

Table of Contents

Administrative Burden Workgroup	1
Accelerate Cures Related to Retina Disease	4
Aging Demographic Research	6
Alcoholism (general update).....	8
Aging Lungs (Alpha-1).....	10
Alternating Hemiplegia of Childhood (AHC)	11
Alzheimer’s Disease	12
Amyloidosis	14
Amyloidosis – Update.....	15
Amyotrophic Lateral Sclerosis (ALS)	16
Angelman Syndrome	17
Anhydramnios.....	19
Antimicrobial Resistance (ARM)	20
Atrial Fibrillation	22
Atrial Fibrillation (AFib)	23
Autism Spectrum Disorder (ASD).....	24
Basic Biomedical Research.....	25
Behavioral Health Science Research in NIMH	26
Biodefense Spend Plan	27
Brain Aneurysms	29
Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative	31
Breast Cancer	33
Bridging Interventional Development Gaps BrIDGs Program.....	35
Burden of Disease	36
Cancer Disparities.....	38
Cannabidiol Research	40
Capacity for Data Collection on Severe Maternal Morbidity.....	41
Capstone Awards	43
Cerebral Palsy (CP).....	45
Children in NIH Research.....	47
Chronic Obstructive Pulmonary Disease (COPD).....	49
Chronic Pain Research.....	50
Chronic Pelvic Pain.....	52

Clinical and Translational Science Awards (CTSA)	53
Clinical and Translational Science Awards (CTSA) – IOM Recommendation	55
Clinical Trial Participation.....	56
Colorectal Cancer.....	58
Common Fund	60
Community Based Participatory Research (CBPR)	62
Conflict of Interest	63
Congenital Heart Disease.....	64
Coordination with CDC	65
Deadliest Cancers.....	67
Diabetes.....	69
Down Syndrome	71
Drug Allergy	73
Duchenne Muscular Dystrophy	74
Early Detection and Prevention of Psychosis	75
Emergency Care Research	77
End-Stage Renal Disease (ESRD)	78
Enhanced NIH Reporting on Research Spending by Disease and Affected Populations –.....	80
Environmental Exposure.....	81
Fetal Alcohol Syndrome (FAS) Research.....	82
Fragile X Research.....	83
Functional Gastrointestinal Disorders (FGID).....	85
Gabriella Miller Kids First Research Act	86
Gastrointestinal Cancer	88
Gastrointestinal Disorders.....	90
Gestational Diabetes	91
Global Infections Disease Health Research	93
Government-Wide Collaborations	95
Grant Review	98
Glaucoma	99
Heart Disease	100
Heavy Ion Cancer Therapy and Research.....	101
Hepatitis B	103
Hereditary Hemorrhagic Telangiectasia (HHT)	105

Hydrocephalus Research.....	106
Immunotherapy Research	107
Institutional Development Award (IDeA)	108
Interstitial Cystitis.....	110
Kennedy’s Disease.....	111
Kidney Cancer	112
Kidney Disease	114
Liver Cancer.....	116
Lupus Research Plan.....	118
Lymphangi leiomyomatosis.....	119
Maternal Morbidity.....	120
Medication Assisted Treatment (MAT).....	122
Medications Development	123
Melanoma	124
Microbicides to Prevent HIV/AIDS.....	126
Minority Research.....	127
Mitochondrial Disease	128
Mother-Infant Relationship.....	130
Muscular Dystrophy.....	132
Nanovaccines	133
National Children’s Study (NCS).....	134
National Children's Study Alternative	136
National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Condition (GenTAC)	138
National Strategy for Combating Antibiotic Resistant Bacteria (CARB)	139
NCI Designated Cancer Centers	141
NCI Precision Medicine Initiative (PMI)	143
Neglected Tropical Diseases.....	145
Neurofibromatosis (NF).....	146
New Initiatives	149
NIDAMED.....	151
NIDCR’s Mission	152
NIH Workforce Study.....	153
Non-Recurring Expenses Fund (NEF).....	154
Office of Cancer Survivorship.....	155

Opioid Drug Abuse.....	157
Pancreatic Cancer.....	158
Pediatric Low Grade Astrocytoma Research (PLGA).....	160
Pediatric Oncology Research.....	161
Pediatric Research Data Collection	163
Pediatric Research Network.....	165
Physician-Scientist Workforce Report Implementation	166
Precision Medicine.....	167
Preeclampsia	169
Preterm Birth.....	171
Prioritization of Funding.....	173
Psychotropic Medications and Children	174
Pulmonary Atresia	176
Reproducibility of Scientific Methods.....	177
Research Facilities	179
Review of Maternal Deprivation Studies.....	181
Science Education.....	182
Science, Technology, Education and Mathematics	183
Scleroderma	184
Sickle Cell Disease (SCD)	186
Sickle Cell Disease – Update.....	187
Sleep and Circadian Health.....	188
Sleep and Circadian Health Coordination Efforts	189
Small Business Innovation Research	190
Spina Bifida	191
Stroke-induced respiratory dysfunction.....	193
Study Sections Pediatric Expertise	194
Sturge-Weber	195
Temporomandibular Disorders (TMD).....	197
Therapeutics for Rare and Neglected Diseases (TRND)	198
Translational Research.....	199
Trans-NIH Strategic Approach.....	200
Tuberous Sclerosis Complex (TSC)	202
Undiagnosed Disease Program (UDP).....	204

Usher Syndrome.....	206
Valley Fever.....	207
Vitiligo	209
Vulvodynia.....	211
Women's Health Research	212
Women's Heart Disease.....	214

Administrative Burden Workgroup

In addition, the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

In the Spring of 2015, NIH reported that it would participate in a study and committee formed by the National Academy of Sciences (NAS) on *Federal Research Regulations and Reporting Requirements: A New Framework for Research Universities in the 21st Century*¹ in fulfillment of this request. The *ad hoc* committee is conducting a study of federal regulations and reporting requirements, with specific attention to those directed at research universities.

The study was commissioned by Congress and funded by the Department of Education and the NIH. The study was initiated amid concerns that federal laws, regulations, rules, policies, and reporting requirements—while essential to a well-functioning, responsible system of research—have led to an environment in which a significant percentage of an investigator’s time is spent complying with regulations, taking time away from research, education, and scholarship.

Although the study was originally planned for 18 months, Senator Lamar Alexander, Chair of the Senate Committee on Health, Education, Labor, and Pensions, asked the committee to deliver an expedited report by the end of summer 2015, as Congress will be considering several legislative actions involving higher education, research policy, and medical innovation. On September 22, 2015, the NAS released a preliminary report entitled, “Optimizing the Nation's Investment in Academic Research: A New Regulatory Framework for the 21st Century: Part 1 (2015).”² The second part of the committee's report will be issued in early 2016.

The initial report reviews the federal regulatory framework for research institutions as it currently exists, considers specific regulations that have placed burdens on the research enterprise, and reassesses the process by which these regulations are created, reviewed, and retired. The report identifies specific actions that Congress, the White House, federal agencies, and research institutions should take to reduce regulatory burden.

NIH concurs with many of these recommendations. In this update, we focus on the recommendations for federal agencies and other areas of greatest impact for NIH. The committee recommended that Congress task a single agency with developing a central database of investigator information, a role that may be well suited for OSTP. The committee noted overlap in data fields collected on biosketches by federal research agencies (page 43) and recommended that this collection be simplified. Further, they recommended on page 45 that a single agency establishes a central database of investigator information. The Federal Demonstration Partnership has made similar requests of the federal research agencies and NIH

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

² http://sites.nationalacademies.org/Pages/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

has been tasked to create Science Experts Network Curriculum Vitae³ ([SciENcv](http://www.ncbi.nlm.nih.gov/sciencv/)) in response. SciENcv is a user-curated database of scientific career information that reduces applicant burden. SciENcv allows investigators to store profile information in a single repository, and generate biosketches formatted to the needs of the agencies they apply to. SciENcv currently creates NIH biosketches, and is piloting the ability to create biosketches for grant applications to the National Science Foundation.

Pursuant to the recommendation that OSTP work with agencies to develop, within the upcoming fiscal year, a single federal-wide conflict of interest policy, NIH suggests that such a federal-wide policy intended to meet the needs of all federal agencies and/or for all types of research may not contain sufficient provisions to be an effective tool for any agency. Furthermore, the financial conflict of interest policy upheld by NIH and other HHS agencies is prescribed in regulation (42 CFR part 50, subpart f). We also note that many of the NAS recommendations are focused on research, which is not a part of every agency's mission. It may be feasible, if planned judiciously, to develop a single, uniform conflict of interest policy that can be upheld in conjunction with the other regulatory provisions of each federal agency. However, it is difficult to envision how such a unified COI policy, implemented across a broad range of federal activities might, in practice, alleviate administrative burden for institutions.

The committee recommendations for federal research agencies (outlined in detail on page 21 of the report)are summarized as: 1) limit research proposals to the minimal information necessary for peer evaluation, allowing other information to be submitted “just-in-time” or when the application is being considered for funding; 2) develop a central repository to house assurances; and 3) reduce and streamline reporting, assurances, and verifications.⁴

NIH uses a just-in-time process to collect some elements of the grant application after peer review, when the application is under consideration for funding. The standard application elements collected just-in-time include other support information (both active and pending) for senior/key personnel; certification of Institutional Review Board (IRB) approval of the project's proposed use of human subjects; verification of Institutional Animal Care and Use Committee (IACUC) approval of the project's proposed use of live vertebrate animals; and evidence of compliance with the requirement for education in the protection of human research participants. Other program-specific information may also be requested using this procedure.

NIH has a repository in its electronic Research Administration system where institutions can store the Federalwide IRB Assurance and the Public Health Service (PHS) Animal Welfare Assurance numbers. NIH provides a listing of institutions⁵ with PHS Assurance on its website. NIH will work with trans-Federal organizations and working groups, including the Research Business Models (RBM) Working Group and the Federal Demonstration Partnership (FDP), to create a federalwide central repository to house assurances.

³ <http://www.ncbi.nlm.nih.gov/sciencv/>

⁴ 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

⁵ <http://grants.nih.gov/grants/olaw/assurance/300index.htm>

The third recommendation proposes to eliminate the Vertebrate Animal section (VAS) of PHS grant applications. NIH has ethical and legal obligations to support the use of the most appropriate models for scientific research, minimize risks, and ensure the welfare of all who participate in NIH-funded research, including both humans and animals. It is necessary to have expert peer review of the PHS grant applications to ensure that proposed animal models and numbers appropriately support the proposed science. The NIH has simplified the VAS as of January 2016 to remove redundancy with IACUC review while ensuring scientific consideration of animal welfare.

The recommendation to defer animal-related noncompliance events is most concerning to NIH. It undermines the mandates of Public Law 99-158, "Animals in Research," requiring prompt reporting by institutions and oversight of corrective actions by NIH when serious noncompliance occurs. Without prompt reporting the opportunity for NIH to ensure prompt correction of serious animal welfare or programmatic issues is lost and more animals may be impacted in the interim. NIH relies upon non-compliance reporting of all events to proactively address weaknesses in institutional animal care practices on an ongoing basis before such deficiencies can become significant and impact animal welfare, and to provide feedback for continual improvement.

NIH is open to exploring the replacement of annual reports to individual agencies about animal care programs with a single annual report under the Federalwide Assurance mechanism. NIH suggests that this endeavor be organized by the RBM or the White House Office of Science and Technology Policy.

Accelerate Cures Related to Retina Disease

The Committee directs NEI to create a challenge program to advance the speed of basic research to cure retina disease by creating a forum for the NEI Director to survey the field of basic retina research discoveries to provide rewards for research not otherwise funded through NEI or other NIH supported competitive awards. The Committee expects NEI to provide an update and timeline in the fiscal year 2017 budget request to describe how the program will be advertised, funding allocated, and criteria to evaluate submissions for possible challenge rewards to further incentive non-NIH supported researchers to accelerate basic research through this mechanism. The Committee further expects NEI to distribute the findings of this program widely to the NEI research community to further promote the leveraging of federal and non-federally supported retina research.

Action taken or to be taken

To accelerate the translation from basic research to disease therapies, NEI will launch a challenge competition to develop retina organoids – advanced 3D tissue engineering models of retinal tissue – as a tool to provide new insights into the development, biology, or disease pathology of retinal diseases and to test pharmaceutical, gene transfer, and regenerative therapies. For many years, drug development has relied on animal models of disease, which have many strengths and drawbacks. However, technological advances in recent years have enabled creation of 3D organoids in a lab dish. Scientists have recapitulated key developmental steps to induce mouse stem cells to self-organize into an optic cup, the tissue that develops into a retina. Biodegradable scaffolds and 3D bioprinting of cells has transformed the way scientists grow tissues in the lab. The NCATS Tissue Chip Program has created bioengineered devices that mimic organs like liver and pancreas to predict whether drugs will be safe or toxic in humans. NEI's program will build on these accomplishments to create retinal organoids from human cells that can be used not only for drug screening and basic research, but may also serve as the foundation for retinal transplantation.

The field of tissue engineering is constantly advancing. To establish technical specifications and minimum requirements for inclusion in the competition, NEI will host a meeting of academic and industry experts in tissue engineering and vision research. Experts at this needs assessment meeting will be encouraged to participate in the competition. The meeting, slated for spring 2016, will allow NEI to survey academia and industry and to design a challenge that will yield useful tools for researchers and serve as faithful models for functional retinal tissue, that have the best opportunity to be adopted widely by the vision research community.

In order to reflect the organization of the human retina and provide the greatest utility for clinically-relevant research, organoids will need to incorporate multiple cell types and should reflect biologically relevant spatial and temporal patterning. They should also be customizable so that scientists can test cell interactions and developmental cues in unique ways that can lead to new insights into the mechanisms of disease and degeneration. In addition, some current cell culture systems derive ocular tissues from individual patients, using induced pluripotent stem cell technology. This allows researchers to test patient-specific therapies for conditions caused by specific gene mutations, such as retinitis pigmentosa, or for diseases which involve a complex interaction of genes and environment, such as age-related macular degeneration.

The challenge competition will be launched this fall and will award \$1 million (FY 2017) over two phases: Phase I is ideation, which will provide four months to outline a concept and provide some preliminary data demonstrating feasibility towards implementing that concept. NEI will provide a total of \$100,000 in prize awards to top ideas, as judged by a panel of subject matter experts. Winners and finalists will then have two years to complete Phase II, proof-of-concept, developing and testing retinal organoids. The three organoid models satisfying eligibility criteria and showing the greatest promise for accelerating disease therapies will be awarded \$500,000, \$300,000 or \$100,000 prizes. Products will be judged based on potential utility and impact, versatility, fidelity for disease modeling, creativity, and potential for adoption by the larger research community. Through advertisements in technical journals, on the NEI website, and at scientific conferences, NEI will target engineers and vision scientists in industry and academia. Although winners can retain some of the intellectual property, the rules of the competition will require them to share their models with the research community. Ultimately, NEI expects this challenge will spur the development of multiple resources and tools to catalyze therapy development for retinal disease.

Aging Demographic Research

In addition, the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

The National Institute on Aging (NIA) supports a robust portfolio of research on the demography of aging in the United States and globally. Areas of interest include: trends in functioning, disability, morbidity, and mortality; age trajectories of health; life expectancy and active life expectancy; causes and consequences of changes in the age-structure of populations; the effect on health of social networks and social contexts; interrelationships between work, family and health; the intersection between demographic processes and social outcomes, including intergenerational relationships; and cohort analyses of aging.

The Health and Retirement Study (HRS), NIA's flagship study of aging demographics, will complete its first 25 years of data collection in FY 2016. HRS consists of a biennial collection of data from a nationally representative, population-based sample of over 26,000 Americans aged 50+ and their spouses. Support from the American Reinvestment and Recovery Act (ARRA) facilitated doubling of the minority sample, and ARRA funding has also enabled HRS researchers to conduct genotyping on approximately 20,000 participants. HRS data are an important resource for researchers, students, and other government agencies, and HRS is a model for numerous similar studies around the world. NIA has taken the lead in building the necessary infrastructure and harmonizing cross-national data resources to facilitate comparative studies and has funded the initial concept work for HRS-like studies in other countries. In addition, NIA has supported the development of an on-line resource that facilitates use and harmonization of data from the HRS and comparable studies around the world.

In 2016, HRS will add respondents born 1960-1965. The study will also implement a new approach to assess trends over time in cognitive impairment and dementia in the United States and across other countries that maintain HRS-like longitudinal studies of aging. Finally, the study will perform assays capturing the aging of the immune system and related molecular and cellular age-related changes that could provide an understanding of some of the mechanisms underlying differences in aging among social and demographic subgroups.

Other relevant initiatives include:

- **Centers on the Demography and Economics of Aging.** NIH currently supports eleven Centers which investigate aspects of health and health care, the societal impact of population aging, and the economic and social circumstances of the elderly. The reach of these Centers is global, with almost all involved in international projects. These will be active during FY 2017.
- **Studies of Old Age Disability Trends and Dynamics.** The National Health and Aging Trends Study (NHATS) replaced the National Long-Term Care Survey as the source of research data on national disability trends and dynamics among the US older population. To date, four rounds of data have been collected, and these data are available to the research community for further analysis. This study will be active during FY 2017.

- **Midlife in the United States (MIDUS) Study.** MIDUS is a national longitudinal study of how behavioral, social, psychological, and biological factors work together to influence health and well-being from midlife into older age. In 2015, NIA issued a call for proposals to support the next five-year cycle of the MIDUS study.

Alcoholism (general update)

In addition to the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Alcohol misuse has profound effects on the health and well-being of individuals, families and communities, and results in substantial economic costs. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) estimates that nearly one-third of adults in the United States have had Alcohol Use Disorder (AUD) at some time in their lives; however, only about 20 percent of them ever sought formal treatment or other help. NIAAA is working to reduce the significant burden of alcohol misuse and AUD by advancing and disseminating evidence-based prevention and treatment for alcohol-related problems alone as well as in the context of co-occurring disorders such as Post-Traumatic Stress Disorder (PTSD).

Three medications have been approved for the treatment of AUD and work well in combination with behavioral therapies; however, these medications are under-used and not effective for all patients. Through its intramural and extramural research programs, NIAAA is working to develop a wider range of AUD medications by capitalizing on research advances in the neurobiology of AUD to identify novel therapeutic targets. NIAAA will pursue promising compounds that act on these targets, and will continue to evaluate new and re-purposed candidate compounds in human laboratory studies and clinical trials. Recognizing that behavioral interventions are a key component of AUD treatment, NIAAA will support research to develop new and improved behavioral therapies for AUD. NIAAA will also continue its efforts to raise public awareness about currently available behavioral and pharmacotherapy treatment options. For individuals with AUD who abstain from or return to low-risk levels of drinking, preventing relapse and sustaining recovery is critical; NIAAA will expand research to elucidate the factors that facilitate the recovery process and build long-term resilience. Considering that individual variability in genes, environment and lifestyle influence the etiology and course of AUD and responsiveness to treatment, NIAAA has launched a new initiative to better understand the heterogeneity of AUD. This initiative holds promise for improving AUD prevention and treatment by informing the development of approaches tailored to an individual's needs.

For individuals who are unable to stop or reduce harmful drinking, the broad range of health consequences that may result can be lifelong and life-threatening. A key priority of NIAAA is to prevent and intervene with the health consequences of alcohol misuse. For example, NIAAA is supporting four research consortia that are pursuing new approaches to diagnosing and treating alcoholic hepatitis. Alcoholic hepatitis is an advanced stage of alcoholic liver disease that results in mortality within the first four weeks of diagnosis in those who are most severely affected.

Prevention of alcohol misuse at all life stages is integral to reducing its harmful consequences. NIAAA will continue to support research to prevent and reduce underage and harmful drinking by young people, and recently released *the College Alcohol Intervention Matrix (CollegeAIM)*, to help college officials select evidence-based alcohol interventions for their campuses. In addition, NIAAA will continue to support research to elucidate the short- and long-term impact of alcohol

on the developing adolescent brain, and to develop novel interventions to prevent and reduce alcohol misuse at all ages, including for populations disproportionately affected by the adverse effects of alcohol misuse.

Aging Lungs (Alpha-1)

The Committee encourages the NHLBI to convene a group of expert stakeholders to establish a treatment algorithm for Alpha-1 Antitrypsin related disease to assist physicians in correctly diagnosing and treating it.

Action taken or to be taken

Alpha-1 Antitrypsin (AAT) is a protein that is made in the liver. Normally, AAT travels the bloodstream to the lungs and other organs, where it helps protect them from the harmful effects of other proteins. AAT deficiency is an inherited condition that results in the AAT proteins not taking the right shape, causing them to get stuck inside liver cells, and, therefore, not move into the bloodstream and reach the lungs. AAT deficiency has no cure, but treatments are available based upon the kind of disease that develops. Many treatments for AAT related lung disease are the same as those for Chronic Obstructive Pulmonary Disease (COPD). They include the use of inhaled bronchodilators and inhaled steroids; flu and pneumonia vaccines; pulmonary rehabilitation; extra oxygen; and lung transplantation.

While the mission of the National Heart, Lung, and Blood Institute (NHLBI) is to support research on diseases such as AAT, NHLBI does partner with other organizations on issues such as the provision of treatment. For example, NHLBI is currently working with the COPD Federal Partners Working Group to develop a National COPD Action Plan. Because AAT deficiency is a risk factor for COPD, AAT related lung disease and its treatment will be among the topics discussed in the development of the Action Plan. Development of the National COPD Action Plan will include patients and their families, health care providers, researchers and representatives of Federal agencies. The working group is currently planning a public town hall meeting to get stakeholder input, and a draft plan describing the expected contribution of Federal agencies to specific goals of the plan will be released in 2016.

Alternating Hemiplegia of Childhood (AHC)

The agreement notes AHC is a rare neurodevelopmental disorder characterized by repeated episodes of weakness or paralysis that may affect one side of the body or the other. It is one of several diseases caused by mutations in the gene ATP1A3. Recently NIH participated in the 4th Symposium on ATP1A3 in Disease. The agreement encourages NINDS to support promising research on AHC and the gene mutation ATP1A3 and to provide a summary of the recent symposium and associated recommendations in the fiscal year 2017 budget request.

Action taken or to be taken

Alternating hemiplegia of childhood (AHC) is one of several diseases caused by mutations in the gene ATP1A3. Others include, for example, types of dystonia-Parkinsonism and epilepsy. Since 2012, scientists, physicians, patients, and parents have met yearly to share the latest on the understanding of ATP1A3 diseases and to accelerate the development of treatments and potentially a cure for AHC. These meetings have facilitated collaborations and led to remarkable progress in the understanding of ATP1A3 diseases. To continue this progress, the *4th Symposium of ATP1A3 in Disease*, organized by Erin Heinzen (Columbia University) and Jeff Wuchich (Cure AHC), was held in Bethesda, Maryland, in August 2015. A summary of the meeting is posted on the Cure AHC's meeting website.

The meeting brought together researchers, including those supported by the NIH, NIH scientific staff, including the NINDS Director, and the international disease advocacy community to share the latest findings, brainstorm about future directions, discuss collaborations, and highlight funding opportunities. The discussions at the symposium illustrated how decades of basic research investment can come to bear on a particular rare disease. ATP1A3 mutations affect the sodium-potassium ATPase, or "sodium pump," which is crucial for electrical activity and other cell functions. Many years of basic studies on the sodium pump conducted before these disease mutations were discovered accelerated understanding of these diseases. Advances in gene sequencing technology have also been essential to progress because there are so many different mutations in this gene (more than 100) that have different effects. Other topics of discussion at the symposium included molecular characterization of ATP1A3 mutations, characterization of the full spectrum of manifestations of these diseases, use of induced pluripotent stem cells (iPSCs) derived from ATP1A3 patients to study the disease, and issues important in preparing for clinical trials for these and other rare diseases. The group formulated research recommendations to help guide efforts over the next year, including assembling clinical characterization standards for patients with ATP1A3 mutation diseases, developing cellular models of ATP1A3 diseases, and sharing resources, including iPSCs, with all interested researchers.

NINDS is currently funding promising research on AHC. This includes research to understand the full range of developmental, motor, cognitive, and psychiatric symptoms that mutations in this gene can cause, which may allow a shared approach to therapy based on the underlying cause. Researchers are also applying advanced brain imaging to identify the brain areas that are affected, which may enhance future clinical trials and the ongoing care of patients by providing objective measures of progress over time, and may point the way to design of future treatments, including deep brain stimulation. Ongoing studies of how the mutations affect cells at the molecular level of analysis will contribute to the design of rational therapies.

Alzheimer's Disease

The Committee looks forward to receiving a report in the fiscal year 2017 CJ that outlines research conducted on Alzheimer's disease relative to the milestones established in the National Plan, as well as the professional judgement budget for Alzheimer's disease for fiscal year 2017. 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.

Action taken or to be taken

NIH's professional judgment budget ("Bypass Budget") for FY 2017 for Alzheimer's disease and related dementias (ADRD) was released on July 27, 2015.⁶ This document provides an estimate of the funds in FY 2017 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. The professional judgment budget also describes initiatives, successes, and plans in the battle against these devastating conditions.

In the Bypass Budget, NIH proposes an increase of \$323.355 million in funding beyond the FY 2017 baseline. This expanded funding will focus on:

- Exploring the complex cellular, molecular, and genetic brain changes that play a role in Alzheimer's and related dementias.
- Development, testing, and validation of tools and methods for diagnosing and monitoring patients with Alzheimer's disease, from the preclinical phase through advanced dementia.
- Development of therapies for all stages of Alzheimer's disease, including studies of interventions already in use for other conditions and nonpharmacological interventions.
- Exploring how genetic, lifestyle, and environmental factors influence the incidence, prevalence, and clinical course of Alzheimer's disease.
- Improving the quality of care and quality of life for dementia patients in a variety of care settings, and alleviating the physical, emotional, and socioeconomic burdens experienced by caregivers.
- Development and dissemination of resources for high-quality Alzheimer's research.
- Creation and support of partnership enterprises to enable major national and international efforts in basic, translational, and clinical research.
- Support for basic, translational, and clinical research on Alzheimer's-related dementias, including frontotemporal degeneration, Lewy body dementia, vascular dementia, and mixed dementia.

NIH supports a number of initiatives to advance translational science and help bring more treatments to more patients more quickly, including for Alzheimer's disease. For example, the Cures Acceleration Network (CAN) at the National Center for Advancing Translational Sciences (NCATS) 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

⁶ <https://www.nia.nih.gov/budget-files/Reaching-for-a-Cure-Alzheimers-Disease-and-Related-Dementias-Research-at-NIH.pdf>.

Research Projects Agency. Current program priorities include: 1) micro-awards for researchers who need to get past a small translational science hurdle; 2) devices and sensors to detect clinical outcomes; and 3) access to compounds, toxicology/pharmacokinetic data, and patient populations.

Amyloidosis

The Committee asks NIH to keep the Committee informed on the steps taken to increase the understanding of the causes of amyloidosis and the measures taken to improve the diagnosis and treatment of this devastating group of diseases. The Committee requests an update in the fiscal year 2017 CJ.

Action taken or to be taken

NIH continues to support research into amyloidosis – the phenomenon of abnormal protein deposits in tissues that result in disease. In response to a solicitation entitled “Systemic Amyloidosis: Basic, Translational, and Clinical Research,” NIH has recently funded two meritorious projects. One project seeks to investigate whether a cellular molecule called ATF6 can play a role in reducing the secretion of amyloid-generating proteins and, therefore, lessen systemic amyloidosis. ATF6 is a factor that participates in the regulation of the “turning on” and “turning off” of genes. The second project utilizes a computer algorithm to identify segments of proteins that have a propensity to form aggregates. Once these “segments” are identified, small molecules will be designed and tested to determine whether they can inhibit aggregate formation.

In another study supported by NIH, investigators are working to determine whether cardiac amyloidosis associated with the V122I variation of the transthyretin (TTR) protein can be differentiated from other causes of heart failure using a simple blood test. V122I has been reproducibly observed in three to four percent of African Americans. However, because TTR cardiac amyloidosis is challenging to diagnose, researchers believe that it is underdiagnosed. This work will provide important information about the burden of disease in African Americans. NIH also supports a study to explore aging as a major risk factor for both the sporadic and inherited forms of TTR amyloidosis.

Recent advances in amyloidosis research include the development of preclinical imaging agents, such as “p5+14” and probe “4”, to detect amyloid deposition in animal model systems, findings which could lead to the development of effective diagnostic tools. Clinically, a recent pilot study provided further evidence that amyloidosis may be treated with the drug tafamidis. Tafamidis works by stabilizing a protein called transthyretin, which is known to contribute to aggregate formation. Specifically, the pilot study found that the blood concentration level of tafamidis is critically important to achieve maximal stabilization of transthyretin and that dosage of this drug may need to be tailored specifically for each patient. NIH remains committed to supporting innovative strategies for improving the health of patients with amyloidosis.

Amyloidosis – Update

In addition, the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

NIH continues to support research into amyloidosis. Two meritorious research projects have recently been funded in response to a solicitation entitled “Systemic Amyloidosis: Basic, Translational, and Clinical Research.” One project will investigate whether a cellular molecule called ATF6 can play a role in reducing the secretion of amyloidogenic proteins and, therefore, ameliorate systemic amyloidosis. ATF6 is a factor that participates in the regulation of the “turning on” and “turning off” of genes. The second project utilizes a computer algorithm to identify segments of proteins that have a propensity to form aggregates that can lead to amyloid fibril formation. Once these “segments” are identified, small molecules will be designed and tested to determine whether they can inhibit aggregate formation. Recent advances in amyloidosis research include the development of preclinical imaging agents such as “p5+14” and probe “4” to detect amyloid deposition in animal model systems. Clinically, a pilot study has suggested that the blood concentration level of the drug tafamidis is critically important to achieve maximal stabilization of transthyretin and that dosage of this drug may need to be tailored specifically for each patient. Transthyretin is a protein in which both mutant and normal forms can contribute to aggregate formation. NIH will continue to pursue research opportunities to improve outcomes for people with amyloidosis.

Amyotrophic Lateral Sclerosis (ALS)

The Committee strongly supports NIH's research in ALS and encourages NINDS to further support promising ALS research related to induced pluripotent stem cells, whole genome sequencing, biomarkers, precision medicine, natural history studies, and translational research that could help identify new treatments for the disease. NINDS also is encouraged to partner with ALS organizations and other Federal agencies and programs, including the ALS Research Program at DOD and the National ALS Registry at CDC. The Committee further encourages NIH to work with FDA to identify opportunities to inform and advance the development of treatments for ALS.

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports research, including collaborative consortia, to better understand ALS and develop new treatments for the disease. NINDS-funded scientists are developing brain imaging, muscle conductivity, and molecular biomarkers to expedite diagnosis or monitor disease progression. In clinical trials, biomarkers may measure the effects of new treatments or help target treatments to specific patient subgroups. Induced pluripotent stem cells (iPSCs) and fibroblasts (a type of skin cell used to generate iPSCs) from people with familial ALS are available to the research community through the NINDS Repository. Researchers are using these and other cell lines to generate iPSC-derived motor neurons and glial (supporting) cells for investigating the cellular processes underlying ALS and for testing potential new therapies.

ALS is a heterogeneous disease that will likely require a precision medicine approach to treatment. To lay the foundation for precision medicine for ALS, NINDS is conducting several natural history studies to better understand the relationship between genes and the disease process in ALS and to develop disease biomarkers. NINDS is funding a collaborative project grant to study neurodegeneration in families with mutations in a gene called "chromosome 9 open reading frame 72 (C9orf72)," the most common genetic cause of ALS, and is supporting a consortium within the NCATS Rare Diseases Clinical Research Network that is conducting whole genome sequencing, biomarker studies, and natural history studies of people with sporadic and familial forms of ALS and related neurodegenerative disorders. NeuroLINCS is another large NINDS-funded study that will enable the exploration of precision medicine approaches for ALS. Using iPSCs, bioinformatics, and state-of-the-art-technology, including whole genome sequencing, NeuroLINCS is investigating the entire complement of genes, gene activity, proteins, and gene modifications in ALS to understand the function of neurons and glia from healthy individuals and people with genetic and sporadic forms of ALS and other neurodegenerative diseases. They are also developing tools that will enable other scientists to analyze similar large complex datasets.

NINDS-funded preclinical therapy development includes genetically-targeted therapies, such as antisense oligonucleotides and gene therapy, as well as broader therapeutic approaches, such as small molecules to induce clearance of toxic accumulations of proteins. NINDS-funded researchers are also conducting an early phase clinical trial to test whether neural progenitor cells can be injected safely into the cervical spinal cord of patients with ALS.

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 and the private partners working diligently to advance the growing body of angel man syndrome research towards practical treatments. Further research in this area holds great promise for both angelman syndrome and forms of autism also linked to misexpression of the UBE3A gene. The Committee encourages NIH to support angelman syndrome research and to consider meritorious research. The Committee encourages NIH to leverage Federal funds with public-private partnerships in the areas of angelman syndrome, autism, and UBE3A-related disorders.

Action taken or to be taken

Since its inception, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) has supported research on intellectual and developmental disabilities, including studies on Angelman Syndrome (AS), a genetic condition that can be associated with developmental delay, loss of language skills, seizures, problems with movement coordination and balance, sleep irregularities, and behaviors that fall within the autism spectrum. A number of genetic changes, including misexpression of the *Ube3a* gene, can lead to AS. This gene must be tightly regulated for normal brain development to occur, since either a decrease or increase from normal activity causes serious developmental problems.

NICHD funds AS-related studies along the entire research spectrum, including studies on gene expression and regulation, a longitudinal study on the natural history of AS, and clinical studies on specific issues such as sleep disturbances among individuals with AS. National Institute of Neurological Disorders and Stroke- (NINDS-) supported studies have focused on the cellular mechanisms through which the *Ube3a* gene affects the development of nerve cell branches, the “plasticity” of synapses (the ability of synapses to adjust through learning), and the expression of other genes that influence development and brain function. AS is an “imprinted” disease; it is caused by the loss or inactivation of the maternally-inherited copy of the gene, while the paternally-inherited gene is “silent,” not compensating for the loss of the maternal gene. Although Assisted Reproductive Technologies (ART) have revolutionized infertility management, some reports suggest that the incidence of various imprinted diseases increases when children are conceived by ART. An NICHD-supported funding opportunity, “Long-Term Outcomes of Medically Assisted Reproduction,” seeks grant applications proposing to study the long-term health outcomes of children conceived after ART.⁷

No therapies for AS have yet addressed the disease process itself, although there has been progress on interventions for some of the symptoms, such as drugs to control seizures and physical and occupational therapies to improve the quality of life for people with AS. Currently supported research is directed toward strategies that target the neurodegeneration and synaptic plasticity that are hallmarks of AS. Several studies include collaborations that involve both university and private partners. One NICHD-funded effort has developed promising treatments for mouse models of AS using genetic tools developed through a collaboration between university-based researchers and a pharmaceutical company. These genetic tools are now being studied as possible treatments for people with AS. Another NICHD-supported research effort is

⁷ <http://grants.nih.gov/grants/guide/pa-files/PAR-14-272.html>

creating a system to facilitate high-throughput screening of drugs for their effects on the *Ube3A* gene. If successful, this effort could serve as a model for public-private partnerships to address a wide variety of genetic conditions.

NICHD also has a particular interest in studies that develop outcome measures – tools to measure results – across clinical trials of treatments for disorders associated with developmental disabilities such as AS. A current NICHD-sponsored funding opportunity, “Outcome Measures for Use in Treatment Trials for Individuals with Intellectual and Developmental Disabilities,” provides a mechanism to support meritorious research that can advance the development of practical treatments of AS, autism, and other *Ube3a*-related disorders.⁸

⁸ <http://grants.nih.gov/grants/guide/pa-files/PAR-13-213.html>

Anhydramnios

The Committee requests NIH conduct a state of the science on anhydramnios research and possible treatments and provide an update in the fiscal year 2017 budget request.

Action taken or to be taken

Anhydramnios is a condition in pregnancy in which there is no amniotic fluid in the amniotic cavity surrounding the developing fetus. It can be caused by a tear in the membranes or lining of the placenta, by a problem with the developing fetus' kidneys or urinary tract, premature rupture of membranes, or placental insufficiency.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) has a long history of supporting research on anhydramnios and related complications. NICHD supports basic research studies to better understand amniotic fluid regulation that could lead to the development of effective interventions for anhydramnios. The regulation of amniotic fluid volume occurs primarily by modulating the rate of transport of water and solutes across the amnion (the membrane enclosing the amniotic cavity) from the amniotic fluid, into fetal blood vessels. NICHD-funded research aims to identify stimulators and inhibitors of this process that could alleviate anhydramnios. Currently, NICHD is supporting research to develop an adhesive patch system to seal amniotic cavity access ports following examination of the pregnant uterus using a fiber-optic tube. Such a system could significantly reduce the risk of preterm fetal membrane rupture in this setting, and thus help to prevent anhydramnios. In addition, the NICHD issued a funding opportunity announcement in FY 2014 to encourage researchers to submit grant applications for research on developmental processes that determine the health of newborns and infants, including fetal kidney development.⁹

NICHD has launched the Human Placenta Project, an initiative whose goal is to increase our understanding of human placental development and function across pregnancy.¹⁰ This effort is expected to lead to a mechanistic understanding of the underlying causes of placental dysfunction and placental insufficiency that are associated with, and may be a cause of, anhydramnios. NIH is investing approximately \$46 million in this effort in FY 2015. In addition, to augment our knowledge about anhydramnios and related conditions, NICHD is planning a scientific workshop on the biology, pathophysiology, and clinical aspects of amniotic fluid abnormalities. This workshop will focus on mechanisms of production and regulation of amniotic fluid, possible causes of anhydramnios, neonatal outcomes, and early diagnostic and treatment approaches, identifying knowledge gaps for future research.

⁹ <http://grants.nih.gov/grants/guide/pa-files/PAR-13-257.html>

¹⁰ <http://www.nichd.nih.gov/research/HPP/Pages/default.aspx>

Antimicrobial Resistance (ARM)

The agreement provides the requested increase of \$100,000,000 for AMR research. The NIAID is directed to work with the Biomedical Advanced Research and Development Authority (BARDA) to develop a joint plan to address the serious threat of antimicrobial resistance. NIAID is also directed to work with the Assistant Secretary for Preparedness and Response on the five-year spending plan for the medical countermeasure (MCM) enterprise, which should provide additional detail on NIAID's biodefense activities, including priorities for MCM candidates in its portfolio and efforts to transition these projects to advanced research at BARDA. The agreement also directs the Department of Health and Human Services to work with the Department of Defense, Agriculture, Veterans Affairs, and the Food and Drug Administration to both track and store AMR genes and the mobile genetic elements from AMR bacteria. The Secretary is directed to include an update in the fiscal year 2017 budget request on the Administration's progress in implementing the National Strategy for Combating Antibiotic Resistance Bacteria.

Action taken or to be taken

As outlined in the 2014 report, the National Institute of Allergy and Infectious Diseases' (NIAID's) Antibacterial Research Program: Current Status and Future Directions, NIAID is pursuing basic, translational, and clinical research on the prevention, diagnosis, and treatment of drug-resistant infections. NIAID and NIH also play a key role in the Administration's comprehensive *National Strategy on Combating Antibiotic-Resistant Bacteria (CARB)*. As part of this effort, NIH is developing a national genomic sequence database of antimicrobial-resistant bacteria; supporting a prize to incentivize development of rapid diagnostic tests; and expanding clinical research capacity to evaluate new antimicrobial products through NIAID's Antibacterial Resistance Leadership Group (ARLG).

NIAID supports basic research to help advance discovery and development of antimicrobial strategies. For example, NIAID-supported researchers used an innovative screening method for unculturable soil bacteria to discover teixobactin, a novel natural product that has shown activity against a variety of Gram-positive bacteria. NIAID's genomic sequencing efforts also have led to improved understanding of antimicrobial resistance and identification of potential drug targets. NIAID has supported the genomic analysis of more than 5,000 antimicrobial-resistant bacteria, including carbapenem-resistant *Enterobacteriaceae* (CRE) and other drug-resistant pathogens of concern. These data are made publicly available to facilitate research and drug discovery.

NIAID also supports basic research examining the bacterial surface and the interactions between bacteria and their hosts to identify promising drug and vaccine targets for drug-resistant pathogens. NIAID researchers have used a rabbit model of methicillin-resistant *Staphylococcus aureus* (MRSA) infection to analyze bacterial and host gene expression to gain a comprehensive picture of the MRSA-host interface. NIAID scientists also characterized the outer surface of carbapenem-resistant *Klebsiella pneumoniae*, identifying 203 previously unreported proteins including new targets for therapeutic and vaccine development. In an effort to discover host factors that could be targeted for therapeutic development, NIAID scientists will partner with researchers from NCI, the NIH Clinical Center, and NHGRI to study the role of the human microbiota in the control of drug-resistant organisms.

Building on basic research discoveries, NIAID is pursuing further development of innovative therapeutics for antimicrobial-resistant infections via platform technologies and other innovative approaches. NIAID has multiple initiatives for novel antimicrobial strategies including non-traditional therapeutics, host-targeted therapeutics, and systems biology efforts. To help lower the risk for drug developers and fill gaps in the product pipeline, NIAID provides preclinical services such as *in vitro* and *in vivo* testing of candidate therapeutics for drug-resistant bacteria. NIAID also supports the development of quorum sensing inhibitors that restore susceptibility to existing drugs in several multi-drug resistant Gram-negative pathogens. In addition, NIAID is working closely with the Biomedical Advanced Research and Development Authority to develop broad-spectrum antibiotics against entire classes of pathogens.

In addition to basic research and drug discovery efforts, NIAID is working to develop novel diagnostics and effective vaccines to combat antimicrobial-resistant infections. NIAID also plans to expand its antimicrobial preclinical support services by enhancing product development capabilities for diagnostics. NIAID will continue to advance discovery and development of new antimicrobial products to address drug resistance through support of basic, translational, and clinical research.

Atrial Fibrillation

In addition to the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Atrial fibrillation, also called AFib, is the most common type of arrhythmia or heart rhythm disorder. About 3-6 million Americans have AFib, and the number of affected individuals is expected to rise with the aging population. Since AFib is often asymptomatic, it frequently goes undetected and untreated, with potentially deadly consequences as it increases the risk for stroke, heart attack, and sudden cardiac arrest. Treatments to restore proper heart rhythm in patients with AFib include electrical cardioversion (low energy shocks); catheter ablation in which a wire is inserted through a vein in the leg or arm and threaded to the heart; pace-makers; and anti-arrhythmic drug therapy.

The National Heart, Lung, and Blood Institute (NHLBI) supports a wide range of research to improve prevention and treatment of AFib. In fact, AFib is one of the first diseases to be included in our landmark Trans-Omics for Precision Medicine (TOPMed) program.¹¹ TOPMed will couple whole genome sequencing and other –omics (e.g., metabolic profiles, protein and RNA expression patterns) data with molecular, behavioral, imaging, environmental, and clinical data to uncover factors that increase or decrease the risk of disease, identify subtypes of disease, and develop more targeted and personalized treatments. Other studies are exploring ways to improve standard catheter ablation procedures; to determine if supplements can lower the risk of repeated episodes of AFib; to optimize dosing strategies for blood-thinners; to test an implantable cardiac monitor for remote and continuous AFib evaluation; and to test the comparative effectiveness and safety of newer anticoagulants.

To address the increased risk of stroke in AFib patients, the National Institute of Neurological Disorders and Stroke (NINDS) supports research to better understand risk factors for AFib and ways to optimize diagnosis and treatment for more effective prevention of AFib-related stroke. Foundational research by the NINDS has also led to the recent success of intra-arterial clot retrieval procedures in reducing disability due to acute cardiogenic embolism. In October 2014, NHLBI and NINDS participated in a meeting organized by the Alliance for Aging Research called “Balancing the Risk of Stroke and the Risk of Bleeding in Older AFib Patients.” The meeting brought experts together to address under-treatment in older patients with AFib due to concerns about medication side effects and misconception about stroke risks.

¹¹ <http://www.nhlbi.nih.gov/research/resources/nhlbi-precision-medicine-initiative/topmed>

Atrial Fibrillation (AFib)

As such, the Committee strongly urges the NIA to work with NHLBI, NINDS, and other relevant NIH Institutes, Centers, and offices to communicate the results of this falls prevention study widely, when available, to inform healthcare providers and patients who are making treatment decisions about AFib-related stroke in older persons.

Action taken or to be taken

Atrial Fibrillation (AFib) is a condition in which the normal beating in the upper chambers of the heart is irregular, compromising blood flow to the lower chambers of the heart and increasing the individual's risk of stroke. Oral anticoagulation therapies can reduce the risk of stroke in these patients. However, physicians may hesitate to prescribe these medications to older individuals due to an associated increase in the risk of bleeding with an injury, such as those that may occur after a fall; according to the CDC, one in three adults ages 65 and older falls each year, and falls are the leading cause of both fatal and nonfatal injuries in older adults.

In 2014, the National Institute on Aging (NIA) and the Patient-Centered Outcomes Research Institute (PCORI) began collaboration on a five-year clinical trial of a multi-component, integrated strategy to reduce risk of serious fall-related injury among older adults. The intervention will include identifying at-risk individuals; defining and developing individually-tailored approaches to modify risk factors; and mitigating risk of injury if the individual does fall.

Adults with AFib will be included in the NIA-PCORI study, and the results of this important study will be useful to these individuals and their healthcare providers. The PCORI/NIA collaboration will be active through 2019, and NIH will communicate the study findings through all appropriate channels upon publication. It is important to note, however, that the study does not directly address the use of anticoagulants in older persons with AFib, and that communications about the study's findings will not reference this issue specifically.

In addition to the PCORI/NIA study, NIH also supports a number of other studies on both falls and AFib. For example, a recently concluded project used Medicare claims data to determine the incidence of fall-related major bleeding among adults over age 75 who receive anticoagulation therapy; we anticipate that findings from this study, when published, will influence clinical practice. NIH also supports research on the etiology, diagnosis, and management of AFib among older adults and on prevention of injurious falls in all populations.

Autism Spectrum Disorder (ASD)

The Committee urges NIEHS to continue its collaboration with NICHD and NIMH to fund new opportunities for research on ASD. NIEHS should also enhance its support for experimental and observational research on potential environmental risk factors that may play a role in the initiation or promotion of ASD at any life stage. Further, with respect to regressive autism, NIEHS is encouraged to focus research on the susceptibility of subpopulations to environmental risk factors and consider approaches to the mitigation of environmental risks associated with ASD.

Action taken or to be taken

ASD is characterized by significant impairments in social communication, which may be expressed as a failure of normal back and forth conversation, reduced sharing of interests and emotions, deficits in nonverbal communication and difficulties in adjusting behavior to meet demands of various social settings. Individuals diagnosed with ASD also show restricted and repetitive patterns of behavior and interests such as repetitive motor movements, inflexible adherence to routines and strong preoccupation with unusual objects. Surveillance data show that ASD affects as many as 1 in 68 children in the United States, a trend that is expected to continue to increase. NIEHS continues to provide strong support for new and ongoing research on environmental risk factors that may play a role in the development of ASD. As with most complex disorders, genes and environment appear to work together, and studies are supporting this idea. For example, multiple studies indicate that exposure to traffic-related air pollution during pregnancy and the first year of life are associated with the development of autism. One project also shows that air pollution exposure during pregnancy and functional variation in the MET receptor gene interact to alter the risk of ASD. Another study of gene-environment interaction in autism showed that periconceptional folic acid may reduce ASD risk in those with inefficient folate metabolism. Furthermore, other projects supported by NIEHS have found evidence linking neurodevelopmental disorders with gestational pesticide exposure, whereas prenatal organic mercury exposure has been ruled out as an autism factor. Finally, NIEHS has also supported a study looking at endocrine-disrupting compounds found in environmental pollutants and whether these compounds interfere with the normal expression of RORA (retinoic acid-related orphan receptor-alpha), a hormonally responsive gene that can potentially regulate as many as 400 genes linked to increased risk of ASD.

More recently, NIEHS has collaborated with NICHD and NIMH to fund the initiative, Environmental Contributors to Autism Spectrum Disorders, the purpose of which is to stimulate research in identification and mechanistic understanding of environmental contributors to risk and expression of ASD. Eight new research projects representing a new investment of \$3 million have been awarded through this initiative. These new awards include both animal and human studies that are addressing a wide range of exposures, from air pollution, diet and nutrition, pesticides, to hormonally active agents. A second group of applications in response to this initiative was received this past August.

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 54 and 57 percent of NIH's research budget, excluding amounts allocated to R&D facilities and training, supported basic research during FYs 2005-2014.¹² NIH agrees that countless medical advances result from curiosity about fundamental questions in biology, physics, and chemistry. Basic research provides the foundational knowledge, often built in small increments, 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.

Continued Federal investment in basic biomedical and behavioral research is critical to improving public health and producing tomorrow's scientific breakthroughs. As the private sector primarily focuses on translational and clinical research, NIH funding for extramural and intramural basic research is a necessary balancing factor for the health of the overall national research enterprise. As such, NIH fosters a broad research portfolio and maintains a strong commitment to support basic science in order to achieve its public health mission. Current NIH research efforts in basic biomedical research include, but are not limited to, model organisms and systems, molecular and cellular imaging, genomics and epigenetics, big data studies, microbiomes, structural and systems biology, as well as behavioral science.

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 that cultivates and maintains a diverse, highly-skilled, scientific workforce.

¹² <https://officeofbudget.od.nih.gov/pdfs/FY15/Basic%20and%20Applied%20FY%202002%20-%20FY%202015%20%28Transmit%29.pdf>

Behavioral Health Science Research in NIMH

In addition to the specific interest items, the Committee requests general update in the FY 2017 budget requests for each of the listed disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Mental illnesses are brain disorders expressed as complex cognitive, emotional, and social behavioral syndromes. As such, the National Institute of Mental Health (NIMH) considers behavioral health science research to be of fundamental importance, with a focus on developing objective and precise measures of behavior. The National Advisory Mental Health Council, which advises NIMH, has formed a new workgroup focused on Behavioral and Social Science Research at NIMH. The workgroup has been charged with addressing how new mobile health (mHealth) technologies can be used to achieve more objective and precise diagnosis and treatment of mental illnesses, and how such technologies can be used to predict and prevent mental illnesses and improve quality of mental health practice. NIMH currently supports mHealth research in areas such as online extensions of individual psychotherapy, tools to move evidence-based interventions into remote communities, and HIV treatment and prevention adherence, including the integration of behavioral science with effective biomedical strategies for HIV prevention.

NIMH participates in a variety of trans-NIH behavioral health initiatives, including the Basic Behavioral and Social Sciences Research Opportunity Network (OppNet) and the Science of Behavior Change (SOBC) program, which is supported by the NIH Common Fund.^{13,14} NIMH currently administers five active OppNet grants: two awards focused on epigenetics, brain, and behavior; two awards focused on improving cross-species translation in the behavioral neurosciences; and, one award focused on self-management of depression. NIMH actively participates in the formal evaluation of OppNet's achievements to date, and will continue to participate in future initiatives.

SOBC is an interdisciplinary program that seeks to establish the groundwork for a unified science of behavior change by supporting basic research to improve our understanding of human motivation and maintenance of behavior change across multiple diseases and conditions. This knowledge will in turn be used to develop more effective and economical behavioral interventions. NIMH was actively involved in the development of four SOBC funding opportunity announcements (released in FY 2015) soliciting projects to validate and document assays of promising behavior change targets: self-regulation, stress reactivity and stress resilience, or interpersonal and social processes. As a result, beginning in FY 2016, NIMH staff will oversee an ongoing project investigating self-regulation in the context of co-occurring depression and obesity.

¹³ <http://oppnet.nih.gov/>

¹⁴ <http://commonfund.nih.gov/behaviorchange/index>

Biodefense Spend Plan

The Committee appreciates ASPR's completion of the 5-year spending plan for the medical countermeasure (MCM) enterprise, but notes concerns on the level of detail included in the spend plan for NIAID's biodefense activities. The spend plan offered little insight into the NIAID's spending priorities for the numerous MCM candidates in its portfolio. The Committee requests NIAID, working with ASPR, to provide more detail on NIAID's future goals for MCM research, including its efforts to transition these projects to advanced research at BARDA, and identify how NIAID coordinates with BARDA's on advanced development and procurement priorities. Further, the Committee requests a summary of this information be included in the fiscal year 2017 budget request. The Committee encourages NIAID to focus on biodefense MCM candidates that have received a Material Threat Determination from the Department of Homeland Security.

Action taken or to be taken

National Institute of Allergy and Infectious Diseases' (NIAID's) strategic approach to biodefense and emerging infectious diseases parallels its successful, longstanding research mission. As an active participant in the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), NIAID collaborates on an ongoing basis with ASPR/BARDA and other Federal partners to address chemical, biological, and radiological/nuclear threats, as well as emerging and re-emerging infectious diseases. NIAID transitions high-priority MCMs to BARDA for advanced development, with the goal of FDA approval and possible inclusion in the Strategic National Stockpile.

NIAID's biodefense budget supports research that aligns with the PHEMCE multi-year budget priorities and includes research on: 1) threats for which the Department of Homeland Security has issued a Material Threat Determination (MTD); 2) "Cross-Cutting Science" including basic and translational research, product development, and animal models that could be used for multiple pathogens; and 3) "Other Threats" including basic and immunological research on more than 50 emerging and re-emerging pathogens not enumerated in the multi-year PHEMCE budget

NIAID-funded biodefense research has contributed to the development of a number of MCM candidates addressing threats with existing MTDs. NIAID and BARDA subject matter experts collaborate extensively to discuss promising candidates and plan for smooth transition of products between the agencies. Recent successes include new NIAID-supported therapeutics for Ebola virus disease that have been transitioned to BARDA for further development. ZMapp, a combination of three monoclonal antibodies against Ebola virus, is currently being evaluated in a clinical trial in West Africa and the United States. BCX4430, a broad-spectrum antiviral drug candidate, began clinical trials in early 2015. NIAID support also has advanced three Ebola vaccine candidates into clinical evaluation. In addition, NIAID research has led to the development of several candidate treatments for radiation exposure that have been transitioned to BARDA for further development. Based largely on NIAID-supported data showing that Neupogen, a drug that promotes white blood cell growth, greatly increases survival in animal models of radiation exposure, the FDA recently approved Neupogen to treat adult and pediatric populations with acute exposure to high-dose radiation. NIAID-funded research also supported the decision to proceed with the first human study of hydroxypyridonate, a drug to help remove radioactive material from the body. Other candidate products recently transitioned from NIAID

to BARDA include vaccines for anthrax, influenza, and smallpox, therapies for plague and influenza, and influenza diagnostic tests.

In addition to threats with existing MTDs, NIAID's biodefense budget supports research on "Cross-Cutting Science," which includes basic and translational research applicable to multiple pathogens. These funds provide drug and vaccine development capabilities for known and existing threats as well as newly emerging threats. This support allows NIAID to respond rapidly to emerging public health threats. Examples include the development and use of animal models to evaluate MCMs; MCM clinical research capability; and MCM development for threats such as Middle East Respiratory Syndrome coronavirus, enterovirus D68, and West Nile Virus.

NIAID's biodefense budget also supports research in the "Other Threats" category, which encompasses basic research and immunological research on more than 50 pathogens. Examples include research on emerging and re-emerging diseases such as Lassa hemorrhagic fever, the foodborne pathogens *Listeria* and highly pathogenic *E. coli*, multi- and extensively drug-resistant tuberculosis, the viral illnesses dengue fever and chikungunya, as well as studies of pathogenesis and host responses to disease. This research provides a critical foundation of scientific discoveries that can be rapidly advanced into candidate MCMs in response to public health need.

NIAID currently plans to transition to BARDA more than thirty MCM candidates through FY 2019. These include a Marburg vaccine, therapeutics for anthrax, several broad spectrum antibiotics and antivirals, and a number of treatments for radiation and chemical exposure. NIAID remains committed to advancing research on high-priority MCMs to combat emerging or re-emerging disease threats and chemical and radiological agents, and will continue to share additional details of this research with the Committee. NIAID and ASPR/BARDA will continue to coordinate on programmatic priorities, research advances, and anticipated product transition dates to ensure smooth scientific progression between agencies.

Brain Aneurysms

The Committee notes that brain aneurysm research appears to be a lower priority. The Committee requests an update in the fiscal year 2017 budget request on on-going and planned research related to this issue.

Action taken or to be taken

Brain aneurysms are weak areas in the walls of blood vessels in the brain. Smaller ones cause no symptoms and often go unnoticed, while larger ones can cause symptoms leading to clinical evaluation and detection. Aneurysms can rupture and release blood into the brain tissue, causing hemorrhagic strokes which have high disability and mortality rates. Research on brain aneurysms and hemorrhagic stroke are high priorities at the National Institute of Neurological Disorders and Stroke (NINDS).

NINDS-funded investigators are exploring the fundamental molecular changes in the brain vessels that lead to the formation of aneurysms, inflammatory processes that may exacerbate aneurysm development, genetic risk factors and associated molecular pathways in aneurysms and hemorrhagic stroke, and other factors that determine aneurysm development and predisposition. NINDS also supports a wide range of studies on fundamental brain vessel biology that are contributing to a better collective understanding of the biological processes underlying this condition.

Pre-clinical research is focused on developing new approaches to medical or surgical management of brain aneurysms. For example, NINDS-funded investigators are using computer-based models to simulate aneurysm flow to improve effectiveness of current aneurysm treatment devices, and to identify the best treatment approach by predicting outcomes of alternative strategies. NINDS is funding the testing of a strategy to improve effectiveness and stability of platinum coils that are commonly placed in aneurysms to prevent future rupture, as well as a novel expandable, space-filling polymer device, which offers the possibility of superior aneurysm healing and less likelihood of recurrence. In other projects, investigators are working to identify medical therapies that could reduce the likelihood of aneurysm development and rupture, and to protect brain cells from the devastating consequences of ruptured aneurysms and hemorrhagic stroke. Recent animal studies by NINDS-supported investigators indicate the potential for aspirin to stabilize aneurysms and reduce the rate of rupture-related hemorrhage, pointing to a potential therapeutic strategy for further investigation. NINDS-supported research has also revealed an apparent higher rate of aneurysm formation in post-menopausal women and animal studies suggest that this could be countered by targeted activation of a novel estrogen receptor.

The 2012, NINDS Stroke Research Priorities Meeting identified the need for more comparative effectiveness research studies for stroke treatments and highlighted coiling versus clipping of unruptured intracranial aneurysms as an important topic.¹⁵ Another important outcome of this planning effort is the NIH StrokeNet, a national network of 25 regional clinical research centers and over 200 affiliated hospitals that serves as the infrastructure for implementing high-quality clinical trials testing new treatments for stroke.¹⁶ This research network is well poised to

¹⁵ www.ninds.nih.gov/strokepriorities

¹⁶ www.nihstrokenet.org

evaluate promising new prevention, treatment, or rehabilitation strategies for patients with ruptured or unruptured intracranial aneurysms.

Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative

The human brain remains one of the greatest mysteries in science and one of the greatest challenges in medicine. Neurological and psychiatric disorders, such as Alzheimer’s disease, Parkinson’s disease, autism, epilepsy, schizophrenia, depression, and traumatic brain injury, exact a tremendous toll on individuals, families, and society. The BRAIN initiative, created with a 10-year plan, was expected to require an annual budget of at least \$400,000,000 by fiscal year 2019. The Committee accelerates the requested funding for BRAIN to \$150,000,000 to ensure the initiative stays on track towards its program goals and objectives. The funds are allocated to NINDS, NICHD, NEI, NIA, NIDCD, NIAAA, NIDA, NIMH, NIBIB, and NCCIH on the same pro-rata bases as provided in the budget request. 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 2017 request provides an appropriate level of funding to keep on this path. 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

NIH continues to utilize the external scientific community’s expert recommendations for achieving the goals of the BRAIN Initiative, articulated in *BRAIN 2025: A Scientific Vision*.¹⁷ 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 FY 2015, NIH issued ten funding opportunities 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 with both each other and funded investigators across the Federal Government, in part, through annual BRAIN Initiative Investigators meetings, the second of which occurred in December 2015.

NIH continues to explore ways to broaden the impact of the BRAIN Initiative. Select applications responsive to BRAIN Initiative funding opportunities may be recommended for co-funding through the NIH Institutional Development Awards (IDeA) program. NIH released FY 2016 BRAIN funding opportunities for short courses; technology sharing and propagation; and development of theories, models, and methods of analysis for data gathered from the brain. Further, NIH announced new international partnerships with research funding agencies from Australia and Canada to advance the BRAIN Initiative.

The first wave of funded awards has already resulted in numerous scientific breakthroughs and insights into how individual brain cells and circuits interact. BRAIN investigators developed new technology that offers a rapid, inexpensive, and precise way to analyze the gene activity of thousands of individual cells, as well as a technique for automated 3D reconstruction of discrete brain areas – including identification of all components therein. Additionally, researchers

¹⁷ <http://braininitiative.nih.gov/>

unveiled a new, non-invasive method called photoacoustic tomography that harnesses light and sound to visualize activity of large groups of brain cells.

NIH is encouraging public-private partnerships with manufacturers to facilitate broad access to novel intracranial stimulating and/or recording devices for conducting clinical research. Finally, NIH is engaging small businesses through the release of a set of FY 2015 BRAIN Initiative-associated SBIR/STTR announcements, potentially funding three applications from SBIR set-aside funds.

Recognizing that the NIH BRAIN Initiative – focused on development of new research tools and technologies – will raise important ethical questions related to the conduct and use of neuroscience research, NIH is establishing a neuroethics workgroup of the BRAIN Multi-Council Working Group. Together, these diverse efforts aim to provide the critical knowledge base for researchers aspiring to treat, cure, and even prevent brain disorders. NIH will continue to submit budget requests at levels appropriate to achieving these goals.

Breast Cancer

The Committee is aware of recent news coverage highlighting studies about mammography screening for breast cancer that questions the use and validity of screening for discovering cancers. Although the majority of scientific studies have corroborated the value of early detection of breast cancers through screening, other studies have concluded that screening sometimes results in false positives and over treatment. This has created a less clear picture of the benefits of screening and may lead women to avoid periodic mammography, an experience some women already view as uncomfortable. From 1990 to 2010, deaths from breast cancer decreased by 34%. This drop in breast cancer mortality has been attributed to both improvements in treatment and earlier detection of cancers. However, in 2013, 230,000 new cases of breast cancer were diagnosed in the United States and almost 40,000 women died from breast cancer. Given the current controversies over screening and the need to validate new screening technologies versus existing technologies, it is clear that a new, comprehensive study of these issues is warranted. The Committee encourages NCI to support research to address these issues and to hopefully provide women and physicians with a clearer, more informed picture of how breast cancer imaging should be considered as part of the overall women's health care environment and urges the Secretary not to implement changes to the breast cancer screening recommendations until this research is completed.

Action taken or to be taken

The National Cancer Institute (NCI) continues to conduct and support high-quality research to understand and improve current screening strategies for breast cancer, to develop new screening techniques that will be more effective than current ones, and to evaluate whether screening strategies used to detect cancer actually save lives. The United States Preventive Service Task Force (USPSTF) consistently uses publicly available NCI research results to inform its cancer-related evidence reviews and recommendations. However, NCI does not directly provide screening services or guidelines for the use of such services.

NCI is aware of the growing concerns about the balance of benefits and harms associated with mammography screening. The concerns fall into two categories. First, the reduction in cancer mortality associated with early detection of breast cancer using mammography may decline over time due to more effective adjuvant therapy that has been developed to treat early- and mid-stages of breast cancer. Much of this unequivocal progress in treatment came from NCI-sponsored randomized trials of adjuvant therapy. Nearly all of the randomized trials testing the efficacy of mammography were conducted decades ago, in the pre-adjuvant therapy era. A recently reported and widely publicized Canadian trial was started early in the era of adjuvant therapy and showed no reduction in breast cancer mortality associated with mammography screening as opposed to screening by physical examination.¹⁸ Second, new evidence of harms associated with mammography has emerged in recent years, particularly one known as over diagnosis – the detection of tumors that are non-life threatening yet cause anxiety and are treated with measures that carry risks, such as surgery, radiation, and chemotherapy.¹⁹

The emerging evidence has led to calls for additional studies in the current modern era of breast cancer therapy aimed at clarifying the balance of benefits and harms of breast cancer screening.

¹⁸ Miller AB, et al.: BMJ 2014; doi: 10.1136/bmj.g366

¹⁹ Pace LE and Keating NL: JAMA 2014;311:1327-1335

The ideal or “gold standard” test would be a large randomized trial comparing screening mammography to a control group that does not receive screening mammography, but such a study would not be feasible in the United States. National surveys show that a large proportion of American women continue to get routine screening mammography, with no change in usage after the USPSTF issued its recommendations against routine screening for women ages 40-49 and for changing the interval of mammography for women age 50-74 from annually to every two years.²⁰ Given current practice, a true control group for an optimally informative “gold standard” trial does not seem feasible. Therefore, NCI is actively funding and planning other types of studies to learn more about the benefits and harms of breast cancer screening, and to try to maximize benefits while limiting the harms. Examples of this research are described below.

NCI supports a collaborative network designed to track outcomes of screening mammography in the community, including recall and biopsy rates, and tumor stages at diagnosis. A goal is to explore ways to achieve optimal and reproducible mammography reading in the community. NCI is also soliciting applications for research on the process of screening and subsequent therapy, with a focus on over-diagnosis. This project will compare tumor biology and clinical aggressiveness with the method of detection, including breast imaging, and with the criteria used for diagnosis. The research aims to identify ways to ensure timely follow-up of abnormal findings and initiation of therapy when necessary. 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 institution of unnecessary aggressive treatments. In October 2015, NCI announced funding for a consortium of multidisciplinary scientists focused on identifying early screen-detected “non-progressor” lesions that can be safely followed, with breast cancer as one of the four primary areas of emphasis for the initiative.

Evaluating other (non-mammography) imaging technologies to detect breast cancer is another important research area supported by the NCI. For example, investigators in NCI’s Breast Cancer Surveillance Consortium are evaluating community practice of advanced imaging technologies such as breast MRI, screening ultrasound, and digital breast tomosynthesis (a form of 3D mammography). Assessments of mammographic density in 3D versus 2D are also in progress. NCI is also supporting a clinical trial entitled “Digital Breast Tomosynthesis Guided Tomographic Optical Breast Imaging (TOBI).” In this study, TOBI is combined with digital breast tomosynthesis to determine whether combined images can be used to diagnose breast cancer with significantly improved sensitivity and specificity compared to digital breast tomosynthesis alone. NCI also has a diverse research grant portfolio focused on the clinical development and evaluation of technologies for breast cancer imaging. NCI supports ongoing early phase feasibility trials evaluating a wide range of new technologies to improve mammography screening.

²⁰ Pace LE, et al.: *Cancer* 2013;119:2518-2523

Bridging Interventional Development Gaps BrIDGs Program

The Committee understands the BrIDGs program has supported new drug interventions and encourages NCATS to look for opportunities to encourage additional success.

Action taken or to be taken

The National Center for Advancing Translational Sciences (NCATS) BrIDGs program collaborates with researchers who are seeking therapy development expertise and resources for the advancement of candidate therapeutics, including small molecule drugs, biologics, and gene therapies. The program's goal is to generate the data and clinical-grade material that will enable researchers to file an Investigational New Drug (IND) application with a regulatory authority, such as FDA, to support the conduct of a clinical trial. Researchers partner with NCATS scientists who devise product development plans and conduct late-stage pre-clinical studies such as compound synthesis, formulation, pharmacokinetic studies, and toxicology studies. The most recent call for proposals²¹ to the BrIDGs program was in October of 2015.

Through September 2015, BrIDGs has generated data to support 17 INDs that have been cleared by FDA and one clinical trial application cleared by Health Canada. A total of 14 projects have been evaluated in clinical trials. Five BrIDGs-supported agents have gone as far as Phase II human clinical trials, in which researchers give an experimental therapy to a group of patients to evaluate the effectiveness and safety of a treatment. Third-party organizations have licensed or invested in 10 therapeutic agents during or after their development by BrIDGs. The following are a few examples of BrIDGs projects:

- In February 2015, BrIDGs data and material enabled investigators at the Children's Hospital of Philadelphia (CHOP) to amend a pre-existing intravenous IND for the study of congenital hyperinsulinism. Congenital hyperinsulinism is a rare, inherited disease affecting about 1 in 25,000 to 1 in 50,000 infants. The amended IND will allow CHOP to evaluate the safety of higher doses and longer infusions of a peptide, exendin-(9-39), and eventually assess a more clinically-practical subcutaneous formulation.
- In August 2015, a California-based company, Signature Therapeutics (in a three-way collaboration with Signature Therapeutics, NCATS and the National Institute on Drug Abuse), used BrIDGs' data and material to successfully apply for an IND to study a novel abuse-resistant opioid treatment for chronic pain. The treatment is designed to limit the effectiveness of simple "kitchen chemistry"-based attempts to inject, snort, or smoke the active opioid ingredient.
- Another potential IND is from investigators at the University of Wisconsin, Madison for a small molecule therapy for epilepsy. BrIDGs investigators have manufactured the drug and assessed its safety in animal models. More than two million people in the United States live with epilepsy and about 15 percent do not respond to any currently available anticonvulsants.

²¹ <https://ncats.nih.gov/news/releases/2015/preclinical-proposals>

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. 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.

Action taken or to be taken

NIH agrees that the burden of disease is an integral aspect of setting priorities for biomedical research. Enhancing health, lengthening life, and reducing illness and disability are central tenets of NIH's mission, and NIH allocates resources with the goal of supporting research that holds the highest potential to reduce disease and disability. NIH believes that the best path to alleviating disease burdens involves making smart investments in research projects that are most likely to contribute to improvements in health. Guiding these decisions requires combining information about disease burdens with knowledge about the broader scientific context in a particular discipline.

NIH considers the burden of a disease one of several factors it takes into account when setting priorities and developing strategic plans. Understanding the burden of a disease is a complex process, involving the integration of many potential measurements and data sources. For example, a chronic illness, such as heart disease and an acute infection like influenza, can cause very different burdens in terms of mortality, long-term disability, and quality of life. The best understanding of disease burden requires careful consideration of multiple measurements and sources on a case-by-case basis, which captures a fuller range of burdens that different diseases impose. NIH announced the new burden of disease page on NIH Research Portfolio Online Reporting Tools (RePORT) website on June 19, 2015.^{22,23} The page provides graphical displays of U.S. and global burden of illness data (disability adjusted life years) for 69 categories of diseases that NIH was able to match to NIH's Research, Condition, and Disease Categorization (RCDC) spending categories.²⁴ NIH is also reporting U.S. and global mortality data for as many of these categories as possible. The source data are also available for download on the burden of disease page.²⁵

In addition to burden, NIH also considers scientific opportunities afforded by recent discoveries and technological advances, scientific merit, and portfolio balance in its priority-setting processes. Fields mature at different rates, and the same amount of funding in two fields can lead to very different scientific returns. Sometimes a field is catapulted forward by an unexpected discovery or an advance in technology, such as a better microscope or a new molecular tool, and other times the progress of a field depends on incremental advances in our understanding of healthy physiology and disease processes. NIH believes that advancing human health requires taking advantage of scientific opportunities as they arise, sometimes unexpectedly. In addition, some fields present unique opportunities: the potential for

²² <http://nexus.od.nih.gov/all/2015/06/19/burden-of-disease-and-nih-funding-priorities/>

²³ http://report.nih.gov/info_disease_burden.aspx

²⁴ <http://www.sciencedirect.com/science/journal/01406736/380/9859>

²⁵ <http://report.nih.gov/FileLink.aspx?rid=892>

eradicating a pandemic, such as a universal flu vaccine, or collecting an unprecedented dataset, such as the Precision Medicine Initiative.

NIH only funds research that has undergone a two-stage peer review process and has been judged as highly meritorious. This process ensures that funded grants are of the highest quality as NIH sets priorities and allocates resources. NIH also strives to ensure the diversity and balance of its research portfolio, in order to cast a broad net to cultivate unexpected opportunities for scientific advancements. For example, basic research targeted towards understanding healthy, normal living systems can have the potential to provide useful breakthroughs in many areas of disease treatment and prevention.

NIH believes that a priority-setting process that incorporates all of these factors provides the nimbleness and breadth necessary to shift resources in response to unexpected scientific breakthroughs, to capitalize on scientific opportunities on the horizon, and to address the most pressing public health needs.

Cancer Disparities

The Committee requests NCI and the National Institute on Minority Health and Health Disparities (NIMHD) to prepare a joint update for the fiscal year 2017 budget request on efforts underway and planned to end this disparity, including activities to focus on research, prevention, and treatment of cancer in minority communities.

Action taken or to be taken

NIH recognizes that health disparities in cancer prevention and treatment affect many Americans. Earlier onset of disease, faster progression, greater incidence/prevalence, and poorer outcomes all impact the quality of life and lifespan for individuals who experience cancer health disparities. Health disparities in cancer care also affect the family and caregivers of patients, increasing the need for culturally competent care. Importantly, health disparities affect individuals from many populations, including rural and low socioeconomic status. NIH conducts research on cancer health disparities, as well as minority health surrounding cancer. Both types of research will continue in FY 2017 and are addressed jointly below.

The National Cancer Institute (NCI) supports a variety of research efforts across the cancer control continuum to better understand and address the disparities that exist in cancer incidence, treatment access, and health outcomes. NCI's Community Oncology Research Program (NCORP) enhances Nation-wide access to clinical trials in cancer control, prevention, screening, treatment, and imaging. NCORP's large national network of research bases and community sites allows individuals to access cancer clinical trials and cancer care delivery research within their own communities. Other NCI-funded research projects seek to better understand and promote health behavior change related to cancer risk factors such as tobacco use, diet, and exercise, as well as care-seeking behaviors like cancer screening and follow-up. NCI also supports research that aims to improve methodologies and selection of appropriate research sample sizes that will allow for generalization of findings to racial and ethnic subpopulations across the United States.

The National Institute on Minority Health and Health Disparities (NIMHD) funds research on cancer disparities at many levels including – prevention interventions, basic biological research, screening, clinical trials, and survivorship research. In addition, NIMHD supports the use of community-based participatory research wherever possible to ensure that the context and impact of health disparities are being included in the research. NIMHD supports research in a diverse array of populations who experience health disparities. For example, currently funded projects include research focused on smokeless tobacco cessation among American Indians to reduce oral cancer disparities, interventions shared through Korean churches to reduce Hepatitis B infection and liver cancer disparities, the creation of a social media platform for health care professionals to reduce prostate cancer disparities among African Americans, nutrition interventions with Native Hawaiian expectant and new mothers to reduce obesity and cancer risk, and research on disparities in advance cancer care planning and end-of-life care among Hispanic patients. In addition to individual research projects, NIH supports centers across the United States to improve cancer treatment and prevention. NCI's Center to Reduce Cancer Health Disparities (CRCHD) coordinates and funds initiatives that include the Partnerships to Advance Cancer Health Equity (PACHE), which enable NCI-designated Cancer Centers and institutions serving health disparity populations and underrepresented students to conduct research in cancer and cancer health disparities, train scientists from diverse backgrounds, and effectively deliver cancer

advances to underserved communities. CRCHD also supports increased workforce diversity through individual training awards to underrepresented trainees.

NCI recently established a new Center for Research Strategy to identify new opportunities for research investment and research areas that deserve increased emphasis. A top priority of the Center will be to focus on catalyzing initiatives focused on the biological factors, lifestyle practices, and access challenges that contribute to the unequal cancer burden in populations experiencing health disparities. Within its first year, the Center will host a Cancer Health Disparities Think Tank to bring together experts in basic science, clinical/ translation research, access to care, and cultural/lifestyle factors to discuss opportunities in health disparities research.

NIH will continue to support a strong portfolio of research to reduce cancer health disparities, including an ongoing focus on understanding the role of biology and the interplay of genetic factors with lifestyle, exposure, or access issues that contribute to differences in the cancer burden experienced by various populations. Advances in cancer molecular tools, biomedical technologies, and computational methods are providing new opportunities to understand how biology contributes to health disparities and how biological factors interact with other relevant factors. New interventions and community-based participatory research efforts are impacting prevention, screening, and treatment rates to continue to reduce cancer health disparities across diverse populations.

Cannabidiol Research

The Committee recognizes the potential therapeutic benefits that marijuana and its components may bring to patients with serious medical conditions, including seizures, multiple sclerosis, Parkinson's disease, Alzheimer's, substance use disorders, and neuropathic and cancer pain. The Committee encourages NIH to coordinate a multi-Institute approach to increase research related to potential therapeutic benefits of marijuana and its components, specifically cannabidiol. The Committee requests an update in the fiscal year 2017 congressional justification on the status of research related to this topic.

Action taken or to be taken

NIH recognizes the need for additional research on the therapeutic effects of cannabidiol (CBD) and other cannabinoids. NIH is currently supporting a number of studies on the therapeutic effects of cannabinoids, including studies of the efficacy of CBD for treatment of substance use disorders; cognitive deficits caused by tetrahydrocannabinol (THC); neuropathic pain; epilepsy; and for mitigating the impact of cannabis use on risk for schizophrenia.

In addition, NIH supports basic research on CBD that will help to elucidate the mechanisms of potential therapeutic action. This includes studies evaluating animal models of epilepsy in order to understand the mechanisms underlying CBD's anti-epileptic effects and studies on brain cannabinoid receptor differences in individuals with post-traumatic stress disorder or anorexia. NIH also has the following active program announcements to encourage further research on the therapeutic potential of cannabinoids:

- Developing the Therapeutic Potential of the Endocannabinoid System for Pain Treatment²⁶
- Clinical Evaluation of Adjuncts to Opioid Therapies for the Treatment of Chronic Pain²⁷

To stimulate additional research in this area, the National Institute on Drug Abuse (NIDA), in partnership with the National Institute of Neurological Disorders and Stroke, National Institute of Mental Health, National Institute on Alcohol Abuse and Alcoholism, and National Center for Complementary and Integrative Health, is convening a scientific conference in March 2016 to review the neuroscience of marijuana and cannabinoids, focusing on the pharmacology of the endocannabinoid system, health effects of marijuana, and potential therapeutic effects of marijuana and its constituent compounds, including CBD.

NIH is committed to encouraging additional research on CBD and is working closely with the Drug Enforcement Administration, the Food and Drug Administration, and the Office of National Drug Control Policy to reduce barriers associated with marijuana and cannabinoid research and facilitates more research in this area.

²⁶ <http://grants.nih.gov/grants/guide/pa-files/PA-15-188.html>

²⁷ [Clinical%20Evaluation%20of%20Adjuncts%20to%20Opioid%20Therapies%20for%20the%20Treatment%20of%20Chronic%20Pain%20-%20See%20more%20at%20http://grants.nih.gov/grants/guide/pa-files/PA-14-225.html#sthash.HVjZ5Np1.dpuf](http://grants.nih.gov/grants/guide/pa-files/PA-15-188.html)

Capacity for Data Collection on Severe Maternal Morbidity

The Committee understands there are no uniform definitions of severe maternal morbidity and that uniform definitions would help Federal, State and local agencies and research institutions establish standardized and interoperable processes for surveillance, data collection, and research. The Committee encourages NICHD to work with CDC to hold a multi-stakeholder consensus workshop to identify uniform definitions for severe maternal morbidity.

Action taken or to be taken

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) includes research on a wide range of severe maternal morbidities (SMM) as a core part of its mission and to lessen the rate of maternal mortality in the United States. Working with Federal and non-Federal partners, NICHD has developed a two-pronged approach to address SMM: 1) continued strong support for research on specific health conditions related to SMM, and 2) collaboration on developing uniform and evidence-based definitions that would promote standardized patient care and population-level surveillance and allow comparisons across research activities.

For example, maternal overweight and obesity have been linked to higher maternal and fetal morbidity and mortality, including pregnancy-induced hypertensive disorders and gestational diabetes mellitus (GDM). NICHD is partnering with other NIH Institutes and Centers (ICs) to fund a consortium of clinical sites to test whether lifestyle interventions during pregnancy among overweight and obese women will improve their gestational weight gain and other metabolic outcomes. The consortium has developed a common set of outcomes to assess common objectives, and initial results are anticipated by 2018. In addition, NICHD partnered with the National Heart, Lung, and Blood Institute to support the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b) sleep study to estimate the prevalence of sleep apnea among 3,700 women during their first pregnancy and to determine whether sleep apnea is a risk factor for adverse pregnancy outcomes. Initial analysis showed that sleep apnea during pregnancy was associated with the development of hypertensive disorders of pregnancy and gestational diabetes. These results are of potential clinical importance, since treating sleep apnea during pregnancy may lessen the risk of these maternal outcomes. In 2013, NICHD organized an NIH Consensus Development Conference to address what criteria to use for the diagnosis of GDM. This effort to standardize the diagnosis of GDM – which is a risk factor for SMM – was endorsed by numerous national and international professional societies.²⁸ In addition, NICHD is supporting a study that explores why there are racial and ethnic health disparities in pregnancy outcomes, and another looking at whether pregnant women with epilepsy are at higher risk for preeclampsia, cesarean delivery, preterm labor, or stillbirth.

NICHD has participated in other efforts to define aspects of SMM. In 2015, the NICHD collaborated with several professional societies on a workshop to define maternal chorioamnionitis, a condition in which there is intrauterine inflammation or infection of the fetal/maternal membranes and the placenta that can lead to SMM. Due to lack of uniform definition, management has been inconsistent. Workshop participants developed consensus recommendations, which are expected to be published by late 2015. In recent years, NICHD also sponsored similar conferences to define the stages of preterm and term birth to prevent non-

²⁸ <https://consensus.nih.gov/2013/gdmstatement.htm>

medically indicated deliveries and unnecessary cesarean births, both well-recognized risk factors for SMM. These definitions have been endorsed and issued as practice guidelines for the field.²⁹

Although SMM is not a discrete condition, NICHD is leading the formation of a working group, in collaboration with Federal and non-Federal partners, including the Centers for Disease Control and Prevention, to refine current definitions of SMM (e.g., develop and stratify specific definitions for severe preeclampsia and hypertensive disorders) and to collect high quality data on the occurrence of uterine rupture, thromboembolic disease including stroke, and uncontrolled diabetes, among others. The working group also plans to address mechanisms to track SMM and to develop processes for prevention.

²⁹ <http://www.acog.org/About-ACOG/News-Room/News-Releases/2013/Ob-Gyns-Redefine-Meaning-of-Term-Pregnancy>

Capstone Awards

The Committee expects NIH to pursue the establishment of new grants, called Capstone Awards. Capstone Awards could be made to promote partnership between a senior and junior investigator, to provide opportunities for acquiring skills needed for transitioning to a new role, or other reasons as determined by the NIH Director in consultation with the IC Directors, patient advocacy groups, and industry leaders. The NIH is expected to develop a duration and amount for each Capstone Award by the NIH Director in consultation with the IC Directors, researchers, patient advocacy groups, and industry leaders.

Action taken or to be taken

NIH strives to support both a productive portfolio of research programs and a talented biomedical research workforce that propels the research enterprise. The biomedical workforce is shaped by a complex interplay of factors, such as long training periods, the number of individuals trained, availability of faculty positions at institutions, retirement rates, and the state of the economy overall. NIH can address many, but not all, of the forces that shape the workforce with its programs and policies. Over the years, NIH has been persistent and creative in its efforts to support early career investigators through policy changes and new programs.

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 proposals discussed by the working group was 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. By facilitating the transition of some investigators out of the NIH-funding pool, this may provide opportunities for early career scientists.

NIH is not the only organization discussing such a concept. In January of 2015, the Federation of American Societies for Experimental Biology, which represents 27 scientific societies and over 125,000 researchers worldwide, issued a report called “Sustaining Discovery in Biological and Medical Sciences” with the following recommendation: “Research sponsors should consider creating a transition award for senior investigators.”^{30,31}

To gauge community interest in such an award program, NIH issued a request for information (RFI) in February 2015, NOT-OD-15-064, that described a few potential ideas for how an Emeritus Award (renamed the Capstone Award) could be used, such as allowing senior investigators to complete their projects and help them close out their laboratories; allowing a senior investigator to transition to a new role, such as full time teaching or executive research administration; or allowing a senior investigator to form a partnership with a junior faculty member in order to hand off his or her line of research inquiry. Feedback from the RFI is being used to develop the concept of the Capstone Award program, including the optimal duration and amount for each award.³²

³⁰ <http://www.faseb.org/About-FASEB/Who-We-Are.aspx>

³¹ <http://www.faseb.org/pdfviewer.aspx?loadthis=http%3A%2F%2Fwww.faseb.org%2FPortals%2F%2FPDFs%2Fopa%2F2015%2FSustaining%2520Discovery%2520Report%2520Final.pdf>

³² <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-064.html>

While some skepticism was voiced over social media, over half of the RFI respondents indicated support for the concept. Taking into account the RFI feedback, NIH is in the process of developing the Capstone award concept for further internal discussion. NIH will continue to consider input from stakeholders, such as IC Directors, patient advocacy groups, and industry leaders to further refine the concept of a Capstone Award.^{33,34}

³³ <http://news.sciencemag.org/funding/2015/02/nih-proposal-create-grant-aging-scientists-hits-nerve>

³⁴ <http://www.nature.com/news/nih-plan-to-give-ageing-scientists-cash-draws-scepticism-1.16895>

Cerebral Palsy (CP)

Over 800,000 Americans are impacted by CP and it is the number one motor disability in children. Currently, there are no identified best practices at diagnosis or through the life span, no organized standards of care, no national CP registry, and few proven therapy protocols. The Committee urges NIH to work with scientists and stakeholders to develop a 5- year strategic plan for research on CP prevention, treatment, and cure through the lifespan with the goal of reducing the number of people impacted by CP overall, as well as improving the opportunity for recovery of those already diagnosed. The Committee urges NIH participation in work groups to develop a research registry of individuals with different forms of CP that could facilitate research related to the impact of diverse impairments and health issues on functioning, participation and well-being across the life span.

Action taken or to be taken

Cerebral palsy (CP) refers to a group of disorders that result from damage to the brain, most often before birth, that may affect movement, muscle tone, and posture. The extent of motor impairment and associated problems varies considerably. Although cerebral palsy is not a progressive brain condition, the affected child's symptoms evolve over time. What leads to cerebral palsy is not fully understood but important contributing factors are primarily prenatal or perinatal. These include stroke, hypoxic injury, infections, and genetic susceptibilities, many of which are associated with low birthweight and prematurity.

The National Institute of Neurological Disorders and Stroke (NINDS) supports a wide spectrum of research on cerebral palsy, from laboratory investigations through clinical trials of interventions. Ongoing laboratory research is investigating how pre- and post-natal insults injure the brain, especially the white matter, and identifying potential targets for repairing or preventing damage. Clinical studies are developing better ways to predict which infants are at risk for cerebral palsy and identifying biomarkers of outcomes that will inform potential interventions. This research includes, for example, development of brain imaging methods, research on brain metabolism, and a major study of more than 900 extremely low gestational age neonates, from birth to age nine, to identify early biomarkers of neurodevelopmental disorders, including cerebral palsy. Therapy development includes preclinical studies of potential drug and stem cell strategies and an ongoing clinical trial of erythropoietin as a neuroprotective agent in extremely low gestational age infants. NICHD research on rehabilitation is extremely important for persons with cerebral palsy and complements the NINDS programs.

To identify gaps in research and identify priorities for advancing progress against cerebral palsy, NIH is convening a series of scientific workshops. The first workshop in November 2014 on "The State of the Science and Treatment Decisions in Cerebral Palsy" brought together more than 100 scientists, clinicians, advocates, and other stakeholders to identify the current gaps in the evidence base for therapeutics and interventions and potential strategies to address those gaps. Among other topics, the participants discussed the importance of comparative effectiveness research, in parallel with registries, to build the evidence base for treatments already in use. To address this issue, NIH is working with cerebral palsy patient organizations, whose close ties with the patient community are essential to development of effective registries.

The group also discussed the importance of basic and translational research to develop new treatment approaches, especially enhancing neuroplasticity and neuromodulation strategies. The next workshop in the series will focus on basic and translational research in cerebral palsy.

Children in NIH Research

The inclusion of children in clinical research is essential to ensure that children benefit from important scientific advances. The Committee understands NIH has a formal policy mandating the inclusion of children in research relevant to child health, but it does not systematically track enrollment data to determine if children are actually being enrolled appropriately in clinical research. The Committee recognizes that without better data collection, the Committee is unable to fully exercise its oversight role and researchers are unable to determine whether children as a whole, or particular pediatric subpopulations, are underrepresented in federally funded biomedical research. The Committee directs NIH to collect data and report publicly on the actual numbers of children in the various pediatric age groups that are enrolled in its clinical studies.

Action taken or to be taken

The NIH is committed to the inclusion of all relevant age groups in the clinical research studies and clinical trials it supports; inclusion is essential to ensure that NIH is supporting sound science that will ultimately inform clinical practice to the benefit of all who are affected by the disease or condition under study. Special attention is warranted for both younger and older (over 65 years) participants in the conduct of health research; their inclusion in research must be considered carefully. As directed by the Committee, NIH is pursuing plans to collect age-related inclusion information for research studies to support enhanced analyses and reporting on inclusion by age, while balancing the interests of the scientific research community to minimize the administrative burden imposed by new reporting requirements.

NIH already collects information in grant applications on the planned age ranges to be included in all clinical research projects. NIH assigns codes to funded research projects to designate the involvement of children only, children and adults, or adults only. These data show that, for FY14, 8 percent of NIH extramural grants involved only children, 30 percent involved only adults, and 62 percent involved both children and adults. NIH also currently identifies the age range for participants of trials in ClinicalTrials.gov. NIH is examining various approaches to adapt its current information collections on age of research participants (particularly children under 18 years and adults 65 and older) to facilitate more in-depth analyses.

The collection of age-related data poses a number of special challenges that require thoughtful consideration, including the following:

- Human development is an intrinsic factor that uniquely influences each of the diseases and conditions studied by NIH. For this reason, age as an inclusion criterion must be considered singularly for every clinical research study. Similarly, the best format for collecting, reporting, and interpreting information on the ages of inclusion in research is also complex. Input from experts will be needed to identify the best way to report on age-related inclusion information.
- Unlike sex, race, and ethnicity, there are no clearly defined, scientifically meaningful categories to describe age or establish useful age-related inclusion guidelines across different diseases/conditions. NIH leadership is discussing hosting a workshop involving experts on pediatric and older populations to provide input on the best approaches to

determine the appropriate age groups to be included in research studies involving human subjects. We hope to conduct this workshop in 2016.

- Because age is a complex variable, uniquely involved in each clinical research study, information collection on age of inclusion must be implemented thoughtfully. There is a very real potential for such an information collection to severely increase the reporting burden imposed upon grantees. NIH will identify and pursue the least burdensome approach that can accomplish our goal of understanding how the NIH research portfolio is performing with respect to inclusion of children and older populations.
- Adding to this complexity, the line between childhood and adulthood has been drawn at different ages for different purposes by different organizations and agencies. NIH recently announced a change to its definition for the age of a child. Currently, the NIH policy on inclusion of children defines a child as an individual under 21 years old.³⁵ The definition will be changed to an individual under 18 years old, effective for NIH grant applications submitted for receipt dates on or after January 25, 2016, to reduce confusion among members of the research community regarding the age of consent and the more widespread practice of considering 18 year-olds as adults. This change also better ensures that grant applicants will focus their inclusion plans to address inclusion of children ages 0-17. NIH has received approval from OMB to make this change in its grant application instructions, and the research community was notified of the new definition in NIH Guide Notice 16-010.³⁶
- NIH is currently considering policy developments in other areas related to clinical research; examples include clinical trials registration, results reporting in ClinicalTrials.gov, data sharing, etc. These activities may offer complementary opportunities to enhance our understanding of age in our portfolio, and coordinated development and implementation of these related policies will reduce confusion and minimize burden on the research community.

³⁵ <http://grants.nih.gov/grants/funding/children/children.htm>

³⁶ <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-010.html>

Chronic Obstructive Pulmonary Disease (COPD)

The Committee commends NHLBI for convening an interagency meeting on federal COPD planning. The Committee is eager to review the forthcoming peer-reviewed publications and urges the NHLBI to move forward efforts to address the rising burden of COPD in the U.S. Further, the Committee is aware that Alpha 1 Antitrypsin Deficiency (Alpha 1) is a major genetic risk factor for developing COPD. The Committee encourages NHLBI to convene a group of expert stakeholders and other federal agencies to develop a treatment algorithm for Alpha 1 related disease and a coordinated federal and private approach to increase knowledge that can improve the diagnosing of this disease.

Action taken or to be taken

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death in the United States and causes serious long-term disability. COPD is a progressive disease that makes it hard to breathe. Risk factors for COPD include smoking, environmental exposure, and genetic factors, such as Alpha-1 Antitrypsin (AAT) deficiency. AAT is a protein that normally protects the lungs, but patients with AAT deficiency may develop COPD.

Research supported by the National Heart, Lung, and Blood Institute (NHLBI) has shown that certain treatments and lifestyle changes – such as quitting smoking – can help people with COPD stay more active and slow the progression of their disease. By the time the disease is identified, however, irreversible damage has often occurred. NHLBI-supported research, such as the COPDGene® study and NHLBI’s Trans-Omics for Precision Medicine (TOPMED) program are combining genomics, imaging, and other data to uncover factors that increase or decrease the risk of disease, identify subtypes of disease, and develop more targeted and personalized treatments.³⁷

As the Committee notes, NHLBI is currently working with the COPD Federal Partners Working Group to develop a National COPD Action Plan. Because AAT deficiency is a risk factor for COPD, AAT related lung disease and its treatment will be among the topics discussed in the development of the Action Plan. While the mission of the NHLBI is to support research on diseases, such as AAT, the NHLBI does partner with other organizations on issues such as the provision of treatment. For example, development of the National COPD Action Plan will include patients and their families, health care providers, researchers and representatives of other federal agencies. The working group is currently planning a public town hall meeting to get stakeholder input, and a draft plan describing the expected contribution of Federal agencies to specific goals of the plan will be released in 2016.

³⁷ <http://www.nhlbi.nih.gov/research/resources/nhlbi-precision-medicine-initiative/topmed>

Chronic Pain Research

The Committee applauds NIH for instituting the NIH Office of Pain Policy and for leading the development of the first Federal pain research strategy with the IPRCC. The Committee remains concerned that NIH's investment in pain research is incommensurate with the significant public health and economic impact of chronic pain. The Committee strongly urges NIH to expand its basic, translational, and clinical research efforts in this area, as well as include chronic pain in ongoing NIH initiatives that have potential for yielding significant advancements in this area.

Action taken or to be taken

NIH appreciates the Committee's recognition of efforts to support chronic pain research and develop a Federal pain research strategy. Multiple NIH ICs fund chronic pain research, ranging from basic research into the molecular, genetic, and bio-behavioral basis of chronic pain to clinical studies of potential treatments. In FY 2014, NIH funded \$499 million on pain research, with a large percentage devoted to chronic pain research at \$402 million. This investment has increased significantly over the past 10 years. NIH-funded pain research has yielded exciting advances including a recently published study of an *in vitro* human pain model that allows researchers to study pain signaling mechanisms and test responses to potential analgesics. Another recent study applied a powerful research tool – optogenetics – to induce or inhibit pain using light to activate light sensitive channels in freely moving mice. These models provide non-invasive means to better understand pain signaling and behaviors.

NIH supports chronic pain research through investigator-initiated studies as well as more targeted Funding Opportunity Announcements (FOAs). NIH's Pain Consortium, a collaboration of 25 Institutes, Centers, and Offices, was established to enhance pain research and promote collaboration across NIH. The consortium develops initiatives, supports the development of research resources and tools, and hosts events to promote collaboration and highlight recent advances. Recent FOAs developed and supported by the Pain Consortium institutes and centers include an initiative to help understand the role of cannabinoids in the management of chronic pain to potentially mitigate the high rate of opioid use; and an initiative to bridge expertise in pain mechanisms with translational and clinical expertise to address overlapping chronic pain conditions. The NIH Pain Consortium supported the Pathways to Prevention workshop "*The Role of Opioids in Chronic Pain*," held in September 2014, to examine the long-term effectiveness, safety and harms, and risk mitigation strategies for opioid use in chronic pain. Pain Consortium members participated in a Federal Partners Meeting in January 2016 to identify actionable items from the workshop recommendations.

Large NIH initiatives such as the NIH Neuroscience Blueprint and the NIH Common Fund-sponsored Health Care Systems (HCS) Research Collaboratory also have supported innovative pain research. Several studies were funded through a Blueprint initiative aimed at understanding the mechanisms underlying the transition from acute to chronic neuropathic pain. The goal of the HCS Research Collaboratory is to strengthen the Nation's capacity to implement cost-effective large-scale research studies that engage health care delivery organizations as research partners. Of the seven project awards, two of them are focused on pain: a study testing collaborative care for chronic pain in a primary care setting; and a pragmatic trial exploring the use of imaging in low back pain.

The development of the Federal Pain Research Strategy (FPRS) is an important step towards advancing the federal pain research agenda and furthering research in chronic and acute pain. Planning for this effort began in 2015 and a steering committee of experts has been convened to coordinate the effort. A Request for Information to seek public input on the development of the strategy has been released. FPRS will emphasize the following areas: 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 disparities in pain and pain care.

Chronic Pelvic Pain

In addition, the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Chronic pelvic pain reduces quality of life and productivity and incurs significant health care costs for millions of Americans. Associated conditions include irritable bowel syndrome (IBS), vulvodynia, uterine fibroids, endometriosis, and urologic pain conditions, such as interstitial cystitis/painful bladder syndrome (IC/PBS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). NIH-supported studies in this area are making strides toward better diagnosis, treatment, and prevention of conditions causing chronic pelvic pain. For example, findings emerging from the NIH-supported Multidisciplinary Approach to the Study of Chronic Pelvic Pain Research Network include new insights into the course of these conditions; potential biomarkers; microbiome differences between patients and healthy controls; different, potentially clinically relevant subgroups among people diagnosed with these conditions; and the importance of self-reported symptom “flares” in assessing these conditions and in patient quality of life. Network scientists recently reported a variety of differences in brain structure and function between women with IC/PBS and healthy counterparts; these findings are now being pursued to determine the potential role(s) of these differences in symptom manifestation, maintenance, and amelioration.

NIH renewed the Network in FY 2014 for a second five-year phase to continue studies that could provide a foundation for effective clinical interventions for IC/PBS and CP/CPPS. NIH is also engaged in efforts to explore whether it may be possible to prevent onset and/or progression of lower urinary tract dysfunction, including conditions resulting in chronic pelvic pain, thereby improving health. NIH continues to support a Specialized Center of Research that is elucidating the interplay between gut and brain pathways in IC/PBS and IBS, focusing on sex differences in the development, clinical manifestation, and treatment response in these pain syndromes. NIH also is supporting the IBS Outcome Study, a multi-center, placebo-controlled randomized clinical trial with the goal of determining whether self-administered cognitive behavioral therapy is as helpful as standard therapy with a therapist in reducing IBS symptoms and overall burden. NIH is supporting a clinical trial to compare the safety and effectiveness of two standard treatments for uterine fibroids. NIH continues to implement a research plan for vulvodynia, and is supporting a clinical trial of gabapentin as a treatment for vulvar pain that is currently recruiting patients.

Clinical and Translational Science Awards (CTSA)

The Committee supports the goals of the CTSA program and believes the principles that serve as the foundation of NCATS – public-private partnerships, community outreach, faster access to clinical trials, and distributed patient cohorts – have tremendous potential for addressing the long-standing scientific and operational problems associated with getting treatments to patients, including those with health disparities. Recognizing the value and importance of supporting the full spectrum of medical research, the Committee encourages NCATS to build meaningful relationships between clinical and translational research programs and the various Institutes and Centers. NCATS is encouraged to work closely with the CTSA community and related stakeholders moving forward to continue to identify emerging opportunities and areas for programmatic improvement. Further, the Committee encourages NIH to fund CTSAAs with a history of serving health disparity populations, as well as CTSAAs that address the unmet needs associated with rare diseases, so that research funding provided through the various Institutes can be leveraged to address the clinical and translational research challenges associated with those populations.

Action taken or to be taken

The National Center for Advancing Translational Sciences (NCATS) has developed several efforts within its CTSA Program that support the inclusion of diverse populations in clinical and translational research. In addition to support of centers or ‘hubs’ of clinical and translational research, the program now includes initiatives to stimulate innovation in collaboration, the CTSA Collaborative Innovation Awards (CCIA), and in research recruitment, the Recruitment Innovation Centers (RIC). These activities encourage research that serves special populations such as those associated with health disparities and rare diseases.

The recent funding opportunity announcement for CTSA Program hubs encourages research proposals that not only study aggregate populations, but also focus on subpopulations with distinct characteristics, such as populations affected by health disparities or rare diseases. Applicants are encouraged to include underserved populations, address health disparities, and approach cultural factors as a variable to be examined when developing translational innovations. CCIA initiative is designed to strengthen the network of CTSA Program institutions by supporting collaborative projects that involve three or more CTSA hubs and address improvements to translational research at any stage along the translational spectrum. Areas of opportunities include innovative methodologies that address translational research roadblocks as they relate to special populations.

The RIC Initiative seeks to improve participant recruitment into multi-site clinical trials, a long-recognized problem seen in both rare diseases and health disparities research. Applicants to this program are asked to describe how they will interact with the broader patient community in the planning and implementation of multi-site research studies across a broad range of diverse populations. The funding announcement encourages development of strategies to ensure adequate representation of under-represented populations in clinical research, such as children, the elderly, or minority populations.

The current CTSA Program hubs have community engagement programs and provide infrastructure for other NIH programs to address health disparities in medically underserved

communities. Eight CTSA Program hubs are co-located with NIGMS-supported Research Centers in Minority Institutions Program sites and work collaboratively to develop and disseminate clinical innovations to improve clinical and translational science. For example, the CTSA Program hub at Vanderbilt University Medical Center partnered with the Meharry Medical College Community Engagement Studios to improve the participation of underrepresented minorities in clinical research. The success of this approach has improved recruitment of underrepresented minorities and lead to changes in the design of clinical research and education of community members about clinical research.

CTSA Program hubs also work directly with members of the Rare Disease Clinical Research Network (RDCRN) and its Data Management and Coordinating Center (DMCC). Twenty one of the 22 RDCRN consortia are at institutions with a CTSA Program hub and several of them utilize the CTSA Program resources. It is anticipated that some of the RDCRN investigators will apply for the CCIA and RIC awards mentioned above, and this will lead to continued development of synergy between the network of rare disease researchers and the CTSA program.

On September 3, 2015, NCATS named Petra Kaufmann, M.D., M.Sc., as director of the Center's Office of Rare Diseases Research (ORDR). She will retain her current position as director of NCATS' Division of Clinical Innovation (DCI), which includes the CTSA Program. Dr. Kaufmann has had a longstanding interest in and commitment to rare diseases research. Because of shared science and shared goals among NCATS' ORDR and DCI programs, placing them both under one person's leadership will enhance synergy, increase NCATS' ability to advance translational science and help bring more treatments to more patients more quickly.

Clinical and Translational Science Awards (CTSA) – IOM Recommendation

The Committee is pleased that NCATS is implementing recommendations from the recent IOM report on the CTSA program. NCATS is encouraged to continue to work closely with the CTSA community and related stakeholders moving forward to continue to identify emerging opportunities and areas for programmatic improvement.

Action taken or to be taken

Conducting multisite clinical research in the United States often is associated with implementation delays and high costs. This is due in part to long-standing challenges such as recruiting trial participants, obtaining approval of a single protocol for a multi-site clinical study by multiple institutional review boards, executing research contracts, qualifying clinical sites and initiating study start-up procedures. To address these issues, the National Center for Advancing Translational Sciences (NCATS) released two new program funding opportunity announcements (FOAs) for the CTSA program in 2015, one for Recruitment Innovation Centers (RICs) and the other for Trial Innovation Centers (TICs). Both initiatives are aimed at overcoming key roadblocks to conducting multi-site clinical trials. In combination with the CTSA program hubs, the RICs and TICs will transform multi-site clinical research by developing and institutionalizing innovations that reduce delays in trial start-up, accelerate participant recruitment and harmonize processes across the CTSA hubs that allow research to be conducted more efficiently.

NCATS also released two new FOAs for CTSA Collaborative Innovation Awards, designed to stimulate team-based research across the CTSA Program network. Through these awards, which will be made in FY 2016, NCATS will foster research collaboration by encouraging teams from multiple CTSA Program hubs to work together to develop, demonstrate and disseminate multi-site experimental approaches that overcome translational science roadblocks.

In developing these FOAs, NCATS carefully considered input about the CTSA Program from the Institute of Medicine's 2013 report, a working group of the NCATS Advisory Council, CTSA investigators, patient groups, other NIH ICs, biotechnology and pharmaceutical development organizations, regulatory agencies, and the broader clinical and translational research community.

Additionally, as recommended by the IOM report, the CTSA Program is developing a set of common metrics that will be used for the collaborative strategic management of the program. A preliminary set of metrics will be ready for implementation at a small number of pilot sites in early CY 2016 with a scale-up to all CTSA Program hubs by the end of CY 2016.

Finally, based on the recommendations of the Advisory Council Working Group on the IOM Report, the CTSA Program established five domain task forces (DTFs) in the following areas: Workforce Development; Collaboration and Engagement; Integration across the Lifespan; Methods and Processes; and Informatics. DTFs include NCATS staff, representatives from the CTSA Program hubs, the broader NIH, FDA, and the community. These new domain-specific collaborations are intended to address translational science roadblocks, encourage participation across CTSA Program hubs, demonstrate multi-site utility of innovative approaches, disseminate effective solutions, and develop new methods that can be applied to different disease areas.

Clinical Trial Participation

The Committee encourages NIH to further the discussion with organizations that participated in the July 2014 NIH Clinical Trial Improvement Workshop as it explores methods to improve participation, enrollment, and retention, in NIH supported clinical trials, especially among underrepresented populations. The Committee requests an update on the steps NIH has taken and planned in the fiscal year 2017 budget request.

Action taken or to be taken

Facilitating patient access to and enrollment in clinical trials is an important issue, and NIH appreciates the Committee's ongoing interest. The 2014 workshop on the enrollment and retention of participants in NIH-funded clinical trials brought together a range of stakeholders involved in clinical trials, and it showcased the many innovative approaches that are being taken to facilitate recruitment and retention, particularly of minority and disadvantaged populations. Since the workshop, NIH has been exploring strategies to expand public awareness of clinical trials, to connect patients and investigators, and to address challenges to clinical trial participation. The following are two examples of those efforts.

The National Cancer Institute (NCI) has made a number of significant changes in the structure of its clinical trials network to enhance its efficiency and improve accrual and trial completion rates, including through changes in the amount of per trial support provided to sites. NCI also recently established AccrualNet, a searchable database that provides strategies, tools, and resources to support accrual to oncology clinical trials that includes resources focused on understanding the perspectives of participants and addressing their needs. The National Center for Advancing Translational Sciences (NCATS) is in the process of establishing Recruitment Innovation Centers (RICs) to improve participant recruitment into clinical trials by using innovative means to assess the availability of potential participants and to enroll them in a timely manner. RICs will be expected to interact with the patient community in the planning and implementation of multi-site research studies across a broad range of diverse populations, to engage research participants as active partners in the research enterprise, and to minimize the burden on participants who are interested in information or access to the trials.

NIH is also taking steps to enhance its stewardship of NIH-funded clinical trials, including efforts to promote the inclusion of women, minorities, and sub-populations, as appropriate, in clinical trials. NIH has a long-established policy promoting the inclusion of women and racial and ethnic minorities in clinical research and clinical trials. It requires investigators seeking NIH funding to address how women and racial and ethnic minorities will be included in their research studies. The proposed inclusion plans are assessed during the peer review process and any concerns are resolved prior to funding. Funded investigators are required to report at least annually how many women and minorities have been recruited into their studies, and NIH staff are responsible for monitoring those enrollment levels as the research proceeds. In the last several years, NIH has taken a number of steps to strengthen the monitoring process, including through the launch of a new data system to facilitate communication between investigators and NIH staff with oversight responsibilities. NIH will be issuing a policy to help speed the initiation of clinical research by ensuring that trials conducted at more than one site need not undergo redundant reviews prior to enrollment. NIH also is working to increase access to information about open clinical trials and results from completed studies through

ClinicalTrials.gov, a web-based resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions.

Colorectal Cancer

The Committee encourages support of meritorious scientific research on colorectal cancer to better understand the biology of young-onset colorectal cancer. Specifically, the Committee requests an update in the fiscal year 2017 budget request related to research activity on the biology of young-onset colorectal cancer in adults under the age of 50.

Action taken or to be taken

Each year in the United States, nearly 70,000 adolescents and young adults between the ages of 15 and 40 are diagnosed with cancer.³⁸ While overall cancer survival rates have increased, there has been little improvement in survival for the adolescent and young adult population since 1975, and the incidence of colorectal cancer in adolescents and young adults has been increasing in recent years.

Recognizing the gap in knowledge about cancer in this population, in 2006 NCI partnered with the LIVESTRONG Young Adult Alliance to produce a report identifying research opportunities and recommendations for improving the care and outcome of adolescents and young adults with cancer. The National Cancer Institute (NCI), LIVESTRONG, and other stakeholders and research partners have continued to support efforts to implement these recommendations. In 2009, NCI and LIVESTRONG convened a workshop entitled: *Unique Characteristics of Adolescent and Young Adult Cancers: Focus on Acute Lymphocytic Leukemia, Breast Cancer, and Colon Cancer*, and in 2013 LIVESTRONG and the Institute of Medicine sponsored a workshop to further explore the needs of adolescents and young adults with cancer. In addition to understanding the psychological and social needs of adolescents and young adults with cancer, examining the current state of basic and translational research has been a focus of these working groups. More specifically, investigating the potential biological basis of age-related differences in outcome for adolescent and young adult cancers is an important part of these efforts because the results of such studies could lead to better understanding of adolescent and young adult cancer biology, facilitate the development of new diagnostic markers, and identify novel therapeutic targets and treatment approaches for adolescent and young adult patients.

The incidence of adolescent and young adult colon cancer is low compared to that of adults, comprising two to six percent of cases; however, the number of deaths is approximately 800 annually. Recent data demonstrates that around five percent of colorectal cancer cases are diagnosed in patients younger than 45 years. Colon cancer in the adolescent and young adult population tends to be detected later, is more aggressive, and is typically more unresponsive to standard treatments. Through its Division of Cancer Treatment and Diagnosis, the NCI is supporting a study to discern any mutation differences between the genomes of colon cancers in adolescent and young adult patients compared to those found in adults. This is being accomplished in collaboration with scientists at two NCI-designated comprehensive cancer centers, the Mayo Clinic and the St. Jude Children's Hospital, along with NCI's Center for Cancer Research and Frederick National Laboratory for Cancer Research. NCI's hypothesis is that the tumors of adolescent and young adult patients with colon cancers will exhibit different mutational profiles from those found in the adult form of the tumor, and thus may reveal novel molecular targets and pathways for diagnosis and treatment. To identify differences in the mutational profile between adolescent and young adult and adult colon cancer tumors, NCI-

³⁸ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3079851/>

supported investigators are using DNA sequencing methods to analyze the tumor genomes from these two groups of patients and then compare their mutational profiles. 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 colon cancer. Investigators are currently working to validate these mutations.

In addition, complimentary efforts are underway through the NCI Specialized Program of Research Excellence, an investigator initiated grant program. NCI supported a pilot project on the genomic features of young onset colorectal cancers. The aim of the study was to examine the molecular characteristics of colorectal tumors diagnosed in young individuals (under the age of 50) with the goal of identifying germline mutations and somatic molecular alterations in tumors that may represent potential drivers of carcinogenesis.

Common Fund

The agreement notes continued support for the Common Fund High Risk High Reward (HRHR) programs, such as the Pioneer, New Innovator, and the Transformative R01 awards. The HRHR awards have shown great success over the years. The agreement requests an update in the fiscal year 2017 budget request on how HrHR awards are supported through the Common Fund and across the NIH ICs.

Action taken or to be taken

Common Fund's (CF) High-Risk, High-Reward (HRHR) program supports exceptionally creative scientists in any area within the NIH mission through four complementary initiatives:³⁹

- Pioneer Award: supports extraordinarily creative scientists proposing bold approaches to address major challenges in biomedical and behavioral research
- New Innovator Award: supports exceptionally creative, early career investigators who propose innovative, high-impact projects
- Transformative Research Award: supports unconventional, paradigm-shifting research projects that are inherently risky; allows teams of investigators
- Early Independence Award: bypasses the traditional post-doctoral training period by helping establish independent scientific careers for newly graduated scientists with the intellect, creativity, drive, and maturity to flourish independently

This program has a strong record of supporting groundbreaking, high-impact research. Recent discoveries funded through these awards include the demonstration that HIV dormancy is controlled by the virus, which helps it escape drug therapies and increase its spread through latent infected cells; brain “rebooting” treats lazy eye in mice; and intestinal bacteria regulate production of a human mood-setting neurotransmitter.

In part as a response to an evaluation of the Pioneer program that demonstrated high levels of innovation and impact, we initiated a budget policy for the HRHR program in 2013 in which Pioneer and Transformative Research Awards were to be co-funded between the Common Fund and the ICs. This led to a gradual decrease in the Common Fund HRHR budget, as ICs paid non-competing commitments on new awards. Although this policy reflected enthusiasm voiced by IC Directors about these initiatives, the budget policy has been difficult to implement in practice, since the work supported by these grants often falls at the interface of multiple ICs. In addition, some ICs have developed similar types of awards. To stabilize the HRHR budget, the Common Fund is beginning in FY 2016 to once again fully fund Pioneer and Transformative Research Awards. As new awards are issued each year, costs for each cohort will build on top of commitments from prior year awards. This will result in a gradual increase in the HRHR budget over the next few years to reach a steady state of approximately \$192 million in FY 2020.

NIH ICs also have their own existing and emerging high-risk, high-reward or flexible “person-focused” initiatives. These include the National Institute on Drug Abuse’s Avant-Garde Award for HIV/AIDS research and Avenir Award for Research on Substance Abuse and HIV/AIDS, the National Institute of Mental Health’s Biobehavioral Research Awards for Innovative New Scientists, the National Institute of Environmental Health Sciences’ Outstanding New

³⁹ <http://commonfund.nih.gov/highrisk/index>

Environmental Scientist Award, the National Cancer Institute's Outstanding Investigator Award, the National Institute of General Medical Studies' Maximizing Investigators' Research Award, and the National Institute of Neurological Disorders and Stroke's Research Program Award.

Through CF and NIH ICs, high-risk research is expanding across NIH, consistent with the intent of the CF to serve as an "incubator" space to pilot new approaches to supporting research. Investigator-initiated (R01) awards are and will continue to be the primary component of NIH-funded research portfolio. However, high-risk, high-reward awards may be particularly useful in stimulating creativity and supporting researchers with transformative and innovative ideas.

Community Based Participatory Research (CBPR)

The Committee is aware that CBPR is an applied collaborative approach that enables community residents to more actively participate in the full spectrum of research. The Committee requests NIMHD to provide an update in the fiscal year 2017 budget request on any CBPR activities its supports and the most appropriate role for CBPR within the NIMHD portfolio.

Action taken or to be taken

The National Institute on Minority Health and Health Disparities (NIMHD) supports community-based participatory research (CBPR) across the NIMHD portfolio. CBPR promotes a collaborative approach that engages both scientific and community partners in the translational research process to improve health and address health disparities. The participatory research process is such that community members, persons affected or impacted, public health and policy professionals, and other key stakeholders in the community's health have the opportunity to be full participants in each phase of the research including conception, design, conduct, analysis, interpretation, communication, and dissemination of the results. Using CBPR approaches provides many benefits, including the creation of bridges between the community, scientists, and policy professionals to facilitate the bidirectional transfer of knowledge and skills, improve community research literacy, and create of appropriate and effective interventions.

Since 2005, NIMHD has supported a unique CBPR initiative which addresses the need for improved transdisciplinary intervention research methods and approaches for addressing health disparities. This initiative also strengthens the science of community engagement in addressing health disparities in socially disadvantaged populations and communities. This initiative uses a unique, three-phase funding process to support the intensive partnership and coalition-building that is needed to develop meaningful, successful research that enhances a CBPR approach. NIMHD's CBPR initiative begins with a three-year planning phase, to allow all stakeholders to develop the strategic relationships, processes, and research framework for a particular disease or condition affecting the community and determine and pilot an intervention. The second phase is a competitive five-year intervention grant, which allows a promising, broad-scale intervention to be implemented and evaluated by the team. The final phase is a competitive three-year dissemination grant, which allows the results of effective intervention to be meaningfully shared within the community and in scientific publications, as well as provides resources for disseminating effective interventions. Grant awards in all three phases are based on scientific merit, progress, quality of the research proposal, and availability of funds.

This eleven-year funding cycle has created long-lasting partnerships between the scientific and community members to address health disparities related to major diseases of public health importance such as diabetes, cancer, cardiovascular diseases, HIV/AIDS, and hepatitis B. These projects will be completing the first cycle of this unique initiative in FY 2016. The second cycle of the CBPR initiative is now underway and the grantees in the planning phase are completing their pilot interventions and have applied to the intervention phase. In May 2015, NIMHD began to solicit applications for the second intervention phase with funding in FYs 2016 and 2017. NIMHD will ensure that CBPR principles and community engagement are included in health disparities research across all relevant NIMHD programs.

Conflict of Interest

The Committee encourages NIH to review and clarify conflict of interest policies to ensure more effective and transparent industry/institutional research collaborations.

Action taken or to be taken

In accordance with the preamble to the financial conflict of interest (FCOI) regulations at 42 CFR part 50 Subpart F, which were revised in 2011, a review on the effect of provisions of the regulation is required within three years of its implementation. NIH is currently considering actions, in conjunction with the American Association of Medical Colleges (AAMC) that can be taken to clarify the regulations. These regulations are intended to increase accountability, add transparency, and enhance regulatory compliance and effective Institutional management of an Investigator's financial conflicts of interests that are related to Public Health Service-funded research.

Following the implementation of the revised FCOI regulation, AAMC conducted a study (the Conflict of Interest Metrics Project) to determine the effect and effectiveness of the revised regulations on institutions, faculty, and staff⁴⁰ and assist in the review of the final rule. The study results were based on annualized FCOI regulation compliance data from member medical schools and teaching hospitals. NIH is currently reviewing the study results in conjunction with its own data to determine if actions should be taken to clarify regulatory requirements, promote efficiency, and reduce administrative burden associated with the regulation while ensuring that proper oversight, transparency and objectivity of research is maintained.

NIH has been actively engaged with the grantee community to ensure appropriate implementation of the 2011 revised FCOI regulations. As a result of NIH's oversight and monitoring efforts over the last three years, NIH has gained valuable insight and information from reviewing and evaluating FCOI report data and grantee FCOI policies. Data maintained by NIH on grantee FCOI reporting has served to identify potential areas where clarification and/or modification could improve efficiency and reduce grantee burden.

In the coming fiscal year, NIH anticipates that it will complete a review of the regulation and identify areas for potential clarification to ensure effective and transparent research collaborations.

⁴⁰ <https://www.aamc.org/initiatives/research/coi/metricsproject/>

Congenital Heart Disease

In addition to the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

The National Heart, Lung, and Blood Institute (NHLBI) supports research on the causes of congenital heart disease (CHD); improved treatments, outcomes, and quality of life; and potential pathways towards prevention. The NHLBI's Bench to Bassinet (B2B) Program fosters translation of basic research findings in heart development and genetics into improved treatment for congenital heart defects through its Cardiovascular Development Consortium (CvDC), which supports basic science research that characterizes the molecular networks and pathways that control heart development; the Pediatric Cardiac Genomics Consortium (PCGC), which is identifying genetic and epigenetic causes of CHD; and the Pediatric Heart Network (PHN), which conducts research studies in children and young adults with CHD or acquired heart disease.^{41,42} PCGC recently showed that about 10 percent of CHD cases are due to new genetic mutations in that individual, rather than inheritance of a disease-causing version of a gene from the mother or father and that these mutations affect a specific biological pathway that is critical to aspects of human development, including the brain and the heart.⁴³ NHLBI recently renewed support for the basic science (CvDC) and genomics (PCGC) components of the program. With its renewed funding, B2B will build upon its successes and seek to understand more about what leads to the development of a healthy heart, and identify potential treatments for children and adults with CHD.

NHLBI also supports research to advance the field of adult congenital heart disease (ACHD) in partnership with the Adult Congenital Heart Association (ACHA) and the Alliance of Adult Research in Congenital Cardiology (AARCC). For example, NHLBI funds an AARCC collaborative pilot study evaluating medical therapy used to treat enlarged aortas in the setting of bicuspid aortic valve, the most common congenital heart defect. To further research in ACHD, in June 2014, a working group hosted by NHLBI and ACHA assessed the current gaps in knowledge about ACHD and identified high-impact research topics for the field.⁴⁴

⁴¹ <http://www.pediatricheartnetwork.com/>

⁴² <http://www.benchtobassinet.com/>

⁴³ <http://www.nature.com/nature/journal/v498/n7453/full/nature12141.html>

⁴⁴ <http://www.nhlbi.nih.gov/research/reports/2014-achd-emerging-research>

Coordination with CDC

The Committee remains concerned regarding the duplication of efforts and overlapping of responsibilities and funding priorities between the NIH and CDC. The Committee encourages NIH and CDC to coordinate further on cross-cutting initiatives, ensuring that each funds programs within its respective core mission. The Committee requests an update in the fiscal year 2017 budget request how each NIH program coordinates with the CDC Centers.

Action taken or to be taken

NIH coordinates and collaborates with the CDC on complementary activities as they align with the mission of each agency, as emphasized in the *NIH-Wide Strategic Plan, Fiscal Years 2016–2020*.⁴⁵

NIH and CDC also work together on U.S. government-wide strategic planning initiatives, such as the development of the *National Strategy for Combating Antibiotic-resistant Bacteria (CARB)*, which includes specified and coordinated activities for different agencies, including NIH and CDC.⁴⁶ Now that *CARB* has been released, NIH and CDC continue to collaborate on the implementation phase. For example, NIH is funding, with technical assistance from CDC, a challenge award for the first group(s) to develop a rapid, point-of-care test that can be easily used by health care professionals in real-world settings.

One way in which NIH coordinates its activities with the CDC is through involvement of both agencies on many federal interagency coordinating committees and working groups which bring together the relevant agencies so that their strategic planning and programmatic activities may be well informed and harmonized. NIH and CDC are together on many such committees, including the HHS Biosafety and Biosecurity Coordinating Council, the Interagency Autism Coordinating Committee,⁴⁷ the Interagency Pain Research Coordinating Committee,⁴⁸ and the Public Health Emergency Medical Countermeasures Enterprise, to name a few.⁴⁹

NIH is also working closely with CDC, and other HHS agencies, to improve clinical research methodologies in a variety of important areas, such as timely reporting of clinical trial results.⁵⁰ These and other steps will increase the rate at which clinical research findings inform current areas of scientific inquiry and stimulate entirely new avenues for biomedical research, which could in turn spark ideas for further treatment and prevention strategies.

NIH and CDC also foster a strong collaborative spirit through the coordination of research initiatives that address topics of mutual interest. Recent collaboration between CDC and NIH on surveillance and initiation of clinical trials of candidate vaccines against Ebola virus disease in West Africa is one noteworthy example.⁵¹ Other initiatives that NIH and CDC are jointly involved in include: the National Collaborative on Childhood Obesity Research,⁵² which aims to

⁴⁵<http://www.nih.gov/about-nih/nih-wide-strategic-plan>

⁴⁶https://www.whitehouse.gov/sites/default/files/docs/carb_national_strategy.pdf

⁴⁷<https://iacc.hhs.gov/>

⁴⁸<http://iprcc.nih.gov/>

⁴⁹<http://www.phe.gov/Preparedness/mcm/phemce/Pages/default.aspx>

⁵⁰<http://www.nih.gov/news-events/news-releases/hhs-nih-take-steps-enhance-transparency-clinical-trial-results>

⁵¹<http://www.niaid.nih.gov/topics/ebolamarburg/research/pages/default.aspx>

⁵²<http://nccor.org/index>

accelerate progress in reducing childhood obesity; the Search for Diabetes in Youth Study, a national multi-center study aimed at understanding more about diabetes in this population;⁵³ 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.⁵⁴ These examples represent just a fraction of the research collaborations involving NIH and CDC.

In order to ensure a strong message reaches the public, NIH and CDC also frequently collaborate on their outreach and education programs designed to communicate biomedical health research findings, and their implications to the public. Examples of these include: Go4Life,⁵⁵ an exercise and physical activity information initiative; and AIDSinfo,⁵⁶ which offers access to the latest, federally approved HIV/AIDS medical practice guidelines, HIV treatment and prevention clinical trials, and other research information.

Looking forward, NIH and CDC will continue to coordinate and collaborate on cross-cutting initiatives, while ensuring that each funds programs within its respective core mission.

⁵³ <https://www.searchfordiabetes.org/dspHome.cfm>

⁵⁴ <http://www.cdc.gov/nchs/nhis.htm>

⁵⁵ <https://go4life.nia.nih.gov/>

⁵⁶ <https://aidsinfo.nih.gov/>

Deadliest Cancers

While overall cancer incidence and death rates are declining, the Committee is concerned that some cancers, often referred to as recalcitrant cancers, continue to have a 5-year survival rate below 50 percent. The Committee is pleased that NCI has released Scientific Frameworks for pancreatic ductal adenocarcinoma [PDAC] and small cell lung cancer, as called for by the Recalcitrant Cancer Research Act. The Committee recognizes that NCI supports critical research efforts exploring potential advances for other recalcitrant cancers and conducts scientific meetings and other horizon scanning efforts to stimulate research in these fields. The Committee looks forward to an update in the fiscal year 2017 CJ on research underway focusing on recalcitrant cancers in addition to PDAC and small cell lung cancer.

Action taken or to be taken

While there have been tremendous advances in cancer prevention, diagnosis, and treatment over the past several decades, a decline in the overall cancer death rate in the United States since the early 1990s, there are some cancer types for which there has not been great progress. When we consider potential for impact on these cancer types, it is important to note that progress in cancer research has changed our understanding of cancer. We now recognize that cancer is a collection of many diseases that no longer fit neatly into organ-specific categories, and data from The Cancer Genome Atlas (TCGA) has enabled extensive characterization of cancer genomes as well as associated analyses across cancer types that have shown that some cancer subtypes may be more similar to each other than to others from the same organ site. These cancer types also 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, but have not yet been considered for that particular subtype. In other words, seemingly dissimilar cancer types may share a vulnerability for which a drug is already available. NCI is supporting new projects to expand on these analyses, including a clinical trial assigning treatment based on the genetic abnormalities of a patient's tumor, rather than on the organ site of the tumor. This trial, NCI's Molecular Analysis for Therapy Choice (MATCH) study, is part of the Precision Medicine Initiative's oncology efforts, and will evaluate 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.

To identify the most promising ideas from the field, we engage in a highly collaborative process that draws upon our external advisory groups and steering committees, the expertise of NCI program leadership, and opportunities to convene expertise via workshops to discuss the state of cancer research in many scientific disciplines, and to consider new opportunities. Topics of such workshops in recent years include pancreatic cancer, small cell lung cancer, liver cancer, pediatric cancer genomics, cancer immunology and immunotherapy, as well as a trans-NIH meeting focused on pancreatitis, pancreatic cancer, and diabetes, convened in partnership with our colleagues at the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute of Diabetes, Digestive Disorders, and Kidney Disease (NIDDK).

NCI's approach to stimulating research in these critical areas is to evaluate the scientific landscape for difficult problems that have a major impact on cancer biology, diagnosis, or treatment, and need additional emphasis. It is important that NCI be alert to new and existing scientific opportunities that could blossom with more support, and retain flexibility to support

research to gain an in-depth understanding of unanticipated successes, as well as why some treatments, diagnostics, or other approaches are ineffective. NCI's considerations must include assessing how changes in molecular classification affect the diagnosis of "cancer," what sort of new tests need to be developed, and how we can reach these ever-smaller subsets of patients.

Diabetes

In addition, the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

NIH supports research to: identify the genetic and environmental causes of type 1 and type 2 diabetes; prevent or reverse these diseases; develop cell replacement therapy to restore insulin production; improve diabetes management and care; and prevent or reduce diabetes complications. For example, tremendous progress has been made toward developing artificial pancreas technologies, which would automate glucose sensing and insulin delivery, and NIH is now making awards for clinical trials to expand further testing of these technologies toward FDA approval.

Strides are also being made in the field of islet transplantation, a promising therapy for people who suffer from severe hypoglycemia unawareness, in which patients are not aware of having dangerously low and even life-threatening blood sugar levels. Researchers have discovered how to generate large quantities of insulin-producing beta cells in the laboratory. Current research efforts through the Human Islet Research Network are building on this progress.

The Environmental Determinants of Diabetes in the Young study is following newborns at high genetic risk of type 1 diabetes until they are 15 years old to identify factors in the environment that may trigger disease onset or protect against it. Such knowledge could revolutionize our ability to prevent the disease.

The Accelerating Medicines Partnership T2D Project has developed and is continuing to augment and expand a Knowledge Portal. This portal will leverage the dramatic NIH-led progress in understanding type 2 diabetes genetics to identify and validate the most promising biological targets for new diagnostic and drug development. The Restore Insulin Secretion Consortium, is assessing whether aggressive glucose lowering in those with prediabetes and early type 2 diabetes will lead to recovery of beta-cell function that will be sustained after treatment. Glycemia Reduction Approaches in Diabetes: An Effectiveness Study is comparing the long-term benefits and risks of four widely used diabetes drugs in combination with metformin, the most common first-line medication for treating type 2 diabetes.

The Diabetes Prevention Program Outcomes Study (DPPOS) continues to monitor the health of participants in the landmark DPP to determine long-term outcomes and efficacy of the DPP interventions for people at high risk of type 2 diabetes. Major findings from this study include: lifestyle intervention is effective for at least 14 years; the health benefits of this intervention are so significant that it reduces the need for other health care so that its net cost at 10 years is very low. Metformin confers less benefit but is so inexpensive that it actually saves a modest amount of money. Finally, although both lifestyle and drug interventions are effective in people with risk genes for diabetes, specific genetic variants were found to influence the effectiveness of metformin, an important precision medicine discovery. NIH will soon launch a new phase of DPPOS to determine whether metformin may prevent cardiovascular disease and cancer. DPPOS also helped show that women who develop gestational diabetes (GDM) during

pregnancy are at greatly increased risk for developing type 2 diabetes in the 5 to 10 years post-partum, and their babies are at increased risk for obesity and diabetes later in life. However, results from the Hyperglycemic and Adverse Pregnancy Outcome (HAPO) study have suggested that elevated blood sugar even below levels diagnostic of GDM is associated with adverse outcomes for mother and newborn around the time of birth. Longer term follow-up of the HAPO participants is ongoing to determine whether having elevated blood sugar (but below GDM levels) during pregnancy influences later levels of body fat in children and development of diabetes in mothers after giving birth.

Down Syndrome

The Committee supports this priority, and urges NIH to take steps to develop a system for measuring the differences in variability related to co-occurring psychiatric or medical conditions and genetic differences among individuals. Further, the NIH Research Plan on Down Syndrome, updated in December 2014, proposes that high priority consideration also be given to developing a Down Syndrome biobank, linked and coordinated with DS–Connect™, the Down Syndrome Registry to systematically collect, store and distribute brain and other tissue samples to Down syndrome researchers. Such a repository could leverage and be linked with the NIH NeuroBioBank and the existing Alzheimer’s Disease Brain Banks so that Down Syndrome tissues can be compared to those obtained from individuals with Alzheimer’s disease and other disorders. The Committee requests an update in the fiscal year 2017 CJ.

Action taken or to be taken

Down syndrome (DS) is a condition caused by having an extra copy of chromosome 21 and is associated with intellectual disability, birth defects, and other adverse health conditions. NIH is currently supporting a wide range of research on DS, including studies aimed at improving our understanding of different medical conditions associated with DS, such as congenital heart defects (which occur in about half of individuals with DS), obesity, and sleep disorders. For example, the *Eunice Kennedy Shriver* National Institute of Child Health and Development (NICHD), in conjunction with the National Institute of Mental Health (NIMH), sponsored a workshop in June 2014 on “Mental Health in Intellectual and Developmental Disabilities: Research Challenges and Opportunities,” to address barriers in the diagnosis, treatment, and management of co-occurring psychiatric conditions in those with intellectual disabilities including DS.

In late 2014, NIH published a revised research plan, “Down Syndrome Directions: The National Institutes of Health Research Plan on Down Syndrome,” which includes a bibliography of 340 publications resulting from NIH funding since the original 2007 plan was published.⁵⁷ Following extensive public comment, the revised plan comprises research objectives covering five broad topics related to DS research, including a new section on “Down Syndrome and Aging.” One objective, identified by the research community as an urgent need, is the development of reliable, validated outcome measures for clinical trials for people with DS, which would be useful for the development of treatments that could improve their lives. A workshop sponsored by NICHD in April 2015, “Outcome Measures for Clinical Trials in Individuals with Down Syndrome,” convened three working groups around the topics of cognition, behavior, and medical/physical issues associated with DS. Work is ongoing within these three groups to validate and develop specific measures in these domains, in preparation for publication.

NICHD, in partnership with the public-private Down Syndrome Consortium, continues to sponsor and promote DS-Connect[®], a patient registry with nearly 3,200 participants with DS. The registry collects voluntary subject- and family-entered demographic and medical information about people with DS, on a secure and confidential web platform.⁵⁸ In addition, since the launch of a professional portal in December 2014, over 100 professional accounts have

⁵⁷ [https://www.nichd.nih.gov/publications/pubs/Documents/DSResearchPlan_2014.pdf#search=Down Syndrome Directions](https://www.nichd.nih.gov/publications/pubs/Documents/DSResearchPlan_2014.pdf#search=Down%20Syndrome%20Directions)

⁵⁸ <https://dsconnect.nih.gov/>

been established, and a growing number of investigators are utilizing the data to recruit for and complete research projects on DS, such as tracking feeding behaviors in children with DS, learning more about how people with DS find their way, and understanding the complication of hypothyroidism in infants with DS. The registry can facilitate linkages to other data repositories and to tissue and brain banks as they are developed, by using a secure Global Unique Identifier that protects personally identifiable information about participants with DS.

NIH has participated in several recent meetings of the DS and Alzheimer's disease (AD) research communities, to understand better the early onset of AD that affects many adults with DS, and increase understanding of both conditions. Discussions are ongoing to develop linkages among DS-Connect[®], the NIH NeuroBioBank, and the brain banks funded as part of the National Institute on Aging (NIA)-supported Alzheimer's Disease Research Centers. To facilitate these efforts, NIA and NICHD jointly issued a Request for Applications in 2015 to identify biomarkers of AD in DS. These awards will help identify relevant and sensitive markers in the adult DS population (a group with pre-existing intellectual disability) that will predict cognitive decline in AD, with the goal of facilitating treatment development.

Drug Allergy

The Committee is pleased that NIAID sponsored a workshop to develop a research agenda on the diagnosis and management of patients with drug hypersensitivity. The Committee requests an update on steps that are being taken to implement the recommendations from the report of that workshop in the fiscal year 2017 CJ.

Action taken or to be taken

Allergic reactions to drugs and their potential to compromise the treatment of infectious or chronic diseases are serious public health concerns. Drug allergy is caused by Immunoglobulin E (IgE)- and non-IgE-mediated mechanisms, and can in part be determined by genetic susceptibility. The clinical manifestations of drug allergy can vary from mild reactions to severe IgE-mediated anaphylaxis or blistering diseases such as toxic epidermal necrolysis (TEN), a potentially life-threatening dermatologic disorder. The National Institute of Allergy and Infectious Diseases (NIAID) has a longstanding commitment to basic, translational, and clinical research on allergic and immune-mediated diseases. These efforts have helped inform our understanding of the mechanisms of allergic reactions, including allergies to medications, and have led to the development of promising prevention and treatment strategies.

NIAID is working in partnership with other NIH ICs to advance research in the field of drug allergy. In March 2013, NIAID sponsored the Drug Allergy Workshop focused on developing a prioritized research agenda for drug allergy. Participants included representatives from NIAID, the National Cancer Institute (NCI), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of General Medical Sciences (NIGMS), and FDA. In March 2015, NIAID published a manuscript in the *Journal of Allergy and Clinical Immunology* describing the research gaps, critical infrastructure needs, and recommendations for future drug allergy research that were identified at the workshop. To assist in implementing these recommendations, NIAID has encouraged research in this area by adding drug allergy as a specific area of interest under the Asthma and Allergic Diseases Cooperative Research Centers (ADCRC). Through the ADCRC program, NIAID supports centers that integrate clinical and basic research to study the mechanisms underlying the onset and progression of asthma and allergic diseases.

In March 2015, NIAID also participated in a workshop led by NHGRI on “Research Directions in Genetically Mediated Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN).” One of the goals of the workshop was to examine the role of genomics and pharmacogenomics in the treatment and eradication of preventable causes of drug-induced SJS/TEN. Following the workshop, participants from NHGRI, NIAID, NIAMS, and NINDS established a trans-NIH working group to enhance collaboration and assess potential mechanisms to stimulate research on adverse drug reactions.

NIAID remains committed to advancing basic, translational, and clinical research on immune-mediated and allergic diseases to provide insight into better ways to identify, treat, and prevent these diseases. NIAID will continue to work with other NIH ICs and public- and private-sector partners to identify opportunities to advance drug allergy research.

Duchenne Muscular Dystrophy

The Committee requests an update in the fiscal year 2017 budget request on NIH's plans to implement the recent changes to the Muscular Dystrophy CARE Act and summary of the outcome from the latest Muscular Dystrophy Coordinating Committee and timeframe for the next two meetings.

Action taken or to be taken

NIH is working to implement the recent changes to the Muscular Dystrophy (MD)-CARE Act, which focus on the membership and activities of the Muscular Dystrophy Coordinating Committee (MDCC). NIH manages the MDCC. The NICHD Director has been chairing the Committee, but recently announced his retirement; MDCC will select a new chair at its next meeting on November 13, 2015. The MD-CARE Act of 2014 requires that representatives from the Social Security Administration and the Administration for Community Living be added to the MDCC roster, and new members from these agencies have been nominated. Representatives from these agencies already attended the MDCC meeting on March 17, 2015, as *ad hoc* members. An additional public member also has been nominated to the Committee in accordance with the membership guidelines required by law. NIH is committed to holding two MDCC meetings per year. In calendar year 2015, one meeting was held in March and one in November.

During the MDCC meeting in March 2015, Federal agencies reported on recent activities including several NIH- and FDA-sponsored workshops, an update on policy issues surrounding newborn screening for neuromuscular disorders, and an overview of programs relevant to the muscular dystrophies at the Department of Defense, the Social Security Administration, the Health Resources and Services Administration, and the Department of Education. The meeting also included a discussion of the draft 2015 Action Plan for the Muscular Dystrophies. MDCC members offered comments on the draft Plan and stressed the need to include a strategy for monitoring progress on the objectives of the Plan. MDCC formed a subcommittee to discuss this issue further. The subcommittee has met via teleconference and based on their input, NIH staff is drafting a proposed strategy for monitoring progress on the Action Plan.

The MDCC meeting in March 2015 concluded with a session on implementation of care guidelines for the muscular dystrophies, since the Action Plan calls for developing, implementing and monitoring the impact of clinical care guidelines for the muscular dystrophies. Representatives from CDC and from patient organizations shared information about their activities in this area and plans for further development and implementation of clinical care guidelines for several of the muscular dystrophies.

Early Detection and Prevention of Psychosis

The Committee applauds NIMH's early detection and intervention efforts involving psychosis in young people and encourages NIMH to coordinate with other ICs to expand these efforts.

Action taken or to be taken

Each year, approximately 100,000 adolescents and young adults have a first episode of psychosis (FEP) in the United States.⁵⁹ The majority of people with such serious mental illnesses (SMIs) experience significant delays in seeking care – nearly two years, on average.⁶⁰ Through a series of major initiatives, the National Institute of Mental Health (NIMH) is striving to improve early identification of individuals at high risk for FEP, to reduce the period of untreated psychosis to less than 12 weeks, and to maximize recovery among persons in the earliest stages of psychotic illness. An NIMH signature project, Early Prevention and Intervention Network (EPINET), will build a learning health care system for early detection and prevention of psychosis beginning in 2016.

NIMH continues to coordinate with other Institutes and Centers to address early detection and prevention of psychosis. For example, in September 2012, NIMH convened a two-day workshop to inform the research agenda on this topic.⁶¹ Staff from the National Cancer Institute (NCI), National Institute on Aging (NIA), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and National Heart, Lung, and Blood Institute (NHLBI) helped plan and participated in the meeting. Staff from the Substance Abuse and Mental Health Services Administration and the Agency for Healthcare Research and Quality also participated. The workshop led to an NIMH-sponsored initiative entitled, *Improving Health and Reducing Premature Mortality in People with Severe Mental Illness*.⁶² As a result, in 2014, NIMH funded five large clinical trials that are rigorously testing innovative service delivery approaches designed to reduce the prevalence and magnitude of common modifiable health risk factors, such as smoking, obesity, and substance use, related to shortened lifespan in adults with SMI.

In August 2015, NIMH released an initiative, *Improving Health and Reducing Cardiometabolic Risk in Youth with Serious Emotional Disturbance and Young Adults with Severe Mental Illness*, which aims to support research that could demonstrably reduce the prevalence and magnitude of common health risk factors related to shortened lifespan in youth with serious emotional disturbance and young adults with SMI.⁶³ Prior to issuing this initiative, NIMH consulted with NIDDK and worked extensively with program staff from NHLBI who shared the latest research on preventing and treating risks for diabetes, heart disease, and stroke in youth, such as low activity level, and poor fitness and diet. NHLBI has also expressed interest in co-funding meritorious applications resulting from this solicitation.

Moving forward, as more data from the Recovery After an Initial Schizophrenia Episode (RAISE) project become available, NIMH plans to hold strategic planning meetings with staff

⁵⁹ <http://www.ncbi.nlm.nih.gov/pubmed/18480098>

⁶⁰ <http://www.ncbi.nlm.nih.gov/pubmed/25588418> and <http://www.ncbi.nlm.nih.gov/pubmed/16143729>

⁶¹ <http://www.nimh.nih.gov/research-priorities/scientific-meetings/2012/research-to-improve-health-and-longevity-of-people-with-severe-mental-illness.shtml>

⁶² <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-060.html>

⁶³ <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-16-600.html>

from other ICs, including National Institute on Drug Abuse (NIDA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), NHLBI, and NIDDK.^{64,65} At these meetings, NIMH will share study findings and discuss implications for substance use onset and treatment among individuals with FEP and SMI as well as implications for health and mortality. NIMH staff and staff from these ICs will also discuss future directions and the potential for additional research opportunities. One such opportunity will be the Adolescent Brain and Cognitive Development study, launched with NIDA, NIAAA, NICHD, NINDS, and NIMH in 2015. The study will track brain and behavioral development in 10,000 children, providing an unprecedented view into the earliest phases of SMI that emerge in adolescence.

⁶⁴ <http://www.nimh.nih.gov/news/science-news/2015/team-based-treatment-is-better-for-first-episode-psychosis.shtml>

⁶⁵ <http://www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml>

Emergency Care Research

While the Committee appreciates the establishment of an Office of Emergency Care Research (OECR) within NIGMS, with a mission to coordinate and foster clinical and translational research and research training for the emergency setting, that office does not directly fund research grants, but must instead work to coordinate and catalyze efforts within other Institutes. The Committee encourages the Director of NIH to help the OECR effectively promote an expanded NIH-wide research agenda on emergency and trauma care.

Action taken or to be taken

The NIGMS Office of Emergency Care (OECR) coordinates efforts to increase the quality of emergency care research at NIH. OECR has produced an inventory that shows that NIH spends about \$66 million per year on emergency care research.

OECR places a great deal of importance on outreach to researchers within the emergency care community. The director travels to academic medical centers and emergency medicine training programs to engage in a dialogue about the emergency medicine research agenda, and how to increase the number of grant applications in this field.

OECR has also worked closely with the other NIH ICs to encourage new opportunities for emergency care research. For example, OECR developed a proposal that played a key role in the creation of the SIREN (Strategies to Innovate EmergENcy Care Clinical Trials) network, an emergency care clinical research network to be supported by NIH and the Department of Defense (DOD). This network will provide the infrastructure to support clinical trials in the areas of emergency neurology, emergency cardiovascular medicine and trauma. This partnership between NIH and DOD demonstrates an investment in emergency care research that did not exist before the establishment of OECR.

OECR was also instrumental in creating the first trans-NIH training program (K12) in Emergency Care. This program, supported by the National Heart, Lung, and Blood Institute, the National Institute of Nursing Research, and the National Institute of Mental Health, will support three clinical training sites. This program will support young investigators who are committed to research careers in emergency cardiovascular medicine, care of patients with emergency psychiatric or mental health care needs, and the provision of emergency nursing care.

In conjunction with the National Cancer Institute (NCI), OECR held a workshop on the research questions that surround the emergency care of patients with cancer. This workshop resulted in the creation of the Comprehensive Oncologic Emergencies Research Network (CONCERN), to be supported by NCI. This network, now in its early stage, will conduct high quality pragmatic clinical trials to improve the care of the cancer patient who needs emergency medical care.

OECR will continue to build on these successes, as the emergency department is increasingly recognized as a critical part of the nation's health infrastructure.

End-Stage Renal Disease (ESRD)

In particular, the Committee encourages investigation regarding genetic, biological, and environmental causes of the health disparities among minority populations. NIDDK should prioritize more investments in kidney research in collaboration with other Federal stakeholders involved in kidney research, including NHLBI, NIA, and the VA.

Action taken or to be taken

Racial and ethnic disparities exist in prevalence and outcomes of kidney disease and its often grave consequence, kidney failure, or end-stage renal disease (ESRD). The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a spectrum of efforts to gain insights into these disparities and thereby develop better prevention and treatments, many in collaboration with other NIH ICs and Federal agencies, including the National Institute on Minority Health and Health Disparities. African Americans have an increased risk of non-diabetic kidney disease, and recent findings emerging from major NIH trials and studies highlight the critical role of the APOL1 gene in this risk. For example, the National Heart, Lung, and Blood Institute (NHLBI), National Institute of Neurological Disorders and Stroke, National Institute on Aging, and NIDDK support the Systolic Blood Pressure Intervention Trial (SPRINT), which has a large proportion of minority group participants, to determine whether reducing blood pressure to a lower level than in currently recommended for adults with hypertension will reduce cardiovascular and kidney diseases, age-related cognitive decline, and dementia. SPRINT investigators recently found that variants in the APOL1 gene are associated with increased risk of kidney disease, but not cardiovascular disease, in African Americans with high blood pressure. Similarly, research leveraging the ongoing Chronic Renal Insufficiency Cohort Study, co-sponsored by NIDDK and NHLBI, and another major research cohort has found that African Americans who have chronic kidney disease (CKD) and two copies of common variants in the APOL1 gene are twice as likely to progress to kidney failure as those without these high-risk variants; also, African Americans with the high-risk variants tend to lose kidney function at twice the rate of those without the variant. In June 2015, NIDDK hosted a scientific workshop focused on APOL1 to develop new ideas regarding and pathways to determining how genetic variants lead to kidney disease susceptibility and other research and clinical issues. NIDDK is also participating in a project to understand risk for CKD in Africans as part of the NIH-Wellcome Trust H3 Africa Research Network; studies in Africa are critical for understanding environmental and genetic interactions influencing APOL1, and complement U.S.-based studies.

NIDDK is also collaborating with the National Center for Advancing Translational Sciences in the recently renewed and expanded Nephrotic Syndrome Study Network (NEPTUNE) observational study, which is focused on nephrotic syndrome resulting from three specific diseases. Complementing NEPTUNE, the new Cure Glomerulopathy Network (CureGN) will conduct translational and clinical research that promotes therapeutic development for primary glomerular diseases. Both Networks have significant participation by U.S. racial and ethnic minority groups, due to greater prevalence of specific glomerular diseases in these groups. NIDDK is also leading ICD-Pieces, a project funded as part of the NIH Healthcare Systems Research Collaboratory – Demonstration Projects for Pragmatic Clinical Trials Focusing on Multiple Chronic Conditions. Conducted in four large healthcare systems, including the Department of Veterans' Affairs, this trial is using a novel IT approach to follow patients with

CKD, hypertension, and diabetes and see whether a model of primary care-subspecialty care collaboration will decrease hospitalizations, cardiovascular events, and deaths in this population when compared to usual care. NIDDK will continue to pursue new efforts with its sister Institutes and other agencies with an interest in kidney disease and kidney failure, especially in racial and ethnic minority populations.

Enhanced NIH Reporting on Research Spending by Disease and Affected Populations –

The Committee reiterates its direction identified in the fiscal year 2015 Explanatory Statement for NIH to make public, on an annual basis, enhanced RCDC spending data with the number of Americans affected by each category of disease according to CDC or other federally-sourced data. Further, the Committee requests NIH to include the number of Americans living with each disease, annual number of newly diagnosed Americans for each disease, and number of Americans who die from each disease annually. The Committee appreciates that NIH may not have all available category data during fiscal year 2016 but expects NIH to upload all available data immediately and to have the full data set on-line no later than May 1, 2016. The Committee requests an update on the process in the fiscal year 2017 budget request. In addition, the Committee encourages NIH to add pediatric cardiomyopathy to the RCDC and spending on the disease for at least the last five year and projected forward.

Action taken or to be taken

In last year's response to the 2015 explanatory statement, NIH indicated that it was examining the feasibility of providing burden of illness information in relation to the disease categories in NIH's Categorical Spending report. The response also indicated that burden of illness measures are a better measure of the impact of diseases than prevalence statistics, since burden of illness measures attempt to reflect a combination of potential rates of mortality, rates of disability, and/or effects on quality of life. For example, equal numbers of Americans might be affected by influenza and cancer, but the rates of mortality, effects of long-term disability, and impact on quality of life are not the same for influenza and cancer.

NIH announced the new burden of disease page on the RePORT web site on June 19, 2015. The page provides graphical displays of U.S. and global burden of illness data (disability adjusted life years) for 69 categories of diseases that NIH was able to match to RCDC spending categories.^{66-67,68} NIH is also reporting U.S. and Global mortality data for as many of these categories as possible. The source data are also available for download on the burden of disease page.⁶⁹

NIH will plan to add pediatric cardiomyopathy as a category for reporting beginning with NIH FY 2016 projects; however, retroactive reporting for previous fiscal years cannot be accurately totaled with the current RCDC system.

⁶⁶ <http://www.sciencedirect.com/science/journal/01406736/380/9859>

⁶⁷ http://report.nih.gov/info_disease_burden.aspx

⁶⁸ <http://nexus.od.nih.gov/all/2015/06/19/burden-of-disease-and-nih-funding-priorities/>

⁶⁹ <http://report.nih.gov/FileLink.aspx?rid=892>

Environmental Exposure

In addition, the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Environmental exposures are a leading cause of morbidity and mortality for mothers and children worldwide. These exposures encompass a broad range of factors from chemical and biological such as air pollution, pesticides, and infectious diseases, to psychosocial factors such as education, stress, and neglect. Exposures during crucial developmental windows, including conception and pregnancy, early childhood, and puberty, can have long lasting effects. NIH has laid a strong foundation for the next phase of research on the effects of environmental exposures on child health and development. Such research can inform strategies to reduce the risk of childhood illnesses and disabilities.

A centerpiece of the NIH efforts is NIEHS Children's Health and Exposure Assessment Resource (CHEAR).⁷⁰ This resource will provide NIH-funded research community access to laboratory and statistical analyses that will allow it to add or expand environmental exposures as a component of ongoing epidemiological and clinical research, thereby creating a public resource of children's exposures across the country. Exposures measured encompass the breadth of the exposome, the term used to refer to the totality of biological, psychosocial, chemical, and physical factors to which humans are exposed. CHEAR infrastructure will have three units: a National Exposure Assessment Laboratory Network that will provide access to state-of-the-art infrastructure for analysis of biological samples and responses associated with those exposures; a Data Repository, Analysis, and Science Center that will provide support for data collection, statistical analysis and interpretation, and the development of community-based data standards, as well as new technologies and metadata standards; and a coordinating center that will provide administrative management, including interface with the research community and an index of additional exposure analysis tools outside of CHEAR. Additional research investments will be used to leverage current studies to expand examination of environmental exposures on later child development.

Two complementary initiatives will enable measurement and analysis of children's exposures in specific settings. The Pediatric Patient Reported Outcomes in Chronic Diseases Consortium will allow researchers to capture the voice and experience of children and their families living with a variety of diseases and conditions.⁷¹ The Human Placenta Project (HPP) will support development of next-generation placental imaging and assessment, as well as use Tox21 technologies to investigate the effects of environmental chemicals on human development using robotic screening of cultured cells.⁷²

⁷⁰ <https://www.niehs.nih.gov/research/supported/dert/programs/chear/index.cfm>

⁷¹ http://www.niams.nih.gov/Funding/Funded_Research/PEPR/default.asp

⁷² <http://www.nichd.nih.gov/research/HPP/Pages/default.aspx>

Fetal Alcohol Syndrome (FAS) Research

The Committee was pleased that NIAAA's budget request proposed increases in research on how alcohol interferes with human development and the various underlying aspects of alcohol-induced fetal damage. The Committee encourages NIH to consider the benefits and methods to support a clearinghouse and improved coordination with federal and private sector partners to best facilitate the translation of science into public health promotion strategies and interventions benefiting individuals living with FAS.

Action taken or to be taken

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) appreciates the Committee's interest in improving coordination of efforts to translate research findings into interventions to help individuals living with Fetal Alcohol Spectrum Disorders (FASD). NIAAA currently collaborates with agencies involved in the Federal effort to address FASD through the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD). The purpose of ICCFASD is to enhance and increase communication, cooperation, collaboration, and partnerships among disciplines and Federal agencies to address health, education, developmental disabilities, research, social services and criminal justice issues that are relevant to FASD. Established in 1996, ICCFASD is sponsored and chaired by NIAAA. Other Federal member agencies include:

- Administration for Children and Families;
- Agency for Healthcare Research and Quality;
- Centers for Disease Control and Prevention;
- Health Resources and Services Administration;
- Indian Health Service;
- National Institute of Child Health and Human Development, NIH;
- National Institute on Drug Abuse, NIH;
- Substance Abuse and Mental Health Services Administration;
- Department of Education; and
- Department of Justice.

ICCFASD, in turn, collaborates with researchers, clinicians, professional associations, advocacy organizations, and others with the goals of increasing awareness of FASD, providing continuing education for professionals and others who interact with FASD-affected individuals, and promoting implementation of evidence-based approaches to address the needs of children and adults who live with FASD.

ICCFASD member agencies provide a wide range of resources targeted to the public, health care professionals and others. NIAAA will work with its federal partners to explore ways to create a centralized resource to help these groups navigate the wealth of available information.

Fragile X Research

The Committee commends NICHD for leading the effort to map the molecular, physiological, biological, and genetic connections between fragile X (FX), the fragile X protein, and autism. The fragile X gene and its protein continue to present important insight into discovering the root cause of autism and disease modifying treatments for FX and autism. The Committee encourages NIH to explore ways to utilize FX and autism research in tandem to accelerate the pace of research toward identification of the commonality between the two conditions and the development of disease modifying treatments that will reduce health burdens.

Action taken or to be taken

Fragile X syndrome (FXS) is the most common heritable form of intellectual disability and most prevalent monogenic (single gene) cause of autism. NIH continues its commitment to research that will advance understanding of the commonalities between Fragile X syndrome and autism, and that will lead to interventions and treatments for these conditions.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), along with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Mental Health (NIMH), funds three Centers for Collaborative Research in Fragile X. Their work benefits both the FXS and autism research communities. One of the centers focuses on sensitivity to sensory stimuli, especially noise, which is of great concern to individuals with FXS and many children with autism. Candidate therapeutics to correct sensory processing deficits will be tested in mice and later in human participants. Because FXS and other diseases, including the autism-spectrum disorders, display aberrant cellular protein synthesis, the second center focuses on molecules that play an important role in protein production. Understanding the role of these molecules may lead to treatments to correct altered protein synthesis. The third center's work aims at identifying genes that modify the severity of symptoms in people with FXS. This is critical, because even though FXS is caused by mutations in a single gene, the severity of symptoms varies among individuals. Sequencing the genes of patients with the Fragile X mutation also will identify additional genes that may affect the likelihood of developing certain health problems, such as epilepsy. Investigators from these Centers met in February 2015 to discuss how to share the data with the National Database for Autism Research and how, by using common data elements, to facilitate comparison of research conducted in individuals with FXS and those with autism.

NICHD continues to fund research in the development of standardized outcome measures for use in clinical trials in FXS. Many of these measures would also be appropriate for use with other developmental disabilities, including autism. Following an NICHD-led effort to develop such measures, several resulting publications have begun to have an impact on the FXS research community by allowing for easier comparisons across studies that are now using similar outcome measures.

The research portfolios of both NICHD and NINDS have continued to grow in the area of FXS, and now include Fragile X-associated tremor/ataxia syndrome and Fragile X-associated premature ovarian insufficiency, with the ultimate goal of identifying and developing targets for treatment. Several currently funded basic research studies using animal models of FXS or patient-derived stem cells focus on understanding the mechanisms underlying deficits in

neuronal development, signaling, and synaptic plasticity that contribute to cognitive and behavioral impairments, and determining whether those mechanisms may also contribute to other forms of autism spectrum disorders. In addition, both NICHD and NINDS supported a 2014 conference, “Fragile X & Autism-Related Disorders: Advances in Human Therapy,” that brought together researchers and clinicians expert in both conditions and helped inform updates for research plans in both areas.

Functional Gastrointestinal Disorders (FGID)

The Committee continues to be concerned by the prevalence of FGIDs and their impact on children. The Committee urges multi-Institute collaborations on FGID research to understand this disease.

Action taken or to be taken

Research to improve understanding of Functional Gastrointestinal Disorders (FGIDs) continues to be a priority for the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). NIDDK supports research to further understand the effects of FGIDs on children and adults. NIDDK's multiple efforts include collaboration with the NIH Office of Research on Women's Health (ORWH), which complements other FGID research funded by the Institute.

The most common FGID, irritable bowel syndrome (IBS), is not fully understood. However, physical and psychological factors are believed to play a role, such as problems in nerve signaling pathways between the gut and the brain and differences in individual responses to stress and other environmental cues. One contributing factor may be the set of bacteria that live in the gut, which differs among individuals. Two NIDDK-sponsored studies have shed light on the microbiome, or the microbes inhabiting the gut, and how it affects the health of children. One preliminary study showed that in some children with IBS, a diet low in certain carbohydrates such as fructose and lactose may decrease abdominal pain frequency; the children who benefitted were more likely to have certain types of gut bacteria. Complementing these results, another study sought to gain a better understanding of the microbiome in healthy children, which will help researchers discern potential differences with the microbiome in children with intestinal disorders and other conditions. The results showed that the healthy pediatric gut microbiome has different components and activities than that of healthy adults, and that a mature gut microbiome may take longer to develop in children than previously suspected.

Although IBS can affect all ages, it is especially common in women. NIDDK continues to collaborate with ORWH to fund a Specialized Center of Research at the University of California, Los Angeles. This Center examines sex and gender differences in the interaction of gut and brain pathways in the development of IBS and other abdominal pain disorders. Additionally, the NIDDK-sponsored IBS Outcome Study (IBSOS) is a multi-center, placebo-controlled randomized clinical trial. IBSOS will determine whether self-administered cognitive behavioral therapy is as helpful as standard therapy with a therapist in reducing IBS symptoms and overall burden. Results from IBSOS show that the fear of IBS symptoms has a large impact on reducing individuals' day-to-day quality of life, even more so than the symptoms themselves. Greater awareness and attention to these complex factors influencing individual experience of IBS may help health care providers in delivery and effectiveness of care, relationships with patients, and patient satisfaction and compliance with medical care.

Gabriella Miller Kids First Research Act

The Committee includes funding within the Common Fund to support the Gabriella Miller Kids First Research Act, named after Gabriella Miller, who died in 2013 as a result of pediatric cancer. The Committee directs the NIH Director to use at least \$12,600,000 of Common Fund resources in fiscal year 2016 to support pediatric research as authorized in the Gabriella Miller Kids First Research Act. The Committee encourages NIH to prioritize research relating to childhood cancer within the Kids First program and requests an update in the fiscal year 2017 budget request on the 10-year program, planned activities, and on-going research.

Action taken or to be taken

The Gabriella Miller Kids First Pediatric Research (Kids First) program is developing a data resource for the pediatric research community to investigate the role of genetics in childhood cancers and structural birth defects.⁷³ This data resource will consist of well-characterized clinical and genetic sequence data that will allow scientists to identify pathways underlying specific pediatric conditions and also to uncover shared pathways between apparently disparate conditions. The fields of pediatric oncology and developmental biology, which studies disorders like birth defects, have made major discoveries to advance our understanding of disease and development. However, we do not fully understand the role of genetics in these conditions. The Kids First data resource will combine genetic data and clinical data so that researchers will be able to investigate the complex role of genetics in childhood cancer and structural birth defects.

In FY 2015, all funds for the Kids First program were dispersed as supplements to NIH-supported DNA sequencing centers at Baylor College of Medicine and Washington University in St. Louis. These centers were selected based on their expertise and available sequencing capacity. Additionally, Kids First solicited applications from researchers with existing pediatric research cohorts to investigate the genetics of structural birth defects and the genetic contributions to childhood cancers, including childhood sarcomas that have failed to respond to treatment.⁷⁴ 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 cohorts to be sequenced were announced in October 2015, and include a range of childhood cancers and structural birth defects.⁷⁵ 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.

NIH is gathering input from the pediatric research community on how best to build and manage the data resource to ensure maximum utility. In future years, subject to availability of funds, NIH plans to support awards to build the data resource, continue genome sequencing of additional cohorts relevant to childhood cancer and structural birth defects, and carry out pilot projects to develop approaches and tools for data analysis to facilitate further studies by the broader pediatric research community that may investigate additional diseases and conditions. Kids First is managed by a trans-NIH working group consisting of members from approximately 12 NIH Institutes and Centers (ICs) and staff from the Office of Strategic Coordination/Division

⁷³ <https://commonfund.nih.gov/KidsFirst/>

⁷⁴ <http://grants.nih.gov/grants/guide/pa-files/PAR-15-259.html>

⁷⁵ <https://commonfund.nih.gov/kidsfirst/fundedresearch>

of Program Coordination, Planning, and Strategic Initiatives, which oversees the NIH Common Fund. 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.

Gastrointestinal Cancer

The Committee continues to be concerned about gastric cancer, particularly among young adults and supports gastric cancer being studied in The Cancer Genome Atlas (TCGA). The Committee notes that research on gastric cancer is less advanced than that of many other cancers. The Committee therefore encourages NCI to consider requesting applications for gastric cancer research that leverages the use of genomic data from the TCGA

Action taken or to be taken

NCI is committed to full exploration of the data from TCGA and similar projects to advance genomic research and translate findings into the clinic to improve the precise diagnosis and treatment of cancers such as gastric cancer. NCI supports a wide range of basic research projects and clinical trials on gastric cancer, including five Specialized Programs of Research Excellence (SPORES) focused on gastrointestinal cancers such as stomach, esophagus, and colon cancers. NCI is currently sponsoring several clinical trials for gastric and gastro-esophageal (GE) cancers. Examples include a study of combination chemotherapy for gastric cancer, a study of a targeted therapy with personalized antibodies for GE cancer, and a phase II study of a drug that inhibits tumor growth receptors for advanced esophageal gastric cancer. In addition, NCI's National Clinical Trials Network (NCTN) is currently supporting several trials for gastric cancer, including a trial of combination therapy for gastric cancers with high MET expression, as well as evaluating whether the addition of molecularly-targeted therapies can enhance the survival of patients treated with combinations of traditional surgical, radiation, and chemotherapeutic approaches.

Sequencing data from TCGA has enabled the extensive characterization of cancer genomes as well as associated analyses across cancer types that have shown that some cancer subtypes may be more similar to each other than to others from the same organ-of-origin. These analyses (called Pan-Can analyses) have also shown that these cancer types might share common genetic features that could be susceptible to some targeted therapies on the market, but not yet considered for the particular subtype. In other words, seemingly dissimilar cancer types may share a vulnerability for which a drug is already available. NCI is supporting new projects to expand on these analyses and to enable researchers to examine a variety of new research hypotheses in this area.

NCI is also supporting the development of new cancer models, including gastric cancer models, sometimes referred to as "organoid" cultures and "conditionally reprogrammed" cells. NCI has completed a pilot program in the development of these organoid models and is co-leading an international consortium effort for broad development of models for many cancer types. When successful, NCI will distribute these new cancer models broadly to cancer researchers to help develop diagnostic and treatment strategies tailored to specific subtypes of cancer and to specific molecular abnormalities.

NCI is fostering many opportunities to study gastric cancer via several different types of funding opportunity announcements (FOAs) supporting a wide variety of investigator-initiated research applications ranging from basic studies of cancer etiology and structural biology to studies of early detection and biomarkers and clinical trials. NCI is also supporting training opportunities for talented individuals who might develop an interest in gastric cancer through individual

fellowships, institutional training awards, and career development awards; and NCI program managers are available to provide guidance to investigators who seek help in finding the most appropriate funding mechanisms to support proposed work on gastric cancer and other types of cancers.

Gastrointestinal Disorders

The Committee recognizes NIDDK's work to create a long-term scientific framework for treating pancreatic, celiac disease, and other gastrointestinal disorders. The Committee requests NIDDK provide an update in the fiscal year 2017 CJ that details how NIDDK is accelerating cures for these diseases.

Action taken or to be taken

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) appreciates the Committee's recognition of the Institute's work to create a long-term scientific framework for treating gastrointestinal disorders. NIDDK is accelerating cures for gastrointestinal disorders by encouraging research to better understand, improve diagnoses, and develop treatments for these diseases. NIDDK also continues to explore new directions toward treating gastrointestinal disorders by holding workshops focusing on opportunities in the development of new diagnostics and treatments.

Due to limitations in detection at the early stages of disease, many chronic pancreatic diseases are typically diagnosed only at advanced stages. In July 2015, NIDDK and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) convened a workshop to encourage research on new ways to detect early pancreatic disease, focusing on recently-developed, noninvasive approaches to the diagnosis of chronic pancreatitis and the detection of pancreatic cancer. Validation of these approaches will help clinicians diagnose these pancreatic diseases at early stages when intervention can reverse the disease or improve the outcome of treatments. In conjunction with the National Cancer Institute (NCI), NIDDK has recently funded a multi-center consortium 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.

NIDDK supports a number of studies devoted to improving treatment for people with celiac disease. For example, in an effort to address the fact that most cases of celiac disease go undiagnosed in the United States, and early detection and intervention is likely to benefit patients, a study evaluated the effectiveness of testing patients with symptoms of irritable bowel syndrome (IBS) for celiac disease. The study showed that symptoms of celiac disease and IBS are common in a U.S. white population, and, contrary to current recommendations in other countries, testing for celiac disease in patients with IBS may not be more effective than a general population-based screening in the United States.

A recent study of more than 32,000 men and women with Crohn's disease or ulcerative colitis – the two most common forms of inflammatory bowel disease (IBD) – has shed light on the genetic underpinnings of these gastrointestinal diseases. An international group of researchers compared the genomes of 18,405 people with Crohn's disease, 14,308 people with ulcerative colitis, and 34,241 people without these diseases. Examining certain genes involved in immunity, the scientists identified a genetic variant that was highly associated with both Crohn's disease and ulcerative colitis, suggesting that it may be involved in the development of both forms of IBD. This finding may lead to new treatments for IBD that target certain features of the immune system. In June 2015, NIDDK released two funding opportunity announcements to encourage research on the human microbiome and its effects on human obesity, nutrition, and digestive and liver diseases.

Gestational Diabetes

The Committee urges NIH to explore additional opportunities for research on gestational diabetes.

Action taken or to be taken

Gestational diabetes mellitus (GDM) is a type of diabetes identified during pregnancy in a woman who had not been diagnosed with other forms of diabetes before she was pregnant. NIH supports a multi-faceted research program to understand and prevent GDM and its immediate and long-term consequences in women and their offspring. Leading these efforts are the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD); these two Institutes work together to synergize GDM research efforts, and also coordinate with the NIH Office of Research on Women's Health (ORWH) in this area.

Because GDM significantly increases a woman's risk of developing type 2 diabetes later in life, a critical area of research focus is finding ways to break this link. NIH is vigorously pursuing opportunities in this area. For example, NIDDK spearheads a study of the long-term effects of the highly successful Diabetes Prevention Program (DPP) clinical trial interventions on development of diabetes and other outcomes in DPP participants, including women with a history of GDM; the robust number of these women recruited into the DPP was made possible with support from ORWH, which continues to partner with NIDDK in the DPP Outcomes Study. In 2015, this study demonstrated that women with and without a history of GDM differ in their responses to the DPP interventions (lifestyle intervention to promote modest weight loss versus the diabetes drug metformin). Both interventions were very effective in reducing progression to diabetes in women who had a history of GDM at baseline. In contrast, only the lifestyle intervention, not metformin, was effective in delaying diabetes onset in women who did not have a history of GDM – a difference that has implications for clinical care. In FY 2016, NIDDK and other NIH components will provide funding to begin phase 3 of the DPP Outcomes Study. This new phase will examine the impact of DPP interventions on development of cardiovascular disease and cancer as well as provide longer term results on progression to diabetes. NIDDK also continues to solicit and support research projects to translate to “real-world” settings, strategies shown in clinical trials to improve outcomes in diabetes and obesity, such as those in the DPP.

GDM also increases risk for obesity and type 2 diabetes in children of affected pregnancies, and NIH is pursuing opportunities to better understand the mechanisms underlying risk. To help address the full extent of risk for both mothers and children, NIDDK and NICHD have built on and extended the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study. An ongoing HAPO Follow-up Study is leveraging the completed NICHD-led HAPO clinical study to help determine whether blood glucose values during pregnancy that are above normal but below the threshold for GDM influence future levels of body fat in children and development of diabetes in mothers after giving birth. Among efforts to develop approaches to mitigate risk of GDM, the Lifestyle Interventions for Expectant Moms consortium, a trans-NIH effort spearheaded by NIDDK, is testing behavioral/lifestyle interventions in overweight and obese pregnant women to try to identify an effective intervention(s) that can control gestational weight gain and potentially reduce health risks for women and their babies during and after pregnancy. Other efforts include

a small clinical trial evaluating a weight loss intervention in overweight and obese women who are likely to become pregnant; such preemptive strategies may help stave off development of GDM in at-risk women. NIH will continue to pursue research opportunities to understand GDM and to improve outcomes for women with or at risk for GDM and their families.

Global Infections Disease Health Research

In addition to the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following 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) supports global research on infectious diseases to help protect the United States from infectious disease threats, such as HIV/AIDS, Ebola, tuberculosis, influenza, malaria, and antimicrobial resistance, among others, and to improve health around the world. NIAID funding supports collaborations between U.S. and international scientists, trains U.S. and foreign investigators to work internationally, and enhances global capacity to address the challenges of infectious diseases. NIAID will continue to support research on diseases of global significance, with the goal of reducing the impact of these diseases. Highlights of this research include, but are not limited to, the following:

HIV/AIDS: Consistent with NIH's updated HIV/AIDS research priorities, including reducing incidence of HIV/AIDS, NIAID supports international HIV/AIDS research that reflects the global impact of the disease. NIAID's HIV/AIDS Clinical Trials Networks, six networks with over 100 global clinical trial sites, are focused on: new HIV prevention methods including microbicides, vaccines, and strategies to prevent mother-to-child transmission; new drug development; and clinical management of HIV/AIDS. NIAID also funds the International Epidemiologic Databases to Evaluate AIDS consortium, seven regional databases containing data from more than one million patients. This information has been critical in evaluating HIV treatment programs and defining new approaches to HIV care in resource-limited settings. In addition, NIAID scientists are investigating features of HIV infection in HIV-endemic regions compared to the United States in order to identify methods to prevent further spread of the epidemic.

Ebola: NIAID responded to the current Ebola virus outbreak in West Africa by leveraging longstanding partnerships to move needed diagnostics, therapeutics, and vaccines into the field through ongoing intramural and extramural research efforts. Working with scientists and officials from affected countries, NIAID is supporting clinical trials in West Africa investigating candidate therapies and vaccines as well as exploring the long-term consequences of Ebola in survivors. Continued international research collaborations will provide the data and tools necessary to control current and future Ebola outbreaks. Emergency funding from the Congress for this purpose is instrumental in these efforts.

Tuberculosis (TB): NIAID's global TB research is contributing to the international fight against TB and drug-resistant TB. NIAID's Tuberculosis Research Units (TBRU) integrate basic and clinical research to study TB in countries where the disease is endemic. In 2015, NIAID reinvested in the TBRU program, funding four institutions that will study latent and persistent TB as part of international, cross-disciplinary, clinical, and animal model research projects. In a co-funding partnership with local biomedical research support organizations, NIAID also is establishing a network of clinical research sites in key countries with high TB and HIV/TB disease burden to enhance global research capacity for collaborative treatment and

prevention trials. In addition, NIAID intramural scientists lead international research on novel therapeutics for TB, including successful partnerships in South Korea, China, and South Africa.

Influenza: To combat the growing global health concerns of seasonal and pandemic influenza, NIAID supports a series of international clinical trials to characterize the natural history and clinical outcomes of patients with influenza and to study new treatment approaches. NIAID also supports the Centers of Excellence for Influenza Research and Surveillance (CEIRS) Program. Domestic and international CEIRS investigators continually monitor cases of animal and human influenza worldwide to rapidly detect and characterize viruses that may have pandemic potential and to lay the groundwork for new and improved influenza control measures. In addition, NIAID intramural researchers are undertaking human influenza challenge studies at NIH's Clinical Center. This human model of influenza pathogenesis provides a foundation for improved vaccines and therapeutics, and complements NIAID efforts to develop a universal influenza vaccine.

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 2017 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 find areas of scientific overlap and collaboration, which has led to many areas of fruitful research. Collaborations can take many forms, including research aimed at supporting the health and wellness of American service members and veterans, and studies aimed at developing specific technologies that address overlaps in mission priorities. Below are a handful of activities describing how the NIH has collaborated, and continues to collaborate, with our DOD and VA partners to conduct needed biomedical research and improve the health of all Americans.

NIH and VA:

- The National Institute on Alcohol Abuse and Alcoholism (NIAAA) collaborates with the VA and others to support the Veterans Aging Cohort Study, addressing the role of alcohol and related behaviors and conditions in determining clinical outcomes in persons living with HIV/AIDS.
- In 2014, the National Center for Complementary and Integrative Health (NCCIH), the National Institute on Drug Abuse (NIDA), and the VA released a joint funding initiative focused on non-pharmacological approaches to improve options for the management of pain and associated problems in military personnel, veterans, and their families. Thirteen research projects totaling approximately \$21.7 million over 5 years are exploring nondrug approaches to managing pain and related health conditions such as post-traumatic stress disorder (PTSD), drug abuse, and sleep issues. This initiative funded thirteen grants (1 NIDA, 1 VA, and 11 NCCIH, including co-funding of 1 by the VA).
- In addition to collaborating on research, the NIH shares access to its established data technology platforms for VA use, thereby allowing information about their supported research to be publicly available. For example, the NIH RePORT Expenditures and Results system is an electronic tool that allows the public to search a repository of NIH-funded research projects, as well as those of other participating federal organizations such as the VA, from the past 25 years and access publications and patents citing this support.

NIH and DOD:

- Research efforts aimed at identifying preventive interventions for suicidal behavior in service members and veterans include the DOD-funded Better Resiliency among Veterans with Omega-3s (BRAVO) study. BRAVO is a large randomized, placebo-controlled clinical trial that is testing nutritional supplementation with omega-3 fatty acids to prevent suicidal behaviors in veterans. Intramural investigators at NIAAA collaborate on the trial.
- Working with the Army, the National Institute of Mental Health (NIMH) has implemented the **Army Study to Assess Risk and Resilience in Servicemembers (Army STARRS)**. This program is identifying behavioral health, risk, and resilience factors to help prevent suicide in the Army. Health data has been collected from more than 113,000 active

duty soldiers, from basic training to separation from the military, at sites across the world, and in many different phases of the Army readiness cycle. Efforts to combine neurocognitive assessments, biospecimen collection, Army and DOD administrative records, and prospective measures of psychiatric correlates, substance use, and suicidality are nearly complete, and data analyses are underway. The first peer-reviewed reports based on Army STARRS analytical methods were published in 2012, and the first papers based on newly-collected data were published in the spring of 2014; details on published articles are available on [the study website](#). Army STARRS has been working with federal partners on establishing the scope of a potential next phase.

- NIH and DOD are building the Federal Interagency Traumatic Brain Injury Research database, to accelerate comparative effectiveness research on brain injury treatment and diagnosis. The \$10 million, four year initiative will serve as a central repository for new data, link to current databases, and allow valid comparison of results across studies. The U.S. Army Medical Research and Materiel Command (USAMRMC) and the National Institute on Neurological Disorders and Stroke (NINDS) will provide programmatic support and foster collaborative research to populate the database.
- The National Institute of Biomedical Imaging and Bioengineering (NIBIB), USAMRMC, and the Office of Naval Research have established the Armed Forces Institute of Regenerative Medicine, which is dedicated to developing advanced treatment options for our severely wounded servicemen and women. Therapies developed here will also serve trauma and burn patients in the public at large. This trans-agency effort includes biotechnology companies, hospitals, two large teams of academic and industry scientists, and the U.S. Army Institute of Surgical Research.
- In 2015, researchers at the National Institute of Allergy and Infectious Diseases (NIAID) and the Walter Reed Army Institute of Research found that [an investigational Ebola vaccine called VSV-ZEBOV](#) was safe and produced robust antibody responses in healthy adults. The vaccine is 1 of 2 experimental Ebola vaccines now being tested in a clinical trial in Liberia.
- Since 2002, NIAID and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) have partnered together to conduct biodefense research. NIAID and USAMRIID have had a productive relationship over the years working on biodefense related diagnostics, drugs and vaccine research. This effort located at Fort Detrick uniquely marshals research capabilities while consolidating resources in response to the nation's changing needs.

NIH and DOD's Defense Advanced Research Projects Agency (DARPA)

- NIH and DARPA, along with a variety of other federal partners, participate in the National Robotics Initiative, which was created by the White House's Office of Science and Technology Policy (OSTP) to promote research in a variety of robot-related topics. The goal of the National Robotics Initiative is to accelerate the development and use of robots in the United States that work beside, or cooperatively with, people. The NIH joined as a major civilian partner of this coordinated interagency plan, which also includes the National Science Foundation (NSF), the National Aeronautics and Space Administration, the U.S. Department of Agriculture and the National Institute of Food and Agriculture. In December

2015, NIH released an updated joint funding announcement to further develop this next generation of robotics, advance the capability and usability of such systems and artifacts, and encourage existing and new communities to focus on innovative application areas. The program aims to address the entire life cycle from fundamental research and development to manufacturing and deployment. Collaboration between academic, industry, non-profit, and other organizations has been strongly encouraged to establish better linkages between fundamental science and technology development, deployment, and use.

- NIH, the Food and Drug Administration (FDA), NSF, and DARPA collaborate on studies of next-generation technologies for Drug Discovery, Testing, and Approval. This collaboration aims to develop 3-D human tissue chips that accurately model the structure and function of human organs, such as the lung, liver and heart. Once developed, researchers can use these models to predict whether a candidate drug, vaccine or biologic agent is safe or toxic in humans in a faster and more cost-effective way than current methods. More than 30 percent of promising medications have failed in human clinical trials because they are determined to be toxic despite promising pre-clinical studies in animal models. These organs-on-chips will enable scientists to predict more accurately how effective a therapeutic candidate would be in clinical studies.
- NIH, FDA, NSF, DARPA, and the Intelligence Advanced Research Projects Activity (IARPA) all collaborate on the President's Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) initiative, which aims to uncover the mysteries of brain disorders, such as Alzheimer's and Parkinson's diseases, depression, and traumatic brain injury (TBI). The initiative will accelerate the development and application of new technologies to produce dynamic pictures of the brain showing how individual brain cells and complex neural circuits interact at the speed of thought. These technologies will open new doors to explore how the brain records, processes, uses, stores, and retrieves vast quantities of information, and shed light on the complex links between brain function and behavior.

Grant Review

The fiscal year 2017 budget request shall provide an update on NIH policies and procedures to ensure appropriate review and approval for grants awarded through the ICs.

Action taken or to be taken

NIH IC directors make all final funding decisions on extramural grants. In making funding decisions, IC directors, as well as their program staff and National Advisory Councils or Boards, weigh four primary factors: peer review of scientific excellence; public health needs; scientific opportunity; and portfolio balance. The decision-making process encompasses several steps of assessment, outlined below, resulting in a funding plan that is formalized and acted upon by each IC director.

A summary of NIH's established peer review processes and policies are published on the NIH Office of Extramural Research website.⁷⁶ In short, the first level of review is carried out by a Scientific Review Group (SRG) composed primarily of non-Federal scientists who have expertise in relevant scientific disciplines and current research areas. The second level of review is performed by the IC advisory council or board, which is composed of both scientific and public representatives chosen for their expertise, interest, or activity in matters related to health and disease.

Following the first level of SRG review, NIH program staff members examine applications, their review scores, and their summary statements and consider these against the IC's needs. Program staff present all applications that may be considered for funding to the Advisory Board/Council, which also review the funding plan in relation to the IC's goals and needs and then advise the IC director. Research grant applications that are favorably recommended by both the SRG and the Advisory Council may be considered for funding. The IC director makes the final decisions on which applications receive funding.

By building priority setting and IC director review into each funding cycle – which occurs three times a year – NIH engages in a process that is responsive to emerging scientific opportunities and health challenges. This multi-stage assessment process ensures that IC directors have answers to key questions, such as how proposed research might expand knowledge to improve human health, how it relates to program goals and objectives, and how it fits into an IC's research portfolio as well as the overall NIH portfolio.

⁷⁶ http://grants.nih.gov/grants/peer_review_process.htm

Glaucoma

The Committee recognizes that NEI's Glaucoma Human Genetics Collaboration has identified five regions of the genome that are strongly associated with primary open-angle glaucoma, the most common form of the disease. It acknowledges new research that suggests that mutations in the myocilin gene can affect development of the myelin sheath that protects the optic nerve, leading to glaucoma, especially the juvenile-onset form of the disease. It is hopeful about new research into a contact lens that releases intraocular pressure-reducing drugs at a steady rate, facilitating better treatment for glaucoma. The Committee requests an update on this research in the fiscal year 2017 CJ.

Action taken or to be taken

Glaucoma is a group of diseases which result in damage to the optic nerve resulting in irreversible vision loss. Over the last decade, NEI scientists have made great progress in discovering risk genes for glaucoma. While the causes of juvenile glaucoma are relatively well understood, allowing clinicians to test for the genes that cause the disease, the genetics are much more complicated for primary open-angle glaucoma (POAG), the most common form of the disease. POAG is highly hereditary and geneticists have identified nine risk genes for POAG. However, these genes do not yet paint a full picture of risk factors. POAG results from the interactions of many genes and environmental factors, each contributing a small but significant effect. The best tool for studying such complex diseases is genome-wide association studies, which requires thousands of patients and healthy controls. The NEIGHBOR (NEI Glaucoma Human genetics collaBORation) consortium, an NEI-led collaborative effort involving 22 investigators at 12 institutions, has included 3,504 POAG patients and 9,746 controls in their analysis, making this the largest such genomic study of glaucoma. They recently added an additional 2,206 POAG patient samples. In 2015, NEIGHBOR investigators reported on the identification of a genetic region shown to be strongly associated with the size of the optic disc, a clinical marker for glaucoma. Patients with POAG often have smaller optic discs.

Patient compliance with prescribed therapy is a challenge with many diseases, including glaucoma, where failure of patients to self-administer eye drops is associated with poorer clinical outcomes. To address this, NEI supports two different projects to develop new drug delivery methods, including a contact lens that directly releases glaucoma drugs into the eye. Both projects are working to increase the duration of drug delivery and to complete pre-clinical safety studies. Regenerating optic nerve axons, which are damaged in glaucoma, is one of the targets of the NEI Audacious Goal Initiative. In 2014, NEI hosted a workshop on optic nerve regeneration and released a funding opportunity in 2015 to discover factors that promote regeneration, which may ultimately help to restore sight lost to glaucoma.

Heart Disease

The Committee recognizes that heart disease presents a grave risk to our Nation's long-term health and economic stability and notes that the prevalence and costs associated with this disease will increase significantly as the population ages. The Committee is concerned that NHLBI's extramural heart research has dropped 17 percent in constant dollars since 2002, and the Committee urges NHLBI to increase heart research commensurate with its impact on public health and scientific opportunity.

Action taken or to be taken

Heart disease is the leading cause of death in the United States. While research conducted by the National Heart, Lung, and Blood Institute (NHLBI) has contributed to the nearly 70 percent decline in deaths from heart disease over the past fifty years, more needs to be done. NHLBI maintains a strong commitment to reducing the burden of heart disease, and heart disease research remains a top priority of the Institute. As the Committee notes, NHLBI funding for heart disease research has dropped 17 percent in constant dollars since 2002. This decline is similar to that of NHLBI's overall budget over the same period – a decrease of almost 20 percent in constant dollars. That decrease has been due primarily to budgetary stagnation and the decline in purchasing power. The fact that funding for heart disease research has decreased 17 percent, while the entire NHLBI budget has decreased by 20 percent, is indicative of NHLBI's efforts to make heart disease research a priority.

One area of great interest and promise is the use of precision medicine to predict patient-specific risk and foster the development of the next generation of more effective drugs that will preempt chronic heart disease. For example, NHLBI-funded research looking for factors that determine the level of low-density lipoprotein (LDL) – so-called bad cholesterol – led to the discovery of PCSK-9, a protein that regulates cholesterol levels in the bloodstream. This finding has now resulted in a new class of drug therapies to prevent heart attacks. To more fully capitalize on the promise of precision medicine, NHLBI recently launched the Trans-Omics for Precision Medicine (TOPMED) program, which will couple whole genome sequencing and other “-omics” (e.g., metabolic profiles, protein and RNA expression patterns) data with molecular, behavioral, imaging, environmental, and clinical data to uncover factors that increase or decrease the risk of disease, identify subtypes of disease, and develop more targeted and personalized treatments.⁷⁷

In a larger context, NHLBI strives to ensure the best use of limited resources. In order to better accomplish this, the NHLBI recently began a strategic visioning process by engaging diverse stakeholders to help shape NHLBI's scientific priorities and guide NHLBI's funding strategies over the next decade. The NHLBI Strategic Research Priorities will be published in early 2016. Please visit the NHLBI website for an overview of the NHLBI strategic visioning process.⁷⁸

⁷⁷ <http://www.nhlbi.nih.gov/research/resources/nhlbi-precision-medicine-initiative/topmed>

⁷⁸ <https://www.nhlbi.nih.gov/about/documents/strategic-visioning>

Heavy Ion Cancer Therapy and Research

The Committee understands NCI recently issued a planning grant for a Heavy Ion Therapy and Research. The Committee encourages NCI to coordinate with other federal agencies on the need and potential funding sources in determining the scientific justification to move forward or retrofit any existing facilities.

Action taken or to be taken

The National Cancer Institute has awarded two exploratory planning grants through the Funding Opportunity Announcement entitled, *Planning for a National Center for Particle Beam Radiation Therapy Research*⁷⁹, to encourage and support planning efforts for the establishment of an independently created and separately funded particle beam radiation therapy facility. These awards were made to the University of Texas Southwestern Medical Center and the University of California, San Francisco. It is expected that this effort will lead to a national research resource capable of successfully competing for and securing the funding required to operate a specialized center for clinical proton and heavier ion beam radiation therapy.

Currently, there are only a few carbon-ion therapy centers operating worldwide with locations in Japan, China, Germany, and Italy. There is a strong interest in the radiation oncology community in the United States to investigate possible application of particle beams (especially carbon – a heavy ion) for cancer treatment, and to compare therapeutic efficacy of different types of charged particles to those of photons and protons. Thus, there is need for a research facility that would allow U.S. scientists to participate in research on oncological applications of a spectrum of particle beams, including carbon-ion beams.

A considerable body of experimental and clinical, treatment-based evidence indicates that in certain settings particle beams might be equally, or more, effective in treating cancer as the most sophisticated photon-based therapies (the current standard approaches) while significantly reducing the volume of normal tissue irradiated. However, there is still a pressing need for more extensive clinical trials to determine appropriate and optimal use of particle beam therapy. To address this need, NCI issued a Sources Sought Notice earlier this year in preparation for a proposed upcoming solicitation for proposals to conduct clinical trials on *Carbon Ion Versus Conventional Radiation Therapy for Locally Advanced, Unresectable Pancreatic Cancer*.⁸⁰ The initiation of clinical trials is a critical next step in validating the benefits of carbon ion therapy.

The Department of Energy has also awarded two grants aimed specifically at developing innovative, particle beam therapy equipment for the treatment of cancer. These awards, along with the two planning grants awarded by the National Cancer Institute, were preceded by a 2013 workshop cosponsored by both agencies on ion beam therapy that helped to define the needs and challenges of the field. Continued collaboration across Federal agencies with related but distinct missions and expertise, including NCI and the Department of Energy, will contribute greatly to researching the potential benefits and advancing the practicality of particle beam approaches to

⁷⁹<http://grants.nih.gov/grants/guide/pa-files/PAR-13-371.html>

⁸⁰https://www.fbo.gov/index/index?s=opportunity&mode=form&tab=core&id=5cbab00c50c3a724a36e3a9fb1f6e24a&_cview=1

cancer treatment.⁸¹ The White House Office of Science and Technology Policy has recognized the efforts of both agencies as important steps to advance this research field.⁸²

⁸¹ <https://www.whitehouse.gov/blog/2015/02/10/targeting-tumors-particle-beams>

⁸² <https://www.whitehouse.gov/blog/2015/04/03/advancing-understanding-particle-beam-therapies-cancer-treatment>

Hepatitis B

The Committee encourages NIAID and NIDDK to continue their long-standing commitment to advancing the scientific knowledge on hepatitis B and chronic hepatitis B. The Committee urges aggressive discovery to find ways to prevent and develop new therapies for hepatitis B that have the potential to be a cure. The Committee requests the NIH Director to consider establishing a hepatitis B specific Integrated Review Group (IRG) to review the grant applications associated with hepatitis B. The Committee also encourages development of an HBV Cure initiative, analogous to the HIV Cure initiative, to coordinate and accelerate the development of a cure for those afflicted with HBV.

Action taken or to be taken

NIAID supports research on the immunology and pathogenesis of hepatitis B virus (HBV) with the goal of identifying new therapeutics to treat and potentially cure HBV infection. NIAID-funded researchers are studying novel HBV antiviral drug strategies, including drugs that utilize alternative mechanisms from currently licensed HBV polymerase inhibitors such as drugs that target the HBV surface antigen, the viral capsid, the covalently closed circular DNA (cccDNA), as well as the host's innate immune system. In addition to these efforts, the NIAID-supported Partnerships for Development of New Therapeutic Classes for Select Viral and Bacterial Pathogens initiative funds research projects to develop new classes of HBV therapeutics to increase treatment choices.

To bridge gaps in the product development pipeline, NIAID offers a broad array of preclinical and clinical research resources and services to academia and industry, including in vitro screening of candidate drugs against HBV. In FY 2014, NIAID screened 302 compounds for HBV antiviral activity. In addition, two NIAID HBV animal model contracts provide researchers with access to a transgenic mouse model and a woodchuck model to evaluate promising HBV antiviral drugs as well as agents to stimulate host immune response to HBV.

While NIAID does not have plans to develop an HBV Cure Initiative, NIAID will continue its current efforts to develop novel therapeutics that have the potential to be a cure and explore opportunities to work with NIDDK and other partners to advance HBV research toward a cure.

NIDDK supports several research programs related to hepatitis B, including a portfolio of investigator-initiated research, intramural research on hepatitis B therapy, and research supported through initiatives, including large, multi-site studies and ancillary studies to clinical trials. The NIDDK-supported Hepatitis B Research Network (HBRN) aims to advance understanding of disease processes and natural history of chronic hepatitis B, as well as to identify effective approaches to treatment with currently available and emerging therapies. Through public-private partnerships and collaboration with the CDC, this multi-center Network, with sites around the United States and Canada, has initiated multiple clinical trials and ancillary studies involving both adults and children with hepatitis B. Additionally, Network investigators target enrollment of special populations, including infected pregnant women, those with acute HBV infections, individuals co-infected with the hepatitis D virus (HDV), and chronically infected individuals experiencing disease flares; an ancillary study to the HBRN focuses on individuals co-infected with both HIV and HBV. The NIDDK's Intramural scientists are advancing research on viral replication and virus-host interactions, as well as translational research related to developing

therapies for infection with HDV, which can infect people with hepatitis B and have severe consequences.

In the Center for Scientific Review over the last two years, about 60 applications per year referred specifically to hepatitis B. We expect each scientific review group to handle more than 200 applications per year, so the number of applications devoted to hepatitis B is about a third of the load we would expect for a single study section, too small a number for a dedicated a scientific review group. The numbers of applications available are further reduced by the need to cluster the small business grant applications in review groups that specialize in these types of applications. What we do in the Center for Scientific Review is to ensure the best investments across many diseases is to focus on either how to attack the infectious mechanism of the specific disease or on the organ most affected. So, HBV applications are reviewed in committees that examine either similar viruses or liver disease. Our experience is that is the best way to foster progress. There are many related diseases and conditions that affect people concurrently. Such groups of diseases and conditions often benefit from being considered as a whole, because the underlying mechanisms, either of the disease or of the body, or both, have common aspects that allows progress in one area to advance other areas. What we learn about liver cancer or HIV, for example, may well lead to new insights about hepatitis B, or vice versa. Such interrelated insights provide some of the most fertile ground for breakthroughs.

Hereditary Hemorrhagic Telangiectasia (HHT)

The Committee encourages multiple NIH Institutes and Centers, including NINDS, NHLBI, NICHD, NHGRI, NIDDK, NIBIB, and NCATS, to explore collaborative research opportunities into improvements for diagnosis and early intervention of HHT and treatment of its manifestations.

Action taken or to be taken

Hereditary Hemorrhagic Telangiectasia (HHT) is a genetic disorder of blood vessels, characterized by fragile connections between arteries and veins that tend to rupture and bleed. When these abnormalities involve small blood vessels, they are called telangiectasias. When larger blood vessels are involved, they are called arteriovenous malformations (AVMs), potentially occurring in multiple organs (e.g., brain, liver, lungs). Symptoms of HHT range from nose bleeds to more serious bleeding conditions.

The National Heart, Lung, and Blood Institute (NHLBI) along with other NIH ICs, such as the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases, support a broad range of research studies to better understand the cellular, molecular, and genetic processes underlying normal and abnormal blood vessel development, with the goal of identifying potential targets for interrupting these pathways to prevent disease progression. NHLBI also supports translational initiatives, such as the NHLBI Vascular Interventions/Innovations and Therapeutics Advances Program, specifically designed to foster translational research in vascular diseases, including the development of new therapeutics for vascular anomalies.

Research projects supported by NINDS and National Institute of Biomedical Imaging and Bioengineering are developing new imaging methods to enable more precise visualization of neurovasculature and detection of vascular malformations. NINDS also collaborates with the National Center for Advancing Translational Sciences to support the Brain Vascular Malformation Consortium (BVMC), which is part of their Rare Diseases Clinical Research Network. 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.

Hydrocephalus Research

The Committee encourages NIH, under the direction of the NINDS, to conduct a state of the science workshop to investigate the status of current federally and non-federal supported hydrocephalus specific research projects. The Committee requests the fiscal year 2017 budget request include a summary of the key recommendations and other findings from the workshop.

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) is committed to funding research to better understand hydrocephalus and to develop new and improved diagnostic methods and treatments. In June 2014 NINDS convened the two-day workshop “Midbrain/Hindbrain Malformation and Hydrocephalus: Understanding the Causes, Consequences, and Gaps in Understanding” in cooperation with the Hydrocephalus Association, Chiari & Syringomyelia Foundation, and the Dandy Walker Alliance. The workshop considered the implications of recent advances in neuroimaging (including sonography, Computed Tomography, and Magnetic Resonance Imaging), which have led to the *in utero* identification of developmental malformation of the brain including those leading to hydrocephalus. The workshop also discussed the remarkable progress in the identification of genes that contribute to these malformations, many of which are related to cilia, which are hair like, often motile, projections from the surface of cells that play important functions in many organs. The meeting discussed not only opportunities arising from these advances, but also potential barriers to progress. For example, inconsistency in detection, diagnosis, and classification of these disorders results in numerous clinical issues, and, despite progress, a clear common biological pathway involved in the development of these disorders is not yet defined. Among the major recommendations of the workshop were the need for an understanding and classification of the disease based on mechanism rather than on just clinical or radiologic findings, centralized biobanking and data repositories, natural history studies of hydrocephalus, and better animal models for study of disease mechanisms and treatment in the laboratory. A white paper, now in preparation, is summarizing the results of discussions, including new paradigms for thinking about hydrocephalus and brain malformation, as well as potential treatments. NINDS is planning a follow up meeting on perinatal/pediatric hydrocephalus focused on understanding the etiology, development of scientific resources (including animal models and cell lines), and potential therapeutics. Together these two workshops will inform NINDS and the scientific community on the state of the science and on priorities for moving forward.

Immunotherapy Research

The Committee is pleased that NIAID has joined AHRQ in co-sponsoring a workshop on allergen immunotherapy effectiveness. The Committee requests an update in the fiscal year 2017 CJ on steps that will be taken to implement the recommendations of the workshop and promote research in this area.

Action taken or to be taken

The National Institute of Allergy and Infectious Diseases' (NIAID's) longstanding support of research to uncover the immunological causes of allergy and asthma is helping to guide the development of better treatments to address these disorders. Allergen immunotherapy is an established approach to treating and a promising approach to preventing allergies by gradually introducing patients to increasing amounts of an allergy-inducing substance to reduce reactions.

NIAID's research efforts on allergen immunotherapy focus on the prevention and treatment of asthma, allergic rhinitis, and food allergy. For example, the Consortium of Food Allergy Research, sponsored by NIAID and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the NIAID-sponsored Immune Tolerance Network (ITN) are developing new approaches to prevent and treat immunoglobulin E-mediated food allergy. A clinical trial conducted by the ITN, which introduced peanut-containing foods in the diet of 4- to 11-month old infants as a means to prevent peanut allergy, resulted in an 81 percent reduction in peanut allergy at age 5, when compared to peanut avoidance. This study indicates that introduction of peanut in infancy is an effective approach to prevent peanut allergies and suggests that similar approaches for other food allergies should be tested. In June 2015, NIAID convened a meeting of experts to begin updating the 2010 food allergy guidelines regarding prevention of peanut allergy in light of this study's findings. NIAID anticipates that this "Guidelines Addendum" will be published in FY 2016.

NIAID also supports research to improve the effectiveness and safety of subcutaneous and sublingual immunotherapy for the treatment of conditions caused by environmental allergens, such as asthma and allergic rhinitis. On June 17, 2015, NIAID cosponsored a workshop with AHRQ on "Improving the Treatment for Allergic Rhinoconjunctivitis and Asthma through Allergen Immunotherapy" to address research needs identified in AHRQ's 2013 *Comparative Effectiveness Review of Allergen-Specific Immunotherapy for the Treatment of Allergic Rhinoconjunctivitis and/or Asthma*. At the workshop, five workgroups presented study proposals and recommendations on future research, including research on sublingual versus subcutaneous immunotherapy; mono- versus multi-allergen immunotherapy; effects of immunotherapy on the progression of childhood asthma and allergies; immunotherapy duration and dosing strategies; and immunotherapy utilization. The workgroups are expected to submit their final study recommendations by November 1, 2015. NIAID plans to publish a manuscript outlining these recommendations in a peer-reviewed journal in FY 2016 to help guide future research on allergen immunotherapy.

NIAID will continue to support research aimed at increasing the effectiveness and safety of immunotherapy, reducing the duration of treatment, and improving our understanding of how immunotherapy helps reduce allergic symptoms. NIAID remains focused on identifying innovative immunotherapeutic approaches to prevent and treat asthma, allergic rhinitis, and food allergies.

Institutional Development Award (IDeA)

The Committee provides a significant increase to the IDeA Program in recognition of the success of this program. The Committee expects NIH to ensure the program is supported at a level of at least 1 percent of total NIH funding in future budget requests. Further, the Committee notes the NIH Centers of Biomedical Research Excellence (COBRE) is proven to successfully increase the number of new scientists at institutions in States eligible for IDeA. The NIH policy has limited the number of COBRE institutions in IDeA States. The Committee expects NIH and NIGMS Directors to jointly review this policy and develop a plan to expand the number of competitively awarded COBREs per institution that include shared funding from outside NIGMS resources. The Committee requests a summary of the outcome of the review and plan forward in the fiscal year 2017 budget request. The Committee expects the NIH Director to ensure all Clinical Translations Science Research awardees actively solicit interaction with IDeA designated states.

Action taken or to be taken

The Institutional Development Award (IDeA) program is designed to enhance the research infrastructure and increase the research capability and competitiveness of investigators in institutions located in states with historically low aggregate grant awards from NIH. Grant awards are made to independent biomedical research institutions that award doctoral degrees in the health sciences or sciences related to health within IDeA-eligible states. The primary objective of the IDeA program is to broaden the geographical distribution of NIH funding for biomedical research.

The IDeA program continues to strive to meet its primary goal to provide biomedical research capacity across all of the IDeA-eligible states and to distribute its resources broadly and appropriately to support cutting edge biomedical research that serves the needs of medically underserved populations in these regions. The program continues to support competing (new and renewals) and non-competing Centers of Biomedical Research Excellence (COBRE) and IDeA Networks of Biomedical Research Excellence (INBRE) awards that constitute the IDeA base. Additionally, support is provided for IDeA Program Infrastructure for Clinical and Translational Research awards and continued co-funding of Independent Research Project (R01 and R15) awards solicited from across the NIH Institutes and Centers (ICs).

Application pressure for IDeA support is high and the program is extremely competitive. Under current program stipulations, the number of COBRE Phase I and Phase II awards that any given institution may have concurrently is limited to three. Phase III COBRE awards or other IDeAs do not contribute to that limit. This limit was put in place to ensure that the funds from the IDeA program had the widest geographic distribution possible among the eligible states. If there were no caps on the number of COBRE awards that could be held by an institution, IDeA funds could become concentrated in a limited number of the larger and more advanced institutions. An eligible institution is defined by its unique Entity Identification Number (EIN) or Data Universal Numbering System (DUNS) number. The larger institutions with many advanced components (e.g., medical school, graduate school, nursing school, school of allied health sciences), each having their own EIN or DUNS identification, may consider each component separately and each component may hold up to three Phase I and II COBRE awards. The IDeA program seeks to raise many institutions in all eligible states to a competitive level rather concentrating IDeA funding in a few institutions in a subset of IDeA states.

In terms of collaboration and shared funding from outside National Institute of General Medical Sciences (NIGMS) sources, NIH ICs are taking increasing interests in and are working with the IDeA program. For instance, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is working with IDeA program staff to develop two funding announcements to support Pediatric Clinical Research Networks in IDeA states. A proposed Data Coordinating and Operations Center (DCOC) will support the activities of the IDeA States Pediatric Clinical Research Network (ISPCRN). The funded DCOC will cooperate with the IDeA Program Directors/Principal Investigators (PDs/Pis) to train pediatric clinical trial teams. These teams will utilize existing infrastructure and networks put in place by the IDeA program in these states to support new research paradigms to address pediatric health, particularly in rural and underserved communities. These initiatives, developed by NICHD in conjunction with NIGMS, will be supported by ECHO funds from the Office of the Director.

IDeA program staff have engaged the Director of the Division of Extramural Research at the National Institute of Dental and Craniofacial Research (NIDCR) in exploring ways to inform dental schools in IDeA states about the funding opportunities for COBRE Phase I. The possibilities discussed were a webinar or having information available at the NIDCR booth in the dental research meeting. The Director will consult with senior staff at NIDCR. Lastly, NIGMS and other ICs will continue to support, through co-funding, meritoriously reviewed research projects that have not made the pay lines of the other ICs. NIGMS is also working on plans to use Small Business Innovation Research/Small Business Technology Transfer funds to set up biotechnology incubators in each of the four IDeA regions.

Clinical and Translational Science Awards (CTSAs) foster collaborations, partnerships, and team science to support a national network of clinical and translational research centers that serve as research hubs by providing expertise, resources, and training that can be leveraged by all the NIH ICs. Institutions within IDeA-designated states are and have always been encouraged to apply for and receive awards through the CTSA program. The National Center for Advancing Translational Sciences (NCATS), which administers the CTSA program, places no restrictions on eligibility related to whether institutions are from IDeA-designated states. Several IDeA-designated states are, in fact, part of the CTSA program hub network: New Hampshire, South Carolina, Kentucky, Arkansas, Kansas, and New Mexico. To contribute to the vision of building an innovative and efficient network for clinical and translational research, NCATS has expanded the capabilities of the CTSA program and will continue to encourage applications from institutions in IDeA-designated states.

Interstitial Cystitis

In addition, the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Interstitial cystitis/painful bladder syndrome (IC/PBS) affects millions of Americans and is characterized by pelvic pain strongly associated with the bladder and with urinary symptoms of frequency and urgency. Current NIH efforts in IC/PBS are focused on understanding the cause(s) of this condition, improving diagnosis, finding more effective treatments, and finding ways to prevent onset. The multi-site Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network is conducting innovative, collaborative studies of IC/PBS and another urologic pelvic pain condition, chronic prostatitis/chronic pelvic pain syndrome.⁸³ The Network is also studying the possible relationships between urologic pelvic pain and other chronic pain disorders, such as IBS and fibromyalgia. Network scientists have recently reported a variety of differences in brain structure and function between women with IC/PBS and healthy counterparts; these findings are now being pursued to determine the potential role(s) of these differences in symptom manifestation, maintenance, and amelioration.

Another Network report describes the burden and impact of self-reported symptom flares on quality of life for women with IC/PBS. Other findings emerging from Network studies include insights into the course of IC/PBS; potential biomarkers; differences in microbes associated with the bladder between patients and healthy controls; characterization of different, potentially clinically relevant sub-groups among people diagnosed with IC/PBS; and tools to track symptom changes and outcomes in people with IC/PBS over time. NIH renewed this very productive Network for a second five-year phase in FY 2014 in order to continue efforts that it is hoped will provide a foundation for effective clinical interventions. Complementing the MAPP Research Network studies, in FY 2015 NIH established the Prevention of Lower Urinary Tract Symptoms Research Consortium. This multi-center, multidisciplinary consortium will plan, perform, and analyze research studies necessary to establish the scientific basis for future prevention-intervention studies for lower urinary tract symptoms and conditions in women.

⁸³ <http://www.mappnetwork.org/>

Kennedy's Disease

In addition, the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following 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 that causes degeneration of the nerve cells in the spinal cord and brain that control muscles of the body. People with SBMA experience slowly progressive muscle atrophy and weakness. Although no treatment has yet proven to alter the course of disease in randomized, controlled clinical trials, the discovery of the gene defect that causes SBMA led to considerable progress in understanding the disease process, the development of cell and animal models to study the disease, and promising strategies for intervention that are now in various stages of testing from the laboratory to the clinic.

The National Institute of Neurological Disorders and Stroke (NINDS) continues to support a full spectrum of extramural and intramural research on SBMA from laboratory studies through clinical trials. Among the key findings, research has demonstrated that the abnormal protein resulting from the defective gene causes disease both by loss of its normal function and by gain of toxic properties, and that muscle cells, as well as nerve cells, may be directly affected by toxicity. In addition to continuing research on the underlying cellular and molecular mechanisms of the disease, investigators are pursuing therapeutic strategies, including a newly funded project on anti-sense oligo-nucleotides in animal models. Complementing extramural research, the NINDS Intramural Research Program continues to make important contributions to SBMA research. Recent intramural activities range from the development of neurons derived from adult stem cells developed from SBMA patient cells, which are valuable for studying disease mechanisms and testing candidate therapies, to validation of clinical rating tools, which are crucial for future clinical trials. The Intramural Program also is continuing a Phase II clinical trial, which started in 2014, that is testing the safety, tolerability, and efficacy of a drug under development by a pharmaceutical company, which reflects how progress from NIH funded research is engaging biotech and pharmaceutical companies to develop treatments for SBMA. In 2015 NINDS also contributed support to a research conference on CAG triplet repeat disorders, a group of genetic diseases sharing a type of genetic error first discovered in SBMA.

Kidney Cancer

The agreement encourages support of meritorious scientific research on kidney cancer, specifically early detection of the disease. The agreement encourages the 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. NCI should provide an update on these efforts in the fiscal year 2017 budget request.

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 (cancer that 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. Advanced RCC frequently spreads to and grows in multiple organs including the brain, liver, and lungs, and has a very poor prognosis. Advances in imaging have increased the percentage of patients eligible for surgical resection, but many still present with disease that is not able to be treated surgically.

Over the last several years, many new agents have been approved by the FDA to treat patients with advanced RCC. Efforts continue in NCI supported clinical trials to use these agents in combination to make treatment more effective, and to explore immunotherapy approaches for RCC. NCI is also supporting research to study potential biomarkers for early detection of RCC, including through its Specialized Program of Research Excellence (SPORE) program. NCI currently supports a Kidney Cancer SPORE at the Dana-Farber/Harvard Cancer Center.⁸⁴ We also anticipate applications from institutions in the near future as NCI has been encouraging investigators to submit applications for Kidney Cancer SPOREs.

Research conducted by the Kidney Cancer SPORE has led to promising recent advances, including a clinical study which showed that patients with treatment-refractory advanced renal cell carcinoma have durable responses to nivolumab, an anti-PD-1 immunotherapy, and that the response remains persistent in some patients after the discontinuation of treatment. This SPORE team is now conducting in-depth investigations on the mechanisms of response and resistance to PD-1 blockade, with the goal of validating RCC biomarkers for early detection and for evaluating response to targeted therapy. Additional projects include studies of combination therapy approaches, drug resistance, and adoptive immunotherapy, as well as a project focusing specifically on prognostic markers to guide treatment of the pediatric kidney cancer Wilms tumor.

The Cancer Genome Atlas (TCGA) research network recently published data analyzing 161 tumors from people with papillary renal cell carcinoma (PRCC) – the second most common form of kidney cancer. Findings from this genomic analysis have confirmed that these subtypes are distinct diseases distinguished by certain genomic characteristics, which could be important in managing patients clinically, identifying new therapies, and designing clinical trials.⁸⁵ TCGA researchers have also studied chromophobe kidney cancer and learned new information about

⁸⁴ <http://trp.cancer.gov/spores/kidney.htm>

⁸⁵ <http://www.ncbi.nlm.nih.gov/pubmed/26536169>

this rare kidney cancer type, including specifics about the tissue origins of the tumor, its low rate of somatic mutations, and key metabolic pathways.

Ongoing research through the SPORE program, along with the other initiatives and programs described above, make up NCI's diverse portfolio of kidney cancer research. NCI continuously strives to stimulate research for specific disease areas and scientific questions and looks forward to receiving proposals for future kidney cancer research efforts.

Kidney Disease

In addition, the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

NIH supports a multi-faceted program of research to identify causes, understand and halt disease progression, develop and improve treatments, and ultimately prevent kidney diseases and kidney failure in adults and children.

The Chronic Renal Insufficiency Cohort (CRIC) Study is evaluating long-term cardiovascular risk and outcomes of over 3,700 persons with chronic kidney disease (CKD). CRIC recently published that systolic blood pressure levels above 130 mm Hg – a lower boundary than current clinical guidelines define as acceptable – is associated with worse kidney outcomes; notably, this finding is consistent with results recently released by the NIH’s landmark Systolic Blood Pressure Intervention Trial (SPRINT) study of blood pressure control in the general adult population.

The Chronic Kidney Disease in Children (CKiD) study in children with mild to moderately decreased kidney function is investigating risk factors for further kidney decline, as well as closely monitoring brain development, examining risk factors for heart disease, and following long-term effects of poor growth in this group; already, CKiD has found that growth is more stunted in lower-income youth with kidney disease. In a related effort, an award was recently issued to an investigator for the planning phase of a trial of phosphate binders in children with bone disease as a result of their CKD; it is anticipated that the trial will be up and running by early 2017.

African Americans have an increased risk of non-diabetic kidney disease, and recent findings emerging from major NIH trials and studies add to the information about genetic contributions to this risk: SPRINT investigators found that variants in the APOL1 gene are associated with increased risk of kidney disease, but not cardiovascular disease in African American participants with high blood pressure; and a study leveraging five NIH-supported cohort studies found evidence suggesting that sickle cell trait may be related to the higher risk of kidney disease in African Americans. To learn more about nephrotic syndrome, NIH recently renewed and expanded the Nephrotic Syndrome Study Network (NEPTUNE) observational study, which now includes a specific pediatric component. Complementing NEPTUNE, the new Cure Glomerulopathy Network (CureGN) consortium 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.

NIH also has launched Improving Chronic Disease Management with Pieces a trial in four large healthcare systems that is using a novel IT approach to follow patients with CKD, hypertension, and diabetes and see whether a model of primary care-subspecialty care collaboration will decrease hospitalizations, cardiovascular events, and deaths in this population when compared to usual care. To help advance potential new CKD therapies, NIH established and is recruiting participants for the CKD Pilot Trials Consortium. Another clinical trial is recruiting participants

to see whether a generic drug (allopurinol) can halt progression of diabetic kidney disease in people with type 1 diabetes. NIH recently renewed a consortium to promote the discovery and validation of biomarkers for CKD, which are greatly needed for research on the causes and course of CKD.

Finally, NIH is supporting ASSESS-AKI, a study of the natural history of patients with acute kidney injury (AKI) that will provide important information about the natural history of AKI and recovery. These are just some of the many efforts NIH is undertaking to overcome the scourge of kidney disease.

Liver Cancer

The Committee continues to be concerned with the lack of a focused liver cancer research program. The NCI is urged to support a Specialized Program of Research Excellence on liver cancer, as well as liver cancer program projects. The Committee encourages more focus on the development of biomarkers to serve as early detection markers of cancer to therefore offer the prospect of improved outcomes

Action taken or to be taken

The incidence of primary liver cancer in the United States is a growing concern, with an estimated 35,660 new cases and 24,500 deaths in 2015. The increased incidence and mortality of liver cancer in the United States is believed to be attributable in large part to Hepatitis C (HCV) infections. Chronic infection with hepatitis B virus (HBV), excessive alcohol consumption, and diabetes and obesity are also important risk factors.

The National Cancer Institute (NCI) is committed to supporting a broad portfolio of research on liver cancer from basic through translational and prevention research. In March of 2014, NCI convened a workshop of experts to explore opportunities in liver cancer research with the goal of identifying research questions and recommendations for coordinated research resources and initiatives. In addition to focusing on biomarkers, screening, and early detection, workshop discussion topics included the molecular pathology and genomics of liver cancer, prevention and treatment, as well as the emergence of obesity and type II diabetes and their associations with liver cancer.

Workshop participants also discussed longitudinal studies (cohort studies) to better define the natural history of liver disease and highlighted research collaborations across NIH as important opportunities. Other topics of discussion included the value of studying cohorts of patients with patients with late-stage liver disease, patients with liver cancer as a result of chronic hepatitis infection, and non-infectious causes of liver cancer, such as steatohepatitis and fatty liver. Research recommendations included focusing on infection and non-infectious risk factors, establishing and validating biomarkers, developing clinically relevant animal models, identifying intervention strategies for prevention and treatment, incorporating obesity research, studying inflammation in animal models and human investigations, and exploring health disparities related to liver cancer. As a result of the workshop, the NCI, National Institute of Allergy and Infectious Diseases (NIAID), and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) are exploring opportunities focusing on developing a liver cancer consortium. This possible activity would study the continuum of the disease from fibrosis to cirrhosis to liver cancer, and would establish biorepositories and cohorts of patients with the goal of improving the screening, detection, prevention, and treatment of liver cancer.

NCI's Specialized Programs of Research Excellence (SPORE) is an investigator-initiated grant program. The number of SPORE grants therefore depends on the scientific merit of applications established by peer review, the availability of funds, and program priorities. Through the workshop noted above and ongoing conversations with the cancer research community, NCI is encouraging investigators to submit applications for Liver Cancer SPOREs and Gastrointestinal (GI) SPOREs with projects on liver carcinoma. NCI anticipates such applications in 2016.

Currently, several of the existing Gastrointestinal SPOREs are studying liver cancer, including studies of genetic changes in hepatocellular carcinoma (HCC), the most common form of liver cancer. Another example includes research focused on comprehensive sequencing for gene mutations in intrahepatic cholangiocarcinomas (ICC), the second most common form of liver cancer, to identify alterations to help understand the fundamental nature of the cancers. Some of these identified mutations are already under investigation as potential targets for intervention by drugs designed to kill cancer cells with specific mutations. In the area of imaging, one GI SPORE developed a tracer designed for Positron Emission Tomography (PET) imaging for tumors. This imaging may allow for improved detection and staging of HCC, as well as provide a novel measure of cancer cell metabolism in these tumors. In addition to being the first study of its kind in the United States, this study will be the first use of this tracer to image a cohort of patients who have benign liver lesions.⁸⁶

NCI's comprehensive research portfolio on liver cancer also includes the Early Detection Research Network's Hepatocellular Carcinoma Early Detection Strategy, a program that is monitoring cirrhotic patients for development of HCC and developing markers for early detection. The NCI-supported National Clinical Trials Network will soon open a Phase III study of focal radiation therapy for unresectable, localized ICC. NCI also supports the Hepatocellular Carcinoma Epidemiology Consortium, an interdisciplinary translational research effort that links liver cancer investigators across the United States to pool their research tools and resources.

NCI intramural investigators are also 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 and are following leads on potential new biomarkers.^{87,88,89,90,91,92}

Through these programs and other initiatives, NCI will continue to encourage research on this important disease.

⁸⁶ <https://clinicaltrials.gov/ct2/show/record/NCT02379377>

⁸⁷ <http://www.ncbi.nlm.nih.gov/pubmed/?term=25758784>

⁸⁸ <http://www.ncbi.nlm.nih.gov/pubmed/?term=25929570>

⁸⁹ <http://www.ncbi.nlm.nih.gov/pubmed/?term=25955255>

⁹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/?term=25833323>

⁹¹ <http://www.ncbi.nlm.nih.gov/pubmed/?term=25953724>

⁹² <http://www.ncbi.nlm.nih.gov/pubmed/?term=26058814>

Lupus Research Plan

The Committee commends NIAMS for leading the effort to review the current state of the science, evaluate progress on the existing lupus research plan and develop a new action plan for lupus research. The Committee applauds the broad solicitation of input across NIH and the greater research and advocacy community, and encourages special attention for efforts in this research area.

Action taken or to be taken

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), on behalf of the NIH, has developed a new plan for lupus research. The Plan, was released on January 13, 2016 and is available on the NIAMS website. The potential research directions presented in the *NIH Action Plan for Lupus Research* have been informed by significant consultation with the research community, patient advocacy groups, and the general public. The Plan includes chapters on etiology, disease mechanisms, development of new treatments, diagnosis and clinical care, special populations, health services research, behavioral and biopsychosocial research, and research training and collaborations.

In December 2014, as a first step in crafting the Plan, NIAMS issued a Request for Information (RFI) to solicit public input on recent progress in lupus research, as well as on the current needs and opportunities for future research. There was a robust response to the RFI, including feedback from researchers, professional societies, and patient advocacy organizations. Through an internal process, the NIAMS also solicited input from the NIH Institutes, Centers, and Offices that conduct or support lupus research. The RFI comments and the NIH input were used to develop a draft of the Plan. In May 2015, NIAMS held a webinar with lupus researchers, professional and health advocacy organizations, as well as experts from across NIH to gather focused input on the draft. After incorporating feedback from webinar participants, in July 2015, NIAMS posted the draft Plan on the Institute website for public comment. Comments received in response to the July 2015 RFI were incorporated, as appropriate. In addition to soliciting public comment, NIAMS also provided regular updates on the process to the Lupus Federal Working Group, NIAMS Advisory Council, and the Congressional Lupus Caucus. The Plan, which reflects a number of diverse perspectives, will help to inform priority setting processes among all lupus-related organizations and serve as a guide for investigators as they develop independent approaches to address promising scientific opportunities in lupus. Basic, translational, and clinical research discoveries and emerging technologies will present additional opportunities to advance our understanding of lupus and how best to manage and ultimately prevent and better treat the condition.

Lymphangiomyomatosis

In addition to the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

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. It is characterized by the proliferation of smooth muscle-like cells and cystic lesions in the lung. LAM may occur sporadically or it may be associated with the genetic disorder, tuberous sclerosis complex (TSC). Most treatments for LAM are aimed at easing symptoms and preventing complications. Lung transplant is one treatment option for women whose lungs have been damaged by LAM. Recent research efforts have focused on finding effective drug therapies for LAM. In fact, sirolimus (rapamycin), the first FDA-approved treatment for LAM, was approved on May 28, 2015, based on research supported by the National Institutes of Health, including the MILES trial.⁹³

The National Heart, Lung, and Blood Institute (NHLBI) continues to support research to identify the causes and other potential treatments of LAM. Although sirolimus has been shown to stabilize lung function, the long-term benefits and side effects of this drug are not clear. In addition, sirolimus causes immunosuppression and once sirolimus is stopped the patient's lung function decline continues. NHLBI is co-funding the Rare Lung Disease Consortium with the National Center for Advancing Translational Sciences (NCATS) to determine the long-term benefits and risks of this drug in LAM patients.⁹⁴ Research is also being done to find additional treatments for this devastating disease. For example, a recent NHLBI-funded study in mice showed that a two drug regimen consisting of sirolimus plus simvastatin prevents growth of LAM-like lung lesions, prevents lung destruction, and can cause a dramatic regression of already established lesions, indicating that this combination treatment may be a promising therapy for LAM.⁹⁵ A follow-up study evaluating the safety of this drug combination in patients with LAM is in progress.⁹⁶ Other studies seek additional treatment targets, to identify molecular markers, and to determine the mechanisms of lung destruction. To promote LAM research, NHLBI co-funds LAM tissue collection, storage, and distribution by the National Disease Research Interchange.⁹⁷ The program has distributed over 2,400 tissue specimens to 31 LAM and TSC investigators, and is open to U.S. and international investigators.

⁹³ <http://www.nejm.org/doi/pdf/10.1056/NEJMoa1100391>

⁹⁴ <https://www.rarediseasesnetwork.org/cms/RLD>

⁹⁵ <http://stm.sciencemag.org/content/4/154/154ra134.full.pdf>

⁹⁶ <https://clinicaltrials.gov/ct2/show/NCT02061397?term=LAM+SOS&rank=1>

⁹⁷ http://www.ndriresource.org/NDRI_Initiatives/Rare_Disease/30/

Maternal Morbidity

The Committee encourages NICHD to work with research institutions and professional societies to identify uniform definitions for severe maternal morbidity.

Action taken or to be taken

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) includes research on a wide range of severe maternal morbidities (SMM) as a core part of its mission and to lessen the rate of maternal mortality in the United States. Working with Federal and non-Federal partners, NICHD has developed a two-pronged approach to address SMM: 1) continued strong support for research on specific health conditions related to SMM; and 2) collaboration on developing uniform and evidence-based definitions that would promote standardized patient care and population-level surveillance and allow comparisons across research activities.

For example, maternal overweight and obesity have been linked to higher maternal and fetal morbidity and mortality, including pregnancy-induced hypertensive disorders and gestational diabetes mellitus (GDM). NICHD is partnering with other NIH Institutes and Centers (ICs) to fund a consortium of clinical sites to test whether lifestyle interventions during pregnancy among overweight and obese women will improve their gestational weight gain and other metabolic outcomes. The consortium has developed a common set of outcomes to assess common objectives, and initial results are anticipated by 2018. In addition, NICHD partnered with the National Heart, Lung, and Blood Institute (NHLBI) to support the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b) sleep study to estimate the prevalence of sleep apnea among 3,700 women during their first pregnancy and to determine whether sleep apnea is a risk factor for adverse pregnancy outcomes. Initial analysis showed that sleep apnea during pregnancy was associated with the development of hypertensive disorders of pregnancy and gestational diabetes. These results are of potential clinical importance, since treating sleep apnea during pregnancy may lessen the risk of these maternal outcomes. In 2013, NICHD organized an NIH Consensus Development Conference to address what criteria to use for the diagnosis of GDM. This effort to standardize the diagnosis of GDM – which is a risk factor for SMM – was endorsed by numerous national and international professional societies.⁹⁸ In addition, NICHD is supporting a study that explores why there are racial and ethnic health disparities in pregnancy outcomes, as well as a study looking at whether pregnant women with epilepsy are at higher risk for preeclampsia, cesarean delivery, preterm labor, or stillbirth.

NICHD has participated in other efforts to define aspects of SMM. In 2015, NICHD collaborated with several professional societies on a workshop to define maternal chorioamnionitis, a condition in which there is intrauterine inflammation or infection of the fetal/maternal membranes and the placenta that can lead to SMM. Due to lack of uniform definition, management has been inconsistent. Workshop participants developed consensus of recommendations, which are expected to be published late 2015. In recent years, NICHD also sponsored similar conferences to define the stages of preterm and term birth to prevent non-

⁹⁸ <https://consensus.nih.gov/2013/gdmstatement.htm>.

medically indicated deliveries and unnecessary cesarean births, both well-recognized risk factors for SMM. These definitions have been endorsed and issued as practice guidelines for the field.⁹⁹

Although SMM is not a discrete condition, NICHD is leading the formation of a working group, in collaboration with federal and non-federal partners, to refine current definitions of SMM (e.g., develop and stratify specific definitions for severe preeclampsia and hypertensive disorders) and to collect high quality data on the occurrence of uterine rupture, thromboembolic disease including stroke, and uncontrolled diabetes, among others. The working group also plans to address mechanisms to track SMM and to develop processes for prevention.

⁹⁹ <http://www.acog.org/About-ACOG/News-Room/News-Releases/2013/Ob-Gyns-Redefine-Meaning-of-Term-Pregnancy>.

Medication Assisted Treatment (MAT)

The Committee understands that NIDA supports 90 research projects totaling over \$41 million related to MAT that include how to incorporate MAT into models of integrated healthcare. The Committee requests an update in the fiscal year 2017 request on research supported across NIH related to MAT, with specific review of MAT in primary care settings. In addition, the Committee expects NIH to conduct a review to identify the scientific gaps related to MAT research.

Action taken or to be taken

Medication assisted treatment (MAT) is available for dependence on opioids, alcohol, and nicotine; for these substance use disorders (SUDs), medications have become an essential component of an ongoing treatment plan. However, despite strong evidence of the efficacy of MAT, these therapies are highly underutilized.¹⁰⁰ The National Institute on Drug Abuse (NIDA) and National Institute on Alcohol Abuse and Alcoholism (NIAAA) support research to:

- Identify and address barriers to MAT implementation in primary care settings;
- Optimize delivery of currently available pharmacotherapies (e.g., optimizing medication formulations, such as transdermal naltrexone and long-acting liposomal buprenorphine for opioid use disorders);
- Develop novel pharmacotherapies, biologics (e.g., vaccines) and non-pharmacological interventions – such as transcranial magnetic stimulation (TMS) – to treat SUDs alone or in combination with other mental health conditions.

In addition, ongoing human laboratory trials are assessing the likelihood of a response to a candidate compound prior to conducting a clinical trial for promising compounds to improve the efficiency of the medication development pipeline.

Given that medications for alcohol use disorders (AUD) are under-utilized in primary care and other settings, NIAAA recently partnered with the Substance Abuse and Mental Health Services Administration to develop Medication for the Treatment of Alcohol Use Disorder: A Brief Guide to assist health care providers in the use of medication-assisted treatment for AUD.¹⁰¹

NIDA and NIAAA will continue to prioritize efforts to increase access to evidence based pharmacotherapies for addiction. In addition, NIH is currently working with the Agency for Healthcare Research and Quality to support a review of current research related to MAT to identify scientific gap areas to guide new research priorities.

¹⁰⁰ Knudsen, H.K.; Abraham, A.J.; and Roman, P.M. Adoption and implementation of medications in addiction treatment programs. *J Addict Med* 2011; 5:21-27.

¹⁰¹ <http://store.samhsa.gov/shin/content/SMA15-4907/SMA15-4907.pdf>

Medications Development

The Committee understands NIDA is considering new technologies for the development of next-generation pharmaceuticals. For example, NIDA is exploring approaches to develop viable immunotherapeutic or biologic (e.g., bioengineered enzymes) approaches for treating addiction. The Committee looks forward to hearing more about work in this area in the fiscal year 2017 budget request.

Action taken or to be taken

In contrast to traditional pharmacological approaches to treat substance use disorders (SUDs), the use of biologics (vaccines, monoclonal antibodies, bioengineered enzymes) is based on the concept of preventing an abused drug from entering the brain. Preclinical studies indicate that biologics are effective in both facilitating abstinence and preventing relapse to abused substances ranging from nicotine to heroin.

One of the most promising areas of biologics development is immune-based approaches for treating addiction. The National Institute on Drug Abuse (NIDA) is continuing to make progress in the development of anti-addiction vaccines, which work by inducing antibodies that target specific drugs and prevent them from entering the brain and exerting their effects. NIDA is supporting research on the development of vaccines to treat cocaine, nicotine, methamphetamine, and opioid addictions. NIDA is also investing in the development of monoclonal antibodies (MAbs) as anti-addiction medications, including ch-mAb7F9 for the treatment of methamphetamine addiction. MAbs bypass the patient's immune system allowing for more precise dosing control.

Another promising area of biologics research is in bioengineered enzymes. Clinical studies have demonstrated the feasibility of using two modified enzymes (a mutated form of a bacterial cocaine esterase and a human butyrylcholinesterase fused to serum albumin (TV 1380)) to treat cocaine intoxication and facilitate abstinence in cocaine dependent subjects. Results are expected this year from a phase II clinical trial of TV 1380 used to facilitate cocaine abstinence.

NIDA has issued two funding opportunity announcements designed to promote partnerships with outside organizations and incentivize high-impact work on development of addiction treatments, including vaccines and biologics: the Strategic Alliances for Medications Development to Treat Substance Use Disorders and the Grand Opportunity in Medications Development for Substance-Use Disorders.^{102,103}

¹⁰² <http://grants.nih.gov/grants/guide/pa-files/PAR-13-334.html>

¹⁰³ <http://grants.nih.gov/grants/guide/pa-files/PAR-13-270.html>

Melanoma

The Committee encourages NCI to develop a 5-year plan across NCI's divisions, and coordinate with other federal agencies and advocates to align melanoma research resources. The Committee understands the NCI MATCH Trial and Exceptional Responders Initiative may provide valuable insight to benefit melanoma subpopulations knowledge and encourages use of these mechanisms. The Committee requests an update in the fiscal year 2017 budget request on these efforts.

Action taken or to be taken

The National Cancer Institute (NCI) recognizes that prevention and early detection are central to reducing mortality and morbidity associated with melanoma. The Institute participated in an NIH-wide effort to endorse the Surgeon General's *Call to Action to Prevent Skin Cancer* (July 2014) and supports these goals by conducting and funding research to strengthen the evidence base that informs public health policy and education efforts. NCI also supports clinical trials to evaluate possible chemopreventive agents and invests in behavioral research to support the development, evaluation, and dissemination of interventions to improve sun protection as a public health priority. Additionally, NCI routinely uses a variety of planning and coordinating mechanisms to manage its cancer research portfolio, within NCI, 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. NCI, like all NIH ICs, relies on a competitive, rigorous peer review process to identify meritorious grant applications. 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. Progress in melanoma research has helped accelerate translation of six new FDA approved drugs to clinical practice between 2011 and 2015 compared to no newly approved drugs in the previous 25 years. The approved drugs included targeted agents and immune checkpoint modulators that have greatly improved clinical response.

The melanoma research community has identified genes altered in melanoma and a higher mutation burden in most melanoma tumors than in other cancers. This high mutational burden is based on changes in DNA characteristic of the effect of UV light. The Cancer Genome Atlas initiative, supported by NCI and the National Human Genome Research Institute, published its comprehensive analysis of the genomes of 333 samples of cutaneous melanoma in June 2015, and identified multiple melanoma subtypes, including BRAF and RAS mutants. These findings have helped clinicians determine which tumors are more aggressive and which are more likely to respond to certain treatments.¹⁰⁴ For example, inhibitory agents targeting BRAF, have significantly improved survival of patients with metastatic melanoma. Furthermore, NCI-sponsored researchers have made great progress in understanding melanoma drug-resistance in BRAF mutants as well as other subtypes, and are working on the development of a new class of anticancer agents that selectively modify cancer cells to make them more susceptible to therapy.

The RAS gene family has also been elusive for direct targeting, forcing indirect targeting of strategies toward other pathway components. Researchers have also identified loss of the tumor suppressor NF1 in some melanomas, and suppression of NF1 leads to increased activation of

¹⁰⁴ <http://www.cell.com/cell/abstract/S0092-8674%2815%2900634-0>

RAS. NCI has initiated a major research effort at the Frederick National Laboratory for Cancer Research with the goal of identifying highly needed approaches therapies targeting RAS and related family genes.¹⁰⁵ Progress in this initiative has the potential to reduce mortality in a broad spectrum of cancers, including melanoma.

NCI continues to develop personalized cancer therapies using novel immunotherapeutic approaches, which include the use of genetically engineered immune cells to destroy cancer cells. Additional efforts are underway to identify biomarkers as predictors of therapeutic success. Moreover, the Institute is supporting two extramural Phase III trials which are using the immuno-modulating antibodies ipilimumab (anti-CTLA-4) or pembrolizumab (anti-PD-1) following surgical resection of melanoma. These therapeutic agents have proven highly effective in treating metastatic melanoma and the final results of these studies will help to establish an effective and new approach for treating melanoma before it metastasizes. Combinations of targeted therapies (anti-BRAF plus anti-PI3K) are being explored, and combinations of immune checkpoint inhibitors ipilimumab and nivolumab (anti-PD-1/PD-L1) have shown promise.

NCI recently launched the Molecular Analysis for Therapy Choice (NCI-MATCH), a clinical trial that analyzes patients' tumors to determine whether they contain genetic abnormalities for which a targeted drug exists, and assigns a treatment based on the abnormality.¹⁰⁶ As part of this trial, oncologists around the country will screen approximately 3,000 patients with advanced solid tumors and lymphomas that are no longer responding (or never responded) to standard therapy. By the end of 2015, NCI-MATCH will have approximately 20 such targeted drugs. NCI MATCH will address several known molecular abnormalities in melanoma. Additionally, NCI's Exceptional Responders Initiative aims to understand the molecular underpinnings of exceptional responses to treatment, primarily via chemotherapy, in cancer patients.¹⁰⁷ NCI continues to collect Exceptional Responder cases from across the cancer research community, in an effort to determine whether certain molecular features of the malignant tissue can predict responses to the same or similar drugs. The initiative is expected to provide important insights about many cancers, including melanoma. So far, 233 cases have been proposed, and 133 have been accepted, including five with melanomas.

¹⁰⁵ <http://www.cancer.gov/research/key-initiatives/ras>

¹⁰⁶ <http://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match>

¹⁰⁷ <http://www.cancer.gov/news-events/press-releases/2014/ExceptionalRespondersQandA>

Microbicides to Prevent HIV/AIDS

In addition to the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

NIAID continues its longstanding effort to identify safe and effective interventions to prevent HIV infection, including microbicides. NIAID's microbicides research program includes basic science to inform improved microbicide strategies and preclinical testing such as pharmacology and toxicology studies to help advance microbicide products toward clinical trials. NIAID also supports microbicides clinical research, including testing of tenofovir- and dapivirine-based vaginal films and rectal microbicide gels for both men and women. NIH's Office of AIDS Research (OAR), which facilitates collaboration among all NIH ICs that support microbicide research, is a key partner in this effort.

NIAID, along with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute for Mental Health (NIMH), supports clinical studies of novel delivery platforms for microbicides through the Microbicide Trials Network (MTN). For example, MTN recently completed one of the first trials to evaluate sustained delivery of an antiretroviral drug from a vaginal ring for HIV prevention. Analysis of data from this Phase III clinical trial, ASPIRE/MTN020, is currently underway to determine whether a vaginal ring containing dapivirine is a safe and effective method to prevent HIV infection. NIAID also is studying the safety of this ring in post-menopausal women and adolescents to provide data for eventual product licensure. In addition, the MTN plans to test rectal microbicide formulations containing tenofovir or dapivirine to identify the most promising candidate to advance into efficacy testing.

NIAID research also seeks to increase the efficacy of microbicide products by combining multiple active agents. MTN expects results in 2016 from a Phase II safety and acceptability study of the oral pre-exposure prophylaxis drug Truvada combined with a rectally applied tenofovir gel in transgender women and men who have sex with men. In addition, MTN is collaborating with Merck to test two products that use the vaginal contraceptive NuvaRing technology to deliver a combination of two classes of antiretroviral agents. MTN also plans to study a vaginal ring containing dapivirine and the hormonal contraceptive levonorgestrel in collaboration with the International Partnership for Microbicides. Building on these efforts, NIAID has initiated a program to develop multipurpose prevention techniques which combine anti-HIV drugs with a contraceptive to increase microbicide use.

In the future, NIAID will continue to support microbicide research in collaboration with OAR, other NIH ICs, and international partners. Planned efforts to investigate the best predictors of safety and efficacy and develop long-acting and easy-to-use formulations will assist NIAID in evaluating a robust pipeline of microbicide products to prevent HIV.

Minority Research

The Committee applauds the NIH Director's efforts to reverse the trend of underrepresentation of researchers from ethnically diverse backgrounds. The Committee encourages NIH to continue newly established programs to enhance NIH-funded workforce diversity.

Action taken or to be taken

In January 2014, and in response to a report and recommendations provided by the NIH Advisory Committee to the Director (ACD) Working Group on Diversity in the Biomedical Research Workforce, NIH appointed Dr. Hannah Valentine as NIH's first Chief Officer for Scientific Workforce Diversity (COSWD) and thus established a centralized agency focus on biomedical research workforce diversity. Scientific workforce diversity (SWD) efforts align with four key strategic goals: expanding inquiry into the science of diversity; weaving diversity inclusion into policy and practice; sustaining career trajectories; and promoting the value of diversity in research excellence. Intramural activities include: development of tools to expand recruitment pools for faculty searches; increased programming for graduate and postdoctoral trainees from underrepresented groups; and an innovative, trans-NIH "Diversity Catalysts" effort to develop, pilot, and scale new diversity approaches at NIH. Extramural activities include: a nationwide consortium for enhancing research training and mentoring (see below for more detail); evaluation of existing programs through monitoring outcomes and tracking; development of standard, trans-NIH policy for including diversity and inclusion language in funding announcements; addressing fairness in peer review; and development of a national strategy for developing sustainability in maintaining scientific workforce diversity.

The Enhancing the Diversity of the NIH-funded Workforce program was launched in FY 2014 and consists of three integrated initiatives operating as the Diversity Program Consortium: 1) Building Infrastructure Leading to Diversity (BUILD); 2) National Research Mentoring Network (NRMN); and 3) Coordination and Evaluation Center (CEC). Collectively, the Diversity Program Consortium represents a critical investment in student development, faculty training and mentoring, infrastructure development, and rigorous assessment and evaluation of intervention strategies that are necessary to achieve the NIH's goal of increased diversity in the biomedical and health professional workforce. The NIH Common Fund has allocated approximately \$250 million over five years to the Diversity Program Consortium. This includes issuing twelve five-year awards (10 BUILD awards, one NRMN award, and one CEC award) totaling approximately \$31 million for FY 2014 in September 2014.

The funded BUILD institutions are partnering with over 80 pipeline or research-intensive partner institutions and the NRMN award includes five core partner institutions and over 100 partner organizations and societies. First-year accomplishments include: developing and implementing summer research programs, faculty development, and infrastructure development; developing consortium-wide hallmarks of success and outcomes for measuring impact; completing evaluation plans for each BUILD and NRMN site and an overall consortium evaluation plan; completing introductory BUILD and NRMN site visits with NIH/CEC; launching the NRMNet.net web portal and enrolling mentors and mentees; and completing mentor training workshops and launching four professional development programs.

Mitochondrial Disease

The Committee continues to support the study of mitochondrial function and primary mitochondrial disease. The Committee understands NIH supported a two-day workshop in March 2012 on primary mitochondrial diseases, which led to the development of a white paper and a working group on mitochondrial disease research with broad participation from various ICs. The Committee requests an update on the steps NIH has taken, on-going, and planned to further each of the white paper recommendations in the fiscal year 2017 budget request.

Action taken or to be taken

NIH continues to support a robust research program in mitochondrial function and dysfunction, which represents a collective effort involving many NIH Institutes and Centers (ICs) and has resulted in significant progress. Augmented by new approaches in imaging technologies and next generation genome sequencing, evidence is growing that genetic or acquired mitochondrial dysfunction contributes to a number of diseases. NIH fosters a wide range of research on these diseases including the development of animal models for primary mitochondrial disorders, natural history and pathophysiology studies, and development of treatment interventions.

Recommendations made during the March 2012 workshop on primary mitochondrial disease are being implemented. These include the establishment of: 1) a patient registry and biorepository that will serve as a basis for natural history studies and clinical trials for new evidence-based interventions; 2) the Mitochondrial Disease Sequence Data Resource Consortium, which is developing a repository of genomic sequencing data for mitochondrial disorders; and 3) an NIH mitochondrial disease working group to coordinate activities within NIH and with investigators and patient representatives. The trans-NIH Mitochondrial Disorders Working Group, which is co-chaired by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and National Institute of Neurological Disorders and Stroke (NINDS), and the public-private North American Mitochondrial Disease Consortium (NAMDC) jointly provide coordination.

Along with these coordinated efforts, many NIH ICs fund research on mitochondrial disease and function relevant to their respective missions and expertise. Longstanding NICHD-supported research has led to an understanding of the natural history of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), including the identification of possible biomarkers for disease progression and clinical trials for potential effective treatments. NICHD and the Office of Dietary Supplements convened a workshop on Nutritional Interventions in Primary Mitochondrial Disease in December 2014 to identify a research agenda to develop evidence-based nutritional interventions for mitochondrial disorders; a publication that lays out the gaps in research and recommendations is pending.

NINDS supports and conducts 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. To facilitate data sharing and aggregation in clinical research, the NINDS has developed a set of standard data types and definitions for mitochondrial disease within the NINDS Common Data Elements project.¹⁰⁸

¹⁰⁸ https://commondataelements.ninds.nih.gov/MITO.aspx#tab=Data_Standards

The National Human Genome Research Institute (NHGRI) is currently supporting three clinical protocols on mitochondrial disorders in its intramural program: 1) the Undiagnosed Diseases program, which is identifying patients with rare or novel mitochondrial disorders; 2) a treatment protocol that is open to patients with primary or secondary mitochondrial dysfunction; and 3) a protocol that includes a cohort of patients who have secondary mitochondrial DNA depletion syndrome. In addition, NHGRI manages the Clinical Genome Research consortium, which coordinates a database of genetic variants related to mitochondrial diseases.

Mother-Infant Relationship

The Committee urges NICHD to continue support for a robust intramural and extramural research portfolio identifying and describing the complex interaction of behavioral, social, environmental, and genetic factors on health outcomes with the ultimate goal of improved understanding of and interventions for disorders such as depression, addiction, and autism.

Action taken or to be taken

A central component of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development's (NICHD's) mission is to conduct and support a broad range of research on the health of mothers and children. For example, NICHD's Child Development and Behavior Branch funds research on the mother-infant relationship. Recently awarded grants are exploring post-partum depression and its impact on parenting; child socio-emotional, cognitive, and physical outcomes; and the development of interventions that may prevent the transmission of risk from depressed mothers to their children. Other studies are examining maternal caregiving and parenting behaviors to identify factors that promote secure attachment; infant stress and emotion regulation; and positive psychosocial development. One recently completed study investigated epigenetic pathways in settings ranging from variations in the quality of early environmental and parental interactions to problem behavior outcomes during adolescence. Additional grants have focused on neuroscience and are looking at brain function and neuroendocrine processes resulting from mother and infant early bonding; how the quality of mother-infant interactions affect health outcomes and cognitive, motor, and language development in low birth-weight preterm infants; the underlying mechanisms by which poverty and chronic stress lead to neurobiological effects in infants and children; and the neurobiology underlying variability in sensitivity of fathers to their infants.

NICHD's Intellectual and Developmental Disabilities Branch supports research on autism spectrum disorder (ASD), a developmental disability that can cause significant social, communication, and behavioral challenges. Some scientists believe that ASD is a result of medical problems that occurred when the child was *in utero*. A recent study by NICHD-funded researchers explored whether there might be a connection between preeclampsia and ASD or developmental delay (DD), finding that children with ASD or DD were twice as likely to have been exposed to preeclampsia as children who did not have ASD or DD. NICHD also recently funded a project to develop and pilot test a parent-delivered intervention for 9- to 15-month-olds at high risk for developing ASD. The 12-week long intervention targets symptoms of ASD such as abnormal repetitive behaviors, visual fixation on objects, and lack of intentional communicative actions. Parents met with professional therapists each week for training on parenting skills to address developmental needs related to the targeted symptoms. The children who received the intervention showed less impairment of autism symptoms and developmental delays at 36 months of age.

The Prenatal Alcohol and SIDS and Stillbirth (PASS) Network was established in 2003 as a partnership between NICHD's Pregnancy and Perinatology Branch and the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The Network is designed to conduct community-linked studies to investigate the role of prenatal exposure to alcohol in Sudden Infant Death

Syndrome (SIDS) and adverse pregnancy outcomes, such as stillbirth and fetal alcohol spectrum disorders, and how these outcomes may be interrelated. This knowledge may help women, families, physicians, and researchers improve pregnancy outcomes and infant health.

Muscular Dystrophy

The Committee is aware that amendments to the Muscular Dystrophy CARE Act were enacted into law in 2014 and requests an update from NIH in the fiscal year 2017 CJ as to the implementation of the updated provisions, particularly a plan to address emerging research opportunities in non-skeletal muscle manifestations such as bone health and endocrine-functioning. The Committee also requests that NIH provide an update on its plans to finalize and implement an updated Action Plan for the Muscular Dystrophies and to convene at least two meetings per calendar year of the Muscular Dystrophy Coordinating Committee.

Action taken or to be taken

NIH is working to implement the recent changes to the MD-CARE Act, which focus on the membership and activities of the Muscular Dystrophy Coordinating Committee (MDCC), which NIH manages. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Director has been chairing the Committee, but recently announced his retirement; MDCC will select a new chair at its next meeting. The MD-CARE Act of 2014 requires that representatives from the Social Security Administration and the Administration for Community Living be added to the MDCC roster, and new members from these agencies have been nominated. Representatives from these agencies already attended the MDCC meeting on March 17, 2015, as *ad hoc* members. An additional public member also has been nominated to the Committee in accordance with the membership guidelines required by law. NIH is committed to holding two MDCC meetings per year. In 2015, the first meeting was held in March and the second one in November. The meetings for the 2016 calendar year will be scheduled soon.

At the March 2015 meeting of MDCC, Federal agencies reported on recent activities including several NIH- and FDA-sponsored workshops, an update on policy issues surrounding newborn screening for neuromuscular disorders, a discussion of the implementation of clinical care guidelines for the muscular dystrophies, and an overview of programs relevant to the muscular dystrophies at the Department of Defense, Social Security Administration, Health Resources and Services Administration, and Department of Education. The meeting also included a discussion of the draft 2015 Action Plan for the Muscular Dystrophies. MDCC members offered comments on the draft Plan and stressed the need to include a strategy for monitoring progress on the objectives of the Plan. MDCC formed a subcommittee to discuss this issue further. The subcommittee has met via teleconference and based on their input, NIH staff is drafting a proposed strategy for monitoring progress on the Action Plan. This was discussed at the November 2015 MDCC meeting.

In 2015, NIH staff met with members of the muscular dystrophy community to discuss issues related to bone defects, appropriate tools for measuring bone health, and strategies to build and preserve bone in boys and young men who have Duchenne muscular dystrophy. NIH expects to continue to work with the muscular dystrophy community to explore ways to encourage investigator-initiated applications in these areas in FY 2016. The 2015 Action Plan for the Muscular Dystrophies also will include language emphasizing the need for understanding the effects of the muscular dystrophies on many organ systems, including the heart, diaphragm and respiration, brain and central nervous system, gut, bones, and endocrine system, as well as the need for treatments that target these organ systems.

Nanovaccines

In addition to the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Research to develop vaccines against bacterial, viral, and parasitic microbes is a longstanding priority of the National Institute of Allergy and Infectious Diseases (NIAID). Nanovaccines are a novel vaccine approach that uses nanotechnology such as nanoparticles or virus-like particles to elicit a response to a pathogen. Nanovaccines are an exciting new field because they have the potential to improve vaccine development and delivery.

NIAID supports basic and clinical research on nanovaccine candidates. For example, scientists with NIAID's Vaccine Research Center developed a hemagglutinin-ferritin nanoparticle that has shown promise as a universal influenza vaccine candidate in preclinical studies. A universal influenza vaccine is of great importance to protect against potential influenza pandemics and it overcomes current seasonal influenza vaccine limitations such as its limited efficacy. As part of NIH's effort to develop an effective Ebola vaccine candidate, NIAID, in partnership with Novavax, Inc., generated an Ebola recombinant nanoparticle vaccine candidate. NIAID is investigating immunogenicity and efficacy of this vaccine in nonhuman primates in a study that began in December 2015. In addition, NIAID researchers have generated two new nanovaccines, currently in clinical trials, that are designed to block transmission of malaria. NIAID also is supporting two Center for HIV/AIDS Vaccine Immunology and Immunogen Discovery projects that use HIV nanovaccine approaches. Other NIAID-supported nanovaccines target the pathogens that cause anthrax, cholera, and dengue fever.

NIAID supports research on nanotechnology to improve vaccine delivery systems, such as transcutaneous and nasal vaccines, vaccines that do not require refrigeration for delivery and storage, and nanotechnology to enhance antigen and adjuvant delivery, improvement of vaccine delivery systems increases their efficacy, decreases cost and broadens the population which can be reach by vaccination. For example, NIAID funded NanoBio Corporation to develop W805EC, a vaccine adjuvant in the form of a nanoemulsion, or small lipid-liquid droplets. In a Phase I clinical trial, W805EC administered with a seasonal influenza vaccine was safe and immunogenic, demonstrating proof of concept for potential application of this technology.

Nanovaccines have the potential to transform the development and delivery of vaccines for a broad spectrum of diseases. NIAID will continue to advance research on nanovaccines to combat infectious diseases of public health concern.

National Children's Study (NCS)

The Committee urges NIH to recalibrate and realign the investment already made in the NCS to initiate new and focus existing longitudinal studies to address the objectives identified for the NCS. The NIH should rely upon a formal scientific advisory mechanism to coordinate efforts across studies. The research efforts should incorporate expertise in population health and environmental epidemiology, integrate basic science, and leverage maternal/infant cohorts. It is also important to study the intertwined biological, behavioral, and social transmission of obesity and obesity-related risk factors across generations and to test intergenerational, exposure-disease associations by linking maternal and infant/child data.

Action taken or to be taken

Following the closure of the National Children's Study in FY 2015, Dr. Francis Collins, NIH Director, emphasized the importance of and need for research addressing the links between the environment and child health and development. To make the best use of the NCS-appropriated funds for FY 2015, NIH established new programs and enhanced existing programs by incorporating more comprehensive environmental assessments, and focusing on tool development and understanding the "seeds" of future diseases and conditions.

The new program under development by the NIH Office of the Director for FY 2016 is called the Environmental influences on Child Health Outcomes (ECHO) program. It continues to leverage investments made in existing programs, including those established in FY 2015, while providing the flexibility to investigate key questions of interest at the intersection of environmental health and pediatric research. NIH will support (through cooperative agreements) multiple synergistic, longitudinal studies using extant maternal/pediatric cohorts that represent a broad range of environmental exposures (e.g., physical, chemical, biological, behavioral, social). All longitudinal studies will collect a standardized, targeted set of data (Core Elements) as a component of the project. These Core Elements will include demographics, typical early health and development, genetic influences on early childhood health and development, and environmental factors. The studies will focus on four key pediatric outcomes (Focus Areas) – upper and lower airway; obesity; pre-, peri-, and postnatal outcomes; and neurodevelopment. Basic mechanistic studies that can only be done using human cohorts will be included and encouraged.

An additional opportunity for creating an IDeA States Pediatric Clinical Trials Network also will be available in FY 2016. This national network will leverage the existing IDeA infrastructure and assist institutions in IDeA-eligible States in establishing and maintaining pediatric clinical trial teams by embedding clinical trials experts at IDeA State locations and facilitating their partnership with academic institutions outside the IDeA consortium. This network will increase recruitment and augment geographic diversity of pediatric clinical trials to help address access gaps for rural children. The IDeA network will be linked, in part, to the ECHO program by prioritizing proposed pediatric trials in one of the four ECHO Focus Areas.

The ECHO program will be overseen by a NIH Program Director with extensive expertise in clinical epidemiology and managing large cohorts. Additional expertise will be gathered through a Steering Committee and an External Scientific Board, both of which will advise and consult on

various issues, including those related to research questions, study design, and cohort harmonization.

The plan described above for FY 2016 is intended to be a multi-year program; therefore, much of it will be continued into FY 2017 and beyond. Additionally, beyond FY 2016, the plan will be assessed to determine whether improvements can be made or additional scientific and/or technological advances can be leveraged. This will be informative in FY 2017, in particular, as it will provide insight into the successes and areas of opportunity during the inaugural year of the program in FY 2016, which could drive its future direction.

National Children's Study Alternative

The Committee was disappointed that NIH determined it was not feasible for NIH to implement the National Children's Study (NCS) as originally conceived. ...The Committee directs and provides funding for continuation of the NCS in an alternative form called the National Children's Study Alternative (NCS–A). The NIH is directed to work in consultation with pediatric groups to develop a series of alternative research activities that build on NCS data and the overarching goals of the NCS to address the developmental origins of health and disease through a series of studies (including longitudinal) that incorporate expertise in biology and epidemiology, integrate basic science, and leverage maternal/infant cohorts, either denovo or from extant networks. NIH is expected to focus on at least prematurity, obesity, autism, asthma, and pediatric rare diseases like cancer. The Committee expects NIH to obtain data, biological samples, and specimens that can ultimately improve child health and well-being. The Committee understands that such a program can be built by leveraging existing cohort studies by expanding or adding study components; supporting projects with smaller cohorts that can investigate unique, disease-specific questions; expanding studies to increase sample size; and using or expanding pediatric networks and extant programs to include a focus on pediatric health.

Action taken or to be taken

Following the closure of the National Children's Study (NCS) in FY 2015, Dr. Francis Collins, NIH Director, emphasized the importance of and need for research addressing the links between the environment and child health and development. To make the best use of the NCS-appropriated funds for FY 2015, NIH established new programs and enhanced existing programs in pediatric research by incorporating more comprehensive environmental assessments, and focusing on tool development and understanding the "seeds" of future diseases and conditions.

To develop the new FY 2016 program, called the Environmental influences on Child Health Outcomes (ECHO) program, the NIH Office of the Director sought extensive feedback from the community through multiple mechanisms, including meetings with key stakeholders, a Request for Information, and a feedback blog. The ECHO program will continue to leverage investments made in existing programs, including those established in FY 2015, while providing the flexibility to investigate key questions of interest at the intersection of environmental health and pediatric research. NIH will support (through cooperative agreements) multiple synergistic, longitudinal studies using existing maternal/pediatric cohorts that represent a broad range of environmental exposures (e.g., physical, chemical, biological, behavioral, social), cohort sizes, and scientific questions. All studies will collect a standardized, targeted set of data (Core Elements) as a component of the project. These Core Elements will include demographics, typical early health and development, genetic influences on early childhood health and development, and environmental factors. The studies will focus on four key pediatric outcomes (Focus Areas) – upper and lower airway; obesity; pre-, peri-, and postnatal outcomes; and neurodevelopment. Basic mechanistic studies that can only be done using human cohorts will be included and encouraged.

An additional opportunity for creating an IDeA States Pediatric Clinical Trials Network also will be available in FY 2016. This national network will leverage the existing IDeA infrastructure and assist institutions in IDeA-eligible States in establishing and maintaining pediatric clinical trial teams by embedding clinical trials experts at IDeA State locations and facilitating their

partnership with academic institutions outside the IDeA consortium. This network will increase recruitment and augment geographic diversity of pediatric clinical trials to help address access gaps for rural children. The IDeA network will be linked, in part, to the ECHO program by prioritizing proposed pediatric trials in one of the four ECHO Focus Areas.

The ECHO program will be overseen by a NIH Program Director with extensive expertise in clinical epidemiology and managing large cohorts. Additional expertise and input will be gathered through a Steering Committee and an External Scientific Board, both of which will be composed of outside experts to advise and consult on various issues, including those related to research questions, study design, and cohort harmonization.

The plan described above for FY 2016 is intended to be a multi-year program; therefore, much of it will be continued into FY 2017 and beyond. Additionally, beyond FY 2016, the program will be assessed to determine whether improvements can be made or additional scientific and/or technological advances can be leveraged, and also to ensure the ECHO program continues to supplement other on-going children's research. This will be informative in FY 2017, in particular, as it will provide insight into the successes and areas of opportunity during the inaugural year of the program in FY 16, which could drive its future direction.

National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Condition (GenTAC)

The Committee recognizes NHLBI for its leadership and support of the GenTAC Registry. The Committee understands this important initiative will be concluding in 2016, and requests an update on the Institute's plans in the fiscal year 2017 CJ.

Action taken or to be taken

The GenTAC registry was established by the National Heart, Lung, and Blood Institute (NHLBI) in 2006 to facilitate research aimed at improving the diagnosis and management of individuals with genetically induced thoracic aortic disease and related cardiovascular and non-cardiovascular conditions. To date, GenTAC houses data and biospecimens from over 3,700 individuals with one of the 13 eligible conditions, including Marfan, Loeys-Dietz, Turner, and Ehlers-Danlos syndromes. Data and biospecimens collected from these individuals are made available to eligible investigators within and outside the GenTAC group of investigators. The registry has already supported over 80 research projects. This program has enlisted and enabled collaborations between U.S. and international academic centers and patients-driven organizations, including the Marfan Foundation, Turner Research Network, Turner Syndrome Society, and Ehlers Danlos Syndrome Network C.A.R.E.S. Foundation.

NHLBI funding for GenTAC will conclude on September 29, 2016. At that time, GenTAC data and biospecimens will be transferred to NHLBI, and will continue to be available to eligible investigators for research through NHLBI-funded BioLINCC (Biologic Specimen and Data Repository Information and Coordinating Center). In addition, GenTAC investigators have been exploring avenues to continue the registry to extend the longitudinal data, such as through patient organizations (e.g., the Marfan Foundation and the Turner Syndrome Society Research Network). Investigators are also pursuing independent R01 funding to continue investigation of specific subsets of the GenTAC cohort.

National Strategy for Combating Antibiotic Resistant Bacteria (CARB)

The Committee directs the Department to work with the Departments of Defense, Agriculture, Veterans Affairs and the Food and Drug Administration (FDA) to both track and store antibiotic resistance (AbR) genes and the mobile genetic elements from AbR bacteria. This information, along with metadata, including geographic information system coordinates describing where they were isolated, is essential to monitor emerging AbR bacteria, assess their threat to public health and develop mitigation strategies. The Committee further directs the Department to include in their fiscal year 2017 request the progress being made in implementing the above language and the overall CARB national strategy initiative.

Action taken or to be taken

National Institute of Allergy and Infectious Disease (NIAID), as the lead NIH Institute for research on antibiotic resistance, has long been committed to addressing the problem of antibiotic-resistant bacteria through basic, translational, and clinical research. In addition, NIAID intramural research explores genetic data and other comprehensive data to understand how antibiotic resistance emerges and identify mitigation strategies. NIAID works closely with many partners within NIH as well as with other Federal agencies to respond to the increasing public health concern of antibiotic resistance.

NIH plays a key role in the Administration's five-year *National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB)*, which outlines specific milestones, timelines, and metrics for implementation of the comprehensive *National Strategy for CARB*. In accordance with the *Action Plan*, NIH is developing a national genomic sequence database of antibiotic-resistant bacteria; supporting a prize award to incentivize development of rapid, point-of-care diagnostics; and expanding its Antibacterial Resistance Leadership Group (ARLG) to increase clinical research capacity to evaluate new antibacterial strategies.

As outlined in the *Action Plan*, NIH is working to develop and maintain the *National Database of Resistant Pathogens* with assistance from FDA, CDC, and DOD. The pilot database will contain genomic data and associated metadata and clinical data for approximately 300 antibiotic-resistant bacterial strains as reference data sets. NIH will work with public and private partners to sequence and add emerging strains and high-priority reference strains identified by CDC and FDA on an ongoing basis. The *National Database* will build upon NIAID's longstanding efforts to collect genomic data on antibiotic-resistant bacteria. For example, NIAID has supported the genomic analysis of more than 5000 antibiotic-resistant bacteria, including newly emerging pathogens of concern such as carbapenem-resistant *Enterobacteriaceae* (CRE). NIH will continue to ensure rapid public release of data from these strains and from the *National Database* to facilitate research and advance drug discovery.

To support the development of enhanced diagnostics for antibiotic-resistant bacteria in accordance with the *Action Plan*, NIH and the Biomedical Advanced Research and Development Authority, in collaboration with FDA and CDC, will fund a \$20 million prize award to incentivize the development of rapid, point-of-care diagnostics. On June 2, 2015, NIH released a request for information seeking public input on the prize criteria. In addition, NIH will hold a public consultation on October 7, 2015, to seek stakeholder comments on the prize criteria. NIH is currently evaluating the public comments received.

The expansion of NIAID's ARLG network will enable clinical studies of antibiotic-resistant strains and facilitate development of new antibacterial strategies. For example, the ARLG is conducting an observational study of carbapenem-resistant *Klebsiella pneumoniae* among hospitalized patients to collect patient metadata and information about infecting strains. The ARLG also hosts a web-based Virtual Biorepository Catalogue to provide researchers with access to well-characterized bacterial strains for the development of diagnostic tests, novel antibacterial compounds, and studies evaluating mechanisms of resistance.

NIH will continue to collaborate with FDA, CDC, DOD, and others to develop and maintain the *National Database of Resistant Pathogens* and sustain longstanding efforts to track and store data on antibiotic-resistant bacteria. NIAID remains committed to supporting the goals of the *National Strategy on CARB* and addressing the emergence of antibiotic-resistant bacteria.

NCI Designated Cancer Centers

The Committee requests an update in the fiscal year 2017 request on how NCI supports or plans to support Institutional Development Award programs in states to broaden the NCI designated cancer center representation within these states.

Action taken or to be taken

The National Cancer Institute (NCI), through its Office of Cancer Centers (OCC), currently supports 69 NCI-designated Cancer Centers in 35 States and the District of Columbia. In addition to monitoring NCI's current portfolio of centers, OCC provides advice to emerging cancer centers and assists them in planning applications to become NCI-designated centers.

To be successful in achieving NCI designation, the center must demonstrate six essential characteristics to peer reviewers and to NCI: depth and quality of its cancer-relevant research; strong institutional commitment from its academic home; organizational capabilities to maximize the center's cancer research capabilities; distinct physical space necessary to carry out the center's mission and give it a unique identity; transdisciplinary research bridging all facets of cancer research; and qualifications of the Center Director as a scientific and administrative leader.

Every NCI-designated center possesses these six essential characteristics. In addition, a center must also specifically address in its research the cancers that occur in the area it serves, known as its catchment area. To meet the six essential characteristics and serve its catchment area in the research it conducts is a substantial task, usually taking years of planning and growth, and considerable institutional funding before a center can be competitive for the NCI designation.

The Institutional Development Award (IDeA) program, supported by the National Institute of General Medical Sciences (NIGMS) since December 2011, is intended to broaden the geographic distribution of NIH funding for biomedical and behavioral research and enhance the competitiveness of investigators at institutions located in states in which the aggregate success rate for applications to NIH has historically been low. The program also serves unique populations in those states, such as rural and medically underserved communities. Specifically, the IDeA program, increases the competitiveness of investigators by supporting faculty development and enhancing research infrastructure at institutions in 23 states and Puerto Rico.

The IDeA program has three main components. One component is the Centers for Biomedical Research Excellence (COBRE) awards, which aim to strengthen institutional biomedical research capabilities through support of a multidisciplinary center led by a peer-reviewed, NIH-funded investigator with expertise central to the theme of the grant proposal. A second component is the IDeA Networks of Biomedical Research Excellence (INBRE) awards, which strengthen the research capabilities of biomedical research faculty and provide access to biomedical resources for promising undergraduate students. The third component is the IDeA Program Infrastructure for Clinical and Translational Research (IDeA-CTR) initiative to encourage applications from IDeA states to develop infrastructure and capacity to conduct clinical and translational research on diseases that affect medically underserved populations and/or diseases prevalent to IDeA states. Additionally, NIGMS will co-fund awards made by another NIH IC to support investigator-initiated research project grants at institutions within

IDeA-eligible states. NCI and NIGMS have co-funded a number of such awards over the years, including an award issued in September 2015 to West Virginia University.

Successful applicants focusing on cancer research would be able to pursue any of the IDeA award mechanisms, as well as other NCI and NIH awards, to further build cancer research capacity. For example, NIGMS supports an IDeA Center for Biomedical Research Excellence at West Virginia University, and the scope of this award focuses specifically on cancer research, building capacity in basic research in particular. West Virginia University, and its Mary Babb Randolph Cancer Center, will use the IDeA award to further strengthen core facilities and faculty, with a long term goal of successfully competing for designation as an NCI Cancer Center. Additionally, eight IDeA states are home to NCI-designated cancer centers, and a number of IDeA COBRE grantees are working within or in collaboration with these centers. For example, the University of Kansas Center for Cancer Experimental Therapeutics COBRE is contributing to the efforts of the University of Kansas Cancer Center, which received NCI designation in 2012. Similarly, the Center for Evolutionary and Theoretical Immunology COBRE at the University of New Mexico supports research efforts that contribute to the activities of the university's NCI-designated comprehensive cancer center.

Given that the IDeA program is administered by NIGMS, NCI and other NIH Institutes and Centers do not establish separate IDeA programs, as that would duplicate NIGMS efforts. NCI and NIGMS expect to continue to co-fund research applications as meritorious proposals identified through peer review. As noted above, NCI's OCC will also continue to provide advice to emerging cancer centers, including those in IDeA-eligible States. For example, OCC recently met with the leadership of the Rockefeller Cancer Institute, based at the University of Arkansas for Medical Sciences (UAMS), for such a discussion. UAMS is home to two IDeA COBRE programs, and is a partner in the Arkansas INBRE. Additionally, as opportunities arise, OCC will make institutions from IDeA-eligible States aware of the IDeA program as a possible source of funding to increase cancer research capacity.

NCI Precision Medicine Initiative (PMI)

The Committee provides the requested funds to support the five-year NCI PMI plan that will support activities such as the pediatric MATCH trial, clinical trials for five major cancer types based on genomic driven data, liquid biopsies, new models of cancer diagnostics, test targeted agents for clinical trials, and related informatics infrastructure. The Committee understands the NCI PMI is a one-time increase of \$70,000,000 for five years.. The Committee requests NCI to provide a breakout in the fiscal year 2017 budget request and future years with the specific science and funding details with these and NCI funds already supporting the PMI activity. The details should include long-term goals, milestones, and annual progress. The Committee encourages NCI, as scientifically feasible, to support existing research networks, especially collaborative efforts among NCI supported cancer centers and institutions serving historically underserved populations, as they have certain attributes of cancer genomic data sharing that may be particularly effective.

Action taken or to be taken

Cancer presents an exceptionally promising opportunity to refine the principles and practices that will serve as the foundation for precision medicine. The additional funding associated with the Precision Medicine Initiative (PMI) will allow the National Cancer Institute (NCI) to expand the NCI-Molecular Analysis for Therapy Choice (MATCH) study. This expansion will include the addition of new genetically targeted therapies to which patients can be matched and an increase in the number of genetic alternations included in the study. PMI funding will also accelerate planning for the Pediatric MATCH study. NCI will continue to provide details and updates to the committee on established NCI programs in precision oncology and the status of NCI progress related to the new and expanded activities under the FY 2016 PMI. A full breakout of these activities for the FY 2017 request and supporting information is included in the budget request.

NCI's PMI efforts will be focused on further developing and expanding research in the following areas:

- Evolution of a new standard for clinical trials in which the molecular characterization of cancers becomes the clinical standard for accurate diagnosis and treatment, and identifying or developing an array of treatments that can be matched to the molecular features of a tumor to successfully control the disease.
- Overcoming drug resistance in cancer treatment by developing cancer models from tissues obtained at the time of diagnosis and at relapse to uncover mechanisms of resistance to treatment, analyzing tumor DNA and tumor cells circulating in blood samples to develop methods to predict relapse before this problem is identified clinically or in radiologic studies, and testing combinations of targeted agents in clinical trials.
- Developing new laboratory models for research by greatly increasing the number of human cancer cell lines and patient-derived tumor xenografts available and providing these and other tools to researchers to gain new insights into tumor biology and better predict patients' responses to cancer treatment.
- Developing a national cancer knowledge system to support precision medicine by building an information platform to support the integration of genetic information about tumors with data on how the tumors respond to therapy, and incorporating genetic, biochemical, environmental and clinical data from patients to define molecular subtypes and to identify the approaches to cancer care that will improve patient outcomes.

NCI will work to achieve these goals by using its existing infrastructure, such as the NCI-Designated Cancer Centers, the National Clinical Trials Network, and the NCI Community Oncology Research Program (NCORP), which supports consortia of community hospitals, oncology practices, and integrated health care systems across the country. This program includes a specific focus on underserved populations, with twelve NCORP

Minority/Underserved Community Sites with patient populations comprised of at least thirty percent racial/ethnic minorities or rural residents. NCI also supports a partnership program between NCI-designated cancer centers and institutions serving underserved health disparity populations that aims to train scientists from diverse backgrounds in cancer research and to effectively deliver cancer advances to underserved communities.

Neglected Tropical Diseases

In addition to the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

The National Institute for Allergy and Infectious Diseases (NIAID) remains a leading global investor in research and development to address neglected tropical diseases (NTDs) that affect more than one billion people worldwide. NIAID supports basic, translational, and clinical research to understand NTD pathogenesis and develop diagnostics, therapeutics, and vaccines to prevent, detect, and treat NTDs. NIAID funds a robust portfolio of research on NTDs such as schistosomiasis, chikungunya, and leishmaniasis, including international research conducted in partnership with scientists from NTD-endemic countries. Notable recent NIAID-supported research advances include:

Dengue: Clinical evaluation of NIAID's-developed single-dose dengue vaccine TetraVax-DV is currently underway by NIAID researchers in Bangkok, Thailand, in collaboration with the Armed Forces Research Institute of Medical Sciences. The vaccine technology developed by NIAID has been licensed to companies and foundations in Brazil, India, and Vietnam, as well as to Merck & Co. in the United States for global distribution. NIAID will continue to support multiple ongoing dengue vaccine evaluation studies.

Trachoma: NIAID researchers successfully used an attenuated strain of *Chlamydia trachomatis* as a vaccine in a non-human primate model to reduce and even prevent potentially blinding eye disease. Work to bring this vaccine candidate to human clinical trials is ongoing, with enrollment expected to begin in early 2016.

Helminth Parasites: NIAID scientists and collaborators have developed CellScope Loa, a video microscope that uses a smartphone application to rapidly screen blood samples for *Loa loa* parasites. Since mass drug administration (MDA) used to treat other NTDs like river blindness and elephantiasis causes severe and often fatal neurological side effects for patients co-infected with *L. loa*, CellScope Loa can be used in the field to identify and exclude those with high *L. loa* parasite burden from the MDA programs.

In FY 2016, NIAID will continue to support research to identify and develop safe and effective diagnostics, therapeutics, and vaccines against NTDs.

Neurofibromatosis (NF)

The Committee continues to support 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 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 notes NF1 can cause vision loss due to optic gliomas and encourages NEI to expand its investment in NF1 basic and clinical research.

Action taken or to be taken

NIH strongly supports research focused on the neurofibromatoses (NF), neurocutaneous genetic disorders that cause multiple morbidities. Neurofibromatosis Type 1 (NF1), a common genetic disorder of deregulated cell growth, affects about 1 in every 3,500 individuals and results in an increased risk of developing a variety of benign and malignant tumors in addition to multiple non-tumor manifestations. Neurofibromatosis Type 2 (NF2) is less common, affecting about 1 in 25,000 individuals, and often causes the development of tumors arising from the nerves important for hearing and balance.

The National Cancer Institute (NCI) is supporting research in this area through numerous efforts, including collaborations with other NIH ICs. The recently developed *NCI Rare Tumors Initiative* aims to accelerate the development of effective treatments for rare tumors, and has a special focus on NF1 tumors.¹⁰⁹ NF1 related manifestations, as well as numerous other rare tumor syndromes, result from activation of the RAS signaling pathway. These disorders are called RASopathies. NCI, Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), and other NIH ICs are collaborating with extramural scientists to accelerate the development of effective treatments for these rare disorders and co-organized a recent meeting with a special focus on RASopathies. 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. NCI is co-chairing an international collaboration called Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS), and is leading the imaging and patient reported outcomes working groups.

NCI continues to support both intramural and extramural research focused on basic and clinical research in NF1 and NF2. NCI's intramural program conducts one of the largest clinical trial programs for children and adults with NF1, including treatment trials for plexiform neurofibromas (pre-cancerous lesions that are present at birth) and for malignant peripheral nerve sheath tumors, or MPNTs (aggressive cancers), as well as an NF1 natural history study. NCI and collaborators are also evaluating the potential role of immunotherapy for NF1 related tumors. In addition, researchers at UC San Francisco recently received an NCI Specialized Programs of Research Excellence (SPORE) program award to integrate data from preclinical studies in genetically engineered mouse models of NF1 with precision medicine technologies. The goal of this research is to generate high-resolution molecular information on NF1-associated tumors

¹⁰⁹ <https://ncifrederick.cancer.gov/events/RareTumors/agenda.asp>

before and after patients are treated with targeted drugs¹¹⁰. NCI-supported clinical trials for NF and related conditions include:

- A Phase I clinical trial of the drug selumetinib (an oral MEK inhibitor) to treat plexiform neurofibromas in children (NCT00924196).¹¹¹ Initial results have been promising with tumor shrinkage in 60 percent of patients. Importantly, several patients experienced a reduction in pain or disfigurement or improvement in function. This degree of activity has not been observed in the past with other agents. An ongoing Phase II trial aims to confirm the responses seen in the Phase I trial and to carefully document clinical improvement.
- A Phase II trial of selumetinib for adults with NF1 and plexiform neurofibromas will soon open for enrollment, and Phase II trials are in development for adults with NF1 and multiple skin neurofibromas, and for gastrointestinal stromal tumors (GIST), for which no effective therapy other than surgery exists.
- The NCI-supported Pediatric Brain Tumor Consortium is conducting a Phase II evaluation of selumetinib for children with low-grade astrocytomas, including children with NF1-associated low-grade astrocytoma (NCT01089101).¹¹²
- The tumor microenvironment has a critical role in the development of NF1 tumors, including plexiform neurofibromas. In a new Phase I and II clinical trial, NCI is testing the effect of an oral agent called PLX3397 on plexiform neurofibromas (NCT02390752).^{113,114}
- NCI is developing strategies to prevent MPNSTs and to evaluate effective treatments for these tumors. These are the most deadly NF1-related tumors, for which only complete surgical resection can be curative. NCI and extramural partners developed several clinical trials specifically for MPNSTs.^{115,116,117}
- NCI investigators are conducting an ongoing study to characterize the genetic changes that occur when benign plexiform neurofibromas become aggressive cancers. Patients undergo detailed clinical and imaging evaluation combined with tumor biopsies for genomic analyses of plexiform neurofibromas, atypical neurofibromas, and MPNST.
- More than 50 percent of patients with NF1 and plexiform neurofibromas have pain, which can be very difficult to treat. NCI developed a novel therapy directed at NF1 pain called *Acceptance and Commitment Therapy*, and this study is ongoing. NCI investigators are also studying the role of genetic modifiers of NF1. This may provide an explanation for why manifestations in NF1 are so variable even within families who carry the same NF1 mutation.

¹¹⁰ <http://cancer.ucsf.edu/news/2015/09/08/childhood-cancer-research-at-ucsf-to-transcend-tissue-types-with-innovative-grant.6756>

¹¹¹ <https://clinicaltrials.gov/ct2/show/NCT00924196>

¹¹² <https://clinicaltrials.gov/ct2/show/NCT01089101>

¹¹³ <https://clinicaltrials.gov/ct2/show/NCT02390752>

¹¹⁴ Volumetric MRI analysis of plexiform neurofibromas, a method developed at the NCI to sensitively measure changes in tumor size, is used centrally at the NCI to evaluate response in most clinical trials nationwide.

¹¹⁵ <https://clinicaltrials.gov/ct2/show/NCT01661283>

¹¹⁶ <https://clinicaltrials.gov/ct2/show/NCT02008877>

¹¹⁷ High throughput screening of agents in MPNST cell lines is performed in collaboration with NCATS, and preclinical trials in mice are performed in collaboration with extramural investigators.

National Institute of Neurological Disorders and Stroke- (NINDS-) supported researchers are also investigating the cellular and molecular processes underlying the development of tumors in NF1, NF2, and schwannomatosis, and are also investigating 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 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 neuromas.

The NIDCD Otopathology Research Collaboration Network includes a study focused on using light microscopy and molecular medicine to investigate disorders of the ear including acoustic neuromas, which could lead to better diagnosis and treatment. In collaboration with NINDS, NIDCD intramural scientists are investigating the relationship between cochleovestibular schwannoma size and hearing, auditory function, vestibular function and postural balance in individuals with NF2, with the goal of improving their clinical management. In addition, NCI also is collaborating with NINDS to better understand the genomics of NF2-associated tumors. These studies may help explain how NF2 related tumors develop and may ultimately identify targets for treatment.

To coordinate research across Institutes, NINDS also organizes biennial Trans-NIH NF Working Group meetings. The most recent meeting in May of 2015, included representatives from ten NIH ICs, the Department of Defense, and advocacy groups.

New Initiatives

The agreement requests NIH provide a table in the fiscal year 2017 and future request reflecting the current year plus five-year planned funding levels for each of the following initiatives: Building Infrastructure Leading to Diversity, BRAIN, Big Data, PMI, CTSA, AMR, Accelerating Medicines Partnership, Human Microbiome, HRHR, Cures Acceleration Network, Biomedical Workforce, and new initiatives proposed in fiscal year 2017. For each initiative, the table should identify, at a minimum, the planned budget level; a list of participating ICs; lineage to the NIH-wide strategic plan, and percentage of the funds focused on basic science.

Action taken or to be taken

Below is a table that shows the FY 2016 and proposed FY 2017 funding levels for the relevant initiatives. All of the initiatives support the new NIH-wide strategic plan; specific linkages are shown in the second table below. NIH does not track funding percentages for basic science at the initiative level. In some cases growth in the out years is expected, but all future funding levels will be subject to the annual budget process. Recommendations for the Precision Medicine Initiative Cohort Program from the Working Group Report to the Advisory Committee to the Director, NIH, can be found at: <http://www.nih.gov/sites/default/files/research-training/initiatives/pmi/pmi-working-group-report-20150917-2.pdf>. Recommendations for the BRAIN Initiative from the Working Group Report to the Advisory Committee to the Director, NIH, can be found at <http://www.braininitiative.nih.gov/2025/BRAIN2025.pdf>.

Initiatives

(Dollars in Millions)

(Dollars in Millions)	FY 2016 Estimate	FY 2017 President's Budget	Institutes and Centers
White House Cancer Moonshot	¹	\$680	NCI
Alzheimer's Disease ²	\$910	\$910	NIA lead, NINDS, and other ICs
Enhancing Diversity	\$57	\$58	Common Fund and all ICs
BRAIN	\$150	\$195	NINDS, NIMH, NIDA, NIBIB, NEI, NIDCD, NIA, NIAAA, NCCIH, NICHD, OD
BD2K (Big Data)	\$102	\$108	Common Fund and all ICs
Precision Medicine Initiative	\$200	\$300	OD (cohort), NCI (oncology)
Antibiotic Resistance ²	\$413	\$413	NIAID lead, and other ICs

¹Funding details not available at time of publication.

²Levels from the Research, Condition, and Disease Categories (RCDC) table.

Initiative	Strategic Plan Objective
White House Cancer Moonshot	Advance Opportunities in Biomedical Research (1)
Alzheimer's Disease	Advance Opportunities in Biomedical Research (1), Enhance Scientific Stewardship (3)
Enhancing Diversity	Enhance Scientific Stewardship (3)
BRAIN	Advance Opportunities in Biomedical Research (1), Foster Innovation by Setting NIH Priorities (2), Enhance Scientific Stewardship (3)
BD2K (Big Data)	Advance Opportunities in Biomedical Research (1), Foster Innovation by Setting NIH Priorities (2), Enhance Scientific Stewardship (3)
Precision Medicine Initiative	Advance Opportunities in Biomedical Research (1), Enhance Scientific Stewardship (3)
Antibiotic Resistance	Advance Opportunities in Biomedical Research (1), Enhance Scientific Stewardship (3)

NIDAMED

The Committee encourages its support for NIDAMED, an initiative designed to reach out to physicians, physicians in training, and other health care professionals to increase especially those treating our youth to better recognize the signs that lead to drug abuse and addiction.

Action taken or to be taken

The NIDAMED initiative was developed to improve the translation of evidence based practices into real world healthcare settings. NIDAMED develops resources to educate healthcare providers on issues related to substance use and addiction and to increase awareness of the impact of substance use on patient health. In 2012, NIDAMED created two continuing medical education (CME) courses, entitled *Safe Prescribing for Pain* and *Managing Pain Patients Who Abuse Prescription Drugs*, to train providers on safe opioid prescribing practices. As of September 2015, more than 100,000 clinicians have completed these modules.

The next phase of the NIDAMED initiative is currently in progress and will focus on developing a CME course on adolescent substance use to train general healthcare providers to identify drug use early and prevent it from escalating to abuse or addiction. NIDAMED Coalition, which includes Coalition organizations, healthcare experts, and National Institute on Drug Abuse (NIDA) staff, met in June 2015 to create learning objectives and draft the content for the CME – which is scheduled to launch in spring 2016. In preparation for the meeting, two surveys, one of clinicians and the other of teens, were conducted by NIDA on how to address substance use in primary care settings; the survey results informed the CME development to ensure that the materials produced will meet the needs of both patients and providers.

Through this project, NIDA is creating multiple online modules that focus on: 1) prescription opioids; 2) marijuana; 3) screening for substance use; 4) key messaging to communicate to adolescents and their caregivers about drugs; 5) successful ways for clinicians to engage in conversations with adolescents (ages 13-18), and their parents; and 6) how best to address issues such as privacy and confidentiality. This CME will also create clinician/patient communication tools that may include brochures/handouts or an in-office, mobile ready game or app that clinicians can use with adolescents to help initiate a conversation about substance use and provide information about the consequences of use. This initiative aims to train 28,000 clinicians in prevention of SUDs in adolescents by October 2019.

NIDCR's Mission

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

NIDCR remains committed to its mission to improve the dental, oral, and craniofacial health of the nation; NIDCR will continue to collaborate on outreach efforts with other HHS agencies to share new scientific information with the community and providers.

NIH Workforce Study

The Committee requests general updates in the fiscal year 2017 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 2008, the National Institutes of Health (NIH) produced a report titled the “NIH New Investigator Projection Report” developed jointly between the NIH Office of Budget (OB) and the Office of Extramural Research (OER). The report was conducted in response to an aging workforce and a desire from NIH leadership to identify ways to maintain a viable and cutting-edge workforce into the future. Since the report, NIH has engaged in multiple activities, studies, and research projects to advance our understanding of workforce dynamics, especially as it relates to new investigators. Examples of these activities include (but are not limited to) various studies and reports from the NIH Advisory Committee to the Director (ACD)¹¹⁸, the development of a new Division for Biomedical Research Workforce Programs (DBRWP) within OER, and a current undertaking of modeling efforts being conducted with economists and physicians at the University of Chicago to expand our ability to understand and, to some extent, predict future workforce dynamics given historical trends. In addition, the FASEB journal recently published an analysis conducted by NIH examining the size and characteristics of the biomedical research workforce associated with its extramural grants.¹¹⁹ This analysis informed and provided evidence demonstrating proof-of-concept for NIH’s further workforce modeling endeavors.

In 2015, NIH initiated modeling efforts similar to that of the NIH New Investigator Projection (PI) report completed in 2008 that examined the Nation’s biomedical research workforce – focusing on the role of new investigators as a pivotal element of our future capacity to sustain scientific discovery. As the modeling efforts move forward, efforts will be made to incorporate an assumption of level funding based on the total budget authority received by NIH Institutes and Centers (ICs) as enacted by appropriations consistent with Congressional direction. The revision effort will access expertise in workforce analysis and capacity modeling equivalent to that used to prepare the original study supported by OER and OB, tapping experiences of ICs where appropriate. In recognition of Congressional concerns regarding scope and content, the NIH report update will consider specific aspects of workforce evolution, such as success rates of new investigators, the success rates of R01 first renewal applications for early stage investigators, and the number of researchers who received funding from NIH Fellowship Awards (F series) or Career Development Awards (K series) who are later employed by industry. In addition, efforts will take into account the historical change over time of policies that impact the length of time needed to achieve Principal Investigator (PI) capability and use that data to adjust the PI projection model assumptions regarding the workforce mix of new and experienced PIs.¹⁵

¹¹⁸ Related working groups include: ACD Working Group on Diversity in the Biomedical Research Workforce, ACD Working Group on Biomedical Workforce, and the ACD Working Group on Physician-Scientist Workforce. For more information on the ACD working groups, see: <http://acd.od.nih.gov/working-groups.htm>.

¹¹⁹ <http://www.fasebj.org/content/early/2015/12/07/fj.14-264358.long>

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 including information technology and facilities infrastructure.

Unfortunately, the Department has chosen to use the majority of NEF funding over the past several years to supplement funding for the Affordable Care Act. Therefore, the Committee includes modified bill language directing funding from the NEF to be expended only by the NIH for carrying out section 301 and title IV of the PHS Act with respect to biomedical research. According to the Department and past expenditures of the NEF, approximately \$650,000,000 should be available in fiscal year 2016. NEF funding shall be transferred to and merged with the accounts for the various Institutes and Centers and the Office of the Director in proportion to their shares of total NIH appropriations made by this act. The NIH shall provide in the fiscal year 2017 CJ actual expenditures from the NEF in fiscal year 2016.

Action taken or to be taken

In FY 2015, NIH received \$10 million in NEF funds to construct a warehouse at the NIEHS RTP campus. NIH obligated all but a little less than \$350 thousand in FY 2015 and plans to obligate the rest in FY 2016.

HHS notified congress of plans to use NEF resources to support the next phase of construction for the NIH Clinical Center E-wing. This project is critical to fulfilling the Clinical Center's research mission. The NEF resources will support decommissioning and relocating labs from the current structure, and construction of modern laboratories and clinical space. The E-Wing will provide new research laboratories that replace obsolete facilities including a vital clinical program now functioning in a deficient space. This renovation will sustain the ability of the clinical center to provide adequately equipped facilities for researchers and patients to continue with patient care, clinical discovery, and research training.

Office of Cancer Survivorship

The Committee requests a report in the fiscal year 2017 budget request on actions planned or ongoing to focus resources and attention to the youngest of cancer survivors.

Action taken or to be taken

The National Cancer Institute (NCI) remains committed to supporting a broad research portfolio related to childhood cancer survivorship. This work remains an important part of NCI's pediatric oncology research efforts overall, particularly as treatment recommendations for children with cancer become more nuanced and children and adolescents are more likely to survive their cancers. Data from the NCI-funded Childhood Cancer Survivor Study (CCSS) in 2015 demonstrated that during the past 30 years, among 5-year survivors of childhood cancer the all-cause mortality rate 15 years from diagnosis dropped from 12.4 percent to 6.0 percent. Researchers found that the strategy of modifying therapy to reduce the occurrence of late-effects, and promote early detection, is successfully translating into a significant reduction in observed late mortality.

CCSS is a multi-institutional, multidisciplinary collaborative research resource. Through the CCSS, 31 institutions across the United States work with a cohort of 34,000 pediatric cancer survivors and their families to gather biospecimens and information on cancer diagnosis, treatment-related exposures, and outcomes. In addition, CCSS collects data on virtually every aspect of cancer survivorship, including late effects of treatment, health-related quality of life, health-related behaviors, and patterns of medical care use. This represents the largest resource available to facilitate the long-term study of pediatric cancer survivors. By characterizing the experience of childhood cancer survivors, the CCSS provides guidance for the medical community on best practices for current and former pediatric cancer patients, and serves as an open resource for the research community. Researchers who have studied the CCSS data so far have identified significant late effects across multiple organ systems such as premature menopause, stroke, cardiovascular diseases, neuropsychological outcomes and subsequent cancers. Intervention studies to reduce preventable risk factors or early identification to avoid or minimize late effects have been completed and are ongoing through CCSS. The importance of the CCSS resource for childhood cancer survivor research is reflected by more than 250 publications using CCSS data and approximately \$37 million of investigator-initiated grants based on applications that utilized CCSS data. NCI has supported CCSS since its launch in 1994, and recently approved another five-year funding cycle for the study. To attract young investigators to the field of childhood cancer survivorship, CCSS also makes available career development awards for early career investigators and trainees with an interest in this area.

Additional CCSS accomplishments include developing a heart failure prediction model for childhood cancer survivors, a descriptive study of the likelihood of developing breast cancer after chest radiation therapy, and identifying genetic risk factors for radiation-associated second cancers. Research from CCSS also informs patient guidelines developed by the NCI-supported Children's Oncology Group (COG), the only pediatric member of NCI's National Clinical Trials Network. The guidelines are a resource for providers and caregivers on best practices for following patients once they have completed therapy to monitor side effects that they may be at risk for due to their treatment. More than 40 percent of the COG guidelines are informed by CCSS publications.

CCSS and NCI's Division of Cancer Epidemiology and Genetics are collaborating on a genome-wide association study (GWAS) using 5,959 biospecimens from CCSS (specimens from childhood cancer survivors who were diagnosed between 1970-1986) to identify genetic variants that modify the effect of radiation therapy and chemotherapy on the risk of developing a second cancer. Once this study is completed, data will be made available for use by other investigators to look at associations between genetic variants and risk of other chronic health conditions.

NCI also recently funded a second childhood cancer survivor cohort, St. Jude Lifetime, that is smaller (approximately 4,000 participants), but highly complementary to CCSS. The St. Jude Lifetime cohort is designed to capture longitudinal, detailed in-person clinical assessment and functional performance information on children treated at St. Jude. Approximately 68 percent of St. Jude Lifetime participants are also enrolled in CCSS. The addition of this valuable new resource will permit: 1) replication of findings from genome-wide association studies; 2) validation of prediction models; and 3) development of collaborative projects to refine risk-based follow-up guidelines and improve outcomes among childhood cancer survivors.

While CCSS is certainly a cornerstone of the pediatric cancer survivorship research portfolio, NCI supports many additional projects. Research topics include characterizing cardiovascular health risks among childhood cancer survivors and examining changes in bone health among patients who received hematopoietic stem cell transplants.

Recognizing that cancer affects patients in a myriad of ways, NCI also promotes research regarding the psychosocial effects of cancer treatment. For example, NCI is funding research examining social-affective, neurocognitive, and family functioning among childhood brain cancer survivors. Additional studies seek to describe behavioral risk factors among adolescent and young adult cancer survivors, to better understand the role that parent-child communication plays in family outcomes, and to develop a curriculum to ensure that pediatric cancer patients receive information about palliative care. NCI is also supporting two new funding opportunities with other NIH Institutes and Centers, posted in August 2015, which aim to foster research on the end-of-life and palliative needs of adolescents and young adults with serious illnesses. Research funded through these announcements will provide evidence-based knowledge to support the development of appropriate models of support and care for adolescents and young adults with serious, advanced illnesses and their family caregivers, and will focus on understanding the unique needs, perspectives, and decision-making processes of these individuals.

Opioid Drug Abuse

The Committee remains concerned about prescription drug abuse, specifically the misuse of orally administered opioid drugs. According to some reports, more than 35 million Americans have abused prescription opioids at some point in their lifetimes. The June 2011 Institute of Medicine report on relieving pain indicates that such abuse and misuse resulted in an annual estimated cost to the Nation of \$72.5 billion. The Committee expects NIDA to continue to support meritorious scientific activities related to research on medications to alleviate pain with reduced abuse liability and, as appropriate, to work with private partners on innovative research into such medications. In addition, NIDA should continue to fund research to better prevent and treat prescription drug abuse and to coordinate with CDC to help identify scientific research gaps. The Committee requests an update in the fiscal year 2017 budget request on the activities related to addressing the opioid drug abuse problem.

Action taken or to be taken

Addressing the opioid epidemic is a high priority issue for the National Institute on Drug Abuse (NIDA) and HHS. NIDA is an active partner in the Secretary's Initiative to address opioid addiction and overdose, focusing 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 pharmacological treatments for opioid use disorders; and 4) develop pain treatments with reduced potential for misuse and diversion including:

- Abuse Resistant Opioid Analgesics: For example, an abuse deterrent formulation of OxyContin that uses prodrug technology – attaching an extension to the opioid molecule that renders it inactive if injected, snorted, or smoked.
- Non-Opioid Medication Targets: For example, fatty acid binding proteins, the G-protein receptor 55 (GPR55), cannabinoids, and transient receptor potential action channel A1.
- Brain Stimulation Therapies: For example, transcranial magnetic stimulation (TMS), transcranial direct current stimulation, and electrical deep brain stimulation (DBS).
- Neurofeedback: A novel treatment modality in which patients learn to regulate the activity of specific brain regions by getting feedback from real-time brain images.

NIDA works closely with CDC and with other Federal agencies to address opioid abuse through the Behavioral Health Coordinating Committee (BHCC), Prescription Drug Abuse Subcommittee. NIDA co-chairs this committee with FDA to coordinate activities related to opioid abuse and overdose across HHS. Additionally, NIDA is working with CDC to develop opioid prescribing guidelines to be released in 2015.

Pancreatic Cancer

The Committee encourages NCI to prioritize support for meritorious research for pancreatic cancer generally and specifically related to early detection of pancreatic cancer. The Committee encourages a focus on promising research to test members of high-risk pancreatic cancer families, including non-invasive screening methods. The Committee requests an update in the fiscal year 2017 budget request on these efforts.

Action taken or to be taken

NCI's 2014 Scientific Framework for Pancreatic Ductal Adenocarcinoma identified four investigational initiatives for consideration by NCI for incorporation into the PDAC research portfolio.¹²⁰ These initiatives focus on PDAC and diabetes, screening protocols for high risk patients, immunotherapy approaches, and methods to target mutations in the RAS gene family. NCI is addressing these research priority areas through a variety of basic and translational research, including clinical trials and the development of new research collaborations. Several of the research projects described below are focused on non-invasive screening methods.

There is consensus that the discovery of biomarkers that can identify early lesions and perhaps serve as therapeutic targets is a critical goal in advancing progress against PDAC; the diagnosis of pre-invasive lesions or even small cancers can improve resectability, the prognosis after resection, and survival. To date, there are no biomarkers or panels of biomarkers that are sensitive and specific enough to allow routine use in the diagnosis of PDAC in its early stages, but recent data has suggested that such capabilities are in development. In July 2015 research by NCI-funded researchers published in *Nature* showed that particles from cancerous cells can be measured in blood samples of patients with pancreatic cancer and therefore could potentially serve as a biomarker of disease.¹²¹ If these results are replicated, this finding may enable development of a blood test to identify early cases of pancreatic cancer, which would improve the chances for surgical interventions as well as overall outcomes. NCI has been investing in the development of early detection biomarkers for many kinds of cancer through the institute's Early Detection Research Network (EDRN).

Regarding screening for high risk patients, NCI issued a new program announcement in June 2015 for creation of the Pancreatic Cancer Detection Consortium (PCDC) to conduct research to improve both the detection of early stage PDAC and the characterization of its precursor lesions. The PCDC is intended to support research for the development and testing of new molecular and imaging biomarkers for identifying patients at high risk for PDAC (because of genetic factors or the presence of precursor lesions) who could be candidates for early intervention. The PCDC will include studies on the following areas: identification and testing of biomarkers measurable in bodily fluids for early detection of PDAC or its precursor lesions; determine which pancreatic cysts are likely to progress to cancer; develop molecular and/or imaging-based approaches for screening populations at high risk of PDAC; conduct biomarker validation studies; and collect biospecimens for establishment of a biorepository. NCI is also taking advantage of new knowledge about genetic and other risk factors such as pancreatic cysts and newly diagnosed diabetes mellitus to test novel approaches to early

¹²⁰ <http://deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/pdacframework.pdf>

¹²¹ <http://www.nature.com/nature/journal/v523/n7559/abs/nature14581.html>

diagnosis. NCI recently approved the development of a Trans-NIH Consortium with NCI, the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the National Institute of Diabetes and Digestive and Kidney Disorders (NIDDK) to support research on probable relationships among chronic pancreatitis, diabetes, and pancreatic cancer, as well as biomarkers and methods for early detection of pancreatic cancer. The Consortium will form multi-disciplinary teams to undertake a comprehensive clinical, epidemiological and biological characterization of patients with chronic pancreatitis, as well as studies on the development of pancreatic cancer in newly diagnosed diabetic patients.

Pediatric Low Grade Astrocytoma Research (PLGA)

The Committee encourages continued research efforts toward the identification of new therapies for PLGA patients, to include clinical trials. The Committee urges NCI and NIH to seek public/private partnerships opportunities on PLGA research. The Committee requests an update in the fiscal year 2017 budget request on on-going and planned activities across NIH.

Action taken or to be taken

The National Cancer Institute (NCI) continues to support research, including clinical trials, to build a greater understanding of Pediatric Low Grade Astrocytoma (PLGA) and to identify new therapies for children with PLGA. PLGA is the most common pediatric brain tumor, and the majority of PLGA cases have genomic alterations in the BRAF gene, a mutation that also occurs in other cancer types targeted for therapy with certain BRAF kinase inhibitors.

In 2011, the NCI Pediatric Preclinical Testing Program developed a model for a subtype of PLGA with the BRAF mutation and identified a targeted therapy, selumetinib, for additional research.¹²² Building upon these findings, the NCI Pediatric Brain Tumor Consortium conducted a Phase I trial of selumetinib (NCT01089101) in children with PLGA who progressed after receiving chemotherapy and/or radiation therapy to study the side effects and the best dose of selumetinib.^{123,124} In this trial, PLGA patients with BRAF mutations responded to treatment as evidenced by tumor shrinkage. Based on these promising findings, the trial is now in a Phase II expansion. The trial is open at 14 sites across the country and is expected to enroll 135 children with PLGA. The NCI-supported investigation of selumetinib to treat PLGA is possible through NCI's partnership with AstraZeneca. AstraZeneca provided the selumetinib for preclinical testing and the Phase I trial, and continues to provide the drug for the Phase II expansion. NCI is also collaborating with Celgene to conduct a randomized Phase II evaluation through the Children's Oncology Group of lenalidomide for children with PLGA (NCT01553149).¹²⁵

NCI also supports four Brain Tumor Specialized Programs of Research Excellence (SPOREs) sites. The University of California, San Francisco (UCSF) Brain Tumor SPORE is leading a project to develop novel approaches to improve outcomes for children with PLGA with mutations in the BRAF gene, specifically a mutation known as BRAFV600E.¹²⁶ The project is studying strategies to inhibit the BRAF gene and to understand how BRAFV600E tumor cells become resistant to BRAF inhibitors. Investigators will also explore combination therapy approaches, both with and without radiation therapy, and will analyze tumor specimens from animal subjects to evaluate adaptation to sustained treatment. Building upon these projects, the researchers aim to evaluate BRAF targeted therapy in patients with BRAFV600E PLGA. An NCI investigator-initiated research project (R01CA169368) is exploring alternative approaches to therapeutically exploiting mutant BRAF to treat pediatric astrocytomas. This project also aims to develop therapeutic approaches with reduced toxicity compared to current therapies, thus reducing the debilitating secondary effects, including late effects, of treatment.

¹²² http://ctep.cancer.gov/MajorInitiatives/Pediatric_Preclinical_Testing_Program.htm

¹²³ <https://clinicaltrials.gov/ct2/show/NCT01089101>

¹²⁴ http://ctep.cancer.gov/MajorInitiatives/Pediatric_Brain_Tumor_Consortium.htm

¹²⁵ <https://clinicaltrials.gov/ct2/show/NCT01553149>

¹²⁶ http://neurosurgery.ucsf.edu/index.php/research_BTRC_SPORE.html

Pediatric Oncology Research

The Committee encourages NCI to continue its important investments in pediatric oncology research, including clinical studies for children with brain tumors, and development of the novel pediatric “MATCH” study, as well as the important pediatric preclinical testing program evaluating new agents for treating pediatric malignancies. The Committee supports NCI’s longstanding investment in the Childhood Cancer Survivor Study and encourages continued childhood cancer survivorship research efforts.

Action taken or to be taken

The National Cancer Institute (NCI) supports a number of key childhood cancer research initiatives, including those cited in the report language. Many of these initiatives have been approved for additional five-year funding cycles in recent years. For example, in March of 2015, NCI’s Board of Scientific Advisors recommended that NCI issue a funding opportunity announcement (FOA) for the Childhood Cancer Survivor Study in FY 2016.¹²⁷ Similarly, NCI previously approved the release of an FOA to support continuation of the research activities of the Pediatric Brain Tumor Consortium (PBTC) for an additional five-year funding period, and the new PBTC award began in April 2014.

NCI will continue to support its pediatric preclinical testing program, and recently renewed funding for the Pediatric Preclinical Testing Consortium (PPTC).¹²⁸ In these examples, NCI initially identified (often with community input) scientific and clinical unmet needs and research opportunities, developed a plan for addressing these needs and opportunities, subjected the plan to internal and external review, and then published FOAs inviting research teams to compete for grant awards to address the specified unmet needs and research opportunities. NCI also supports the Children’s Oncology Group (COG) as a member of the NCI National Clinical Trials Network (NCTN) to conduct high priority clinical trials for children with cancer. The most recent five-year COG award began last year. More information about these and other NCI-supported pediatric oncology research efforts is available at NCI’s website on the *Childhood Cancers Research* page.¹²⁹ NCI’s Pediatric Oncology Branch, part of its intramural program, also continues to conduct translational research in an effort to develop new treatments for pediatric cancers.¹³⁰

NCI is in the process of developing a pediatric precision medicine trial, the Pediatric Molecular Analysis for Therapy Choice (NCI Pediatric MATCH) trial, which aims to generate new knowledge to help address a number of challenges associated with pediatric cancer.¹³¹ NCI Pediatric MATCH will provide a tremendous opportunity to test a range of 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 relapse in pediatric cancers. Additionally, NCI continues to support pediatric drug development through the preclinical testing and clinical trials networks noted above (PPTC,

¹²⁷ Please see the update provided in response to the “*Office of Cancer Survivorship*” Significant Item for a detailed description of research underway through the CCSS, as well as additional NCI-supported childhood cancer survivorship research efforts.

¹²⁸ <http://www.ncipptc.org/>

¹²⁹ <http://www.cancer.gov/research/areas/childhood>

¹³⁰ <https://ccr.cancer.gov/Pediatric-Oncology-Branch>

¹³¹ <http://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match>

PBTC, and COG). For example, the recent FDA approval of dinutuximab to treat high-risk neuroblastoma would not have been possible without decades of NCI support, from early funding for investigator-initiated research, to the COG Phase III trial that led to dinutuximab's approval by FDA, and to the NCI Cooperative Research and Development Agreement (CRADA) with United Therapeutics that brought this drug to market for patients.¹³² In addition to these efforts, NCI has prioritized the development of new treatments for pediatric cancer in the NCI Experimental Therapeutics (NExT) Program.¹³³ 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.

NCI is also supporting new research opportunities and collaborations in pediatric oncology. In February 2015, NCI brought together experts to identify critical gaps in our knowledge about the genetic changes underlying childhood cancers.¹³⁴ The *Childhood Cancer Genomics Gaps and Opportunities* workshop included researchers and clinicians, members of regulatory agencies, and advocates for research on childhood cancers.¹³⁵ Participants continue to collaborate to pursue opportunities identified at the workshop, and the workshop discussions have informed NCI's decision to support Provocative Questions (PQ) meetings focused specifically on pediatric cancers.¹³⁶ NCI's PQ initiative aims to promote cancer research on important yet understudied areas or research questions that have proven difficult to address. NCI launched the PQ effort in 2011 to build on specific advances in cancer biology and cancer control, and to address critical questions about cancer biology that were largely unresolved. The questions are generated from the cancer research community through NCI-sponsored interactive workshops with researchers. Two of the most recent PQ workshops focused exclusively on identifying questions to advance pediatric oncology research.

¹³² <http://www.cancer.gov/news-events/cancer-currents-blog/2015/dinutuximab-neuroblastoma>

¹³³ <http://next.cancer.gov/about/mission.htm>

¹³⁴ <http://www.cancer.gov/news-events/cancer-currents-blog/2015/childhood-genomic-workshop>

¹³⁵ <http://www.cancer.gov/types/childhood-cancers/research/childhood-genomics-workshop-summary.pdf>

¹³⁶ <http://provocativequestions.nci.nih.gov/>

Pediatric Research Data Collection

The Committee directs NIH to collect, assess, and report publicly information about the inclusion of individuals from appropriate age groups throughout the lifespan and on relevant gaps in pediatric and older population involvement in the NIH portfolio of clinical research. Pg 106

Action taken or to be taken

NIH is committed to the inclusion of all relevant age groups in the clinical research studies and clinical trials it supports; inclusion is essential to ensure that NIH is supporting sound science that will ultimately inform clinical practice to the benefit of all who are affected by the disease or condition under study. Special attention is warranted for both younger and older (over 65 years) participants in the conduct of health research; their inclusion in research must be considered carefully. As directed by the Committee, NIH is pursuing plans to collect age-related inclusion information for research studies to support enhanced analyses and reporting on inclusion by age, while balancing the interests of the scientific research community to minimize the administrative burden imposed by new reporting requirements.

NIH already collects information in grant applications on the planned age ranges to be included in all clinical research projects. NIH assigns codes to funded research projects to designate the involvement of children only, children and adults, or adults only. These data show that, for FY 2014, 8 percent of NIH extramural grants involved only children, 30% involved only adults, and 62 percent involved both children and adults. NIH also currently identifies the age range for participants of trials in ClinicalTrials.gov. NIH is examining various approaches to adapt its current information collections on age of research participants (particularly children under 18 years and adults 65 and older) to facilitate more in-depth analyses.

The collection of age-related data poses a number of special challenges that require thoughtful consideration, including the following:

1. Human development is an intrinsic factor that uniquely influences each of the diseases and conditions studied by NIH. For this reason, age as an inclusion criterion must be considered singularly for every clinical research study. Similarly, the best format for collecting, reporting, and interpreting information on the ages of inclusion in research is also complex. Input from experts will be needed to identify the best way to report on age-related inclusion information.
2. Unlike sex, race, and ethnicity, there are no clearly defined, scientifically meaningful categories to describe age or establish useful age-related inclusion guidelines across different diseases/conditions. NIH leadership is discussing hosting a workshop involving experts on pediatric and older populations to provide input on the best approaches to determine the appropriate age groups to be included in research studies involving human subjects. We hope to conduct this workshop in 2016.
3. Because age is a complex variable, uniquely involved in each clinical research study, information collection on age of inclusion must be implemented thoughtfully. There is a very real potential for such an information collection to severely increase the

reporting burden imposed upon grantees. NIH will identify and pursue the least burdensome approach that can accomplish our goal of understanding how the NIH research portfolio is performing with respect to inclusion of children and older populations.

4. Adding to this complexity, the line between childhood and adulthood has been drawn at different ages for different purposes by different organizations and agencies. NIH recently announced a change to its definition for the age of a child. Currently, the NIH policy on inclusion of children defines a child as an individual under 21 years old.¹³⁷ The definition will be changed to an individual under 18 years old, effective for NIH grant applications submitted for receipt dates on or after January 25, 2016, to reduce confusion among members of the research community regarding the age of consent and the more widespread practice of considering 18 year-olds as adults. This change also better ensures that grant applicants will focus their inclusion plans to address inclusion of children ages 0-17. NIH has received approval from OMB to make this change in its grant application instructions, and the research community was notified of the new definition in NIH Guide Notice 16-010.¹³⁸
5. NIH is currently considering policy developments in other areas related to clinical research; examples include clinical trials registration, results reporting in ClinicalTrials.gov, data sharing, etc. These activities may offer complementary opportunities to enhance our understanding of age in our portfolio, and coordinated development and implementation of these related policies will reduce confusion and minimize burden on the research community.

¹³⁷ <http://grants.nih.gov/grants/funding/children/children.htm>

¹³⁸ <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-010.html>

Pediatric Research Network

The Committee notes the enactment of the National Pediatric Research Network Act that authorizes collaborative and multi-institution pediatric research network to accelerate the pace of pediatric disease discovery. The Committee requests the NIH Director to provide an update in the fiscal year 2017 budget request on the specific steps on-going and planned towards the aims of the Act and describe how the network can participate in the alternative approach to support the goal of increasing biomedical knowledge on children's diseases to accelerate cures, treatment, and prevention activities as anticipated in the National Children's Study.

Action taken or to be taken

Through a collaboration of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and National Institute of General Medical Sciences (NIGMS), and in conjunction with the Institutional Development Award (IDeA) program and the proposed Environmental influences on Child Health Outcomes (ECHO) program, NIH is developing a national network for pediatric clinical trial teams/hubs to address the access gap for rural-dwelling and underserved children. The IDeA Program provides support for institutions in many states that historically have not received extensive NIH funding. The opportunity for children in rural locations and underserved communities to participate in clinical trials that are testing new therapies is limited. Providing such access would aid in addressing health disparities through recruitment of diverse populations. The network would include teams of dedicated pediatric research staff at participating IDeA locations, provision of professional development activities to ensure competency and consistency in conducting pediatric clinical trials, and oversight by a central data coordinating and operations center (DCOC).

This "IDeA States Pediatric Clinical Trials Network" would partner with academic institutions outside the IDeA consortium to facilitate recruitment and augment geographic diversity of clinical trials. Such enhanced pediatric research capacity would provide a portal of entry to populations historically not included in multisite studies, particularly rural and American Indian communities. The research staff would be capable of recruiting for and implementing almost any pediatric clinical trial. A mentoring and professional development component would leverage existing activities within the IDeA program. Researchers interested in augmenting their clinical trials by including IDeA sites would contact the IDeA DCOC. Priority would 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.

Physician-Scientist Workforce Report Implementation

A committee has been convened to determine how this report's recommendations should be implemented at NIH. The Committee would like NIH to report on the implementation status of this report's recommendations in the fiscal year 2017 CJ.

Action taken or to be taken

NIH is pleased to provide the following update on the implementation of the recommendations made by the Advisory Committee to the Director's Working Group on the Physician-Scientist Workforce. For FY 2016, NIH plans to:

- Issue new funding opportunity announcements designed to ensure strong support for training of M.D./PhDs through individual predoctoral fellowships.
- Provide a data dashboard to track the role that physician-scientists play in the NIH-funded workforce – and in the research workforce overall, using national statistics from sources, such as the Bureau of Labor Statistics.
- Standardize the minimum NIH salary contribution for career development awards commonly used by physician-scientists (e.g., the Mentored Clinical Scientist Research Career Development Award (Parent K08) at \$100,000, and vigorously enforce the requirement for protected time for career development.¹³⁹
- Modify the funding opportunity announcement for the flagship “Pathway to Independence” career transition award (K99/R00) to encourage more physician-scientists to apply.¹⁴⁰
- Convene a meeting of stakeholders to consider potential pilot programs to streamline and improve the research training of physician-scientists.

In addition, NIH is planning to take the following steps in FY 2017, as appropriate:

- If granted the authority to do so, NIH plans to raise the maximum annual amount of loan repayment awards to health professionals pursuing research careers and to establish a new loan repayment program for veterinary-scientists.
- Pilot a career navigation program for underrepresented physician-scientists, to foster diversity in the physician-scientist workforce.
- Leverage its national network of Clinical and Translational Science Awards to provide additional training and career development opportunities for physician-scientists.

¹³⁹ <http://grants.nih.gov/grants/guide/pa-files/PA-14-046.html>

¹⁴⁰ <http://grants.nih.gov/grants/guide/pa-files/PA-15-083.html>

Precision Medicine

The Committee recommendation strongly supports the new Precision Medicine Initiative and has provided \$70,000,000 to NCI and \$130,000,000 to various Institutes and Centers in support of this Initiative. The Committee looks forward to NIH providing further details and information on the Initiative as the Working Group of the Advisory Committee to the NIH Director reports in September 2015. In particular, as further details are developed, the Committee remains particularly interested in short and long-term milestones of the program and expects these milestones to be specified in the fiscal year 2017 CJ.

Action taken or to be taken

NIH is grateful for the strong support of the Committee for the new Precision Medicine Initiative (PMI). Since the President announced the Precision Medicine Initiative during the State of the Union address in January 2015, NIH worked rapidly to develop a plan for the national research cohort. On March 30, the NIH Director, Dr. Francis Collins, created a PMI Working Group of the Advisory Committee to the NIH Director. The committee's members represent participants from industry, multiple research disciplines, academia, and other Federal agencies. Their charge is to develop a design for PMI national research cohort. Since its launch, the Working Group has convened four major national workshops to help inform its deliberations about the design of the national cohort:

- April 28-29, 2015 Workshop on Unique Scientific Opportunities for the National Research Cohort (NIH, Bethesda, Maryland)
- May 28-29, 2015 Workshop on Digital Health Data in a Million-Person Precision Medicine Initiative (Vanderbilt University, Nashville, Tennessee)
- July 1-2, 2015 Workshop on Participant Engagement and Health Equity (NIH, Bethesda, Maryland)
- July 27-28, 2015 Workshop on Mobile and Personal Technologies in Precision Medicine (Intel Corp., Santa Clara, California)

The PMI Working Group presented to the Advisory Committee to the NIH Director (ACD) on September 17 its report entitled *The Precision Medicine Initiative Cohort Program – Building a Research Foundation for 21st Century Medicine*.¹⁴¹ The ACD supported the report's recommendations and it was subsequently accepted by the Dr. Collins. The cohort design developed in the report will be the basis for short and long-term actionable milestones. The NIH immediately began work preparing to implement the recommendations, contingent on FY 2016 funding. Since September 17, the following milestones have been met:

- NIH issued four (4) Requests for Applications to establish cooperative agreements for a coordinating center (RFA-PM-16-001), a set of healthcare provider organization enrollment centers (RFA-PM-16-002), a participant technologies center (RFA-PM-16-003), and a biobank (RFA-PM-16-004).^{142,143,144,145} NIH expects these awards to be issued by July 2016.

¹⁴¹ <https://www.nih.gov/sites/default/files/research-training/initiatives/pmi/09172015-pmi-working-group-report.pdf>

¹⁴² <http://grants.nih.gov/grants/guide/rfa-files/RFA-PM-16-001.html>

¹⁴³ <http://grants.nih.gov/grants/guide/rfa-files/RFA-PM-16-002.html>

¹⁴⁴ <http://grants.nih.gov/grants/guide/rfa-files/RFA-PM-16-003.html>

¹⁴⁵ <http://grants.nih.gov/grants/guide/rfa-files/RFA-PM-16-004.html>

- NIH issued two (2) funding opportunities for Other Transaction awards to provide the services and systems needed for direct volunteers pilot (OT-PM-16-001) and communications experience and expertise to support NIH PMI research efforts (OT-PM-16-002).^{146,147} NIH expects these awards will initiated in early 2016.
- Dr. Collins named Dr. Josie Briggs, Director of the National Center for Complementary and Alternative Medicine, as Acting PMI Cohort Program Director. A search for the permanent director was launched and closes on December 24.

NIH expects that these actions will quickly establish the firm foundation for this national research treasure and enable it to provide an unequaled resource to bring precision medicine into the daily lives of individuals, families, and clinicians.

¹⁴⁶ <http://www.nih.gov/sites/default/files/research-training/initiatives/pmi/20151116-pmi-pilot-phase-studies-ota-sow.pdf>

¹⁴⁷ <http://www.nih.gov/sites/default/files/research-training/initiatives/pmi/20151116-pmi-comms-ota-sow.pdf>

Preeclampsia

In addition to the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Preeclampsia is a disorder of pregnancy, characterized by high blood pressure, which can have serious health consequences, including preterm birth, fetal and maternal morbidity and mortality. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is supporting a wide range of research on the risks associated with preeclampsia, and factors that may cause the condition.

Preeclampsia affects about five percent of pregnancies and contributes to nearly 15 percent of maternal deaths and 25 percent of deaths of infants during or shortly after birth. To determine when the fetuses of mothers with preeclampsia are at the most risk, NICHD-supported researchers analyzed data from a large birth cohort study in which, a significant portion of the pregnancies had preeclampsia. The researchers found that the risk of stillbirth to a pregnant woman with preeclampsia at 26 weeks of gestational age – around the time that preeclampsia is usually diagnosed – is 86 times greater than in pregnancies without preeclampsia, and that even at 40 weeks of gestational age, stillbirth is seven times more likely if a woman has preeclampsia.

Autism spectrum disorder (ASD) is a developmental disability that can cause significant social, communication, and behavioral challenges. Some scientists believe that ASD is a result of medical problems that occurred when the child was *in utero*. A new study conducted by NICHD-funded researchers explored whether there might be a connection between preeclampsia and ASD or developmental delay and found that children with ASD or Developmental Disorders (DD) were twice as likely to have been exposed to preeclampsia.

Researchers supported by NICHD have shown that preeclampsia is associated with a vascular defect in the placenta that results in reduced blood flow between the mother and the fetus by producing factors that result in systemic vascular damage and development of preeclampsia. NICHD is currently funding a number of studies in relevant basic science areas, including the process of uterine invasion and the role of signaling molecules, the interaction of the trophoblast (the outermost cells of a blastocyst, which provide nutrients to the embryo) with immune cells, and remodeling of the uterine spiral arteries. Restoring normal blood flow in pregnancy is currently a major area of study with potential clinical promise. One study, for example, is developing a device to remove detrimental anti-angiogenic proteins (which can inhibit growth of new blood vessels) from a woman's blood stream in a process similar to dialysis called apheresis.

In addition to these specific research efforts, NICHD has launched an initiative, the Human Placenta Project, whose goal is to increase understanding of human placental development and function across pregnancy.¹⁴⁸ This effort is expected to lead to a mechanistic understanding of the underlying causes of placental dysfunction and placental insufficiency that are associated with, and may be a cause of, conditions such as preeclampsia. NIH is investing approximately

¹⁴⁸ <http://www.nichd.nih.gov/research/HPP/Pages/default.aspx>

\$46 million in this effort in FY 2015. Two scientific conferences focused on the Human Placenta Project, which brought together the experts in placental biology, were held in 2014 and 2015, with a third meeting scheduled for April 2016.

Preterm Birth

The Committee applauds NICHD's work with leading global health organizations to develop a research agenda aimed at reducing preterm birth. Public and privately funded research that spans the range of discovery, development, and delivery science is needed in order to identify the causes of premature birth. The Committee urges NICHD to continue to invest in biomedical and clinical research related to the prevention of preterm birth and the care and treatment of preterm infants.

Action taken or to be taken

To understand what causes preterm birth, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports a large portfolio of clinical, translational, and epidemiological research. NICHD-supported Maternal Fetal Medicine Units (MFMU) Network has a long history of conducting clinical research on the prevention of preterm birth and treatment for associated medical problems. For example, the Antenatal Late Preterm Steroids Trial is aimed at determining if the administration of antenatal corticosteroids will reduce the respiratory support needed for newborns. Although twins account for only three percent of all live births, they are responsible for 15 percent of infant deaths, largely due to the much higher rate of preterm birth. To date, no screening or intervention strategy has proven effective in reducing the risk of preterm birth in twins, although limited data suggest that progesterone may decrease preterm birth in women with a twin gestation and a short cervix. In a randomized trial, the MFMU will assess whether any specific form of delivery of progesterone does, indeed, reduce the risk of preterm delivery in twins.

Another NICHD initiative is the *Genomics and Proteomics Network for Preterm Birth Research*. By using state-of-the-art genetic and protein approaches, new biomarkers are being identified that may correlate with the risk of preterm delivery. Following up on a study that suggested that an increase in genomic copy number variation is correlated to an increase in preterm birth, NICHD is working with an international consortium of patient cohorts to validate these results. The *Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b)* is a prospective observational study of over 10,000 nulliparous women (pregnant women with no previous children) who were followed from the first trimester through delivery. The purpose of the study is to understand the causes and mechanisms of adverse pregnancy outcomes, including preterm birth. The data obtained, currently being analyzed, will be used to answer questions regarding risk factors, underlying mechanisms, and causes of preterm birth in women who have little or no pregnancy history to help guide their treatment.

Care of newborns born preterm is also a primary research focus for NICHD. One recent NICHD-funded study focused on brain development of premature babies, showing that brain scans done near the time of the babies' due dates are more informative than earlier scans in predicting delays in development and disabilities. Another study indicated that "cord milking," a technique that pushes the umbilical cord blood to the infant's abdomen to allow the blood vessels in the infant's lungs to fill and help protect infants from intraventricular hemorrhage, offers health-related advantages to those preterm infants delivered by cesarean.

NICHD-funded Neonatal Research Network (NRN) facilitates the advancement of neonatal care through a network of 18 academic centers that can provide answers more rapidly than individual

centers acting alone. NRN studies have informed clinical practice by showing that preterm infants are at risk of language delay, and that differences in hospital practice regarding the initiation of active treatment in infants born at 22, 23, or 24 weeks of gestation explain some of the between-hospital variation in survival, and survival without impairment, among such patients.

Prioritization of Funding

The agreement expects NIH to consider burden of disease when setting priorities and developing strategic plans across its ICs to address conditions (such as Alzheimer's disease, diabetes, heart disease, and cancer) with significant opportunity to improve the current or future health of the American population by targeting funding toward cures and better treatments. Further, the agreement expects NIH to prioritize funds on medical research discovery over outreach and education. The agreement expects NIH to continue policies to distribute funding based on the merit of researchers' ideas and productivity, and to ensure consistent application of scientific policies between extramural and intramural researchers. The agreement requests NIH provide an updated in the fiscal years 2017 budget request on how it plans to use the NIH 5-year scientific strategic plan as part of its resource allocation process to improve the health of the American population.

Action taken or to be taken

The same principle of scientific merit review applies to extramural and intramural research review systems using the same review criteria, even though the two research programs serve different functions and have different cost accounting systems. The intramural review system assures that highly innovative discovery research with significant impact on current and future public health is being conducted often by teams of basic, translational, population-based, and clinical researchers. The mission of the intramural program is to conduct the most creative and innovative biomedical research in Government laboratories with distinctive attributes, including the ability to initiate new research programs swiftly, sustain long-term projects, respond to public health emergencies, and address unmet needs in support of the composite NIH research enterprise. Prioritization of intramural research is done by Institute and Center leadership and reviewed by National Advisory Councils.

Oversight of intramural research is continual and direct, and changes in budget and research priorities can be effected quickly as the need arises. Within the Intramural Research Program, resources of each principal investigator are regularly reviewed and allocated by IC leadership that is responsible for implementation of the NIH five-year strategic plan. At least once every four years, outside experts review the work of each Principal Investigator mainly in a retrospective fashion but also with attention to future research plans. Reviewers that are constituted as external peer review panels called Boards of Scientific Counselors recommend resource adjustments to IC leadership. The extramural program is primarily based on prospective long-term grant reviews with direct oversight provided by the institutions to which the funds are granted. In summary, both intramural and extramural systems are subject to regular, rigorous, competitive peer review, and oversight.

Psychotropic Medications and Children

The Committee encourages NICHD, NIMH, CDC and FDA to undertake a concerted effort to identify the research gaps and work with these agencies to determine the safety and efficacy of these medications, and to explore research into the biological evidence-base of psychosocial interventions that can be used instead of, or in combination with, psychotropic medications.

Action taken or to be taken

Given the potential behavioral, metabolic, and neurological adverse effects of antipsychotics, it is important to ensure their safe and optimal use, especially for children and adolescents. A recent National Institute of Mental Health (NIMH) report demonstrated that these medications were being used mostly for non-psychotic disorders in children and adolescents.¹⁴⁹ In February 2015, NIH issued a request for proposals entitled, *A Targeted Approach to a Safer Use of Antipsychotics in Youth*.¹⁵⁰ The initiative addresses the common and increasing use of antipsychotic medications to treat youth who do not have a psychotic disorder, but rather suffer from non-psychotic mood and behavioral disturbances. NIH expects to award a contract to develop and test a treatment algorithm for youth aged 5-17 years who have a non-psychotic disorder, but who present with severe behavioral and mood disturbances for which antipsychotics are frequently used. In the algorithm, psychosocial interventions and medications other than antipsychotics will be preferentially tried. Review of submitted proposals is currently ongoing.

One obstacle to testing the safety and efficacy of psychotropic medications – and interventions of all types – is the lack of reliable biomarkers for predicting response to treatment. NIH is partnering with the Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services, non-profit organizations, and pharmaceutical companies through the Foundation for the NIH (FNIH)-sponsored Biomarkers Consortium to identify disease-specific biomarkers and develop targeted technologies and treatments, with the ultimate goal of precision medicine.¹⁵¹ One such recently funded project will develop and improve clinical research tools for studying autism spectrum disorder (ASD). The project will receive \$28 million over the next four years to test and refine clinical measures of social impairment in ASD in order to better evaluate potential behavioral and drug therapies.¹⁵²

The importance of determining the biological evidence-base of psychosocial interventions has captured the attention of the National Advisory Mental Health Council (NAMHC), which advises NIMH. A new NAMHC workgroup on Behavioral and Social Science Research at NIMH has been charged with addressing how new mobile health technologies can be used to achieve more efficient and effective diagnosis and treatment of mental illnesses, and how such technologies can be used to predict and prevent mental illnesses and improve quality of mental health practice. NIMH also has several ongoing funding initiatives on the development and testing of cognitive, behavioral, and other psychosocial interventions for children, adolescents,

¹⁴⁹ <http://www.ncbi.nlm.nih.gov/pubmed/26132724>

¹⁵⁰ <http://contract-opportunities.insidegov.com/l/325783/A-Targeted-Approach-to-a-Safer-Use-of-Antipsychotics-in-Youth-HHS-NIH-NIDA-MH-14-005>

¹⁵¹ <http://www.biomarkersconsortium.org/whatwedo.php>

¹⁵² <http://www.nimh.nih.gov/news/science-news/2015/nih-joins-public-private-partnership-to-fund-research-on-autism-biomarkers.shtml>

and adults.¹⁵³ In addition, the NIH Best Pharmaceuticals for Children Program supports pediatric drug testing on medications that are currently being used off-label.¹⁵⁴ Researchers supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) recently completed a pediatric clinical trial on the correct dosage of lithium for children with acute mania in bipolar disorder, and submitted the necessary data for pediatric labeling to FDA in August 2015.

¹⁵³ <http://www.nimh.nih.gov/funding/opportunities-announcements/clinical-trials-foas/index.shtml>

¹⁵⁴ See <http://bpca.nichd.nih.gov/Pages/Index.aspx> and <http://www.pediatrictrials.org/>

Pulmonary Atresia

In addition to the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Pulmonary atresia is a rare congenital heart defect in which the heart's pulmonary valve (which sends blood from the heart to the lungs) lacks an opening for blood to pass through. Because of this defect, blood from the right side of the heart cannot go to the lungs to pick up oxygen. There is no known cause of this defect. Treatments include heart catheterization, open heart surgery to repair or replace the valve, reconstructing the heart, or heart transplant. The National Heart, Lung, and Blood Institute (NHLBI) supports a broad portfolio of grants investigating abnormal cardiac development, including those focused on the pulmonary valve. For example, NHLBI recently renewed the Bench to Bassinet Program (B2B), which is focused on congenital heart disease (CHD) and aims to accelerate the translation of scientific research discoveries into clinical practice.¹⁵⁵ One of B2B protocols, CHD GENES, is analyzing the genetic causes of congenital heart disease, and includes over 100 patients with various types of pulmonary atresia. In addition to research conducted within the B2B program, B2B creates resources that are available to the scientific community at large to further research in this area. For example, another B2B project developed mouse models of pulmonary atresia that are now available for researchers to use to study mechanisms of disease and identify new targets for interventions.

¹⁵⁵ <http://www.benchtobassinet.org/>

Reproducibility of Scientific Methods

The Committee notes that the gold standard of good science is the ability of a lab to reproduce a method and finding and therefore continues to be concerned with reports that some published biomedical research cannot be easily reproduced. The Committee expects NIH to continue to stress the importance of experimental rigor and transparency of reporting of research findings in order to enhance the ability of others to replicate them. The Committee requests an update in the fiscal year 2017 budget request on how NIH is measuring the effectiveness of each step NIH has taken to develop and implement best practice guidelines to better facilitate the conduct of replicable research and research transparency in the reporting of methods and findings.

Action taken or to be taken

NIH has several efforts under way – both new and ongoing – to address reproducibility, rigor, and transparency in biomedical research. To raise awareness, Drs. Francis Collins and Larry Tabak published a commentary in *Nature* in January 2014 describing concerns surrounding reproducibility and rigor in preclinical research and the potential steps to address the issues.¹⁵⁶ NIH has continued to engage various stakeholder communities to prompt a dialogue and solicit feedback, co-sponsoring a meeting with the publishers of *Science* and *Nature* that challenged editors representing more than 30 major journals to identify opportunities in the scientific publishing arena to enhance rigor and further support research that is reproducible, robust, and transparent. This meeting led to the development of NIH's Proposed Principles and Guidelines for Reporting Preclinical Research, which have been endorsed by more than 130 journals, publishing groups, and societies and apply to both intramural and extramural researchers.¹⁵⁷ Within NIH Institutes and Centers, ongoing pilots continue to test and assess efforts aimed at addressing reproducibility and rigor – for example, through improving research training, enhancing the reporting of methods in applications and publications, and educating reviewers to better evaluate the strength of methodological approaches in grant applications.

The Office of Intramural Research hosted workshops to discuss the potentials and pitfalls of modern advanced technologies and the kinds of reproducibility problems that can arise. The workshops focused on genomics, structural biology, and cell biology^{158-159,160}. By educating researchers on the limitations of these cutting edge technologies, new users of these approaches are better able to employ them in a manner that ensures more reproducible reporting. These workshops are publically available on the NIH website.¹⁶¹

In early 2015, NIH released a series of training videos to highlight common issues related to reproducibility and rigor in the research endeavor, such as bias, blinding, and exclusion criteria.¹⁶² These videos have been incorporated into required training within the NIH intramural program. In FY2015, NIH solicited applications and made awards for creative educational activities to enhance data reproducibility. These awards will help train the biomedical workforce and develop skills to enhancing data reproducibility.

¹⁵⁶ Collins, FS, Tabak, LA. Policy: NIH plans to enhance reproducibility. *Nature*. 505, 612–613. (30 January 2014).

¹⁵⁷ <http://www.nih.gov/science/reproducibility/principles-guidelines.htm>

¹⁵⁸ <https://www.training.nih.gov/rdca-y2015m06>

¹⁵⁹ <http://videocast.nih.gov/summary.asp?Live=15910&bhcp=1>

¹⁶⁰ <http://videocast.nih.gov/summary.asp?Live=15277&bhcp=1>

¹⁶¹ <http://www.nih.gov/science/reproducibility/meetings-workshops.htm>

¹⁶² <http://www.nih.gov/science/reproducibility/training.htm>

NIH has implemented modifications to the NIH biographical sketch that complement SciENCv and better reflect researcher contributions, including the magnitude and significance of the scientific advances associated with a researcher's discoveries and the specific role the researcher played in those findings, rather than listing his or her publications.^{163,164} These changes were implemented for all grant applications received after May 25, 2015. NIH submitted new instructions and review questions emphasizing rigor and transparency to OMB in 2015 for implementation NIH-wide in 2016 applications.¹⁶⁵ The instructions and review questions include information on scientific premise, rigorous experimental methods to achieve robust and unbiased results, consideration of relevant biological variables with an expectation that both sexes will be included unless there is strong justification to use a single sex, and that all key biological and/or chemical resources will be authenticated.¹⁶⁶ NIH is currently in the planning stages for evaluating these efforts and will move forward with assessing the effect of these policy changes. Experimental rigor and transparency are integral components of what is expected and undertaken by NIH ICs in pursuit of their IC-specific missions and the broader mission of NIH.

¹⁶³ <http://www.ncbi.nlm.nih.gov/sciencv/>

¹⁶⁴ <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-085.html>

¹⁶⁵ <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-103.html>

¹⁶⁶ <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html>

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 NIH research facilities are in compliance with all laws and regulations that supports its 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.

Review of Maternal Deprivation Studies

The Committee is aware that prominent experts and animal advocacy organizations have raised concerns about the scientific and ethical justifications for maternal deprivation studies involving baby monkeys being conducted in both intramural and extramural NIH funded laboratories. The Committee is further aware that the NIH Office of Laboratory Animal Welfare opened an investigation in response to these allegations on September 9, 2014. The investigations consulted with research investigators, the USDA, nonhuman primate center scientists, veterinarians, animal care staff and other relevant experts. As a result of the investigation, several modifications were made to the protocol and several procedures removed. Accordingly, the Committee requests NIH to conduct a review of its ethical policies and processes with respect to nonhuman primate research subjects, in consultation with outside experts, to ensure it has appropriate justification for animal research protocols and to provide an update on these efforts in the fiscal year 2017 budget request.

Action taken or to be taken

Research with non-human primates and other animal species is key to helping us understand and improve human health in a multitude of ways, including the development of treatments and interventions. NIH takes animal welfare concerns seriously, and has numerous policies and protocols in place to assure the ethical treatment and use of these invaluable resources. All NIH-funded research with animals is reviewed to ensure that (1) the science is highly meritorious, and (2) the welfare of the animals is protected. To ensure that this research continues to be conducted responsibly and in accordance with the highest ethical standards, the NIH will convene an expert workshop in Fiscal Year 2016 to review the ethical policies and procedures associated with the conduct of research with non-human primates. This meeting will include experts across scientific disciplines such as primatology and animal behavior, as well as ethicists and experts in animal health and welfare. This meeting will ensure that NIH continues to have appropriate justification for animal research protocols in the future. The NIH will provide the summary of this meeting to the Senate and House Appropriations Subcommittees on Labor, HHS, Education, and Related agencies.

Science Education

Therefore, NIH is directed to continue funding the SEPA program at no less than last year's level.

Action taken or to be taken

NIH continues to support the Science Education Partnership Award (SEPA) program located within the Office of Science Education, 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 2015, SEPA made 10 new awards and funded two administrative supplements to current SEPA awards. NIH will continue to fund a total of 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.

Science, Technology, Education and Mathematics

In addition, the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

The FY 2015 President's Budget proposed a reorganization of all Federal Science, Technology, Engineering, and Mathematics (STEM) education programs. Consistent with the Government-wide STEM reorganization, NIH eliminated four of its smaller STEM programs. This decision to discontinue or eliminate these programs follows the recommendations contained in the 2013 Federal STEM Education 5-Year Strategic Plan (Appendix Table A6: STEM Education Funding in Millions by Agency, page 98). NIH will continue to support the Office of Science Education and coordinate NIH's science education efforts through the distribution of curriculum supplements and the funding of the Science Education Partnership Awards (SEPA) program. The NIH Curriculum Supplement Series provides teacher guides with two-weeks of lessons that combine information on cutting-edge biomedical discoveries with state-of-the-art instructional materials. Since the beginning of 2015, NIH distributed over 12,400 supplements and plans to continue this effort. NIH's SEPA program invests in educational activities for underserved and low socioeconomic status communities enhancing the training of a diverse workforce to meet the nation's biomedical, behavioral, and clinical research needs. NIH will continue funding approximately 70 SEPA projects to create partnerships among biomedical and clinical researchers and pre-K to grade 12 teachers and schools, museums, and other educational organizations.

Scleroderma

The Committee notes that while meaningful scientific progress has been made through NIAMS-led scleroderma research, there remains no cure and treatment options are limited. NIAMS is encouraged to consider advancing research projects to improve the understanding of the mechanisms of this disease.

Action taken or to be taken

Scleroderma is a complex group of diseases involving inflammation, vascular defects, and fibrosis – a pathological thickening and scarring of connective tissue. It often manifests as hard, tight skin, but in some individuals, may affect blood vessels and internal organs, such as the heart, lungs, and kidneys. Scleroderma is considered an autoimmune disease, in which the immune system attacks the body's own tissues. Currently available treatments help control symptoms, but are limited in their effectiveness because they do not alter underlying disease mechanisms. To foster new therapies, NIAMS, along with other NIH Institutes, such as the National Institute of Allergy and Infectious Diseases (NIAID) and the National Heart, Lung, and Blood Institute (NHLBI), are funding basic, translational, and clinical research relating to scleroderma.

NIAMS-funded researchers have recently reported several advances related to understanding the biological mechanisms of scleroderma. Scientists studying the molecules involved in scleroderma pathology found that a protein called Fn^{EDA} is present at elevated levels in scleroderma patients. Using a variety of techniques to inhibit the protein's activity, the researchers were able to reduce scarring in a scleroderma mouse model. Other investigators, funded by a NIAMS Center of Research Translation (CORT) focused on scleroderma disease mechanisms, have shown that people with scleroderma also produce high levels of another protein called CXCL4. Scleroderma patients with the highest levels of CXCL4 develop signs of serious lung complications much earlier than those with lower levels. The findings suggest that CXCL4 could be used both as a predictive marker to help clinicians decide which patients might benefit from aggressive therapy and as a therapeutic target for development of new treatments. More recently, investigators supported by CORT conducted a small clinical study in 15 patients to investigate the role of the protein TGF-beta, an important molecular mediator of pathological scarring, in scleroderma. When treated with an experimental drug that blocks TGF-beta, the patients experienced a marked decrease in skin scarring. Although a larger study is needed to confirm the findings, the results show promise for preventing one of the underlying molecular processes that drives the disease.

Researchers at NIAID are studying the immunological mechanisms of abnormal scarring with the goal of identifying a first-in-class fibrosis disease therapy. Current NIAID intramural research includes the identification of the IL-13 signaling pathway leading to fibrosis and investigation of induced pluripotent stem cells as a potential therapy. NIAID-supported researchers are evaluating new treatments for scleroderma in clinical trials. The Scleroderma: Cyclophosphamide Or Transplantation (SCOT) study is investigating the benefit of high-dose immunosuppressive therapy followed by stem cell transplantation compared to monthly high-dose cyclophosphamide therapy for treatment of early, severe disease. This study will conclude in 2016. In addition, NIAID funds the SCOT Scleroderma Treatment Alternative Registry to compare outcomes of SCOT study participants to non-participants following a physician-

prescribed treatment course. A Phase II clinical trial is also underway to evaluate the effect of standard of care plus rituximab, a monoclonal antibody treatment, on disease progression in patients with a life-threatening lung condition called pulmonary arterial hypertension (PAH).

NHLBI supports research on interstitial lung disease (ILD) and PAH – both serious lung complications that are the major causes of morbidity and mortality in scleroderma patients. Active projects include an investigation of the pathogenic processes of PAH and ILD in people with scleroderma and a project to develop biomarkers for scleroderma-associated ILD. NHLBI also is completing a clinical trial comparing treatment with two immunosuppressive drugs, and starting a pilot clinical trial to test the efficacy of an anti-fibrotic drug. In addition, NHLBI recently issued a funding opportunity announcement, *Collaborative Projects to Accelerate Research in Organ Fibrosis*, for research to characterize and compare mechanisms of fibrosis in multiple organ systems and fibrotic diseases such as scleroderma.

Despite recent advances in understanding scleroderma mechanisms, translating basic research findings into new therapies remains challenging. To facilitate translation, in February 2015, NIAMS held a roundtable, *Scleroderma: Advancing Potential Drugs to Patient Care*. The meeting included representatives from academia, regulatory and funding agencies, patient organizations, industry, and several other NIH ICs. Participants discussed the current status of scleroderma research leading to drug development; opportunities and obstacles to evaluating new therapeutic targets; and potential approaches to move candidate drugs into robust clinical trials and eventually clinical care.

Sickle Cell Disease (SCD)

The Committee encourages the NIH to create a Trans-NIH program focusing on SCD and fund interdisciplinary research initiatives at hospitals and universities experienced in treating SCD patients.

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 1 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. SCD has no widely available cure; however, the results of clinical trials supported by the National Heart, Lung, and Blood Institute (NHLBI) have led to the use of penicillin to prevent fatal infections, chronic blood transfusions to reduce stroke risk, and hydroxyurea to reduce pain.

As SCD can affect multiple organ systems and cause stroke, many NIH ICs support research efforts to address this disease. For example, NIH has identified SCD as an important initial priority of the Therapeutics for Rare and Neglected Diseases (TRND) Program, housed at the National Center for Advancing Translational Sciences, which involves a wide array of diseases and partnerships with renowned academic hospitals, patient advocacy groups, pharmaceutical and biotechnology companies, and other government agencies. The National Institute of Neurological Disorders and Stroke (NINDS) also support SCD research, with a focus on SCD-related stroke. For example, one recent study showed that regular blood-transfusion therapy significantly reduced the incidence of cerebral infarct recurrence in children with SCD, for whom infarcts are the most common neurologic injury.

NHLBI continues to support innovative research programs, such as the Excellence in Hemoglobinopathies Award Program to promote basic and translational research in SCD. Researchers are also investigating 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 treatments for SCD are underutilized. Therefore, NHLBI is seeking to form a Sickle Cell Disease Implementation Consortium to develop and test multi-sector interventions, involving community and academic health care institutions, to improve the rate at which SCD patients receive routine primary care.¹⁶⁷

In addition, NHLBI is committed to involving the entire sickle cell disease community in addressing this devastating disease. Between June 25 and 26, 2015, NHLBI held a Sickle Cell Disease Forum *Engaging the Community: Developing Solutions*, which welcomed over 450 participants including people living with SCD, family members, health professionals, researchers, and advocates.¹⁶⁸ Focus areas included finding a widely available cure and alleviating the pain caused by the disease; the resources available to patients; and the groups devoted to raising awareness about SCD. Next steps are to craft a research agenda that may include additional trans-NIH initiatives.

¹⁶⁷ <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-16-010.html>

¹⁶⁸ <https://www.nhlbi.nih.gov/news/events/sickle-cell-disease-forum>

Sickle Cell Disease – Update

In addition to the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

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, 1 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. SCD has no widely available cure; however, the results of clinical trials supported by the National Heart, Lung, and Blood Institute (NHLBI) have led to the use of penicillin to prevent fatal infections, chronic blood transfusions to reduce stroke risk, and hydroxyurea to reduce pain.

NHLBI is currently funding a major program to promote innovative basic and translational research in the hemoglobinopathies, which are diseases caused by abnormal hemoglobins, such as SCD. Research areas in this program include 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.¹⁶⁹ Researchers also are investigating 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 also requesting applications to form a Sickle Cell Disease Implementation Consortium to develop and test multi-modal, multi-sector interventions aimed at improving the rate at which patients with SCD receive routine primary care.¹⁷⁰

¹⁶⁹ <http://www.nhlbi.nih.gov/news/spotlight/fact-sheet/nhlbi-funded-research-centers-target-hemoglobinopathies>

¹⁷⁰ <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-16-010.html>

Sleep and Circadian Health

In addition to the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

Insufficient sleep affects approximately 30 percent of employed adults and as many as 60 percent of high school students in the United States. Sleep deficiency and disorders are associated with an increased risk of cardiovascular disease, stroke, diabetes, certain cancers, and mortality. The National Center on Sleep Disorders Research (NCSDR), located within the National Heart, Lung, and Blood Institute (NHLBI), was established in 1993 to combat this serious public health concern through research, training, and technology transfer programs.¹⁷¹

Recent NHLBI-supported research link untreated sleep apnea to health risks specific to women and minorities. For example, findings from NHLBI Multi-Ethnic Study of Atherosclerosis (MESA) provide the first evidence of racial/ethnic differences in the contribution of sleep apnea to the risk of metabolic dysfunction.¹⁷² Sleep apnea increased the risk of abnormal fasting glucose four fold in African-Americans and three fold in Caucasians but posed no additional risk in Chinese and Hispanics after adjusting for differences in sleep duration and demographic factors. This and other recent findings indicate that inadequate sleep are prevalent in minority and low-income populations, and may be fundamental to racial and socioeconomic status inequities that contribute to a range of health conditions, including cardiovascular disease.

While sleep disorders and sleep deprivation are significant threats to public health and productivity, there are no practical tools for the objective measurement of sleepiness. Biomarkers of sleepiness could be invaluable in diagnosing sleep problems, evaluating the effectiveness of treatment, and developing policies to reduce risks to public safety. A 2015 workshop jointly organized by NHLBI, the National Institute on Aging, and the Sleep Research Society, articulated opportunities to develop point-of-care assessment technologies for the evaluation of acute sleep deprivation, chronic sleep deficiency, sleep disorders, and circadian risks to health.

¹⁷¹ <http://www.nhlbi.nih.gov/about/org/ncsdr/>

¹⁷² http://www.atsjournals.org/doi/abs/10.1164/rccm.201502-0366OC?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed#.VgCqCIVViko

Sleep and Circadian Health Coordination Efforts

The Committee recognizes the immense public health burden of sleep and circadian disorders and encourages the Office of the Director to foster collaboration on sleep and circadian research across ICs and to support NCSDR efforts to coordinate this important research.

Action taken or to be taken

The National Center on Sleep Disorders Research (NCSDR) was established within the National Heart, Lung, and Blood Institute (NHLBI) via a provision of the National Institutes of Health Revitalization Act of 1993. NCSDR was mandated to:

- Conduct and support research, training, health information dissemination, and other activities with respect to a basic understanding of sleep and sleep disorders; and
- Coordinate the activities of NCSDR with similar activities of other Federal agencies, including the other components of NIH, and similar activities of other public and nonprofit entities.

NCSDR coordinates NIH-supported sleep and circadian research through monthly meetings of a trans-NIH Sleep Research Coordinating Committee (SRCC), which includes a dozen NIH ICs.¹⁷³ In FY 2015, NIH organized workshops and symposia on the role of sleep problem in pain, the significance of caffeine and stimulants on health, and the development of objective measures of sleep health (biomarkers) for acute/chronic sleep deprivation, sleep apnea, and circadian phase disorders. NCSDR also led the trans-NIH SRCC involvement in collaboration with the National Geographic on a documentary to help educate the public about advances in sleep research. In addition, NHLBI hosts the Sleep Disorders Research Advisory Board, which provides a public venue in which stakeholder needs and opportunities are discussed with the representatives of NIH ICs and the “Sleep Health” working group in Healthy People 2020 providing an inter-agency focus for potential research coordination.

NHLBI also partners with other NIH ICs and Federal agencies to support sleep disorder research, in addition to its NHLBI-specific portfolio. For example, an NHLBI-initiated collaboration with the *Eunice Kennedy Shriver* National Institute on Child Health and Human Development is now underway to investigate sleep apnea during pregnancy, how apnea severity changes during the postpartum period, and if gestational apnea increases future maternal risk of cardiovascular disease. A new NHLBI partnership with the National Institute of Diabetes and Digestive and Kidney Diseases in FY 2015 measures sleep and sleep apnea in young adults with type 2 diabetes to determine whether comorbid sleep problems increase the severity of diabetic symptoms and reduces the effectiveness of glucose management strategies. In addition, NHLBI sponsored sleep data collection in selected surveillance studies of CDC (such as the National Health Interview Survey and the National Health and Nutrition Examination Survey) is helping to quantify the national burden of epidemic sleep deprivation and understand the potential impact of trans-NIH programmatic coordination activities.

¹⁷³ <https://dpcpsi.nih.gov/collaborations/committees.aspx?TID=2#182>

Small Business Innovation Research

The Committee encourages NIH to consider new clinical indications that leverage developed devices when soliciting proposals and awarding funds through competitive grant programs, including the Small Business Innovation Research program.

Action taken or to be taken

NIH provides grant opportunities for small businesses in any biomedical or behavioral research area that falls within the agency's mission to improve human health. NCATS small business funding is designed specifically to transform the translational science process so that new treatments and cures for disease can be delivered to patients more efficiently.

NCATS seeks to increase small business participation in federally supported research and development as well as private-sector commercialization of technology developed with federal support. The Center also supports the development of clinical technology, instruments, devices and related methodologies that may have broad application to clinical research and better patient care.

NCATS will consider for possible funding applications that propose new clinical indications that leverage developed devices. Specifically, NCATS has several SBIR/STTR research priorities that include the development of devices to be used in clinical settings. These priorities are further described on the NCATS' website at: <https://ncats.nih.gov/smallbusiness/priorities>.

Spina Bifida

The Committee encourages NIDDK, NICHD, and NINDS to study the causes and care of the neurogenic bladder and kidney disease to support research to address issues related to the treatment and management of Spina Bifida and associated secondary conditions, such as hydrocephalus; and to understand the myriad co-morbid conditions experienced by children with Spina Bifida, including those associated with both paralysis and developmental delay.

Action taken or to be taken

NICHD continues its longstanding research commitment on spina bifida, a serious congenital disorder that occurs when the spinal cord does not close properly before birth.

Myelomeningocele, the most severe form of spina bifida, causes lifelong disability with concomitant quality-of-life challenges.

The NICHD-funded Management of Myelomeningocele Study (MOMS) was initiated to determine whether pre- or postnatal surgery was more effective in treating myelomeningocele. As reported in the *New England Journal of Medicine*, death or the need for a shunt to drain excess cerebrospinal fluid accumulating within the skull (hydrocephalus) within 12 months was much less likely in those who had prenatal surgery compared to the traditional, postnatal, surgery group. Children in the prenatal surgery group were also twice as likely to be able to walk without orthotics or crutches at 30 months. Following up on this groundbreaking trial, the MOMS 2 trial is now in progress, aimed at determining whether prenatal repair of myelomeningocele affects adaptive behavior, cognitive functioning, motor level and function, brain morphology and microstructure, and urologic health. The impact of having had prenatal surgery on the reproductive health of the mother, and on family well-being, also is being assessed. The study should be completed by late 2016.

Spina bifida often causes paralysis of the lower limbs. One recent NICHD-funded study used magnetic resonance imaging to show that muscle fat content (a reflection of muscle strength and function) varied widely among children with spina bifida. Knowing which muscles have better tissue integrity may help improve rehabilitation therapies for those with spina bifida. Another NICHD-supported study that assessed health-related quality-of-life issues for children with spina bifida showed the importance of including not only parents' perspectives, but also children's.

NINDS supports basic research to understand the mechanisms regulating spinal cord development and to understand and prevent spina bifida and other neural tube developmental problems and conditions that are secondary to them. The NINDS also funds research to treat such secondary conditions, including hydrocephalus and neurogenic bladder. Recent examples include a small business grant for the development of a pharmaceutical therapy to treat the loss of voluntary bladder control, and several Small Business Innovation Research grants for improved monitoring and use of shunts for hydrocephalus.

NIDDK supports basic and clinical research important to addressing the bladder and kidney problems of spina bifida. A major NIDDK-supported effort in this area is the GenitoUrinary Development Molecular Anatomy Project (GUDMAP), which 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, NIDDK plans to renew and expand GUDMAP for a third five year period. In February 2015, the NIDDK hosted a scientific meeting, “Research Needs for Effective Transition in Lifelong Care of Congenital Genitourinary Conditions,” to define research needs for improving the quality of care provided for adolescents/young adults with spina bifida and other conditions as these persons transition to the adult health care delivery system.

NIH works closely with its sister agencies on spina bifida and related health issues. NIH sits with CDC and other agency representatives on the Urology Interagency Coordinating Committee, which meets on a regular basis to discuss such issues as large cohort studies involving participants with spina bifida and the feasibility of a national spina bifida registry.

Stroke-induced respiratory dysfunction

In addition to the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) and the National Heart, Lung, and Blood Institute (NHLBI) support research that is elucidating the cellular and physiological mechanisms of how normal respiratory rhythms are generated and controlled by brain regions responsible for respiration. These projects are also providing insight into mechanisms underlying disrupted breathing patterns that may be a consequence of several neurological conditions including stroke. Breathing disorders such as sleep apnea also can increase the risk of stroke, including recurrent strokes. NINDS-funded investigators are studying the effects of sleep apnea on blood flow in the brain to better understand the mechanisms underlying its effect on stroke risk. NINDS also is supporting research to understand the influence of sleep apnea on the excess burden of stroke in Mexican American populations as a potential avenue for reducing stroke disparities.

Study Sections Pediatric Expertise

In addition, the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

NIH has populated its regular (chartered) study sections in the Center for Scientific Review (CSR) with pediatric expertise appropriate for the applications under review. For example, CSR used more than 400 reviewers with pediatric expertise during the May 2015 council review cycle. These reviewers were spread across 78 (about 45 percent) of CSR's regular (chartered) study sections as well as numerous Special Emphasis Panels. These reviewers span the full range of science covered by CSR's study sections -- from basic (40 reviewers) to physiological (110) to clinical (95) and to behavioral and populations sciences (155). Furthermore, CSR engaged another 200 reviewers in child development and 117 reviewers in developmental psychology for the May council. It is noteworthy that all five of CSR's review divisions are represented: Physiological and Pathological Sciences, Translational and Clinical Sciences, AIDS, Behavioral and Population Sciences, Neuroscience, Development, and Aging, and Basic and Integrative Biological Sciences.

While pediatric expertise across CSR study section is broad, it is important to note that CSR has two study sections with particularly strong concentrations of expertise in pediatrics, child development and developmental psychology: Child Psychosocial Risk and Developmental Disabilities; and Psychosocial Development, Risk and Prevention.

Given the number and distribution of pediatric reviewers, CSR is confident that there is appropriate pediatric expertise included on its study sections and panels and that it is well positioned to meet future needs. It has the flexibility to rapidly recruit additional experts to meet evolving needs, given the way it routinely recruits additional reviewers to fill the unpredictable needs that come with new applications each round.

Sturge-Weber

In addition, the specific interest items, the Committee requests general update in the FY 2017 budget requests for the following disease, condition, or topic to describe the latest efforts ongoing and planned.

Action taken or to be taken

NIH-supported research on Sturge-Weber Syndrome (SWS) and other vascular malformation conditions is comprehensive in scope and includes elucidation of disease mechanisms, experimental disruption of the disease processes, development of research and diagnostic tools, and development of new or improved treatment strategies.

The National Institute of Neurological Disorders and Stroke (NINDS), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Heart, Lung, and Blood Institute (NHLBI), and other NIH ICs support studies to better understand the cellular, molecular, and genetic processes underlying normal and abnormal blood vessel development, with the ultimate goal of interrupting these pathways to prevent disease progression. The NHLBI VITA Program (Vascular Interventions/Innovations and Therapeutics Advances Program) is specifically designed to foster translational research in vascular diseases, including the development of new therapeutics for vascular anomalies. NINDS-funded investigators are exploring ways to inhibit a growth factor involved in brain vascular malformation pathology, and others are investigating interventions that target novel signaling pathways gone awry in inherited forms of cerebral cavernous malformations (CCM). Several translational and clinical studies are also specifically focused on SWS. For example, NIAMS-funded investigators are working to improve current treatments, such as laser therapies to address port-wine stain birthmarks, to enhance effectiveness and longevity of the intervention. NINDS-funded investigators are exploring a new treatment paradigm with potential to reduce or prevent neurological consequences of SWS in children. Projects supported by NINDS and the National Institute of Biomedical Imaging and Bioengineering are developing new imaging methods to enable more precise visualization of neurovasculature and detection of vascular malformations. The Brain Vascular Malformation Consortium (part of the Rare Diseases Clinical Research Network) is supported by the NINDS and the National Center for Advancing Translational Sciences. Investigators in this project are developing imaging, genetic, and biochemical markers for vascular malformation conditions, including SWS, in order to build the foundation for future clinical research studies. Recently, this work has led to the discovery of a single gene mutation underlying the majority of cases of SWS and port-wine stain birthmarks, a finding which has catalyzed new research avenues for this field.

NIH serves an important role in supporting and stimulating collaboration among researchers and the community. NIAMS, the National Eye Institute, the National Cancer Institute, and NINDS supported a research workshop held in April 2015 to explore new research opportunities in SWS that have emerged as a result of the recently discovered gene discovery described above. The meeting brought together experts in SWS, researchers in allied fields, young investigators and trainees, and representatives from the Sturge-Weber Foundation to create new collaborations and chart research priorities for SWS. NINDS has sponsored several annual Angioma Alliance scientific meetings, an organization dedicated to research and advocacy for vascular malformation conditions that affect the brain. Finally, the Pediatric Dermatology Research

Alliance was established within the pediatric dermatology community and, through support from the NIAMS and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, has hosted annual scientific planning meetings to identify research needs and facilitate interactions between clinicians and basic scientists.

Temporomandibular Disorders (TMD)

The Committee encourages NIBIB, NIAMS, and NIDCR to consider the recommendation that resulted from their jointly sponsored Roundtable on the Temporomandibular Joint in Health and Disease 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

Temporomandibular disorders (TMDs) are a group of conditions that cause pain and dysfunction in the jaw joint and the associated muscles and supporting tissues. The National Institute of Dental and Craniofacial Research (NIDCR) funds a diverse research portfolio related to the development, structure, function, regeneration, and replacement of the temporomandibular joint (TMJ), as well as studies on chronic pain, which is associated with TMD. In a continued effort to identify safe and effective therapeutics that can be used for TMD and a variety of other pain conditions, NIDCR, through support of a small business grant, is developing a promising compound, called AQU-118, which has been found to block neuropathic pain in various animal models.

Damage or displacement of the disc that cushions the jaw joint can occur in TMD. The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports research to repair damaged disc tissue in other regions of the body, such as the spine, that should translate into efforts to improve the treatment of TMD. NIAMS-funded research is also providing insight into bone-loss caused by tiny implant particles, which is the most common reason for implant failure following joint replacement surgery. Researchers are developing and testing more durable or biologically compatible materials and generating new approaches for the early detection of complications following joint replacement surgery.

NIDCR co-funds a project with the National Institute of Biomedical Imaging and Bioengineering (NIBIB) to develop imaging methods for diagnosing and classifying bone damage in TMJ osteoarthritis in order to improve early diagnosis and monitoring of treatment outcomes. NIDCR and NIBIB also co-sponsor initiatives 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 additional novel approaches to prevent, diagnose, assess risk, and treat TMD.

In September 2014, NIDCR partnered with other NIH ICs and the TMJ Association to sponsor a meeting on the genetic and epigenetic basis of TMD and related chronic overlapping conditions.¹⁷⁴ In a related effort, NIDCR has launched a new initiative to better define the genetic basis of variability in drug responses and adverse events in individuals with painful conditions of the dental, oral, and craniofacial region. These types of precision medicine studies are critical to developing effective and personalized pain management for acute and chronic pain patients.

¹⁷⁴ <http://www.molecularpain.com/content/pdf/1744-8069-10-72.pdf>

Therapeutics for Rare and Neglected Diseases (TRND)

The Committee encourages NCATS to focus on additional neglected diseases through the TRND program. The Committee expects NCATS' contributions to neglected disease research be included in the joint CDC, FDA and NIH global health strategy describing coordination and prioritization of global health research activities within the three agencies.

Action taken or to be taken

The TRND program aims to encourage and speed the development of new treatments for rare and neglected diseases. The program is designed to advance the entire field of therapeutic development by encouraging scientific and technological innovations to improve success rates in the crucial pre-clinical stage of development.

TRND is an NCATS intramural program that supports collaborations with external investigators in the pre-clinical development of therapeutic candidates for rare and neglected diseases. Currently, NCATS scientists are collaborating with an academic research partner to develop a new treatment for malaria, a mosquito-borne infection of global importance that affects an estimated 250 million people worldwide. The purpose of this project is to develop a novel class of drugs that will not only relieve symptoms in affected patients, but also block mosquito-borne transmission from person to person. Blocking transmission represents a key step toward eradication of the disease. NCATS scientists have performed medicinal chemistry studies to identify a candidate compound suitable for further development, and are supporting pharmacology, drug metabolism, and other studies necessary to enable clearance by FDA to begin eventual human clinical trials. The TRND program announced a solicitation¹⁷⁵ in October 2015 to accept new collaborative research proposals on a rolling basis that address the development of candidate treatments for rare and neglected diseases.

TRND program supports several of the objectives of the HHS Global Health Strategy, particularly "Objective 6: Catalyze Health Research Globally" and one of its key priorities to "support the rapid translation of research results into new or improved preventive, diagnostic, and treatment products and processes..." TRND program's efforts on neglected disease research will continue to contribute to the successful implementation of HHS' global health strategy.

¹⁷⁵ <https://ncats.nih.gov/news/releases/2015/preclinical-proposals>

Translational Research

The Committee understands NIH has undertaken an expansion of translational research and sciences over the past several years. The Committee requests an update on the specific results of these efforts, current activities, a plan for future activities, and the fiscal year 2013 through 2016 annual NIH expenditures on translational sciences in the fiscal year 2017 budget request.

Further, the updates should provide the definition for Translational Research and how it applies the definition as it makes awards to various institutions.

Action taken or to be taken

The National Center for Advancing Translational Sciences (NCATS) defines *translation* as the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public – from diagnostics and therapeutics to medical procedures and behavioral changes. Translation is part of the mission of every NIH Institute and Center and each year NIH as a whole spends approximately 46 percent of its research budget on applied research, including translational research.

NCATS studies translational science, the field of investigation focused on understanding the scientific and operational principles underlying each step of the translational process. NCATS studies translation on a system-wide level as a scientific and operational problem and utilizes the definition when identifying applications that have a strong potential to advance the translation process across the full spectrum of biomedical research.

Highlights of NCATS' translational science milestones, programs and initiatives are described in its Annual Report for 2014.¹⁷⁶ The 2015 Annual Report is in preparation and will be sent to the Congressional Appropriations Committees when it is available.

¹⁷⁶ https://ncats.nih.gov/files/NCATS_2014_report.pdf

Trans-NIH Strategic Approach

The Committee directs the Director of DPCPSI to develop a trans-NIH strategic approach to improve coordination and facilitation of trans-NIH research with measurable objectives. The Director should also take specific steps with the ICs to strengthen to reduce duplication and increase effectiveness and efficiency of research.

Action taken or to be taken

The Director of DPCPSI has developed and refined trans-NIH strategic approaches to improve the coordination and facilitation of trans-agency research, including the identification of measurable objectives. In addition, the Director has initiated innovative approaches to assessing the efficiency and effectiveness of the Agency's research programs and to identify potential duplication in grant proposals and funded activities.

One model for trans-NIH research coordination and facilitation is the Common Fund (CF), which is managed by DPCPSI. CF supports research in areas of emerging scientific opportunities, rising public health challenges and knowledge gaps that deserve special emphasis and would benefit from strategic coordination and planning across NIH ICs. DPCPSI organizes a trans-NIH process to establish priorities for CF that engages IC Directors and their staff. During the planning for new CF programs, NIH and external research portfolios are carefully analyzed to avoid duplication of efforts and identify synergistic partnerships or opportunities for enhancement. All CF programs have specific goals and milestones, and progress towards these goals and milestones is assessed on a regular basis. Further information about the process is available in the 2015 Common Fund Strategic Planning Report.¹⁷⁷

DPCPSI's Director has initiated activities that promote and facilitate portfolio analysis at NIH. Information gleaned from these analyses can be used to identify and minimize the potential for duplication in NIH-supported research, resulting in greater efficiency and effectiveness in NIH's support for research. In its Office of Portfolio Analysis (OPA), DPCPSI develops new computational tools that can: retrieve and clean data used to analyze information about NIH investments, funded collaborations, and publication records; 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. These tools and analyses support the overall effort to help ensure that the NIH research portfolio is balanced, free of unnecessary duplication, and takes advantage of collaborative, cross-cutting research. DPCPSI also encourages and coordinates portfolio analysis across NIH by planning and hosting seminars, workshops, and symposia. OPA has developed a web-based training portal with courses that range from introductory portfolio analysis to advanced offerings in content analysis; network analysis and bibliometrics courses are forthcoming. OPA training activities are offered regularly in formal classes and are supplemented with ad hoc training sessions, user manuals, FAQs, and instructional videos available to NIH staff on the DPCPSI website.

In addition to the above efforts, DPCPSI and its Program Offices lead other trans-NIH research coordination and facilitation activities including:

¹⁷⁷https://commonfund.nih.gov/sites/default/files/2015%20Common%20Fund%20Strategic%20Planning%20Report_final%20-%20508.pdf

- Coordinating multi-IC workshops that result in multi-IC funding opportunity announcements (FOAs).
- Convening Research Coordinating Committees to strengthen collaborative efforts, facilitate information sharing, and coordinate and disseminate research goals and priorities.
- Providing or hosting detailees from other IC and OD offices to develop and/or implement multi-IC collaborative projects or activities.
- Analyzing significant investments in shared resources. NIH supports core research facilities – centralized, shared research resources that provide access to instruments, technologies, and expert consultation, as well as other services to scientific and clinical investigators. To better understand the efficiencies of core facilities, DPCPSI led a multi-IC Working Group to review the state of existing NIH-funded research core facilities and sponsored a workshop develop options to maximize their use and efficiency.^{178,179,180}
- Initiating, updating, and implementing DPCPSI Program Office Strategic Plans. The Offices have actively sought input from the ICs and other OD offices in the development of these plans, which has resulted in enhanced coordination of trans-NIH research activities.

¹⁷⁸ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4310223/>

¹⁷⁹ <http://nexus.od.nih.gov/all/2015/09/10/core-facts-about-core-facilities/>

¹⁸⁰ https://dpcpsi.nih.gov/sites/default/files/NIH-ABRF%20Workshop%20Report_Complete_06-22-15.pdf

Tuberous Sclerosis Complex (TSC)

The Committee continues to encourage NIH to coordinate a multi-Institute approach to finding a cure for TSC. NINDS and NCATS should play leading roles, given the promising translational potential of new therapeutics or treating the neurological conditions of TSC, including autism and epilepsy. The Committee encourages NINDS to lead the development of NIH programs to implement consensus recommendations developed at the NIH-sponsored TSC workshop, “Unlocking Treatments for TSC: 2015 Strategic Plan.”

Action taken or to be taken

Several NIH ICs fund research aimed at understanding and developing treatments for tuberous sclerosis complex (TSC). Communication among these ICs is facilitated by the Trans-NIH TSC Working Group, which is led by the National Institute of Neurological Disorders and Stroke (NINDS) and includes 10 NIH ICs, as well as representatives from the Department of Defense’s Tuberous Sclerosis Complex Research Program (DOD TSCRCP) and the Tuberous Sclerosis Alliance. The group meets biannually to share information and to discuss opportunities for collaboration. NIH ICs also support conferences and workshops to facilitate interaction among researchers. For example, NINDS and the National Center for Advancing Translational Sciences (NCATS) recently helped support the *2015 International Tuberous Sclerosis Complex Research Conference: From Treatment to Prevention*.

NINDS is dedicated to advancing promising new therapeutics to treat the neurological conditions of TSC, including epilepsy and autism. Several NINDS-funded studies are identifying early biomarkers of autism spectrum disorders and epilepsy in infants and children with TSC, which may facilitate earlier treatment or prevention. One NINDS-funded study, part of the NIH Autism Centers of Excellence, is determining whether state-of-the-art imaging along with quantitative EEG – a test that measures electrical activity in the brain – can predict the development of autism in infants with TSC. Another NINDS-funded project, part of the NINDS Epilepsy Centers Without Walls Program, is studying whether EEG during infancy is a reliable biomarker to identify TSC infants who will develop infantile spasms. If successful, this would lead to a preventive treatment trial. Other NINDS studies are using imaging techniques to identify epileptogenic anatomical lesions, or tubers, in the brains of TSC patients. NINDS also supports basic disease research to understand the signaling mechanisms and cellular processes underlying the disease as well as projects to improve preclinical models for TSC to help advance translational research and therapy development.

TSC research also is supported through NCATS’ Rare Diseases Clinical Research Network (RDCRN), which is designed to advance research on rare diseases by providing support for clinical studies and facilitating collaboration, study enrollment, and data sharing. The *Developmental Synaptopathies Consortium* is part of the RDCRN and is co-funded by NICHD, NIMH, and NINDS. The consortium is currently recruiting for the study *Autism Spectrum Disorder (ASD) and Intellectual Disability (ID) Determinants in Tuberous Sclerosis Complex (TSC)*. The goal of this study is 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, with the goal of developing effective interventions. This longitudinal study is taking place at five

institutions throughout the country: Boston Children's Hospital; Cincinnati Children's Hospital Medical Center; University of Alabama at Birmingham; University of Texas at Houston; and University of California at Los Angeles.

NIH, with the DOD TSCRP and the Tuberous Sclerosis Alliance, held a workshop “Unlocking Treatments for TSC: 2015 Strategic Plan” in March 2015.¹⁸¹ The goal of the workshop was to review research progress in TSC, identify key challenges and needs, and update the recommendations in the 2003 Research Plan for Tuberous Sclerosis. Prior to the workshop, four working groups (Molecular Pathways & Therapeutics, Growth/Tumor Biology, Neurocognition, Epilepsy in TSC) developed preliminary recommendations which were further deliberated and refined at the workshop. NINDS is currently developing a publication communicating the final research recommendations for the field, and discussions of next steps will follow.

¹⁸¹ <https://meetings.ninds.nih.gov/Home/Index/9540>

Undiagnosed Disease Program (UDP)

The Committee continues support for the Undiagnosed Disease Network (UDN) within the UDP. The Committee requests an update in the fiscal year 2017 budget request on steps NIH has taken to develop public/private partnership for the UDN and how it can support physicians who are handling cases of undiagnosed diseases with new knowledge, consistent with applicable privacy laws, including HIPAA privacy and security law, through an ability to search for similar cases and to network and collaborate with physicians handling similar cases in order to accelerate the diagnosis, treatment options, and improve patient outcomes across the country. Further, the update should describe the criteria NIH uses to allow various level of access to the database based on the circumstances of the users' requirements.

Action taken or to be taken

NIH's initiation and continued support of UDN is aimed at improving the level of diagnosis and care for patients with undiagnosed diseases, facilitating research into the causes of undiagnosed diseases, and creating an integrated and collaborative research community to identify improved options for patient care and treatments of these new and rare diseases. To facilitate access to this research program, UDN has opened an online patient application portal, the UDN Gateway. This portal streamlines the application process, improving upon the previous system of applications being submitted via individual clinical network sites. To enable patients to submit these applications to UDN, the National Organization for Rare Disorders (NORD; rarediseases.org) has set up a patient assistance fund that will also help qualifying patients pay for the preliminary diagnostic testing necessary for application to the UDN in a limited number of cases. The network has also incorporated new sequencing facilities, such as Baylor College of Medicine and the HudsonAlpha Institute for Biotechnology with Illumina Corporation.

With regards to data sharing, important clinical insights learned through UDN cases will be available to physicians and the public via NIH public and controlled access databases. UDN has a form available for outside investigators to request a research collaboration. De-identified data will be made available on a case-by-case basis to qualified investigators. In addition, UDN is also collecting phenotypes, or observable characteristics, data through PhenoTips, a specialized software program used for collecting this type of information. This data will then be deposited in Matchmaker Exchange, with a goal of providing a database that can be searched to identify other patients with similar phenotypes and connect clinicians to help advance our efforts to understand and identify the condition and improve care.¹⁸² Next, in order to provide guidance to healthcare professionals regarding which individual differences in the DNA code have clinical relevance for patient care, links discovered between specific variants and diseases will be made available through the Clinical Genome Resource (ClinGen) database (a growing catalog of variants in the human genome associated with disease).¹⁸³ All UDN research data provided through NIH databases will be managed in accord with rigorous data security and privacy practices regarding access and minimization of any identifiable data held, in compliance with relevant Health Insurance Portability and Accountability Act and Federal Information Security Management Act (FISMA) regulations. Patient-participants will be informed during the research consent process that every effort will be made to minimize the risk to their privacy, but that this risk cannot be completely eliminated. It is important to note that the UDN coordinating center,

¹⁸² <http://www.matchmakerexchange.org/>

¹⁸³ www.clinicalgenome.org

which hosts the UDN Gateway, is a FISMA moderate database due to the types of data being collected. The intent of the program is to deposit UDN data in a variety of resources that physicians and patients can access long term.

UDN also disseminates its expertise and resources for researching undiagnosed diseases across the country through its distribution of thirteen geographically diverse clinical and research centers. These centers simultaneously broaden the UDN's diagnostic expertise while expanding opportunities for patients to participate. Private physicians who have patients that they believe have undiagnosed diseases may collaborate directly with the researchers and physicians at the UDN clinical sites. These activities are encompassed within the UDN mission and supported through the UDN grants and NIH intramural research program, as funds permit.

Usher Syndrome

The Committee continues to encourage support for research activities to prevent and correct the health related issues of Usher Syndrome. The Committee requests an update in the fiscal year 2017 budget request on the planned and on-going activities related to this syndrome. The update should address the funding level and manner in which the various ICs coordinate on common goals and objectives.

Action taken or to be taken

NIH spends an estimated \$19 million annually on research projects directly related to Usher Syndrome (USH). Since USH is a hereditary disease that affects hearing, balance, and vision, multiple institutes at NIH are studying the disease and coordinate research on different aspects of the disorder based on each NIH IC's research mission. For example, the National Institute on Deafness and Other Communication Disorders (NIDCD) funds research on deafness and balance disorders, while the National Eye Institute (NEI) supports research on blindness.^{184,185}

NIDCD is investing in basic research projects to understand the underlying genetic basis of deafness and balance disorders in USH. To date, NIH support has enabled molecular geneticists to identify at least 11 gene mutations that cause USH, and NIDCD intramural scientists are also conducting studies to search for new USH genes. NIDCD-funded researchers continue to develop mouse and zebrafish models of USH similar to the human types of USH. NIDCD intramural scientists are also working on methods to deliver genes to the inner ear for treating hereditary hearing loss. They are using a mouse model of USH in which the *whirlin* gene is mutated. In another study, an investigator is testing treatments for blindness, balance problems, and deafness in a mouse model of USH. Translational research efforts focus on better diagnosis for children with USH, and on how to slow and/or prevent hearing loss. NIDCD clinicians are expanding testing options to characterize vestibular and balance function in individuals with USH. NIDCD and NEI intramural scientists are collaborating on clinical research with individuals with USH, focusing on neural mechanisms underlying balance and vision.

NEI research explores the relationship between USH genes and the structure and function of photoreceptors. Two current studies at the NEI Eye Clinic are testing the genes of individuals with USH and their family members and closely monitoring disease progression over time. NEI is also developing gene therapies for inherited retinal diseases and has had success in recent clinical trials. However the genes mutated in USH are presently too large for scientists to package into existing gene therapy vectors with current technology. Thus, NEI researchers are developing new viral vectors and delivery systems, such as DNA nanoparticles, for use with large genes that cannot fit into traditional vectors. These experiments will include two animal models of USH, type 2.

National Institute of General Medical Sciences (NIGMS) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) support basic research on protein structure, cell biology, and development involving USH genes. For example, using a novel zebrafish model of USH, NICHD-supported researchers suggest that defects in the biological pathway leading to USH may cause cellular dysfunction and death.

¹⁸⁴ <http://www.nidcd.nih.gov/health/hearing/pages/usher.aspx>

¹⁸⁵ <https://www.nei.nih.gov/health/ushers>

Valley Fever

The Committee commends NIH and CDC on the continued joint efforts to combat coccidioidomycosis, also known as Valley Fever. Specifically, the Committee supports ongoing efforts by NIH and CDC to conduct a Randomized Controlled Trial (RCT) to identify an effective treatment for Valley Fever, encourage development of a vaccine, and help increase awareness of this disease among medical professionals and the public. The Committee looks forward to when patients can begin enrolling in the RCT later this year.

Action taken or to be taken

Coccidioidomycosis, or Valley Fever, is a fungal infection caused by airborne spores of several soil-dwelling *Coccidioides* species. In the United States, Valley Fever occurs primarily in the Southwest. Most Valley Fever patients experience mild flu-like symptoms and recover spontaneously; however, for some individuals, the infection may be severe and life-threatening, emphasizing the importance of research addressing this disease.

The National Institute of Allergy and Infectious Disease (NIAID) and CDC continue to prepare for the expected initiation in FY 2016 of a randomized controlled trial (RCT) to address key unanswered questions regarding treatment of the initial infection of Valley Fever. RCT will study patients with community-acquired pneumonia (CAP). Since CAP may be caused by bacteria or by fungi like *Coccidioides*, RCT will compare outcomes in patients receiving the standard-of-care antibacterial drug such as azithromycin with or without treatment with the antifungal drug fluconazole. The primary goal of the trial will be to assess the safety and effectiveness of early treatment of Valley Fever with fluconazole in patients with CAP in Valley Fever-endemic regions. CDC has identified where cases of Valley Fever commonly occur in order to enroll patients in the trial as they first seek care for CAP, while NIAID is working closely with subject matter experts from Valley Fever-endemic regions to finalize the clinical trial protocol. In addition to determining the safety and efficacy of fluconazole to treat Valley Fever, RCT will likely help increase awareness of the disease in the endemic area, prompting those experiencing symptoms to seek medical care earlier in the course of the disease.

NIAID also conducts research to better understand why some Valley Fever patients develop more severe forms of the disease. NIAID intramural researchers are leading an ongoing clinical trial to identify underlying factors, including the strains of *Coccidioides* causing the infection that may increase a patient's susceptibility to develop chronic disease. The objective of this research is to better understand mechanisms of the disease and explore the development of novel ways to prevent and treat Valley Fever.

To encourage the development of a vaccine for Valley Fever, NIAID included the topic in the current Small Business Innovation Research solicitation, *Vaccines against Pathogens with Small Market Potential*, which highlights NIAID's interest in the development of vaccines against pathogens with a small or limited market, including *Coccidioides*. While the segment of the overall population affected by these pathogens may be small, the impact to affected communities in morbidity and/or mortality can be quite substantial. To address these pathogens, the program encourages collaborations between academic researchers and small businesses to discover, validate, and produce vaccines.

NIAID will continue to support Valley Fever research to increase basic understanding of the infection and develop new therapies and vaccines to prevent and treat the disease. Continued engagement with Federal partners and the scientific, public health, and affected communities will be essential to these efforts.

Vitiligo

The Committee is concerned that although vitiligo is not a terminal or debilitating disease, it nonetheless can have serious effects on the lives of those afflicted with this skin-discoloring condition. The Committee is further concerned that this may lead to other conditions that have not been thoroughly considered including the impact on behavior and mental health consequences. The Committee requests an update in the fiscal year 2017 budget request on the epidemiology of the disease including incidence, causal factors, any associations with racial populations and hereditary occurrence. The update should include planned and on-going medical research to move towards a cure.

Action taken or to be taken

Vitiligo is a progressive disease in which the skin cells that impart color (melanocytes) are destroyed, resulting in white patches on the face, hands, and other parts of the body. The condition affects about 0.5-1.0 percent of the world's population. It affects both sexes and all races equally; however, it is more noticeable in people with dark skin. Although vitiligo is usually not harmful medically, its emotional and psychological effects can be devastating. People with vitiligo can experience emotional stress, and may find it helpful to get counseling from a mental health professional or to participate in a vitiligo support group.

Although the precise cause of vitiligo is not fully understood, research suggests that it is an autoimmune disease in which the immune system attacks the body's own organs or tissues. In vitiligo, abnormal immune cells specifically target melanocytes. To foster more effective therapies, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports basic and translational research to understand the molecular mechanisms of vitiligo and the underlying immune system defects involved in the disease. NIAMS also supports clinical research to test new interventions. In addition, other NIH ICs, such as the National Cancer Institute and the National Institute of Allergy and Infectious Diseases support research on vitiligo.

NIAMS has a long-standing commitment to fostering research on the genetics of vitiligo. Over 15 years ago, as part of an international collaboration, the Institute funded the first studies to search for genes linked to vitiligo in families affected by the disease. Those studies led to the identification of a number of genes that may be altered in vitiligo. More recently, researchers have used new approaches, such as genome-wide association studies (GWAS), to learn more about the genetic underpinnings of vitiligo. One ongoing NIAMS-funded study seeks to identify additional genetic factors that increase the risk of developing the disease. Another is focused on determining how different vitiligo-associated genetic changes influence specific clinical characteristics and disease biomarkers in order to facilitate the development of interventions that are tailored to a patient's specific genetic makeup.

Findings from a NIAMS-funded translational research study showed that altering a protein involved in the development of vitiligo may protect against – or even reverse – the pigmentation loss associated with the skin disorder in mice. When researchers administered the mutated protein as a vaccine to mice that were genetically predisposed to develop vitiligo, the vitiligo-prone mice did not develop the disorder at all. When the protein was given to mice that already had developed vitiligo, seventy-six percent of normal pigment returned, essentially reversing the

disease. Currently, NIAMS is funding researchers' efforts to determine how the vaccine exerts its effects and to generate a form of the protein that would be suitable for the next step in preclinical testing. In addition to this work, NIAMS also is funding research using a vitiligo mouse model, as well as human skin samples, to improve understanding of the natural mechanisms the body uses to control autoimmunity. Through such research, scientists hope eventually to harness the body's innate protective responses to prevent and treat vitiligo and other autoimmune diseases.

In addition to developing new drugs for vitiligo, researchers also are exploring whether existing drugs may be beneficial. Researchers have identified biological processes involved in disease pathology that could be modified using available drugs. For example, NIAMS-funded scientists recently reported that an FDA-approved cholesterol-lowering medication reverses and prevents depigmentation in a mouse model of the disease.

Vulvodynia

The Committee encourages NICHD to implement the recommendations from the May 2013 NICHD workshop to develop research diagnostic criteria and common data elements to standardize vulvodynia research efforts. The Committee is pleased with NICHD's involvement in the Trans-NIH effort to advance research on chronic overlapping pain conditions and encourages the Institute's continued and expanded involvement.

Action taken or to be taken

Vulvodynia is a complex, multifactorial clinical syndrome of unexplained vulvar pain lasting more than three months. Recent population estimates indicate that seven to eight percent of women will self-report burning or pain on contact consistent with vulvodynia by the age of 40. As part of a recent restructuring, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) established the Gynecologic Health and Disease Branch, which includes vulvodynia as an important focus area in its research portfolio.

To address this common pain syndrome that detrimentally affects quality of life, NICHD worked over several years with the NIH Office of Research on Women's Health, experts, non-profit organizations, and women with vulvodynia to create the NIH Research Plan on Vulvodynia in 2012.¹⁸⁶ With public input from the research, clinician, and patient communities, the plan addressed gaps in research, identified the need to build more research capacity, and suggested creating a better understanding of vulvodynia as a chronic pain condition by improving its diagnosis and treatment through various types of research. A funding opportunity announcement was released shortly thereafter, further informed by the Institute of Medicine report, "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research."¹⁸⁷

Because of the importance of pain treatment and management, NICHD continues to explore opportunities for new and innovative collaborations to augment pain research in conditions that affect women. For example, the research community has called for the development of common data elements and noted the absence of standardized and validated patient reported outcomes, all of which are needed to construct clinical, translational, and basic science strategies to improve the clinical care of women with vulvodynia. NICHD sponsored a meeting on developing common terminology related to vulvodynia, and a final report is forthcoming from a consortium of professional societies on updated terminology for vulvodynia and vulvar pain disorders. NICHD also is participating in two new funding opportunity announcements on developing potential therapies for pain treatment and on chronic overlapping pain conditions that will be open to researchers studying vulvodynia. NICHD also eagerly awaits the development of the Federal Pain Research Strategy and has encouraged researchers in vulvodynia to respond to the notice, "Request for Information: Input on the Development of the Federal Pain Research Strategy, Notice Number: NOT-NS-16-038."

¹⁸⁶[https://www.nichd.nih.gov/publications/pubs/documents/NIH_Vulvodynia_Plan_April2012.pdf#search=vulvodynia research plan](https://www.nichd.nih.gov/publications/pubs/documents/NIH_Vulvodynia_Plan_April2012.pdf#search=vulvodynia%20research%20plan)

¹⁸⁷ <http://iom.nationalacademies.org/Reports/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research.aspx>

Women's Health Research

The Committee appreciates NIH's recent work to improve the gender balance in pre-clinical research and continues to encourage all future NIH-funded research to include both sexes unless there is a specific reason not to include them. The Committee requests an update on NIH's new policy to require that both sexes be represented in preclinical research; that report should include an analysis of the impact on applications for funding in fiscal year 2015, the projected impact in 2016, and NIH's plan to ensure the analysis of data by sex and other subgroup demographics as a part of grant progress reporting and the compliance of institute directors for funding studies on sex differences and conditions that predominantly impact women.

Action taken or to be taken

Throughout FY 2015 NIH developed changes to instructions and review criteria for research grant applications, which reflect NIH's new policy on the study of both sexes. Pending approval of these changes by the Office of Management and Budget, grant application instructions will state that NIH expects that sex as a biological variable will be factored into proposed research with vertebrate animals and humans. Beginning in FY 2016 peer reviewers will be directed to evaluate applicants' consideration of sex as a variable within the context of the overall proposed research program. Strong scientific justification will be required for studying only one sex. Thus, for research funded in FY 2017 and beyond, the influence of sex will be considered in vertebrate animal and human studies as scientifically appropriate and year-to-year progress of awarded grants will be assessed in progress reports. .

Throughout FY 2015 NIH has communicated the scope and intent of the changes to various NIH Advisory Councils, at national and international scientific meetings, and posted supporting documentation on the NIH website. To facilitate dissemination of research conducted on males and females, NIH has worked with journal editors to clarify guidelines for publications including specification of the sex or sexes studied in preclinical research.^{188,189} NIH continues to explore innovative options for expanding reporting of data from research on males and females, where scientifically relevant. For example, NIH hosted a workshop on methods and techniques for integrating sex as a biological variable into preclinical research, which highlighted the knowledge to be gained when both sexes are included in appropriately designed studies.¹⁹⁰

NIH has longstanding policy on the inclusion of women and minorities in research involving human subjects. Currently, applicants for NIH-defined Phase III trials must address plans for a valid analysis of potential differences by sex, race, and/or ethnicity.¹⁹¹ These plans are initially assessed during peer review, and enrollment information is reported by investigators no less than annually from the time of award through award closeout. NIH recognizes that complete information about potential group differences sometimes becomes available after the award is closed out, and therefore is outside of the NIH's direct purview. To address this, NIH is actively engaging with journal editors to enhance the publication of sex-specific results, through strategies such as data sharing and sex-stratified analyses.¹⁹² In addition, for clinical trials that

¹⁸⁸ <http://www.nih.gov/about/reporting-preclinical-research.htm>

¹⁸⁹ <http://orwh.od.nih.gov/resources/policyreports/pdf/Sex-Specific-Reporting-Scientific-Research-2011.pdf>

¹⁹⁰ <http://orwh.od.nih.gov/sexinscience/researchtrainingresources/methodstechniquesbiovar.asp>

¹⁹¹ http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm

¹⁹² http://www.ncbi.nlm.nih.gov/books/NBK84192/pdf/Bookshelf_NBK84192.pdf

are subject to registration and reporting in ClinicalTrials.gov, if sex is a primary or secondary outcome of the trial design, results on that basis will be reported in ClinicalTrials.gov.

In FY 2015, NIH also continued the Administrative Supplements for Research on Sex/Gender Differences, which provide additional funding for studying both sexes in existing NIH-funded research programs. Co-funded by the Office of Research on Women's Health and 19 NIH ICs, these grantees are among the vanguard in enhancing preclinical research via consideration of sex as a biological variable, which in turn leads to appropriate treatments and interventions for both men and women.

Women's Heart Disease

Heart disease is the number one killer of women in the United States, and increased research on women's heart disease, including sex-specific analysis in clinical trials is needed to make progress against the disease. Therefore, the Committee urges NHLBI to prioritize research on women and heart disease. Further, the Committee urges NIH, when making research awards, to ensure inclusion of women and minority groups in clinical research in a manner that is appropriate to the scientific question under study. For those studies where sex is identified as a primary or secondary outcome measure, with stratification on that basis, the NIH should continue to ensure that sex-based analysis of results is reported on clinicaltrials.gov. Furthermore, the Committee encourages NIH to continue to work with scientific journals to report sex-specific data in its publications.

Action taken or to be taken

National Heart, Lung, and Blood Institute (NHLBI) has a long-standing commitment to women's health research, starting with the Framingham Heart Study, begun in 1948, and continuing through many pioneering studies that have greatly contributed to improving women's health and our knowledge about women and heart disease. The Women's Health Initiative (WHI), for example, changed how postmenopausal hormone therapy is used in this country, reducing heart disease and breast cancer cases and resulting in a net economic return of \$140 for every dollar invested in the trial. In addition to studies focused solely on women's health, such as the WHI, NHLBI is committed to including women in cardiovascular clinical trials more generally. In FY 2013, nearly half of participants (46 percent) in NHLBI cardiovascular clinical trials (excluding the WHI) were women. But more needs to be done to prioritize heart disease research in women. NHLBI recently hosted a "Working Group on Sex Bias in Cardiovascular Research," which highlighted barriers to the study of both sexes, as well as scientific opportunities in studying sex differences in cardiovascular disease. NHLBI also held a scientific roundtable, "Optimizing Cardiovascular Health of Women: Public Health Challenges and Scientific Opportunities," to assess the current state of research on the cardiovascular health of women and to provide input into the desired future state of research and the scientific priorities to be reflected in NHLBI's strategic visioning process.

The role of sex as a biological variable in both health and disease is an important focus of the NIH in all types of research, from basic to clinical. Recently, NIH developed changes to instructions and review criteria for research grant applications that will require applicants to explain how sex as a biological variable is factored into research designs and analyses for vertebrate animal and human studies (pending OMB approval). NIH expects that enhancing the study of both sexes in basic and preclinical research will lead to more precise hypotheses for clinical research, and therefore to more appropriate treatments and interventions for both men and women.

To ensure that women are included in clinical research in a manner that is appropriate to the scientific question, Scientific Review Groups across the NIH are directed to consider inclusion plans as part of the overall priority score, which directly affects funding decision-making.¹⁹³ With respect to reporting, ClinicalTrials.gov currently collects the number of enrolled participants in a trial by sex/gender. In addition, if analyses of sex/gender effects on primary or

¹⁹³ http://grants.nih.gov/grants/peer/guidelines_general/Review_Human_Subjects_Inclusion.pdf

secondary outcome measures have been proposed, and the study is subject to registration and reporting requirements in ClinicalTrials.gov, then those results must be reported in ClinicalTrials.gov after trial completion. In November 2014, HHS published a Notice of Proposed Rulemaking that would require more types of trials to be registered and additional trial registration information, including results, to be submitted.¹⁹⁴ NIH also is working to draft a policy, expected to be finalized by May 2016, which would expand registration and results submission to all NIH-funded clinical trials thereby strengthening the reporting of results, including sex-specific results when a primary or secondary outcome measure.¹⁹⁵

In addition, NIH continues to work with scientific journals to encourage the reporting of sex-specific data in their publications. NIH held a joint workshop in June 2014 with the Nature Publishing Group and Science on the issue of reproducibility and rigor of research findings. The workshop included journal editors representing over 30 science journals in which NIH-funded investigators have most often published. The editors came to consensus on a set of principles to enhance rigor and reproducibility in research, which over 70 journals have agreed to endorse.^{196,197}

¹⁹⁴ <https://www.federalregister.gov/articles/2015/02/13/2015-02990/clinical-trials-registration-and-results-submission>

¹⁹⁵ <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-019.html>

¹⁹⁶ <http://www.nih.gov/about/reporting-preclinical-research.htm>

¹⁹⁷ <http://www.nih.gov/about/endorsing-journals.htm>