,000,000 for activities as part of the CARB initiative. These funds will support the development and expansion of antibiotic stewardship programs specifically focused on ambulatory and long-term care settings. In addition, the Committee directs AHRQ to collaborate with NIH, BARDA, CDC, FDA, VA, DOD, and USDA to leverage existing resources to increase capacities for research aimed at developing therapeutic treatments, reducing antibiotic use and resistance in animals and humans, and implementing effective infection control policies.

Action Taken or to be Taken

AHRQ is promoting the expansion of antibiotic stewardship programs in ambulatory and long-term care settings, as well as in hospitals, through its 5-year nationwide CUSP for Antibiotic Stewardship project, which AHRQ is coordinating with CDC and CMS. On the research front, AHRQ and CDC have collaborated in co-hosting a meeting of experts to identify knowledge gaps for the prevention of antibiotic-resistant healthcare-associated infections, which will help inform these agencies' research efforts. AHRQ is participating in the activities of the Presidential Advisory Council on CARB, together with NIH, BARDA, CDC, FDA, DOD, and USDA, and AHRQ has discussed its research innovations with the Council. AHRQ is also coordinating its activities with NIH, CDC, and CMS in collaborative activities which aim to increase the percent of hospitals that have antibiotic stewardship programs that incorporate all the CDC core elements of such programs.

Heart Disease

The Committee is aware of the enormous burden heart disease inflicts on our Nation's population and economy, particularly as the population ages. The Committee requests an update in the fiscal year 2018 budget request on the IC's strategic vision for heart research.

Action taken or to be taken

Heart disease is the leading cause of death in the United States, and as such, is a high priority for the National Heart, Lung, and Blood Institute (NHLBI). NHLBI recently released its Strategic Vision for the next five to ten years, which identifies strategic research priorities for all the research topics related to our mission, including research on heart disease. The Vision resulted from a unique online crowdsourcing process that allowed NHLBI stakeholders to submit and comment on compelling scientific questions that must be answered and critical challenges that must be overcome to achieve scientific progress. Participants from all 50 states contributed and developed a set of 132 research priorities based on timeliness, feasibility, and potential to advance science related to heart, lung, and blood disorders.

The Strategic Vision identified the following priorities related to heart disease:

- Investigating whether early intervention — during childhood or adolescence — can protect against development of atherosclerosis (clogging of the arteries) and other heart diseases during middle age.
- Determining how to predict and prevent the conversion of stable, manageable atherosclerosis into a heart attack.
- Developing new technologies and tests to better manage treatment with anticoagulants (drugs to prevent blood clots), and to reduce the risk of adverse side effects such as internal bleeding.
- Harnessing the power of electronic medical records and data from genetics and other fields to learn more about modifiable risk factors for heart disease and how they interact, to develop more predictive models of heart disease and treatment responses, to identify new targets for therapy, and to better understand population differences in heart disease. (These developments would be especially helpful in improving prevention and treatment of heart disease in women, African Americans, Latinos, and Native Americans. These groups have higher rates of death and disability from heart disease and have been historically understudied.)
- Understanding how social conditions and psychosocial stress contribute to the onset and progression of heart disease and peripheral arterial disease.
- Harnessing the body's own repair processes to promote repair and regeneration of the heart.

These are just a few of the priorities that stand to significantly advance our understanding and treatment of heart disease. In addition, as NHLBI moves forward with implementing the Strategic Vision, the Institute will remain open to new ideas and developments and will adjust its priorities as science evolves. The Vision further positions the Institute to take advantage of emergent technologies and approaches as well as to address new challenges.

Healthy Housing

The Committee encourages NIEHS to further study the impact healthy housing has on reducing environmental exposures that lead to health risks such as asthma and lead poisoning.

Action taken or to be taken

NIEHS continues to support a wide variety of studies on the impact of environmental exposures, including exposures in the home, on health risks like asthma and lead poisoning. NIEHS also supports outreach activities, which focus on engaging communities to help mitigate the effects of environmental agents. A new study is specifically testing whether an indoor environmental control strategy, including reductions of air particulate matter and indoor allergens, is associated with actual reductions in the use of asthma control medications. To help test asthma interventions in real time, a consortium of university researchers is developing wearable, lightweight, personal sensing arrays and a handheld portable spirometer that can be used jointly to measure asthma exacerbation and asthma control in a variety of settings.

Secondhand smoke is a common and well-known trigger of asthma and other adverse health outcomes in the home; a new study is looking at better ways to encourage individuals to ban smoking in their homes, including a test of financial incentives, to see if they have enough of an effect to be adopted as a public health intervention.

An ongoing study aims to determine how perinatal and early childhood lead exposure combined with social stressors can negatively impact neurodevelopment in children. We continue to expand our understanding of the ways that these indoor exposures are important for health; for example, a December 2015 NIEHS-funded study found that elevated blood lead levels in early childhood are associated with insomnia, night waking, use of sleeping pills, and excessive daytime sleepiness in late childhood.⁷⁴

NIEHS supports Healthy Housing outreach through initiating programs and funding studies aiming at community engagement. One program initiated by NIEHS is titled, “Research to Action: Assessing and Addressing Community Exposures to Environmental Contaminants.” The purpose of this program is to use community-engaged research methods to investigate the potential health risks of environmental exposures of concern to the community and to implement an environmental public health action plan. Another ongoing study is using community-engaged research methods to improve the health of Latino children living in the Yakima Valley of Washington State by reducing exposure to substances that cause asthma symptoms. In addition to these efforts, eligible researchers can apply to have biological samples analyzed free of charge for chemicals and biomarkers of exposures through the NIEHS-led Children’s Health Exposure Analysis Resource (CHEAR). This resource will enable researchers to expand their studies with environmental assessments, including the home environment and its effects on health.

⁷⁴ Liu J, Liu X, Wang Y, Yan C, Pinto-Martin J, Dinges D. Early Blood Lead Levels and Sleep Disturbance in Preadolescence. *Sleep*, 2015 Dec 1. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4667382/>

Hemophilia

The Committee encourages NHLBI to include rare diseases such as hemophilia in its work through the Precision Medicine Initiative. For patients with hemophilia, there is wide variation in disease severity and therapeutic outcomes not readily explained by the disease-causing gene mutations. Genome-wide studies would yield new insights into the pathogenesis of hemophilia and patient responses to therapies, benefiting patients with bleeding disorders and broader patient communities.

Action taken or to be taken

Hemophilia A is a rare bleeding disorder affecting one in 5,000 male births. The disease is caused by an insufficient level of clotting factor VIII (FVIII) in the circulating blood. As a result, individuals with hemophilia are at significant risk for bleeding, particularly into their muscles and joints. The disease is frequently diagnosed within the first year of life, particularly when infants become more active and mobile. Treatment of patients with intravenous FVIII has significantly improved patient quality of life and led to a near normal life span. However, treatment with FVIII remains very expensive and about 30 percent of patients with severe disease develop antibodies to FVIII. These FVIII antibodies can greatly reduce the effectiveness of therapy and represent a major obstacle in treating hemophilia patients. Alternative therapies for patients with FVIII antibodies can cost up to \$1 million each year per patient.

The National Heart, Lung, and Blood Institute (NHLBI) is sponsoring a wide spectrum of hemophilia research grants that range from basic and translational research to testing new therapies in human clinical trials, such as curative gene therapies. As part of the NHLBI Trans-Omics for Precision Medicine (TOPMed) program, whole genomic sequencing is currently being performed on 2,100 patients with hemophilia. This DNA sequencing data will provide an unprecedented look into the complex interaction of factors that influence the severity of hemophilia and response of patients to therapies.

The TOPMed DNA sequencing database, expected to be completed in 2017, will provide researchers with a new tool to examine not only genetic risk factors, but also how genetic backgrounds specifically interact with environment factors and clinical factors. Combining disease characteristics and genetic sequencing data in hemophilia will complement the broader participant database anticipated to be collected in the NIH Precision Medicine Initiative. Studies such as these will provide the research community with unique opportunities to evaluate risk factors and to develop better treatment options for patients with hemophilia.

Hepatitis B

The Committee is aware that it is now possible to study the entire Hepatitis B virus life cycle, and, therefore, a research program to identify life cycle vulnerabilities. The Committee encourages NIAID to collaborate with NIDDK to advance innovative research to discover and develop new therapies and treatments to interrupt the life cycle of the Hepatitis B virus to eliminate the infection and to help cure this deadly disease.

Action taken or to be taken

Hepatitis B virus (HBV) infection is a significant public health concern due to the development of potentially fatal virally-induced liver cirrhosis and liver cancer. While hepatitis vaccines effectively prevent HBV infection in nearly all individuals who complete the vaccine series, and available therapeutics are able to suppress HBV replication, there is currently no permanent cure for chronic HBV infection.

NIAID supports a broad portfolio of basic and translational research on the pathogenesis and immunology of HBV that is helping to advance novel therapeutics for chronic HBV infections. NIAID-supported researchers are investigating new therapeutic approaches that use different mechanisms than those of the currently licensed HBV drugs. These approaches target key structures or processes in the HBV life cycle including the HBV surface antigen, viral capsid, viral covalently closed circular DNA, and host immune response. In these efforts, NIAID works closely with NIDDK, which supports a wide range of research programs related to HBV. For example, with support from both NIDDK and NIAID, a team of extramural and intramural scientists showed how a type of immune cell mounts an early defense against HBV infection, pointing to new approaches to prevent and treat chronic HBV infection by targeting these cells.

Complementary efforts by NIAID and NIDDK aim to identify and advance promising HBV therapeutic candidates and potential cures. NIAID investigators recently developed a powerful method to identify the dysregulation of gene expression in patients with HBV-associated acute liver failure (ALF). By assessing ribonucleic acid (RNA) expression in the livers of these patients, the researchers identified key regulatory networks that could contain novel drug targets for HBV-associated liver disease. In addition, NIAID is working to increase HBV treatment options by providing access to comprehensive preclinical and clinical research resources and services. In fiscal year 2015, NIAID screened 187 compounds for therapeutic activity against HBV for academic and industry partners. Ten of these candidates were advanced to a secondary screening round. NIAID also provides evaluation of candidate therapeutics in an HBV transgenic mouse model and a woodchuck model. One promising candidate, SB 9200, was tested using NIAID preclinical services and is now being evaluated further by Spring Bank Pharmaceuticals in a Phase IIa clinical trial.

The NIDDK-supported Hepatitis B Research Network also aims to advance understanding of disease processes and disease progression, as well as to identify effective approaches to treatment with currently available and emerging therapies. The Network has initiated multiple clinical trials and ancillary studies involving both adults and children with HBV. In addition, NIDDK-supported investigators have developed a “humanized” mouse model – an immune-deficient mouse transplanted with human immune and liver cells – in which to study early events in HBV infection and test new treatment approaches. Finally, in April 2016, NIDDK experts participated in an NIAID-organized workshop on Cures for Chronic Hepatitis B. The workshop

convened leading scientists to discuss promising research toward advancing cures for chronic HBV.

NIAID will continue to work with partners in academia, industry, and the Federal government, including NIDDK, to identify novel therapeutics and potential cures for HBV. These collaborative efforts, along with NIAID's continued support of basic, translational, and clinical research, are crucial to understanding and ultimately eliminating HBV.

Hepatitis Research Related to Minorities

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned:

Action taken or to be taken

Viral hepatitis remains a silent epidemic in the United States. Most of the 3 to 5 million Americans living with chronic viral hepatitis do not know that they are infected, placing them at greater risk for severe, even fatal, complications from the disease and increasing the likelihood that they will spread the virus to others. As a result, viral hepatitis is a leading infectious cause of death and claims the lives of 12,000 to 18,000 Americans each year. It is the leading known cause of liver cancer and the most common reason for liver transplantation.

Hepatitis B virus (HBV) infection is a major preventable health problem in the United States with a disproportionate burden on Asians and Native Hawaiians and other Pacific Islanders. While these groups constitute only 5 percent of the overall U.S. population, at least 50 percent of all individuals with chronic HBV infection come from these groups. From 2000 to 2014, American Indians and Alaska Natives had the highest incidence of hepatitis C virus (HCV). African Americans represent about 12 percent of the U.S. population, but about 22 percent of the chronic HCV cases. Chronic liver disease, often hepatitis C-related, is a leading cause of death among African Americans ages 45–64. Puerto Ricans have more than 3 times the rate of HCV infection compared to other Latinos and Whites.

The considerable racial and ethnic disparities in hepatitis incidence and outcomes present a significant need for interventions and future research. Insufficient insurance coverage, limited access to health information, cultural and linguistic barriers, and social isolation represent both contributors to these disparities and potential avenues of addressing these disparities.

NIMHD is supporting a collaborative project among a group of stakeholders that include health organizations, community organizations, and academic institutions to assess the impact of culturally appropriate health information technology (HIT) strategies on access to HBV screening and vaccines for underserved Asians in Seattle, WA. This project serves as an important model for developing culturally appropriate screening, vaccination, and linkage to care approaches that integrate health services, HIT, support services, and self-advocacy for Asian communities. These approaches are aimed at reducing disparities in hepatitis incidence and outcomes, as well as reducing preventable health events and costs to the health system.

Despite significant advances in preventing HBV-related liver cancer, substantial disparities remain in incidence and mortality rates between Koreans and the general population. Koreans experience the second highest incidence rate of HBV and liver cancer in the United States. An NIMHD-supported HBV intervention trial using a community health worker-led group education, patient navigation, and bilingual health provider engagement increased HBV screening and vaccination rates by more than 10 times among underserved Koreans. The intervention is designed to scale-up to the Korean community at-large, potentially reducing incidence and saving significant healthcare dollars by reducing avoidable liver conditions.

Hereditary Hemorrhagic Telangiectasia (HHT)

The Committee supports the formation of an HHT coordinating committee of multiple ICs, including NINDS, NHLBI, NICHD, NHGRI, NIDDK, NIBIB, and NCATS. The Committee urges the coordinating committee to initiate a workshop to explore collaborative research opportunities into the diagnosis and treatment of HHT, including efforts to foster translational research in the development of new therapeutics for vascular anomalies, the identification of potential targets for interrupting pathways to prevent HHT progression, and new imaging methods to enable more precise detection of vascular malformations. The Committee requests an update in the fiscal year 2018 CJ on the status of research related to this topic.

Action taken or to be taken

Hereditary Hemorrhagic Telangiectasia (HHT) is a rare, inherited bleeding disorder caused by genetic mutations that affects approximately one in 5,000 to 8,000 people in the United States and 1.4 million individuals worldwide. The development of HHT involves formation of arteriovenous malformations (AVM), or abnormal connections between the arteries and veins. These fragile connections are highly prone to bleeding, and occur in several tissues and organs including the brain, lung, liver and mucosal membranes. Recurrent nosebleeds and gastrointestinal (small bowel) bleeding are common, and can lead to dependence on transfusion and iron therapy, with some patients requiring more than 200 blood transfusions in a year. In addition, AVMs are linked to hemorrhage, anemia, brain abscess, and stroke.

A number of NIH Institutes and Centers support research in this area through coordinated efforts across the agency and with private foundations representing patients with different types of vascular malformation disorders. For example, the National Heart, Lung, and Blood Institute (NHLBI) supports a substantial basic and translational research portfolio on the development of new blood vessels from pre-existing vessels. NHLBI has expanded the scope of research in HHT to include clinical studies and trials to provide clinicians with the appropriate evidence needed to better treat HHT patients. To further maximize the efficiency of such trials, in May 2016, NHLBI hosted a multidisciplinary Working Group on Designing Trials for Uncommon Diseases and Therapeutics. The HHT Foundation (Cure HHT) participated in the Working Group, lending a patient perspective to how NHLBI can better support clinical trials in rare diseases.

The National Institute of Neurological Disorders and Stroke (NINDS) supports research on brain AVMs, focused on understanding the underlying cellular, molecular, and genetic mechanisms of brain AVMs, as well as potential interventions for disrupting their formation. NINDS collaborates with the National Center for Advancing Translational Sciences (NCATS) to support the Brain Vascular Malformation Consortium (BVMC), which is part of the Rare Diseases Clinical Research Network. The BVMC is developing clinically relevant imaging, genetic, and biochemical markers for HHT and other vascular malformation disorders in order to build the foundation for future clinical research studies. The BVMC also has active collaborations with the Angioma Alliance, the Sturge-Weber Foundation, and the HHT Foundation, and NIH program staff interact with these groups and participate in the Angioma Alliance's annual scientific meeting on a regular basis.

In addition, the National Institute of Biomedical Imaging and Bioengineering (NIBIB) is supporting research to improve evaluation of AVMs. For example, NIBIB-supported researchers

are developing a noninvasive imaging technique called arterial spin labeling, which can be used to assess the vascular architecture and hemodynamics of AVMs without the use of contrast agents. Recent testing using this technique in the liver shows promise.

HIV/AIDS

The Committee appreciates that NIAID has made reducing the incidence of HIV/AIDS, including the development of safe and effective vaccines, a high priority. The Committee is aware of several promising HIV vaccine candidates, including candidates that use novel immunogens and vaccine platforms, such as cytomegalovirus (CMV). The Committee supports NIAID efforts to advance such innovative and promising vaccine candidates into early clinical testing.

Action taken or to be taken

NIAID is committed to conducting and supporting basic, translational, and clinical research to develop a safe and effective vaccine to prevent HIV/AIDS, including ongoing clinical trials of promising vaccine strategies. NIAID, in collaboration with the Pox-Protein Public-Private Partnership, conducted HVTN 100, a Phase I/II clinical trial in South Africa to evaluate an investigational HIV vaccine regimen designed to improve upon the RV144 vaccine regimen which had demonstrated modest protection against HIV. Early data from HVTN 100 showed the improved vaccine regimen was safe and produced a robust immune response. NIAID launched HVTN 702, a Phase IIb/III clinical trial, in late 2016 to further evaluate vaccine efficacy. This is the first new HIV vaccine efficacy study in seven years. NIAID also is collaborating with Janssen Pharmaceuticals, Inc., to evaluate new candidate vaccines and optimize vaccine regimens. For example, two Phase I studies are evaluating the ability of vaccines containing a key HIV protein, gp140, to induce protective antibodies against HIV. Several of these NIAID-supported vaccine candidates and regimens may move forward into Phase IIb studies if early results are promising.

NIAID also supports preclinical research to identify new HIV vaccine candidates. The NIAID-supported Centers for HIV/AIDS Vaccine Immunology and Immunogen Discovery are accelerating HIV vaccine development by supporting multidisciplinary research into immune responses that prevent or control HIV infection in order to generate novel vaccine concepts. The Centers are focused on identifying the ways in which HIV may be vulnerable to targeting by the immune system. In particular, the Centers are using animal models to develop vaccine immunogens directed at the immune response of B cells to induce protective antibodies.

NIAID also is working to develop novel methods to prevent HIV infection. NIAID researchers have shown that a single injection containing four anti-HIV-1 antibodies effectively protects against infection for extended periods in an animal model. In addition, two NIAID-supported clinical trials are testing the safety, tolerability, and effectiveness of VRC01, a potent anti-HIV neutralizing antibody, in preventing HIV infection in women in sub-Saharan Africa as well as in men and transgender people who have sex with men in the United States, Brazil, and Peru.

The development of a safe and effective HIV vaccine remains key to realizing a durable end to the HIV/AIDS pandemic. NIAID remains committed to advancing research to develop such a vaccine. In addition, NIAID will continue to pursue the goal of reducing the incidence as well as the morbidity and mortality of HIV/AIDS through the support of research to develop the next generation of HIV therapies and prevention strategies, reduce HIV-associated co-morbidities and co-infections, and ultimately develop a cure.

Human Trisome

The Committee looks forward to the results of NIH's feasibility report on a multi-year study to examine the molecular, cellular, and physiological mechanisms that predestine individuals born with a third copy of human chromosome 21 to either live with-or be protected from- a range of diseases that cause nearly 60 percent of U.S. deaths. The Committee encourages NIH to focus on whether aspects of the project, from accrual of children and adults with T21, to analysis of biological samples at the genetic, epigenetic, biochemical, and cellular levels, to advanced bioinformatics analysis of large genomics datasets, fit within the priorities set in the NIH research plan published in 2014.

Action taken or to be taken

The Conference Report accompanying the fiscal year (FY) 2016 Omnibus Appropriations measure, under the Department of Health and Human Services, requested that the NIH submit a report within one year of enactment of the Act to the Committees on Appropriations on the feasibility of a multi-year study of children and adults with trisomy 21. The NIH submitted the report to Congress within that timeframe.

In brief, the NIH feasibility report describes the myriad of research efforts being supported on aspects of health associated with trisomy 21 (Down syndrome, or DS), including the development and evaluation of animal models to help study the syndrome, examination of specific genes and groups of genes that may be factors in developing features of DS, understanding the role of maternal age, biomarker, neuroimaging, and neuropsychological studies of aging in adults with DS, and the causes and treatments of DS-related conditions. The report also notes that the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) works across the NIH with other Institutes and Centers that support research on DS, and with national and international stakeholders that are members of the NICHD-led Down Syndrome Consortium. In addition, the report states that in 2014, the NIH published a revised version of its research plan on Down syndrome, which identifies short- and long-term research objectives in five main categories: Pathophysiology of Down Syndrome and Disease Progression, Down Syndrome-Related Conditions, Treatment and Management, Down Syndrome and Aging (a new section), and Research Infrastructure.

To assess the feasibility of a multi-year study of children and adults with DS, the NICHD identified and addressed component aspects that could be part of such a study. Research on many of these components is already underway with NIH support. These include:

- *Recruitment of a cohort of individuals with DS that represent a range of ages and diversity*
- *Biosamples/biorepository/brain banking*
- *Whole genome sequencing from biospecimens*
- *Comprehensive biomarker studies from biospecimens*
- *Cognitive assessments and outcome measures*
- *Biomarkers/risk factors for cognitive decline and Alzheimer's Disease*
- *Neuroimaging*
- *Congenital Heart Disease (CHD) and other heart defects*
- *Research infrastructure*

- *Publicly available datasets for analyses by researchers*
- *“Catalogue” of phenotypes associated with DS*

Many of these components dovetail with objectives in the NIH Research Plan, whose aim is to identify the gaps in research still needed in the field of DS. Given its many competing priorities, the NIH must carefully consider the most cost-effective and non-duplicative ways to fill the research gaps. Careful coordination among all supporters of DS research will be necessary to move this work.

Imaging

The Committee notes that imaging research occurs in multiple ICs throughout the NIH and is an integral component of the BRAIN Initiative. The Committee requests NIH provide an overview of imaging research throughout all NIH activities, including collaborations with other HHS and non-HHS agencies. The Committee requests this information be included in the fiscal year 2018 CJ.

Action taken or to be taken

Over the past few decades, imaging technology has revolutionized healthcare, allowing for early detection of disease, monitoring of disease progression, and response to treatment. Using image-guidance, minimally invasive approaches can be used for the treatment of cancer, cardiovascular, neurological, and musculoskeletal diseases. NIH invests heavily in imaging research and supports advances that will continue to transform medicine. Imaging research is a multi-disciplinary effort among researchers from different federal agencies and public and private institutions that come together to collaborate to improve healthcare.

As a critical component of the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative⁷⁵, imaging research is developing new tools and technologies to improve our understanding of brain structure and function. Researchers seeking new ways to detect, treat, cure, and even prevent brain disorders are working to address major gaps in our current knowledge. This will provide unprecedented opportunities for exploring exactly how the brain enables the human body to record, process, utilize, store, and retrieve vast quantities of information, all at the speed of thought. One of many examples of research in this area is the development of photoacoustic imaging, a technique that blends the sensitivity and instant precision of light with the penetrating ability of sound to reveal the activity of neurons. The BRAIN initiative is also creating a data archive of brain images that will be available for researchers to utilize in future projects.

The Interagency Working Group on Medical Imaging (IWGMI), 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, is working 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. The IWGMI, which includes twelve federal agencies, has determined key strategic directions through a series of stakeholder meetings. Areas identified as important for joint focus include deep/machine learning, quantitative and high-value imaging, and inter-agency collaboration to accelerate translation.

The BRAIN Initiative and IWGMI are examples of national efforts to address gaps in tools and technologies. NIH leads collaborative efforts such as these and coordinates and participates in workshops, meetings, and other forums to identify and help close scientific gaps in knowledge. These joint efforts provide the opportunity for researchers at NIH to collaborate with each other and engage in efforts across NIH, HHS, and with the broader research community. Important research opportunities are also identified through Requests for Information, reports, and community feedback and proposed as potential new programs that are then evaluated against priorities.

⁷⁵ <https://www.braininitiative.nih.gov/index.htm>

Imaging research at NIH covers a vast spectrum of efforts to develop, improve, and validate tools and technologies to see the unseen—from the subcellular level to whole organs to imaging in 4D (space and time). These efforts are coordinated both at the level of individual institutes and across NIH as a whole in both the intramural and extramural research programs. For example, the NIH Common Fund recently launched a program to develop and increase access to the new cryo-electron microscopy (Cryo-EM) systems that are being used to observe subcellular structures, such as proteins, while other microscopy techniques can be used to observe very small and extremely fast biological interactions in real time. With the development of new materials and manufacturing processes, NIBIB has supported imaging research to produce pocket-sized ultrasound devices and screen-printed, flexible MRI coils that can be woven into fabric to improve pediatric imaging. The NIH has also recognized opportunities to encourage research in specific areas. For example, NIBIB launched an initiative to reduce radiation exposure from CT exams and is funding a project to develop low-cost MRI machines that produce an image quality equal to the best available high-end commercial machines.

Today's research is employing new strategies to collect, analyze, and share increasingly complex biomedical data sets. Examples include the Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) Consortium⁷⁶ which uses imaging research combined with genomic studies to discover genetic biomarkers, determine how lifestyle impacts the brain's wiring, and identify potential risk and protective factors in the development of disease. The Neuroimaging Informatics Tools and Resources Clearinghouse Computational Environment (NITRC-CE)⁷⁷ provides researchers with a high-quality image repository along with software tools and a cloud based computing environment.

NIH is collaborating with many agencies, including the Department of Energy, to address the availability of research isotopes for imaging and identify and prioritize radioisotopes needed for biomedical research. Many other NIH collaborative efforts to advance science and medicine are ongoing and include, but are not limited to, the Human Connectome Project⁷⁸, Human Placenta Project, Quantitative Imaging Biomarkers Alliance (QIBA)⁷⁹, Image Share⁸⁰, National Biomedical Imaging Archive⁸¹, and Imaging Tools for Cancer Research.⁸²

⁷⁶ <http://enigma.ini.usc.edu/>

⁷⁷ <https://www.nitrc.org/>

⁷⁸ <http://www.humanconnectomeproject.org/>

⁷⁹ <http://www.rsna.org/qiba/>

⁸⁰ http://www.rsna.org/image_share.aspx

⁸¹ <http://ncia.nci.nih.gov/ncia/>

⁸² http://lhncbc.nlm.nih.gov/project/imaging-tools-cancer-research_

Immunotherapy

Recent NCI research demonstrates that new cancer immunotherapy approaches that specifically attack tumor cells with characteristics unique to a certain cancer could be effective against a wide range of cancers. The Committee encourages NCI to further explore new interventions, such as immunotherapy, as a promising new treatment strategy for children with cancer.

Immunotherapy of Childhood Cancer

The Committee encourages NCI to continue to further explore new interventions, such as immunotherapy, as a promising new treatment strategy for children with cancer.

Action taken or to be taken

The National Cancer Institute (NCI) is dedicated to accelerating progress for pediatric cancer patients and is supporting research on a number of emerging treatments that restore or enhance the immune system's ability to attack cancer cells.

NCI's ongoing research priorities include the investigation of why some patients respond better to immunotherapy than others, the combination of immunotherapy with other types of treatment, and the use of immunotherapies in earlier disease stages and more disease types. By continuing to build upon the foundation of decades of basic research into immunological processes, NCI-supported researchers seek to better describe the immune system and determine potential therapeutic pathways and strategies. Scientists work to translate this knowledge into treatments through the NCI-supported Cancer Immunotherapy Trials Network (CITN). Co-sponsored by the Fred Hutchinson Cancer Research Center and comprised of 30 member sites, the CITN selects, designs, and conducts early phase immunotherapy trials.

Similarly, the over 200 member institutions of the NCI-supported Children's Oncology Group (COG) oversee nationwide clinical trials for pediatric patients. Several of these trials introduce new immunotherapy agents, representing a broad spectrum of immunotherapy mechanisms, into evaluation for children with cancer. For example, one study is currently testing the use of genetically modified T-cells (a type of immune cell) to treat chemotherapy-resistant leukemia, while another is testing the use of a monoclonal antibody to treat leukemia and lymphoma.

In addition, the Pediatric Oncology Branch (POB) in NCI's Center for Cancer Research, dedicated to conducting high-risk, high-impact basic, translational, and clinical research on childhood cancers, and has successfully treated several children with acute lymphoblastic leukemia (ALL). Researchers in the POB continue to conduct clinical trials evaluating chimeric antigen receptor (CAR) T-cell therapy (a type of immunotherapy) for certain high-risk leukemias and lymphomas, and for certain solid tumors with cells that express a protein called GD2.

Additionally, the Beau Biden Cancer Moonshot Initiative is an important opportunity to speed progress on childhood cancers. Not only is childhood cancer research one of the seven core elements within the initiative, several other elements are also important to advancing progress for children with cancer. A key recommendation from the Blue Ribbon Panel Pediatric Working Group is to improve our understanding of these unique molecular drivers of pediatric cancers - fusion oncoproteins - and to use new preclinical models to develop therapies that target them. The Blue Ribbon Panel report also encourages pediatric immunotherapy research efforts to enhance the speed by which new immunotherapies can be tested in children. A specific focus on

pediatric immunotherapy targets is essential, as many of the immunotherapy treatments being developed to more effectively treat adult cancers may have no role in treating childhood cancers. The NCI remains committed to further expanding existing treatment options for children with cancer, particularly in promising fields such as immunotherapy.

Inclusion of Children

The Committee appreciates the commitment made by the NIH in its fiscal year 2017 budget request to pursue plans to collect age-related inclusion information for research studies to support enhanced analyses and reporting on inclusion by age. Reporting study participation by age will assist the Committee, researchers, and other stakeholders in understanding whether children as a whole, or particular pediatric subpopulations, are underrepresented in federally funded biomedical research. The Committee believes that the implementation challenges cited by the NIH, including determining the appropriate format for collecting age-related data and establishing meaningful age-based categories, are addressable with appropriate expertise and stakeholder input. The Committee directs the NIH to develop a detailed plan to collect data and report publicly on the actual numbers of children and age distribution that are enrolled in its clinical studies.

Action taken or to be taken

The NIH remains committed to ensuring that relevant scientific questions are appropriately considered for different age groups, particularly children and older populations (65+). Although the Committee notes particular interest in pediatric populations, NIH is taking approaches that will address age across the lifespan with particular emphasis on pediatric and older groups. The NIH recognizes that both the young and the old are vulnerable populations in health research and their inclusion in clinical research and trials is an important aspect to ensure sound science is supported that will ultimately inform clinical practice. The NIH is interested in further understanding age as an important biological variable in its research portfolio and identifying where gaps exist in the inclusion of certain age groups.

NIH will host a workshop in 2017 to engage with internal and external stakeholders on the inclusion of pediatric and older populations in clinical research. A trans-NIH workgroup was established to plan the meeting. Discussion is anticipated on the following issues:

- How investigators address age variables in designing their studies
- Ethical considerations of including pediatric and older populations
- Ways to avoid excluding pediatric and older populations that are not scientifically or ethically driven
- Approaches to collect individual age-related information

NIH is considering alternative strategies to collect information on participant age that would make the best use of the information for reporting purposes as well as for performance assessment. As mandated in Section 404N of the 21st Century Cures Act, NIH must ensure that age-related data reported in the triennial report are made publically available on the NIH website. With input from the planned workshop and policy implementation, NIH will develop a system to facilitate collection of de-identified, individual-level information on participants' age, sex, race, and ethnicity. The age-reporting system will provide a standardized way to collect this information that utilizes NIH's existing reporting process for investigators, minimizes administrative burden, and maximizes the NIH's flexibility to use age-related information to better understand how different age groups are included in our research portfolio as well as to identify gaps and opportunities within the NIH clinical research portfolio.

Inflammatory Bowel Disease Genetics Consortium

The Committee is pleased by NIDDK's work on the Inflammatory Bowel Disease Genetics Consortium and supports this ongoing initiative. The Committee also urges NIDDK to expand its portfolio on pediatric IBD research through existing and new initiatives.

Action taken or to be taken

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) appreciates the Committee's recognition of the Inflammatory Bowel Disease Genetics Consortium (IBDGC). In collaboration with the International IBD Genetics Consortium, of which it is a member, the IBDGC has enrolled thousands of patients and identified about 200 regions of the human genome that are associated with risk of IBD. This work has provided important new insights into the nature of the disease. For example, IBDGC researchers recently found variations in several genetic regions that are more common in IBD patients from certain populations across the world, which could enable tailoring of future treatments based in part on genetic background. Another study found that there are actually two genetically distinct types of Crohn's disease, which could help guide targeted treatments in the future. To continue investigations into the genetic underpinnings of IBD, and to build upon the successes of the initial phase of the IBDGC, support for the consortium will be renewed in 2017. A goal of the next phase is not only to continue identifying regions of the genome associated with genetic risk for IBD, but also to identify precisely specific genes and genetic variants within these regions that are involved in IBD susceptibility. The consortium will also delve into how genetic factors influence the development of IBD by investigating the functions of candidate genes.

The NIDDK also continues to support research in pediatric IBD. For example, NIDDK-sponsored researchers recently discovered that different treatments for Crohn's disease have varying effects on the microbes that inhabit the guts (the microbiome) of children and teens—a new finding with implications for approaches to monitor treatment response and for potential development of future microbiome-targeted therapies. This could open new avenues for developing ways to modify the microbiome as potential treatments for people with Crohn's disease. It could also potentially be used to predict who will respond to different therapies, toward a longer-term goal of personalizing treatments. The NIDDK also recently completed enrollment of Predicting Response to Pediatric Colitis Therapy, a multi-center study of children and adolescents who have been newly diagnosed with ulcerative colitis. Samples gathered from study participants are currently being used to understand better the effects of genetics, inflammation, Vitamin D, and the microbiome on clinical outcomes.

Infrastructure

The Committee understands that Federal agencies such as NIH need to maintain and upgrade parts of their physical infrastructure every year. The NIH facilities budget has been relatively flat since 2009. Over time, only the most essential maintenance and repairs for health and safety have been addressed, leaving an increasing backlog of projects requiring attention. To ensure the Committee is informed of NIH's critical facility needs and inform future infrastructure budgets, the Committee has included up to \$1,000,000 for NIH to enter into a contract with the National Research Council, Division of Engineering and Physical Sciences, 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. The Committee directs NIH to provide the report with its recommendations to the House and Senate Committees on Appropriations no later than 1 year from the date of the contract agreement on the statement of work between NIH and the National Research Council.

Action taken or to be taken

The NIH conducted an exploratory meeting with the National Research Council (NRC), Division of Engineering and Physical Sciences, in October 2016. The NRC explained what building, infrastructure, and census data they would need and what preparatory steps NIH could take in the interim while we are awaiting funding. The NIH has undertaken those steps and believe in collaboration with NRC that it is possible to begin the study soon after receiving funding.

Intellectual and Developmental Disabilities Research Centers (IDDRC)

The Committee recognizes the outstanding contributions of the IDDRCs toward understanding why child development goes awry, discovering ways to prevent developmental disabilities, and discovering treatments and interventions to improve the lives of people with developmental disabilities and their families. The Committee urges NICHD to continue to support the IDDRCs to conduct basic and translational research to develop effective prevention, treatment, and intervention strategies for children and adults with developmental disabilities.

Action taken or to be taken

The 14 Intellectual and Developmental Disabilities Research Centers (IDDRCs), located at academic institutions throughout the United States, conduct research to advance the diagnosis, prevention, treatments, and amelioration of intellectual and developmental disabilities (IDD). These research efforts cover a broad spectrum of scientific approaches ranging from basic laboratory research on the fundamental processes of normal and abnormal development to clinical and behavioral research. Individuals with a wide array of conditions including Down syndrome, autism, genetic syndromes, metabolic and biochemical disorders, newborn conditions, muscular dystrophies, and others, participate in this work.

For the first 50 years of its existence, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supported IDD-related research through infrastructure support for centers in the form of core services accessed by a broad spectrum of individual researchers to support their research grants, some funded through NIH. In 2013, the NICHD switched to a cooperative agreement approach to allow for closer partnerships with NIH scientific staff, and to move toward a refocusing the research network of IDDRC sites toward integrated programs to support clinical trials. As part of this change, each IDDRC now is required to have a Clinical Translational Core to facilitate clinical research on IDDs, providing research-related services such as a biorepository, patient registry, or recruitment assistance. Each center also is required to have at least one cutting-edge research project that addresses one of the five priority areas identified during NICHD's 2012 workshop on charting a new course for the IDDRC program. These focus areas include comprehensive genomic or proteomic approaches to an IDD condition; development of outcome measures for interventions; multimodal treatment approaches; shared resources across IDDRCs; and strategies for improving public health. This new formulation of the IDDRC program completed its fourth and final year of competition for funding in FY2016.

In these "new" IDDRCs, a strong emphasis remains on the promotion of collaborative, multidisciplinary, and interdisciplinary research programs that are not only providing core facilities and support for research in IDD, but also are advancing the development of therapeutics and interventions for these conditions. The NICHD remains committed to this program. To review past successes, identify remaining gaps, and set priorities for the field of IDD research, a workshop is being planned for the end of April 2017. The NIH recognizes that the evolution of the field has much to offer in informing our next steps, and will seek the wisdom of the IDD community in formulating the next iteration of the program.

Interagency Pain Research

The Committee encourages the Director to intensify and coordinate fundamental, translational, and clinical research 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 made by the Federal Pain Research Strategy, an ongoing effort coordinated by the Interagency Pain Research Coordinating Committee and the NIH Demographic.

Action taken or to be taken

The NIH understands that a coordinated interagency effort is necessary to improve fundamental, translational, and clinical research with respect to the understanding of pain, and the discovery and development of therapies for chronic pain, including alternatives to opioids for effective pain treatments.

The HHS Secretary's 2016 portfolio brief⁸³ and research agenda on opioids and pain management recognizes the pressing need to encourage the development of new pain treatments, especially treatments with reduced risk for misuse, and for opioid addiction and overdose. The portfolio brief summarizes ongoing interagency research in these areas and identifies the most pressing research opportunities. NIH and other agencies have already taken steps to enhance and expand the research highlighted in this strategic agenda.

The Interagency Pain Research Coordinating Committee (IPRCC) was established to coordinate all pain research efforts across HHS agencies and departments. It includes federal (six agencies and departments), public, clinical and scientific members. Collaborative efforts across the participating federal members have resulted in several trans-agency/department research initiatives on pain management in the military population, for example a Funding Opportunity Announcement to encourage research on health services and observational studies of non-pharmacological approaches to managing pain and co-morbid conditions in US military personnel.

An ongoing IPRCC initiative is development of the Federal Pain Research Strategy (FPRS). This effort supports the mandate of the committee to identify critical gaps in basic and clinical research on the symptoms and causes of pain and make recommendations to ensure that the activities of the NIH and other Federal agencies are free of unnecessary duplication of effort.

Planning for the FPRS began in 2015 with the establishment of a steering committee and request for public comments. The FPRS is structured thematically with respect to the temporal continuum of pain, from prevention, to acute pain, to the transition to a chronic pain disease state. Five working groups made up of a diverse and balanced group of scientific experts, patient advocates, and federal representatives have been meeting since early 2016 to examine the current federal research portfolio and to identify and prioritize future research recommendations. Their ultimate goal is to provide an evidence base to improve pain care. Their recommendations will serve as a long term strategic plan to coordinate and advance the federal pain research agenda. Their final report of the FPRS was presented March 2017 to the IPRCC for review and to federal agencies that support pain research.

⁸³ <http://www.hhs.gov/sites/default/files/opioid-report-v4-remediated.pdf>

International Agency for Research on Cancer (IARC)

The Committee recognizes that understanding the relationship among chemical agents and other hazardous substances and cancer is an important area of research. The Committee requests an update on NIH support for the IARC on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans.

Action taken or to be taken

The International Agency for Research on Cancer (IARC) is a specialized cancer agency of the World Health Organization (WHO). Its purpose is to promote international collaboration in cancer research and to identify the causes of cancer so that preventive measures may be adopted and the burden of disease and associated suffering reduced. For over 45 years, the IARC Monographs program has been highly regarded within the scientific community for its systematic, rigorous, comprehensive reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures based on the current state of the science. Over the course of its history, the program has evaluated more than 1,000 potentially harmful substances and identified hundreds of carcinogens that today are widely known to be hazardous, such as asbestos, tobacco, and benzene. The IARC Monographs program is an independent entity that conducts evaluations using a well-respected and transparent review process.

The National Cancer Institute (NCI) has funded the IARC Monographs program⁸⁴ under a cooperative agreement (U01) through the NIH peer review process since 1982. In this agreement, the NIH assumes a partnership role with the awardee but does not assume direction, prime responsibility, or a dominant role in awardee activities. NCI's award to IARC supports two of IARC's Working Groups each year. The Working Groups are comprised of scientific experts who have published significant research related to the carcinogenicity of the potential cancer agent being reviewed. These experts examine the published data to evaluate whether an agent has the potential to cause cancer in humans and perform what is called a "hazard classification," an assessment that indicates the strength of evidence suggesting that the agent can cause cancer. It is important to note that the Working Groups do not assess the risks associated with exposure to a given agent, and do not make evaluations regarding the probability of developing cancer, which depends on a variety of factors, including levels and duration of exposure.

The Monographs provide important assessments of evidence to national and international health agencies to inform their public health programs that may undertake such risk assessments. The conclusions and published content of each Monograph are the sole responsibility of the IARC Working Group. Consistent with NIH Grants Policy, the contents of the monograph volumes, like the findings of any individual research project grant, do not represent the official views of NIH or the NCI.

⁸⁴ <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-14-503.html>

Irritable Bowel Syndrome (IBS)

The Committee is encouraged by the work of NIDDK to explore symptoms of IBS among various patient populations and urges NIDDK to further explore the etiology of IBS and the efficacy of treatments for IBS symptoms.

Action taken or to be taken

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) continues to support studies that explore the causes of IBS and the efficacy of treatments for this disorder, one of the most common functional bowel disorders. NIDDK continues to support a Specialized Center of Research at the University of California, Los Angeles, to examine sex and gender differences in the interaction of gut and brain pathways in the development of IBS and other abdominal pain disorders. A recent study from this center suggests that people with IBS engage brain regions involved in threat appraisal and emotion more than healthy people do when facing an uncertain threat of pain. These results provide clues into the role of brain response to uncertainty in symptom experience in those with IBS. Another study from the Specialized Center of Research has shown that early adverse life events are associated with IBS, providing evidence of a strong relationship between several types of childhood trauma and the risk of developing IBS later in life. Likewise, further research from this center showed that, in an animal model, stress in early life causes changes in the brain that cause the animals to be more sensitive to abdominal pain later in life. In addition to supporting these studies, NIDDK is also leveraging this Specialized Center of Research to build upon the success of the IBS Outcome Study, a multi-center clinical trial with the goal of determining whether self-administered cognitive behavioral therapy is helpful in reducing IBS symptoms and overall burden. NIDDK is supporting a study that will combine the recruitment, assessment and treatment components of the IBS Outcome Study with the brain imaging technology at the Specialized Center of Research to investigate the neurobiological mechanisms underlying cognitive behavior therapy for IBS. The study will also develop tools to predict which patients may benefit from these treatments.

Also, on June 23-24, 2016, NIDDK convened a meeting titled “Functional Bowel Disorders Workshop: Future Directions in Pathophysiology, Diagnosis, and Treatment.” The workshop’s goal was to review recent advances in functional bowel disorders, including IBS, and to identify new directions for research. Among the topics discussed were new findings on the roles of gastrointestinal muscle and nerve cells in the development of IBS. Also discussed were recent advances in the understanding of genetic and environmental factors, including the microbiome and psychosocial factors that could contribute to IBS. The workshop participants discussed current and emerging strategies to manage and treat IBS, such as changes in diet and the effectiveness of current pharmaceutical therapies. New ways to diagnose IBS were also discussed, including efforts to identify and detect physiological changes associated with IBS. A summary of the workshop is planned to be published in a major scientific journal.

Kennedy's Disease

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned

Action taken or to be taken

Kennedy's disease, also known as spinal bulbar muscular atrophy (SBMA), is a rare genetic disorder. SBMA primarily affects men, who experience slowly progressive muscle atrophy and weakness as motor neurons, the nerve cells that control muscles, degenerate in the spinal cord. Symptoms usually begin in midlife, though sometimes as early as 18 years. The discovery of the gene defect that causes SBMA by Dr. Kenneth Fischbeck, now at the NINDS intramural program, provided the crucial starting point to develop treatments, but the path from gene to therapy is difficult. Developing a treatment requires understanding of how defective genes cause the disease, testing agents that target those mechanisms in cell and animal models, and validating clinical measures that can reliably detect whether a treatment is effective. Research on SBMA has shown encouraging progress in all of these steps. A clinical trial of a drug developed by a pharmaceutical company was recently completed at the NIH Clinical Center and other sites, and researchers are now analyzing the results. In addition to clinical research, intramural and extramural NIH laboratory research is also continuing on several fronts, using genetically engineered mice and fruit flies, as well as cell cultures derived from people with SBMA via stem cell techniques. Researchers, for example, are following up a key finding that, contrary to the longstanding view that the mutant protein acts directly on motor neurons, this protein also harms muscle cells, which then indirectly affect the neurons. Research on antisense therapy, which reduces the production of the mutant protein, is also promising. Several studies are dissecting the various steps at which the mutant protein is toxic to cells and how natural protein quality control systems in cells reduce the toxic effects. Each advance in understanding the disease mechanism potentially reveals additional targets for intervention.

Kidney Cancer

The Committee is concerned that the amount of meritorious scientific research on kidney cancer is not commensurate with the growing number of diagnoses, and encourages NCI to support a Specialized Program of Research Excellence in kidney cancer and other research programs for subtypes of kidney cancer, such as papillary and chromophobe, as well as diagnostic tests for early detection of the disease. The Committee requests an update in the fiscal year 2018 budget request on these efforts.

Action taken or to be taken

Kidney cancer includes renal cell carcinoma (RCC), a cancer that forms in the lining of very small tubes in the kidney that filter the blood and remove waste products, and renal pelvis carcinoma (RPC), which forms in the center of the kidney where urine collects. It also includes Wilms tumor, which is a type of kidney cancer that usually develops in children under the age of five. RCC is the most common cancer arising in the kidney. The increase in kidney cancer incidence in the U.S. is generally acknowledged to be due to increased screening from the growing use of imaging, with most of the increase being in localized disease and smaller tumors less than 4 centimeters. Renal cancer mortality rates have remained essentially unchanged during the same time period.

Many new agents have been approved by the FDA to treat patients with advanced RCC in the past several years, including drugs developed to inhibit pathways known as c-Met and VEGF that were approved in 2016. The National Cancer Institute (NCI) continues to support clinical trials that use these agents in combination to make treatment more effective, and to explore the efficacy of immunotherapy for RCC. NCI is also supporting research to identify biomarkers for the early detection of RCC.

The NCI Specialized Program of Research Excellence (SPORE) program supports kidney cancer research and currently funds two SPOREs focused on this disease⁸⁵. Research conducted by the Dana Farber/Harvard Kidney Cancer SPORE focuses on exploring tumor genetics, minimally invasive therapy, and immune immunotherapy for adult renal cell carcinoma. In August 2016, the NCI awarded a new Kidney Cancer SPORE grant to the University of Texas Southwestern Medical Center's Harold C. Simmons Comprehensive Cancer Center (UTSW). The investigators from this SPORE lead efforts to evaluate drugs to block the HIF2 protein, a driver of kidney cancer; to identify new subtypes of kidney cancer; to apply new technologies to predict the aggressiveness of imaging-diagnosed small renal masses in adult renal cancer; and to identify microRNAs that drive tumorigenesis in pediatric Wilms tumors.

The NCI-supported The Cancer Genome Atlas (TCGA) program published in January 2016 a comprehensive molecular characterization of papillary renal cell carcinoma (PRCC)—the second most common form of kidney cancer. The researchers confirmed that PRCC is at least two genetically and clinically distinct diseases; the authors further classified these distinct diseases into subtypes based on molecular and phenotypic features.⁸⁶ Other NCI-supported researchers are using the extensive kidney cancer genomic data from TCGA to advance our understanding of

⁸⁵ <http://trp.cancer.gov/spores/kidney.htm>

⁸⁶ <http://www.ncbi.nlm.nih.gov/pubmed/26536169>

genetic, molecular, metabolic, and clinical presentations of the heterogeneous disease of kidney cancer.

The examples highlighted above represent key research efforts from across NCI's diverse and expanding portfolio of kidney cancer research. The Institute continues to stimulate research to address important scientific questions relevant to kidney cancer and all cancer types, and looks forward to receiving proposals for future research efforts.

Liver Cancer

The Committee notes that the number of liver cancer cases has more than tripled since 1980 and the death rate for this cancer has continued to increase. The Committee continues to be concerned with the increasing incidence of liver cancer and its low 5-year survival rate.

Therefore, the Committee encourages NCI to continue to support liver cancer research across its portfolio, including research focused on the development of biomarkers to serve as early detection markers of cancer to offer the prospect of improved outcomes.

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

NCI continues to support research across its broad liver cancer portfolio, including research aimed at prevention and related risk factors, in conjunction with other NIH Institutes and Centers. Basic through translational and prevention research help the NCI identify biomarkers to improve health outcomes.

In 2014, NCI convened a workshop of experts to explore liver cancer research with the goal of identifying research questions and recommendations for coordinated research resources and initiatives. Building upon this effort, the NCI, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Allergy and Infectious Diseases (NIAID) and other NIH Institutes and Centers continue to explore collaborative research opportunities focusing on liver cancer and related conditions. The objectives of this future initiative include formation of a consortium to improve the surveillance of hepatocellular carcinoma (HCC) in high-risk populations, to increase the proportion of HCC detected at an early stage, and to better stratify patients at risk of developing HCC.

Additional highlights from NCI's comprehensive research portfolio include:

- Hepatocellular Carcinoma Epidemiology Consortium – This NCI-supported consortium is an interdisciplinary translational research effort that links liver cancer investigators across the United States to pool their research tools and resources. Currently, a Genome-Wide Association Study (GWAS) in HCC is investigating how the unique host genetic factors can predict HCC risk in non-viral cases. The study also examines how other markers may predict HCC development in patients with chronic HCV infection and clinical outcome in HCC, including response to therapy.
- Early Detection Research Network (EDRN) –The EDRN - a national infrastructure that supports the integrated development, validation, and clinical application of biomarkers for the early detection of cancer - includes the Hepatocellular Carcinoma Early Detection Strategy program that monitors cirrhotic patients for development of HCC and developing markers for early detection.
- National Clinical Trials Network (NCTN) – The NCI-supported NCTN recently launched a Phase III clinical trial⁸⁷ to study stereotactic radiation therapy for HCC. The trial is currently

⁸⁷<https://clinicaltrials.gov/ct2/show/NCT01730937?term=stereotactic+radiation&cond=hepatocellular+carcinoma&phase=2&rank=1>

open at 31 sites across the United States, as well as at four sites within NCTN's partnering Canadian Network Group. Additionally, patients with cholangiocarcinoma have enrolled into NCI's Molecular Analysis for Therapy Choice (MATCH) precision medicine clinical trial.

- The NCI has developed a series of phase II clinical trials designed to compare the outcomes of patients with HCC treated with either conventional radiation therapy or proton therapy. The goal of this trial is to show an improvement in survival for patients with non-surgically resectable cancer treated with proton therapy.⁸⁸
- Recently approved curative therapies for hepatitis C are expected to lead to a decrease in HCC incidence, as hepatitis C is a major underlying cause of this cancer.
- NCI intramural investigators are leading several cohort studies to examine risk factors for liver cancer in the United States, China, and Thailand. These studies also aim to identify clinically and biologically relevant biomarkers for early detection and molecular classification for HCC, and to define key cancer drivers for therapeutic intervention. Moreover, intramural teams are examining new ways to target treatments using antibodies,⁸⁹⁹⁰⁹¹ and are following leads on potential new biomarkers.⁹²⁹³⁹⁴

⁸⁸https://clinicaltrials.gov/ct2/results?term=hepatocellular+carcinoma&recr=Open&type=&rslt=&age_v=&gndr=&cond=&intr=proton+therapy&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=&rcv_e=&lup_s=&lup_e=

⁸⁹ <http://www.ncbi.nlm.nih.gov/pubmed/?term=25758784>

⁹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/?term=25929570>

⁹¹ <http://www.ncbi.nlm.nih.gov/pubmed/?term=25955255>

⁹² <http://www.ncbi.nlm.nih.gov/pubmed/?term=25833323>

⁹³ <http://www.ncbi.nlm.nih.gov/pubmed/?term=25953724>

⁹⁴ <http://www.ncbi.nlm.nih.gov/pubmed/?term=26058814>

Liver Disease

The Committee continues to be concerned by the morbidity and mortality of Hepatitis C-related liver disease and the development of cirrhosis, liver failure, and liver cancer in chronically infected persons with viral hepatitis. The Committee urges NIDDK to enhance multi-Institute collaborations on liver research to understand these diseases. The Committee encourages NIDDK and NIAID to collaborate research efforts in this area.

Action taken or to be taken

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a vigorous research portfolio related to viral hepatitis and other forms of liver disease. For hepatitis C-related liver disease, ground-breaking new direct-acting antiviral agents have demonstrated safety and efficacy in treating infection with the hepatitis C virus (HCV). NIDDK-supported research has contributed to past HCV treatment development and continues to advance understanding of how HCV infects cells and interacts with the host immune system to identify potential new therapeutic targets. Currently, NIDDK intramural researchers, in collaboration with intramural scientists at the National Cancer Institute (NCI), are developing a cohort of 200 patients with cirrhosis – a condition in which the liver slowly deteriorates and is unable to function normally due to chronic, or long lasting, injury – who will be treated with direct-acting antiviral drugs against hepatitis C and followed with biomarkers and advanced imaging for evidence of liver cancer using genomic data. For other major causes of chronic hepatitis-related liver disease for which therapeutic options are more limited—such as the hepatitis B and D viruses—NIDDK supports a wide range of research programs. For example, the Hepatitis B Research Network aims to advance understanding of disease processes and how the disease progresses over time, as well as to identify effective approaches to treatment with currently available and emerging therapies. In addition, NIDDK’s intramural scientists are advancing the development of ground-breaking therapies for hepatitis D, which can infect people with hepatitis B and have potentially severe consequences.

NIDDK has collaborated with other NIH Institutes and Centers to support research on viral hepatitis and other liver diseases. For example, together with National Heart, Lung, and Blood Institute (NHLBI) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), NIDDK supported recent initiatives to encourage small businesses to address viral hepatitis research opportunities. One of the grants currently supported through this initiative is developing a therapeutic vaccine for chronic hepatitis B designed to stimulate an immune response sufficient to clear the virus from the body. Staff from NIDDK and the National Institute on Drug Abuse (NIDA) also co-lead the Trans-NIH Committee on Viral Hepatitis, with participation from many NIH Institutes and Centers with an interest in viral hepatitis research, including the National Institute of Allergy and Infectious Diseases (NIAID). The Committee provides coordinated NIH input to HHS on its development of viral hepatitis action plans and progress toward the plans’ research goals.

NIAID-supported basic research on viral hepatitis is focused on understanding the biology of these viruses and how they can lead to liver disease. NIAID actively engages with NIDDK and other scientific partners to advance critical areas of viral hepatitis research. NIAID also supports translational and clinical research on viral hepatitis to inform the development and use of vaccines and therapeutics to prevent or treat associated liver disease. NIAID supports the Hepatitis C Cooperative Research Centers, which aim to understand the immune response to

HCV to identify factors critical to protection against HCV and successful clearance of HCV infection. In addition, NIAID scientists have identified key immune signatures in response to treatment with the currently available direct-acting HCV antiviral drugs. These signatures could potentially serve as biomarkers for relapse in patients undergoing HCV treatment. NIAID also is funding a Phase II clinical trial of a candidate HCV vaccine, as well as screening compounds to discover candidate therapeutics for viral hepatitis. Additionally, NIAID supports research to understand the relationship between HIV and HCV in co-infected individuals, including a partnership with NIDDK and other NIH Institutes and Centers to support projects under the *Multidisciplinary Studies of HIV and Viral Hepatitis Co-Infection* funding opportunity announcements.

Lung Cancer

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

The National Cancer Institute (NCI) continues to focus on cutting edge lung cancer research. The Specialized Program of Research Excellence (SPORE) program expanded to four Lung Cancer SPOREs across the United States last year, with the funding of the Yale SPORE in Lung Cancer focusing on projects in immunotherapy, precision medicine, drug development, and smoking cessation. Recent studies by Lung Cancer SPORE investigators have looked at various pathways and molecular targets as new avenues to understand and treat lung cancer.

The NCI-supported, public-private collaboration “Lung Cancer Master Protocol” (Lung-MAP)⁹⁵ continues to progress its multi-drug, multi-sub-study, biomarker-driven squamous cell lung cancer precision clinical trial. This innovative adaptive design allows for additional sub-studies to be added to evaluate new promising treatment approaches. Accordingly, the Lung-MAP team announced in 2016 that the trial now includes new immunotherapy drugs and treatment methodologies.⁹⁶

Among the NCI-supported lung cancer clinical trials are several within the “Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST)⁹⁷ precision medicine program. The ALCHEMIST trials involve genetic screening of tumors and testing of post-surgical drug treatments to evaluate if specific genetic markers can be used to effectively target FDA-approved drugs to improve patient outcomes. As of 2016, there are active ALCHEMIST trials currently enrolling patients to investigate the genetic screening component and two targeted treatments—with ALK and EGFR inhibitors. In addition, a new treatment arm with immunotherapy was added recently to the ALCHEMIST. Patients whose tumors do not have the EGFR or ALK gene change may be able to enroll in this study arm, which compares the immunotherapy drug nivolumab (Opdivo®) with observation.

The Cancer Genome Atlas (TCGA) has completed the sample collection and made public all the data for lung adenocarcinoma, lung squamous cell carcinoma, and mesothelioma. TCGA researchers also published in *Nature* a comprehensive molecular profile of lung adenocarcinoma.⁹⁸ NCI-supported scientists used TCGA data to show in their March 2016 *Science* article that chemotherapy-induced tumor mutations can reduce sensitivity to immunotherapy in some lung cancer patients.⁹⁹ TCGA data is also helping advance drug discovery efforts in the private sector—Loxo Oncology used TCGA data to identify fusions of the TRK gene as a prime target,¹⁰⁰ and in July 2016, the FDA designated their drug LOXO-

⁹⁵ <http://www.lung-map.org/about-lung-map>

⁹⁶ <http://www.lung-map.org/media/press/lung-map-precision-medicine-trial-makes-exciting-changes-new-science-and-treatment>

⁹⁷ <http://www.cancer.gov/types/lung/research/alchemy>

⁹⁸ <http://www.nature.com/nature/journal/v511/n7511/full/nature13385.html#group-1>

⁹⁹ <http://science.sciencemag.org/content/early/2016/03/02/science.aaf1490.full>

¹⁰⁰ <http://www.cancer.gov/about-nci/organization/ccg/blog/2016/tcga-loxo-101-targeted-therapy-development>

¹⁰¹ <http://cancergenome.nih.gov/researchhighlights/tcgainaction/tcga-data-used-for-loxo101-drug-development>

101 as a “breakthrough therapy.” Clinical trials with LOXO-101 have demonstrated tumor regression in lung cancer, as well as five other cancer types.

Lung Disease

The Committee applauds NHLBI's efforts on primary lung disease prevention, from prenatal lung development through the aging process. The Committee requests that NHLBI report on its efforts to prevent lung disease, which is now the third leading cause of death in the United States, in the fiscal year 2018 CJ.

Action taken or to be taken

The National Heart, Lung, and Blood Institute (NHLBI) recognizes that primary prevention strategies may ultimately provide the most effective means of reducing the substantial morbidity and mortality of lung diseases. Although research into the early origins of pulmonary disease is challenging, recent advances in technology and in understanding lung biology have made it possible to envision a new era of primary prevention for chronic lung diseases. To that end, NHLBI convened a workshop of expert pulmonary scientists in 2013, entitled "Primary Prevention of Chronic Lung Diseases," to explore opportunities for research that would define and promote optimal lung health by identifying modifiable molecular, cellular, and physiological events that represent a departure from optimal function. Recommendations developed in this workshop identified many opportunities and provided a rationale for interventions that may restore normal function or abrogate progression to clinical lung disease.

Based on the workshop's recommendations, NHLBI released two funding opportunity announcements in 2015 that focused on better definition of pre-symptomatic stages of chronic lung diseases. Studies funded in response to these announcements are defining and validating specific markers of pulmonary health that could serve to distinguish pre-symptomatic lung disease(s) from normal variability in lung function. That information will facilitate development of appropriate strategies to prevent disease and optimize and promote lung health.

In addition to these initiatives, NHLBI is funding two primary prevention trials in young children at increased risk for asthma. Since the majority of persistent asthma presents as repeated wheezing events during the preschool years, a highly effective approach to prevention may be to eliminate predisposing pulmonary and immune system changes during this time period. These studies are particularly important for addressing health disparities since racial and ethnic minority populations are disproportionately affected by asthma.

NHLBI continues to support basic, translational, and clinical research for the primary prevention of chronic lung diseases. Our strategic leadership of investigations by the pulmonary research community is fostering a paradigm-changing approach to enhancing lung health and preventing chronic lung disease. Long term goals of NHLBI-supported research on lung disease include both a reduction in the number of people affected, and an overall improvement in the respiratory health of those who are affected.

Lymphangiomyomatosis (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 means of expanding research on LAM and urges NHLBI to use all available mechanisms as appropriate to stimulate a broad range of clinical and basic research. The Committee commends NIH for supporting multi-center LAM trials and encourages additional support of such trials.

Action taken or to be taken

Lymphangiomyomatosis (LAM) is a rare, slowly progressive disease that affects women almost exclusively and gradually destroys the lungs, often leading to death from respiratory failure. LAM is characterized by the proliferation of smooth muscle-like cells and cystic lesions in the lung; it may occur sporadically or in association with tuberous sclerosis complex (TSC). While lung transplant is a treatment option for LAM, recent research efforts have focused on finding effective drug therapies. Sirolimus (rapamycin), the first FDA-approved treatment for LAM, was approved in 2015, based on research supported by the NIH, including the Multicenter International LAM Efficacy of Sirolimus (MILES) trial.¹⁰²

The National Heart, Lung, and Blood Institute (NHLBI) continues to support research to identify the causes and treatments of LAM. Although the MILES trial showed that sirolimus can stabilize lung function in LAM patients with advanced disease, it is not known if low-dose sirolimus can safely prevent disease progression in LAM patients with well-preserved lung function. The NHLBI recently funded the Multicenter Interventional Lymphangiomyomatosis Early Disease (MILED) trial, which is designed to answer this important question. The NHLBI has also partnered with the National Center for Advancing Translational Sciences (NCATS) to co-fund the Multicenter International Durability and Safety of Sirolimus (MIDAS) study, which will examine long-term outcomes of sirolimus treatment among LAM patients.

Additional research is uncovering the molecular mechanisms of LAM and revealing potential new treatment options. For example, an NHLBI-funded study found that metastasis (proliferation and spreading) of LAM cells appears to depend on a rise in the activity of certain kinases (a type of enzyme). The researchers also found that kinase inhibitor compounds reduced LAM metastasis in mice, which suggests that the inhibitors might be an effective treatment for LAM. Following up on these promising results, researchers are conducting a clinical trial to evaluate the potential benefit of the kinase inhibitor saracatinib in LAM patients.

NHLBI also supports research on biomarkers for LAM. In one such project, intramural and extramural investigators are collaborating to determine if LAM biomarkers can be used to develop personalized strategies for sirolimus dosing, and whether circulating LAM cell burden can be used as a quantitative biomarker of LAM progression. Other NHLBI-funded studies are seeking to better understand why LAM affects women almost exclusively and to determine the mechanisms of lung destruction in LAM.

To further promote LAM research, the NHLBI co-funds LAM tissue collection, storage, and distribution by the National Disease Research Interchange. This program has distributed more

¹⁰² (<http://www.nejm.org/doi/pdf/10.1056/NEJMoa1100391>)

than 700 tissue specimens to 15 LAM investigators in the past four years. The NHLBI also provided funding for the 2016 International LAM Research Conference during which experts in the field presented state-of-the-art research and charted new research directions.

Lymphatic Research and Lymphatic Disease

The Committee commends the trans-NIH Coordinating Committee for Lymphatic Research, which sponsored a historic Lymphatic Symposium in 2015. The Committee supports building on this momentum 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 greater 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 Lymphatic Symposium in 2015 was to increase multidisciplinary collaborations and encourage interest by new investigators in lymphatic research. Since the symposium, the National Heart, Lung, and Blood Institute (NHLBI) has seen an increase in grant applications from trainees, new investigators, and multidisciplinary research teams interested in lymphatic disease. Some of these research projects have started to address the role of the lymphatic system in pathogenesis of cardiovascular and pulmonary diseases, and organ transplantation.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) also continues to support research on lymphatics in the digestive tract, which are crucial for major functions of digestion and immunity, including transport of lipids to the vascular system and the rest of the body, recovery of excess fluid from digestive tissues, and immunity in the face of the resident microbiome and invading organisms. The NIDDK has continued its Funding Opportunity Announcement, PAR-15-306, Lymphatics in Health and Disease in the Digestive System, Kidney, and Urinary Tract (R01), which offers special review of lymphatics projects within the Center for Scientific Review.

In addition, NIH continues to receive grant applications investigating the development of the lymphatic system, and genetic mutations and other conditions that result in its malfunction observed in congenital lymphatic diseases and lymphedema. We expect these trends will continue in the coming year. As we continue to receive more applications in lymphatic research, study sections in the Center for Scientific Review have been including more expertise in lymphatic biology and diseases.

In 2017, the North American Vascular Biology Organization will be holding a Lymphatics Symposium to continue the theme of the 2015 Symposium. In collaboration with the NIH, they plan to continue this symposium series every other year, which we anticipate will also help to encourage interest and collaboration in lymphatic research.

Marijuana Research

The Committee is concerned that marijuana public policies in the States are being changed 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. The Committee requests a report in the fiscal year 2018 budget request on these efforts.

Action taken or to be taken

Regular use of marijuana among adolescents is correlated with changes in the developing brain and negative social and behavioral outcomes¹⁰³ however it is currently unclear how changes in local, state, and national policies will impact adolescent use and related outcomes. There are many open questions related to marijuana legalization that research can help to address. Over the last few years the National Institute on Drug Abuse (NIDA) issued three funding opportunity announcements to explore the impact of changes in state marijuana policies on health outcomes including:

- 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

NIDA funded 24 grants resulting in over 160 publications so far that have examined how state policy changes have affected:

- 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 specific details of these policies and their implementation makes a big difference for the impact on society. Factors such as registration requirements, the breadth of medical 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. 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 going forward.

More research is also needed to develop prevention interventions that target marijuana use among youth in the context of changing norms, 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.

¹⁰³ 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.

NIDA-supported science aims to address these gaps and to help inform decision making related to state and federal marijuana policies. 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 therapeutic potential of marijuana-derived compounds for pain and addiction.

Medical Foods

The Committee is encouraged by the opening of a new Office of Nutrition Research. The Committee requests the Office develop research initiatives that explore the impact of medical foods on nutrition and digestive disease management.

Action taken or to be taken

Research to determine the impact of nutrition status on disease prevention and management, including the role of medical foods,¹⁰⁴ is one of the priorities of the NIH and its Office of Nutrition Research, which is housed administratively within the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), but works collaboratively to coordinate nutrition research across the NIH. As of August 2016, the NIH had 597 active research projects related to nutrition and digestive diseases, and 14 active projects specifically related to medical foods and/or inborn errors of metabolism. Inborn errors of metabolism are rare genetic disorders caused by defects in enzymes that metabolize food components; common examples of these disorders include phenylketonuria, lysosomal storage diseases, and urea cycle disorders. The studies of inborn errors of metabolism also include investigations into the disease processes and new technologies for earlier screening, which may help to improve the timely treatment of these disorders. These grants also include research on medical foods and other conditions, such as nonalcoholic fatty liver disease, diabetes, and iron-deficiency anemia.

Assessing the impact of medical foods will continue to be an integral part of the Office of Nutrition Research's future research agenda. The Office is currently working to develop a strategic plan for NIH nutrition research, to be crafted with help from staff of the Institutes and Centers across the NIH, as well as from key stakeholders in the scientific and patient advocacy communities. An important area for the research plan will be applied and medical nutrition research, including research related to medical foods and the management of digestive and liver diseases (e.g., Crohn's disease, eosinophilic esophagitis, and biliary atresia), as well as disorders related to inborn errors of metabolism such as those of fatty acid oxidation, amino acid metabolism, and organic acid metabolism. The NIDDK, in conjunction with *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute of Neurological Disorders and Stroke (NINDS), has an existing initiative to encourage research on "Innovative Therapies and Tools for Screenable Disorders in Newborns," which includes research into therapies such as medical foods for inborn errors of metabolism.

¹ This response uses the term "medical food" according to its definition in the Orphan Drug Act, which defines it as "formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."

Melanoma

Melanoma is the most responsive tumor type to the new generation of immune therapies. As many phase 3 trials-the essential platform to provide high quality annotated biospecimens for biomarker discovery-are launched under the aegis of the NCI, and industry has specimens that have not been fully analyzed, the Committee urges a coordinated effort to analyze biospecimens across NCI and industry trials and treatment type with the most advanced technologies. The current Exceptional Responders Initiative has been focused primarily on chemotherapy which has been proven to be ineffective in improving outcomes for the majority of patients with melanoma. This initiative could be extended to exceptional responders to targeted therapies and/or immunotherapies. The Committee continues to encourage efforts to use advances in genomic, proteomic, and digital imaging technologies for early detection, research to understand genetic changes that occur in melanogenesis and mechanisms that underlie clinical dormancy to provide effective means of preventing recurrence. The Committee requests an update on these requests in the fiscal year 2018 CJ.

Melanoma

The Committee encourages consideration of a coordinated effort to analyze biospecimens across clinical trials. The Committee continues to encourage efforts to use advances in genomic, proteomic and digital imaging technologies for early detection research to understand genetic changes and mechanisms that underlie clinical dormancy. The Committee encourages NCI to consider convening a multisector, multidisciplinary strategic planning committee to provide recommendations and chart a collaborative path forward to support evidence for melanoma screening. The Committee requests an update on melanoma activities ongoing and planned in the fiscal year 2018 budget request.

Action taken or to be taken

The National Cancer Institute (NCI) recognizes that early detection, screening, and prevention are critical to reducing the mortality and morbidity from melanoma. NCI routinely uses a variety of planning and coordinating mechanisms to manage its cancer research portfolio, within the Institute, across NIH and other Federal agencies, and in collaboration with the research and advocacy communities. These efforts address factors such as public health priorities, burden of disease, and scientific gaps and opportunities of greatest potential by examining current knowledge and pursuing approaches that build on basic scientific discoveries. This strategic approach guides NCI's ongoing planning efforts, while allowing the Institute the needed flexibility to respond to scientific opportunities that have emerged in the melanoma research field in recent years.

In addition to funding research to better understand the disease, NCI invests in behavioral research to support the development, evaluation, and dissemination of interventions to improve sun protection as a public health priority. In May 2016, NCI launched the Moles to Melanoma online tool¹⁰⁵ to educate the public about the appearance and features of common moles (which rarely pose a health risk), those of atypical moles (which are markers of increased melanoma risk), and actual melanomas. This tool is based on four decades of research and photographs

¹⁰⁵ <http://analysistools.nci.nih.gov/nevustool/>

from patients enrolled in the NCI Familial Melanoma Study run by the Division of Cancer Epidemiology and Genetics (DCEG).

The collaborative NCI Specialized Program of Research Excellence (SPORE) program currently funds five SPOREs focused on melanoma, supporting translational activities such as the development of highly promising immunotherapies and combinational targeted pathway therapy approaches are addressing tumor resistance and recurrence. The SPOREs use extensive genomic analysis of tumor samples to characterize risk and prognostic biomarkers, and novel animal and cell culture models are used to test therapeutic or preventative agents. The SPOREs collaborate to share ideas, biospecimens, results, data, resources, and clinical populations.

NCI-supported scientists are leveraging the public melanoma “The Cancer Genome Atlas Network” (TCGA) data to advance our understanding of the disease. For example, in their March 2016 *Cell* article¹⁰⁶, researchers at the UCLA Jonsson Comprehensive Cancer Center utilized TCGA data to define genomic features of responsiveness to immunotherapies in metastatic melanoma. NCI has also initiated a major research effort at the Frederick National Laboratory for Cancer Research with the goal of identifying innovative approaches for cancers driven by mutations of the RAS family of genes. Progress in this initiative has the potential to reduce mortality in a broad spectrum of cancers, including melanoma.

NCI continues to focus on developing novel and personalized cancer therapies in its support of melanoma clinical trials. Current efforts are underway to evaluate the combination of autologous, melanoma-targeted cytotoxic T-lymphocytes with immunotherapy drugs (ipilimumab, aldesleukin) in patients with metastatic melanoma. Additional clinical trials are focused on using tumor vaccines as a monotherapy in patients with advanced accessible solid tumors, or using tumor vaccines in combination with immune checkpoint inhibitors in metastatic melanoma patients.

In January 2016, the NCI entered into a cooperative research and development agreement (CRADA) with the private biotech company SolaranRx to develop a new class of precision radiopharmaceutical therapies and companion imaging agents for metastatic melanoma.¹⁰⁷ The drug, SRX-1177, targets melanocortin-1 (MC1) receptors that are overexpressed in about 80% of human melanoma. NCI’s Center for Advanced Preclinical Research (CAPR) is working with the private biotech company to develop the novel, precision-targeted diagnostic and therapeutic compound.

NCI’s Exceptional Responders Initiative aims to understand the molecular underpinnings of exceptional responses to treatment, primarily via chemotherapy, in cancer patients. These cases can be rare cases of complete or partial response, or cases whose responses lasted an exceptionally long time. The initiative is expected to provide important insights about many

¹⁰⁶ Willy Hugo, Jesse M. Zaretsky, Lu Sun, Chunying Song, Blanka Homet Moreno, Siwen Hu-likeskovan, Beata Berent-Maoz, Jia Pang, Bartosz Chmielowski, Grace Cherry, Elizabeth Seja, Shirley Lomeli, Xiangju Kong, Mark C. Kelley, Jeffrey A. Sosman, Douglas B. Johnson, Antoni Ribas, Roger S. Lo. Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma. *Cell*. Volume 165, Issue 1, 24 March 2016, Pages 35-44.

¹⁰⁷ Melanie Lux. SolaranRx Signs Research Agreement with the National Cancer Institute to Advance Metastatic Melanoma Theranostic. *SolaranRx Newsroom Press Releases*. 7 January 2016.

cancers, including melanoma. So far, five cases of melanoma have been accepted in to the Exceptional Responder study.

Metastatic Brain Tumor Research

The incidence of metastatic brain tumors has been increasing, largely due to the fact that more Americans are surviving and living longer after treatment for other cancer diagnoses. While the increased incidence is a significant cause of concern, brain metastases are often treatable if diagnosed in a timely manner. The Committee encourages NCI to continue to involve stakeholders in the brain tumor community in its research efforts to develop strategies that improve our understanding of the molecular basis for cancer metastasis to the brain, detection through enhanced imaging, early intervention, and treatment.

Action taken or to be taken

The National Cancer Institute (NCI) provides support for five Specialized Programs of Research Excellence (SPoREs) focused on brain cancer, located at Duke University Medical Center, Massachusetts General Hospital, the Mayo Clinic, the University of California, San Francisco, and the University of Texas/MD Anderson. SPoRE projects include studies focused on identifying chromosomal and genetic variants that can be used for diagnosis and targeted therapies, non-invasive brain imaging, the tumor microenvironment, cell signaling pathways, and the use of immunotherapies to treat brain tumors.

The Neuro-Oncology Branch (NOB), a critical component of the Brain Tumor Program at NCI's Center for Cancer Research (CCR), is an integrated clinical, translational, and basic research program that engages the strengths and resources of both the NCI and the National Institute of Neurological Disorders and Stroke (NINDS) to develop novel experimental therapeutics for children and adults with tumors of the brain and spinal cord. The Brain Tumor Clinic, part of the NOB, has developed close relationships with outside institutions and with the extramural research groups, specifically the Central Nervous System (CNS) Tumor Consortium, and provides a referral base for patients with CNS neoplasms and their physicians to obtain information and advice about potential therapeutic options.

Recognizing that a more robust understanding of cell biology may elucidate new therapeutic pathways, NCI's Tumor Metastasis Branch, in the Division of Cancer Biology (DCB), funds research centered on how variations in cellular structure, the endocrine system, a patient's immune environment, and the tumor microenvironment contribute to metastases. Since 2006, DCB has supported the Tumor Microenvironment Network (TMEN) through ten cooperative agreements across eleven institutions. The TMEN encourages collaborative efforts between its network members to stimulate research aimed at a comprehensive understanding of the composition of the stroma in normal tissues, as well as its roles in tumor initiation, progression, and metastasis.

The NCI continues to involve various stakeholders from the brain tumor community in our research efforts to increase our knowledge and understanding of metastatic brain tumors. The Brain Tumor Epidemiology Consortium (BTEC), for example, is an open scientific forum organized to foster the development of multi-center, international, and interdisciplinary collaborations that will lead to a better understanding of the etiology, outcomes, and prevention of brain tumors. The Institute also includes advocates from the brain tumor community in the NCI research process. Advocates participate in a wide range of NCI activities, including peer review panels, advisory boards, educational materials review, and scientific steering committees. The

unique viewpoint that research advocates bring to the cancer research process helps make scientific advances more timely and effective for people living with cancer.

Military Hospitals and Cancer Centers Collaboration

The Committee is aware that formal alliances between American military hospitals and NCI-designated cancer centers would provide an ideal context to facilitate research on the causes, prevention, and treatment of cancer in military personnel and their families. The Committee encourages NCI to explore opportunities for collaborative clinical research efforts between American military hospitals and NCI-designated cancer centers. The Committee urges NCI to focus on populations with significant health disparities, including multiethnic populations.

Action taken or to be taken

There are several National Cancer Institute (NCI) programs that have made collaborations between American military hospitals and NCI-Designated Cancer Centers possible, including the NCI Cancer Centers Program, the NCI Community Oncology Research Program (NCORP), and several partnership opportunities, such as the Feasibility Studies to Build Collaborative Partnerships in Cancer Research and Comprehensive Partnerships to Advance Cancer Health Equity (CPACHE). NCI's Center for Cancer Research's partnership with Walter Reed National Military Medical Center serves a strong example of such collaborations.

The 69 NCI-Designated Cancer Centers, located in 35 states and the District of Columbia, are the backbone of NCI's programs for studying and controlling cancer, with research studies ranging from basic laboratory research to clinical assessments of new treatments. Many of the NCI-Designated Cancer Centers are engaged in collaborations with military hospitals. For example, the University of Colorado Cancer Center is a consortium center, representing universities, an HMO, and the Denver Veterans Affairs Medical Center. In addition, the Case Comprehensive Cancer Center at Case Western Reserve University, another NCI-Designated Cancer Center, is organized into nine interdisciplinary scientific programs that together include more than 350 members across its affiliated institutions, including the Louis Stokes Cleveland VA Medical Center.

The NCI NCORP is a national network of investigators, cancer care providers, academic institutions, and other organizations that conduct multi-site cancer clinical trials and studies in diverse populations in community-based healthcare systems across the United States and Puerto Rico. Several NCORP community sites include NCI-Designated Cancer Centers and military hospitals as collaborators. For example, the Hawaii Minority Underserved NCORP includes the University of Hawaii Cancer Center and the Tripler Army Medical Center; the Columbia University Minority Underserved NCORP includes the Herbert Irving Cancer Center and the Bronx Veterans Administration Medical Center; the Medical University of South Carolina Minority Underserved NCORP includes the Hollings Cancer Center and the Ralph H. Johnson Veterans Administration Medical Center; and the South Texas Pediatric Minority Underserved NCORP includes the University of Texas Health Science Center at San Antonio and Brooke Army Medical Center. Each of these examples are comprised of patient populations that include at least 30 percent racial/ethnic minorities or rural residents.

In 2011, NCI's Center for Cancer Research (CCR) established a memorandum of understanding with Walter Reed National Military Medical Center (WRNMMC) with the goals of establishing protocols for cross-agency participation in cancer-related research and clinical trials, providing training and skills enhancement for members of both the DoD and CCR workforces, and encouraging material and professional resource sharing. This partnership led to the Tri-Federal

Cancer Initiative, which includes CCR, WRNMMC, and the Uniformed Services University of the Health Sciences (USUHS). The Initiative has established working groups focused on prostate cancer, breast cancer, lung cancer, bioinformatics, pediatric oncology, gynecologic cancers, and cancer prevention.

Mitochondrial Disease

The Committee commends 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 understands numerous ICs are involved in a variety of research efforts related to mitochondrial disease and dysfunction. The Committee requests an update on the steps NIH has taken, on-going, and planned in the fiscal year 2018 budget request.

Action taken or to be taken

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

Basic science related to mitochondrial biology is also conducted in NCI's intramural program, where researchers examine the roles of the protein ubiquitin system in mitochondria and focus on mitochondrial stress responses. 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. 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 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 respond 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. 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. NCI also supports four Outstanding Investigator Awards (OIA) 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 Disorders 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 and a new activity under development on the Molecular Mechanisms of Fatigue.

Mitochondrial Disease

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. The Committee looks forward to the pending publication of a report in follow up to the December 2014 workshop on Nutritional Interventions in Primary Mitochondrial Disease that will identify a research agenda for evidence-based nutritional interventions for mitochondrial disorders. With the growing recognition mitochondrial disease provides a window into understanding and treating many conditions that afflict large segments of the population, the Committee strongly encourages the Director to urge an aggressive research effort around primary mitochondrial disease as well as mitochondrial function and dysfunction.

Action to be taken:

The NIH funds a wide range of research on mitochondrial disease and function, facilitated by the Trans-NIH Mitochondrial Disease Working Group, which is led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute of General Medical Sciences (NIGMS), and the National Institute of Neurological Disorders and Stroke (NINDS), and which meets quarterly to coordinate research efforts. In addition, NINDS, NICHD, and the Office of Dietary Supplements (ODS) support the North American Mitochondrial Disease Consortium (NAMDC), which conducts research on primary mitochondrial diseases and has developed a patient registry, a biorepository, consensus criteria for diagnosis, infrastructure for clinical research across 18 centers, and a clinical fellowship training program to help foster the future workforce in mitochondrial disease research. Ongoing clinical studies within the consortium include natural history studies of three mitochondrial disorders, a phase I clinical trial for mitochondrial neurogastrointestinal encephalomyopathy, and studies to investigate nutritional supplementation for mitochondrial diseases.

Conference proceedings for the 2014 workshop on Nutritional Interventions in Primary Mitochondrial Disorders: Developing an Evidence Base were published in the November 2016 issue of *Molecular Genetics and Metabolism*.¹⁰⁸ The summary outlines a mitochondria research agenda developed at the workshop, which has already yielded some concrete results to advance the field. To address challenges in clinical trial design for rare mitochondrial disorders, a Critical Path Innovation Meeting (CPIM) was held at the Food and Drug Administration in October 2015. Attended by representatives from the North American Mitochondrial Diseases Consortium, academia, constituency groups, and industry, meeting participants addressed several important clinical trials design issues, including specific challenges of research on therapeutics in mitochondrial diseases; clinical outcome measure selection; mitochondrial treatments as dietary supplements, medical foods, or drugs; and biomarker selection in mitochondrial disease.

Another outcome of the 2014 workshop was the establishment of the Mitochondrial Model Organisms and Cellular Systems Working Group to promote rigorous research of nutritional interventions for mitochondrial dysfunction. This Working Group, co-led by the ODS and the National Cancer Institute and composed of experts in pre-clinical and clinical investigations of mitochondrial function, has drafted a comprehensive review manuscript that identifies areas of

¹⁰⁸ Camp KM, Krotoski D, Parisi MA, Nutritional Interventions in Primary Mitochondrial Disorders: Developing an Evidence Base. *Mol. Genet. Metab.* 119 (2016) 187-206.

research needs and assesses current and emerging model systems for investigating mitochondrial dysfunction, disease states, and health outcomes. This manuscript will be submitted to a peer-reviewed journal in early 2017.

NIH Institutes and Centers also are pursuing mitochondrial-related research specific to their missions. NICHD supports basic research on mitochondrial morphology and function, animal models of primary mitochondrial disorders, studies of natural history and pathophysiology, the role of mitochondria in reproductive function, neuroprotection in neonatal hypoxia, and development of treatment interventions for mitochondrial diseases. In FY 2016, NICHD issued a new funding opportunity announcement to stimulate research on oocyte mitochondrial function. NINDS funds research on normal mitochondrial function in the nervous system and on disease mechanisms and potential interventions for primary mitochondrial diseases and neurological conditions associated with mitochondrial dysfunction, including seizures and neurodegenerative diseases.

Muscular Dystrophy Action Plan

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned

Action taken or to be taken

The interagency Muscular Dystrophy Coordinating Committee (MDCC) coordinates muscular dystrophy activities across the NIH and with other federal agencies. The *2015 MDCC Action Plan for the Muscular Dystrophies* was approved by the MDCC in November 2015. The 2015 plan, like the 2005 plan before it, contains specific research objectives and other goals for understanding the causes of the dystrophies and its impact on patients, families and society, accelerating diagnosis and treatment, and improving the lives of individuals living with muscular dystrophies. The updated plan reflects research advances and new scientific methodologies such as in-depth genetic analyses, emphasizes similarities among different forms of muscular dystrophy, and includes patient perspectives in a number of objectives.

The Action Plan is meant to serve as a guide map for all MDCC member agencies and organizations and thus is a central focus for coordination of research and other patient-centered activities in the muscular dystrophies. While the Action Plan includes some objectives for specific types of muscular dystrophies, most objectives address shared needs of the field as a whole. The 2015 MDCC Action Plan for the Muscular Dystrophies has added value in that it can serve as both a starting point and a guide for individual disease communities to tailor strategic plans for their specific types of muscular dystrophy. Much of NIH's currently funded portfolio addresses many of the Action Plan objectives, and NIH welcomes research proposals to address objectives in the Plan that fall within NIH's mission. A newly formed subgroup of the MDCC on Access to Care and Services hopes to identify strategies to overcome some of the obstacles that patients and families experience in accessing care and services; many of these issues were touched on in the 'Living with Muscular Dystrophy' section of the Action Plan and discussed in more detail at the April 2016 MDCC meeting.

Multiple Sclerosis Research – Update

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

NINDS funds research to understand the disease processes and to develop treatments for relapsing-remitting and progressive forms of multiple sclerosis (MS). NINDS-funded scientists are conducting studies to identify genetic and environmental risk factors for MS, and to determine whether factors linked to MS risk in adults, such as specific immune system genes, Epstein-Barr virus infection, cigarette smoke, and vitamin D levels, also are linked to pediatric MS. Because two to three times as many women have MS as men, researchers are studying how estrogen affects MS. Researchers are investigating how myelin (the fatty sheath that insulates axons) forms and breaks down in MS, immune system function and dysfunction in the brain, blood-brain-barrier breakdown in MS, and factors that repair or protect against neurodegeneration. NINDS funds preclinical therapy development that is focused on finding treatments that stop or reverse the course of the disease by modulating immune system function, by repairing damaged myelin, or by protecting neurons from damage. Years ago NINDS intramural researchers conducted initial studies showing that daclizumab, a monoclonal antibody therapy, could benefit MS patients. After further development and testing by private industry, the FDA approved daclizumab (brand name Zinbryta) in May of 2016 for the treatment of relapsing-remitting MS.

Although multiple therapies have been shown effective for relapsing-remitting MS, there are no treatments for progressive MS. As part of a public-private partnership with the pharmaceutical company Medicinova and the National MS Society, the NINDS NeuroNEXT phase II clinical trials network is testing a potential neuroprotective drug for progressive MS called ibudilast (MN-166). Enrollment is complete, and initial results are expected soon. Within the NIH Clinical Center, NINDS investigators are conducting early-stage clinical trials to test treatments for progressive MS, including a trial testing the safety and effectiveness of the experimental drug idebenone in patients with secondary progressive MS. The lack of a biomarker that can assess the underlying neurodegeneration that is associated with progressive MS has slowed the development of treatments. The NINDS and the National MS Society held a workshop in February 2016 to identify the highest priority research questions for developing progressive MS biomarkers and to identify ways to leverage current resources to address those priorities, and they expect to publish the recommendations in the coming months. NIAID supports research to better understand the immunologic basis of MS. In a recent NIAID-supported study in a mouse model of MS, researchers showed that an inflammatory signal drives the expression of a protein that is essential for disease development. This finding suggests a potential link between environmental stimuli that cause inflammation, such as infection, and the development of MS. In a separate study, NIAID-funded researchers found that specific types of immune cells (myelin-reactive T cells) in patients with MS caused higher levels of inflammation compared to healthy individuals, suggesting that underlying differences in these immune cells between healthy individuals and those with MS may be fundamental to MS disease development. This research may help us understand the mechanisms of these cells and identify targets for the development of new therapeutics for MS.

Muscular Dystrophy (MD)

The Committee understands the MD Action Plan was updated in 2015. The Committee encourages NIH consider meritorious research projects aligned to the updated plan.

The Committee requests an update in the fiscal year 2018 budget request on activities NIH is planning to facilitate clinical trial and research infrastructure to improve performance of clinical trial endpoints and validate biomarkers of the disease. The Committee encourages NIH, in coordination with FDA and other agencies, to consider a Duchenne follow-on meeting to examine the current state-of-the-science of exon skipping and targeted therapeutics.

Action taken or to be taken

The *2015 Muscular Dystrophy Coordinating Committee (MDCC) Action Plan for the Muscular Dystrophies* is meant to serve as a guide for all MDCC member agencies and organizations. While NIH's current portfolio in muscular dystrophy addresses many of the Plan objectives, NIH continues to welcome additional proposals that address objectives that fall within NIH's mission. The Action Plan includes a focus on evaluating biomarkers and endpoints needed for clinical trials, particularly non-invasive methods to measure disease progression and treatment response.

The NIH currently funds several research projects in this regard. Investigators at the NIH-funded University of Florida Wellstone Center are refining methods to assess skeletal muscle health in patients with muscular dystrophies, using magnetic resonance imaging and spectroscopy (MRI/S). They are using MRI/S approaches to characterize changes in cardiac and respiratory muscles in boys with Duchenne Muscular Dystrophy (DMD), and to compare these changes to genetic factors that affect progression of the disease. Biomarkers developed through this research are currently being used in DMD clinical trials, including an industry-sponsored trial testing a small molecule investigational new drug. NIH-funded studies are also using methods to study 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. Another NIH-funded project is focused on developing imaging biomarkers to track disease progression in the central nervous system in patients with myotonic dystrophy.

Several NIH activities are aimed at ensuring clinical trial readiness, as more therapies near clinical testing. A project at the University of Iowa Wellstone Center is addressing clinical trial readiness for the class of muscular dystrophies known as the dystroglycanopathies. A NINDS Funding Opportunity Announcement (FOA) invites proposals to facilitate the design of clinical trials for any rare neurological or neuromuscular disorder by validating outcome measures or biomarkers, and/or by characterizing cohorts of relevant patients. A NIAMS FOA requests proposals for *Core Centers for Clinical Research (CCCR)* to foster the development, implementation, and inclusion of methods, metrics, and outcome measures into clinical studies; NIAMS plans to fund up to five new CCCRs in FY 2017 that support clinical research within and across the NIAMS' portfolio of diseases. NINDS Common Data Elements (CDEs) have been developed for several muscular dystrophies; CDEs are common definitions and data sets that help insure data is consistently captured and recorded across clinical studies. To facilitate discussions regarding clinical trials, NIH organized a session at the November 2016 MDCC meeting focused on challenges in designing clinical trials for the muscular dystrophies, including pediatric trials.

NIH-funded studies were an important part of the research that contributed to the development of the first exon-skipping drug for DMD. However, given the recent FDA approval of Exondys 51 (eteplirsen; Sarepta Therapeutics, Inc.), further testing of this drug and development of related drugs has now moved to industry. NIH expects that the industry groups involved in this research will continue to examine the state-of-the-science for these therapies. In addition, the MDCC provides an ongoing forum for member organizations and agencies to discuss new research advances relevant to the development of this and other therapies for the muscular dystrophies.

Myotonic Dystrophy Research

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Myotonic dystrophy research makes up a robust component of the NIH-funded muscular dystrophy portfolio. Researchers at the NIH-funded Paul D. Wellstone Muscular Dystrophy Cooperative 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 are identifying clinical endpoints and biomarkers for use in future clinical trials. With support from NIH, private foundations, and industry collaborators, investigators at this Wellstone Center have developed candidate therapeutics that are currently under testing in clinical trials. The University of Rochester's National Registry for Myotonic Dystrophy and Facioscapulohumeral Dystrophy contains information about more than 2,100 patients, and facilitates patient recruitment for clinical studies. In addition to its effects on skeletal muscle and the heart, myotonic dystrophy also affects the brain, and NIH currently supports a longitudinal study to assess changes in the brain during progression of the disease using MRI. The NIH portfolio in myotonic dystrophy also includes studies to further understand the underlying genetic mechanisms of myotonic dystrophy, the identification of small molecules to reverse the pathology of disease in patient-derived muscle cells and in animal models, and a multi-project grant to understand neurological features of the disease including defects in brain development and cognitive deficits.

NIH interacts with the Myotonic Dystrophy Foundation patient organization on a regular basis. National Institute of Arthritis and Musculoskeletal and Skin Diseases Director Dr. Stephen Katz presented an overview of the NIH investment in myotonic dystrophy research at a congressional briefing hosted by the Foundation in September 2016. Dr. Katz and National Institute of Neurological Disorders and Stroke Director Dr. Walter Koroshetz will meet with Foundation representatives in November 2016. Finally, objectives in the *Muscular Dystrophy Coordinating Committee's 2015 Action Plan for the Muscular Dystrophies* address shared needs of the field as a whole but also include objectives for specific types of muscular dystrophy, including myotonic dystrophy.

National Pediatric Research Network - Update

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

The opportunity for children in rural locations and underserved communities to participate in clinical trials that are testing new therapies historically has been limited. Providing such access would increase the numbers of children, many of whom have rare conditions, who can participate in cutting edge research aimed at addressing their conditions. Under the auspices of the new Environmental Influences on Child Health Outcomes (ECHO) program, the NIH announced in September 2016 17 awards to institutions across the country for a national network of pediatric clinical trial teams/hubs to address this access gap for rural-dwelling and underserved children. The network includes teams of dedicated pediatric research staff at participating Institutional Development Award (IDeA) locations, provision of professional development activities to ensure competency and consistency in conducting pediatric clinical trials, and oversight by the central data coordinating and operations center (DCOC). The underlying IDeA Program provides support for institutions in many states that historically have not received extensive NIH funding.

This “IDeA States Pediatric Clinical Trials Network” will partner with academic institutions outside the IDeA consortium to facilitate recruitment and augment geographic diversity of clinical trials. At the same time, this approach will allow children who have a disease or condition to stay closer to home but still participate in research. Such enhanced pediatric research capacity will provide a portal of entry to populations historically not included in multisite studies, particularly rural and American Indian communities. The research staff will be capable of recruiting for and implementing almost any pediatric clinical trial, and a mentoring and professional development component will leverage existing activities within the IDeA program. Researchers interested in augmenting their clinical trials by including IDeA sites would contact the IDeA DCOC. Priority will be given, but not limited to, proposed pediatric trials on one of the four ECHO focus areas: (1) upper airway conditions, (2) obesity, (3) pre-, peri-, and postnatal outcomes, and (4) neurodevelopment.

National Strategy for Combating Antibiotic Resistance Bacteria (CARB)

The Committee directs the Department to continue to collaborate with the Department of Defense, United States Department of Agriculture, Department of Veterans Affairs, and the Food and Drug Administration, to develop and maintain the National Database of Resistant Pathogens; broaden and sustain efforts to track and store data on AbR genes and the mobile genetic elements from AbR bacteria and metadata. Geographic information systems describing where the AbR are isolated is also essential to monitor emerging AbR and to assess their threat to public health and develop mitigation strategies. The Committee further directs consideration of best evidence on the environmental locations for the influx of antibiotic resistance into bacteria of medical importance, and surveillance methodologies that ensure the greatest chance of detecting the influx of new antibiotic resistance elements as early as possible. The Committee requests a comprehensive update in the fiscal year 2018 budget request on the progress being made in areas described above and advancements being made on the CARB national strategy initiative.

Action taken or to be taken

NIAID is the lead NIH institute for research on antimicrobial resistance and is a key implementer of the Administration's National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB). NIAID activities span multiple goals in the National Action Plan, including pivotal efforts to advance basic research on antimicrobial resistance, foster innovation in diagnostics for resistant pathogens, and support clinical trials of promising antimicrobial products and strategies.

NIAID is committed to improving the national data reporting infrastructure for antibiotic-resistant pathogens. As part of the National Action Plan, NIH and NIAID are working with CDC, FDA, DoD, and other partners to establish and maintain the National Database of Resistant Pathogens. The National Database will serve as a comprehensive resource of genomic information for surveillance, epidemiology, and basic research into the mechanisms of antibiotic resistance. As part of this effort, NIAID is supporting the sequencing of high-priority reference strains, incorporating antibiotic resistance genes, mobile genetic elements, and associated metadata where relevant. The National Database also will help foster development of improved diagnostics, therapeutics, and vaccines for drug-resistant bacteria, and identify strategies to optimize and preserve the use of existing antibiotics.

NIAID works with multiple partners to support the development of tools to identify sources of antibiotic-resistant pathogens and better treatments for the infections they cause. For example, NIAID is working with academic and industry researchers to develop diagnostic tests to detect both drug-sensitive and drug-resistant bacteria, including those found in healthcare settings. These diagnostics would facilitate antibiotic stewardship by allowing clinicians to swiftly determine appropriate treatments for infected individuals. In addition, NIAID is supporting research to investigate how food and/or food-producing animals could serve as reservoirs for multidrug-resistant infections. These efforts will inform critical surveillance activities for antibiotic resistance led by CDC, FDA, and USDA.

NIAID is collaborating with BARDA to advance the development of novel antimicrobial drugs and strategies. Together the agencies have established the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator, or CARB-X. CARB-X is a new global public-private partnership to accelerate promising antibacterial products from preclinical to clinical development. In addition, NIH, in partnership with BARDA, recently announced the

Antimicrobial Resistance Diagnostic Challenge. This prize competition aims to foster the development of rapid, point-of-care diagnostic tests for drug-resistant bacteria. These types of diagnostic tools would provide real-time information about drug-resistant strains so that they can be quickly monitored and appropriately treated early in the course of infection as patients first seek care. Additional diagnostic development is facilitated through the NIAID Antibacterial Resistance Leadership Group (ARLG), which is working to increase clinical research capacity to investigate novel diagnostics and therapeutics for resistant pathogens. Ongoing clinical studies by the ARLG are designed to validate new diagnostics, including those intended to differentiate between viral and bacterial respiratory tract infections.

NIAID remains committed to working with Federal and other partners to advance critical research on the identification and characterization of antibiotic-resistant pathogens. NIAID will continue to leverage the knowledge gained by these efforts to support the development of new diagnostics, therapeutics, and vaccines for antibiotic-resistant bacteria.

Natural Products Collections

The Committee continues to urge NIH to increase access to comprehensive and professionally organized natural products libraries.

Action taken or to be taken

Comprehensive and professional organized natural product libraries provide valuable research resources. Both the National Cancer Institute (NCI) and the National Center for Complementary and Integrative Health (NCCIH) provide support to advance research on natural products by enhancing access to comprehensive natural product libraries. The NCCIH encourages further enhancement of natural product libraries within NIH and increased use of these libraries by the research community.

Since 1986, the NCI's Natural Products Branch has collected, extracted and stored natural product extracts in a central repository. This collection contains approximately 230,000 extracts from plant, marine, and microbial sources. These extracts are available for screening by NIH-supported researchers and can be made available to other researchers. The Developmental Therapeutics Program collections also include plated pure natural product libraries and a recently plated collection of organic and aqueous extracts of traditional Chinese medicinal plants. The NCI encourages broader utilization of these extracts in high throughput screens to identify new extracts and molecules of interest.

NCCIH is committed to the understanding of basic biological mechanisms of action of natural products as outlined in its 2016 Strategic Plan. NCCIH continues to sponsor research on compounds isolated from natural products, as well as on the complex mixtures from which they originate. This support includes funding for screening of natural product libraries.

For example, NCCIH is funding a five-year research award to Virginia Polytechnic Institute and State University to discover novel antimalarial compounds from plants supplied by the Natural Products Discovery Institute (NPDI). As part of this award, researchers will screen approximately 22,000 extracts for antimalarial activity. For the most promising agents, the investigators will seek to determine the mechanisms of action. This research award builds on an earlier study, also funded by NCCIH, to screen the NPDI library for compounds that may lead to the development of new drugs and/or advance our understanding of the mechanism of action of specific natural products.

In addition to supporting specific research grants, NCCIH facilitates access to publicly available natural products libraries by creating and maintaining an online listing of nearly 20 natural product libraries. The website <https://nccih.nih.gov/grants/naturalproducts/libraries> provides the name of the natural product library, contact information, and a brief description of the materials available and helps connect researchers to the natural product resources they need.

NCI Designated Cancer Centers

NCI Designated Cancer Centers.—The Committee requests an update in the fiscal year 2018 budget request on how NCI supports or plans to support IDeA States to broaden NCI’s designated cancer center representation within these States.

Action taken or to be taken

The National Cancer Institute’s (NCI) Office of Cancer Centers (OCC) supports 69 NCI-designated Cancer Centers in 35 states (8 of which have NCI-designated cancer centers)¹⁰⁹ and the District of Columbia to act as the backbone of NCI’s programs for studying and controlling cancer. These Centers, along with their community partners, serve as critical infrastructure for support of the national cancer program and for ensuring cancer patients have access to clinical trials whether they live in urban, suburban, or rural communities. In addition to supporting and monitoring the NCI’s current portfolio of designated centers, the OCC advises emerging cancer centers as they navigate the application process to become an NCI-designated center. Discussion about applying for NCI designation are currently underway between the OCC and representatives of cancer centers in Oklahoma, Arkansas, and other rural communities.

The Institutional Development Award (IDeA) program serves unique populations by broadening the geographic distribution of NIH funding and enhancing investigator competitiveness. A number of IDeA Centers for Biomedical Research Excellence (COBRE) grantees are working within or in collaboration with their state’s NCI-designated Center. Examples include the University of Kansas Center for Cancer Experimental Therapeutics COBRE that contributes to the efforts of the University of Kansas Cancer Center, which received NCI designation in 2012, and the Center for Evolutionary and Theoretical Immunology COBRE 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. Although West Virginia does not presently have any NCI Community Oncology Research Program (NCORP) or National Clinical Trials Network (NCTN) sites within its borders, they do have a number of sites for NCI-supported clinical trials, including seven sites for NCI-Molecular Analysis for Therapy Choice (MATCH).

In addition to the Cancer Centers, NCI’s NCTN and NCORP serve as partners for the Cancer Centers to provide cancer patients with access to NCI-supported clinical trials across the country. Although NCI-designated cancer centers are an important part of NCI’s portfolio, the NCI supports cancer research through numerous other programs and mechanisms. There are many ways for a cancer center to connect with NCI’s clinical trials networks, regardless of whether they achieve NCI-designation status. In addition, regardless of whether a center has achieved designation, researchers at all institutions can apply for funding for individual research projects through the NIH/NCI competitive application and peer review process. More information about

¹⁰⁹ (Maine, New Hampshire, Kentucky, South Carolina, Hawaii, Kansas, Nebraska, New Mexico)

active NCI funding opportunities across the cancer research portfolio are available on NCI's website.¹¹⁰

¹¹⁰ <https://www.cancer.gov/grants-training/grants/funding-opportunities>

NCI's Precision Medicine Initiative (PMI)

The Committee continues support for pediatric oncology research, including clinical studies for children with brain tumors, pediatric preclinical testing program, evaluating new agents for treating pediatric malignancies, and the pediatric Molecular Analysis for Therapy Choice (MATCH) study. The Committee is pleased a goal of the NCI MATCH trial is for at least 25 percent of the total patients enrolled in the trial to have rare cancers, and that results of NCI's recent interim analysis demonstrate the goal is exceeded. The Committee encourages NCI to continue to prioritize rare cancers in the MATCH trial. The Committee requests NCI provide an update on its plans to utilize the PMI and MATCH to identify and test more effective, less toxic treatments, and to improve the targeting of treatments for children battling brain cancer in the fiscal year 2018 budget request.

Action taken or to be taken

Recognizing the unique scientific questions surrounding pediatric oncology, the National Cancer Institute (NCI) shares the Committee's interest in supporting research aimed at developing novel treatment options for childhood cancer patients. NCI is particularly enthusiastic about the Pediatric MATCH (Molecular Analysis for Therapy Choice) Trial, which expects to begin enrolling patients in 2017. The trial is being led by the NCI-funded Children's Oncology Group (COG) and will screen children with cancer for 143 genetic abnormalities that suggest that they may respond to one of the investigational targeted therapies included in one of the eight initial treatment arms. The MATCH Trial is structured so that new arms, representing new treatment agents, can be added over time. Children and adolescents, ages 12 months to 21 years of age, who have tumors for which no standard therapy is available, are eligible to participate. With the goal of targeting treatments based on the unique genetic profile of each patient, Pediatric MATCH is one of the key features of NCI's Precision Medicine Initiative for Oncology.

While children with brain tumors are eligible to participate in the Pediatric MATCH Trial, NCI also conducts and funds many research projects that seek to identify the most effective and least toxic treatment options for children with brain cancers. The Pediatric Brain Tumor Consortium (PBTC), a multidisciplinary cooperative research organization, is devoted to the identification of superior treatment strategies for children with primary brain tumors through conducting novel phase I and II clinical evaluations of new treatments, studying tumor specimens to further understanding of pediatric brain tumor biology, and developing innovative neuro-imaging techniques. NCI also provides support for five Specialized Programs of Research Excellence (SPOREs) with a focus on brain cancer, which seek to translate basic science findings into novel therapies through promoting collaboration between teams of scientists with expertise in cancer prevention, early detection, diagnosis, and treatment.

NCI-supported clinical trials for childhood brain cancer patients are conducted both intramurally and extramurally. The COG, part of the NCI National Clinical Trials Network (NCTN), develops and coordinates pediatric cancer clinical trials that are available at over 200 member institutions, including cancer centers, throughout the United States, Canada, Australia, and New Zealand. Additionally, the PBTC was formed by NCI in 1999 as a multidisciplinary cooperative research organization devoted to identifying superior treatment strategies for children with primary brain tumors. The participating academic centers and children's hospitals are responsible for the diagnosis and treatment of the majority of children with primary brain tumors in the United States. The PBTC has a direct working relationship with the COG to ensure that

results from phase I and II trials can be confirmed through additional phase II and multi-agent phase III clinical trials in the COG.

In addition to studying the basic biology of pediatric brain tumors, the neuro-oncology team within the intramural Pediatric Oncology Branch in NCI's Center for Cancer Research (CCR) conducts a number of high-risk, high-impact clinical trials for childhood cancer patients. Current trials include a phase I trial (with collaboration from the PBTC) of the drug panobinostat in children with diffuse intrinsic pontine glioma (DIPG), one of the most lethal forms of pediatric brain cancer, and a comparative study of imaging techniques that can be used to assess central nervous system tumor activity.

NCI also supports research with relevance to pediatric cancer more broadly. The Pediatric Preclinical Testing Consortium (PPTC) works to identify new, more effective agents for treating childhood cancers through systematic evaluation of novel agents against genomically characterized pediatric solid tumors and leukemia *in vivo* models. Through the efforts of the PPTC, NCI hopes to accelerate the rate at which potential new treatments for pediatric cancers can be identified. NCI also prioritizes the development of new treatments for pediatric cancer through the NCI Experimental Therapeutics (NExT) Program. This program focuses on advancing breakthrough discoveries in basic and clinical research into new therapies, and several new inhibitors with potential to treat pediatric cancer are being studied for this purpose. There are currently nine agents from the NExT program being studied in pediatric clinical trials. In addition, childhood cancer research is one of the seven core elements within the Beau Biden Cancer Moonshot Initiative; key recommendations from the Blue Ribbon Panel Pediatric Working Group that will be implemented in 2017 are the encouragement of pediatric immunotherapy research and the study of fusion oncoproteins, unique molecular drivers of pediatric cancers. Finally, in 2017, NCI hopes to announce the first round of grants funded through the Pediatric Provocative Questions Initiative, designed to generate innovative approaches to childhood cancer research challenges.

Additionally, the Childhood Cancer Survivor Study (CCSS) examines the long-term effects of cancer and cancer therapy in approximately 35,000 survivors of childhood cancer diagnosed between 1970 and 1999; one goal of this research is to examine the long-term toxicity of cancer treatments and identify which treatments are least likely to lead to negative health outcomes. In addition, the CCSS also conducts intervention studies in survivors to examine the best ways to screen for and prevent subsequent malignancies and to improve health outcomes, including early identification of cardiac toxicity. The St. Jude Lifetime Cohort Study, a smaller but complimentary effort funded by the NCI, will allow for replication of findings from genomic studies (from the CCSS) and the development of collaborative projects to refine risk-based follow-up guidelines and improve outcomes among childhood cancer survivors.

Neurofibromatosis [NF]

The Committee continues to support NF research and treatment at multiple NIH ICs, including NCI, NINDS, NIDCD, NHLBI, NICHD and NEI. Children and adults with NF are at risk for the development of many forms of cancer. The Committee encourages NCI to continue its NF research portfolio in fundamental basic science, translational research and clinical trials focused on NF. The Committee encourages all the funded ICs to continue to explore meritorious research. The Committee appreciates NCI support to centers, clinical trials consortia, preclinical mouse models consortia and other NF-associated tumor sequencing efforts. The Committee encourages NIDCD activities in NF2 basic and clinical research. Further, the Committee understands NF1 may cause vision loss and encourages NEI to explore research in NF1.

Neurofibromatosis [NF] - The Committee supports NIH's commitment to NF research and treatment at multiple ICs, including NCI, NINDS, NIDCD, NHLBI, NICHD, NIMH, NCATS, and NEI. The Committee encourages NCI to continue to support its NF research portfolio in fundamental basic science, translational research and clinical trials focused on NF. The Committee also encourages the NCI to support NF preclinical mouse models 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 support 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 continue to support 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 continue its investment in NF2 basic and clinical research. NF1 can cause vision loss due to optic gliomas; the Committee encourages NEI to continue 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. Neurofibromatosis Type 1 (NF1), the most common NF, affects about 1 in every 3,000 individuals and results in an increased risk of developing a variety of benign and malignant tumors in addition to multiple non-tumor manifestations. NF1 is a progressive disorder whose symptoms include skin abnormalities like freckling in the armpit or groin shortly after birth. Neurofibromatosis Type 2 (NF2) is less common, affects approximately 1 in 25,000 individuals, and often causes the development of slow-growing tumors on the nerves that are important for hearing and balance.

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. The work of this SPORE, conducted across nine research institutions, seeks to implement effective new targeted therapies for *NF1* tumors. In addition to these genetic studies, NCI's intramural program conducts a large clinical trial program for children and adults with NF1. It includes treatment trials for plexiform neurofibromas (pre-cancerous lesions which arise from nerves that are present at birth) and for

aggressive cancers like malignant peripheral nerve sheath tumors (MPNTs), as well as an NF1 natural history study. In collaboration with the NIH Clinical Center and other NIH institutes and centers, the NCI Center for Cancer Research (CCR) and its Rare Tumor Initiative accelerate the development of effective treatments for rare tumors with a special focus on NF1 tumors.¹¹¹ Some of the NCI-supported clinical trials for NF and related conditions include:

- A Phase II trial that studies how well the cancer drug selumetinib works in treating patients with NF1 and plexiform neurofibromas that cannot be removed by surgery. Selumetinib may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth.¹¹²
- A Phase I/II study of an experimental drug called AZD6244 hydrogen sulfate for plexiform neurofibromas. Some of these tumors cannot be completely removed surgically. This experimental drug may be able to prevent them from growing, slow down their growth, or shrink them.¹¹³
- The NCI-supported Pediatric Brain Tumor Consortium is conducting a Phase II evaluation of selumetinib for children with low-grade astrocytomas (tumors that arise in star-shaped brain cells called astrocytes that hold nerve cells in place), including children with NF1-associated low-grade astrocytoma.¹¹⁴

Additionally, with increasing numbers of clinical trials conducted in NF, there is a need for meaningful and 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 within the NF community about the design of future clinical trials. REiNS includes seven working groups that focus on imaging of tumor response; functional, visual, patient-reported, and neurocognitive outcomes; whole-body MRI; and disease biomarkers. The NCI leads the imaging and patient reported outcomes working groups.

The National Institute of Neurological Disorders and Stroke (NINDS) supports researchers investigating the cellular and molecular processes underlying the development of tumors in NF1, NF2, and Schwannomatosis (a rare form of neurofibromatosis), as well as the role of NF genes in brain development and their effect on cognitive and motor/sensory function. NINDS-funded investigators are conducting preclinical studies of a potential gene therapy for Schwannomatosis and of combinations of small molecules and biologics as potential therapies for NF1. NIDCD-supported scientists who are using genetically engineered mice to study the pathophysiology of the NF2 pathway and to identify potential therapeutic targets. In another study, scientists are developing robotic technology to help surgeons safely remove acoustic neuroma (non-cancerous tumors that affect the nerves supplying the inner ear).

The National Institute on Deafness and Communication Disorders (NIDCD) continues to support both basic and clinical research to prevent and treat NF2. NIDCD-supported scientists are using genetically engineered mice to study the pathophysiology of the NF2 pathway and to identify potential therapeutic targets. Another NIDCD-supported project will conduct a Phase I clinical

¹¹¹ <https://ncifrederick.cancer.gov/events/RareTumors/agenda.asp>

¹¹² <https://clinicaltrials.gov/ct2/show/NCT02407405>

¹¹³ <https://clinicaltrials.gov/ct2/show/NCT01362803>

¹¹⁴ <https://clinicaltrials.gov/ct2/show/NCT01089101>

safety study testing the use of a new two-shank auditory midbrain implant (AMI) device in NF2 patients. If the AMI proves safe, the trial will be expanded to test its efficacy, with the hope that the AMI can help NF2 patients improve their ability to hear and understand spoken language.

The *Eunice Kennedy Shriver* National Institutes of Child Health and Human Development (NICHD) continues to support research pertaining to NF1. Individuals 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. Recent research results are promising, showing that school-age children with NF1 and reading disabilities respond positively to tutoring, and that the use of the drug Lovastatin reverses cognitive deficits in humans with NF1. NICHD recently funded a clinical study to examine the possible synergistic effects of this therapy combination, which may also have broader applicability to further elucidating learning mechanisms in developmental disorders.

Finally, to coordinate NF research across institutes, NINDS organizes biennial Trans-NIH NF Working Group meetings. The most recent meeting included representatives from ten NIH ICs, the Department of Defense, and advocacy groups.

Neurogenic Bladder and Kidney Disease

The Committee encourages NIH 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 and management of Spina Bifida and associated secondary conditions, such as hydrocephalus; and to support research to understand 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 NIH supports research on various aspects of spina bifida to understand better this condition and improve health and health outcomes for children and adults who are affected. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports basic and clinical research important to addressing causes and care of bladder and kidney problems of spina bifida. For example, basic research on how proper nerve connections are established in the bladder and lower urinary tract during early life development may contribute to greater understanding and improved treatment of neurogenic bladder from spina bifida and other causes. The NIDDK-supported GenitoUrinary Development Molecular Anatomy Project (GUDMAP) has been cataloging and assembling a functional and dynamic map of the cells, nerves, and tissues in the genitourinary tract from early life to adulthood in mice. In FY 2016, the NIDDK renewed and expanded GUDMAP for a third 5-year period; its new scope includes a comprehensive analysis of the developing human kidney and lower urinary tract and comparisons with such development in mice.

On the clinical side, findings and research recommendations from a February 2015 meeting hosted by the NIDDK, “Research Needs for Effective Transition in Lifelong Care of Congenital Genitourinary Conditions,” which focused on ways to improve urologic and reproductive care as people with spina bifida and other conditions transition to adulthood, have now been submitted for publication in a peer-reviewed journal. In addition, planning is currently under way for a meeting to be held on March 30-31, 2017, entitled “Individualizing Treatment – Broadening the Framework for Urinary Incontinence Research;” it is hoped that this meeting will attract researchers who care for adult and children with spina bifida. In a recent advance, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)-funded Management of Myelomeningocele Study (MOMs) demonstrated that children who had prenatal surgery were much less likely than those who had their spinal cords repaired postnatally to need a shunt or assistive devices to walk. Although surgery in the womb was associated with its own risks, the study showed a clear benefit from the prenatal repair. Currently, MOMS 2 is examining the children who were part of the original study to determine whether those who received prenatal surgery have better physical and mental health outcomes than those who had had postnatal repair. Finally, National Institute of Neurological Disorders and Stroke (NINDS)-funded investigators are investigating the genetic and molecular mechanisms underlying neural tube closure and the processes that lead to disruption and subsequent neural tube defects such as spina bifida. NINDS-funded scientists are also exploring molecular and cellular mechanisms that lead to hydrocephalus, a common secondary condition with spina bifida. Shunts are the most common treatment for hydrocephalus; however, failure is frequent, requiring surgical revision and leading to increased risk for infection. NINDS-supported researchers are exploring mechanisms of shunt failure and infection to enable better prevention, detection, and

management strategies. The NINDS is also contributing to the long-term follow-up of the NICHD-led MOMS.

New Innovative Awards

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed diseases, condition, or topics to describe the latest efforts ongoing and planned.

Action taken or to be taken

The NIH Director's New Innovator (DP2) Award¹¹⁵ initiative, first launched in 2007, supports a small number of early stage investigators of exceptional creativity who propose bold and highly innovative new research approaches that have the potential to produce a major impact on broad, important problems in biomedical and behavioral research. Since its inception, this program has continued to support 30-45 New Innovators each year (48 awardees in FY 2016¹¹⁶). In keeping with this model, other new, innovative award programs that focus on investigators have been developed.

The Maximizing Investigators' Research Award (MIRA)¹¹⁷ is a unified grant to provide support for the program of research in an investigator's laboratory that falls within the mission of the National Institute of General Medical Sciences (NIGMS). Once investigators have MIRAs, they cannot receive additional research grants from NIGMS, with certain exceptions. The MIRA program involves two distinct funding opportunities: one for experienced investigators and one for new and early stage investigators. A key goal of the program is to enhance support for early career scientists. In order to free up funds to do this, the budgets of extremely well-funded senior investigators who received MIRAs were reduced 12 percent (on average) relative to the levels they historically had through R01 funding. For both established and early career investigators, the benefits of MIRAs relative to traditional R01s include:

- MIRAs are for 5 years instead of the current NIGMS average of 4 years for R01s;
- More flexibility to pursue new ideas and opportunities as they arise during the course of research because the award is not tied to specific aims;
- Increases the stability of funding for NIGMS-supported investigators, which could enhance their ability to take on ambitious scientific projects and approach problems more creatively;
- Reduces administrative burden associated with managing multiple grants;
- Reduces the time spent by researchers writing and reviewing grant applications, allowing them to spend more time conducting research; and
- Enables investigators to devote more time and energy to mentoring trainees in a more stable research environment.

Applications from new and established investigators are reviewed separately from one another using distinct evaluation criteria, which allows the potential of early career scientists to be judged more fairly.

¹¹⁵ <http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-16-004.html>

¹¹⁶ <https://commonfund.nih.gov/newinnovator/Recipients16>

¹¹⁷ <http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-16-003.html>

In FY 2016 NIGMS was able to fund 135 experienced investigator MIRAs. From the savings due to consolidating multiple research grants for these investigators into single MIRAs, NIGMS was also able to fund 93 new investigator MIRAs.

NIH's other investigator-based activities support career development in preparation to become an independent researcher in the biomedical, behavioral, and clinical sciences. Examples of such programs include the Pathway Independence award (K99/R00)¹¹⁸ and the Early Independence Award (DP5)¹¹⁹. These targeted programs focus on early stage investigators and make initial awards at a lower average age than other research project grants. K99/R00 awards, for reference, provide up to 5 years of support and are limited to postdoctoral trainees to facilitate a timely transition from a mentored postdoctoral research position to a stable independent research position with NIH support at an earlier stage than is currently the norm. A 2015 outcomes study on the K99/R00 awards indicated success in promoting transition to independent research project grant (RPG) funding at 39 years of age, which is a lower age than the average age at first R01 (42 years old).

The NIH Early Independence Award (DP5), established in 2010, provides an opportunity for exceptional junior scientists to "skip the post-doc" and start an independent research career at a supportive institution directly following the completion of their graduate degree or clinical residency. The evaluation process for this activity emphasizes the qualities of the investigator and the environment provided by the host institution, while de-emphasizing preliminary data in the proposal. NIH announced sixteen recipients of this award in FY2016.¹²⁰

¹¹⁸ <https://grants.nih.gov/grants/guide/pa-files/PA-15-083.html>

¹¹⁹ <http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-16-006.html>

¹²⁰ <https://commonfund.nih.gov/earlyindependence/Recipients16>

NIDAMeD

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Educating patients, families, and healthcare providers is a critical component in curbing substance use and associated health consequences, including addiction. The National Institute on Drug Abuse (NIDA) continues to support these efforts through the NIDAMED initiative by partnering with leaders in clinician education to provide training and other resources on substance use prevention, early intervention, and treatment tailored to the specific needs of primary care providers.

Since 2007, NIDA has engaged in three initiatives to create and disseminate educational information to practicing healthcare providers and clinicians in training. These efforts began with seven NIDA Centers of Excellence for Physician Information (2007-2014) at medical schools across the country. These Centers created twelve medical education resources including lectures, web modules, and workshops for medical students and resident physicians in primary care specialties. NIDA, with funding from the Office of National Drug Control Policy, broadened these educational efforts by partnering with Medscape Education (2012-2015) to create two continuing medical education (CME) modules to promote safe opioid prescribing practices and tools to help manage pain patients who misuse prescription opioids. These courses trained well over 100,000 clinicians.

Most recently, NIDA formed the NIDAMED Coalition of Healthcare Organizations (2014-current) consisting of leading experts and medical associations including the American Academy of Pediatrics, the California Academy of Family Physicians, the American Osteopathic Association, the American Academy of Physician Assistants, and the American Association of Nurse Practitioners. In 2016, the Coalition will launch a CME that provides evidence-based information and clinical strategies to help prevent and address substance use disorders and prescription medication misuse in adolescent patients. The CME includes information on screening adolescent patients prior to prescribing controlled substances, working with parents and caregivers to manage appropriate use of prescriptions, using Prescription Drug Monitoring Programs (PDMPs), and safe ways to dispose of medications with abuse potential. This web-based CME/CE is expected to launch prior to January, 2017.

NIH-CDC-AHRQ Coordination

The Committee remains concerned regarding the duplication of efforts and overlapping of responsibilities and funding priorities between the NIH, CDC, and AHRQ. The Committee encourages NIH, AHRQ, and CDC to coordinate further on crosscutting initiatives, ensuring that each funds programs within its respective core mission. The Committee requests an update in the fiscal year 2018 budget request on how each NIH program coordinates with CDC and AHRQ.

Action taken or to be taken

NIH coordinates and collaborates with the CDC and AHRQ on complementary activities as they align with the mission of each agency, as noted in the *NIH-Wide Strategic Plan, Fiscal Years 2016–2020*.¹²¹ To help focus resources on the highest priority research and reorganize federal activities in a more effective manner, the FY 2018 Budget consolidates AHRQ into NIH as the as the National Institute for Research on Safety and Quality. This new Institute will help conduct a review of coordination of health services research at NIH.

The three agencies interact via many federal interagency coordinating committees and working groups to ensure that programmatic activities are well informed and harmonized. For example, NIH, AHRQ, and CDC work together on committees, such as the Advisory Committee for Heritable Disorders in Newborns and Children,¹²² the Chronic Fatigue Syndrome Advisory Committee,¹²³ ICARE: Interagency Collaborative to Advance Research in Epilepsy,¹²⁴ and the Diabetes Mellitus Interagency Coordinating Committee,¹²⁵ to name a few.

NIH, AHRQ, and CDC also foster a collaborative relationship through the coordination of research-based activities that address topics of mutual interest. In one such instance, NIH staff in the Office of Disease Prevention work closely with AHRQ staff to help identify and address evidence gaps in disease prevention. This collaborative work helps inform and is responsive to the U.S. Preventive Services Task Force (USPSTF), an independent panel of non-Federal experts in prevention and evidence-based medicine, which conducts evidence reviews of clinical preventive health care services and develops recommendations for primary care clinicians and health systems. NIH and CDC are also jointly involved in several initiatives, including: the National Collaborative on Childhood Obesity Research,¹²⁶ which aims to accelerate progress in reducing childhood obesity; efforts to develop a universal influenza vaccine that would increase the breadth and duration of protection; and the National Health Interview Survey, which has collected data on the nation's health since 1957 through personal household interviews.¹²⁷ In addition, both AHRQ and CDC collaborate with NIH on its Health Care Systems Research Collaboratory program, which is improving the way clinical trials are conducted by creating a

¹²¹ <http://www.nih.gov/about-nih/nih-wide-strategic-plan>

¹²² <http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/>

¹²³ <http://www.hhs.gov/ash/advisory-committees/cfsac/index.html>

¹²⁴ <http://www.ninds.nih.gov/research/epilepsyweb/researchers/ICARE/index.htm>

¹²⁵ <https://www.niddk.nih.gov/about-niddk/advisory-coordinating-committees/diabetes-mellitus-interagency-coordinating-committee/Pages/background.aspx>

¹²⁶ <http://www.nccor.org/>

¹²⁷ <http://www.cdc.gov/nchs/nhis.htm>

new infrastructure for collaborative research with healthcare systems.¹²⁸ These examples represent just a fraction of the research collaborations involving NIH, AHRQ, and CDC.

Furthermore, NIH, AHRQ, and CDC frequently collaborate on national outreach and education programs designed to communicate biomedical health research findings and their implications to the public. For instance, all three agencies collaborated on Go4Life,¹²⁹ an exercise and physical activity information initiative, as well as on the National Kidney Disease Education Program,¹³⁰ aimed at improving the understanding, detection, and management of kidney disease. NIH and CDC, along with other agencies, launched the Mind Your Risks¹³¹ campaign in 2015 to educate the public about the risks of high blood pressure.

NIH believes that there are always opportunities to strengthen and improve our collaboration and coordination with sister agencies. To that end, NIH is currently evaluating its research portfolio to explore opportunities for greater strategic collaboration. These coordination efforts will intensify and expand as a result of the consolidation of AHRQ into NIH.

¹²⁸ <https://www.nihcollaboratory.org/about-us/Pages/default.aspx>

¹²⁹ <https://go4life.nia.nih.gov/>

¹³⁰ <https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/Pages/default.aspx>

¹³¹ <https://mindyourrisks.nih.gov/>

Non-Recurring Expenses Fund (NEF)

Created in fiscal year 2008, the NEF permits HHS to transfer unobligated balances of expired discretionary funds into the NEF account for capital acquisitions. For fiscal year 2017, the Committee transfers \$300,000,000 from the NEF to OD for carrying out activities associated with biomedical research. The OD shall provide actual expenditures based on activity in the fiscal year 2018 CJ.

Action Taken or to be taken

The National Institutes of Health (NIH) will invest in new emergency power generators to enable the startup of the main NIH campus cogeneration plant, in the event of a power outage. This will address a key vulnerability of the Bethesda campus by guaranteeing uninterrupted cooling and steam service needed to sustain NIH's most critical facilities when power outages occur. Additionally, NIH will invest in new chillers in NIH's Central Utility Plant to comply with the Environmental Protection Agency (EPA) requirements under the Clean Air Act to stop using an ozone layer-destroying chlorofluorocarbon refrigerant. NIH will replace obsolete chillers that are approximately twenty years old, with new more efficient and environmentally friendly chillers that do not use ozone destroying refrigerants.

Total Project Cost: The total estimated project cost for construction, post design, CIT, CQM, commissioning and ORF management fees is \$51.752M.

Nursing Research

The Committee supports NINR's Strategic Plan, *Bringing Science to Life*, as well as its efforts to bolster the new NIH-Wide Strategic Plan. The Committee applauds NINR's aim to enhance health promotion and disease prevention. The Committee supports NINR's commitment to improving quality-of-life by managing symptoms of acute and chronic illness; improving palliative and end-of-life care; enhancing innovation in science and practice; and developing the next generation of nurse scientists. The Committee remains particularly interested in NINR's efforts to invest in young nurse scientists who will produce the evidence to improve quality of care nationally and globally.

Action taken or to be taken

In FY 2016, NINR released its new strategic plan laying out NINR's research vision. The NINR Strategic Plan: *Advancing Science, Improving Lives* was developed using input from interdisciplinary scientists, clinicians, experts across the Nation, and members of the public. The plan reflects long-standing focus areas of nursing science, including symptom science, wellness, self-management, and end-of-life and palliative care; calls for the continued development of the 21st-century nurse scientists workforce; and incorporates the ways in which technology and innovation can contribute across all of these areas. The strategic plan will guide NINR's efforts to support research to advance nursing science and improve the lives of individuals, families, and communities.

NINR has long emphasized training the next generation of nurse scientists by supporting various training opportunities for scientists at all career levels. In particular, NINR supports those at an early career stage who are so critical to sustaining the future of innovative research and high quality health care. NINR devotes significant support to individual and institutional pre- and postdoctoral research fellowships, as well as career development awards. For example, the Ruth L. Kirschstein National Research Service Awards (NRSAs), as well as career development awards, support nurse scientists to conduct independent research and to address health care challenges. NINR supports the NIH-wide K99/R00 Pathway to Independence program, which provides mentored and independent research support to postdoctoral nurse scientists.

NINR sponsors "research intensives" for nurse scientists at all career levels. NINR's Summer Genetic Institute is an intensive training program that provides graduate students and faculty with a foundation in molecular genetics to enhance their research and clinical practice. The NINR's Graduate Partnerships Program is a doctoral fellowship program that coordinates training and funding for nursing students in basic or clinical research. The Symptom Methodologies Boot Camp, a one-week intensive training course, increases the research capability of graduate students and faculty in symptom methodologies and covers topics including pain, fatigue, sleep, data science methods, genetics, and omics. The Institute also developed a video series for the NINR website to introduce students and early career scientists to the NIH grant application process and to provide tools for writing a successful grant application, as well as a video series with information to support midcareer scientists on building and sustaining a scholarly career.

NINR is committed to preparing a scientific workforce that is diverse, innovative, multidisciplinary, and well-prepared to meet national and global health care challenges. For

instance, NINR supports research conducted by investigators at early to advanced career stages to improve health outcomes globally, including projects that are: examining cardiovascular risk factors and treatment outcomes for individuals in South Africa with both tuberculosis and HIV; implementing a community-based prevention intervention for HIV in Malawi; and testing a diabetes self-management education and mobile health intervention for Type 2 diabetes in Mexico. NINR will continue its commitment to addressing the health challenges of today and tomorrow, supporting the next generation of nurse scientists, and improving quality of life for all.

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

In 2013, the Office of Disease Prevention (ODP) formally retired the Consensus Development Program (CDP), which produced consensus statements representing an unbiased, evidence-based assessment of controversial medical issues important to researchers, healthcare providers, policymakers, patients, and the general public. The consensus statements were used by numerous professional organizations to develop guidelines for clinical practice. The CDP was created during a time when few other organizations were providing evidence reviews of relevance to clinical practice. Today, there are many other organizations that conduct such reviews, including other federal agencies, academic institutions, and private organizations. Although the program has been retired, over 160 consensus statements are available in an online archive.¹³²

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. Unlike the CDP, P2P workshops are designed for topics that have incomplete or underdeveloped research and for which it is difficult to produce a report synthesizing published literature. Each P2P workshop results in a systematic evidence review and a Panel Report on the workshop's findings. P2P workshop panel reports are disseminated through numerous channels, including online postings, publication in a peer-reviewed journal, and a variety of NIH and HHS outreach programs. 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 website¹³³, in addition to the P2P workshop pages¹³⁴, includes extensive resources for researchers¹³⁵ 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.¹³⁶

¹³² <https://consensus.nih.gov>

¹³³ <https://prevention.nih.gov/>

¹³⁴ <https://prevention.nih.gov/programs-events/pathways-to-prevention>

¹³⁵ <https://prevention.nih.gov/resources-for-researchers>

¹³⁶ @NIHprevents

Opioid Drug Abuse

The Committee is concerned about the escalating epidemic of prescription opioid and heroin use, addiction and overdose in the United States. The Committee appreciates the important role that research can and should play in the various Federal initiatives aimed at this crisis. The Committee urges NIDA to continue supporting research on medications to alleviate pain, including the development of those with reduced abuse liability. In addition, the Committee urges NIDA, as appropriate, to work with private companies on innovative research and to provide an update in the fiscal year 2018 budget request on what is known on the transition from opioid analgesics to heroin abuse and addiction within affected populations.

Action taken or to be taken

While there are many strategies currently being utilized to address the opioid crisis – including requiring use of prescription drug monitoring programs, improving access to evidence based treatments for opioid use disorders, improving prescriber education, and expanding access to the overdose reversal drug naloxone – there remains a pressing need to develop safer and more effective treatments for pain while ensuring careful use of opioids when medically necessary.

The National Institute on Drug Abuse (NIDA) worked with the CDC to develop its *Guideline for Prescribing Opioids for Chronic Pain*¹³⁷, published in March of 2016, which provides evidence-based recommendations for opioid prescribing. NIDA also contributes to the Interagency Pain Research Coordinating Committee, which fosters collaboration between NIH, AHRQ, CDC, CMS, DoD, FDA, SAMHSA, and VA as well as a number of HHS staff divisions, including the Office of the Secretary (OS), the Office of the Assistant Secretary for Financial Resources (ASFR), the Office of the Assistant Secretary for Planning and Evaluation (ASPE), and the Office of the Assistant Secretary for Health (OASH).. In March of 2016, this committee published the National Pain Strategy¹³⁸, the government’s first coordinated plan to reduce the burden of chronic pain. The *Strategy* focuses on safer opioid use and research to better optimize pain care.

NIH supports a significant research portfolio to foster the development of better pain therapies. Researchers have long sought opioid analgesics without abuse liability, and NIDA-funded research published in 2016 described progress toward this goal.^{139,140} Some other promising therapies include non-opioid medications, brain stimulation therapies, and neurofeedback. NIH has initiated multiple strategic partnerships to advance development of medications for pain and opioid addiction, leveraging NIH funds with the strengths and resources of outside organizations, including academic institutions, pharmaceutical and biotechnology companies, private and public foundations, and small businesses to identify safer and more effective treatment options. For example, NIDA is partnering with Elysium Therapeutics to develop abuse-resistant opioid pain medications using a novel molecular deactivation technology. In addition, in May of 2016, the FDA approved the buprenorphine implant Probuphine, a novel formulation for treating opioid use disorders developed with NIDA support that provides stable around-the-clock dosing for six months. Further, US World Meds, funded in part through NIDA grants, is in late stage

¹³⁷ <http://www.cdc.gov/drugoverdose/prescribing/guideline.html>

¹³⁸ https://iprcc.nih.gov/docs/HHSNational_Pain_Strategy.pdf

¹³⁹ Manglik A, Lin H, Aryal DK, et al. Structure-based discovery of opioid analgesics with reduced side effects. *Nature*. 2016;537(7619):185-190. doi:10.1038/nature19112.

¹⁴⁰ ¹⁴⁰ Ding H, Czoty PW, Kiguchi N, et al. A novel orvinol analog, BU08028, as a safe opioid analgesic without abuse liability in primates. *Proc Natl Acad Sci*. August 2016;201605295. doi:10.1073/pnas.1605295113.

development of lofexidine, a medication for the treatment of opioid withdrawal symptoms that might also hold promise for the treatment of other addictions.

Heroin and prescription opioid pain relievers both belong to the opioid class of drugs, and their euphoric effects are produced by their binding with mu opioid receptors in the brain. This shared mechanism is one reason prescription opioid use is a risk factor for heroin use, with about 80 percent of current heroin users reporting previous prescription opioid misuse.¹⁴¹ A relatively small number of people who misuse prescription opioids ever transition to heroin use (about four percent), but prescription opioid use disorders are associated with a 40-fold increased risk of heroin use disorder.¹⁴² Three paths to heroin use include a shift from prescription opioid misuse, a shift from cocaine, or a shift from polydrug use; the transition from polydrug use to heroin is most common.¹⁴³ Heroin use is driven in part by its low cost and high availability, and a recent survey of patients in treatment determined that accessibility was one of the main factors identified in the decision to start using heroin.¹⁴⁴ Ongoing research will help to determine the factors that increase the risk of transition from prescription opioid to heroin use, as prevention and treatment efforts continue to target a reduction in overall opioid morbidity and mortality.

¹⁴¹ Muhuri PK, Gfroerer JC, Davies MC. Associations of nonmedical pain reliever use and initiation of heroin use in the United States. August 2013. <http://www.samhsa.gov/data/2k13/DataReview/DR006/nonmedical-pain-reliever-use-2013.htm>.

¹⁴² Jones CM, Logan J, Gladden RM, Bohm MK. Vital Signs: Demographic and Substance Use Trends Among Heroin Users - United States, 2002-2013. *MMWR Morb Mortal Wkly Rep.* 2015;64(26):719-725.

¹⁴³ Kane-Willis K, Schmitz S, Bazan M, Narloch V, Wallace C. Understanding suburban heroin use. https://www.robertcrown.org/files/Understanding_suburban_heroin_use.pdf.

¹⁴⁴ Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The Changing Face of Heroin Use in the United States: A Retrospective Analysis of the Past 50 Years. *JAMA Psychiatry.* 2014;71(7):821. doi:10.1001/jamapsychiatry.2014.366.

Opioid Misuse and Addiction

The Committee appreciates the important role that research plays in the various Federal initiatives aimed at addressing the opioid crisis. The Committee urges NIDA to continue to fund research on medications to alleviate pain, including the development of those with reduced abuse liability, and continue to work with industry to fund innovative research into such medications. The Committee requests an update in the fiscal year 2018 CJ on these initiatives.

Action taken or to be taken

The National Institute on Drug Abuse (NIDA) is an active partner in the Secretary's Initiative to address opioid addiction and overdose. Our efforts are focused on supporting and disseminating research to (1) improve opioid prescribing practices, (2) expand the use of the opioid overdose reversal drug naloxone, (3) improve implementation of evidence-based practices for treatment of opioid use disorders, and (4) develop pain treatments with reduced potential for misuse and diversion.

NIDA is one of multiple institutes of the NIH supporting research into novel pain treatments, including abuse resistant opioid analgesics, non-opioid medication targets, and non-pharmacological treatments. 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 drugs that minimize diversion and misuse (e.g., by preventing tampering) and reduce the risk of overdose deaths. Two recent publications of NIDA-funded research in high-profile journals detail recent progress made in the discovery of opioid analgesics with reduced abuse liability.^{145,146}
- *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.

NIDA has initiated multiple strategic partnerships to advance development of medications for pain, leveraging NIDA funds with the strengths and resources of outside organizations, including academic institutions, pharmaceutical and biotechnology companies, private and public foundations, and small businesses to identify safer and more effective treatment options. For example, NIDA worked in partnership with Lightlake Therapeutics Inc., Adapt Pharma, and the

¹⁴⁵ Manglik A, Lin H, Aryal DK, et al. Structure-based discovery of opioid analgesics with reduced side effects. *Nature*. 2016;537(7619):185-190. doi:10.1038/nature19112.

¹⁴⁶ Ding H, Czoty PW, Kiguchi N, et al. A novel orvinol analog, BU08028, as a safe opioid analgesic without abuse liability in primates. *Proc Natl Acad Sci*. August 2016;201605295. doi:10.1073/pnas.1605295113.

FDA to develop a user-friendly intranasal formulation of the opioid overdose reversal drug naloxone that became commercially available in February 2016. In addition, in May of 2016, the FDA approved the buprenorphine implant Probuphine, a novel formulation for treating opioid use disorders developed with NIDA support that provides stable around-the-clock dosing for six months. Further, US World Meds, funded in part through NIDA grants, is in late stage development of lofexidine, a medication for the treatment of opioid withdrawal symptoms that might also hold promise for the treatment of other addictions.

Otolaryngology

The Committee urges NIDCD to work with the otolaryngology community to facilitate new and innovative therapies that examine the pathology of the ear and to ensure that hypothesis driven research is retained in pathology centers.

Action taken or to be taken

The National Institute on Deafness and Other Communication Disorders (NIDCD) has a long history of supporting research on human temporal bone tissues. In 1992, the Institute established the NIDCD National Temporal Bone, Hearing and Balance Pathology Resource Registry to promote human temporal bone utilization for research on human hearing and balance disorders, and to serve as an information resource for researchers and the public. NIDCD continues our longstanding support of the Registry to benefit studies on the pathology of the human auditory and vestibular systems by both scientific investigators and clinicians. The Registry keeps extensive biomedical and clinical information on thousands of temporal bones available to scientists and disseminates information to the public on temporal bone donation and research.

From 2005 to 2016, NIDCD funded two Requests for Application (RFAs) for temporal bone research: the Human Temporal Bone Consortium for Research Resource Enhancement and the Otopathology Collaboration Network. Each RFA provided set-aside dollars specifically to fund three cooperative agreements targeting activity between temporal bone labs to develop techniques and complementary approaches, to promote more collaborative modern biomedical research across the community of otopathology and inner ear researchers, and to provide the basis for subsequent new research project applications. Within the terms of the cooperative agreement, NIDCD staff worked closely with the principle investigators of the labs to facilitate both their research and their transition to an independent research project.

In 2016, NIDCD released an additional RFA to help support even broader community use of temporal bone tissues through a new National Human Ear Tissue Laboratory Resource for Hearing and Balance Research, to be awarded in December 2016. This RFA has set-aside funding of \$750,000/year for a five-year period. It will provide a national technological resource for a range of auditory and vestibular researchers who use human inner and middle ear tissues for a variety of basic and clinical studies. The laboratory will develop and provide technical services for procuring, preparing, sectioning and distributing high-quality human ear tissues; develop and disseminate techniques for improved tissue preservation and for imaging human middle and inner ear structures, including cellular and membranous components; and provide opportunities for technical instruction in the special skills needed to prepare tissues from post-mortem human temporal bones. Research on the ear will be enhanced by providing a critical link towards the translation of basic and directed animal studies to the human ear and eventually to the clinic.

NIDCD recognizes the value of human temporal bones to auditory and vestibular researchers as well as for clinicians. The Institute continues its commitment to this area through support of the new National Human Ear Tissue Laboratory, the Temporal Bone Registry, and a variety of research projects that include studies using tissues from temporal bone preparations. In addition, NIDCD welcomes individual investigator-initiated research grant applications using techniques of otopathology with the hope that scientists will incorporate such studies into their research programs.

Ovarian Cancer

The Committee notes that despite scientific advancements, ovarian cancer remains the fifth most prevalent disease for women with 5-year survival rates still below 50 percent. The Committee encourages NCI to continue to support clinical trials with emerging genomics-driven immunotherapies applied to human ovarian cancer, with particular emphasis on treatments that target the molecular characteristics of each tumor. The Committee requests an update in the fiscal year 2018 CJ.

Ovarian Cancer

The Committee requests serious consideration be given to Ovarian Cancer in any “Moonshot” effort given the emerging genomics-driven immunotherapies success. The Committee requests NCI provide an update in the fiscal year 2018 budget request on the on-going and planned research in this area.

Action taken or to be taken

The National Cancer Institute’s (NCI’s) ovarian cancer research portfolio reflects efforts to optimize therapeutic options for patients by understanding underlying molecular mechanisms of ovarian tumors. In 2011, gene sequencing on 316 ovarian cancer tumors was completed through The Cancer Genome Atlas (TCGA) program. Researchers confirmed that mutations in a single tumor-suppressing gene, TP53, are present in nearly all cases of serous adenocarcinoma, which accounts for about 85% of ovarian cancer deaths. Scientists are now developing and testing therapies that restore the function of this gene. TCGA investigators also noted that one type of drug, a PARP (Poly ADP ribose polymerase) inhibitor, might be able to counteract the DNA repair gene mutation observed in half of the ovarian tumors studied. Several NCI-supported clinical trials are underway to determine the effectiveness of these agents in treating ovarian cancer.

NCI’s Center for Cancer Research (CCR) currently has several active clinical trials for ovarian cancer patients. These projects include phase I and phase II studies investigating the use of a PARP inhibitor in combination with other therapeutic agents, including the immunotherapy drug PD-L1 (MEDI4736). Another trial is testing to see if monocytes, a type of white blood cell that supports immune system activity, can be used to target ovarian cancer tumor cells. Ovarian cancer patients are also eligible to participate in the NCI-Molecular Analysis for Therapy Choice (MATCH) Trial, which analyzes patients’ tumors to determine whether they contain genetic mutations for which a targeted therapeutic agent exists. If a specific genetic mutation is found, patients receive a targeted therapy that has been approved for another cancer site (a tumor’s location in the body).

While clinical trials represent a vital aspect of NCI’s investment in ovarian cancer research, NCI also supports basic and pre-clinical research focused on better understanding the biology of ovarian cancers and improving early detection and diagnosis. Recognizing that the high ovarian cancer mortality rate is due in part to late diagnosis, NCI supports the work of the Early Detection Research Network (EDRN) Breast and Gynecologic Cancers Research Group, a collaboration whose goal is to identify and test new biomarkers to enhance cancer detection and risk assessment. The group’s work, in cooperation with industry partners, has led to two FDA approved diagnostic tests: OVA1, which is used to predict ovarian cancer risk in women with an

adnexal (uterine) mass; and ROMA (Risk of Ovarian Cancer Malignancy), which is used to predict risk for women with a pelvic mass. Early detection is also a major focus of the five NCI-supported ovarian cancer Specialized Programs of Research Excellence (SPOREs) across the country. Other SPORE research priorities also include imaging technologies, risk assessment, and novel therapeutic approaches.

The Cancer Moonshot Blue Ribbon Panel released a report in September 2016, outlining 10 scientific recommendations that the panel believes have the potential to accelerate cancer research to make ten years of progress over the next five years. These recommendations encourage researchers to advance the science of a number of priority areas, including expanding clinical trials and advancing immunotherapy treatment approaches; precision prevention and early detection; efforts to overcome drug resistance; and enhanced data sharing and analysis. These cross-cutting recommendations aim to advance progress in understanding and treating all types of cancers, including ovarian cancer.

Overlapping Pain Conditions

The Committee commends the NIDCR for its ongoing support for the Orofacial Pain Prospective Evaluation and Risk Assessment program, which is yielding valuable information on many physiological aspects of temporomandibular disorders and overlapping pain conditions. The Committee encourages continued research on overlapping pain conditions and increased collaboration across NIH Institutes on epidemiological, basic, clinical and translational research related to pain conditions.

Action taken or to be taken

The National Institute of Dental and Craniofacial Research (NIDCR) actively collaborates with other NIH Institutes, Centers, and Offices (ICOs) to support research on temporomandibular disorders (TMDs) and overlapping pain conditions. In 2014 NIDCR, along with eight other NIH ICOs, released an initiative to encourage studies that will increase our understanding of multiple chronic overlapping pain conditions. One of the projects that resulted from this initiative is using stored bio-specimens from the NIDCR-funded Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study to examine the role of proteins, microRNAs (small RNA molecules that can change gene activity), and genes in the development of TMDs and five overlapping pain conditions (migraine, low back pain, irritable bowel syndrome, pelvic pain, and widespread body pain). These new biologic data will be combined with existing psychological and social data to identify the underlying mechanisms common to overlapping pain conditions. In 2016 NIDCR released an initiative to encourage research to understand the genetic basis of variability in an individual's responses to therapeutic pain drugs used in orofacial pain management and adverse events. Findings from these studies could also aid in the treatment of other chronic pain conditions that overlap with TMDs.

To enhance the coordination of pain research across the NIH, a number of ICOs actively participate in the NIH Pain Consortium. The Consortium encourages pain research on topics of shared interest among NIH ICOs. For example, there is a critical need for standardized data elements to accelerate the identification of common risk factors in chronic pain conditions. To begin to address this pressing issue, the Investigator's Meeting on Chronic Overlapping Pain Conditions¹⁴⁷ was held in 2015 to develop a standardized definition for chronic overlapping pain conditions and identify common data elements that could be collected across research studies. Following this meeting the Office of Research on Women's Health (ORWH), NIDCR, and the National Institute of Neurological Disorders and Stroke (NINDS) supported the expansion of a tool called the Complex Medical Symptoms Inventory that collects standardized pain data across relevant chronic pain conditions that often co-occur. Increased use of this new tool will enhance the ability of scientists to collect consistent data across studies and better understand the shared mechanisms of overlapping pain conditions to improve the clinical care and quality of life of individuals living with chronic pain.

¹⁴⁷ https://painconsortium.nih.gov/Conferences_and_Seminars/9-16-2014_Inv.MtgonCOPC.html

Pain Management

The Committee is encouraged by the ongoing collaboration between NCCIH, VA, DOD, and other NIH Institutes 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 to support research on nonpharmacological 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.

Action taken or to be taken

Evidence-based non-pharmacologic, complementary, and integrative pain management approaches are needed to reduce the Nation's reliance on opioid medications for treating chronic pain. This need is further amplified for service members and veterans who often suffer from chronic pain as well as comorbid conditions including traumatic brain injury and post-traumatic stress disorder. Non-pharmacologic interventions may provide new, practical choices for pain management, which may reduce or eliminate the need for, and the risks associated with, opioid medications. The NIH, the Departments of Defense (DoD), and Veterans Affairs (VA) have a long-standing interest in the role of complementary and integrative strategies to reduce pain, improve function, and potentially reduce the need for opioid medications.

In 2014, NCCIH convened a working group of its Advisory Council to provide recommendations regarding development and implementation of a large scale initiative and suggest strategies for collaboration among Federal agencies. In 2015, the working group report entitled, *Strengthening Collaborations with the DoD and VA: Effectiveness Research on Mind and Body Interventions*¹⁴⁸, recommended that NCCIH assess the feasibility to undertake a coordinated effort aimed at conducting large-scale studies on the use of integrative approaches in pain management and in cooperation with the VA and DoD through its Defense Health Agency.

In response to these recommendations, NCCIH, in collaboration with the VA, DoD, and several other NIH Institutes and Offices, developed a joint research funding initiative to implement a large-scale pragmatic clinical research program in military and veteran health care delivery organizations. Funding opportunity announcements were released in December 2016 with awards anticipated to be made starting in late FY 2017. The overall goal of the program is to determine if non-pharmacological approaches to pain management and other comorbid conditions are safe, effective, and can be delivered successfully within "real world" military and veteran health care delivery organizations.

The initiative will support a coordinating center and a set of demonstration projects that will conduct pragmatic clinical trials on non-pharmacological approaches to pain management and comorbidities with patients who are service members, veterans, and/or their families. Ultimately, it is expected that findings from these research efforts, along with future research initiatives, will have the potential to transform clinical decisionmaking about the use of non-pharmacological approaches, including complementary and integrative approaches, for pain

¹⁴⁸ (<https://nccih.nih.gov/about/naccih/military-report>)

and other co-morbid conditions, leading to improved symptom management and, overall, enhanced patient care.

Pancreatic Cancer

The Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC) made four important recommendations for expanding pancreatic cancer research: understanding the biological relationship between PDAC and diabetes mellitus; evaluating longitudinal screening protocols for biomarkers for early detection of PDAC and its precursors; studying new therapeutic strategies in immunotherapy; and developing new treatment approaches that interfere with RAS oncogene-dependent signaling pathways. The Committee looks forward to receiving the fiscal year 2018 CJ to learn how the specific recommendations included in the report are being implemented.

Action taken or to be taken

Pancreatic cancer remains a major clinical challenge claiming more than 40,000 lives yearly in the United States. Despite many advances in understanding the biology of pancreatic cancer, the disease still imposes challenges in its early detection and effective therapy. In 2014, the National Cancer Institute (NCI) released a Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC), which accounts for 95% of pancreatic cancer cases. 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 mellitus of recent onset; (2) evaluation of longitudinal screening protocols, concomitant with the development of new molecular and imaging biomarkers, for patients at high risk for PDAC (because of genetic factors or the presence of mucinous pancreatic cysts) who could be candidates for early surgical intervention; (3) implementation of new immunotherapy approaches based on a deeper understanding of how PDAC interacts with its potentially immunosuppressive microenvironment; and (4) development of new treatment strategies that interfere with RAS oncogene-dependent signaling pathways.

To further our understanding of PDAC and diabetes, NCI has partnered with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to create two initiatives aimed at establishing a consortium to examine chronic pancreatitis (CP) and factors that increase the risk of pancreatic cancer in patients with newly diagnosed diabetes. Based on preclinical studies indicating that metformin, a commonly used diabetes drug, may destroy cancer cells, NCI funds research on combining metformin with standard chemotherapy treatments.

The framework also called for the evaluation of longitudinal screening protocols, based on emerging knowledge of molecular and imaging biomarkers, for patients at high risk for PDAC who could be candidates for early surgical intervention. The NCI has issued a funding opportunity announcement to support the formation of a Pancreatic Cancer Early Detection Consortium (PCDC), which will focus on the identification and validation of biomarkers for early detection of PDAC or its precursor lesions, the determination of which pancreatic cysts are likely to progress to cancer, the development of molecular- and/or imaging-based approaches for screening populations at high risk of PDAC, and the collection of biospecimens for the establishment of a biorepository. To date, the PCDC consortium consists of three clinical centers and it is expected that more centers will be added to this consortium.

Several NCI-funded projects have already supported the discovery of biomarkers that may lead to less invasive and more accurate pancreatic cancer screening tests. Intramural scientists in NCI's Center for Cancer Research (CCR) have also identified potential new biomarkers and

therapeutic targets.^{149,150,151,152} These findings, combined with those anticipated from the study of the recently completed PDAC reference set of serum and plasma from patients with pancreatic cancer, chronic pancreatitis, acute benign biliary obstruction, and healthy controls, may lead to the identification of candidates for early intervention. In addition to these biomarker-focused efforts, NCI has also awarded grants to create a consortium focused on pancreatic imaging advances. These awards are part of a larger effort to identify the molecular and cellular characteristics of screen-detected pre-cancers and early cancers. The investigators are combining CT imaging, genomic profiles, and immune response measurements in an effort to determine which pancreatic cysts have the greatest potential to become malignant.

The framework also encouraged the implementation of new immunotherapy approaches to treating pancreatic cancer. Initial testing of the GVAX vaccine, funded in part by NCI, indicates that the vaccine is able to trigger the growth of immune cell nodules within pancreatic cancer cells, which may potentially make these cells susceptible to immune therapies. At the NCI CCR, researchers are conducting a pilot study to evaluate immune checkpoint inhibitors in combination with radiation therapy in patients with unresectable pancreatic cancer.¹⁵³ In addition, the NCI-funded Cancer Immunotherapy Trials Network (CITN) is actively accruing patients with pancreatic cancer in a phase I clinical trial investigating an anti-CD40 antibody. The NCI recently approved a new funding opportunity for a consortium focused on the interaction between tumors and the microenvironment in order to design new immunotherapy and combination interventions.

The framework also suggested the development of new treatment strategies that interfere with RAS oncogene-dependent signaling pathways, as 95% of pancreatic cancers are driven by mutations in cell signaling pathways that are controlled by RAS genes (specifically the KRAS subtype). NCI's RAS research initiative is led by researchers at NCI's Frederick National Laboratory for Cancer Research. Current projects include an investigation of the structural biology and biochemistry of KRAS proteins, understanding the biology of mutant KRAS cell lines, RAS signal pathway analysis, and characterizing cell surface features of KRAS cancers.

In addition to efforts directly tied to the Scientific Framework, NCI coordinates and supports several other pancreatic cancer-focused scientific programs, including the Pancreatic Cancer Epidemiology Consortia, the Pancreatic Cancer Interest Group, the Regional Chemotherapy in Locally Advanced Pancreatic Cancer (RECALP) Trial, and three pancreatic-cancer-specific Specialized Programs of Research Excellence (SPOREs). Also, as part of the Precision Medicine Initiative, NCI has funded nine 1-year supplements to cancer centers and SPOREs in support of studies that elucidate the complex relationship between PDAC and its microenvironment. The projects are geared toward a better design of immunotherapy of PDAC. A Request for Applications soliciting for translational studies in this area is in its final phases of NCI approval and is anticipated to be launched in 2017.

¹⁴⁹ <https://www.ncbi.nlm.nih.gov/pubmed/?term=27367029>

¹⁵⁰ <https://www.ncbi.nlm.nih.gov/pubmed/?term=27401251>

¹⁵¹ <https://www.ncbi.nlm.nih.gov/pubmed/?term=27197190>

¹⁵² <https://www.ncbi.nlm.nih.gov/pubmed/?term=26479921>

¹⁵³ <https://clinicaltrials.gov/ct2/show/NCT02311361>

Pancreatitis and Pancreatic Cancer

The Committee is encouraged by NIDDK's consortium for the Study of Chronic Pancreatitis Diabetes and Pancreatic Cancer in collaboration with NCI. The Committee urges additional efforts to utilize the diverse data of patients within the consortium in precision medicine to inform targeted treatment and prevention.

Action taken or to be taken

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), with support from the National Cancer Institute (NCI), recently funded the multi-center consortium for the Study of Chronic Pancreatitis Diabetes and Pancreatic Cancer to pursue clinical research on pancreatic diseases, including chronic pancreatitis, acute recurring pancreatitis, pancreatic cancer, and the type 3c diabetes that may result from these diseases. The consortium is enabling researchers to make strides towards the goals of earlier diagnosis, targeted treatment, and prevention of pancreatic disease in a diverse population of patients. For example, in the largest study of its kind, researchers at one of the consortium's clinical centers recently found that genetics, birth defects, and ethnicity may play important roles in the occurrence of pancreatitis in children. Other studies from the consortium will identify physiological changes that may signal the onset of pancreatitis, pancreatic cancer, or type 3c diabetes, such as changes in the community of microbes inhabiting the gut. These studies could eventually allow health care providers to use improved screening tools to diagnose pancreatic diseases earlier, which is a critical step towards better prevention. They could also lead to targeted treatments for a diverse population of patients with pancreatic disease.

In addition to its important role in supporting this consortium, NCI continues to develop and test targeted therapies to treat pancreatic cancer. The NCI-sponsored National Clinical Trials Network is conducting a 950-patient, phase III trial of adjuvant therapy for pancreatic cancer, the largest study of its kind, assessing the value of adding radiation to chemotherapy, with or without the addition of targeted drug therapy. A phase II trial, supported by NCI and conducted by Georgetown University, is testing seven targeted therapies that will be selected for pancreatic cancer patients based upon their tumor profiles. Pancreatic cancer patients are also eligible to participate in the NCI-Molecular Analysis for Therapy Choice Trial, a novel clinical trial that analyzes patients' tumors to determine whether they contain a genetic mutation for which a targeted therapy exists. Currently, 24 drugs are part of the trial, and the trial is designed for the addition of more treatment arms as new treatments are developed. To aid in the development of future treatment options, NCI plans to create a Consortium for Pancreatic Ductal Adenocarcinoma Translational Studies on the Tumor Microenvironment through a cooperative agreement, scheduled to be awarded in late 2017.

Parkinson's Disease

The Committee commends NINDS for taking critical steps in identifying priority research recommendations to advance research on Parkinson's disease, which impacts between 500,000 and 1,500,000 Americans and is the second most prevalent neurodegenerative disease in the United States. The Committee recognizes that NINDS is prioritizing public health concerns with severe gaps in unmet medical needs and supports the research recommendations set forth by the NINDS planning strategy to bring us closer to better treatments and a cure for Parkinson's disease. The Committee also encourages NINDS to submit an update of its progress on implementing these recommendations in the fiscal year 2018 CJ.

Action taken or to be taken

NINDS convened the conference, *Parkinson's Disease 2014: Advancing Research, Improving Lives* (PD2014), on January 6 -7, 2014. At this conference, expert clinicians and scientists, with input from the broader scientific and lay communities (including people with PD, their caregivers, family members and advocates), developed a set of 31 recommendations to inform basic, translational, and clinical research efforts. To follow up on specific PD2014 recommendations NINDS organized the *PD Genetics and Systems Biology Workshop* in June of 2014 to develop strategies for maximizing resources for advancing research on PD genetics and systems biology, and NIEHS, in collaboration with NINDS, convened *Parkinson's Disease: Understanding the Environment and Gene Connection* in November of 2014.

NINDS is using a variety of methods to encourage and facilitate research projects that address the recommendations from these planning efforts. NINDS staff actively encourage researchers to submit investigator-initiated proposals that will address PD2014 recommendations, and NINDS continues to assess whether funded investigator-initiated grants and incoming grant applications advance the priorities established by the PD2014 recommendations. In recent Funding Opportunity Announcements for the NINDS Morris K. Udall Centers of Excellence for Parkinson's disease Research program, applicants are encouraged to address the PD2014 recommendations in their research proposals (These announcements include RFA-NS-17-001, RFA-NS-16-002, RFA-NS-15-002, RFA-NS-14-011, and RFA-NS-14-003). NINDS is soliciting applications for grants to assist in planning new Udall Centers Without Walls that will engage research teams across institutional and geographic boundaries to address the most pressing challenges in PD (RFA-NS-16-024). The NINDS PD Biomarkers Program (PDBP) has developed data management, clinical, and biospecimen resources that are essential tools for implementing many of the PD2014 recommendations. As part of this program, NINDS is also soliciting new projects focused on discovering novel biomarkers for PD and related diseases, which was a key component of several PD2014 recommendations (PAR-14-259, RFA-NS-16-022, and PAR-16-112). The NIH BRAIN Initiative is funding the development of new tools and technologies to study and therapeutically modulate brain circuit activity, potentially leading to improved deep brain stimulation technology and safer and more effective deep brain stimulation therapy for PD (RFA-NS-16-008, RFA-NS-16-009, RFA-NS-16-010, and RFA-NS-16-011).

Through these targeted initiatives and investigator-initiated research, NINDS is funding a variety of projects that address the PD2014 recommendations. These include studies to expand our understanding of the genetic risk for PD motor and non-motor symptoms and their progression, to bridge the gap between molecular clues of PD pathology and mechanisms of disease process, to develop better animal and cell models for PD, and to understand the brain circuits involved in

PD and how deep brain stimulation affects those circuits. Other projects aim to develop methods to diagnose PD before motor symptoms occur, to improve technologies to measure PD pathology, and to develop new approaches to and stronger rationale for testing interventions to prevent, slow, or stop PD.

Partnership to find Partners for Unfunded Research

The Committee commends NIH for its leadership to move forward with and expand the request for NIH to develop a new mechanism for public-private organizations to directly fund high quality unfunded applications from one IC to all ICs. The program will not only benefit applicants by helping connect them with potential funders, it allows the private funders to take advantage of NIH's peer review system and reduce researcher application drafting time. The Committee requests that in fiscal year 2018 budget request, and future year budget requests, NIH report the annual number of applications supported and total annual dollar level of support provided through this mechanism to expanded research.

Action taken or to be taken

NIH is very excited to have entered into a public private partnership with Leidos Life Sciences as an inaugural member of the Online Partnership to Accelerate Research (OnPAR). OnPAR was created to find alternate funding options for unfunded NIH peer reviewed applications.

NIH Institutes and Centers are encouraged to announce the OnPAR program to high-scoring, unfunded applicants and invite them to submit a public abstract. Leidos Life Sciences then independently identifies potential matches, extends invitations to applicants to submit additional information (e.g. same NIH application and summary statement), as well as selects applications to be funded. OnPAR members, including foundations, pharmaceutical companies, and venture capitalists, review the applications and make funding decisions.

This project had a soft launch in March 2016 with five committed funders. To date, approximately 200 unfunded investigators have entered onto the OnPAR. The private funders have not yet made any awards thus far.

Though not part of the funding decision itself, Leidos Life Sciences will provide an annual update to the NIH regarding who has been funded by the private organizations involved in OnPAR. NIH looks forward to reporting our progress on this partnership in future budget requests.

Pediatric Cancer Research Funding

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

NCI is eager to accelerate progress in childhood cancer research by attempting to define potentially game-changing scientific questions that could influence research directions in the future. To this end, NCI held two childhood cancer Provocative Questions workshops in 2015 to identify questions that address gaps in the pediatric oncology research field. NCI released the pediatric oncology provocative questions in April 2016 through program announcements designed to generate innovative approaches to address childhood cancer research challenges. NCI is also supporting an active funding opportunity focusing on the study of gene fusions in pediatric sarcomas. This is a particularly important area of research to inform future pediatric drug development, as targeted agents being developed for adult cancers do not target these changes.

The developing NCI-Pediatric Molecular Analysis for Therapy Choice (MATCH) precision medicine trial will provide a tremendous opportunity to test molecularly targeted therapies in children with advanced cancers who have few other treatment options. 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. As in the adult NCI-MATCH trial, DNA sequencing will be used to identify children and adolescents whose tumors have a genetic abnormality for which either an approved or investigational targeted therapy exists. NCI-Pediatric MATCH, which is jointly led by NCI and the NCI-funded Children's Oncology Group, is under development and is expected to launch in the first half of 2017.

Additionally, the Beau Biden Cancer Moonshot is an important opportunity to speed progress on childhood cancers. Not only is childhood cancer research one of the seven core elements within the initiative, several other elements are also important to advancing progress for children with cancer. Based on scientific recommendations from the Cancer Moonshot Blue Ribbon Panel, NCI hopes to support new research efforts to study the unique molecular changes that drive many childhood cancers, specifically those that arise in transcription factors and other cellular targets that are often considered "undruggable," with the goal of delivering advances and new treatments for pediatric cancers. A key recommendation from the Blue Ribbon Panel Pediatric Working Group is to improve understanding of these unique molecular drivers of pediatric cancers – fusion oncoproteins – and to use new preclinical models to develop therapies that target them. The Blue Ribbon Panel report also encourages pediatric immunotherapy research efforts to enhance the speed by which new immunotherapies can be tested in children.

NCI has prioritized the development of new treatments for pediatric cancer in the NCI Experimental Therapeutics (NExT) Program. This program focuses on advancing breakthrough discoveries in basic and clinical research into new therapies, and several new inhibitors with potential to treat pediatric cancer are being studied for this purpose. There are currently nine agents from the NExT program being studied in pediatric clinical trials.

In addition to soliciting applications in areas of scientific focus, NCI also remains committed to supporting a number of key research efforts focused specifically on childhood cancers. NCI has

been renewing many of these programs for numerous five-year funding periods. Examples of these critical long-term investments in childhood cancer research include:

- The Children's Oncology Group (COG)
- COG Phase 1 and Pilot Consortium
- The Pediatric Preclinical Testing Consortium (PPTC)
- The Childhood Cancer Survivor Study (CCSS)
- The Pediatric Brain Tumor Consortium
- The Pediatric Oncology Branch (POB) in NCI's Center for Cancer Research, part of NCI's intramural research program.

Specific funding figures that NIH and NCI are able to track and report each year reflect only research projects identified as specifically focused on childhood cancer in a given fiscal year, such as the research data reported in the NIH Research, Condition, and Disease Categorization (RCDC) database. While RCDC is a useful tool, it does not provide the complete picture of NIH and NCI investments that are critical to advancing childhood cancer research. For example, approximately half of the NCI budget – and half of the overall NIH budget – supports basic research that may not be specific to one type of cancer. By its nature, basic research cuts across many disease areas, and makes important contributions to our knowledge of the underlying biology of cancer. This knowledge supports the ability of the research community to make advances against many cancer types. Additionally, it is important to clarify that NCI does not make decisions about funding based on predetermined targets for a specific disease area or research category. Rather, NCI relies heavily on scientific peer review, in which highly trained outside scientists review research proposals and judge them on factors such as scientific merit, potential impact, and likelihood of success. NCI leadership further evaluates proposals to consider additional factors such as scientific novelty and overall representation of the research topic within the NCI portfolio. In some cases, the National Cancer Advisory Board also reviews the NCI research funding recommendations.

This response provides a summary of NCI-supported childhood cancer research efforts. Additional information about current NCI research is also available through the Childhood Cancers Research webpage on Cancer.gov where additional details about current research, including more comprehensive descriptions of some of the programs mentioned above, are posted.

Pediatric Inflammatory Bowel Disease Safety Registry - Update

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

The NIH supports research into new treatments for children and adolescents with Inflammatory Bowel Disease (IBD). While NIH does not manage a pediatric IBD safety registry, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) partners on some clinical trials with the Crohn's & Colitis Foundation of America (CCFA), which is collecting data, including adverse effects from treatments, from pediatric IBD patients across North America. The data will be housed and organized in what will become the largest registry of IBD patients in the world, being developed by CCFA. This registry will include data from some of the research that involves NIDDK partnership. CCFA is currently supporting a pediatric risk stratification study that is following over one thousand pediatric Crohn's disease patients for complications and response to therapies. The NIDDK-supported Predicting Response to Pediatric Colitis Therapy, a multi-center study of children and adolescents who have been newly diagnosed ulcerative colitis, is utilizing the infrastructure established by the CCFA risk study. Data from both studies will be integrated into the CCFA registry.

Pediatric Kidney Disease

The Committee continues to encourage NIDDK to work collaboratively with other ICs, including NICHD and NHLBI to encourage multi-disciplinary research for children and young adults with kidney disease.

Pediatric Kidney Disease

The Committee is encouraged by NIDDK's plans to conduct pilot studies of candidate therapies for Pediatric Chronic Kidney Disease. These studies will further optimize study designs for larger trials of new pediatric chronic kidney disease treatments. Further, the Committee continues to support NIDDK efforts to work collaboratively with other NIH Institutes, including the NICHD and NHLBI, to encourage multi-disciplinary research for children and young adults with kidney disease. Such collaborative efforts will aid in identifying childhood antecedents of chronic kidney disease, including modifiable risk factors that could be critical to developing interventions for pediatric kidney disease.

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 identify the causes, understand and halt disease progression, develop and improve treatments, and ultimately prevent kidney diseases and kidney failure in children. In July of 2016, NIDDK convened a workshop to discuss the possibilities for full-scale clinical trials in children with chronic kidney disease (CKD), and to explore potential therapeutic target areas for this group. Based on discussion at the workshop, NIDDK issued a Request for Applications to initiate and implement a network of clinical centers to conduct pilot and feasibility studies of therapies to slow or reverse the progression of CKD in children. These pilot studies will seek to optimize critical elements of a full-scale randomized control trial design – the most promising study question, agent(s), target population, dosing, data collection, and appropriate outcomes. The ultimate goal of this initiative is to obtain the necessary information to design and implement one or more full-scale randomized controlled clinical trials of therapies to reduce morbidity in children with CKD.

In an ongoing collaboration, the National Heart, Lung, and Blood Institute (NHLBI) continues its support of NIDDK's Chronic Kidney Disease in Children (CKiD) study, with particular interest in its aim of evaluating cardiovascular outcomes in children with CKD. This multi-center study in children with mild to moderately decreased kidney function is investigating risk factors for further kidney function 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. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) also supports the CKiD study. Included in the cohort analysis will be a variety of potential modifiable risk factors for CKD, such as excess protein in the urine and elevated levels of lipids in the blood.

To address the concern about acute kidney injury (AKI) in children, the NIDDK is collaborating with the National Institute of Neurological Disorders and Stroke (NINDS) in a study to collect kidney data in a cohort of premature neonates who are part of a study to examine neurological developmental issues [Preterm Epo Neuroprotection Trial (PENUT)]. This is of particular significance because there is evidence that AKI early in life can lead to increased risk of subsequent CKD.

The NICHD continues its longstanding research commitment to many conditions affecting children, including pediatric kidney disease. One recently funded study focuses on AKI, a condition common in critically ill neonates and in infants and children following cardiopulmonary bypass. Although treatment with aminophylline has been shown to improve renal function in these populations, better understanding of the pharmacokinetics (PK) and pharmacodynamics (PD) of using aminophylline in neonates and children with AKI is critical to direct customized dosing strategies that optimize safety and treatment response. The NICHD is leading a trans-NIH effort to implement the Best Pharmaceuticals for Children Act (BPCA), last reauthorized in 2012, which provides mechanisms for studying on- and off-patent drugs in children. AKI has been prioritized as a therapeutic area under the BPCA program, and NICHD will be supporting a study to collect PK data on the drugs prescribed to children with AKI through its Pediatric Trials Network.

Pediatric Rare Diseases

Further, the Committee suggests NIH evaluate how the National Pediatric Research Network Act and the Gabriella Miller Kids First Research Act activity would benefit from a single Program Management Office (PMO) to improve the coordination of pediatric research efforts.

Action taken or to be taken

Pediatric research is an important priority across the NIH. In FY 2015, NIH supported over \$3.6 billion in research grants and projects for pediatric research. Approximately 25 NIH Institutes and Centers (ICs) support pediatric research, demonstrating the breadth of the research portfolio dedicated to improving the health of children everywhere. This robust and diverse research portfolio is strengthened by close coordination among the many different pediatric research efforts to identify areas that would benefit from collaboration and to avoid duplication.

One component of the broad NIH pediatric research portfolio is the NIH Common Fund's Gabriella Miller Kids First Research program (Kids First)¹⁵⁴, which aims to catalyze pediatric research by making large amounts of high-quality genetic and clinical data from pediatric patient cohorts widely available and easy to use for scientists and clinicians. In order to maximize the impact of this program, NIH staff overseeing this program are closely coordinating with myriad pediatric research efforts across NIH. Members of the Kids First Working Group belong to approximately 12 different NIH ICs¹⁵⁵ and the Office of the Director, and Kids First staff are working with other programs making critical investments in pediatric research, including the Precision Medicine Initiative and the Environmental influences on Child Health Outcomes (ECHO) program.

Implementation of the National Pediatric Research Network Act is being carried out through the creation of the IDEa States Pediatric Clinical Trials Network (ISPCTN)¹⁵⁶ within the ECHO program¹⁵⁷. The ISPCTN will provide medically underserved and rural populations with access to state-of-the-art clinical trials, apply findings from relevant pediatric cohort studies to children in IDEa state locations, and build pediatric research capacity at a national level.

The ECHO and Kids First program staff are actively engaged in ongoing discussions about how they can work together to accelerate pediatric research. Both programs are housed within the NIH Office of the Director, facilitating close collaboration. Thus, the creation of a separate Program Management Office to improve coordination is unnecessary and duplicates activities that are already occurring. Additional levels of oversight may also hinder the flexible and fluid interactions that need to occur between ECHO, Kids First, and other pediatric research efforts across the NIH to capitalize on emerging scientific opportunities in this rapidly advancing research area.

¹⁵⁴ <https://commonfund.nih.gov/KidsFirst>

¹⁵⁵ <https://commonfund.nih.gov/KidsFirst/members>

¹⁵⁶ <https://www.nih.gov/echo/clinical-sites-idea-states-pediatric-clinical-trials-network>

¹⁵⁷ <https://www.nih.gov/echo>

Peripheral Neuropathies

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

NINDS supports a broad array of research aimed at understanding and treating peripheral neuropathies, a wide-ranging group of disorders in which the nerves that transmit sensory and motor signal to and from the brain are damaged. NINDS-funded scientists are studying the mechanisms by which genetic mutations, metabolic problems (e.g. diabetes), autoimmune disorders, infections, physical injury, or exposure to toxins (e.g. chemotherapy drugs) damage nerves or myelin (the fatty sheath that insulates and protects nerves). In addition, they are developing ways to prevent or repair this damage as well as tools to diagnose neuropathy early in the disease process. NINDS is also funding research to identify the brain circuits and cellular and molecular mechanisms underlying neuropathic pain, and to develop new therapies for relieving it. Below are a few examples of research on different types of peripheral neuropathies.

Charcot-Marie-Tooth (CMT) comprises a group of disorders caused by mutations in any of 80 or more genes that cause abnormalities in nerve axons or myelin. NINDS funds research to understand the genetic basis of and cellular mechanisms underlying multiple forms of CMT, including: the mechanisms of myelination/demyelination; intracellular trafficking of myelin proteins; and the role of cytoskeletal (structural) proteins in the maintenance of myelinated axons. NINDS funds the Inherited Neuropathies Consortium, one of the NCATS Rare Disease Clinical Research Networks, which brings together clinical researchers with expertise in CMT. The Consortium's activities include: natural history studies of various forms of CMT, a training program for post-docs and junior faculty members involving all Consortium sites, and the development of an international registry.

In people with Guillain-Barre Syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP), the body's own immune system damages peripheral nerves. Current projects are investigating particular types of antibodies (anti-ganglioside antibodies) that are present in GBS patients, how they bind to receptors, and whether blocking this binding is a potential therapeutic approach. In genetic mouse models that develop disorders similar to CIDP, NINDS-funded researchers are determining which nerve proteins are targets of autoimmune attack and which components of the immune system contribute to the autoimmune response with the goal of identifying potential therapeutic targets. Zika virus infection is one of many microbial infections that increase the risk of developing GBS. NINDS issued a notice to clarify NIH's interest in supporting research on GBS and other neurological consequences of Zika infection (NOT-NS-16-027).

Diabetic peripheral neuropathy is one of the most prevalent and debilitating complications of diabetes. NINDS-funded researchers are studying why diabetic neuropathy sometimes causes pain and other times causes numbness without pain, determining whether skin biopsy analyses can be used to predict changes associated with painful neuropathy in persons with pre-diabetes, identifying which metabolic syndrome components are associated with neuropathy, and investigating how metabolic and other molecular pathways contribute to neuropathy. Through the NINDS Blueprint Neurotherapeutics and the Small Business Innovation Research (SBIR)

programs, several small businesses are developing novel therapeutics for treating diabetic neuropathy.

Phelan-McDermid Syndrome

Phelan-McDermid Syndrome is a genetic disorder caused by a partial deletion of chromosome 22 and a loss of the *SHANK3* gene. The Committee encourages NIH to continue its multi-Institute approach to research into the Syndrome and related "shankopathies." Some topics of interest, if feasible, include the correlation of the syndrome with mental health disorders, including autism, schizophrenia, catatonia, and bipolar disorder; the study of *SHANK3* as a target for better understanding risk factors for mental health problems that occur in adolescence; phenotype studies of the syndrome as a model for studying prodromes as indicators of later manifestations in disorders; and gastro-intestinal complications associated with Phelan-McDermid Syndrome and related disorders. The Committee requests an update in the fiscal year 2018 CJ on the status of research related to this topic.

Action taken or to be taken

At the National Institutes of Health, the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Mental Health (NIMH), and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) all are engaged in research projects to better understand Phelan-McDermid syndrome and related autistic features. Phelan-McDermid syndrome is caused in most cases by a deletion of genetic material on chromosome 22 in a region known to harbor the *SHANK3* gene. Most affected individuals have intellectual disability and autism spectrum disorder (ASD); consequently, *SHANK3* serves as a useful genetic model to understand autism and other related cognitive and behavioral disorders. The term used to describe such disorders related to deficiency of *SHANK3* is "shankopathies." Research funded by NINDS and NIMH includes studies to characterize mouse models of Phelan-McDermid syndrome that harbor either mutations in this gene or knockouts (i.e., deletions) of the complete gene. These experiments shed light on the basic pathophysiology of the conditions, and have allowed researchers to uncover the molecular and cellular effects of this condition. Studies of *SHANK3* now are being conducted in rats, which allows researchers to evaluate better the complex phenotypes that underlie the behaviors associated with shankopathies. Several studies are focused on the motor deficits that occur in these conditions, with the ultimate goal of developing productive and successful treatments for some of the symptoms of Phelan-McDermid syndrome. In fact, one small business grant funded by the NICHD is developing small molecules to treat the irritability in autism with *SHANK3* as a specific target.

NIMH supports research on the shared mechanisms and symptoms of Phelan-McDermid Syndrome (PMS) and autism spectrum disorder (ASD). For example, one NIMH-funded study is designed to examine visual and sensory processing abnormalities in PMS and ASD using behavioral and electrophysiological measures. The overarching goal of this project is to develop reliable measures of visual-sensory reactivity, which can be used as objective outcome measures in treatment studies. One of the newer approaches being utilized to study Phelan-McDermid syndrome and other related conditions is the use of induced pluripotent stem cells (iPSCs), derived from skin or white blood cells, which are coaxed to develop into neurons of different types to determine the role of *SHANK3* in neuronal function. Such cell-based models also may form the basis of efficient drug screens that will result in therapeutics for this condition.

One of the key methods for understanding relatively rare genetic disorders such as Phelan-McDermid syndrome is to follow subjects with these conditions over time. A natural history and biomarker study of Phelan-McDermid syndrome is being carried out in conjunction with

comparable studies of related disorders; all share the features of developmental abnormalities of the brain coupled with high rates of autism and associated behavioral and medical conditions. NINDS, NICHD, and NIMH support the Developmental Synaptopathies Consortium, which includes teams of researchers conducting mechanistic studies of genetic conditions related to autism spectrum disorders and intellectual disability. One of the projects is focused on *SHANK3* mutations and involves a cohort of patients with Phelan-McDermid syndrome. Researchers aim to track and characterize the natural history of the condition using medical, behavioral, and cognitive measures; to use advanced imaging methods for development of biomarkers; and to understand how genetic factors contribute to the diversity of phenotypes observed in individuals with Phelan-McDermid syndrome. In addition, the Consortium has received funding from the Phelan-McDermid Syndrome Foundation to conduct a pilot study within the cohort to identify visual and auditory neurophysiological biomarkers that could potentially be used as outcome measures in clinical studies. Finally, the Consortium has developed a contact registry for the Phelan-McDermid syndrome community, including patients, families, researchers, and clinical care providers.

Physician-Scientist Workforce

The Committee is concerned about the impact of the decrease in the number of physician-scientists who can accelerate the translation of science to the treatment of widespread chronic, and currently incurable diseases such as diabetes and other diseases.

The Committee expects a report in the fiscal year 2018 CJ on the specific steps NIH has taken and their effect, as well as the path forward to implement the recommendations of the Physician-Scientist Workforce Working Group.

Action taken or to be taken

NIH continues to address the composition and size of the physician-scientist biomedical workforce and the recommendations to help sustain and strengthen a robust and diverse workforce. NIH recognizes that the training and career paths of physician-scientists were different from those of the non-clinician PhD workforce. Here, NIH presents actions taken to continue addressing the physician scientist workforce.

Sustain strong support for training of MD/PhDs and physicians through fellowships. NIH will sustain support for the dual-degree Medical Scientist Training T32 Program (MSTP) which trains MD/PhD and other health professionals. All NIH Institutes and Centers (IC) support fellowship training for physician scientists through the F30 (MD/PhD, other dual degree) and F31 (PhD) fellowships. Between 2011 and 2015 the number of new F30 awards doubled, and new F31 awards increased by 30 percent. Furthermore, new funding opportunity announcements¹⁵⁸ ensured broader availability of individual F30 fellowships at institutions with and without an NIH-funded institutional MSTP program.

Continue to address the gap in RPG award rates between new and established investigators. In 2015, NIH had similar award rates for new and established investigators. Regarding research project grant award rates for new and early stage investigators, physician scientists had similar or higher award rates compared with PhD scientists. NIH recognizes the need to identify additional programs and pathways to support physician scientists. In FY 2015, for reference, physician scientists were named as principal investigators on over 15,000 research applications (24 percent of all applications) down from 2001 when physician scientists made up 29 percent of the applicant pool.

Assess and track the strength of the biomedical workforce. In 2017, a new publicly facing Biomedical Workforce Data Dashboard will be available that includes NIH data on PhD, MD, MD/PhD, dentist, veterinarian, and nurse scientists as well as data from the American Association of Medical Colleges on medical students and medical school faculty.

Establish a new physician scientist specific grant mechanism to facilitate the transition to independence. In 2016, career development award programs specifically for physician scientists (K08 and K23)¹⁵⁹ were modified to facilitate the transition to independence. These mechanisms standardize the minimum salary contributions to \$100,000 and allow ICs to provide increased research resources during years 4-5 of the K award. In addition, the Eligibility of Physician

¹⁵⁸ <http://grants.nih.gov/grants/guide/pa-files/PA-16-305.html>; <http://grants.nih.gov/grants/guide/pa-files/PA-16-306.html>

¹⁵⁹ <http://grants.nih.gov/grants/guide/pa-files/PA-16-191.html>; <http://grants.nih.gov/grants/guide/pa-files/PA-16-198.html>

Scientists for the NIH Pathway to Independence (K99/R00) award was clarified¹⁶⁰ to encourage applications from physician scientists.

Expand the Loan Repayment Program (LRP) and amount of loans repaid.

The 21st Century Cures Act (H.R 34, section 2022) authorizes NIH to increase the maximum amount that can be repaid through the NIH loan payment program to \$50,000 per year. It further authorizes the NIH Director to change the number of LRP recipients to reflect workforce needs. A new public website¹⁶¹ was also developed to facilitate applications and efficiency. Finally, NIH initiated a strategic plan for continuous evaluation of program impact.

Support pilot programs to improve/shorten physician research training.

Two workshops held in 2016 brought together early and established physician scientists, those transitioning to independence, residents, representatives of professional societies, board certification organizations, and NIH representatives to identify flexible approaches to address gaps in training support and new programs for physician scientists. NIH is developing pilot programs to expand research opportunities during residency, support PhDs after clinical training, and mechanisms to retain and accelerate independence of promising physician scientists in research. On December 16th 2016, the NIH Director hosted a meeting of experts to prioritize the programs under development. Prioritized programs include support for Research in Residency, PhD or Masters Degrees for physician scientists at different career stages after their clinical (health professional) degree and enhancements to the Medical Scientist Training Programs (MSTP) which support MD/PhD, DVM/PhD and DDS/PhD training. NIH leadership will review the Plans for implementation (currently under development). A public report summarizing steps already taken by NIH or to be taken in the future to improve physician scientist training will be prepared in 2017.

Intensify efforts to increase physician scientist diversity.

In 2015, NIH published a Request for Information to identify strategies to enhance diversity in the physician-scientist workforce¹⁶². Input prioritized partnerships between NIH and professional organizations to enhance networking and retention of faculty and trainees from under-represented groups. A new NIH website¹⁶³ will be used to increase awareness of NIH-supported activities and programs, as well as provide information about best practices and other diversity-related programs.

Leverage the existing resources of the Clinical Translational Science Awards (CTSA) Program to maximize benefit for training and career development of clinician scientists.

In 2016, the National Institute of Dental and Craniofacial Research and National Institute of Biomedical Imaging and Bioengineering supported new partnerships with CTSA. Multiple

¹⁶⁰ <http://grants.nih.gov/grants/guide/pa-files/PA-16-193.html>

¹⁶¹ <https://www.lrp.nih.gov/>

¹⁶² <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-027.html>

¹⁶³ <https://extramural-diversity.nih.gov>

Lastly, the CTSA One Health Alliance partnership is a direct partnership between the NIH CTSA program and the extramural veterinary medicine research community. This activity seeks to advance understanding of diseases shared by humans and animals. The alliance will leverage the expertise of physicians, research scientists, veterinarians, and other professionals to solve medical problems and address the well-being of humans, animals and the environment.

Preterm Birth and Prevention of Preterm Birth

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) continues to actively support a large and diverse research portfolio related to the cause and prevention of prematurity as well decreasing the complications that can be a consequence of preterm delivery. New research shows that the smallest preterm infants also 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 percent of all live births but are responsible for 15 percent 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, there is promising, but limited, data that pessary and vaginal progesterone may decrease preterm birth in women with a twin gestation and short cervix. This randomized clinical trial is designed to assess whether either of these approaches reduces the risk of preterm delivery prior to 35 weeks in women who are carrying twins.

The NICHD also is looking at what impact various exposures may have on the likelihood of delivering a baby preterm. Infection-mediated preterm birth accounts for 25-40 percent of preterm births in the U.S. and is the primary cause of preterm birth in underdeveloped countries. Studies to diagnose and treat these conditions are being supported by the NICHD. For example, babies infected with CMV may develop permanent disabilities including hearing loss, and a small number will die from the infection. A study being conducted by the MFMU is designed to determine whether treating pregnant women who are infected with Congenital Cytomegalovirus (CMV) with CMV antibodies prior to 24 weeks of gestation could reduce the number of babies infected with CMV, thus preventing morbidity and mortality in these infants. Another recent 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 nitrogen oxides and carbon monoxide. It found that when women are exposed to these pollutants just before conception and in the early weeks of pregnancy, they faced an even greater risk of preterm birth.

Based on earlier research supported by the NICHD, administration of antenatal corticosteroids to women at risk of delivering prematurely has reduced neonatal morbidity and mortality in the U.S. Steroids are now a standard treatment for women likely to deliver before 34 weeks of pregnancy because these drugs are known to reduce respiratory and other complications, as well as death, among infants born early preterm. However, not all neonates respond similarly to this therapy. Recently, the NICHD supported a study that showed that steroids reduce the occurrence of serious respiratory complications in late preterm infants (born at 34-36 weeks). Previously, it was believed that these late preterm infants could thrive without their mothers having received steroid treatment. 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 encourages further efforts into treatments for men with advanced disease as well as diagnostic and imaging methodologies common in other hormone driven cancers with similar disease burden. The Committee encourages NCI to coordinate its response to these needs with other Federal agencies, and collaborators as appropriate, including the Department of Defense, as well as private research foundations and advocacy groups.

Prostate Cancer

The Committee is aware of NCI's ongoing investment in prostate cancer research, but 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. The Committee encourages NCI to coordinate with other Federal agencies, including the Department of Defense, private research foundations, and other stakeholders. Further, the Committee encourages NIH and CDC to consider how to develop a joint public/private partnership aimed at reducing the prevalence of prostate cancer in African American men. The Committee requests NIH and CDC provide a joint response on this type of effort in the fiscal year 2018 budget request.

Prostate Cancer

The Committee encourages CDC and NIH to examine how to develop a joint public-private partnership to reduce the prevalence of prostate cancer in African-American men. Specifically, CDC and NIH should consider how to develop support via coordinated meritorious scientific competitive research and public health outreach awards. The Committee requests that the CDC and NIH provide a joint report on this potential type of effort with a notional timeline and expected outcome measures in the fiscal year 2018 budget request on these efforts. (CDC)

Action taken or to be taken

Prostate cancer is the third most commonly diagnosed cancer in the United States, accounting for approximately 11% of new cancer cases. In 2016, an estimated 180,100 men were diagnosed with prostate cancer, and approximately 26,100 men died from the disease. While early stage prostate cancer is highly treatable, the survival rate for men who are diagnosed at advanced stages of the disease is much lower than those men who are diagnosed in earlier disease stages. Therefore, NCI has a number of research initiatives focused on treating late-stage disease. Within NCI's intramural Center for Cancer Research (CCR), the Urologic Oncology Branch, the Genitourinary Malignancies Branch, and the Radiation Oncology Branch have active clinical trials to test new prostate cancer therapies. For example, CCR has developed clinical trials to test the use of anti-angiogenic agents that block tumor blood supply, small molecules that impair the growth of tumors, and anti-tumor vaccines to be used in combination with radiotherapy and chemotherapy.

Through the extramural Division of Cancer Treatment and Diagnosis (DCTD), NCI also supports eight prostate cancer Specialized Programs of Research Excellence (SPOREs), a team science program focused on translational research in prostate cancer. Among its therapeutic contributions is the development and the clinical evaluation of second-generation hormonal therapies for the treatment of advanced prostate cancer and establishment of a precision

oncology framework for selecting treatment based on the molecular profiling to tumors. In addition to research conducted by SPOREs, DCTD provides support for a number of clinical trials for prostate cancer treatment.

Prostate cancer incidence and survival rates vary widely by race and ethnicity, with African American men experiencing the highest incidence and mortality rates. NCI conducts and supports a number of research initiatives with a focus on understanding both the biological and behavioral factors that lead to these outcomes. For example, the NCI Maryland Prostate Cancer Case Control Study, which has been ongoing through the Laboratory of Human Carcinogenesis in CCR since 2005, consists of 975 cases and over 1000 controls, with an equal number of Caucasian and Black participants. The study examines potential causes of prostate cancer (including risk factor exposures and environmental factors) and biomarkers for prognosis, with the identification of gene signature and interferon activity differences between races being of particular interest. Additionally, through the Division of Cancer Control and Population Science (DCCPS), NCI supports population level prostate cancer research on topics such as prostate cancer decision-making for low-income African American men, mitochondrial genetic susceptibility to prostate cancer, prostate cancer information disparities, and the genome-wide sequencing of prostate cancer in men of African ancestry. The division also supports the Cancer Intervention and Surveillance Modeling Network (CISNET) Prostate Working Group, which is modeling prostate cancer progression, screening, and treatment in the U.S. population, assuming biologically plausible assumptions validated against various data sources. Currently, the working group is examining efficiency gains of screening only high-risk individuals, benefits of avoiding or delaying treatment for low-risk cancers, and feasible approaches for reducing racial disparities. This research will advance the evidence necessary to make informed decisions about screening and treatment for this most common cancer in men.

In addition, NCI has an ongoing collaboration with the Center for Prostate Disease Research (CPDR) at the Walter Reed National Military Medical Center. CPDR's patient population of 28,000 military health care recipients, including 4,500 military members, is 20 percent African-American, providing opportunities for racial/ethnic health disparities research. Additional research priorities include the investigation of genomic markers, the use of hormonal receptors as prognostic markers, and MRI-ultrasound fusion image technology.

NCI invests heavily in research focused on improving diagnosis techniques, particularly through imaging research. Studies focus not only on detecting disease, but developing methods to determine which lesions are potentially lethal in order to prevent overtreatment. NCI's CCR is currently undertaking multiple clinical trials, many of which focus on prostate cancer and involve a variety of imaging systems, including PET/CT scans and enhanced MRI techniques. Through the National Clinical Trials Network (NCTN), NCI supports the work of the Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN), a collaboration whose recent projects include the study of best practices for the use of MRI imaging. The Cancer Imaging Program (CIP), in DCTD, manages an extramural portfolio that also includes projects exploring the nuances of using MRI in prostate cancer diagnosis and treatments, as well as projects to develop new agents for use in PET scans and potentially new imaging technologies.

NCI and CDC continue to collaborate across programs that address various areas of cancer control and prevention research. For example, the Population-based Research Optimizing Screening through Personalized Regimens (PROSPR) initiative includes external stakeholders as advisors, and CDC colleagues are a part of this effort. Both the PROSPR consulting committee and the PROSPR information network include CDC colleagues.

Another example of NCI and CDC collaboration is the Cancer Prevention Research Network (CPRN). CPRN is a national network of academic, public health, and community partners who work together to reduce the burden of cancer, especially among those disproportionately affected. Its members conduct community-based participatory cancer research across its eight network centers, crossing academic affiliations and geographic boundaries. The CPRN is a thematic research network of the Prevention Research Centers (PRCs), which are CDC's flagship program for preventing and controlling chronic diseases. The CPRN represents a collaboration of cancer divisions from two federal agencies: The Division of Cancer Prevention and Control of the CDC's National Center of Chronic Disease Prevention and Health Promotion, and the Division of Cancer Control & Population Sciences of the National Cancer Institute.

NCI also collaborates with stakeholders across the cancer research community to incorporate a collective patient perspective in the cancer research process. Patient advocates serve on a number of NCI advisory groups and steering committees, and NCI recognizes individual advocates and organizations as important partners in the research process, as well as in providing education and outreach about cancer risk, screening, treatment, and survivorship.

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 implement distress screenings in the NIH Clinical Center and in NCI-funded clinical trials

Action taken or to be taken

The National Cancer Institute (NCI) is committed to reducing patients' psychological distress and improving overall quality of life. In addition to supporting research on psychosocial and behavioral interventions to reduce psychological distress and promote adaptation to illness, the NCI encourages the use of distress screening in NCI-funded clinical trials and provides this screening at the NIH Clinical Center.

NCI's Community Oncology Research Program (NCORP) is a national network of investigators, cancer care providers, academic institutions, and other organizations that conducts multi-site clinical trials across the cancer control spectrum and facilitates patient and provider access to treatment and imaging trials in the National Clinical Trials Network (NCTN). One of the requirements for funded NCORP sites is the ability to screen for distress and refer individuals to appropriate psychosocial care as needed.

The NIH's Pain and Palliative Care consultation service, established in 2000, is available to all patients who are actively participating in a research study within the NIH Clinical Center. This service provides skilled management of disease symptoms and treatments to alleviate suffering (psychosocial, emotional, and spiritual) and improve patient and family quality of life while allowing NIH researchers to continue to focus on conducting clinical trials. Pediatric patients are also seen by experts in NCI's Psychosocial Support and Research Program, which is dedicated to studying how to best help patients and their families prepare for, adjust to, and cope with the effects of cancer and other related medical conditions. One study in this program seeks to develop a brief electronic screening tool, *Checking In*, which would assist clinicians in assessing the presence of psychological distress in children and adolescents with cancer and other serious medical illnesses.¹⁶⁴

The NCI also seeks to further scientific understanding of psychosocial distress in patients with cancer and supports the development of appropriate interventions through the support of extramural grantees. For example, one study is testing a stepped-care approach tailored to symptom severity for reducing emotional distress and improving secondary outcomes in rural, post-treatment cancer survivors in community oncology settings.¹⁶⁵ Recognizing that psychosocial support is also necessary after treatment ends, the Office of Cancer Survivorship (OCS) works to enhance the quality and length of survival of all persons diagnosed with cancer and to minimize or stabilize adverse effects. In 2016, OCS solicited research applications to

¹⁶⁴ <https://ccr.cancer.gov/Pediatric-Oncology-Branch/psychosocial/science>

¹⁶⁵ https://projectreporter.nih.gov/project_info_description.cfm?aid=9100255&icde=31538937

stimulate research evaluating the effect of care planning on self-management of late effects of cancer therapy; adherence to medications, cancer screening, and health-behavior guidelines; utilization of follow-up care; and survivors' health and psychological outcomes. The NCI also supports psychosocial oncology training initiatives, such as the Ohio State University's "From Cancer to Health" program, to educate cancer care professionals on how to implement screening programs at their respective institutions to recognize and treat cancer patients who experience significant distress.¹⁶⁶

¹⁶⁶https://projectreporter.nih.gov/project_info_description.cfm?aid=8920516&icde=31538937&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC

Psychosocial Issues and Chronic Disease Management

People with chronic diseases have an elevated risk of psychosocial issues such as depression, anxiety, and eating disorders. These issues correlate with an increase in negative outcomes for disease management. The Committee urges NIDDK to devote resources toward investigating the psychosocial burdens related to chronic diseases, particularly as it relates to type 1 diabetes, and identify steps that can be taken to help improve disease management.

Action taken or to be taken

Psychosocial issues in type 1 diabetes is an area of focus for research supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Daily management of type 1 diabetes is a challenge for people with the disease, as well as their caregivers. There is great need for new tools and strategies to help people achieve the recommended levels of blood glucose control with less burden and fewer episodes of dangerously low blood glucose, so that they can reduce their risk for long-term disease complications. People of all age groups—from babies to adults—are burdened with type 1 diabetes, and each age group has different obstacles to overcome for disease management. The NIDDK supports research to identify barriers to care across the lifespan and to develop and test strategies to help people with the disease and their caregivers. In FY 2016, three funding opportunity announcements were re-issued to support development of innovative strategies to improve type 1 diabetes management in different age groups: young children; preteens, adolescents, and young adults; and adults.

NIDDK supports a diverse portfolio of research to improve diabetes management, especially in adolescents, a population in which achieving the recommended levels of blood glucose control is particularly challenging. Improving disease management for adolescents is critical because NIDDK-supported research has shown that early and intensive blood glucose control is key to preventing complications and reducing risk of premature death. These efforts include the ongoing FL3X clinical trial to test an innovative behavioral approach to address the challenges to optimal diabetes self-management in youth with type 1 diabetes, and five other ongoing studies testing different approaches to deal with the psychosocial and biological complexities of adolescence and managing a chronic disease. Results from these studies could inform future interventions to help adolescents manage their disease, thus improving blood glucose control and long-term health outcomes.

Behavioral research on how best to utilize new blood glucose control technology is also a focus of NIDDK support. New technologies for disease management—such as artificial pancreas technologies, which link a continuous glucose monitor to an insulin pump with a computer that instructs delivery of an appropriate amount of insulin—will only be beneficial if people know how to and are willing to use them. In FY 2016, NIDDK announced a funding opportunity for clinical, behavioral, and psychological research to improve usability of current and novel artificial pancreas technologies. NIDDK also awarded three grants to study the impact of diabetes management technologies on health outcomes and quality of life in older adults with type 1 diabetes. In addition, NIDDK released a funding opportunity announcement to study neurocognitive effects of type 1 diabetes, which can influence mental health, quality of life, and disease management.

Pulmonary Hypertension (PH)

The Committee applauds NHLBI for leading research efforts that have helped prolong life for individuals affected by PH. NHLBI is encouraged to further study the underlying mechanisms of PH, particularly idiopathic pulmonary arterial hypertension, so that additional gains can be made that benefit patient health and wellness.

Action taken or to be taken

Pulmonary hypertension (PH) represents a spectrum of fatal lung diseases without a known cure or unifying cause. Prognosis and treatment efficacy differ greatly among patients with different subtypes of the disease. PH is also often diagnosed late in the disease process, which further limits treatment effectiveness. Pulmonary arterial hypertension (PAH) is a particularly insidious and devastating subtype of PH. In 1985, the NIH-estimated median survival for PAH was only 2.8 years from diagnosis. With the advent of medications in the mid-1990s, mean one-year survival has improved from 68 percent in 1985 to 85 percent today. However, the National Heart, Lung, and Blood Institute (NHLBI) recognizes a continued need for better understanding of and treatments for PH, and ultimately, a need for a cure.

New discoveries and emerging technologies supported by NHLBI offer unprecedented opportunities to understand PH pathogenesis and disease progression, to allow for earlier identification of PH patients, and to develop targeted disease prevention and treatment strategies. In addition, rapid advances in understanding disease mechanisms, improved imaging techniques, "omics" technologies, and methods for biomarker discovery have enabled us to improve the PH classification system, which will help standardize methods across clinical trials.

In 2014 and 2015, the NHLBI partnered with the Pulmonary Hypertension Association (PHA) to launch the Pulmonary Vascular Disease Phenomics (PVDOMICS) Program. This program aims to identify more sensitive measures of PH. Success could transform future clinical trials by allowing more timely diagnosis, thus enabling potential new therapies to be tested earlier in the disease, with improved odds of preempting or forestalling it. In addition, new measures of PH severity derived from this large endeavor, including biomarkers and clinical characteristics, could be used as surrogate outcome measures in future trials. Disease and mechanism-specific biomarkers could help enhance patient enrollment and allow investigators to determine whether study cohorts respond more uniformly to mechanism-based therapies. As of late 2016, the program includes one data coordination center and six clinical centers, which have begun recruiting patients.

Also in partnership with the PHA, NHLBI used supplemental funding for clinical and patient-oriented career development awards to foster training of clinical investigators and strengthen the pipeline of future PH researchers. NHLBI also has actively engaged the PH community via joint workshops and symposia and through our recent strategic planning process. As a result of community input, one of the research priorities in the NHLBI's newly released Strategic Vision is to explore novel PH biomarkers in order to better identify individuals at high risk for PH, reveal underlying mechanisms, and guide treatment. This priority aligns with several other current efforts, including PH research conducted by the NHLBI Centers for Advanced Diagnostics and Experimental Therapeutics (CADET), translational program projects, and the Vascular Interventions/Innovations and Therapeutic Advances programs.

Radiation Oncology

The Committee encourages support for high quality meritorious radiation oncology research. The Committee requests an update in the fiscal year 2018 budget request on efforts to support radiation therapy's role in the development and adoption of new combination therapies.

Action taken or to be taken

Radiation therapy uses high-energy radiation delivered by a machine outside the body (external-beam radiation therapy and particle therapy), by using radioactive material given intravenously (systemic radiotherapy), or by internal applicators (brachytherapy) to shrink tumors and kill cancer cells. Radiation therapy is given with a curative or a palliative intent and can be used in combination with other treatments like surgery, chemotherapy, and immunotherapy. Radiation therapy used in partnership with chemotherapy can kill more cancer cells and increase the likelihood of a cure, but in order to minimize the toxicity, innovative radiation therapy technology may be used, such as image guided radiation therapy and proton/particle therapy. Radiation, when used in combination with immunotherapy approaches, may also substantially enhance immune responses, inhibit immunosuppression, and/or alter the phenotype of tumor cells, thus rendering them more susceptible to immune-mediated killing. The National Cancer Institute (NCI) is supporting research examining how to exploit radiation-induced changes to tumor-cell antigens, how to induce effective immune responses to these cumulatively immunogenic stimuli, and how to use radiation in unique doses and schedules to enhance the efficacy of drugs, including repurposing drugs that have been used in the clinic.

For example, NCI's recent funding opportunity announcement, Cooperative Agreements to Develop Targeted Agents for Use with Systemic Agents Plus Radiotherapy, encourages researchers to submit a cooperative agreement (U01) application that proposes studies to enhance pre-clinical *in vitro* and *in vivo* testing of NCI-prioritized molecularly targeted anti-cancer agents for use with radiation therapy combined with systemic chemotherapy. The goal of this project is to generate high-quality preclinical data on the effects of molecular therapeutics when added to standard-of-care for solid tumors. Research data from these studies will accelerate the pace at which combined modality treatments are identified and incorporated into standard practices for treatments of patients with solid tumors.

Additionally, the funding opportunity announcement will establish a Preclinical Chemo-Radiotherapy Testing Consortium (PCRTC) that will support several individual research programs for *in vivo* and *in vitro* testing of investigational anti-tumor drugs administered concurrently to chemo-radiotherapy. Reliable data will be reproduced within the PCRTC and used for new agent prioritization decisions, in addition to informing clinical trial designs.

Ongoing research at the NCI includes a number of clinical trials evaluating radiation therapy in combination with immunotherapy and other approaches. Examples of clinical trials include:

- A pilot study to evaluate immune checkpoint inhibitors in combination with radiation therapy in patients with unresectable pancreatic cancer.¹⁶⁷
- A phase II trial studying radiation therapy and cisplatin (chemotherapy) with triapine (a targeted therapy that inhibits the activity of certain enzymes) to see how well they work

¹⁶⁷ <https://clinicaltrials.gov/ct2/show/NCT02311361>

compared to the standard radiation therapy and cisplatin alone in treating patients with newly diagnosed stage IB2, II, or IIIB-IVA cervical cancer or stage II-IVA vaginal cancer.¹⁶⁸

- A phase I/II trial studying the side effects and how well localized radiation therapy or recombinant interferon beta (a recombinant protein with antiviral and anti-tumor activities) and avelumab (an antibody that may stop the growth of tumor cells) with or without cellular adoptive immunotherapy works in treating patients with Merkel cell carcinoma, a rare type of skin cancer, that has spread to other parts of the body.¹⁶⁹

NCI will continue to support research to better understand and enhance combination therapies, including radiation therapy, to improve outcomes for all cancer patients.

¹⁶⁸ <https://clinicaltrials.gov/ct2/show/NCT02466971?term=NRG-GY006&rank=1>

¹⁶⁹ <https://clinicaltrials.gov/ct2/show/NCT02584829?term=radiation+and+immunotherapy&rank=6>

Raising Awareness of 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, patients, and families. Through its NIDAMED initiative, NIDA is advancing addiction awareness, prevention, and treatment in primary care practices through seven Centers of Excellence for Physician Information. Intended to serve as national models, these centers target physicians-in-training, including medical students and resident physicians in primary care specialties. NIDA also developed, in partnership with the Office of National Drug Control Policy, two online continuing medical education courses on safe prescribing for pain and managing patients who abuse prescription opioids. The Committee is pleased with NIDAMED and urges NIDA to continue its focus on activities to provide 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

Educating patients, families, and healthcare providers is a critical component in curbing substance use and associated health consequences, including addiction. The National Institute on Drug Abuse (NIDA) continues to support these efforts through the NIDAMED initiative by partnering with leaders in clinician education to provide training and other resources on substance use prevention, early intervention, and treatment tailored to the specific needs of primary care providers.

Since 2007, NIDA has engaged in three initiatives to create and disseminate educational information to practicing healthcare providers and clinicians in training. These efforts began with seven NIDA Centers of Excellence for Physician Information (2007-2014) at medical schools across the country. These Centers created twelve medical education resources including lectures, web modules, and workshops for medical students and resident physicians in primary care specialties. NIDA, with funding from the Office of National Drug Control Policy, broadened these educational efforts by partnering with Medscape Education (2012-2015) to create two continuing medical education (CME) modules to promote safe opioid prescribing practices and tools to help manage pain patients who misuse prescription opioids. These courses trained well over 100,000 clinicians.

Most recently, NIDA formed the NIDAMED Coalition of Healthcare Organizations (2014-current) consisting of leading experts and medical associations including the American Academy of Pediatrics, the California Academy of Family Physicians, the American Osteopathic Association, the American Academy of Physician Assistants, and the American Association of Nurse Practitioners. By January 2017, the Coalition will launch a CME that provides evidence-based information and clinical strategies to help prevent and address substance use disorders and prescription medication misuse in adolescent patients. The CME includes information on screening adolescent patients prior to prescribing controlled substances, working with parents and caregivers to manage appropriate use of prescriptions, using Prescription Drug Monitoring Programs (PDMPs), and safe ways to dispose of medications with abuse potential. This web-based CME/CE is expected to launch prior to January, 2017.

Rare Disease Clinical Research Network

The Committee is encouraged by the work of the Rare Disease Clinical Research Network (RDCRN). The Committee encourages NIH to have ICs consider how they can work with RDCRN 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), is designed to advance medical research on rare diseases by providing support for clinical studies and facilitating collaboration, study enrollment and data sharing. Through the network, scientists from multiple disciplines at hundreds of clinical sites around the world work together with patient advocacy groups to study more than 280 rare diseases. Several of the RDCRNs focus on rare diseases that primarily affect children. One example is the Lysosomal Disease Network. In lysosomal diseases, there is a deficiency in or absence of an enzyme that breaks down unwanted cellular waste, which results in the inappropriate buildup of waste in the body's cells. This buildup kills the cells, which can lead to illness and often eventual death of the patient. The Lysosomal Disease Network brings together doctors, researchers, and patient advocacy groups for a large number of lysosomal diseases, including Batten disease, Fabry disease, Gaucher disease, Krabbe disease, mucopolysaccharidosis, Niemann–Pick disease, Pompe disease, Tay-Sachs disease, and Wolman disease, to solve major challenges in diagnosis and disease management and treatment. All of the diseases are genetic and affect children and young adults—in some cases the disease is fatal in children, in others patients live to adulthood but with severe disabilities. NCATS supports each of the RDCRNs in collaboration with other NIH Institutes and Centers.

NCATS also supports the Clinical and Translational Science Awards (CTSA) Program, which is working to strengthen the entire spectrum of our nation's clinical and translational research enterprise. This includes ensuring that populations across the entire lifespan, including pediatrics, are part of research studies. As such, the CTSA Program is working on ways to enhance the participation in research of pediatric and other special populations, and, in some instances, making them the focus of study.

In 2013, Congress passed the Pediatric Research Network Act, which NIH is implementing through the new Institutional Development Award (IDeA) States Pediatric Clinical Trials Network Program (ISPCTN). This program is part of the new Environmental Influences on Child Health Outcomes (ECHO) program, which will investigate environmental exposures on child health and development. The ISPCTN will give medically underserved and rural populations access to state-of-the-art pediatric clinical trials. The network's clinical trials sites, which will be located in states eligible for funding through the IDeA program, will receive support for the development of appropriate research infrastructure as well as supervised professional development in all aspects of clinical trials research and implementation. The ISPCTN will help strengthen pediatric research opportunities, including research on pediatric rare diseases, and capacity in IDeA states, which historically have not received extensive NIH funding. Any institution in the country conducting a pediatric clinical trial can supplement their recruitment by using this new network—allowing children in IDeA states, many of whom have rare conditions, to participate in cutting edge clinical trials.

NIH funds over 100 pediatric research centers and networks, several of which are working on rare conditions, so an additional pediatric rare disease center of excellence might be duplicative of current efforts especially in times when there are limited resources.

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. The Committee encourages the National Center for Medical Rehabilitation Research 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) in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), as well as other Institutes and Centers at the National Institutes of Health (NIH) who support rehabilitation research, recognize the need to extend the reach of rehabilitation services to rural or remote settings. The NCMRR is funding currently, or has recently funded, 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.

One project, recently funded by the NCMRR, will assess 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 rural and remote areas. The investigators are ensuring that the program meets the needs of specific populations who are often underserved, including American Indian/Alaska Native and Hispanic/Latino individuals. Another project is examining a mobile health extension of a wellness coordinator program for persons with spina bifida that includes two-way communications between providers and participants.

Specific to tele-rehabilitation, the NCMRR is co-funding a large trial of tele-rehabilitation for upper extremity weakness or paralysis as compared to an in-clinic rehabilitation therapy in partnership with the National Institute of Neurological Disorders and Stroke (NINDS). This project will provide an intervention for weakness or paralysis of the hand or arm, and will provide stroke prevention and health education information for participants in the trial. The investigators will monitor participants' compliance with the therapy through self-report measures and body-worn sensors at nine sites throughout the country. In addition, the NCMRR is supporting a home-based cycling protocol that uses body sensors and mobile health applications to provide feedback and training for patients after stroke. The NCMRR also supports a number of research grants under the Small Business Innovation Research program that are aimed at developing devices to deliver physical rehabilitation in the home environment for patients with stroke.

The development of assistive technologies appropriate for home use is another priority of the NCMRR. Some examples of recently funded grants include: virtual occupational therapy interventions for remote rehabilitation of daily living activities; game-based training systems for navigating uneven surfaces for patients with Parkinson's disease; game-based training for upper extremity amputees learning to use prosthetic devices; remote delivery of a physical activity

program for individuals with physical disability; and robust toy-based rehabilitation techniques for children with cerebral palsy using remote controlled cars and computers. Projects within the NCMRR research portfolio that could ultimately be used in the home include prevention of complications for individuals with disability, such as remote biofeedback systems to help prevent pressure ulcers in manual wheelchair users, promotion of physical activity through sensor-based or mobile health technologies, and interactive self-management systems to help people manage chronic conditions associated with disability.

Reproducibility of the Scientific Method

The Committee requests an update on the progress made and the plan for additional activities in the fiscal year 2018 budget request.

Action taken or to be taken

NIH continues to expand its efforts to address reproducibility, rigor, and transparency in biomedical research. Updates to NIH grant application instructions and review language were implemented for most research grant and mentored career development award applications submitted for the January 25, 2016 due date and beyond. Attention must focus on the scientific premise of the proposed research, rigorous experimental design, consideration of relevant biological variables, such as sex, and authentication of key biological and/or chemical resources. The biomedical research community was notified of the upcoming updates in FYs 2015 and 2016^{170,171,172}, including the expectation that Research Performance Progress Reports emphasize rigorous approaches¹⁷³.

In preparation for the updated application guidelines, NIH published both staff and community resources online (e.g., eLearning modules, infographics, and FAQs)¹⁷⁴, several blog posts on the application updates¹⁷⁵, and reviewer guidance in many forms (e.g., online guidance)¹⁷⁶. Resources continue to be developed as needs are identified. NIH conducted training for all Scientific Review Officers on the new standards, and Scientific Review Officers trained all of their reviewers on the new standards.

Additionally, multiple Institutes, Centers, and the Office of the Director recently released a Funding Opportunity Announcement to address the problem of misidentified cell lines¹⁷⁷. Small businesses were invited to submit applications to improve existing technologies, and/or develop novel, reliable, and cost effective tools to simplify the process to confirm the identity and/or sex of the cells used.

The first set of NIH grants reviewed under the new guidance to emphasize rigor and transparency were awarded between August and October 2016, with the next cycle currently under review. The reviewer guidance is being refined and will incorporate lessons learned from early reviews. NIH is in the early stages of evaluating these efforts to increase rigor and transparency in NIH-funded research. Over the next two years, over 1,500 NIH grant applications and reviewer summary statements will be assessed for adherence to the policy.

NIH is also taking steps to strengthen research training. In December 2015, NIH notified the research community of upcoming requirements for formal instruction in rigorous experimental design and transparency to enhance reproducibility, to be implemented as early as FY 2017¹⁷⁸. To help prepare institutions in developing instruction, the National Institute of General Medical

¹⁷⁰ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-103.html>

¹⁷¹ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-011.html>

¹⁷² <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-012.html>

¹⁷³ <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-031.html>

¹⁷⁴ <https://grants.nih.gov/reproducibility/index.htm>

¹⁷⁵ <https://nexus.od.nih.gov/all/tag/rigor/>

¹⁷⁶ https://grants.nih.gov/grants/peer/guidelines_general/Reviewer_Guidance_on_Rigor_and_Transparency.pdf

¹⁷⁷ <http://grants.nih.gov/grants/guide/pa-files/PA-16-186.html>

¹⁷⁸ <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-034.html>

Sciences (NIGMS), along with eight other Institutes and Centers, funded projects aimed at developing exportable training modules designed to promote expertise in rigorous experimental design and transparency which are targeted to graduate students, postdoctoral fellows, and other investigators early in their careers¹⁷⁹. A public NIGMS website¹⁸⁰ currently hosts the first set of funded products that highlight common issues related to reproducibility and rigor in the research endeavor, such as minimizing unintended bias in experimental design and execution by random sampling, blinding, and balancing experiments to reduce bias¹⁸¹. In FY 2016, NIGMS also funded training grant supplements to (1) provide graduate students with training in rigorous experimental design and statistical and quantitative approaches that will enhance reproducibility, (2) broaden training to better prepare students for research careers in a variety of venues^{182,183,184}, (3) develop skills needed to be a competitive biomedical research scientist, and (4) promote the reworking and revitalization of biomedical predoctoral research education and training¹⁸⁵.

In March 2016, NIH hosted a workshop to discuss potential pitfalls that might lead to irreproducible research, with emphasis on assays that generate large volumes of data. Moreover, NIH plans to reconvene a workshop with journal editors (originally held in 2014) that produced a consensus document, Principles and Guidelines for Reporting Preclinical Research¹⁸⁶. This follow-on workshop will be an opportunity for journal editors to share experiences and lessons learned and to discuss how funders and journals can continue to work together to promote rigorous, transparent, and reproducible research.

¹⁷⁹ <http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-15-006.html>

¹⁸⁰ Clearinghouse for Training Modules to Enhance Data Reproducibility

¹⁸¹ <https://www.nigms.nih.gov/training/pages/clearinghouse-for-training-modules-to-enhance-data-reproducibility.aspx>

¹⁸² <http://grants.nih.gov/grants/guide/pa-files/PA-15-136.html>

¹⁸³ <http://grants.nih.gov/grants/guide/pa-files/PA-16-060.html>

¹⁸⁴ <http://grants.nih.gov/grants/guide/pa-files/PA-16-133.html>

¹⁸⁵ <http://grants.nih.gov/grants/guide/pa-files/PA-16-142.html>

¹⁸⁶ <http://www.nih.gov/science/reproducibility/principles-guidelines.htm>

Research Centers in Minority Institutions (RCMI)

The Committee continues to recognize the critical role played by minority-serving institutions in addressing minority health and health disparities, while also providing training for a diverse health workforce. 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 \$1 invested being leveraged to generate an additional \$5 to \$6 in competitive research funding. The RCMI program has the capability to promote solutions to the significant gap in R01 grant funding among black and other minority researchers when compared to non-minority researchers. The Committee remains concerned NIMHD may be considering changing RCMI's configuration and funding structure without adequate congressional or stakeholder input. Therefore, the Committee directs NIH to maintain the existing vital infrastructure support provided through the RCMI program and make available not less than last year's level for the RCMI program. Further, NIMHD is directed to provide an update to the Committee no later than 90 days after enactment of this act on any proposed changes to the program and prior to any changes being implemented.

Action taken or to be taken

The Research Centers in Minority Institutions (RCMI) program plays a unique and essential role in assisting eligible institutions to become more competitive in seeking funding for biomedical research and contributing to the National Institutes of Health's (NIH) goal of turning discovery into health. The leadership of the NIMHD has engaged in a year-long dialogue regarding the RCMI Program with key stakeholders, including current principal investigators, other RCMI scientists, and institutional leaders, as well as the advocacy community and academic and scientific leaders, and has incorporated feedback into the future plans for the RCMI program.

The RCMI programmatic content requirements remain essentially the same with support for research infrastructure and capacity as the largest allowable component of an institution's overall project. NIMHD has not proposed any changes to the RCMI program that contradict Congressional intent. The few changes are meant to strengthen the ability of eligible institutions to: a) conduct world-class biomedical research; and b) produce well-trained, new investigators from underrepresented groups who will help enhance diversity to the biomedical research workforce. The RCMI program has been modified to better align with the Institute's vision to advance the science of minority health and health disparities. The new RCMI funding opportunity announcement (<https://grants.nih.gov/grants/guide/rfa-files/RFA-MD-17-003.html>), released on December 9, 2016, is more flexible with options for one to three types of research studies for basic, clinical, and/or behavioral research. Eligible institutions include those with a historical and current documented commitment to serving students from underrepresented populations that receive less than \$50 million average annual NIH funds within the 3 years prior to the time of application. Further, the specialized centers will emphasize workforce diversity by enabling all levels of investigators, especially new and early career investigators, to experience rigorous, mentored research experiences focused on diseases that disproportionately affect minority and other health disparity populations. At least one research project will be included, as well as funds allocated to support pilot projects by postdoctoral fellows and assistant professors.

The addition of a requirement to conduct a scientific research project is designed to provide opportunities for faculty investigators to directly conduct important research projects which is invaluable in enhancing the scientific and technical expertise of faculty investigators as they

compete for additional research funding and to strengthen opportunities for graduate students and postdoctoral trainees. Building upon the prior significant NIMHD investment in many of these institutions, it may also address the significant gap in research project grants (R01) funding for African American and other researchers from underrepresented groups, as defined by the National Science Foundation. Awards are expected to be made in September 2017.

Furthermore, increasing biomedical research capacity and training a diverse biomedical research workforce continue to be priorities for the NIH. The NIMHD sees the RCMI program as an outstanding vehicle by which to promote diversity in the biomedical scientific workforce. The single most significant predictor of a young person choosing a scientific career is whether they participated in a rigorous, mentored, research experience.

NIMHD reassures the Committee that the FY 2017 funding level for the RCMI program will be not less than the FY 2016.

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

NIH's Building and Facilities program ensures that the campus research facilities are in compliance with all laws and regulations that supports NIH's mission. The Division of Technical Resources (DTR) review process checks for compliance with the latest edition of the NIH Design Requirements Manual, National Standards, as well as for technical accuracy, constructability, sustainability, good lab/engineering practice, and programmatic acceptability.

DTR provides a multidisciplinary peer review of design documents prepared by grant recipients. The review may consist of all or any part of the following discipline areas: Civil, Structural, Architectural, Mechanical, Plumbing, Electrical, Telecommunications, Fire protection, Health and Safety and Sustainability compliance.

The DTR team assists in resolution of construction related matters as necessary, performs site visits and on-site technical reviews as well as project close out.

To ensure safety of the NIH environment, all high containment facility (i.e. BSL-3) projects are required to conduct a Bio-safety Risk Assessment which describes the technologies, procedures and practices for preventing unintentional (i.e. accidental) exposure and/ or release of pathogens and toxins.

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.

According to Federal regulations and NIH policy, grant applications submitted to the NIH undergo a two level peer review process; these procedures are followed for all construction applications managed by ORIP. 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 NIH 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) for their architectural and engineering compliance with the NIH Design Requirement Manual. Design documents must be approved by the NIH before funds are released for the

construction activities. In addition, in accordance with Federal regulations, ORIP conducts site visits to check for agreement between the approved design documents and the final product. NIH monitors the long-term use of the facility for its intended functions under the Notice of Federal Interest.

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.

Finally, NIH leadership is reviewing recommendations made by the NIH Research Advisory Committee, Space Review Board, and the Facilities Working Group, to seek funds sufficient to underwrite the cost of construction and renovation of NIH intramural facilities that support clinical and disease research that will maintain the high standards for accreditation of such facilities.

Safe Prescribing

The Committee notes 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. The Committee encourages NIDA to continue its work with Federal partners to further engage the medical community, including physicians-in-training, medical students and resident physicians in primary care specialties (e.g. internal medicine, family practice, and pediatrics), to help provide the tools and skills needed to incorporate drug abuse screening and treatment into their clinical practices. The Committee also encourages NIDA and CDC to develop strategies for increasing participation in its online continuing medical education courses on safe prescribing for pain and managing patients who abuse prescription opioids.

Action taken or to be taken

Educating patients, families, and healthcare providers is a critical component in curbing substance use and associated health consequences, including addiction. The National Institute on Drug Abuse (NIDA) continues to support these efforts through the NIDAMED initiative by partnering with leaders in clinician education to provide training and other resources on substance use prevention, early intervention, and treatment tailored to the specific needs of primary care providers.

Since 2007, NIDA has engaged in three initiatives to create and disseminate educational information to practicing healthcare providers and clinicians in training. These efforts began with seven NIDA Centers of Excellence for Physician Information (2007-2014) at medical schools across the country. These Centers created twelve medical education resources including lectures, web modules, and workshops for medical students and resident physicians in primary care specialties. NIDA, with funding from the Office of National Drug Control Policy, broadened these educational efforts by partnering with Medscape Education (2012-2015) to create two continuing medical education (CME) modules to promote safe opioid prescribing practices and tools to help manage pain patients who misuse prescription opioids. These courses trained well over 100,000 clinicians.

Most recently, NIDA formed the NIDAMED Coalition of Healthcare Organizations (2014-current) consisting of leading experts and medical associations including the American Academy of Pediatrics, the California Academy of Family Physicians, the American Osteopathic Association, the American Academy of Physician Assistants, and the American Association of Nurse Practitioners. In 2016, the Coalition will launch a CME that provides evidence-based information and clinical strategies to help prevent and address substance use disorders and prescription medication misuse in adolescent patients. The CME includes information on screening adolescent patients prior to prescribing controlled substances, working with parents and caregivers to manage appropriate use of prescriptions, using Prescription Drug Monitoring Programs (PDMPs), and safe ways to dispose of medications with abuse potential. This web-based CME/CE is expected to launch prior to January, 2017.

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. Therefore, NIH is directed to continue funding the SEPA program at no less than \$17,100,000, the fiscal year 2016 level. Further, because of the central role NIGMS plays in managing programs that support the development of the biomedical research workforce, the Committee transfers the SEPA program from OD to NIGMS.

Action taken or to be taken

NIH continues to support the Science Education Partnership Award (SEPA) program located within the Office of Research Infrastructure Programs, Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI). NIH's SEPA program invests in educational activities for underserved and low socioeconomic status communities to enhance the training of a diverse workforce to meet the Nation's biomedical, behavioral, and clinical research needs. In FY 2016, SEPA made 22 new awards and funded two administrative supplements to current SEPA awards. In total, NIH funds approximately 70 SEPA projects to create partnerships among biomedical, behavioral, and clinical researchers and pre-K to grade 12 teachers and schools, museums, and other educational organizations.

In accordance with the Senate Appropriations Committee's recommendation, DPCPSI is working with the National Institute of General Medical Sciences (NIGMS) to ensure a smooth transition of the SEPA program in FY 2017.

Severe Acute Shock and Multi-Organ Failure

There are an estimated 1,300,000 cases in the United States each year of severe, acute shock, which can trigger multi-organ failure, often resulting in death. Despite the number of Americans affected by this condition and the lack of a proven treatment for shock, the Committee notes that there is no dedicated Federal research focused on addressing these challenges. The Committee encourages NIH to support research to develop treatments for severe, acute shock, including septic shock, cardiogenic shock, hypovolemic shock, and hemorrhagic shock.

Action taken or to be taken

NIH continues to support research to develop new treatments for severe, acute shock, including septic shock, cardiogenic shock, hypovolemic shock, and hemorrhagic shock through investments by the National Institute of General Medical Sciences (NIGMS) and National Heart, Lung, and Blood Institute (NHLBI). NIGMS supports research in certain clinical areas that affect multiple organ systems, and NHLBI supports research in areas that focus on cardiovascular and pulmonary organ systems.

In FY2014, NIGMS partnered with NHLBI to support several research projects focused on multi-disciplinary research approaches to the blood/vascular systems response to sepsis/septic shock through a funding initiative designed to support collaborations that pave the way for the identification of new treatment targets, pathways to target validation, and development of innovative anti-sepsis therapeutics. This funding initiative which will be active until FY2020 has already led to the identification of new molecular targets for the treatment of septic shock and new microfluidic assay devices that may be useful in the treatment of hemorrhagic and septic shock.

NIGMS supports several clinical trials that test treatments for septic shock. Results of a clinical trial of Protocolized Care for Early Septic Shock (ProCESS)¹⁸⁷, which demonstrated that aggressive resuscitation protocols that require invasive monitoring procedures to regulate fluid administration are not superior to other less invasive resuscitation protocols were published in the New England Journal of Medicine. A clinical trial of carnitine administration in septic shock¹⁸⁸ is actively enrolling patients.

¹⁸⁷ ClinicalTrials.gov Identifier: NCT00510835

¹⁸⁸ ClinicalTrials.gov Identifier: NCT01665092

Sickle Cell Disease (SCD)

The Committee encourages NHLBI to devote more research to the study of SCD. 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, which is currently the only therapy that can cure the disease. However, more focused research is needed to augment the limited treatment options available. The Committee notes recent advances in treatment of SCD and urges the Institute to support clinical trials for prenatal and postnatal treatment of SCD, which includes multiple promising approaches to eradicate the disease, save lives, and reduce dramatically the substantial health care costs associated with SCD for children and adults.

Action taken or to be taken

Sickle cell disease (SCD) is a genetic blood disorder that affects approximately 100,000 people in the United States, among them, one in 365 African Americans. Individuals living with SCD have red blood cells (RBCs) that contain abnormal hemoglobin that causes them to become rigid and crescent-shaped, blocking small blood vessels and causing inflammation, pain, and strokes. Research supported by the National Heart, Lung, and Blood Institute (NHLBI) has led to the use of penicillin to prevent fatal infections, chronic blood transfusions to reduce stroke risk, and hydroxyurea to reduce pain. In NHLBI-funded clinical trials, bone marrow transplantation has reversed SCD in children and has shown promise for adults. Because most patients lack an immunologically identical relative (e.g., a twin) who can serve as a bone marrow donor, NHLBI is funding trials to test the efficacy and safety of bone marrow transplants from partially matched donors.

The NHLBI is currently funding a major program to promote innovative basic and translational research in SCD and other hemoglobinopathies¹⁸⁹. The Excellence in Hemoglobinopathies Research Award (EHRA) program is supporting eight multidisciplinary research centers that are investigating new therapeutics to elevate the level of fetal hemoglobin (the most powerful known modifier of the severity of SCD); new therapeutics for sickle cell pain; novel modulators of inflammation; and treatments for SCD-associated kidney disease.

NHLBI is also supporting research into the use of gene-editing technologies to correct the sickle cell gene in patients with SCD. While still only in the proof-of-concept stages, this technology could ultimately lead to the ability to correct the SCD gene in a patient's own bone marrow, providing hope for a widely available cure for SCD in the future. However, these new treatments will only be useful if they reach those in need. Currently, many of the existing evidence-based treatments for SCD are underutilized. Therefore, NHLBI is now coordinating the Sickle Cell Disease Implementation Consortium to develop and test multi-modal, multi-sector interventions aimed at improving delivery of routine primary care to patients.¹⁹⁰ The consortium includes eight centers in seven geographic areas to conduct needs-based community assessment of the barriers to SCD treatment.

¹⁸⁹ <http://www.nhlbi.nih.gov/news/spotlight/fact-sheet/nhlbi-funded-research-centers-target-hemoglobinopathies>

¹⁹⁰ <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-16-010.html>

In addition, the NHLBI intramural program has hired world renowned researchers to lead a newly formed Sickle Cell Disease Branch where researchers study early SCD mortality prevention, bone marrow transplants, and gene therapy.

Most recently, NIH convened a workshop on March 10, 2017, entitled “Accelerating Cures for Hemoglobinopathies,” with the goal of leveraging advances in genetic therapies and gene editing to accelerate the development of potentially curative therapies for SCD. Individual investigators and commercial enterprises are working toward such therapies, and recent scientific advances support that the timing is ideal to enhance coordination toward a common goal. The NIH workshop brought together thought-leaders in genetic therapies and gene editing, including representatives from academia and the pharmaceutical industry, to explore current challenges and opportunities for curative therapies and further explore the state of the science and how NIH could be catalytic and facilitate a framework for scientific collaborations. 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 chances for a cure. Curing SCD has broad-reaching implications for other disorders similarly caused by a change in a single gene.

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 explore the role of sleep in cancer development and progression.

Action taken or to be taken

The National Cancer Institute (NCI) recognizes the vital role sleep plays in overall health and well-being in cancer patients and survivors. Recent studies have revealed that chronic lack of sleep may lead to higher risk of prostate,¹⁹¹ breast,¹⁹² and colorectal¹⁹³ cancer. In people living with cancer, physical illness, pain, hospitalization, and drugs and other treatments, as well as the psychological impact of malignant disease, may disrupt sleeping patterns.¹⁹⁴ Anxiety and depression – common psychological responses to the diagnosis of cancer, cancer treatment, and hospitalization – are highly correlated with insomnia.

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 a broad portfolio of cancer research and sleep health as noted in the observational and interventional study examples below:

- A prospective study of the impact of breast cancer on the relationships between inflammation and symptoms of fatigue, depression, sleep, and cognition that compares breast cancer survivors and age-matched controls.
- A study of breast cancer survivors that examines the relationships between sleep disturbances, cellular and genomic markers of inflammation, and depression occurrence.
- A proposed phase II trial that examines the impact of Brief Behavioral Therapy (BBT) on insomnia, mood, and quality of life, as well as circadian rhythm disruption, autonomic dysfunction, and sleep-wake cycles, in a clinical oncology community clinic.
- A phase III trial exploring the use of a BBT for patients with insomnia who are receiving chemotherapy for breast cancer.
- A phase I study that uses cognitive-behavioral treatment (CBT) to target the specific needs of cancer survivors with insomnia to significantly improve quality of life. Phase II and phase III of the study will include a randomized controlled trial of 50 cancer survivors to compare the efficacy of the CBT intervention.
- A phase III trial study on yoga or stretching and relaxation in improving physical function in patients with stage 0-III breast cancer undergoing radiation therapy.

¹⁹¹ <http://cebp.aacrjournals.org/content/22/5/872.full>

¹⁹² <http://link.springer.com/article/10.1007/s10549-012-2144-z/fulltext.html>

¹⁹³ <http://onlinelibrary.wiley.com/doi/10.1002/cncr.25507/full>

¹⁹⁴ Berger AM: Update on the state of the science: sleep-wake disturbances in adult patients with cancer. *Oncol Nurs Forum* 36 (4): E165-77, 2009.

- A phase III randomized controlled trial comparing yoga to cognitive behavioral therapy and a health education control on insomnia in cancer survivors 6-12 months following adjuvant treatment.

NCI will continue to support promising research opportunities that reveal the connection between sleep health and cancer development, progression, and remission in order to help cancer patients and survivors live healthier lives.

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 NHLBI's efforts to improve our understanding of sleep disorders and urges NHLBI 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), continues to support research on how differences in sleep health contribute to racial, ethnic, gender, and socioeconomic disparities in cardiovascular health. In 2016, NCSDR published the recommendations of an NHLBI workshop entitled [“Reducing health disparities: the role of sleep deficiency and sleep disorders.”](#) Ongoing NHLBI-supported studies are investigating the importance of sleep to disparities in cardiovascular disease risk in African Americans, Hispanics, and other diverse populations. A joint initiative between NHLBI and the *Eunice Kennedy Shriver* National Institute on Child Health and Human Development (NICHD) has identified sleep health risks that are specific to pregnant women. These studies indicate that untreated sleep apnea and sleep deficiency increase the risk of gestational hypertension and diabetes by three- to five-fold. A follow-up study is underway to determine whether sleep problems during pregnancy increase the future maternal risk of cardiovascular disease. A new NHLBI-NICHD partnership is planned for Fiscal Year 2017 to determine whether treating sleep apnea during pregnancy can reduce cardiometabolic risks to pregnant women (such as gestational diabetes and high blood pressure).

The NHLBI also leads efforts to stimulate the development of sleep biomarkers. A workshop funded by NHLBI and the National Institute on Aging, held in partnership with the Sleep Research Society, examined the need for biomarkers of chronic sleep loss, sleep apnea screening, and circadian phase. A resulting study was funded to identify specific changes in metabolism that consistently occur during insufficient sleep. Further, the NHLBI's Trans-Omics for Precision Medicine (TOPMed) program supports gene sequencing and state-of-the-art molecular analyses in cohorts where sleep health has been studied.

Recent advances suggest a need to identify biomarkers for sleep disturbances related to artificial light exposure. With NCSDR input, the National Toxicology Program of the National Institute of Environmental Health Sciences (NIEHS) has completed an evidence-based review of health risks associated with artificial light at night; a report summarizing the findings is in preparation. In August 2016, an NHLBI Workshop on Light and Circadian Health evaluated preliminary findings from the review, and concluded that light, circadian rhythm, and sleep are essential physiological requirements for optimal human development, health, and wellness across the lifespan. In 2017, NHLBI is sponsoring the first nationally representative survey of sleep schedules and health risks among U.S. adults, and will work with the Sleep Disorders Research Advisory Board and scientific program staff across NIH to update the NIH Sleep Disorders Research Plan.

Small Business Research Funding

The Committee supports the initiative to direct small business research funding to IDeA States to foster the development of products to advance public health. The Committee asks 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. NIH shall not use funding from its IDeA allocation for these grants.

Action taken or to be taken

The Committee supports the initiative to direct small business research funding to IDeA States to foster the development of products to advance public health. The Committee asks 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. NIH shall not use funding from its IDeA allocation for these grants.

Action taken or to be taken

NIH appreciates the Committee's support to develop an initiative to direct small business research funding to IDeA states to foster the development of products to advance public health. NIGMS is supportive of fostering small business research in the IDeA states, which historically have few funded Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) grants. We recognize the importance of using available resources efficiently to provide maximal benefit in IDeA states considering the vast geographical distances involved and the uneven entrepreneurial ecosystems present in the IDeA states. Many of the academic institutions in IDeA states are not aware of existing assistance programs for small businesses and the infrastructure needed to assist moving scientific and technological discoveries out of the laboratories towards the marketplace. The Small Business Administration supports Small Business Development Centers in every state with the purpose of aiding existing and prospective small business owners. NIGMS does not seek to replicate or compete with existing resources, although many of these may not have the expertise or knowledge specific for biomedical sciences.

Our goal is to set up one shared innovation incubator/accelerator in each of the four IDeA regions that would provide infrastructure and build an entrepreneurial culture. These regional accelerators would support entrepreneurial environments to facilitate networking and team formation, sharing and transfer of information, best practices and guidelines, and provide assistance, mentoring, and access to resources and services.

This initiative will leverage the funded IDeA programs with efforts that can identify and specifically assist academic investigators or groups by providing knowledge, development of business skills, information, networking, and business strategies that can result in more successful SBIR and STTR applications and new startups.

NIGMS is investigating any statutory, regulatory, or budgetary requirements that would need to be satisfied to support this initiative. NIGMS will actively seek partners from other Institutes and Centers of NIH.

To ensure the success of this initiative, we plan to continue our current outreach efforts to enhance the IDeA participation with the SBIR and STTR programs at IDeA regional meetings, National IDeA symposium and the Annual NIH SBIR STTR conference.

Spina Bifida - Update

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) continues its longstanding research commitment on spina bifida (SB), a serious congenital disorder that occurs when the spinal cord does not close properly before birth. Myelomeningocele (MM), the most frequent and severe form of spina bifida (one in 2,500 live births in the U.S.), causes lifelong disability with concomitant quality-of-life challenges. In addition to paralysis and problems with nerve function, many infants with MM experience hydrocephalus, an excess of cerebrospinal fluid placing pressure on the brain. The NICHD-funded Management of Myelomeningocele (MOMs) study demonstrated that children who had prenatal surgery for MM were much less likely to need either a shunt or assistive devices to walk. Although surgery in the womb was associated with its own risks the study showed a clear benefit from the prenatal repair; results were so clear that the study was stopped early. The MOMs 2 study, supported by both the NICHD and the [National Institute of Neurological Disorders and Stroke](#) (NINDS), is now examining the original MOMs children to determine whether school-age children who received prenatal surgery have better physical and mental health outcomes and can function more independently. In addition, the impact of prenatal surgery on the reproductive health of the mother is being assessed. If the benefits of prenatal surgery last into childhood (and potentially longer), the study will provide further scientific evidence for offering this intervention to pregnant women in the future. Conversely, if long-lasting benefits cannot be proven, women can be discouraged from undergoing an invasive and expensive procedure.

Genetic, environmental, and nutritional factors all are involved in the genesis of neural tube defects (NTD) including SB. NINDS-funded investigators are investigating the genetic and molecular mechanisms underlying neural tube closure and the processes that lead to disruption and subsequent neural tube defects such as spina bifida. In particular, a strong link between maternal folic acid status and NTD susceptibility has been shown. The NICHD's Epidemiology Branch is conducting birth defect studies in collaboration with the Health Research Board and Trinity College in Dublin to determine the relationship between folate and birth defects. Recent advances in genomics and computational genetics, together with the creation of genetic mouse models, offer unique opportunities to examine the genetic component of NTDs including SB. A NICHD-supported study is performing exome sequencing to identify unique variations in genes and pathways influencing MM susceptibility to facilitate improved diagnostics and treatment. Another study is using an animal model to determine how mutations in certain key genes affect the process of neural tube closure.

In the U.S., infants with "open" NTDs, where the spinal cord or brain is exposed at birth, are more likely to be delivered by caesarean section than infants with other types of birth defects. However, it is not known whether caesarean delivery actually reduces the high risk of early death infants by limiting trauma and the risk of infection. A NICHD-supported study is identifying obstetric procedures associated with improved survival for this group of infants.

NINDS-funded scientists also are exploring molecular and cellular mechanisms that lead to hydrocephalus, a common secondary condition with spina bifida. Shunts are the most common treatment for hydrocephalus; however failure is frequent, requiring surgical revision and leading to increased risk for infection. NINDS-supported researchers are exploring mechanisms of shunt failure and infection to enable better prevention, detection, and management strategies.

Spinal Muscular Atrophy

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Spinal muscular atrophy (SMA) is a rare inherited disease that varies widely in severity. SMA can cause severe muscle weakness, muscle atrophy, and death in infancy, or weakness that progresses slowly over many years in adults. Although there is still no cure, progress is encouraging. More than a dozen drug, cell, and gene therapies are at various stages of the development pipeline in the public and private sector. In December 2016, the FDA approved the first drug to treat SMA in children and adults, a landmark for this disease. The discovery of the underlying gene defect led to improved diagnosis, animal and cell models to study the disease, and rational strategies to develop therapies, including the newly approved private sector drug. NIH is continuing to support research to better understand what goes wrong in SMA and to develop treatments. Laboratory researchers are investigating the normal functions of SMN (the protein that is deficient in SMA), why nerve cells that control muscles are specifically affected by loss of SMN, what other genes modify the severity of SMA, how the disease affects early development of the nervous system, when and where normal SMN protein is needed, and many other questions about how the gene defect leads to the disease. NIH is also supporting laboratory studies of several promising therapeutic strategies, including small molecules, biologics, and gene therapy. Clinical research is laying the groundwork for rehabilitation interventions for people with milder SMA, and an NINDS NeuroNEXT clinical network study, which focused on biomarkers to expedite testing of therapies for SMA, published its first results this year. NIH, together with private groups, sponsored a June 2016 meeting that brought together public and private sector researchers to discuss the newest findings and how best to move forward toward therapies that can treat all people with SMA. As part of its activities to encourage talented young investigators to tackle the challenges of SMA, this year NINDS made three diversity supplements to grants in this disease, an unusual number for a rare disease research community.

Stroke

The Committee recognizes the immense burden stroke places on our Nation's population and economy, and strongly support NINDS increase its stroke research efforts. NINDS is also encouraged to 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.

Action taken or to be taken

Stroke research continues to be a high priority at the National Institute of Neurological Disorders and Stroke (NINDS). In addition to the large investments in investigator-initiated research covering the spectrum of basic, translational, and clinical research, the NINDS has also made concerted efforts to stimulate research based on the priorities identified in the 2012 stroke research planning effort.

The NIH StrokeNet is currently enrolling patients in six stroke clinical trials that are testing new prevention, treatment, and rehabilitation interventions. The network infrastructure has been instrumental in the ability of the trials to meet or exceed enrollment targets. NINDS expects to fund additional trials to begin in the network in order to maximize use of the infrastructure and expedite stroke clinical research.

StrokeNet has developed international partnerships to strengthen the capacity for international stroke clinical research studies. The Global Alliance of Interdependent Networks focused on Stroke Trials (GAINS) workshop, scheduled for December, 2016, is being hosted by two Canadian stroke research organizations in close collaboration with NINDS and the NIH StrokeNet to identify strategies to coordinate stroke research efforts. NINDS also provided funds for the US-Japan Brain Research Cooperative Program workshop that was held in Tokyo in June, 2016, to identify collaborative projects of mutual interest that could be developed between Japan's stroke trials network and the NIH StrokeNet. Connecting StrokeNet with other national and international networks will help synergize and accelerate stroke clinical research worldwide.

Activities within StrokeNet to strengthen the network have also been robust. The training core within StrokeNet has been actively developing junior investigators through educational and professional development webinars and mentorship activities. The StrokeNet team has also recently signed a Memorandum of Understanding with the Department of Veterans Affairs (VA) to establish a central Institutional Review Board model for the VA sites within the network.

Stroke recovery and rehabilitation research is another priority that was identified in the stroke research planning effort. The NIH StrokeNet provides a centralized resource for stroke rehabilitation trials, and NINDS program staff members have participated in an international effort to identify priority research topics and foster a global community of researchers committed to advancing stroke recovery and rehabilitation research. NINDS and the National Center for Medical Rehabilitation Research (NCMRR) are also planning a 2017 workshop to identify stroke recovery and rehabilitation research priorities.

NINDS has also been focused on identifying how best to stimulate progress in stroke translational research, another important area that emerged in the stroke planning effort. For the past two years, NINDS has been involved in a European activity to consider the design and

feasibility of a multi-site preclinical research network that would enable standardized approaches and identification of high priority therapeutic candidates. NINDS is leveraging the findings from that pilot planning initiative to stimulate discussions about improved coordination of preclinical stroke research within the U.S. NINDS hosted a workshop on November 1-2, 2016 to identify an overall vision for stroke translational research best practices and to promote enhanced collaboration with the clinical research community.

Temporomandibular Disorders (TMD)

The Committee understands that NIH- funded research has demonstrated that TMD is primarily a multisystem disorder with overlapping co-morbid 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. Therefore, the Committee strongly supports research to examine the safety and efficacy of current clinical treatments of TMD, the burden and costs associated with TMD, and the development of future scientific and clinical, professional and policy directions for TMD. Further, the Committee encourages NIH ICs with pertinent expertise on the temporomandibular joint to collaborate and implement the recommendations from the Temporomandibular Joint in Health and Disease Round Table held in 2013. Research to develop safe and effective techniques for joint repair and regeneration is essential. An analysis of problems associated with current joint replacements should provide guidance in these efforts.

Action taken or to be taken

To provide the evidence base needed to improve temporomandibular joint disorder (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, which is associated with TMDs. NIDCR-supported scientists have discovered a type of stem cell in the TMJ bone that can be used to regenerate and repair cartilage, a promising discovery that could lead to new approaches to regenerate the TMJ. The Institute also supports research that brings together clinicians, computer scientists, and engineers to develop more precise bone imaging techniques to measure TMJ disease progression and ultimately improve diagnosis and treatment. In addition, promising new coating materials for implant devices are being created to improve joint repair strategies by combatting bacterial infections, enhancing implant biocompatibility with surrounding tissues, and increasing implant performance and wear-resistance.

In collaboration with other NIH Institutes, Centers and Offices (ICO)s, NIDCR is implementing the research recommendations from the 2013 Temporomandibular Joint in Health and Disease Roundtable, including funding studies on the biology of the TMJ in health and disease. NIDCR and NIBIB participate in funding announcements to encourage research grant applications on the “Biology of the Temporomandibular Joint in Health and Disease.” Research on the biology of joint function and the tissues that make up the TMJ will provide the basis for developing safe and effective techniques for joint repair and regeneration. NIDCR-supported scientists are building a model to help identify healthy individuals at risk for developing TMDs by examining whether mechanics, behavior, and genes can be used to predict differences in TMJ disc position and orofacial pain in men and women. And to understand why women are much more likely to have chronic orofacial pain, NIDCR has launched an initiative to encourage studies on the underlying biological factors that lead to differences in the presentation of dental, oral, and craniofacial diseases between men and women. Moving forward, the Institute will encourage investigations on how the nervous system influences the dental and craniofacial skeletal system, including the TMJ, a key research area identified in the Roundtable.

NIDCR recognizes the need to engage with key stakeholders to evaluate the state of TMJ science and identify gaps and opportunities for future investigation and collaboration. To this end, NIDCR senior leadership participated in a first-of-its-kind TMJ Patient Roundtable in 2016.

Participants included patients, patient advocates, industry, clinicians, and representatives from the NIH, the U.S. Food and Drug Administration (FDA), and the Agency for Healthcare Research and Quality (AHRQ). The Roundtable brought these stakeholders together to discuss a number of topics, including advancements in TMJ implants and medical devices, and the development of patient-centered outcomes to improve therapies and clinical care. These types of inclusive discussions are essential to develop future scientific and clinical, professional, and policy directions for TMD. In addition, NIDCR, along with a number of other NIH ICOs, provided funding for a recent meeting of the TMJ Association, bringing together scientists, clinicians, and patients to explore how precision medicine strategies can inform the treatment of TMD and co-occurring pain conditions. As we continue to gain new insights into the biological, environmental, and behavioral influences on an individual's health, precision medicine approaches can be leveraged to treat and prevent TMDs more effectively.

Thoracic Aortic Disease

The Committee is concerned by 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) has funded the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) since 2006 to enable research on genetically triggered thoracic aortic aneurysms and to improve the management of individuals with these conditions. GenTAC has created a data and biospecimen repository from over 3,700 individuals with one of the 13 eligible conditions, including Marfan syndrome, Loeys-Dietz syndrome, Turner syndrome, and Ehlers-Danlos syndrome. Data and biospecimens collected from these individuals are available to eligible investigators through the NHLBI-funded Biologic Specimen and Data Repository Information and Coordinating Center (BioLINCC).

The GenTAC repository has enabled more than 90 research projects that have resulted in a number of advances, including the discovery of new gene mutations that predispose individuals to thoracic aortic aneurysms and the identification of potential biomarkers to aid clinical decision making for treatment of these syndromes. In addition, one project is evaluating factors contributing to quality of life for individuals with Marfan Syndrome, and another is evaluating cardiovascular and surgical outcomes in the entire cohort. Discoveries made through GenTAC also have contributed to our understanding of the pathology of non-genetic thoracic aortic disease.

In addition, GenTAC has built a lasting infrastructure and patient cohort, enabling several foundations and universities to establish new registries for thoracic aortic disease. These registries will extend the longitudinal data collection initiated by GenTAC and expand the original GenTAC cohort by enrolling new participants. These new registries include the Marfan and Related Disorders Registry, funded by the Marfan Foundation; the Knight Cardiovascular Institute Aortic Disease Registry and International Bicuspid Aortic Valve Consortium, both funded by the Knight Cardiovascular Institute at the Oregon Health & Science University; the Vascular Ehlers–Danlos Syndrome Registry, funded by the Ehlers-Danlos Syndrome Network C.A.R.E.S., Inc.; and the Familial Thoracic Aortic Aneurysm Disease and Sporadic Aortic Dissection Cohorts at the University of Texas at Houston, funded by the John Ritter Foundation.

The NHLBI is exploring additional opportunities to leverage the activities of these new registries. In addition to the new registries, future efforts could include other stakeholders, such as patients and the representatives of scientific societies and companies whose mission includes treatment of thoracic aortic disease, to define a research agenda that aligns with patient needs and improves patient health.

Moving forward, the NHLBI will also continue to fund investigator-initiated basic and translational research on thoracic aortic disease.

Tick-Borne Diseases - NIH

The Committee encourages NIH, in coordination with CDC, to intensify research on 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 and to intensify basic research that can be used to focus on the development of more sensitive and accurate diagnostic tests for Lyme and tick-borne diseases.

Action taken or to be taken

Lyme disease, caused by the bacterium *Borrelia burgdorferi*, is the most prevalent tick-borne disease in the United States. The National Institute of Allergy and Infectious Diseases (NIAID) has a longstanding commitment to basic and clinical research to expand our knowledge of Lyme and other tick-borne diseases to inform the development of vaccines, therapeutics, and diagnostics.

NIAID supports and conducts basic and translational research to understand the biology of the tick, the pathogens it transmits, and the diseases that result from these infections. For example, NIAID researchers studying Lyme disease have discovered that the bacterial enzyme FtsH is an essential factor in *B. burgdorferi* infection in both mice and ticks. This finding reveals key aspects of the Lyme disease process and suggests that FtsH could be a novel target for the development of therapeutics. NIAID also solicits fundamental research on tick-borne pathogens including *B. burgdorferi* and other *Borrelia* species, such as *B. mayonii*, through the Novel Approaches to Understanding, Preventing, and Treating Lyme Disease and Tick-borne Coinfections initiative. Key areas of focus include disease transmission and pathogenesis; host and bacterial factors that contribute to post-treatment symptoms; and the development of vaccines, therapeutics, and diagnostics.

In addition, NIAID is conducting clinical trials to identify biomarkers of *B. burgdorferi* infection and to explore whether bacterial replication persists after treatment. An ongoing NIAID natural history study of patients with Lyme disease is assessing biological markers of disease, patient outcomes, and the immunological response to *B. burgdorferi* infection. Evaluation, treatment, and follow-up of study participants will help scientists learn more about the range of Lyme disease processes. NIAID researchers also are conducting a clinical study to determine whether patients who continue to experience Lyme disease symptoms following treatment still harbor live *B. burgdorferi* bacteria. The information from this study could inform diagnostic criteria for Lyme disease and future therapeutic trials.

The development of more sensitive and accurate diagnostic tests for Lyme and other tick-borne diseases continues to be a priority for NIAID. NIAID is partnering with the Centers for Disease Control and Prevention (CDC) to coordinate efforts to improve the diagnosis of Lyme disease, including a standardized serum repository, which is a valuable tool for the evaluation of new and improved diagnostic tests. Additionally, in collaboration with CDC, NIAID is working to engage patients and researchers to foster the development of rapid and easy-to-use diagnostic tests. Furthermore, NIAID is supporting targeted research initiatives and Small Business Innovation Research (SBIR) awards to develop improved Lyme disease diagnostics, including a point-of-care test. Ongoing research focuses on identifying Lyme disease biomarkers to enable rapid diagnosis early in the course of infection as well as detect signals of disease progression and successful treatment. Of particular interest is xenodiagnosis, a strategy that uses the tick

vector to detect disease. NIAID scientists are using xenodiagnosis to investigate whether *B. burgdorferi* is more likely to be detected post-treatment in people with ongoing symptoms, such as fatigue and joint pain.

NIAID will continue to support basic and clinical research on Lyme and other tick-borne diseases to provide insight into better means of diagnosing, treating, and preventing these diseases. NIAID will foster ongoing collaborations with CDC and other partners to identify opportunities to advance research to combat tick-borne diseases.

Tick-borne Diseases AHRQ

The Committee encourages AHRQ to determine when the last time a bibliography of peer-reviewed tick-borne diseases literature was last completed and to work with CDC and NIH to determine how best to develop a tool for use by the scientific community, treating physicians, and the public. The review should also evaluate the science related to persistent infection with *borrelia burgdorferi* or other types of *borrelia*.

Action Taken or to be Taken

In 2012, AHRQ received a nomination to review information on chronic Lyme disease, and at that time, AHRQ conducted a review of existing guidelines and determined that there was consistency across in their recommendation and concluded that a complete systematic evidence review would not change practice.

AHRQ does not currently have funding to conduct a systematic evidence review on tick-borne diseases. However, AHRQ staff will reach out to CDC and NIH/NIAID to determine their interest in supporting a systematic evidence review which AHRQ could conduct through its Evidence-based Practice Center program, and in developing tools based on this review.

Traumatic Brain Injury (TBI)

The Committee encourages research related to technologies using biomarkers to distinguish trauma to the brain. The Committee requests an update in the fiscal year 2018 budget request on TBI research.

Action taken or to be taken

Extensive research to develop biomarkers for traumatic brain injury (TBI) is an integral part of NIH research on TBI, which spans basic, translational, and clinical research. Development of biomarkers is also a major theme and among the successes of the National Research Action Plan for PTSD and TBI, which coordinates research across Federal Agencies. A significant challenge for NIH research is to address the full range of TBI, from mild to severe, consider special populations, including children and the elderly, and attend to consequences that may be immediate or delayed for decades. The importance of multiple dimensions of TBI (e.g., severity, age, and injury type) suggests that multiple types of biomarkers (e.g., fluids, brain imaging, behavioral) will be essential. One of the most important issues is that conventional brain imaging does not detect most mild TBI (concussions). This hampers physicians and athletic trainers who need markers to diagnose concussions, for assessment of readiness to return to sports and other activities, and to predict who is likely to suffer persistent symptoms. Markers are likewise key to developing prevention and early intervention for persons with persistent post-concussion symptoms. For more severe TBI, biomarkers will help physicians to predict outcomes, assess risk for post-traumatic epilepsy, guide treatment decisions, and monitor whether new candidate treatments are engaging their intended targets and improving outcomes. Biomarkers will also significantly improve clinical trials by selecting patients who are likely to benefit from a given intervention. Similarly, biomarkers are essential for chronic traumatic encephalopathy (CTE), a degenerative brain disease that can result from repetitive trauma. CTE can now only be diagnosed at autopsy, so better CTE diagnostics are essential to develop prevention and treatment for CTE, as well as to determine who is most at risk.

NIH research is underway for all of these biomarker needs using a wide array of technologies. Researchers are, for example, testing an extraordinary array of advanced brain imaging methods, innovative technologies to measure biochemical markers in the blood circulation, brain electrical activity monitoring, artificial intelligence analysis of clinical features, and increasingly sensitive behavioral measures, including virtual reality testing. Major multicenter studies are investigating better diagnostic markers for CTE. NINDS is funding the “Biomarkers of Injury and outcome in PROTECT III” to validate markers of brain tissue breakdown. PROTECT III is a large completed multicenter randomized clinical trial in TBI. The Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK TBI) project, which coordinates clinical research across multiple centers, is providing a wealth of high quality clinical, imaging, genomic, proteomic, and outcome biomarkers data. Data from TRACK TBI is now being used, for example, to validate both neuroimaging and blood based markers for excluding the need for CT scanning, with its inherent costs and radiation exposure. In March 2016, NIH and NIH-supported investigators contributed to an FDA workshop on biomarkers for TBI that examined potential biomarkers, discussed challenges and solutions, and considered strategies for standardization, which include the NINDS Common Data Elements for TBI and the NIH and DOD led Federal Interagency Traumatic Brain Injury Research (FITBIR) database. The NINDS Biomarkers Repository and NeuroBioBank are also key resources for research on TBI

biomarkers. Together these programs have yielded encouraging progress, but the heterogeneity of TBI and the necessity for several types of biomarkers will require NIH to continue intensive investment in this area in the coming years.

Translational Science and Clinical Trials

The Committee commends NIH's continued focus on clinical and translational science, but is concerned with the need to expand this work to geographic regions with the highest burdens of chronic disease, limited access to health care providers, and minority populations. By providing support for the necessary infrastructure for translational science across the spectrum from drug and natural product discovery to clinical trial implementation to community and population health, citizens with significant needs in these underserved regions will benefit. Therefore, NIH is directed to support efforts to build and sustain integrated clinical and translational science infrastructure to optimize the movement of drug and natural product discoveries across the translational spectrum in States where funding has not previously been provided, but where there is significant disease burden.

Action taken or to be taken

NIH is committed to building and sustaining integrated clinical and translational science infrastructure across the nation, including in states that historically have received limited NIH funding, so that all communities and patients may be part of and benefit from biomedical research discoveries. Two major NIH programs, the Clinical and Translational Science Awards Program (CTSA Program, supported by the National Center for Advancing Translational Sciences, NCATS) and the Research Centers in Minority Institutions Infrastructure for Clinical and Translational Research (RCTR, supported by the National Institute on Minority and Health Disparities, NIMHD), are working towards this common goal in a complementary fashion. The NCATS CTSA Program addresses roadblocks common to all clinical and translational research, while the NIMHD RCTR program looks to broaden opportunities for clinical and translational research specific to areas of minority health and health disparities.

The CTSA Program is comprised of more than 50 distinct academic medical centers (hubs) across the country, which work to improve clinical and translational research to get more treatments to more people more quickly. CTSA Program hubs collaborate locally, regionally and nationally, to foster innovation in training, patient involvement and new methodologies. NCATS relies on the individual strengths of the CTSA Program hubs, partnering with them to develop and implement innovative, collaborative solutions intended to transform clinical and translation research.

Through collaborative innovation efforts, the CTSA Program supports a national network to address the common scientific and operational bottlenecks that affect all clinical research. In doing so, the program facilitates clinical research needs for all clinical research populations. The program also supports clinical and translational research for underserved populations and health disparities when developing translational innovations. The CTSA Program supports biomedical research institutions from states that have historically received less NIH funding, such as New Hampshire, South Carolina, Kentucky, Arkansas, Kansas, and New Mexico. For example, the University of New Mexico Clinical and Translational Science Center is a founding partner in the CTSA Program Mountain West Research Consortium (MWRC). The MWRC is a network of 11 universities spanning seven states and has a goal of building and enhancing this region's clinical and translational research capacity.

NIMHD recognizes the need to promote a transdisciplinary, culturally appropriate, community driven research framework to address health disparities. The RCTR was established to develop

capacity, foster training, and support basic, clinical, and translational research addressing minority health and health disparities. A number of minority serving institutions support research across the clinical and translational research continuum, focusing on health conditions that significantly impact racial/ethnic minorities, rural populations, and other medically underserved populations. Select examples of health conditions being addressed by this program include: HIV/AIDS, cancer, cardiovascular disease, diabetes, mental health/psychiatric disorders, neurological diseases, and cancer. In addition to the RCTR program, NIMHD also supports investigator-initiated research in clinical and translational research. Select examples of currently supported research initiatives include: a translational research project aimed at reducing the risk for a recurrent stroke in Hispanics; and a multi-pronged approach in translating evidence-based strategies to eliminate health disparities in diabetes prevention and control.

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

One of DPCPSI's central functions is to facilitate planning and strategic coordination of a wide range of trans-NIH programs and activities. DPCPSI tailors the approaches used to coordinate and facilitate different areas of trans-NIH research.

Under the leadership of the DPCPSI Director, the Office of Portfolio Analysis (OPA) undertakes efforts that promote and facilitate the development of trans-NIH portfolio analysis activities. For example, OPA hosted a Grand Challenges Workshop at which outside experts in scientific portfolio analysis identified approaches to improve coordination and facilitation of trans-NIH research. Key topics included automated categorization of research topics, identification of overlap, scientific gaps, and emerging areas, and evaluation of research productivity and cost-effectiveness. To facilitate trans-NIH research assessment, OPA published a standardized metric of scientific influence, the Relative Citation Ratio,¹⁹⁵ and a website, *iCite*,¹⁹⁶ which provides open access to this metric. OPA offers training for NIH staff, and has user manuals, FAQs, and instructional videos available on the OPA website. The tools and approaches taught by OPA contribute to strategic planning activities across NIH.

OPA also develops new computational tools that can retrieve and clean data used to analyze information about NIH investments, funded collaborations, publication records, and bench-to-bedside translation; leverage advanced data mining and knowledge discovery techniques to link people, funding, and research outputs across data sets; and analyze the content of grant applications, awards, publications, and patents to help ensure that the NIH research portfolio is balanced, free of unnecessary duplication, and takes advantage of collaborative, cross-cutting research. Since the peer-reviewed publication of the development and validation of the RCR metric in *PLoS Biology*¹⁹⁷ on September 6, 2016, it has seen widespread adoption in measuring the scientific influence of research publications, both domestically and internationally¹⁹⁸. At the NIH, Mike Lauer^{199,200} (Deputy Director for Extramural Research) and Jon Lorsch²⁰¹ (Director, NIGMS) have used the RCR method as a measure of grant productivity in strategic planning. Newer OPA analytics designed to identify duplication and improve strategic planning, including

¹⁹⁵ <http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002541>

¹⁹⁶ <https://icite.od.nih.gov/>

¹⁹⁷ 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.

¹⁹⁸ Naik, G. (2016). The quiet rise of the NIH's hot new metric. *Nature* 539, 150.

¹⁹⁹ Lauer, M. (2016a). Measuring Impact of NIH-supported Publications with a New Metric: the Relative Citation Ratio. In: Open Mike. <https://nexus.od.nih.gov/all/2016/09/08/nih-rcr/>

²⁰⁰ Lauer, M. (2016b). Applying the Relative Citation Ratio as a Measure of Grant Productivity. In: Open Mike. <https://nexus.od.nih.gov/all/2016/10/21/applying-the-relative-citation-ratio-as-a-measure-of-grant-productivity/>

²⁰¹ Basson, J., Lorsch, J., and Dorsey, T. (2016). Revisiting the Dependence of Scientific Productivity and Impact on Funding Level. NIGMS Feedback Loop Blog. <https://loop.nigms.nih.gov/2016/07/revisiting-the-dependence-of-scientific-productivity-and-impact-on-funding-level/#more-9927>

iSearch, the OPA NextGen portfolio analysis platform, are likewise being received enthusiastically, as evidenced by overflow attendance at ongoing demos, training sessions, and workshops.

In the area of prevention research, new tools have been developed for systematically monitoring NIH investments and assessing the progress and results of that research. To that end, the Office of Disease Prevention (ODP) created a prevention research taxonomy and accompanying protocol to enable accurate and standardized classification of funded prevention research grants. ODP has used the Taxonomy and Protocol to analyze type 1 R01s funded in fiscal years 2010-15 and has presented the results of that analysis to the NIH leadership. At their request, ODP is now analyzing other research project grant mechanisms using the same methods to provide a more complete picture of the NIH prevention research portfolio in humans. ODP is also extending that work to include grants funded in FY2016. At the end of this process, ODP will have the most complete picture of the NIH prevention research portfolio ever developed. ODP will use it to identify levels and trends in awards and dollars as a function of the grant's rationale, exposures, outcomes, population focus, study design, and type of human prevention research. ODP will share the results with colleagues at NIH, with the extramural research community, and with the general public.

DPCPSI program offices have made effective use of trans-NIH and cross-government coordinating committees. For example, input from formal research coordinating committees—composed of IC and OD Office representatives and, as appropriate, external representatives—are being used for multiple purposes, including:

- To identify the need for and develop new collaborative prevention research through creation of new NIH Special Interest Groups via the Prevention Research Coordinating Committee. Anticipated outputs include Funding Opportunity Announcements (FOAs), workshops, and identification of relevant research resources—these new processes will help ensure that efforts are not being duplicated and resources are being used most effectively. Measurable objectives include the number of new FOAs and workshops.
- To ensure continuing communication about Sexual and Gender Minority (SGM) research and systematically track implementation of the SGM Research Strategic Plan across the ICs. This is being accomplished via the SGM Research Coordinating Committee and its four subcommittees. Outputs and outcomes of strategic plan implementation will be tracked through an annual portfolio analysis and a companion SGM Research Office annual update.
- To coordinate and facilitate collaboration among the ICs in programmatic and scientific activities in NIH behavioral and social sciences research. The Behavioral and Social Sciences Research Coordinating Committee serves as the central coordination point among the ICs, OD Offices, NIH OBSSR, and the external scientific community. This includes facilitating and promoting exchange of information and planning for and implementation of collaborative programmatic and scientific activities and initiatives.
- To enhance the trans-NIH planning, portfolio analysis, and research budget processes for AIDS research. The Office of AIDS Research has streamlined and clarified its analytical, planning, and budget allocation processes and strengthened the NIH AIDS Executive Committee in these deliberations. These steps are facilitating the ICs planning efforts related to support of AIDS research.

- To strengthen collaborative efforts among federal government agencies by sharing information and discussing issues related to dietary supplement research and education. The Federal Working Group on Dietary Supplements meets with the goals of stimulating co-funding; expanding opportunities for research training; and strengthening collaborative federal-wide efforts involving dietary supplement research, education, and communication.
- To facilitate implementation of the NIH Strategic Plan for Women’s Health Research by improving its interactions with the ICs. This was done through the Office of Research on Women’s Health (ORWH) Scientific Research Planning Committee which designed a new streamlined approach for submission and review of co-funding requests which allows the ICs to more efficiently and effectively prioritize their requests and plan their research agendas. ICs will identify and ORWH will track how the co-fund and/or scientific partnership meets specific goals/objectives of the Plan.

In the past year, several DPCPSI program offices either developed new or updated existing Strategic Plans. Development of these plans involves extensive public input and internal coordination, facilitated by the offices within DPCPSI, which helps to avoid duplication and promote collaboration.

- The Office of Research Infrastructure Programs released its first Strategic Plan (2016-2020).²⁰² ORIP’s research infrastructure support includes the physical, intellectual, and human resources that advance biomedical research funded by the NIH ICs. ORIP partners with the ICs to create and support a variety of research resources and to explore creative ways to partner with other Federal agencies and nongovernmental organizations.
- The Office of Dietary Supplements (ODS) will be releasing its fourth strategic plan in 2016. ODS uses its strategic planning cycles to communicate and evaluate the outcomes of its investments, consider research priorities, and offer an opportunity for the public input. Covering 2017-2021, the plan capitalizes on ODS’s progress in advancing tools for successful research, builds on collaborations with ICs and Offices and other federal agencies, and encourages public-private partnerships.
- The Office of Behavioral and Social Sciences Research (OBSSR) initiated a strategic planning process, and the FY 2017-2021 strategic plan will focus 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.

Within DPCPSI, the Office of Strategic Coordination (OSC) manages the Common Fund (CF), which supports research in areas of emerging scientific opportunities, rising public health challenges, and knowledge gaps that deserve special emphasis; that would benefit from strategic coordination and planning across the NIH ICs; and are designed to address specific, high-impact goals and milestones within a 5 to 10 year timeframe. OSC orchestrates an NIH-wide process to establish priorities for the CF that engages IC Directors and their staff. CF programs are designed and implemented by trans-NIH Working Groups (WG), ensuring that broad expertise is brought to bear on program management and that the resources developed by these programs advance the missions of multiple ICs. During the planning for new CF programs, NIH and external research portfolios are analyzed to avoid duplication of efforts and identify synergistic

²⁰² <https://dpcpsi.nih.gov/sites/default/files/ORIP%20Strategic%20Plan%20Final-%20April%202016.pdf>

partnerships or opportunities that could enhance the program. Ongoing discussions with IC leadership and members of the trans-NIH WGs help prevent duplication and facilitate collaborations. All CF programs have specific goals and milestones, and progress towards these goals and milestones is assessed on a regular basis. The 2015 Common Fund Strategic Planning Report is available on the OSC website.²⁰³

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https://commonfund.nih.gov/sites/default/files/2015%20Common%20Fund%20Strategic%20Planning%20Report_fi%20-%2008.pdf

Trisomy

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Trisomy is an abnormal number of chromosomes (aneuploidy) marked by three copies of a particular chromosome (or parts of a chromosome), instead of the normal two. Trisomies can occur with any chromosome; however, such a condition often results in miscarriage of a pregnancy. Trisomy 21 or Down Syndrome (DS) is one of the most common chromosome abnormalities in humans; other trisomies include Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13). Both of these syndromes are rarer than DS and are characterized by intellectual disability, and heart and kidney defects. Klinefelter syndrome is a sex chromosomal abnormality in which males have two or more X chromosomes (XXY) instead of one X chromosome.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports a broad range of research studies to understand better both DS and non-DS trisomies. For example, a study funded by the NICHD study is using next-generation sequencing of maternal plasma DNA for the detection of aneuploidy in a non-invasive manner. Another NICHD-supported study is modeling Klinefelter Syndrome in XXY mice to identify genes on the X chromosome that cause features related to the syndrome.

The NICHD, along with other NIH Institutes and Centers that comprise the NIH Down Syndrome Working Group, support a myriad of research efforts on aspects of health associated with DS, including the development and evaluation of animal models to help study the syndrome, examination of specific genes and groups of genes that may be factors in developing features of DS, understanding the role of maternal age, biomarker, neuroimaging, and neuropsychological studies of aging in adults with DS, and the causes and treatments of DS-related conditions. The NIH also works with national and international stakeholders that are members of the NICHD-led Down Syndrome Consortium. The Consortium is discussing implementation of the revised NIH Research Plan on Down Syndrome, published in 2014, which identifies short- and long-term research objectives in five main categories: Pathophysiology of Down Syndrome and Disease Progression, Down Syndrome-Related Conditions, Treatment and Management, Down Syndrome and Aging (a new section), and Research Infrastructure.

The National Institute of Neurological Disorders and Stroke (NINDS) supports two of the leading research labs using mouse models to determine which of the genes triplicated in DS are responsible for cognitive deficits. A study is examining the role of microRNAs, which are small pieces of RNA that can silence other RNA, in gene regulation in a DS mouse model. NINDS recently supported a study to develop a small molecule as a potential therapeutic to alleviate memory deficits and neurodegeneration in DS. Through the NINDS Cooperative Program in Translational Research, NINDS supported a milestone-driven preclinical project on a potential drug therapy (PTZ) for DS that targets inhibitory brain circuitry and improves learning and memory in a mouse model. Investigators are completing preclinical toxicology studies and plan for an IND meeting with the FDA later this year. Recent publications supported by NINDS funding link expression of triplicated genes with neurodevelopmental deficits in the peripheral

nervous system and white matter development, as well as an increased presence in DS brains of an enzyme that facilitates amyloid production, which advances our understanding of the increased risk for Alzheimer's disease in individuals with DS.

Tuberculosis (TB)

The Committee encourages NIAID to continue prioritizing and implementing the National Action Plan for Combating Multi-drug Resistant Tuberculosis, including addressing the Plan's objectives, and coordinating with other TB research agency partners including USAID and CDC.

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) plays a key role in the Administration's National Action Plan for Combatting Multidrug-Resistant Tuberculosis. In collaboration with USAID and CDC, NIAID is participating in comprehensive Federal efforts to address the domestic and global challenges posed by multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB). NIAID is leveraging its strengths in TB research to address Goal 3 of the National Action Plan, "Accelerate Basic and Applied Research and Development to Combat MDR-TB," in order to stimulate innovation in the diagnosis, treatment, and prevention of drug-resistant TB.

NIAID supports fundamental research on *Mycobacterium tuberculosis*, the bacterium that causes TB, to understand how it causes disease and how it develops resistance to the drugs used to treat it. NIAID also provides preclinical services to mycobacterial researchers around the world to uncover biological mechanisms of TB and to advance countermeasure development. These services include testing of drug candidates, animal model studies for vaccine development, and provision of adjuvants, immune modulators, and other reagents. In addition, NIAID offers access to bioinformatics tools and bacterial genome sequence data, including the genomes of more than 3,800 drug-resistant and drug-sensitive TB strains.

NIAID also is working to identify new classes of TB drugs and improve the use of existing treatments to help prevent the development of resistance. As part of the TB Drug Accelerator, a public-private partnership led by the Bill & Melinda Gates Foundation, NIAID is evaluating small molecule candidates provided by drug companies to identify new TB treatments. In collaboration with CDC, NIAID is supporting a clinical trial in Peru and South Africa to determine the appropriate dosage of the antibiotic levofloxacin, in combination with a standardized antibiotic regime, to more effectively treat MDR TB. NIAID also is supporting studies of host-directed TB therapies designed to enhance the ability of the immune system to kill the bacteria and decrease tissue damage caused by inflammation.

In addition, NIAID is pursuing the development of TB vaccines that protect against both, drug-susceptible and drug-resistant infections. NIAID has released four ongoing funding announcements soliciting research to advance the science of TB vaccines, including studies of vaccines for patients co-infected with TB and HIV who are at high risk for morbidity and mortality. NIAID also supports research to develop and evaluate a broad array of TB diagnostic tests, including those capable of detecting drug resistance and characterizing the genetic diversity, evolution, and underlying patterns of TB drug resistance. NIAID scientists recently demonstrated that positron emission tomography/computed tomography (PET/CT) scans have the potential to be used early in the course of treatment of patients with pulmonary MDR TB to determine whether treatment will be successful. This technology represents a novel approach to predict MDR TB treatment outcomes that will be explored for potential use in future clinical trials. Additional NIAID-supported clinical trials include a TB household contact study

investigating the immune system response to TB in collaboration with a CDC-supported clinical research site in Kenya.

NIAID remains committed to supporting basic, translational, and clinical research to develop and evaluate novel and improved TB drugs, vaccines, and diagnostics. NIAID will continue to advance the biomedical research goals and objectives of the National Action Plan by engaging with multiple stakeholders, including academic and industry collaborators, and by leveraging the clinical trial infrastructures established by CDC and USAID.

Tuberous Sclerosis Complex (TSC)

The Committee is encouraged by progress on updating NIH's 2003 TSC Research Plan, including a March 2015 workshop sponsored by NINDS and the Tuberous Sclerosis Alliance that assessed progress and prioritized new opportunities for research in TSC. Building on this progress, the Committee encourages the Director to coordinate the participation of multiple ICs on a research strategy aimed at addressing the numerous medical and neuropsychological burdens associated with TSC while deciphering the biology underlying phenotypic heterogeneity. Manifestations of TSC are highly variable among affected individuals, and TSC can be a model condition for developing precision medicine approaches to treat each individual's symptoms to maximize the benefit-risk ratio. NIH should encourage research opportunities in the five key areas prioritized by workshop participants: understanding phenotypic heterogeneity in TSC, gaining a deeper knowledge of TSC signaling pathways and the cellular consequences of TSC deficiency, improving TSC disease models, developing clinical biomarkers for TSC, and facilitating therapeutics and clinical trials research.

Action taken or to be taken

On March 10-12, 2015, the National Institute of Neurological Disorders and Stroke (NINDS) and the Tuberous Sclerosis (TS) Alliance sponsored a workshop to assess progress and new opportunities for research in tuberous sclerosis complex (TSC). Additional participants included representatives from six other NIH Institutes, the Department of Defense Tuberous Sclerosis Complex Research Program, basic scientists and clinicians, and representatives from the pharmaceutical industry. Workshop participants developed recommendations focused around the five broad themes described in the committee's request above. Following the workshop, a research plan, including short- and long-term goals and recommendations, was published in *Pediatric Neurology*²⁰⁴.

Making progress toward the goals in the report will require coordinated efforts of basic scientists, clinical researchers, and public and private partners. NIH currently supports research in all five priority areas of the report and welcomes additional research proposals in all of these areas. Currently funded research includes projects to: understand and develop therapeutic targets of components of the molecular signaling networks involved in TSC; better decipher the variable phenotypes of TSC and related disorders; develop imaging and other biomarkers of the disease; understand the neurological and neuropsychological components of TSC; identify novel therapeutic targets; and understand the contributions of different cell types to the TSC disease pathology. NINDS recently funded a clinical trial, "*Preventing epilepsy using vigabatrin in infants with TSC*" (PREVeNT) that will utilize EEG to identify TSC infants at risk for epilepsy and study the effectiveness of early intervention on preventing seizures and improving neurocognitive outcomes in infants with TSC.

Given the multi-system nature of TSC and shared mechanisms with other disorders, several NIH Institutes fund research relevant to TSC, and coordinate through regular informal interactions among program officials as well as through meetings of the trans-NIH TSC working group.

²⁰⁴ Sahin, et al., Advances and Future Directions for Tuberous Sclerosis Complex Research: Recommendations From the 2015 Strategic Planning Conference, <http://www.sciencedirect.com/science/article/pii/S0887899416301679>

Because TSC is often associated with autism and epilepsy, planning and coordinating activities in these areas are also relevant. Collaboration across Institutes also occurs through co-funding of projects or initiatives. For example, the *Developmental Synaptopathies Consortium*, part of the National Center for Advancing Translational Sciences' Rare Diseases Clinical Research Network (RDCRN), is co-funded by several NIH Institutes with an interest in TSC. The consortium is currently recruiting for a longitudinal study to identify early signs of autism and intellectual disability to gain a better understanding of why people with TSC are more prone to these conditions. NIH Institutes will also continue to work closely with the TS Alliance as the organization develops several important initiatives to address the recommendations in the plan, including the TS Alliance's Preclinical Consortium, a collaboration with academia and industry to test the efficacy of candidate therapeutic drugs and advance the best candidates to clinical testing.

Tuberous Sclerosis Complex - Update

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

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²⁰⁵ Sahin, et al., Advances and Future Directions for Tuberous Sclerosis Complex Research: Recommendations From the 2015 Strategic Planning Conference, <http://www.sciencedirect.com/science/article/pii/S0887899416301679>

U.S. Preventative Task Force [USPSTF]

The Committee strongly urges the Secretary to ensure greater transparency and inclusion of appropriate physician experts in the development of USPSTF recommendations. The Committee is concerned about the lack of communication with relevant stakeholders and inconsistency with recommendations by other Federal agencies or organizations. Therefore, the Committee emphasizes the need for the USPSTF to conduct outreach to relevant stakeholders, including provider groups, practicing specialists that treat the specific disease or condition under review, and relevant patient and disease advocacy organization before voting on a draft recommendation statement. To promote greater transparency, the Committee urges that any final recommendation statement include a description of comments received on the draft recommendation statement and relevant recommendations of other Federal agencies and organizations.

Action Taken or to be Taken

AHRQ is committed to the Committee's request to promote greater transparency of the recommendations of the U.S. Preventive Services Task Force (USPSTF or Task Force) and the inclusion of appropriate topic experts, including physician experts in the development of USPSTF recommendations.

All of the Task Force's recommendations are informed by topic experts, including provider groups, disease-specific experts, and practicing specialists that treat the specific disease or condition under review, such as radiologists, oncologists, cardiologists, and surgeons. For all topics, experts review and provide input at critical points in the recommendations development process. For example, experts provide guidance on key questions, populations of concern, and the research approach for the evidence reviews; help develop the evidence review; and provide peer review. This type of expert engagement happens prior to the Task Force voting on a grade for the draft recommendation.

In addition, for all topics, the Task Force invites comments from the public on draft materials at least three times throughout the recommendations' development process. Each public comment opportunity is publicized on the Task Force's website and promoted through its many communication vehicles. This comment period remains open for four weeks; anyone—including additional specialists, advocacy organizations, and others—can comment by visiting the [Opportunities for Public Comment page](#) on the USPSTF's website. The "Response to Public Comment" section of the final recommendation statement summarizes the themes of the public comments and details any changes that were made to the recommendation as a result.

The Task Force partners with relevant stakeholders—including specialists, patient and disease advocacy groups, and Federal agencies—throughout the recommendation development process. At the start of each topic, the Task Force alerts national primary care, specialty, patient, advocacy, and other stakeholder organizations with interest in and relevance to the topic and invites them to submit feedback on its work during the public comment periods. At each additional stage in the development of a recommendation, stakeholders are notified of progress and public comment opportunities through the Task Force's 42,000+ member email list. As a result of this comprehensive outreach, the USPSTF receives thousands of comments each year, all of which are carefully reviewed and considered. In addition, the Task Force has formal partnerships with 17 organizations that represent primary care clinicians, patients and disease

advocates, and other stakeholders. Partners contribute their expertise, communicate about Task Force’s work to their constituents, and help put the recommendations into practice. A complete list of partners is available on the [Our Partners page](#) on the Task Force’s Web site.

All final recommendation statements include a section covering relevant recommendations of other organizations and Federal agencies. The Task Force routinely examines recommendations from other organizations (e.g., American College of Obstetricians and Gynecologists, American Cancer Society) as part of its review of the evidence. It also communicates and partners with 12 Federal agencies and institutions, which keep the Task Force informed of major Federal initiatives that may produce new evidence. A complete list of the Task Force’s Federal partners is available on the [Our Partners page](#) of its Web site.

At times, there are differences between the Task Force’s evidence-based recommendations and those prepared by other organizations. These differences can often be attributed to differences in processes and procedures for developing recommendations. The Task Force uses independent systematic evidence reviews, as recommended by the Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine (formerly known as the Institute of Medicine). The [standards for guideline development](#) are described on the USPSTF Web site. The Task Force makes recommendations only for those populations without signs or symptoms of disease and in U.S. primary care settings. Nevertheless, the Task Force includes a section in each recommendation statement titled “Recommendations of Others,” which summarizes topic recommendations from other professional societies, advocacy organizations, and Federal agencies (where applicable). This section serves to promote greater transparency and help educate the public and clinicians about the work of relevant external stakeholders.

Usher Syndrome

The Committee continues to encourage the NIDCD to prioritize Usher syndrome research. The Committee requests an update on NEI and NIDCD basic, clinical, and translational research that will lead to additional treatment options and improved patient outcomes for individuals with Usher syndrome. The update should include a description of the criteria used by NIH to evaluate grant submissions to ensure that prioritization of those that accelerate human treatment options that would benefit individuals with Usher syndrome.

The Committee continues to urge the prioritization of Usher syndrome research at NEI. The Committee requests an update on NEI and NIDCD basic, clinical, and translational research that will lead to additional treatment options and improved patient outcomes for individuals with Usher syndrome. The update should include a description of the criteria used by NIH to evaluate grant submissions to ensure that prioritization of those that accelerate human treatment options that would benefit individuals with Usher syndrome.

The Committee continues to urge NIH to prioritize Usher syndrome research at NEI and NIDCD. The Committee requests an update in the fiscal year 2018 budget request on steps NIH has taken to date and future plans to accelerate treatment options and improve patient outcomes.

Action taken or to be taken

Usher syndrome (USH) is a hereditary disease that affects hearing, balance, and vision. NIH funds basic, translational, and clinical research on USH at several institutes and centers (ICs), primarily at the National Institute on Deafness and Other Communication Disorders (NIDCD) and the National Eye Institute (NEI). NIH uses scientific peer review to identify the most meritorious grant proposals based on significance, approach, innovation, clinical impact, and likelihood of success based on the investigator and his/her research environment²⁰⁶. A second level of peer-review at each IC helps prioritize proposals. Top priority is given to proposals identified as having high program relevance, such as addressing goals in the ICs' strategic plans. For example, one NEI strategic plan²⁰⁷ aim is to develop animal models for pathological features of vision disorders "including syndromic disorders such as Usher's disease." The NIDCD strategic plan²⁰⁸ objectives include "genetic causes of hearing loss." NIDCD and NEI have research aims 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. NIH is committed to funding all investigator-initiated USH research that scores well in peer review. 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 and NEI intramural scientists are collaborating to identify and characterize additional USH genes and are also collaborating on clinical research with individuals with USH, focusing on neural mechanisms underlying hearing, balance, and vision. NIDCD intramural scientists are also using

²⁰⁶ http://grants.nih.gov/grants/peer_review_process.htm

²⁰⁷ <https://www.nei.nih.gov/sites/default/files/nei-pdfs/VisionResearch2012.pdf>

²⁰⁸ <https://www.nidcd.nih.gov/about/strategic-plans>

gene therapy to restore hearing and balance in an USH2 animal model, and look to move from animals to gene delivery to the human inner ear. Collaborations between NIDCD and NEI grantees include using gene therapy to rescue auditory response in a zebrafish model of USH type 3 (USH3) and a visual response in a new USH mouse model, caused by mutations in a gene called clarin-1. Based on this work, NEI recently awarded funding to a young investigator building her career in this field. Another NEI- and NIDCD-funded study is developing a drug therapy for USH3. The researchers discovered a small molecule, BF844, that can slow progressive hearing loss and prevent deafness in a USH3 animal model. This small molecule targeted therapy could, in principle, be used to prevent both deafness and blindness in children with USH3, and could even be started preemptively before the onset of their hearing loss and vision loss. Further, NIH-funded research on genetics, gene therapy, regenerative medicine, and rehabilitation may also lead to future treatment options for individuals with USH.

Valley Fever

The Committee continues to commend NIH and CDC on the joint efforts to combat Valley Fever, specifically by conducting a Randomized Controlled Trial (RCT) to identify an effective treatment for Valley Fever. The Committee understands establishing and conducting an RCT is complex and recognizes the effort NIH and CDC have committed to this project. The Committee encourages NIH to finalize the RCT so patients in endemic areas can begin to enroll in the trial this year. Further, the Committee encourages the development of a vaccine.

Action taken or to be taken

Coccidioidomycosis, or Valley Fever, is a fungal infection resulting from the inhalation of airborne spores of several *Coccidioides* species found in the soil. Most Valley Fever patients experience mild flu-like symptoms and recover naturally; however, many individuals require one or more weeks to recover enough to return to routine activities, and some individuals develop severe and life-threatening complications, emphasizing the importance of research addressing this disease.

In December 2015, NIAID, the component of the NIH with the lead for research on emerging and re-emerging infectious diseases, initiated a randomized controlled trial (RCT) to evaluate the impact of early treatment of Valley Fever. The trial aims to enroll patients early in the course of community-acquired pneumonia (CAP), a condition caused by a variety of pathogens, including *Coccidioides* species. The RCT is designed to compare patients receiving the standard-of-care for CAP, azithromycin, with patients receiving both azithromycin and fluconazole, a drug used to treat fungal infections like Valley Fever. In addition to evaluating the impact of early antifungal treatment for Valley Fever, the trial will promote awareness of the disease in the highest areas of occurrence, encouraging residents who are experiencing symptoms to seek medical care early.

The NIAID-funded Duke University Vaccine and Treatment Evaluation Unit is conducting the trial. Currently, three RCT sites are open for patient screening and enrollment at the University of Arizona in Tucson, Arizona; the Mayo Clinic in Phoenix, Arizona; and Kern Medical in Bakersfield, California. Additional sites in Arizona and California are being assessed for potential inclusion in the trial. CDC helped NIAID to facilitate site planning for the RCT by identifying medical facilities that treat the highest volume of CAP patients in Valley Fever-endemic areas of California and Arizona.

Additional NIAID research efforts on Valley Fever aim to better understand disease progression as well as develop both vaccines and therapeutics against the disease. An ongoing clinical trial led by NIAID scientists seeks to identify underlying factors that may increase a patient's susceptibility to develop chronic or severe forms of Valley Fever. This research will clarify underlying disease mechanisms, including differences between *Coccidioides* strains, and explore the development of novel ways to prevent and treat Valley Fever. In addition, NIAID-supported scientists are developing a plant-based, orally delivered vaccine candidate and evaluating candidate therapeutic compounds for activity against *Coccidioides* species in preclinical studies.

NIAID looks forward to continued engagement with CDC and other Federal partners and the scientific, public health, and patient communities to advance research efforts against Valley Fever, particularly the ongoing RCT. NIAID remains committed to research to understand Valley Fever pathogenesis and to develop new therapies and vaccines.

Women's Health Research

The Committee appreciates the efforts undertaken by NIH, specifically, the Office of Women's Health, to ensure policies related to gender and sex in clinical and pre-clinical research are in place. The Committee requests an update in the fiscal year 2018 budget request on how the ICs are implementing the changes, the impact of these new guidelines, the plans to improve public availability of this data, and the status of implementing GAO recommendations related to this issue.

Action taken or to be taken

This inquiry is related to two distinct National Institutes of Health (NIH) policies: Consideration of Sex as a Biological Variable (SABV) and the NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. SABV is a component of the NIH Policy to Enhance Reproducibility through Rigor and Transparencyⁱ. Under SABV, the NIH expects that SABV will be factored into research designs, analyses, and reporting in vertebrate animal and human studies. *Inclusion* refers to recruitment and participation of women and underrepresented minorities in clinical trialsⁱⁱ.

In FY 2015 and FY 2016, the NIH issued public notices explaining new requirements regarding SABV.^{iii,iv} Beginning in January 2016, NIH research program and career development grants must include a discussion of relevant biological variables, such as sex. The policy has been implemented for only one of the NIH's three annual funding cycles. Therefore, it is too soon to fully understand the impact of the policy on research outcomes. However, as the policy was implemented, the NIH hosted numerous training opportunities for NIH staff. Qualitative feedback thus far indicates that uptake of the policy by applicants and reviewers has been robust. This round highlighted certain aspects of the policy that the NIH is working to clarify. The NIH is also in the early stages of evaluating the efforts to increase rigor and transparency in NIH-funded research.

The goal of the NIH Inclusion Policy is to ensure that individuals are included in clinical research in a manner that is appropriate to the scientific question under study. In October 2015, the Government Accountability Office (GAO) issued a final report entitled "*National Institutes of Health: Better Oversight Needed to Help Ensure Continued Progress Including Women in Health Research*" (GAO-16-13).^v The GAO identified five recommendations the NIH Director should take to ensure effective implementation of the Inclusion Policy. In February 2016, the NIH submitted its Statement of Action in response to the report. Recommendation Three has been implemented and is considered closed by the GAO. Recommendation One^{vi} has been implemented by the NIH, but will not be considered closed until the NIH issues its Statement of Action report in FY 2017 to the GAO. Recommendations Two, Four, and Five are in various stages of implementation. Along with the NIH Office of Research on Women's Health (ORWH) and the Office of Extramural Research, the NIH's Inclusion Governance Committee, which is co-chaired by the Director of ORWH, is involved in addressing the GAO recommendations and the NIH's progress in meeting them.

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 2018 budget request and future budget requests. In addition, the NIH shall submit an accompanying plan outlining concrete steps to lower the median age at which individuals receive their first R01 award within 180 days of enactment. The Committee further expects NIH to convene a working group consisting of stakeholders from academia, young researchers, industry leaders, and government officials to move forward on this goal.

Action taken or to be taken

In 2016 NIH engaged in several activities to address concerns about the average age at independence, with an emphasis on Physician Scientists, whose median age at independence is older than for PhDs. In February, July and December 2016, NIH hosted workshops to identify new mechanisms to encourage recruitment, retention, and diversity within the physician scientist workforce and accelerate achievement of independence. These workshops engaged young physician scientists, leaders in research training, representatives of licensing and accreditation boards, representatives of professional societies and NIH leadership.

Based on input from the workshops several programs are under consideration for development with goals to reduce age at independence for Physician scientists. These include the following:

New Pathway to Independence Awards (K99/R00) via some ICs, which will be targeted to Physician Scientists, who to date have not had high representation in the applicant pool.

Enhancements to the Medical Scientist Training Programs (MSTP) via a new funding opportunity announcement to encourage reduced duration of training.

New trans-NIH Research in Residency programs under development to provide research training continuity for those health professionals (MD or MD-PhD) who have had some research experience, but need additional experience in order to apply for independent research awards.

In 2017 NIH and the National Academies initiated a study to identify and recommend solutions to any barriers that may extend periods of training, time-to-independence, or that impede sustained success in research for the next generation of biomedical researchers. This opportunity has engaged early and mid-career researchers, academic and industry leaders, as well as government officials to address the issue. A report is scheduled for release by March 30, 2018. NIH will consider actions to take after that report.

NIH defines new investigators as those who have not yet competed successfully for a substantial NIH research grant (e.g. R01). Early Stage Investigators (ESIs) are new investigators who have completed their terminal degree or medical residency within the last 10 years. Since 2009, NIH has strengthened new investigator policies to encourage research applications at an early career stage. The policy specifies that funding rates of new investigators should be approximately equal to the funding rate of established investigators and that ESIs comprise approximately half

of the new investigator pool. Applications from new investigators and ESIs are grouped and reviewed in a separate cluster during the review meeting. Peer reviewers are instructed to focus more on the proposed research question, significance, innovation, and approach as well as expect less preliminary data rather than focusing on the investigator's track record.

Recent data confirm that these policies continue to be successful in ensuring comparable funding rates NIH-wide between new and established investigators, and that approximately half of the new investigators are ESIs. Since the new investigator policy was revised in FY 2009, NIH has awarded over 23,000 research project grants to investigators who were receiving their first NIH award, representing 35 percent of the investigators who received competing awards during this time. This represents a significant increase over the previous seven-year period, when only 30 percent of funded investigators were first-time awardees.

NIH programs that focus on Early Stage Investigators include the Pathway to Independence Award (K99-R00), Early Independence Award (DP5), and the NIH Director's New Innovator Award (DP2). These targeted programs make initial awards at a lower average age. Despite the success of these specific new programs, the overall age at first award has been resistant to change. A 2016 study suggests that some major determinants of the age at scientific independence are external to NIH.²⁰⁹

²⁰⁹ Heggeness et al. Policy Implications of Aging in the NIH-Funded Workforce. [Cell Stem Cell](#). 2016 Jul 7;19(1):15-8. 016.06.012.

Zika Therapeutic Treatment Research - Update

In addition to the specific items of interest above, the Committee requests general updates in the fiscal year 2018 budget request for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases (NIAID) is the lead NIH Institute for conducting and supporting research on emerging and re-emerging infectious diseases, including flaviviruses such as Zika virus. Currently, no vaccines or specific therapeutics are available to prevent or treat Zika virus disease. NIAID is building on its longstanding commitment to flavivirus research to better understand Zika virus and how it causes disease. This research is informing NIAID's efforts to develop novel treatments, improved diagnostics, and effective vaccines for Zika virus infection.

NIAID is pursuing several strategies to develop therapeutics against Zika virus as well as broad-spectrum antiviral drugs that could be effective against multiple flaviviruses. For example, a recent NIAID-supported study showed that the broad-spectrum antiviral drug BCX4430, originally developed by BioCryst Pharmaceuticals as a therapeutic candidate for the Ebola and Marburg viruses, protected immune-deficient mice infected with Zika virus. NIAID also is supporting the identification of monoclonal antibodies that could be used to treat or prevent Zika virus infection. In addition, NIAID, in collaboration with the National Center for Advancing Translational Sciences and academic and industry researchers, is screening FDA-approved drugs for activity against Zika virus infection. Furthermore, NIAID has developed an assay to test candidate therapeutics for antiviral activity against Zika virus. As of November 10, 2016, NIAID has evaluated antiviral compounds, antibodies, and peptides in 388 primary tests; of those, 29 candidates yielded moderate to high activity. Promising antiviral candidates are being evaluated further in cell culture and animal models, including in a rodent animal model for Zika virus infection developed with NIAID support.

In addition to Zika therapeutics, NIAID also is pursuing the development and testing of multiple Zika virus vaccine candidates. An NIAID-developed DNA-based Zika virus vaccine candidate is being tested in a Phase I trial and, if successful, is anticipated to move to Phase II clinical trials in early 2017. In addition, NIAID is collaborating with Walter Reed Army Institute of Research (WRAIR) and the Biomedical Advanced Research and Development Authority to advance an inactivated virus vaccine candidate developed by WRAIR. As part of this effort, NIAID is co-funding an ongoing Phase I clinical trial of this vaccine candidate with WRAIR. NIAID researchers also are developing a live-attenuated Zika virus vaccine candidate and are planning to start Phase I trials of this candidate as well as a universal mosquito saliva vaccine developed by SEEK for Zika and other mosquito-borne diseases. An effective vaccine against Zika would provide a valuable tool to help stop the spread of infections and prevent future outbreaks. NIAID will continue to support this research, as well as vital research on Zika therapeutics, to help combat the ongoing Zika virus outbreak.

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- i <https://www.nih.gov/research-training/rigor-reproducibility>
 - ii <https://www.gpo.gov/fdsys/pkg/USCODE-2011-title42/pdf/USCODE-2011-title42-chap6A-subchapIII-partH-sec289a-2.pdf>
 - iii <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html>
 - iv <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-011.html>
 - v <http://www.gao.gov/products/GAO-16-13>
 - vi https://report.nih.gov/recovery/inclusion_research.aspx