

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

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### **Addressing the Opioid Crisis in Rural Regions**

The Committee encourages NIDA to continue its partnership with CDC, SAMHSA, and the Appalachian Regional Commission in support of research to help communities develop comprehensive approaches to prevent and treat consequences of opioid injection, including substance use disorders, overdose, HIV, and hepatitis infections, as well as sexually transmitted infections. These projects will serve as models for addressing the consequences associated with opioid injection that can be implemented by health systems in similar rural communities in the United States.

#### **Action taken or to be taken:**

The National Institute on Drug Abuse (NIDA) is committed to researching the most effective ways to implement addiction and overdose prevention and treatment interventions in populations with unique needs, including those living in rural areas. Often these areas have specific challenges due to lack of access to key prevention and treatment services and to personnel trained to deliver these services. To address the challenges posed by addiction in rural settings, NIDA partnered with the Appalachian Regional Commission (ARC), CDC, and SAMHSA to issue eight grants, supported by a laboratory site and a coordinating center to help rural communities develop comprehensive approaches to prevent and treat consequences of opioid injection, including substance use disorder (SUD), overdose, HIV, Hepatitis C Viral (HCV) infections, and syphilis. Funded in FY 2017 and continuing into FY 2022, investigators will work with state and local communities to develop best practices that can be implemented by public health systems in these regions and rural areas in other parts of the country.

NIDA's commitment to addressing addiction in rural areas extends beyond this partnership. NIDA funds research examining approaches to implement evidence-based SUD treatment, overdose prevention, and the prevention and treatment of infectious disease consequences of opioid injection in rural areas of the U.S. For example, NIDA supports a study to increase access to treatment for HCV, which often co-occurs with opioid injection, in a rural Appalachian community in Kentucky. NIDA also supports a project studying the effects of linking treatment for HIV, HCV, and opioid addiction in a community in rural northern New England. These are just two examples of NIDA-funded studies in rural areas across the country, which extend from California and the Pacific Northwest, to Midwestern states like Wisconsin, Illinois, and Ohio, to Appalachia and New England.

Rural communities are also represented in flagship projects of the NIH HEAL (Helping to End Addiction Long-term) Initiative<sup>SM</sup>. For example, the HEALing Communities Study, a multi-site implementation study testing a set of proven prevention and treatment interventions across 67 communities in four states hard hit by the opioid crisis, was designed from the outset to include rural communities. In order to qualify for funding, each research site had to demonstrate both that their communities were disproportionately impacted by the opioid crisis, and that at least 15 percent of opioid overdose deaths occurred in rural communities. In addition, NIDA's efforts to expand its Clinical Trial Network under the NIH HEAL Initiative<sup>SM</sup> included both the creation of

an Appalachian Node of the Network, allowing for dedicated staff and infrastructure for clinical trials in Appalachian populations, and the addition of a trial protocol aimed specifically at expanding medication-based treatment for opioid use disorder in rural areas. These efforts, alongside the partnership with the ARC, represent a commitment to supporting research that addresses the specific challenges that come with SUD in rural areas.

### **Advancement of Non-Opioid Chronic Pain Therapies**

Fifty million Americans suffer from chronic pain; living with chronic pain can be life-altering, deeply impacting people on many levels. The current state of chronic pain management is often inadequate for many patients and places an economic burden on the health care system, costing the U.S. \$560 billion annually. Management of chronic pain often requires both non-pharmacological treatment as well as medicines. Unfortunately, the current pharmacological options do not meet the needs of all patients, and additional treatments are needed. The Committee requests in the fiscal year 2021 Congressional Justification an update on the progress of the development and advancement of non-opioid chronic pain therapies.

#### **Action taken or to be taken:**

The National Institutes of Health (NIH) recognizes the need to improve pain management without the risk of addiction or dangerous side effects. NIH is moving forward on research priorities through a multi-pronged approach to develop safe and effective therapies to reduce our reliance on opioids. Three key areas of interest are to understand the biological underpinnings of pain, accelerate discovery and development of non-addictive treatments, and rapidly advance new treatments to the clinic.

Studies are underway to identify compounds that target receptors and ion channels integral to non-opioid pain pathways in the nervous system. People with gene mutations that switch off function in pain relevant nerve ion channels are unable to sense pain, while others with mutations in the same channel that switch on function suffer from devastating pain. These channels are now targets for pharmaceutical development. In addition, NIH supports studies on anti-inflammatory compounds to treat chronic pain conditions such as neuropathic pain and osteoarthritis. Through the NIH Blueprint Neurotherapeutics Program for drug discovery and development, the National Institute of Neurological Disorders and Stroke (NINDS) funds studies to develop non-addictive kappa opioid receptor antagonists for treatment of migraine and a safe, non-opioid analgesic, which is a soluble epoxide hydrolase inhibitor that can be taken orally to reduce diabetic nerve pain. NIH supported basic science research that led to the understanding of the role of calcitonin gene-related peptide therapy for migraine and nerve growth factor therapy for inflammatory pain. Drugs that target these molecules' function are now approved by the FDA to treat migraine and osteoarthritis pain, respectively.

The NIH Helping to End Addiction Long-term (HEAL) Initiative significantly expands research to discover and accelerate development of non-addictive pharmacological and non-pharmacological pain treatments. In September 2019, NIH announced \$945 million in research awards (using FY 2018 and FY 2019 appropriations) to improve treatments for chronic pain and address opioid use disorder, overdose and addiction. Through the HEAL initiative, NIH supports programs to discover and accelerate development of new medications and devices to treat pain. To test new non-addictive pain treatments, newly established preclinical screening platforms will use animal-based and human cell-based models such as neural tissue chips for rapid screening of molecules or devices for analgesic relevant biological and behavioral activity. Through HEAL,

NIH is also partnering with academia and industry to bring in promising new drugs and devices for early phase testing of novel therapeutics in the newly established Early Phase Pain Investigation Clinical research network (EPPIC-NET) which supports trials on the safety and efficacy of novel drugs and devices. This network also will support discovery research on different pain conditions. NIH also established the Pain Management Effectiveness Research Network to support phase 3 effectiveness trials and will support a range of trials on pharmacological and nonpharmacological therapies for many different pain conditions.

NIH is working with federal partners to address research gaps for non-pharmacological treatments by providing the foundation for implementing these treatments into health care systems and leading ultimately to their broader dissemination. The NIH Health Care Systems Research Collaboratory, which supports pragmatic trials, will be leveraged to support trials on how best to imbed effective non-pharmacological treatments for pain into large health care settings through PRISM (Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing).

NINDS also leads the NIH Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, a major effort to develop tools to map, monitor, and modulate neural circuits, which may lead to treatment of disorders such as chronic pain that alter neural circuits. Advanced technologies from the BRAIN Initiative will enable powerful approaches to diagnose and treat pain through knowledge of normal and altered circuits and discovery of ways to modify circuit changes.

### **Alopecia Areata**

The Committee notes NIAMS leadership is continuing autoimmune research to advance treatment development for alopecia areata and related conditions. The Committee requests an update from NIAMS on developments from cross-cutting autoimmune research projects in the fiscal year 2021 Congressional Justification.

#### **Action taken or to be taken:**

Alopecia areata (AA) is an autoimmune disease in which the immune system mistakenly attacks hair follicles, leading to hair loss. Hair loss caused by AA can have substantial negative effects on a patient's quality of life. There is no cure for AA, and no current therapies are approved specifically for the disease. NIAMS supports the development of new treatments for AA through continued support for the Alopecia Areata Center of Research Translation (AACORT). The Center seeks to apply recent discoveries about the genetics and pathogenesis of alopecia areata into translational studies that will advance the development of new drugs or the repurposing of existing drugs to treat AA. NIAMS also continues to fund a career development award to an investigator who is exploring the role of a specific immune signaling pathway in AA. Another NIAMS funded-study examining the genomics of AA is expected to shed light on how genetic factors contribute to the development of AA. This data could also help researchers understand how genetic influences may give rise to other autoimmune diseases, and reveal whether drugs currently in use for those conditions could also be effective in treating AA.

### **Alzheimer's Disease (Senate)**

The Committee provides an increase of \$350,000,000 for Alzheimer's research, bringing the total funding level in fiscal year 2020 to \$2,818,000,000. By 2050, the cost to treat and care for those suffering from Alzheimer's disease is expected to rise to as high as \$1,100,000,000,000 a year. Without a medical breakthrough to prevent, slow, or stop the disease, Medicare- and Medicaid-related costs could more than quadruple.

#### **Action taken or to be taken:**

In addition to the severe medical and psychological costs to patients and their families, Alzheimer's disease and related forms of dementia (AD/ADRD) impose significant economic costs in many forms. For example, National Institute on Aging (NIA)-funded economists found total health care spending in the last five years of life for people with dementia was more than a quarter-million dollars per person, some 57 percent greater than costs associated with death from other diseases, including cancer and heart disease. This analysis estimates that total health care spending was \$287,000 for those with probable dementia and \$183,000 for other Medicare beneficiaries in the study.

More recently, investigators used data from the NIA-funded Health and Retirement Study (HRS) to estimate the incremental costs of dementia to the Medicare program. They found that the 480,000 patients newly diagnosed with Alzheimer's disease in 2017 cost traditional Medicare \$2.7 billion in that year alone and will add an additional \$3.2 billion to Medicare spending by 2022. As the population ages, incremental spending in the first year of diagnosis among newly diagnosed patients could exceed \$3.5 billion by 2030 and \$5.5 billion by 2050, without accounting for inflation, and ignoring costs beyond the first year after diagnosis (which can themselves be significant). The authors note that interventions that aid in earlier identification of dementia, if coupled with effective preventive interventions, could lead to substantial savings within the program.

At present, NIA supports research on over 40 compounds that are currently under study for the prevention and treatment of AD, mild cognitive impairment, and age-related cognitive decline. NIH also supports approximately 140 clinical trials, including both pilot and large-scale trials, of a wide range of interventions to prevent, slow, or treat AD and cognitive decline. Over 60 of these studies are testing cost-effective non-pharmacological interventions, including diet, exercise, and cognitive training.

Other investigators are exploring the application of relatively inexpensive treatments already in use for other conditions. For example, NIA-supported investigators have found that people with mild cognitive impairment (MCI), often a precursor to AD, who took metformin, a safe and commonly-used diabetes drug, performed better on some cognitive tests (although not others) than MCI patients who did not take the drug—results that justify further study of this widely-used agent. Elsewhere, NIA-supported investigators with the Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults (PREVENTABLE) Trial are determining whether lowering cholesterol could prevent MCI, dementia, physical disability, major cardiovascular events, or death in adults age 75 and older without cardiovascular disease.

A promising finding recently emerged from the NIH-supported Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension (SPRINT MIND). The investigators found that intensive lowering of blood pressure did not significantly reduce dementia risk but did have a measurable impact on MCI. These results are the first to demonstrate an intervention that significantly reduces the occurrence of MCI and—potentially—the risk for later dementia.

NIA-supported investigators are also using cutting-edge techniques to identify treatment targets and develop new compounds that are exquisitely tailored to engage those targets. NIA is currently supporting a team of experts in economics, neuroscience, and AD/DRD care as they identify and quantify alternative reimbursement strategies that could ensure better access to therapies and more rapid innovation. These investigators are identifying novel reimbursement strategies to ensure AD/DRD patients gain access to the most promising treatment alternatives, and quantify their social benefits and costs, including to caregivers.

### **Alzheimer's Disease (House)**

In recognition that Alzheimer's disease poses a serious threat to the nation's long-term health and economic stability, the Committee recommends a total of no less than \$2,392,000,000 for Alzheimer's disease research, as recommended in the NIH Bypass Budget Proposal for Fiscal Year 2020. NIA should continue to address the research goals set forth in the National Plan to Address Alzheimer's disease, as well as the recommendations from recent research summits on Alzheimer's disease and related dementias and care and services for individuals living with these conditions. The Committee commends NIA for its leadership in supporting longitudinal, population-based cohort studies into the causes of dementia. Because rural, poor, and minority populations may be at enhanced risk for dementia, the value and application of these studies is enhanced when they include individuals from various geographic, ethnic, socio-economic and generational backgrounds. The Committee directs NIA to support diversity in its cohort studies, with the specific goal of better understanding disease burden and biomarkers by race and geographic region. The Committee believes this could be accomplished through enhanced partnerships between existing NIA-funded Alzheimer's Disease Research Centers (ADRC) and non-ADRC dementia centers in high-risk geographic regions or through the creation of new long-term cohorts in under-represented groups/regions. The Committee also recognizes that as participants in these studies have aged, much has been learned about cognitive decline and the role of mid-life risk factors, but key challenges remain, particularly in the identification of biomarkers and in understanding the role of environmental versus genetic factors. The Committee encourages NIA to support a pilot program to test community-based clinical trials for the prevention of cognitive decline. Such a longitudinal study should include an ethnically representative sample, incorporate genomic and environmental Alzheimer's disease risk factors, and monitor cognitive and motor function, disability, and morbidity over time.

#### **Action taken or to be taken:**

We have now passed the halfway point between the establishment of the National Plan to Address Alzheimer's Disease and the target date of effectively preventing and treating Alzheimer's disease and related dementias (AD/ADRD) by 2025. Although we have not yet achieved this ambitious goal, we have made significant progress. Notably, additional appropriations over the past few years have enabled NIH to address many of the research goals and milestones in the Plan in advance of their scheduled implementation. For example, the additional \$414 million received in FY 2018 helped to accelerate implementation of many FY 2019 AD/ADRD research milestones, and the additional \$425 million received in FY 2019 may enable the acceleration of many FY 2020 milestones.

Consistent with recommendations from the triennial AD Research Summits, a major focus at the National Institute on Aging (NIA) since the substantial funding increases began has been building a solid yet flexible infrastructure upon which the Institute can continue to maintain its research footprint. Ongoing initiatives include:

- Alzheimer’s Clinical Trial Consortium (ACTC), to accelerate and expand trials of AD/ADRD therapies;
- Resilience-AD, a new program bringing together experts from multiple disciplines to understand why some high-risk individuals remain dementia-free;
- Molecular Mechanisms of the Vascular Etiology of Alzheimer’s Disease (M<sup>2</sup>OVE-AD) Initiative, exploring how metabolic and vascular risk factors influence brain aging and AD pathology and identifying blood-based markers of the disease;
- Alzheimer’s Biomarker Consortium – Down Syndrome (ABC-DS), in which researchers use biomarkers to track disease progression in people with DS, a uniquely vulnerable population at high risk for developing AD;
- The Model Organism Development and Evaluation for Late-onset AD (MODEL-AD) project to develop better animal models of late-onset AD;
- The Alzheimer’s Disease Centers, which translate research advances into improved prevention, diagnosis, treatment, and care for people with AD/ADRD.

Research on care and services for people with dementia and their caregivers remains an important focus of the NIH AD/ADRD research portfolio. As such, NIA acknowledges the guidance and insights provided by the participants in the October 2017 National Research Summit on Care, Services, and Supports for Persons with Dementia and Their Caregivers. One outcome of this Summit has been the establishment in October 2019 of the NIA Imbedded Pragmatic AD/ADRD Clinical Trials (IMPACT) Collaboratory, which will build the nation’s capacity to conduct pragmatic clinical trials of interventions embedded within health care systems for people living with dementia and their caregivers. The Collaboratory brings together a multidisciplinary group of over 60 investigators representing over 30 academic institutions. NIA anticipates that as many as 40 pilot clinical trials testing non-drug, care-based interventions for people living with dementia will be established through the IMPACT Collaboratory within the next five years. The next AD/ADRD Care and Services Summit will take place in March 2020.

Complementing the NIA-led AD Research Summits, the National Institute of Neurological Disorders and Stroke (NINDS) hosted the third triennial Alzheimer’s Disease and Related Dementias (ADRD) Summit in March 2019 to identify research priorities in ADRDs, such as Lewy body, frontotemporal, vascular, and mixed dementias. In addition, several NIH institutes are addressing vascular contributions to cognitive impairment and dementia (VCID). The National Heart, Lung, and Blood Institute (NHLBI), NINDS, and NIA co-hosted a workshop in November 2019 to strategize on future VCID clinical trials, with a focus on primary and secondary prevention trials to reduce vascular risk. NINDS also recently funded the DISCOVERY project, a new 6-year prospective clinical research study, which includes a strong focus on diverse populations, to determine the specific subsets of stroke events that cause (or do not cause) cognitive impairment and dementia in post-stroke populations in the US.

*The Committee commends NIA for its leadership in supporting longitudinal, population-based cohort studies into the causes of dementia.*

NIA-supported demographic, epidemiologic, and longitudinal studies provide the critical data necessary to understand trends, track incidence and prevalence of disease, and identify potential risk and protective factors for Alzheimer's and related dementias. For example, the Health and Retirement Study (HRS), the ground-breaking population-based study that follows over 20,000 Americans from age 50 until death, was renewed in FY 2019. As part of this renewal, NIA-supported investigators are conducting follow-up dementia assessments using the innovative Harmonized Cognitive Assessment Protocol to update data on the national prevalence of Alzheimer's disease and related forms of dementia. In 2017, NIA issued a solicitation for research proposals to leverage existing cohort studies to clarify risk and protective factors into AD/ADRD. Eighteen studies have been funded under this solicitation to date, with others currently undergoing expert review.

*Because rural, poor, and minority populations may be at enhanced risk for dementia, the value and application of these studies are enhanced when they include diversity across geographic, ethnic, socio-economic, and generational parameters. The Committee directs NIA to support diversity in its cohort studies, with the specific goal of better understanding disease burden and biomarkers by race and geographic region. The Committee believes this could be accomplished through enhanced partnerships between existing NIA-funded Alzheimer's Disease Research Centers (ADRC) and non-ADRC dementia centers in high-risk geographic regions or through the creation of new long-term cohorts in under-represented groups/regions.*

NIH is committed to ensuring that Americans from every segment of the population have access to the benefits of participation in clinical research. A number of the Institute's ongoing studies are highly diverse by design. For example, investigators with the NIA-supported, ethnically diverse Washington Heights-Inwood Columbia Aging Project (WHICAP) are searching for potential mediators and modifiers of dementia risk among adult children of WHICAP participants. The degree to which markers of AD pathology are associated with cognition in midlife, as well as the role of cerebrovascular disease in promoting AD pathology, are also being determined in this group. NIA is also funding the addition of cognitive testing to NHLBI's Coronary Artery Risk Development in Young Adults (CARDIA) study, which has been following a diverse cohort of young Americans (mean age 24 at baseline) for over 30 years. As the participants reach midlife, the investigators can now assess how cardiovascular disease risk and preclinical markers beginning in early adulthood (20s and 30s) may affect midlife cognitive functioning and brain aging. Elsewhere, NIA-supported investigators are working with the Bogalusa Heart Study, which follows a biracial, semi-rural population in the South, to determine whether blood sugar levels in childhood and adolescence are an important trigger of cognitive changes decades later.

One of the priorities discussed at the Alzheimer's Disease and Related Dementias (ADRD) Summit in March 2019 was closing the gap on health disparities in AD/ADRD, which is the goal of several current and planned NINDS initiatives. For example, NINDS supports several long-running epidemiological studies of disparities in neurological health outcomes, including the

Reasons for Geographic and Racial Differences in Stroke (REGARDS) study and the Northern Manhattan Study (NOMAS). Looking forward, NINDS has recruited a new program director to coordinate and develop targeted initiatives in global health and health disparities research.

NINDS is also diversifying existing cohorts within the Biomarkers for the Lewy Body Dementias projects, which are expanding the collection of clinical data and biospecimens in the Parkinson's Disease Biomarkers Program to include data from individuals with Lewy body dementias, including Hispanic populations in the U.S. Due to the growing appreciation that the biological and behavioral changes underlying dementia can vary substantially from person to person, it is critical to develop sensitive, culturally-tailored screening and diagnostic tests to detect early signs of cognitive decline irrespective of dementia sub-type, which is the goal of the recently launched DetectCID initiative.

Finally, ensuring diversity of study participants in our AD/ADRD studies is one of the cornerstones of the new National Strategy for Recruitment and Participation in AD/ADRD Clinical Research. The overarching goal of the National Strategy is to engage broad segments of the public in the Alzheimer's and related dementias research enterprise, with a particular focus on underrepresented communities, so that studies with an aim to better understand and eventually cure these disorders can successfully and more quickly enroll and retain participants. NIA has also developed the Alzheimer's and Dementia Outreach, Recruitment, and Engagement (ADORE) resources, a searchable online "toolbox" containing materials to support recruitment and retention into AD/ADRD research. ADORE stems from the National Strategy and contains materials developed and tested at NIA/NIH, NIA-supported Alzheimer's Disease Centers, and other organizations.

*The Committee also recognizes that as participants in these studies have aged, much has been learned about cognitive decline and the role of mid-life risk factors, but key challenges remain, particularly in the identification of biomarkers and in understanding the role of environmental versus genetic factors. The Committee encourages NIA to support a pilot program to test community-based clinical trials for the prevention of cognitive decline. Such a longitudinal study should include an ethnically representative sample, incorporate genomic and environmental Alzheimer's disease risk factors, and monitor cognitive and motor function, disability, and morbidity over time.*

In 2018, NIA issued a Funding Opportunity Announcement (FOA) inviting applications for planning awards to develop and finalize protocols for well-powered cognitive training intervention trials to remediate or prevent age-related cognitive decline as well as possibly prevent or delay the onset of mild cognitive impairment and dementia. One large grant was awarded, and as a crucial first step the grantee is developing a recruitment plan incorporating community engagement to enroll a sample representative of the U.S. older adult population with respect to sex, ethnicity, race, and education. Multiple cognitive training approaches will be tested, and the study will incorporate imaging and possibly blood-based biomarkers to objectively track the interventions' effectiveness.

In addition, as noted previously, NIH supports a variety of longitudinal studies that explore the role of mid-life risk factors and their potential reversibility. Cohorts from studies such as the Wisconsin Longitudinal Study, the Midlife in the U.S. Study, and the National Longitudinal Study of Adolescent to Adult Health, among others, are being followed as they move through middle age to older adulthood in order to identify both genetic and environmental risk and protective factors for age-related disease and dysfunction, including cognitive decline and dementia. Other initiatives, including the Alzheimer’s Disease Neuroimaging Initiative, the Accelerating Medicines Partnership-Alzheimer’s Disease, and the Alzheimer’s Biomarker Consortium—Down Syndrome, are identifying biomarkers for use both in diagnosing dementia and in tracking treatment response.

NIA also supports a number of trials for the prevention of cognitive decline and dementia, and many of these have a community-based focus. Currently active examples include:

- A study of Tai Ji Quan, an exercise intervention, to slow cognitive decline in community-dwelling older adults with amnesic Mild Cognitive Impairment (MCI; frequently a precursor to Alzheimer’s disease)
- A study of the effects of regular physical exercise on cognition as well as other physical parameters among older, community-dwelling African Americans
- A study to determine whether “enhanced conversational engagement” can reduce incidence of MCI among homebound elders aged 80 and older. Potential study participants will be recruited through the local Meals on Wheels apparatus.

The recently released National Strategy for Recruitment and Participation in AD/ADRD Research, discussed above, also contains a wealth of information about engaging community audiences in clinical research.

### **Alzheimer’s Disease and Vascular Dementia**

The Committee recognizes the value that well-characterized, longitudinal, population-based cohort studies provide in bringing to light more information about the risk factors related to dementia. By studying participants over time, much can be learned about cognitive decline and early biomarkers that will help us understand the role of environmental and genetic factors in disease development and progression. In time, however, mature cohorts naturally dwindle as participants pass away, requiring that the research mission be adjusted to continue to leverage the previous science and build upon it. Therefore, the Committee urges NHLBI to fund a pilot project on next generation cohorts, with the goal of determining the feasibility of recruiting descendant cohort participants to continue study into the development and progression of risk factors and to detect early signs of cognitive decline.

#### **Action taken or to be taken:**

The National Heart, Lung and Blood Institute (NHLBI) is committed to understanding the cardiovascular risk factors that contribute to cognitive decline and vascular dementia, as well as finding ways to mitigate such risks. For example, the Framingham Heart Study (FHS)—first established in 1948—expanded its scope in 1975 to include ongoing surveillance of cognitive impairment and dementia. The study also grew to include the descendants of the original cohort—the second generation in 1975 and third generation in 2002. Continued follow-up of these cohorts is helping investigators probe early signs and risk factors for cognitive decline. For example, a recent analysis of second-generation cohort data spanning more than 40 years found that elevated blood pressure in mid-life is associated with an increased risk of dementia later in life.<sup>1</sup>

NHLBI also supports several long-term studies of cardiovascular health that are modeled after FHS. Similar to ongoing follow-up of the FHS second- and third-generation cohorts, it is hoped that as these cohorts age, investigators will gain new insights into the potential causes of age-related cognitive decline. For example, NHLBI’s Coronary Artery Risk Development in Young Adults (CARDIA) study began in 1985 with participants aged 18-30. Now that the participants are in their early 50s and 60s, the study is well poised to analyze how cardiovascular risk factors detected in early adulthood affect the risk of cognitive decline later in life. The National Institute on Aging (NIA) funds the study’s cognitive component.

NHLBI also supports several long-term studies to better understand risk factors for cardiovascular disease and cognitive decline in diverse populations. For example, the Atherosclerosis Risk in Communities (ARIC) Study is examining cardiovascular disease in several racially diverse communities and has expanded to include the ARIC Neurocognitive Study (NCS), which is co-funded by NHLBI, NIA, the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute on Deafness and Other Communication Disorders. NHLBI’s Jackson Heart Study, the largest longitudinal study of

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<sup>1</sup> [www.ncbi.nlm.nih.gov/pubmed/291179549](http://www.ncbi.nlm.nih.gov/pubmed/291179549)

heart disease in African Americans, will begin a new clinical exam in 2020 that will include detailed assessments of cognitive function as well as brain magnetic resonance imaging (MRI).

NHLBI's Hispanic Community Health Study/Study of Latinos (HCHS/SOL) and the Multi-Ethnic Study of Atherosclerosis (MESA) have continued to examine cardiovascular risk factors in multiethnic communities. These ongoing studies have incorporated cognitive testing, brain MRI, and positron emission tomography (PET) imaging to detect the brain amyloid deposits that occur in Alzheimer's disease. Recent results suggest that abnormally low or high daily sleep may predict a risk of cognitive decline in Latinos.<sup>2</sup>

NIA supports several projects with descendent cohorts, such as the Chicago Health and Aging Project (CHAP). CHAP is examining cognitive resilience in participants as well as midlife biomarkers of brain and cardiovascular health in their adult children. In addition, NIA's Washington Heights-Inwood Columbia Aging Project is looking for potential mediators and modifiers of dementia risk among the cohort's adult children.

NINDS funds the DISCOVERY project, a new six-year study of diverse populations to determine the types of stroke that cause cognitive impairment and dementia. In addition, NINDS supports several studies of vascular risk factors in African Americans and Hispanic/Latinos, including the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, Northern Manhattan Study (NOMAS), and the Brain Attack Surveillance in Corpus Christi (BASIC) Project. In November 2019, NHLBI, NINDS and NIA will convene a workshop to strategize on future clinical trials, with a focus on preventing vascular risks.

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<sup>2</sup> [www.ncbi.nlm.nih.gov/pubmed/27450689](http://www.ncbi.nlm.nih.gov/pubmed/27450689)

## **Amyloidosis**

The Committee encourages NIH to continue its expansion of research efforts into amyloidosis, a group of rare diseases characterized by abnormally folded protein deposits in tissues. Amyloidosis is often fatal, and there is no known cure. Left untreated, there is an average survival of 15 months. Current methods of treatment are risky and unsuitable for many patients. The Committee directs NIH to inform the Committee 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 in the fiscal year 2021 Congressional Justification.

### **Action taken or to be taken:**

NIH supports research on the pathogenesis, diagnosis, and treatment of systemic amyloidosis. National Institute on Aging (NIA)-supported investigators are working to determine why and how misfolded proteins clump together to cause disease. Other NIA-supported investigators have elucidated the structures of transthyretin (TTR) and immunoglobulin light chain fibrils—proteins associated with different forms of amyloidosis—and developed compounds that cap the ends of the developing fibrils, preventing their further growth. Some of these compounds have advanced to preclinical testing in model systems. In addition, investigators are binding some of these novel capping compounds to nanoparticles that enable visualization by magnetic resonance imaging, facilitating diagnosis of these diseases. Other investigators are developing small-molecule activators of a cellular pathway involved in protein maintenance. These compounds could potentially be used to treat a range of conditions including amyloidosis, cardiovascular disease, diabetes, and Alzheimer’s disease. Finally, researchers are exploring a possible connection between TTR amyloidosis, heart failure, and lumbar spinal stenosis (LSS), the most common cause of spinal surgery in older adults. Studies have shown that in older patients with TTR amyloidosis and LSS, spinal symptoms may appear several years before damage to the heart is evident. Validation of the association between LSS and TTR amyloidosis may facilitate early diagnosis of cardiac amyloidosis in some patients undergoing spinal surgery, which could lead to earlier disease-modifying treatments for heart failure.

National Institute on Diabetes and Digestive and Kidney Diseases (NIDDK) intramural scientists are investigating how various “chaperones” (proteins that assist in the folding or unfolding of other proteins) may affect amyloid formation and/or propagation in a yeast model system, and are studying the biology of chaperones in the hope one day manipulating their activities as a potential therapeutic strategy in amyloid diseases. NIDDK-supported extramural projects seek to better understand how the process of protein aggregation leads to dysfunction and, ultimately, the death of tissue in amyloid disease. A long-term goal of this research is to develop rational therapeutics including small molecules to slow or prevent amyloid formation. In addition, a recently awarded project to a Ph.D. trainee aims to employ induced pluripotent stem cells (iPCSs) from patients with a hereditary form of transthyretin-based amyloidosis, as a robust new disease model for the development of universal gene correction strategies and novel pharmacologic approaches to treatment.

### **Aortic Aneurism and Fibrosis**

The Committee is encouraged by the focus on fibrosis research within NHLBI's strategic plan, and further supports research in fibrosis, which is a significant comorbidity with conditions that cause aortic aneurysm, like Marfan syndrome, vascular Ehlers Danlos, and Loeys-Dietz syndrome. The Committee requests updates from NHLBI on this research in the fiscal year 2021 CJ.

#### **Action taken or to be taken:**

The National Heart, Lung, and Blood Institute (NHLBI) is committed to research on disorders associated with aortic aneurysm and the role of fibrosis in these disorders. In Marfan syndrome (MFS), vascular Ehlers Danlos syndrome (vEDS), and Loeys-Dietz syndrome, weakening of the connective tissues supporting the aorta—the artery from the heart to the rest of the body—can lead to an aortic aneurysm—a balloon-like bulge prone to rupture. Fibrosis, which is the growth of scar-like connective tissue, may also contribute to poor outcomes in these disorders.

From fiscal years 2006-2016, NHLBI funded the National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) Registry. The GenTAC Registry has accumulated data and biospecimens from more than 3,700 individuals with one of 13 eligible conditions, including MFS, vEDS, Loeys-Dietz syndrome, and Turner syndrome. These data and biospecimens are available to eligible investigators through the NHLBI-funded Biologic Specimen and Data Repository Information and Coordinating Center (BioLINCC).

In FY 2016, when GenTAC funding ended, NHLBI facilitated establishment of the GenTAC Alliance—a consortium of researchers, patients, professional and patient advocacy groups, and other stakeholders. The GenTAC Alliance leverages an established research infrastructure and patient cohort, enabling several foundations and universities to establish new registries for thoracic aortic disease. It also promotes collaboration among stakeholders to achieve improved outcomes for patients with genetic aortic diseases, and is developing strategic goals to enhance research, training, and education to address genetically triggered aortic diseases. An NHLBI representative serves on the GenTAC Alliance Operations Committee.

NHLBI encourages investigators to leverage the GenTAC Registry in research to develop improved approaches for diagnosing, monitoring, and treating people who are at risk for aortic aneurysms. A current NHLBI-supported study recruited patients from the GenTAC registry to evaluate whether computed tomography (CT) scans can be used to detect and monitor fibrotic, twisted blood vessels in children and young adults at risk for aortic dissection. If successful, this approach could be used to help determine the optimal timing of aortic surgery in young patients.<sup>3</sup> Another ongoing study has recruited patients with MFS to investigate whether aortic wall

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<sup>3</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9673762](https://projectreporter.nih.gov/project_info_description.cfm?aid=9673762)

inflammation and/or stiffness—measured through hybrid positron emission tomography (PET) and magnetic resonance imaging (MRI)—can predict abnormal aortic growth.<sup>4</sup>

NHLBI also continues to support robust research into the molecular mechanisms of aortic aneurysm, which could lead to effective targets for precision medicine. For example, one study is using mouse models to examine how aortic cells sense and adapt to mechanical stress and how these responses in turn affect blood vessel integrity.<sup>5</sup> Another study in mouse models is investigating a theory that aortic aneurysm involves abnormal signaling by TGF $\beta$ —a molecule that supports tissue repair but can also contribute to fibrosis.<sup>6</sup>

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<sup>4</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9743846](https://projectreporter.nih.gov/project_info_description.cfm?aid=9743846)

<sup>5</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9658555](https://projectreporter.nih.gov/project_info_description.cfm?aid=9658555)

<sup>6</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9704039](https://projectreporter.nih.gov/project_info_description.cfm?aid=9704039)

## **Brain Cancer in Children**

The Committee recognizes that brain cancer remains the most fatal of all pediatric cancers. Despite progress in other diseases, pediatric brain cancer survival rates have not improved for decades and have lagged behind the strides made in other cancers. The majority of children who survive may experience lifelong impairments and disabilities that result from high levels of toxicity associated with treatment. The committee strongly encourages NIH to support additional research on pediatric brain cancer, including but not limited to drug delivery methods and new therapies with reduced levels of toxicity and long-term complications.

### **Action taken or to be taken:**

The National Cancer Institute (NCI) is pleased to share the news of renewal and expansion of the Pediatric Brain Tumor Consortium (PBTC).<sup>7</sup> The NCI has supported this program since 1999 and the 2019 expansion will grow the consortium from 12 institutions to 18 with St. Jude Children's Research Hospital serving as the operations, biostatistics, and data management center of the consortium. The PBTC is the primary source of NCI-sponsored clinical trials for children with relapsed or refractory brain tumors and the expansion will include increasing capacity for clinical trials. The PBTC has served a key role in evaluating agents with immunological mechanisms of action for pediatric brain tumor populations and has brought novel agents into clinical testing. Most of PBTC's work involves performing initial studies in children based on prior studies on adult tumors. The PBTC is conducting the first prospective safety and feasibility trial in children for Optune, a device currently approved for adults with high-grade glioblastoma.

Current scientific directions for the PBTC include developing novel agents based on the distinctive biology of pediatric brain tumors, local therapies, and immunotherapies. The expansion aims to enhance opportunities to evaluate novel treatment approaches based on research opportunities arising within PBTC institutions, within the Children's Oncology Group, or within biopharma companies. This includes exploring novel treatment options for brain tumors with specific genomic and epigenomic features and for children with diffuse intrinsic pontine glioma (DIPG).

One example is local administration of novel agents using convection enhanced delivery for children with DIPG. Convection-enhanced delivery involves inserting a small tube (catheter) into a tumor during a surgical procedure in an operating room and then delivering a therapeutic agent through that tube. The PBTC is currently testing convection enhanced delivery of radioactive iodine attached to a molecule called 8H9 which homes to tumor cells. Once 8H9 binds to a tumor cell, the radioactive iodine can kill the cell. The Consortium is uniquely positioned to pursue this type of drug administration and expansion will support efforts to train pediatric neurosurgeons in this technique so that the therapy can be tested more widely at multiple PBTC sites.

Recently, the PBTC worked to enable St. Jude's to serve as an Investigational New Drug sponsor for trials, which facilitates the testing of a wider range of pharmaceutical agents. Overall, the PBTC represents a distinct and critical role within the NCI portfolio for pediatric brain tumor

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<sup>7</sup> [www.pbtc.org/index.html](http://www.pbtc.org/index.html)

research for its ability to conduct timely evaluation of innovative therapeutic approaches in cooperation with other research groups. Overall, this renewal and expansion is aimed at developing a more robust pipeline of clinical trials and more expansive access to these trials for pediatric brain tumor patients.

The National Institute of Neurological Disorders and Stroke (NINDS) supports a broad array of research aimed towards defining the molecular and cellular processes underlying the growth of pediatric brain tumors. Most of these studies are focused on basic and translational research on very aggressive brain tumors, ranging from the most common, medulloblastoma, to one of the rarest, DIPG. This portfolio has grown significantly at NINDS over the past 10 years and has supported a number of promising breakthroughs. NINDS-funded investigators have discovered that neurons, as well as neuronal factors, can contribute to the growth of gliomas, uncovering a novel cohort of therapeutic targets. NINDS also funds pediatric brain tumor studies aimed at manipulating the immune system or enhancing blood-brain-barrier penetration to enable therapeutic agents into the brain.

### **Brain Research through Advancing Innovative Neurotechnologies [BRAIN] Initiative**

The Committee recommendation provides \$500,000,000 for the BRAIN initiative, an increase of \$71,000,000. In the initial BRAIN 2025 report, released in June 2014, the working committee recommended an escalating budget to reach \$500,000,000 per year by fiscal year 2019, which this bill achieves. Since the BRAIN Initiative's inception, over 550 awards have been granted to hundreds of investigators from a wide range of fields, with the aim to find more effective treatments for a wide variety of brain disorders and diseases, such as Alzheimer's disease, Parkinson's, and epilepsy. BRAIN's unique capacity to bring large, multi-disciplinary teams together, to generate and scale-up innovative technologies, and to produce large datasets that are available to scientists worldwide is revolutionizing our understanding of the human brain. The Committee has provided additional resources in fiscal year 2020 to significantly expand efforts to working with the BRAIN data, which up to this point has been a lower priority. Neuroscience and biosciences in general need additional focus on how to consolidate and deliver data to the research community in a more usable and computationally minable form. As an example, the BRAIN Initiative Cell Census Network represents a major NIH commitment to profiling the basic cellular components of the nervous system, but the bulk of funding is committed for data generation to a growing portfolio of independent laboratories, without sufficient resources for data processing, standardization, and robust analysis. The Committee expects to receive a report in the fiscal year 2021 CJ on the initiative's achievements in its first 5 years of operation and its objectives for the next 5 years, including NIH's plans to address the challenge of making large datasets usable.

#### **Action taken or to be taken:**

The Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is developing and applying tools to understand how circuits of brain cells enable us to think, feel, and act, and ultimately to restore impaired circuits that underly neurological, psychiatric, and substance use disorders. A stellar group of independent, interdisciplinary scientists, under the aegis of the NIH Advisory Committee to the Director (ACD), developed the report *BRAIN 2025: A Scientific Vision*, which provides an overarching vision, operating principles, and milestones for the Initiative. Following that report's advice to monitor progress, a new ACD external scientific working group, the BRAIN Initiative Working Group 2.0, assessed progress and reported to the ACD in June 2019 that the Initiative is advancing on all major priorities of the plan, with many milestones already accomplished, remarkable advances in some areas, and new opportunities emerging.

Progress on identifying all brain cell types, a major Initiative priority, is well ahead of what was anticipated. The BRAIN Initiative Cell Census Network is now developing a comprehensive mouse brain cell atlas and identifying cell types in human brains. Brain mapping and activity monitoring tools have dramatically improved, from advances in human brain imaging, to genetic "barcodes" for mapping connections among nerve cells and automated 3D reconstruction of "connectomes" (comprehensive maps of neural connections) from electron microscopy sections. Optical monitoring methods enable researchers to simultaneously observe the activity of

thousands of brain cells, capturing the activity of every nerve cell in simple experimental animals as they behave. Likewise, the BRAIN Initiative is enhancing methods to modulate brain circuits, using electromagnetic, ultrasound, chemical, and optical techniques.

From its inception, the BRAIN Initiative focused on the normal brain, largely in laboratory animals, with the expectation that this will, in due course, provide the tools and knowledge to combat human brain diseases. Technological advances are already opening new avenues for progress against human disease. Researchers can now determine which brain cells are affected by diseases such as Alzheimer's, autism, and Zika virus infection and why so many drugs work in mouse models of brain diseases but not in humans. New methods point the way toward delivering drugs precisely where needed in the brain. Devices such as "closed-loop" deep brain stimulation (DBS), which monitors brain activity and automatically adjusts stimulation, have shown promise for treating Parkinson's disease and other neurological and psychiatric disorders. Brain computer interfaces are also advancing, for example, decoding speech directly from brain activity and developing a feasible approach to restore lost vision.

The main recommendation of the BRAIN 2.0 group was that the Initiative stay on its productive path, continuing technology development and increasing application of new methods to understand brain circuits. As the group recommended, the Initiative is placing a high priority on ensuring that the increasingly valuable data that it generates is FAIR (Findable, Accessible, Interoperable, and Reusable). To that end, in 2019 the Initiative established a very strong data sharing policy, enabled by the authorities in the 21st Century Cures Act and substantially increased support for the development of data standards, archives, and analysis tools. The group also noted that, given the remarkable progress to date, the BRAIN Initiative could now consider investing in larger scale, transformative projects that might propel neuroscience far into the future. The BRAIN Initiative is considering the feasibility and impact of these large-scale scientific opportunities for its next five years.

## **Building and Facilities Backlog**

### Capital Facilities Asset Management Needs of the NIH Bethesda Campus

In fiscal year 2017, the Committee included a directive to NIH to enter into a contract with the National Academies of Sciences, Engineering, and Medicine (NASEM) to assess the capital needs of NIH's Bethesda Campus. NIH's Bethesda Campus houses the majority of the Intramural Research Program and comprise a multi-billion dollar public investment, including a 200-bed research hospital, numerous laboratories, outpatient clinics, administrative space, and facilities providing research support services, energy and transportation services, and other utilities. On August 26, 2019, NASEM released a report that stated there is a \$1,300,000,000 backlog that is rapidly growing. In particular, the report states that the 12,000,000 facility square feet have an average "condition index" in the poor range, and that 72 percent of facilities are more than 20 years old.

The Committee takes this issue seriously and provides an increase of \$100,000,000 in annual Buildings and Facilities (B&F) funding. Since fiscal year 2018, the Committee will have more than doubled B&F funding for NIH. Unfortunately, these increases will make only a small dent in the increasing backlog. Therefore, the Committee has included new bill language to allow the Institutes and Centers (IC) of NIH to use up to 1 percent of IC funding for facility maintenance and construction. All 27 IC Directors have agreed to this funding structure.

Finally, the Committee directs NIH to provide a report with the fiscal year 2021 CJ describing the steps it has and will take to implement the report's recommendations. The Committee is especially interested in the actions NIH is taking to apply the recommendations to update the B&F prioritization model, develop an annual budget request for Backlog of Maintenance and Repair (BMAR), and strengthen its internal governance process, including assigning and empowering a senior leader to manage capital planning. In addition, the Committee directs NIH to provide quarterly update of its B&F maintenance and construction plans, including specific milestones for advancing projects, status of the project, cost, and priority. These updates should also highlight and explain any potential cost and schedule changes affecting projects.

### **Action taken or to be taken:**

The NIH Office of Research Facilities (ORF) will lead the implementation of the NASEM committee's recommendations, which fall into the following categories: governance, prioritization, BMAR reduction, and alignment with Research goals. ORF will take steps to improve the B&F project review and prioritization model in both the short and long term. The current extensive review process for work requests includes engaging the relevant Subject Matter Experts (SMEs). The information is tracked in a database, which includes budget amounts for studies, design, and construction, as well as the timing of the intended expenditures. Projects are indexed by category and location and prioritized by urgency. Comments are added regularly based on communication with SMEs. SmithGroup, a national architecture/engineering/planning firm, has been engaged to work on the database and develop it into a five-year plan. Facility Condition Assessments of real property and site infrastructure are performed by the consulting

firm Nelson Engineering on a four-year cycle. Nelson Engineering manages a database which informs existing BMAR reports. ORF management meets regularly with the Facilities Working Group (FWG), which provides input from the perspective of the facility users.

In the short term, ORF will alter the five-year plan methodology in several ways. Individual deficiencies will be combined into larger projects and programs under single contracts. Deficiencies will be cross-referenced by building, site location, and construction trade, with the intent of streamlining the planning and execution of programs. Budgets will include reviews by category as a cost control method. NIH will continue to use BMAR reduction as a high-priority criterion in planning capital projects. Quarterly reporting will be submitted based on categories. Included in the report will be the current BMAR and the status of notable projects.

Several long-term improvements are already in the planning stages. To advance the goal of consulting other Government agencies to identify methods for improvement, NIH held joint meetings with the Environmental Protection Agency (EPA), National Aeronautics and Space Administration (NASA), National Institute of Standards and Technology (NIST) and Naval Research Lab (NRL), Centers for Disease Control and Prevention (CDC), Smithsonian Institution, United States Department of Agriculture (USDA), and Food and Drug Administration (FDA), with the main agendas to see other portfolio asset management tools including a tool SmithGroup is developing for the EPA. The tool will track the existing project information, along with customized priorities and a ranking of projects to be organized into a five-year plan. ORF is also reviewing well-established portfolio management and capital planning software, such as IBM Tririga and VFA Capital Planning.

A key approach to reduce BMAR is the consolidation of building envelope deficiencies into one contract with a phased plan. The Building Technology Studio of SmithGroup gave a presentation, also in early November, on campus envelope assessment and improvement which will inform a Request for Proposal (RFP) for the project.

ORF has formed a group consisting of representatives from 4 divisions that is tasked with addressing all 14 NASEM recommendations. The group has started meeting regularly and assigned individuals to lead efforts to address each recommendation.

NIH is still in the process of comparing the organizational structure to other government agencies; once this comparison is completed, the recommendation will be addressed.

## **Celiac Disease**

The Committee recognizes the serious issue of Celiac disease which affects more than 3,000,000 Americans, and that the number afflicted is growing. To that end, the Committee urges NIH to devote sufficient, focused research to the study of Celiac disease. Today, the only known treatment for this disease is a gluten-free diet. However, recent private sector research has revealed that such a treatment is insufficient for many who suffer from Celiac disease. Therefore, the Committee strongly encourages NIDDK to dedicate sufficient resources to better coordinate existing research and focus new research efforts toward understanding causation and ultimately, finding a cure. The Committee requests an update on these activities in the fiscal year 2021 CJ.

### **Action taken or to be taken:**

NIH supports a robust portfolio of projects that are investigating potential causes of and treatments for celiac disease. As the lead institute for celiac disease at NIH, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) engages in multiple activities to advance research to gain insight into the disease's underpinnings and to enable the development of improved diagnostics and treatments. For example, building upon groundbreaking NIDDK-supported research that implicates a common type of virus in the development of celiac disease, scientists are investigating other viruses that may similarly trigger the disease. Understanding how these infections contribute to gluten sensitivity could open doors to new treatments and preventative strategies. Other NIDDK-funded research includes investigating the role of resident gut bacteria in celiac disease; elucidating the molecular basis of celiac disease to identify new diagnostic and therapeutic targets; and developing a swallowable pill-like capsule that captures microscopic pictures of the intestine, which could offer a more accurate test for celiac disease that is faster, less expensive, and better tolerated than endoscopic biopsies.

The NIDDK also supports broad research into the biology of the gastrointestinal tract, providing insight into the causes and complications of celiac disease. For example, an NIDDK-supported program project award on gastrointestinal inflammation, which supports several collaborative laboratories, has provided insight into how chronic inflammation from celiac disease may lead to permanent changes in the gut's immune system. This suggests that new treatment strategies may be necessary for people with a long history of celiac disease. Notably, some of the knowledge gained through NIDDK-funded basic research has moved into translational, industry-funded research that aims to improve the lives of people with celiac disease. For example, NIDDK-supported research led to the development of a drug that could help people with celiac disease digest and tolerate gluten; a clinical trial in the private sector is currently examining its safety and efficacy.

The NIDDK also supports celiac disease research through The Environmental Determinants of Diabetes in the Young (TEDDY) study. TEDDY is a long-term, international study that is investigating both type 1 diabetes and celiac disease, because both are autoimmune diseases sharing some of the same genetic risk factors. The goal of TEDDY is to understand

environmental factors, such as diet and the microbiome, that could contribute to these diseases in children with high genetic risk. Bolstered by the vast amount of data being collected in this study, TEDDY researchers are investigating the causes of type 1 diabetes and celiac disease, which could pave the way to new prevention and treatment strategies.

In addition to NIDDK's efforts, the National Institute of Allergy and Infectious Diseases (NIAID), which works in close coordination with the NIDDK, supports a broad portfolio of basic, translational, and clinical research on autoimmune diseases such as celiac disease. NIAID also facilitates the identification and development of new research opportunities and potential collaborations to address autoimmune diseases through the Autoimmune Diseases Coordinating Committee (ADCC). NIAID plans to convene a meeting of the ADCC to explore additional opportunities for collaboration in the field of celiac disease research among NIH Institutes and Centers, other federal agencies, professional societies, and patient and advocacy organizations.

### **Childhood Cancer Data Initiative**

The Committee includes \$50,000,000 for the first year of the Childhood Cancer Data Initiative, as proposed in the fiscal year 2020 budget request. The development of new therapies is important to finding a cure for childhood cancers, many of which have not seen new therapies in decades.

#### **Action taken or to be taken:**

NCI understands the need for pediatric cancer data to be collected, analyzed, and shared in order to address the critical issue of the burden of cancer in children, adolescents, and young adults (AYAs). Through the newly proposed Childhood Cancer Data Initiative (CCDI), NCI will focus efforts on enhancing and integrating data collection and ensuring data accessibility for childhood cancers.<sup>8</sup> The CCDI aims to build a connected data infrastructure that would enable the sharing of childhood cancer data from various sources. By integrating different types of data from these various sources, including biospecimen repositories, clinical trials, basic research, pre-clinical models, real-world patient data, and population studies, NCI envisions researchers better understanding the etiology of childhood cancers and advancing research to develop new and better treatments.

The CCDI is complementary to other NCI initiatives working to advance the study of childhood cancer, including the efforts aligned with the implementation of the Childhood Cancer STAR Act (see STAR Act response).<sup>9</sup> In May 2019, NCI hosted the Enhancing Biobanking for Childhood Cancers meeting, which brought researchers and advocates together to discuss the challenges and opportunities in the field. Tumor tissue samples from childhood cancer patients are both limited yet incredibly valuable, making the accessibility of the sequencing data generated from these samples crucial to researchers. NCI-supported biospecimen collection and associated data would all contribute to the aggregated data resources NCI plans to develop through the CCDI.

This past July, over 250 scientific stakeholders gathered at the CCDI Symposium to discuss the current issues and opportunities in childhood cancer research that can be addressed through enhanced data collection and maximum utilization of that data.<sup>10</sup> The Symposium focused on four areas: prioritizing data needs, creating meaningful data sets for both clinical care and research progress, creating an infrastructure to connect pediatric data repositories, and the development of tools and methods to extract and utilize the data. The goal of such efforts is to make it easier to identify opportunities for the data to work better for patients, clinicians, and researchers. It is envisioned that the CCDI could integrate NCI-funded data stored in various repositories, including data from Children's Oncology Group, the Childhood Cancer Survivorship Study, Pediatric MATCH trial, TARGET trial, Gabriella Miller Kids First Research Program, and cancer registries such as the Surveillance, Epidemiology, and End Results (SEER)

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<sup>8</sup> <https://www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative>

<sup>9</sup> <https://www.congress.gov/bill/115th-congress/senate-bill/292/text?q=%7B%22search%22%3A%5B%22S292%22%5D%7D&r>

<sup>10</sup> [https://www.cancer.gov/news-events/cancer-currents-blog/2019/lowy-ccdi-symposium-childhood-cancer?cid=eb\\_govdel](https://www.cancer.gov/news-events/cancer-currents-blog/2019/lowy-ccdi-symposium-childhood-cancer?cid=eb_govdel)

Program. These integrated data could potentially be used to answer scientific questions related to the prevention and treatment of secondary cancers and long-term treatment side effects, understand the continuum of care into survivorship, discover novel therapeutic options, and generate and validate data to support pre-clinical and treatment efforts.

The CCDI initiative is a promising opportunity to enhance our ability to improve outcomes for children with cancer by optimizing data sharing and maximizing data use. In the coming year, NCI plans to publish a perspectives paper that describes the CCDI data science and data sharing approaches. A Working Group of the NCI Board of Scientific Advisors has been established and will convene to advise NCI on next steps for the CCDI. Priority activities that NCI plans to implement include determining the criteria needed for the best datasets, including existing data and potential perspective data that could be collected; creating and maintaining a resource catalog for reference to and reuse of data, biospecimens, and tools; and conducting pilot projects connecting pediatric data repositories and registries containing NCI-funded data.

### **Childhood Post-Infectious Neuroimmune Disorders**

The Committee is concerned that children, following streptococcal and other infections, are experiencing the onset of neuropsychiatric and behavioral disorders. These auto-inflammatory encephalopathic conditions, including Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) and Pediatric Acute onset Neuropsychiatric Syndrome (PANS), are often misdiagnosed. Delays in diagnosis and lack of developed avenues of treatment result in a devastating escalation of mental health symptoms and associated costs. The Committee encourages NIH to prioritize research efforts in this area and report to the Committee on the current understanding of incidence, causes, diagnostic criteria, and treatment of these conditions and to describe the status of research related to this area in the fiscal year 2021 Congressional Justification.

#### **Action taken or to be taken:**

When children show a sudden onset of obsessive-compulsive disorder (OCD) symptoms, accompanied by other behavior problems, cognitive changes, and physical symptoms, they may be classified as having Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) or its subset Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS). Health care providers examine patients for both PANS and PANDAS via clinical interview, as there is no definitive ‘test’ available. Although the disorders share certain core features, there are some key differences. The diagnostic criteria for PANS include sudden onset of OCD and/or an eating disorder and specific changes in mood, behavior, and sensory or motor function. The criteria for PANDAS include sudden onset (or worsening) of OCD and/or a tic disorder following a streptococcal (strep) infection, accompanied by changes in behavior and motor function. Although many children show symptoms of OCD and most children will have strep throat, few children will show clear symptoms of PANS or PANDAS, and the number of children impacted is difficult to determine.

Findings from National Institute of Mental Health (NIMH) intramural research and NIMH-funded studies suggest that Post Infectious Neuroimmune Disorders occur when the body mounts an immune response to fight an invading infection but gets tricked into attacking healthy cells – an autoimmune response – causing inflammation in the brain and other parts of the body. In the case of PANDAS, this autoimmune response is associated specifically with Group A streptococcal (strep) infections, such as strep throat and scarlet fever. In some cases, clinicians can treat strep-related PANDAS episodes by prescribing antibiotics to eliminate the strep infection and ameliorate symptoms. Children with PANS- or PANDAS-related OCD symptoms may also benefit from standard OCD treatment, which includes symptom-related medication and behavioral therapy.

The NIMH intramural research program has been instrumental in identifying the immune mechanisms that lead to brain dysfunction in PANS and PANDAS,<sup>11</sup> and NIMH continues to support lines of research that are exploring the biological pathways involved in the disorders. For example, in one NIMH-funded project, researchers are investigating how T-helper cells – critical

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<sup>11</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9790789&icde=46937455](https://projectreporter.nih.gov/project_info_description.cfm?aid=9790789&icde=46937455)

components of a typical immune response – contribute to brain inflammation and dysfunction following strep infection.<sup>12</sup> In other NIMH-funded research, investigators are examining whether individuals’ immune proteins to a specific type of neuron.<sup>13</sup> These lines of research aim to provide a more precise understanding of the link between autoimmune processes and PANS/PANDAS, and may identify new targets for treatment.

NIMH intramural researchers are also conducting ongoing clinical trials that include individuals diagnosed with PANS or PANDAS, with the aim of developing comprehensive clinical profiles of the disorders. These large-scale longitudinal trials are collecting data on multiple levels using a variety of measures, including: medical and psychiatric histories; measures of judgment, thinking, and behavior; imaging of brain structure and function; and assessments of physiological and biological functioning. As a primary outcome, one clinical trial aims to establish a national database and repository of biological samples for PANS.<sup>14</sup> Another clinical trial is evaluating patient characteristics that are associated with symptom profiles and responses to standard interventions.<sup>15</sup> The clinical, behavioral, and biological data collected in these clinical trials may provide an invaluable resource for future investigations into the causes, consequences, and treatment of Post Infectious Neuroimmune Disorders, including PANS and PANDAS.

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<sup>12</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9775457&icde=46891708](https://projectreporter.nih.gov/project_info_description.cfm?aid=9775457&icde=46891708)

<sup>13</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9726837&icde=46891708](https://projectreporter.nih.gov/project_info_description.cfm?aid=9726837&icde=46891708)

<sup>14</sup> <https://clinicaltrials.gov/ct2/show/NCT03507218>

<sup>15</sup> <https://clinicaltrials.gov/ct2/show/NCT01778504>

### **Chronic Conditions and Health Disparities**

Kidney disease, type 2 diabetes, and obesity are among the most common, costly, and preventable of all health conditions. As of 2012, about half of all adults had one or more chronic health conditions, with 25 percent of adults suffering with two or more chronic health problems. The Committee strongly believes that NIH needs to focus chronic disease efforts on those populations most affected, particularly vulnerable populations and underrepresented minorities. Therefore, the Committee has included sufficient funding for an initiative to address chronic diseases and health disparities in these areas. The program must focus on kidney disease, obesity, diabetes, exercise medicine, and health disparities. Programs should have a strong existing track record of NIH funding in all of these areas, such as NIH-funded Nutrition Obesity Research Center, Diabetes Research Center, Obesity Health Disparities Research Center, and O'Brien Kidney Center. Additionally, regional multi-institutional consortiums are strongly encouraged.

#### **Action taken or to be taken:**

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) continues to support research efforts on chronic health conditions that are sources of health disparities such as kidney disease, type 2 diabetes, and obesity. These conditions disproportionately affect minorities and are also overrepresented in rural areas and in the Southern United States. In 2019, as part of a trans-NIH effort to stimulate research on these and other conditions, NIH issued a new funding opportunity (FOA) to support projects with a focus on chronic diseases and the reduction of health disparities that could benefit from leveraging the existing capacity of certain NIH-supported research centers.<sup>16</sup> As a result of the announcement, NIDDK funded five applications for expanded research on chronic diseases and health disparities that were submitted by NIDDK-supported research centers. These include the NIDDK Diabetes Research Center at Vanderbilt University and four research centers at the University of Alabama at Birmingham: NIDDK Diabetes Research Center, NIDDK O'Brien Center for Acute Kidney Injury Research, NIDDK Nutrition Obesity Research Center, and NIDDK Cystic Fibrosis Research and Translation Core Center. The NIDDK Nutrition Obesity Research Center is planning to build capacity for developing personalized lifestyle interventions, evaluating their efficacy, and implementing them in clinical and community settings. The NIDDK Cystic Fibrosis Center is planning to test whether a cystic fibrosis drug could treat chronic obstructive pulmonary disease, another chronic disease associated with health disparities. In addition, other NIH Institutes funded applications from this funding opportunity that are relevant to their missions. These new awards could significantly catalyze research on some of the most costly and burdensome chronic diseases that disproportionately affect minorities and underserved communities in the United States and complement other NIH research efforts in these areas.

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<sup>16</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-070.html>

## Chronic Fatigue Syndrome

The Committee commends the NIH on its new ME/CFS efforts, including its plans for a 2019 conference on accelerating research into ME/CFS and its formation of the National Advisory Neurological Disorders and Stroke (NANDS) Council Working Group. The Committee encourages NIH to expand ME/CFS efforts such as (1) new ME/CFS disease specific funding announcements, including those with set-aside funds, to deliver needed diagnostics and treatments as quickly as possible, (2) an initiative to reach consensus on the ME/CFS case definition, and (3) mechanisms to incentivize researchers to enter the field.

### **Action taken or to be taken:**

The National Institutes of Health appreciates the need to expand and advance myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) research. The trans-NIH ME/CFS Working Group has been seeking the community's input through the National Advisory Neurological Disorders and Stroke (NANDS) Council Working Group as well as workshops to identify priorities that would help guide research directions and energize the ME/CFS field. On April 4-5, 2019, NIH held a conference, "Accelerating Research on ME/CFS," which brought together researchers, clinicians, patients, and advocates to review the current state of ME/CFS research and the latest findings, and discuss challenges or gaps that need to be addressed to move the field forward. Presentations at this conference focused on analyses of genetic, metabolic, immunological, microbiome, and brain imaging data to identify distinct patterns found in patients with ME/CFS compared to control groups with the goal of gaining new clues to disease processes or potential biomarkers. One day prior to the conference, NIH also sponsored another meeting, "Thinking the Future: A Workshop for Young/Early Career ME/CFS Investigators," the goal of which was to help improve the critical shortage of new and young investigators studying ME/CFS by encouraging trainees and early career scientists to network and present their research findings.

Recently, the NANDS Council Working Group for ME/CFS Research released a report<sup>17</sup> of the group's recommendations on how best to advance ME/CFS research. Public input gathered through a Request for Information informed these recommendations. The report was presented to the NANDS Council in September 2019, and focused on several topics, including research gaps and opportunities, potential strategies to attract and train a pipeline of new investigators, and approaches to enhance research collaboration, coordination, and communication. One of the top research priorities in the report was reaching consensus on the ME/CFS case definition to enable clearly defined eligibility criteria and/or subtyping of participants for clinical research. The Trans-NIH ME/CFS Working Group, led by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Allergy and Infectious Diseases (NIAID), is working to prioritize the recommendations outlined in this report and develop an implementation plan.

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<sup>17</sup>[https://www.ninds.nih.gov/sites/default/files/report\\_of\\_nands\\_council\\_working\\_group\\_for\\_mecfs\\_research\\_508c\\_0.pdf](https://www.ninds.nih.gov/sites/default/files/report_of_nands_council_working_group_for_mecfs_research_508c_0.pdf)

NIH continues to support investigator-initiated research to understand the pathogenesis and causes of ME/CFS, such as genetic factors, microbial infections, and immune mechanisms. For instance, NIAID is supporting studies to characterize immune cell subsets and investigate mucosal and systemic immune responses in ME/CFS. Thanks to the community outreach from ME/CFS advocacy organizations to improve recruitment and retention of participants in the NIH intramural study on ME/CFS, the NIH Clinical Center also continues to conduct research to evaluate patients with ME/CFS to learn more about the clinical and biological markers and mechanisms of the disease. In addition, NIH continues to fund three ME/CFS Collaborative Research Centers (CRCs) and an accompanying Data Management and Coordinating Center. The CRC researchers are using a wide range of tools and technologies to search for underlying causes of ME/CFS, particularly the role of genes, inflammation, and the immune system. Established in 2017, CRCs aim to develop new diagnostics, novel biomarkers, and ways to stratify patients into subgroups based on clinical presentation. In Fiscal Year 2020, NIH is releasing funding opportunities to stimulate investigator-initiated research on ME/CFS.

## **Combating Antibiotic-Resistant Bacteria/ Antimicrobial Resistance [AMR]**

### **Combating Antibiotic-Resistant Bacteria (House)**

The Committee includes sufficient funding to maintain NIAID research related to combating antibiotic-resistant bacteria at no less than the fiscal year 2019 enacted level. These funds enable NIAID to support research on antimicrobial (drug) resistance, including basic research on how microbes develop resistance, new and faster diagnostics, and clinical trials designed to find new vaccines and treatments effective against drug-resistant microbes.

### **Antimicrobial Resistance (Senate)**

The Committee recommendation includes \$600,000,000 within NIAID for research related to combating AMR, an increase of \$50,000,000. The Committee remains deeply troubled by the growing threat posed by antimicrobial resistant pathogens. In April, the United Nations issued a report that, like the 2016 review sponsored by the government of the United Kingdom and Wellcome Trust, warned that rampant overuse of antibiotics and antifungal medicines in humans, livestock, and agriculture could erase much of the improvement in public health achieved since the development of the first antimicrobials in the 1940s. The Committee recommendation includes \$1,700,000 to fund a National Academies of Sciences, Engineering, and Medicine study to examine and quantify the long-term medical and economic impacts of increasing AMR in the United States. The review should examine progress made on the U.S. National Strategy and Action Plan for Combating Antibiotic-Resistant Bacteria including domestic and international strategies employed by NIH, CDC, FDA, ASPR, USDA, and USAID. The National Academies' report should make recommendations to address any gaps in research and development of therapeutics and diagnostics; efforts to move new products to market; animal and human surveillance, prevention efforts, international coordination and collaboration; and any other recommendations the Academies finds relevant to stopping the spread of AMR. The Committee directs NIAID to report on trends in AMR-related Research Project Grants, including the success rates for such grants, and requests an update on these activities in the fiscal year 2021 CJ, including an overall assessment of the progress to date of efforts to address AMR.

### **Action taken or to be taken:**

The National Institute of Allergy and Infectious Diseases (NIAID) supports a comprehensive portfolio of basic, clinical, and translational research to enable new and improved products to prevent and treat drug-resistant infections. This work supports the U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB). There has been a 31 percent increase in the number of NIAID-funded research project grants (RPGs) focused on antimicrobial resistance (AMR) from fiscal year (FY) 2016 to 2019. Additionally, the success rate of AMR-focused RPG applications (26 percent in FY 2019) continues to exceed the overall NIAID RPG application success rate (22 percent in FY 2019). NIAID encourages additional grant applications that are focused on innovative approaches for addressing AMR. Highlights of progress to date in NIAID-supported AMR research are summarized below.

NIAID conducts and supports basic research to better understand the fundamental biology of disease-causing microbes and provide insight into the mechanisms used to evade antimicrobial drugs. Building on this knowledge, NIAID-supported researchers are exploring novel microbiome-based approaches to treat recurrent *Clostridium difficile* infections. NIAID scientists are examining the use of probiotic approaches as a simple and safe *Staphylococcus aureus* decolonization strategy, as well as an immunotherapy-based approach to prevent and treat carbapenem-resistant *Klebsiella pneumoniae*.

NIAID supports research on the development of novel diagnostic tools to distinguish between bacterial and viral infections, identify AMR pathogens, and determine optimal treatment strategies. NIAID has supported development of five diagnostic products recently cleared by the FDA, including tests for urinary tract infections, sexually transmitted infections, and pneumonia. NIH is partnering with the Biomedical Advanced Research and Development Authority (BARDA) on the AMR Diagnostic Challenge prize competition seeking innovative, rapid point-of-need diagnostic tests. In FY 2019, five finalists were selected to move on to the final phase of this competition; in FY 2020, up to three winners will be chosen to split prize funding of \$19 million.

The NIAID-supported Antibacterial Resistance Leadership Group (ARLG) is a clinical research network that conducts interventional and observational clinical studies to reduce the public health threat of AMR. The ARLG is conducting a Phase I clinical trial of a novel combination therapy for carbapenem-resistant Enterobacteriaceae. NIAID also has supported the development of zoliflodacin, a novel therapeutic for uncomplicated gonorrhea that has been awarded Fast Track status by the FDA. In addition, NIAID recently established Cooperative Research Centers focused on the development of vaccines to prevent sexually transmitted infections that can become drug-resistant, including syphilis, chlamydia, and gonorrhea. NIAID further works to increase the pipeline of antibacterial products through support for CARB-X. This public-private partnership led by BARDA aims to advance the development of antimicrobial candidates from the target identification stage through Phase I clinical trials.

NIAID will continue to advance the field of AMR research. In addition, NIAID will work with its CARB partners to address any future recommendations from the National Academies of Sciences, Engineering, and Medicine.

## **Congenital Heart Disease [CHD]**

The Committee commends NHLBI for its continued work to better understand causation, improve treatments and outcomes, and integrate registry data and research datasets to facilitate research on congenital heart disease across the lifespan. The Committee encourages NHLBI to prioritize CHD activities outlined in its strategic plan, including improving understanding of outcomes and co-morbidities, modifying treatment options across the lifespan, and accelerating discovery, analysis, and translation by leveraging CHD registries and networks. The Committee requests NHLBI include in its fiscal year 2021 CJ a report on steps being taken on these efforts.

### **Action taken or to be taken:**

Congenital heart disease (CHD) is the most common birth defect in the United States and describes a constellation of problems with the heart's structure that are present at birth. The National Heart, Lung, and Blood Institute (NHLBI) supports research focused on understanding the causes of CHD and its co-morbidities, and improving treatment outcomes as part of its efforts to meet the goals and objectives established in the NHLBI Strategic Vision.

NHLBI's Bench to Bassinet Program, which comprises the Pediatric Heart Network (PHN), the Cardiovascular Development Consortium, and the Pediatric Cardiac Genomics Consortium (PCGC), focuses on all aspects of CHD. Current research supported by the program includes investigating the genomic basis of neurodevelopmental disabilities associated with CHD,<sup>18</sup> whole-genome sequencing of hundreds of children with CHD and their parents, and a large clinical trial to evaluate a medication that may delay heart failure symptoms in adolescents with a complex heart disease.<sup>19</sup>

NHLBI also co-leads with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the trans-NIH Investigation of Co-occurring conditions across the Lifespan to Understand Down Syndrome (INCLUDE) Project,<sup>20</sup> which was established in 2018. Approximately 50 percent of all children born with Down syndrome have CHD. Through the INCLUDE Project, NHLBI is expanding the PCGC to conduct genome sequencing that will shed light on the genetic factors that contribute to CHD in people with and without Down syndrome. Although not part of INCLUDE, a recent NHLBI-funded study shows just how complex the genetics of CHD can be. The study found that in a family with early-onset heart disease, the parents each harbored distinct genetic mutations that were not impactful on their own, but combined to cause CHD in their children.<sup>21</sup> Genome sequencing through the PCGC could help unravel such complexity on a large scale.

In FY2019, NHLBI participation in the INCLUDE Project led to awards ranging from basic science to clinical trials designed to understand CHD in individuals with Down syndrome. INCLUDE Project funding also went toward establishing a new training program within the

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<sup>18</sup> [https://benchtoassinet.com/wp-content/uploads/2018/05/PCGC-CHD-Brain-and-Genes-Protocol- v4.0\\_08Mar2018\\_clean-1.pdf](https://benchtoassinet.com/wp-content/uploads/2018/05/PCGC-CHD-Brain-and-Genes-Protocol- v4.0_08Mar2018_clean-1.pdf)

<sup>19</sup> [www.ncbi.nlm.nih.gov/pubmed/29910047](http://www.ncbi.nlm.nih.gov/pubmed/29910047)

<sup>20</sup> [www.nih.gov/include-project](http://www.nih.gov/include-project)

<sup>21</sup> [www.ncbi.nlm.nih.gov/pubmed/31147515](http://www.ncbi.nlm.nih.gov/pubmed/31147515)

PHN for young investigators focused specifically on Down syndrome research and associated heart issues; a PHN study to compare neurodevelopmental and behavioral outcomes between children with Down syndrome who have had heart surgery and children with Down syndrome who do not have CHD; and using animal models to validate gene candidates that may cause heart defects in these individuals.

NHLBI-funded research is also leading to the development of improved treatment and care of children with CHD. For example, a clinical trial is currently underway to test the use of tissue-engineered vascular grafts (TEVG) to repair a specific type of CHD. The TEVG vessel is made from a child's own cells and can grow with the heart.<sup>22</sup> Another clinical study—the Pumps for Kids, Infants and Neonates (PumpKIN) trial—is currently enrolling patients to assess the feasibility of a compact artificial heart device for children who are in need of a heart transplant.<sup>23</sup> Because of advances in diagnosis and treatment across the lifespan, more children with CHD are living well into adulthood, and there are now more adults than children living with CHD. NHLBI's investments helped inform the 2018 Guidelines for Management of Adults with Congenital Heart Disease, developed by the American Heart Association and the American College of Cardiology.<sup>24</sup> The PHN is also partnering with the Alliance for Adult Research in Congenital Cardiology to launch a study of neurocognitive function and genetics in adults with congenital heart disease.

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<sup>22</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9616876](https://projectreporter.nih.gov/project_info_description.cfm?aid=9616876)

<sup>23</sup> <https://clinicaltrials.gov/ct2/show/NCT02954497>

<sup>24</sup> <https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000602>

### **Cumulative Investigator Rate**

The Committee is pleased that its sustained investments in NIH in recent years have reversed the troubling decline in grant applicant funding rates that began in 2003 as the number of applicants dramatically increased while funding remained relatively flat. Applicants' funding rates (as measured over 5-year windows) began to improve in fiscal year 2015 and reached 36 percent in fiscal year 2018 for NIH Research Project Grants and 41 percent for R01-equivalent grants. The Committee is encouraged by this trend, and directs NIH to include information on the Research Project Grant, R21, P01, and R01–Equivalent Cumulative Investigator Rate by NIH Institute/Center in its fiscal year 2021 CJ.

#### **Action taken or to be taken:**

The NIH's cumulative investigator rate is a person-based metric that looks at the likelihood that unique investigators are funded over a five-year window.<sup>25</sup> NIH calculates this rate by taking the number of unique principal investigators who were designated on a research project grant, activity or mechanism divided by the number of unique principal investigators who were designated on applications over a five-year period. This timeframe was chosen because most research grants last for more than one year and most applicants submit applications over a period of time measured in years, not just 12 months, that may overlap with their periods of funding, if they are funded. The most recent data on the NIH-wide cumulative investigator rate is available on the NIH Data Book.<sup>26</sup>

NIH appreciates the opportunity to provide Institute/Center (IC) level cumulative investigator rate information when fiscal year (FY) 2019 data are available. As the President's Budget was under development, NIH was in the process of reviewing FY 2019 grants data for accuracy. NIH anticipates providing the IC-level data to the Committee shortly after release of the Budget.

Of note, the cumulative investigator rate is an NIH-wide metric.<sup>27</sup> An investigator may be designated on separate awards from multiple ICs in a particular five-year timeframe, but will only be counted a single time across the entire period at the NIH level.

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<sup>25</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-129.html>

<sup>26</sup> <https://report.nih.gov/nihdatabook/category/22>

<sup>27</sup> <https://nexus.od.nih.gov/all/2019/04/22/how-many-researchers-revisitedthe-fy-2018-nihs-cumulative-investigator-rate/>

### **Diversity in the *All of Us* Research Program**

The Committee recognizes the importance of including populations historically underrepresented in biomedical research in the *All of Us* program. By ensuring meaningful and broad inclusion, the program ensures more equitable benefit from future medical discoveries using *All of Us* data, including those in the field of cancer research. The Committee was pleased to learn that as of May 2019, 50 percent of the more than 193,000 participants who completed the initial steps of the protocol self-identified as members of racial/ethnic minority groups. Within the amount provided to *All of Us*, the Committee directs NIH to continue its efforts to recruit and retain participants from these historically underrepresented populations so that the *All of Us* scientific resources reflect the rich diversity of our country.

### **Action taken or to be taken:**

NIH appreciates the Committee's support of the *All of Us* Research Program's efforts to recruit and retain participants who previously have been underrepresented in biomedical research. The program remains committed to engaging, enrolling, and retaining these participants. To date, the program already has created the largest, most diverse cohort in NIH history. To further these efforts, the program is developing strategies for precision engagement and retention such as focusing on participant centeredness, building a network of national community partners, creating research capacity convenient to diverse participants, and driving culturally relevant education and communications materials. For example, *All of Us* is currently funding two awards under its Engagement and Retention Innovators funding opportunity. These awards will be used to sustain a robust national network of multicultural community organizations and health care provider associations that support the *All of Us* mission by leading grassroots engagement and retention activities across the country. The funding also enables the creation of an Engagement Incubator to support the development, implementation, and evaluation of culturally sensitive experiential learning and engagement experiences designed to enhance the knowledge, interest, enrollment, and retention of diverse individuals, communities, and providers in the program. The outcomes of this work will be of significant benefit to the program and can also be utilized to inform future research efforts designed to enhance participation in research by individuals who have been historically underrepresented in biomedical research.

## Electronic Cigarettes

The Committee recognizes that the increased use of electronic cigarettes and similar devices pose possible threats to public health, particularly for teenagers and young adults. While these devices are often promoted as safe alternatives to tobacco, studies suggest they may still contain chemicals that pose health risks to the user. The Committee urges NIH to expand research on the oral health consequences of e-cigarettes, and to consider interdisciplinary collaboration between schools of dentistry and traditional cancer researchers.

### **Action taken or to be taken:**

Electronic cigarettes (e-cigs) are often thought of as a safer alternative to conventional cigarettes. This unsupported view has contributed to increasing popularity amongst high schoolers, including never smokers, and has become a public health crisis. The National Institute of Dental and Craniofacial Research (NIDCR) was an early leader in supporting e-cig research, and in 2016 launched an initiative to understand the biological and physiological effects of e-cigs on cells, tissues and organs of the oral cavity.<sup>28</sup> Due in part to this early research, evidence of the harmful effect of e-cigs is quickly accumulating.

NIDCR-supported researchers uncovered molecular clues demonstrating chronic e-cig use likely contributes to oral cancer. By comparing oral cells from the mouths of e-cig users and non-users they found that over 60 percent of the abnormally expressed genes from e-cig users' oral cells were associated with cancer.<sup>29</sup> Another group of scientists tested the effects of aerosolized e-cig liquids in the craniofacial frog model *Xenopus laevis*. They found that e-cig exposure during embryonic development induces a variety of craniofacial defects.<sup>30</sup> Future research on this topic will address whether e-cig use by pregnant women increases the risk of having a child with craniofacial defects. Several other NIDCR-supported researchers are focused on the effects of e-cig use on the oral microbiome – the collection of bacteria, fungi, and viruses in the mouth crucial to oral health and disease. One group is investigating specific microbial and oral host defense changes, like salivary gland and immune cell function caused by e-cigs, in young adults,<sup>31</sup> another is working to identify biological markers of e-cig exposure,<sup>32</sup> and a third is focused on the link between e-cigs and oral cancer.<sup>33</sup>

NIDCR continues to support research and foster interdisciplinary collaborations to understand how e-cigarettes contribute to oral diseases and to develop novel strategies to reduce their use, especially among young adults and pregnant women. This includes the Institute's commitment to supporting dentist researchers and promoting interdisciplinary collaborations between dental researchers and other scientists and clinicians. For example, NIDCR supports collaborative supplements to bring together ideas, theories, methods, and approaches from different scientific

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<sup>28</sup> [www.grants.nih.gov/grants/guide/rfa-files/RFA-DE-16-005.html](http://www.grants.nih.gov/grants/guide/rfa-files/RFA-DE-16-005.html); [www.grants.nih.gov/grants/guide/rfa-files/RFA-DE-16-004.html](http://www.grants.nih.gov/grants/guide/rfa-files/RFA-DE-16-004.html)

<sup>29</sup> [www.ncbi.nlm.nih.gov/pubmed/30744164](http://www.ncbi.nlm.nih.gov/pubmed/30744164)

<sup>30</sup> [www.ncbi.nlm.nih.gov/pubmed/28957438](http://www.ncbi.nlm.nih.gov/pubmed/28957438)

<sup>31</sup> [www.projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9665257&icde=46827893](http://www.projectreporter.nih.gov/project_info_description.cfm?aid=9665257&icde=46827893)

<sup>32</sup> [www.projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9833771&icde=46827800](http://www.projectreporter.nih.gov/project_info_description.cfm?aid=9833771&icde=46827800)

<sup>33</sup> [www.projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9665258&icde=46827837](http://www.projectreporter.nih.gov/project_info_description.cfm?aid=9665258&icde=46827837)

and clinical disciplines to advance oral health research.<sup>34</sup> Further, over 70% of NIH research support to dental schools is from NIDCR,<sup>35</sup> and many of the e-cig research projects NIDCR supports are conducted at dental schools. NIDCR is currently collaborating with NCI and other ICs and Offices on Funding Opportunity Announcements to support basic research on e-cigs<sup>36</sup> and research to examine population-based prevention of disease, including potential risks, benefits, and impacts on e-cig use behavior among different populations.<sup>37</sup>

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<sup>34</sup> <https://www.nidcr.nih.gov/grants-funding/reissuance-administrative-supplement-collaborative-science-asc>

<sup>35</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28033063>

<sup>36</sup> [www.grants.nih.gov/grants/guide/pa-files/PAR-17-475.html](http://www.grants.nih.gov/grants/guide/pa-files/PAR-17-475.html); [www.grants.nih.gov/grants/guide/pa-files/PAR-17-476.html](http://www.grants.nih.gov/grants/guide/pa-files/PAR-17-476.html); [www.grants.nih.gov/grants/guide/pa-files/PAR-18-846.html](http://www.grants.nih.gov/grants/guide/pa-files/PAR-18-846.html); [www.grants.nih.gov/grants/guide/pa-files/PAR-18-845.html](http://www.grants.nih.gov/grants/guide/pa-files/PAR-18-845.html)

<sup>37</sup> [www.grants.nih.gov/grants/guide/pa-files/PAR-17-472.html](http://www.grants.nih.gov/grants/guide/pa-files/PAR-17-472.html); [www.grants.nih.gov/grants/guide/pa-files/PAR-17-473.html](http://www.grants.nih.gov/grants/guide/pa-files/PAR-17-473.html); [www.grants.nih.gov/grants/guide/pa-files/PAR-18-611.html](http://www.grants.nih.gov/grants/guide/pa-files/PAR-18-611.html); [www.grants.nih.gov/grants/guide/pa-files/PAR-18-612.html](http://www.grants.nih.gov/grants/guide/pa-files/PAR-18-612.html); [www.grants.nih.gov/grants/guide/pa-files/PAR-18-848.html](http://www.grants.nih.gov/grants/guide/pa-files/PAR-18-848.html); [www.grants.nih.gov/grants/guide/pa-files/PAR-18-847.html](http://www.grants.nih.gov/grants/guide/pa-files/PAR-18-847.html)

### **Enhanced Partnerships for Alzheimer's Studies**

The Committee commends NIA for its leadership in supporting longitudinal, population-based cohort studies into the causes of dementia. Because rural, poor, and minority populations may be at enhanced risk for dementia, the value and application of these studies is enhanced when they include individuals from various geographic, ethnic, socio-economic, and generational backgrounds. Therefore, the Committee directs NIA to diversify its cohort studies, with the specific goal of better understanding disease burden and biomarkers by race and geographic region. The Committee believes this could be accomplished through enhanced partnerships between existing NIA-funded Alzheimer's Disease Research Centers [ADRC] and non-ADRC dementia centers in high-risk geographic regions or through the creation of new long-term cohorts in under-represented groups/regions.

#### **Action taken or to be taken:**

Demographic, epidemiologic, and longitudinal studies supported by the National Institute on Aging (NIA) provide the critical data we need to understand trends, track incidence and prevalence of disease, and identify potential risk and protective factors for Alzheimer's and related dementias (AD/ADRD). For example, the Health and Retirement Study (HRS), the ground-breaking population-based study that follows over 20,000 Americans from age 50 until death, was renewed in FY 2019. As part of this renewal, NIA-supported investigators are conducting follow-up dementia assessments using the innovative Harmonized Cognitive Assessment Protocol to update data on the national prevalence of Alzheimer's disease and related forms of dementia. In addition, 18 studies have been funded under a 2017 solicitation for research proposals to leverage existing cohort studies to clarify risk and protective factors into AD/ADRD, and others are currently undergoing expert review.

NIH is committed to ensuring that Americans from every segment of the population have access to the benefits of participation in clinical research. A number of our ongoing studies are highly diverse by design. For example, investigators with the NIA-supported, ethnically diverse Washington Heights-Inwood Columbia Aging Project (WHICAP) are searching for potential mediators and modifiers of dementia risk among adult children of WHICAP participants. The degree to which markers of AD pathology are associated with cognition in midlife, as well as the role of cerebrovascular disease in promoting AD pathology, are also being determined in this group. NIA is also funding the addition of cognitive testing to NHLBI's Coronary Artery Risk Development in Young Adults (CARDIA) study, which has been following a diverse cohort of young Americans (mean age 24 at baseline) for over 30 years. As the participants reach midlife, the investigators can now assess how cardiovascular disease risk and preclinical markers beginning in early adulthood (20s and 30s) may affect midlife cognitive functioning and brain aging. Elsewhere, NIA-supported investigators are working with the Bogalusa Heart Study, which follows a biracial, semi-rural population in the South, to determine whether blood sugar levels in childhood and adolescence are an important trigger for later cognitive changes.

One of the priorities discussed at the Alzheimer's Disease and Related Dementias (ADRD) Summit in March 2019 was closing the gap in health disparities in AD/ADRD, which is the goal

of several current and planned National Institute of Neurological Disorders and Stroke (NINDS) initiatives. For example, NINDS supports several long-running epidemiological studies of disparities in neurological health outcomes, including the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study and the Northern Manhattan Study (NOMAS). Looking forward, NINDS has recruited a new program director to coordinate and develop targeted initiatives in global health and health disparities research.

NINDS is also diversifying existing cohorts within the Biomarkers for the Lewy Body Dementias projects, which are expanding the collection of clinical data and biospecimens in the Parkinson's Disease Biomarkers Program to include data from individuals with Lewy body dementias, including Hispanic populations in the U.S. Due to the growing appreciation that the biological and behavioral changes underlying dementia can vary substantially from person to person, it is critical to develop sensitive, culturally-tailored screening and diagnostic tests to detect early signs of cognitive decline irrespective of dementia subtype, which is the goal of the recently launched DetectCID initiative.

Finally, ensuring diversity of study participants in NIA's AD/ADRD studies is one of the cornerstones of the new National Strategy for Recruitment and Participation in AD/ADRD Clinical Research. The overarching goal of the National Strategy is to engage broad segments of the public in the Alzheimer's and related dementias research enterprise, with a particular focus on underrepresented communities, so that studies to better understand and eventually cure these disorders can successfully and more quickly enroll and retain participants. NIA has also developed the Alzheimer's and Dementia Outreach, Recruitment, and Engagement (ADORE) resources, a searchable online "toolbox" containing materials to support recruitment and retention into AD/ADRD research. ADORE stems from the National Strategy and contains materials developed and tested at NIA/NIH, NIA-supported Alzheimer's Disease Centers, and other organizations.

### **Fertility Issues for Rare Disease Patients**

Patients with rare diseases like thalassemia face a number of issues related to reproductive health due to complications both from their conditions and from their treatments. Because of medical advances, many rare disease patients are now living long enough to contemplate fertility, when it may previously not have been feasible. The Committee requests that NICHD provide an report on current research and future initiatives to address these issues in the fiscal year 2021 Congressional Justification and continue to provide updates to the Committee on advances being made.

#### **Action Taken or to be Taken:**

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) recognizes that, thanks to the advent of new screening protocols and treatment options, children born with severe, debilitating rare diseases, such as thalassemia, cystic fibrosis, and sickle cell disease are now routinely surviving into adulthood. They are healthy enough to consider starting a family. However, by that time, their underlying condition and the consequences of its treatment have often severely compromised their fertility, which can be a devastating loss. As more patients born with these diseases survive to reproductive age and beyond, there will be an increasing demand for the same potential for robust reproductive health and the same options to build a family as enjoyed by their healthy peers. Apart from fertility, good reproductive health is a component of favorable quality of life for all adults, and its provision should be an important consideration for patients with rare diseases as well.

Because this is a relatively new issue, reproductive health, fertility preservation, and fertility treatment options for patients born with chronic diseases that previously precluded reproduction have been understudied. However, scientific advances made through NICHD and the National Institutes of Health (NIH) Roadmap funding include fertility preservation for cancer survivors. Technical advances in gamete cryopreservation/vitrification and *in vitro* maturation of gametes, among other techniques, can now be applied or adapted as needed to serve this new population of patients. Research at multiple institutes at NIH, including the NICHD-supported development of EVATAR, a functional, human-tissue-based model of the full female reproductive system, also can be leveraged for future research.

The state of the science varies by disease. For some of these rare diseases, clear epidemiological evidence for infertility is lacking; even when infertility has been documented, the proximate cause may not be known. Initial fertility preservation options for different conditions currently are modeled around treatments for cancer patients, but more work needs to be done to determine their efficacy. In partnership with NIH's Office of Rare Diseases, the NICHD is meeting with constituency organizations to discuss the best ways to approach and address research gaps related to particular conditions. In addition, two NICHD-supported consortia within the Rare Diseases Clinical Research Network (urea cycle disorders and brittle bone diseases) are

collecting information about pregnancy outcomes in their patients, which will provide evidence on the scope of the challenges faced by these patients.

NICHD is expanding its efforts to foster research in reproductive health and fertility options for patients with rare diseases. For example, a funding opportunity announcement<sup>38</sup> was published in the fall of 2019. The purpose of the announcement is to encourage studies on reproductive health, fertility and fertility preservation, or fertility treatment options in patients born with a serious chronic condition who are healthy enough to consider their reproductive health and fertility options. The Funding Opportunity Announcement encourages teams of scientists with expertise in their respective fields to work together to understand the effects of the diseases and/or their treatments on parameters of reproductive health, and to identify ways to preserve, protect, or treat reproductive deficits in these patients. Specific areas of research could include development of new animal models for these conditions and pilot clinical trials for development or optimization of protocols for fertility protection or preservation. Awards are expected to be made in FY2020.

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<sup>38</sup> <https://grants.nih.gov/grants/guide/rfa-files/RFA-HD-20-021.html>

## Fibrotic Diseases

The Committee also encourages NIH to enhance its patient-centered clinical research into pulmonary fibrosis to include traditional observational and interventional studies looking at reducing healthcare utilization such as hospitalizations, improving symptoms such as cough, and prolonging life, and directs NIH to include an update in its fiscal year 2021 CJ on its work relating to idiopathic pulmonary fibrosis following the November 2012 NHLBI workshop: “Strategic Planning for Idiopathic Pulmonary Fibrosis.” The Committee also commends CDC on its recent work identifying and studying clusters of pulmonary fibrosis in workers, including dentists and miners, and encourages NIH and CDC to collaborate on such findings to include further research efforts and data sharing that could lead to better understanding of this disease and life-saving treatments. The Committee also encourages NIH to create a funding mechanism to fund fibrosis research across all organs, building on the progress and leveraging data that has and may result from NHLBI funded projects.

### **Action taken or to be taken:**

The National Heart, Lung, and Blood Institute (NHLBI) remains committed to supporting patient-centered observational and interventional clinical research projects focused on pulmonary fibrosis. In FY 2019, NHLBI began supporting PRECISIONS, which will recruit patients with idiopathic pulmonary fibrosis (IPF) and use genetic testing to identify those most likely to respond to an experimental treatment, the antioxidant N-acetylcysteine (NAC). The trial builds on an earlier retrospective analysis suggesting that a gene called TOLLIP influences patients’ responses to NAC, and will enroll only those patients who carry a certain TOLLIP gene variation, in order to increase the likelihood of detecting a benefit.<sup>39</sup> This first-of-its-kind precision medicine study in IPF will also include molecular analyses on biospecimens obtained from the Pulmonary Fibrosis Foundation Patient Registry. These analyses are intended to uncover novel genetic risk factors that will improve IPF diagnosis, prediction of its course, and understanding of its underlying mechanisms. In FY 2019, NHLBI also funded a new trial that includes a dose-response safety study of the antioxidant, epigallocatechin-3-gallate (EGCG), in healthy volunteers and a subsequent open-label pilot mechanistic trial of EGCG in patients with lung fibrosis.<sup>40</sup>

Based on findings that IPF may involve autoimmunity (the immune system attacking the patient’s own body), NHLBI also continues to support two multi-site clinical trials, STRIVE-IPF<sup>41</sup> and ART-IPF,<sup>42</sup> which are examining whether treatments to target and reduce autoantibodies can improve survival and lung function in IPF. In addition, through its Pulmonary Trials Cooperative, NHLBI continues to fund the CleanUP-IPF trial evaluating the

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<sup>39</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9822535](https://projectreporter.nih.gov/project_info_description.cfm?aid=9822535);  
[https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9822307](https://projectreporter.nih.gov/project_info_description.cfm?aid=9822307)

<sup>40</sup> <https://clinicaltrials.gov/ct2/show/NCT03928847>

<sup>41</sup> <https://clinicaltrials.gov/ct2/show/NCT03286556>

<sup>42</sup> <https://clinicaltrials.gov/ct2/show/NCT03286556>

use of antimicrobial therapy as an add-on medication to reduce the risk of hospitalization and death from IPF.<sup>43</sup>

Beyond clinical trials, NHLBI continues to fund observational studies with the potential to yield new insights into lung diseases, including pulmonary fibrosis. For example, the new American Lung Association Lung Health Cohort is the first national adult cohort focused on respiratory health and will follow 4,000 healthy millennials (aged 25-35) to identify early risk factors and signs of lung disease, to allow for earlier and more effective intervention.<sup>44</sup> NHLBI also recently invited researchers to propose new cohort studies of rare heart, lung, blood, and sleep disorders.<sup>45</sup>

NHLBI also collaborates with other agencies, including CDC to advance research on pulmonary fibrosis. For example, NHLBI and the National Institute for Occupational Safety and Health (NIOSH), part of the CDC, have collaborated on research related to understanding the risks for pulmonary fibrosis in first responders to the World Trade Center attacks in New York City.

The NHLBI-sponsored 2012 Strategic Planning for IPF workshop identified a critical need for better laboratory models of IPF. To address this need, in June 2019, NHLBI announced the availability of funds for up to five research projects to develop research models that effectively reproduce the pathologic features of human IPF.<sup>46</sup> These models will serve as a resource for the IPF research community and are expected to advance our understanding of IPF disease mechanisms and enable more rigorous study of potential new therapies prior to human trials.

Also, in follow-up to the 2012 workshop, the NHLBI and the National Institute of Allergy and Infectious Diseases (NIAID) launched an initiative in 2015 to support Collaborative Projects to Accelerate Research in Organ Fibrosis.<sup>47</sup> This initiative aims to characterize mechanisms of fibrosis in different organ systems, develop novel therapeutic strategies to prevent or reduce organ fibrosis, and improve technologies to study fibrosis. Six grants were awarded, including projects focused on fibrotic diseases of the lung, heart, liver, kidney, and skin. The grantees came together at a meeting of the American Thoracic Society in 2018 and presented preliminary findings, which suggest that although there may be some overlap in clinical manifestations across organ-specific fibrotic diseases, the disease pathways appear to be different in each organ. The grants remain active, and NHLBI-NIAID will continue to monitor their progress, which will inform the potential for future cross-cutting opportunities in fibrotic disease research.

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<sup>43</sup> <https://clinicaltrials.gov/ct2/show/NCT02759120>

<sup>44</sup> <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-20-007.html>

<sup>45</sup> <https://grants.nih.gov/grants/guide/rfa-files/rfa-hl-20-014.html>

<sup>46</sup> <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-20-007.html>

<sup>47</sup> <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-16-003.html>

## **Food Allergy Research/Food Allergies**

### **Food Allergy Research (House)**

The Committee recognizes the serious issue of food allergies which affect approximately eight percent of children and ten percent of adults in the U.S. The Committee commends the ongoing work of NIAID in supporting clinical sites for this critical research, including seven sites as part of the Consortium of Food Allergy Research (CoFAR). The Committee urges NIH to support robust investment to expand its clinical research network to add new centers of excellence in food allergy clinical care and to select such centers from those with a proven expertise in food allergy research.

### **Food Allergies (Senate)**

The Committee recognizes the serious issue of food allergies, which affect approximately 8 percent of children and 10 percent of adults in the United States. The Committee commends the ongoing work of NIAID in supporting approximately 17 clinical sites for this critical research, including seven sites as part of the Consortium of Food Allergy Research. The Committee urges NIH to support robust investment to expand its clinical research network to add new centers of excellence in food allergy clinical care and to select such centers from those with a proven expertise in food allergy research.

### **Action taken or to be taken:**

The National Institute of Allergy and Infectious Diseases (NIAID) supports a broad portfolio of basic, translational, and clinical research to better understand food allergy and to develop preventive and therapeutic options. In recent years, NIAID has fostered the growth of the food allergy prevention and treatment research community and is currently evaluating potential food allergy research centers and clinical sites to help expand existing clinical research capacity.

NIAID supports a cadre of clinical sites that conduct food allergy clinical research through multiple initiatives, including the Immune Tolerance Network (ITN) and the Consortium for Food Allergy Research (CoFAR). The research findings of these NIAID-supported clinical sites can have a direct impact on patient care. For example, groundbreaking research findings of the ITN informed an NIAID-convened expert panel's development of the Addendum Guidelines for the Prevention of Peanut Allergy in the United States. NIAID-supported researchers are investigating ways to enhance implementation of these guidelines, which are being used to aid healthcare providers in the early introduction of peanut-containing foods to infants to prevent the development of peanut allergy. ITN investigators are now building on earlier peanut allergy prevention research with two clinical trials to prevent food allergy in infants and one to treat peanut allergy in older children and adults. CoFAR scientists also are evaluating new approaches that may contribute to future advances in food allergy treatment, such as using oral immunotherapy (OIT) for simultaneously treating multiple food allergies and combining OIT with an anti-immunoglobulin E (IgE) monoclonal antibody.

NIAID also supports the Asthma and Allergic Diseases Cooperative Research Centers (AACRC), which promote multidisciplinary basic and clinical research on the immunological basis, pathobiology, diagnosis, treatment, and prevention of asthma and allergic diseases. The AACRCs are conducting two clinical trials to evaluate peanut allergy interventions. These trials also are utilizing state-of-the-art techniques, such as high-throughput sequencing and bioinformatic analysis, to assess the mechanisms of food allergy. In addition, NIAID is supporting studies at two clinical sites to better understand peanut, milk, shrimp, and cashew allergy through the T Cell Reagent Research for the Study of Allergic Diseases program. NIAID also supports research on eosinophilic esophagitis, a food allergy-related inflammatory condition, through the Consortium of Eosinophilic Gastrointestinal Disease Researchers.

NIAID scientists are conducting basic and clinical research on food allergy and related comorbidities such as eczema, also known as atopic dermatitis (AD). NIAID researchers have shown that the levels of specific IgE antibodies and the pattern of IgE reactivity can be used to predict food allergy status in patients with moderate to severe AD. NIAID has launched a clinical trial to establish a threshold of IgE antibody reactivity to milk and peanut that can predict an allergic response and serve as a helpful tool to guide clinical management of these AD patients.

NIAID remains committed to mentoring and training academic clinicians and scientists involved in basic, translational, and clinical food allergy research. NIAID will continue to support these efforts through multiple NIAID-funded clinical sites and explore opportunities to expand clinical research on the treatment and prevention of food allergy.

## **Foreign Threats to Research**

The Committee remains deeply concerned about foreign threats to the research infrastructure in the United States. In particular, the Chinese government has started a program to recruit NIH-funded researchers to steal intellectual property, cheat the peer-review system, establish shadow laboratories in China, and help the Chinese government obtain confidential information about NIH research grants. As the Federal Bureau of Investigation, HHS, and NIH continue to investigate the impact the Thousand Talents and other foreign government programs have had on the NIH research community, the Committee expects to be notified quarterly on the progress of the investigation, as well as institutions, scientists, and research affected. Further, the Committee directs NIH to carefully consider the NIH Advisory Committee's recommendations, including to implement a broad education campaign about the requirement to disclose foreign sources of funding and develop enhanced cybersecurity protocols. As recommended, NIH should use this campaign to help institutions develop best practices for how to handle these challenges, including training, communications materials, and how to improve vetting, education, and security. Further, NIH shall evaluate the peer-review system and their internal controls through a lens that takes into account national security threats. This includes holding those accountable who inappropriately share information from the peer-review process or illegally share intellectual property. The Committee appreciates the partnership between NIH and HHS' Office of National Security [ONS] on this issue and ONS's implementation of a formal NIH CI/Insider Threat program on NIH's behalf. The Committee believes this work should be expanded in fiscal year 2020 and directs NIH to allocate no less than \$5,000,000 for this work that ONS does on behalf of NIH.

### **Action taken or to be taken:**

NIH continues to focus its efforts on enhancing research integrity across all of its processes and systems. NIH, as requested, will notify the Committee quarterly to discuss these efforts. NIH is working closely with other Federal agencies, and with institutions, to strive to assure an environment of compliance and ethical conduct of research.

NIH will continue to actively partner with other federal departments and agencies, as recognized by the Committee, to address concerns related to undue foreign influence on the biomedical research enterprise. These federal partners include the Central Intelligence Agency, Federal Bureau of Investigation, HHS Office of Inspector General (OIG), Department of Defense, Department of State, Department of Energy, and the National Science Foundation. Moreover, NIH will continue engaging the HHS' Office of National Security and the NIH Counterintelligence and Insider Threat program to address security issues appropriately for the protection of all NIH-funded assets, including data.

**Overall Approach:** NIH's commitment to tackling these important challenges is reflected in a variety of recent actions, including the convening of an NIH Advisory Committee to the Director (ACD) Working Group for Foreign Influences on Research Integrity. Acting on ACD

recommendations, NIH is increasing awareness with institutions on their need to disclose all affiliations and other support, mitigate and prevent risks, and work with federal partners on issues of research security and integrity. Moreover, NIH is clarifying long-standing policies that require disclosure of all other support (including support from foreign entities), foreign components, and financial conflicts of interest.

NIH is employing a multi-pronged approach to minimize the likelihood of problems in the future. To date, informing the research community and the extramural staff at NIH to raise awareness, and partnering with other agencies have been effective strategies. These partnerships have led to extensive discovery about the nature of the threats, actions by the relevant institutions against certain investigators, referrals to the OIG, and institutional implementation of additional internal systems control measures.

**Extramural Institutions:** NIH continues to strongly encourage universities to look closely at their organizations to mitigate unscrupulous practices by individuals and entities that aim to capitalize on the collaborative nature of the U.S. biomedical enterprise. Regular communications to the extramural community over the last several years have focused on protecting the integrity of U.S. biomedical research and the imperative to inform NIH of any foreign support. These communications have included several notices and statements to the community (most recent notice on other support and foreign components<sup>48</sup>), including the unprecedented step of the NIH Director issuing a letter to officials at approximately 10,000 recipient institutions.<sup>49</sup> This letter informed the research community that the agency is aware that some foreign entities have mounted systematic programs to influence NIH-supported researchers and peer reviewers, as well as to take advantage of the long tradition of trust, fairness, and excellence of NIH- supported research activities.

NIH has contacted more than 70 institutions regarding specific scientists who may have failed to disclose substantial foreign research support or financial conflicts of interest or who may have engaged in substantial breaches of peer review integrity. This outreach has led to referrals to the OIG, communications with FBI, disciplinary actions by the relevant institutions (including terminations or resignations), revisions of grant terms, and new efforts on the part of institutions to enhance oversight and security of their research operations.

Furthermore, NIH regularly communicates with grantees to provide training and compliance support for issues involving financial conflict of interest requirements at NIH-led conferences such as the NIH Regional Seminars. NIH also communicates this information through professional organizations such as the Society for Research Administrators, and the National Council of University Research Administrators. There have been a number of special meetings involving these groups and others to address the recent concerns on foreign influence. In addition, NIH has recently updated an online

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<sup>48</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-114.html>

<sup>49</sup> <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/statement-protecting-integrity-us-biomedical-research>

training module<sup>50</sup> on Financial Conflict of Interest as a resource for both NIH staff and the extramural community. NIH's outreach and engagement have facilitated extensive faculty outreach at research organizations as well as led to developing and sharing best practices.

A strong indication that these communication strategies are proving to be successful is a report on *Actions Taken by Universities to Address Growing Concerns about Security Threats and Undue Foreign Influence on Campus*<sup>51</sup>, issued by the American Association of Universities and the Association of Public and Land-Grant Universities, and updated in April 2019. This report shares practices that universities are employing to “ensure the security of research, protect against intellectual property theft and academic espionage, and prevent actions or activities by foreign governments and/or other entities that seek to exert undue foreign influence or that infringe on core academic values.”

**Integrity of Peer Review:** In recent years, NIH has taken numerous steps to protect the integrity of the peer review process. All participants in the NIH peer review system are responsible for promoting integrity. Maintaining integrity in the peer review process – including keeping application data confidential and secure – is essential for ensuring robust exchange of scientific opinions and evaluations without fear of reprisal; protecting trade secrets and other proprietary, sensitive and/or confidential information; providing reliable input to NIH about which research projects it should support; and maintaining public trust in science.

In addition to issuing several Guide Notices and blogs on the confidentiality and integrity of peer review, NIH has referred several cases to the HHS OIG for consideration of debarment or suspension as well as removed the violating individuals from peer review service. Also, in 2018, reviewer conflict of interest certifications were converted to a completely electronic format, enabling a more thorough assessment of compliance across the agency and in cases of individual breaches.

The NIH Office of Extramural Research (OER) has expanded its internal training for NIH Scientific Review Officers (SROs) to raise their awareness of integrity concerns. OER held three interactive training sessions on peer review integrity in the last year, each event drawing hundreds of SROs. These events covered case studies largely based on actual events and stimulated lively discussion of the best course of action in each scenario. NIH is also working to implement recommendations from the NIH Advisory Committee to the Director on Foreign Influences on Research Integrity that focus on peer review integrity.

NIH continues to explore new technologies and ideas to protect the integrity and security of the peer review process. For example, a new electronic forensics dashboard is being developed to assist the Office of the Director in identifying data needed to investigate possible peer review integrity violations. Other electronic systems are being enhanced which investigators used to

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<sup>50</sup> <https://nexus.od.nih.gov/all/2018/12/03/new-financial-conflict-of-interest-training-module-available/>

<sup>51</sup> <https://www.aplu.org/members/councils/governmental-affairs/Effective-Sci-Sec-Practices-What-Campuses-are-Doing.pdf>

submit applications, two-factor authentication for electronic research system logins for peer reviewers to access applications for evaluation, as well as using an all-electronic conflict-of-interest certification. Finally, policies for permissions to access certain information such as the preliminary score matrix are being re-assessed, and a new application is being developed to more efficiently implement those rules. Taken together, these efforts to communicate internally and externally, as well as modernize controls, are raising the profile on peer review integrity concerns and reducing risks.

### **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 2021 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:**

In keeping with NIH's strategic objective to capitalize on cross-cutting opportunities to advance biomedical research,<sup>52</sup> NIH continues to work closely with the Department of Defense (DoD) and the Department of Veterans Affairs (VA) on research activities that support the organizations' mutual scientific and clinical missions.

In 2018, there was a focus on forging new innovative collaborations, including jointly serving on multi-organization committees and workgroups, partnering on research initiatives, and collaborating on resource development. Highlighted below are four ongoing initiatives that leverage the expertise and resources of NIH, DoD, and VA to address the needs of military personnel and veterans and to accelerate specific research areas through strategic partnerships.

NIH, DoD, and VA are working closely toward the goal of providing excellent state-of-the-science cancer care to military personnel, veterans, and civilians through the Collaborative Efforts Statement, Multi-Federal Cancer Initiative.<sup>53</sup> Renewed on December 1, 2017, the collaboration between the NIH, DoD's Walter Reed National Military Medical Center, and the Uniformed Services University of the Health Sciences was also extended to include the VA. The partnership aims to optimize resources and expertise, develop and leverage new technologies, collaborate on clinical trials, accelerate discoveries in cancer research, and increase education and training opportunities for military personnel, veterans, and other Americans.

In addition, the NIH, DoD, and VA, as part of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), are collaborating to enhance infection prevention and antibiotic stewardship in humans and animals.<sup>54</sup> In 2018, PACCARB released a report with recommendations to support best practices in research, implementation strategies, and workforce education and competencies. These recommendations are designed to ensure that the reduction and prevention of antimicrobial resistance in animals and people is conducted through well-supported federal and non-federal programs.

To promote data sharing on traumatic brain injury, NIH and DoD co-lead the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System, which partners with other federal agencies, including the VA.<sup>55</sup> Data from the Concussion Assessment Research

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<sup>52</sup> [www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf](https://www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf)

<sup>53</sup> <https://www.cancer.gov/news-events/cancer-currents-blog/2018/sharpless-va-dod-collaborations>

<sup>54</sup> <https://www.hhs.gov/sites/default/files/final-ips-report-10-03-2018.pdf>

<sup>55</sup> <https://fitbir.nih.gov/>

Education (CARE) Consortium on more than 34,000 subjects were submitted to FITBIR to enable researchers to gain new insights on traumatic brain injury and treatments for military personnel, veterans, and other Americans.

The NIH, DoD, and VA are also continuing their partnership through the National Clinical Care Commission (NCCC) to evaluate and provide recommendations on the coordination and leveraging of federal programs and activities related to complex metabolic or autoimmune diseases that result from insulin-related issues.<sup>56</sup> These diseases and their complications represent a significant burden in the United States, where more than one out of three adults have pre-diabetes and consequently elevated risk of heart attack and stroke. The NCCC will release a final report to Congress and the Secretary of HHS in October 2021 with recommendations to address gaps in federal efforts to provide integrated, high-quality care to individuals with these diseases and complications.

NIH's collaborations with DoD and VA highlight the importance of tackling complex medical challenges through strategic partnerships. By creating and fostering cross-cutting research opportunities, NIH can help accelerate the search for effective treatments for cancer, chronic pain, and other diseases and conditions that affect military personnel, veterans, and other Americans.

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<sup>56</sup> <https://health.gov/hcq/national-clinical-care-commission.asp>

## **Gynecologic Cancer Clinical Trials**

Clinical trials have significantly improved survival for women with gynecologic cancers, including ovarian, endometrial, cervical, and vulvar cancers. The Committee supports continued investment in federally-funded clinical trials for gynecologic cancers and encourages NCI to work with stakeholders to address priorities for the gynecologic oncology clinical trials scientific agenda, including consideration of the availability of trials for these patients. Given the high mortality rates for certain gynecologic cancers, the Committee requests NCI provide an update on access to gynecologic cancer clinical trials in its fiscal year 2021 CJ.

### **Action taken or to be taken:**

The National Cancer Institute (NCI) remains dedicated to improving outcomes for all women diagnosed with gynecologic cancers through basic, translational, and clinical research. NCI supports clinical trials in several ways, including through networks such as the National Clinical Trials Network (NCTN)<sup>57</sup> and the NCI Community Oncology Research Program (NCORP).<sup>58</sup>

Overall, a greater understanding of cancer at the molecular level has allowed scientists to develop a new generation of targeted and immune-based therapies, identify biomarkers that can be used to guide therapy and select patients who are most likely to respond, and develop novel strategies to detect difficult-to-treat cancers early. The practice of clinical trials is evolving to keep pace with these advances in the scientific understanding of cancer. For example, investigators are conducting fewer very large trials in which all patients, regardless of the underlying biology of their cancers, are randomly assigned to receive an experimental or control treatment. This is, in part, because these types of trials often require large numbers of participants to detect an effect due to the diversity of the broad population in these “one-size-fits-all” trials. Thus, more patients are required for an overall benefit to be detected. The move away from these types of trials is resulting in fewer overall trials with more targeted patient enrollment.

For gynecologic cancers, molecular analysis has led to the identification of many types and subtypes of ovarian, endometrial, and invasive cervical cancers. These require different clinical approaches, and more targeted (and typically smaller) clinical trials. For example, tissue-agnostic studies are becoming more common – meaning based on a biomarker found across different tumor types versus the location in the body where the tumor originated, (e.g., ovarian). NCI supports several tissue-agnostic precision medicine trials open to patients with specific molecular alterations from any advanced solid tumor cancers, including ovarian, endometrial, and cervical. Examples include the Molecular Analysis for Therapy Choice (NCI-MATCH),<sup>59</sup> that has enrolled 1,262 gynecologic cancer patients, and DART: Dual Anti-CTLA-4 and Anti-

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<sup>57</sup> <https://www.cancer.gov/research/areas/clinical-trials/nctn>

<sup>58</sup> <https://ncorp.cancer.gov/>

<sup>59</sup> <https://www.cancer.gov/news-events/press-releases/2018/nci-match-first-results>

PD-1 Blockade in Rare Tumors Trial,<sup>60</sup> that has enrolled 101 gynecologic cancer patients. Importantly, trials such as NCI-MATCH and DART are run through the NCTN and the NCORP. This infrastructure supports patient enrollment for these trials at hundreds of hospitals, cancer centers, and community clinics across the United States meaning that cancer patients have access to receive investigational drugs, through trial participation, in their local communities.

NCI's Coordinating Center for Clinical Trials (CCCT)<sup>61</sup> plays a key role in supporting NCI's clinical and translational research programs to advance science and patient care and coordinates numerous scientific steering committees tasked with evaluating and prioritizing clinical trials disease-specific areas. The NCTN Gynecologic Cancer Steering Committee (GCSC) meets monthly to evaluate and prioritize proposed phase 2 and phase 3 clinical trials that will be conducted through the NCTN.<sup>62</sup> The GCSC is composed of gynecologic oncology experts from academic medical centers across the country, NCI program leaders, and patient advocates.

In 2018, the GCSC released updated strategic priorities for NCTN clinical trials in cervical, uterine corpus, and ovarian/fallopian tube cancers.<sup>63</sup> The GCSC updates these priorities yearly and continues to work with stakeholders to assure that NCTN gynecologic cancer clinical trials align with the updated priorities. The 2018 priorities recognized the need for the development of novel trial designs to facilitate the efficient screening of novel targeted therapeutic and new therapeutic strategies within well-defined cancer populations across all gynecologic cancers.

Accordingly, since the beginning of FY 2019, the NCTN has newly activated or revised (e.g., expanded number of trial arms; added trial sites; re-opened to broader accrual) 10 clinical trials for gynecologic cancers, including ovarian, fallopian tube, peritoneal, uterine, cervical, vaginal, and endometrial cancers. Several of these are phase 3 trials, some of which aim to seek approval from the U.S. Food and Drug Administration for a new therapy or the new use of a therapy previously approved for another cancer type. These trials examine the efficacy of a variety of therapies – including immunotherapy, targeted therapies, surgery, and combination approaches – in treating these diseases. In total, these trials seek to enroll over 2,200 patients at hundreds of sites across the United States.

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<sup>60</sup> <https://clinicaltrials.gov/ct2/show/NCT02834013?term=dart&draw=4>

<sup>61</sup> <https://www.cancer.gov/about-nci/organization/ccct>

<sup>62</sup> <https://www.cancer.gov/about-nci/organization/ccct/steering-committees/nctn/gynecologic>

<sup>63</sup> <https://www.cancer.gov/about-nci/organization/ccct/steering-committees/nctn/gynecologic/nctn-gcsc-2018-strategic-priorities.pdf>

## **Harassment**

The Committee recognizes that recent events make clear that harassment occurs in all workplaces, including science and medicine, and that changing the culture that fosters sexual harassment will require sustained commitment and resources. The National Academies of Sciences, Engineering, and Medicine report released last year found that sexual harassment is rampant in the labs and institutions supported by NIH and American taxpayers. The Committee commends NIH for taking steps to remind institutions of the agency's expectation that they implement and enforce policies for reporting sexual harassment and notify NIH when key personnel named on an NIH grant award have been removed because of sexual harassment concerns. However, as the funder of the vast majority of biomedical research conducted in the U.S., the Committee believes NIH must play a more active role in changing the culture that has long perpetuated the problem. The Committee directs NIH to require institutions not just to notify the agency when key personnel named on an NIH grant award are removed cause of sexual harassment concerns, but also when they are placed on administrative leave for such concerns, and to submit to the Committee plans to implement measures that attend to harassment in extramural settings with the same level of attention and resources as those devoted to other research misconduct. The Committee also directs NIH to support research in the areas identified in the Report, including the psychology underlying harassment and the experiences and outcomes of diverse groups when subjected to harassment. Additionally, the Committee directs NIH to collaborate with the National Academies to develop best practices for developing more diverse and inclusive cultures in the grantee research environments, including training individuals in institutions that receive NIH funds to recognize and address sexual harassment, and evaluating the efficacy of various sexual harassment training programs.

### **Action taken or to be taken**

As noted in a February 2019 statement<sup>64</sup> from NIH leadership, sexual harassment is morally indefensible, is unacceptable, and presents a major obstacle that is keeping women from achieving their rightful place in science. NIH is concerned that it has been part of the problem and is determined to become part of the solution.

NIH will continue working with all its communities to stop harassment, including sexual harassment, and facilitate awareness to drive the culture that fosters a research environment that is free from harassment and conducive to high-quality research. To that end, NIH grant recipients must comply with federal laws, regulations, and policies that protect the rights and safety of individuals working on NIH-funded projects. For a complete list of NIH's anti-sexual harassment policies for NIH awardees, please visit <https://grants.nih.gov/grants/policy/harassment.htm>.

NIH requires institutions to notify the agency immediately of any changes that have a significant impact on a grant award, including removal of a principal investigator (PI), or any change that will impact his/her ability to carry out the approved research at the location of, and on behalf of,

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<sup>64</sup> <https://www.nih.gov/about-nih/who-we-are/nih-director/statements/update-nih-efforts-address-sexual-harassment-science>

the recipient institution, including administrative leave. Institutions must request prior approval from NIH for changes to the PI and/or other senior key personnel identified on the grant award. Generally, NIH views a replacement PI as the best course of action in harassment cases, when possible, to allow scientific progress of a peer-reviewed project and allow other personnel working on the grant, including in some cases the victim of harassment, to continue their research.

NIH continues to pursue actions within its existing authorities to address findings of sexual harassment in the extramural research community and aims to send a clear message to NIH-funded institutions and researchers supported by NIH grants that sexual harassment is unacceptable. Failure to comply with the terms and conditions of the award, such as those requirements that protect the rights and safety of individuals working on NIH-funded projects, may cause NIH to take one or more actions, depending on the severity and duration of noncompliance. These actions may include but are not limited to removing senior personnel, including the PI, from participating in ongoing grant awards; replacing PIs to allow research to continue; and imposing specific terms and conditions on an award. NIH also reaches out to institutional leadership when allegations of harassment are received. The agency requests the following: an exploration of the issue, a report back to the agency on the results of the institutional analysis, a description of any impact on NIH-funded research, a list of corrective actions taken, and information on grantee organization's policies and procedures to assure compliance with the terms and conditions of NIH grant awards that require a workplace conducive to the safe conduct of research.

In December 2018, NIH Director Dr. Francis Collins convened a working group of his Advisory Committee to address “Changing the Culture to End Sexual Harassment.” This Working Group presented interim recommendations to the Advisory Committee in June 2019, including an interim recommendation to treat professional misconduct, including sexual harassment, as seriously as research misconduct. Additionally, the Working Group was charged with, among other things, developing strategies for encouraging research on anti-harassment policies, procedures, and training, including measures and evaluations of their effectiveness. The Working Group presented its report<sup>65</sup> and final recommendations to the Advisory Committee in December 2019. The key themes from the report include:

1. Increase Transparency and Accountability in Reporting of Professional Misconduct, especially Sexual Harassment;
2. Establish Mechanisms for Restorative Justice;
3. Ensure Safe, Diverse, and Inclusive Research and Training Environments; and
4. Create System-wide Change to Ensure Safe, Diverse, and Inclusive Research Environments

NIH will continue working with stakeholders to develop best practices for establishing safe, diverse, and inclusive research environments. Notably, Dr. Carrie Wolinetz, Acting NIH Chief of Staff and Associate Director for Science Policy, co-chairs the Subcommittee on Safe and Inclusive Research Environments (SIRE), a subcommittee of the National Science and

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<sup>65</sup> [https://acd.od.nih.gov/documents/presentations/12122019ChangingCulture\\_Report.pdf](https://acd.od.nih.gov/documents/presentations/12122019ChangingCulture_Report.pdf)

Technology Council (NSTC) Joint Committee on Research Environments. SIRE has representation from a number of Federal departments and agencies and builds upon previous and current interagency or agency-specific efforts, and one goal of the committee is to coordinate and facilitate sharing of best practices. In addition, NIH also continues to develop best practices<sup>66</sup> with its own workforce, guided by the efforts of an internal NIH Anti-Harassment Committee.

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<sup>66</sup> <https://www.nih.gov/anti-sexual-harassment/nih-staff>

## **Headache Disorders**

The Committee recognizes that migraine is the second leading cause of global disability, and that migraine and other headache disorders are poorly responsive to opioids, but that these drugs are often inappropriately prescribed for these diseases. Under the HEAL Initiative, the NIH has recently issued Funding Opportunity Announcements for research relevant to all types of pain, including migraine and headache disorders, and a few specific announcements that focus specifically on increasing research on back pain and hemodialysis-related pain. The Committee strongly urges the Director of NIH to consider a similar focused group of HEAL Initiative Requests for Applications to fund fundamental, translational, and clinical research on headache disorders, including migraine, post-traumatic headache, the trigeminal autonomic cephalalgias, and intracranial hypo/hypertension.

### **Action taken or to be taken:**

The National Institutes of Health (NIH) recognizes the global burden of migraine and other headache disorders and the need for better therapies. The NIH Helping to End Addiction Long-term (HEAL) Initiative provides an unparalleled opportunity to revolutionize research in the US that will lead to better treatments for a multitude of pain conditions, including headache.

In 2018, NIH launched the HEAL initiative to address the opioid crisis. HEAL priorities include enhanced understanding of pain, discovery and validation of novel pain targets, testing therapies in clinical settings, and accelerating development of better therapies for patients. NIH has released many HEAL funding opportunity announcements for research from biomarker discovery to device and drug optimization, to clinical trials to compare effectiveness of interventions and to determine how best to bring effective therapies into large health care systems. Headache research is within the scope of all these solicitations, and NIH encouraged the headache research community to submit applications. HEAL has funded studies on headache and trigeminal pain that, for example, aim to discover markers that predict persistent headache after head trauma, explore how dysfunction of an ion channel called TRESK mediates headache and other trigeminal pain and predisposes women to migraines, explore the therapeutic potential of TRP channels for temporomandibular joint pain, and study a novel CGRP receptor, AMY1, that mediates migraine induced behaviors to optimize the family of CGRP- targeted therapies. Many other compounds are being developed and tested as safe analgesics for a broad spectrum of chronic pain conditions, which might be helpful in relieving headache and other trigeminal pain.

An important HEAL objective is to improve pain management to reduce our reliance on opioids. Only a few HEAL research solicitations called for research on specific pain conditions low back pain and hemodialysis pain, both of which are associated with high rates of opioid prescribing. Research in these two disorders, lack essential research resources such as accurate diagnostic tools, common data elements, and case definitions necessary to perform quality research. These research essentials are better established for headache disorders.

In addition, many NIH Institutes and Centers support initiatives whose scope includes headache research and a broad range of research, from neural mechanisms that cause headache, to development of treatments, to dissemination of effective therapies into the clinic.

Exploration by NIH investigators of potassium and transient receptor potential (TRP) channels, delta and kappa opioid receptors, all components of neural signaling, has increased our understanding of the role of trigeminal nerve circuitry in migraine and other pain disorders and provided novel targets for therapy development. The seminal NIH research on CGRP, a small molecule involved in migraine pain, led to development of CGRP antibody drugs approved recently by the Food and Drug Administration (FDA) for treatment of migraine headaches. NIH research on how the auras that many people experience before a migraine attack activate pain sensing nerves and initiate the headache has led to new avenues for therapy development. NIH investigators are testing therapies for headache that include electrical stimulation of peripheral and cranial nerves and the brain.

A pivotal NIH clinical trial in children and adolescents showed that medications frequently used to treat chronic migraine are no more effective than placebo, but behavioral therapies do reduce headache frequency. This study contributed to changes in clinical practice. The National Institute of Neurological Disease and Stroke (NINDS) recently launched the “Migraine Trainer” a mobile app to help children understand and manage their migraines.

NIH continues to solicit research on pain and pain management and has established communication channels to ensure that the headache research community is up to date on funding opportunities.

## **HEALthy Brain and Child Development Study**

### **Senate**

The Committee recognizes and supports the NIH HEALthy Brain and Child Development (HEALthy BCD) Study, which will establish a large cohort of pregnant women, including those affected by the opioid crisis, and follow them and their children for at least 10 years. This knowledge will be critical to help predict and prevent some of the known impacts of pre- and postnatal exposure to drugs or adverse environments, including risk for future substance use, mental disorders, and other behavioral and developmental problems. The Committee recognizes that the HEALthy BCD Study is supported in part by the HEAL Initiative, and encourages other NIH Institutes, such as NICHD, NIMH, NHLBI, NCI, NIAAA, NIMH, NINR, as well as the Office of the Director, to support this important study.

### **House**

The Committee recognizes and supports the HEALthy BCD Study, which will establish a large cohort of pregnant women including those affected by the opioid crisis and follow them and their children for at least 10 years. This knowledge will be critical to help predict and prevent some of the known impacts of pre- and post- natal exposure to drugs or adverse environments, including risk for future substance use, mental disorders, and other behavioral and developmental problems.

### **Action taken or to be taken:**

The first few years of life are a period of exponential brain growth and development. While some effects of early exposure to opioids and other substances on infant and child development are known, understanding the exact nature and full extent of those effects requires additional rigorous research. To address this knowledge gap, NIH is supporting research to understand typical brain development better, beginning in the prenatal period and extending through early childhood, including variability in development and how it contributes to cognitive, behavioral, social, and emotional function. Knowledge of normative brain trajectories is critical to understanding how brain development may be affected by exposure to opioids and other substances (e.g., alcohol, tobacco, cannabis), stressors, trauma, and other significant environmental influences, including those that promote resilience.

The HEALthy Brain and Child Development (HBCD) Study will establish a large cohort of pregnant women and follow them and their children for at least 10 years. Findings from this cohort will help researchers understand normative childhood brain development as well as the long-term impact of prenatal and postnatal opioid and other drug and environmental exposures. The study will collect: data on pregnancy and fetal development; infant and early childhood structural and functional brain images; measurements of body growth; medical history; family history; biospecimens; and information on social, emotional and cognitive development.

Knowledge gained from this research will be critical to help predict and prevent some of the known effects of prenatal and postnatal exposure to certain drugs or environmental exposures, including risk for future substance use, mental disorders, and other behavioral and developmental problems.

Currently, grants have been awarded for Phase I of the study, which is an 18-month planning phase during which awardees will test the experimental design and feasibility of methodological approaches. Awardees will conduct multisite pilot and feasibility studies around recruitment and retention, approaches to structure the study and its data ethically, and methodologies for brain imaging and other assessments, to provide a foundation to launch Phase II in fiscal year 2021. Phase II will incorporate lessons learned from Phase I to create a fully integrated, collaborative infrastructure to support the collection and analysis of brain development and other data in opioid-exposed and non-drug-exposed infants and children across a variety of regions and demographics. NIH looks forward to continuing to support the study and reporting its progress and results as they continue to move ahead.

### **Impact of Technology and Digital Media on Children and Teens**

The Committee recognizes that children and teens' lives increasingly involve widespread technology use and consumption of digital media. The Committee is aware of the need for robust research into how young people's use of technologies and media sources such as social media, mobile devices, and interactive video games impact development of children and adolescents. The Committee encourages NIH to prioritize research into how these types of stimuli affect young people's cognitive, physical, and socio-emotional outcomes, including attention, sleeping routines, and anxiety.

#### **Action taken or to be taken:**

In this age of increased digital media consumption, the NIH is committed to understanding the effects, both positive and negative, of increasing media exposure on the development of children. Several NIH Institutes and Centers are currently supporting research on the effects of the rapidly evolving use of media technologies by children and adolescents.

The American Academy of Pediatrics recommends that children 18 months and younger should avoid the use of screen media and that children 8-11 years of age should have less than two hours of recreational screen time per day. In 2019, the World Health Organization issued new guidelines emphasizing that screen time should be replaced with interactive non-screen-based activities. Nonetheless, as today's children enter adolescence, media exposure is increasing; 95 percent of teens have access to smartphones, and 45 percent say they are online "almost constantly." Data from the NIH-funded Adolescent Brain Cognitive Development study show that only 37 percent of children in the study consume less than the recommended two hours per day of recreational screen time. Additionally, a recent study funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) found that exposure to media violence is a strong predictor of aggression, but that parental monitoring can be a significant factor against aggressive behavior. Nonetheless, the use of digital media can have positive effects. For example, NICHD's Adolescent Trials Network is exploring the use of an interactive smartphone app as an intervention to help prevent the spread of HIV.

Recently, NICHD hosted a workshop on Media Exposure and Early Child Development, bringing together experts from several fields to review the neuroscientific perspectives on media exposure, discuss implications for learning and language development, and explore the impact of technology on the lives of young children and parent-child interactions. While identifying current knowledge gaps and promising directions for future research, ideas offered by the participants included long-term longitudinal studies of media exposures of diverse groups of children (including children with intellectual and developmental disabilities) beginning at young ages, how to use neuroimaging to examine variations in early brain development associated with electronic media exposure, and how to apply multidisciplinary approaches to these continually evolving technologies.

NICHHD also has made the effects of childhood exposures to media a major focus of its newly-released strategic plan for the next five years.<sup>67</sup> The plan specifically identifies sensitive periods during childhood, such as transitioning into early adolescence, as a focal point of research, since these periods may provide optimal windows for prevention and treatment strategies. Among NICHHD's refreshed goals are to determine how exposures to social and environmental factors, including technology and digital media use, affect neurodevelopment, neuroplasticity, and health outcomes. As a first step, NICHHD will work with the scientific community to develop and harmonize measures of technology and electronic media exposure, promoting the use of age-appropriate measures at different stages across child development (such as neuroimaging, executive function, language development) and health outcome measures (such as body mass index, physical activity, cortisol levels). Such measures will allow researchers to examine the impact of these technologies on children at different ages as well as those from different racial, ethnic, and economic backgrounds.

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<sup>67</sup> <https://www.nichd.nih.gov/about/org/strategicplan>

### **Increasing Diversity in NIH Clinical Trials**

The Committee recognizes efforts by NIH to reduce health disparities by addressing significant barriers to clinical trial participation and directs the agency to ensure eligibility criteria for clinical trials funded by NIH do not create unintentional barriers to participation for racial and ethnic minorities as well as for patients with certain healthcare conditions. Specifically, the Committee directs NIH to revise existing protocol templates and guidelines for clinical trials that receive funding by the agency to include eligibility criteria that avoids inappropriate exclusions of racial and ethnic minorities by taking steps to account for variations in health status across racial and ethnic minority groups when determining eligibility criteria as well as ensuring exclusions based on health status are scientifically justified and appropriate.

#### **Action taken or to be taken:**

NIH is committed to supporting clinical research that benefits individuals of all sexes/genders, races, ethnicities, and ages. NIH has longstanding policies to ensure the appropriate inclusion of women, minorities,<sup>68</sup> and children<sup>69</sup> in its supported clinical research studies. In December 2017, NIH announced a revision<sup>70</sup> to its existing policy to address the inclusion of research participants of all ages. Additionally, as part of implementing the 21<sup>st</sup> Century Cures Act, all NIH Institute and Center strategic plans must now account for women and minorities as well as be focused on reducing health disparities.

In January 2018, NIH introduced a new PHS Human Subjects and Clinical Trials section of the NIH application form, which consolidates human subjects, inclusion enrollment, and clinical trial-related information in one place, and expands the information required for proposed clinical research studies. The new form requires applicants to provide participant age limits and inclusion/exclusion criteria, as well as plans for the inclusion of women, minorities, and individuals across the lifespan. Applicants are instructed<sup>71</sup> to describe the planned distribution by sex/gender, race, ethnicity, and age; and to provide a scientific or ethical rationale for excluding any groups based on these characteristics. When considering the appropriate distribution of participants, NIH encourages applicants to consider not only explicit exclusions based on sex/gender, race, ethnicity, and age, but also factors such as health of the subjects and scientific issues, e.g., high prevalence of a condition, different disease characteristics, or gap(s) in knowledge in a racial or ethnic minority subpopulation. Inclusion plans are evaluated by peer reviewers, who are instructed<sup>72</sup> to consider the subject selection criteria and rationale for selection considering the population at risk for the disease/condition under study, the scientific objectives, and the proposed study design. If inclusion plans are missing or inadequate, an award

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<sup>68</sup> [https://grants.nih.gov/grants/funding/women\\_min/women\\_min.htm](https://grants.nih.gov/grants/funding/women_min/women_min.htm)

<sup>69</sup> <https://grants.nih.gov/grants/funding/lifespan/lifespan.htm>

<sup>70</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-116.html>

<sup>71</sup> <https://grants.nih.gov/grants/how-to-apply-application-guide/forms-e/general/g.500-phs-human-subjects-and-clinical-trials-information.htm#2.4>

<sup>72</sup> [https://grants.nih.gov/grants/peer/guidelines\\_general/Review\\_Human\\_Subjects\\_Inclusion.pdf](https://grants.nih.gov/grants/peer/guidelines_general/Review_Human_Subjects_Inclusion.pdf)

cannot be made until acceptable plans are submitted, and any concerns raised during peer review are resolved.

In May 2017, NIH and FDA released an optional clinical trial protocol template<sup>73</sup> with instructional and example text for NIH-funded investigators to use when writing Phase 2 and 3 Investigational New Drug (IND)/Investigational Device Exemption (IDE) clinical trials. This template was expanded to include behavioral and social science clinical trials in 2019. The templates instruct investigators to consider NIH inclusion policies when determining eligibility criteria, provide justification for any exclusions based on demographic factors, to describe strategies for recruitment and retention of historically underrepresented populations, and to provide a clear and compelling rationale and justification when inclusion is inappropriate with respect to the health of the participants or the purpose of the research. The NIH Office of Extramural Research (OER), Office of Science Policy (OSP), and National Library of Medicine (NLM) continue to collaborate to improve integration with other NIH forms and systems and to enhance the usability of the templates.

Appropriate inclusion of research participants is essential to ensuring 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. By ensuring the inclusion of individuals from the sex/gender, racial, ethnic, and age groups affected by the condition, NIH aims to ensure study results are generalizable across populations.

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<sup>73</sup> <https://osp.od.nih.gov/clinical-research/clinical-trials/>

### **Induced Pluripotent Stem Cell [iPSC]**

The Committee continues to stress iPSC technology as a critical tool in the realm of personalized medicine. The Committee notes that iPSCs are derived from adults or skin-sourced biopsies, providing increased opportunities to tailor human medicine, reduce clinical trial costs, and pre-screen for patient-specific efficacy. To date, inadequate funding is available for the translation of iPSC research into new therapeutics, diagnostics, and cures. The Committee is especially concerned that a funding gap between basic science and clinical trials may hinder the timely discovery of treatments for a wide range of diseases that currently lack clinical solutions. Accordingly, the Committee directs NIH to provide funding to support translational research, as well as promote regional, collaborative consortiums to advance scientific knowledge in the area of iPSC basic research. The Committee further instructs NIH to conduct an assessment of agency efforts to:

(1) address the existing funding gap between basic science and clinical trial research; and (2) develop a framework that provides both new and existing grantees with funded opportunities for translational research. The Committee expects this information to be included in the fiscal year 2021 CJ.

#### **Action taken or to be taken:**

NIH is providing substantial support for translational research using induced pluripotent stem cell (iPSC) technology as well as other adult stem cells. The 21st Century Cures Act authorized a total of \$30 million to be appropriated over FY 2017-2020 for regenerative medicine clinical research. As part of Cures Act implementation, NIH established the Regenerative Medicine Innovation Project (RMIP) in coordination with the Food and Drug Administration (FDA) to accelerate the field by supporting clinical research on adult stem cells, which include iPSCs.<sup>74</sup> The first RMIP awards supported testing the therapeutic potential of cells from iPSCs for treating epidermolysis bullosa (a devastating inherited blistering disorder), as well as for insulin-dependent diabetes, sickle cell disease, lung disease, anemia of chronic kidney disease, and generating platelets for blood transfusions.<sup>75</sup>

NIH is also actively supporting scientific discussions with key stakeholders in the regenerative medicine and cellular therapy fields to promote and facilitate clinical development of interventions that utilize iPSCs. NIH and FDA jointly hosted a Regenerative Medicine Innovation Workshop in December 2017 on the development of safe and effective products. The workshop informed development of the subsequent round of NIH funding opportunity announcements, which supported both late-stage investigational new drug or device applications (INDs and IDEs) enabling clinical research projects and clinical trials to advance treatments for conditions that included retinitis pigmentosa, age-related macular degeneration, and ischemic heart disease.<sup>76</sup>

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<sup>74</sup> <https://www.nih.gov/research-training/medical-research-initiatives/rmi>

<sup>75</sup> <https://www.nih.gov/rmi/fy-2017-funded-awards>

<sup>76</sup> [https://projectreporter.nih.gov/Reporter\\_Viewsh.cfm?sl=15EFCC084B8AC4D17598B8961CAA4A01A2FFCEB861BF](https://projectreporter.nih.gov/Reporter_Viewsh.cfm?sl=15EFCC084B8AC4D17598B8961CAA4A01A2FFCEB861BF)

The ultimate goal of translational research is the development of clinically useful treatments and cures. In August 2019, as part of the RMIP, NIH published an announcement to specifically fund clinical trial applications to develop safe and effective regenerative medicine interventions using adult stem cells, including iPSCs.<sup>77</sup> In addition, NIH established the Regenerative Medicine Innovation Catalyst program to provide critical clinical services to support RMIP awardees. The Catalyst program offers source and product cell characterization services, regulatory support services, and manufacturing assistance for the development of clinical-grade products.<sup>78</sup>

Overall, NIH has a large investment in all types of human iPSC research—basic, translational, and clinical projects totaling \$468 million in FY 2018.<sup>79</sup> Some outcomes of NIH-funded research with iPSCs include the development of personalized human blood-brain barrier chips to model inheritable neurological disorders and use in drug screening; human cerebral organoids with a mutation associated with schizophrenia; human gut and liver organoids to study disease and find treatments; and development of an anti-cancer immunotherapy to provide “off-the-shelf” cell therapy.

Collaborative research is of high value to NIH, and thus the agency has built multiple collaborative iPSC translational research networks. Examples include the (Re)Building a Kidney consortium, funded by the National Institute of Diabetes and Digestive and Kidney Diseases, which coordinates studies to generate or repair kidney cells, including kidney cells from iPSCs.<sup>80</sup> The National Institute of Dental and Craniofacial Research’s Dental, Oral and Craniofacial Tissue Regeneration Consortium is translating iPSC-based projects to clinical trials.<sup>81</sup> The National Heart, Lung, and Blood Institute’s Cardiovascular Cell Therapy Research Network provides infrastructure for multicenter clinical trials of stem cell-based therapies for cardiovascular disease.<sup>82</sup>

The NIH intramural program has several important activities to translate iPSC research to the clinic. An intramural researcher at the National Eye Institute has filed an IND application with FDA for an iPSC-derived cell therapy he developed for age-related macular degeneration.<sup>83</sup> The Stem Cell Translation Laboratory (SCTL) within the National Center for Advancing Translational Sciences is a state-of-the-art research facility that utilizes a collaborative team-based model - including scientists in academia, biotechnology, and industry to overcome hurdles to translating iPSCs research into treatments.<sup>84</sup> The SCTL is a participating laboratory in the NIH Helping to End Addiction Long-term (HEAL) Initiative through research collaboration

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<sup>77</sup> <https://www.nih.gov/rmi/funding-opportunities>

<sup>78</sup> <http://rmiatahub.org/>

<sup>79</sup> [https://report.nih.gov/categorical\\_spending.aspx](https://report.nih.gov/categorical_spending.aspx)

<sup>80</sup> <https://www.rebuildingakidney.org/about/>

<sup>81</sup> <https://www.nidcr.nih.gov/grants-funding/funding-priorities/dental-oral-and-craniofacial-tissue-regeneration-consortium>

<sup>82</sup> <https://sph.uth.edu/research/centers/ccct/cctm/about-us.htm>

<sup>83</sup> <https://irp.nih.gov/pi/kapil-bharti>

<sup>84</sup> <https://ncats.nih.gov/stemcell>

opportunities for Developing Drugs and Human Cell-Based Testing Platforms for Pain, Addiction and Overdose.<sup>85</sup>

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<sup>85</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-TR-19-018.html>

### **Interdisciplinary Rural African-American Aging Research**

Although racial and rural disparities in health have been well-documented, there remain major gaps in our understanding of how psycho-social stressors, particularly those salient and unique to the experiences of rural African-Americans, contribute to multi-system aging across biological systems. The committee urges NIMHD to work with extramural partners to develop the infrastructure needed for conducting interdisciplinary aging epidemiologic studies in rural contexts despite the above challenges. The committee encourages NIMHD to prioritize efforts focused on establishing partnerships with rural stakeholders and service providers; implementing a multistage probability sampling design for rural populations, and creating a sophisticated recruitment and project management and database system; and conducting research involving collection of biological and physiological aging measures, specifically in rural areas through the application of novel methods to collect biospecimens in participants' homes.

#### **Action taken or to be taken:**

Residing in certain rural areas presents several challenges including social and geographic isolation, limited access to clinicians and hospitals, fewer economic opportunities, and sometimes lower quality of life especially for older individuals. Many chronic health conditions may develop or intensify with aging including cardiovascular disease, chronic lung disease, cognitive impairment, and arthritis that limit activities of daily living irrespective of geographic location. However, management of these health conditions may be more challenging for rural residents who lack easy access to health care services and are poor. The National Institute on Minority Health and Health Disparities (NIMHD) recognizes the unique health disparities that rural communities face, and as such, rural health is an important area of research.

NIMHD conducts and supports research to improve minority health and eliminate health disparities in collaboration with multiple partners across distinct disciplines, sectors, agencies, and communities including rural areas. NIMHD supports several programs which offer investigators the flexibility to conduct research on aging among rural African Americans. The Research Centers in Minority Institutions (RCMI) Program and the Specialized Centers of Excellence (COE) Program offer unique opportunities through pilot project research grants to early-stage investigators to target important aspects of rural health. Furthermore, community engagement activities and collaborations among institutions create synergistic effects in the pursuit of improving minority health and eliminating health disparities. The RCMI institutions such as Morehouse School of Medicine, Clark Atlanta University, Howard University, Morgan State University, Tuskegee University, and North Carolina Central University have the expertise and capacity to advance the state of the science pertinent to African Americans living in rural areas. Recently, the NIMHD-supported COE at the University of Alabama-Birmingham directed its attention to chronic diseases such as obesity in African Americans living in rural Alabama.

Other examples of NIMHD-funded rural health research include a partnership with academic researchers who are investigating cardiovascular disease (CVD) prevention in a rural county. The Using Agent-based Modeling to Compare Strategies that can Reduce Rural-Urban

Disparities in Cardiovascular Disease<sup>86</sup> study will test the health impact of healthcare delivery and access using home-based telemonitoring programs focused on hypertension, obesity, and diabetes, three CVD risk factors that disproportionately affect African Americans. The researchers will also use a population-based CVD epidemiology simulation model to translate the benefits on the risk factors and lifestyles examined in the study. The results of this study will help to enhance understanding of rural-urban disparities in the incidence and mortality of CVD and direct medical costs.

Another study, Telehealth Treatments for Depression with Low-Income Homebound Seniors,<sup>87</sup> is testing the effectiveness of two telehealth models to provide depression care for homebound low-income seniors from racially diverse backgrounds to identify a sustainable approach to delivering evidence-based mental health services to older adults. A NIMHD-funded technology business has developed a multiplexed biosensor system that can quickly measure multiple urinary biomarkers of dietary intake, such as sodium-to-creatinine ratios, in a home-care setting using a mobile app. The IoT-Based Smart-Toilet and Mobile App for Passively Quantifying Objective Urinary Biomarkers of Dietary Intake and Personalizing Nutrition Guidance study<sup>88</sup> integrates the Internet of Things (IoT) system to develop an automated, passive smart-toilet design to provide personalized dietary recommendations for individuals in rural and low socioeconomic communities who often lack access to nutrition counseling. The Acute Ischemic Stroke Neuroprotection Platform to Overcome Care Disparities for Rural Populations study<sup>89</sup> is developing a novel nanoparticle-based mobile-health platform to treat individuals who have had a stroke with neuroprotective agents prior to transfer to a hospital or stroke center. In rural communities, travel to a healthcare facility can take at least two hours and consequently may contribute to the worse neurological outcomes among stroke patients from rural communities. This novel technology can potentially improve stroke outcomes among rural populations who often lack access to early thrombectomy or a procedure to remove the blood clot causing the stroke.

In addition, NIMHD is partnering with the National Heart, Lung, and Blood Institute (NHLBI) to support clinical research on HIV-related co-morbidities among older adults, through the NHLBI Multi-Center AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS) Combined Cohort Study.<sup>90</sup> Overall, the studies will offer insights into the effect of aging with HIV. The research is examining a range of HIV-related issues such as psychosocial, behavioral,

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[https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9716311&icde=46809688&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pbball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9716311&icde=46809688&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pbball=)

<sup>87</sup>

[https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9617158&icde=46809839&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pbball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9617158&icde=46809839&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pbball=)

<sup>88</sup>

[https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9780334&icde=46809932&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pbball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9780334&icde=46809932&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pbball=)

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[https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9794241&icde=46811441&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pbball=](https://projectreporter.nih.gov/project_info_description.cfm?aid=9794241&icde=46811441&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pbball=)

<sup>90</sup> <https://grants.nih.gov/grants/guide/rfa-files/RFA-HL-19-008.html>

structural and genetic determinants of HIV and co-morbidity-related outcomes, cardiovascular disease, the microbiome, and neurocognition among aging persons living with HIV.

NIMHD is committed to ensuring that there are opportunities for African Americans in rural communities to access the benefits of research as they age. In its efforts to advance the science of minority health and health disparities, NIMHD will develop and strengthen collaborations and partnerships with diverse stakeholders including those in rural communities to ensure that NIMHD is responding to the strengths, challenges, and needs of rural populations. NIMHD will continue to build on its current research portfolio to conduct and support interdisciplinary research pertaining to the health of aging African Americans living in rural communities. As NIMHD works with the other NIH Institutes and Centers to implement the next NIH Minority Health and Health Disparities Research Strategic Plan, it will seek new opportunities and partnerships to address rural health.

## Kidney Cancer

The Committee is concerned with the growing number of kidney cancer diagnoses and lack of early detection of the disease. The Committee encourages NCI to continue to prioritize meritorious research that could assist in developing diagnostic tests and early detection techniques.

### **Action taken or to be taken:**

Research to improve the early detection, diagnosis, and treatment of kidney cancer is a high priority for the National Cancer Institute (NCI). Although the age-adjusted rate of kidney cancer incidence increased annually from 1992 through 2008, this rate has plateaued over the past eight years.<sup>91</sup> This stabilization in incidence might be explained by the increased use of advanced imaging techniques, such as computed tomography (CT) scans, to evaluate abdominal symptoms and/or changes in the prevalence of kidney cancer risk factors. With regard to imaging, research has shown that the frequent use of abdominal CT scans is associated with an increased risk of undergoing a nephrectomy (removal of one or both kidneys) because current imaging methods cannot reliably distinguish between benign and malignant renal masses. Consequently, more intensive workup is performed for all solid kidney tumors, regardless of size.<sup>92</sup> Despite this leveling in kidney cancer incidence, it is estimated that more than 73,000 new cases of kidney cancer will be diagnosed in the United States in 2019 and that nearly 15,000 people will die from the disease.<sup>93</sup> These statistics indicate a clear need for sensitive and accurate methods to detect and diagnose kidney cancer early to reduce the morbidity and mortality associated with this disease.

Current research on the early detection and diagnosis of kidney cancer is focused on novel imaging approaches and the identification of blood and tissue biomarkers. One such new imaging approach, hyperpolarized <sup>13</sup>C (radioactive carbon) magnetic resonance imaging (MRI), takes advantage of differences in cellular metabolism and blood supply to distinguish malignant masses from benign ones. For example, preclinical studies using MRI with hyperpolarized <sup>13</sup>C-pyruvate or hyperpolarized <sup>13</sup>C-urea found significant differences between malignant kidney cells and normal cells in their rate of conversion of pyruvic acid to lactic acid and their blood supply, respectively.<sup>94</sup> Although studies of hyperpolarized MRI for the early detection of kidney cancer have not yet been conducted in humans, these preclinical findings are highly promising and demonstrate the feasibility of this approach.

NCI also supports research to identify biological markers for the early detection of kidney cancer. For example, NCI-supported researchers recently determined that elevated concentrations of the protein kidney injury molecule-1 (KIM-1) (a type 1 transmembrane protein) measured in blood samples up to five years before diagnosis were associated with an

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<sup>91</sup> <https://seer.cancer.gov/statfacts/html/kidrp.html>

<sup>92</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30391138>

<sup>93</sup> <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf>

<sup>94</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30456188>

increased risk of a subsequent kidney cancer diagnosis. The researchers also found that elevated KIM-1 concentrations in prediagnostic blood samples were associated with higher risk of death for patients with kidney cancer.<sup>95</sup> Other NCI-supported researchers have recently developed a classification model based on DNA methylation markers that enables normal and malignant kidney tissue to be distinguished. When they applied this model to needle biopsy specimens from small renal masses and adjacent normal tissue, they found that 98 percent of adjacent normal tissue specimens were correctly classified as normal; 92 percent of malignant tumors were correctly classified as malignant; and 86 percent of benign masses were correctly classified as benign.<sup>96</sup> The researchers hope this model will enable the earlier detection of kidney cancer, allowing for improved patient management, and the avoidance of unnecessary surgical procedures for patients with benign masses.

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<sup>95</sup> <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6239904/>

<sup>96</sup> <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5354921/>

## Kratom

The Committee requests that NIH expand research on all health impacts of kratom, including its constituent compounds, mitragynine, and 7-hydroxymitragynine. The Committee is aware of the potential promising results of kratom for acute and chronic pain patients who seek safer alternatives to sometimes dangerously addictive and potentially deadly prescription opioids.

### **Action taken or to be taken:**

Finding new, less addictive therapies for pain, as well as effective treatments for opioid use disorder, is essential to addressing the current crisis of opioid addiction and overdose facing the nation. Compounds derived from kratom, the leaves of a tropical tree (*Mitragyna speciosa*) native to Southeast Asia, may hold therapeutic potential.

Early research suggests that kratom could have the potential for treating pain and OUD, and some people report using kratom to self-treat both opioid withdrawal symptoms and depression/anxiety associated with chronic pain. However, there is concern that kratom may be addictive, and that products that contain kratom could be dangerous. Early evidence from cultured heart cells suggests that there may be risks of cardiovascular effects from mitragynine and related compounds, but these findings have not been confirmed in humans or animals. While deaths have occurred in people using kratom, most appear to have resulted from adulterated products or taking kratom with other potent substances. More research is required to better understand the effects and risks of kratom and its constituent compounds.

Mitragynine represents 50 to 67 percent of the alkaloids found in kratom. When consumed, it produces sensations of stimulation and relaxation, with decreased pain and sedation at higher doses. Mitragynine affects several types of receptors in the brain. While the pain relief and sedation at higher doses may be due to stimulation of opioid receptors, the stimulant and relaxing effects likely involve non-opioid receptors. Mitragynine activates the same pathway as opioids, but at a weaker level. However, it is converted in the body into 7- $\alpha$ -hydroxymitragynine, which is 10 times more potent, suggesting that it may have a higher potential for misuse and addiction than mitragynine. 7- $\alpha$ -hydroxymitragynine is generally found in low amounts in kratom products, except in cases of contamination or poor storage conditions, and it is unclear what amount is produced in the body. Both compounds are of particular interest because they appear to selectively stimulate the opioid signaling pathway responsible for pain relief rather than the signaling pathway that causes slowed breathing rate, which could reduce the danger of an overdose. However, more research is needed to confirm these findings.

To better understand kratom and its constituents, NIH currently funds research on these compounds, both to understand their properties and to evaluate them for therapeutic potential. Several studies focus on the diverse array of compounds within kratom, to better understand the effects of each individually, as well as how different compounds work together to create unique effects on the body. Several studies on Kratom are funded as part of medications development efforts under the NIH HEAL (Helping to End Addiction Long-term<sup>SM</sup>) Initiative, examining whether the properties of mitragynine and related molecules make them a viable starting point

for developing therapeutics. Potential applications include the development of pain medications with lower risk of addiction and overdose, and potential treatments for opioid withdrawal, opioid use disorder, and alcohol use disorder.

Mitragynine, as the most abundant psychoactive compound in kratom, is of particular interest. Currently, one of the largest barriers to rigorous research on kratom is the lack of a formulation of its constituent active alkaloids of sufficient dose, purity, and ability to be absorbed by the body to allow for the study of its pharmacology and safety in humans. To address this major hurdle, NIH is developing a purified mitragynine dosage formulation with established purity, stability, safety, and ability to be reproducibly absorbed. Assuming the project is successful in delivering a product that meets FDA standards to allow human trials, the National Institute on Drug Abuse will use it to conduct rigorous clinical studies to advance the understanding of kratom's safety, addiction potential, effects on pain sensitivity, and effects on opioid withdrawal and relapse.

The information gleaned from the efforts described above will allow researchers to better understand the properties of kratom and the compounds within it and will catalyze additional research towards therapeutic applications.

## Liver Cancer

The Committee commends NCI for supporting research on liver cancer and for its inter-institute work to encourage more research focused on liver cancer, but urges greater priority to address the threat of liver cancer, the second deadliest cancer with a five-year survival rate of 20 percent. The Committee also notes that the link between hepatitis B infection and primary liver cancer is well established with up to 60 percent of global liver cancer cases caused by the hepatitis B virus (HBV) and, therefore, encourages continued close collaboration with National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and active participation in the Director's newly-established Trans-NIH Hepatitis B working group. The Committee requests an update on NCI's activities in these areas in the fiscal year 2021 Congressional Justification.

### **Action taken or to be taken:**

The National Cancer Institute (NCI) conducts and supports research to improve the prevention, detection, diagnosis, and treatment of liver cancer, or hepatocellular carcinoma (HCC), including research on viral hepatitis, caused by the hepatitis B and C viruses, and its link to liver cancer. For early detection, NCI supports several translation programs working to develop strategies to detect liver cancer early. For example, the Translational Liver Cancer Consortium established in 2018 conducts studies to better stratify patients at risk of developing liver cancer, improve the surveillance of liver cancer in high-risk populations, and increase the fraction of liver cancer detected at an early stage.<sup>97</sup> In addition, NCI has issued funding opportunity announcements to support epidemiological research investigating novel and innovative hypotheses on emerging risk factors (biological, environmental, and social) for the development of liver cancer and their interplay with established risk factors such as viral hepatitis.<sup>98</sup>

While several targeted treatments have been approved by the U.S. Food and Drug Administration for liver cancer, they usually extend patients' lives by just a few months, and the prognosis for the disease remains poor. NCI supports and conducts research to develop better therapeutic approaches. Recent NCI-funded research has revealed an alternate approach by which cancer cells evade the immune response which can be exploited for new immunotherapies.<sup>99</sup>

The NCI Center for Cancer Research Liver Cancer Program is a multidisciplinary network that collaborates with extramural investigators to develop diverse approaches to the prevention, early detection, diagnosis, and treatment of liver cancer.<sup>100</sup> Recently, NCI researchers uncovered a clear relationship between a liver tumor's level of cellular diversity and the response to immunotherapy that can better inform patient prognosis.<sup>101</sup> A component of this program is to

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<sup>97</sup><https://prevention.cancer.gov/major-programs/translational-liver-cancer-tlc-consortium>

<sup>98</sup><https://grants.nih.gov/grants/guide/pa-files/pa-18-677.html>; <https://grants.nih.gov/grants/guide/pa-files/PA-18-678.html>

<sup>99</sup><https://www.ncbi.nlm.nih.gov/pubmed/30643286>

<sup>100</sup><https://ccr.cancer.gov/liver-cancer-program>

<sup>101</sup><https://ccr.cancer.gov/news/article/diversity-of-liver-cancer-cells-can-impede-tumors-response-to-immunotherapy>; <https://www.ncbi.nlm.nih.gov/pubmed/31588021>

conduct research to explore whether immunotherapies can be effective for treating liver cancer and to develop novel ways to boost a patient’s immune response. New research revealed that gut microbes might play a role in antitumor immunity. Based on these data, NCI initiated clinical trials to determine whether antibiotics in combination with other drugs enhance antitumor immune responses in patients with HCC or liver metastasis and whether antibiotics treatment affects the progression of unresectable Fibrolamellar Hepatocellular Carcinoma, a rare liver cancer that usually occurs in adolescents and young adults who have no history of liver disease and for which there are no effective therapies.<sup>102</sup>

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a wide range of research programs related to hepatitis B, including investigator-initiated extramural research, intramural research, and research supported through initiatives, such as large, multi-site studies and ancillary studies to clinical trials. For example, the NIDDK-supported Hepatitis B Research Network has aimed to advance understanding of disease processes and progression over time, as well as to evaluate approaches to treatment with available and emerging therapies. The Network recently completed two clinical trials of a combination drug therapy—one in adults and another in children—and found it was of limited benefit at the early stage of chronic hepatitis B infection. The Network also completed enrollment for an ongoing study of long-term outcomes of hepatitis B therapy to investigate whether it is possible to clear the infection and stop antiviral therapy, as part of efforts toward developing a “cure.”

NCI, NIDDK, the National Institute of Allergy and Infectious Diseases (NIAID), and other NIH Institutes and Centers (ICs) collaborate on research related to hepatitis B and progression to liver cancer. Intramural researchers at NCI, NIDDK, NIAID, and the NIH Clinical Center are conducting ongoing translational research studies on the molecular mechanisms of disease processes in acute and chronic liver disease aimed at investigating the role of hepatitis viruses in liver carcinogenesis. In addition, collaborative research supported by NCI, the National Institute on Minority Health and Health Disparities (NIMHD), and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) continues to understand the underlying etiologic factors and the mechanisms that result in disparities in chronic liver diseases and cancer in the United States as HCC disproportionately affects racial and ethnic minorities.<sup>103</sup>

Lastly, NCI, NIDDK, NIAID, and others participate in the Trans-NIH Hepatitis B Cure Working Group, the Trans-NIH Committee on Viral Hepatitis, and the HHS National Viral Hepatitis Action Plan to coordinate efforts on hepatitis B and related liver cancer across the NIH and HHS. The recently established Trans-NIH Hepatitis B Cure working group is currently drafting a Strategic Plan for Trans-NIH Research to Cure Hepatitis B. For additional information on the activities of this working group, please see the response on the Trans-NIH Hepatitis B working group and other Hepatitis B Viral-related activities.

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<sup>102</sup><https://clinicaltrials.gov/ct2/show/NCT03785210>; <https://clinicaltrials.gov/ct2/show/NCT04025567>

<sup>103</sup>[https://projectreporter.nih.gov/project\\_info\\_details.cfm?aid=9688365](https://projectreporter.nih.gov/project_info_details.cfm?aid=9688365),  
[https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9650567](https://projectreporter.nih.gov/project_info_description.cfm?aid=9650567),  
[https://projectreporter.nih.gov/project\\_info\\_details.cfm?aid=9662802](https://projectreporter.nih.gov/project_info_details.cfm?aid=9662802),  
[https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9679122](https://projectreporter.nih.gov/project_info_description.cfm?aid=9679122).

## **Lyme and Other Tick-Borne Diseases**

### **Lyme and Other Tick-Borne Diseases (House)**

The Committee encourages NIAID to intensify research and development on Lyme and other tick-borne diseases, including research that will increase understanding of the full range of processes that cause Lyme disease infection. This should include research on the physiology of *Borrelia burgdorferi* and *Borrelia mayonii*, including the mechanisms of possible persistent infection, potential treatment protocols for extended or long-term symptoms attributed to Lyme and other tick-borne diseases, and development of more sensitive and accurate diagnostic tests for Lyme and tick-borne diseases, including next generation polymerase chain reaction (PCR) and new testing methodologies such as proteomics and metabolomics. The Committee directs NIAID to support research on the heightened incidence of Lyme Disease and vector-borne diseases due to global warming.

The Committee encourages NIH to improve early diagnosis and treatment of Lyme and other tick-borne diseases (TBD) to prevent the development of late stage disease and more serious and longer-term disability, but also intensify research on diagnosis and treatment of late stage and chronic disease. In addition to development of highly sensitive and specific diagnostics for all stages of disease, a goal should be to develop diagnostics with appropriate sensitivity and specificity for the detection of infection. Treatments also should be developed for all stages of Lyme and other TBD, determining optimal combinations of new candidate or older drugs and exploring novel combinations. The Committee strongly encourages NIH to hold a workshop on the numerous molecular and functional mechanisms that *Borrelia burgdorferi* (*Bb*) employs to evade and subvert the immune system of the human host and the immune responses and consequences. The Committee supports inclusion of other TBD pathogens to consider shared and unique characteristics of the pathogens as NIH determines practical for the workshop, with participation by researchers who have published peer-reviewed articles describing such mechanisms and immune cell responses, particularly for *Bb*.

### **Lyme and Other Tick-Borne Diseases (Senate)**

With an estimated 300,000 new cases of Lyme disease each year in the United States, and tens of thousands more suffering from other tick-borne diseases, improved understanding and treatment of these diseases is essential for the health and well-being of Americans. The Committee encourages NIH to issue requests for grant applications for research to investigate causes of all forms and manifestations of Lyme disease and other high-consequence tick-borne diseases, including post-treatment symptoms, as well as research to develop diagnostics, preventions, and treatments for those conditions, including potential vaccine candidates. The Committee notes that in patients who suffer from long-term complications associated with Lyme disease, clear treatment pathways are not yet defined. The Committee urges NIAID, in coordination with CDC, to study the long-term effects on patients suffering from post-treatment Lyme disease syndrome, or “chronic Lyme disease.” Specifically, the Committee urges NIAID to evaluate the effectiveness of laboratory tests associated with the detection of *Borrelia burgdorferi* to diagnose the disease early, which can improve the treatment of patients suffering from Lyme disease. The Committee is also aware of promising vaccine innovations to combat *Borrelia* and requests a

report within 90 days of enactment on agency activities to support Lyme vaccine development. The Committee also encourages NLM, in coordination with NIAID, to update its terminology in line with new research to more accurately reflect the long-term effects of Lyme disease.

**Action taken or to be taken:**

NIAID is the NIH lead for basic, translational, and clinical research on Lyme and other tickborne diseases (TBDs). Recently, the NIH published a strategic plan for TBD research that focuses on five key areas: basic research, diagnosis and detection, prevention, therapeutics, and research resources. The plan was developed in response to recommendations from the Department of Health and Human Services (HHS) Tick-Borne Disease Working Group, a Congressionally established federal advisory committee that includes federal and non-federal members.

In alignment with the strategic plan, NIAID is supporting research to develop and improve tools to detect early stage and acute infection, assess treatment success, and identify individuals more likely to develop post-treatment symptoms. Lyme disease diagnostics developed with NIAID support are now being used, beginning in 2019, in a simplified testing approach that may help improve early stage detection of the disease. NIAID also supported development of a serological assay that tests for exposure to eight common tickborne pathogens from a single blood sample. NIAID scientists are conducting a clinical trial to evaluate patients with post-treatment Lyme disease syndrome (PTLDS) to look for evidence of *Borrelia* bacteria and are assessing the use of xenodiagnosis, which uses disease-free laboratory-bred ticks to detect the presence of *B. burgdorferi* following treatment. NIAID also is supporting research on a number of additional diagnostic strategies including an optimized PCR-based test; metabolic biomarkers and biosignatures; direct visualization of *Borrelia* in early disease; and a serologic test to measure Lyme disease treatment effectiveness.

NIAID is conducting and supporting research towards the development of new and improved vaccines and therapeutics for Lyme and other TBDs, including research to better understand newly emerging species of *Borrelia*. NIAID-supported scientists are exploring Lyme disease prevention strategies by adapting a canine vaccine approach for use in humans, researching new vaccine antigens, and investigating vector and reservoir-targeted vaccines. NIAID also is supporting evaluation of antibiotics and drug combinations for activity against *B. burgdorferi* in cell culture and in animal models.

NIAID-supported scientists are addressing key questions regarding *B. burgdorferi* persistence, including how bacterial surface proteins are altered to evade the host immune response. NIAID is currently in the early stages of planning a Lyme disease scientific workshop that will include the key topic of genetic and biochemical mechanisms of immune evasion. In addition, NIAID conducts research on tick biology to better understand disease transmission and supports scientists examining the environmental and climatic factors associated with population growth and geographic expansion of ticks and the pathogens they carry.

NIAID remains committed to the development of diagnostics, vaccines, and therapeutics for Lyme and other TBDs. NIAID will continue to pursue opportunities to advance research on *B.*

*burgdorferi* and other tickborne pathogens via participation in the HHS Tick-Borne Disease Working Group and membership in the longstanding interagency HHS Tick-Borne Disease Partners. NIAID also will continue to work with NLM, which in 2019 updated the Medical Subject Headings (MeSH) terminology for Lyme disease and PTLDS to reflect the current state of scientific knowledge.

## Maternal Mortality

The Committee encourages NICHD to continue its support of research into the leading causes of maternal morbidity and mortality. As black women experience maternal mortality at nearly four times the rate of white women, the Committee strongly urges NICHD to support research that investigates factors contributing to this disparity, and tests evidence-based interventions to address this disparity. NICHD should collaborate with NIMHD as appropriate.

### Action taken or to be taken:

Research into the leading causes of maternal morbidity and mortality is a priority for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD),<sup>104</sup> Through a wide range of investigator-initiated grants and contracts, NICHD research on this topic is aimed at identifying and addressing the biomedical causes of maternal mortality and morbidity and understanding the social and behavioral contexts that can lead to these conditions. For example, an NICHD-supported study found that pretreating women with an antibiotic before delivery lowered rates of infection after cesarean delivery.<sup>105</sup> NICHD researchers are also investigating treatments to reduce death attributed to hemorrhage that have worked in low-to-middle income countries.<sup>106</sup> To better track spending on this critically important public health issue, NIH created an official reporting category in 2017 for maternal health, which includes both maternal morbidity and death.<sup>107</sup> This new resource clearly shows that NIH currently funds research to address knowledge gaps in risk prediction, severe morbidity, optimal timing for delivery, long-term outcomes, and data collection.

Even with these existing research efforts, far more work is needed to reduce maternal morbidity and mortality rates in the U.S., especially among black women. NICHD is leading the development of a research agenda to address maternal morbidity and mortality. In 2019, NICHD led two national meetings to gather information on the contexts of maternal mortality. The first meeting<sup>108</sup> brought together representatives from community-based and professional health groups to discuss what is needed to help improve maternal health. The second meeting<sup>109</sup> focused on the research needed to reverse the increasing rates of both maternal mortality and severe maternal morbidity. Much of the discussion centered on health disparities and how to reach populations that are disproportionately affected. The third meeting, planned for spring 2020, will develop a research agenda to address the clinical causes and co-occurring conditions that increase the risk of morbidity and mortality. Experts will present information about why women die from these conditions and the research gaps that must be addressed to reduce maternal morbidity and mortality in the U.S. In the meantime, NICHD is also supporting a study<sup>110</sup> conducted by the National Academy of Sciences to examine the impact of different birth

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<sup>104</sup> [https://www.nichd.nih.gov/sites/default/files/2019-09/NICHD\\_Strategic\\_Plan.pdf](https://www.nichd.nih.gov/sites/default/files/2019-09/NICHD_Strategic_Plan.pdf)

<sup>105</sup> <https://doi.org/10.1056/NEJMoa1602044>

<sup>106</sup> <https://doi.org/10.1016/j.ajog.2019.05.050>

<sup>107</sup> [https://report.nih.gov/categorical\\_spending.aspx](https://report.nih.gov/categorical_spending.aspx)

<sup>108</sup> <https://videocast.nih.gov/summary.asp?Live=31665&bhcp=1>

<sup>109</sup> <https://videocast.nih.gov/summary.asp?Live=31709&bhcp=1>

<sup>110</sup> <https://www8.nationalacademies.org/pa/projectview.aspx?key=51457>

settings on maternal mortality and morbidity and social determinants that influence risk and outcomes.

To coordinate its research efforts on maternal mortality and morbidity, NICHD created the trans-NIH Maternal Health Coordinating Committee through its Office of Health Equity to facilitate collaboration with the other NIH Institutes and Centers, including the National Institute of Minority and Health Disparities, which focus on some aspect of this issue. NICHD is also a leading member of other committees at the NIH and HHS levels.

In addition, NICHD conducts several activities to address maternal health during pregnancy. These efforts may help to inform research on maternal morbidity and mortality. They include:

- The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) submitted a report<sup>111</sup> to the Secretary of Health and Human Services in 2018 with recommendations about how to improve gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women. Phase II of the Task Force is expected to issue a plan on how to implement those recommendations in 2020.
- The Human Placenta Project (HPP)<sup>112</sup> is a collaborative research effort that aims to develop new tools to study the placenta in real-time to learn how it develops and functions.
- PregSource®<sup>113</sup> is a crowdsourcing research project that will help researchers learn how women from a variety of backgrounds experience pregnancy, which may lead to improvements in care.
- NICHD is also a leading participant in trans-NIH and trans-HHS working groups that are aimed at coordinating and addressing maternal mortality and severe maternal morbidity.

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<sup>111</sup> [https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC\\_Report.pdf](https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf)

<sup>112</sup> <https://www.nichd.nih.gov/research/supported/HPP/default>

<sup>113</sup> <https://www.nichd.nih.gov/research/supported/pregsource>

## **Melanoma**

### **Melanoma (House)**

The Committee encourages NCI to support research from development of experimental models to identify mechanisms and associated biomarkers of risk for development of melanoma, new technologies for early detection as well as trials that develop population-based evidence for screening, including ophthalmologic, and sun protection practices. The Committee also encourages collaboration with the FDA to develop scientific review pathways that more efficiently evaluate new sunscreen ingredients.

Discovery of biomarkers of response and resistance is critical at this point in melanoma research. The Committee urges NCI to support mechanistic research into response and resistance to therapy, and to develop a strategic plan across the public and private sector to systematically focus on biomarker research with the most advanced technologies (genetic, gene expression, or protein-based), so that physicians have the diagnostic tools to deliver personalized medicine to each patient. The Committee also urges NCI to continue the advances in adjuvant therapy by extending research to earlier stage disease and testing shorter, less toxic and more economical regimens. The Committee further encourages research to understand mechanisms that underlie clinical dormancy to provide an effective means of preventing tumor recurrence and improving quality of life and longevity of survivors.

The Committee is aware symptomatic brain (CNS) and leptomeningeal (LMD) metastases remain difficult to treat and may become the last frontier in systemic therapy in melanoma and other cancers. The Committee urges expanding research to identify treatments for CNS and LMD melanoma, which may pave the way for advances in other cancers.

Melanoma is a heterogeneous cancer and includes rare subtypes such as uveal melanoma, the most common cancer of the eye, as well as mucosal and pediatric melanoma. States have difficulty capturing and defining cases due to the complex nature of arriving at the true diagnosis. The Committee encourages NCI to support research through national registries to better understand natural history, epidemiology, as well as patient reported and clinical outcomes in these rare melanoma subtypes. The Committee requests an update on these requests in the fiscal year 2021 Congressional Justification.

### **Melanoma (Senate)**

The Committee encourages NCI to support research from development of experimental models to identify mechanisms and associated biomarkers of risk for development of melanoma, new technologies for early detection as well as trials that develop population-based evidence for screening, including ophthalmologic, and sun protection practices. Discovery of biomarkers of response and resistance is critical at this point in melanoma research. The Committee urges NCI to support mechanistic research into response and resistance to therapy. The Committee further encourages research to understand mechanisms that underlie clinical dormancy to provide an effective means of preventing tumor recurrence and improving quality of life and longevity of

survivors. The Committee is aware symptomatic brain [CNS] and leptomeningeal [LMD] metastases remain difficult to treat and may become the last frontier in systemic therapy in melanoma and other cancers. The Committee urges expanding research to identify treatments for CNS and LMD melanoma, which may pave the way for advances in other cancers. Melanoma is a heterogeneous cancer and includes rare subtypes such as uveal melanoma, the most common cancer of the eye, as well as mucosal and pediatric melanoma. States have difficulty capturing and defining cases due to the complex nature of arriving at the true diagnosis. The Committee encourages NCI to support research through national registries to better understand natural history, epidemiology, as well as patient reported and clinical outcomes in these rare melanoma subtypes. The Committee requests an update on these requests in the fiscal year 2021 CJ.

**Action taken or to be taken:**

Clinical advances in melanoma—including the development of molecularly targeted therapies and immunotherapies—have emerged from decades of National Cancer Institute (NCI) and NIH-funded basic, preclinical, and clinical research. Because of these highly effective therapies, from 2012 through 2016, melanoma saw the largest decrease in death rates compared to any other major cancer type—an average five percent per year.<sup>114</sup> To build on this progress, NCI is supporting research to improve the prevention, early detection, and treatment of melanoma.

Understanding drug resistance is a high priority for NCI. Development of biomarkers for immunotherapies is an important research area that cuts across many cancer types. NCI is supporting this work through research projects and the public-private research collaboration Partnership for Accelerating Cancer Therapies (PACT).<sup>115</sup> In 2018, with NCI funding, three research teams developed methods to predict which patients with melanoma are most likely to respond to immune checkpoint therapies.<sup>116,117,118</sup> These approaches may lead to lab tests that can help guide treatment decisions in the future.

NCI funds research to better understand cancer cell dormancy (a process where cancer cells exist in a non-growing state) and metastasis across cancer types, such as the Human Tumor Atlas Network and Cancer Systems Biology Consortium. In addition, much of NCI’s portfolio in this area is investigator-initiated research funding through the Tumor Metastasis Branch in NCI’s Division of Cancer Biology.

To address the needs of patients with brain metastases, multiple completed and ongoing clinical trials—including those supported by NCI<sup>119,120</sup>—are testing the use of molecularly targeted therapies and immune checkpoint inhibitors. These agents show activity in patients with brain

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<sup>114</sup> [https://seer.cancer.gov/report\\_to\\_nation/infographics/mortality.html](https://seer.cancer.gov/report_to_nation/infographics/mortality.html)

<sup>115</sup> <https://fnih.org/what-we-do/programs/partnership-for-accelerating-cancer-therapies>

<sup>116</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30127393>

<sup>117</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30089911>

<sup>118</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30127394>

<sup>119</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30134131>

<sup>120</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30407895>

metastases,<sup>121</sup> and ongoing research aims to investigate additional approaches, including combination therapies.<sup>122</sup> NCI-funded research has revealed distinct biology underlying leptomeningeal disease (LMD),<sup>123</sup> which is important to inform new therapeutic development strategies.

Adjuvant therapy for melanoma has also improved since 2015 with FDA approval of ipilimumab, nivolumab, and pembrolizumab as well as dabrafenib in combination with trametinib for patients with BRAF mutations. There is growing interest in understanding the role for these therapies in the neoadjuvant setting, i.e., giving them to patients before surgery. For example, NCI is supporting an ongoing Phase 2 trial testing how pembrolizumab works when given to patients both before surgery and after surgery.<sup>124</sup>

To better understand the biology of rare melanoma subtypes and identify potential therapeutic targets, recent NCI-funded research has revealed molecular mechanisms underlying ocular (uveal)<sup>125,126</sup> and mucosal melanomas.<sup>127</sup>

Population data on melanomas and other cancers are captured through NCI's SEER registries. A series of innovative pilot studies are setting the stage for SEER to routinely collect far more clinically relevant pieces of data than previously,<sup>128</sup> including information about cancer treatments and genomic tests.

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<sup>121</sup> <https://www.ncbi.nlm.nih.gov/pubmed/29703161>

<sup>122</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30231345>

<sup>123</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28283064>

<sup>124</sup> <https://clinicaltrials.gov/ct2/show/NCT03698019>

<sup>125</sup> <https://www.ncbi.nlm.nih.gov/pubmed/31253977>

<sup>126</sup> <https://www.ncbi.nlm.nih.gov/pubmed/31555735>

<sup>127</sup> <https://www.ncbi.nlm.nih.gov/pubmed/31320640>

<sup>128</sup> <https://www.cancer.gov/news-events/cancer-currents-blog/2018/nci-seer-enhancements-creating-opportunities>

## **National Commission on Lymphatic Diseases**

The Committee applauds the Office of the Director, NHLBI, NIDDK, and NIAID for facilitating the 2015 Trans-NIH Lymphatics Symposium. The Committee notes the scientific potential that lymphatics research has to treat a wide variety of severe diseases, including heart disease, AIDS, diabetes, rheumatoid arthritis, Alzheimer's, and cancer. The Committee recommends continuing and extending the efforts of the trans-NIH Coordinating Committee for Lymphatic Research, with participation from other relevant institutes, to explore scientific directions that might expand and advance research in this field.

### **Action taken or to be taken:**

The trans-NIH Coordinating Committee for Lymphatic Research continues to support collaboration across many NIH Institutes and Centers, led by the National Heart, Lung, and Blood Institute (NHLBI), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute of Allergy and Infectious Diseases (NIAID). The committee recently expanded its membership to include additional expertise from NHLBI and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Expanding the reach of the committee may serve to more broadly address the various diseases that involve lymphatics.

Another trans-NIH effort that will improve understanding of the lymphatic system is the Human BioMolecular Atlas Program (HubMap) supported by the NIH Common Fund. HubMap is building an open and global platform to map the cells of nine major human organ systems including the lymphatic system.<sup>129</sup>

Lymphatic research is further advanced by the focus of individual Institutes on specific aspects of the lymphatic system. For example, NHLBI supports research to understand the cellular and molecular processes that control lymphatic function in order to develop better treatments for lymphatic disease and dysfunction. NHLBI also coordinates with the nonprofit Lymphatic Education and Research Network to improve awareness of lymphatic diseases and to assist scientists interested in lymphatics research in navigating the NIH funding process. NHLBI also supported the North American Vascular Biology Organization's Lymphatic Forum 2019<sup>130</sup> and assists with the American Venous Forum's annual meeting.

NIDDK supports research on the role of lymphatics in regulating digestive health and disease.<sup>131</sup> Recent advances include a study showing dramatic remodeling of the intestinal lymphatic vessels in a mouse model of short gut syndrome—a condition resulting from surgical removal of a diseased portion of the small intestine. This work could provide new insights into treating short

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<sup>129</sup> <https://commonfund.nih.gov/HuBMAP/fundedresearch>

<sup>130</sup> [www.navbo.org/events/lymphatic-2019](http://www.navbo.org/events/lymphatic-2019)

<sup>131</sup> <https://grants.nih.gov/grants/guide/rfa-files/RFA-DK-17-016.html>; <https://grants.nih.gov/grants/guide/rfa-files/rfa-dk-18-021.html>

gut syndrome, a major cause of morbidity and mortality in children with nutritional deficiencies or intestinal failure-associated liver disease.<sup>132</sup>

NIAID currently supports research aimed at understanding the mechanisms controlling the migration of cells through the lymphatic system; the role of the lymphatic system in pathogenesis and spread of infectious, radiation-induced, or immune-mediated diseases; and how the lymphatic system affects the development, activation, and control of immune responses.

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<sup>132</sup> [www.ncbi.nlm.nih.gov/pubmed/30879758](http://www.ncbi.nlm.nih.gov/pubmed/30879758)

## Neurofibromatosis

The Committee supports efforts to increase funding and resources for NF research and treatment at multiple Institutes, including NCI, NINDS, NIDCD, NHLBI, NICHD, NIMH, NCATS, and NEI. Children and adults with NF are at significant risk for the development of many forms of cancer, as well as deafness, blindness, developmental delays and autism; the Committee encourages NCI to increase its NF research portfolio in fundamental laboratory science, patient-directed research, and clinical trials focused on NF-associated benign and malignant cancers. The Committee also encourages NCI to support clinical and preclinical trials consortia. Because NF can cause blindness, pain, and hearing loss, the Committee urges NINDS to continue to aggressively fund fundamental basic science research on NF relevant to restoring normal nerve function. Based on emerging findings from numerous researchers worldwide demonstrating that children with NF are at significant risk for autism, learning disabilities, motor delays, and attention deficits, the Committee encourages NINDS, NIMH, and NICHD to increase their investments in laboratory-based and patient-directed research investigations in these areas. Since NF2 accounts for approximately 5 percent of genetic forms of deafness, the Committee encourages NIDCD to expand its investment in NF2-related research. NF1 can cause vision loss due to optic gliomas. The Committee encourages NEI to expand its investment in NF1-focused research on optic gliomas and vision restoration.

### **Action taken or to be taken:**

The National Cancer Institute (NCI) is pleased to provide an update on the development of selumetinib, an oral anti-cancer drug that continues to show promises in patients with Neurofibromatosis Type 1 (NF1) tumors.

Based on the results of a phase II trial called SPRINT, the FDA recently awarded selumetinib “breakthrough designation” for the treatment of pediatric patients aged three years and older with NF1 symptomatic and/or progressive, inoperable plexiform neurofibromas (PN), which is a rare, incurable genetic condition.<sup>133</sup> This designation allows FDA to accelerate the path to the possible approval of this drug.

Data from the multicenter, phase II, SPRINT trial, which was led by the NCI Pediatric Oncology Branch (POB) confirmed the results of a smaller NCI-led trial in 2016 that demonstrated for the first time that the selumetinib could shrink large tumors.<sup>134,135</sup> In addition, the researchers found that selumetinib led to improvements in clinical outcomes such as pain, strength, and quality of life. After a year of treatment, most patients (or their parents) reported improved pain scores, strength, and range of motion.

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<sup>133</sup> [https://ccr.cancer.gov/news/article/mek-inhibitor-selumetinib-granted-breakthrough-designation-by-fda-to-treat-neurofibromatosis-type-one-in-pediatric-patients?cid=eb\\_govdel](https://ccr.cancer.gov/news/article/mek-inhibitor-selumetinib-granted-breakthrough-designation-by-fda-to-treat-neurofibromatosis-type-one-in-pediatric-patients?cid=eb_govdel)

<sup>134</sup> <https://www.cancer.gov/news-events/cancer-currents-blog/2018/selumetinib-nf1-neurofibromas>;  
<https://ccr.cancer.gov/news/article/fda-grants-orphan-drug-status-to-selumetinib-for-neurofibromatosis-type-1-nf1-treatment>;  
[https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15\\_suppl.10503](https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.10503)

<sup>135</sup> <https://ccr.cancer.gov/Pediatric-Oncology-Branch/nf>

Selumetinib, developed by AstraZeneca, blocks a protein called MEK that is part of the RAS oncogene signaling pathway. This pathway is improperly activated in patients with NF1, leading to the growth of tumors. Multiple clinical trials are testing selumetinib as a treatment for NF1 patients, including the SPRINT trial. In addition, the POB directs a large clinical trials program for children and adults with NF1 to develop and improve treatments.<sup>136</sup>

These findings and FDA's "breakthrough designation" offer a way forward to better survival and quality of life for individuals with NF1. Those with NF1 have a high predisposition to develop plexiform neurofibromas (PN), a premalignant tumor that can progress to an invasive tumor, and to other cancers. Children and young adults that develop NF1 tumors often suffer from chronic pain that is hard to control, restricted motion, loss of vision, disfigurement, and other complications.

The National Institute on Deafness and Other Communication Disorders (NIDCD) remains committed to supporting basic and clinical research on Neurofibromatosis Type 2 (NF2). NIDCD-supported investigators aim to improve auditory prosthesis devices to have the ability to restore hearing for individuals who are profoundly deaf, including individuals with NF2. Several additional NIDCD-supported research teams are working to identify drug targets that can slow or prevent the growth of the tumors that cause hearing loss and balance problems in individuals with NF2.

The National Institute of Neurological Disorders and Stroke (NINDS) supports and conducts research to understand disease mechanisms in NF and to inform new and improved treatments. An ongoing natural history study led by NINDS intramural investigators is providing new insights into factors affecting tumor growth, clinical symptoms, and optimal treatment timing in patients with NF2. In future years, the study aims to find better ways to prevent hearing loss in NF2 and further explore the biologic basis for speech and swallowing dysfunction in this disease. NINDS funds research on NF1, NF2, and schwannomatosis (a rare form of NF), including studies in animal models and patient-derived cells to understand benign and malignant tumor growth, to define factors influencing symptom variability across individuals, and to conduct preclinical tests of potential treatments to slow or prevent tumor growth and associated impairments, such as hearing loss. Mechanisms underlying neurological symptoms and neurodevelopmental disabilities in NF1 are an important area of NINDS-funded research, with studies focused on autism, hyperactivity and repetitive behaviors, and sleep abnormalities. In addition, recent studies on pain pathways in NF1 suggest a promising therapeutic target.

In addition to the role of the NF1 gene in vision loss due to optic nerve gliomas, the National Eye Institute (NEI) is also exploring its role in Retinopathy-of-Prematurity (ROP), a leading cause of childhood blindness in very premature, low birthweight infants. In both ROP and NF1, patients are at risk for abnormal blood vessel growth and inflammation. Neurofibromin, the protein encoded by the NF1 tumor suppressor gene, regulates inflammatory cells called monocytes and macrophages. A recent NEI study showed that a mutation or deficiency in the protein Neurofibromin has been linked to abnormal growth of blood vessels in the eye. In FY 2019, NEI

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<sup>136</sup> <https://clinicaltrials.gov/ct2/show/NCT02407405>; <https://clinicaltrials.gov/ct2/show/NCT03109301>; <https://clinicaltrials.gov/ct2/show/NCT01362803>; <https://clinicaltrials.gov/ct2/show/NCT01089101>

awarded a new grant to study the NF1 molecular pathways leading to aberrant inflammation, metabolism, and blood vessel growth in animal models and in neonates with severe ROP.

### **Office of Behavioral and Social Sciences Research**

The OBSSR was established to coordinate and promote basic, clinical, and translational research in the behavioral and social sciences in support of the NIH mission. The Committee supports OBSSR's activities aimed at strengthening these sciences by enhancing trans-NIH investments in longitudinal datasets, technology in support of behavior change, innovative research methodologies, and promoting the inclusion of behavioral and social sciences in initiatives at the NIH Institutes and Centers. In partnership with other Institutes and Centers, OBSSR co-funds highly-rated grants that the ICs cannot fund alone. While the NIH budget has grown in recent years, OBSSR funding has remained stagnant. Therefore, the Committee encourages NIH to provide OBSSR funding commensurate with increases given to the ICs.

#### **Action taken or to be taken:**

- From FY 2015 through FY 2019, the budget for the Office of Behavioral and Social Science Research (OBSSR) increased from \$26.1 million to \$27.9 million, a 6.9 percent increase. During this same five-year period, the corresponding increase for NIH as a whole was from \$30.3 billion to \$39.2 billion, an increase of 29.3 percent.
- As OBSSR's budget has increased, the office has underscored its commitment to co-fund impactful and innovative behavioral and social science grants awarded by the NIH Institutes and Centers (ICs). In FY 2018, OBSSR provided \$19.8 million or 71% of its total budget, to co-fund behavioral and social science research grants awarded by the NIH ICs. Via co-funding, OBSSR supports various trans-NIH initiatives including the Environmental influences on Child Health Outcomes (ECHO) and the Adolescent Brain and Cognitive Development (ABCD) longitudinal cohort.
- OBSSR's budget priorities align with its behavioral and social science scientific priorities to: 1) improve the synergy of basic and applied research, 2) enhance and promote research infrastructure, methods, and measures, and 3) facilitate adoption of findings in research and practice. OBSSR is the primary funder of OppNet<sup>137</sup>, a trans-NIH initiative to accelerate basic behavioral and social sciences research. OBSSR developed and leads the Intensive Longitudinal Health Behavior Network,<sup>138</sup> which leverages sensor technologies and computational modeling to understand better changes in health risk behaviors over time. OBSSR also funded the Eureka Platform,<sup>139</sup> which provides mobile health researchers with a test-bed platform to rapidly test and evaluate their applications. OBSSR also commits considerable resources to advanced methodology training in the behavioral and social sciences through its R25 Training Institutes<sup>140</sup> and its T32 grant on advanced data analytics<sup>141</sup> and behavioral and social science predoctoral training

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<sup>137</sup> <https://oppnet.nih.gov/>

<sup>138</sup> <https://ilhbn.ssri.psu.edu/>

<sup>139</sup> <http://info.eurekaplatform.org/platform/>

<sup>140</sup> <https://grants.nih.gov/grants/guide/rfa-files/RFA-OD-19-012.html>

<sup>141</sup> <https://grants.nih.gov/grants/guide/rfa-files/rfa-od-19-011.html>

programs, designed to build and expand the capacity of the field to employ cutting edge and innovative research methods.<sup>142</sup>

- OBSSR's priorities going forward are not only to be able to co-fund additional meritorious behavioral and social sciences research grants, but also to initiate or accelerate a number of key initiatives that OBSSR is uniquely positioned within the NIH to lead. For example, a more cumulative and integrated field of behavioral and social sciences requires more relevant and extensive controlled vocabularies, taxonomies, and ontologies to facilitate data sharing, data integration, and reproducibility of findings. A comprehensive evaluation of the NIH basic behavioral and social sciences research portfolio can help identify specific research gaps that currently hinder the translation of novel health behavior intervention development. More extensive partnerships and combined initiatives with agencies and entities that translate research findings to practice can be used to increase the adoption of effective social and behavioral interventions in healthcare practices and community services.

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<sup>142</sup> <https://obssr.od.nih.gov/training/training-supported-by-the-obssr/>

## **Pain Management**

The Committee is encouraged by the continued collaboration between NCCIH, VA, DOD, and other NIH Institutes to develop and test efficacious non-pharmacological approaches to pain management and comorbidities—including opioid misuse, abuse, and disorder—in military personnel, veterans, and their families. The Committee is particularly encouraged by recent studies assessing brain activity and pain receptors associated with mindfulness meditation and studies that will assess provider adherence to CDC opioid prescribing practices. While VA has made some notable progress in advancing more appropriate opioid prescribing practices, opioid abuse continues to persist among young veterans. As such, the Committee believes it is critical that we continue to support research on non-pharmacological treatments to ensure the best quality of care for our Nation’s veterans and servicemembers, and urges NIH, VA, and DOD to continue to expand this research. The Comprehensive Addiction and Recovery Act (Public Law 114–198) calls for an expansion of research and education on and delivery of complementary and integrative health to veterans, and the NCCIH can play an important role in coordinating efforts with the VA, DOD, and other relevant agencies. The Committee requests an update on these studies and the activities of the multi-agency partnership with DOD and VA in the fiscal year 2021 CJ.

### **Action taken or to be taken:**

In 2017, NCCIH partnered with the Department of Defense (DoD), the Department of Veterans Affairs (VA) and seven other Institutes and Centers at the NIH to launch the NIH-DoD-VA Pain Management Collaboratory (PMC). The PMC seeks to support the development, implementation, and testing of cost-effective, large-scale, real-world research on nonpharmacologic approaches for pain management and related conditions in military and veteran health care delivery organizations. The PMC is currently supporting 11 pragmatic, large-scale clinic trials within the military and veteran health care delivery organizations. Of these trials, the NIH is supporting six, the DoD is supporting four, and the VA is supporting one. “Pragmatic” clinical trials are an emerging type of research that involves a real-world distribution of patients in a real-world healthcare setting; this type of research is critical to apply the knowledge derived from “explanatory” clinical trials that test an intervention in strictly controlled, but less generalizable conditions. These grants are funded through a phased mechanism, meaning that an awardee has two years to plan and test the feasibility of their study design. After this time, they must meet specific milestones to move on to the larger, more comprehensive implementation phase of the award. The award is terminated if an investigator fails to meet their milestones. This phased mechanism helps ensure only studies with the highest likelihood of success will continue. The two-year planning and feasibility phase of the current trials ended in FY 2019, and five of the six NIH-supported grants have met their milestones. The sixth is expected to transition in early FY 2020. The grant supported by the VA will be evaluated in FY 2020 with transition pending soon after. The four grants supported by the DoD are on a similar timeline for milestone review and possible approval of the implementation phase

of the project. The trials that transitioned to the implementation phase in FY 2019 and 2020 will run through FY 2024.

Researchers at Yale University are investigating the effect of early resource education on pain management by enrolling veterans at the time that they are seeking disability for a pain condition. The intervention involves education on the different types of pain medications, information on the importance of treating both the physical and psychological aspects of pain, and information and connection to the many services available to them, including nonpharmacologic interventions. Researchers also assess the risk for substance use disorders and depression and refer the veterans to the appropriate treatment. If this intervention is successful, it can be quickly scaled up and made available nationwide to veterans seeking disability. This early education and referral paradigm could also be adapted to other healthcare systems. Other interventions being investigated as part of the PMC include cognitive behavioral therapy delivered by phone, stepped care management, manual therapies, and percutaneous peripheral nerve stimulation, which is an alternative method of pain control involving the insertion of an electrical lead through an introducing needle followed by the introduction of electric current to produce analgesia. The PMC is also supporting a coordinating center that provided technical, design, and other support to the research teams during this demonstration phase. It also helps coordinate research teams and disseminates Collaboratory-endorsed policies, best practices, and lessons learned from the demonstration projects. The knowledge gained from these studies will not only show if specific nonpharmacologic approaches are effective for pain management and how they can be integrated into a healthcare system, but will also demonstrate how to design and conduct these types of clinical trials.

In total, the PMC is investing \$81 million over 6 years on this effort, with NCCIH contributing more than half of these funds. NIH is supporting 6 of the 11 pragmatic clinical trials and the coordinating center. The DoD is funding four trials, and the VA is supporting one.

The PMC is not the only avenue NCCIH is taking to investigate nonpharmacologic approaches for pain management in pragmatic clinical trials. NCCIH is leading NIH's Helping to End Addiction Long Term (HEAL) Initiative's Pragmatic and Implementation Studies for the Management of Pain to Reduce Opioid Prescribing (PRISM) program, which seeks to take interventions and treatment guidelines that have already been shown to work for specific pain conditions and integrate them into healthcare delivery systems. The PRISM program builds on the lessons learned from the PMC and other pragmatic trials (i.e., The NIH Collaboratory Initiative) and applies them to the civilian healthcare system. NCCIH is overseeing two PRISM grants that focus on nonpharmacologic approaches, like acupuncture and mindfulness meditation, for pain management and one grant to support the PRISM Resource Coordinating Center. The PRISM acupuncture study will help develop evidence to inform the Centers for Medicare & Medicaid Services as they make decisions about future Medicare coverage determinations for acupuncture treatment for beneficiaries with chronic low back pain.

NCCIH is also leading the HEAL Initiative's Behavioral Research to Improve Medication Assisted Treatment (BRIM) program, which seeks to understand whether adding behavioral interventions such as cognitive behavioral therapy or meditation approaches can help improve

outcomes for patients with opioid use disorder (OUD) by helping them stay on their medications for treating OUD. NCCIH is overseeing 14 HEAL grants in this area. While the activities of PRISM and BRIM are not solely focused on the military and veteran populations, the knowledge gained will be applicable to these populations.

## **Pancreatic Cancer Research**

In 2016, pancreatic cancer rose to become the third leading cause of cancer-related death in the U.S., claiming the lives of nearly 42,000 Americans. Despite progress in combatting other forms of cancer, the 5 year survival rate for pancreatic cancer is just 9 percent, in large part because there are no reliable early detection methods or effective treatment options. To help turn the tide against this deadly cancer, Congress in 2012 passed the Recalcitrant Cancer Research Act (Public Law 112–239), calling for the development of a scientific framework for certain recalcitrant cancers. The Committee looks forward to NCI’s submissions of the 5 year updates to the reports required by the Recalcitrant Cancer Research Act of 2012. The Committee encourages NCI to continue to support research efforts to advance progress for patients diagnosed with pancreatic cancer and other cancers with low 5 year survival rates. The Committee requests an update on pancreatic cancer research in the fiscal year 2021 CJ.

### **Action taken or to be taken**

In response to the Recalcitrant Cancer Research Act, and in collaboration with the extramural research community and advocacy groups, the National Cancer Institute (NCI) developed a Scientific Framework for Pancreatic Ductal Adenocarcinoma (PDAC) in 2014.<sup>143</sup> NCI continues to establish and support research opportunities identified through the PDAC framework and to fund meritorious grant proposals in all areas of pancreatic cancer that include prevention, detection, and treatment. Several of these NCI-funded initiatives are described in more detail in a recent report from the Progress in PDAC Research Working Group.<sup>144</sup>

NCI continues to support existing research efforts to improve detection and diagnosis of cancer and to test new molecular and imaging biomarkers that may be useful in the early detection of pancreatic cancer through the Early Detection Research Network and the Pancreatic Cancer Detection Consortium, respectively.<sup>145</sup> In partnership with the National Institute of Diabetes and Digestive and Kidney Diseases, the NCI Community Oncology Research Program (NCORP) is helping to enroll 4,000 patients in the New-Onset Diabetes Cohort study to investigate the link between new-onset diabetes and pancreatic cancer. In addition, investigators supported by the NCI Pancreatic Cancer Cohort and the Pancreatic Cancer Case-Control Consortium (PANC4) are focusing on better understanding the etiology of pancreatic cancer and identifying risk factors for PDAC development.<sup>146</sup> Results from a recent PANC4 study have revealed new insights on the importance of rare and common genetic differences that are linked to pancreatic cancer risk.<sup>147</sup>

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<sup>143</sup><https://deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/pdacframework.pdf>

<sup>144</sup><https://deainfo.nci.nih.gov/advisory/ctac/workgroup/PDAC/WGreport2019.pdf>

<sup>145</sup><https://prevention.cancer.gov/major-programs/early-detection-research>; <https://prevention.cancer.gov/major-programs/pancreatic-cancer-detection>

<sup>146</sup><https://epi.grants.cancer.gov/PanScan/>

<sup>147</sup><https://www.ncbi.nlm.nih.gov/pubmed/?term=PMID%3A+31015203>

NCI supports and conducts research to identify ways to improve the treatment of pancreatic cancer. For example, results from three independent studies (which include a study led by researchers of the NCI-RAS initiative and one led by NCI intramural researchers) have revealed a potential way to kill cancer cells in oncogenic KRAS-driven pancreatic tumors by simultaneously blocking the activity of proteins that interact with the mutant KRAS proteins and disrupting an energy-creating process called autophagy.<sup>148</sup> The findings have led to the design of two clinical trials of such combination treatments in people with pancreatic cancer.

NCI currently supports three pancreatic cancer Specialized Programs of Research Excellence (SPOREs) and three gastrointestinal cancer SPORE that include a focus on pancreatic cancer.<sup>149</sup> Several recent advances have been made by these SPORE investigators. For example, one of the gastrointestinal SPORE teams, in collaboration with others, developed an artificial intelligence diagnostic tool that shows promise in detecting pancreatic cysts that are pre-cancerous from others that have little risk of developing into invasive pancreatic cancer.<sup>150</sup> The use of this tool could prevent unnecessary surgeries in patients with pancreatic cyst. A second study, led in part by one of the pancreatic SPORE teams, showed promising results in reducing pancreatic tumor growth when using a combinatory treatment consisting of stereotactic body radiation therapy (SBRT) and a local immunotherapy to reduce pancreatic cancer growth.<sup>151</sup> Results from another study unveiled a new mechanism to sensitize the immune system and potentially overcome resistance to immunotherapy in PDAC.<sup>152</sup>

In addition, results from an NCI-funded study suggest that altering the makeup of bacteria that populate pancreatic tumors may be a way to improve the treatment of pancreatic cancer.<sup>153</sup> Based on these results, an early-stage clinical trial is being planned to test fecal bacterial transplants as a way to treat pancreatic cancer.

NCI also supports and oversees numerous early- and late-phase clinical trials to develop effective treatments for pancreatic cancer and improve patient care. The Cancer Immunotherapy Trials Network (CITN) has prioritized pancreatic cancer immunotherapy studies and four research teams of the Pancreatic Cancer Microenvironment Network (PaCMEN), a Cancer Moonshot project, are investigating the role of the immune system in PDAC to develop approaches that enhance the immune response against pancreatic cancer.<sup>154</sup> An early-phase clinical trial has shown promising results for patients with locally-advanced pancreatic cancer

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<sup>148</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30709910>;  
<https://www.ncbi.nlm.nih.gov/pubmed/30833752>; <https://www.ncbi.nlm.nih.gov/pubmed/30833748>

<sup>149</sup> <https://trp.cancer.gov/spores/pancreatic.htm>

<sup>150</sup> <https://www.ncbi.nlm.nih.gov/pubmed/31316009>

<sup>151</sup> <https://www.ncbi.nlm.nih.gov/pubmed/?term=31597100>

<sup>152</sup> <https://www.ncbi.nlm.nih.gov/pubmed/?term=31270275>

<sup>153</sup> <https://www.cancer.gov/news-events/cancer-currents-blog/2019/pancreatic-cancer-tumor-microbiome-survival>;  
<https://www.ncbi.nlm.nih.gov/pubmed/31398337>

<sup>154</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9449550](https://projectreporter.nih.gov/project_info_description.cfm?aid=9449550);  
[https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9449587](https://projectreporter.nih.gov/project_info_description.cfm?aid=9449587);  
[https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9450411](https://projectreporter.nih.gov/project_info_description.cfm?aid=9450411);  
[https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9457862](https://projectreporter.nih.gov/project_info_description.cfm?aid=9457862)

that were treated with a combination of chemotherapy, radiation therapy and a common blood pressure drug.<sup>155</sup> In addition, more than 400 pancreatic cancer patients have been enrolled in Molecular Analysis for Therapy Choice (NCI-MATCH), an ongoing precision medicine trial that is expected to provide new research ideas for advances in all many cancer types, including pancreatic cancer.<sup>156</sup>

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<sup>155</sup> <https://jamanetwork.com/journals/jamaoncology/article-abstract/2734827>; <https://clinicaltrials.gov/ct2/show/NCT01821729>

<sup>156</sup> <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match>

## Parkinson's Disease

The Committee commends NINDS for taking critical steps in identifying priority research recommendations to advance research on Parkinson's disease, which impacts between 500,000 and 1,500,000 Americans and is the second most prevalent neurodegenerative disease in the U.S. The Committee recognizes that NINDS is prioritizing public health concerns with severe gaps in unmet medical needs and supports the research recommendations set forth by the NINDS planning strategy to bring us closer to better treatments and a cure for Parkinson's disease. The Committee also encourages NINDS to submit an update of its progress on implementing these recommendations in the fiscal year 2021 Congressional Justification.

### **Action taken or to be taken:**

The National Institute for Neurological Disorders and Stroke (NINDS) is using a range of coordinated approaches to encourage and facilitate research projects that address the Parkinson's disease (PD) research recommendations from the *Parkinson's Disease 2014: Advancing Research, Improving Lives* (PD2014) conference.<sup>157</sup>

The NINDS Morris K. Udall Centers of Excellence for Parkinson's Disease Research program as well as investigator-initiated basic research projects are expanding our knowledge of the genetic and environmental risk factors for PD, connecting the molecular clues of PD pathology to mechanisms of disease process, characterizing symptomatic, pathophysiologic and genetic heterogeneity in people with PD, investigating how gastrointestinal pathology as well as the brain immune response contribute to PD, developing better animal and cell models for PD, and characterizing the brain circuits involved in PD. The pathologic signature of PD is Lewy bodies (aggregates of the protein synuclein). Major efforts are underway to understand how and where synuclein aggregates form and how they spread throughout the nervous system. Preventing and treating the dementia that occur in persons with Lewy bodies is also a subject of intense study in the NINDS led Alzheimer's Disease-Related Dementia initiatives.

These basic science discoveries are being translated into innovative treatments for PD. The NINDS intramural research program recently completed a phase I open-label safety study that demonstrated that they could safely deliver a gene for GDNF (a neuroprotective protein) to specific brain regions in people with PD, and that the treatment may increase dopamine production and stabilize the disease. Industry partners are building on these promising initial results to determine whether GDNF gene therapy slows the progression of PD. NINDS-funded researchers are testing whether gene therapy can restore function of AADC, an enzyme that is essential for the production of dopamine and other neurotransmitters in children with a genetic AADC deficiency. If successful, this same approach may be used to restore dopamine levels in PD. NINDS is funding a large, phase III trial to determine whether high-intensity exercise alters disease progression and to facilitate patient-specific exercise prescriptions. Another clinical study is determining whether telemedicine and smartphone platforms can be used to measure PD

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<sup>157</sup> <https://www.ninds.nih.gov/About-NINDS/Strategic-Plans-Evaluations/Strategic-Plans/Parkinsons-Disease-2014-Advancing-Research>

progression, potentially improving the data quality of future PD clinical trials while reducing the patient burden and costs to funders. The NIH BRAIN Initiative is funding several projects to improve deep brain stimulation (DBS) technology, which is currently used to treat motor symptoms in people with PD. Recent improvements in DBS electrode and implantable pulse generator design, stimulation patterns, and computational models are accelerating the development of novel treatment approaches, including closed-loop paradigms that enable devices to respond to abnormal brain activity in real time, which could improve DBS efficacy and reduce unwanted side-effects. In November of 2019, NINDS will hold a workshop to identify methods to increase the chance of identifying successful new treatments for PD in NIH-funded clinical trials.

The NINDS PD Biomarkers Program (PDBP) has developed data management, clinical, biospecimen and cell line resources that are essential tools for implementing many of the PD2014 recommendations. The NIH Accelerating Medicines Partnership for Parkinson's Disease (AMP PD) is a public-private partnership that is utilizing existing cohorts and biomarkers resources, including PDBP resources, to perform large scale analyses of genes, gene transcription and proteins to identify and validate biomarkers and new therapeutic targets for PD. AMP data and analyses will be publicly accessible to the broad biomedical community via the AMP PD Knowledge Portal, which will be launched in the fall of 2019.

## Pediatric Cancer

“The Committee encourages NCI and NIH to continue to prioritize pediatric cancer research. The Committee recognizes NCI’s efforts to implement sections of the Childhood Cancer STAR Act, develop a new Childhood Cancer Data Initiative, and continue to support and expand new and innovative research efforts to advance progress for children with cancer. These include the Pediatric MATCH precision medicine trial and a pediatric immunotherapy translational science network established through the Cancer Moonshot, in addition to NCI’s long-standing support for the Children’s Oncology Group, the Childhood Cancer Survivor Study, the Pediatric Preclinical Testing Consortium, and several other critical programs. The Committee also commends NIH for its efforts to coordinate pediatric research across its Institutes and Centers through the recently established Trans-NIH Pediatric Research Consortium. The Committee understands NCI participates in the Consortium, and that childhood cancer research is an important part of the pediatric research portfolio across NIH. The Committee requests an update in the fiscal year 2021 CJ on opportunities to enhance childhood cancer research efforts, including coordination efforts already underway through the Trans-NIH Pediatric Research Consortium.”

### **Action taken or to be taken:**

Pediatric cancer research remains a top priority for the National Cancer Institute (NCI) and the Institute continues its commitment to addressing the unique scientific challenges and opportunities that pediatric cancers pose. The portfolio of pediatric cancer research spans from basic studies that seek to understand the mechanisms of cancer formation, to the development of more effective treatments, to research focusing on the long-term consequences of cancer and its treatment to improve the quality of life of children and adolescent and young adult (AYA) cancer survivors. Recent activities underway to support implementation of research provisions in the Childhood Cancer Survivor, Treatment, Access, and Research (STAR) Act,<sup>158</sup> planning for the Childhood Cancer Data Initiative (CCDI),<sup>159</sup> and continued expansion of the Pediatric MATCH study,<sup>160</sup> and pediatric brain tumor research are described in accompanying Significant Items.

Numerous targeted programs supported by NCI aim to advance research in pediatric oncology. The Cancer Moonshot initiative has several pediatric focused projects, including the Center for a Pediatric Tumor Cell Atlas, part of the Cancer Moonshot Human Tumor Atlas Network, which over the past year made progress with biospecimen collection and analysis studies.<sup>161</sup> The Center, located at the Children’s Hospital of Philadelphia, focuses on three high-risk cancer subtypes that combined, account for 50 percent of all pediatric cancer deaths: high-grade glioma, high-risk neuroblastoma, and very high risk acute lymphoblastic B-cell precursor leukemia.<sup>162</sup> The Pediatric Immunotherapy Discovery and Development Network and the Fusion

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<sup>158</sup> <https://www.congress.gov/bill/115th-congress/senate-bill/292/>

<sup>159</sup> <https://www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative>

<sup>160</sup> <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match>

<sup>161</sup> <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/implementation/human-tumor-atlas>

<sup>162</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9627531&icde=0](https://projectreporter.nih.gov/project_info_description.cfm?aid=9627531&icde=0)

Oncoproteins in Childhood Cancers Consortium (FusOnC2) are additional Cancer Moonshot initiatives, both are focused on developing new treatments for children and adolescents with cancer.<sup>163</sup>

Other large NCI-supported programs focusing on therapeutic developments for childhood cancer include the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program,<sup>164</sup> Pediatric Preclinical Testing Consortium,<sup>165</sup> Pediatric Early Phase Clinical Trials Network,<sup>166</sup> the NCI Pediatric Brain Tumor Consortium, and the Children's Oncology Group (COG).<sup>167</sup>

NCI continues to support the ongoing longitudinal Childhood Cancer Survivor Study (CCSS),<sup>168</sup> which looks at the long-term effects of cancer and therapy in a cohort of more than 35,000 childhood cancer survivors. With the new efforts of the CCDI focused on data collection and integration, NCI aims to integrate data from the CCSS and St. Jude Lifetime Study<sup>169</sup> with other resources. These new data linkages and resources would enable investigators to study the long-term effects of new immunotherapy and targeted chemotherapy treatments and to improve tracking of second cancers among childhood cancer survivors.

Pediatric cancer research is a large portion of NIH-wide pediatric research portfolio, which has grown steadily in recent years. Because of the breadth of pediatric research across the institutes and centers (ICs), the NIH Director asked the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to create and lead a new group to harmonize pediatric research efforts across NIH, resulting in the establishment of the NIH Pediatric Research Consortium (N-PeRC).<sup>170</sup> Nearly all of the ICs and offices appointed senior level representatives to N-PeRC, including both extramural and intramural scientists. In just over a year, N-PeRC has already made significant progress on identifying some early areas for potential collaborations. Among the emerging issues are several of clear importance to multiple ICs, such as research on issues faced by adolescents in transitioning to adult health care, drug and device development appropriate for pediatric use, consolidated pediatric data resources, and pediatric research training.

NCI is represented at N-PeRC by the Chief of the Pediatric Oncology Branch (POB)<sup>171</sup> at the Center for Cancer Research, part of NCI's intramural research program that conducts high-risk, high-impact basic, translational, and clinical research. The MyPART (My Pediatric and Adult Rare Tumor) Network<sup>172</sup> is one initiative out of the POB and involves enhancing biospecimen collection amongst pediatric cancer patients, aligning with the STAR Act provisions. The POB is

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<sup>163</sup> <https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/implementation/pediatric-immunotherapy-network>

<sup>164</sup> <https://ocg.cancer.gov/programs/target>

<sup>165</sup> <http://www.nciptc.org/>

<sup>166</sup> <https://ctep.cancer.gov/initiatives/Programs/pep-ctn.htm>

<sup>167</sup> <https://www.childroncologygroup.org>

<sup>168</sup> <https://ccss.stjude.org/>

<sup>169</sup> <https://www.stjude.org/treatment/survivorship/participate-in-st-jude-life-study.html>

<sup>170</sup> <https://www.nichd.nih.gov/research/supported/nperc>

<sup>171</sup> <https://ccr.cancer.gov/Pediatric-Oncology-Branch>

<sup>172</sup> <https://www.cancer.gov/pediatric-adult-rare-tumor/about/what-is-mypart>

dedicated to improving outcomes for children and AYA with cancer through translational research that spans basic science to clinical trials.

NCI will continue to support basic, translational, and clinical research to help develop new and less toxic therapies for children with cancer, and is committed to supporting cancer survivorship research to better understand and develop interventions to address the late effects of cancer and its treatment in childhood and AYA cancer survivors.

### **Pediatric Clinical Trials Authorized under Best Pharmaceuticals for Children Act**

The Committee directs that no less than \$25,000,000 be used toward research in preparation for clinical trials authorized by the Best Pharmaceuticals for Children Act.

#### **Action taken or to be taken:**

Although progress has been made in recent years, approximately three-quarters of all medicines marketed still do not carry Food and Drug Administration (FDA) approved labeling for their use in neonates, infants, children, and adolescents. The goal of the Best Pharmaceuticals for Children (BPCA) program, first authorized by Congress in 2002, is to increase the number of drugs prescribed for children that have specific, evidence-based pediatric labeling.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) leads the trans-NIH BPCA program, coordinating the research efforts of 23 NIH Institutes and Centers (ICs), with the overall goal of identifying and addressing therapeutic gaps in pediatric diseases, disorders, or conditions for which more complete knowledge of drugs and biologics would benefit specific pediatric populations. In consultation with pediatric experts from the Food and Drug Administration (FDA), academia, industry, and other ICs, NICHD regularly publishes an updated, prioritized list of drugs or indications that require further investigation.

For most drugs, dosing derived from adult clinical studies cannot be safely extrapolated for use by infants and children. Consequently, scientists must first conduct clinical research that will inform the design of clinical trials so that they can determine the safety and efficacy of drug dosages, such as pharmacokinetic and pharmacodynamic studies (how drugs are metabolized by different age groups and body types). Investigators who will be conducting these studies must be trained in how to conduct pediatric clinical trials to meet rigorous regulatory requirements for pediatric labeling.

NIH has been making full use of the funds made available by participating ICs through the BPCA program, which are disseminated primarily through contracts. The Pediatric Trials Network (PTN)<sup>173</sup> was established in 2010 to create an infrastructure for investigators to conduct clinical trials to improve pediatric drug labeling. Data from the PTN's clinical studies are submitted to the FDA for potential label modification and made available to investigators and clinicians by posting on NICHD's public website.<sup>174</sup>

Since its inception, the NIH BPCA program has:

- Enrolled more than 7,000 children in 160 sites across five countries, including the NICHD-sponsored PTN;
- Sponsored 40 clinical trials to date; data from 25 of these trials have been submitted to the FDA for potential labeling changes; and

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<sup>173</sup> <https://pediatrictrials.org/>

<sup>174</sup> <https://www.nichd.nih.gov/research/supported/bpca/pediatric-clinical-trials>

- Consequently, eight drugs often prescribed to children now have pediatric labeling, the most recent being Lithium, whose label was updated in October 2018. Studies on four other drugs are now in the final stages of review.

NICHHD is also engaging with the research community to develop additional study designs and simulations, including biomarkers for response to treatment.

### **Pediatric Kidney Disease**

The Committee is encouraged by the research funded by NIDDK on pediatric kidney disease and continues to urge the Institute to support research toward multicenter clinical and translational research focused on clinical approaches to children with kidney disease. However, the Committee believes that NIDDK could do more to support research toward the development of novel therapeutic strategies that utilize genomics and personalized medicine in this patient population. To this end, the Committee urges NIDDK to fund additional research and support clinical trials in this area. The Committee requests that NIDDK report back in the fiscal year 2021 Congressional Justification on the progress made towards additional pediatric focused clinical trials and novel therapeutic development.

#### **Action taken or to be taken:**

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a multi-faceted program of research to identify the causes, understand and halt disease progression, develop and improve treatments, and ultimately prevent kidney diseases and kidney failure in children. The multicenter Chronic Kidney Diseases in Children (CKiD) study is continuing to investigate growth (*e.g.*, physical measures of height and weight), neurocognitive function, and early evidence of cardiovascular disease in children ages 1 to 16 with chronic kidney disease (CKD). The study is also examining the progression of CKD to kidney failure in children with congenital and acquired kidney disease. The CKiD study was recently extended to follow the cohort into young adulthood; this represents a unique opportunity to study individuals with different needs and outcomes than those with adult-onset kidney disease. The CKiD study also continues to refine the newest and most reliable measures of kidney function and outcomes of kidney disease in children.

In addition, NIDDK is continuing to support other research investigating glomerular diseases in children. The Cure Glomerulopathy Network (CureGN) consortium is a multi-site, prospective observational research network of children and adults with established glomerular disease; the consortium includes studies that will help inform new diagnostic and treatment strategies. Close to 40 percent of CureGN participants are children. The Nephrotic Syndrome Study Network (NEPTUNE) is a multidisciplinary, multicenter collaborative research network that complements CureGN and includes many children with nephrotic syndrome. This study applies a personalized medicine approach and genomics research to glomerular disease and will promote novel therapeutic developments. NEPTUNE has assembled clinical, histological, genetic and molecular data on a large sample of children and adults with nephrotic syndrome and will now use this data to evaluate the specific causes of glomerular disease and to choose optimal treatment trials.

Along with the research networks and studies described above, NIDDK continues to support investigator-initiated projects; for example, NIDDK supports research to identify the genetic basis of human kidney malformation—a common cause of pediatric end-stage renal failure. Another team of NIDDK-supported researchers recently reported that sequencing portions of the

genome could help diagnose the underlying cause of chronic kidney disease in children and young adults receiving a kidney transplant, enabling clinicians to use personalized medicine strategies to improve outcomes. These initiatives and projects will continue to yield insights to lay the groundwork for pediatric-focused clinical trials in kidney disease, leading to improved treatment strategies. Further, knowledge gained from kidney disease research in children, where complications are not obscured by other aging-related diseases, will advance understanding of the disease in all populations.

## Pediatric MATCH

The Committee recognizes that cancer is the leading cause of death by disease amongst children and, after accidents, cancer is the second leading cause of death in children ages 1 to 14. In 2018 alone, cancer will affect over 17,000 children, and many of these diagnoses will be rare forms, which lack sufficient therapeutic options. Moreover, children with cancer can suffer more severe side effects from aggressive treatments than adult patients, and the majority of pediatric cancer survivors live with chronic conditions because of their treatments. Improvements in treatment are urgently needed to address this childhood health crisis. The Committee commends NCI's efforts on the novel pediatric MATCH study to address some of these challenges, and appreciates that it will add to the body of scientific evidence necessary to determine the molecular targets substantially relevant to the growth or progression of pediatric cancer as required by the FDA Reauthorization Act of 2017. The Committee encourages NCI to continue its efforts on the pediatric MATCH study and trials. The Committee requests an update in the fiscal year 2021 CJ.

### **Action taken or to be taken:**

The National Cancer Institute (NCI) supports many clinical trials of novel and targeted therapies, including immunotherapies, and trials for cancer control and survivorship studies for children and adolescents. In partnership with the Children's Oncology Group (COG), one of the five NCI National Clinical Trials Network (NCTN) groups, the Pediatric MATCH (Molecular Analysis for Therapy Choice) study focuses on matching pediatric patients with therapies targeted to the molecular abnormalities found in their tumor. Patients will also have their blood (normal genome) sequenced to determine if there are any germline (inherited) mutations present, which can help doctors in informing families about cancer risk.

Launched in July 2017, the Pediatric MATCH study is a precision medicine cancer treatment trial accessible through the 200 COG sites located across the United States, made up of several phase 2 study arms, each evaluating a molecularly targeted therapy.<sup>175</sup> Children and adolescents ages 1 to 21 who have solid tumors that no longer respond to standard treatment or experience reoccurrence are eligible to have a sample of their tumor sequenced to detect genetic abnormalities in over 160 genes, which could be targeted by one or more of the drugs being studied in the trial.<sup>176</sup> Investigators originally expected only 5 to 10 percent of the screened tumors to have one of the key mutations for which experimental drugs are currently available, and therefore they planned on screening 1,000 patients in order to enroll at least 20 patients to each treatment arm.

At the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting held in June, investigators presented an in-depth update on the trial based on accrual data through December 2018.<sup>177</sup> At this point in time, there were 422 patients with a median age of 13 years enrolled from 93 different COG sites. Patients enrolled were diagnosed with greater than 60 different

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<sup>175</sup> <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match>

<sup>176</sup> <https://www.childrensoncologygroup.org/index.php/pediatricmatch>

<sup>177</sup> <https://meetinglibrary.asco.org/record/170951/abstract>

types of cancer, including 101 patients with brain tumors, 300 with other solid tumors, and 21 with lymphomas/histiocytoses. Tumor sequencing was completed on 357 patients, with 112 of those patients identified as having a targetable genetic mutation, and 95 eligible to be assigned to a treatment arm. The match rate of 24 percent was significantly higher than the expected 10 percent, which investigators say demonstrates that through public-private collaboration and partnerships across federal agencies, tumor screening to match children with both common and rare cancers to targeted therapies can be successful. By the end of 2018, 38 of those patients had begun treatment, with the median time from tumor sequencing to treatment assignment being 15 days.

As of September 30, 2019, there have been 721 children and adolescents enrolled into the screening protocol and there are 10 different treatment arms available,<sup>178</sup> 9 open to enrollment and 1 closed as it has met its target accrual. Three more treatment arms are currently in development and should be activated by the end of 2019. There has been at least 1 patient enrolled from 41 states as well as the District of Columbia, and at least 4 patients enrolled in each of the 10 treatment arms.

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<sup>178</sup> <https://clinicaltrials.gov/ct2/show/NCT03155620>

### **Pediatric Physician-Scientist Workforce**

The Committee is concerned about the challenges in attracting and retaining researchers, particularly physician-scientists, to careers in pediatrics and the impact these challenges will have on the pace of innovation and discovery. The Committee directs NIH to build upon the formation of the Trans-NIH Pediatric Research Consortium (N-PeRC) to develop a framework for expanded pediatric research training that would supplement and not supplant existing programs, cut across multiple Institutes and Centers, and focus on supporting individual physician-scientists who have not yet achieved a level of research independence so they can be qualified to meet current and future needs in pediatric research.

#### **Action taken or to be taken:**

NIH remains committed to understanding the healthy development of children, as well as the causes of and treatment for diseases, illnesses, and conditions affecting children. Funding for pediatric research has increased steadily over the past few years; in FY 2018, NIH spent \$4.5 billion in this research area.<sup>179</sup> The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) provides approximately 18 percent of the total amount, joined by 24 other Institutes and Centers (ICs). Because of this breadth, in 2018, NIH Director Dr. Francis Collins asked NICHD to create and lead a new group to harmonize pediatric research efforts across NIH, resulting in the establishment of the NIH Pediatric Research Consortium (N-PeRC). Nearly all of the ICs and offices appointed senior-level representatives to N-PeRC, including both extramural and intramural scientists. In just over a year, N-PeRC has already made significant progress in identifying some early areas for potential collaborations. Among the emerging issues are several of clear importance to multiple ICs, such as research on issues faced by adolescents in transitioning to adult health care, drug and device development appropriate for pediatric use, consolidated pediatric data resources, and pediatric training.

N-PeRC discussions about trans-NIH support for pediatric research training have focused on increasing the cohort of physician-scientists interested in this area of research. A recent analysis conducted on the NICHD portfolio, published in *JAMA Pediatrics*,<sup>180</sup> highlights the importance of individual career development awards to physician-scientists. The study showed that researchers with an M.D. degree who received an individual career development award (as opposed to those who were supported as part of an institutional career development award) from NICHD were more likely to receive subsequent project grant funding. Based on these data, the NICHD intends to provide a greater proportion of its career development fund allocation to individual awards. NICHD currently is leading an additional analysis of pediatric training needs and career opportunities for pediatric scientists across the NIH; this analysis will be published to provide even greater awareness of these opportunities.

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<sup>179</sup> <https://report.nih.gov/rcdc/>

<sup>180</sup> Twombly et al. "Association of national Institute of Child Health and Human Development Career Development Awards with Subsequent Research Project Grant Funding." *JAMA Pediatrics* 2018;172(3):226-231

In the meantime, NICHD is engaging in other efforts to foster the development of pediatric physician-scientists. The NICHD Clinician-Scientist Investigators Conference is an annual meeting held to facilitate the career development of junior academic physician-scientists in pediatrics, obstetrics and gynecology, and rehabilitation medicine. This meeting brings together physicians who have recently completed clinical training with an outstanding faculty of established investigators and NICHD staff to exchange information on grant funding opportunities, career development topics, and research approaches. The goal is to enhance communication, promote interaction, and foster interest in a research career, as well as collaboration in research. The feedback from the fellows and junior faculty who have attended this meeting has been overwhelmingly positive, indicating that the meeting has been instrumental in helping them to achieve their goals of pursuing a career in academic medicine and research.

In addition to increasing the awarding of individual training awards to physician-scientists specializing in pediatrics, panels that review grant applications focused on pediatrics must have the appropriate pediatric expertise. A representative from NIH's Center for Scientific Review was recently added to N-PeRC facilitate the addition of pediatric experts to scientific review panels so that physician-scientists applying for pediatric grants who are at the beginning of their research careers will be judged by those with the most appropriate expertise.

## **Platform Technologies**

There is growing evidence of the importance of the role that “platform technologies” play in accelerating the pace of biomedical research and improving our ability to diagnose, treat, cure, and prevent diseases. Platform technologies can often lead to orders of magnitude improvement in dimensions of cost and performance, such as accuracy, resolution, throughput, flexibility, and ease-of-use. The Human Genome Project, for example, helped drive down the cost of sequencing the human genome from \$100,000,000 to roughly \$1,000, while today the BRAIN Initiative is investing in new and improved platform technologies to increase our understanding of how the brain encodes and processes information. The Committee is interested in whether, given the growing importance of platform technologies, there is more that NIH could and should do to increase the national investment in them. To help answer this question, the Committee directs NIH to provide a report in the fiscal year 2021 CJ that identifies: (1) the challenges that currently limit NIH’s ability to support the development of platform technologies, and how these might be addressed. Potential examples include: (a) low levels of engagement with researchers in the physical sciences, engineering, math, and computer science; (b) a culture that prioritizes hypothesis-driven as opposed to technology-driven proposals; (c) the structure of the NIH, which is organized primarily around specific diseases or organs of the body; (d) a typical size and duration of research grants that may not be aligned with the level of investment required for advances in platform technologies; and (e) difficulty in supporting high-risk, high-return ideas; (2) the specific unmet needs for basic, clinical and translational research that might motivate investment in transformational platform technologies that could be high-impact and timely, given recent scientific and technological advances and unmet medical needs; and (3) changes that NIH and Congress should consider with respect to its ability to identify and fund promising research proposals for platform technologies. Examples include: (a) recruiting NIH personnel and members of study sections with relevant expertise; (b) supporting workshops and the development of roadmaps for platform technologies; (c) increasing funding mechanisms that are appropriate for platform technologies that are relevant to multiple NIH Institutes, such as the Common Fund or NIBIB; (d) increasing NIH’s capacity to partner with industry on the development of platform technologies, such as use of Other Transactions authorities; (e) experimentation with different models for funding and managing research, such as the DARPA model for recruiting and empowering world-class program managers; (f) use of incentive prizes, milestone payments and open innovation techniques; and (g) funding non-profit research institutes that have an increased capacity to manage more complex research projects that require professional scientists, engineers, and product managers, not just graduate students and postdoctoral researchers. Given the importance of this issue, the Committee encourages NIH to engage the research community and industry as it develops its response to these questions and options.

### **Action taken or to be taken:**

As part of the NIH Strategic Plan for Data Science, teams across NIH are developing and enhancing platform technologies to increase data access and usability. These activities are

highlighted here in brief and are described in depth in the trans-NIH Big Data/STRIDES section of the Overview volume of the FY 2021 Congressional Justification. The Overview section also highlights examples of how institutes, centers, and offices are working together to advance platform technologies.

Using Other Transaction Authority, the Science and Technology Research Infrastructure for Discovery, Experimentation, and Sustainability (STRIDES)<sup>181</sup> Initiative is leveraging the commercial cloud space. It will continue to increase access to industry expertise by engaging current partners under STRIDES and engaging additional platform and software analytics partners in the coming year. Changes to NIH's identity and access management (IAM) systems and the STRIDES Initiative will lay the foundations for scientists to search across research datasets on various disease types, minimizing the silo effect created by having unique disease-specific platforms. HL7® Fast Healthcare Interoperability Resources® (FHIR®)<sup>182</sup> will achieve similar goals by implementing standards for clinical research data. NIH workforce development efforts are recruiting experts from computational, mathematical, and related backgrounds and are also opening more opportunities to partner with those communities and engage them in our research. Through workshops on emerging technologies such as artificial intelligence, NIH will continue to engage technical experts and bring them together with the biomedical research community to foster new ideas and adopt emerging technologies. As we increase our capacity for platform technologies, a major challenge will be bringing the tools and software needed for usability to the platforms. As part of the strategic plan, NIH has a team working on multi-pronged approaches to address this issue, including potential new funding opportunities and industry partnerships. These and other activities will push NIH and the researchers it supports to continue to leverage advancing platform technologies while working to harness the power of computational and technical advances to promote integration and collaboration across scientific disciplines, health topics, and communities.

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<sup>181</sup> <https://datascience.nih.gov/strides>

<sup>182</sup> <http://hl7.org/fhir/>

### **Population Research (House)**

The Committee applauds NIA for supporting an innovative and productive population aging research portfolio. The Committee urges NIA to pursue its plans to renew and expand the Demography and Economics of Aging Centers Program and to reaffirm the Institute's commitment to supporting population aging research overall as part of its revised strategic directions document, *Aging Well in the 21st Century: Strategic Directions for Research on Aging*.

#### **Action taken or to be taken:**

Demographic, epidemiologic, and longitudinal studies supported by the National Institute on Aging (NIA) provide the critical data we need to understand trends, track incidence and prevalence of disease, and identify potential risk and protective factors for Alzheimer's and related dementias. For example, the Health and Retirement Study (HRS), the ground-breaking population-based study that follows over 20,000 Americans from age 50 until death, was renewed in FY 2019. During this phase of the study, HRS will continue to collect comprehensive and high-quality data while reducing the burden on study participants by introducing new modes of data collection. HRS will establish a repository of blood samples for future study and strengthen collaborations with genetics consortia, which will further enable researchers to link genetic information to social, behavioral, and economic outcomes. In addition, HRS investigators will conduct follow-up dementia assessment using the innovative Harmonized Cognitive Assessment Protocol (HCAP) to update data on the national prevalence of Alzheimer's disease and related forms of dementia. A newly awarded Research Network will bring together investigators from an international group of studies implementing the HCAP to collaborate on methods and measures to enhance comparability across countries. Importantly, the first Generation X respondents will be added to the study in 2022, and the study will continue the same expanded minority oversample design for the Gen-X cohort as was implemented in 2010 and 2016 for the baby boom cohorts.

Also in FY 2019, NIA solicited applications for the renewal of the Centers on the Demography and Economics of Aging. NIA currently funds 11 of these prestigious Centers, which support pilot research and over 35 U.S.-based and international data resources relevant to aging, including the HRS, the National Health and Aging Trends Study, the National Long-Term Care Survey, the Panel Study of Income Dynamics, and longitudinal and/or population studies in China, India, Latin America, Europe, and Africa. Applications are currently in review, and NIA anticipates funding 9 to 12 Centers in FY 2020.

In addition, NIA has expanded the program to include Centers on the Demography and Economics of Alzheimer's Disease and Related Dementias (AD/ADRD). These unique and highly specialized Centers will focus on issues relevant to AD/ADRD demography, economics, and health services research. Topics of interest include (but are not limited to) national and international population trends in cognitive aging and AD/ADRD; demography of dementia care and caregiving; economic burden of AD/ADRD; and impact of health care systems and long-

term supports and services on outcomes for persons with dementia and their care providers. Applications for the AD/ADRD Demography and Economics Centers are also currently in review, and NIA anticipates funding up to two of these Centers in FY 2020.

Those living in rural areas are disproportionately older and less healthy than urban areas, and the disparity is growing. To address the need to understand the mechanisms that drive rural health and health disparities, NIA awarded a new Interdisciplinary Network on Rural Population Health and Aging (INRPHA) to bring together researchers studying health, aging, spatial disparities and rural well-being to initiate new research on rural U.S. population health and aging.

Finally, population research will be well-represented in NIA's forthcoming update of its strategic directions document. As with the current document, one of NIA's top-line goals articulates its commitment to improving understanding of the consequences of an aging society to inform intervention development and policy decisions. Subgoals re-affirm NIA's interest in supporting epidemiological, behavioral, social, and economic research, including population studies of AD/ADRD. The document has entered the review process, and is planned to be released, pending approval by the National Advisory Council on Aging, early in 2020.

### **Population Research (Senate)**

The Committee applauds NIA for supporting an innovative and productive population aging research portfolio. In particular, the Committee praises the Institute for sustaining its investment in demographic surveys, such as the Health and Retirement Survey and the National Health and Aging Trends Study, critical behavioral and social research infrastructure programs, such as the Centers on the Demography and Economics of Aging and the Roybal Centers for Translational Research, and high priority research networks focused on topics such as the biodemography of aging, stress measurement, and early adversity and later life reversibility. These surveys, programs, and networks are instrumental to the NIA mission. In fiscal year 2020, the Committee urges NIA to pursue its plans to renew and expand the Demography and Economics of Aging Centers Program and to reaffirm the Institute's commitment to supporting population aging research overall as part of its revised strategic directions document, *Aging Well in the 21st Century: Strategic Directions for Research on Aging*.

#### **Action taken or to be taken:**

The National Institute on Aging (NIA) supports demographic, epidemiologic, and longitudinal studies that provide the critical data we need to understand trends, track incidence and prevalence of disease, and identify potential risk and protective factors for diseases and conditions including Alzheimer's disease and related forms of dementia (AD/ADRD). For example, the ground-breaking Health and Retirement Study (HRS), which follows over 20,000 Americans from age 50 until death, was renewed in FY 2019. During this phase of the study, HRS will continue to collect comprehensive and high-quality data while reducing the burden on study participants by introducing new modes of data collection. HRS will establish a repository of blood samples for future study and strengthen collaborations with genetics consortia, which will further enable researchers to link genetic information to social, behavioral, and economic outcomes; and conduct follow-up dementia assessment using the innovative Harmonized Cognitive Assessment Protocol (HCAP) to update data on the national prevalence of AD/ADRD. A newly awarded Research Network will bring together investigators from an international group of studies implementing the HCAP to collaborate on methods and measures to enhance comparability across countries. Importantly, the first Generation X respondents will be added to the study in 2022, with the same expanded minority oversample design for the Gen-X cohort as was implemented in 2010 and 2016 for the baby boom cohorts.

Funding for the National Health and Aging Trends Study (NHATS), a longitudinal study that gathers data at both the individual and population levels on how daily life changes as we age, was also renewed in FY 2019. In addition to replenishing the study population, NHATS investigators will begin collecting measurements of cognitive and sensory capacity and physical activity, which will foster the study of how physical, cognitive, and sensory capacity interact with behavioral accommodations to sustain activities and wellbeing.

Also in FY 2019, NIA solicited applications for the renewal of the Centers on the Demography and Economics of Aging. NIA currently funds 11 of these prestigious Centers, which support

pilot research and provide support to over 35 U.S.-based and international data-resources relevant to aging, including the HRS, NHATS, and others. Applications are currently in review, and NIA anticipates funding nine to 12 Centers in FY 2020. In addition, NIA has expanded the program to include Centers that focus on issues relevant to AD/ADRD demography, economics, and health services research. NIA anticipates funding up to two of these Centers in FY 2020.

Funding for the Roybal Centers for Translational Research was renewed in September 2019. Nine of the 13 currently-funded Roybal Centers focus on the development of interventions in domains such as improving mobility and prolonging independent living, fostering appropriate prescription medicine use, promoting physical activity, and managing pain. Four of the Roybal Centers focus on the development of interventions for dementia care, including palliative care for persons with dementia.

NIA funded five new High-Priority Behavioral and Social Research Networks in FY 2019 to provide infrastructure support for developing specific high-priority areas of aging research. Exploring topics such as health disparities (including rural health), optimal stress measurement, and genetics of behavioral health, these networks will be active until 2023.

Finally, population research will be well-represented in NIA's forthcoming update of its strategic directions document. As with the current document, one of NIA's top-line goals articulates its commitment to improving understanding of the consequences of an aging society to inform intervention development and policy decisions. Subgoals re-affirm NIA's interest in supporting epidemiological, behavioral, social, and economic research, including population studies of AD/ADRD. The document has entered the review process, and NIA anticipates that it will be released, pending approval by the National Advisory Council on Aging, early in 2020.

### **Psycho-Social Distress Complications**

According to the Institute of Medicine, nearly 50 percent of all cancer patients experience distress. Further, studies suggest that distress in cancer patients leads to higher healthcare costs, less compliance with treatment pathways, and poorer health outcomes. While significant advancements have been made in cancer care, the Committee is concerned that the unaddressed psycho-social needs of patients are adversely impacting the effectiveness and cost of care, as well as the individuals' overall well-being. As such, the Committee encourages NCI to ensure that all of its designated cancer centers are managing and measuring patients for distress as an integral piece of their treatment and follow-up care. The Committee requests an update on NCI's activities in this area in the fiscal year 2021 CJ, especially as they relate to recommendations made in the 2008 Institute of Medicine report, "Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs."

### **Action taken or to be taken**

The National Cancer Institute (NCI) is committed to supporting research to improve the quality of life of cancer patients and survivors. The Coordinating Center for Clinical Trials plays a key role in supporting NCI's clinical and translational research programs including coordinating numerous scientific steering committees to advance science and patient care. Research on psychosocial care is informed by the Symptom Management and Health-Related Quality of Life Steering Committee.<sup>183</sup> The committee addresses the design, prioritization, and evaluation of clinical trials on symptom management and quality of life for trials in NCI Community Oncology Research Program (NCORP) and the NCI National Clinical Trials Network. To be eligible to become an NCORP site, institutions must demonstrate that they are able to provide distress screening to patients.

The NCI-funded Screening for Psychosocial Distress Program supported implementation of distress screening at institutions.<sup>184</sup> Results of this program were recently published. Participants from 72 cancer centers, including community and NCI-designated cancer centers, in the United States participated in the program. The program significantly improved each center's ability to successfully implement psychosocial distress screening.<sup>185,186</sup>

NCI is supporting many ongoing research projects to address cancer-related psychosocial distress in patients and caregivers, including various projects that align with research priorities identified in the 2008 Institute of Medicine report, "Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs." Areas of emphasis included research to develop reliable, valid, and efficient tools and strategies for provision of care, along with a focus on vulnerable populations. NCI has supported research relevant to these areas of emphasis over many years. Examples include ongoing research to better understand and measure distress and to develop and test interventions in different populations, such as survivors and their caregivers,<sup>187</sup> parents of

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<sup>183</sup> <https://www.cancer.gov/about-nci/organization/ccct/steering-committees/ncorp/symptom-management>

<sup>184</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9283237&icde=47203002](https://projectreporter.nih.gov/project_info_description.cfm?aid=9283237&icde=47203002)

<sup>185</sup> <https://www.ncbi.nlm.nih.gov/pubmed/30968987>

<sup>186</sup> <https://www.ncbi.nlm.nih.gov/pubmed/29880068>

<sup>187</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9741129&icde=47202742](https://projectreporter.nih.gov/project_info_description.cfm?aid=9741129&icde=47202742)

children with cancer,<sup>188</sup> adolescents and young adults with cancer,<sup>189,190</sup> and cancer survivors who live in rural areas.<sup>191</sup>

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<sup>188</sup>[https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9655009&icde=47202742](https://projectreporter.nih.gov/project_info_description.cfm?aid=9655009&icde=47202742)

<sup>189</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9750647&icde=47202797](https://projectreporter.nih.gov/project_info_description.cfm?aid=9750647&icde=47202797)

<sup>190</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9733171&icde=47202797](https://projectreporter.nih.gov/project_info_description.cfm?aid=9733171&icde=47202797)

<sup>191</sup>[https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9548182&icde=47202797](https://projectreporter.nih.gov/project_info_description.cfm?aid=9548182&icde=47202797)

### **Rare Cancers (including the Therapeutic Research and Development Program)**

Rare cancers, defined as those cancers that have fewer than six new cases per 100,000 Americans per year, represent over 30 percent of all cancers. Pediatric cancers, all forms of which are rare, account for around 1 percent of new patients per year. Rare cancers present unique research challenges for many reasons, including the difficulty in accruing enough patients to clinical trials, and the lack of industry focus on these cancers due to the relatively small number of patients diagnosed with each cancer. The Committee commends NCI's investment in the Rare Tumor Patient Engagement Networks, including NCI CONNECT and MyPART, and in particular in the NCI Experimental Therapeutics Program, with a focus on supporting the most promising new drug discovery and development projects, with priority given for development of therapeutic agents for pediatric cancers. The Committee is particularly interested in the preliminary results of the NCI DART trial ("Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors Trial"), the first federally-funded immunotherapy study devoted entirely to rare cancers, with over 35 cohorts targeting very rare to exceedingly rare types of cancers. The Committee requests an update on the DART study in the fiscal year 2021 budget request. Finally, the Committee encourages a trans-NIH collaboration, which includes NCATS, to accelerate therapies for rare cancers and to support broader sharing of genomic-related rare cancers data to accelerate research and drug development for these cancers.

#### **Action taken or to be taken:**

Cancer is the term used for a collection of diseases that are characterized by abnormal cell growth. Ongoing research on the molecular characterization of cancer continues to reveal that there are hundreds, if not thousands, of different types and subtypes of the disease. This fact, and the facts that no two patients' cancers are identical and approximately 20 percent of patients diagnosed in the United States have a rare form of cancer,<sup>192</sup> makes it challenging to study and develop effective treatments for every cancer. Nonetheless, it is NCI's mission to lead, conduct, and support research on all cancers to help all people live longer, healthy lives.

The Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors or DART<sup>193</sup> trial is one example of a study focused on rare cancers. Since it opened in 2017, the DART trial has enrolled over 550 patients – an uncommon success for a rare cancers trial. The trial is open at over 800 hospitals, cancer centers, and community clinics across the U.S., widespread availability that is a unique feature of trials run through the NCI National Clinical Trials Network (NCTN) and the NCI Community Oncology Research Program (NCORP). This infrastructure allows cancer patients, including those with rare cancers, to receive investigational drugs, through trial participation, in their local communities.

DART is testing the immunotherapy combination of ipilimumab and nivolumab in a "basket" trial design. A basket trial tests a drug or a combination of drugs in multiple tumor types in the same trial as opposed to a more traditional clinical trial design that focus on a single tumor type.

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<sup>192</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28542893>

<sup>193</sup> <https://clinicaltrials.gov/ct2/show/NCT02834013>

The first results from the trial, released in the spring of 2019, showed a significant clinical benefit for patients with high-grade neuroendocrine tumors, a cancer of the neuroendocrine cells (cells that signal for the release of hormones into the blood) that often forms tumors in the lungs and along the digestive tract.<sup>194</sup> There are currently 37 different types of rare cancers being studied in the DART trial.

The NCI collaborates with many other NIH institutes to advance cancer research, including NCATS. NCI is partnering with NCATS, and utilizing its unique expertise and technologies, to work on several projects focused on rare cancers. Examples of collaborative efforts include:

- Studying the rare childhood brain tumor, diffuse intrinsic pontine glioma (DIPG). These aggressive, hard-to-treat tumors are a leading cause of brain cancer death among U.S. children. The teams used NCATS' matrix screening technology, which rapidly tests the effects of thousands of different drug combinations on key disease processes, to examine single compounds and combinations of compounds against DIPG patient cells. Several promising leads were identified.<sup>195</sup>
- Examining drugs for the two different forms of Rhabdomyosarcoma (RMS). RMS is a rare muscle cancer that often affects children and adolescents. There are two main forms of the disease in children that have been shown to develop through different biological mechanisms. NCATS, NCI, and an international team examined drugs for their activity against both types of RMS. They found combinations of compounds that were more active against each form of cancer.<sup>196 197</sup>
- Research showing the drug, metarrestin can selectively attack metastatic tumors in an animal model of pancreatic cancer. In mice with metastatic pancreatic cancer, treatment with metarrestin shrank metastatic tumors and extended the lifespan of the mice.<sup>198</sup> The research team is currently planning a clinical trial.<sup>199</sup>

In addition, there are efforts ongoing focused on drug repurposing, developing better animal models of rare and common cancers, and investigating natural products as anti-cancer drugs. NCI and NCATS will continue to work together on rare cancer projects, with the goals of both finding treatments for rare cancers and developing research tools and platforms that can improve translational research and have a much larger impact on biomedical research and health.

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<sup>194</sup> <https://www.swog.org/news-events/news/2019/03/31/immuno-combo-shrinks-neuroendocrine-tumors>

<sup>195</sup> <https://ncats.nih.gov/pubs/features/childhood-cancer>

<sup>196</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28446439>

<sup>197</sup> <https://www.ncbi.nlm.nih.gov/pubmed/29973406>

<sup>198</sup> <https://www.ncbi.nlm.nih.gov/pubmed/29769289>

<sup>199</sup> <https://www.cancer.gov/news-events/cancer-currents-blog/2018/metarrestin-metastatic-tumors>

## **Deadliest/Recalcitrant Cancers (including Recalcitrant Childhood Cancers)**

### **Deadliest Cancers (House)**

The Committee notes that while more effective screening methods and treatments have lowered overall cancer incidence and death rates, several cancer types with particularly low survival rates have limited screening methods, and effective treatments for these cancers are also limited. The Recalcitrant Cancers Research Act of 2012 defined “recalcitrant cancers” as those with a five-year survival rate below 50 percent. These cancers account for nearly half of all cancer deaths in the U.S. and include cancers of the brain, esophagus, liver, lung, ovary, pancreas, and stomach. The Committee notes that in fiscal year 2020, NCI will report on the effectiveness of the scientific framework process NCI undertook to carry out implementation of the Recalcitrant Cancers Research Act.

### **Recalcitrant Cancers (House)**

The Committee encourages NCI to incorporate the deadliest forms of childhood cancers into the recalcitrant cancer’s category, and to prioritize research on such cancers, which include anaplastic astrocytoma, diffuse intrinsic pontine glioma, glioblastoma, Juvenile myelomonocytic leukemia, high risk neuroblastoma, recurrent osteosarcoma, rhabdomyosarcoma, and diffuse anaplastic Wilms tumors. The Committee urges NCI to utilize available resources to aid in the discovery of better treatments and cures to improve overall childhood cancer survival rates. The Committee requests that NCI include an update on the progress being made to increase childhood cancer research in the Fiscal Year 2021 Congressional Justification.

### **Deadliest Cancers (Senate)**

The Committee remains concerned that while more effective screening methods and treatments have lowered overall cancer incidence and death rates, several cancer types with particularly low survival rates have limited screening methods, and effective treatments for these cancers are also limited. The Recalcitrant Cancers Research Act of 2012 defined “recalcitrant cancers” as those with a 5 year survival rate below 50 percent. These cancers account for nearly half of all cancer deaths in the United States and include cancers of the brain, esophagus, liver, lung, ovary, pancreas, and stomach. The Committee notes that in 2020 NCI will report on the effectiveness of the scientific frameworks process NCI undertook for pancreatic adenocarcinoma and small cell lung cancer to improve prevention, detection, diagnosis and treatment. NCI developed these frameworks at Congress’ direction for cancers with a 5 year survival rate of less than 20 percent and expected toll of at least 30,000 deaths per year in the United States. The Committee appreciates that NCI has led scientific planning efforts in recent years to explore research opportunities related to pancreatic cancer, small cell lung cancer, liver cancer, and glioblastoma. Given the high cost recalcitrant cancers exact on society and the lack of diagnostic and treatment resources currently available to help patients, the Committee directs NCI develop a scientific framework using the process outlined in the Recalcitrant Cancer Research Act of 2012 for stomach and esophageal cancers. These cancers have 5 year survival rates below 50 percent and are collectively expected to kill approximately 27,000 Americans in 2020. The Committee also urges NIH and NCI to continue to support research with an emphasis on developing screening

and early detection tools and more effective treatments for all recalcitrant cancers. The Committee expects to receive an update on NCI-supported research to advance these goals in the fiscal year 2021 CJ. Also, the Committee directs NIH to add esophageal and stomach cancers to future Research, Condition, and Disease Categorization reports. Finally, the Committee recognizes that while overall cancer death rates continue to decline, successful treatment for some cancers, including many forms of childhood cancer, remains elusive. The Committee encourages NCI to place a high priority on researching these cancers, which include anaplastic astrocytoma, diffuse intrinsic pontine glioma, glioblastoma, Juvenile myelomonocytic leukemia, high-risk neuroblastoma, recurrent osteosarcoma, rhabdomyosarcoma, and diffuse anaplastic Wilms tumors. The Committee requests an update on the progress being made for childhood cancer research in the fiscal year 2021 CJ.

**Action taken or to be taken:**

The overall rate of cancer deaths in the United States has declined steadily for more than two decades. Advances in detecting and diagnosing certain cancers at an early stage, improvements in treatment, and public health initiatives that encourage people to adopt proven cancer prevention and screening strategies have all contributed to the progress made against cancer to date. Yet, progress in preventing, diagnosing, and treating cancer is not uniform for all types of the disease.

Developing a better understanding of cancers with high mortality rates remains a high priority for the National Cancer Institute (NCI). NCI's strategy to advance progress against these and all cancers is based on careful planning, coordination, collaboration, and fiscal stewardship of federal resources. NCI supports progress against cancer by supporting investigator-initiated research, targeted funding opportunities, national research infrastructures, and other mechanisms.

A recent advance in the prevention and early detection of esophageal cancers was supported by the NCI through the Early Detection Research Network, the Specialized Programs of Research Excellence (SPOREs) in gastrointestinal cancer, and the Barrett's Esophagus Translational Research Network.<sup>200</sup> In 2019, the U.S. Food and Drug Administration (FDA) cleared a new swallowable balloon device, EsoCheck, to detect Barrett's esophagus (BE) and esophageal cancers. BE is the only established precursor lesion for esophageal cancer and detecting it early provides an opportunity to remove the lesions and prevent the development of esophageal cancer. The device collects a sample (DNA) that is used for genomic analysis to identify BE.<sup>201</sup> This represents a sensitive and well-tolerated way of screening at risk individuals.

The Early Detection Research Network also supported the development of CancerSEEK, a blood test that measures the levels of eight proteins and the presence of mutations in 16 cancer-related genes to detect early-stage cancers.<sup>202</sup> This test received breakthrough designation by the FDA

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<sup>200</sup> <https://edrn.nci.nih.gov/>, <https://prevention.cancer.gov/major-programs/barretts-esophagus>

<sup>201</sup> <https://www.ncbi.nlm.nih.gov/pubmed/29343623>

<sup>202</sup> <https://www.ncbi.nlm.nih.gov/pubmed/29348365>

for the detection of genetic mutations and proteins associated with pancreatic and ovarian cancers. It also has the potential to detect esophagus, liver, ovarian, and stomach cancers.

In addition to the gastrointestinal SPOREs (comprised of colon, rectal, stomach, esophageal, small intestine, liver, gallbladder, and other digestive organ cancers), NCI supports SPOREs focused on brain, lung, ovarian and pancreatic cancers (please see the separate response on the Specialized Programs of Research Excellence for more information).<sup>203</sup> NCI also supports other early detection and treatment networks and consortium focused on high-mortality cancers. Examples of these include the Small-Cell Lung Cancer Consortium,<sup>204</sup> Comparative Brain Tumor Consortium,<sup>205</sup> Pancreatic Cancer Detection Consortium,<sup>206</sup> Pancreatic Ductal Adenocarcinoma (PDAC) Translational Studies on the Tumor Microenvironment Consortium,<sup>207</sup> and a Consortium on Translational Research in Early Detection of Liver Cancer.<sup>208</sup> For additional information on pancreatic and liver cancers, please see separate responses for each of these cancer types.

For pediatric cancers, NCI supports a comprehensive research portfolio that spans from understanding the mechanisms of cancer formation to developing more effective and less toxic treatments and improving cancer survivorship. In addition to funding unsolicited, investigator-initiated research, NCI supports several large programs focused on childhood cancers. For example, therapeutic discovery and development efforts are supported through the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program,<sup>209</sup> Pediatric Preclinical Testing Consortium,<sup>210</sup> Pediatric Early Phase Clinical Trials Network,<sup>211</sup> NCI Pediatric Brain Tumor Consortium (see separate Brain Cancer in Children response), and Children's Oncology Group (COG).<sup>212</sup> As part of NCI's efforts to implement research provisions within the Childhood Cancer Survivorship, Treatment, Access and Research (STAR) Act, NCI is issuing funding opportunity announcements to support new research to improve outcomes for pediatric, adolescent, and young adult cancer survivors.<sup>213</sup> The new Childhood Cancer Data Initiative (CCDI) will enhance the collection, sharing, and analysis of data to address the burden of cancer in these populations.<sup>214</sup> For additional information, please see separate responses for the STAR Act and the CCDI, respectively.

Recent examples of NCI-funded advances in pediatric cancer research include a randomized clinical trial conducted by COG that supported a new standard of care for patients with high-risk

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<sup>203</sup> <https://trp.cancer.gov/>

<sup>204</sup> <https://www.mskcc.org/research-programs/nci-small-cell-lung-cancer-consortium>

<sup>205</sup> <https://ccr.cancer.gov/comparative-oncology-program/research/cbtc>

<sup>206</sup> <https://prevention.cancer.gov/major-programs/pancreatic-cancer-detection>

<sup>207</sup> <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-015.html>; <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-016.html>

<sup>208</sup> <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-025.html>; <https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-028.html>

<sup>209</sup> <https://ocg.cancer.gov/programs/target>

<sup>210</sup> <http://www.ncipptc.org/>

<sup>211</sup> <https://ctep.cancer.gov/initiativesPrograms/pep-ctn.htm>

<sup>212</sup> <https://childrensoncologygroup.org/>

<sup>213</sup> <https://grants.nih.gov/grants/guide/rfa-files/RFA-ca-19-033.html>

<sup>214</sup> <https://www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative>

neuroblastoma.<sup>215</sup> In 2019, an NCI-funded Phase 2 clinical trial showed that the drug selumetinib was active in patients with recurrent, refractory, or progressive pilocytic astrocytoma with BRAF aberrations and patients with NF-1 associated low-grade glioma.<sup>216</sup> This drug is now being tested in COG Phase 3 trials.<sup>217</sup> NCI also is supporting the development of an investigational drug to treat diffuse intrinsic pontine glioma and other brain tumors in pediatric and adult patients.<sup>218</sup> Finally, the ongoing NCI-COG Pediatric Molecular Analysis for Therapy Choice (MATCH) trial is exploring whether targeted therapies can be effective for children and adolescents with solid tumors that harbor specific gene mutations.<sup>219</sup> More information on selumetinib is provided in the Neurofibromatosis response, and also in the general Pediatric Cancer and Pediatric MATCH responses.

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<sup>215</sup> <https://www.ncbi.nlm.nih.gov/pubmed/31454045>

<sup>216</sup> <https://www.ncbi.nlm.nih.gov/pubmed/31151904>

<sup>217</sup> <https://clinicaltrials.gov/ct2/show/NCT01089101>

<sup>218</sup> <https://www.ncbi.nlm.nih.gov/pubmed/31456142>

<sup>219</sup> <https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/pediatric-match>

### **Research Centers at Minority Institutions**

The Committee recognizes the important role of the RCMI program in developing the infrastructure required to enhance biomedical research conducted at historically minority serving institutions. This infrastructure is critical to supporting the development of new investigators and sustaining an established workforce conducting world-class biomedical research that emphasizes the advancement of minority health and the reduction of health disparities. Therefore, the Committee includes \$75,000,000, an increase of \$11,186,000, for RCMI to ensure that critical capacity development in historically minority graduate and health professional schools continues to be enhanced to meet these critical needs. In addition, the Committee recognizes the importance of the RCMI Translational Research Network in ensuring that collectively, institutions can engage in multi-site collaborative research.

#### **Action taken or to be taken:**

The Research Centers in Minority Institutions (RCMI) program<sup>220</sup> supports NIMHD's vision to advance the science of minority health and health disparities research by providing all investigators within the program the resources to engage in rigorous research experiences focused on diseases that disproportionately affect racial and ethnic minorities, and other health disparity populations. RCMI institutions provide shared resources including research infrastructure, research and technical training, mentorship, career development, grant writing, database support for community-based research studies, and opportunities for professional networking to foster collaboration across RCMI sites. NIMHD funding to RCMI institutions also supports neurogenetics research, cell culture facilities, imaging and image analysis instrumentation, state-of-the-art analytical facilities for proteomics research, high-throughput screening, molecular modeling techniques, informatics, and statistical support.

RCMI institutions are a critical link to establishing a diverse biomedical workforce. These institutions support post-doctoral fellows, early-stage investigators, and mid-career scientists with an interest in advancing their scientific careers in basic, translational, clinical, behavioral and populations sciences. RCMI institutions also provide trainees and scholars access to the necessary tools to conduct their proposed research projects to be successful.

The RCMI program has been strengthened to offer more flexibility with respect to the types of research studies conducted to include basic, clinical, and behavioral research. The RCMI Specialized Centers program expands the national capacity for research in the health sciences by providing cooperative agreement support to eligible institutions. An example of the type of research the RCMI program supports is a study that aims to identify new treatment for triple-negative breast cancer, which is the most aggressive type of breast cancer and disproportionately affects African American and Latina women. The study discovered that Monocyte Chemoattractant Protein-1 (MCP-1) mediated pathways could have the potential for treating triple-negative breast cancer and consequently reducing cancer health disparities. Another study is conducting research to identify candidate genes and genetic pathways associated with type 2

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<sup>220</sup> <https://www.nimhd.nih.gov/programs/extramural/research-centers/rcmi/>

diabetes and Hepatitis C virus infection. The goal is to gain insights into possible mechanisms by which the Hepatitis C virus may contribute to the burden of type 2 diabetes, and potentially identify novel treatment and prevention avenues for health disparity populations with both conditions. Other research taking place at RCMI Centers focus on topics such as environmental factors, substance use, HIV-AIDS, prostate cancer, racial and ethnic differences in periodontal disease microbiomes, and adversity-driven chronic pain.

The RCMI program has transitioned from a grant award mechanism, designed for research-related support, to a cooperative agreement, which supports meritorious research projects as well as access to core facilities resources. This also allows NIH staff to have more substantial programmatic involvement. NIMHD staff have met with representatives from RCMI institutions to develop the best strategies for the RCMI institutions to coordinate collaborative efforts among the institutions and leverage their respective capabilities to maximize their impact.

NIMHD will continue to support the RCMI program to leverage the diverse expertise of the RCMI-funded institutions as important partners in advancing the mission of NIMHD to improve minority health and eliminate health disparities.

### **Research in Pregnant and Lactating Women**

The Task Force on Research in Pregnant Women and Lactating Women issued a report to the Secretary of HHS outlining 15 recommendations to facilitate the inclusion of pregnant and lactating women in clinical research. The Committee commends the Secretary for extending the Task Force and believes this extension should be for at least an additional 2 years to continue to work towards healthcare professionals and consumers having accurate information on the safety and efficacy of drugs taken by these populations. NICHD should oversee its part of the implementation of the already released recommendations working with other relevant Institutes, CDC, and FDA. The Committee requests a progress report be provided in fiscal year 2021 CJ.

#### **Action taken or to be taken:**

Most prescription medications have not been tested in, nor are labeled for, use by pregnant and lactating women. Yet, on average, women take between three and five prescription medications during their pregnancies. The 21st Century Cures Act established The Task Force on Research in Pregnant Women and Lactating Women (PRGLAC or Task Force) to advise the Secretary of Health and Human Services (HHS) about gaps in current knowledge and research on safe and effective therapies for pregnant women and lactating women. As required, in September 2018, the Task Force submitted a report on its findings to the Secretary and Congress, along with 15 recommendations for addressing these gaps in knowledge. On March 13, 2019, the federal charter for the Task Force was renewed for an additional two years. The HHS Secretary requested that the Task Force provide advice and guidance related to the implementation of recommendations that were set forth in the 2018 report.

NICHD continues to lead the Task Force for this next phase, which includes a wide range of federal health agencies, including representatives from CDC and FDA, professional societies, patient organizations, and representatives from industry to provide additional advice to the HHS Secretary on the development and use of therapeutics by pregnant women and lactating women, including appropriate inclusion of pregnant and lactating women in clinical research.

In August 2019, PRGLAC members met in person to begin working on an implementation plan. Four working groups – Research, Regulatory, Communications, and Discovery – were established; the recommendations were divided among the groups to describe the steps needed to implement each of them. These working groups will present their findings at the February 2020 PRGLAC meeting for discussion by the full Task Force and to obtain public input. A final implementation plan will be sent to Secretary Azar in the summer of 2020.

In the meantime, NIH continues to support research on therapeutics used by pregnant and lactating women. To better track research that NIH funds, three new public reporting categories were developed: Pregnancy; Maternal Health; and Breastfeeding and Lactation, and Breastmilk.<sup>221</sup> To gain a more thorough understanding of what medications and dosages women take during their pregnancies and postpartum, NICHD added a new feature – a medications

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<sup>221</sup> [https://report.nih.gov/categorical\\_spending.aspx](https://report.nih.gov/categorical_spending.aspx)

tracker – to PregSource®, its online pregnancy research registry.<sup>222</sup> This new tool allows women enrolled in PregSource to report on the name, frequency, and dosage of their medications. In addition, NICHD’s Obstetric-Fetal Pharmacology Research Network continues to support research aimed at improving the safety and effective use of therapeutic drugs in women during pregnancy and lactation through enhanced understanding of obstetric pharmacokinetics and pharmacodynamics. The Network takes a multidisciplinary approach to pharmacologic and clinical research to explore the mechanisms of drug disposition and response in pregnancy and during lactation.

In the coming years, NICHD will remain committed to advancing research on therapeutics used during pregnancy and lactation. The Institute’s new strategic plan, published in September 2019, will be used to guide its research activities for the next five years. It addresses five broad research themes, one of which is Advancing Safe and Effective Therapeutics and Devices for Pregnant and Lactating Women, Children, and People with Disabilities.

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<sup>222</sup> <https://pregsource.nih.gov/>

## **Research Transparency**

As demonstrated over the past 5 years, the Committee remains committed to funding NIH research and ensuring that our Nation's researchers, particularly our scientists early in their career, have the support to make the scientific breakthroughs that may transform healthcare. However, it is critical that NIH can ensure funds are used for the most meritorious biomedical and behavioral research possible that fulfill the core research mission of NIH. Over the last 4 fiscal years, Members of the Committee have provided several examples of questionable spending stemming from research grants awarded by NIH, showing the need for enhanced oversight in the review and approval process. Therefore, NIH is directed to justify, in writing made available on a publicly accessible website, that each grant or agreement promotes efforts to seek fundamental knowledge about the nature and behavior of living systems and/or the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.

### **Action taken or to be taken:**

NIH's mission, as the Committee recognizes, is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability. Moreover, NIH must support the most meritorious biomedical and behavioral research possible as part of its proper stewardship of public funds. In so doing, NIH must also be transparent with the research grants awarded in support of the NIH mission.

NIH provides access to reports, data, and analyses of NIH research activities, including information on NIH expenditures and the results of NIH-supported research, through a suite of public web tools. One of these tools, the NIH Research Portfolio Online Reporting Tools Expenditures and Results (RePORTER)<sup>223</sup>, allows users to review non-sensitive information on the grants that NIH funds. The non-sensitive information on RePORTER includes a statement justifying the relevance of the specific research project to public health. Instructions for applicants explain that the public health relevance section must reflect NIH's mission and NIH's support of a diverse research portfolio that may have short-term or long-term contributions to human health. On RePORTER, public health relevance information is taken directly from the project narrative section of the funded application and written in plain language for the general public to understand. Users may find this information on the RePORTER webpage following the project abstract for each funded grant.

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<sup>223</sup> <https://projectreporter.nih.gov/reporter.cfm>

### **Sickle Cell Disease (House)**

Sickle cell disease (SCD) is the most common inherited blood disorder in the U.S. Academic medical centers located in states with significant populations of sickle cell patients have made progress in treating the disease through NIH-sponsored clinical trials and through blood and marrow transplantation, which is currently the only therapy that can cure the disease. The Committee urges NHLBI to prioritize and implement robust investment to drastically spur, strengthen, accelerate and coordinate sickle cell disease research. The Committee also encourages NIH to support clinical trials for treatment of SCD, which includes multiple promising approaches to eradicate this disease, save lives, and reduce dramatically the substantial health care costs associated with SCD for children and adults. Finally, the Committee encourages NIH to consider programs both domestically and globally to evaluate the effectiveness of screening technologies for infants and children with the sickle cell trait and disease.

#### **Action taken or to be taken:**

The National Heart, Lung, Blood Institute (NHLBI) has a long history of supporting research that has improved health outcomes for people with sickle cell disease (SCD), an inherited blood disorder. NHLBI-supported clinical trials established that bone marrow transplantation can cure SCD when an immune-matched, unaffected sibling serves as the donor.<sup>224</sup> A more recent study showed that the drug hydroxyurea can reduce pain crises and correct a key predictor of stroke in pediatric patients, and now the drug is approved by the Food and Drug Administration (FDA) for these indications.<sup>225</sup>

Today, NHLBI's continuing investments have laid the groundwork for novel approaches to cure the disease, such as gene replacement or repair to correct disease-causing mutations in the hemoglobin gene. Building on this strong foundation, in September 2018, NIH launched a bold, collaborative effort to help speed the development of cures for SCD. The Cure Sickle Cell Initiative builds on the latest genetic discoveries and technological advances to move the most promising gene-based curative therapies safely into clinical trials within 5-10 years.<sup>226</sup> Projects recently funded through the initiative include preclinical studies that may lead to FDA approval to advance into clinical trials, a new platform to manufacture therapeutic products in large quantities, and a national patient data resource that will help provide a more comprehensive picture of SCD. In March 2019, the CBS news show *60 Minutes* featured progress toward a cure, highlighting the story of a young woman who appears to be free of SCD after receiving gene therapy at NIH.

In addition to gene-based therapies, NHLBI continues to support basic, translational, and clinical research to improve the lifespan and quality of life for patients with SCD. For example, a fetal version of hemoglobin made during early life has the capacity to substitute for the mutant

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<sup>224</sup> [www.ncbi.nlm.nih.gov/pubmed/8663884](http://www.ncbi.nlm.nih.gov/pubmed/8663884)

<sup>225</sup> [www.ncbi.nlm.nih.gov/pubmed/26670617](http://www.ncbi.nlm.nih.gov/pubmed/26670617)

<sup>226</sup> [www.nhlbi.nih.gov/science/cure-sickle-cell-initiative](http://www.nhlbi.nih.gov/science/cure-sickle-cell-initiative)

hemoglobin that causes SCD. New insights into the switch from fetal hemoglobin to adult hemoglobin are providing researchers with potential new targets for therapy. Other efforts include development of new bone marrow transplantation techniques for patients who lack an immune-matched donor or face a higher risk of complications from transplant. NHLBI is also supporting an analysis to better understand the clinical and economic benefits and risks of established treatment options, such as bone marrow transplants, and new interventions, including gene-based therapies.

NHLBI is also committed to improving the care and long-term survival for children and adults with sickle cell disease in other parts of the world. This includes Sub-Saharan Africa, where more than 75 percent of SCD births occur and where most patients die before age 5. NHLBI supports 3 major programs in Sub-Saharan Africa across 9 countries and 11 cities: The Sickle Pan-African Research Consortium, the Sickle Cell Disease Genomics Network of Africa, and the Realizing Effectiveness across Continents with Hydroxyurea (REACH) Program. All are working to build research capacity and develop an infrastructure to enhance disease surveillance and delivery of care. The REACH program recently completed a dose-escalation trial of hydroxyurea, and found that hydroxyurea treatment is feasible and safe for children in this region, with many of the same benefits it has for American patients.<sup>227</sup> In other global efforts, the Institute is working with partner organizations to support newborn screening programs for SCD, so that treatments can begin as early as possible. With support from NHLBI's Small Business Innovation Research program, researchers have developed a rapid result test kit for sickle cell mutations, and recently showed that it could be used to screen for SCD and sickle cell trait in low, medium, and high-resource settings, including Sub-Saharan Africa.<sup>228</sup>

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<sup>227</sup> [www.ncbi.nlm.nih.gov/pubmed/30501550](http://www.ncbi.nlm.nih.gov/pubmed/30501550)

<sup>228</sup> [www.ncbi.nlm.nih.gov/pubmed/30290004](http://www.ncbi.nlm.nih.gov/pubmed/30290004)

### **Sickle Cell Disease (Senate)**

Sickle cell disease is an inherited disorder affecting red blood cells that impacts approximately 100,000 African-Americans in the United States. The disease causes extensive bone and organ damage. It is a disabling disease on many levels. Frequent, chronic, and progressive pain crises, along with other medical complications of the disease, make living a normal existence for afflicted individuals very difficult. Advances in medical care have increased the average life expectancy to 45 years, but many individuals succumb to the disease long before, and significant variations exist in the standard of care provided across the country. The Committee encourages NHLBI to continue to make the study of sickle cell disease a priority. The Committee strongly encourages NHLBI to prioritize and implement robust investment to drastically spur, strengthen, accelerate, and coordinate sickle cell disease research. Academic medical centers located in States with significant populations of sickle cell patients have made progress in treating the disease through NIH sponsored clinical trials and through blood and marrow transplantation for sickle cell disease, which is currently the only therapy that can cure the disease. However, more research is needed to augment the limited treatment options available if we are to have a real impact on sickle cell disease. Further, while the Committee is aware that NHLBI is funding very promising areas of innovation related to curative gene therapies, the Committee strongly encourages NHLBI to increase its focus on disease-modifying therapies that could improve day-to-day care for the vast majority of patients and address issues such as organ damage and pain management. Lastly, the Committee encourages NHLBI to support translational research and implementation science to improve the care of patients as they transition from childhood medical care to adult.

#### **Action taken or to be taken:**

The National Heart, Lung, Blood Institute (NHLBI) has a long history of supporting research that has improved health outcomes for people with sickle cell disease (SCD). Early research funded by NHLBI helped establish that SCD is caused by mutations affecting hemoglobin (Hb), a protein essential in red blood cells. Subsequent research has contributed to interventions that have improved life expectancy and quality of life for the approximately 100,000 people with SCD in the United States. NHLBI will continue to build on this foundation of discovery by funding basic and translational research to develop new SCD therapies, as well as implementation science to find new ways to bring evidence-based care to patients of all ages.

Catalyzing a new generation of treatments is an important part of NHLBI's multi-faceted approach to addressing SCD. NHLBI launched the Cure Sickle Cell Initiative in September 2018 to build on recent advances in gene therapy and gene editing technologies, and to help accelerate the application of these technologies for SCD. Through this Initiative, NIH will undertake a coordinated approach that provides access to scientific expertise and resources to advance the most promising genetic therapies. The Initiative links the SCD patient community with academia, federal agencies, biotechnology companies, and clinicians, all working together to safely move the most promising gene-based therapies into clinical trials within 5-10 years. Projects recently funded through the Initiative include preclinical studies of emerging therapies

and a new platform to manufacture therapeutic products in large quantities. Researchers funded through NHLBI's Excellence in Hemoglobinopathies Research Award (EHRA) program continue to increase our understanding of the mechanisms of SCD and to translate this knowledge into new therapeutic approaches.<sup>229</sup> For example, one EHRA-funded group has developed an approach to compensate for sickled Hb by reactivating another version of Hb that is active only during fetal life. The group has found that a gene called BCL11A is responsible for turning off fetal Hb, and that by blocking BCL11A function, it is possible to prevent SCD in a mouse model. More recently, the group characterized how the BCL11A gene is regulated and how it, in turn, regulates the fetal Hb gene,<sup>230</sup> which has provided the basis for gene-based and small molecule-based therapeutic approaches to target these pathways.

To improve care and the quality of life for adolescents and adults with SCD, NHLBI established the Sickle Cell Implementation Consortium in 2016. The Consortium includes eight regional centers (in Chicago; Memphis; St. Louis; Augusta, Ga.; Charleston, S.C.; New York City; Durham, N.C.; Oakland, Calif.) that are using implementation science to enhance the delivery of evidence-based care for SCD. Because managing SCD is particularly complicated when patients are transitioning from pediatric to adult care, improving adolescent care is an important focus of this project. Phase I included an assessment of barriers to care and the development of an SCD patient registry. Phase II will seek solutions to these barriers, with the first three protocols to begin this year (Identifying teens and adults not receiving ongoing care by a primary care physician or specialist; Improving emergency room care of patients in crisis; Redesigning outpatient care and ensuring compliant use of the medication hydroxyurea).<sup>231</sup> Additionally, NHLBI is supporting research to address organ damage and the painful episodes known as sickle cell crisis, including projects to evaluate new biomarkers of crisis that can help predict disease severity and prognosis.<sup>232</sup> In addition, to address pain management, NHLBI is leveraging the NIH Helping to End Addiction Long-term (HEAL) Initiative to support research on the mechanisms of pain and development of non-addictive pain therapeutics.

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<sup>229</sup> [www.nhlbi.nih.gov/news/spotlight/fact-sheet/nhlbi-funded-research-centers-target-hemoglobinopathies](http://www.nhlbi.nih.gov/news/spotlight/fact-sheet/nhlbi-funded-research-centers-target-hemoglobinopathies)

<sup>230</sup> [www.ncbi.nlm.nih.gov/pmc/articles/PMC5889339/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5889339/)

<sup>231</sup> [www.ncbi.nlm.nih.gov/pmc/articles/PMC6020469/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6020469/)

<sup>232</sup> [www.projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9792193&icde=47100387](http://www.projectreporter.nih.gov/project_info_description.cfm?aid=9792193&icde=47100387)

### **Specialized Programs of Research Excellence [SPORE]**

The Committee notes that the SPORE program is one of NCI's cornerstone efforts to promote collaborative, interdisciplinary, translational cancer research, as it works to bring basic research findings into practical treatments. The Committee commends NCI's investment in this area and notes the increasing multicenter nature of this program, with now over 70 percent of the NCI SPOREs being multicenter (involving more than one institute), and 45 percent of those multicenter sites involve more than two institutes. Likewise, the Committee notes that several of the existing SPOREs focus on related organ site diseases (such as the Gastrointestinal, Neuroendocrine, and Sarcoma SPOREs), and another SPORE focuses on a specific pathway called hyperactive RAS in the context of mutations in the NF1 gene. The Committee requests an update on the NCI SPOREs program in the fiscal year 2021 CJ.

#### **Action taken or to be taken:**

The Specialized Programs of Research Excellence (SPOREs), a key component of NCI's Translational Research Program, currently include SPOREs in 23 states, housed at 34 different research institutions. SPORE grants require research efforts in both basic and applied/clinical science. The supported projects are expected to result in new and diverse approaches to the prevention, early detection, diagnosis, and treatment of cancer. NCI supports 63 SPOREs focusing on 20 organ sites, groups of related cancers, or diseases that share a common pathway or molecular characteristic.<sup>233</sup> In 2019, NCI re-issued a Funding Opportunity Announcement that invites applications for the development of translational research programs that are focused on cancer health disparities.<sup>234</sup> The awarded grants will support feasibility and planning activities to build comprehensive cancer health disparities research programs. All applications must propose translational research that will contribute to improved prevention, early detection, diagnosis, and/or treatment of cancers found to disproportionately affect specific racial/ethnic minority populations.

Selected examples of recent advances made by SPORE investigators include:

- Yale Lung Cancer SPORE investigators have discovered that the level of “dormant” tumor-infiltrating T lymphocytes is a predictive biomarker of overall survival in patients with non-small cell lung cancer who are undergoing immunotherapy with immune checkpoint inhibitors. The researchers also demonstrated that these dormant immune cells, which are characterized by low levels of activation and proliferation, can be reinvigorated upon treatment with immune checkpoint inhibitors that target the protein PD-1 in mice bearing patient-derived xenograft tumors.<sup>235</sup>
- Washington University Pancreatic SPORE investigators and their colleagues at the University of Rochester, the University of North Carolina at Chapel Hill, and Johns Hopkins University have determined that stereotactic body radiation therapy (SBRT) of

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<sup>233</sup> [trp.cancer.gov](http://trp.cancer.gov)

<sup>234</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-CA-19-034.html](http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-19-034.html)

<sup>235</sup> [www.ncbi.nlm.nih.gov/pubmed/30097571](http://www.ncbi.nlm.nih.gov/pubmed/30097571)

pancreatic tumors followed by intratumoral administration of the cytokine interleukin-12 (IL-12) can eradicate tumors and effect cures in preclinical mouse models of pancreatic ductal adenocarcinoma. SBRT kills tumor cells, leading to the release of tumor-associated antigens, which in the presence of IL-12, prime potent and durable antitumor immune responses.<sup>236</sup>

UCLA Brain Cancer SPORE investigators found in a clinical trial that administering the anti-PD-1 immune checkpoint inhibitor pembrolizumab before (neoadjuvant) and after (adjuvant) surgery in patients with recurrent, resectable glioblastoma brain tumors significantly improved overall and progression-free survival compared with adjuvant pembrolizumab alone. In addition, the researchers found that neoadjuvant pembrolizumab enhanced both local and systemic antitumor immune responses. These findings suggest that neoadjuvant immune checkpoint inhibitor therapy may be a more efficacious approach in treating this deadly brain tumor.<sup>237</sup>

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<sup>236</sup> [www.ncbi.nlm.nih.gov/pubmed/31597100](http://www.ncbi.nlm.nih.gov/pubmed/31597100)

<sup>237</sup> [www.ncbi.nlm.nih.gov/pubmed/30742122](http://www.ncbi.nlm.nih.gov/pubmed/30742122)

## STAR Act

The Committee includes \$25,000,000 in funding for continued implementation of sections of the Childhood Cancer Survivorship, Treatment, Access, and Research [STAR] Act. Funding is in addition to the funds allocated in fiscal year 2019 to expand existing biorepositories for childhood cancer patients enrolled in NCI sponsored clinical trials to collect and maintain relevant clinical, biological, and demographic information on children, adolescents, and young adults, with an emphasis on selected cancer subtypes (and their recurrences) for which current treatments are least effective. Funding provided this year will allow NCI to continue to conduct and support childhood cancer survivorship research as authorized in the STAR Act. The Committee was pleased to see NCI issue a Request for Applications in fiscal year 2019 to encourage research proposals directly aligned with areas of emphasis outlined in the STAR Act.

### **Action taken or to be taken:**

The National Cancer Institute (NCI) continues to conduct and support pivotal childhood and adolescent and young adult (AYA) cancer survivorship research. Over the past year, NCI has worked diligently to implement the provisions of the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act that aim to further enhance the research portfolio, primarily through additional awards of pediatric survivorship research and enhancements to biospecimen collection and research efforts. These areas of research are important in addressing the unique needs of this population and the STAR Act research provisions build upon the existing infrastructure and ongoing research. In addition to these efforts, NCI continues to implement other provisions of the STAR Act to ensure pediatric expertise on NCI Advisory Boards, applicable committees and panels (Sections 111 and 112 of the STAR Act), and to continue reporting on childhood cancer research activities (Section 121).<sup>238</sup>

NCI continues to conduct and support childhood cancer survivorship research and has expanded support for new research projects that aim to improve outcomes for pediatric and AYA cancer survivors through a new request for applications (RFA) funding announcement.<sup>239</sup> Three projects were funded from the first round of applications. One study will integrate a program, Symptom Monitoring & Systematic Assessment and Reporting System in Young Survivors (SyMon-SAYS), into the electronic health records of children with cancer.<sup>240</sup> The project will evaluate the effectiveness of the program's ability to decrease patients' symptom burden, decrease parent-perceived barriers in managing their child's symptoms, increase patients' and parents' self-efficacy, and increase patients' quality of life. Another project will evaluate the effectiveness of a physical activity intervention consisting of a combination of a wearable activity tracker integrated with individualized goal setting and a private Instagram account for virtual peer support.<sup>241</sup> Researchers aim to determine if the intervention increases physical activity, improves biomarkers of cardiovascular health, and improves overall quality of life in AYA survivors, with

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<sup>238</sup> [www.congress.gov/bill/115th-congress/senate-bill/292](http://www.congress.gov/bill/115th-congress/senate-bill/292)

<sup>239</sup> [grants.nih.gov/grants/guide/rfa-files/RFA-ca-19-033.html](http://grants.nih.gov/grants/guide/rfa-files/RFA-ca-19-033.html)

<sup>240</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9893629&icde=46897427](http://projectreporter.nih.gov/project_info_description.cfm?aid=9893629&icde=46897427)

<sup>241</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9895223&icde=46897607](http://projectreporter.nih.gov/project_info_description.cfm?aid=9895223&icde=46897607)

plans to scale-up if efficacious. The third project aims to determine whether administering an oral medication called memantine to children receiving cranial radiotherapy for brain tumors is associated with reduction in decline of cognitive function.<sup>242</sup> The drug has been used with adult dementia patients and has been shown to decrease changes in thinking and memory that occur after whole brain radiotherapy in adults with brain metastasis. Based on the mechanism of action and animal models, researchers expect memantine to be effective and safe for reducing short and long-term changes in brain function for children receiving radiation for brain tumors. NCI looks forward to receiving additional applications to the RFA in 2020.

Progress in enhancing biospecimen collection and biobanking resources for childhood cancer, as specifically encouraged in the STAR Act, was also made over the past year. In May 2019 the Institute held a scientific meeting to bring together researchers and advocates to discuss pediatric specimen collection and biobanking challenges and opportunities. Conversations focused on issues with access and the sharing of specimens, standardization of specimen annotation, and specimen quality control. Opportunities to further enhance specimen collection, particularly with high-priority specimens collected outside of clinical trials and specimens from cancer types/subtypes for which treatments are least effective, were also discussed. NCI also awarded Nationwide Children's Hospital an additional \$1.5 million in August 2019 to support specimen collection, analyses, and overall enhancements to the Children's Oncology Group Biospecimen Core Resource, the nation's largest pediatric biospecimen bank.<sup>243</sup>

NCI anticipates continuing the implementation of the STAR Act provisions regarding pediatric survivorship research and biospecimen collection and enhancement through activities that will expand emphasis on these research areas for pediatric and AYA patients in the coming year.

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<sup>242</sup> [projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9892593&icde=46897678](https://projectreporter.nih.gov/project_info_description.cfm?aid=9892593&icde=46897678)

<sup>243</sup> [www.childrensoncologygroup.org](http://www.childrensoncologygroup.org)

## Stroke

Due in large part to NIH-funded research, the stroke mortality rate has decreased by 71 percent since 1969. Despite this remarkable progress, strokes cost Americans \$37 billion annually in health care bills and lost productivity at work. Unfortunately, after more than four decades of steep decline, stroke death rates in the U.S. have recently slowed, stalled, or reversed among some groups. The Committee encourages the NINDS to prioritize studies that help develop interventions to reduce health disparities in stroke and to advance promising stroke prevention, treatment, and rehabilitation research, including endovascular therapy and tele-rehabilitation. The Committee also urges continued collaboration with the other Institutes and Centers on research related to vascular contributions to cognitive impairment and dementia.

### **Action taken or to be taken:**

The National Institute of Neurological Disorders and Stroke (NINDS) shares the Committee's concern about the vast burden of stroke and continues its robust investments to advance the most promising science. Several high-impact trials funded through the national NIH Stroke Trials Network (NIH StrokeNet) have changed practice and influenced patient care, including the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) 3 trial which is using a novel neuroimaging approach to deliver life-saving endovascular stroke therapy. In StrokeNet's first completed recovery trial, investigators found that home-based tele-rehabilitation was effective at improving arm motor status in stroke survivors, offering a potential strategy for improving access to quality rehabilitation services. Another recently completed NINDS trial, the Stroke Hyperglycemia Insulin Network Effort (SHINE), found that intensive glucose management after acute ischemic stroke is no more effective than standard care, providing clinical evidence on how best to manage blood sugar in acute stroke patients. NINDS also launched the Stroke Preclinical Assessment Network that uses animal models to identify and validate treatments that might protect the brain in ischemic stroke patients prior to and during emergency reperfusion therapy.

Several NIH initiatives are aimed at better understanding the link between vascular risk factors and stroke as well as dementia. The National Heart, Lung, and Blood Institute (NHLBI)-directed Framingham Heart Study (FHS)—established in 1948—identified some of the earliest known risk factors for stroke and includes ongoing surveillance of cognitive impairment and dementia. Recent FHS findings show that elevated blood pressure in mid-life is associated with an increased risk of dementia later in life. Similarly, recent findings from the Systolic Blood Pressure Intervention-Memory and Cognition in Decreased Hypertension (SPRINT-MIND) trial—supported by NHLBI, NINDS, and the National Institute on Aging (NIA)—show that aggressive blood pressure treatment reduces the risk of cognitive impairment and accumulation of brain white matter lesions. In addition, NINDS and NIA have launched a consortium—called MarkVCID—to identify biomarkers related to the vascular contribution to cognitive impairment and dementia (VCID) to inform prevention trials. NINDS also recently funded the DISCOVERY project, a new six-year prospective clinical research study, which includes a strong focus on diverse populations, to determine the specific subsets of stroke events that cause

(or do not cause) cognitive impairment and dementia in post-stroke populations in the United States.

Decades of research, including several studies funded by NINDS and NHLBI, have provided evidence of disparities in stroke incidence, health outcomes, and excessive mortality, particularly in African Americans and Hispanics as well as individuals from rural areas and low socioeconomic background. To improve understanding of health disparities in stroke, NINDS supports several studies, including the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, Northern Manhattan Study (NOMAS), and the Brain Attack Surveillance in Corpus Christi (BASIC) Project, which are diverse epidemiological studies of black and Hispanic participants. NHLBI supports several long-term studies modeled after FHS to better understand and reduce the risk of cardiovascular disease, including stroke, in diverse populations. These include the Jackson Heart Study, the largest longitudinal study of heart disease in African Americans, which will soon include tests of cognitive function as well as brain magnetic resonance imaging (MRI); the NHLBI-funded Strong Heart Study, the largest study of cardiovascular disease in American Indians; and the Atherosclerosis Risk in Communities (ARIC) Study, which is examining cardiovascular disease risk factors in several racially diverse communities, with joint funding from NHLBI, NINDS, NIA, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD). Using stroke surveillance data from 1988-2008, these studies recently reported that American Indians and blacks have a higher incidence of and higher rates of death from stroke compared to whites.

## **Suicide Prevention and Risk Detection Algorithms**

The Committee is alarmed by new data from CDC that indicates that suicide rates have increased nationwide by 30 percent since 1999. Data also shows that the suicide rate among children, and especially minority children, has significantly risen over the past decade. NIMH has made some encouraging breakthroughs in research on risk detection algorithms. These tools hold promise for developing assessments that will improve the understanding of when people are at higher risk for suicide and prevention efforts to address future attempts. The Committee continues to encourage NIMH to prioritize its suicide screening and prevention research efforts to produce models that are interpretable, scalable, and practical for clinical implementation, including mental and behavioral healthcare interventions, to combat suicide in the United States. In assessing research opportunities, the Committee encourages NIMH to consider the recommendations included in the Action Alliance for Suicide Prevention's A Prioritized Research Agenda for Suicide Prevention. The Committee directs NIMH to provide an update on these efforts in the fiscal year 2021 CJ.

### **Action taken or to be taken:**

Given the troubling rise in the national suicide rate over the past two decades, suicide prevention research is a top priority for the National Institute of Mental Health (NIMH). NIMH-funded research has produced suicide screening tools to improve the identification of individuals at risk for suicide. Further, NIMH-funded researchers are examining ways to implement these evidence-based practices into healthcare systems and communities effectively, leveraging partnerships to save lives.

Emergency departments (EDs) are critical settings for suicide prevention efforts. In the United States, there are nearly half a million visits to EDs for self-injury and many more visits that involve suicide ideation.<sup>244,245</sup> Current ED practices identify only half of all patients at risk for suicide.<sup>246</sup> The NIMH-funded Emergency Department Safety Assessment and Follow-up Evaluation (ED-SAFE) study demonstrated that a three-item screening tool improved providers' ability to identify adults at risk for suicide.<sup>247</sup> When the screening was conducted for all patients – regardless of the reason for their ED visit – suicide risk detection increased nearly twofold. ED-SAFE represents a scalable and practical set of practices. NIMH is currently supporting a follow-up to ED-SAFE, ED-SAFE-2, which includes sustainability studies of successfully implemented universal suicide risk screening, as well as the implementation of the Safety Planning Intervention. Safety Planning is a practical, brief intervention that is being tested in various settings and populations,<sup>248</sup> in which the patient and provider work together to reduce access to lethal means and to identify coping strategies and a contact list of people and resources that could help in a crisis. To date, NIMH-funded researchers have shown that this combination

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<sup>244</sup> <https://webappa.cdc.gov/sasweb/ncipc/nfirates.html>

<sup>245</sup> <https://www.sciencedirect.com/science/article/pii/S016383431200103X?via%3Dihub>

<sup>246</sup> <https://www.ncbi.nlm.nih.gov/pubmed/26654691>

<sup>247</sup> <https://www.ncbi.nlm.nih.gov/pubmed/26654691>

<sup>248</sup> <https://www.nimh.nih.gov/news/science-news/2015/embracing-the-spirit-of-reducing-suicide.shtml>

of screening, brief intervention, and follow-up contact reduced suicide attempts in the following year by about 30 percent.<sup>249</sup> Further, NIMH is funding the Emergency Department Screen for Teens at Risk for Suicide (ED-STARS), a study that has employed a 4-item universal screening tool and other innovative approaches to screening and assessment, such as the development of computerized adaptive screen (CAS) for predicting suicide attempts. CAS will generate individualized sequences of screening questions conditional on previous responses and may enable researchers to identify acute suicide risk indicators in teens.<sup>250,251</sup>

NIMH is a member of the National Action Alliance for Suicide Prevention (NAASP), a public-private partnership among federal agencies, state governments, companies, and national suicide prevention advisory and advocacy groups. NAASP is committed to reducing the suicide rate by 20 percent by the year 2025. NIMH co-leads the Research Prioritization Task Force (RPTF) and helped develop the Prioritized Research Agenda for Suicide Prevention.<sup>252</sup> NIMH has solicited studies to address gaps identified in the Agenda, encouraging efforts to develop and test screening approaches for use in EDs to identify youth at risk for suicide, and studies to develop methods to help assign youth who are identified as at risk to appropriate interventions.<sup>253</sup> NIMH partnered with other NIH Institutes and Centers to support projects leveraging existing data sets to improve understanding of suicide risks and mortality outcomes.<sup>254,255</sup> NIMH has also issued a notice of special interest to expand the number of mental health researchers—both established scientists, as well as early-career scientists—who engage in suicide research.<sup>256</sup>

To address implementation research, NIMH partners with NAASP to support the Zero Suicide initiative.<sup>257</sup> Zero Suicide is a commitment, a goal, and a campaign to prevent suicide among individuals receiving treatment within healthcare systems. NIMH is funding several projects aimed at achieving the goals of Zero Suicide to create a stronger evidence base for suicide prevention practices in real world settings.<sup>258</sup> This effort is also consistent with the NIMH Strategic Plan for Research, Objective 4, improving public health through more practice-ready suicide prevention interventions.<sup>259</sup>

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<sup>249</sup> <https://www.ncbi.nlm.nih.gov/pubmed/28456130>

<sup>250</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=8755416&icde=21651658](https://projectreporter.nih.gov/project_info_description.cfm?aid=8755416&icde=21651658)

<sup>251</sup> <https://www.nimh.nih.gov/news/science-news/2014/personalized-screen-to-id-suicidal-teens-in-14-ers.shtml>

<sup>252</sup> <https://theactionalliance.org/resource/prioritized-research-agenda-suicide-prevention-action-plan-save-lives>

<sup>253</sup> <https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-070.html>

<sup>254</sup> <https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-18-400.html>

<sup>255</sup> <https://grants.nih.gov/grants/guide/rfa-files/rfa-mh-18-410.html>

<sup>256</sup> <https://grants.nih.gov/grants/guide/notice-files/NOT-MH-19-026.html>

<sup>257</sup> <http://zerosuicide.sprc.org/>

<sup>258</sup> <https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-16-800.html>

<sup>259</sup> <https://www.nimh.nih.gov/about/strategic-planning-reports/strategic-objective-4.shtml>

### **Temporomandibular Disorders [TMD]**

The Committee commends NIDCR for its work with the Office of the Director and the National Academies of Sciences, Engineering, and Medicine in the comprehensive project, Temporomandibular Disorders: From Research Discoveries to Clinical Treatment. It also appreciates NIDCR's participation in the TMJ Patient-Led RoundTable to advance collaboration to work toward the common end of providing safe and effective treatments that improve patients' quality of life. The Committee encourages continued collaboration with governmental agencies and other stakeholders in the project. The Committee continues to be concerned that over 36,000,000 people, primarily women in their childbearing years, are affected physically, financially, and emotionally by TMD. The Committee is aware that TMD are primarily a multisystem disorder with overlapping conditions influenced by multiple biological and environmental factors rather than solely an orofacial pain condition. The Committee is cognizant that NIDCR's budget on TMD is a small percent of its overall budget despite the burden of this condition on individuals and society at large. The Committee urges NIDCR to increase funding that will expand the science base and enable increasing multidisciplinary research to advance this field. The Committee requests an update on TMD funding and the preliminary recommendations that came forth from the multiple TMJ public- private scientific meetings supported by NIH and NIDCR in the fiscal year 2021 CJ.

#### **Action taken or to be taken:**

Fostering collaborations is key to tackling the challenges posed by Temporomandibular Disorders. NIDCR is a lead participant in the TMJ Patient RoundTable to advance partnerships to work toward the common goal of providing safe and effective treatments that improve patients' quality of life. Over the past year, NIDCR has continued its participation in the monthly RoundTable meetings, which are producing documents aimed at advancing TMD research and disseminating research results.<sup>260</sup> For example, to characterize the current state of TMD treatments and the strength of supporting data, the group identified and published abstracts of 94 meta-analyses and systematic review articles.<sup>261</sup>

In addition, NIDCR and the NIH Office of the Director are supporting a National Academies of Sciences, Engineering, and Medicine (NASEM) consensus study titled "Temporomandibular Disorders: From Research Discoveries to Clinical Treatment."<sup>262</sup> This project began in fall 2018, convening an expert committee to review and address the current state of knowledge regarding TMD research, education and training, safety and efficacy of clinical treatments of TMD, and burden and costs associated with these disorders. The committee held five meetings throughout 2019. It also held a two-day public workshop and two additional webinars that covered the following TMD-related topics: scope and definitions, public health burden, basic and clinical research, current state of care, provider perspectives on patient care, and clinical education. Importantly, the voice of patient advocates was prominent at the workshop, and all participants expressed a sincere appreciation for the patient point of view. The committee will release its final report in March 2020. NIDCR will carefully consider the study findings and

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<sup>260</sup> <http://www.tmj.org/Page/450/48>

<sup>261</sup> [http://mdepinet.org/wp-content/uploads/TMD-Treatment-MA-and-SRs\\_Final.pdf](http://mdepinet.org/wp-content/uploads/TMD-Treatment-MA-and-SRs_Final.pdf)

<sup>262</sup> [www.nationalacademies.org/hmd/Activities/PublicHealth/TemporomandibularDisorders.aspx](http://www.nationalacademies.org/hmd/Activities/PublicHealth/TemporomandibularDisorders.aspx)

plans to use the report, in partnership with stakeholders, to inform approaches to advance fundamental, translational, and clinical TMD research and help guide the development of policies related to evidence-based treatment and clinical management of TMD patients.

NIH has increased investments in pain research through the Helping to End Addiction Long-term (HEAL) Initiative. In FY19, NIH published over 40 funding opportunity announcements as part of HEAL. Further, NIDCR is collaborating with many other NIH ICs to support efforts to promote the discovery of robust candidate biomarkers and endpoints for pain conditions, including TMD, that can be used to facilitate the development of non-opioid therapeutics. For example, researchers are determining whether non-invasive methods that modulate the nervous system, such as direct current stimulation of specific brain regions, can reduce pain in TMD patients.<sup>263</sup> Another HEAL project is investigating the role of neuronal ion channels – proteins responsible for transmitting nerve signals – in mediating TMD pain, with the hope that these proteins can be drug-targeted as a non-opioid pain treatment.<sup>264</sup> These increased investments in TMD pain research will allow scientists working on TMD to leverage findings from related pain research to advance the field and accelerate the development of evidence-based strategies to prevent, diagnose, and treat TMD. The ultimate goal is to improve the lives of those affected physically, financially, and emotionally by these disorders.

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<sup>263</sup> [www.projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9751247&icde=46779531&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](http://www.projectreporter.nih.gov/project_info_description.cfm?aid=9751247&icde=46779531&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=)

<sup>264</sup> [www.projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9998160&icde=46779633&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=](http://www.projectreporter.nih.gov/project_info_description.cfm?aid=9998160&icde=46779633&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pball=)

## **Threat of Emerging Infectious Diseases**

### **Threat of Emerging Infectious Diseases (Senate)**

The Committee notes NIH's progress in advancing scientific discovery and public health by leveraging the incredible growth in the volume, speed of delivery, and complexity of large biomedical datasets. The Strategic Plan for Data Science released by NIH in June 2018, articulates a vision for making big data sustainable, interoperable, accessible, and usable by the broader scientific community. The usage of machine learning, data-driven dynamical modeling, and other big data techniques to identify early warning signals for outbreaks of rare diseases is an integral part of scientific research on the ecology and evolution of infectious diseases. The Committee recognizes the threat of Emerging Infectious Diseases from animals and urges NIH to support further research in disease mapping and forecasting in order to identify early warning signals for outbreaks of emerging diseases. The Committee expects the fiscal year 2021 budget request to include a progress report on the use of machine learning and validated mechanistic models to advance critical biomedical research, improve decision support for epidemiological interventions and enhance human health.

### **Threat of Emerging Infectious Diseases (House)**

The usage of machine learning, data-driven dynamical modeling, and other big data techniques, to identify early warning signals for outbreaks of rare diseases, is an integral part of scientific research on the ecology and evolution of infectious diseases. The Committee recognizes the threat of Emerging Infectious Diseases (EID) from animals and urges NIH to support further research in disease mapping and forecasting in order to identify early warning signals for outbreaks of emerging diseases. The Committee directs NIH to include a progress report on the use of machine learning and validated mechanistic models to advance critical biomedical research, improve decision support for epidemiological interventions, and enhance human health in the fiscal year 2021 Congressional Justification.

### **Action taken or to be taken:**

The in-house scientists at the NIH Fogarty International Center use mathematical modeling, integrating large-scale demographic, economic, environmental and geographic datasets to analyze, visualize and better understand the disease dynamics of epidemics with implications for U.S. health. Fogarty scientists have recently modeled the global migration of emerging viral threats, including Ebola, Zika and influenza, and their potential for causing large outbreaks in the U.S. Fogarty scientists are also using machine-learning based regression model fitting and validation methods developed for internet-based surveillance to monitor open-source internet data streams such as search queries, social media and internet newswire data to detect epidemic onset, trajectory, peak and other aspects of disease dynamics earlier than traditional public health surveillance methods.

The National Institute of Allergy and Infectious Diseases (NIAID), through its Centers of Excellence for Influenza Research and Surveillance program, is supporting the use of computer modeling to evaluate the dynamics of influenza virus transmission. In addition, researchers in the NIAID-supported International Centers for Excellence in Malaria Research program are utilizing mathematical modeling to assess the impact of interventions on malaria transmission.

### **Traumatic Brain Injury (House)**

The Committee understands that regenerative medicine, including the use of adult stem cells and neuroplasticity may play an important role in developing treatment of Traumatic Brain Injury (TBI). The Committee strongly encourages NINDS to work with all relevant parts of NIH, including NIA, to support a robust and coordinated portfolio of TBI research that explores all promising avenues to facilitate functional repair of damaged circuitry in TBI, including research on regenerative medicine and neuroplasticity. The Committee requests an update in the fiscal year 2020 Congressional Justification on efforts in these specific areas of TBI research.

#### **Action taken or to be taken:**

Basic research on neuroplasticity, stem cells, and regenerative medicine has opened several avenues to understand how the brain recovers after TBI and how that process might be enhanced. NINDS leads NIH TBI research and coordinates with several NIH Institutes and Centers that are exploring opportunities in regenerative medicine. The NIH-wide Regenerative Medicine Innovation Project has boosted this field of research and cross-fertilization.

A variety of cellular processes are set in motion after brain injury that lead to recovery of function to a variable extent. Research in stroke and TBI animal models has demonstrated that the generation of new nerve cells, neurogenesis, and their movement into the region of injury contributes to self-repair. Return of function occurs primarily by rewiring of remaining brain circuits to take on new functions. This neuroplasticity contributes to recovery via establishment of new connections between different brain regions. Neuroplasticity may also go awry, for example by contributing to the development of post-traumatic epilepsy. NINDS is currently supporting a major national study to understand how seizures develop after TBI. NIH research to better understand neuroplasticity following TBI, includes studies of how uninjured movement control regions of the brain reorganize following injury, how TBI triggers neurogenesis, what regulatory pathways interfere with spontaneous regeneration, which changes increase risk for later dementia, and how TBI disrupts the normal balance of excitation and inhibition in the brain.

NIH research across multiple Institutes is building on advances in stem cell biology and neurogenesis to develop interventions that improve outcomes from TBI. Current candidate therapies, mostly at various stages of testing in laboratory animals, are testing small molecule drugs, gene transfer, or biologics to stimulate neurogenesis in the damaged brain's own neuronal precursor cells, brain cells that are capable of generating new cells. Other research is attempting to stimulate glial cells, the versatile non-neuronal supporting cells of the brain, to repair white matter damage or reprogram to replace lost nerve cells, and to understand how plasticity of brain blood vessels, or the lack thereof, may affect recovery. Various transplantation strategies employ stem cells, cells derived from stem cells, or membrane bound portions of stem cells that can release beneficial substances. Hydrogels and other engineered biomaterials enhance survival and integration of transplanted cells. NINDS is currently funding a Phase 2 clinical trials using bone marrow derived cells to help preserve injured brain tissue in children with severe TBI.

The National Center for Medical Rehabilitation Research, which is within the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), coordinates NIH rehabilitation research, which also relies on brain plasticity. Ongoing projects supported by NIH Institutes, including NIA, are designed to optimize the plasticity that underlies TBI recovery using behavioral interventions, virtual reality, brain machine interfaces, exercise, and enhancing behavioral training with drugs or electrical stimulation.

Beyond neuroplasticity and regenerative medicine, NINDS also collaborates extensively on TBI research with other NIH Institutes and Centers. Recent examples include a workshop and joint initiatives on pediatric concussion with NICHD, joint initiatives on TBI and dementia with NIA, and a focus on concussion within the NIDA and NIAAA led Longitudinal Study of Adolescent Brain Cognitive Development (ABCD Study).

### **Traumatic Brain Injury (Senate)**

The Committee is aware that TBI and post-traumatic stress disorder [PTSD] continue to pose significant health challenges for many individuals in the United States, and that these medical conditions especially affect combat veterans. The Committee directs NIH to enhance its research efforts on alternative treatment methods for PTSD and TBI, including hyperbaric oxygen treatment [HBOT]. The Committee encourages NIH to partner with VA and DOD to research treatment alternatives such as HBOT for veterans living with PTSD and/or TBI.

#### **Action taken or to be taken**

NIH supports extensive research to understand the underlying causes of and to develop treatments for traumatic brain injuries (TBI) and post-traumatic stress disorder (PTSD), including research on TBI and PTSD among military personnel and veterans. The National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Mental Health (NIMH) lead NIH research on TBI and on PTSD, respectively. NINDS supports, for example, a study of long-term brain imaging and clinical outcomes of concussive TBI sustained during deployment of military personnel, and NIMH research is investigating suicide risk prevention strategies for combat veterans. Because of the multi-faceted nature of TBI and PTSD and the variety of potential treatment strategies, several other parts of NIH also support research. For example, the National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) support research on the intersection of PTSD with substance and alcohol use disorders and on behavioral treatments, including studies in veterans. The National Center for Complementary and Integrative Health (NCCIH) supports research on mindfulness training, hypnosis, and meditation for veterans, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development's National Center for Medical Rehabilitation Research supports research on the use of service dogs for military veterans with PTSD and their spouses. Similarly, in addition to research on drugs, cell, and device strategies for treatment for TBI, NIH supports research on cognitive and behavioral therapies, exercise, computer-mediated communications support, virtual reality-based rehabilitation, and other interventions.

In 2013, the DOD, VA, Department of Education, and the Department of Health and Human Services, with NIH participation, released the National Research Action Plan (NRAP) for TBI, PTSD, and other co-occurring mental health conditions. Since then, NIH has continued to coordinate research with the DOD, VA, and other agencies. NINDS convened the scientific community and other agencies to develop Common Data Elements (CDEs) to facilitate sharing of data, and NIH and DOD co-lead the Federal Interagency TBI Research (FITBIR) Informatics System, which uses these CDEs. NIH and DOD have overseen the alignment of large natural history studies in TBI (TRACK-TBI) and PTSD (AURORA) via FITBIR. Because discriminating PTSD and TBI symptoms and their interactions is quite complex, the NIH has worked with the VA to provide funding opportunities to probe existing Electronic Health Records to inform understanding of comorbidity of TBI and PTSD better. NIH also funds multiple VA researchers to investigate TBI/PTSD and outcomes. In addition to collaborations

with other Federal agencies on TBI, NIH and DOD work through the International Initiative for TBI Research (InTBIR) with the European Commission, the Canadian Institutes of Health Research, and One Mind, a non-governmental organization.

As in other areas of TBI and PTSD research, NIH research on hyperbaric oxygen treatment (HBOT) complements studies by other agencies, notably including recent clinical trials on HBOT that DOD has conducted. NINDS has supported clinical trials on HBOT for TBI in the past, and the Institute is currently supporting the multicenter Hyperbaric Oxygen Brain Injury Treatment (HOBIT) trial. The HOBIT trial is designed to determine what hyperbaric oxygen dose schedule is most effective for patients with severe TBI without producing toxicity and clinical complications that can occur with hyperbaric oxygen.

## Trisomy 21

The Committee commends NIH for its support of the Investigation of Co-Occurring Conditions Across the Lifespan to Understand Down Syndrome (INCLUDE) Initiative. The Committee includes no less than \$60,000,000 within the Office of the Director for the INCLUDE Initiative, an increase of \$22,000,000 above the expected fiscal year 2019 funding level. The Committee expects that this multi-year, trans-NIH research initiative may yield scientific discoveries that could significantly improve the health and quality of life of individuals with Down syndrome as well as millions of typical individuals.

### **Action Taken or to be Taken**

In June 2018, a trans-NIH effort was launched: INvestigating Co-occurring conditions across the Lifespan to Understand Down syndrome, or INCLUDE. In its first year (FY 2018), over \$22 million was spent on projects under this new initiative alone. The FY 2019 awards totaling approximately \$35 million were made in September 2019. Combined with increased baseline funding, overall NIH funding for Down syndrome (DS) research rose to \$77 million.<sup>265</sup>

Research conducted under the INCLUDE project is investigating conditions that affect both individuals with DS and the general population, such as Alzheimer’s disease (AD)/dementia, autism, cataracts, celiac disease, and congenital heart defects. Applying the expertise and resources from multiple NIH Institutes and Centers, INCLUDE will:

- Conduct* targeted, high-risk, high-reward basic science studies on chromosome 21.
- Assemble* a large study population (cohort) of individuals with DS.
- Include* individuals with DS in new and existing clinical trials.

To give just a few examples, from the first round of awards, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is funding a project to create a cohort of infants with DS. Data from this project will be used to investigate co-occurring autism, provide details about cardiovascular and other potential physical health characteristics, and conduct future analyses on individual samples, including genetic analyses. Another study will develop and test the feasibility and accuracy of a home-based sleep assessment tool to diagnose obstructive sleep apnea in adolescents with DS, a condition that many families cite as having a major impact on quality of life and learning. The National Institute on Aging (NIA) is developing a DS module for its Alzheimer’s centers, and building an AD-DS clinical trials network. In addition, two major scientific workshops will coalesce the DS scientific community around the goals of INCLUDE. The first, held in September 2019, fostered discussions on how to “knit together” many datasets on DS to develop a large cohort to benefit the research community, and the second, which will take place in the spring of 2020, will focus on how to include people with DS in clinical trials.

NIH continues to fund a wide range of research related to Down syndrome, across many of the Institutes and Centers, coordinating their efforts through the trans-NIH Down Syndrome

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<sup>265</sup> <https://www.nih.gov/include-project/funding>

Working Group. For example, NICHD is partnering with NIA on a major project – over \$30 million – on DS and AD, known as the ABC-DS study. One of the studies, which has almost completed initial enrollment of nearly 450 adults with Down syndrome across 7 different sites, is poised to uncover the biological signature of Alzheimer’s disease in those with Down syndrome, who are predisposed to develop the condition at an early adult age.

NICHD is also taking on the issue of inclusion of people with Down syndrome in clinical trials, supporting its established Pediatric Trials Network (PTN) in efforts to add children with DS to their trials aimed at determining optimal pediatric dosing. In addition, a training program is being developed that will engage the expertise of researchers who work in Down syndrome to provide training and best practices for PTN site investigators about unique aspects of clinical care and consent for children with Down syndrome. These and other clinical trials have frequently had success in recruiting participants with DS through the NICHD-sponsored DS-Connect®, a Web-based health registry that serves as a national health resource for people with Down syndrome and their families, researchers, and health care providers. As of September 2019, over 4,700 participants have registered.

NIH continues to actively engage the broader DS community through the Down Syndrome Consortium, a public-private group that includes the Trans-NIH DS Working Group, 13 national and international organizations whose missions focus on Down syndrome, and individuals with Down syndrome and family members. The consortium also works toward implementing and updating the 2014 NIH Research Plan on Down Syndrome,<sup>266</sup> which sets research goals for Down syndrome.

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<sup>266</sup> <https://www.nichd.nih.gov/publications/product/441>

### **Undiagnosed Disease Network**

The Committee continues to support the work of the Undiagnosed Diseases Network (UDN) and urges the UDN to continue efforts to enhance access to patients, caregivers, and other stakeholders as well as make information obtained through the UDN available to other Federal agencies.

#### **Action taken or to be taken:**

The NIH appreciates Congress' interest in the UDN and has recently taken steps to enhance access to this program. In 2018, the UDN program was renewed for a second phase with the intention of expanding the network's geographic reach and developing a plan for the network's sustainability. NIH Common Fund support for the network concludes in 2023 after the maximum 10 years of Common Fund support. The network now contains 12 clinical sites (there were 7 sites previously), 2 model organisms screening centers (1 site previously), a biorepository, a metabolomics core (new), a DNA sequencing core, and a coordinating center.

Disseminating research is an important component of the UDN. As of September 2019, the UDN has published 72 research manuscripts; submitted 326 entries to ClinVar, a public database that collects information about the clinical significance of genetic variants; submitted the data of 450 study participants to the NIH database of Genotypes and Phenotypes (dbGaP), which is an archive of research data from other NIH-funded studies for the purpose of enabling secondary research; and submitted 1,045 participants' information to PhenomeCentral, an international data repository for researchers investigating rare diseases. These databases are easily accessible for researchers and clinicians seeking to use UDN data for further research or diagnose other patients.

As opportunities arise, UDN will collaborate with Federal agencies to share findings and build upon the work of the network to enhance the long-term sustainability of the UDN as a national resource.

## Women and Lung Cancer

Committee notes that lung cancer has a disparate impact on women, particularly younger women who have never smoked. Additional research strategies are needed to explore the differences in women with respect to lung cancer risk factors, incidence, and histology. The Committee urges NCI to accelerate research into treatments and implementation of lung cancer preventive services for women. The Committee requests an update on these activities in the fiscal year 2021 Congressional Justification.

### **Action taken or to be taken:**

Research on gender-related differences in lung cancer risk factors, incidence, histology, and mortality remains a priority for NCI. In 2019, NCI launched the *Sherlock-lung* study, a comprehensive genomic epidemiologic study of lung cancer in never smokers.<sup>267</sup> Previous research has shown that approximately 20 percent of women who have never smoked develop lung cancer compared with about 9 percent of nonsmoking men. This difference is further accentuated in Asian populations, where 60 to 80 percent of women with lung cancer have never smoked.<sup>268</sup> In *Sherlock*, genomic and other molecular data will be analyzed to identify processes involved in lung tumorigenesis, and these data will be combined with histologic and imaging features to develop a more refined classification of lung cancer in never smokers and provide insights into prognosis and treatment strategies.

In addition, other research has shown that there are gender-specific differences in lung cancer histology and biology that might be due to gender-specific differences in susceptibility to certain molecular alterations caused by smoking or other carcinogens.<sup>269</sup> Research has also suggested that the female hormone estrogen and/or its metabolites may influence the histologic and molecular features of lung cancer and may explain some of the observed intergender differences in these characteristics. For example, in 2017, NCI-funded researchers determined that the level of the estrogen metabolite 4-hydroxyestrogen (4-OHE), a putative carcinogen, is higher in the tumor tissue of never-smoking women than in the surrounding normal lung tissue and is elevated in the normal lung tissue of current smoking women compared with never-smoking women.<sup>270</sup> These findings and others suggest that changes in estrogen metabolism in the lung during tumorigenesis may contribute to the risk conferred by smoking, sex, or race/ethnicity.

Currently, NCI has three active R01 grants that are exploring the relationship between estrogen and its metabolites and lung cancer in never smokers.<sup>271</sup> Additional research has shown that the uptake of lung cancer screening among eligible individuals in the United States remains

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<sup>267</sup> <https://dceg.cancer.gov/research/cancer-types/lung/sherlock-lung-study>

<sup>268</sup> <https://www.uptodate.com/contents/lung-cancer-in-never-smokers>

<sup>269</sup> Some data indicate that women with lung cancer have reduced DNA repair capacity, regardless of smoking status, and differences in tobacco carcinogen metabolism.

<sup>270</sup> <https://www.ncbi.nlm.nih.gov/pubmed/29290988>

<sup>271</sup> [https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9653154&icde=47488256;](https://projectreporter.nih.gov/project_info_description.cfm?aid=9653154&icde=47488256;)

[https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9477685&icde=47488296;](https://projectreporter.nih.gov/project_info_description.cfm?aid=9477685&icde=47488296;)

[https://projectreporter.nih.gov/project\\_info\\_description.cfm?aid=9606459&icde=47108635](https://projectreporter.nih.gov/project_info_description.cfm?aid=9606459&icde=47108635)

exceedingly low, and a 2019 analysis<sup>272</sup> of data from NCI’s Health Information National Trends Survey (HINTS) indicates that more needs to be done to develop communication strategies to promote screening among eligible smokers. Implementing these strategies is of particular importance for women because recent follow-up data from NCI’s National Lung Screening Trial (NLST) and the European NELSON trial have demonstrated that the mortality benefit from lung cancer screening is substantially higher for women than for men.<sup>273</sup>

Finally, since 80 percent of lung cancers among women can be attributed to smoking, NCI’s ongoing efforts to reduce the uptake and use of tobacco are paramount in female lung cancer prevention. This includes supporting *Smokefree Women* as part of the larger Smokefree.gov website.<sup>274</sup> Women face unique challenges when quitting smoking, and the women.smokefree.gov site addresses these challenges by providing information and tools that specifically address women’s experiences as they become smokefree.<sup>275</sup> The site has information about common issues for female smokers, such as concerns about weight gain, getting support while quitting, relationship changes, or how to quit while pregnant. It also offers customized tools like the SmokefreeMOM text message program for pregnant smokers.<sup>276</sup> Overall, the Smokefree.gov initiative offers information, resources, and support to help all smokers quit—wherever they are on their quit journey.

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<sup>272</sup> <https://www.ncbi.nlm.nih.gov/pubmed/31023697>

<sup>273</sup> <https://www.ncbi.nlm.nih.gov/pubmed/31260833> and <https://www.ascopost.com/issues/october-25-2018/nelson-trial/>

<sup>274</sup> <https://smokefree.gov>

<sup>275</sup> <https://women.smokefree.gov>

<sup>276</sup> <https://women.smokefree.gov/tools-tips-women/text-programs/smokefreemom>

## Women in Research

### Women in Research (House)

Women represent half of the U.S. population. As such, conditions and diseases that are specific to women's health, or those that present differently in women than men, must be a priority for Federally-funded research. The Committee encourages the NIH, under the leadership of the Office of Research on Women's Health and the NICHD, to do the following: report on the total dollar amount of research invested in health conditions specific to women over the last ten years, including but not limited to pregnancy, gynecologic oncology, and infertility; provide a list of which Institutes provide the highest amount of funding toward health research on conditions specific to women; and report on how and whether funding for research in this area is coordinated across the NIH. The Committee looks forward to a report from the NIH in the fiscal year 2020 Congressional Justification.

### Women's Health Research (Senate)

Women represent half of the U.S. population. As such, conditions and diseases that are specific to women's health, or those that present differently in women than men, must be a priority for federally-funded research. The Committee encourages NIH, under the leadership of the Office of Research on Women's Health and NICHD, to: (1) report on the total dollar amount of research invested in health conditions specific to women over the last 10 years, including but not limited to pregnancy, gynecologic oncology, and infertility; (2) provide a list of which Institutes provide the highest amount of funding toward health research on conditions specific to women; and (3) report on how and whether funding for research in this area is coordinated across the NIH. The Committee looks forward to a report from NIH in the fiscal year 2021 CJ.

### Action taken or to be taken:

#### **Total Investment in Women's Health-Related Research, FY 2008 – FY 2018**

Table 1 shows the annual dollar amount invested in women's health-related research from FY 2008 to FY 2018 according to funding statistics documented annually by the NIH Research, Condition, and Disease Categorization (RCDC) system<sup>277</sup>. The Institute with the highest dollar amount investment is the National Cancer Institute (NCI). The Institutes with the next four highest overall investments during this time period are: the National Heart, Lung, and Blood Institute (NHLBI); the National Institute of Diabetes and Digestive and Kidney Diseases

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<sup>277</sup> The NIH Research, Condition, and Disease Categorization (RCDC) system uses sophisticated text data mining (categorizing and clustering using words and multiword phrases) in conjunction with NIH-wide definitions used to match projects to categories. RCDC use of data mining improves consistency and eliminates the wide variability in defining the research categories reported. The definitions are a list of terms and concepts selected by NIH scientific experts to define a research category. The research category levels represent the NIH's best estimates based on the category definitions.

(NIDDK); the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD); and the National Institute on Aging (NIA).

### **Research Investment in Diseases and Conditions Specific to or Predominately Affecting Women, FY 2008 – FY 2018**

Table 2 shows total annual investments tracked in the official NIH RCDC system for diseases and conditions specific to or predominately affecting women, by year from FY 2008 to FY 2018. Diseases and conditions specific to women are displayed in the top 11 rows, and those that predominately affect women but also affect men to a lesser extent are identified in the bottom 13 rows.

For each of the diseases and conditions listed in Table 2, Table 3 shows the top five NIH Institutes and Centers (ICs) in terms of the amount invested in these diseases and conditions specific to or predominately affecting women (FY 2016 – FY 2018). The highest-investing IC is given in the ‘1st’ column of Table 3, with the next four ICs listed in descending order. IC rankings for all but three of the diseases and conditions are based on average funding from FY 2016 to FY 2018. The rankings for (i) Breastfeeding, Lactation, and Breastmilk; (ii) Maternal Health; and (iii) Pregnancy are based on funding from FY 2017 to FY 2018, because these three categories were newly added in FY 2017.

### **Coordination of Research on Health Conditions Specific or Related to Women across the NIH**

The Office of Research on Women’s Health (ORWH) is the focal point for coordinating women’s health research across NIH. The Director of ORWH chairs the NIH Coordinating Committee on Research on Women’s Health (CCRWH), which is composed of the NIH Institute, Center, and Office (ICO) Directors or their senior-level designees. The CCRWH is charged with coordinating women’s health research efforts and priorities NIH-wide. The ORWH Director and the ICO Directors also collaborate on the identification of research gaps and emerging opportunities in women’s health research. However, IC Directors are the ultimate decision makers on how much of the ICs’ budgets are allocated to biomedical research on diseases and conditions specific to women.

The NIH Advisory Committee on Research on Women’s Health (ACRWH) is a chartered committee that was established by the 1993 NIH Revitalization Act.<sup>278</sup> This committee is comprised of a wide range of experts from the external scientific community appointed by the NIH Director. Their charge is to advise the ORWH Director on priorities, gaps, and opportunities in research that is focused on the health of women. The ACRWH publishes a biennial report,<sup>279</sup> which details women’s health research programs and advances across NIH. The biennial report also includes information on NIH budget allocations for diseases and conditions specific to women, as well as data on the inclusion of women and minorities in NIH-funded clinical research.

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<sup>278</sup> Public Law 103-43, Sec. 486.

<sup>279</sup> <https://orwh.od.nih.gov/research/funded-research-and-programs/research-reports/biennial-report>.

As mandated by the 21st Century Cures Act,<sup>280</sup> each IC must include details on how it will account for women and reduce health disparities for women within its IC-specific strategic plan.<sup>281</sup> Recently, the NIH implemented a *2019-2023 Trans-NIH Strategic Plan for Research on Women's Health*<sup>282</sup> as a framework for scientific planning within the ICs, and for coordinating women's health research priorities across the NIH. This strategic plan emphasizes the importance of taking a life course approach in research to improve the health of girls and women.

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<sup>280</sup> Public Law 114-255, Sec. 2031.

<sup>281</sup> IC-specific strategic plans are available at <https://report.nih.gov/strategicplans/>.

<sup>282</sup> [https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH\\_Strategic\\_Plan\\_2019\\_02\\_21\\_19\\_V2\\_508C.pdf](https://orwh.od.nih.gov/sites/orwh/files/docs/ORWH_Strategic_Plan_2019_02_21_19_V2_508C.pdf).

**Table 1: NIH total investment in Women’s Health-Related Research<sup>(1)</sup>, FY 2008 – FY 2018**

<b>Fiscal Year</b>	<b>Total NIH investment tracked by RCDC Women’s Health Research category (dollars in millions)</b>	<b>Top five Institutes/Centers funding support levels in RCDC Women’s Health Research category (in descending order)</b>
2008	\$3,514	NCI, NIDDK, NHLBI, NICHD, NINDS
2009 <sup>(2)</sup>	\$3,725	NCI, NIDDK, NHLBI, NICHD, NIDA
2010 <sup>(2)</sup>	\$3,691	NCI, NICHD, NHLBI, NIDDK, NIDA
2011	\$3,891	NCI, NHLBI, NICHD, NIDDK, NIA
2012	\$3,833	NCI, NHLBI, NICHD, NIDDK, NIA
2013	\$3,745	NCI, NHLBI, NIDDK, NICHD, NIA
2014	\$3,935	NCI, NHLBI, NIDDK, NICHD, NIA
2015	\$3,989	NCI, NHLBI, NIA, NIDDK, NICHD
2016	\$4,540	NCI, NIA, NHLBI, NIDDK, NICHD
2017	\$4,769	NCI, NIA, NHLBI, NIDDK, NICHD
2018	\$5,048	NCI, NIA, NHLBI, NIDDK, NICHD

Data Source: NIH RCDC Budget Estimating Tool (RBET) Data Repository.

- (1) Includes diseases that are specific to or that predominately affect women, as well as conditions that have an impact on both sexes, however, with a specific focus on the female population.
- (2) The reported amount excludes American Recovery and Reinvestment Act (ARRA) funds. ARRA associated women’s health research spending was \$506 million in FY 2009 and \$449 million in FY 2010, respectively.

**Table 2: NIH total investments from RCDC tracked diseases and conditions specific to women or predominately affecting women (in millions of dollars): FY 2008 – FY 2018<sup>(1)</sup>**

Disease Category	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2008-2018 Total <sup>(5)</sup>
Diseases and conditions specific to women												
Breast Cancer	726	722	763	715	800	657	682	674	656	689	721	7,805
Ovarian Cancer	96	102	122	138	147	133	131	118	144	151	159	1,441
Cervical Cancer	69	84	93	119	112	98	116	99	99	114	112	1,115
Maternal Health <sup>(3)</sup>	--	--	--	--	--	--	--	--	--	249	303	552
Uterine Cancer	16	25	26	40	42	39	57	52	50	45	47	439
Violence Against Women	45	39	36	34	36	31	35	31	30	30	32	379
Fibroid Tumors (Uterine)	16	18	12	12	14	10	9	10	12	11	13	137
Endometriosis	15	15	15	14	9	7	7	10	10	6	7	115
Vaginal Cancer	--	--	--	--	8	7	7	6	5	5	12	50
Pelvic Inflammatory Disease	3	3	4	4	3	3	2	4	3	2	7	38
Vulvodynia	--	1	2	2	4	4	3	2	2	1	2	23
Diseases and conditions predominately affect women <sup>(2)</sup>												
Breastfeeding, Lactation and Breast Milk <sup>(3)</sup>	--	--	--	--	--	--	--	--	--	92	77	169
Pregnancy <sup>(3)</sup>	--	--	--	--	--	--	--	--	--	319	419	738
Teenage Pregnancy	21	23	22	19	18	17	16	14	14	14	17	195
Estrogen	245	235	231	227	221	218	203	194	205	220	230	2,429
Rett Syndrome	9	9	13	12	13	13	12	12	14	15	16	138
Interstitial Cystitis	10	11	12	13	10	10	9	10	9	10	13	117
Lupus	126	115	112	106	108	92	99	90	97	109	123	1,177
Osteoporosis	183	198	181	179	181	164	141	146	141	139	152	1,805
Scleroderma	20	21	19	25	24	21	24	22	18	17	23	234
Chronic Fatigue Syndrome (ME/CFS)	4	5	6	6	5	5	5	6	8	15	14	79
Rheumatoid Arthritis <sup>(4)</sup>	--	--	--	--	--	--	--	59	91	93	92	335
Fibromyalgia	12	11	9	11	13	11	10	8	11	14	14	124
HPV and/or Cervical Cancer Vaccines	19	25	25	24	26	25	38	31	38	59	37	347

Data Source: RePORT- Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC) summary table at [https://report.nih.gov/categorical\\_spending.aspx](https://report.nih.gov/categorical_spending.aspx).

- (1) The research categories are not mutually exclusive. Individual projects can be included in multiple categories. Therefore, amounts presented within each column do not add up to 100% of NIH-funded research.
- (2) Rankings of diseases/conditions that predominately affect women based on scientific relevance and disease prevalence, in descending order.
- (3) RCDC categories introduced in FY 2017.
- (4) RCDC category introduced in FY 2015.
- (5) Amount not adjusted for cumulative effect of inflation from FY 2008 through FY 2018.

**Table 3: Top five NIH Institutes and Centers in terms of amount invested in diseases and conditions specific to or predominately affecting women, in descending order<sup>(1)</sup>**

Disease Category	1st	2nd	3rd	4th	5th
Diseases and conditions specific to women					
Breast Cancer	NCI	NIEHS	NIGMS	NIBIB	NIMHD
Ovarian Cancer	NCI	NIGMS	NCATS	NIBIB	NHGRI
Cervical Cancer	NCI	NIAID	NICHD	NIMHD	NIBIB
Maternal Health <sup>(1)</sup>	NICHD	NHLBI	NIMH	NIAID	NIEHS
Uterine Cancer	NCI	NHGRI	NIEHS	NICHD	NIGMS
Violence Against Women	NICHD	NIAAA	NIDA	NIMH	OD
Fibroid Tumors (Uterine)	NIEHS	NICHD	NIMHD	NCCIH	NCI
Endometriosis	NICHD	NIEHS	NCCIH	NCI	NINDS
Vaginal Cancer	NCI	NIAID	NICHD	FIC	(3)
Pelvic Inflammatory Disease	NIAID	NINR	NICHD	NIGMS	OD
Vulvodynia	NICHD	NIDDK	NIGMS	NIAID	(3)
Diseases and conditions predominately affect women <sup>(2)</sup>					
Breastfeeding, Lactation and Breast Milk <sup>(1)</sup>	NICHD	NIDDK	NIAID	NIEHS	OD
Pregnancy <sup>(1)</sup>	NICHD	OD	NIEHS	NHLBI	NIAID
Teenage Pregnancy	NICHD	NIDA	NINR	NIGMS	NIMH
Estrogen	NCI	NIEHS	NIA	NICHD	NHLBI
Rett Syndrome	NINDS	NIMH	NICHD	NCATS	NHLBI
Interstitial Cystitis	NIDDK	NIA	OD	NCI	NCCIH
Lupus	NIAMS	NIAID	NHLBI	NIEHS	NIGMS
Osteoporosis	NIAMS	NIA	NHGRI	NIDDK	NIDCR
Scleroderma	NIAMS	NHLBI	NHGRI	NIAID	NEI
Chronic Fatigue Syndrome (ME/CFS)	NIAID	NINDS	OD	NINR	NHLBI
Rheumatoid Arthritis	NIAMS	NHGRI	NIAID	NHLBI	NIGMS
Fibromyalgia	NIAMS	NCCIH	NINDS	NIDA	NINR
HPV and/or Cervical Cancer Vaccines	NCI	NIAID	NIMHD	NICHD	NIGMS

Data Source: RePORT- Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC) summary table at [https://report.nih.gov/categorical\\_spending.aspx](https://report.nih.gov/categorical_spending.aspx).

- (1) Institute and Center rankings for disease categories are based on average funding from FY 2016 – FY 2018, except for Breastfeeding, Lactation and Breastmilk; Maternal Health; and Pregnancy, which were new categories in FY 2017.
- (2) Ranking of diseases and conditions that predominately affect women are based on scientific relevance and disease prevalence, in descending order.
- (3) Only four ICs provided funding in this category.