TABLE OF CONTENTS

ACADEMIC RESEARCH ENHANCEMENT AWARD ................................................................. 7
ADMINISTRATIVE BURDENS IN GRANT PREPARATION .................................................. 9
ADULT STEM CELL TECHNOLOGY .................................................................................. 10
AGE-RELATED MACULAR DEGENERATION ....................................................................... 12
ALCOHOL'S ROLE IN OPIOID OVERDOSE ...................................................................... 14
ALOPECIA AREATA .............................................................................................................. 16
ALZHEIMER'S DISEASE AND VASCULAR DEMENTIA ..................................................... 17
ALZHEIMER'S DISEASE DISPARITIES ............................................................................. 19
ALZHEIMER'S DISEASE .................................................................................................... 21
ALZHEIMER'S DISEASE .................................................................................................... 23
AMYLOIDOSIS .................................................................................................................... 28
ANGELMAN SYNDROME ................................................................................................... 29
AUDACIOUS GOALS INITIATIVE ..................................................................................... 31
AVERAGE COST OF NIH GRANTS .................................................................................... 33
BARRIERS TO RESEARCH ............................................................................................... 34
BIODEVICES ...................................................................................................................... 36
BIOMARKERS .................................................................................................................... 37
BIOMEDICAL RESEARCH FACILITIES ......................................................................... 39
BLEPHAROSPASM ............................................................................................................ 40
BRAIN INITIATIVE ............................................................................................................ 41
BRAIN RESEARCH THROUGH ADVANCING INNOVATIVE NEUROTECHNOLOGIES [BRAIN] INITIATIVE .......................................................................................... 42
BSL-4 LABORATORY .......................................................................................................... 44
CAREGIVER DEMENTIA INITIATIVE ............................................................................... 45
CEREBRAL PALSY ............................................................................................................. 46
CHILDHOOD CANCER STAR ACT ................................................................................ 48
CHILDREN’S ONCOLOGY GROUP .................................................................................. 49
CHRONIC FATIGUE SYNDROME .................................................................................... 50
CHRONIC OVERLAPPING PAIN CONDITIONS ............................................................... 52
CLINICAL AND TRANSLATIONAL SCIENCE AWARDS .......................................................... 53
CARB .................................................................................................................................. 55
COLLABORATION BETWEEN AGENCIES REGARDING PEDIATRIC
INVESTIGATION OF APPROPRIATE NEW DRUGS .......................................................... 57
COLORECTAL CANCER ....................................................................................................... 58
CONGENITAL HEART DISEASE ........................................................................................ 60
CYSTIC FIBROSIS ............................................................................................................. 62
DATA SHARING OF RARE DISEASES RESEARCH .......................................................... 63
DEADLIEST CANCERS ...................................................................................................... 65
DEPARTMENT OF ENERGY [DOE] COLLABORATION ..................................................... 68
DIABETES .......................................................................................................................... 69
DIVERSITY IN ONCOLOGY ............................................................................................... 71
DUAL PURPOSE WITH DUAL BENEFIT PROGRAM (SENATE) ....................................... 72
DUCHENNE MUSCULAR DYSTROPHY ........................................................................... 73
DYSTONIA .......................................................................................................................... 75
EATING DISORDER RESEARCH ...................................................................................... 76
ENDOMETRIOSIS ............................................................................................................. 77
END-STAGE RENAL DISEASE ......................................................................................... 79
EPIDERMOLYSIS BULLOSA ............................................................................................. 80
FERTILITY ISSUES FOR RARE DISEASE PATIENTS .................................................... 81
FIBROSIS ............................................................................................................................ 82
FIBROTIC DISEASES .......................................................................................................... 83
FOCAL SEGMENTAL GLOMERULOSCLEROSIS RESEARCH ........................................... 85
FOOD ALLERGIES ............................................................................................................ 86
FOOD IS MEDICINE .......................................................................................................... 88
FRAGILE X ........................................................................................................................ 89
FRONTOTEMPORAL DEGENERATION ............................................................................ 92
GABRIELLA MILLER KIDS FIRST RESEARCH ACT ...................................................... 94
GASTRIC CANCER ............................................................................................................ 96
GENERAL CARDIAC RESEARCH .................................................................................... 98
GESTATIONAL DIABETES ................................................................................................. 100
GLAUCOMA ............................................................................................................................ 102
GOVERNMENT-WIDE COLLABORATIONS ................................................................. 103
GYNECOLOGIC CANCER CLINICAL TRIALS ......................................................... 105
HEADACHE DISORDERS ......................................................................................... 107
HEALTHY BRAIN AGING ....................................................................................... 109
HEART DISEASE ......................................................................................................... 111
HEAVY ION CANCER THERAPY AND RESEARCH ............................................... 113
HEMOGLOBINOPATHIES ......................................................................................... 114
HEPATITIS B ................................................................................................................... 116
HEPATITIS B (NIMHD) ............................................................................................... 117
HEPATITIS B VIRUS ...................................................................................................... 118
HEPATITIS B VIRUS (NIMHD) ................................................................................... 120
HEREDITARY HEMORRHAGIC TELANGIECTASIA ........................................ 121
IMPROVING PATIENT ACCESS TO CANCER CLINICAL TRIALS .................. 122
IMPROVING THE TREATMENT OF MENTAL ILLNESS ....................................... 124
INCREASING DIVERSITY IN CLINICAL TRIALS ............................................... 126
INDUCED PLURIPOTENT STEM CELL TECHNOLOGY ......................................... 128
INFLAMMATORY BOWEL DISEASES (HOUSE) ..................................................... 130
IMMUNOTHERAPY ....................................................................................................... 131
INFLAMMATORY BOWEL DISEASES ................................................................... 133
INSTITUTIONAL DEVELOPMENT AWARD .............................................................. 134
INSTITUTIONAL DEVELOPMENT AWARD [IDEA] STATE AND CANCER TRIALS ......................................................................................................................... 137
INTERSTITIAL CYSTITIS .......................................................................................... 139
JOHN E. FOGARTY INTERNATIONAL CENTER ..................................................... 140
LIVER CANCER ........................................................................................................... 141
LONG-TERM AND DEVELOPMENTAL HEALTH EFFECTS OF ZIKA .......... 143
LUPUS ......................................................................................................................... 145
LYMPHANGIOLEIOMYOMATOSIS ........................................................................ 146
LYMPHATIC RESEARCH ........................................................................................... 147
MARIJUANA RESEARCH ......................................................................................... 148
<table>
<thead>
<tr>
<th>Research Area</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic Cancer Research</td>
<td>150</td>
</tr>
<tr>
<td>Microbicides</td>
<td>152</td>
</tr>
<tr>
<td>Mitochondrial Disease Research</td>
<td>154</td>
</tr>
<tr>
<td>Mucopolysaccharide Diseases</td>
<td>156</td>
</tr>
<tr>
<td>National Center for Complementary and Integrative Health</td>
<td>158</td>
</tr>
<tr>
<td>National Chronic Obstructive Pulmonary Disease (COPD) Action Plan</td>
<td>160</td>
</tr>
<tr>
<td>National Commission on Digestive Disease</td>
<td>161</td>
</tr>
<tr>
<td>National Eye Institute 50th Anniversary</td>
<td>162</td>
</tr>
<tr>
<td>Native American Research Centers for Health</td>
<td>164</td>
</tr>
<tr>
<td>Neglected Tropical Diseases</td>
<td>165</td>
</tr>
<tr>
<td>Neonatal Abstinence Syndrome</td>
<td>167</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>169</td>
</tr>
<tr>
<td>Neuromyelitis Optica Spectrum Disorder</td>
<td>172</td>
</tr>
<tr>
<td>Neuroscience Research</td>
<td>174</td>
</tr>
<tr>
<td>Next Generation Researchers Initiative</td>
<td>175</td>
</tr>
<tr>
<td>Non-Addictive Pain Treatments</td>
<td>177</td>
</tr>
<tr>
<td>Office of Cancer Survivorship</td>
<td>179</td>
</tr>
<tr>
<td>Opioid Misuse and Addiction</td>
<td>180</td>
</tr>
<tr>
<td>Opioid Research Centers</td>
<td>183</td>
</tr>
<tr>
<td>Opioid Use Disorders during Pregnancy and Neonatal Abstinence Syndrome</td>
<td>185</td>
</tr>
<tr>
<td>Opioid-Related Infectious Diseases Research</td>
<td>187</td>
</tr>
<tr>
<td>Opioids (HEAL Initiative)</td>
<td>189</td>
</tr>
<tr>
<td>Opioids (HEAL Initiative)</td>
<td>191</td>
</tr>
<tr>
<td>Opioids</td>
<td>193</td>
</tr>
<tr>
<td>Palliative Care</td>
<td>195</td>
</tr>
<tr>
<td>Pancreatic Cancer Research</td>
<td>197</td>
</tr>
<tr>
<td>Parkinson's Disease</td>
<td>199</td>
</tr>
<tr>
<td>Pediatric Kidney Disease</td>
<td>201</td>
</tr>
<tr>
<td>Peripheral Neuropathies</td>
<td>203</td>
</tr>
<tr>
<td>Topic</td>
<td>Page</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>PHELAN-MCDERMID SYNDROME</td>
<td>204</td>
</tr>
<tr>
<td>POPULATION RESEARCH</td>
<td>205</td>
</tr>
<tr>
<td>POPULATION RESEARCH</td>
<td>207</td>
</tr>
<tr>
<td>POST-TRAUMATIC STRESS DISORDER</td>
<td>209</td>
</tr>
<tr>
<td>PRECISION ONCOLOGY</td>
<td>211</td>
</tr>
<tr>
<td>PRENATAL OPIOID USE DISORDERS AND NEONATAL ABSTINENCE SYNDROME</td>
<td>213</td>
</tr>
<tr>
<td>PRE-TERM BIRTH</td>
<td>215</td>
</tr>
<tr>
<td>PROSTATE CANCER</td>
<td>217</td>
</tr>
<tr>
<td>PEDIATRIC RARE CANCER</td>
<td>219</td>
</tr>
<tr>
<td>PSYCHO-SOCIAL DISTRESS COMPLICATIONS</td>
<td>221</td>
</tr>
<tr>
<td>PULMONARY HYPERTENSION</td>
<td>223</td>
</tr>
<tr>
<td>RAISING AWARENESS AND ENGAGING THE MEDICAL COMMUNITY IN DRUG ABUSE AND ADDICTION PREVENTION AND TREATMENT</td>
<td>225</td>
</tr>
<tr>
<td>REHABILITATION RESEARCH</td>
<td>227</td>
</tr>
<tr>
<td>RESEARCH INITIATIVE ON ETHNIC AND RACIAL DIVERSITY IN CANCER</td>
<td>229</td>
</tr>
<tr>
<td>RESEARCH TRANSPARENCY</td>
<td>231</td>
</tr>
<tr>
<td>RURAL HEALTH OUTCOMES AND HEALTH DISPARITIES</td>
<td>233</td>
</tr>
<tr>
<td>SCLERODERMA</td>
<td>235</td>
</tr>
<tr>
<td>SICKLE CELL DISEASE RESEARCH</td>
<td>237</td>
</tr>
<tr>
<td>SICKLE CELL</td>
<td>238</td>
</tr>
<tr>
<td>SLEEP DISORDERS</td>
<td>240</td>
</tr>
<tr>
<td>SLEEP DISORDERS</td>
<td>242</td>
</tr>
<tr>
<td>SPASMODIC DYSPHONIA</td>
<td>244</td>
</tr>
<tr>
<td>SPINA BIFIDA</td>
<td>246</td>
</tr>
<tr>
<td>STROKE RESEARCH</td>
<td>248</td>
</tr>
<tr>
<td>STROKE</td>
<td>250</td>
</tr>
<tr>
<td>SUICIDE PREVENTION AND RISK DETECTION ALGORITHMS</td>
<td>252</td>
</tr>
<tr>
<td>TASK FORCE ON RESEARCH SPECIFIC TO PREGNANT WOMEN AND LACTATING WOMEN</td>
<td>255</td>
</tr>
<tr>
<td>TECHNOLOGY AND OPHTHALMIC DISORDERS</td>
<td>257</td>
</tr>
<tr>
<td>TEMPOROMANDIBULAR DISORDERS</td>
<td>259</td>
</tr>
<tr>
<td>Section</td>
<td>Page</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>TICK-BORNE DISEASES</td>
<td>261</td>
</tr>
<tr>
<td>TRANSFORMATIVE HIGH-RESOLUTION CRYO-ELECTRON MICROSCOPY</td>
<td>263</td>
</tr>
<tr>
<td>TRANSLATIONAL RESEARCH PROGRAM</td>
<td>264</td>
</tr>
<tr>
<td>TRANSLATIONAL RESEARCH</td>
<td>266</td>
</tr>
<tr>
<td>TRANSLATIONAL VACCINE RESEARCH</td>
<td>268</td>
</tr>
<tr>
<td>TRAUMATIC BRAIN INJURY</td>
<td>270</td>
</tr>
<tr>
<td>TRISOMY 21</td>
<td>272</td>
</tr>
<tr>
<td>TUBEROUS SCLEROSIS COMPLEX</td>
<td>274</td>
</tr>
<tr>
<td>UNDIAGNOSED DISEASES</td>
<td>276</td>
</tr>
<tr>
<td>UNIVERSAL INFLuenZA VACCINE</td>
<td>278</td>
</tr>
<tr>
<td>VACCINATION ACCELERATION</td>
<td>280</td>
</tr>
</tbody>
</table>
Academic Research Enhancement Award
The Committee believes that biomedical discoveries can occur anywhere, and continues to support programs that foster biomedical research and opportunities for students at institutions who may not receive significant NIH funding. In particular, the Committee continues its long-standing support of the IDeA program. However, the Committee notes that many institutions that may benefit from the IDeA program are ineligible because they reside in States that are not IDeA States. The Committee encourages NIH to enhance support for the AREA program and is urged to develop ways to improve ties between institutions that receive significant NIH funding and AREA-eligible institutions.

Action taken or to be taken:
NIH appreciates the Committee’s support for the Institutional Development Award (IDeA) program and recognition of the importance of the Academic Research Enhancement Award (AREA) program to support meritorious research, expose students to research, and enhance the research environment at institutions not receiving significant NIH support. NIH will continue to support the both programs and improve ties between NIH-funded institutions through the following initiatives:

- The NIH AREA Program Advisory Committee (APAC), with staff from each NIH Institute and Center, regularly discuss how best to reach out to the AREA-eligible community and to meet their needs. The APAC members regularly address questions from eligible investigators, and the committee chair has made many presentations to AREA universities to directly discuss the program with leadership, professors, and administrators, and to discuss preparing grant applications. In September 2018, the APAC chair made a presentation to grantees of the IDeA Networks of Biomedical Research Excellence (INBRE) program, which is focused on IDeA-eligible states.

- NIH organizes and participates in regional meetings\(^1\) across the country at least once per year to discuss preparing grant applications and developing undergraduate research. Participants learn how to prepare AREA grant applications; receive responses to questions about collaborations, budgets, and scope of projects; and can join networking events held for investigators from AREA institutions.

- NIH staff present at national, professional meetings on topics ranging from grant application writing to time management tips for teaching and research. Of note, this includes the Council on Undergraduate Research, which seeks to enhance and provide undergraduate research opportunities for faculty and students at all institutions serving undergraduate students.

NIH will continue to ensure the success of these programs. NIH aims to build active biomedical research environments in IDeA states and improve access to modern, state-of-the-art biomedical research for students and researchers. Collaborations are encouraged among IDeA research

\(^1\) https://grants.nih.gov/news/contact-in-person/seminars.htm
resource centers when appropriate, as well as between research intensive institutions and AREA universities. This allows NIH to achieve research goals while preserving the goals of the AREA program. For example, investigators can use AREA funds for equipment or involve collaborators at research intensive institutions.

By taking steps such as these, NIH will continue supporting activities across the nation to enhance the competitiveness of AREA-eligible investigators for research. Importantly, NIH will also provide opportunities through these programs for talented undergraduate students to participate in research training and careers in the biomedical sciences.
Administrative Burdens in Grant Preparation
The Committee recognizes that certain administrative tasks are critical to the research process and applauds the NIH's efforts to identify and reduce sources of administrative burden for researchers. The Committee encourages NIH to identify additional ways to enable researchers to spend more productive time working on science, rather than applying for and reporting on grants. The Committee notes that the modular budget cap has not increased with inflation, and that grant applications with necessary costs above the modular budget cap incur additional administrative responsibilities. The Committee requests an update from NIH in the fiscal year 2020 CJ regarding the effect of modular budget cap increases on reducing administrative burdens while maintaining appropriate fiscal oversight of grant costs.

Action taken or to be taken:

We appreciate the interest in increasing the modular budget cap. Since 1999, NIH has required the use of the modular budget cap for new, renewal, and resubmission applications as well as for revisions for grants requesting up to a total of $250,000 of direct costs per year (excluding consortium Facilities and Administrative costs). All other grant applications require detailed budgets in various forms.

It is possible that increasing the modular budget cap may lead to reduction in administrative burden, and NIH will consider this. However, we anticipate that an increase in the modular budget cap may lead to a substantial decrease in the number of research awards NIH is able to fund.
Adult Stem Cell Technology
The Committee continues to recognize adult stem cell technology (including induced pluripotent stem cells, mesenchymal stem cells, and other types of adult stem cells) as a critical tool in the realm of personalized medicine. The Committee notes that adult stem cells provide promising opportunities to develop sources of cells with great therapeutic value and potential for curing human diseases. The Committee also recognizes that basic science leads to pre-clinical studies and clinical trials, which may in turn generate new diagnostics, treatments and cures. The Committee encourages NIH to further explore additional basic science opportunities. The Committee requests an update in the fiscal year 2020 Congressional Justification on NIH efforts to foster basic research on adult stem cell technology, including through collaborative consortiums and other approaches to leveraging existing research capabilities to further advance scientific knowledge.

Action taken or to be taken:

In recognition of tremendous promise for treating and even curing a variety of diseases and injuries, NIH supports a wide range of basic and preclinical research on adult stems cells, such as induced pluripotent stem cells (iPSCs) and other types of adult stem cells, including mesenchymal stem cells from bone marrow, dental, and adipose tissues. These studies range from basic research, such as developmental and regulatory mechanisms of stem cells, cell fate determination, and control of stem cell niche, to translational projects addressing scale up of stem cell populations, development of approaches and assays for effective stem cell delivery and cellular function in vivo. Stem cells are often used as tools to help understand and target the underlying mechanisms of illness, analyze genetic and cellular dysfunction (e.g., in patient-derived versus control lines), identify targets for intervention or diagnostic classification, and develop new small molecule therapeutics. NIH also supports a broad range of bioengineering projects to develop biomaterials and scaffolds that can modulate stem cell survival and function in vitro and in vivo as well as the development of tissue chips and “disease-in-a-dish” systems that utilize patient-derived stem cells (iPSCs and mesenchymal stem cells) to model human organ and tissue functionality, elucidate mechanisms of disease, and predict human responses to drugs.

NIH supports a wide variety of highly collaborative stem cell research, including research consortiums. Some of these collaborative initiatives focus broadly on stem cell development and use, such as the National iPSC Network, which freely shares iPSC lines and their reprogramming reagents with more than 500 laboratories across the globe. Its goals are to make patient-derived iPSCs, together with the tools and expertise for their genetic manipulation, available to the greater research community on a large scale to facilitate understanding of disease and development of new therapies. Other consortiums are focused on the development and validation of iPSC-based human tissue chips that closely mimic the normal physiology of key metabolic tissues such as pancreatic islet, liver, skeletal muscle, and fat. In the future, such tissue chips could advance drug development, disease biomarker discovery, and development of personalized treatments. Some NIH-supported consortiums focus on specific diseases or tissues. For example, consortiums focus on treatments for type 1 diabetes, seeking to induce pluripotent stem cells to become new beta cells, develop microdevices to support functional human islets, and develop innovative approaches to model type 1 diabetes immunobiology. The Intestinal
Stem Cell Consortium supports projects that use iPSCs to generate “mini-intestines” in the lab, which could serve as models for gastrointestinal disorders and platforms for developing novel therapies. The (Re)Building a Kidney consortium is investigating how to induce pluripotent stem cells to become kidney cells and the recently established Dental, Oral and Craniofacial Tissue Regeneration Consortium is helping to move iPSC-based projects toward initiation of clinical trials. NIH is also generating iPSCs from patients with age-related eye diseases and will make these lines available to the extramural research community along with phenotypic and genotypic information to elucidate disease mechanisms and correlate them with clinical pathology. Another collaborative study focuses on pre-clinical safety and efficacy of a novel adipose-derived cell therapy for the treatment of pressure ulcers, which can be a life-threatening condition in elderly patients.

Ongoing efforts to expand stem cell-based research include the development of autotherapy strategies to improve patient outcomes. These strategies rely on a patient’s own stem and progenitor cells rather than on stem cells manipulated ex vivo and injected into tissues. Other research will focus on development of biofabricated iPSC-derived tissue models of sensory neurons for pain drug development. Additionally, the Tissue Chips for Disease Modeling initiative will support further development of tissue chip models that mimic disease pathology of major human organs and tissues. These model systems will use primary tissue or iPSC-derived patient cell sources on tissue/organ-on-chip platforms to test the effectiveness of candidate drugs. For example, tissue chip research on three-dimensional heart ventricle chamber models are being tested to understand heart disease mechanisms and to screen small molecules and gene therapies for improved patient outcomes.
Age-Related Macular Degeneration
The Committee recognizes the tremendous strides in the treatment of patients with the "wet" form of AMD resulting from anti-Vascular Endothelial Growth Factor therapies—which emerged from initial NIH-funded research—that stabilize vision loss and may improve lost vision. The Committee commends NEI for establishing an AMD Pathobiology Working Group within its National Advisory Eye Council to evaluate knowledge learned from its extensive AMD portfolio and identify what is still uncertain, such as the relationship between genes and biological pathways, therapies for the more-prevalent "dry" form of the disease, and how to diagnose and treat the disease much earlier. The Committee is pleased that NEI has launched a prospective international study of patients that uses the latest advances in retinal imaging to identify biomarkers of the disease and targets for early therapeutic interventions.

Action taken or to be taken:

Age-related macular degeneration (AMD) causes damage to the macula, a small spot near the center of the retina and the part of the eye needed for sharp, central vision used in reading, driving, and recognizing faces. While AMD is the leading cause of irreversible vision impairment and blindness in Americans 65 years of age and older, many exciting advances in the past decade have transformed patient care. Genomic studies have identified 52 independent genetic variants associated with AMD as well as environmental risk factors, which have opened up new avenues for developing therapies. While no therapies currently exist for the “dry” form of AMD, NIH clinical trials are testing two new drug compounds for dry AMD. Furthermore, NEI scientists are also launching a cutting-edge stem-cell clinical trial to treat dry AMD patients with stem-cell based tissue transplants derived from the patients’ own cells. For the “wet” form of AMD, anti-Vascular Endothelial Growth Factor (anti-VEGF) therapies have prevented vision loss and, in many cases, restored lost vision. NEI research showed that after 5 years of anti-VEGF treatment, 50 percent of patients had 20/40 vision or better, compared with studies before these treatments when less than 10 percent of patients retained 20/40 vision after one year.

The NEI-led Age-Related Eye Disease Studies (AREDS) identified dietary supplements that can delay progression to advanced disease in about a quarter of early- and mid-stage AMD patients. This NEI team of investigators just launched the AMD Ryan Initiative Study (ARIS), an international study of AMD progression, which will follow 500 people over five years to learn about the natural history of early AMD. By using the latest technologies to visualize structures within the eye and measure their function, researchers hope to identify biomarkers of disease progression, well before it advances to late-stage disease and causes vision loss. The study is named after the late Stephen Ryan, M.D., a widely recognized expert in retinal disease. To help

---

2 The International AMD Genomics Consortium, “Insights into Rare and Common Genetic Variation from a Large Study of Age-Related Macular Degeneration,” Nature Genetics, online December 21, 2015. DOI:10.1038/ng.3448
4 For more information, https://www.nei.nih.gov/content/nih-launches-international-study-amd-progression
coordinate all these exciting activities, the AMD Pathobiology Workgroup reviews AMD research advances and opportunities and provides updates to the National Advisory Eye Council.

As part of the newly launched AMD Systems Biology Project, NEI scientists are also generating stem cell lines from tissue donated by consenting AREDS participants; these lines can be converted into adult tissues to elucidate AMD disease mechanisms, which can also be correlated with genetic and clinical data from the participants, once personally identifiable information has been removed. This research resource will be made available to the scientific community.
Alcohol's Role in Opioid Overdose

The Committee is concerned that the role of alcohol in opioid and other drug overdoses is not receiving the attention it should. CDC estimates that alcohol contributes to over 8,000 annual overdose deaths that are primarily attributed to other substances, and that data suggest alcohol is commonly omitted from death certificates leading to underreporting. To address the opioid crisis, all avenues of investigation must be addressed. The Committee directs NIAAA to work with NIDA and any other appropriate agencies to better understand these linkages and to support research that will help to address this aspect of the problem.

Action taken or to be taken:

Alcohol misuse contributes to 88,000 deaths each year\(^5\), including thousands due primarily to alcohol poisoning and to overdose attributed to other substances, including illicit and prescription opioids, benzodiazepines, and cocaine\(^6\). These figures are likely an underestimate given data suggesting that alcohol use is often omitted from death certificates\(^7\). The co-use of alcohol and opioids or benzodiazepines can be especially lethal. Each of these substances suppresses brain stem areas that control vital functions such as breathing; using them in combination synergistically increases respiratory depression and the risk for overdose.

Understanding the role of alcohol in opioid overdose is important, particularly in the context of the national opioid crisis. Analyses conducted by NIAAA find that alcohol is involved in 15% of emergency department visits\(^8\), 20% of hospitalizations\(^9\), and 15% of all deaths due to opioid overdoses\(^10\). Between one-quarter to one-third of people with opioid use disorder (OUD) meet diagnostic criteria for alcohol use disorder (AUD)\(^11\). Moreover, chronic pain is present in a significant portion of people who misuse opioids and/or alcohol. Alcohol produces significant analgesia at doses that exceed moderate drinking\(^12\), and withdrawal from excessive alcohol use produces pain\(^13\). Thus, research suggests a bidirectional relationship between pain and both opioid and alcohol use such that pain contributes to alcohol\(^14\)\(^15\), and opioid use\(^16\), and alcohol and opioid use contribute to pain\(^17\). Indeed, emerging evidence suggests that, for some, OUD, AUD, and chronic pain may be facets of an integrated syndrome involving common biological


\(^{6}\) CDC Wonder Multiple Cause of Death database: https://wonder.cdc.gov/mcd-icd10.html


\(^{8}\) Nationwide Emergency Department Sample: www.hcup-us.ahrq.gov/nedsoverview.jsp

\(^{9}\) Nationwide Inpatient Sample: www.hcup-us.ahrq.gov/nisoverview.jsp

\(^{10}\) CDC WONDER Multiple Cause of Death database. https://wonder.cdc.gov/mcd-icd10.html


\(^{15}\) Thompson T (2017) *J Pain* 18:499-510

\(^{16}\) Hipólito L (2015) *J Neuroscience* 35:12217–12231

mechanisms\textsuperscript{18}. Additional studies are needed to clarify the relationships among these conditions and drug overdose.

NIAAA supports research on the relationship between alcohol and opioid use\textsuperscript{19,20}, and is exploring collaborative opportunities to stimulate research on the effects of alcohol on opioid-induced respiratory depression and overdose; how alcohol-opioid interaction contributes to the misuse of each substance and to pain; and the effects of pain on alcohol and opioid use, interactions, and overdose. Under the newly launched Helping to End Addiction Long-term (HEAL) initiative, NIAAA is encouraging studies on candidate biomarkers that can be used to facilitate the development of non-opioid pain therapeutics for individuals with comorbid chronic pain and AUD\textsuperscript{21}. In addition, as part of Collaborative Research on Addiction at NIH (CRAN), NIAAA is partnering with the National Institute on Drug Abuse (NIDA) and the National Cancer Institute (NCI) to develop a comprehensive understanding of substance use, misuse, and addiction. NIAAA, NIDA, and NCI seek to elucidate the adverse consequences of polysubstance use; develop interventions for screening individuals for multiple drug use; and develop treatments for multi-substance addictions and related conditions, including chronic pain\textsuperscript{22}.


\textsuperscript{19} https://projectreporter.nih.gov/project_info_description.cfm?aid=9584519&icde=40701419&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC&pbali


\textsuperscript{22} CRAN Strategic Plan: 2016-2021www.addictionresearch.nih.gov/cran-strategic-plan-2016-2021
Alopecia Areata
The Committee applauds NIAMS for its leadership in autoimmune research breakthroughs that have advanced treatment development for alopecia areata. The Committee requests an update from NIAMS on new alopecia areata research advances in the fiscal year 2020 Congressional Justification.

Action taken or to be taken:

Alopecia areata (AA) is an autoimmune disease that leads to disfiguring hair loss on the scalp and elsewhere. The condition occurs when the immune system, which normally protects the body from foreign invaders such as viruses and bacteria, mistakenly attacks one’s own hair follicles, the structures from which hairs grow. Ongoing research aims to fully understand the immune cells and signaling pathways that are involved in autoimmune diseases, and to apply this knowledge to the development and testing of new treatments.

Researchers supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases have previously identified a particular gene (IKZF1) that is overactive in AA and promotes overproduction of so-called killer T cells (white blood cells that kill cells that are infected or cancerous) that target the hair follicle. Based on this finding, the researchers reasoned that IKZF1 might be relevant to cancer, which presents a different challenge than autoimmune disease—evasion of cancer cells by killer T cells. The researchers hypothesized that cancers that lack IKZF1, an important immune signaling factor, would be less responsive to immunotherapies. Utilizing computational models, as well as in vitro and in vivo techniques, the research team demonstrated that IKZF1 expression in certain cancers suppressed tumor growth and enhanced the efficacy of two immunotherapeutic approaches. In addition, the researchers found that mutations to IKZF1 could predict poor prognosis in certain cancer patient cohorts. This work supports the emerging concept that there is a balance within the immune system between overactivity leading to autoimmunity and underactivity leading to immune evasion in cancer. Ongoing studies are searching for additional genes that can predict immunotherapy response and enhance the accuracy of patient prognosis.
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 and their descendants over time, much can be learned about cognitive decline and early biomarkers that will help the understanding of the role of environmental versus genetic factors in disease development and progression. Therefore, the Committee commends NHLBI for its work to follow its current and future cohort study participants for the development and progression of risk factors and to detect signs of cognitive decline in order to provide new insights into risk identification and accelerated prevention efforts.

Action taken or to be taken:

The National Heart, Lung, and Blood Institute (NHLBI) has a long history of supporting large observational studies that have provided fundamental insights into environmental and genetic determinants of cardiovascular disease (CVD) and related health outcomes. As the participants in these studies age, there is a need and opportunity to understand their risk of cognitive decline and dementia and the role that heart, lung, blood, and sleep disorders play in cognitive decline.

The Framingham Heart Study (FHS), a multi-generational study of CVD that began in 1948, has expanded to include three generations of participants, that are helping to answer new questions about how heart health relates to brain health. The FHS has shown that many of the risk factors for dementia are the same as those for heart disease, such as high blood pressure, cigarette smoking, lack of physical activity, obesity, diabetes, and aging. Such findings suggest that vascular dementia—a decline in brain function precipitated by vascular risk factors and chronic CVD—is a major contributor to cognitive decline with aging. A recent NIH-supported analysis of the Framingham Offspring cohort data has shown that high blood pressure during mid-life increases dementia risk, suggesting that there are potential cognitive benefits from managing blood pressure in mid-life.23

Recently, FHS investigators also identified new metabolic biomarkers that correlate with the incidence and progression of dementia. With further study, such biomarkers could offer a means of earlier diagnosis and treatment for dementia.24 A similar National Institute of Aging cohort study, the Baltimore Longitudinal Study of Aging (BLSA) explores trajectories of changes of multiple physiological, medical, psychological, and behavioral parameters over the lifespan in the same individuals, with some individuals having participated since the study’s establishment in 1958. BLSA data are available to qualified researchers and are particularly useful for identifying at an early, still asymptomatic stage, biomarkers that predict the development of diseases conditions, including dementia.

The Jackson Heart Study, the largest longitudinal study of CVD in African Americans in the Jackson, Mississippi area, has begun investigating the links between heart health and brain health. The study was renewed in August 2018, and new clinical exams beginning in 2020 will include tests of cognitive function as well as magnetic resonance imaging of the brain.

The National Institute of Neurological Disorders and Stroke (NINDS) also supports several large cohort studies of stroke and vascular dementia, including the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study and the Northern Manhattan Study (NOMAS), which focus on African American and Hispanic populations, respectively. In May 2018, NHLBI and NINDS convened a workshop to identify gaps and opportunities in research on vascular cognitive impairment and dementia. The workshop concluded there is a need for further research on genetic and socioeconomic factors that contribute to racial and geographic disparities in vascular dementia.

NHLBI has announced the availability of funding to continue existing cohort studies of CVD that will enable additional clinical exams, laboratory testing, and biospecimen collection potentially relevant to Alzheimer’s and related dementias. NHLBI also released a funding opportunity for new prospective cohort studies focused on CVD that could contribute to our understanding of vascular dementia.

In addition to population studies that identify risk factors that contribute to CVD and related comorbidities, NHLBI supports intervention studies to better understand the relationship between CVD and cognitive decline. Funded in part by NHLBI, the SPRINT Memory and Cognition in Decreased Hypertension (MIND) study is investigating whether intensive blood pressure control protects against global cognitive decline and dementia in people 50 years of age or older without diabetes. Preliminary findings suggest that intensive lowering of blood pressure may reduce the risk of mild cognitive impairment (MCI) and the combined risk of MCI and dementia.

---

5 NINDS, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute on Aging, and the U.S. Department of Veterans Affairs also fund SPRINT MIND.
Alzheimer’s Disease Disparities
The Committee commends the 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 encourages NIA to diversify its cohort studies, with the specific goal of better understanding disease burden and biomarkers by race and geographic region. Additionally, the Committee is concerned about the racial and ethnic disparities that exist in Alzheimer’s disease diagnoses and encourages NIA to support research exploring the disproportionate impact Alzheimer’s disease has on people of color, particularly African Americans who are two times more likely to develop late-onset Alzheimer’s disease than whites.

Action taken or to be taken:

NIA supports a number of cohort studies that include participants from a range of geographic, ethnic, socioeconomic, and generational backgrounds, and has planned additional substantive efforts to determine the diverse factors underlying variation in dementia risk.

For example, proposals to enhance the power of multi-ethnic cohort studies were specifically invited in a NIA issued 2016 Funding Opportunity Announcement (FOA) soliciting research applications addressing the epidemiology of AD and protective factors for cognitive health and resilience. NIA also issued an FOA in FY 2017 for research aimed at leveraging existing cohort studies to clarify risk and protective factors for Alzheimer’s and related dementias. Three projects have been funded to date, one of which draws information from the Honolulu-Asia Aging Study, the Nun Study, and the 90+ Study, which will allow the investigators to compare and contrast brain pathology associated with cognitive and motor impairment among people of differing age, sex, and race/ethnicity.

A priority identified at the ADRD Summit in 2016 was to close the gap on health disparities in Alzheimer’s disease and related dementias (AD/ADRD). To help address this gap, NINDS is supporting DetectCID, a national consortium that tests and validates tools that are quick and easy to use in primary care settings to increase accurate detection of cognitive impairment and dementia among high-risk populations, particularly in minority and underserved populations.

Decades of research have suggested a strong link between cerebrovascular disease, such as stroke, and subsequent dementia, and evidence suggests that mixed dementias with cerebrovascular disease are more prevalent in African Americans. To improve understanding of this disparity and further explore the relationship between cardiovascular/cerebrovascular risk factors and dementia, the National Institute of Neurological Disorders and Stroke (NINDS) is supporting Reasons for Geographic and Racial Differences in Stroke (REGARDS) study and the Northern Manhattan Study (NOMAS) which are longitudinal cohort studies of whites, African Americans, and Hispanics, and related projects that utilize the data from these studies. NINDS is also diversifying existing cohorts by supporting 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.

Finally, NIA supports several studies that explore the reasons behind the increased dementia risk seen in African Americans. For example, investigators with the long-running Washington Heights-Inwood Community Aging Project have identified unique genetic risk factors among African American and Caribbean Hispanic study participants, and investigators with the Monongahela-Youghiogheny Healthy Aging Team (MYHAT) are exploring risk factors for mild cognitive impairment and dementia in an economically disadvantaged, majority-African American population in Pennsylvania. These studies will continue in FY 2019.
Alzheimer’s Disease

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 at least $2,250,000,000 for Alzheimer’s disease research. NIA should continue to address the research goals set forth in the National Plan to Address Alzheimer’s disease, as well as the recommendations from the Alzheimer’s disease Research Summit in 2015.

Action taken or to be taken:

As we approach 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, significant progress has been made. Additional generous 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 $400 Million received in FY17 helped to accelerate implementation of many FY18 AD/ADRD research milestones, and the additional $414 Million received in FY18 will enable acceleration of many FY19 milestones.

Consistent with recommendations from the 2015 AD Research Summit, a major focus at the NIA since the substantial funding increases began has been building a solid yet flexible infrastructure upon which we can continue to expand our 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 (M²OVE-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;
- **Initiatives supporting reprogramming human cells** as a tool for AD/ADRD research.

Increased funding for AD/ADRD research has accelerated research at other ICs, including the National Institute of Neurological Disorders and Stroke (NINDS). In FY 2018, NINDS created new funding opportunities that provide support for biomarker and drug target discovery studies, Lewy body dementia clinical trial design and planning, and mechanistic research to advance our understanding of ADRD’s basic biology. NINDS also leads the triennial ADRD Summits to identify research priorities for Lewy body, frontotemporal, vascular, and mixed dementias.
NIH’s blueprint for addressing the research goals set forth in the National Plan is presented in our professional judgment budget ("Bypass Budget") for AD/ADRD. The latest Bypass Budget, for FY 2020, was released July 30, 2018. Its development was informed by many strategic planning efforts, including but not limited to: the 2012, 2015, and 2018 AD Research Summits; the 2013 and 2016 ADRD Summits; the 2013 meeting on Advancing Treatment for Alzheimer's Disease in Individuals with Down Syndrome; and the 2017 AD Care and Services Summit. The next ADRD Summit is planned for 2019; the next Care and Services Summit, for 2020.
Alzheimer’s Disease
The Committee provides an increase of $425,000,000 for Alzheimer's research, bringing the total funding level in fiscal year 2019 to $2,340,000,000, meeting and surpassing the $2,000,000,000 goal laid out in the National Plan to Address Alzheimer's Disease 6 years earlier than the 2025 goal. The NIA is encouraged to continue addressing the research targets outlined in the fiscal year 2019 Professional Judgement Budget. Further, the Committee applauds the work of NIH to support Alzheimer's disease clinical trials and for recognizing the need to reduce the time and cost of such trials, including those involving patients who are asymptomatic or in the earliest stages of the disease. The Committee is concerned about the under-representation of minority populations in these trials and directs NIMHD to collaborate with the NIA and other Institutes to develop an action plan to address this gap. The action plan should include a review of the NIA's current public reporting practices of the recruitment and retention of underrepresented populations in Alzheimer's research. In addition, the Committee recognizes the Institute's leadership in driving greater access to research data and investing in data infrastructure to accelerate the discovery of treatments for Alzheimer's disease and related dementias. The Committee encourages NIA to consider a comprehensive approach to expand and enhance these efforts through policies that prioritize data sharing, new funding that supports data sharing and harmonization, and partnerships with other Alzheimer's disease data efforts to promote a coordinated data ecosystem.

Finally, 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 an 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.

Action taken or to be taken:

The NIA is encouraged to continue addressing the research targets outlined in the fiscal year 2019 Professional Judgement Budget.

The additional generous appropriations directed at Alzheimer’s disease and related dementias (AD/ADRD) over the past few years have enabled the NIH to establish and pursue ambitious and exciting milestones toward the ultimate goal of identifying an effective prevention or treatment intervention by 2025. A major focus at the NIA since the substantial funding increases began has been building an infrastructure upon which we can continue to expand our 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 (M²OVE-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 Alzheimer’s Disease Centers, which translate research advances into improved prevention, diagnosis, treatment, and care for people with AD/ADRD.

Initiatives supporting reprogramming human cells as a tool for AD/ADRD research.

These large, focused programs will continue in FY2019 and beyond.

Further, the Committee applauds the work of NIH to support Alzheimer’s disease clinical trials and for recognizing the need to reduce the time and cost of such trials, including those involving patients who are asymptomatic or in the earliest stages of the disease.

Reducing the time and cost of clinical trials is an important goal of the NIH and the impetus for NIH’s groundbreaking Accelerating Medicines Partnership (AMP), a collaboration between NIH, biopharmaceutical and nonprofit organizations, and the Foundation for the NIH. This innovative program is expected to transform the way we develop new diagnostics and treatments by jointly identifying and validating promising targets of disease. Importantly, all data are being made publicly available to qualified researchers, further facilitating and accelerating research on the diseases and conditions under study, including AD/ADRD. To date, investigators with AMP-AD have identified over 100 potential new drug targets for AD/ADRD.

AMP resources are currently being used to include novel biomarkers such as PET imaging of tau in three major clinical trials:

- The Dominantly Inherited Alzheimer’s Network Trials Unit (DIAN-TU) trial is assessing the safety, tolerability, and biomarker efficacy of two experimental drugs, gantenerumab and solanezumab, in people who are genetically at high risk for the disease.
- The Alzheimer’s Prevention Initiative APOE4 trial is testing two anti-amyloid drugs, an active vaccine and a beta-secretase inhibitor, in cognitively normal older volunteers who are at increased risk of developing late-onset Alzheimer’s.
- The Alzheimer’s Disease Cooperative Study Anti-Amyloid Treatment in Asymptomatic AD (A4) trial is assessing the efficacy of solanezumab in clinically normal older people with neuroimaging biomarker evidence of brain amyloid.

NIA anticipates that these trials will be completed between 2020 and 2022.

In 2018, NIA also solicited applications for collaborative networks to target gaps in recruitment methods and outcomes and to establish the community infrastructure needed to accelerate studies. In addition, the Global Alzheimer’s Platform Trial-Ready Cohort for Preclinical/Prodromal Alzheimer’s Disease (GAP TRC-PAD) is an innovative public-private partnership between NIA and the Global Alzheimer’s Platform (GAP) Foundation to recruit a large number of “trial-ready” potential participants at high risk of developing AD/ADRD.
Investigators anticipate that this approach will markedly shorten recruitment timelines, potentially from years to months.

The Committee is concerned about the under-representation of minority populations in these trials and directs NIMHD to collaborate with the NIA and other Institutes to develop an action plan to address this gap. The action plan should include a review of the NIA's current public reporting practices of the recruitment and retention of underrepresented populations in Alzheimer's research.

The National Plan to Address Alzheimer’s Disease specifically directs NIH to monitor and identify strategies to increase enrollment of racial and ethnic minorities in AD/ADRD studies. In response, NIA has worked with nationally recognized experts to develop a National Strategy for Recruitment and Participation in Alzheimer’s Disease Clinical Research. As part of this process, NIA employed a cutting-edge crowd-sourcing program that drew input and feedback from respondents around the world. We anticipate implementing the National Strategy beginning in fall 2018. NIA also works with NIMHD on a number of initiatives aimed at studying health disparities in Alzheimer’s disease, including two active funding opportunity announcements soliciting research on a range of issues related to health disparities in AD/ADRD.

NIA is currently analyzing recruitment and retention of underrepresented population in AD/ADRD clinical trials. Preliminary results of this analysis were presented at the 2018 Alzheimer’s Association International Conference, and we anticipate publication in a peer-reviewed journal in 2019.

Most additional public reporting on recruitment and retention is coordinated by the NIH Office of Extramural Research (OER). As part of NIH efforts to comply with 21st Century Cures requirements to enhance accountability and transparency in NIH clinical research, NIH has implemented a new Human Subjects System (HSS), which consolidates human subjects and clinical trial information in one place. The HSS will streamline collection and reporting of recruitment/retention data and will promote transparency by displaying accurate and timely information to grantees and staff simultaneously.

In addition, the Committee recognizes the Institute's leadership in driving greater access to research data and investing in data infrastructure to accelerate the discovery of treatments for Alzheimer's disease and related dementias. The Committee encourages NIA to consider a comprehensive approach to expand and enhance these efforts through policies that prioritize data sharing, new funding that supports data sharing and harmonization, and partnerships with other Alzheimer's disease data efforts to promote a coordinated data eco-system.

NIA and other NIH Institutes are harnessing the tremendous power of big data to gain insight into the basic biology of AD/ADRD, as well as factors that may confer resilience to these diseases; accelerating the discovery of the next generation of new targets and biomarkers; and establishing new translational infrastructure programs to enable rapid sharing of data and research models and enhancing research rigor and reproducibility.
For example, the Accelerating Medicines Partnership-AD (AMP-AD) Knowledge Portal is a big-data hub that allows researchers to access and analyze human as well as cell-based and animal-model datasets on a scale that would not be possible by individual research teams, academic institutions, or pharmaceutical companies. Initially developed to enable data sharing for the AMP-AD Target Discovery Consortium, today the portal is an NIH-designated repository hosting data from multiple NIH-supported Alzheimer’s systems biology consortia and is open to data contributions from other researchers. To date, the knowledge portal has more than 1,300 users and contains contributions from 42 investigators across 22 institutions, representing samples from 36 research studies.

Finally, 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 an 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 back-grounds. 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.

NIA supports a number of cohort studies that include participants from a range of geographic, ethnic, socioeconomic, and generational backgrounds, and has planned additional substantive efforts to determine the diverse factors underlying variation in dementia risk.

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

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

In addition, NIA supports the COhort Studies of Memory in International Consortium (COSMIC), an international consortium of prospective longitudinal population based cohorts examining the risk and protective factors for cognitive decline and the development of dementia. Established in 2012, COSMIC has developed into a consortium of 26 studies from 16 countries in five continents, with a combined sample size of >70,000, and is now uniquely placed to address some of the salient questions in relation to the epidemiology and biomarkers of neurocognitive disorders.
A priority identified at the ADRD Summit in 2016 was to close the gap on health disparities in Alzheimer’s disease and related dementias (AD/ADRD). To help address this gap, NINDS is supporting DetectCID, a national consortium that tests and validates tools that are quick and easy to use in primary care settings to increase accurate detection of cognitive impairment and dementia among high-risk populations, particularly in minority and underserved populations.
Amyloidosis
The Committee encourages NIH to continue to expand its research efforts into amyloidosis, a group of rare diseases characterized by abnormally folded protein deposits in tissues. Amyloidosis is often fatal and there is no known cure. Current methods of treatment are risky and unsuitable for many patients. The Committee requests that NIH provide an update 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 2020 Congressional Justification.

Action taken or to be taken:

NIH continues to support research into amyloidosis. The National Institute on Diabetes and Digestive and Kidney Diseases (NIDDK) funds one project seeking to further understand the process by which amyloids (which are abnormally folded forms of certain proteins) aggregate to form deposits that can build up and damage organs and tissues. This project, in an animal model of a form of amyloidosis involving aggregation of the protein transthyretin (TTR), is studying how amyloid formation leads to loss of function and, ultimately, the death of tissue. Recent results from this project demonstrated that neuronal dysfunction can be worsened when a degradation pathway is eliminated or ameliorated when properly folded TTR is stabilized. Building on these types of studies, a retrospective study funded by the National Institute on Aging (NIA) reported, in 2018, that treatment with TTR stabilizers is associated with reduced risk of death and lower rates of heart transplant among individuals with cardiac amyloidosis. The promising results of this small study next require confirmation in randomized clinical trials. A second group of projects is characterizing the fundamental molecular events involved in the mis-folding and aggregation of amyloid that leads to disease. NIDDK supports one of these projects, which recently described a key step in the TTR aggregation pathway using a sensitive fluorescent probe that has the potential to provide new insights into disease pathology.

NIH also supports research on light chain amyloidosis (AL), the most common type of the disease. A group of projects in this area is evaluating potential treatments to remove amyloid buildup in AL patients. One of these studies funded by NIDDK has shown that a newly identified chemical inhibitor significantly decreases movement out of the cell, which might potentially reduce the associated pathology. Another NIDDK-supported project is using a mouse model system to test whether a small synthetic protein designed to interact both with AL and with a therapeutic antibody can be used to improve immunotherapy in AL amyloidosis. NIA also held a November 2018 workshop on “Specificity of Protein Aggregation in Alzheimer’s Disease and Related Neurodegenerative Diseases Relevant to Other Pathologies,” to discuss a wide range of diseases characterized by abnormal protein folding, including systemic amyloidosis.
Angelman Syndrome

The Committee recognizes the promising scientific gains made in the pursuit of treatments for Angelman Syndrome. The Committee applauds the significant contributions of the Angelman Syndrome Natural History Study, funded by NIH, and the private partners working diligently to advance the growing body of Angelman Syndrome research towards practical treatments. Further research in this area holds great promise for both Angelman Syndrome and forms of autism also linked to misexpression of the UBE3A gene. With two innovative new treatments poised for clinical trials, the Committee urges NIH to support Angelman Syndrome research, and specifically to advance research in the roles of the UBE3A gene in brain functions.

Action Taken or to be Taken

Angelman syndrome (AS) is a complex neurodevelopmental disorder that results from the loss of function or deletion (misexpression) of the maternally inherited copy of the *UBE3A* gene and is linked to intellectual and developmental delays, speech impairment, and problems with movement and balance. There are three forms of the *UBE3A* gene in human neurons, and basic studies supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) are designed to understand the specific function for each so that targeted gene therapy approaches will be most effective. Studies supported by the National Institute of Neurological Disorders and Stroke (NINDS) and NICHD are examining the role of the *UBE3A* gene in regulating the proteins that underlie the circadian clock, important for the sleep/wake cycle in mammals, ultimately aimed at potential treatments to correct circadian rhythm disorders. Another study is determining the mechanism by which loss of *UBE3A* leads to dysfunction of synapses (the region where neurons communicate with one another), and how this may affect neural development. Researchers supported by both NINDS and NICHD are testing a drug to target molecules that interact directly with *UBE3A*, particularly proteins that are critical for learning and memory. In a mouse model of AS, the drug is being tested on tasks measuring learning, memory, and executive function. These approaches have the goal of identifying pharmacologic therapies and restoring the cognitive and behavioral deficits created by AS. Further, several of NICHD’s Intellectual and Developmental Disabilities Research Centers are supporting AS-related translational studies to capitalize on potential new treatments under development.

To prepare for clinical studies, NICHD and NINDS support efforts to identify biomarkers for use in research aimed at development of therapies for AS. For example, one research group recently described a specific pattern of abnormal brain activity during sleep in children with AS, which could serve as a biomarker in future studies to assess the effectiveness of treatments for AS. In December 2017, NINDS and NICHD led a scientific workshop on development of such biomarkers for a range of neurodevelopmental disorders, including AS, bringing together leading researchers from academia and industry, federal agency representatives, and patient advocacy groups.

In addition, the NICHD has supported a Rare Diseases Clinical Research Consortium that has tracked the natural history of AS over a 10-year period in over 300 individuals with the condition; a recently funded extension of this study is evaluating cognition, communication, functional mobility, adaptive functioning, anxiety, maladaptive behaviors, seizure frequency, and
sleep disturbance in this cohort and modifying a standard developmental assessment for this largely nonverbal population.
Audacious Goals Initiative
The Committee commends NEI’s leadership through its AGI, which aims to restore vision through regeneration of the retina by replacing cells that have been damaged by disease and injury and restoring their visual connections to the brain. The Committee is pleased that, to-date, NEI has funded novel imaging technologies to help clinicians observe the function of individual neurons in human patients and follow them over time as they test new therapies, as well as identifying new factors that control regeneration and comparing the regenerative process among model organisms. The Committee is pleased that NEI has launched a third funding mechanism to stimulate development of models for evaluating survival and integration of regenerated photoreceptors and retinal ganglion cells in model systems that are closer to human visual anatomy and function than current models.

Action taken or to be taken:

Working towards a 15-year goal of restoring vision through regeneration of neurons and neural connections in the eye and visual system, the NEI Audacious Goals Initiative (AGI) recently assembled its third research consortium to develop translation-enabling models for evaluating survival and integration of regenerated neurons in the visual system. The objective is to establish new animal models that emulate critical aspects of human blinding diseases amenable to regenerative therapy. Individual research teams will collaborate, sharing methodology, scientific resources, and data across different model systems. Teams will be modeling genetic forms of retinal degeneration, optic nerve degeneration (glaucoma), and damage due to trauma. Once models are developed, the teams will attempt to correct the disease conditions with cell replacement therapies. They will evaluate how well neurons integrate and connect to other cells in the retina anatomically, and how successfully function is restored.

A different AGI consortium is looking at animals that naturally regenerate vision after trauma to discover new factors that can be used to promote regeneration in mammalian visual systems, which don’t regenerate naturally. NEI scientists published a new study in *Nature* in which they reversed congenital blindness in mice by changing supportive cells in the retina called Müller glia into rod photoreceptors\(^{29}\). Photoreceptors are the light-sensitive neurons in the retina. In mammals, including mice and humans, photoreceptors fail to regenerate on their own. Like most neurons, once mature they don’t divide. Scientists have long studied the regenerative potential of Müller glia because in other species, such as zebrafish, they divide in response to injury and can turn into photoreceptors and other retinal neurons. The zebrafish can thus regain vision after severe retinal injury. In the lab, however, scientists can coax mammalian Müller glia to behave more like they do in the fish. In the first phase of a two-stage reprogramming process, scientists spurred Müller glia in normal mice to divide by injecting their eyes with a gene to turn on a protein called beta-catenin. Weeks later, they injected the mice’s eyes with factors that encouraged the newly divided cells to develop into rod photoreceptors. Under a microscope, these regenerated cells looked identical to real photoreceptors. By testing their treatment in mice

---

born without functional rod photoreceptors, they were able to confirm these regenerated neurons were communicating with other neurons and responding to light.

In April, *eNeuro* published a white paper of recommendations from an AGI workshop entitled “Creating a Cellular Environment for Neuroregeneration.”30 The AGI also held a workshop on September 24-25 on “Pathways for Retinal Cell Replacement Therapy”. The meeting brought together representatives from biomedical manufacturing and industry with vision researchers poised to translate their regenerative medicine research into therapies.

30 http://www.eneuro.org/content/early/2018/04/06/ENEURO.0035-18.2018
Average Cost of NIH Grants

The Committee recommendation does not include the general provision proposed in the FY 2019 budget request to limit the percentage of a researcher's salary that may be paid for using NIH grant funds, as the impact of this policy change is unclear. The Committee requests an analysis of the projected impact of such a policy change on the number and average cost of NIH grants, as well as on academic institutions, in the fiscal year 2020 Congressional Justification.

Action taken or to be taken:

Reductions in the NIH contributions to the salary of researchers may free up funds for additional scientists and equipment to carry out research. No previous research examines the impact of reducing the salary cap on the number of grants and the average cost per grant. Data limitations preclude findings from such analyses from extending to the entire NIH extramural funding. However, these data can have implications for subgroups of grants and investigators that the NIH funds. The NIH will consult with outside stakeholders (e.g. AAMC and UMETRICS) to explore possible data and analyses and will report back on findings.

A previous policy example from NIH can illustrate that there is not necessarily a correlation between a reduction in the amount of available salary and a decrease in the number or average cost of grant awards. The salary cap was reduced from $199,700 in December 2011 to $179,900 for the remainder of FY 2012. Over the period from December 2011 to September 30, 2012 there was a 10 percent reduction in the salary compensation provided on Federal grants from NIH. Despite the reduced salary cap, there was no significant change in the number of grants and average award amount that the NIH made during FY 2012. Although the NIH awarded 142 fewer Research Grants in FY 2012 than in FY 2011 (from 44,642 to 44,500), the average cost per grant increased by approximately $5,000 (from $449,644 to $454,588 in unadjusted for inflation dollars). The NIH appropriation increased by $232 million in nominal dollars and decreased by $165 million in real dollars (adjusted for inflation) between FY 2011 and 2012, thus changes in budgets did not affect the result. In this example, the number of grants did not increase in the year the salary cap was lowered. However, there are a number of other factors that could have affected the number of grants in these cases. Holding other factors constant, a reduction in the salary cap would free up additional resources for more grants in general.

An unintended consequence of limiting the percentage of a researcher's salary that may be paid for using NIH grant funds is that recipient institutions will be required to contribute increasing amounts of their institutional funds to make up the difference in researcher’s’ salary support. The amount of salary that can be charged to a grant is already limited by the salary cap. Further reduction of available salary, in addition to the unreimbursed costs of increasing administrative burden and other capped costs, may limit the number of applicants with sufficient resources to participate in Federally-funded research.
Barriers to Research
The Committee is concerned that restrictions associated with Schedule 1 of the Controlled Substance Act effectively limit the amount and type of research that can be conducted on certain Schedule 1 drugs, especially marijuana or its component chemicals and certain synthetic drugs. At a time when we need as much information as possible about these drugs, we should be lowering regulatory and other barriers to conducting this research. The Committee directs NIDA to provide a short report on the barriers to research that result from the classification of drugs and compounds as Schedule 1 substances.

Action taken or to be taken:

With Americans across the country consuming marijuana and its components for health-related conditions, the National Institute on Drug Abuse (NIDA) believes there is a pressing need for more research in this area. The potency of marijuana has risen over the years, as has the use of higher potency modes of administration (hash oil, edibles, etc.) and research is needed to understand what this means for individual and public health. The progress of therapeutics development and clinical trials has been slow, in part due to the increased time, costs, and administrative efforts associated with the regulatory framework for conducting research on these and other Schedule 1 compounds.

The Schedule 1 registration process can take more than a year to complete and creates administrative burdens that can serve as disincentives to researchers. Some of the factors that contribute to this issue include:

- Separate registrations are required for marijuana and each constituent compound studied;
- The application process is complex; approximately 70 percent of applications are incomplete when submitted, suggesting that there is a need for better guidance on the application process;
- The requirement for protocol review by the DEA can be redundant with the review that occurs through the FDA Investigational New Drug (IND) process and with federal grant review;
- The requirement for review by DEA of changes to an approved protocol can further delay research;
- There is variability in experiences with the application of rules and regulations. For example, whether a laboratory can operate under a single registration or whether a registration is required of each researcher in the laboratory who works with the Schedule I substance;

There are also additional barriers to research on marijuana and constituent compounds beyond the process for other Schedule I drugs:

- All cannabinoids in marijuana are considered Schedule I compounds regardless of evidence of addiction liability. Evidence suggests that cannabidiol (CBD) is non-psychotropic, and a CBD-based drug, epidiolex, was recently approved by the FDA to treat rare forms of epilepsy. However, removing CBD from Schedule I will require a
study to assess psychotropic effects and addiction potential of CBD in humans, with an estimated cost of $2 million; a study is currently underway;

- Additionally, despite a stated policy change and a solicitation to increase the number of marijuana providers for research purposes, the DEA has only issued one license for marijuana cultivation, to the University of Mississippi, which cultivates marijuana under a contract with NIDA. While the NIDA supply of marijuana has diversified, it is both costly and time consuming to grow new products;

- NIH is currently unable to fund researchers to analyze marijuana products available in state dispensaries, since obtaining these samples would violate federal law. Understanding the characteristics of the marijuana that is being dispensed, including the potency (i.e., amount of tetrahydrocannabinol (THC) in the plant) and concentration of other components (e.g., CBD), is important for studying the impact of potential therapeutic and recreational use of marijuana on individual and public health;

- In addition, there are legal barriers to conducting research using marijuana from state dispensaries. Universities and researchers are concerned about the potential impact of this type of research on their ability to obtain DEA licenses or federal funding, even if they are not using federal funds to purchase marijuana.

On January 18, 2018, DEA announced that they are streamlining the application process for researchers interested in studying Schedule I substances, a step which has been welcomed by the research community. NIDA will continue to work with Department of Health and Human Services (HHS), FDA, Department of Justice (DOJ)/DEA, and Office of National Drug Control Policy (ONDCP) colleagues to identify policy and regulatory changes that can facilitate research using Schedule I substances, address specific barriers to research on marijuana and its constituent compounds (e.g., lack of researcher access to marijuana products available in state dispensaries), and identify alternative strategies to controlling distribution of new psychoactive substances without impeding research.
Biodevices
The Committee is pleased that NIDCR is exploring how to leverage oral biodevices for overall health, including developing tools to detect bone loss. The Committee encourages NIDCR to continue focusing on novel products, such as imaging technologies and dental restorative materials, which can improve individuals’ oral and overall health and well-being.

**Action taken or to be taken:**

Oral biodevices have immense potential for real-time monitoring of oral health and overall health, in addition to delivery of local and systemic treatments. Recent progress in wireless capability, nanotechnology, and microfabrication can now be leveraged to develop oral biosensors for a variety of uses. Since these devices will be placed in the mouth, they must be capable of withstanding the unique challenges of the oral environment — like chewing forces, microorganisms, and salivary enzymes. National Institute of Dental and Craniofacial Research (NIDCR)-supported researchers are creating oral biodevices such as an orthodontic pressure sensor capable of monitoring and controlling tooth movement, and a device for detecting bone loss to improve periodontal disease management and treatment. In addition, scientists are developing biosensors to measure salivary biomarkers to understand important aspects of overall health in real time. In pilot studies, researchers are measuring melatonin levels in patients with sleep disorders, and monitoring cortisol to detect changes in psychological stress levels, such as in post-traumatic stress conditions. These early studies will be expanded so that the biosensors can be tested further with a goal of facilitating the translation of clinically-validated oral biosensors into everyday practice.

NIDCR has been a leader in supporting the development of new products and devices to solve some of the challenging problems that dentists face in their clinical practice. For example, it is difficult for practitioners to diagnose cracked teeth and undetected cracks can result in tooth loss. NIDCR is supporting a small business to develop improved imaging tools that automatically visualize and measure cracks in teeth in 3D. NIDCR is also investing in research to improve the longevity and durability of the restorative materials that dentists use to treat dental decay. NIDCR-supported researchers are developing prototypes of new restorative materials such as resins, fillers, and adhesives. These new materials are not only stronger and longer-lasting, but researchers are also developing new features like the ability to self-heal and anti-microbial properties. Building on this momentum, NIDCR is launching a new initiative on digital dentistry that will advance research in personalized imaging, procedures, products, and devices.
Biomarkers
The Committee commends the efforts of NIDDK to prioritize the discovery and validation of biomarkers and urges NIDDK to continue to prioritize this important work that will accelerate the designing and conducting of clinical trials to prevent, treat, and cure type 1 diabetes. Given the growing prevalence of diabetes, the Committee is concerned that additional research is needed to determine how to improve the treatment of a common complication, diabetic foot ulcers, to reduce amputations, and urges NIDDK to support such efforts. Further, given the aging population, the Committee urges NIDDK to work with NIA to explore the relationship between diabetes and neurocognitive conditions, such as dementia and Alzheimer's disease.

Action taken or to be taken:
The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) continues to support biomarker research through multiple efforts. In addition to conducting clinical trials to prevent or reverse type 1 diabetes, NIDDK’s Type 1 Diabetes TrialNet conducts mechanistic studies alongside these trials to identify and validate new biomarkers. Discovery of biomarkers is also a goal of NIDDK’s The Environmental Determinants of Diabetes in the Young (TEDDY) study, which aims to identify environmental triggers of type 1 diabetes by following over 6,000 children at high genetic risk. Results from TrialNet and TEDDY studies are refining understanding of type 1 diabetes risk, and identifying intermediate endpoints for trials, which could facilitate smaller, shorter, and simpler trials.

To overcome the lack of biomarkers that predict diabetic wound healing, NIDDK plans to launch the Diabetic Foot Consortium, a group of clinical research centers that will conduct coordinated studies to validate biomarkers for diabetic foot ulcers. Through its Diabetic Complications Consortium, NIDDK solicited pilot studies for biomarkers of diabetic foot ulcers; these and other biomarkers will be discussed at an October 2018 meeting that will inform studies of the Diabetic Foot Consortium. In a recent study of wound healing with implications for biomarker discovery, NIDDK-supported scientists found that a type of inflammatory response cell—macrophages—converts into a skin-like cell at wound sites and that this process is crucial for wound closure and may be impaired in diabetic wound healing.

To identify new and emerging research opportunities to unravel the complex relationship between diabetes and neurocognitive conditions, including efforts to identify biomarkers of neurocognitive change, NIDDK, in conjunction with the National Institute on Aging (NIA) and other NIH Institutes and Offices, recently supported several workshops to solicit input from scientific experts. In addition, neurocognitive function is being measured by multiple tests in NIDDK’s recently extended Epidemiology of Diabetes Interventions and Complications (EDIC) study, the observational follow-up study of the landmark Diabetes Control and Complications Trial, and magnetic resonance imaging is being used to measure brain volume and detectable vascular, neurodegenerative, and functional changes. NIDDK and NIA partnered to continue the Diabetes Prevention Program Outcomes Study (DPPOS), the observational follow-up to the landmark Diabetes Prevention Program, and to include cognitive tests. Measurements taken in EDIC and DPPOS will not only determine the impact of diabetes and other factors on neurocognitive function, but will also inform discovery, prioritization, and validation of biomarkers of neurocognitive change. With funding for Alzheimer’s disease research managed
by NIA, NIDDK was also able to expand several existing grants that were not originally focused on Alzheimer’s disease and its related dementias to allow them to develop a focus on those areas.

The NIA Intramural Research Program (IRP) is also collaborating with extramural and other intramural and extramural scientists and industry to develop and test a class of diabetes drugs (GLP-1 receptor agonists) in neurological disease. Significantly, however, in separate research, investigators with the Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes follow-up study (ACCORDION MIND) found no effect of an intensive blood glucose intervention on cognitive outcomes or brain MRI approximately 80 months after the intervention was completed; trial participants were ages 55-80, with long-standing diabetes that was treated at least to the standard guidelines. ACCORDION MIND was supported by the IRPs of the NIA and the National Heart, Lung, and Blood Institute, with support from other NIH Institutes including NIDDK.
Biomedical Research Facilities

The Committee believes that the Nation's biomedical research infrastructure, including laboratories and research facilities at academic institutions, is out of date and insufficient. Therefore, the Committee has provided $50,000,000 for grants or contracts to public, nonprofit, and not-for-profit entities to expand, remodel, renovate, or alter existing research facilities or construct new research facilities as authorized under 42 U.S.C. section 283k. The Committee urges NIH to consider recommendations made by the NIH Working Group on Construction of Research Facilities, including making awards that are large enough to underwrite the cost of a significant portion of newly constructed or renovated facilities.

Action taken or to be taken:

The Office of Research Infrastructure Programs (ORIP), located in the Division of Program Coordination Planning and Strategic Initiatives (DPCPSI) within the NIH Office of the Director, is authorized to issue and manage construction awards to biomedical extramural research institutions, when funds for such awards are appropriated by Congress pursuant to authorities in 42 U.S.C. Section 283k.

Consistent with Federal regulations, NIH submits all construction grant applications to a two-level peer review process. The first level of review is for scientific merit and is conducted by the Scientific Technical Review Board (STOD) authorized by 42 U.S.C. Section 283k; the second level is overseen by the DPCPSI’s Council of Councils. Following funding decisions and issuing of the Notice of Award, applicants are required to submit design construction documents; these documents are reviewed by the NIH Office of Research Facilities (ORF) Division of Technical Resources (DTR) to ensure compliance with the NIH Design Requirement Manual. Grant recipients are allowed to proceed with construction only after the design documents have been accepted by DTR. This formal review process ensures that taxpayers receive the full value of investments in biomedical research.

In addition, in accordance with Federal regulations, NIH provides construction surveillance to ensure that construction is compliant with the approved design documents. Lastly, NIH monitors the long-term use of the facility for its intended functions under the Notice of Federal Interest.
Blepharospasm
The Committee is pleased that NEI is expanding research on blepharospasm, a form of dystonia. The Committee encourages NEI to work with NINDS and stakeholders on cross cutting research opportunities that affect all forms of dystonia.

Action taken or to be taken:

Blepharospasm is a condition characterized by sustained and involuntary eye twitching and blinking that interferes with vision. It is associated with an abnormal function of the basal ganglion from an unknown cause. The basal ganglion is the part of the brain responsible for controlling the muscles. In rare cases, heredity may play a role in the development of blepharospasm, but most people develop the condition without any warning symptoms. The onset may begin with a gradual increase in blinking or eye irritation. Some people may also experience fatigue, emotional tension, or sensitivity to bright light. As the condition progresses, the symptoms become more frequent, and patients may develop facial spasms. Interestingly, blepharospasm may decrease or cease while a person is sleeping or concentrating on a specific task.

At the National Eye Institute (NEI), blepharospasm research is funded within the Oculomotor Systems Program. NEI research is applying new tools in genetics, immunology and neuroscience to expand understanding of various causes and develop treatments for blepharospasm. Additionally, the NEI Corneal Diseases Program, which covers ocular surface conditions, includes research on the causes and treatments of blepharitis, an inflammation of the eye lids, which can cause eye twitching. NEI works together with the National Institute of Neurological Disorders and Stroke (NINDS) and other neuroscience institutes on tools and resources common to neurological conditions. The NINDS dystonia research portfolio includes blepharospasm. NINDS studies are identifying genetic and environmental factors and metabolic markers associated with dystonia to improve accurate diagnosis and effective treatment. A large international genomics study31 funded by NINDS, as well as the National Institute of Aging, National Institute of General Medical Sciences, the Department of Defense, and private funders, recently sequenced the DNA that provides the instructions for the entire set of proteins in 31 individuals with blepharospasm from 21 independent pedigrees. By comparing variants of genes that differed in these individuals, they identified 14 new candidate genes that may play a role in blepharospasm. The National Center for Advancing Translational Sciences funds the cross-cutting Dystonia Coalition, a large international network of scientists focused on developing new therapies for primary dystonias, including blepharospasm, and Meige syndrome, a rare disorder that involves blepharospasm and dystonia of the mouth. The coalition has projects to understand the natural history of dystonias, to provide universal diagnostic guidelines and rating scales to monitor progression and to identify biomarkers of disease.

BRAIN Initiative
The Committee recommendation includes bill language transferring $57,500,000 from the NIH Innovation Account to NINDS to support the BRAIN Initiative. These funds were authorized in the 21st Century Cures Act (PL 114–255). The Committee recognizes the importance of neuroscience research funded by NIH, which is fueling a vital scientific endeavor and is the essential foundation for understanding and treating diseases that impact over 100 million Americans each year. The Committee also commends NIH for its successful implementation of the BRAIN Initiative, and for its 5 year partnership with an array of agencies. This collaborative effort is revolutionizing the understanding of how neural components and their dynamic interactions result in complex behaviors, cognition, and disease, while accelerating the development of transformative tools to explore the brain in unprecedented ways making information previously beyond reach accessible. The Committee encourages NIH to continue to build off its 5 years of success as a leader and partner on the BRAIN Initiative bringing together various disciplines and funding meritorious research to advance our knowledge of the brain.

Action taken or to be taken:
To date, the BRAIN Initiative has launched more than 450 research projects, large and small, led by nearly 600 principal investigators. Funding the most meritorious research has always been at the heart of NIH success, and the special challenges of advancing our knowledge of brain circuits warrant a strong emphasis on engaging experts from many scientific disciplines. NIH recognizes that the remarkably collaborative and trans-disciplinary nature of the BRAIN Initiative has been the key to its encouraging progress to date, and NIH will continue to build on that strategy. At the Federal level, the NIH has developed effective working relationships with other agencies, including the National Science Foundation, the U.S. Food and Drug Administration, the Defense Advanced Research Projects Agency, and the Intelligence Advanced Research Project Activity. Non-governmental organizations, including the Allen Institute for Brain Science, Janelia/Howard Hughes Medical Institute, and the Kavli Foundation, and several Industry and University partners are also integral to the project. The BRAIN Initiative Alliance helps coordinate activities of federal and non-federal partners and inform the public and engage the scientific community about scientific successes from BRAIN Initiative projects. Within NIH, the Initiative is managed by teams of scientific program managers who bring diverse expertise from across NIH. And, most importantly, the research projects themselves bring together as many experts from physics, chemistry, materials science, engineering, molecular and cellular biology, mathematics, and computer sciences as from across the breadth of neuroscience. For example, more than 1,000 scientists and engineers participated in the most recent annual BRAIN Initiative investigators meeting to exchange information and extend their growing networks of collaboration across the various types of projects and consortia that make up the Initiative.

Development of the BRAIN 2025 plan, which guides the BRAIN Initiative, was itself led by a team of scientists of diverse expertise, through extensive consultation with the broader scientific community. As the Initiative moves into its second five years, in keeping with the advice of that original group, the NIH Director has tasked a BRAIN 2.0 Working Group of external experts as well as a new team of scientific advisors to assess progress to date and consult with the scientific community to ensure that the BRAIN Initiative takes advantage of newly emerging opportunities to advance toward its ambitious goal.
Brain Research through Advancing Innovative Neurotechnologies [BRAIN] Initiative

The Committee continues its strong support of the BRAIN Initiative, providing $429,380,000. Deciphering the complexity of the human brain is a tremendous endeavor that requires large-scale, collective efforts. The focus of the initiative, to accelerate technology development to show the brain's structure and function at the level of its cellular components and the functional circuits they form, is a grand challenge that can only be approached as a Big Science effort. Like the Human Genome project and its impact on genetics, the Initiative will be transformative for neuroscience. The Committee encourages a continuation of this unique opportunity to do Big Science in which large, multi-disciplinary teams work together to generate and scale up innovative technologies to produce large, publicly available datasets. As the BRAIN Initiative moves from its early emphasis on development of technologies to greater investment in production and analysis of data, the Committee encourages NIH to work with its Federal, academic and private partners, as well as leaders in the technology sector, to continue to jointly develop and adequately fund integrated, scalable data analysis hubs for BRAIN data as well as methods for tool dissemination. The goal of such an effort would be a network that has at its core an interconnected open platform of imaging, neurophysiological, behavioral, clinical, and molecular data along with the metadata essential for its interpretation. This collaborative effort would guide development and sharing of best practices in data acquisition, analysis, and choices in computational pipelines. Open sharing on this scale would enable data analysis and visualization across institutional boundaries to accelerate understanding of brain function and dysfunction.

Action taken or to be taken:

Sharing of data and dissemination of technological advances are at the heart of the BRAIN Initiative, as noted in the BRAIN 2025 strategic plan that guides the Initiative. In its early phase, the Initiative emphasized these principles through management of individual projects and consortia, encouraging collaborative projects, and networking activities, such as the annual BRAIN Initiative investigators meeting. As new tools emerge from early BRAIN investments and pilot projects are maturing to larger scale data generation, NIH is focusing direct support to enhance tool dissemination and data sharing. In fiscal year 2018, the BRAIN Initiative is funding the first targeted resources focused on technology dissemination, with specific projects on advanced capabilities for brain mapping, high resolution connectomics, simultaneous monitoring of large numbers of neurons’ activity, behavioral quantification, and other methods. Likewise, in fiscal year 2018, the initiative is scaling up data resources, including: 1) web-accessible data archives to capture, store, and curate data, 2) standards for different types of data that will facilitate sharing, 3) informatics tools for analyzing, visualizing, and integrating. Through these activities, the BRAIN Initiative is building the data infrastructure one experimental area at a time to ensure that the data are immediately useful to the research community, but with a longer-term goal of creating linkages among these various domain specific informatics efforts.

This strategy arises because the BRAIN Initiative faces data challenges that are quite different from the Human Genome Project. Research on brain cell types illustrates the complexity. A comprehensive characterization of brain cell types is critical for understanding how brain circuits generate behaviors and for gaining access to specific cell types to control them and analyze
active brain circuits. The initial 10 pilot projects of the BRAIN Initiative Cell Census Consortium made remarkable progress in developing, validating, and scaling up genomic and anatomical mapping technologies. This laid the groundwork for the larger scale BRAIN Initiative Cell Census Network, now underway, whose integrated centers, collaborating laboratories, and data resources will provide researchers with a comprehensive reference atlas of the diverse cell types in human, monkey, and mouse brain. Unlike the Human Genome Project, which captured mainly gene sequence data, characterizing cell types requires multiple modalities of data, including a cell’s location, anatomical structure, connectivity, gene expression, and physiological characteristics, such as its electrical behavior, as well as developmental changes. Other aspects of the BRAIN Initiative add yet more types of data.

As the BRAIN Initiative moves forward to its second half, the NIH Director has engaged a BRAIN 2.0 Working Group of external experts, who are assessing progress to date and emerging opportunities for the BRAIN Initiative. Optimizing data sharing and dissemination of technologies are a key part of their focus, which includes extensive consultation with the research community.
BSL-4 Laboratory
The Committee encourages NIH to evaluate the need for additional BSL--4 laboratory space for the purpose of addressing the growing threat posed by current and emerging infectious diseases. Priority should be given to organizations with a history of efficiently and successfully conducting this complex research.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) has the lead for the National Institutes of Health (NIH) in conducting and supporting research to address emerging and re-emerging infectious diseases, as well as potential bioterrorism threats. The goals of this research are to advance our understanding of the underlying pathogenesis, and to develop new and improved diagnostics, vaccines, and treatments for these diseases. To facilitate the conduct of this research, NIAID supports state-of-the-art facilities where research on these pathogens can be safely conducted, including four biosafety level (BSL)-4 laboratories capable of housing research on pathogens requiring high levels of containment. These specialized facilities are designed to protect the laboratory workers as well as the surrounding community in the unlikely event of an accidental exposure to infectious agents such as Ebola, Lassa, or Marburg viruses.

While infectious disease outbreaks can lead to an increase in research addressing the pathogens causing these outbreaks, the current capacity of BSL-4 facilities allows for a surge in high-containment research in response to an outbreak. This was demonstrated during the 2014-2015 Ebola virus outbreak in West Africa, which was accompanied by a substantial increase in NIH-funded Ebola research requiring high-containment facilities. With the recent addition of the BSL-4 laboratory at Boston University, which became fully operational in 2018, there is sufficient capacity at existing BSL-4 laboratories in the United States to carry out the NIH mission to develop medical countermeasures for biodefense and emerging and re-emerging infectious diseases.

At this time, it is the assessment of NIAID and the NIH that there is not a need for additional BSL-4 facilities to conduct NIH-funded research. NIAID will continue to closely monitor infrastructure needs, including BSL-4 facilities, to enable the safe conduct of NIH-funded research in support of the development of medical countermeasures for emerging and re-emerging infectious diseases and potential bioterrorism threats. NIAID remains committed to supporting a robust basic and translational research portfolio while also responding rapidly to infectious disease threats of public health concern.
Caregiver Dementia Initiative
At any given time, more than 15 million Americans are providing informal care to an older relative with dementia. However, dementia caregivers experience considerable stress and depression and impaired subjective well-being, self efficacy, and physical health. The Committee encourages NIA to fund a pilot community-based peer support program designed to develop an accessible, feasible, and sustainable program that capitalizes on the expertise of former caregivers. Persons who previously cared for a person with dementia but have transitioned out of that role can provide one-on-one problem-solving, or coaching, for current dementia caregivers. Family care is preferred by both family members and persons with dementia themselves, and removes a substantial burden from the US healthcare system.

Action taken or to be taken:
NIA currently supports a pilot project to develop and test an evidence-based peer support program in which persons who previously cared for an elder relative but have transitioned out of that role provide one-on-one problem-solving support for current family caregivers similar to themselves. The “Caregivers Help In Problem-Solving” (CHIPS) program will be based in an adaptation of a well-known technique, problem solving therapy, for use by lay peer counselors. The study will identify benefits not just for current caregivers, but also for the former caregivers who serve as their peer counselors. This intervention is not specific to dementia caregivers, and further research will be needed to ensure that the results, when produced, are generalizable to that specific population.

NIA supports a wide range of additional research on caregiving, including population-based research that provides important insight into the unique challenges and needs of dementia caregivers. For example, researchers with the longitudinal National Study of Caregiving interview caregivers of older persons with and without dementia about multiple facets of the caregiving experience. The Health and Retirement Study also collects data on caregiving.

Investigators funded by NIA are also developing and testing a variety of interventions to reduce caregiver burden and improve outcomes. Some are leveraging new technologies, including robotics, to assist people with Alzheimer’s disease and related dementias (AD/ADRD) and their caregivers with a range of daily activities. Others are testing mindfulness meditation and cognitive interventions to enhance well-being in caregivers. Still others are identifying and addressing the specific needs of caregivers from underserved racial, ethnic, and socioeconomic populations.

In FY 2018, NIA solicited applications for new Edward R. Roybal Centers for Translational Research on Dementia Care Provider Support. Roybal Centers conduct preliminary research to develop behavioral interventions, programs, or practices that promote healthy aging, and the new Dementia Care Centers will focus on behavioral interventions that improve the health, well-being and/or capacity of individuals and/or systems that provide care to persons with AD/ADRD.

NIA’s research on caregiving is strongly informed by the priorities established at the October 2017 National Research Summit on Dementia Care. Recommendations from the Summit were released in April 2018, and the next Care and Services Summit is scheduled for March 2020.
Cerebral Palsy
The Committee commends NINDS for developing the CP 5-year Strategic Plan and urges NINDS to implement Funding Opportunity Announcements in support of the top research priorities and increase its CP research efforts for prevention, treatment, and cure through the lifespan. The Committee encourages funding for basic, translational, and implementation research (including regenerative medicine and genomic research) for understanding mechanisms underlying CP and improving outcomes for patients with CP, and recommends collaboration with the research and advocacy community to accelerate clinical research in CP. Furthermore, the Committee recommends that NIH form a trans-NIH working group of program officers who manage their institute's CP portfolio and that the group regularly interact with CP patient advocacy groups.

Action taken or to be taken:

The 2017 Strategic Plan for Cerebral Palsy (CP) Research developed by the National Institute of Neurological Disorders and Stroke (NINDS) and the Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD) outlines priorities for research to advance the prevention and treatment of CP across the lifespan. NINDS and NICHD work together to foster research focused on these priorities and partner with other NIH Institutes in areas of shared interest. NINDS and NICHD interact often with the CP research and advocacy communities at scientific conferences and other events, and CP experts serve on advisory groups for NINDS and NICHD’s National Center for Medical Rehabilitation Research (NCMRR). NINDS and NICHD will initiate working group meetings among NIH program staff whose portfolios include CP to promote more opportunities to work together and collaborate with the CP community.

NINDS supports research on mechanisms leading to CP, health outcomes for those affected, and interventions for treatment and prevention. As an early response to the strategic plan, NINDS developed Common Data Elements for CP research to facilitate high-quality clinical studies and data harmonization. NINDS continues to work with CP researchers to update this resource. Two clinical trials are testing whether erythropoietin, a commercially available hormone, can prevent death or neurodevelopmental disability in infants born very premature or with hypoxic/ischemic encephalopathy (HIE) due to blocked oxygen/blood flow to the brain. An NINDS-funded study on outcomes, including CP, after extremely premature birth is now part of the Environmental influences on Child Health Outcomes (ECHO) Program, an NIH initiative leveraging several clinical cohorts. In ECHO, the study will add new analyses on prenatal environmental exposures, inflammation effects on the placenta, and neurodevelopmental outcomes at 15 and 18 years. A major focus of NINDS CP research is understanding how early insults, such as HIE, intrauterine infection, and hemorrhage, affect brain and spinal cord development. Researchers are identifying mechanisms that could be harnessed in future protective or regenerative therapies, including changes in early neural circuits and a signaling pathway that disrupts repair following neonatal white matter injury. For example, an NINDS Translational Research Program project is developing a nanotechnology-enabled drug that showed neuroprotective effects in an animal model of CP. NINDS also joined the National Heart, Lung, and Blood Institute (NHLBI) in a funding opportunity for research on perinatal stroke, a significant cause of CP, and four new projects were funded on potential treatments, rapid stroke detection in newborns, and disease mechanisms. Beyond prematurity and early brain injuries, little is known about the role of
NINDS supports a new project to look for gene variants linked to CP in 500 parent-child trios, an effort involving patient advocacy and research organizations as partners.

NICHD funds CP research on the prevention of preterm birth, the causes of early brain insults, and the development of interventions to improve motor and intellectual skills. An NICHD-supported randomized controlled trial found that intraventricular hemorrhage, which often leads to CP, could be prevented or ameliorated by delayed umbilical cord clamping, alone or combined with approved medical therapy. Through NCMRR, NICHD supports research on rehabilitative approaches for CP, including studies in children with CP to evaluate vibration devices to improve muscle function and balance, electrical stimulation to address paralysis in the hands, and intense physiotherapies to promote function very early in development. Studies in adults with CP are examining new neuromodulation therapies, such as transcranial direct current stimulation, in conjunction with robotic therapies to promote hand and arm function. NICHD also supports three trials on improving upper limb function through constraint induced therapies.
Childhood Cancer STAR Act
The Committee has included sufficient additional funding for implementation of the Childhood Cancer Survivorship, Treatment, Access, and Research [STAR] Act. The Committee has included additional funding for HHS operating divisions consistent with the various programs authorized in the bill. This includes funding for NCI to support childhood, adolescent, and young adult cancer survivorship research, as well as biospecimen research in these populations and funding for CDC to enhance pediatric, adolescent, and young adult cancer surveillance.

Action taken or to be taken:
The NCI is actively working to implement provisions of the Childhood Cancer STAR Act directed toward the Institute and recognizes the importance of research focusing on cancer survivorship of children and adolescents and young adults (AYA), and the need for robust biospecimens from these patients and related research tools. The provisions in the STAR Act build upon NCI’s vast portfolio in these areas, including initiatives recently launched as part of the Cancer MoonshotSM. NCI currently supports a portfolio of programs and grants in the survivorship field that focus on both prospective and retrospective studies with childhood and AYA cancer survivors. These studies often focus on determining the differences in adverse outcomes of survivors, risk of subsequent cancers and other medical conditions, psychosocial issues and outcomes, and the late effects of treatment for childhood cancer, which includes reproductive complications. Please see the Significant Item on the Office of Cancer Survivorship for more details about ongoing research in this area. NCI will continue to fund childhood and AYA survivorship research to address the unique needs of this population.

In addition, NCI plans to enhance NCI-supported biorepositories and biospecimen collection from pediatric and AYA cancer patients to build upon existing research efforts in this area. The Children’s Oncology Group32, part of the NCI-sponsored National Clinical Trials Network, has a biorepository which maintains the largest pediatric cancer biospecimen bank in the nation. This valuable resource will be important to NCI’s strategy to enhance biospecimen collection of pediatric and AYA tumors, as well as related biorepository and data resources. Also, Cancer Moonshot initiatives to identify novel pediatric immunotherapy approaches and create human tumor atlases will provide new biospecimens for analysis.

---

32https://www.childrensoncologygroup.org
Children’s Oncology Group
The Committee continues to support the important work of the Children’s Oncology Group and other pediatric research efforts to advance drug development. Pediatric cancer patients and their families rely heavily on the trials run by the Children’s Oncology Group. The vast majority of childhood cancer patients are enrolled in trials conducted by the Children’s Oncology Group and advances in treatment are dependent on the cancer research community’s ability to conduct trials quickly and enroll as many pediatric patients as possible.

Action taken or to be taken:

The NCI thanks the committee for their support of the Children’s Oncology Group (COG). COG is part of the NCI National Clinical Trials Network.33 This network provides the infrastructure for NCI-funded treatment, screening, and diagnosis trials to improve the lives of all cancer patients. Specifically, COG develops and coordinates pediatric cancer clinical trials that are available at over 200-member institutions, including cancer centers throughout the United States and Canada. COG hospitals treat over 90% of children with cancer in the United States.

NCI and COG are supporting many clinical trials of novel and targeted therapies, including immunotherapies, and trials for cancer control and survivorship studies. This includes the Pediatric MATCH trial launched in July 2017. The goal of the trial is to screen at least 1,000 children and adolescents 1-21 years of age who have refractory or recurrent solid tumors. The aim of Pediatric MATCH is to determine whether identifying genetic changes in a patient’s tumor and using an agent to target the specific genetic changes will result in the tumor shrinking in size. Currently, 9 treatment arms are open to accrual, with 4 more opening in the next year. At least 20 patients may be enrolled on each treatment arm. Since the study opened, close to 300 children and adolescents have been enrolled for screening. The Pediatric MATCH Trial is accessible at over 200 COG sites across the country.

33https://childrensoncologygroup.org
Chronic Fatigue Syndrome

The Committee is pleased that NIH has begun to expedite research into ME/CFS. However, NIH itself has acknowledged that there are too few centers and that 10 to 20 times more funding is required to make progress in the field. The Committee is concerned that NIH’s current plans to increase research activities and funding will take too long to produce the FDA-approved treatments and diagnostic tests critically needed by patients and their doctors. The Committee urges NIH to collaborate with disease experts and the patient community to identify additional opportunities to expedite progress on this understudied disease. Specifically, the Committee recommends that NIH increase research to: (1) identify underlying causes of the illness to enable therapies that would effectively prevent or treat the illness; (2) identify biological markers linked to the various forms of the illness to optimize selection of specific patient sub-groups for trials; (3) increase investigator-initiated studies and early stage investigator awards; (4) develop mechanisms to incentivize researchers to enter the field.

Action taken or to be taken:

NIH appreciates the need to continue to expand and advance ME/CFS research and is working to better understand the causes of this disease and to grow the field of researchers in this area.

In 2017, NIH announced funding for three ME/CFS Collaborative Research Centers (CRCs) and an accompanying Data Management and Coordinating Center. Studies being carried out in the CRCs 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. The CRCs are working to develop new diagnostics and identify novel biomarkers of the disease and will also develop ways to stratify patients into subgroups based on clinical presentation. The NIH portfolio of investigator-initiated research in ME/CFS also includes studies to understand the causes of the illness, such as genetic factors, immune mechanisms, and the role of gender. In addition, the National Institute of Neurological Disorders and Stroke (NINDS), together with clinicians, researchers, individuals with ME/CFS, and caregivers, has developed and released the first set of Common Data Elements (CDEs) for ME/CFS. These data standards enable investigators to systematically collect data and help facilitate study start-up, data aggregation, and data sharing across studies. This will be particularly important as new therapies move into clinical testing. An NIH intramural study on ME/CFS is underway at the NIH Clinical Center to evaluate individuals with ME/CFS with the goal of learning more about the clinical and biological markers and mechanisms of the disease. NIH appreciates the continued work of ME/CFS advocacy organizations to improve recruitment for this study.

NIH is eager to provide funding to investigators in ME/CFS who submit meritorious grant applications and continues to encourage new research projects, especially from trainees and early-stage investigators. NIH program officials regularly give presentations at professional meetings to educate researchers about the grant application process and to underscore NIH’s commitment to funding high-quality research in this area. NIH hopes that the CRCs will help build a strong foundation for research and attract new researchers to the ME/CFS field.

Twenty-four NIH Institutes, Centers, and Offices, led by NINDS and the National Institute of Allergy and Infectious Diseases (NIAID), contribute to the effort to advance ME/CFS research, and coordinate their activities through the Trans-NIH ME/CFS Working Group. The Working
Group continues to host regular telebriefings with the patient and research communities, providing updates from NIH and highlighting currently-funded NIH research activities.

Two new activities at NIH will help guide research directions in ME/CFS. The Trans-NIH ME/CFS Working Group will host “Accelerating Research on ME/CFS,” a research conference on April 4-5, 2019 at NIH. In addition, a new Working Group of the NINDS Advisory Council is being formed to make recommendations for improving collaboration between research agencies and ME/CFS stakeholders. This Working Group will include researchers, clinicians and patient advocates.
Chronic Overlapping Pain Conditions
The Committee is concerned with the lack of progress in advancing a comprehensive initiative on Chronic Overlapping Pain Conditions, especially in light of recent findings from major studies funded by the agency demonstrating the significant prevalence and cost of Chronic Overlapping Pain Conditions, as well as the associated disability and detrimental health and quality of life outcomes for those with these debilitating disorders. The Committee strongly encourages the Director to continue to assess the state of science on Chronic Overlapping Pain Conditions and use the findings to continue to advance the scientific understanding of Chronic Overlapping Pain Conditions, as well as the development and discovery of safe and effective treatments.

Action taken or to be taken:

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

The NIH Pain Consortium addressed the objectives of a Workshop, sponsored by the Office of Research on Women’s Health, on chronic overlapping pain conditions (COPCs). The goal of the workshop was to develop research resources to facilitate harmonization of data collection and analysis across clinical studies. Based on recommendations from the workshop, NIH awarded supplements to ongoing studies to expand a standardized research tool, the Complex Medical Symptoms Inventory (CMSI). This tool currently is used to define six of the ten most common overlapping pain conditions. The awards supported modification of the CMSI to include diagnostic criteria for all ten COPCs. The tools have been completed and plans are being considered to validate them in a clinical population and host them on a publicly available website.

NIH supports a study in a large health care system to assess the effect of chronic pain on patient lifestyle and disability. Early findings show that those patients with chronic overlapping pain conditions are more severely affected than those with single pain conditions.

The NIH Pain Consortium also sponsored two Funding Opportunity Announcements (FOAs) to solicit applications in this area: Research on Overlapping Pain Conditions, R01 (PA-14-244)\(^\text{34}\) and R21 (PA-14-243)\(^\text{35}\), for which renewals are pending. Three projects funded through these FOAs aim to elucidate shared mechanistic pathways across overlapping pain conditions. The projects collectively are searching for circulating and tissue markers that occur in more than one chronic overlapping pain condition. These markers will provide clues to common biological mechanisms that underlie COPCs. In addition, a comprehensive longitudinal study to understand the mechanisms by which acute pain transitions to chronic pain is collecting predictive biomarkers that will identify those at risk to develop chronic pain. The ultimate goal is to guide chronic pain prevention strategies and benefit those at risk for COPCs.

\(^{34}\) http://grants.nih.gov/grants/guide/pa-files/PA-14-244.html
Clinical and Translational Science Awards
The Committee encourages the NCATS to fund, through the existing CTSA Program hubs, expanded efforts to improve translational research that address health disparities and the significant burden of conditions that disproportionately affect minority and special populations. Accelerating translational research by making it more efficient and effective will reduce the burden of disease and promote health equity. Applying the CTSA model to address long-standing regional health disparities can provide innovative, multi-disciplinary approaches to reducing the burden of disease among vulnerable populations. The Committee supports the goals of the NCATS program and believes the principles that serve as the foundation of NCATS; public-private partnerships, community outreach, faster access to clinical trials, have tremendous potential for addressing the long-standing diseases associated with health disparities. The Committee encourages NCATS to fund institutions with a history of serving health disparity populations.

Action taken or to be taken:

The National Center for Advancing Translational Sciences (NCATS) funds multiple efforts within the Clinical and Translational Science Awards (CTSA) Program that support the inclusion of diverse populations, particularly minority and special populations, in clinical and translational research. In addition to supporting ‘hubs’ of clinical and translational research (which fund academic clinical and translational science centers, including their career development and training efforts), the program includes initiatives to stimulate and encourage innovation via collaboration, the CTSA Collaborative Innovation Awards (CCIA), and recruitment approaches, the Recruitment Innovation Center (RIC). These activities encourage research to serve a wide range of populations, especially those associated with health disparities that disproportionately affect minority and special populations.

Outreach to various groups such as minority and other underrepresented populations encompasses a major effort towards community engagement activities. For example, the Georgetown / Howard University CTSA initiated a collaboration with African-American faith communities towards improving engagement and recruitment in mental health comparative effectiveness research. These efforts have led to two awards from the Patient Centered Outcomes Research Institute (PCORI). The Stanford CTSA, through its Stanford Precision Health for Ethnic and Racial Equity (SPHERE) Transdisciplinary Collaborative Center, is studying chronic arthritis biomarkers in Native Americans, weight reduction strategies among obese Mexican-American children, and developing communication strategies to discuss genetic cancer risks for Latinos and Asian-American populations.

The four Massachusetts CTSAs (Boston University, Harvard University, Tufts University, and University of Massachusetts) have partnered to address persistent city-wide mortality disparities in breast cancer mortality among minority, low-income women by overcoming barriers to widespread implementation of previously identified evidence-based strategies that reduce delays in care. Systematic deployment of regional patient registries, screening for social barriers to care, and integrated patient navigation services will improve the quality and effectiveness of care delivery.
The University of California at Los Angeles (UCLA) CTSA recently demonstrated outstanding results in a hypertension trial in a nontraditional health care setting (African-American barbershops). Researchers are pairing pharmacists with barbershops to offer high blood pressure care for customers, and the results show that this approach can dramatically lower blood pressure. The researchers will next attempt to replicate these findings in collaboration with other CTSA's in different geographic locations for future widespread dissemination.

The RIC has been involved with multiple clinical trials supported by other NIH ICs to promote and enhance minority recruitment. Examples include recruitment efforts towards African-Americans and Latino populations for a Washington University study addressing age-related cognitive decline and recruitment and retention efforts of African-Americans, Native Americans, Hispanics, and Asian populations for a University of Texas Southwestern Medical Center study evaluating hydroxychloroquine (originally used to treat malaria) as a treatment for lupus.

NCATS and the CTSA Program will continue to emphasize and support clinical and translational research involving minority and special populations, particularly by funding institutions with a history of supporting health disparities research.
CARB
The Committee remains deeply troubled by the global rise of drug-resistant bacteria, and provides $550,000,000, an increase of $37,000,000 to expand efforts to develop new antimicrobials, rapid diagnostics, and other tools and strategies against drug-resistant bacterial infections. The Committee is encouraged by the potential for novel approaches to addressing antimicrobial resistance, such as vaccines, bacteriophages, and antitoxins, but aware that these may be best suited as adjuncts and not as replacements for antibiotics. In an analysis issued last September, the World Health Organization noted that, despite the efforts made in recent years, treatment options remain "lacking for the most critical resistant bacteria, especially for multidrug and extensively drug-resistant Gram-negative pathogens." The Committee encourages NIAID to increase its efforts to support basic science, rapid point-of-need diagnostics, drug discovery, and clinical trials related to Gram-negative carbapenem-resistant bacteria. It commends NIAID for its leadership to address the threat posed by antibiotic resistant bacteria, and its collaboration with Federal partners to increase antibiotic stewardship, including ASPR and CDC, as well as its support for efforts like CARB-X and its international partnerships. The Committee directs NIAID to track trends in Research Project Grants supporting CARB, and requests an update on these activities in the fiscal year 2019 CJ, including an overall assessment of the progress to date of efforts to address the rising threat of drug-resistant bacteria. Senate Report

Antimicrobial Resistance
The Committee recommendation includes at least $538,000,000 within NIAID for research related to combating antibiotic-resistant bacteria. Many infectious organisms have adapted to the drugs designed to kill them, making the products less effective. Because most bacteria, viruses, and other microbes multiply rapidly, they can quickly evolve and develop resistance to antimicrobial drugs. Overusing or misusing antimicrobial drugs can make resistance develop even faster. 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. The Committee requests an update on these activities in the fiscal year 2020 Congressional Justification. House Report

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) continues to support basic research to understand the fundamental biology of disease-causing microbes and the microbial mechanisms used to block antibacterial drugs. This research fosters the development and clinical testing of novel diagnostics, therapeutics, and vaccines to address drug-resistant infections.

The recent funding increases for National Institutes of Health (NIH) antimicrobial resistance research provided by Congress have encouraged additional grant applications that are focused on new and innovative approaches for addressing antimicrobial resistance. NIAID will continue tracking funding trends in research project grants on antimicrobial resistance as well as the outcomes from these studies.
NIAID supports research on the development of novel diagnostic tools to rapidly distinguish between bacterial and viral infections; identify drug-resistant pathogens; and determine optimal treatment strategies at the point-of-need. NIAID is implementing a master diagnostics protocol to enable validation of multiple tests simultaneously in partnership with medical diagnostics companies and academic investigators from the NIAID-supported Antibacterial Resistance Leadership Group (ARLG). NIH is partnering with the Biomedical Advanced Research and Development Authority (BARDA) on the Antimicrobial Resistance Diagnostic Challenge prize competition to identify innovative and rapid point-of-need diagnostic tests, which help inform appropriate antibiotic treatment and facilitate antimicrobial stewardship efforts.

NIAID is advancing the discovery, development, and clinical testing of novel antibiotics and new antibiotic formulations, including therapeutics for difficult to treat infections with carbapenem-resistant Enterobacteriaceae (CRE), methicillin-resistant *Staphylococcus aureus*, and *Neisseria gonorrhoeae*. NIAID also supports clinical trials of strategies to optimize and preserve the use of existing antibiotics for pediatric community-acquired pneumonia, urinary tract infections, and multi-drug resistant (MDR) Gram-negative bacterial infections. The ARLG, which has initiated more than 35 wide-ranging clinical studies in antimicrobial resistance, is developing a Phase 1 clinical trial to evaluate a novel combination therapy for CRE. NIAID also supports CARB-X, a public-private partnership led by BARDA that is funding the development of 28 therapeutic candidates, including 10 new antibiotic classes, as well as 5 diagnostics.

NIAID conducts and supports research on the development of innovative alternatives to antibiotics including bacteriophages, microbiome-based approaches, immune-based therapies, and vaccines. NIAID-supported scientists are working to identify protective bacterial strains that could serve as antimicrobial products to prevent and treat *Clostridium difficile* infection. In addition, NIAID intramural investigators have identified a potential host-directed therapy using an antibody to boost the activity of neutrophils, a type of white blood cell, against carbapenem-resistant *Klebsiella pneumoniae*. NIAID also is supporting development of a new vaccine platform against multiple pathogens, a novel vaccine candidate to prevent *Pseudomonas* infections, and a novel immunoprophylactic against MDR Gram-negative pathogens.

NIAID will continue to build on the significant progress made through intramural and extramural research, as well as through partnerships with other Federal agencies, academia, and industry, to develop medical countermeasures to address the public health threat of antimicrobial resistance.
Collaboration Between Agencies Regarding Pediatric Investigation of Appropriate New Drugs

The Committee recognizes that Title V of the Food and Drug Administration Reauthorization Act (FDARA) amended the Pediatric Research Equity Act to support the early evaluation of potentially effective drugs by requiring pediatric investigation of appropriate new drugs intended for adults with cancer. The law directs the FDA, in collaboration with the NCI, to establish, publish, and regularly update a list of molecular targets considered on the basis of data the Agency determines to be adequate, to be substantially relevant to the growth or progression of pediatric cancers, and that may trigger the requirement for pediatric investigations. The Committee encourages NCI to collaborate with FDA as well as the patient community, providers, and manufacturers, and conduct a transparent and inclusive process to implement FDARA in a timely manner.

Action taken or to be taken:

The NCI and FDA are working together on a variety of activities, including implementation of the Research to Accelerate Cures and Equity (RACE) for Children Act. On August 17, 2018, the FDA, in collaboration with the NCI, released the initial version of the Pediatric Molecular Targets List.\(^\text{36}\) The list contains molecular targets for which existing evidence and/or biologic rationale exist to determine their potential relevance to the growth or progression of one or more pediatric cancers. Currently, it includes 62 gene abnormalities and over 100 other genes that are potential targets for pediatric cancer. Prior to the release, the FDA Oncology Center of Excellence held a public meeting in April 2018, “Relevant Molecular Targets In Pediatric Cancers: Applicability to Therapeutic Investigation FDARA 2017” to collect input from stakeholders in the pediatric cancer research community. NCI staff participated in this meeting, sharing their expert opinions and taking part in panel discussions. During this same time, NCI issued a Request for Information\(^\text{37}\) to collect additional input. FDA held a second public meeting in June 2018, a “Meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee” to review and discuss the list of molecular targets prior to publication in August. NCI experts also participated in this meeting. NCI supports a robust portfolio in pediatric cancer research specifically, and in basic cancer biology, that will continue to inform the molecular targets added to the list. NCI will continue to work with colleagues at the FDA to update the list regularly as scientific advances are made that increase our understanding of the biology of pediatric cancers. NCI is committed to bring the promise of precision medicine to children with cancer through effective targeted therapies.

\(^\text{36}\)https://www.fda.gov/downloads/AboutFDA/CentersOffices
Colorectal Cancer
The Committee notes African-Americans have colorectal cancer incidence and mortality rates significantly higher than other racial groups. Furthermore, the Committee recognizes that research into systemic inflammation may be important for the prevention and treatment of colorectal cancer.

Action taken or to be taken:
Research on the causes, prevention, screening, diagnosis, and treatment of colorectal cancer, including research to address racial/ethnic and urban/rural disparities, remains a priority for NCI. In 2017 NCI launched the Detroit Research on Cancer Survivors (ROCS) study, the largest study to date of African-American cancer survivors in the United States, to examine the major factors affecting cancer progression, recurrence, mortality, and quality of life among African-American cancer survivors, with a focus on lung, breast, prostate, and colorectal cancers.38

Colorectal cancer arises from a complex interplay of several factors, including genetics, inflammation, the gut microbiome, and environmental exposures. NCI supports a broad portfolio of research into each of these factors and their interrelationships, including research conducted by three of NCI’s four Gastrointestinal (GI) Specialized Programs of Research Excellence (SPOREs). The Case Western Reserve University GI SPORE is studying a subtype of colorectal cancer that arises uniquely in African Americans and is characterized by mutations in 15 different genes. The researchers are focusing on the biological basis for developing the mutations that define this subtype and to determine the impact on disparities in outcomes.39 Research also indicates that nonbiological factors, including differences in insurance coverage, uptake of cancer screening tests, and access to quality care, are major contributors to racial disparities in colorectal cancer incidence and mortality. In 2018, results from an NCI-supported study reported a 9 percent difference in 5-year survival between African American and white patients and showed that differences in insurance coverage accounted for nearly half of this disparity. Differences in tumor characteristics accounted for another quarter of the disparity.40

Increasing the rate of colorectal cancer screening in underserved populations is also a goal of the Cancer Moonshot. Recently, NCI-supported researchers conducted a randomized trial testing the use of an iPad application that lets patients order their own colorectal cancer screening tests and provides follow-up reminders. The trial showed that users of the iPad application completed screening at twice the usual rate.41

Researchers are investigating the role of inflammation in cancer development, including colorectal cancer development. Studies have shown that obesity, which causes a state of low-grade chronic inflammation, is associated with increased colorectal cancer risk. In 2018, NCI-supported investigators reported findings from a large study of diet and colorectal cancer risk, showing that participants with diets associated with increased markers of inflammation had higher risk of colorectal cancer (44 percent increase for men, 22 percent increase for women).42

39 https://trp.cancer.gov/spores/abstracts/case_gi.htm
Strategies to mitigate the adverse effects of pro-inflammatory dietary patterns are being explored.
Congenital Heart Disease

The Committee commends NHLBI for its continued work to better understand causation and appropriate treatments for those with the most life-threatening congenital heart defects through its biomedical research program Bench to Bassinet and the critical multi-centered infrastructure of the Pediatric Heart Network. The Committee urges NHLBI to continue its work with other Federal agencies and professional and patient organizations to expand collaborative activities targeted toward prevention and treatment of the diverse lifelong needs of children and adults living with congenital heart disease. The Committee requests a report on these efforts in the fiscal year 2020 Congressional Justification.

Action taken or to be taken:

Congenital heart disease (CHD), the most common birth defect in the United States, is a constellation of conditions that affect the structure of the heart, such as abnormal communications between the heart’s chambers, improperly formed heart valves and blood vessels leaving the heart, or even the absence of one of the two pumping chambers of the heart. CHD remains a leading cause of mortality associated with birth defects. However, because of advances in diagnosis and treatment, children with CHD are living longer lives well into adulthood and there are now more adults than children living with CHD.

The National Heart, Lung, and Blood Institute (NHLBI) supports research focused on understanding the causes of CHD, its natural history, and its co-morbidities across the lifespan. NHLBI’s Bench to Bassinet Program, which comprises the Pediatric Heart Network, the Cardiovascular Development Consortium, and the Pediatric Cardiac Genomics Consortium (PCGC), is leading these efforts. In 2018, the PCGC launched a study to investigate the genomic basis of learning disabilities and developmental delays associated with CHD, as these have a major impact on quality of life.

Many newborns and infants with CHD require surgery, but the care of these babies around the time of surgery varies, which can lead to different health outcomes. NHLBI’s Pediatric Heart Network worked with the Georgia Institute of Technology to develop and implement best practices to speed recovery after heart surgery in infants and children, which have improved recovery times, including earlier removal of assistive breathing devices, after surgery. These improvements in care also have led to decreases in opioid-based pain medications and lower medical costs.43

Approximately fifty percent of all babies born with Down Syndrome have CHD. The new trans-NIH Investigation of Co-occurring conditions across the Lifespan to Understand Down Syndrome (INCLUDE) Project will focus on the critical health needs of individuals with Down Syndrome, including CHD. Appropriate to the multi-organ system nature of Down syndrome and its co-occurring conditions, 18 NIH Institutes and Centers will leverage their expertise and resources in this effort. Given the significance of CHD in Down syndrome, the NHLBI Director is serving as a co-chair of the INCLUDE steering committee. As part of this trans-NIH initiative, two NIH funding two Notices of Availability of Administrative Supplements were

released in the summer of 2018 to supplement existing NIH grants that can advance scientific progress on this disease, as well as other co-morbid diseases.\textsuperscript{44,45} As a result, NHLBI awarded several supplements, including one that increases the number of individuals with both Down syndrome and CHD in the PCGC study to identify genes involved in Down syndrome-related heart malformations. Additionally, the INCLUDE project will build an integrated effort across NIH and engage stakeholders to inform the agenda. Several workshops are planned that will involve scientific and clinical research experts, individuals with Down syndrome, their families and caregivers, and industry partners. These workshops will focus on development of a cohort of individuals with Down syndrome across the lifespan and on the current state of the science for development of clinical trials.

In addition to working with other parts of NIH, NHLBI collaborates with other Federal agencies. NHLBI was instrumental in working with HHS agencies to have critical congenital heart disease added to the Recommended Uniform Screening Panel (RUSP) for newborns in 2011.\textsuperscript{46} The RUSP is a list of disorders that are recommended by the Secretary of the Department of Health and Human Services (HHS) for states to screen as part of their state universal newborn screening programs. NHLBI also partners with the Centers for Disease Control and Prevention (CDC) and the National Institute of Neurological Disorders and Stroke to co-fund the Sudden Death in the Young Case Registry, which collects data on sudden and unexpected death among children (up to age 20), including sudden cardiac death and sudden unexpected death in epilepsy.\textsuperscript{47} NHLBI also participates as a Federal Advisor with the CDC and the Agency for Healthcare Research and Quality in the Congenital Heart Public Health Consortium. The Consortium is made up of individuals and organizations across federal, state, and local communities working together to prevent CHD and improve outcomes for affected children and adults by using public health principles to effect change.\textsuperscript{48}

\textsuperscript{44}https://grants.nih.gov/grants/guide/notice-files/NOT-OD-18-194.html
\textsuperscript{46}https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html
\textsuperscript{47}https://www.sdvregistry.org/
Cystic Fibrosis
The Committee applauds the work of NIH to support research aimed at correcting the genetic defect that causes cystic fibrosis (CF), including recent Requests for Applications that will advance the fields of gene editing, lung stem cell biology, and nucleic acid delivery. Cystic fibrosis is a rare, life-threatening genetic disease that impacts the lungs and digestive system. There are more than 1,700 mutations that cause CF, some of which may only be effectively overcome through genetic repair approaches. The Committee also encourages the continuation of collaborative initiatives to overcome current barriers to implementing genetic repair approaches for treating human diseases. One such project, a joint workshop between the NHLBI and the Cystic Fibrosis Foundation, focused on identifying barriers and proposing solutions to deliver gene editing technologies to the lungs of people with CF as a means to cure the disease.

**Action taken or to be taken:**

The National Heart, Lung, and Blood Institute (NHLBI) continues to support a robust basic and clinical research portfolio for many lung diseases, including cystic fibrosis (CF). This includes research to identify strategies that advance approaches to gene-based therapy. Because CF is a single-gene disease, caused by mutations in the CFTR gene, it is an ideal focus for gene-based therapies, including gene delivery to replace the mutated CFTR gene and gene editing to repair the affected gene. NHLBI is investing in research to develop and test both approaches. For example, in a recent study, researchers used peptide nucleic acids (PNAs), synthetic molecules similar to DNA, to trigger editing and repair of the affected gene in a mouse model of CF.49

The lung airway surface has natural barriers to foreign particles, which has presented a challenge to the development of effective delivery methods for gene replacement therapy and gene editing systems. However, recent NHLBI-funded studies have demonstrated that nanoparticles carrying a molecule designed to attach to the CFTR gene and stimulate DNA repair could correct CFTR mutations in mouse airway epithelium. Such nanoparticles might be used to deliver other *in vivo* gene editing technologies.

NHLBI also participates in the NIH Somatic Cell Genome Editing Program, which aims to develop quality tools to perform effective and safe genome editing in patients.50 The products under development have the potential to impact the future of genome editing strategies for CF and other diseases. The program has issued 12 funding opportunity announcements to develop these research tools, with the first round of funding decisions made in September 2018.

In addition, NHLBI is continuing to form collaborations with organizations such as the Cystic Fibrosis Foundation to help move genetic repair approaches forward. In March 2018, NHLBI partnered with the CF Foundation to hold a workshop on "Advancing Gene Editing Technologies for the Treatment of Cystic Fibrosis." A publication summarizing the workshop recommendations is being developed.

---


50 [https://commonfund.nih.gov/editing](https://commonfund.nih.gov/editing)
Data Sharing of Rare Diseases Research

The Committee is aware that NIH funded projects require a data-sharing plan to encourage transparency and leverage Federal investments in research. At the same time, project leaders and their institutions often cite barriers to implementing these plans in a timely and cost-effective manner. The Committee believes that a focused initiative to show commitment and to improve data-sharing performance in rare disease research, including conditions that disproportionately impact the pediatric population, can create a model for the broader research community and recommends that the NIH develop this initiative in collaboration with patient, provider, and research organizations.

Action taken or to be taken:

NIH reaffirms its support for the concept of data sharing and believes that data sharing is essential for expedited translation of research results into knowledge, products, and procedures to improve human health. NIH endorses the sharing of final research data to serve these and other important scientific goals. NIH expects and supports the timely release and sharing of final research data from NIH-supported studies for use by other researchers. Starting with the October 1, 2003, receipt date, investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why data sharing is not possible.

The National Center for Advancing Translational Sciences (NCATS) Office of Rare Diseases Research (ORDR) partners with multiple NIH Institutes and Centers to support the Rare Diseases Clinical Research Network (RDCRN). The RDCRN was established through the Rare Diseases Act of 2002 and its intent is to advance the diagnosis, management, and treatment of rare diseases with a focus on clinical trial readiness.

The RDCRN currently consists of 21 consortia studying a multitude of rare diseases that impact individuals across the life span, particularly pediatric diseases which are a high proportion of rare diseases. Each of the consortia within the network promotes highly collaborative, multi-site, patient-centric, translational and clinical research. To promote collaboration among rare disease patient and stakeholder organizations and the RDCRN, a Coalition for Patient Advocacy Groups (CPAG) was established to facilitate better access to, and earlier benefit from, research conducted on rare diseases. Each consortia must be actively engaged with the CPAG.

NCATS is taking steps to facilitate the advancement of rare disease research through the sharing of high-value data as a critical goal of the RDCRN. Deidentified data collected within this network and housed within cloud services provisioned by NCATS will become a resource for the greater rare disease research community and will be made available to the scientific community, stakeholders and other relevant partners in a timely manner that meets all NIH human subjects protection, data safety, and data sharing requirements. RDCRN participants will be required to share their data within the Data Management and Coordinating Center (DMCC) of the RDCRN.
The DMCC Data Management Core will provide Cloud Computing Services and Engineering Support provisioned by the Information Resources Technology Branch within NCATS. The DMCC will also coordinate and support efforts, in collaboration with representatives of the consortia, to develop and monitor data standards for clinical and research data and will assist in facilitating the use of common data elements. Through its Engagement and Dissemination Core, the DMCC will establish a broad outreach plan for the RDCRN that will extend to basic and clinical researchers, academic and practicing physicians, patients, and the general public.

The RDCRN, and its efforts to identify and solve data sharing issues, may serve as a future model for data sharing across the entire biomedical research community.
Deadliest Cancers
The Committee remains concerned that while more effective screening methods and treatments have lowered overall cancer incidence and death rates, some forms of cancer remain extremely difficult to diagnose and treat. Defined in statute as "recalcitrant cancers"—those whose 5-year survival rate is below 50 percent—they account for nearly half of all cancer deaths in the U.S. and include cancers of the pancreas, liver, ovary, brain, stomach, esophagus, and lung. Given the toll these types of cancer exact on society, the Committee urges NIH and NCI to continue to support research with an emphasis on developing improved screening and early detection tools and more effective treatments. The Committee expects to receive an update in the fiscal year 2020 CJ of how NCI is advancing these goals.

**Action taken or to be taken:**

The National Cancer Institute (NCI) is dedicated to advancing science for all cancer patients and their families and to supporting cancer control interventions that will help prevent thousands of cancer deaths each year. This includes identifying preventive measures that have the potential to save even more people from ever experiencing a cancer diagnosis. As part of these efforts, NCI is especially committed to advancing research on cancers that have a high mortality rate and a low five-year relative survival, including cancers of the pancreas, liver, ovary, brain, stomach, esophagus, and lung. In 2017 and 2018, NCI funded over 100 grants and awarded a research and development contract aimed at developing improved prevention, screening, and early detection methods, as well as more effective treatments, for these cancers.

Early detection is vital to reducing cancer mortality. In general, patients whose cancers are diagnosed at early stages have more treatment options available to them. Rapid progress has been made in developing liquid biopsy approaches for the early detection of the deadliest cancers, including 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. When this test was applied to blood samples from 1,005 patients with eight different types of nonmetastatic cancer, the presence of cancer was correctly identified 70 percent of the time. For five of the eight cancer types for which no screening tests are currently available (i.e., ovary, liver, stomach, pancreas, and esophagus), the sensitivity of detecting cancer ranged from 69 percent (esophageal cancer) to 98 percent (ovarian cancer).

In addition, researchers are exploring ways in which liquid biopsies can be used to manage the treatment of cancer patients. For example, researchers have shown that analyzing blood samples from patients with early-stage lung cancer for circulating tumor DNA can identify the presence of residual tumor cells or recurrent disease approximately five months earlier than standard-of-care evaluations (CT scan or PET scan). Earlier detection of residual or recurrent disease could facilitate the delivery of interventions earlier when the disease burden is lowest, and hopefully lead to better outcomes for patients.

Researchers have developed new methods of genomic analysis to detect and monitor the progression of Barrett’s esophagus (BE), a precursor to esophageal adenocarcinoma caused by

---

51 www.ncbi.nlm.nih.gov/pubmed/29348365  
52 www.ncbi.nlm.nih.gov/pubmed/28899864
chronic acid reflux disease.53,54 Since BE progresses to cancer at a rate of less than 1 percent per year, these methods will enable doctors to monitor BE patients and intervene before cancer develops.

To encourage additional research to advance the early detection and treatment of high-mortality cancers, NCI has issued funding announcements to establish a Consortium on Translational Research in Early Detection of Liver Cancer55 and a Consortium for Pancreatic Ductal Adenocarcinoma (PDAC) Translational Studies on the Tumor Microenvironment.56 These consortia join existing programs, including the Small-Cell Lung Cancer Consortium,57 the Pancreatic Cancer Detection Consortium,58 the Comparative Brain Tumor Consortium,59 and Pediatric Brain Tumor Consortium.60 In addition, NCI supports Specialized Programs of Research Excellence (SPOREs) focused on specific cancer types, including pancreatic, ovarian, brain, lung, and gastrointestinal cancers (comprised of colon, rectal, stomach, esophageal, small intestine, liver, gallbladder, and other digestive organ cancers).61

NCI strongly encourages the development and use of cancer prevention and early detection methods. NCI also supports a robust array of clinical trials for aggressive, late-stage cancers. For example, in a phase I trial, researchers at Duke University tested a modified poliovirus as part of immunotherapy for adult patients with recurrent glioblastoma and found that 21 percent of the patients remained alive 36 months after treatment, compared with 4 percent of historical control patients. Some of these patients remained alive 57 months or more following treatment.62 The genetically modified virus is infused directly into the brain, where it targets cancer cells to kill them and induce an immune response.63 This therapy, developed after a longstanding collaboration with NCI,64 is now being tested for the treatment of glioblastoma in a phase II trial for adults65 and a phase I trial for children.66 In addition, NCI’s Experimental Therapeutic Clinical Trials Network (ETCTN) is conducting a phase I/II study of olaparib, an inhibitor of certain DNA repair proteins (PARPs) in combination with ramucirumab, an inhibitor of tumor blood vessel formation, in patients with metastatic stomach cancer.67 Investigators at NCI’s Center for Cancer Research also conduct clinical trials focused on low survival rate cancers, including a phase II trial of a new immunotherapy drug (M7824) combined with chemotherapy in the treatment of patients with relapsed lung cancer68 and a phase I/II trial of an investigational

54 www.ncbi.nlm.nih.gov/pubmed/29343623
57 www.mskcc.org/research-programs/nci-small-cell-lung-cancer-consortium
58 www.preventiion.cancer.gov/major-programs/pancreatic-cancer-detection
59 www.ccr.cancer.gov/comparative-oncology-program/research/cbtc
60 www.pbtc.org/
61 www.trp.cancer.gov/
63 www.ncbi.nlm.nih.gov/pubmed/28931654
64 www.today.duke.edu/2018/06/poliovirus-therapy-glioblastoma-has-three-year-survival-rate-21-percent
65 www.clinicaltrials.gov/ct2/show/NCT02986178
66 www.clinicaltrials.gov/ct2/show/NCT03043391
67 www.clinicaltrials.gov/ct2/show/NCT03008278
68 https://clinicaltrials.gov/ct2/show/NCT03554473
immunotherapy (checkpoint inhibitor) in combination with targeted therapies for advanced or recurrent ovarian, lung, breast, prostate, and colorectal cancers.\textsuperscript{69}

Department of Energy [DOE] Collaboration

In 2016, DOE and NCI began a collaboration to develop advanced computational solutions applied to specific areas of cancer research, including pre-clinical drug response, molecular dynamics, and population level surveillance. The Committee encourages NCI to continue this collaboration with DOE and its high performance computing facilities to bring state-of-the-art computational and data analytics capabilities to cancer research, and to continue discussions with potential future collaborators in the ATOM consortium.

Action taken or to be taken:

NCI thanks the Committee for their recognition and encouragement of the highly unique collaborations with the DOE. At the intersection of high-performance computing and cancer research we have an opportunity to advance basic, translational, and population-based research that will benefit both agencies as well as the American people. In addition to the Accelerating Therapeutics for Opportunities in Medicine (ATOM) consortium, NCI has several other partnerships with the DOE. The Joint Design of Advanced Computing Solutions for Cancer (JDACS4C) is one program.\(^{70}\) JDACS4C began with three pilot programs in June of 2016. The commitment to this collaboration has been renewed with DOE, and NCI is pleased to report that many advances are being made in the pilot projects. For example, the exquisite computational abilities contributed by the DOE are being applied to the challenge of understanding the behavior of a mutant protein called RAS in cell membranes. This knowledge will add to the knowledge base essential for helping scientists discover novel ways to intervene in RAS driven cancers. More than 30 percent of all human cancers — including 95 percent of pancreatic cancers and 45 percent of colorectal cancers — are driven by mutations of the RAS family of genes and proteins.

NCI is also leveraging its significant, longstanding investment of coordinating cancer surveillance across the United States. The collaboration with DOE is enabling the extraction of data from novel sources, such as pharmacies, and its integration with existing and newly collected data to increase the breadth and depth of information related to cancer patients, their treatments, and outcomes. The sharing and aggregation of this data will further enable cancer researchers to increase the precision with which every cancer patient is identified, treated, and followed.

Additionally, the CANcer Distributed Learning Environment (CANDLE), builds upon the JDACS4C program and the collaboration between NCI and DOE. CANDLE is a high capacity (exascale) computing initiative that will provide essential new computing capabilities to support the three pilot projects, while delivering critical technologies that are essential to understand, accelerate, and inform the design of future computing solutions in precision oncology.\(^{71}\)

\(^{70}\) https://cbiit.cancer.gov/ncip/hpc/jdacs4

\(^{71}\) https://cbiit.cancer.gov/ncip/hpc/candle
Diabetes
The Committee recognizes the important work of NIDDK, the lead Federal agency conducting research to find a cure for diabetes and improve diabetes care. Individuals with and at risk for diabetes benefit from life-sustaining advancements in preventing and treating diabetes that result from NIDDK studies. The Committee also recognizes the success of the NIDDK supported research in the development of essential tools to manage diabetes, including insulin pumps and blood glucose monitors, ongoing development of artificial pancreas technologies, and new and better medications to treat diabetes. The Committee urges NIDDK to commit resources commensurate with the severity and escalating costs of the epidemic to further diabetes research that will build upon these past successes, improve prevention and treatment, and bring the Nation closer to a cure.

Action taken or to be taken:
Building on past National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-supported research, considerable recent progress has been made toward prevention, treatment, and cure of diabetes. For example, NIDDK-supported research has contributed to the development or testing of new continuous glucose monitors (CGMs) that were recently approved by the Food and Drug Administration (FDA), including the first fully implantable CGM and the first CGM designed to be used as part of an integrated system with other compatible devices and electronic interfaces. These recently approved devices are being tested in NIDDK-supported clinical trials examining novel artificial pancreas (AP) technologies, which link glucose sensing and insulin delivery. Results from these studies could advance interoperability of AP components, so that newly developed insulin pumps and glucose sensors could be paired with existing algorithms, speeding development of next-generation AP devices. Additionally, CGMs that NIDDK supported early in development are now being covered by the Centers for Medicare & Medicaid Services (CMS), further demonstrating how NIDDK-supported research has contributed to new management technologies that are now available to people with diabetes.

The NIDDK also supports research conducted by small businesses to improve diabetes management tools, such as research to develop more accurate and less burdensome devices and AP components. NIDDK-supported research developing AP and other diabetes management tools is being done in conjunction with research developing behavioral interventions, because new tools will only benefit people if they can use them.

NIDDK’s Restoring Insulin Secretion Study showed that in youth 10-19 years of age, rapid progression of prediabetes or recent onset type 2 diabetes is not slowed by early combined use of the two approved medications for pediatric type 2 diabetes; analyses of participants’ metabolic tests are showing how the disease differs in young people versus adults, which can inform new therapies. Research is also showing that complications develop more rapidly when type 2 diabetes begins in youth. Another NIDDK-supported study found that bariatric surgery to treat severely obese adolescents with type 2 diabetes led to improved outcomes, even remission of diabetes, compared to medical therapies. Additional knowledge about type 2 diabetes treatments in adults are expected from NIDDK’s ongoing Glycemia Reduction Approaches in Diabetes: An Effectiveness Study, which is comparing the long-term benefits and risks of four widely used type 2 diabetes drugs in combination with metformin. The Accelerating Medicines Partnership
T2D (type 2 diabetes) Project has developed a Knowledge Portal to identify and validate the most promising biological targets for new diagnostic and drug development.

Toward curing diabetes, the NIDDK’s Human Islet Research Network (HIRN) is studying multiple approaches to replace insulin-producing beta cells destroyed by type 1 diabetes. For example, HIRN is examining the possibility of “editing” cells’ DNA to reprogram pancreatic cells to replace lost beta cells or to otherwise modify the pancreatic environment to protect beta cell health.

Regarding diabetes prevention, CMS is now covering a group-based adaptation of an intensive lifestyle intervention for beneficiaries with prediabetes; this type 2 diabetes prevention approach was first pioneered in NIDDK’s Diabetes Prevention Program clinical trial. An NIDDK-led trial testing whether vitamin D supplementation can delay the onset of type 2 diabetes in people at risk is complete and data are now being analyzed. NIDDK’s Type 1 Diabetes TrialNet just began a new type 1 diabetes prevention trial using hydroxychloroquine, a drug that has long been used safely as a malaria therapeutic and has shown benefit in autoimmune diseases like lupus.
Diversity in Oncology
The Committee is aware of the lack of diversity in the field of medicine and, particularly, in oncology, and is also aware of the program supported by the NCI to increase the diversity in this area. The Committee is supportive of these actions and encourages the Institute to continue and expand its work on this issue.

Action taken or to be taken:
NCI is committed to reducing the unequal burden of cancer in our society via research, including community-based participatory research, and to train the next generation of competitive researchers from diverse populations in cancer and cancer health disparities research. In 2017, NCI trained more than 1,400 underrepresented minority students and investigators through the CURE (Continuing Umbrella of Research Experiences) and PACHE (Partnerships to Advance Cancer Health Equity) programs. Nearly 60% of research projects supported by PACHE over the life of the program have focused directly on disparities research. In the semiannual CURE Distinguished Scholars Seminar in 2017 and 2018, three former CURE scholars were recognized for their seminal contributions to the fields of cancer and cancer health disparities research and for being role models for other scientists from backgrounds that are underrepresented in cancer research. Additional training opportunities include an exploratory grant to promote workforce diversity in basic cancer research and institutional awards to support cancer research education programs (e.g., Youth Enjoy Science and awards to support American Indian and Alaskan Native researchers).

NCI also supports research programs that aim to reduce cancer disparities in underserved populations, including the NCI Community Oncology Research Program (NCORP), planning grants for Cancer Health Disparities Specialized Programs of Research Excellence (SPORE), and the RESPOND (Research on Prostate Cancer in Men of African Ancestry: Defining the Roles of Genetics, Tumor Markers, and Social Stress) study. For more information about these initiatives, please see the Significant Item on Research Initiatives on Racial and Ethnic Diversity in Cancer and on Prostate Cancer.

---

72 https://www.cancer.gov/about-nci/organization/crchd/diversity-training/cure
73 https://www.cancer.gov/about-nci/organization/crchd/diversity-training/pache
74 https://www.cancer.gov/about-nci/organization/crchd/blog/2017/inaugural-cure-seminar
Dual Purpose with Dual Benefit Program (Senate)
The Dual Purpose with Dual Benefit Research in Biomedicine and Agriculture Using Agriculturally Important Domestic Species is an interagency partnership grants program funded by NICHD and the U.S. Department of Agriculture [USDA]. Both USDA and NIH should be commended for developing this important interagency program. The Committee strongly urges continuation of this partnership because it sponsors use of farm animals as dual-purpose models to better understand developmental origins of disease, fat regulation and obesity, stem cell biology, assisted reproductive technologies, and infectious disease which directly benefits both agriculture and biomedicine. This program also strengthens ties between human medicine, veterinary medicine, and animal sciences, which is key to success of the One Health Initiative.

Action taken or to be taken

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the U.S. Department of Agriculture (USDA) established the Dual Purpose with Dual Benefit Program in 2010. The objective of this important interagency program is to stimulate and encourage research investigations in the four areas identified as high priority issues for both biomedicine and agriculture using pertinent domestic farm animal species that mimic specific human developmental, physiological, or disease states. The four areas are: 1) reproduction, stem cell biology, and regenerative medicine; 2) metabolism; 3) developmental origins of adult diseases (DOHAD); and 4) infectious disease. Thus far, the program has awarded 51 grants with 27 focused on the reproduction, metabolism, and DOHAD areas, and 24 in the infectious disease area. Notably, eight of the NIH awards have been given to new (to the NIH) investigators with four being early-stage investigators (an additional 11 new investigators received funding through the USDA).

Excellent progress has been made thus far. In one study, pigs exposed to early weaning stress exhibited increased vulnerability to gastrointestinal disorders that were sexually dimorphic (females more susceptible than males) and mimicked some of the key pathophysiologic findings in human functional gastrointestinal disorders. In another study, obesity of pregnant sheep resulted in increased body mass in male offspring and insulin insensitivity in female offspring that is transmitted to the progeny of those offspring without the requirement that the offspring be obese. Finally, investigators have shown that development of the female reproductive tract can be permanently impaired in offspring that do not receive sufficient amounts of the mother’s milk. This latter finding has implications for development of better milk replacers for livestock offspring and infant formulas for humans.

The research emphasis areas stated in the report language originally were identified in a workshop held in 2007. Given that 11 years have elapsed since that workshop, both the NICHD and USDA staff have begun planning for another workshop to be convened in 2019 to revisit and reassess these emphasis areas with the goal of identifying new areas for future investigation.
Duchenne Muscular Dystrophy
Duchenne muscular dystrophy is a severe type of muscular dystrophy for which there is no cure and for which the average life expectancy is 26 years. The Committee strongly encourages NIH to significantly expand its support for research on Duchenne muscular dystrophy.

Action taken or to be taken:

NIH funds a broad portfolio of basic, translational, and clinical research in many forms of muscular dystrophy, including Duchenne Muscular Dystrophy (DMD). For over 15 years, the Senator Paul D. Wellstone Muscular Dystrophy Research Centers Program has served as a flagship program for muscular dystrophy research at NIH. Several Wellstone Centers are conducting research on DMD, including understanding and modulating fibrosis (formation of excess connective tissue and non-muscle fibers) in a mouse model of DMD, studying the role of genetics in disease progression using imaging biomarkers, and developing gene editing techniques and testing them in DMD mouse models. NIH reissued the Request for Applications for the Wellstone Centers and expects to announce the most recent awards soon. In addition, NIH is carrying out an evaluation of the Wellstone Program, which will be completed in early 2019, to provide insights on how to enhance the program.

NIH also funds a robust portfolio of investigator-initiated research in DMD outside of the Wellstone Program. Several studies are aimed at developing non-invasive imaging biomarkers for DMD, some of which are currently being used as exploratory biomarkers in clinical trials. Other studies focus on the discovery of genetic modifiers potentially associated with the severity and progression of DMD. Additionally, some of the NIH-funded research is for therapy development projects, which include gene and muscle cell therapy studies in animal models, genome editing approaches, and pharmacologic approaches to promote muscle regeneration. NIH also supports active clinical trials in DMD, including a study to determine the optimal steroid dosing regimen, a trial of a novel compound aimed at increasing the efficacy of steroids while reducing side effects, and a first-in-human gene therapy trial to deliver an enzyme that modifies muscle membrane proteins to compensate for the lack of the protein dystrophin in DMD.

One of the goals of NIH’s research support in the muscular dystrophies is to lay the scientific foundations for further investments by industry. For example, NIH supported several projects that uncovered the potential of antisense oligonucleotides (synthetic molecules often used to disrupt disease processes by altering protein synthesis) to modify exon skipping - a way to ‘skip over’ or bypass the faulty part of a gene - in DMD. This research led Sarepta Therapeutics to develop the exon skipping drug Exondys 51, which was approved by the FDA in 2016. Other DMD clinical trials being conducted by industry that are built on NIH research include studies to develop other exon skipping strategies, gene delivery of a micro-dystrophin construct (a way to produce a shorter, but functional, version of the dystrophin protein, which is lacking in patients with DMD), and a trial of an inhibitor of myostatin, a negative regulator of muscle growth.

The interagency Muscular Dystrophy Coordinating Committee has hosted numerous discussions at its recent meetings on topics relevant to research in DMD. At the most recent meeting in April 2018, the Committee discussed lessons learned from recent drug approvals in neuromuscular disease and heard about ways the patient voluntary groups are helping to facilitate access to treatments, particularly for DMD patients. Previous meetings have
highlighted advances in the treatment of cardiopulmonary complications in DMD and biomarkers and outcome measures for the muscular dystrophies.

NIH will continue to fund the most meritorious research applications in all the muscular dystrophies to help ensure a robust portfolio and a pipeline of research to help inform the development and testing of new therapies.
Dystonia
The Committee encourages NINDS to work with stakeholders to revitalize and expand the dystonia research portfolio. The Committee understands the importance of a state of the science conference and continues to encourage NINDS to work with stakeholders and other IC's that research forms of dystonia to examine collaborative research opportunities.

Action taken or to be taken:
In October 2018 NINDS convened a scientific workshop to identify research opportunities to advance the understanding and treatment of dystonia. Participants included researchers in dystonia and other relevant fields of science, clinicians who treat dystonia, representatives of NGOs focused on dystonia, and scientific staff from NIH. The workshop discussed existing data and resources, as well as new tools and techniques that might be brought to bear on dystonia. Topics included the underlying neurobiology of dystonia, animal models that mimic some aspects of the disease, genetics, natural history, neuropathology, and therapeutic approaches. Following up the workshop, the participants are developing a summary for the research and patient community of opportunities for research and collaboration that emerged from the discussion.

NIH continues to support a broad range of research relevant to dystonia, from genetic studies through neuro-engineering approaches. As for all diseases, NINDS relies heavily on investigators at universities, medical centers, and small companies throughout the United States to seek out opportunities and propose research to advance understanding and treatment of dystonia, with rigorous peer review guiding selection of the most meritorious proposals. NIH offers a variety of grant mechanisms, including those that support collaborative projects. We expect that the opportunities emerging from the October workshop will stimulate high quality applications from the research community.

As the workshop discussed, the NIH’s Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative is likely to advance dystonia research in the future. Dystonia symptoms arise from malfunction of the brain circuits that control movement. The Initiative is providing new insights about how brain circuits work, developing new methods to study brain circuits, and exploring new therapies to intervene when circuits malfunction.
Eating Disorder Research
Eating disorders are a serious mental illness that affect 30 million Americans during their lifetime and has the highest mortality rate of any psychiatric illness. The Committee encourages NIH to continue to support eating disorders research, with a focus on applied research in prevention, early identification, and innovative treatment.

**Action taken or to be taken:**

NIMH is committed to funding studies on eating disorders that inform prevention, early identification, and treatment. NIMH will continue to invest in research that helps to clarify the basic biological mechanisms, including genetic factors and neural circuitry associated with eating, reward, and impulsivity that underlie the behavioral dysregulation found among individuals with eating disorders. For example, NIMH-funded researchers plan to calculate the genetic risk for anorexia nervosa as well as risk for comorbidity with obsessive-compulsive disorder using a population-based cohort (~8,000 participants) to better prevent, detect, and treat these disorders.77 Another NIMH-funded study aims to examine the neural mechanisms involved in goal-directed versus habit-based eating behavior across a full spectrum of dietary restriction, ranging from healthy dieters to individuals with anorexia nervosa, which may open new avenues for treatment research.78 Additionally, the microbiome-gut-brain axis plays a critical role in metabolic function and weight regulation, and NIMH-funded researchers are currently exploring the potential relationship between gut microbiota and eating disorder psychopathology.79 This research may enhance current weight restoration therapy and improve treatment outcomes.

Furthermore, NIMH supports research on innovative interventions for eating disorders. For example, NIMH-funded researchers are testing a novel, brief, and relatively inexpensive dissonance-based treatment that focuses on reducing valuation of a body ideal.80 These researchers also propose to examine the neural processes that maintain eating disorder psychopathology and the mechanism of action through which this dissonance-based treatment may produce therapeutic benefit. If efficacious, this treatment may see broad use and address a major need for evidence-based eating disorder treatment. NIMH is also supporting research into the optimization of a large-scale smart phone application to reduce relapse in individuals recovering from eating disorders.81 These researchers are developing and testing application content that may help individuals challenge distorted thinking based on their unique symptom profiles and potentially improve outcomes.

Moving forward, NIMH will continue to support eating disorders research, in alignment with the NIMH mission to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure.

---

Endometriosis.
The Committee is aware that endometriosis is a serious chronic condition that impacts one in ten women in the US between the ages of 10 and 49. Women with this condition can suffer up to ten years before being properly diagnosed, often due to lack of awareness and limited treatment options available. The Committee encourages NICHD to develop a report on the current state of endometriosis. Further, the Committee encourages NICHD, through research and in collaboration with CDC, to continue to support education, outreach, and awareness to promote early and accurate diagnosis of endometriosis.

Action taken or to be taken:

Research on women’s health, including the common disorder, endometriosis, is a research priority for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The Institute supports scientific investigations into the risk factors, etiology, diagnosis, management, and associated morbidity (e.g., infertility and pelvic pain) of this condition. In addition to NICHD support, studies on aspects of endometriosis are funded by other Institutes and Centers (ICs) at the National Institutes of Health (NIH), including research on environmental toxicology (the National Institute of Environmental Health Sciences), physical activity as a therapeutic intervention (the National Center for Complementary and Integrative Health), and the relationship of endometriosis to endometrioid and clear ovarian cancers (the National Cancer Institute).

Currently, the NICHD funds studies across the research spectrum, including an array of basic, translational, and clinical work, ultimately aiming to develop treatments for this painful condition. For example, the Reproductive Medicine Clinical Trials Program is planning a large-scale clinical trial to assess nonsurgical, noninvasive methods of diagnosing and monitoring treatment of endometriosis. In addition, the NICHD is working to encourage even more participation from the field, recently publishing Funding Opportunity Announcements (FOAs) on endometriosis. One FOA is soliciting grant applications to elucidate the role of stem cells in the pathogenesis and treatment of gynecologic disorders, focusing on the cellular dysfunction that may lead to the development of endometriosis. Recognizing that diagnosis of endometriosis is often delayed, another FOA, using the Small Business Innovation Research mechanism, is eliciting applications for non-invasive diagnostics to improve gynecologic health, including endometriosis. The focus of this grant opportunity is to encourage small businesses to collaborate with scientists and clinicians to develop, advance, and validate new devices and methods to shorten the time to diagnosis, decrease the invasiveness of current techniques, and/or improve accessibility, safety, convenience, and costs of diagnosis. The value of using the small business grant mechanism can be seen with the recent FDA approval of Elagolix for moderate-to-severe pain often associated with endometriosis. This compound was developed, in part, through a NICHD-funded small business award.

Investigator-initiated studies have led to important advances in endometriosis. A recent NICHD-funded study showed that childhood abuse is linked to the risk of endometriosis, indicating that it is important to identify the biologic impacts of abuse and the related pathophysiology of various diseases including endometriosis. Multiple ICs at the NIH, including the NICHD, supported the development of EVATAR™, a functional, 3-D human-tissue based model of the full female reproductive system, but which can fit into the palm of a hand. This technology gives scientists a
new tool to understand diseases such as endometriosis and fibroids, both of which can lead to infertility, as well as allowing for pre-clinical testing of drugs in a “human” model.

NICHD is committed to the identification of gaps in our understanding of normal and abnormal menstruation (i.e., painful menses due to endometriosis) as well as improving health literacy among patients and health care providers. To this end, a meeting on “Menstruation: Science and Society” will be held in the fall of 2018 to bring together basic scientists, clinicians, advocacy groups, and global health specialists.
End-Stage Renal Disease

The Committee recognizes NIDDK’s accomplishments in supporting critical kidney research, including research on end-stage renal disease. The Committee notes the recent GAO report on research funding and encourages NIDDK to continue working with stakeholders to disseminate critical information and discuss new opportunities for research.

Action taken or to be taken:

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) continues to work with stakeholders to disseminate critical information and discuss new opportunities for research. The NIDDK-supported U.S. Renal Data System (USRDS\textsuperscript{82}) is a national data system that collects, analyzes, and distributes an Annual Data Report (ADR) about chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the United States. Using data provided by the USRDS, researchers have published peer-reviewed scientific articles that improve our understanding of kidney disease. The 2017 ADR contains substantial information on CKD and on ESRD and covers topics such as prevalence, incidence, acute kidney injury, hospitalization, morbidity, transplantation, and mortality. To spur additional research, the USRDS produces a Researcher’s Guide to the USRDS Database. NIDDK’s ongoing basic kidney research on regeneration and bioengineering functional nephrons is optimizing approaches for isolation, expansion, and differentiation of appropriate kidney cell types and their integration into complex structures that replicate human kidney function and provides a foundational research opportunity to begin to address corrective strategies in kidney disease. The Kidney Precision Medicine Project (KPMP) includes several research teams developing then deploying single-cell or single-nucleus analysis methods to interrogate the heterogenous cell populations in human kidney tissue, in health and in acute and chronic kidney diseases. These tools for discovery will inform KPMP researchers on compelling targets to map back to tissue with multiplex 3D microscopy methods, to understand their location in kidney structures, and improve our understanding of the pathophysiology of kidney disease. NIDDK recently sponsored two workshops to disseminate critical information and discuss new opportunities for research. The Renal Imaging workshop was held July 12-13, 2018, to chart a path forward to functional renal imaging. The workshop had several presentations on state-of-the-art magnetic resonance imaging (MRI) as well as a presentation on biomarkers by staff from the Food and Drug Administration. The Chronic Kidney Diseases in Agricultural Communities workshop was held June 25-26, 2018, and brought together clinicians, basic scientists, epidemiologists, and public health officials to discuss the current gaps in knowledge and to identify research opportunities toward a better understanding of the causes and potential treatments of chronic kidney diseases in agricultural communities.

\textsuperscript{82} http://www.usrds.org/
Epidermolysis Bullosa
The Committee recognizes the promising scientific gains and applauds private partners advancing research in pursuit of treatments for Epidermolysis Bullosa. The Committee encourages NIH to continue to support such research at NIAMS.

Action taken or to be taken:

Epidermolysis bullosa (EB) is a family of inherited disorders of the skin and internal mucosal membranes, and individuals with a severe form of EB often carry mutations in the gene encoding type VII collagen, leading to a nonfunctional protein. For people with EB, the skin and mucosal surfaces are so fragile that even minor rubbing can cause blistering. NIAMS supports a wide range of research to identify the causes of EB and determine new treatments. For example, earlier studies supported by NIAMS and other federal and non-profit organizations have revealed that gentamicin, a common antibiotic, can induce production of functional collagen type VII in skin from patients with a specific genetic mutation. When applied topically to or injected just under the skin of EB patients, the treatment improved wound closure and was durable for three months. To build on this work, NIAMS is supporting a pilot study to examine the safety and efficacy of intravenous administration of gentamicin, which may allow simultaneous treatment of all skin as well as other mucosal sites. If successful, gentamicin therapy could provide a non-invasive treatment option for individuals that carry this type of genetic anomaly, approximately 30 percent of EB patients.

Regenerative medicine technologies have also shown promise in the treatment of EB. Recently, NIAMS-supported scientists have shown that induced pluripotent stem cells (iPSCs) derived from EB patient skin can be genetically corrected and produce functional collagen VII. However, the lengthy process to create the genetically corrected iPSCs can introduce off-target changes to other genes, and the long-term effects of those changes is unknown. NIAMS is supporting research to develop novel techniques that will simplify derivation of therapeutic iPSCs, reducing the number of off-target mutations and enhancing the safety of iPSC-based therapies for EB and, potentially, other genetic diseases.
Fertility Issues for Rare Disease Patients
Patients with rare diseases like thalassemia face a number of issues related to reproductive health, often due to complications from their conditions or treatments. As a consequence of improved treatment options, 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 report on current research and future initiatives to address these issues and provide an update in the fiscal year 2020.

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 serious, debilitating rare diseases such as thalassemia, cystic fibrosis, and sickle cell disease, now are routinely surviving into adulthood and are healthy enough to consider starting a family. However, by the time they reach their reproductive years, individuals with these underlying conditions and/or the consequences of treatment often have severely compromised their fertility, which can be a devastating loss for both the individuals and their families. 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.

Scientific advances made under the auspices of the NICHD and the National Institutes of Health (NIH) Roadmap funding for research into fertility preservation for patients with cancer have built a foundation of evidence for similar issues that patients with rare diseases face. These advances, encompassing cryopreservation (freezing) of eggs and sperm, and the means to fully mature eggs and sperm outside of the body, along with other techniques, provide possible avenues for fertility preservation, including in patients with rare diseases. Multiple Institutes and Centers at the NIH, including the NICHD, supported the development of EVATAR™, a functional, 3-D human-tissue based model of the full female reproductive system that can fit into the palm of a hand. This technology gives scientists a new tool to understand diseases such as endometriosis and fibroids, both of which can lead to infertility, as well as allowing for pre-clinical testing of drugs in a “human” model.

In partnership with NIH’s Office of Rare Diseases, the NICHD is discussing the best ways to approach and address research gaps regarding fertility of patients with rare diseases. Currently, two NICHD-supported consortia within the Rare Diseases Clinical Research Network (urea cycle disorders and brittle bone diseases consortia) are collecting information about pregnancy outcomes in their patients, and this will provide some evidence as to the scope of the issues these patients face. The NICHD plans to expand current research in the Fertility Preservation portfolio specifically to include research in reproductive health and fertility options for patients with rare diseases.
Fibrosis
The Committee recognizes NIH for their work on addressing the need for coordination across ICs on fibrotic research. The Committee encourages NIH to continue working across ICs and with stakeholders to advance critical priorities.

Action taken or to be taken:

The NIH Fibrosis Interest Group comprises more than 50 NIH scientists and trainees with expertise in fibrosis who represent multiple NIH Institutes and Centers, enabling them to discuss the latest advances and opportunities in the field. The monthly interest group meetings promote scientific discovery, generate innovative concepts to improve our understanding of fibrotic diseases, and enhance therapeutic approaches for the improved treatment of disorders that share a common endpoint of organ fibrosis. The group will continue its efforts to enhance coordination and communication across federal and non-federal fibrosis research entities. This includes inviting distinguished speakers from the extramural academic community to present at meetings, engage with NIH investigators, and facilitate research collaboration in strategic areas.

NIH also formed the Inflammatory Disease Interest Group in 2016 to encourage better communication, thoughtful discussions, and NIH-wide collaboration regarding research on the many chronic inflammatory and fibrotic diseases that affect human health. The group convenes two to three day-long symposia per year on various inflammatory disease topics, and hosts a bimonthly seminar series on basic and translational research focused on inflammation. All staff at NIH and other federal health and science agencies who share an interest in basic and translational inflammation research are welcome to participate.  

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

Scientists at NIAID are also conducting novel analyses of gene expression in patients with systemic sclerosis (scleroderma) to better understand signaling pathways involved in scleroderma and other fibrotic diseases that involve excess collagen production.

NHLBI continues to put considerable focus on pulmonary fibrosis research and in September 2018, participated in an all-day patient education day involving a wide range of key stakeholders.

83 https://www.niaid.nih.gov/research/inflammatory-disease-interest-group
Fibrotic Diseases
The Committee encourages the Fibrosis Interest Group to continue its efforts to bring together key stakeholders, at the NIH and elsewhere, to develop strategic paths forward to maximize efforts in fibrotic disease research. The Committee also directs NIH to include an update in its fiscal year 2020 CJ on its work relating to idiopathic pulmonary fibrosis following the November 2012 NHLBI workshop, "Strategic Planning for Idiopathic Pulmonary Fibrosis." The Committee 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. As noted in previous years, the Committee directs NIH to report to the Committee on its progress in meeting the goals enumerated in the November 2014 NHLBI report on Future Directions in Idiopathic Pulmonary Fibrosis Research. The Committee applauds increases in funding for pulmonary fibrosis at the Institute, but remains concerned that funding lags in relation to the devastating impact of the disease and funding for other diseases with similar patient populations and morbidity rates. In addition, the Committee recommends that NHLBI continue to encourage the use of patient registries that are accessible to the pulmonary fibrosis research community and operates in coordination with major medical centers and patient organizations.

Action taken or to be taken:

The National Heart, Lung, and Blood Institute (NHLBI) continues to play an active role in bringing together researchers, clinicians, and patients to strategically support development of life-saving treatments for fibrotic diseases through the trans-NIH Fibrosis Interest Group and unique NHLBI initiatives. In particular, NHLBI is committed to research on pulmonary fibrosis (PF), a progressive, lethal scarring of the lungs, and supports a multi-pronged approach to improve treatments for PF. Guided by the recommendations of the 2014 NHLBI report on the “Strategic Planning for Idiopathic Pulmonary Fibrosis,” NHLBI supports basic and clinical research to reduce the devastating impact of the disease. NHLBI’s current basic research grants focus on the importance of a variety of lung cell types in disease development, progression, and mitigation, as well as specific molecular and genetic determinants of fibrotic diseases. In fiscal year 2018, NHLBI funded two new Program Project Grants focused on identifying and inhibiting cellular mechanisms of lung fibrosis, and continued funding three projects developing therapeutics to treat PF within the Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Diseases (CADET).

Additionally, because some patients with PF have been found to have antibodies directed against their own lung tissue, NHLBI is supporting research to understand the role that these auto-antibodies play in short-and long-term disease progression. To test new therapeutics, NHLBI supports two multi-site clinical studies investigating a combination of therapies that target and reduce autoantibodies known to cause acute exacerbations or serious breathing attacks in patients with PF. Through NHLBI’s Pulmonary Trials Cooperative, a study of antimicrobial therapy for PF is ongoing. Results of a recently completed trial evaluating treatment of PF with laparoscopic anti-reflux surgery were published.
in August 2018, showing a slight, yet not statistically significant, benefit.\textsuperscript{84} The surgery was found to be safe, so further study of this intervention may be warranted.

NHLBI strongly encourages the use of patient registries as a valuable resource for the research community. In July of 2018, the Pulmonary Fibrosis Foundation (PFF) announced that it had achieved its enrollment goal for the initial phase of the PFF Patient Registry with participation of more than 2,000 patients.\textsuperscript{85} The Registry, launched in 2016, is a collection of comprehensive anonymized data from patients living with PF. The registry is an example of a critical open-access resource containing phenotypic clinical data and biospecimens that can be leveraged by investigators to enhance recruitment and retention of patients for clinical trials, as well as support ancillary or independent mechanistic studies to better understand PF’s etiology.

Finding better treatment options for patients with PF is very important to NHLBI. Over the past few years, there has been a steady increase in NHLBI funding for pulmonary fibrosis, in particular, from about $45 million in each of FY 2012 and 2013 to more than $64 million in FY 2017. This funding increase demonstrates not only the number of high-quality grant applications received by the NHLBI, but also a continued commitment to supporting outstanding research on this devastating disease.

\textsuperscript{84} https://www.sciencedirect.com/science/article/pii/S2213260018303011
\textsuperscript{85} https://www.pulmonaryfibrosis.org/medical-community/pff-patient-registry
Focal Segmental Glomerulosclerosis Research
The Committee recognizes the work that NIMHD and NIDDK are doing to address the connection between the APOL1 gene and the onset of Focal Segmental Glomerulosclerosis (FSGS). The Committee encourages NIMHD to work with community stakeholders caring for the affected population to identify areas of collaboration.

Action taken or to be taken:
The National Institutes of Health (NIH) supports research to increase understanding of the association between the APOL1 gene and the onset of Focal Segmental Glomerulosclerosis (FSGS), a rare disease that affects the filtering units of the kidneys and can cause significant scarring that leads to kidney damage or failure. This work includes the launch of the APOL1 Long-term Kidney Transplantation Outcomes Network (APOLLO) Clinical Centers program, one year ago, led by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and co-funded by the National Institute on Minority Health and Health Disparities (NIMHD). The multi-center multidisciplinary network of investigators provides an opportunity for NIMHD to support the program’s community engagement efforts to reach and involve racial and ethnic minorities in the project.

The APOLLO Consortium has made important progress in its first year, including the development of a protocol and a Manual of Procedures, and presentation of its research plan to an External Evaluation Panel. A key element of the Consortium’s work was the initiation of a Community Advisory Council (CAC) which includes individuals of African ancestry who have personal experience with chronic kidney disease, kidney transplantation or kidney donation, and a CAC member who serves as a full voting member of the Steering Committee. The CAC participated in meetings of the Steering Committee, provided input to the Consortium regarding recruitment, sharing of results, and the informed consent process.

In another NIH project, supported in part by NIDDK and NIMHD, researchers sought to understand why high-risk APOL1 gene variants do not always lead to kidney disease. The study found that individuals with a high-risk APOL1 gene variant who developed FSGS are more likely to have other genetic sequences, found in people of African ancestry, that lead to lower levels of a protein called UBD, which interacts with APOL1. Lower UBD levels may lead to reduced protection from APOL1-mediated cell death, and thus may modify APOL1-driven kidney disease.

NIH also supports research on the mechanism leading to the development and predisposition of Hispanics or Latinos to chronic kidney disease. This research explores the roles of ancestry in chronic kidney disease susceptibility and identifies ancestry-specific loci, and their corresponding rare and common genetic variants, that explain the higher susceptibility for chronic kidney disease in Hispanics or Latinos beyond the established risk factors of uncontrolled diabetes and hypertension.

NIH will continue to foster community engagement and collaborations through the work of NIMHD and NIDDK to advance research efforts to garner insights into the connection between the APOL1 gene and the initiation of FSGS.
Food Allergies

Food allergies affect 15 million Americans, can be life threatening, and have no cure. Currently, the Consortium of Food Allergy Research network includes seven clinical sites/centers. In addition, approximately 10 other NIH-supported centers are conducting basic, translational, and clinical research on food allergies. The Committee encourages NIH 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 food allergy research that includes basic, clinical, and translational studies to understand the causes of food allergy and develop preventive and therapeutic options. The field of food allergy prevention and treatment continues to grow rapidly, and NIAID has facilitated an expansion of clinical research capacity, developing a cadre of investigators and institutions to pursue research on food allergy, including clinical trials evaluating pioneering new therapies.

NIAID supports 14 centers that conduct food allergy clinical research through the Consortium for Food Allergy Research (CoFAR), the Immune Tolerance Network (ITN), and the Asthma and Allergic Diseases Cooperative Research Centers (AADCRC). CoFAR evaluates new approaches to treat food allergy such as the use of immunotherapy for treating milk, egg, and peanut allergy. The ITN is a collaborative network for clinical research that is pursuing three clinical trials to prevent food allergy in infants and two to treat peanut allergy in young children. The AADCRCs are conducting several clinical trials to treat food allergy to peanut, including a state-of-the-art study to assess the mechanisms of food allergy. NIAID also supports three centers that conduct research on eosinophilic esophagitis, an inflammatory condition that can be caused by food allergy. NIAID continues to encourage scientists with promising approaches to the treatment and prevention of food allergy to seek NIAID research funding. For example, NIAID is supporting ongoing investigator-initiated food allergy clinical trials.

NIAID also conducts intramural clinical research on food allergy and eczema, also known as atopic dermatitis (AD), which can be a precursor to development of food allergy as well as a challenging co-morbidity. NIAID scientists recently completed a first-in-human trial evaluating a novel treatment for AD using commensal bacteria to alter the skin microbiome and relieve affected individuals from the burden of topical steroid therapy. NIAID investigators also have shown that growth may be significantly impaired in children with AD and concurrent IgE food allergy, particularly milk allergy. This finding, along with the observation that patients with moderate-severe AD alone are often more likely to have elevated body mass index and weight, suggests that children with moderate-severe AD may benefit from close nutritional follow-up. In addition, NIAID scientists found that unexplained anaphylaxis in a group of patients was due to allergy to a sugar molecule found in mammalian meat known as alpha-gal. Lone Star tick bites were previously identified to be associated with this allergy, and NIAID researchers found that patients with unexplained anaphylaxis had a history of tick bites and that a diet free of red meat prevented anaphylaxis recurrence.
NIAID remains committed to supporting the development of academic clinicians and scientists involved in basic, clinical, and translational food allergy research. NIAID has the clinical research capacity to support groundbreaking research on food allergies. Should a need for additional clinical research capacity for food allergy arise, NIAID will work though its existing networks to add clinical sites with proven expertise in food allergy research. NIAID will continue to support clinical research on food allergy through the 14 centers within CoFAR, ITN, and AADCRCs as well as intramural and extramural investigator-initiated food allergy clinical trials.
Food is Medicine

The Committee recognizes the important role of nutrition in health outcomes and encourages OD to work with relevant ICs, including NIDDK, NHLBI, NIA, and NICHD, to report on the research that has been conducted on Food is Medicine related topics. This may include, but is not limited to, medically tailored meals, medical nutrition therapy, produce prescription programs, the role of proper nutrition in aging, and the role of proper nutrition in reproductive health. The Committee further encourages additional collaboration among the ICs on these topics.

Action taken or to be taken:

The NIH supports substantial research on nutrition in health and disease, funded by several of its Institutes, Centers, and Offices (ICOs).

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports research on the impact of diet and nutritional status on prevention and treatment of diseases within its mission, including diabetes, obesity, and digestive and kidney diseases. Examples of NIDDK-sponsored studies and programs in this area include the Vitamin D and Type 2 Diabetes Study, the Chronic Renal Insufficiency Cohort Study (including identification of nutritional risk factors related to declining kidney function), and the Nutrition Obesity Research Centers. The NIDDK Office of Nutrition (ONR) has also sponsored recent scientific meetings to advance nutrition research, such as a mini-symposium on advances in personalized nutrition and a workshop to stimulate research on human milk composition held in collaboration with the Department of Agriculture and HHS’s Office of Disease Prevention and Health Promotion, with participation from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Currently, NIDDK collaborates with several other NIH ICOs in leading three funding opportunity announcements related to nutrition in disease prevention and treatment. Additionally, NIDDK ONR helps coordinate nutrition research efforts among the ICOs and led the development of the first NIH-wide nutrition research strategic plan. As part of the NIH’s ongoing interest in supporting research on nutrition for disease prevention, the plan recognizes the need for more research focused on nutritional support in clinical settings, for premature infants, and for those with special nutritional requirements, including older adults, as well as on interactions between nutrition, disease states, and treatments.

The National Heart, Lung, and Blood Institute (NHLBI) has a robust commitment to research evaluating how food and nutrient intake relate to cardiovascular disease and obesity, including landmark clinical trials such as Dietary Approaches to Stop Hypertension (DASH), DASH-Sodium, OmniHeart, Dietary Intervention Study in Children, and the multigenerational Framingham Heart Study. NHLBI also collaborates with other NIH components to support trials investigating how specific nutrients may reduce the risk of cancer, heart disease, and stroke in people without a prior history of these conditions. NHLBI is also supporting many other investigator-initiated research studies, including trials examining the effects of a Mediterranean diet on weight loss and cognition in obese older adults and effects of protein on cardiometabolic risk factors. In addition, NHLBI’s Division of Intramural Research is actively engaged in basic research to better understand how nutritional components affect health.

NICHD supports research to better understand human milk composition, including the importance of its non-nutritive compounds, and how nutrition promotes growth and development from pregnancy through adolescence to better inform dietary choices. Studies include research
to gain a better understanding of maternal nutrition and its effects on pregnant women and offspring. According to the Federal Task Force on Research Specific to Pregnant Women and Lactating Women, many women use dietary supplements without an adequate evidence base, pointing to the need for further work in this area. Additionally, NICHD is engaged in research focused on better delineating nutrient requirements of infants and older children.

The National Institute on Aging (NIA) supports a variety of projects on the role of nutrition in healthy aging, including cognitive aging. In particular, current research focuses on the efficacy of various diets, supplements, and dietary modifications to prevent or delay the onset of Alzheimer’s disease and related dementias (ADRD). Other NIA-funded research is investigating gut microbial changes as a potential mechanism through which diet exerts its effects on brain health.
Fragile X
The Committee commends NIH for supporting research to understand the nature of FX and its association with other conditions such as autism. The Committee encourages NIH to continue to fund at least three FX research centers, supporting interdisciplinary research in important new areas. The Committee urges NIH to assure that the FX research centers program includes clinical and translational research that directly addresses the needs of affected children and their families, and that applicants for new centers may propose clinical trials as part of their research portfolio. Given the inextricable connection between the FX protein and autism, the Committee urges the Director and each Institute Director with Fragile X and autism portfolios to explore ways to create greater efficiency and synergy among these two research tracks to accelerate translational research toward a better understanding of both conditions and to shorten the time to bring effective treatments for both conditions to market including the funding for clinical trials for both disorders.

Action taken or to be taken:

Fragile X Syndrome (FXS), which is caused by mutations in the \textit{FMR1} gene on the X chromosome, is the most common form of inherited intellectual disability. Mutations in the \textit{FMR1} gene also play a role in several other medical conditions that affect children, adults, and seniors, including Fragile X-associated Tremor/Ataxia Syndrome, which leads to disabling neurological symptoms in middle-aged and elderly adults. Fragile X-associated Primary Ovarian Insufficiency a condition also generated by the gene, can lead to infertility and/or early menopause in affected women.

The National Institutes of Health (NIH) continues to have a high level of interest in supporting basic, translational, and clinical research on FXS and other \textit{FMR1}-associated conditions. A centerpiece of NIH’s support for Fragile X and \textit{FMR1}-related research is the Fragile X Research Centers Program. This program is supported by multiple NIH Institutes and Centers, including the \textit{Eunice Kennedy Shriver} National Institute of Child Health and Human Development (NICHD), the National Institute on Mental Health, and the National Institute of Neurological Disorders and Stroke (NINDS). For example, NIH-funded researchers at the University of Texas Southwestern, in collaboration with center investigators, identified electroencephalographic (EEG) signatures that are common to both individuals with FXS and mouse models of FXS, and which show similar responses to medications that act on molecular pathways known to be altered in FXS. These EEG signatures appear to correlate to clinical symptoms seen in FXS, such as hypersensitivity to certain sounds and noises, thus showing considerable promise as a potential biomarker for future clinical trials, both in animals and humans. Scientific findings such as these may dramatically accelerate the pace at which researchers can develop and test potential treatments for FXS and related conditions.

NINDS and NICHD also support a collaborative research center focused on understanding the variability of Fragile X-associated diseases across affected individuals. One of the center’s projects will search for genetic factors that influence the occurrence of epilepsy in boys with FXS. Since FXS increases the risk for both epilepsy and autism, possibly through shared mechanisms, this project may identify genetic modifiers of autism in FXS as well. Other
NINDS-funded research at the cellular, neuronal circuit, and behavioral levels will yield insights into how mutations in the \textit{FMR1} gene lead to intellectual disability and autism, and into strategies for future therapies. In addition, NINDS, NICHD, and the National Institute on Deafness and Communication Disorders, are supporting a new trial through the NINDS NeuroNEXT clinical trials network to assess whether a drug (AFQ056) that blocks the cell receptor implicated in FXS (mGluR5) will improve language learning in young children with FXS, as compared to speech and language therapy alone. To facilitate translational research and clinical trials, a workshop held by NINDS in December 2017, in collaboration with other NIH Institutes and Centers and non-profit organizations, developed recommendations for discovering and validating robust biomarkers for the field. NIH shares the Committee’s interest in assuring that the Fragile X Research Centers continue to support research that can accelerate the process of making effective treatments available to individuals and families affected by FXS and \textit{FMR1}-associated conditions. Multiple NIH Institutes that support Fragile X research, both through the Fragile X Centers and through other funding opportunities, also have specific mechanisms for funding clinical trials that are open to proposals for clinical trials on FXS and autism and autism-related conditions. These clinical trials programs are especially well-suited to building synergy between research programs on conditions that share clinical features, such as FXS and autism.

Over the last year, the Trans-NIH Fragile X Research Working Group, which coordinates NIH’s efforts to implement research priorities, has been working on a substantive update of the NIH Research Plan for FXS, expected to be published in late 2018. Developed with extensive public input from expert researchers and family organizations, the new plan will provide recommended priority research areas for use by the entire Fragile X community.
Frontotemporal Degeneration
The conferees encourage NIH to maintain and expand a multi-site infrastructure and network of clinical sites to extend the study of genetic and sporadic FTD cohorts. By supporting this research, researchers may increase our knowledge of the natural history of the disease and build an infrastructure for biomarker discovery and clinical trials in defined FTD cohorts. A key component of this will be to leverage recent advances in information technology to create an infrastructure for FTD research that will collect and record data and samples in a uniform manner, incorporate patient-reported data, and take advantage of new technologies that enable remote monitoring. Development of a data biosphere that supports broad sharing of robust datasets, generated with powerful -omic platforms, will enable the broader community of researchers, including younger investigators and scientists from a wide array of fields, to bring their expertise and intellectual curiosity to bear on the challenges currently confronting the Alzheimer's disease and related dementias disorders. In this way, the conferees hope to accelerate the understanding of basic disease mechanisms that may be common across forms of dementia and speed the translation of this information into much-needed therapeutics.

Action taken or to be taken:

The National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA), and the National Center for Advancing Translational Sciences (NCATS) support two natural history studies in frontotemporal lobar degeneration (FTLD): the Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) Consortium and the Longitudinal Evaluation of Familial Frontotemporal Dementia (LEFFTDS). ARTFL consists of fourteen clinical sites in the United States and Canada and has recruited over 1,200 individuals with genetic and sporadic forms of diseases that encompass the FTLD spectrum. LEFFTDS examines the natural history of individuals from families with known mutations in FTD-related genes with a goal of identifying biomarkers that can track disease progression more accurately. These collaborative efforts aim to support the development of diagnostic tools and new treatments by conducting clinical research to improve our knowledge of the differences among diseases on the FTLD spectrum, as well as facilitating other research by providing a large infrastructure and resources for the research community. In 2018, NINDS and NIA released a Notice emphasizing the interests of both Institutes in supporting clinical trial-ready cohorts for FTLD.

The additional funds for Alzheimer’s disease and Alzheimer’s disease-related dementias (AD/ADRD) research that NIH has received in the recent years have enabled NINDS to announce new funding opportunities and programs to fill gaps in FTD research and encourage investigators to leverage existing resources such as ARTFL/LEFFTDS. In 2018, NINDS released a funding opportunity to support research that uses advanced information technologies for large-scale data analysis to discover and validate potential biomarkers and therapeutic targets for ADRD, including FTD. A research team supported through this program will use a multi-omics approach to analyze brain samples from people with AD/ADRD in hopes of identifying unique molecular signatures that may help differentiate between different dementias. NIH is also supporting Tau Center without Walls, a multi-center project to investigate molecular mechanisms that contribute to abnormal, toxic forms of tau that are found commonly in the brains of people with FTD and Alzheimer’s. To accelerate the discovery and validation of genetic factors that increase FTD risk, NIH is supporting the FTD Sequencing Consortium in
collaboration with non-government organizations. The genomes from ARTFL and LEFFTDS will be sequenced through this Consortium, and, to complement this effort, researchers at NIA and NINDS are performing genome sequencing in 300 individuals diagnosed with FTD and 3,000 individuals diagnosed with Lewy body dementia, another type of ADRD, to identify gene locations that alter disease risk as well as age at onset. The resulting genome sequence data will be made broadly available to qualified researchers via a new online resource.

The Accelerating Medicines Partnership for Alzheimer’s Disease (AMP-AD), a groundbreaking collaboration between NIH and the private sector, is enabling rapid and broad data sharing in AD/ADRD research. The AMP-AD Knowledge Portal, an informatics platform, provides access to multi-omic datasets and clinical and pathology data from thousands of subjects across all stages of AD, and hosts data on a smaller collection of brain samples from individuals with ADRD, including FTD. Researchers are using these resources to discover and study disease pathways that are specific to AD as well as common across AD/ADRD; to identify novel therapeutic targets and biomarkers; and to make better predictions about drug repurposing and combination therapy development. The Portal is being enhanced with cloud computing capabilities and web-based tools to ensure that the data can continue to be widely used by the research community, including young researchers with varying degrees of expertise.
Gabriella Miller Kids First Research Act.
The bill provides the full request of $12,600,000. The Committee requests that NIH provide information on how it has disbursed fiscal year 2016, fiscal year 2017, and fiscal year 2018 funding for the Gabriella Miller Kids First Research Act, including any personnel that are responsible for overseeing the allocation of designated research dollars, the criteria that NIH employed to ensure awards will advance the objectives of the act, and a description of the research projects that were funded at the end of fiscal year 2018. The criteria and process for grant awards that NIH intends to use for fiscal year 2019 and subsequent years of funding under the act should also be included.

Action taken or to be taken:
The NIH Common Fund’s Gabriella Miller Kids First Research program (Kids First) aims to catalyze pediatric research by making large amounts of high-quality genetic and clinical data from pediatric patient cohorts widely available and easy to use for scientists and clinicians. For example, the Kids First program supports a data resource that integrates data from patients with childhood cancer, structural birth defects, or other childhood conditions that have profound, lifelong effects on patients and their families. Importantly, the Kids First data resource will aggregate Kids First-generated data together with many additional existing data sets, increasing researchers’ ability to detect rare genetic changes that contribute to these conditions.

Consistent with the requirements of the Gabriella Miller Kids First Research Act, all available funds have been disbursed as grants to support pediatric research. In FY 2016, Kids First provided $12.6 million to research centers at Broad Institute and Hudson-Alpha Institute for Biotechnology to determine the genetic sequence of patient samples, with each center receiving a $6.3 million award for the year. In FY 2017, Kids First provided approximately $4.8 million to the Broad Institute sequencing center and approximately $4.7 million to the Hudson-Alpha sequencing center. Kids First also launched the Kids First Data Resource Center with an award for approximately $3.1 million to the Children’s Hospital of Philadelphia. In FY 2018, Kids First awarded approximately $4.7 million to the Broad Institute sequencing center, $4.9 million to the Hudson-Alpha sequencing center, and $3.0 million to the Kids First Data Resource Center at the Children’s Hospital of Philadelphia. Sequencing centers were chosen based on their expertise and available sequencing capacity. The criteria for selection of the Data Resource Center were their experience in handling large amounts of data, ability to organize these data so other researchers can use it, and their expertise in pediatrics.

In FYs 2016, 2017, and 2018 Kids First solicited applications from researchers with childhood cancer or structural birth defects patient cohorts. Successful applicants do not receive funds from Kids First but do gain access to the sequencing capabilities of the Kids First-supported centers. The genome sequence data and associated clinical data from these cohorts form the basis for the Kids First data resource. Data from the first set of Kids First cohorts is now publicly available and data from subsequent cohorts will be made available to the research community on an ongoing basis. Cohorts were selected based on scientific criteria that included, but were not limited to, the robustness of the cohort, evidence for a genetic component, potential to provide new information and address important questions, and significance to human health and/or understanding of biology.
In FY 2019 and beyond, pending availability of funds, the Kids First program plans to support sequencing of additional pediatric cohorts and will explore opportunities to leverage the Common Fund’s “New Models for Data Stewardship” program to establish a Pediatric Data Commons, providing a pathway to efficiently share and analyze trans-NIH pediatric data. If this proves feasible, it would allow analysis of many more pediatric conditions. Collectively, rigorous scientific criteria, peer review by experts, and robust discussions between NIH, pediatric researchers, and patient advocates ensures that the program initiatives and awards will advance pediatric research and the objectives of the Kids First Act.

Because all appropriated Kids First funds were used to support pediatric research over FYs 2015-2018, no appropriated Kids First funds were used to support personnel overseeing allocation of designated research dollars. Research Management Support for the Kids First program totaled $401,000 in FY 2018, of which $342,500 was used for personnel support. The remaining funds supported peer review activities and meetings with scientific experts. All Research Management Support for Kids First came from the NIH Common Fund budget.
Gastric Cancer
The Committee continues to be concerned about the deadly outcomes of gastric cancer, particularly among young adults. The 5-year survival rate for stomach cancer is 30 percent. The Committee encourages NCI to consider developing a scientific framework for advancing stomach cancer research.

Action taken or to be taken:
NCI is committed to improving outcomes for gastric cancer patients and supports a comprehensive gastric cancer research portfolio that spans from understanding the biological mechanisms that lead to gastric cancer through the development of new treatments to improve outcomes for patients. NCI regularly conducts scientific horizon scanning efforts to identify opportunities to advance cancer research in all areas, ranging from basic science opportunities to disease-specific projects. This is a highly collaborative process that draws upon NCI’s external advisory groups and steering committees, the expertise of NCI program leadership, and opportunities to convene extramural experts to evaluate and discuss new scientific opportunities. In addition, NCI’s Division of Cancer Treatment and Diagnosis maintains twelve disease-specific Scientific Steering Committees focused on treatment and imaging for specific cancer types, including gastrointestinal cancers such as gastric cancer. The Steering Committees include leading cancer experts, community oncologists, biostatisticians, translational scientists, and advocates as well as NCI senior investigators. These committees work to evaluate unmet clinical needs and discuss strategic priorities for a given disease or research area.

Research highlights in gastric cancer from the past year include the discovery of a new potential therapeutic target; researchers in the NCI Center for Cancer Research identified a pathway that acts as a growth suppressor in gastric cancer cells. Several clinical trials of immunotherapy and targeted therapy for gastric cancer are being sponsored by NCI. For example, an ongoing clinical trial is testing a new cancer therapy, called gene transfer, to treat cancers driven by amplification of the KRAS gene, including gastric and gastroesophageal cancers. Another NCI-supported trial is currently recruiting patients to study the effectiveness of combining an antibody and a targeted therapy in patients with gastric cancer that has spread to other places in the body, has recurred, or that cannot be removed by surgery.

NCI also continues to support new and ongoing research efforts focused specifically on opportunities in gastric cancer research, such as four Specialized Programs of Research Excellence (SPORE), focused on translational research in the gastrointestinal system, including cancers of the stomach. Recently, one of the Gastrointestinal SPORE research teams showed that, in cancers driven by amplification of the KRAS gene, which are resistant to treatment with drugs that target a protein called MEK, it is possible to target another protein, called SHP2, and force the tumor to be sensitive to therapies that target and inhibit MEK. This work showed the

86 https://www.cancer.gov/about-nci/organization/ccct/steering-committees/nctn
87 https://www.cancer.gov/about-nci/organization/ccct/steering-committees/nctn/gastrointestinal
89 https://clinicaltrials.gov/ct2/show/NCT03190941
90 https://clinicaltrials.gov/ct2/show/NCT03008278
91 https://trp.cancer.gov/spores/gi.htm
therapeutic potential of combination targeted therapy for cancers of the stomach, esophagus and ovaries that have amplification of KRAS.
General Cardiac Research

The Committee encourages NIH to pursue highly translational basic and clinical research that will have a near-term impact on health care of aging populations in States with high numbers of patients with cancer suffering from cardiovascular complications of chemotherapy, severe peripheral vascular disease, genetic cardiac diseases, and clotting disorders associated with aging and cardiac arrhythmias. Research should be conducted across the disciplines of medicine, immunology, imaging, chemistry, biomedical engineering, physics, statistics, mathematics, and entrepreneurship to design new drugs and drug delivery systems and strategies that are safer, more effective, and improve patient compliance, while seeking to move technologies from bench to bedside with private partners and local health care and community organizations.

Action taken or to be taken:

The National Heart, Lung, and Blood Institute (NHLBI) supports comprehensive research to improve, diagnosis, treatment, and prevention of cardiovascular diseases, and places a high priority on multi-disciplinary research to develop innovative therapies. In addition to support for investigator-initiated grants, NHLBI supports the translation of research discoveries into medical treatments by offering grants to small businesses, forging alliances between federal and private stakeholders, and providing researchers with product development resources. In fiscal year 2020, NHLBI will launch Catalyze, a comprehensive program that will offer researchers mentoring, coaching, technical services, and funding to advance early-stage discoveries toward new therapies. NHLBI also supports efforts to improve dissemination and adoption of existing, evidence-based therapies, and has announced plans to fund new research into strategies for delivering proven community-level interventions to reduce disparities in CVD.93

The Institute’s translational and implementation research programs are integrated with programs to support fundamental discovery science and clinical research to test the safety and efficacy of potential new therapies. Below are select, specific NHLBI-funded research advances toward improved treatment of age-related CVD.

**Cardiovascular complications of chemotherapy:** The 14 million pediatric and adult cancer survivors living in the United States are living proof of improvements in cancer treatment; however, this success has been tempered by a parallel rise in the incidence of cancer treatment-related toxicity, including cardiotoxicity. To reduce the cardiac risks from chemotherapy while optimizing cancer outcomes, NHLBI and the National Cancer Institute (NCI) are partnering to fund research toward new methods to evaluate cardiac risk before cancer treatment and to integrate this information into treatment regimens.94 NHLBI also is funding a multi-center clinical trial that leverages an NCI-funded community oncology program to determine whether a low-cost, widely available statin can prevent cardiovascular toxicity from chemotherapy for breast cancer.95 Another NHLBI-funded trial is investigating whether a drug used to prevent thromboembolism can prevent blood clots in patients with cancer.96

---

96 [https://clinicaltrials.gov/ct2/show/study/NCT02195232](https://clinicaltrials.gov/ct2/show/study/NCT02195232)
Peripheral Artery Disease
An estimated 8.5 million people in the United States have peripheral artery disease (PAD), which reduces blood flow to the limbs, and is associated with a risk of heart attack, stroke, and limb amputation. To reduce these risks, NHLBI is supporting research into earlier diagnosis of PAD through ultrasound imaging to detect clogged arteries. To improve treatment, an NHLBI-funded trial is comparing the use of surgical bypass, the historical gold standard for treating PAD, versus a newer minimally invasive procedure.

Genetic CVD: Heritable birth defects can contribute to CVD in old age, even if they remain undetected throughout most of life. For example, congenital cardiomyopathies (heart muscle weakness) and valve disorders can manifest as heart failure late in life. NHLBI-funded researchers are beginning to identify the genetic bases of these heart defects; some have been traced to mutations in single genes needed in heart muscle, while others are more complex and appear to involve the interplay of several genetic risk variants. It is hoped that this research will lead to more effective, targeted therapies for congenital heart disease and for other causes of heart failure.

Clotting Disorders: Arrhythmias can cause blood to pool in the atria of the heart, which can lead to clot formation. A recent NHLBI-funded retrospective study showed that in older patients with atrial fibrillation (AFiB), a type of arrhythmia, surgery to reduce the risk of blood clots entering the bloodstream was associated with lower risk of blood clots known as a thromboembolism, clots that originated elsewhere in the circulation. A current NHLBI-funded study is using biophysical modeling of blood flow patterns to develop a more personalized assessment of clotting and stroke risk in patients with AFiB. Additionally, NHLBI recently solicited projects to better understand the mechanisms by which female sex hormones and sex hormone-based therapies can increase the risk of venous and arterial thromboembolism in pre-menopausal women. Four new projects were funded.

97 https://projectreporter.nih.gov/project_info_description.cfm?aid=9047293
98 https://clinicaltrials.gov/ct2/show/NCT02060630
100 https://projectreporter.nih.gov/project_info_description.cfm?aid=9433677
101 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5833567
102 https://projectreporter.nih.gov/project_info_description.cfm?aid=9584773

99
Gestational Diabetes
The Committee recognizes the importance of research funded by NIH related to gestational diabetes, a disease affecting up to 9.2 percent of all pregnant women. Given that both women with gestational diabetes and their babies face long-term health consequences as a result of the disease, such as increased risk of developing type 2 diabetes, the Committee urges NIH to explore additional opportunities for research on gestational diabetes.

Action taken or to be taken:
The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institutes of Health (NIH) Office of Research on Women’s Health (ORWH) lead NIH support for research on gestational diabetes mellitus (GDM) and its health effects on women and their children. GDM is associated with adverse perinatal outcomes, with risks posed by both severe and mild forms of the disease. NICHD-supported studies include exploring mechanisms to explain adverse outcomes in women with GDM and their infants, the role of the placenta and intrauterine environment in modulating the effects of GDM, and various components of diagnosis and management of GDM. Recent research has shown that treatment of mild GDM with dietary interventions, and insulin when necessary, proved to be effective in reducing the risks of some adverse outcomes. One study that looked at the relationship of maternal glycemia to childhood obesity and metabolic function, conducted by investigators from NICHD’s Maternal-Fetal Medicine Units (MFMU) Network, found that maternal glycemia was associated with some childhood obesity. This study has many clinical implications, including a need for close surveillance of glycemic levels during pregnancy. In 2016, another MFMU study evaluated the relationship among excessive gestational weight gain, neonatal adiposity, and adverse obstetric outcomes in women with mild gestational diabetes mellitus. It showed that this combination posed higher risk factors for the pregnant women, including preeclampsia and cesarean delivery, and concluded that for women with both treated and untreated mild gestational diabetes mellitus, excessive gestational weight gain is a risk factor, associated with both greater birth weight and adiposity in the infant and higher rates of maternal complications.

The NICHD- and NIDDK-supported Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study demonstrated in 2008 a strong linear relationship between increased maternal blood glucose concentrations and adverse neonatal outcomes, although without any clear glucose level threshold. The HAPO Follow-Up Study, sponsored by NIDDK and supported by NICHD, recently reported that in utero exposure to glucose levels found harmful at the time of childbirth continued to be harmful a decade later. The study results show a strong relationship between glucose levels during pregnancy and subsequent type 2 diabetes in the mothers and obesity in the offspring. However, the study did not find a significant relationship between maternal glucose levels during pregnancy and the combined outcome of overweight and obesity in offspring. The NIDDK has led the development of a new initiative to build a comprehensive picture of maternal glucose levels during pregnancy, aiming to establish a research consortium that can recruit pregnant women in their first trimester to examine maternal blood glucose levels across the span of pregnancy, and detect and characterize the development of abnormal glucose levels during
that time. This initiative builds upon a GDM research workshop convened by NIDDK and ORWH in 2017, and upon advances in continuous glucose monitoring technology made possible with support from the Special Statutory Funding Program for Type 1 Diabetes Research. The workshop identified the importance of research to better understand whether early diagnosis and treatment of abnormal maternal glucose levels would improve the health of mothers and their children. It is expected that the consortium study will yield information that can lead to improved approaches for screening for GDM and help inform the development of future clinical trials of interventions to decrease adverse short and long-term outcomes for mothers and their children.
Glaucoma

The Committee commends the recent FDA approval of two new drug therapies emerging from decades of NEI research into the role of high intraocular pressure [IOP] as a causal risk factor for primary open-angle glaucoma, the most common form of the disease and a leading cause of vision loss and blindness. Targeting the eye's trabecular meshwork which is one of the pathways responsible for regulating fluid flow within the eye the new generation of therapies reflects an expanding menu of drugs that lower IOP and better meet the needs of patients.

Action taken or to be taken:

The recent approval of two novel medications for glaucoma – the first new medications for the disorder in nearly 18 years – are fruit borne from decades of foundational scientific research supported by the National Eye Institute (NEI). The two medications, Vyzulta and Rhopressa, treat elevated eye pressure. High intraocular pressure is a causal risk factor for primary open-angle glaucoma, the most common form of glaucoma and a leading cause of vision loss and blindness in the U.S. and worldwide. This condition causes the bundles of nerve fibers connecting the eye and the brain, known collectively as the optic nerve, to die. The two newcomers to the market have novel mechanisms of action acting on the trabecular meshwork, the eye tissue that is directly responsible for increased intraocular pressure. The drugs inhibit an enzyme called rho kinase, which triggers the contractile machinery of cells; inhibiting this enzyme relaxes the meshwork cells, allowing fluid to leave the eye.

In May, researchers participating in the NEI NEIGHBORHOOD glaucoma consortium announced the identification of 133 genetic variants that predict with 75 percent accuracy a person’s risk for developing glaucoma related to intraocular pressure. Of these 133 gene variants, 68 had not previously been associated with the condition. The consortium compared DNA from almost 140,000 participants. Future genetic tests could identify high-risk individuals who could benefit from closer monitoring and early interventions. Additionally, NEI research has expanded the use of a powerful imaging tool called Optical Coherence Tomography (OCT) for early detection and treatment decisions. In a 2017 study, OCT detected glaucoma in 60 percent of 356 patients with suspected glaucoma, compared to 27 percent with the standard-of-care vision test. OCT significantly improved detection for cases of mild glaucoma. With genetics information to predict disease risk, imaging tools to detect mild and early disease, and new therapies, clinicians are now armed with a new arsenal to attack this blinding disease.
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 2020 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 research104, 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 2017, NIH participated in at least 126 collaborations with DoD and at least 80 collaborations with VA, including 53 collaborations that included both DoD and VA. The collaborations took several forms, including jointly serving on multi-organization committees and workgroups, partnering on research initiatives, and collaborating on resource development. In addition, NIH partnered with DoD and/or VA on at least 11 activities undertaken by the National Academies of Sciences, and worked with DoD and/or VA, along with other Federal agencies, on 25 activities of the National Science and Technology Council in the White House Office of Science and Technology Policy.

NIH shares many areas of interest with DoD and VA, including research on cancer, chronic pain, suicide, and substance use disorders. Highlighted below are two ongoing research 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 creating the first nationwide program for systematically integrating proteogenomics, in which genomic data is used to better detect various proteins, into cancer care. The Applied Proteogenomics Organization Learning and Outcomes (APOLLO) network105, established in 2016 as part of the Cancer MoonshotSM, utilizes proteogenomics to better predict how cancer patients will respond to therapy by screening their tumors for both genetic abnormalities and protein information. APOLLO’s first phase is underway and is focused on the full proteogenomic profiling of selected cancer types. APOLLO’s next phase will bring proteogenomics into the DoD and VA clinical systems in which donated patient tissue is routinely profiled with the goal of characterizing both gene and protein expression and matching tumor types to targeted therapies. In this phase, all cancer types will be studied.

NIH, DoD, and VA are also continuing their partnership to find solutions for treating chronic pain. Beginning in 2014, NIH and VA funded 13 grants to study the health of veterans and service members with a focus on nondrug approaches to managing pain and related conditions. This collaboration was later expanded to include DoD, forming the NIH-DoD-VA Pain

105 [www.proteomics.cancer.gov/node/13](http://www.proteomics.cancer.gov/node/13)
Management Collaboratory\textsuperscript{106}. In September 2017, the partners announced a multi-component research effort to provide approximately $81 million over six years to support 12 large-scale and cost-effective pragmatic clinical trials. These studies are being conducted in DoD and VA healthcare systems and are expected to provide critical information on the feasibility, acceptability, safety, and effectiveness of nondrug approaches in treating pain\textsuperscript{107}.

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 is able to help accelerate the search for effective treatments for cancer, chronic pain, and other diseases and conditions that affect military personnel, veterans, and other Americans.

\textsuperscript{106} \url{www.nccih.nih.gov/research/blog/partnering-on-pain}

\textsuperscript{107} \url{www.nih.gov/news-events/news-releases/federal-agencies-partner-military-veteran-pain-management-research}
Gynecologic Cancer Clinical Trials
Clinical trials have significantly improved survival for women with gynecologic cancers, including ovarian, endometrial, cervical, and vulvar cancers. The Committee 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. The Committee requests that NCI provide an update to the Committee in the fiscal year 2020 CJ.

Action taken or to be taken:
The National Cancer Institute (NCI) is a leader in developing and supporting clinical trials of promising new treatments, including treatments for gynecologic cancers. NCI supports clinical trials in several ways, including through networks such as the National Clinical Trials Network (NCTN) and the Early Therapeutics Clinical Trials Network (ETCTN).

NCI’s Gynecologic Cancer Steering Committee (GCSC) evaluates and prioritizes proposed randomized phase 2 and phase 3 clinical trials in adult gynecologic cancers that will be conducted through the NCTN. The GCSC is composed of gynecologic oncology experts from academic medical centers across the country, NCI program leaders, and a patient advocate representative. In 2015, the GCSC identified strategic priorities for NCTN clinical trials in cervical, uterine corpus, and ovarian/fallopian tube cancers.108 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 NCTN has initiated 54 gynecologic cancer clinical trials since its inception in March 2014. Currently, there are 19 active clinical trials for women with gynecologic cancers, an increase from the 15 clinical trials reported last year. In addition, six new trials for gynecologic cancer are nearing activation.

The ETCTN has a portfolio of clinical trials focused on early drug development and currently has 12 trials focused specifically on accruing women with gynecologic cancer. In addition, 24 studies are accruing patients who have any type of solid tumor, providing additional opportunities for women with gynecologic cancers.

In the NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) Trial, more than 18% of the screened patients had gynecologic cancers, which is an over-representation compared with the proportion of gynecologic cancer patients nationally. The NCI-MATCH Trial enrolls patients based on the molecular abnormalities found in their tumors rather than cancer type. On average, 75% of women who have been screened and invited to enroll in an NCI-MATCH treatment arm have done so.

The NCTN is also conducting a unique trial, DART (Dual Anti-CTLA-4 & Anti-PD-1 Blockade in Rare Tumors), combining two immunotherapy drugs (ipilimumab and nivolumab) to treat rare cancers. Several treatment cohorts in DART are dedicated to rare subsets of gynecologic cancers. Since its activation in January 2017, DART has accrued 69 patients with rare gynecologic cancers.

NCI’s intramural program also conducts gynecologic cancer clinical trials. Since January of 2017, 6 trials have opened at the NIH Clinical Center. These studies are evaluating new treatments for ovarian, fallopian tube, and endometrial cancers.\textsuperscript{109}

Headache Disorders

The Committee commends NIH for including consideration of disease burden as a 'crucial' factor for aligning its research priorities within the NIH-Wide Strategic Plan. The Committee notes that migraine is the top cause of global disability for people aged 15 to 49 years old in the 2016 Global Burden of Disease study, but that migraine and headache are among the very least funded disease categories, relative to disease burden, in the NIH "Research, Condition, and Disease Categorization." The Committee, therefore, encourages NIH to prioritize substantial increases in fundamental, translational, and clinical research funding towards migraine, cluster headache, post-traumatic headache, and other headache disorders.

Action taken or to be taken:

NIH recognizes the large burden of headache disorders and will continue to fund meritorious basic, translational, and clinical research to better understand and treat headache disorders. Current NIH research into the causes of migraine includes the roles of genetics, gender, and hormones, and how pain nerve fibers in the brain and brain lining contribute to migraine. NIH also funds research to understand the mechanisms, including the role of inflammation, underlying headaches following mild traumatic brain injury. Imaging research funded by NIH is detecting brain changes in headache disorders, including post-traumatic headache in children. NIH also funds several projects to develop animal models of headache pain and migraine.

NIH-funded research is identifying potential targets for therapy development. For example, scientists are exploring the role of proteins involved in sending signals between neurons in migraine. A project funded through the NIH Blueprint Neurotherapeutics Program, dedicated to the discovery and development of small molecule compounds, is developing drug candidates for migraine prevention that block the action of a protein which has been linked to stress—a potent migraine trigger. NIH-funded research into non-drug approaches to relieve migraine include the use of different colored room lighting and a clinical trial to test if dietary omega-3 polyunsaturated fatty acids improve clinical outcomes. A clinical trial supported by National Institute of Neurological Disorders and Stroke (NINDS), the Childhood and Adolescent Migraine Prevention Study (CHAMP), compared two commonly prescribed medications to prevent recurrent migraines in children and adolescents, and found that these medications were no more effective than placebo in reducing the frequency of migraines. These findings have important implications for clinical practice. In addition, the NINDS website Brain for Life will soon feature a migraine management app for adolescents that will enable them to better identify triggers and take charge of management of their own migraine headaches.

Several large NIH initiatives include activities relevant to headache research. A notice issued through the NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative encourages applications focused on understanding the neural circuits associated with pain, including headache, and on ways to modulate this circuitry to reduce pain. The NIH Common Fund—a resource that addresses research challenges of high priority for the NIH as a whole—is launching a large-scale study to identify “biosignatures” of chronic pain following an initial acute injury. These biosignatures may help to understand how headache pain develops and will be important tools for headache-focused research. In addition, the NIH Helping to End

---

Addiction Long-Term (HEAL) initiative includes research activities to develop more effective treatments for pain, including headache, while reducing the potential for addiction and abuse.

Coordination of pain research activities is accomplished on a trans-NIH level through the NIH Pain Consortium, and on an interagency level through the Interagency Pain Research Coordinating Committee. The Federal Pain Research Strategy, a long-term plan to advance the federal research agenda in pain, is helping to guide NIH and other agencies’ research agendas. The discussions and recommendations from these groups will continue to guide NIH pain research, including research relevant to understanding and treating headache.
Healthy Brain Aging
In the context of NIA’s robust Alzheimer’s Disease research portfolio, the Committee recognizes
the need to understand healthy brain aging and risk factors for Alzheimer’s Disease. The
Committee encourages NIA to continue to address the research goals and recommendations
related to healthy brain aging and cognitive resilience identified during the NIH’s 2015
Alzheimer’s Policy Summit.

Action taken or to be taken:

The National Institute on Aging (NIA) supports a number of studies to increase our
understanding of healthy brain aging and cognitive resilience. For example, a 2017 Funding
Opportunity Announcement (FOA) solicited applications for interdisciplinary studies to
understand the complex biology of resilience to Alzheimer’s disease risk. Six projects were
funded and will be active in FY 2020.

In April 2017, the NIA, with the support of Foundation for the NIH on behalf of the McKnight
Brain Research Foundation, conducted the Cognitive Aging Summit III, the specific focus of
which was the concepts of cognitive reserve and resilience. The Summit brought together a
multidisciplinary group of investigators with shared interest in research on age-related cognitive
decline as well as cognitive reserve and resilience, as compared to cognitive impairment or
dementia.

Recommendations from the Summit included the specific suggestion to establish a network to
study cognitive super-agers; this was viewed as a way to escalate the research enterprise for
discovery of factors for resilience, reserve, compensation, and/or preservation of cognition.
Because the numbers of individuals identified and followed at any one site to date are small, a
structure to allow uniform identification of individuals and uniform data collection would allow
the field to push forward more quickly in our understanding of factors that promote sustained
cognitive health and those that do not. An FOA to establish such a network has been approved in
concept by the National Advisory Council on Aging and will be issued later this year in
anticipation of an FY 2019 award.

Summit participants also recommended creation of a collaboratory on research definitions for
cognitive reserve and resilience to Alzheimer’s disease. This initiative will be established in
2018.

NIA supports the NIH Neuroscience Blueprint Lifespan Human Connectome Project (LHCP) to
map structural and functional connectivity in the developing, adult and aging human brain. The
overall goals of this project are to:

• capture change and variability in brain connectivity across the lifespan;
• link connectivity to behavior and genetic variation;
• share knowledge of the lifespan connectome; and
• provide a reference ‘normative’ dataset for research on understanding normal and
pathological changes in brain networks and behavior across the lifespan.
Other active research on cognitive resilience includes studies of the genetic, molecular, and structural underpinnings of healthy cognitive aging and clinical studies of both drug and non-drug interventions to protect brain function during aging. Currently open FOAs are also soliciting research on “normal” age-related brain changes, from cellular changes to alterations in brain structure, that may influence risk of dementia. Research funded under these FOAs will be active in FY 2019.
Heart Disease
Heart disease is our Nation's leading cause of death and a key source of disability, yet NIH funding is not commensurate with its burden on long-term health outcomes, financial stability, and novel scientific opportunities. Concerned that NHLBI extramural heart research has dropped 17 percent in constant dollars since 2002, the Committee encourages NHLBI, to prioritize and implement robust investment to drastically spur, strengthen, accelerate and coordinate heart research. This investment shall focus on expediting innovative basic, clinical, population, and translational research through all pertinent mechanisms. The Committee urges NHLBI to intensify the implementation of heart research recommendations and priorities, including promotion of cardiovascular health and prevention of heart failure, high blood pressure, and vascular dementia in its Strategic Vision. On NHLBI's 70th anniversary, the Committee commends the Institute for leadership in advancing its mission of improving prevention and treatment of heart, lung, blood, and sleep disorders.

Action taken or to be taken:

Research supported by the National Heart, Lung, and Blood Institute (NHLBI) has contributed to a 70 percent decline in the death rate for heart disease in the United States over the past 50 years. Nevertheless, heart disease remains the leading cause of death and a serious public health concern. Guided by NHLBI’s Strategic Vision, released in 2016, the Institute supports a robust portfolio of cardiovascular disease (CVD) research to significantly advance our understanding and treatment of heart disease and improve long-term outcomes.

NHLBI’s support for large population-based cohort studies that began with the Framingham Heart Study in the 1940s continues with recently announced funding opportunities to support new investigator-initiated cohort studies and to fund follow-up data collection and other activities in established cohorts. Data from these cohort studies are being used by NHLBI’s TransOmics for Precision Medicine (TOPMed) program to improve understanding of the fundamental biological processes that underlie heart disease.

Research has shown that hypertension management and control is a major strategy for promoting cardiovascular health and prevention of heart disease, heart failure, and vascular dementia. For example, the landmark NHLBI-funded Systolic Blood Pressure Intervention Trial (SPRINT) found that intensive blood pressure control can reduce heart attacks and strokes in at-risk patients. Given the efficacy of aggressive blood pressure control in the SPRINT cohort, implementation research on effective hypertension management is a high priority. An ongoing study is investigating the benefits of this treatment approach for a high-risk population in Louisiana. NHLBI continues to encourage similar research projects under the “Strategies to Increase Delivery of Guideline-Based Care to Populations with Health Disparities” grant.

111 www.jamanetwork.com/journals/jama/fullarticle/2626552?utm_campaign=articlePDF&utm_medium=articlePDF link&utm_source=articlePDF&utm_content=jama.2017.4150#jed170031r3
115 www.projectreporter.nih.gov/project_info_description.cfm?aid=9376903
program. To address hypertension in African American men, who have the highest rate of hypertension-related death in the nation, NHLBI-supported researchers found blood pressure screenings and pharmacist referrals at barbershops helped reduce high blood pressure among African American men. In another trial, NHLBI-funded researchers added pharmacist case management, including prescribing of drug therapy, and found that participants who had access to a pharmacist through their barbershop had a marked reduction in blood pressure.

NHLBI supports several studies focused on primary and secondary prevention and implementation science of CVD. The NHLBI Improved Cardiovascular Risk Reduction to Enhance Rural Primary Care (I-CARE) study is a multi-center study in which researchers provide telemedicine-based access to pharmacists to support private medical offices in rural areas that lack large integrated health plans. NHLBI is supporting clinical trials of strategies to increase use of cardiovascular rehabilitation by eligible patients. Additionally, a recent NHLBI funding opportunity calls for the development of multidisciplinary research teams to study the effectiveness and implementation of new evidence-based practices for managing heart disease in inpatient settings.

Finally, the SPRINT Memory and Cognition in Decreased Hypertension (MIND) study is investigating whether intensive blood pressure control protects against global cognitive decline and dementia in people 50 years of age or older without diabetes. Recent preliminary findings suggest that intensive lowering of blood pressure may reduce the risk of mild cognitive impairment (MCI) and the combined risk of MCI and dementia.

Ongoing advancements continue to show that controlling blood pressure, cholesterol, and diabetes, eating a healthy diet, not smoking, and exercising are some of the things a person can do to improve cardiovascular health, including maintaining their memory and cognitive abilities.

---

117 clinicaltrials.gov/ct2/show/NCT01983813
119 SPRINT MIND is supported by NHLBI, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke, the National Institute on Aging, and the Department of Veterans Affairs.
Heavy Ion Cancer Therapy and Research

The Committee supports NIH’s continued exploration of advanced therapeutic cancer research, specifically heavy ion irradiation technology. This technology will introduce a novel treatment option to cancer patients that is currently not available in the US. The Committee supports NIH’s work with the heavy ion planning grant recipients to further advance access to novel heavy ion treatment within the US. The Committee encourages NIH to explore further the establishment of a state-of-the-art heavy ion research facility in the US. Furthermore, the Committee encourages NIH to work with the Departments of Defense and Energy, and other applicable Federal agencies to equip the first US heavy ion research center. The Committee urges NIH to capitalize on the expertise and potential of the heavy ion facility planning grant recipients in order to foster a multidisciplinary approach and advance heavy ion research that would produce novel, cutting edge treatments for cancer patients.

Action taken or to be taken:

A considerable body of experimental and clinical evidence indicates that in certain settings particle beam therapy (including carbon – a heavy ion) might be equally, or more, effective in treating cancer as the most sophisticated photon-based therapies. Particle beam therapy also significantly reduces the radiation exposure to normal surrounding tissue. However, no randomized phase III clinical trials comparing carbon ion therapy to other treatment modalities have been reported. Randomized trials are essential to establishing clinical benefit for any new cancer treatment, and since a typical heavy ion treatment facility may cost well over $100 million to build, and millions each year to operate, there is a pressing need for more research to determine appropriate use of particle beam therapy to maximize its benefit to cancer patients.

In 2015, NCI awarded a contract to the Albert Einstein College of Medicine through the solicitation Carbon Ion Versus Conventional Radiation Therapy for Locally Advanced, Unresectable Pancreatic Cancer to conduct a phase III clinical trial, however the results have not yet been published.\(^{121,122}\) Also, the University of Texas Southwestern Medical Center is planning to begin a trial of Carbon Ion Versus Photon Radiotherapy for Locally Advanced, Unresectable Pancreatic Cancer (CIPHER) in December of 2018.\(^{123}\) This will be a multicenter randomized phase III trial and is estimated to be completed in 2023.

---

122 [https://clinicaltrials.gov/ct2/show/NCT03403049](https://clinicaltrials.gov/ct2/show/NCT03403049)
123 [https://clinicaltrials.gov/ct2/show/NCT03536182](https://clinicaltrials.gov/ct2/show/NCT03536182)
Hemoglobinopathies
The Committee acknowledges NHLBI’s leadership on gene therapy and gene editing research, and the Institute’s investment in using these transformative technologies to seek cures for patients with hemoglobinopathies and other genetic disorders. The Committee encourages NHLBI to continue to support multi-centered research for expanded treatments for thalassemia, sickle cell disease, and other hemoglobinopathies, with specific attention paid to gene therapy and gene editing.

Action taken or to be taken:

The National Heart, Lung, and Blood Institute (NHLBI) is committed to the development of genetic and cell-based therapies to treat and cure genetic disorders, including thalassemia, sickle cell disease (SCD), and other hemoglobinopathies.

Both SCD and thalassemia are caused by mutations in hemoglobin, a protein used by red blood cells to carry oxygen. Decades of research on the Hb gene family have helped yield promising approaches to genetic therapy. In ongoing trials, French researchers recently reported that delivery of an adult Hb gene to the bone marrow – where red blood cells are produced – reversed symptoms in a teenage boy with SCD for more than one year.124 NHLBI intramural researchers are conducting trials of a similar approach. Meanwhile, NHLBI-funded researchers recently found that a gene editing system delivered using nanoparticles can correct Hb mutations and ameliorate disease in a mouse model of β-thalassemia.125

In September 2018, NHLBI launched a Cure Sickle Cell Initiative, a collaborative research effort that is expected to accelerate the development of genetic therapies to cure SCD and other hemoglobinopathies. The Initiative grew out of an NIH-sponsored workshop, “Accelerating Cures in Hemoglobinopathies,” held in March 2017, that brought together thought-leaders in genetic therapies and gene editing, including representatives from academia and the pharmaceutical industry, to accelerate the development of potentially curative therapies for SCD. With new advancements in genetic therapy approaches, the time is right to push toward cures that are more accessible to approximately 100,000 Americans, and over 20 million people worldwide, who have SCD.

As part of the Cure Initiative, NHLBI will work with its partners to accelerate movement of the most promising genetic therapies for SCD into trials and assess factors that affect their adoption. NHLBI will also work with others to establish national networks to make it easier for patients and providers to learn and engage with the research, clinical trials, and other activities happening across the country. Scientific advances and other lessons learned from the Cure Initiative are also expected to accelerate development of new therapies for thalassemia and other hemoglobinopathies.

In addition to supporting new treatments for blood disorders, NHLBI is supporting research to identify barriers that impede access to care. In particular, many adolescents and adults with SCD do not receive ongoing, high-quality care. There are many contributing causes, including patient

125 www.nature.com/articles/s41467-018-04894-2
knowledge, lack of qualified providers, and difficulties in negotiating the health care system. The NHLBI-funded Sickle Cell Disease Implementation Consortium consists of eight geographically diverse centers that are systematically assessing the barriers to care, to be followed by interventional clinical trials that will implement methods to overcome these barriers. To support the critical need for ongoing research and specialized care in hemoglobinopathies, NHLBI is supporting a pilot program to attract more physician scientists to the field of blood science.

Additionally, researchers funded through NHLBI’s Excellence in Hemoglobinopathies Research Award program are working to understand mechanisms of SCD, thalassemia, and other blood disorders and to translate these insights into new drug therapies and new ways to treat pain. Eight centers are being funded through this program.

Hepatitis B
The Committee notes that the Hepatitis B virus (HBV) research community convened a virtual consensus conference that resulted in articles published in 2018 in two peer reviewed scientific journals identifying the most urgent research questions that must be answered to find a cure for HBV. The Committee urges NIDDK to pursue multiple critical research opportunities towards improved treatments and a cure for HBV and to provide an update in the fiscal year 2020 Congressional Justification.

Action taken or to be taken:

NIH remains committed to addressing hepatitis B virus (HBV) infection and HBV-related diseases such as cirrhosis and liver cancer. In pursuit of this goal, several NIH Institutes, Centers, and Offices maintain robust, complementary HBV research portfolios that span a broad array of research areas, including efforts aimed at developing new treatments and an effective cure.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a variety of HBV research programs, including investigator-initiated extramural research, intramural research at NIH, and research supported through initiatives, such as large, multi-site studies and ancillary studies to clinical trials. For example, the Hepatitis B Research Network aims to advance understanding of disease processes and progression over time, as well as to identify effective approaches to treatment with available and emerging therapies. The Network’s 13 sites across the U.S. and Canada have initiated multiple clinical trials and ancillary studies in both adults and children with hepatitis B; two of the trials have been completed with results to be published in the near future. The study involves participation from the Centers for Disease Control and Prevention. These studies can help drive development of new strategies to manage and treat chronic hepatitis B. The Network is currently completing a 5-year study of long-term outcomes of hepatitis B therapy to investigate whether it is possible to clear HBV infection and stop antiviral therapy, coming close to a “cure.” The NIDDK Intramural Research Program also conducts ongoing research to develop model systems for the development of new drugs to treat chronic hepatitis B.

Additionally, the National Institute of Allergy and Infectious Diseases (NIAID) supports basic, translational, and clinical research on HBV to better understand the disease and to develop novel therapeutics with the potential to serve as a functional cure. NIDDK is continuing to work with representatives of NIAID and the National Cancer Institute (NCI) on efforts to advance research on hepatitis B and its sequelae, such as cirrhosis and liver cancer. NIDDK, NIAID, NCI, and other NIH Institutes, Centers, and Offices also participate in the Trans-NIH Committee on Viral Hepatitis and the HHS National Viral Hepatitis Action Plan to coordinate efforts on hepatitis B and related liver cancer across the NIH and HHS. NIDDK will continue to be informed by hepatitis B research priorities identified by the wider research community as it pursues collaborative efforts with other funders of hepatitis B research at NIH to advance development of novel HBV therapeutics that could serve as a functional cure.
Hepatitis B (NIMHD)
The Committee notes that half of all HBV patients in the US are immigrant Asian-Americans or
Pacific Islanders, though these groups only accounts for about six percent of the population.
Further, among African immigrants, the prevalence of chronic HBV is about 10 percent. The
Committee urges NIMHD to fund research to test scale-up model programs that increase HBV
awareness, knowledge, testing and linkage to care for treatment among the disproportionately
HBV-impacted communities.

Action taken or to be taken:

Hepatitis B is a growing public health concern for racial and ethnic minorities in the United
States. Chronic hepatitis B can result in cirrhosis or scarring of the liver, liver failure, or liver
cancer. Asian Americans and Pacific Islanders make up less than five percent of the total
population in the U.S., but account for more than 50 percent of nearly one million Americans
living with chronic hepatitis B. Furthermore, African Americans bear a disproportionate burden
do disease and are 2.5 times more likely to die from hepatitis B than Whites. Foreign-born
persons account for approximately 95 percent of newly reported chronic infections in the United
States, especially immigrants from East Asia and Africa.

Prevention, screening, and early detection of hepatitis B and liver disease are key focus areas of
NIH research efforts to address health disparities among Asian Americans and other Pacific
Islanders, African Americans, as well as those of African descent, and other immigrant
populations. NIH supports hepatitis B projects focused on prevention as well as projects that
investigate hepatitis B as a risk factor for liver cancer among racial and ethnic minority
populations. NIH also supports research on multilevel ecological interactions between and across
population social conditions, social and physical contexts, and individual demographic and
biological determinants to this disparate health outcome.

One NIH-funded study aimed at improving hepatitis B virus (HBV) screening and vaccination
among Korean Americans who had never been screened for HBV used a community-based
participatory research approach to deliver a multi-level intervention. Participants in the
intervention were exposed to educational sessions on HBV prevalence, risk factors, transmission,
screening and vaccination, as well as prevention strategies. The study found that 92.5 percent of
the participants in the intervention were more likely to be screened for HBV compared to
participants who did not receive the intervention. The findings illustrate the potential of
community-based participatory research in increasing awareness and knowledge, as well as
screening and vaccination rates among communities disproportionately impacted by HBV.

NIH will continue to support collaborative efforts to advance awareness agendas, prevention
strategies, testing, and treatment among those disproportionately affected by hepatitis B.
Hepatitis B Virus
The Committee notes that infection with HBV is a serious public health threat and 1 in 20 Americans has been infected and more than 2,000,000 are chronically infected, increasing by 80,000 a year. Left undiagnosed and untreated, 1 in 4 or over 500,000 of those with chronic HBV infection will die prematurely from cirrhosis, liver failure, and/or liver cancer. In view of this public health threat, the Committee remains concerned that NIH research spending on HBV research was only $48,000,000 in 2013 and has remained flat funded since then. The Committee notes that both the World Health Organization in 2016 and the National Academies of Science, Engineering and Medicine in 2017 have declared that the elimination of HBV is possible. Subsequently, the HBV research community convened a virtual consensus conference that resulted in articles published in 2018 in two peer-reviewed scientific journals, Hepatology and Antiviral Research, identifying the most urgent research questions that must be answered to find a cure for HBV. NIDDK is urged to pursue multiple critical research opportunities toward improved treatments and a cure for Hepatitis B.

Action taken or to be taken:

NIH remains committed to addressing hepatitis B virus (HBV) infection and HBV-related diseases such as cirrhosis and liver cancer. In pursuit of this goal, several NIH Institutes, Centers, and Offices maintain robust, complementary HBV research portfolios that span a broad array of research areas, including efforts aimed at developing new treatments and an effective cure.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a variety of HBV research programs, including investigator-initiated extramural research, intramural research at the NIH, and research supported through initiatives, such as large, multisite studies and ancillary studies to clinical trials. For example, the Hepatitis B Research Network aims to advance understanding of disease processes and progression over time, as well as to identify effective approaches to treatment with available and emerging therapies. The Network’s 13 sites across the U.S. and Canada have initiated multiple clinical trials and ancillary studies in both adults and children with hepatitis B; two of the trials have been completed with results to be published in the near future. The study involves participation from the Centers for Disease Control and Prevention. These studies can help drive development of new strategies to manage and treat chronic hepatitis B. The Network is currently completing a 5-year study of long-term outcomes of hepatitis B therapy to investigate whether it is possible to clear HBV infection and stop antiviral therapy, coming close to a “cure.” The NIDDK Intramural Research Program also conducts ongoing research to develop model systems for the development of new drugs to treat chronic hepatitis B.

Additionally, the National Institute of Allergy and Infectious Diseases (NIAID) supports basic, translational, and clinical research on HBV to better understand the disease and to develop novel therapeutics with the potential to serve as a functional cure. NIDDK is continuing to work with representatives of the NIAID and the National Cancer Institute (NCI) on efforts to advance research on hepatitis B and its sequelae, such as cirrhosis and liver cancer. NIDDK, NIAID, NCI and other NIH Institutes, Centers, and Offices also participate in the Trans-NIH Committee on Viral Hepatitis and the HHS National Viral Hepatitis Action Plan to coordinate efforts on hepatitis B and related liver cancer across the NIH and HHS. NIDDK will continue to be informed by hepatitis B research priorities identified by the wider research community as it
pursues collaborative efforts with other funders of hepatitis B research at NIH to advance development of novel HBV therapeutics that could serve as a functional cure.
Hepatitis B Virus (NIMHD)

The Committee notes that HBV infection is a serious public health threat with 1 in 20 Americans infected and more than 2,000,000 chronically infected, increasing by 80,000 a year. Left undiagnosed and untreated, 1 in 4, or over 500,000, of those with chronic HBV infection will die prematurely from cirrhosis, liver failure, and/or liver cancer. The Committee notes that half of all hepatitis B patients in the U.S. are Asian-American immigrants or Pacific Islanders, though these groups only account for about 6 percent of the population. Further, among African immigrants, the prevalence of hepatitis B is about 10 percent. The Committee urges NIMHD to fund research to test scale-up model programs that increase hepatitis B awareness, knowledge, prevention through vaccination, testing, and treatment through linkage to care among the disproportionately hepatitis B impacted communities.

Action taken or to be taken:

Hepatitis B is a growing public health concern for racial and ethnic minorities in the United States. Chronic hepatitis B can result in cirrhosis or scarring of the liver, liver failure, or liver cancer. Asian Americans and Pacific Islanders make up less than five percent of the total population in the U.S., but account for more than 50 percent of nearly one million Americans living with chronic hepatitis B. Furthermore, African Americans bear a disproportionate burden of disease and are 2.5 times more likely to die from hepatitis B than Whites. Foreign-born persons account for approximately 95 percent of newly reported chronic infections in the United States, especially immigrants from East Asia and Africa.

Prevention, screening, and early detection of hepatitis B and liver disease are key focus areas of NIH research efforts to address health disparities among Asian Americans and other Pacific Islanders, African Americans, as well as those of African descent, and other immigrant populations. NIH supports hepatitis B projects focused on prevention as well as projects that investigate hepatitis B as a risk factor for liver cancer among racial and ethnic minority populations. NIH also supports research on multilevel ecological interactions between and across population social conditions, social and physical contexts, and individual demographic and biological determinants to this disparate health outcome.

One NIH-funded study aimed at improving hepatitis B virus (HBV) screening and vaccination among Korean Americans who had never been screened for HBV used a community-based participatory research approach to deliver a multi-level intervention. Participants in the intervention were exposed to educational sessions on HBV prevalence, risk factors, transmission, screening, and vaccination, as well as prevention strategies. The study found that 92.5 percent of the participants in the intervention were more likely to be screened for HBV compared to participants who did not receive the intervention. The findings illustrate the potential of community-based participatory research in increasing awareness and knowledge, as well as screening and vaccination rates among communities disproportionately impacted by HBV.

NIH will continue to support collaborative efforts to advance awareness agendas, prevention strategies, testing, and treatment among those disproportionately affected by hepatitis B.
Hereditary Hemorrhagic Telangiectasia
The Committee encourages NHLBI to examine heart manifestations of HHT, including the correlation between liver arteriovenous malformations caused by HHT and heart failure.

Action taken or to be taken:

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

The National Heart, Lung, and Blood Institute (NHLBI) funds basic research to understand the molecular mechanisms of AVMs. Genetic causes of HHT are linked to a common signaling pathway in cells, the TGFβ pathway. One study is investigating the mechanism by which the loss of signaling to a gene regulating protein in this pathway leads to AVM and HHT.\textsuperscript{127}

This project seeks to explain the molecular and cellular mechanisms driving AVM/HHT pathogenesis and the downstream effects of the TGFβ pathway that promote AVM/HHT. Another group is investigating which cells are involved in AVM formation and progression and determining how the genes linked to the TGFβ pathway are contributing to the disorder.

Other researchers are implementing a screening and characterization strategy to identify FDA-approved drugs that might have a therapeutic potential in the cellular and mouse models of HHT. This drug repurposing strategy has the potential to fast-track new clinical investigations for HHT.

NHLBI funds animal models of HHT to study heart development and heart defects caused by HHT. One study is looking at the relationship between HHT and genes involved in producing a necessary signaling molecule that is decreased in HHT patients. They use the zebrafish animal model where the signaling molecule gene is inactivated to evaluate vascular and heart defects.\textsuperscript{128}

Lastly, an NHLBI-supported scientist recently reported promising results on testing a new therapy to prevent hemorrhage of brain AVMs in mice with HHT-like disorders.\textsuperscript{129}

\textsuperscript{127}projectreporter.nih.gov/project_info_description.cfm?aid=9594924&icde=40450398&ddparam=&ddvalue=&dds
ub=&cr=7&csb=default&cs=ASC&pball=
\textsuperscript{128}projectreporter.nih.gov/project_info_description.cfm?aid=9522067&icde=40450398&ddparam=&ddvalue=&dds
ub=&cr=9&csb=default&cs=ASC&pball=
\textsuperscript{129}www.ncbi.nlm.nih.gov/pubmed/29593101
Improving Patient Access to Cancer Clinical Trials

The Committee supports NCI efforts to improve patient access to and participation in cancer clinical trials across the country. One of the underappreciated barriers to enrollment in cancer clinical trials is the ancillary costs associated with participating in clinical trials, especially for underserved and minority patients. NCI is encouraged to explore research opportunities to improve accrual and retention by collaborating with its NCTN and the NCORP. NCTN is the cornerstone of NCI’s clinical trials program that conducts phase II and III clinical trials, and NCORP is a national network that brings clinical trials and cancer care delivery studies to people in their own communities. These programs encompass over 3,000 clinical trials sites across the country, as well as collaborations with many NCI-Designated Cancer Centers. The Committee also supports the NCI-Designated Cancer Centers working with their local community organizations to encourage enrollment of underrepresented populations onto cancer trials. The Committee requests an update on these efforts in the fiscal year 2020 CJ.

Action taken or to be taken:

The National Cancer Institute (NCI) is committed to helping cancer patients access NCI-supported clinical trials and is working to effectively leverage its networks and programs related to clinical trials. The cornerstone of NCI’s clinical trials program is the National Clinical Trials Network (NCTN), which includes five U.S. clinical trials research groups and several international member sites that constitute approximately 2,400 NCTN sites across the country. In addition, the NCI Community Oncology Research Program (NCORP) conducts research and clinical trials in community-based health care systems. Both NCTN and NCORP work with NCI-Designated Cancer Centers across the country to provide cancer patients with access to clinical trials.

NCORP brings clinical trials to patients in their own communities, generating broadly applicable evidence-based knowledge to improve patient outcomes and reduce cancer disparities. The program includes a network of seven Research Bases, twelve Minority/Underserved Community Sites, and thirty-four Community Sites that are associated with over nine hundred public hospitals, physician practices, academic medical centers, and other groups across the nation. The Minority/Underserved Sites provide access to a diverse patient population, allowing enhanced accrual of underrepresented populations such as racial and ethnic minorities, adolescent and young adult (AYA) patients, and rural communities. The success of this program can be seen through its impact on enrollment to the NCI Molecular Therapy of Choice Trial (MATCH). The MATCH trial enrolled patients from all 50 states, with 44% of the patients enrolled through NCORP community sites.

NCI has recently launched a new collaboration with the Veteran’s Administration (VA) to enhance the ability of veterans with cancer to receive investigational treatments locally, to increase clinical trials participation, and to allow for more rapid completion of trials. This program, entitled the NCI and VA Interagency Group to Accelerate Trials Enrollment (NAVIGATE), opened at twelve VA sites in 2018.130 NAVIGATE will enhance the ability of

---

veterans to participate in trials carried out through NCTN and NCORP. NCI will provide infrastructure funding support needed for the VA facilities to participate in NCI-sponsored trials, and VA will manage activities within its national healthcare system to establish a network to focus on NCI trial goals.

NCI is also exploring innovative ways to increase overall participation in clinical trials. Social media is facilitating multi-directional communication among patients, advocates, clinicians, and the research community. NCI is engaging the cancer research community in devising social media strategies for clinical trials and in June of 2018, held a workshop titled, “At the Crossroads of Social Media and Clinical Trials: A Workshop on the Future of Clinician, Patient and Community Engagement.” The workshop aimed to synthesize new ideas for improving education and awareness about clinical trials using social media in the community, including ways to reach and engage minorities and other communities traditionally underrepresented in clinical trials. Currently, NCI is working to convene a stakeholder group to implement and carry forward key recommendations.

To identify ways to make cancer clinical trials easier to find, NCI’s Coordinating Center for Clinical Trials recently launched the Finding Clinical Trials Collaborative. Working with the cancer community, NCI will focus on developing optimal, standard language and terminology for structuring clinical trials eligibility criteria. Building consensus on standard language to drive more machine-readable eligibility criteria will allow for improved accuracy of clinical trials searches and opens the possibility of matching patients to trials based on data in electronic health records. In addition, the longstanding NCI Contact Center provides accurate, up-to-date, and easily understandable information on cancer. The service is available by phone, e-mail or live chat from the cancer.gov website.

---

131 https://dctd.cancer.gov/NewsEvents/20180706_Social_Media_and_Clinical_Trials.htm
132 Also known as the Cancer Information Service
Improving the Treatment of Mental Illness

The Committee encourages NIMH to continue to ensure a diverse research portfolio of basic neuroscience, applied, and translational research, with a continued focus on excellent science.

Action taken or to be taken:

The National Institute of Mental Health (NIMH) maintains its commitment to a diverse research portfolio that prioritizes excellent science across the basic, translational, and intervention and services pipeline.133 This commitment is reflected in the objectives outlined in the NIMH Strategic Plan for Research,134 all aimed at improving treatment for mental illnesses. NIMH efforts to improve treatments for mental illnesses includes pharmacological, device-based, and psychosocial and behavioral intervention strategies.

The path to novel pharmacological treatments begins with basic research. The NIMH Drug Discovery and Clinical Therapeutics Program supports research to develop and test novel therapeutic agents for the treatment of mental illnesses.135 Early-stage therapeutic discovery and development spans the drug development pipeline, including first-in-human and early efficacy trials.136 Recent pharmacological approaches include new drug compounds to improve cognition in people with schizophrenia, two of which are now at the stage of safety and tolerability testing.137,138,139 NIMH Fast-Fail Trials evaluate novel drug compounds for mood and anxiety spectrum disorders, psychotic spectrum disorders, and autism spectrum disorders.140

Translational research sheds light on mechanisms that underlie mental illnesses and therapeutic response. The North American Prodrome Longitudinal Study (NAPLS and NAPLS2) examines the conversion from the prodromal stage to the psychotic stage of schizophrenia to inform the development of treatments that may prevent that conversion.141 Large clinical trials are designed to test the efficacy of new treatments, and a recent study is examining how well a novel device-based intervention works for the treatment of depression.142

To develop and test prevention and treatment strategies, intervention and services research aims to benefit those who are living with mental illnesses now. These research efforts encompass a wide spectrum of care, and examples include suicide prevention in health care systems,143 early identification and rapid engagement in evidence-based services,144 treatment for persons at

---

134 www.nimh.nih.gov/about/strategic-planning-reports/index.shtml
137 projectreporter.nih.gov/project_info_description.cfm?aid=9339822&icde=32296266
138 projectreporter.nih.gov/project_info_description.cfm?aid=9140071&icde=32296291
139 projectreporter.nih.gov/research-priorities/research-initiatives/fast-fast-fail-trials.shtml
140 projectreporter.nih.gov/project_info_description.cfm?aid=9533695&icde=40746163
141 projectreporter.nih.gov/project_info_description.cfm?aid=9536150
142 projectreporter.nih.gov/project_info_description.cfm?aid=9536150
clinical high risk for psychosis\textsuperscript{145}, and research to optimize practice-based research infrastructure for youth and adults with mental illnesses.\textsuperscript{146}

In the context of a balanced portfolio based on excellent science, NIMH will continue to support basic, translational, and intervention and services research to advance its mission to transform the understanding and treatment of mental illnesses.

\textsuperscript{145} grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-211.html
\textsuperscript{146} grants.nih.gov/grants/guide/pa-files/PAR-16-354.html
Increasing Diversity in Clinical Trials

Inclusivity in clinical trials is a critical solution to ensure that patients receive the safest, most efficacious and precise care possible. The Committee requests that the Director report to the Committee in the fiscal year 2020 CJ regarding the status of these efforts, also including major successes, barriers, and best practices.

Action taken or to be taken:

For over two decades, NIH has required that the research it supports include women, members of racial and ethnic minority groups, and children unless there is a scientific or ethical rationale for the exclusion of these groups. In fiscal year (FY) 2016, over 50 percent of participants in NIH-supported clinical research were women, while about 37 percent were racial and ethnic minorities. NIH supports increased enrollment of diverse populations through activities such as the All of Us Research Program, a momentous research effort to advance individualized prevention, treatment, and care for people of all backgrounds, which opened to national enrollment in May 2018. NIH also has refined methods for reporting data on inclusion of participants by sex/gender, race, and ethnicity by research condition and disease category and plans to include these data in its next triennial inclusion report expected in FY 2020.

In 2017, as part of implementing the 21st Century Cures Act, NIH announced policy changes related to best practices for considering inclusion variables in study design and reporting. NIH is requiring that applications for all NIH-supported research submitted on January 25, 2019 or later address inclusion of individuals across the lifespan (including children and older adults). Awardees will also be required to report de-identified individual-level participant data by sex/gender, race, ethnicity, and the age at enrollment in their progress reports. Furthermore, NIH issued a policy amendment to require recipients conducting applicable NIH-defined Phase III clinical trials ensure results of stratified analyses by sex/gender, race, and ethnicity are submitted to ClinicalTrials.gov at the completion of the study. This policy aims to ensure the dissemination of clinical trial results to assess if variables being studied affect women or members of minority groups differently than other trial participants.

In January 2018, NIH also began collecting the planned age range of participants in its new grant application forms and deployed a new electronic system that allows submission of de-identified individual-level participant data in progress reports. This new functionality will allow for analysis of the intersection of participant age, sex/gender, race, ethnicity, and research condition or disease category of the project in which the participant is enrolled.

Although NIH has taken many steps to improve the inclusion of diverse groups in its clinical research studies, inclusion of certain populations, such as pregnant and lactating women, continues to be a challenge. The Task Force on Research Specific to Pregnant Women and

---

147 Trends in inclusion in NIH research: https://report.nih.gov/recovery/inclusion_research.aspx
Lactating Women, established by the 21st Century Cures Act, developed 15 recommendations\textsuperscript{150} aimed at increasing scientific knowledge of therapeutic product safety, effectiveness, and dosing for pregnant and lactating women. NIH looks forward to continuing to work with the scientific community to ensure that the knowledge gained from NIH-funded research is applicable to all those affected by the conditions under study.

\textsuperscript{150} The Task Force on Research Specific to Pregnant Women and Lactating Women report which includes these recommendations will be submitted to the Department of Health and Human Services Secretary and Congress in September 2018.
Induced Pluripotent Stem Cell Technology

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 adult skin cells, providing increased opportunities to develop sources of cells with great therapeutic value and potential for curing human diseases. The Committee recognizes that basic science leads to pre-clinical trials, cures, diagnostics, and treatments. It encourages NIH to further explore additional basic science opportunities. The Committee requests an update in the fiscal year 2020 CJ on NIH efforts to expand iPSC technology basic research, including through collaborative research activities.

Action taken or to be taken:

NIH supports a wide range of basic and preclinical research focused on induced pluripotent stem cells (iPSCs). These studies range from basic research, such as developmental and regulatory mechanisms of stem cells, cell fate determination, and control of stem cell niche, to translational projects addressing scale up of stem cell populations, development of approaches and assays for effective stem cell delivery and cellular function in vivo. iPSCs are often used as tools to help understand and target the underlying mechanisms of illness, analyze genetic and cellular dysfunction (e.g., in patient-derived versus control lines), identify targets for intervention or diagnostic classification, and develop new small molecule therapeutics. NIH also supports a broad range of bioengineering projects to develop biomaterials and scaffolds that can modulate stem cell survival and function in vitro and in vivo as well as the development of tissue chips and “disease-in-a-dish” systems that utilize patient-derived iPSCs to model human organ and tissue functionality, elucidate mechanisms of disease, and predict human responses to drugs. Correcting defective genes in iPSC-derived tissues is a promising approach for cell therapies for inherited diseases and could lead to new treatment strategies to maintain or restore organ function in a variety of diseases or provide new tools for diagnostics and drug discovery and testing. However, the process to create the genetically corrected iPSCs can introduce mutations to off-target genes, and the long-term effects of those mutations is unknown. Consequently, NIH supports the development of novel processing techniques that will simplify derivation of therapeutic iPSCs, reduce the number of off-target mutations, and enhance the safety of such therapies for genetic diseases.

NIH supports a wide variety of highly collaborative iPSC research, including research consortiums. Some of these collaborative initiatives focus broadly on iPSC development and use, such as the National iPSC Network, which freely shares iPSC lines and their reprogramming reagents with more than 500 laboratories across the globe. Its goals are to make patient-derived iPSCs, together with the tools and expertise for their genetic manipulation, available to the greater research community on a large scale to facilitate understanding of disease and development of new therapies. Other consortiums are focused on the development and validation of iPSC-based human tissue chips that closely mimic the normal physiology of key metabolic tissues such as pancreatic islet, liver, skeletal muscle, and fat. In the future, such tissue chips could advance drug development, disease biomarker discovery, and development of personalized treatments. Some NIH-supported consortiums focus on specific diseases or tissues. The Intestinal Stem Cell Consortium supports projects that use iPSCs to generate “mini-intestines” in the lab, which could serve as models for gastrointestinal disorders and platforms for developing novel therapies. The recently established Dental, Oral and Craniofacial Tissue
Regeneration Consortium is helping to move iPSC-based projects toward initiation of clinical trials. NIH is also generating iPSCs from patients with age-related eye diseases and will make these lines available to the extramural research community along with phenotypic and genotypic information to elucidate disease mechanisms and correlate them with clinical pathology. Another collaborative study focuses on pre-clinical safety and efficacy of a novel adipose-derived cell therapy for the treatment of pressure ulcers, which can be a life-threatening condition in elderly patients.

Ongoing efforts to expand iPSC-based research include development of biofabricated iPSC-derived tissue models of sensory neurons for pain drug development. Additionally, the Tissue Chips for Disease Modeling initiative will support further development of tissue chip models that mimic disease pathology of major human organs and tissues. These model systems will use primary tissue or iPSC-derived patient cell sources on tissue/organ-on-chip platforms to test the effectiveness of candidate drugs. For example, tissue chip three-dimensional heart ventricle chamber models are being tested to understand heart disease.
Inflammatory Bowel Diseases (House)
The Committee is pleased by NIDDK's support of research into inflammatory bowel diseases and notes recent CDC prevalence data, which suggests inflammatory bowel disease (IBD) is twice as prevalent as originally thought. The Committee encourages NIDDK to respond to these findings by providing enhanced support for research on IBD. Research should include a focus on the environmental triggers and epigenetics of IBD as well as interventions for the rising prevalence of IBD, and be targeted at both pediatric and adult patients.

Action taken or to be taken:
The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supports a robust portfolio of projects that are investigating potential causes of inflammatory bowel diseases (IBD). Several studies are exploring environmental causes, such as diet and the composition of the gut microbiome (which is affected by diet, antibiotics, and other environmental factors). For example, NIDDK is supporting a study to examine whether a diet low in fiber could exacerbate IBD by disrupting the intestine’s protective barrier. Another study recently found that an enzyme produced by certain gut bacteria could potentially play a significant role in the development of IBD by disrupting the microbiome. Also, several studies in the NIDDK-supported IBD Genetics Consortium are identifying epigenetic changes that could play roles in the development of IBD. These studies are examining how IBD risk is influenced independently from variations in active genes, such as through changes in the 3-dimensional structure of chromosomes or in the regions of DNA that do not code for protein. These investigations into the environmental and epigenetic causes could lead to the development of new therapies for IBD.

NIDDK is also supporting clinical trials to test the safety and effectiveness of IBD interventions. The Methotrexate Response in Treatment of Ulcerative Colitis (MERIT-UC) study is investigating the safety and therapeutic value of methotrexate, an inexpensive yet potentially toxic drug that is used in adult ulcerative colitis patients in whom established therapies have failed. Recent results from this study showed that methotrexate did not improve ulcerative colitis symptoms compared to a placebo, suggesting that this drug, which could lead to chronic liver disease and liver fibrosis, is not beneficial for colitis patients. Another study is examining the safety and effectiveness of a protein called interleukin-2, which has been shown to restrain the immune response in other autoimmune diseases, as a treatment for adults with moderate to severe ulcerative colitis. The Predicting Response to Standardized Pediatric Colitis Therapy (PROTECT) study is evaluating whether a combination of clinical, genetic, and immunologic tests can be used to predict response to standard medical therapy for children newly diagnosed with ulcerative colitis. Recent results from the PROTECT study found that higher amounts of an immunologic biomarker called pANCA in the blood correlates with disease severity, which means this biomarker could potentially be used as a diagnostic tool to help plan treatments for pediatric patients. The PROTECT study also found that ulcerative colitis correlates with vitamin D deficiency in pediatric patients, raising the possibility that vitamin D deficiency might contribute to the progression of the disease.
**Immunotherapy**

The Committee continues to be encouraged by new breakthroughs in cancer immunotherapy, built upon decades of NCI-funded research on the immune system and the ways in which it can be harnessed to find and destroy tumors. This new wave of treatment options has the potential to revolutionize treatment for a growing number of cancers. Yet much remains unknown about how immunotherapy works on a cellular level, and especially why such treatments are successful for some patients, but not for others. Furthermore, some patients experience side effects that are far different than those associated with chemotherapy. Without a better understanding of the immune system’s response to cancer, the knowledge of how cancer escapes immune-based therapy, the capacity to quickly recognize and manage side effects, and the ability to predict which patients are most likely to respond well to therapy, further advances in this field will be slowed. Therefore, the Committee urges NCI to continue to prioritize basic research on the mechanisms of action involved in immunotherapy, including a focus on tumor resistance to immunotherapy and the underlying mechanisms of cancer immunotherapy toxicities. The Committee also recognizes the need for more basic and clinical researchers who have the necessary education to develop new breakthroughs in immunotherapy. The Committee encourages NCI to continue to support training for both young and mid-career researchers interested in immunotherapy.

**Action taken or to be taken:**

Recent clinical advances in cancer immunotherapy have emerged from decades of NCI and NIH-funded basic, translational, and clinical research on the immune system and cancer. For example, the recent 2018 Nobel Prize in Physiology and Medicine was awarded to NCI-grantee Dr. James Allison of MD Anderson Cancer Center and Dr. Tasuku Honjo of Kyoto University, Japan, “for their discovery of cancer therapy by inhibition of negative immune regulation.”¹⁵¹ NCI has supported Dr. Allison’s research for many years and continues to do so today as NCI recognizes the need to continue to advance research in this area. This includes better understanding of basic mechanisms of how the immune system interacts with cancer, biomarkers of immunotherapy response and resistance, identification of new therapeutic targets, development of novel agents (to be used alone or in combination therapies), and mechanisms of toxicities and how to manage them clinically. A comprehensive description of each of these research areas is available on our website.¹⁵²

Physicians need more biomarkers that reliably and accurately predict which patients are more likely to benefit from immunotherapies. For example, recently NCI extramural and intramural scientists developed new methods for predicting which patients are most likely to respond to immune checkpoint therapies. These approaches may lead to tests that can help guide treatment decisions.¹⁵³ Immunotherapy biomarker research is being supported by investigator-initiated grants as well as through clinical trials networks and public-private partnerships.

NCI is also funding research on immunotherapy induced toxicities, including identifying genetic factors that may make some patients particularly susceptible to toxicities, studying the biological mechanisms underlying toxicities in different tissues, and developing diagnostic tests to identify

---


¹⁵² [https://www.cancer.gov/research/key-initiatives/immunotherapy](https://www.cancer.gov/research/key-initiatives/immunotherapy)

toxicities earlier. NCI supports other tools and resources to aid researchers and clinicians in this area. For example, in 2017, the Common Terminology Criteria for Adverse Events—a standard classification of adverse effects of cancer drugs—added terminology for reporting on immunotherapy clinical trials.

Supporting and retaining investigators in all areas of cancer research, including immunoncology, is critical for advancing NCI’s mission. NCI supports training through extramural grants and through its intramural program, which has strength in the field of cancer immunotherapy. As an example of one activity, NCI has recently supported an immunotherapy fellowship with a non-profit organization.154

Inflammatory Bowel Diseases
The Committee is pleased by NIDDK's past support of research into inflammatory bowel diseases (i.e. Crohn's disease and ulcerative colitis). The Committee encourages NIDDK to build upon this foundation by exploring "bedside-to-bench" approaches to regenerative medicine by clearly defining the clinical need and subsequent research agenda and bringing multi-disciplinary experts together to advance progress toward new therapeutic benefit for IBD patients.

Action taken or to be taken:

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) continues to encourage research to explore new therapies for inflammatory bowel diseases (IBD), including using regenerative medicine approaches. In 2018, for example, NIDDK hosted a year-long series of forums, which took place during meetings of the National Diabetes & Digestive & Kidney Diseases Advisory Council, to receive advice on the Institute’s programs and research directions related to regenerative medicine. These discussions involved experts from various academic fields and included consideration of overlapping interests and possibilities for collaboration. The January 2018 Advisory Council forum included a presentation from a member of the NIDDK-sponsored Intestinal Stem Cell Consortium who highlighted the clinical need for regenerative medicine approaches as potential therapies for digestive diseases, including IBD.

Other members of the multidisciplinary Intestinal Stem Cell Consortium, whose ultimate vision is to develop novel therapies by using intestinal stem cells to regenerate and rebuild the human intestine, recently developed methods to generate “mini-intestines” in the laboratory from adult stem cells. One eventual goal of such an approach would be to replace damaged intestinal tissues in IBD patients and reduce the odds of transplant rejection by using the patients’ own cells as starting material. Another “bedside to bench” approach to IBD research is being undertaken by the IBD Genetics Consortium, which has analyzed samples from thousands of IBD patients and identified over 200 genetic regions associated with the disease. The IBD Genetics Consortium is combing through these regions to identify specific genes implicated in IBD, along with their physiological functions, which could open the door to personalized therapies that would be based on the patients’ genetics.

These activities align with the goals established by the National Commission on Digestive Diseases Research Plan, the development of which included key input from external scientists across many disciplines relevant to digestive diseases, as well as several digestive disease-related professional and patient advocacy organizations. This Plan continues to serve as a resource for NIDDK’s planning for IBD research. NIDDK will also maintain awareness of the IBD research plans of advocacy organizations, with particular attention to areas aligning with NIDDK’s mission where partnerships may be possible and ways to avoid duplicative efforts.
Institutional Development Award
The Committee provides $361,763,000 for the IDeA program, an increase of $11,188,000. The Committee believes the IDeA program has made significant contributions to biomedical research and has led to the creation of a skilled workforce and made the IDeA program an essential component of NIH's research portfolio. The Committee recognizes the IDeA program's significant contributions to biomedical research and to the development of our Nation's biomedical research infrastructure and workforce. The Committee supports efforts to update IDeA eligibility to be based on the median NIH-funding level for all States. The Committee continues to believe that Primarily Undergraduate Institutes in States that do not reside in an eligible State, but that have been eligible for the National Science Foundation's Experimental Program to Stimulate Competitive Research program for the past 2 consecutive years, would benefit from being able to apply to an entity that currently holds an IDeA Networks of Biomedical Research Excellence award for inclusion in its IDeA network.

Action taken or to be taken:
NIH/National Institute of General Medical Sciences (NIGMS) appreciates the Committee’s continued support of the Institutional Development Award (IDeA) Program and for recognizing the critical role that the Program plays in developing and enhancing the biomedical research workforce and infrastructure across the nation. Currently, institutions in 23 states\textsuperscript{155} and Puerto Rico are eligible for funding from the IDeA Program. The Department of Health and Human Services has submitted to the Congress a legislative proposal seeking authorization for a revision to the IDeA Program eligibility criteria. The revised eligibility criteria are based on a State’s total NIH funding instead of aggregate success rate as the eligibility criteria, which makes the lower half of the 55 States/Jurisdictions receiving NIH funding eligible for the IDeA Program. Also included in the legislative proposal is a provision that would allow Primarily Undergraduate Institutions (PUIs) that do not reside in IDeA-eligible states but have been eligible for the Established Program to Stimulate Competitive Research (EPSCoR) of the National Science Foundation (NSF) for the past 2 consecutive years to participate as partnering/collaborating institutions in established INBRE awardees. Their participation would be supported by supplementing the budgets of existing IDeA Networks of Biomedical Research Excellence (INBREs).

For FY 2019, the IDeA Program will continue to support investigators in eligible states/jurisdictions through the following initiatives:

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

\textsuperscript{155} Alaska, Arkansas, Delaware, Hawaii, Idaho, Kansas, Kentucky, Louisiana, Maine, Mississippi, Montana, Nebraska, Nevada, New Hampshire, New Mexico, North Dakota, Oklahoma, Rhode Island, South Carolina, South Dakota, Vermont, West Virginia, Wyoming.
knowledge in the states' workforces. In FY 2018, NIGMS supported 24 INBRE awards, one in each eligible state and Puerto Rico. For FY 2019, NIGMS will continue support for INBRE Networks.

(2) Centers of Biomedical Research Excellence (COBRE – Phases I, II, and III). The goal of the COBRE initiative is to strengthen institutional biomedical research capabilities in IDeA states through three 5-year phases of infrastructure and faculty development of thematic and multidisciplinary research centers. In FY 2018, NIGMS supported 116 COBRE awards. For FY 2019, NIGMS will continue to support non-competing awards and consider new COBRE awards to outstanding applications.

(3) IDeA Program Infrastructure for Clinical and Translational Research (IDeA-CTR). The IDeA-CTR initiative develops network infrastructure and capacity in eligible states to conduct clinical and translational research focused on health concerns that affect medically underserved populations and/or that are prevalent in IDeA states. IDeA-CTR awards support mentoring and career development activities in clinical and translational research. In FY 2018, NIGMS renewed the funding of two IDeA-CTR awards and funded one new IDeA-CTR award, bringing the total number of IDeA-CTR awards supported to 11. Furthermore, administrative supplements were awarded to four IDeA-CTR programs to address the opioid epidemic. In FY 2019, NIGMS will continue to support non-competing awards and consider funding new, meritorious IDeA-CTR applications.

(4) Research co-funding. IDeA co-funding is provided to eligible applications that have already been judged meritorious by NIH peer-review committees and national advisory councils but are outside the range of applications under consideration for funding by the other NIH Institutes and Centers (ICs). In FY 2018, the IDeA Program is co-funding 31 awards for research project grants (R01) and Academic Research Enhancement Awards (AREA, [R15])156, as well as four shared instrumentation (S10) awards with 18 NIH ICs. In FY 2019, NIGMS is again soliciting applications from other ICs for co-funding.

In addition to the four ongoing IDeA initiatives described above, NIGMS also funded four STTR Regional Technology Transfer Accelerator Hubs in FY 2018 that will provide the necessary infrastructure to build and foster an entrepreneurial culture in IDeA states/jurisdictions. These STTR awards are in response to the HHS Committee Report in FY 2016 that asked NIH/ NIGMS ‘to consider allocating funding for one shared innovation incubator in each of the four IDeA regions that would be competitively bid among IDeA States and would serve IDeA States.’ Consistent with report language that further indicates that ‘NIH shall not use funding from its IDeA allocation for these grants;’ these awards are funded from the SBIR/STTR allocation.

In FY 2019, the IDeA Program will provide continuing support for the non-competing INBRE, COBRE, and IDeA-CTR awards that constitute the IDeA Program budget base. The IDeA

156 https://area.nih.gov/
Program will also support competing new and renewal awards to COBRE, INBRE, IDeA-CTR, and IDeA co-funding of meritorious applications from other ICs.
Institutional Development Award [IDeA] State and Cancer Trials

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

Action taken or to be taken:

NCI remains committed to providing cancer patients with access to NCI-supported clinical trials throughout the United States. NCI-supported networks and programs operate in collaboration to achieve this goal. NCI supports 70 designated cancer centers in 36 states and the District of Columbia; this includes nine in IDeA states. The newest NCI cancer center, the University of Oklahoma Stephenson Cancer Center, awarded in 2018, is one of those. Staff in NCI’s Office of Cancer Centers worked closely with the Stephenson staff over several years to assist them in developing their application and encourages other interested centers to contact NCI to learn more about the application and designation process.

The National Clinical Trials Network (NCTN) is the cornerstone of NCI’s clinical trials enterprise and provides access to clinical trials through 2,400 sites that are connected through six network groups (five in the U.S. and 1 in Canada). Along with the NCTN, the NCI Community Oncology Research Program (NCORP) conducts research and clinical trials in community-based health care systems, including rural communities. NCORP currently supports 34 Community Sites, 12 Minority/Underserved Community Sites, and seven research bases. Nineteen IDeA states are involved in the NCORP network in some way and there are over 4,000 investigators and over 900 public hospitals, physician practices, academic medical centers, and other groups across the nation associated with the network. NCORP was launched in 2014 and in 2018 NCI renewed its commitment to the program with the re-issuance of the Funding Opportunity Announcement (FOA) for Research Bases, Community Sites and Minority/Underserved Community Sites to continue and expand the program. Each of these FOAs require a clinical trial component. NCI held pre-application webinars to answer questions and provide technical assistance to potential applicants and additional resources are available on the NCORP website. Applicants from IDeA states are encouraged to apply.

The reach of these programs is exemplified by the enrollment statistics for the NCI Molecular Analysis for Therapy Choice (MATCH) trial. More than 1,100 institutions across the United States have enrolled patients for screening in NCI MATCH, representing all 50 states, the

160 https://ncorp.cancer.gov/resources/applicants.html
District of Columbia, and Puerto Rico. Forty-four percent of those patients were from NCORP community sites and eight of the eleven highest enrolling states were IDeA states.

NIGMS continues to support Institutional Development Awards to build research capacities in IDeA states. Of note, in 2018, an IDeA Program Infrastructure for Clinical and Translational Research grant was awarded to the Dakota Cancer Collaborative on Translational Activities at the University of North Dakota. The goal of the project is to create a center to support and expand our ability to conduct full-spectrum clinical and translational research on various cancers.

NCI encourages researchers at all institutions to apply for funding for individual and team research projects through the NIH/NCI competitive application and peer review process. More information about active NCI funding opportunities across the cancer research portfolio are available on NCI’s website.

---

161 https://projectreporter.nih.gov/project_info_description.cfm?aid=9574221
162 https://www.cancer.gov/grants-training/grants/funding-opportunities
Interstitial Cystitis

The Committee is pleased with the progress of interstitial cystitis research and continues to encourage NIDDK and stakeholders to collaborate on a comprehensive scientific conference to examine mechanisms for scientific opportunity.

Action taken or to be taken:

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) research efforts on interstitial cystitis/bladder pain syndrome (IC/BPS) are focused on understanding the cause(s) of this condition, which affects millions of Americans; improving diagnosis; finding more effective treatments for the pelvic pain and urinary frequency and urgency that affect people with this condition; and finding ways to prevent onset. The innovative, multi-site Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, supported by NIDDK and the NIH Office of Research on Women’s Health, is spearheading the evolution in our understanding of IC/BPS and another urologic chronic pelvic pain syndrome, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Based upon the many important insights already gained, NIDDK has published three Funding Opportunity Announcements with the intent to support a 3 year MAPP Research Network Extension Phase beginning in late FY 2019 that would enable characterization of participants currently enrolled in Network studies for an additional 12 months. The additional research will greatly enrich the Network’s unique clinical dataset and biological sample archive and allow for unprecedented assessment of disease progression over time. This initiative will also allow additional time and resources for collaborative studies to further the goals of the Network, including establishing a foundation for future clinical studies and trials. At the same time, NIDDK is planning to hold a multi-day scientific conference in conjunction with an official Network leadership meeting in fall 2019. The conference will focus on research advances in urologic chronic pelvic pain syndromes and how they can inform the next generation of clinical studies. Goals for this meeting include:

- Providing a forum for the exchange of current, key scientific insights from both MAPP Research Network and non-Network investigators, as well as from non-urologic chronic pain studies that may inform the urologic pain field
- Developing recommendations for effective translation of these insights into an improved evidence base for future clinical studies and ultimately improved patient care
- Developing improved strategies for disseminating Network findings
- Initiating development of new research definitions for urologic pain conditions, based upon the evolving insights into patient characteristics emerging from Network and other studies.

Research opportunities important for IC/BPS should be identified through this effort and, importantly, will inform efforts during the extension phase. At this time, meeting planning is being led by NIDDK scientific staff and MAPP Research Network leadership, and will later expand to include representatives from patient advocacy groups, such as the Interstitial Cystitis Association, that have been active partners in various aspects of Network activities, as well as additional NIH and external scientific experts.
John E. Fogarty International Center
Recent disease outbreaks such as Ebola, Zika, and Dengue have shown the importance of the Center’s essential role in global infectious disease health research training to help developing countries advance their own research and health solutions and tools. FIC has developed important partnerships to not only fight malaria, neglected tropical diseases, and other infectious diseases but also to have the capabilities to detect and treat infectious diseases that are not endemic to the United States before they travel to the United States thus protecting Americans here at home. The Committee urges FIC to continue this important work building relationships with scientists abroad to foster a stronger and more effective science workforce and health research capacity on the ground, helping to detect infectious diseases and building the capacity to confront those diseases while improving the image of the U.S. through health diplomacy in their countries.

Action taken or to be taken:

The Fogarty International Center (FIC) is committed to continuing to invest in building leaders in global health research and strengthening the capacity of research institutions in low-and middle-income countries (LMICs) to be sustainable platforms for cutting-edge science and catalyzing meaningful collaborations between U.S. and foreign institutions. This commitment is articulated in the most current Fogarty International Center Strategic Plan.163

FIC’s investments comprise a range of capacity-strengthening programs which include, for example, the longstanding HIV Research Training Program and the Global Infectious Disease Research Training Program (GID). For more than 15 years, GID has strengthened capacity (through partnerships between U.S. and LMIC institutions) to conduct research directly related to prevention, treatment and control of infectious diseases causing major morbidity and mortality. The recent epidemics of Ebola and Zika have highlighted the need for better global preparedness and response to disease epidemics. FIC is funding collaborations between U.S. and West African academic institutions, through the Emerging Epidemic Virus Research Training Program for West African Countries with Widespread Transmission of Ebola, to develop programs that would strengthen the skills required to evaluate vaccines, develop new diagnostic tests and treatments, and identify the most effective intervention strategies for disease outbreaks.

FIC efforts also include programs that strengthen the global health research workforce generally and are designed to foster partnerships between US and LMIC institutions. Programs like the International Bioethics Research Training Program, the Emerging Global Leader Award, and the Global Health Program for Fellows and Scholars provide research training support for both US and LMIC scientists across the career development pipeline.

Liver Cancer

The Committee commends the NCI on recent efforts to encourage more research focused on liver cancer, but urges greater priority to address the threat of liver cancer, which has a 5-year survival rate of less than 20 percent. Unlike many other cancers, the rates of liver cancer deaths and incidence are rising. The Committee urges NCI to support liver cancer research across its portfolio using a variety of methods to stimulate research proposals. The Committee also notes that the link between hepatitis B infection and primary liver cancer is well established with up to 60 percent of global liver cancer cases caused by the hepatitis B virus [HBV] and, therefore, urges collaboration with NIAID and NIDDK on issues related to HBV research. The Committee requests an update on these activities in the fiscal year 2020 CJ.

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. NCI has funded several new programs in 2018 for HCC, including the NCI Liver Consortium, and the launch of a Specialized Program of Research Excellence (SPORE) in hepatobiliary (liver, gallbladder, bile ducts) cancers. The SPORE will develop translational strategies to improve the detection, diagnosis, and treatment of patients with these malignancies. The NCI Liver Cancer Consortium, which includes five research centers plus a centralized data center, aims to conduct studies to increase the early diagnosis of liver cancer and better stratify patients at risk of developing this cancer. A specific focus area will be the identification and validation of biomarkers of early stage HCC arising from different causes, such as viral, non-alcoholic fatty liver disease; non-alcoholic steatohepatitis; and alcoholic liver disease.

NCI’s intramural Center for Cancer Research has recently established the NCI Liver Cancer Program, a multidisciplinary, translational research program that collaborates with extramural investigators to develop diverse approaches to the prevention, early detection, diagnosis, and treatment of liver cancer. One area of emphasis involves new diagnostics and treatments for liver cancer that use precision medicine strategies, such as molecular analyses for subgrouping patients and biomarker-guided molecularly-targeted therapies. In addition, patient recruitment is underway for several NCI-supported clinical trials testing new therapies, including immunotherapies, for liver cancer.

NCI also collaborates with the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) to advance research to understand hepatitis B virus (HBV) infection and its associated liver cancer. Collaborative work includes understanding how the virus contributes to the development of liver cancer and developing novel therapies that target HBV. Additionally, research to understand the mechanisms of liver

---

166 [www.ccr.cancer.gov/liver-cancer-program](http://www.ccr.cancer.gov/liver-cancer-program)
destruction by HBV in HIV-infected individuals is supported.\textsuperscript{168} The NIDDK-supported Hepatitis B Research Network, in collaboration with the Centers for Disease Control and Prevention, has initiated multiple clinical trials and ancillary studies in both adults and children infected with HBV. Additional research is focused on the possibility of clearing HBV and establishing model systems for new drugs to treat chronic HBV infections. NCI, NIDDK, and NIAID further collaborate on efforts to advance research on HBV infection and its sequelae, such as cirrhosis and liver cancer. Because HCC disproportionately affects racial and ethnic minorities, NCI also supports collaborative research to understand the underlying etiologic factors and the mechanisms that result in disparities in chronic liver diseases and cancer in the United States.\textsuperscript{169}

\begin{footnotesize}
\begin{itemize}
\end{itemize}
\end{footnotesize}
Long-Term and Developmental Health Effects of Zika

The Committee recognizes the unique nature of NICHD research into how the Zika virus infection affects pregnancy and the long-term and developmental health effects on children exposed to the Zika virus. The Committee urges NICHD to prioritize investment in long-term and developmental health effects of the Zika virus as the fight against the virus continues.

Action taken or to be taken:

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) continues its strong research commitment to address the long-term and developmental health effects of Zika virus infection (Zika). Zika is a primarily mosquito-borne flavivirus first isolated in 1947. In 2015, the virus began spreading rapidly in South and Central America and started to appear in the United States. In addition to transmission by mosquitoes, the virus is transmitted sexually and, most critically, transmitted vertically from mother to child during pregnancy. New research in animal models has indicated that infection with Zika during pregnancy may result in at least a 25 percent miscarriage rate. In completed pregnancies, it can cause serious health outcomes, including microcephaly and other birth defects. A recent study from the Centers for Disease Control and Prevention of children born to mothers with laboratory evidence of Zika found that six percent had at least one virus-related birth defect, and nine percent had at least one developmental abnormality. Many of the neurodevelopmental abnormalities of Zika-infected children are not always evident at birth, highlighting the need for continued evaluation of prenatal exposure to Zika and the importance of identifying prevention and treatment strategies.

NICHD, in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Environmental Health Sciences (NIEHS), and Fundacao Oswaldo Cruz-Fiocruz in Brazil, launched the Zika in Infants and Pregnancy (ZIP) Cohort study in 2016, a multi-country study aimed at evaluating the magnitude of health risks that Zika infection poses to pregnant women and their offspring. Over 5,300 participants have been enrolled to date at sites in Brazil, Colombia, Guatemala, Nicaragua, Peru, and Puerto Rico (United States). Women participating in the study are being followed throughout their pregnancies to determine if they become infected with Zika and the health outcomes of those mothers and their children. Participating infants also are followed for at least one year after birth. The next phase of the ZIP Cohort Study will focus on understanding the longer-term health effects of Zika infection by extending the follow-up of infants to at least 4-5 years of age. Recent data in a mouse model indicated that infection can affect testis and sperm quality, so the ZIP study is being leveraged to also evaluate male partners and symptomatic men in Zika-endemic areas.

To address questions concerning the impact of Zika co-infection with other viral infections, NICHD also launched the Prospective Cohort Study of HIV in Zika in Infants and Pregnancy (ZIP-HIV Cohort study) with a focus on HIV/Zika co-infected individuals. The goal of this study is to determine the risk of adverse maternal and child health outcomes associated with co-infection across clinical sites in the continental United States, Puerto Rico, and Brazil.
NICHD is also supporting investigator-initiated research on Zika and its effects on children and mothers. Along with other NIH Institutes and Centers, a funding opportunity was published to encourage investigations of Zika-related complications, specifically focusing on children’s health outcomes such as vision, hearing, neurological, and neurodevelopmental complications. Experiments with pregnant mice have enabled NICHD-funded researchers to describe the variable effects of maternal exposure to Zika depending on the stage of pregnancy when infection occurs. The placenta and fetus appear to be more susceptible to Zika infection at earlier gestational ages and lead to placental insufficiency and fetal demise, but later, in mid-gestation, the infection led to infants with undersized heads. Another study, funded in part by NICHD, has led to Food and Drug Administration approval of a drug, hydroxychloroquine, that appears to reduce transmission of Zika from pregnant mice to their fetuses. In addition, vaccinations recently have begun in a first-in-human trial of an experimental live, attenuated Zika virus vaccine developed by scientists at NIAID.
Lupus
The Committee recognizes NIAMS for implementing the Action Plan for Lupus Research and for leading the Lupus Federal Working Group. The Committee is concerned about the substantial racial disparities in the incidence and prevalence of lupus and notes that African American women experience the highest lupus rate. Therefore, the Committee encourages NIAMS to continue to support lupus research, including studies to understand why the disease disproportionately affects women of color.

Action taken or to be taken:

Systemic Lupus Erythematosus (SLE or lupus) is an autoimmune disorder – a condition where the body’s immune system mistakenly attacks healthy tissues. Population-based research has consistently demonstrated that the disease disproportionately affects women 9:1 versus men, and African American women 3-5 times more frequently than White women. SLE is also more common among Latinas and Asians and more severe among all minority groups studied compared with Whites.

A significant amount of NIH lupus research seeks to understand how lupus develops and to identify potential targets for interventions. Such research into the basic mechanisms of disease development may also reveal clues as to why lupus disproportionately affects women in general, and especially women of color. For example, NIAMS is supporting research to identify genetic risk factors for lupus specifically within African American populations. While more than 50 genetic risk loci have already been identified through genomic studies of European or Asian populations, enhanced understanding of risk factors among African American populations may provide new insights for better prevention approaches or clinical interventions in the future.

In addition, NIAMS is supporting research to understand how sociodemographic factors also may contribute to disparities in lupus incidence and severity. Current research is examining the role that psychosocial stressors (e.g., racial discrimination, financial strain, and inadequate social support) may play in lupus disease progression, as well as the biological consequences of such stressors, such as enhanced inflammation or atherosclerosis. Another project is investigating how potentially modifiable social and behavioral factors (e.g., diet, obesity, and depression symptoms) may contribute to increased SLE incidence among black and low socioeconomic status women. The findings from these and other studies will shed light on the biologic mechanisms underlying lupus and its racial disparities, and potentially inform lifestyle interventions for lupus prevention.

NIAMS also is supporting clinical research centers focused on improving minority health in rheumatic diseases, such as lupus. The centers foster translational, clinical and outcomes research centered on African Americans to improve disease diagnosis, management, and treatment, and ultimately reduce racial disparities in rheumatic diseases. The centers also serve as a resource to educate African American patients and their families, health care providers, and others about rheumatic diseases.
Lymphangioleiomyomatosis
The Committee requests an update on Lymphangioleiomyomatosis research in the fiscal year 2020 Congressional Justification

Action taken or to be taken

The National Heart, Lung, and Blood Institute (NHLBI) is committed to identifying the causes of lymphangioleiomyomatosis (LAM) and improving treatment for patients. LAM is a rare, slowly progressive disease that affects women almost exclusively, and gradually destroys the lungs, often leading to death from respiratory failure. It is characterized by the proliferation of smooth muscle-like cells and cystic lesions in the lung. LAM may occur sporadically, or it may be associated with the genetic disorder tuberous sclerosis complex (TSC).

Lung transplant is a treatment option for women whose lungs have been damaged by LAM, but recent research efforts have focused on finding effective drug therapies. The first FDA-approved treatment for LAM (Sirolimus) was based on research supported by NIH.

NHLBI is currently supporting the Multicenter Interventional LAM Early Disease (MILED) trial which is a Phase III trial investigating whether early, low dose Sirolimus, an immunosuppressive agent, can prevent disease progression in LAM patients with preserved lung function.170 The study is being conducted using the infrastructure created for the Rare Lung Disease Clinic Network, which is currently following over 1200 patients with LAM in the United States.

The Resveratrol and Sirolimus in LAM Trial (RESULT) is an NHLBI-funded phase II trial to test whether a combination of resveratrol and sirolimus in patients with LAM is safer and more effective than sirolimus alone.171 Other NHLBI-funded researchers are conducting studies to determine whether aspirin and sirolimus can prevent lung destruction and restore pulmonary function in preclinical animal models of LAM.172

NHLBI continues to work with the LAM patient community and supports conferences to educate researchers, clinicians, patients and family members. For example, NHLBI and the National Center for Advancing Translational Sciences (NCATS) co-funded the 2017 International Research Conference on TSC and LAM, which brought together leading researchers to focus on accelerating the translation of research advances into benefits for LAM patients.173 In 2018, NHLBI and NCATS supported the International Rare Lung Diseases Conference and LAMposium which is the largest conference in the world that brings together patients, clinicians and LAM experts. The 2018 LAMposium focused on bringing cutting edge technologies to rare lung disease research.174

170 https://clinicaltrials.gov/ct2/show/NCT03150914
171 https://clinicaltrials.gov/ct2/show/NCT03253913
174 http://www.thelamfoundation.org/Events-Conference-Overview
Lymphatic Research
The Committee applauds NHLBI's work on lymphatic diseases and encourages further collaboration and coordination amongst relevant Institutes and Centers conducting important research in this area.

Action taken or to be taken:

Through the Trans-NIH Coordinating Committee for Lymphatic Research, the National Heart, Lung, and Blood Institute (NHLBI), along with several other institutes including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Allergy and Infectious Diseases (NIAID) develops collaborative NIH activities to support research in lymphatic biology and diseases.

The committee organized a symposium in 2015 entitled "The Third Circulation: Lymphatics as Regulators in Health and Disease" to explore how the lymphatic system contributes to function and dysfunction in other organ systems. The committee also has worked with the non-profit Lymphatic Education and Research Network to ensure that NIH peer review sections have sufficient expertise to fairly evaluate grant proposals in lymphatic biology.

NHLBI continues to support multidisciplinary research investigating the development of the lymphatic system, as well as genetic mutations and other conditions that contribute to congenital lymphatic diseases and lymphedema. NHLBI-funded research also addresses the role of the lymphatic system in cardiovascular and pulmonary diseases and in lung transplant outcomes.

NIDDK funds basic and translational research on the role of lymphatics in regulating the digestive system in health and disease, and announced new funding for this area in fiscal year 2017. NIAID currently supports research aimed at understanding the mechanisms that control the migration of cells through the lymphatic system and their role in health and disease, and studies to determine how cells of the lymphatic system contribute to, and regulate, immune responses.

Finally, NHLBI and the National Center for Advancing Translational Sciences (NCATS) co-fund the Rare Lung Disease Consortium (RLDC), a collaboration among patient organizations, clinical investigators, and NIH that supports clinical research studies in people with rare lung diseases. The RLDC supports the development of novel diagnostic tests, therapies, and outcome measures for individuals with rare lung diseases including lymphangioleiomyomatosis (LAM), a disease with lymphatic involvement. The RLDC also provides opportunities for patients to be engaged and participate in research as well as training opportunities for researchers and doctors in rare lung disease clinical research.

176 https://www.rarediseasesnetwork.org/cms/rld
Marijuana Research
The Committee is concerned by the lack of research on marijuana and marijuana products, especially increasing potency. The Committee is concerned with the rapidly changing landscape regarding the recreational use of marijuana the effects that the drug can have on brain development; addiction; the long-term health effects in both youth and older individuals. The Committee directs NIH to coordinate a multi-Institute approach to increase research related to the effect of increasing delta-9-tetrahydrocannabinol levels on the human body as well as the effect of various delta-tetrahydrocannabinol levels on cognitive abilities that are required to, for example, operate motor vehicles. The Committee requests an update on the status of research related to these topics be included in the fiscal year 2020 CJ. Further, the Committee remains concerned that NIDA ceased funding for analysis of marijuana samples seized by law enforcement in 2014. Without dedicated funding for this activity, the number of analyzed seized samples has plummeted, meaning that available data is no longer current or robust. The Committee believes that such re-search, along with analysis of marijuana and marijuana-derived products sold commercially in dispensaries or online, is essential for informing substance misuse and addiction prevention efforts, public health policy, and law enforcement tactics across the Federal Government. The Committee continues to direct NIDA to coordinate efforts with the DEA and other law enforcement agencies to monitor Schedule I marijuana and marijuana-derived products.

Action taken or to be taken:
The increasing potency of marijuana (plant varieties are reported to contain 15-25% tetrahydrocannabinol (THC) or more), and the highly concentrated extracts (e.g., shatter, butter) raise important questions about the health effects of their administration. There are also edibles, tinctures, transdermal, and other formulations. And products are reported to contain differing concentrations of non-THC components, such as cannabidiol (CBD), which does not appear to have rewarding or addictive properties, and is being used for a wide variety of medical conditions, despite little to no evidence supporting most of these uses.

In addition, NIDA has been diversifying its products available for research by varying the cannabinoid concentrations of its plants, allowing for varieties with relatively high THC content (~12%) and low CBD, and vice versa; as well as others in between. However, given current funding availability (and DEA-approved quotas) NIDA is not manufacturing the types of extracts that researchers are interested in studying, particularly for medicinal purposes. At this time, we do not have sufficient products for a large clinical trial of a CBD extract for psychosis, anxiety, or other potential therapeutic applications.

In addition, under the Collaborative Research on Addiction at the NIH (CRAN) initiative, NIDA and the National Institute on Alcohol Abuse and Alcoholism (NIAAA), along with nine other components of the NIH and the Centers for Disease Control and Prevention, are supporting a longer-term, longitudinal study that will not only examine how substance use, including

177 https://www.drugabuse.gov/researchers/research-resources/nida-drug-supply-program-dsp/marijuana-plant-material-available-nida-drug-supply-program
marijuana use, affects neural development, but also identify risk factors and biomarkers that make adolescents vulnerable to substance use disorder. The Adolescent Brain Cognitive Development (ABCD) study will follow the biological and behavioral development of more than 10,000 children beginning at ages 9-10 through adolescence into early adulthood. Scientists will use advanced brain imaging, interviews, and behavioral testing to determine how childhood experiences interact with each other and with a child’s changing biology to affect brain development and—ultimately—social, behavioral, academic, health and other outcomes, including both substance use and broader health outcomes. This groundbreaking research promises to inform future substance use prevention strategies, educational priorities, child development innovations, research priorities, and public health interventions. The ABCD study has currently enrolled more than 10,000 participants and released curated data on the first approximately 4,500–4,500 participants to the scientific community in February 2018.

NIDA and others, including international stakeholders, support a variety of research projects on the effects of marijuana on cognitive and psychomotor performance, including abilities required for safe driving. Examples are:

- studies of the cognitive/attention skills required for safe driving;
- studies of the effects of cannabis (alone or in combination with alcohol) on driving performance in driving simulators;
- studies of the effects of cannabis use on real on-road driving, usually on closed courses;
- epidemiological studies of the presence of markers of cannabis use among injured and fatally-injured drivers who are or are not culpable; and
- meta-analyses of the individual epidemiological studies.

Meta-analyses of epidemiological studies suggest that cannabis use is associated with a modest increase in the risk of a crash (up to twofold). In addition, cannabis use impairs skills related to driving in laboratory settings, performance in driving simulators and in on-road driving studies but there is uncertainty about how these changes translate into real world crash risk. There is also a synergistic effect of marijuana combined with alcohol—worsening the impairment caused by either substance alone. Notably, the research on the risks associated with cannabis on driving need to be interpreted with caution. Tests of injured and killed drivers that detect blood THC or metabolites are usually performed hours after the crash and may either under-report (since THC levels can drop quickly after recent use), or over-report THC levels at the time of the crash, since chronic users will test positive even a month after last use. Thus, it can be difficult to establish the causality for any given crash.
Metastatic Cancer Research

The Committee remains supportive of early detection and prevention activities, but also notes that research into controlling and eliminating cancer that has already disseminated is of critical importance to many affected individuals and families. The Committee recognizes recent breakthroughs and innovative treatments in this area; and requests an update in the fiscal year 2020 CJ.

Action taken or to be taken:

Metastatic disease is a major cause of death from cancer, and NCI supports basic, translational, and clinical research to develop ways to prevent or block metastasis and better treat patients with metastatic disease. The goal is to improve patient outcomes by pursuing scientific opportunities to better understand the metastatic process, to prevent the spread of tumor cells to distant locations in the body, and when metastasis does occur, to detect it early and determine optimal treatment for patients with metastatic disease.

NCI supports a number of networks and initiatives that conduct research into tumor metastasis. These include the Tumor Microenvironment Network, the Physical Sciences Oncology Network (PS-ON), the Cancer Systems Biology Consortium (CSBC) and the Oncology Models Forum. In addition, much of NCI’s portfolio in this area is investigator-initiated research funded through the Tumor Metastasis Branch, in the Division of Cancer Biology and other divisions within NCI.

Examples of recent scientific advances from NCI-supported research include:

- 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. The research team is currently planning a clinical trial. This work was the result of a collaboration between intramural and extramural NCI supported researchers and researchers at the National Center for Advancing Translational Sciences.

- Scientists in the NCI intramural research program discovered that tumor cells send signals to cells that support blood vessels (perivascular cells) in distant organs. These signals prompt the perivascular cells to alter the structure of the tissue in the organ to render it more hospitable to metastasizing tumor cells. In addition, they showed metastasis was dramatically reduced by disabling this behavioral transformation in the perivascular cells in mice.

- A collaborative research team from the PS-ON and CSBC uncovered how chromosomal instability, a hallmark of cancer cells, plays a role in initiating metastasis. This new information suggests novel targets for the treatment of metastatic disease exist and drugs could be developed to target them.

In the clinical setting, two recent studies highlight progress for the treatment of patients with brain metastasis. Brain metastases are particularly difficult to treat and increasing survival and quality of life for these patients is critical. A recent analysis of melanoma patients with brain metastases showed that use of a type of immunotherapy called a checkpoint inhibitor (PD-1 inhibitor) significantly increased overall survival.\textsuperscript{182} Another study compared two types of radiation to determine if a more targeted form of radiation treatment (stereotactic radiosurgery) would have less harmful side effects and still be as effective as standard of care (whole brain radiotherapy). In this Phase 3 clinical trial conducted at 48 institutions in the United States and Canada, patients who were randomized to stereotactic radiosurgery suffered less cognitive dysfunction and had equivalent survival to those who received whole brain radiotherapy. This indicated that stereotactic radiosurgery could be considered a less toxic standard of care for patients with brain metastasis.\textsuperscript{183}

Finally, an exciting new initiative, the Human Tumor Atlas Network, launched in 2018 as part of the Cancer Moonshot\textsuperscript{SM}, will create four-dimensional atlases of human tumors that map the evolution of tumors from development to metastasis and response to treatment. This project will increase our knowledge of the metastatic process and enable researchers to create predictive models of tumor progression and response to treatment that will ultimately help oncologists make better informed treatment decisions for each patient.\textsuperscript{184}

\textsuperscript{182} https://www.ncbi.nlm.nih.gov/pubmed/29703161
\textsuperscript{183} https://www.ncbi.nlm.nih.gov/pubmed/28687377
\textsuperscript{184} https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-17-034.html
Microbicides
The Committee recognizes that with NIH and United States Agency for International Development (USAID) leadership, research has shown the potential for antiretroviral (ARV) drugs to prevent HIV infection in women. The Committee encourages NIAID to continue coordination with USAID, the Department of State, and others to advance ARV-based microbicide development efforts with the goal of enabling regulatory approval of the first safe and effective microbicide for women and supporting an active ARV-based microbicide pipeline to produce additional solutions to prevent HIV and to help end the epidemic.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) supports basic, translational, and clinical research into the development of topically applied microbicides to prevent sexually transmitted HIV infection that are safe, effective, long-acting, desirable, and inexpensive. NIAID, in collaboration with product developers and implementers including the United States Agency for International Development (USAID) and the Department of State, will continue to play a key role in facilitating the evaluation of microbicidal products to prevent HIV.

NIAID conducts and supports basic and preclinical research into the development of novel microbicide therapies against HIV and other common sexually transmitted infections (STIs). NIAID scientists have developed uniquely potent neutralizing antibodies that may be used as topical microbicides to prevent sexually transmitted HIV infection. NIAID grantees are investigating the use of pH- and temperature-responsive nanoparticles – as well as other nanoengineering techniques – to improve HIV and STI prevention products. In addition, NIAID offers comprehensive preclinical resources to HIV researchers to support development and testing of novel microbicides. NIAID preclinical services currently are being used to provide data in support of regulatory approval of the dapivirine intravaginal ring (IVR).

NIAID is furthering clinical development of microbicide products through its Microbicide Trials Network (MTN), which is co-funded with the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health. The NIH-supported MTN is working to understand how people use microbicide products in order to maximize their efficacy, including an ongoing Phase 3b clinical trial to assess participants’ desire to use the dapivirine IVR. A large MTN study in young African women evaluating the safety and desirability of dapivirine IVR use, along with daily pre-exposure prophylaxis, is expected to begin in 2019. NIAID also is supporting research into the use of longer acting (90-day) dapivirine IVRs to enhance cost-effectiveness and facilitate use of this microbicide product. The NIH-supported MTN also is evaluating the use of microbicides administered rectally, where HIV acquisition per exposure is thought to be higher.

NIAID is supporting the development of multipurpose prevention technologies (MPTs) that protect against HIV as well as other STIs. NIAID-funded researchers are developing an IVR to prevent HIV and gonorrhea infections, as well as a contraceptive IVR to prevent HIV and herpes simplex virus-2 (HSV) infections. NIAID also is supporting the development of a novel contraceptive IVR manufactured with 3-D printing technology to prevent HIV, HSV-2, and
human papillomavirus (HPV) infections. NIAID also coordinates with USAID to understand the needs of potential end-users to ensure that microbicide products, including MPTs, are designed for optimal use and effectiveness.

NIAID is committed to basic, translational, and clinical research facilitating the development of safe and effective microbicides to prevent HIV and other STIs. NIAID will continue to coordinate with USAID, the Department of State, and other longstanding partners to advance microbicides through the product development pipeline to enable their regulatory approval.
Mitochondrial Disease Research
The Committee understands that no fewer than 17 ICs are involved in research efforts related to mitochondrial disease and dysfunction. The Committee appreciates the NIH’s support of the trans-NIH Mitochondrial Disorders Working Group, the North American Mitochondrial Disease Consortium, the Mitochondrial Disease Sequence Data Resource Consortium, and its support for investigator-initiated intramural and extramural studies. The Committee encourages NIH to continue its efforts to ensure that individuals with mitochondrial disease participate in both the All of Us research program and the ECHO study. The Committee understands that the NIH is funding research relevant to mitochondrial disease through the Office of Research Infrastructure Programs (ORIP). The Committee encourages the Director to promote mitochondrial disease research within ORIP and to provide an update to the Committee in the fiscal year 2020 Congressional Justification on progress made through this research. The Committee applauds the efforts made by the agency’s Office of Dietary Supplements (ODS) on nutritional interventions for those with mitochondrial disease and requests the agency include mitochondrial disease as a focus of its future practice and to reengage its trans-NIH research through the ODS on these issues. The Committee further encourages the Director to competitively fund mitochondrial disease centers of excellence that combine a critical mass of clinical care and research on mitochondrial disease.

Action taken or to be taken:

NIH will continue efforts to ensure that individuals with mitochondrial disease participate in the All of Us Research Program (All of Us) and the Environmental influences on Child Health Outcomes (ECHO) program. All of Us will gather data to advance individualized prevention, treatment, and care for people of all backgrounds from one million or more volunteers. By enrolling a large and diverse set of volunteers, All of Us will enable research for a wide range of common and rare diseases, including mitochondrial diseases. ECHO leverages existing cohorts of children to study the impact of early life exposures on health, including pre-, peri-, and postnatal outcomes, upper and lower airway disorders, neurodevelopment, obesity, and positive child health. These cohorts will likely be useful for studying mitochondrial diseases in children.

Several NIH Institutes, Offices, and Centers support research related to mitochondrial disease and dysfunction. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), together with the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of General Medical Sciences (NIGMS), co-chair the trans-NIH Mitochondrial Disorders Working Group, which convenes three times per year to coordinate efforts on mitochondrial disorder research across the NIH and develop trans-NIH workshops on novel areas of investigation. The Working Group has also strengthened NIH’s communication and coordination with the research and patient communities.

NIGMS supports research on whether nutritional supplements can mitigate mitochondrial dysfunction in animal models of mitochondrial disease. The Office of Research Infrastructure Programs (ORIP) supports the creation of animal models of human disease including mitochondrial diseases. The Office of Dietary Supplements (ODS) promotes scientific study of the benefits of dietary supplements for preventing disease and maintaining health and provides...
information regarding nutritional interventions for inborn errors of metabolism, including mitochondrial diseases.

NINDS, NICHD, ODS, and the National Center For Advancing Translational Sciences (NCATS) support the North American Mitochondrial Disease Consortium (NAMDC), which is part of the NIH Rare Diseases Clinical Research Network. NAMDC conducts research on primary mitochondrial diseases, trains future clinician scientists, and has established a network of 18 clinical centers connecting investigators and clinicians who see patients with mitochondrial diseases. NAMDC has created a patient registry, a biorepository, and consensus criteria for diagnosis to further promote research to improve care and treatment for mitochondrial diseases. Current NAMDC research includes natural history studies of three mitochondrial diseases and a study on nutritional supplementation.

The NICHD continues to actively support a large and diverse research portfolio on mitochondrial disorders. Basic research on the genetics, bioenergetics, and cell biology in both animal models and humans provides a basis on which therapeutic interventions for mitochondrial disease are being developed. Translational research includes gene therapy for mitochondrial disorders, as well as the identification of biomarkers, development of diagnostics, and nutritional and pharmacological interventions for mitochondrial diseases and disorders. The NICHD-supported Mitochondrial Disease Sequence Data Resource Consortium (MSeqDR) organizes expert panels that select genes and genomic variants associated with pediatric mitochondrial diseases to determine their clinical significance and utility for diagnosis and treatment.

NINDS extramural and intramural research includes studies on mitochondrial quality control, normal mitochondrial function in the nervous system, and mechanisms and interventions for primary mitochondrial diseases and other neurological disorders in which mitochondria play a role, such as stroke, epilepsy, neurodegenerative diseases, and brain injury. Among current projects are efforts to develop a drug that increases mitochondria creation in cells and to find new disease mutations by sequencing whole exomes from 200 patients with mitochondrial encephalopathy. In 2015, NINDS led the development of Common Data Elements (CDEs) for clinical mitochondrial disease research, to facilitate high-quality studies and data harmonization. NINDS is now working with expert investigators to update these CDEs and increase their utility.

The National Institute of Diabetes and Digestive and Kidney Diseases supports research to explore the role of brain, liver, skeletal muscle, and fat mitochondria in maintaining glucose and energy homeostasis, mitochondrial dysfunction that either predisposes people toward diabetes and obesity, or the impact of drugs on mitochondrial functions that are used to treat these diseases. Collectively, these projects demonstrate NIH’s commitment to mitochondrial disease research.

NIH will continue to explore other potential avenues to competitively fund mitochondrial disease centers of excellence that combine a critical mass of clinical care and research on mitochondrial disease.
Mucopolysaccharide Diseases

Mucopolysaccharide (MPS) diseases are inherited, with death occurring for many in early childhood. This systemic disease causes progressive damage to the bones, heart, respiratory system, and brain, causing permanent disability and early death. The Committee continues to urge NIH to put a high priority on better understanding and treating MPS diseases. The Committee commends NIH for allocating funds to discover, develop, define, and make available for research animal models of human genetic disease. The Committee encourages expanded research of treatments for neurological, chronic inflammation, cardiovascular and skeletal manifestations of MPS, with an emphasis on gene therapy. The Committee thanks NCATS, NINDS, and NIDDK for again funding the Lysosomal Disease Network through the Rare Disease Clinical Network and for funding lysosomal research meetings. The Committee encourages NIH to expand support to incentivize MPS research. Understanding the manifestations and treatments of both the skeletal and neurological disease continues to be an area of great unmet need.

[Senate] MPS and mucolipidosis [ML] are inherited, with death occurring for many in early childhood. These systemic diseases cause progressive damage to the bones, heart, respiratory system, and brain. The Committee continues to urge NIH to put a high priority on better understanding and treating MPS and ML diseases. The Committee commends NIH for allocating funds to discover, develop, define, and make available for research animal models of human genetic disease. The Committee encourages expanded research of treatments for neurological, chronic inflammation, cardiovascular and skeletal manifestations of MPS, with an emphasis on gene therapy. The Committee thanks NINDS, NIDDK, and the Office of Rare Diseases Research for again funding the Lysosomal Disease Network through the Rare Disease Clinical Network and for funding lysosomal research meetings. The Committee encourages NIH to increase funding to grantees to incentivize MPS research, particularly given the age and small population of current researchers. Understanding the manifestations and treatments of both the skeletal and neurological disease continues to be the greatest areas of unmet need.

Action taken or to be taken:

NIH supports research on mucopolysaccharidoses (MPS), mucolipidoses (ML), and other lysosomal storage disorders to understand how they affect multiple organ systems and to develop innovative treatments. In the last two years, three new therapies enabled by NIH were FDA-approved for lysosomal storage disorders: enzyme replacement therapies (ERT) for MPS VII and CLN2 (a form of Batten disease) and a drug for Fabry disease. These successes hold promise for the use of similar treatment strategies for other types of MPS and for ML.

National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK), and the National Center for Advancing Translational Sciences (NCATS) support the Lysosomal Disease Network (LDN), part of the NIH Rare Disease Clinical Research Network. LDN research includes longitudinal studies of brain structure and function and of bone and endocrine disease in children with different MPS types, to understand disease progression and inform diagnosis, monitoring, and treatment. Network investigators are also conducting an open label clinical trial in MPS I to determine if delivering
ERT to the spinal fluid will safely treat memory loss and language and learning difficulties. Intravenous ERT for MPS I does not address neurological symptoms because it does not cross the blood-brain barrier. The recently approved ERT for CLN2 disease overcomes this challenge with direct delivery to the nervous system, and the LDN study will provide safety and efficacy data on the use of a similar approach for MPS I. Another LDN pilot study will examine inflammation and oxidative stress in brain abnormalities that continue in MPS I patients even with ERT or hematopoietic cell transplants.

Additional NINDS-supported research on gene therapy and ERT for MPS includes efforts by academic and small business investigators to optimize gene therapy vectors, improve ERT delivery to the brain, and increase enzyme uptake into cells. Other studies focus on different treatment approaches, such as small molecule drugs to enhance enzyme production and ways to genetically modify patient-derived blood and neural stem cells to make missing enzymes. NINDS-funded researchers are also studying how MPS and ML lead to brain pathology and neurodevelopmental abnormalities, which may suggest novel targets for treatment. A suite of funding opportunities through the NINDS Translational Research Program are available to support therapy development research for MPS, ML, and other lysosomal storage disorders, including programs tailored to biological products such as ERT and gene and cell-based therapies. To promote the success of clinical trials for future therapies for rare diseases like the lysosomal storage disorders, another program supports clinical trial readiness studies, such as characterizing relevant patient cohorts or validating outcome measures. NIDDK also funds research on gene therapy approaches for MPS. In addition, a test that simultaneously screens for six related lysosomal storage diseases (MPS-I, Pompe, Fabry, Niemann-Pick-A/B, Gaucher, and Krabbe diseases) was developed with NIDDK support and is now available worldwide. Other NIDDK-funded studies are examining the shape and stability of the proteins that are damaged in these diseases and determining how the diseases progress and how to improve their treatment.

To bring new investigators to lysosomal storage disease research, the LDN supports training for postdoctoral research fellows. NIH-wide and Institute-specific programs are also available for research training and career development, and NIH funding policies for early stage investigators could foster additional researchers. Scientific conferences are another way to fuel new research. The LDN holds an annual international conference for which it provides travel grants to young investigators, and NIH supports other conferences relevant to lysosomal storage disease research, including a recent NCATS symposium on gene therapy approaches for rare diseases.
National Center for Complementary and Integrative Health

The Committee is encouraged by the ongoing collaboration between NCCIH, VA, DOD, and other Institutes across the NIH to develop and test efficacious non-pharmacological approaches to pain management and comorbidities—including opioid misuse, abuse, and disorder in military personnel, veterans, and their families. The Committee is particularly encouraged by the ongoing studies that will assess provider adherence to CDC opioid prescribing practices and develop integrated pain care approaches to reduce pain and opioid use in patients enrolled in a large healthcare system. In addition, the Committee believes it is critical to support research on non-pharmacological treatments to ensure the best quality of care for our Nation's veterans and servicemembers, and urges the NIH, VA, and DOD to continue this vital research. The Comprehensive Addiction and Recovery Act (Public Law 114--198) calls for an expansion of research and education on and delivery of complementary and integrative health to veterans, and the NCCIH can play an important role in coordinating efforts with the VA, DOD, and other relevant agencies. The Committee requests an update on these studies in the fiscal year 2020.

Action taken or to be taken:

The NIH-DOD-VA Pain Management Collaboratory (PMC), focuses on implementing and testing cost-effective, large-scale, real-world research on nondrug approaches for pain management and related conditions in military and veteran health care delivery organizations. The PMC funds 11 pragmatic clinical trial research project grants and a resource coordinating center, totaling approximately $81 million over six years, with the NCCIH contributing more than half of these funds.

The research projects will provide valuable information about the safety and effectiveness of nondrug approaches in treating pain within VA and DOD health care systems. Types of approaches being studied include mindfulness/meditative interventions, movement interventions (e.g., structured exercise, tai chi, yoga), manual therapies (e.g., spinal manipulation, massage, acupuncture), psychological and behavioral interventions (e.g., cognitive behavioral therapy), integrative approaches that involve more than one intervention, and integrated models of multimodal care.

The Resource Coordinating Center provides leadership and serves as a national resource for development and refinement of innovative tools, best practices, and other tools to facilitate research partnerships to conduct pragmatic trials in the PMC. The PMC Coordinating Center addresses issues that span the pragmatic trials and provides input on the development of policies and processes to facilitate research in both the VA and DOD health care systems. To achieve this goal, the Resource Coordinating Center established seven workgroups addressing biostatistics and study design; ethics and regulatory issues; phenotype and outcomes; stakeholder engagement; electronic health records; data sharing; and implementation science, which meet monthly via teleconference to discuss each of the trials and provide scientific input to improve the studies during the planning phases. The PMC Steering Committee meets via monthly teleconferences and met in person on January 23-24, 2018, and September 17-18, 2018, with plans for yearly in person meetings beginning in 2019.
The pragmatic trial research project grants have been funded for a 2-year planning phase, working with the PMC Coordinating Center to test methods that will be used, optimize the study design, harmonize some common outcome measures, and obtain all regulatory approvals. Trials that successfully achieve the planning milestones will move into full trial implementation as early as September 2019. The results of these studies may inform new pain management practices within the DOD and VA and support the use of nondrug approaches for pain management in the general population.
National Chronic Obstructive Pulmonary Disease [COPD] Action Plan
The Committee commends NHLBI for leading the effort to craft the comprehensive COPD National Action Plan requested by Congress. The action plan outlines research, public health, patient care, and awareness activities that can be supported by Federal agencies and strategic partners. The Committee has provided additional funding for NHLBI to begin facilitating agency-wide implementation of the action plan by supporting research activities and collaborating with other PHS agencies to advance implementation of the plan's recommendations. The Committee expects regular updates from NHLBI on the implementation of the COPD Action Plan.

Action taken or to be taken:

The National Heart, Lung, and Blood Institute (NHLBI) is committed to helping address the national burden of chronic obstructive pulmonary disease (COPD) through a comprehensive COPD National Action Plan (NAP), which was released in May 2017. NHLBI expects to facilitate agency-wide implementation of this action plan by directly supporting research on COPD and collaborating with other Public Health Service (PHS) agencies to advance implementation of the plan’s other recommendations. Pressing opportunities for research include clinical trials of pulmonary rehabilitation, studies of the early development of COPD, epidemiological studies of why this condition is more prevalent in rural settings, and studies investigating mechanisms of aging in the lung.

An ongoing collaboration between NHLBI and the Centers for Disease Control and Prevention (CDC) has yielded new data showing that COPD is almost twice as common in rural areas as in urban settings. To address this disparity, NHLBI established a collaboration with the Health Resources and Services Administration (HRSA) on issues related to COPD and hosted a COPD and Rural Health Workshop in March 2018. Participants discussed how to manage the distinctive issues of COPD in rural America through implementation of the COPD NAP. A report of this workshop is in preparation. NHLBI also joined the Federal Office of Rural Health Policy to moderate a Congressional briefing on the burden of COPD in rural America on March 20, 2018 with the American Lung Association, American Thoracic Society, and the COPD Foundation.

In June 2018, NHLBI organized a second workshop on COPD in rural communities in collaboration with HRSA and CDC’s National Institute for Occupational Safety and Health. Among the participants were the National Rural Health Association (NRHA), the American Lung Association, the American Thoracic Society, the COPD Foundation, the National Rural Health Resource Center, the COPD Coalition, the Dorney-Koppel Foundation, Appalachian Regional Healthcare (serving Eastern Kentucky and Southern West Virginia), and representatives of rural health offices from Kentucky, Tennessee, and Pennsylvania. Outcomes of the meeting include plans for promoting COPD awareness and pulmonary rehabilitation in rural settings using telemedicine, organizing a COPD education session at the NRHA’s annual conference, and discussing national perspectives on rural COPD at HRSA’s National Advisory Committee on rural health and human services.
National Commission on Digestive Disease

The Committee applauds NIDDK for the implementation of the recommendations of the 2009 National Commission on Digestive Diseases and looks forward to hearing how these recommendations have led to new findings with respect to emerging research in digestive diseases.

Action taken or to be taken:

The National Commission on Digestive Disease Research’s 2009 digestive diseases research plan represented a trans-NIH effort to identify research goals for pursuit by the NIH and the broader digestive diseases research community. The plan is being actively implemented by many of NIH’s Institutes, Centers, and Offices, as well as other federal and non-federal partners involved in digestive diseases research.

Within the NIH, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has contributed to addressing the Commission’s recommendations by advancing emerging digestive disease research. For example, the Institute supports cutting-edge research on the role of intestinal stem cells in digestive health through such efforts as the Intestinal Stem Cell Consortium. Recent advances in this area include identifying factors that support intestinal stem cell renewal and thus, help maintain a healthy gut lining. Additionally, studies supported by the NIDDK and an NIH Common Fund program, called Stimulating Peripheral Activity to Relieve Conditions, are mapping the gastrointestinal (GI) nervous system and using stem cells to develop intestinal organoids with functional nervous systems for the study of digestive disorders.

Another emerging area of digestive diseases research responsive to the Commission’s plan concerns the microbiome’s role in sustaining a healthy digestive system. Recent advances by NIDDK-supported researchers have shown how factors such as nutrient availability or antibiotics determine which microbes occupy the gut, whether they are pathogenic bacteria such as Clostridium difficile (C. difficile) or potentially beneficial bacteria, as well as predictors of how well donor microbes colonize the GI tract in fecal microbial transplant recipients with recurrent C. difficile infection. Studies also continue to yield new insights into microbial impacts on inflammatory bowel disease (IBD) risk, including that gut microbial communities altered by antibiotics can be passed from pregnant mice to offspring, conferring increased IBD susceptibility.

Other examples of new research responsive to the Commission’s recommendations include the NIDDK’s recently expanded support for the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer, in collaboration with the National Cancer Institute, to conduct studies in adults and children with chronic pancreatitis to improve understanding of disease processes and related outcomes, such as diabetes and pancreatic cancer. Researchers also recently utilized data from the NIDDK’s Childhood Liver Disease Research Network to identify a possible biomarker in infants with biliary atresia that may enable early detection of this potentially fatal disease. Additionally, the NIDDK stimulated research to understand the role of lymphatic vessels in digestive health through a new funding opportunity announcement.
National Eye Institute 50th Anniversary
The Committee acknowledges that 2018 marks the 50th anniversary of Congress creating the NEI as NIH’s institute leading the Federal commitment to sight-saving and vision-restoring research. The Committee recognizes NEI’s role in basic research as a leader in determining the genetic basis of eye disease, having identified genes associated with both common and rare eye diseases. The Committee also recognizes NEI’s leadership in clinical research, such as with the current Diabetic Retinopathy Clinical Research Network, which has been instrumental in developing the standard of care for diabetic eye disease.

Action taken or to be taken:

The National Eye Institute (NEI) enjoyed a busy year celebrating the 50th anniversary since the Institute was created by Congress in 1968. As NEI looked back at a half-century of progress in preventing, diagnosing, and treating common and rare eye diseases, it also looked forward toward continuing its mission to protect and prolong vision through cutting-edge research. With so many constituencies and audiences that wanted to mark the milestone year, NEI organized a menu of interactive activities. For the research community and the public, NEI organized a series of four cross-cutting, star-studded, scientific symposia. Kicking off the year-long celebration, the “Vision and the Brain” symposium featured two Nobel Prize laureates. Recognizing research in recent years identifying the role of the immune system in diseases like age-related macular degeneration (AMD), the second symposium highlighted “Vision and Immunology.” The third symposium, “Low Vision and Vision Rehabilitation,” included live demonstrations of assistive and adaptive devices developed by NIH grantees for people with low vision. The final symposium, entitled “Future of Vision Research” featured stem cell regenerative medicine and other technologies that represent the future of eye care.

To reach the patient community and the public, NEI developed a series of “Then and Now” videos, which demonstrated progress by comparing the vision care in the past with the remarkable capabilities today. In preparing these videos, NEI interviewed scientific leaders critical to the success of NEI and vision research over the years. NEI also published a history book documenting key accomplishments, not just for vision, but that propelled biomedical endeavor overall. These achievements include the first successful application of genomics to discover genes involved in AMD; pioneering gene therapy in the eye; and comparing the effectiveness of remarkable new drugs for AMD and diabetic retinopathy (DR), through clinical trial networks such as the DR Clinical Research Network, a public-private partnership that expedites protocols in community clinics and academic centers. NEI highlighted accomplishments through leadership at public events such as Brain Awareness Week and the USA Science & Engineering Festival. Members of the public enjoyed learning about eye diseases through a new NEI virtual reality (VR) tool, which employed VR goggles to demonstrate dynamic real-world scenes, as they are experienced by individuals with different eye diseases.

185 For a list of NEI Anniversary activities, visit nei.nih.gov/neiat50 to find a list of events, an anniversary toolkit, a history book and timeline of milestones with archival images.
One of the highlights of the year was a Congressional reception for NEI, hosted by Congressman Pete Sessions and sponsored by the Alliance for Eye and Vision Research. The event included Congressional Members and staffers, the NIH Community led by NIH Director Francis Collins and NEI Director Paul Sieving, scientists, advocacy groups, and members of the public. Congressman Sessions presented the Inspirational Vision Research Award, established in recognition of the 50th Anniversary of NEI, honoring research to preserve the independence and quality of life of individuals with low vision or blindness. The recipient was Dr. Gordon Legge, a Psychology professor at the University of Minnesota who has devoted his career to developing tools for individuals with low vision.
Native American Research Centers for Health
The Committee commends NIGMS for supporting the Native American Research Centers for Health program, which provides opportunities for Tribes and Tribal organizations to build the capacity to support research, research training, and faculty development to address health disparities in American Indian/Alaska Native communities.

Action taken or to be taken:

The National Institute of General Medical Sciences (NIGMS) thanks the Committee for recognizing the important role that the Native American Research Centers for Health (NARCH) Program plays in supporting research and research training that meet the needs of American Indian/Alaska Native (AI/AN) communities. The NARCH program funds research projects that are prioritized by the tribal communities. These projects address health issues disproportionately affecting the AI/AN communities, enhance health research partnerships, and reduce distrust of research by AI/AN communities while developing a cadre of AI/AN scientists and health research professionals. In FY 2018, NIGMS contributed $6.0 million and coordinated an additional $3.8 million contributed by 11 other NIH Institutes, Centers, and Offices to the NARCH program, which funded 17 NARCH grants with 46 different research, student development, faculty development, capacity building and administrative coordination projects.

The NARCH program has begun to support research capacity building projects, following the effective model developed by the Institutional Development Award (IDeA) program, in the AI/AN communities. Among new NARCH grants in FY 2018, three infrastructure/capacity building projects were funded. Furthermore, collaborations between NARCH programs and IDeA programs are encouraged and supported. For example, the Cherokee Nation investigators supported by an NARCH award are participating in collaborative research led by the Oklahoma IDeA-Clinical Translational Research program.

In FY 2019, NIGMS plans to continue to support non-competing awards and develop a new NARCH Funding Opportunity Announcement.
Neglected Tropical Diseases
One-sixth of the world’s population suffers from one or more NTDs. In the United States, we have seen Chikungunya and Dengue emerge. Only 10 percent of global health science resources are directed towards 90 percent of the global disease burden, and as such, world-class research conducted by NIH is a key component to ensuring there are tools to treat, control, and eventually eradicate many neglected diseases. The Committee urges NIAID to continue its investment in NTD research, including work in late-stage and translational research for NTDs, and to work with other agencies to foster research and ensure that basic discoveries are translated into much needed solutions.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) maintains a longstanding research program devoted to combating neglected tropical diseases (NTDs). This program includes basic, translational, and clinical research to better understand NTDs and advance novel diagnostics, therapeutics, and vaccines. NIAID also engages in critical partnerships with agencies and organizations that are key to developing improved tools to treat, control, and ultimately eradicate NTDs. For example, NIAID collaborated with the Coalition for Epidemic Preparedness Innovations and the Indian Department of Biotechnology to hold a workshop on chikungunya vaccine research.

NIAID supports basic research to better understand how NTDs are transmitted and cause disease, and to develop vector control methods. NIAID is investigating novel tools to limit the ability of mosquitoes to proliferate and/or transmit NTDs, including Wolbachia bacteria to prevent mosquitoes from transmitting viruses. Building on technologies developed by the Centers for Disease Control and Prevention, NIAID is exploring the use of traps to lure and eliminate egg-laden female mosquitoes. NIAID also is planning a clinical trial to assess the impact of genetically modified mosquitoes on dengue and chikungunya incidence in Brazil. In addition, NIAID is supporting development of several diagnostic tests for lymphatic filariasis, leishmaniasis, Chagas disease, dengue, and chikungunya.

NIAID supports discovery and development efforts for new NTD treatments. NIAID-supported investigators recently conducted early-stage clinical trials of a broad-spectrum antiparasitic drug that could be used to treat soil-transmitted helminths, echinococcosis, and filarial diseases. NIAID also supported the development of a therapeutic dengue antibody that has been shown to neutralize the four known types of the virus in animal models. In addition, NIAID is planning a Phase 2 clinical trial to determine the dose of the drug imatinib required to lower levels of Loa loa infection to a level at which L. loa-infected individuals can safely participate in mass drug administration programs for river blindness. NIAID also supports Tropical Medicine Research Centers that conduct a variety of in-country clinical and field-oriented research on NTDs.

NIAID is advancing the development of several NTD vaccine candidates, including an ongoing Phase 3 trial of a dengue vaccine candidate in Brazil. NIAID also is conducting a Phase 2 clinical trial of an NIAID-developed investigational chikungunya vaccine that uses non-infectious virus-like particles to simulate an infection and generate a protective immune response. NIAID, through its Vaccine and Treatment Evaluation Units, is supporting a Phase 1 clinical trial of another chikungunya vaccine candidate, and supported a recently completed Phase 1 clinical trial of an experimental schistosomiasis vaccine. In addition, NIAID scientists
are investigating novel saliva-based vaccine approaches designed to trigger protective immune responses to insect saliva to prevent infections transmitted by mosquitoes or sand flies. NIAID investigators also are building on the development of a novel chimeric Zika vaccine approach to develop a second-generation vaccine that could protect against both Zika and dengue viruses.

NIAID remains committed to supporting basic, translational, and clinical research into the development of diagnostics, therapeutics, and vaccines against NTDs. NIAID will continue to work with Federal, academic, and industry partners to address the global challenge of NTDs.
Neonatal Abstinence Syndrome

The Committee is aware that the rising untreated use of opioids by pregnant mothers is one of the main causes for the Nation's opioid epidemic and that it causes death or sometimes critical mental and physical health problems in babies who do survive. The Committee understands that until the need for interventions to reduce the use and abuse of opioids during pregnancy is addressed, the problem is likely to continue, with post-delivery effects on mothers and infants continuing to be a medical, social, and financial burden. The Committee encourages NIDA and NICHD to continue to support research that will help clinicians and academic research institutions to develop a comprehensive approach to the prevention and treatment of NAS.

Action taken or to be taken:

In communities severely affected by the opioid crisis, as many as 10% of newborns are affected by Neonatal Abstinence Syndrome/Neonatal Opioid Withdrawal Syndrome (NOWS). The National Institutes of Health (NIH), especially through its National Institute on Drug Abuse (NIDA) and the Eunice Kennedy Shriver National Institute on Child Health and Human Development (NICHD), are committed to finding the best approaches to address the needs of these children. For instance, the National Institutes of Health (NIH) through the NAS/NOWS Working Group of the Opioid and Controlled Substances Subcommittee of the Behavioral Health Coordinating Council convenes members from across the agencies of HHS to best address the needs of mothers who use opioids and infants who are exposed to opioids in utero, and has completed the report mandated by the Protecting Our Infants Act (POIA) and the POIA Final Strategy.

Although NAS/NOWS is known to increase the risk for neurodevelopmental problems as infants grow older, little is known about its long-term effects. To address this gap in care, the Advancing Clinical Trials in Neonatal Opioid Withdrawal Syndrome (ACT NOW) program, launched in 2017 and expanded as part NIH HEAL (Helping to End Addiction Long-term) Initiative, aims to inform clinical care of infants who are exposed to opioids before birth. ACT NOW is a collaborative effort of two networks supported by NIH:

- NICHD’s Neonatal Research Network, which has more than 30 years of experience designing and implementing clinical trials involving infants; and
- NIH’s Environmental influences on Child Health Outcomes (ECHO) Program’s Institutional Development Award (IDeA) States Pediatric Clinical Trials Network, which focuses on rural and medically underserved communities, including those reporting a higher incidence of NOWS.

---

188 The POIA Final Strategy is available here: https://www.samhsa.gov/sites/default/files/topics/specific_populations/final-strategy-protect-our-infants.pdf
ACT NOW pilot studies are assessing the prevalence of NOWS across more than 20 clinical research sites and are surveying current management approaches in preparation for developing research protocols for large-scale studies. Currently, two large studies are under development: a medication weaning study and a non-drug intervention to improve care for newborns with NOWS. Further efforts focusing on the long-term outcomes of NOWS, and these interventions, are being planned.

Additional research interests announced by NICHD and NIDA also encourage clinically-oriented research proposals that address the research gaps for opioid use disorder in pregnancy, and proposals that advance scientific knowledge about the consequences of opioid agonist or antagonist exposure during pregnancy on embryonic, fetal, and post-natal brain and behavioral development, as well as other health outcomes and the mechanisms underlying these consequences.
Neurofibromatosis
The Committee supports efforts to increase funding and resources for Neurofibromatosis (NF) research and treatment at multiple NIH ICs, including NCI, NINDS, NIDCD, NHLBI, NICHD, NIMH, NCATS, and NEI. Children and adults with NF are at significant risk for the development of many forms of cancer. The Committee encourages NCI to increase its NF research portfolio in fundamental basic science, translational research and clinical trials focused on NF. The Committee also encourages the NCI to support NF centers, NF clinical trials consortia, NF preclinical mouse models consortia and NF-associated tumor sequencing efforts. Because NF causes brain and nerve tumors and is associated with cognitive and behavioral problems, the Committee urges NINDS to continue to aggressively fund fundamental basic science research on NF relevant to nerve damage and repair. Based on emerging findings from numerous researchers worldwide demonstrating that children with NF are at significant risk for autism, learning disabilities, motor delays, and attention deficits, the Committee encourages NINDS, NIMH, and NICHD to expand their investments in laboratory-based and clinical investigations in these areas. Since NF2 accounts for approximately five percent of genetic forms of deafness, the Committee encourages NIDCD to expand its investment in NF2 basic and clinical research. NF1 can cause vision loss due to optic gliomas, the Committee encourages NEI to expand its investment in NF1 basic and clinical research.

Action taken or to be taken:
The NIH supports a wide range of research focused on Neurofibromatosis (NF) across several of its Institutes with the goal of developing effective treatments and improving the overall care of individuals with NF.

NF type 1 (NF1) is the most common NF and individuals with NF1 have a high predisposition to plexiform neurofibromas, a premalignant tumor that can progress to an invasive tumor and to other cancers. The mechanisms of NF1 tumor development are poorly understood. The NCI intramural program conducts genetic studies to improve our understanding of NF etiology, in particular to identify genes that promote the progression of NF tumors from benign to malignant peripheral nerve sheath tumors (MPNST). In addition, the NCI Pediatric Oncology Branch (POB) is leading a study at the NIH Clinical Center to follow individuals with NF1 longitudinally to better understand the natural history of NF1-related tumor and other manifestations. Findings from this study will help to develop more effective treatments.

Mutations in NF1 result in a “RASopathY.” RASopathies are a group of syndromes caused by mutations in genes involved in the regulation of the RAS pathway. The NCI intramural program launched an initiative to accelerate the understanding of RASopathies and RAS mutated tumors, including NF1 tumors. This will involve a natural history study to better understand the spectrum of disease characteristics, and studies to develop more effective therapies and prevention strategies for RAS-driven cancers. Furthermore, the NCI RAS initiative aims to understand the functional role of RAS genes and to identify and optimize drugs that can effectively treat RAS-driven cancers, including NF1 tumors. A project supported by this

190 [https://clinicaltrials.gov/ct2/show/NCT00924196](https://clinicaltrials.gov/ct2/show/NCT00924196)
191 [https://ccr.cancer.gov/Pediatric-Oncology-Branch/nf](https://ccr.cancer.gov/Pediatric-Oncology-Branch/nf)
192 [https://www.cancer.gov/research/key-initiatives/ras](https://www.cancer.gov/research/key-initiatives/ras)
initiative focuses on using experimental imaging techniques coupled with computer modeling to investigate the structure of NF1. In addition, NCI also continues to support translational research through the Developmental and HyperActive Ras Tumor (DHART) Specialized Program of Research Excellence (SPORE), conducted across nine research institutions including the POB. Recent findings from the program suggest that preventing inflammation and nerve injury could be a new therapeutic approach for preventing the progression of neurofibroma to malignant tumors.

The POB also conducts a large clinical trials program for children and adults with NF1 to develop and improve treatments. Multiple clinical trials are testing seluminib as a treatment for NF1 patients. An NCI clinical trial for patients with NF type 2 (NF2) and progressive vestibular schwannomas is expected to open for accrual soon. The hallmark feature of NF2 is the development of bilateral tumors arising from the nerves important for hearing and balance (vestibular schwannomas), but individuals with NF2 also develop other tumors.

Individuals with NF1 and plexiform neurofibromas tumors often have chronic pain that is hard to control and affects daily activities. NCI is investigating approaches to better address and alleviate NF1 patients’ symptoms. Examples include studies to develop and validate Patient Reported Outcome (PRO) measures for NF1 patients to understand how well people with NF1 follow their treatment plan for plexiform neurofibromas, and to test a new strategy called Acceptance and Commitment Training that may help these people cope with chronic pain.

NINDS supports basic and translational science research focused on defining the roles of NF1 and NF2 not only in tumor formation but also specifically in nerve damage. For example, several studies are using mouse models to determine how mutations in NF1 gene that are identified in humans affect cell growth, differentiation, and survival. Additionally, two new projects are attempting to develop novel treatments for NF2 by targeting the development of nerve-insulating support cells, which form tumors in NF2. NINDS also supports research projects to identify links between NF and co-occurring neurological disorders. One project has shed light on the biological basis for the high co-occurrence of autism spectrum disorder with NF1 by discovering impairments in communication behavior in a mouse model of NF1. Sleep disturbances also frequently co-occur with NF1, particularly in children, and one NINDS-funded study has helped to explain this link by identifying a novel role for NF1 in regulating circadian rhythms.

NIDCD continues to support research to prevent and treat hearing loss caused by inner ear tumors that develop in individuals who inherit gene mutations that cause NF2. Previous findings determined that hearing loss severity is correlated with a protein called TNF-alpha, secreted by the inner ear tumors. NIDCD-supported researchers are testing a molecule that blocks TNF-alpha in animal studies of NF2 to evaluate if this molecule prevents the correlated hearing loss.

193 https://trp.cancer.gov/spores/hyperactive_ras.htm
196 https://ccr.cancer.gov/Pediatric-Oncology-Branch/nf
197 https://clinicaltrials.gov/ct2/show/NCT02544022
198 https://clinicaltrials.gov/ct2/show/NCT03531814
199 https://clinicaltrials.gov/ct2/show/NCT02471339
NEI continues to support NF basic research, such as developing genetically engineered NF1 and NF2 disease models in fish and rodents to identify molecular mechanisms of cellular functions, tumor formation, and metabolic diseases involved in optic nerve dysfunction and regeneration. To expand clinical NF research capabilities, NF is presented in NEI’s Ophthalmic Genetics Fellowship, which trains early stage clinicians to pursue research careers. NEI and NCI scientists collaborate at the NIH Clinical Center in drug trials to prevent or slow growth of neurofibromas in patients with inherited mutations of NF1.

Individuals that have mutations in the NF1 gene are four times more likely to experience learning disabilities compared to the 15 percent of the general population who have such disabilities. NICHD continues to support research pertaining to NF1 and has a clinical trial to evaluate the synergistic effects of a medication called Lovastatin and reading intervention (tutoring) in treating reading disabilities in school-age children with NF1. Since the last reporting period, NICHD has funded a new fellowship grant focused on NF1 to identify underlying neurocognitive and social skills deficits and to examine risk and resilience factors for social interactions in youth with NF1.
Neuromyelitis Optica Spectrum Disorder
The Committee directs NEI to provide an update in the fiscal year 2020 Congressional Justification on research related to Neuromyelitis Optica Spectrum Disorder (NMO/SD), a rare autoimmune disease that causes blindness and/or paralysis. The Committee strongly encourages NEI to work with other ICs, including NINDS and NIAID, to support basic research into the causes and treatment of NMO/SD.

Action taken or to be taken:

In neuromyelitis optica spectrum disorder (NMOSD), a patient’s own immune system attacks astrocytes, key supportive cells in the optic nerve and spinal cord. Damage to the astrocytes triggers a process known as demyelination, the breakdown of the myelin sheath necessary for nerve function. Demyelination is also a hallmark of a related disease, Multiple Sclerosis (MS); both conditions lead to nerve dysfunction and degeneration, and ultimately blindness and/or paralysis. While there is no cure, treatment usually involves administering corticosteroids or other drugs to dampen the immune attacks. NIH supports a portfolio of NMO basic and translational research projects at four different institutes, the National Eye Institute (NEI), National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Allergy and Infectious Diseases (NIAID), and National Institute of General Medical Sciences (NIGMS).

NEI projects range from understanding the biology behind the autoimmune mechanisms that initiate inflammation and tissue damage in the optic nerve (optic neuritis), to basic understanding of the molecules and neural activity involved in optic nerve development and myelination, to characterizing the structure of the optic nerve. Studies are looking at the interplay between the immune system, neurons, and astrocytes and other support cells. Many of the projects are testing new therapies and treatment strategies, with a focus on protecting vulnerable retinal ganglion cells, which form the optic nerve, and regenerating and reconnecting the damaged nerve fibers. An additional project in MS patients is using an advanced imaging technique, called spectral domain optical coherence tomography, to conduct high resolution images, which could identify biomarkers for disease detection. Early diagnosis is critical in NMO to prevent acute episodes, which can irreversibly and severely impact function.

NINDS-funded scientists are studying immune system function in the optic nerve and spinal cord, which may provide insights into what causes the immune system to attack myelin in autoimmune diseases like NMO. Most, but not all, patients with NMO have antibodies against a particular protein called aquaporin 4 (AQP4), which is expressed on the outside surface of astrocytes. NINDS-funded researchers are examining the function of these antibodies and the mechanisms by which they cause NMO and are investigating whether particular genes predispose people to develop NMO or other autoimmune and inflammatory neurological diseases.

NIGMS research is exploring the atomic structure of AQP4 binding to antibodies, to provide insights into function and rational therapy design. NIAID has a large portfolio studying ways to treat autoimmune diseases. Specifically, one research team has created a mouse model of NMO
that may help them address why NMO targets the optic nerve and spinal cord, when other tissues that express AQP4, like lung and kidneys, are spared.
Neuroscience Research

The Committee recognizes the importance of neuroscience research funded by the NIH, which is fueling a vital scientific endeavor and is the essential foundation for understanding and treating diseases that impact over 100,000,000 Americans each year. The Committee also commends the NIH for its successful implementation of the BRAIN Initiative, and for its 5 year partnership with an array of agencies. This collaborative effort is revolutionizing our understanding of how neural components and their dynamic interactions result in complex behaviors, cognition, and disease, while accelerating the development of transformative tools to explore the brain in unprecedented ways making information previously beyond our reach accessible. NIH should continue to build on its 5 years of success as a leader and partner on the BRAIN Initiative, bringing together various disciplines and funding meritorious research to advance our knowledge of the brain.

Action taken or to be taken:

To date the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative has launched more than 450 research projects, large and small, led by more than 600 principal investigators. Funding the most meritorious research has always been at the heart of NIH success, and the special challenges of advancing our knowledge of brain circuits warrant a strong emphasis on engaging experts from many disciplines. NIH recognizes that the remarkably collaborative and trans-disciplinary nature of the BRAIN Initiative has been the key to its encouraging progress to date, and NIH will continue to build on that strategy. At the Federal level, the NIH has developed effective working relationships with other agencies, including the National Science Foundation, the Food and Drug Administration, the Defense Advanced Research Projects Agency, and the Intelligence Advanced Research Project Activity. Non-governmental organizations, including the Allen Institute for Brain Science, Janelia/Howard Hughes Medical Institute, the Kavli Foundation, and several industry and university partners are also integral to the project and the BRAIN Initiative Alliance helps coordinate activities. Within NIH, the Initiative is managed by teams of scientific program managers who bring diverse expertise from across NIH. And, most importantly, the research projects themselves bring together as many experts from physics, chemistry, materials science, engineering, molecular and cellular biology, mathematics, and computer sciences as from across the breadth of neuroscience. As one indication, more than 1000 scientists and engineers participated in the most recent BRAIN Initiative investigators meeting to exchange information and extend their growing networks of collaboration across the various types of projects and consortia that make up the Initiative.

Development of the BRAIN 2025 plan, which guides the BRAIN Initiative, was itself led by a team of scientists of diverse expertise, through extensive consultation with the broader scientific community. As the Initiative moves into its second five years, in keeping with the advice of that original group, a new team of scientific advisors is assessing progress to date and consulting with the scientific community to ensure that the BRAIN Initiative takes advantage of progress to date and newly emerging opportunities to advance toward its ambition.

200 https://www.braininitiative.nih.gov/2025/
Next Generation Researchers Initiative
The Committee urges NIH to continue to prioritize robust implementation of the Next Generation Researchers Initiative within the Office, as established in the 21st Century Cures Act, and to continue to expand the activities under the Initiative to improve and accelerate transitions into independent careers and enhance workforce diversity. The Committee directs NIH to collect, evaluate, and disseminate data, including best practices, on implementation of the Initiative's policies as well as programs and pilots across all Institutes and Centers aimed at promoting the next generation of researchers, and to coordinate with relevant agencies, professional and academic associations, and others to inform programs related to the training, recruitment, and retention of biomedical researchers, as required under the law. The Committee applauds the National Academy of Sciences publication of the study, the Next Generation of Biomedical and Behavioral Sciences Researchers: Breaking Through and urges NIH to advance the recommendations in the study.

Action taken or to be taken:
The NIH has long recognized that the most essential resource in the biomedical research enterprise is the scientists that make-up our workforce. For the past 10 years NIH has taken steps to improve funding for our early-stage investigators to support and sustain the next generation of researchers. In September 2017, with support from the 21st Century Cures Act (P.L. 114-255), NIH launched the Next Generation Researchers Initiative (NGRI). This initiative aims to bolster opportunities for early-stage investigators, defined as those within ten years of completing postgraduate clinical training or their most recent advanced research degree. Through this initiative, NIH Institutes and Centers are requested to prioritize funding for additional early-stage investigators and track the impact of funding decisions for early-stage investigators to ensure that this new strategy is effectively implemented. As of September 17, 2018 NIH has met its goal of funding 1,100 ESIs in FY 2018, which is the largest number to date. In addition, NIGMS introduced a Maximizing Investigators' Research Award for Early Stage Investigators (R35) program which provides more stable funding and flexibility for ESIs to follow new research directions.

Additionally, a working group of the Advisory Committee to the NIH Director is assessing the success of the new NGRI-related programs in a systems-oriented data-driven manner. This group is expected to recommend strategies in December 2018 to enhance training, mentorship, and diversity across the biomedical workforce.

NIH is closely reviewing recommendations from the National Academies of Science, Engineering, and Math (NASEM) report on ‘Next Generation of Biomedical and Behavioral Sciences Researchers’ which provides a rigorous, data-driven assessment of the biomedical research workforce. Among NASEM’s recommendation is a call for more data to be collected on the workforce. Consistent with NASEM recommendations, NIH recently published a report

201 https://grants.nih.gov/ngri.htm
202 https://grants.nih.gov/ngri.htm
204 https://www.nap.edu/catalog/25008/the-next-generation-of-biomedical-and-behavioral-sciences-researchers-breaking
on trends in the demographics of early stage investigators, new investigators and established investigators between 2009 and 2016.\textsuperscript{205} In addition, NIH regularly collects data on demographics and outcomes of NIH-supported biomedical pre- and postdoctoral trainees and fellows and regularly performs outcomes evaluations of NIH-supported training and career development programs. Recent evaluations have demonstrated positive outcomes regarding successful transitions to independent careers for individuals appointed to National Research Service Award (NRSA) postdoctoral fellowships\textsuperscript{206} as well as individual mentored career development (K) awards (Accepted for publication in Academic Medicine)\textsuperscript{207}. NIH will continue to consider ways to enhance NRSA mechanisms and K awards aligning NIH’s work with recommendations from NASEM. In addition, NIH will continue to collect workforce related data and perform outcomes analyses as well as interact with external stakeholders to rigorously assess biomedical workforce trend.

Additionally, NIH, as part of the NGRI program and other related activities, is considering effective strategies to increase diversity in the biomedical research workforce. For example, multiple NIH Institutes and Centers are piloting new programs (using the K99-R00 award mechanism)\textsuperscript{208, 209} to enhance workforce diversity which is consistent with provisions within the 21\textsuperscript{st} Century Cures Act.

NIH remains strongly committed to the goals of NGRI to fund more early career investigators, protect and retain meritorious at-risk scientists, and enhance the diversity of the biomedical research workforce. Through thoughtful implementation of the recommendations detailed above, NIH will be better equipped to design, test, implement, and evaluate policies that will assure the success of the next generation of talented biomedical researchers.

\textsuperscript{205} https://www.ncbi.nlm.nih.gov/pubmed/29920223
\textsuperscript{206} http://www.nber.org/papers/w24508
\textsuperscript{207} Nikaj, S, Lund PK. The impact of individual mentored career development (K) awards on the research trajectories of early career scientists. Academic Medicine (accepted for publication)
\textsuperscript{208} https://grants.nih.gov/grants/guide/pa-files/PAR-18-813.html
Non-Addictive Pain Treatments
The Committee is aware that many people who suffer from acute pain are exposed to opioids, leading to addiction, and many others who suffer from chronic pain turn to opioids for relief because they lack alternative pain treatments and management. This is a particular challenge in Appalachia. The Committee encourages NINDS to prioritize the development of non-addictive treatments for pain, recognizing that there are regions of the country with high per capita rates of opioid deaths.

Action taken or to be taken:

NINDS is moving forward on research priorities to meet the urgent needs of people with pain through a multi-pronged approach to develop safe and effective therapies that reduce our reliance on opioids. Three key areas of interest include: understanding the biological underpinnings of pain, accelerating discovery and development of non-addictive treatments, and rapidly advancing new treatments to the clinic. These programs will help to improve the quality and safety of pain care nationwide, and the focus on acceleration of research discoveries into the clinic will be especially beneficial to those communities hardest hit by the opioid crisis.

NINDS co-leads a large-scale clinical study to understand the mechanisms that lead to chronic pain after an acute injury. Data on many different bio-psychosocial characteristics, such as gene variants, altered neural circuitry, inflammation, and mental health will be correlated with risk for chronic pain. This information will provide targets for novel drugs for acute pain treatment and guidance for precision medicine approaches to reduce opioid use for those who are not likely to develop chronic pain.

NINDS supports studies ranging from early-stage drug target discovery focused on molecular pathways of pain signaling to exploration of receptors and channels as potential non-addictive analgesic targets and testing of novel treatments in behavioral models. For example, NINDS researchers identified nerve growth factor receptor and pain-related ion channels targets, which have led to industry-sponsored clinical trials for safe pain treatments. NINDS supported early development of calcitonin gene receptor protein, the precursor to a compound recently approved for migraine. NIH programs for discovery of new formulations, combinations of medicines, and re-purposing molecules developed for other disorders are being expanded rapidly to find new pain medications. Through the NIH Blueprint Neurotherapeutics Program, which provides support for small molecular drug discovery and development, NINDS funds research to develop a non-addictive treatment for headache and non-opioid analgesics for diabetic nerve pain.²¹⁰

NINDS leads the NIH BRAIN Initiative, a major effort to develop tools to map neural circuits, monitor and modulate circuit activity, and characterize neural circuit disorders. Chronic pain is a disorder of the neural pain circuitry, and technologies discovered through the BRAIN Initiative to better understand and modify neural circuits will enable powerful new approaches to diagnose and treat pain.

The NIH Helping to End Addiction Long-term (HEAL) Initiative\textsuperscript{211} significantly expands research to develop non-addictive pain treatments. As a part of this initiative, NINDS is establishing resources to identify new pain medications through rapid screening of molecules for pain-relevant biological activity. NINDS also is developing a platform for pain biomarker discovery and validation to inform clinical studies of potential drug effectiveness and safety. In addition, NINDS is working to facilitate the sharing of data on past and future drug development across industry and academia to promote more research and improve success in bringing medications to the clinic. To accelerate testing of novel pain treatments in humans, NINDS is establishing a Pain Clinical Trial Network to optimize trial design, target appropriate patients for trials, and engage experts in performing clinical trials. These programs collectively are part of an NIH-wide aggressive effort to stem the opioid public health crisis nationwide.

\footnote{211} https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative
Office of Cancer Survivorship
The Committee recognizes that the needs of childhood cancer survivors are unique. By 2020, there will be at least 500,000 childhood cancer survivors in the US. Two thirds of childhood cancer survivors suffer from at least one health problem caused from their treatment. The Committee urges NCI to continue to support childhood cancer survivorship, including research on survivorship following targeted and immune-therapies as well as a standard of care. The research should focus on the specific needs for childhood cancer survivors such as psycho-social treatments.

Action taken or to be taken:

The NCI Office of Cancer Survivorship was established in 1996 and provides a scientific home for the support and direction of research designed to improve the length and quality of life of individuals treated for cancer. This includes all individuals—children, adolescents and young adults (AYA), and adults, including the elderly. NCI currently supports a portfolio of programs and grants in the survivorship field that focus on both prospective and retrospective studies with childhood and AYA cancer survivors. These studies often focus on determining the differences in adverse outcomes of survivors, risk of subsequent cancers and other medical conditions, psychosocial issues and outcomes, and the late effects of treatment for childhood cancer, which includes reproductive complications. The Childhood Cancer Survivor Study (CCSS) coordinated through St. Jude Children's Research Hospital is part of a longstanding study that looks at the long-term effects of cancer and therapy in a cohort of more than 35,000 childhood cancer survivors. An ongoing CCSS study is conducting genomic analysis of tumor DNA from nearly 6000 survivors to identify genetic factors that influence the risk of second cancers and other long-term adverse effects to help doctors develop appropriate survivorship care plans for childhood cancer survivors. NCI also currently funds numerous projects exploring the psychosocial needs for childhood cancer survivors through assessments and implementation of evidence-based methods and programs. One recently funded study aims to develop methods to identify acute lymphoblastic leukemia patients with emerging cognitive problems before significant impairments develop to provide early intervention. Similarly, another newly funded study is testing methods to reduce anxiety and depression and increase adherence to oral medications in AYA cancer survivors who underwent a hematopoietic cell transplant as part of their cancer treatment. These are just a few examples of NCI supported research to understand the long-term consequences of cancer and its treatment to improve the quality of life of children and AYA cancer survivors.

212 https://projectreporter.nih.gov/project_info_description.cfm?aid=9415425
213 https://projectreporter.nih.gov/project_info_description.cfm?aid=9524839
214 https://projectreporter.nih.gov/project_info_description.cfm?aid=9493159
Opioid Misuse and Addiction
The bill includes $250,000,000 for targeted research related to opioid misuse and addiction, development of opioid alternatives, pain management, and addiction treatment. The Committee remains concerned about the growing epidemic of opioid misuse and addiction in this country. The widespread availability of prescription opioids has contributed to the millions of Americans who suffer from addiction disorders. Although NIH has studied the effectiveness and risks associated with long-term opioid use for chronic pain, little research has been done to investigate new and alternative treatment options to treating chronic pain, other than with highly addictive opioid painkillers and muscle relaxants. The Committee directs NIH to expand scientific activities related to research on medications used to treat and reduce chronic pain, and the transition from acute to chronic pain. Further, the Committee urges NIH to: (1) continue funding research on medication development to alleviate pain and to treat addiction, especially the development of medications with reduced misuse liability; (2) as appropriate, work with private companies to fund innovative research into such medications; (3) report on what we know regarding the transition from opioid analgesics to heroin and synthetic opioid use and addiction within affected populations; (4) conduct pilot studies to create a comprehensive care model in communities nationwide to prevent opioid misuse, expand treatment capacity, enhance access to overdose reversal medications, and enhance prescriber practice; (5) test interventions in justice system settings to expand the uptake of medication assisted treatment and methods to scale up these interventions for population-based impact; and (6) develop evidence-based strategies to integrate screening and treatment for opioid use disorders in emergency department and primary care settings. In addition, NIH should continue to sponsor research to better understand the effects of long-term prescription opioid use, especially as it relates to the prevention and treatment of opioid misuse and addiction.

Action taken or to be taken:
To put an end to the opioid crisis, the National Institutes of Health (NIH) is committed to play a central role in the multi-agency effort to advance HHS’s 5 strategic priorities of:

- Improving access to treatment and recovery services;
- Promoting use of overdose-reversing drugs;
- Strengthening our understanding of the epidemic through better public health surveillance;
- Providing support for cutting edge research on pain and addiction; and
- Advancing better practices for pain management.

These strategic areas delineate and guide all of NIH’s specific initiatives to maximize the public health impact of the funds allocated for targeted research related to opioid misuse and addiction, development of opioid alternatives, pain management, and addiction treatment. In April 2018, NIH launched the HEAL (Helping to End Addiction Long-term) Initiative to speed scientific solutions to stem the national opioid public health crisis. The initiative is centered around two strategic goals: a) preventing addiction through enhanced pain management and 2) improving treatments for opioid misuse disorder and addiction. HEAL will build on extensive, well-established NIH research, including basic science of the complex neurological pathways involved in pain and addiction, implementation science to develop and test treatment models, and research to integrate behavioral interventions with medication-assisted treatment for opioid
use disorder (OUD). The following components of the HEAL Initiative, along with NIH’s existing portfolio in opioids research, will seek to address many of the issues mentioned above.

**Developing Better Treatments for Pain and Addiction**
The HEAL initiative is establishing extensive research infrastructure to accelerate the development of safe, non-addictive analgesics through collaboration with industry and academic partners. This effort includes building a clinical trials network to support pain research to test the safety of new drugs, explore patient characteristics that predict treatment response, and test the effectiveness of a broad range of pain therapies, including non-pharmacological approaches. The pain research clinical trials infrastructure is expected to be established and active in running studies in FY 2019. The HEAL Initiative is also supporting promising candidates for new addiction treatments through focused medication development efforts, as well as the expansion of the size and scope of the National Drug Abuse Treatment Clinical Trials Network (CTN), a cooperative venture of the National Institute on Drug Abuse (NIDA), academic researchers, and community providers to develop, validate, refine, and translate into practice new treatment options for patients with substance use disorders.

**Understanding the Trajectory of OUD**
NIDA recognizes the importance of investigating the factors that influence opioid use disorder trajectories and of educating all stakeholders about evidence-based treatment options. Through NIDA-supported research, for example, we have learned that both daily participation in sports and exercise \(^{215}\) and trait mindfulness \(^{216}\) may serve as protective factors with respect to nonmedical prescription opioid use (NPOU). On the other hand, most NPOU users transitioned to regular heroin use (79%) and heroin injection (64%) about 3½ years after onset, \(^{217}\) while young adults in the club scene, which display high levels of NPOU, are at particularly high risk of transition to heroin a year later. \(^{218}\) These types of studies provide critical insight that can be translated into effective public health policies to prevent or mitigate the impact of opioid misuse.

**Integrated Care: The HEALing Communities Study**
The HEALing Communities study is a national research effort that will support a multi-site, national research effort to develop approaches for the implementation of effective interventions for opioid misuse, OUD, and opioid overdose. The study, still in development, will test integration of prevention, treatment, and recovery support services in healthcare, justice, and community-based settings. This study will be developed in close collaboration with the Substance Abuse and Mental Health Services Administration and other federal partners to avoid duplication and leverage complementary ongoing efforts. The findings will establish best practices for integrating evidence-based strategies in highly-affected communities that can be replicated nationwide.

\(^{215}\) [http://pediatrics.aappublications.org/content/early/2016/07/21/peds.2016-0677](http://pediatrics.aappublications.org/content/early/2016/07/21/peds.2016-0677)


Interventions in Justice Settings
Through the NIDA Justice Community Opioid Innovation Network, NIH will establish a network of research investigators to rapidly conduct studies on the quality of care for opioid misuse and OUD in justice populations by facilitating partnerships between local and state justice systems and community-based treatment providers. Specifically, this will include (1) implementing a national survey of addiction treatment delivery services within the justice system; (2) conducting studies on the effectiveness and adoption of new medications, prevention and treatment interventions, and technologies in justice system settings; and (3) leveraging existing data sources and developing innovative research methods to address the opioid crisis.

OUD Screening
In order to initiate treatment for OUD, it is essential that the disorder be successfully detected and that such screening processes are integrated into both emergency and primary care settings. Part of the HEALing communities study will involve an integrated approach to both screening and treatment. In addition, NIDA also funds studies to develop, test, and improve processes for screening and initiating treatment in such settings. For example, NIDA funds a grant to develop emergency-department based surveillance programs for clandestine opioids such as fentanyl after an overdose.
Opioid Research Centers
The Committee supports the creation of one or more research centers to study the effectiveness of policies related to combatting prescription opioid use. Preference should be given to research done in States with high levels of prescription opioid use, opioid overdose deaths, and racial and ethnic diversity.

Action taken or to be taken:

In April 2018, the National Institutes of Health (NIH) launched the HEAL (Helping to End Addiction Long-term) Initiative to speed scientific solutions to stem the national opioid public health crisis. This Initiative will build on extensive, well-established NIH research, including basic science of the complex neurological pathways involved in pain and addiction, implementation science to develop and test treatment models, and research to integrate behavioral interventions with medication-assisted treatment for opioid use disorder (OUD). The HEALing Communities study is a national research effort that is part of the NIH HEAL Initiative described above. By deploying sites in geographical areas with high levels of prescription opioid use/overdose deaths, the overall goal of the study is to determine if an integrated set of evidence-based interventions within healthcare, behavioral health, justice systems, and community organizations can work to decrease opioid overdoses and to prevent and treat opioid use disorders. The study will build the necessary research infrastructure to develop approaches for the implementation of effective prevention and treatment interventions to address the opioid crisis and decrease opioid overdose fatalities.

In 2018, as part of the HEAL Initiative, the National Institute on Drug Abuse (NIDA) is also working to expand the size and scope of research conducted by the National Drug Abuse Treatment Clinical Trial Network (CTN) to address emergent needs presented by the opioid crisis. The CTN is a cooperative venture of NIDA, academic researchers, and community providers to develop, validate, refine, and translate into practice new treatment options for patients with substance use disorders. The CTN has already generated important findings on the effectiveness and safety of medication treatments for OUD, the utility of behavioral interventions for OUD management, and the use of medication-assisted treatment (MAT). By incorporating new research sites and investigators into existing research nodes and centers, the CTN will incorporate OUD-related research questions into studies currently underway, expedite new studies of OUD treatment in general medical and other settings, and enhance clinical and research training opportunities. In 2019, NIDA will begin to leverage this expansion to rapidly address the urgent clinical questions arising from the opioid crisis.

NIH is also launching a pain-centric clinical trial network, which will focus primarily on Phase II clinical trials, validating specific biomarkers in a multi-site setting, accommodating novel trial designs, and research on specific well-phenotyped pain conditions with a high unmet medical need. Organized in a “hub and spoke” model, the network design will promote effective training and consistency among clinical sites and streamlined selection and approval of protocols. The network will include a clinical coordinating center, data coordinating center, and hubs identified as “centers of excellence” able to recruit participants with specific pain conditions. Through its standing infrastructure, the clinical trial network will reduce start-up times, incentivize testing,
and de-risk the challenges of Phase II clinical trials to accelerate the approval of effective, non-addictive therapies for treating pain.

Additionally, NIDA has partnered with states and several other federal agencies to address the opioid crisis in rural U.S. regions, issuing funding opportunities to help communities develop ways to comprehensively prevent and treat substance use disorder, overdoses, and infectious disease transmission related to injection drug use. These projects support the work of state and local communities in developing best-practice responses that rural public health systems can implement. The grants are co-funded by the Appalachian Regional Commission, the Centers for Disease Control and Prevention, and the Substance Abuse and Mental Health Services Administration.
Opioid Use Disorders During Pregnancy and Neonatal Abstinence Syndrome
The Committee recognizes the growing burden of NAS and the health care costs associated with it. The Committee is aware of the need for more information regarding long-term health and developmental outcomes related to NAS, the wide variation in clinical practice and health systems support, as well as the challenges associated with post-discharge care. The Committee encourages NIH to coordinate with other agencies at HHS to support additional research on prevention, identification, and treatment of prenatal opioid exposure and NAS, including the best methods for screening and treating pregnant women for opioid use disorder and the best methods for screening for NAS. Additionally, the Committee encourages NIH to build on the ACT NOW study to enhance understanding of the impact of pharmacological and non-pharmacological treatment techniques on costs and outcomes in the short-term and longitudinally. The Committee further encourages NIH to coordinate with other agencies at HHS to support research on innovative care models to optimize care and long-term outcomes for families. NICHD is encouraged to coordinate with other agencies, including CDC and HRSA, to support additional research on pre-venting, screening, and treating NAS. The Committee supports research regarding long-term health and development outcomes related to NAS, best practices for screening and treating pregnant women for opioid use disorder, and challenges associated with post-discharge care.

Action taken or to be taken:

According to the Centers for Disease Control and Prevention, national rates of opioid use disorder at time of delivery more than quadrupled from 1999 to 2014.219 Newborns who are exposed prenatally to opioids are at risk for withdrawal symptoms after birth. Symptoms of Neonatal Opioid Withdrawal syndrome (NOWs - also called Neonatal Abstinence Syndrome) often include tremors, excessive crying and irritability, and problems sleeping, feeding, and breathing. Although NOWs is known to increase the risk for neurodevelopmental problems as infants grow older, little is known about its long-term effects. No standard evidence-based treatment for NOWs currently exists in the United States, even though the number of reported cases is far higher than in recent years.

To lay the groundwork for this emerging public health issue, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) conducted a workshop in April 2016 to evaluate opioid use in pregnancy and health and developmental outcomes for children who had been prenatally exposed to opioids and experienced NOWs. Experts identified research gaps and opportunities to improve outcomes for families; these findings were subsequently published in Obstetrics and Gynecology in 2017. They agreed that routine screening for substance use, including misuse of prescription opioids, should be provided to all women throughout pregnancy, and that reducing unnecessary opioid use in healthy women after delivery is an important goal for preventing future opioid misuse. The primary recommendation called for more research to determine best practices for screening and treating pregnant women.

---

219 https://www.cdc.gov/mmwr/volumes/67/wr/mm6731a1.htm?s_cid=mm6731a1_x
for opioid use disorder and to understand additional problems, such as poor nutrition and mental illness, which can accompany opioid use disorder in pregnancy.

In 2017, NICHD and the National Institute of Drug Abuse (NIDA) issued a funding opportunity announcement (RFA-HD-18-036) seeking projects related to the following topics:

- Clinical studies of medically supervised opioid withdrawal that evaluate potential outcomes such as maternal complications, fetal complications, pregnancy loss, and neonatal opioid withdrawal syndrome.
- Pharmacokinetic and pharmacodynamic studies to optimize management of medications used to treat opioid use disorder in pregnant and/or postpartum women.
- Observational or cohort studies evaluating the effects of medication-assisted opioid cessation (such as methadone) on maternal, fetal, and neonatal outcomes.
- Studies of genetic and/or epigenetic factors associated with the effects of opioid use during pregnancy on fetal and neonatal outcomes.

To address this gap in care, the Advancing Clinical Trials in Neonatal Opioid Withdrawal syndrome (ACT NOW) program, launched in 2017, aims to inform clinical care of infants who are exposed to opioids before birth. ACT NOW is a collaborative effort of two networks supported by the National Institutes of Health (NIH), the NICHD’s Neonatal Research Network, which has more than 30 years of experience designing and implementing clinical trials involving infants, and the NIH Office of the Director’s Environmental influences on Child Health Outcomes (ECHO) Program’s Institutional Development Award (IDeA) States Pediatric Clinical Trials Network, which focuses on rural and medically underserved communities, including those reporting a higher incidence of NOWs. ACT NOW pilot studies are assessing the prevalence of NOWs across more than 20 clinical research sites and are surveying current management approaches in preparation for developing research protocols for large-scale studies. Currently, two large studies are under development: a medication weaning study and a non-drug intervention to improve care for newborns with NOWS. Further efforts that will focus on the long-term evaluation of these interventions on the health outcomes of infants with NOWs are being planned.
Opioid-Related Infectious Diseases Research
The Committee urges NIAID, NIDA, NHLBI, NICHD, and NIMHD to expand research on opioid-related infectious diseases to include endocarditis, osteomyelitis, bacteremia, skin and soft tissue infections, and cerebral infections, in addition to HN and hepatitis B and C, and respond to the unique barriers to care and treatment for justice-involved individuals and rural populations. Implementation studies should be conducted in collaboration with CDC, AHRQ, and HRSA to understand the best approaches for preventing and treating opioid related infections.

Action taken or to be taken:

The National Institutes of Health (NIH) is committed to supporting evidence-based implementation science research to integrate treatment of the addiction underlying the opioid crisis and comorbidities associated with opioid use disorder (OUD), including coinfections. Transmission of bloodborne infections, particularly hepatitis C virus (HCV) and the bacterial pathogens that cause endocarditis, osteomyelitis and septicemia are an emerging public health challenge of the opioid epidemic. The incidence of HIV and hepatitis B virus (HBV) infections, syphilis and other sexually transmitted infections are also rising among injection drug users but occur at lower prevalence.

NIH supports research that aims to characterize and ultimately prevent these infections among injection drug users. These studies range from finding ways to prevent individuals from initiating injection drug use, to testing interventions for reducing the risk of co-occurring infections. Mitigating this complex public health problem requires a trans-NIH approach to implementation research, in collaboration with the Centers for Diseases Control and Prevention (CDC), the Agency for Healthcare Research and Quality (AHRQ), and the Health Resources and Services Administration (HRSA). There is a particular need to integrate OUD treatment into hospital settings, in parallel with interventions for OUD-related infections. Evidence-based medication-assisted treatment for OUD during hospital care for OUD-related infections may help to reduce post-hospital relapse into illicit opioid use and resulting OUD-related morbidity and mortality.

The National Institute of Allergy and Infectious Diseases (NIAID) maintains a longstanding program of basic, translational, and clinical research into the development of vaccines, therapeutics, and diagnostics for infectious diseases, including those acquired through injection drug use. For example, NIAID, along with the National Institute on Drug Abuse (NIDA) and the National Institute of Mental Health (NIMH), is supporting research to prevent HIV acquisition in drug-using populations through the use of opioid substitution therapy and other treatment and prevention methods. In addition, NIAID is pursuing new or improved vaccines to prevent HBV and HCV infections, including a Phase 1/2 clinical trial of a vaccine candidate to prevent acute and chronic HCV infection in injection drug users. NIAID continues to support a robust research program on viral and bacterial pathogens to facilitate the development of medical countermeasures.
The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is actively collaborating with NIDA, other NIH Institutes and Centers, and its federal partners to ensure that the at-risk populations of pregnant women, infants, and adolescents are included in studies and clinical trials regarding the prevention and treatment of opioid-related infectious diseases. The National Heart, Lung, and Blood Institute (NHLBI) funds research on endocarditis that may help reduce the risk of opioid-related heart infections, as well as poor outcomes. An integrated strategy is needed because treatment of endocarditis is resource-intensive and nearly half of patients are uninsured or on Medicare. Furthermore, without effective treatment of the underlying OUD, patient readmission for endocarditis occurs with unacceptably high frequency. To address HIV-related comorbidities, as of FY 2019, NHLBI is leading the MACS and WIHS Combined Cohort Study, a trans-NIH initiative to understand and reduce the burden of chronic comorbidities among people living with HIV.

While preventing such infections is important to combating their spread, it is equally essential that patients be able to access effective treatment. NIH funds studies which examine both the access to care and the quality of care for individuals who may face unique barriers to care and treatment, and are testing ways to improve the care those individuals receive. One major component of NIH’s efforts to address opioid use, the Helping to End Addiction Long-term (HEAL) initiative, will use the Justice Community Opioid Innovation Network (JCOIN), which will establish a network of research investigators to rapidly conduct studies on quality care for opioid misuse and opioid use disorder in justice populations by facilitating partnerships between local and state justice systems and community-based treatment providers. Using JCOIN, NIH will conduct studies on the effectiveness and adoption of new medications, prevention and treatment interventions, and technologies in justice system settings. JCOIN will build on NIDA’s existing portfolio of justice research, much of which has developed interventions for reducing infectious diseases such as HIV and Hepatitis C that are associated with injecting opioids such as heroin. JCOIN will provide an opportunity to scale these interventions and enhance integration with addiction treatment.

As NIH continues to respond to the evolving state of opioid use, misuse and overdose in the United States, it will continue to consider co-occurring infections as part of both the problem and the response, and to find new ways to ensure that effective treatment and prevention interventions are able to reach the individuals who need them.
Opioids (HEAL Initiative)
The Committee commends NIH for launching the HEAL (Helping to End Addiction Long-Term) Initiative, a trans-NIH effort to speed scientific solutions to stem the national opioid public health crisis. This initiative will build on extensive, well-established NIH research, including basic science of the complex neurological pathways involved in pain and addiction, implement science to develop and test treatment models, and research to integrate behavioral interventions with medication-assisted treatment for opioid use disorder. The Committee continues to support opioid-related research at NINDS and expects NINDS to expand this research in fiscal year 2019.

Action taken or to be taken:

NIH launched the HEAL (Helping to End Addiction Long-term) Initiative to improve treatments for opioid misuse and addiction and enhance pain management. HEAL is a trans-NIH effort, for which the National Institute on Drug Abuse (NIDA) leads the research effort on opioid misuse and addiction, and the National Institute of Neurological Disorders and Stroke (NINDS) leads the research effort on better pain management to reduce our reliance on opioids.

NINDS in collaboration with the NIH Pain Consortium is launching a set of research projects to meet the pain relevant objectives of HEAL: to increase our understanding of the biological underpinnings of pain, accelerate discovery and development of non-addictive treatments, and rapidly advance new pain treatments to the clinic.

The Acute to Chronic Pain Signatures Program is an effort, co-led by NINDS, to better understand the mechanisms that drive the transition from acute to chronic pain. A comprehensive clinical study is planned to determine a set of predictive characteristics, such as gene variants, altered neural circuitry, inflammation, and mental health that will identify those at risk for chronic pain after an acute pain event. This information will provide mechanistic targets for novel drugs for acute pain treatment and guidance for precision medicine practices to reduce opioid use for those who are not likely to develop chronic pain.

HEAL initiatives also will establish resources to accelerate discovery and development of non-addictive treatments for pain. NINDS will support projects to discover and optimize new biological targets for small molecules, biologics, natural products, and devices for the treatment of pain. NINDS is establishing a preclinical testing platform with models that more closely mimic human pain conditions, to test non-addictive treatments and is working with the National Center for Advancing Translation Sciences to engineer human cell-based screening platforms that approximate human pain physiology. NINDS also is facilitating the sharing of data on past and future drug development across industry and academia to promote more research and improve success in bringing medications to clinic.

NINDS is spearheading programs to rapidly advance new non-addictive pain treatments to the clinic. To accelerate testing of novel treatments - medications and devices, NINDS is establishing a Pain Clinical Trial Network to optimize trial design, target appropriate patients for trials, and engage experts in performing clinical trials. The network will support NINDS led biomarker discovery and validation programs to define patient populations and treatment response and will test interventions from academic and industry partners. These programs
collectively, are part of the aggressive efforts of the NIH-wide HEAL Initiative to stem the opioid public health crisis.
Opioids (HEAL Initiative)
The Committee commends NIH for launching the HEAL (Helping to End Addiction Long-Term) Initiative, a trans-NIH effort to speed scientific solutions to stem the national opioid public health crisis. This Initiative will build on extensive, well-established NIH research, including basic science of the complex neurological pathways involved in pain and addiction, implementation science to develop and test treatment models, and research to integrate behavioral interventions with medication-assisted treatment for opioid use disorder. The Committee continues to support opioid related research at NIDA and expects NIDA to expand this research in fiscal year 2019.

Action taken or to be taken:

In April 2018, the National Institutes of Health (NIH) launched the HEAL (Helping to End Addiction Long-term) Initiative to identify effective ways for enhancing pain management approaches and improving treatments for opioid use disorder and addiction in communities affected by the opioid crisis. NIH is working on several fronts to speed scientific solutions to this public health crisis.

The National Institute on Drug Abuse (NIDA) is working to expand therapeutic options for opioid addiction, overdose prevention, and reversal. NIDA is soliciting grants to develop new treatment strategies for Opioid Use Disorder (OUD), including creating longer-acting formulations of existing addiction treatment medications, such as buprenorphine and naltrexone, to promote adherence to treatment while preventing medication misuse. NIDA is also investing in the development of stronger, longer-acting formulations of opioid antagonists (including longer-lasting naloxone formulations and novel compounds) to reverse overdose caused by opioids and combinations of drugs including opioids.

Additionally, NIDA is investing in the development of novel medications, immunotherapies, and devices to treat addiction, withdrawal, craving, progression, and relapse. New therapeutic approaches to treat OUD may result from 1) repurposing already-approved medications such as lorcaserin, which is approved by the Food and Drug Administration (FDA) for controlling appetite, to reduce opioid seeking; 2) evaluating medications already in use internationally but not in the United States; and 3) discovery and validation of novel biological targets to prevent compulsive drug taking. To reduce drug craving in people with OUD, NIDA will assess novel therapeutic agents targeting the brain’s reward pathway. Studies will test the safety, efficacy, and underlying mechanisms of craving reduction as a strategy to prevent opioid misuse, dependence, and relapse, and reduce morbidity and mortality risk for people with OUD. NIDA will also pursue promising candidates for new addiction treatments through focused medication development efforts. Meritorious preclinical target identification and validation efforts will reveal new mechanisms of action for OUD treatments.

In 2018, NIDA is also working to expand the size and scope of research conducted by the National Drug Abuse Treatment Clinical Trials Network (CTN) to address emergent needs presented by the opioid crisis. The CTN is a cooperative venture of NIDA, academic researchers, and community providers to develop, validate, refine, and translate into practice new treatment options for patients with substance use disorders. The CTN has already generated

191
important findings on the effectiveness and safety of medication treatments for OUD, the utility of behavioral interventions for OUD management, and the use of medication-assisted treatment (MAT). By incorporating new research sites and investigators into existing research nodes and centers, the CTN will incorporate OUD-related research questions into studies currently underway, expedite new studies of OUD treatment in general medical and other settings, and enhance clinical and research training opportunities. In 2019, NIDA plans to begin leveraging this expansion to more smoothly and rapidly begin testing possible OUD treatments.

Improving the quality of OUD treatment within the justice system will be critical to address the opioid crisis. Through the NIDA Justice Community Opioid Innovation Network (JCOIN), NIH will establish a network of research investigators to rapidly conduct studies on quality of care for opioid misuse and OUD in justice populations by facilitating partnerships between local and state justice systems and community-based treatment providers. Specifically, this will include (1) implementing a national survey of addiction treatment delivery services within the justice system; (2) conducting studies on the effectiveness and adoption of new medications, prevention and treatment interventions, and technologies in justice system settings; and (3) leveraging existing data sources and developing innovative research methods to address the opioid crisis.

Workgroups have already met to begin the process of designing the HEALing Communities Study, a multi-site, national research effort to develop approaches for the implementation of effective interventions for opioid misuse, OUD, and opioid overdose, and funding opportunity announcements for components of the study are targeted for dissemination in September 2018 with review in January 2019.
Opioids
The Committee continues to be extremely concerned about the epidemic of prescription opioids, heroin, and synthetic opioid use, addiction, and overdose in the US. Approximately 144 people die each day in this country from opioid overdose, making it one of the most common causes of non-disease-related deaths for adolescents and young adults. This crisis has been exacerbated by the availability of fentanyl and its analogs in many communities. The Committee appreciates the important role that research can and should play in the various Federal initiatives aimed at this crisis. The Committee urges NIDA to continue funding research on medication development to alleviate pain, especially the development of medications with reduced abuse liability, and to report on what we know regarding the transition from opioid analgesics to heroin and synthetic opioid abuse and addiction within affected populations.

Action taken or to be taken:

The National Institutes of Health (NIH) is committed to supporting a broad portfolio of pain research ranging from cell and molecular mechanisms of acute and chronic pain to safe, effective therapy development, to large scale clinical trials. The portfolio includes many projects that address the pressing need to develop new non-opioid, non-addictive pain treatments. Studies range from early-stage drug target discovery focused on molecular pathways of pain signaling including exploration of receptors and channels as potential non-addictive analgesic targets to testing in behavioral models. Several targets identified through NIH basic science research, such as the nerve growth factor receptor and pain-related ion channels, are now being pursued in industry sponsored clinical trials of non-addictive treatments. NIH is also supporting discovery projects to reveal novel targets for small molecules, biologics, natural products, and devices for the treatment of pain. These targets will encompass all levels of the pain processing pathway from a basic biology perspective. Multidisciplinary tools and multi-site validation will validate pain targets. This research will increase opportunities to commercialize small molecules, biologics, and neuromodulation devices that engage targets for the treatment of pain.

In addition, NIH is working to develop opioids with reduced risk of addiction and misuse. NIH-supported investigators are developing new compounds that exhibit novel properties as a result of their combined activity at different opioid receptors (mu, delta, and kappa). Compounds with combined activity at the mu and delta receptors or at all three receptors can induce strong analgesia without producing tolerance or dependence in animal models. In addition, discovery of adjunct medications that can be combined with opioids to reduce the needed dose, promise to result in lower potential for dependence and addiction. Innovative methods are being explored for drug delivery to increase specificity and efficacy and to reduce analgesic side effects, as well as modified formulations to enhance delivery.

NIH is also launching a pain-centric clinical trial network, which will focus primarily on Phase II trials with assets from companies through partnerships established as part of the NIH Helping to End Addiction Long-term (HEAL) Initiative but will be open to viable assets from academia and other sources. The network also will validate specific biomarkers in a multi-site setting and accommodate novel trial designs and will focus on specific well-phenotyped pain conditions with a high unmet medical need. Organized in a “hub and spoke” model, the network design will promote effective training and consistency among clinical sites and streamlined selection...
and approval of protocols. The network will include a clinical coordinating center, data coordinating center, and hubs identified as “centers of excellence” able to recruit participants with specific pain conditions. Through its standing infrastructure, the clinical trial network will reduce start-up times, incentivize testing, and de-risk the challenges of Phase II clinical trials to accelerate the approval of effective, non-addictive therapies for treating pain.

Finally, the National Institute on Drug Abuse (NIDA) recognizes the importance of investigating the factors that influence opioid use disorder trajectories and the transition from medical or non-medical prescription opioid use (NPOU) use to heroin use. NIDA-supported research in this important area has been gathering speed in recent years. For example, research has shown that both daily participation in sports and exercise and mindfulness may serve as protective factors with respect to NPOU. When combined, these types of studies provide critical insight that can be translated into effective public health policies to prevent or mitigate the impact of opioid misuse.
Palliative Care
The Committee recognizes the importance of palliative care research to strengthen clinical practice and improve healthcare delivery for patients with serious or life-threatening illness or multiple chronic conditions, as well as their families/caregivers. Research funding for palliative care, including pain and symptom management, comprises less than 0.1 percent of the NIH annual budget. Therefore, the Committee strongly urges NIH to develop and implement a trans-Institute strategy to expand and intensify national research programs in palliative care to address quality of care and quality of life for the rapidly growing population of individuals in the United States with serious or life-threatening illnesses.

Action taken or to be taken:

NIH is committed to supporting palliative care research to improve quality of life and health care for people with serious or life-threatening illness, or multiple chronic conditions, and their families and caregivers.

As the lead NIH Institute for end-of-life research, the National Institute of Nursing Research (NINR) supports research to assist individuals, families, and health care professionals in relieving the symptoms and suffering of serious or life-threatening illness, understanding the potential benefits of palliative care, and planning for end-of-life decisions. In shaping a comprehensive palliative care research program, NINR recognizes that high-quality, evidence-based palliative care is a critical component of maintaining quality of life at any stage of illness, not just at the end of life, as well as across the life span from infants to older adults.

NINR’s Office of End-of-Life and Palliative Care Research (OEPCR) coordinates and supports ongoing NINR and NIH research efforts in end-of-life and palliative care science. A major program priority of OEPCR is to coordinate the development, implementation, and evaluation of end-of-life and palliative care research in direct collaboration with other NIH Institutes and Centers (ICs), federal research agencies, and outside constituencies.

For example, NINR will continue to support the expansion of a palliative care research cooperative (PCRC) to build the science of end-of-life and palliative care. The PCRC brings together a network of over 400 multidisciplinary palliative care scientists and includes over 160 clinical trial research sites across the U.S. The PCRC was established to develop rigorous research methods to improve quality of life for patients with serious, life-limiting illnesses and their caregivers. The PCRC provides extensive networking, training, and data resources to palliative care researchers nationally. NINR also continues to build the Palliative Care: Conversations Matter® campaign to increase the use of palliative care for children living with serious illness, by providing evidence-based information and resources to give children, families, and providers the tools they need to start and manage conversations about palliative care.

In addition, NINR works in partnership with other NIH ICs to enhance knowledge of the benefits of palliative care across different illnesses, contexts, settings, populations, and the life span. For instance, NINR and the National Cancer Institute (NCI) launched an initiative to increase understanding of palliative care in advanced rare diseases. Also, NINR, along with NCI, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the Office of Research on Women's Health, lead an initiative to encourage research on the unique needs and wishes of adolescents and young adults with serious, life-threatening illness. Another
initiative, involving several NIH ICs, focuses on increasing research on palliative care in older adults across a variety of healthcare and community settings, such as hospitals, doctor’s offices, patients’ homes, assisted living facilities, nursing homes, and hospice.

These are just a few examples of the collaborative efforts underway across NIH to expand palliative care research. Moving forward, NIH will continue to undertake comprehensive efforts to advance palliative care science to improve quality of life for individuals with serious or life-threatening illness, and their family members and caregivers. These efforts could encompass a broad range of illnesses and conditions, such as cancer; heart, kidney, liver, lung, and infectious diseases; as well as neurodegenerative diseases such as dementia, Parkinson’s disease, and amyotrophic lateral sclerosis
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 combating other forms of cancer, the 5-year survival rate for pancreatic cancer is just nine 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 requests an update on pancreatic cancer research in the fiscal year 2020 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. 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 research.

Through the Early Detection Research Network (EDRN) and the Pancreatic Cancer Detection Consortium, NCI supports multi-disciplinary research to improve detection and diagnosis of cancer and to test new molecular and imaging biomarkers that may be useful in the early detection and treatment of pancreatic cancer, respectively. In addition, NCI supports three pancreatic cancer Specialized Programs of Research Excellence (SPOREs), and one of four gastrointestinal (GI) cancer SPOREs includes pancreatic cancer. The pancreatic and GI SPORE teams collaborate to develop screening protocols and to investigate novel targets, drugs, vaccines, and strategies to benefit pancreatic cancer patients. For example, an NCI-supported research team from EDRN and several SPOREs has developed a new blood test (liquid biopsy) called CancerSEEK, which is a non-invasive test to detect eight common cancer types, including pancreatic cancer. CancerSEEK can identify the presence of cancer at an early stage and determine the organ of origin. It was originally tested in people known to have one of the eight cancers and is currently being evaluated in a large study of healthy volunteers to determine whether the test will be as effective in identifying new cases of cancer.

To investigate the etiology of pancreatic cancer and identify risk factors for PDAC development, multiple investigators supported by the NCI Pancreatic Cancer Cohort and the Pancreatic Cancer Case-Control (PANC4) Consortium collaborated with other researchers to conduct the largest pancreatic cancer genome study to date. This study identified five new regions of the genome that are associated with pancreatic cancer risk.

Because a better understanding of the role of diabetes in the development of PDAC is needed, NCI has partnered with the National Institute of Diabetes and Digestive and Kidney Diseases.

220 https://prevention.cancer.gov/major-programs/early-detection-research
221 https://prevention.cancer.gov/major-programs/pancreatic-cancer-detection
222 https://trp.cancer.gov/spores/pancreatic.htm
223 https://projectreporter.nih.gov/project_info_description.cfm?aid=9569170
225 https://epi.grants.cancer.gov/PanScan/, http://panc4.org
(NIDDK) to support the New Onset Diabetes Cohort for the Diagnosis of Pancreatic Cancer. NCI plans to accrue a cohort of 10,000 newly diagnosed diabetes patients in concert with the Pancreatic Cancer Action Network (PanCAN). Blood samples will be collected to establish probability of developing pancreatic cancer, and a biobank of annotated specimens will be collected for validation of emerging early detection tests.

In 2017, NCI established the PDAC Translational Studies on the Tumor Microenvironment Consortium to study the interaction between pancreatic tumors and their microenvironment. NCI, through the Cancer Moonshot Initiative, funded four multi-disciplinary research teams to understand the role of the immune system in PDAC development and to develop new effective treatments by enhancing the immune response against pancreatic cancers.

New approaches are needed to improve treatment and quality of life of pancreatic cancer patients. NCI supports research to develop novel models and identify biomarkers to predict treatment response. For example, a study, supported in part by the NCI Human Cancer Models Initiative, showed that patient-derived organoid models could be useful in predicting treatment response. Other NCI-funded researchers identified a new biomarker, called angiogenin, which could be useful in predicting the response of PDAC patients to treatments used to target the epidermal growth factor receptor. Through the RAS Synthetic Lethal Network, part of the RAS Initiative, NCI is supporting novel research to test drug combinations in RAS mutated pancreatic cancers.

NCI supports numerous clinical trials to identify effective treatments for pancreatic cancer. Clinicians at the NIH Clinical Center are recruiting pancreatic cancer patients to evaluate the combination of a new immunotherapy drug (M7824) and chemotherapy. A phase II clinical trial is recruiting patients to investigate the drug selumetinib for patients with advanced pancreatic cancer whose tumors harbor a specific genetic marker in the RAS family. This trial is a collaborative, multi-institutional effort, with 11 Cancer Centers participating. In addition to providing experimental therapy, clinicians will screen participants for the presence of more than 50 cancer-associated genes to identify pancreatic cancer biomarkers and novel drug targets.

---

228 https://projectreporter.nih.gov/project_info_description.cfm?aid=9449550
229 https://projectreporter.nih.gov/project_info_description.cfm?aid=9449587
230 https://projectreporter.nih.gov/project_info_description.cfm?aid=9450411
231 https://projectreporter.nih.gov/project_info_description.cfm?aid=9457862
234 https://projectreporter.nih.gov/project_info_description.cfm?aid=9513499
235 https://clinicaltrials.gov/ct2/show/NCT03451773
236 https://clinicaltrials.gov/ct2/show/NCT03040986
Parkinson's Disease
The Committee commends NINDS for taking critical steps in identifying priority research recommendations to advance research on Parkinson's disease, which impacts between 500,000 and 1,500,000 Americans and is the second most prevalent neurodegenerative disease in the United States. The ultimate success of these recommendations will depend upon targeted research initiatives and increased research capacity, even if innovative support and funding mechanisms are required. The Committee recognizes that NINDS is prioritizing public health concerns with severe gaps in unmet medical needs and believes any funding increase for NINDS in fiscal year 2019 should support the research recommendations set forth by NINDS planning strategy towards better treatments and, ultimately, a cure for Parkinson's disease. The Committee also encourages NINDS to submit a report of its progress on implementing these recommendations in the fiscal year 2020 CJ.

Action taken or to be taken:

NINDS is using a range of coordinated approaches to encourage and facilitate research projects that address the 31 basic, translational, and clinical Parkinson’s disease (PD) research recommendations from the Parkinson’s Disease 2014: Advancing Research, Improving Lives (PD2014) conference on January 6 -7, 2014.

Investigator-initiated research is a crucial component of the NIH’s efforts to address PD2014 research recommendations. NINDS staff actively encourage researchers to submit investigator-initiated proposals that will address PD2014 recommendations, and NINDS continues to assess whether funded investigator-initiated grants advance the priorities established by the PD2014 recommendations. Investigator-initiated research projects are expanding our knowledge of the genetic and environmental risk factors for PD, bridging the gap between molecular clues of PD pathology and mechanisms of disease process, developing better animal and cell models for PD, and characterizing the brain circuits involved in PD and how deep brain stimulation affects those circuits. Other projects aim to develop methods to diagnose PD before motor symptoms occur, to improve technologies to measure PD pathology, and to test interventions to prevent, slow, or stop PD.

NIH has also leveraged established programs and resources and developed new initiatives to coordinate these larger projects. Recent Funding Opportunity Announcements for the NINDS Morris K. Udall Centers of Excellence for Parkinson’s Disease Research program encourage applicants to address the PD2014 recommendations in their research proposals. The NINDS PD Biomarkers Program (PDBP) has developed data management, clinical, and biospecimen resources that are essential tools for implementing many of the PD2014 recommendations. As part of this program, NINDS is also soliciting new projects focused on discovering novel biomarkers for PD and related diseases, which was a key component of several PD2014 recommendations. In January 2018, NIH launched the NIH Accelerating Medicines Partnership for Parkinson's Disease (AMP PD) to provide the expertise and support needed to determine which biomarkers show the greatest potential for predicting PD and the progression of the disease. This public-private partnership will leverage 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. The NIH BRAIN Initiative is funding the development of new tools and technologies to study and
therapeutically modulate brain circuit activity, potentially leading to improved deep brain stimulation technology and safer and more effective deep brain stimulation therapy for PD. Newly available Alzheimer’s disease and Alzheimer’s disease-related dementias (AD/ADRD) funds are being used to expand the NINDS PDBP to Lewy body dementias (LBDs) such as PD dementia, to employ cutting edge tools to study the structure of proteins associated with LBD and PD, and to study the molecular signatures of LBD and other ADRDs at the level of single cells.
Pediatric Kidney Disease

The Committee is encouraged by the research funded by NIDDK on pediatric kidney disease. However, the Committee continues to urge the NIDDK to plan and work toward multicenter clinical trials and translational studies that will focus on the unique needs of children with kidney disease. Pediatric patients and the entire pediatric nephrology community have benefited extensively from the previous two large pediatric focused clinical studies, RIVUR and CKiD. These studies not only addressed important clinical questions but also established large biorepositories and databases, which can be used by the research community to gain important additional knowledge from the study populations. The Committee also encourages NIDDK to fund research aimed at establishing new prognostic indicators such as genomics and personalized medicine, novel diagnostics, and therapeutics that may help further understanding in pediatric kidney disease that may also lead to breakthroughs and applications in adult kidney disease. The Committee requests that NIDDK report back in the fiscal year 2020 Congressional Justification on the progress made towards additional pediatric focused clinical studies.

Action taken or to be taken:

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 has been renewed to continue investigation into growth, neurocognitive function, early evidence of cardiovascular disease, and progression of chronic kidney disease (CKD) to transplantation and dialysis in children with congenital and acquired kidney disease. The CKiD study will be extended to follow the cohort into young adulthood where they represent a unique group with different needs and outcomes compared to those with adult-onset kidney disease. The CKiD study continues to refine the newest and most reliable measures of kidney function and outcomes of kidney disease in children.

NIDDK will continue to support research investigating childhood glomerular disease, a condition in which kidney function is impaired due to injury to glomeruli, the fundamental filtering units of the kidney that keep blood cells and larger molecules, such as proteins, in the blood while allowing wastes and excess fluid to pass through. The Cure Glomerulopathy Network (CureGN) consortium is a multi-site, prospective observational research network of children and adults; it has expanded to include ancillary studies which will help inform new diagnostic and treatment strategies. One of the main recruitment centers for CureGN is the MidWest Pediatric Nephrology Consortium, assuring robust pediatric participation. The Nephrotic Syndrome Study Network (NEPTUNE), a multidisciplinary, multicenter collaborative research network that complements CureGN, 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. Both of these NIDDK-funded efforts will benefit children with kidney disease.

Recognizing the unique needs of children to learn to assume responsibility for their chronic disease as they transition into adulthood, the NIDDK funds research in medication adherence in pediatric and adolescent patients with chronic kidney disease and kidney transplants.
Along with the research networks and studies described above, NIDDK continues to nurture and guide 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. These initiatives and projects will yield insights to lay the groundwork for pediatric-focused clinical trials in kidney disease. 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.
Peripheral Neuropathies

The Committee is pleased at the continued progress of ongoing research into Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, and related conditions. The Committee encourages NINDS to work with NIAID and stakeholders on a state of the science conference on evolving research and scientific mechanisms.

Action taken or to be taken:

The National Institute of Neurological Disorders and Stroke (NINDS) supports a broad array of research aimed at understanding and treating Guillain-Barre Syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP), and related inflammatory peripheral neuropathies. In people with GBS and CIDP, the body’s immune system attacks peripheral nerves, damaging the nerve cells or the fatty covering (myelin) that insulates and protects them. This damage diminishes the nerve’s ability to conduct electrical signals, resulting in weakness, numbness, tingling sensations or even paralysis. NINDS-funded researchers are investigating the mechanisms by which the body’s immune system starts attacking peripheral nerves and are studying the molecular factors that mediate axon repair after inflammatory injury with the goal of developing new treatments for these diseases.

Despite progress, more research is needed in these disease areas, and more researchers need to be encouraged to engage in GBS and CIDP research. NINDS is currently in discussions with outside stakeholders regarding a research conference that would examine the state of the science for GBS and CIDP research and would include scientists from related research fields with the hope of identifying key research obstacles and potential strategies for overcoming them.
Phelan-McDermid Syndrome
The Committee continues to support a multi-Institute approach to support research into Phelan-McDermid Syndrome and encourages NIH to continue to examine the correlation between SHANK3 and neurological diseases and the mental health manifestations of Phelan-McDermid Syndrome. The Committee requests an update in the fiscal year 2020 CJ on the status of research related to this topic.

Action taken or to be taken:

The National Institute of Neurological Disorders and Stroke (NINDS) joins the National Institute of Mental Health (NIMH) and other Institutes in supporting research on the basic science of how mutation of the SHANK3 gene leads to Phelan-McDermid Syndrome (PMS) and other neurodevelopmental disorders. For example, both NINDS and NIMH fund projects using neurons derived from the stem cells of PMS patients to investigate the role of SHANK3 mutations in the development of autism, intellectual disability, and epilepsy in PMS. NIMH also recently funded a research center that will compare alterations of neuronal connectivity caused by the loss of SHANK3 and other ASD mutations, using three different experimental paradigms. A common goal of these basic research projects is to guide the discovery of novel therapeutic targets by revealing the cell signaling pathways that underlie PMS.

NINDS, NIMH, and other Institutes also support activities aimed at better understanding the developmental time course and heterogeneity of PMS. For example, NINDS, NIMH, and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) support the National Center for Advancing Translational Sciences (NCATS)-sponsored Rare Disease Clinical Research Network Study, mapping the genotype, phenotype, and natural history of PMS, as part of the Developmental Synaptopathies Consortium. This Consortium is also conducting research on other genetic disorders that share strong associations with autism and epilepsy, with the goal of identifying shared biological pathways and more versatile treatment strategies. Another project funded by NINDS, NIMH, and NICHD is using mouse models of autism, including SHANK3 mutant mice, to guide future treatments of PMS and other autism-related disorders by identifying the critical brain regions and time windows in which these disorders emerge. An NINDS-funded study of children with PMS is searching for patterns of electrical brain activity that can be used as biomarkers to identify those children who will go on to develop autism, in turn enabling earlier therapeutic intervention. Finally, NINDS led a workshop in December 2017 on biomarker development for neurodevelopmental disorders including PMS, bringing together leading researchers from academia and industry, federal agency representatives, and patient advocacy groups to develop recommendations for future research in this area.

NINDS will continue to partner with other Institutes in supporting meritorious research focused on enhancing our fundamental understanding of how SHANK3 gene mutations affect brain development and function, with the ultimate goal to improve the outcomes for individuals with PMS.
Population Research
The NICHD Population Dynamics Branch fosters scientific understanding of changes in human health and development at the population level by supporting research and research training in demographic or population research. Through the Population Dynamics Centers Research Infrastructure Program, the Branch promotes the development of young scientists, efficient use of scientific resources, development of new scientific methods, and identification and response to emerging public health crises, such as the increased incidence of maternal mortality in parts of the United States. The Committee encourages NICHD to continue its commitment to this program as well as other population research activities, including support for longitudinal studies and efforts to advance data sharing, all of which promote an understanding of how the demography and health of our Nation are fundamentally intertwined.

Action taken or to be taken

The Eunice Kennedy Shriver National Institute on Child Health and Human Development (NICHD) continues to fund major, longitudinal studies that provide the underpinnings of much of what we know about family health and well-being. Included among these are the Child Development Supplement of the Panel Study of Income Dynamics (PSID), the Indian Health and Development Survey, the National Longitudinal Survey of Youth 1979 (NLSY79), the Fragile Families and Wellbeing Study, and the National Longitudinal Study of Adolescent to Adult Health (Add Health)—as well as the population-representative National Survey of Family Growth. The data from these projects has produced major scientific breakthroughs over the past year. In addition, NICHD’s Population Research Infrastructure Program continues to be highly competitive, currently supporting 20 research centers around the country. One recent research finding demonstrated that the expansion of Medicaid eligibility in the 1980s to low-income pregnant women and their children in the first year of life increased the likelihood that, by young adulthood, these children’s economic status surpassed their parents.

For example, recent research results linked the social and behavioral health of parents to the health of children. Adverse childhood experiences (ACEs) are stressful and potentially traumatic events that occur during childhood. Using multi-generational data from the PSID, NICHD-supported researchers demonstrated that parents exposed to high levels of ACES in their own childhood were more likely to have children with behavioral problems. Other researchers examining the long-term effects of Hurricane Katrina found that more than 12 years later, some displaced survivors proved to be more resilient than others; those who were re-housed quickly recovered at a higher rate.

Population dynamics studies may also shed light on health outcomes for our most vulnerable populations. This year, a NICHD-supported study provided new evidence that pregnant women’s exposure to air pollution is associated with adverse pregnancy outcomes. Using pollutant monitoring data and birth records, these researchers found that exposure to pollutants during weeks 3-6 of pregnancy is associated with an increase in the probability that the infant may be born with a cleft palate defect. Another study found that black and Hispanic infants who
were born very preterm are more likely to be born at hospitals that have higher neonatal morbidity-mortality rates; these differences in hospitals may be contributing to the disproportionate morbidity and mortality among these infants.

Additionally, population research has addressed the urgent public health issue of around opioid use disorder and the epidemic of drug fatalities. Researchers found that drug-related mortality was higher in counties that had high levels of economic distress, family distress, and high economic dependence on mining. Drug-related mortality was found to be lower in counties that had a high density of religious establishments, high levels of recent in-migration, and high levels of employment in the public sector. The availability of healthcare did not contribute to county differences in drug-related mortality rates.
Population Research
The Committee applauds NIA for including the population sciences in its Alzheimer’s disease research portfolio. Specifically, the Committee is pleased to learn that NIA is collecting nationally representative data via the Health and Retirement Study to measure cognitive function, which will inform our understanding of national trends and differences. In addition to enhancing data collection, NIA is commended for developing a dementia care research agenda and adding an Alzheimer’s disease research component as part of the Roybal Centers of Translation Research in Behavioral and Social Sciences of Aging, Resource Centers for Minority Aging Research, and Demography and Economics of Aging Centers program. The Committee urges NIA to sustain these activities while also encouraging more research from the field related to the underlying causes of regional health disparities, including differences in U.S. adult mortality rates.

Action taken or to be taken:

NIA-supported investigators first fielded the Health and Retirement Study Harmonized Cognitive Assessment Protocol (HRS HCAP) in 2016 in order to provide the research community with new and richer data to study the prevalence, predictors, and outcomes of cognitive impairment and dementia. These investigators recently received funding to field the HCAP as part of the 2020 HRS data collection. We anticipate the HCAP 2020 follow-up study will provide extensive new data to better assess trajectories of cognitive decline among older U.S. adults, including the incidence of new cognitive impairment and dementia. These data will also provide an unprecedented opportunity to better understand trends in the incidence and prevalence of dementia in the United States and around the world.

In FY 2018, NIA solicited applications for new Edward R. Roybal Centers for Translational Research on Dementia Care Provider Support. Roybal Centers conduct preliminary research to develop behavioral interventions, programs, or practices that promote healthy aging; the new Dementia Care Centers will focus on interventions that improve the health, well-being and/or capacity of individuals and/or systems that provide care to persons with Alzheimer’s disease and related dementias (AD/ADRD). The new Centers will be established in 2019.

NIA also solicited applications for Alzheimer’s Disease-focused Resource Centers for Minority Aging Research (RCMARs) in FY 2018. RCMARs focus on increasing the number of researchers from underrepresented groups who study AD/ADRD and developing infrastructure to promote advances in this area and increase the number of researchers focused on AD/ADRD minority elders. Seven Centers have been funded. We also expect to increase attention to the fields of demography and economics of aging and recruit new researchers into the field with new ADRD-focused Demography and Economics of Aging Centers, the establishment of which reflects recommendations from the October 2017 Dementia Care Summit to increase research efforts on the impact of health care organizations and health care financing policies on outcomes for persons with dementia and on inequality in access and quality of care. These new Centers will be active beginning in FY 2020.
The existing Demography and Economics of Aging Centers are also investigating underlying causes of regional health disparities. Other studies are seeking explanations—including education, employment opportunities, inequality, health behaviors, and health care—for increased rates of premature death, including “deaths of despair,” among certain populations. Still others are focusing on the roles of health behaviors and behavioral risk factors, health care access and quality, and domestic and international migration in geographic variations in mortality, and investigating the biological underpinnings of socioeconomic status.
Post-Traumatic Stress Disorder
The Committee supports NIMH's efforts to support a diverse portfolio of research on post-traumatic stress conditions, including research to identify risk and protective factors, develop and test interventions, and implement models for delivering care across settings. The Committee encourages NIMH to continue to support the Aurora study, a comprehensive 5-year study of mental health outcomes following trauma exposure to understand how mental illnesses like PTSD develop to understand modifiable factors that may be targets of new treatments. This and similar efforts have the potential to greatly impact care for individuals with and at-risk for PTSD.

Action taken or to be taken:

NIMH is the lead federal agency for research on mental disorders and supports a diverse research portfolio on post-traumatic stress disorder (PTSD). The NIMH Traumatic Stress Research Program currently supports over 120 research projects. The program encompasses research spanning and integrating basic science, clinical practice, and health care system factors regarding mass trauma and violence (e.g., war, terrorism, natural and technological disaster). The portfolio includes translational (basic, clinical, and genomic) research on the mental health consequences of traumatic stress to elucidate the nature, causes, and pathophysiology of posttraumatic psychopathology; the development and testing of interventions to assist victims and survivors at risk for and experiencing posttraumatic psychopathology; and models for delivering care effectively and efficiently across settings, contexts, and populations.

NIMH specifically continues to support the Aurora study, a longitudinal assessment of post-traumatic syndromes engaging 5,000 individuals who arrive in emergency departments after experiencing trauma. In this study, researchers are acquiring data on the emergence and course of diverse post-traumatic clinical phenomena to enhance early prediction and classification of conditions, as well as to identify targets for prevention. Further, NIMH-funded researchers recently identified brain changes in response to effective treatment for PTSD and are working on establishing biomarkers for early diagnosis and treatment.

To address the mental health needs of active duty, National Guard, and Reserve service personnel, veterans, and their families, NIMH works with the Department of Defense (DoD), the Veterans Administration (VA), and academic clinicians and researchers. These efforts aim to accelerate progress on the treatment and prevention of PTSD by developing highly predictive sets of risk indicators that may help identify trauma survivors at highest risk for developing PTSD, and may also help identify biological mechanisms and novel treatment targets.

NIMH also partners with the DoD, the VA, and other NIH Institutes and Centers to implement the interagency National Research Action Plan (NRAP). With the goal of enhancing prevention, diagnosis, and treatment of PTSD and traumatic brain injury, NRAP aims to implement a set of common data elements for use in research to facilitate comparison across

---

239 www.projectreporter.nih.gov/project_info_description.cfm?aid=9174752
studies, enable meta-analyses across projects, and avail smaller projects of larger datasets for more powerful analyses. NIMH will continue to support research opportunities in the area of post-traumatic stress conditions, as such research investments have the potential to revolutionize prevention, care, and treatment for individuals with, or at high risk for, PTSD.
Precision Oncology
The Committee recognizes the potential for significant advancements in cancer treatments from the NCI-MATCH trial. It remains the central pillar of the precision medicine research focused on oncology for cancers that are unresponsive to standard interventions. NCI should also continue to focus on the important pediatric-MATCH trial as pediatric oncology mechanisms are very different from mutations seen in adults. The Committee requests an update in the fiscal year 2020 CJ.

Action taken or to be taken:
Precision oncology continues to propel medicine toward the goal of treating patients with therapies targeted to the genetic/molecular features of their cancers. While the National Cancer Institute (NCI) supports a diverse research portfolio in precision oncology, the NCI-MATCH and Pediatric MATCH trials remain cornerstones of NCI’s Precision Medicine Initiative. Both NCI-MATCH and Pediatric MATCH are phase 2 trials open to patients for whom standard treatments failed or who have a rare cancer for which no standard treatment exists. Patients who enter the trials first undergo genomic sequencing/screening of their tumors. Those who have a genetic abnormality that matches one of the therapeutic agents available in the trial are then enrolled in a treatment arm.

Launched in 2016, the NCI-MATCH trial is open to adults with solid tumors, lymphomas, and myelomas. Notably, among the first 6,000 patients enrolled for screening, more than 60 percent had tumors other than the four most common cancer types (i.e., breast, colorectal, non-small cell lung, and prostate cancers), providing more research opportunities for less common and rare tumors. As of August 2018, 821 patients have been enrolled in a treatment arm. Almost half of the 39 treatment arms have already reached their enrollment goal of at least 35 patients. Currently, 18 arms are enrolling patients, and four new arms are in development. More than 1,100 institutions across the United States have enrolled patients for screening, representing all 50 states, the District of Columbia, and Puerto Rico.

The NCI-MATCH trial met and exceeded its screening goal of 6,000 patients in 2017. However, some of the treatment arms had not reached their accrual goal because the tumor gene variant is very rare. Continuing to accrue to these treatment arms is a high priority. In NCI-MATCH, 13 genomic testing laboratories around the country are identifying patients at participating trial sites. Tumor testing by one of these labs is now the only pathway for new patients to enroll in the trial.

To date, four treatment arms have released preliminary findings. These early results included evidence of promising activity for the immunotherapy drug, nivolumab, in patients with a loss of mismatch repair proteins in tumors other than colorectal cancer, e.g., endometrial, prostate, and breast cancer.

In recognition that childhood cancers are genetically distinct from adult cancers, NCI, through the Children’s Oncology Group (COG), launched the Pediatric MATCH trial in July 2017.

242 www.jitc.biomedcentral.com/track/pdf/10.1186/s40425-017-0297-3
Structured like its adult counterpart, the goal of the trial is to screen at least 1,000 children and adolescents 1-21 years of age who have refractory or recurrent solid tumors. The aim of Pediatric MATCH is to determine whether identifying genetic changes in a patient’s tumor and using an agent to target the specific genetic changes will result the tumor shrinking in size. Currently, nine treatment arms are open to accrual, with four more in various stages of development that will open over the next year. At least 20 patients may be enrolled on each treatment arm. Since the study opened, close to 300 children and adolescents have been enrolled for screening. The Pediatric MATCH Trial is accessible at approximately 200 COG sites across the country, where the majority of pediatric cancer patients receive treatment.
Prenatal Opioid Use Disorders and Neonatal Abstinence Syndrome

The Committee recognizes the growing burden of NAS and the health care costs associated with it. The Committee is aware of the need for more information regarding long-term health and developmental outcomes related to NAS, the wide variation in clinical practice and health systems support, as well as the challenges associated with post-discharge care. The Committee encourages NIH to coordinate with other agencies at HHS to support additional research on prevention, identification, and treatment of prenatal opioid exposure and NAS, including the best methods for screening and treating pregnant women for opioid use disorder and the best methods for screening for NAS. Additionally, the Committee encourages NIH to build on the ACT NOW study to enhance understanding of the impact of pharmacological and non-pharmacological treatment techniques on costs and outcomes in the short- and long-term. The Committee further encourages NIH to coordinate with other agencies at HHS to support research on innovative care models to optimize care and long-term outcomes for families.

Action taken or to be taken:

According to the Centers for Disease Control and Prevention, national rates of opioid use disorder at time of delivery more than quadrupled from 1999 to 2014. Newborns who are exposed prenatally to opioids are at risk for withdrawal symptoms after birth. Symptoms of Neonatal Opioid Withdrawal syndrome (NOWs - also called Neonatal Abstinence Syndrome) often include tremors, excessive crying and irritability, and problems sleeping, feeding, and breathing. Although NOWs is known to increase the risk for neurodevelopmental problems as infants grow older, little is known about its long-term effects. No standard evidence-based treatment for NOWs currently exists in the United States, even though the number of reported cases is far higher than in recent years.

To lay the groundwork for this emerging public health issue, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) conducted a workshop in April 2016 to evaluate opioid use in pregnancy and health and developmental outcomes for children who had been prenatally exposed to opioids and experienced NOWs. Experts identified research gaps and opportunities to improve outcomes for families; these findings were subsequently published in Obstetrics and Gynecology in 2017. They agreed that routine screening for substance use, including misuse of prescription opioids, should be provided to all women throughout pregnancy, and that reducing unnecessary opioid use in healthy women after delivery is an important goal for preventing future opioid misuse. The primary recommendation called for more research to determine best practices for screening and treating pregnant women for opioid use disorder and to understand additional problems, such as poor nutrition and mental illness, which can accompany opioid use disorder in pregnancy.

In 2017, NICHD and the National Institute of Drug Abuse (NIDA) issued a funding opportunity announcement (RFA-HD-18-036) seeking projects related to the following topics:

---

244 https://www.cdc.gov/mmwr/volumes/67/wr/mm6731a1.htm?s_cid=mm6731a1_x
Clinical studies of medically supervised opioid withdrawal that evaluate potential outcomes such as maternal complications, fetal complications, pregnancy loss, and neonatal opioid withdrawal syndrome.

Pharmacokinetic and pharmacodynamic studies to optimize management of medications used to treat opioid use disorder in pregnant and/or postpartum women.

Observational or cohort studies evaluating the effects of medication-assisted opioid cessation (such as methadone) on maternal, fetal, and neonatal outcomes.

Studies of genetic and/or epigenetic factors associated with the effects of opioid use during pregnancy on fetal and neonatal outcomes.

To address this gap in care, the Advancing Clinical Trials in Neonatal Opioid Withdrawal syndrome (ACT NOW) program, launched in 2017, aims to inform clinical care of infants who are exposed to opioids before birth. ACT NOW is a collaborative effort of two networks supported by the National Institutes of Health (NIH), the NICHD’s Neonatal Research Network, which has more than 30 years of experience designing and implementing clinical trials involving infants, and the NIH Office of the Director’s Environmental influences on Child Health Outcomes (ECHO) Program’s Institutional Development Award (IDeA) States Pediatric Clinical Trials Network, which focuses on rural and medically underserved communities, including those reporting a higher incidence of NOWs. ACT NOW pilot studies are assessing the prevalence of NOWs across more than 20 clinical research sites and are surveying current management approaches in preparation for developing research protocols for large-scale studies. Currently, two large studies are under development: a medication weaning study and a non-drug intervention to improve care for newborns with NOWS. Further efforts that will focus on the long-term evaluation of these interventions on the health outcomes of infants with NOWs are being planned.
Pre-Term Birth
Preterm birth affects approximately 380,000 babies each year in the U.S. and is the leading cause of infant mortality. The Committee applauds NICHD’s research portfolio spanning the range of discovery, development, and delivery of science in order to identify the causes of premature birth and infant mortality. The Committee encourages NICHD to continue to provide robust support to extramural preterm birth prevention research, the Maternal-Fetal Medicine Units Network, the Neonatal Research Network, and the intramural research program related to prematurity.

Action taken or to be taken:

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) continues to support a large and diverse research portfolio related to the causes and prevention of prematurity, as well as to decreasing the complications that can be a consequence of preterm deliveries. Preterm birth infants, or those born before 37 weeks of gestation, suffer from significantly increased risk for neonatal mortality, and long-term pulmonary and neurodevelopmental morbidities. According to the Centers for Disease Control and Prevention, in 2016, about one in 10 infants were born preterm in the United States, with a 50 percent higher incidence for African-American infants.

The NICHD-supported Maternal Fetal Medicine Units (MFMU) Network has a long history of conducting large-scale clinical research studies on the prevention of preterm birth and improved treatments for associated medical problems. Having the ability to enroll large populations of pregnant women in MFMU-supported clinical trials is critical in helping to decipher the factors involved in preterm birth. One possible predictor of preterm birth is cervical length of the pregnant woman. An ongoing MFMU clinical trial is testing whether the use of a cervical pessary in women who have short cervical length will reduce the risk for preterm birth in singleton pregnancies. A second study is assessing whether pessary and/or progesterone treatment may decrease preterm birth in women with a twin gestation and a short cervix.

Several other NICHD-funded studies are aimed at the prevention of preterm births. One study showed that overweight or obese pregnant women, who had no history of chronic disease before pregnancy, were at significant risk of preterm birth compared to normal weight women. Another study of 10,000 nulliparous women (women who had never before given birth), co-funded by the NICHD and the National Heart, Lung, and Blood Institute, showed that sustained low leisure-time physical activity during pregnancy is associated with excess risk of gestational diabetes and overall preterm birth compared to higher patterns of activity. These findings raise the possibility that increases in activity early during pregnancy may be associated with improved pregnancy health. A NICHD-supported randomized controlled trial found that intraventricular hemorrhage, which typically occurs in preterm birth, could be prevented or ameliorated by delayed umbilical cord clamping, alone or in combination with an approved medical therapy.

NICHD-supported investigators have also determined that women with high blood levels of the retinol-binding protein 4 (RBP4) at less than 22 weeks of pregnancy were about eight times more likely than others to develop preterm preeclampsia. The results suggest that measuring RBP4 early in pregnancy may allow clinicians to identify patients at risk for preeclampsia and monitor these at-risk patients more closely.
The NICHD is funding multiple initiatives to better diagnose and understand preterm birth. The “Human Placenta Project” (HPP) aims to better understand the placenta, arguably the least understood human organ and one that greatly influences the health of a woman and fetus during pregnancy. One goal of the HPP is to identify non-invasive biomarkers for prediction of adverse pregnancy outcomes, including preterm birth. The NICHD's newly launched PregSource® project uses a crowd-sourcing approach to learn about typical pregnancies, asking pregnant women who wish to participate to enter information regularly throughout gestation and the early infancy of their babies into online surveys and trackers via a website. A large resource library that includes evidence-based information about pregnancy management, issues, and complications are available to participants.
Prostate Cancer
The Committee is concerned that prostate cancer lacks treatments for men with advancing
disease as well as adequate diagnostic and imaging methodologies common in other hormone-
driven cancers with similar disease burden. In order to ensure Federal resources are leveraged to
the greatest extent possible, the Committee encourages NCI to coordinate its response to these
needs with other Federal agencies, including the Department of Defense, as well as private
research foundations and advocacy groups.

Action taken or to be taken:
Research on the diagnosis, treatment, and prevention of prostate cancer remains a priority for
NCI. The institute coordinates and collaborates across NIH, as well as with other Federal
agencies, private research organizations, and advocacy groups.

In July of 2018, NCI launched the RESPOND study, or Research on Prostate Cancer in Men of
African Ancestry: Defining the Roles of Genetics, Tumor Markers, and Social Stress. This
$26.5 million study is the largest coordinated research effort to study biological and
nonbiological factors associated with aggressive prostate cancer in African-American men, who
disproportionately experience aggressive disease compared with men of other racial and ethnic
groups. RESPOND is supported by NCI, the National Institute on Minority Health and Health
Disparities, and the Prostate Cancer Foundation, a philanthropic organization dedicated to
funding and accelerating prostate cancer research. NCI’s support is provided through the Cancer
MoonshotSM.

The partnership between NCI and the Center for Prostate Disease Research (CPDR) at the
Walter Reed National Military Medical Center, a Department of Defense (DoD) research center,
remains vital to advancing prostate cancer research. NCI experts coordinate and collaborate
with their DoD scientific colleagues by serving as peer reviewers for the DoD Congressionally
Directed Medical Research Program (CDMRP) Prostate Cancer Research Program and on the
CDMRP Prostate Cancer Programmatic Panel. Similarly, DoD colleagues serve as peer
reviewers for NCI research proposals. Patient advocates also participate in reviews of research
proposals and serve on advisory committees such as NCI’s Council of Research Advocates, the
NCI National Clinical Trials Network’s Genitourinary (GU) Cancers Steering Committee, and
the GU Steering Committee’s Prostate Task Force. These collaborative efforts provide important
opportunities for both federal scientific colleagues and the cancer research advocacy community
to share expertise and experience for the benefit of NCI’s cancer research portfolio.

In February of 2018, the Food and Drug Administration approved the targeted drug apalutamide
for the treatment of nonmetastatic prostate cancer that is resistant to hormonal therapy.
Importantly, funding from the NCI and DOD supported the initial development and early clinical
testing of this drug.

Additionally, NCI supports a robust portfolio of intramural and extramural research programs
that are aimed at better preventing, detecting, and treating prostate cancer. This research allows
NCI to advance prostate cancer research more effectively with its partners. In the area of

improving prostate cancer imaging and diagnosis, for example, an interdisciplinary team of NCI scientists pioneered the use of magnetic resonance imaging (MRI) combined with transrectal ultrasound imaging to enhance the precision of prostate biopsies and continues to refine the application of this method. One goal is to reduce the biopsy rate for men who ultimately are found to have benign or low-grade tumors which may not need treatment, thereby sparing them from the potential complications of a prostate biopsy. In 2018, this NCI team and their extramural colleagues reported the development of an MRI-based risk prediction model capable of reducing the number of unnecessary biopsies by more than a third while still detecting nearly 90% of cancers that need treatment.249 NCI also supports a wide range of research programs aimed at developing new interventions for the treatment and prevention of prostate cancer, including research carried out by nine prostate cancer Specialized Programs of Research Excellence (SPOREs) located across the country.250 These SPOREs are highly collaborative translational research teams, sharing resources and conducting inter-institutional clinical studies. The SPOREs in prostate cancer play a central role in advancing translational cancer research with academia, industry, other government agencies, and the international research community.

250 https://trp.cancer.gov/spores/prostate.htm
Pediatric Rare Cancer
After accidents, cancer is the second leading cause of death in children ages one to fourteen. In 2018 alone, cancer will affect over 15,000 children and adolescents, and most of those diagnoses will be for rare forms which lack therapeutic options. While children face dozens of cancers, only one pediatric-specific cancer has a targeted therapeutic. Moreover, children with cancer can suffer more severe side effects from aggressive treatments than adult patients. The Committee strongly encourages NIH to expand funding for research that may contribute to the development of new treatments for pediatric rare cancers.

Action taken or to be taken:

NCI supports a comprehensive portfolio of pediatric cancer research that spans from understanding the mechanisms of tumor formation to developing more effective and less toxic treatments for children with cancer and improving cancer survivorship. NCI remains committed to continuing to address the unique scientific challenges posed by pediatric cancers.

A very brief overview of NCI’s pediatric cancer research efforts is outlined below. For additional information on NCI’s pediatric cancer research portfolio, please also refer to the Significant Items on the Children's Oncology Group (COG), the Childhood Cancer Star Act, the Office of Cancer Survivorship, and Collaboration Between Agencies Regarding Pediatric Investigation of Appropriate New Drugs. Also, NCI prepared reports on pediatric cancer research and transmitted them to the Appropriations Committees in FY17 and FY18; these reports provide in depth information on many of the programs named below.

NCI conducts and supports pediatric cancer research through investigator-initiated research, consortia/networks, and programs. These include COG, the Pediatric Brain Tumor Consortium, the Pediatric Preclinical Testing Consortium, the NCI Human Genetics Program, the intramural Pediatric Oncology Branch, and the Pediatric Provocative Questions Initiative. Also, in 2018, through the Cancer Moonshot™ Initiative, NCI funded two new initiatives exclusively devoted to pediatric cancer research and several others that include pediatric cancer research. The Pediatric Immunotherapy Discovery and Development Network and the Fusion Oncoproteins in Childhood Cancers Consortium are focused on deepening our knowledge of the biology of and developing novel treatments for pediatric cancers. In addition, the Rare Tumor Patient Engagement Network will leverage the unique resources of the NIH Clinical Center and bring together national and international investigators, patients, advocacy groups and industry to comprehensively study rare tumors and provide exceptional patient care. The Human Tumor Atlas Network will construct detailed maps, or atlases, of various components of tumors over time for specific pediatric and adult cancers.

Clinical trials are also an important component of NCI’s pediatric cancer research portfolio. The NCI sponsors pediatric clinical trials in collaboration with COG, at the NIH Clinical Center, and through other mechanisms. The NCI-COG Pediatric MATCH Trial, opened in 2017, continues to enroll patients. Since the study opened, close to 300 children and adolescents have been enrolled for screening and 9 treatment arms are open.
Long term, NCI hopes to use the data generated from all pediatric cancer research to identify children and adolescents at risk for developing cancer, detect cancer at the earliest possible stage or prevent its development altogether, develop more effective and less toxic treatments, and improve survivorship outcomes and quality of life.
Psycho-Social Distress Complications
According to the Institute of Medicine, nearly 50 percent of all cancer patients experience distress. Further, studies suggest that distress in cancer patients leads to higher healthcare costs, less compliance with treatment pathways, and poorer health outcomes. While significant advancements have been made in biomedical treatments in cancer care, the Committee is concerned that the unaddressed psycho-social needs of patients are adversely impacting the effectiveness and cost of care, as well as the individuals’ overall well-being. The Committee encourages NCI to continue to implement distress screenings in the NIH Clinical Center and in NCI-funded clinical trials as appropriate, coordinate and share information on this effort with the FDA, and to support the development of appropriate interventions through the support of extramural grantees, including by encouraging extramural grantees to implement such screenings.

Action taken or to be taken:
NCI is committed to encouraging the use of distress screenings in clinical trials, supporting research to identify the best methods of providing support to individuals affected by cancer, and promoting known best practices among cancer care providers. NCI supports the implementation of psychosocial distress screening in both its intramural and extramural programs. NCI also collaborates extensively with the FDA in regard to clinical trial design across intramural and extramural clinical research efforts—these collaborations span various aspects of trial design and data collection and include information about relevant distress screening research efforts as appropriate.

Patients who receive treatment at the NIH Clinical Center may be recommended for distress screening through the Pain and Palliative Care Consultation Service, an NIH-wide program that provides skilled management of symptoms from the burden of disease and treatments. In addition, the Psychosocial Support and Research Program provides comprehensive care and support services to pediatric patients on intramural clinical trials. The program also conducts research on how to best support pediatric patients and their families. For example, current projects include the development and validation of an electronic psychosocial distress screening measure.251

NCI’s research on psychosocial care is informed by the Symptom Management and Health-Related Quality of Life Steering Committee, established in 2006.252 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. The committee’s most recent set of strategic priorities, released in 2015, identifies psychosocial distress as a priority area for research. NCORP conducts health-related quality of life studies for patients on treatment trials and delivers cancer prevention, supportive care and symptom management, screening, and surveillance clinical trials to communities throughout the country. To be eligible to become an NCORP site, institutions must demonstrate that they are able to provide distress screening to patients.

NCI also supports extramural research on cancer-related psychosocial distress. The NCI-funded Screening for Psychosocial Distress Program was recently developed to support implementation

---

251 [https://clinicaltrials.gov/ct2/show/NCT02423031](https://clinicaltrials.gov/ct2/show/NCT02423031)
of comprehensive distress screening at institutions. The NCI Distress Measurement Initiative is focused on creating a repository of distress screening tools with user ratings to assist clinicians and researchers in making decisions about measures of distress and to promote data harmonization. NCI is supporting and encouraging the development of additional tools and technologies for cancer-related psychosocial distress and management.

In the setting of pediatric cancer, the Bright IDEAS Problem-Solving Skills Training is a research-tested intervention program that helps mothers of children with cancer reduce emotional distress and improve decision-making about complex medical therapies. Currently available to caregivers at medical centers, investigators are developing an online version to increase access to caregivers directly.

253 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5984040/
255 https://projectreporter.nih.gov/project_info_description.cfm?aid=9272369
258 https://rtips.cancer.gov/rtips/programDetails.do?programId=546012
259 https://clinicaltrials.gov/ct2/show/NCT01711944
Pulmonary Hypertension
The Committee recognizes the work NHLBI is doing to advance research into pulmonary hypertension especially with attention on idiopathic pulmonary arterial hypertension. The Committee encourages NHLBI to continue working with stakeholders to advance critical research priorities.

Action taken or to be taken:

Pulmonary hypertension (PH) is high blood pressure in the arteries that supply blood to the lungs. In PH, these arteries become narrower and can no longer effectively carry blood from the heart to the lungs to pick up oxygen. Early symptoms of this chronic disease include difficulty in breathing and fatigue, and later manifestations include reduced tolerance to exercise, chest pain, palpitations, fainting, and swelling of the ankles or legs. Pulmonary arterial hypertension (PAH) is a particularly insidious and devastating type of PH.

The National Heart, Lung, and Blood Institute (NHLBI) is dedicated to discovering the underlying disease causes and effective treatments for PH and PAH. NHLBI supports research on these disorders at every level from basic biology to diagnosis and treatment. As understanding of PH and PAH improves, NHLBI is working toward moving research efforts away from a one-size-fits-all treatment approach to developing precision medicine approaches targeted to the unique manifestations of PA and PAH in individual patients.

NHLBI has partnered with the Pulmonary Hypertension Association to establish the Pulmonary Vascular Disease Phenomics (PVDOMICS) program to better understand patient differences so more personalized approaches for interventions and/or preventions of PVD can occur. This multi-center program is investigating disease mechanisms that can lead to PH, PAH and other lung diseases. This includes research to identify biomarkers and clinical characteristics that could serve as surrogate outcome measures in future PH clinical trials; if validated, such measures also could be used to develop a refined PH classification to better inform precision therapy. Since its inception, 811 patients have been enrolled in the PVDOMICS program, with a goal to enroll approximately 1,500 patients by September 2019.

NHLBI recently partnered with the Cardiovascular Medical Education and Research Fund to hold a workshop on leveraging scientific opportunities emerging from the PVDOMICS program. Stakeholders, including basic, translational, and clinical investigators; clinicians; patient advocacy organizations; regulatory agencies; and pharmaceutical industry experts, joined to discuss the application of precision medicine to clinical trials on pulmonary vascular disease. A high-priority recommendation from the workshop is to establish a web-based repository of data and biological samples from studies of PH, to be shared and integrated across research sites. The repository could build on existing programs such as PVDOMICS, the Pulmonary Hypertension Breakthrough Initiative, the National Biological Sample and Data Repository for PAH, and the NIH All of Us precision medicine initiative.

---

Additionally, NHLBI continues to support clinical trials to improve understanding and treatment of PH through many of its translational research programs.
Raising Awareness and Engaging the Medical Community in Drug Abuse and Addiction Prevention and Treatment

The Committee notes that education is a critical component of any effort to curb drug use and addiction, and it must target every segment of society, including healthcare providers (doctors, nurses, dentists, and pharmacists), patients, and families. Medical professionals must be in the forefront of efforts to curb the opioid crisis. The Committee continues to be pleased with the NIDAMED initiative, targeting physicians-in-training, including medical students and resident physicians in primary care specialties (e.g., internal medicine, family practice, and pediatrics). The Committee encourages NIDA to continue its efforts in this space, providing physicians and other medical professionals with the tools and skills needed to incorporate drug abuse screening and treatment into their clinical practices. The Committee encourages NIDA and CDC to develop strategies for increasing participation in its online continuing medical education course on safe prescribing for pain and managing patients who abuse prescription opioids. The Committee also encourages NIDA and CDC to develop strategies for increasing participation in its online continuing medical education courses on safe prescribing for pain and managing patients who abuse prescription opioids.

Action taken or to be taken:

The National Institute on Drug Abuse (NIDA) is committed to continuing its efforts to engage the medical community, and intends to continue the NIDAMED initiative, which has been highly effective in this area.

For example, almost a year (11 months) after the NIDAMED Continuing Medical Education/Continuing Education (CME/CE) course “Adolescent Substance Use and RX Misuse Course” went live, 17,418 clinicians have engaged with the course including nurse practitioners, physician assistants, osteopathic physicians, family physicians, addiction medicine specialists and pediatricians. To date, 7,455 clinicians have received a CME/CE certificate for taking the course. The course was built by a coalition of adolescent health providers, with NIDA providing scientific input.

In addition, NIDAMED also facilitated a national partnership between the National Institutes of Health and the American Dental Association on ways to enhance and support dentistry’s role in preventing opioid misuse. NIDA’s Director wrote a blog on the groundbreaking partnership. And a joint article between NIDA and the National Institute of Dental and Craniofacial Research (NIDCR) was published in the August issue of the Journal of the American Dental Association.

As part of NIDA’s continuing support of NIDAMED, a new initiative, “Science to Medicine,” has just been launched to help engage the clinician community in integrating cutting-edge

---

261 www.drugabuse.gov/nidamed/adolescent-substance-use-rx-drug-misuse-cmeces
263 https://jada.ada.org/article/S0002-8177(18)30419-7/fulltext
research into their practice. The first topic in the series addressed how to integrate medication treatment for opioid use disorder into various practice settings. To create the materials, NIDAMED interviewed six clinicians in a variety of practice settings (e.g., a federally qualified health center, primary care, emergency medicine, pediatrics). NIDAMED’s clinician partners, including major health care Associations and other federal partners (e.g., American Osteopathic Association, American Association of Nurse Practitioners, American Association of Physician Assistants, and the Health Resources and Services Administration, among others), are helping to disseminate this series to clinicians nationwide.

NIDAMED will continue to disseminate the Centers for Disease Control and Prevention (CDC) materials on pain and opioids education primarily through the NIDAMED portal\(^\text{265}\). On the Portal, there is a section on “Opioid Prescribing” where NIDAMED links to the CDC Guidelines for Prescribing Opioids for Chronic Pain\(^\text{266}\) including the sections on “Training for Providers”\(^\text{267}\). NIDAMED staff and CDC staff involved in CDC Opioid guideline implementation and education are coordinating their efforts to ensure that the actions of both agencies are synergistic in pursuit of the goal of educating providers about responsible opioid prescribing and managing patients who misuse opioids.


\(^{266}\) [www.cdc.gov/drugoverdose/prescribing/guideline.html](http://www.cdc.gov/drugoverdose/prescribing/guideline.html)

\(^{267}\) [www.cdc.gov/drugoverdose/training/index.html](http://www.cdc.gov/drugoverdose/training/index.html)
Rehabilitation Research

The Committee recognizes the significant challenges faced by patients with neurological impairments who live in rural areas, where access to assistive devices, medical advice, and community resources can be limited. Proper rehabilitation, with the help of patient ‘‘navigators’’, is critical to improving patients’ quality of life and preventing further, and more costly, health problems. The Committee encourages the National Center or Medical Rehabilitation Research to provide greater support for research efforts on assistive health technology, particularly in underserved rural settings.

Action taken or to be taken:

According to a new report from the Centers for Disease Control and Prevention, one in four adults in the United States has a disability and many experience disability-specific disparities in health care access. The National Center for Medical Rehabilitation Research (NCMRR), within the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and other Institutes and Centers at the National Institutes of Health that support rehabilitation research, are actively engaged in the promotion of rehabilitation therapies that reach the person where they live. The NCMRR continues to support assistive technology development, telehealth and e-health approaches, and coordination with patient navigators or care partners to support the use of rehabilitation therapies in the community, especially reaching out to rural areas that may lack the services that may be more readily available in urban and suburban settings.

Often the needs of a person with functional impairment are not limited to rehabilitation, but also include therapies for their mood, sleep, or health needs. NCMRR recently awarded funding for research focused on developing an accessible cognitive behavioral therapy for insomnia that could be delivered via the internet. This adaptation of the gold standard therapy for individuals who have sleep difficulties, particularly tailored to those with multiple sclerosis, could promote access to these therapies by those with limited mobility and those in rural areas.

Another approach to improving delivery of therapy is to encourage involvement of the person’s care partner in their therapy. Therapies originally delivered in the clinic that are enhanced by home use and collaboration between the person with disability and their care partner is critical to advancing and maintaining improvements in function. For example, investigators are exploring the effectiveness of home-based constraint-induced movement therapy for individuals with stroke provided via telehealth and involving the person’s care partner. Testing this combination will verify the effectiveness of the therapy, the delivery method, and the impact of the way the therapy is delivered for the person who is recovering from a stroke.

Finally, health and wellness approaches that encourage exercise and physical activity are sometimes difficult for people to access in their communities. NCMRR recently funded an e-health intervention to expand physical activity and exercise in the home environment for people with a broad range of disabilities. This project also promotes social networking with other individuals with disability to build community and enhance adherence to exercise. The protocol

268 https://www.cdc.gov/mmwr/index.html
will evaluate not only the impact on overall health, but also whether the participants make changes in their social support and interaction with their community.
Research Initiative on Ethnic and Racial Diversity in Cancer

The Committee recognizes that NIH's Cancer Moonshot initiative aims to accelerate the discovery of new ways to cure cancers, including through an understanding and application of cancer genetic information to the prevention and treatment of cancer. The Committee urges NIH to facilitate research on the causes, prevention, and treatment of cancer in populations with diverse cultural, racial, and ethnic composition.

Action taken or to be taken:

Advances in cancer research do not benefit all people equally. As noted by the Committee, the Cancer MoonshotSM provides a unique opportunity for NCI to expand its cancer disparities research portfolio. The Cancer Moonshot Blue Ribbon Panel report highlighted reducing cancer disparities as a cross-cutting theme of all its recommendations. Accordingly, all Cancer Moonshot funding opportunity announcements (FOAs) include language highlighting the need for research in cancer health disparities and where applicable, the research strategies of proposed work must address how data from racially and ethnically populations will be integrated into the studies.

Examples of Cancer Moonshot FOAs that specifically emphasize disparities research include Accelerating Colorectal Cancer Screening and follow-up through Implementation Science (ACCSIS), improving smoking cessation in socioeconomically disadvantaged populations via scalable interventions, and Minority Patient-Derived Xenograft (PDX) Development and Trial Centers (M-PDTCs). ACCSIS will support research to test implementation strategies to substantially improve colorectal cancer screening and follow-up rates in populations where rates remain low, particularly underserved groups, including racial and ethnic minorities and people living in rural or difficult-to-reach areas. In 2018, three awards were made for ACCSIS projects in Illinois, Kentucky, and North Carolina. The Minority PDX Development and Trial Centers will join the larger PDX Research Network and be focused on development and pre-clinical testing of models derived from racial and ethnic minority populations. This is a critical need as the majority of models currently used in discovery science and pre-clinical drug testing are derived from white or Asian individuals. Two minority centers were awarded in 2018.

To promote cancer disparities research in other areas, NCI issued a funding opportunity announcement in 2017 to invite applications for feasibility and planning studies to develop Specialized Programs of Research Excellence (SPOREs) to investigate cancer health disparities. The aim is to build programs to improve the prevention, early detection, diagnosis, and treatment of cancers that disproportionately affect specific racial and ethnic

272 https://projectreporter.nih.gov/project_info_description.cfm?aid=9627196
273 https://projectreporter.nih.gov/project_info_details.cfm?aid=9627516
274 https://projectreporter.nih.gov/project_info_description.cfm?aid=9627357
275 https://projectreporter.nih.gov/project_info_details.cfm?aid=9627765
minority populations that can compete for SPORE funding in future years. Four awards were made in 2018 for projects focused on breast cancer, prostate cancer, and colon cancer.²⁷⁸

Research Transparency
As shown over the past 4 years, the Committee remains committed to funding NIH research and ensuring that our Nation's researchers, particularly those early in their career, have the support to make the scientific breakthroughs that may transform health care. It is critical that NIH can ensure funds are used to support the most meritorious research. Members of this Committee have raised concerns and provided examples of questionable research. 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. The Committee continues to urge a focus on research that will yield further advancement in life-saving treatments and cures.

Action taken or to be taken:

NIH remains committed to supporting research that leads to life-saving treatments and we appreciate the Committee’s support for investing in the health and well-being of all Americans. NIH will continue to cultivate a carefully balanced research portfolio as outlined in the NIH-Wide Strategic Plan for Fiscal Years 2016-2020.²⁷⁹  By identifying the most meritorious research through its rigorous peer review process, NIH funds research on understanding how healthy living systems function as well as basic science research that identifies underlying disease mechanisms. Indeed, many important medical advances have grown from the pursuit of fundamental questions in biology, physics, and chemistry, including studies on how bacterial “scissors” chop up DNA from invading viruses, for example, which led to the revolutionary discovery and development of the CRISPR/Cas9 gene editing system. This system could be used to correct genetic diseases such as Duchenne muscular dystrophy, sickle cell disease, and cystic fibrosis, as well as to develop therapies for cancer, such as chimeric antigen receptor T (CAR T) cell therapy.

NIH has numerous strategies for investing in the training and career development of early-stage investigators (e.g., undergraduates, graduate students, postdoctoral researchers), such as dedicated training grants, fellowships, and programs, as this investment is essential to maintaining the best and brightest scientific workforce and ultimately sustaining the infrastructure of the biomedical research enterprise. NIH also aims to bolster its infrastructure for supporting early-career investigators through the Next Generation Researchers Initiative (NGRI), which includes a suite of initiatives to help researchers by improving access to NIH funding opportunities to make scientific breakthroughs that advance life-saving treatments and cures.

NIH agrees with the committee that scientific transparency is important to ensure the highest level of public accountability and has implemented numerous strategies to demonstrate its commitment to making its research publicly accessible. NIH has a website dedicated to publishing information on NIH expenditures and the results of NIH supported research (Research

Portfolio Online Reporting Tool (RePORT)\textsuperscript{280}, which provides access to reports, data, and analyses of NIH research activities. Regarding the Committee’s request, NIH intends to include a statement on the main page of the RePORT website, which is a portal to all NIH-funded grants, to reassert its commitment that each grant or agreement, in accordance with NIH’s mission, 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.

\footnotetext[280]{https://report.nih.gov/}
Rural Health Outcomes and Health Disparities

The Committee notes translational science and education is critical to developing new treatments and healthcare approaches that can be disseminated to underserved and special populations to improve health outcomes across the life span. The Committee continues and encourages NCATS, through its CTSA program, to enhance its commitment to the value of translational science and funding for universities to continue to innovate by leveraging statewide resources and capabilities to improve rural health outcomes and eliminate health disparities. The Committee requests an update on the actions within the CTSA program to improve rural health outcomes and health disparities in the fiscal year 2020 Congressional Justification.

Action taken or to be taken:

The National Center for Advancing Translational Sciences (NCATS) funds multiple efforts within the CTSA Program that support the inclusion of diverse populations, particularly underserved and special populations, especially rural populations, in clinical and translational research. In addition to supporting ‘hubs’ of clinical and translational research (which fund academic clinical and translational science centers, including their career development and training efforts), the program includes initiatives to stimulate and encourage innovation via collaboration, through the CTSA Collaborative Innovation Awards (CCIA), and recruitment approaches, through the Recruitment Innovation Center (RIC). These activities encourage research that serves a wide range of populations, especially those associated with health disparities that disproportionately impact rural populations.

Five CTSAs (The Ohio State University, University of Cincinnati, University of Kentucky, Penn State University, and Wake Forest University), along with affiliated partner institutions (Marshall University, Ohio University, West Virginia Clinical and Translational Science Institute, and East Tennessee State University), created the Appalachian Translational Research Network (ATRN) to catalyze translational research towards improving the health of Appalachian communities. While much of the ATRN focus has been directed towards the opioid crisis, other areas such as pollution and childhood health are being studied.

The Indiana University CTSA, through the state Community Health Coalition Development Program, is working with individual rural counties to develop specific program / project goals addressing a wide range of issues such as mental health, chronic disease prevention, smoking cessation, substance abuse, childcare, etc. The University of Arkansas for Medical Science CTSA has developed a Community Scientist Academy that trains community leaders in research methodology resulting in research advocates located in rural communities and more easily creating partnerships between researchers and community members. The University of Alabama at Birmingham CTSA has a focus on obesity, a significant issue especially in rural communities. Recently published work has demonstrated intermittent fasting benefits towards blood sugar control and blood pressure regulation go beyond eating less or weight loss, suggesting alternative dietary strategies that may be more suitable for long term use.
These are just a few of the numerous examples of rural health research being supported by the CTSA Program. NCATS will continue to strive to support CTSA hubs located in and focused on rural regions that support clinical and translational research in this populations.
Scleroderma
The Committee recognizes the work that NIAMS is doing to support research of fibrotic disease and continues to encourage prioritizing research including scleroderma. The Committee also encourages NIAMS to work with other ICs on collaborative opportunities where feasible to advance critical research.

Action taken or to be taken:

NIAMS supports a robust portfolio of research on scleroderma, a chronic autoimmune disease characterized by excessive fibrosis (scarring) that damages the skin, blood vessels, and internal organs. NIAMS funds scleroderma research through investigator-initiated grants, Institute initiatives, and other collaborative efforts that cover a broad spectrum of areas from basic research on the role of genes, molecules, and cells, to translational projects, and clinical studies of potential new therapies.

NIAMS-sponsored investigators are studying the causes of and potential treatments for scleroderma and its complications. For example, a grant funded in FY 2018 will investigate the role of immune cells known as regulatory T cells in influencing the activity of fibroblasts, the cells that drive tissue fibrosis. Other researchers supported by NIAMS reported that a drug called dimethyl fumarate (DMF), which is FDA-approved for the treatment of multiple sclerosis, modulates skin fibrosis. The researchers isolated skin fibroblasts from either healthy donors or scleroderma patients, treated the cells to induce expression of pro-fibrotic genes, and found that follow-up treatment with DMF efficiently blocked the fibrosis. Related to this work, NIAMS recently funded an exploratory study by another research group to generate preliminary data on the safety and efficacy of adding DMF to standard therapy for patients with scleroderma and pulmonary arterial hypertension (PAH), a serious complication that occurs in some patients. In addition, in FY 2018, NIAMS funded a Small Business Innovation Research Award to generate preclinical data on the use of a novel therapeutic small molecule inhibitor as a potential treatment for interstitial lung disease (ILD), another potential complication of scleroderma.

Because the severity and symptoms of scleroderma vary widely, an important goal of research is to identify biomarkers that could help physicians tailor treatment to individual patients and enable researchers to identify groups of patients with similar features for clinical trials. For example, results from a recent NIAMS-funded study showed that assessing the production of five specific genes in skin samples from scleroderma patients could help predict the course of skin fibrosis. A separate group of researchers supported by NIAMS, the National Center for Advancing Translational Sciences, the Department of Defense, and a private foundation, recently made progress toward predicting which systemic sclerosis patients will experience a rapid decline in pulmonary function due to ILD. The researchers examined samples and data collected through two studies of scleroderma patients and found an association between higher blood levels of a molecule called CCL2, and faster declines in lung function. The findings support earlier work that indicated CCL2 as a potential target for systemic sclerosis therapies, and suggest that CCL2 could identify patients at highest risk of rapidly progressing ILD.
Additionally, NIAMS continues to work with other NIH Institutes and Centers that share an interest in scleroderma, including understanding the disease course and co-occurring conditions. For example, researchers across various disciplines have begun to explore the potential linkages between autoimmune diseases and cancer. In FY 2018, NIAMS funded a grant to understand why certain subgroups of scleroderma patients are at increased risk of developing cancer. This study may help identify those patients at high or low risk of cancer and provide insights into how best to manage and treat them. One of the principal investigators for the project was a featured speaker at a March 2018 NIH-wide workshop on Cancer, Autoimmunity, and Immunology, sponsored by the NIAMS, the National Cancer Institute, and the National Institute of Allergy and Infectious Diseases. The meeting brought together researchers from several disciplines to advance research by sharing insights across fields.
Sickle Cell Disease Research
The Committee encourages NHLBI to devote more research to the study of sickle cell disease. Academic medical centers located in States with significant populations of sickle cell patients have made progress in treating the disease through NIH-sponsored clinical trials and through blood and marrow transplantation, which is currently the only therapy that can cure the disease. However, more focused research is needed to augment the limited treatment options available.

Action taken or to be taken:
Approximately 100,000 Americans and over 20 million people worldwide have sickle cell disease (SCD). The National Heart, Lung, and Blood Institute (NHLBI) is committed to building on its legacy of research excellence to find new treatments, cures, and personalized care for patients with sickle cell disease and remains committed to engaging patients and stakeholders in the research process.

In September 2018, NHLBI launched the Cure Sickle Cell Initiative to accelerate the development of genetic therapies to cure SCD. The Initiative grew out of a March 2017 NIH-sponsored workshop, “Accelerating Cures in Hemoglobinopathies,” that brought together thought-leaders in genetic therapies and gene editing, including representatives from academia and the pharmaceutical industry, to accelerate the development of potentially curative therapies for SCD. Workshop participants endorsed the concept of a collaborative consortium of academia and private sector partners advancing multiple genetic and cellular strategies simultaneously to optimize and accelerate progress toward a cure. The Cure SCD Initiative will intensify the focus on genetic-based curative strategies for SCD, identify the most promising ones, and move them safely into clinical trials within five to 10 years. Through this Initiative NIH will provide access to scientific expertise and resources that will catalyze the production of genetic therapies to improve lifespan and quality of life for people with SCD.

Researchers are investigating the use of gene therapy or gene editing to repair the mutations in hemoglobin that cause SCD. Another possible target for gene therapy is fetal hemoglobin, because increased fetal hemoglobin helps protect against the effects of sickled hemoglobin. Researchers are exploring whether gene editing can help reactivate expression of fetal hemoglobin genes already in blood cells. They are also looking at whether they can introduce and express new fetal hemoglobin genes in blood cells of patients with SCD.

Additionally, as part of the Cure Sickle Cell Initiative, NHLBI seeks to support the development of cell and genetic therapy resources, clinical trials, comparator analyses of different management strategies, data repositories and resources, and stronger engagement of patients and advocates in research toward a cure.

With respect to bone marrow transplants (BMT), NHLBI-supported researchers are working to expand treatment options for adults with SCD and for patients who do not have immunologically matched donors. Since many people cannot find matches, developing other safe, effective BMT protocols would greatly expand the number of people with SCD who could receive a transplant.
Sickle Cell

The Committee understands the burden sickle cell disease places on more than 100,000 Americans. 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, Federal research spending on sickle cell disease has been disproportionately lower than other medical conditions that affect fewer Americans. The Committee encourages the NHLBI to consider an increased focus and innovation in treatment of sickle cell disease and continued support for highly meritorious research on sickle cell disease.

Action taken or to be taken:

Sickle cell disease (SCD) is a genetic blood disorder caused by a variation in one of the genes that encodes hemoglobin, the protein that carries oxygen in red blood cells. It is one of few disorders whose genetic underpinnings are well understood. The sickle-cell gene variant can cause hemoglobin to aggregate and distort red blood cells into a sickle shape, blocking small blood vessels and causing extreme pain, organ damage, and, often, life-threatening complications such as strokes. SCD affects approximately 100,000 people in the United States, among them, one in 365 African Americans. Globally, mortality, particularly in young children, is very high.

Although there is no widely available cure for SCD at this time, several therapies whose development was supported by the National Heart, Lung, and Blood Institute (NHLBI) have improved the longevity and well-being of people living with the disease. Drugs developed through NHLBI-supported research, such as hydroxyurea, can reduce pain and are effective at reducing blood flow velocities in the brain, a key predictor of stroke in pediatric patients. Additionally, clinical trials have established that bone marrow transplantation can cure SCD when a genetically well-matched, unaffected sibling serves as the donor. However, few patients (less than 25 percent) have a genetically well-matched related sibling who could provide bone marrow with the immunological compatibility necessary for a successful transplant. NHLBI is now funding trials to test the efficacy and safety of bone marrow transplants from unrelated, but fully matched donors, and related partially matched donors. If successful, these new transplant strategies could allow almost all patients to benefit from a transplant, regardless of whether they have a fully matched sibling.

In September 2018, NHLBI launched the Cure Sickle Cell Initiative to accelerate the development of gene therapies to cure SCD. The Initiative will identify and support the most promising gene therapies, so they can be safely used in clinical research in the next 5 to 10 years. Through this Initiative, NIH will provide access to scientific expertise and resources that will catalyze the production of these genetic therapies to improve lifespan and quality of life for people with SCD.

Additionally, researchers funded through NHLBI’s Excellence in Hemoglobinopathies Research Award program are working to understand mechanisms of SCD and other blood disorders and translate these insights into new therapies and new ways to treat pain. Eight centers are being funded through this program.

NHLBI also supports research to develop new strategies that will assure that patients with SCD receive high-quality longitudinal health care. Many adolescents and adults with SCD do not receive ongoing, high-quality care, and damage to the lung, kidney, and heart begin to manifest. Many patients also experience severe chronic pain and require access to care. NHLBI’s Sickle Cell Disease Implementation Consortium consists of eight geographically diverse centers that are systematically assessing the barriers to care, to be followed by interventional clinical trials that will implement methods to overcome these barriers.
Sleep Disorders

CDC estimates that between 50,000,000 and 70,000,000 Americans suffer from sleep and wakefulness disorders. Insufficient sleep is associated with diseases including diabetes, cardiovascular disease, obesity, and depression. To address the public health burden of sleep deficiency and untreated sleep disorders, there is an urgent need to improve our understanding of these diseases, including the identification of biomarkers to predict and manage risks to individual health and public safety. The Committee urges the Institute to expand discovery science efforts into sleep and wakefulness disorders.

Action taken or to be taken:

Fundamental research on sleep is advancing rapidly. Groundbreaking discoveries regarding the genetics of sleep and circadian (daily) rhythms, which were funded in part by NIH and recognized by the 2017 Nobel Prize in Medicine, have opened doors to a better understanding of the physiological mechanisms through which sleep deficiency and sleep disorders contribute to chronic disease and mortality.

The National Heart, Lung, and Blood Institute (NHLBI) is funding studies to understand how poor sleep health contributes to the risk of heart, lung, and blood diseases. This includes research on many sleep disorders, such as sleep apnea, narcolepsy, insomnia, restless legs syndrome, as well as jet lag and other disturbances of the body’s internal clocks or circadian rhythms. The Trans-NIH Sleep Research Coordinating Committee, which comprises representatives from 10 Institutes and Centers and the NIH Office of the Director, is working to foster research on biomarkers to measure, predict, and manage sleep disorders and sleep deficiency. The National Center on Sleep Disorders Research (NCSDR), housed at NHLBI, is also coordinating sleep biomarker development through meetings of the Department of Transportation (DOT)-organized Federal Inter-Agency Fatigue Management Working Group, which includes representatives from DOT, the Department of Defense, the National Aeronautics and Space Administration, and NIH.

Researchers have discovered patterns in groups of metabolic biomarkers that are linked to regular sleep-wake schedules. For example, studies looking at changing sleep schedules have revealed that varying levels of certain metabolites in blood are associated with changes in the timing and duration of sleep. With further characterization, these metabolites could be used as biomarkers to show how sleep deficiency and sleep disorders influence the risk of metabolic conditions such as obesity and high cholesterol.

Brain imaging has led to the discovery that the cumulative effects of sleep deficiency and circadian rhythm may have more adverse effects than previously thought. In a small study, NIH researchers found that even one night without sleep increased brain levels of beta-amyloid, a biomarker associated with Alzheimer’s disease.\(^\text{282}\) NHLBI continues to expand its programs to better understand the link between sleep and brain health. For example, NHLBI is part of a National Institute on Aging effort to study sleep disorders and circadian clock disruption in Alzheimer’s disease.\(^\text{283}\) NHLBI also organized a two-day workshop with other NIH Institutes

\(^\text{282}\) [http://www.pnas.org/content/early/2018/03/29/1721694115.short](http://www.pnas.org/content/early/2018/03/29/1721694115.short)

and Centers in August 2018 on the Role of Sleep Deficiency and Sleep Disorders in Aging, Cognition and Neurodegeneration. The workshop brought together researchers from the fields of aging, neuroscience, cardiology, pulmonology, immunology, and sleep to identify new directions and opportunities for collaborative research focused on sleep and brain health.

In addition, NHLBI supports research to examine the impact of poor sleep during adolescence on neurological and cardiovascular health risk factors. A survey of 2,000 adolescents revealed that only two percent obtained the 8-10 hours of sleep recommended by the American Academy of Sleep Medicine. Adolescents with the least sleep had the highest cardiovascular risk based on waist size, blood pressure, and biomarkers including cholesterol, lipids, and insulin resistance. Further study is needed to determine whether these biomarkers could be used to assess sleep problems and to determine the potential benefits of sleep interventions. New NHLBI-funded studies of adolescent populations are examining how sleep deficiency affects body fat, and the role that chronic poor sleep can play in elevating stress hormones, which in turn can increase cardiovascular risk. In October 2018, NHLBI partnered with other NIH Institutes, as well as the NIH Office of Research on Women’s Health and the HHS Office of Women’s Health to organize a two-day public conference exploring progress and gaps in understanding gender differences in sleep, sleep disorders, and the impact of sleep deficiency on families and children.

Sleep Disorders
The Committee continues to recognize sleep disorders as a public health concern, and is
couraged by the ongoing implementation of the NIH Sleep Disorders Research Plan. The
Committee recognizes that sleep and circadian research play an important role across all
Institutes and Centers, and notes that the 2017 Noble Prize in Physiology or Medicine was
awarded to an NIH grantee for breakthroughs in studying the internal biological clock. The
Committee encourages NIH to explore opportunities to appropriately incorporate cross-cutting
efforts into activities supported by the Common Fund and the All of Us research program.

Action taken or to be taken:

The National Center on Sleep Disorders Research (NCSDR), housed within the National Heart,
Lung, and Blood Institute (NHLBI), administers NIH support for sleep research projects and
sleep science training programs. Together with the Trans-NIH Sleep Research Coordinating
Committee, which comprises representatives from 10 Institutes and Centers and the NIH Office
of the Director, NCSDR works to identify and coordinate cross-cutting sleep research
opportunities across NIH. This includes support for research on the circadian rhythm (the body’s
daily internal clock), how it is regulated, and its relationship to the risk of chronic disease.

Disruption of sleep and circadian rhythms can impair daily health and performance and
contribute to the risk of chronic disease. The discoveries in circadian biology that were
recognized by the 2017 Nobel Prize in Medicine, and funded in part by NIH, figure prominently
in new cross-cutting initiatives in which NHLBI has partnered with other Institutes to better
understand the intersection between circadian rhythm, health, and disease states.

For example, an NHLBI partnership with the National Institute of Diabetes and Digestive and
Kidney Diseases led to a new program to better understand how circadian-dependent
mechanisms contribute to obesity and to the risk of heart and lung disorders linked to obesity.286
NHLBI also has joined with the National Institute on Minority Health and Health Disparities in
an initiative to identify specific sleep and circadian mechanisms contributing to health
disparities.287 A new cross-cutting partnership with the Eunice Kennedy Shriver National
Institute on Child Health and Human Development in 2018 led to a phase III clinical trial to
determine whether the treatment of sleep apnea during pregnancy reduces the risk of gestational
diabetes and hypertension.288

NIH-supported researchers have found that the brain’s circadian rhythm does not easily adapt to
externally imposed sleeping and waking schedules, such as night-shift work. In contrast,
researchers have found levels of metabolites that tend to ebb and flow with the sleep-wake
schedule.289 Researchers are beginning to study the role that these metabolic patterns may play
in irregular sleep schedules and how they may increase the risk of metabolic diseases such as
type 2 diabetes. Meanwhile, brain imaging has revealed that the cumulative effects of sleep

288 https://clinicaltrials.gov/ct2/show/NCT02299414
289 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6065025/
deficiency and circadian rhythm disturbance may have more adverse effects than previously thought. In a small study, NIH researchers found that even one night without sleep increased brain levels of beta-amyloid, a biomarker associated with Alzheimer’s disease.290 Growing evidence points to systems that work during sleep to clear away metabolites and potential toxins, such as beta-amyloid, that accumulate during waking. NHLBI is committed to better understanding the role that sleep patterns and circadian rhythms play in regulating these systems.

Although the timing, intensity, and spectrum of light strongly influences circadian biology and sleep, relatively little is known about the relationship between health and lighting in public buildings, schools, and hospitals. A recent report on this topic sponsored by NCSDR recommends further study of the neural mechanisms through which light influences brain and behavior, and the optimal doses and types of light exposure for maintaining healthy sleep.291

The momentum and scale of sleep disorders research is expected to grow under the NIH All of Us Research Program. This large study, seeking to enroll more than one million people, will survey all participants on sleep habits and is developing technologies that will enable collection of sleep data from wearable devices. These data, coupled with electronic health records from All of Us participants, will help NIH better quantify the real-world burden of sleep deficiency and untreated sleep disorders in the United States, as well as the benefits of treatment.

Support for sleep research is also gaining momentum through the NHLBI Trans-Omics for Precision Medicine (TOPMed) initiative. TOPMed is piloting a whole-genome sequencing project to identify genetic variants and biochemical pathways associated with sleep disorders, including sleep apnea and insomnia. The pilot will analyze DNA samples from 1,000 participants of African and European descent in the Cleveland Family Study which is the largest family-based study of sleep apnea worldwide, consisting of 2284 individuals (46 percent of whom are African American) from 361 families being studied over 16 years. Data from TOPMed will be included in a pilot of the new NIH Data Commons, a public-private partnership to bring research findings into a cloud-computing environment to enhance data sharing.

290 http://www.pnas.org/content/early/2018/03/29/1721694115.short
291 http://journals.sagepub.com/doi/pdf/10.1177/0748730418789506
Spasmodic Dysphonia
The Committee continues to encourage NIDCD to expand research on spasmodic dysphonia, a form of dystonia. The Committee also encourages NIDCD to meet with stakeholders to link research with the needs of the community.

Action taken or to be taken:

NIDCD supports basic and clinical research studies that focus on understanding the nature of voice disorders and determine prevention and treatment of voice disorders. Spasmodic dysphonia (SD), also referred to as laryngeal dystonia, is a voice disorder that belongs to a family of neurological disorders called focal dystonias. When a person with SD attempts to speak, the muscles in the larynx spasm involuntarily and cause the voice to break up and sound strained or breathy. It is a rare disorder, occurring in roughly one to six of every 100,000 people. More women than men are affected. Currently, there is no cure for SD, and the most common treatment is repeat injections of very small amounts of botulinum toxin directly into the affected muscles of the larynx every few months to lessen the muscle spasms. Surgical procedures, like the selective laryngeal adductor denervation-reinnervation have yielded good results in people with adductor spasmodic dysphonia. Voice therapy can also be helpful, especially when a patient has developed compensation techniques.

NIDCD currently funds research to determine the causes and pathophysiology of SD to develop new diagnostics and better treatment options. NIDCD is supporting a new clinical trial on a non-invasive intervention to improve SD voice quality. In this study, scientists will apply vibratory motor stimulation to the neck of individuals with SD to activate underlying muscles. This vibrotactile stimulation therapy could induce laryngeal muscles to change the aberrant neuronal signaling which is thought to be the cause of SD. If this trial is successful, it would lay the foundation to examine this approach and long-term outcomes in a larger group of individuals with SD. In a series of other studies, NIDCD voice researchers used brain imaging, neural recordings, and genetic analysis to elucidate further the neural processes of speech production. The researchers examined the structural organization, connectivity, and neurotransmitter signaling of brain areas involved in producing speech. They found differences in connectivity between specific sub-regions that may explain different clinical manifestations of disordered speech production in individuals with SD.

NIDCD has been supporting voice disorders research guided by recommendation from an NIDCD-sponsored workshop on voice sciences and disorders. The research portfolio includes projects that are developing biomaterials for engineering vocal fold tissue and ambulatory biofeedback approaches for management of individuals with voice disorders. It also includes projects aimed to improve patient outcomes, health services, and community-based research with special attention to the following topic areas: health disparities, rural health, second language populations, and women’s health. Further, NIDCD scientific staff meet with grantees and patient advocacy groups at annual scientific conferences and on an ad hoc basis to keep informed on the needs of the SD community. In 2018, NIDCD will participate in an NINDS-organized Dystonia

meeting. Public stakeholders, grantees, and NIH scientific program staff will discuss a range of research topics, including SD.
Spina Bifida
The Committee encourages NIA, NIDDK, NICHD, and NINDS to study the causes and care of the neurogenic bladder and kidney disease in order to improve the quality of life of children and adults with Spina Bifida; to support research to address issues related to the treatment and management of Spina Bifida and associated secondary conditions, such as hydrocephalus; and to invest in understanding the myriad co-morbid conditions experienced by individuals with Spina Bifida, including those associated with both paralysis and developmental delay.

Action taken or to be taken:

National Institute of Health (NIH) Institutes and Centers continue to collaborate on research efforts related to Spina Bifida (SB). The Eunice Kennedy Shriver National Institutes of Child Health and Human Development (NICHD) continues to actively support research on SB. Through its efforts and those of others, the prevalence rate of SB has declined 31 percent from 1995 to 2006; this translates into 1,000 fewer babies born with a neural tube defect each year. The original NICHD-funded Management of Myelomeningocele (MOM) study reported that surgically correcting the spinal defect while the fetus was still in the womb greatly reduced the need to divert fluid away from the ventricles to relieve hydrocephalus, improving health and mobility outcomes. The recently-completed “MOMS 2” study, co-funded by NICHD and the National Institute of Neurological Disorders and Stroke (NINDS), followed children in the original MOMS study to school age to assess health and mental health outcomes as well as capacity to live more independently and function more safely and appropriately in daily life, compared with those treated with surgery after birth. The follow-up study is determining the effects of prenatal repair on adaptive behavior, cognitive and motor function, brain morphology and microstructure, urologic health, and other aspects at school age. Initial results suggest the fetal surgery improves long-term functional outcome, with the majority of children able to successfully complete daily tasks. In addition, long-term ambulatory status is improved. Multiple papers to share the results will be published within the next few months.

Even with the significant decrease in children born with a neural tube defect each year, there are still over 150,000 individuals with SB living in the United States, about half of whom are adults. Common manifestations of SB include motor and sensory neurological deficits, neurogenic bladder and bowel, spasticity, and pressure ulcers. A multidisciplinary care team consisting of neurosurgery, neurology, urology, orthopedics, physical medicine and rehabilitation and others is required to manage this complex disorder. A NICHD-funded study of patterns of fat accumulation in children with myelomeningocele (the most severe form of SB) detected a pattern that correlated with an increased risk of developing type 2 diabetes. This finding could alert doctors to the importance of tailoring their care of young patients with SB to reduce muscle-related fat and thus reduce diabetes risk. Research in NICHD’s intramural branch is looking at how nutritional and other interventions might prevent neural tube defects such as SB. Recent advances in genomics and computational genetics, together with the creation of genetic mouse models, offer unique opportunities to examine the genetic components of SB. For example, a NICHD-supported study is performing exome sequencing to identify unique variations in genes
and pathways influencing myelomeningocele susceptibility to facilitate improved diagnostics and treatment.

Considering the condition’s complexity and issues associated with aging with SB, self-management and self-reporting is critical; yet, this approach has received little attention. NICHD recently funded a skin care self-management study to address the chronic skin conditions such as wounds on lower extremities experienced by individuals with SB. Investigators developed a mobile health (mHealth) system for supporting self-care and management of skin problems, called SkinCare, which was shown to be capable of supporting self-care and adherence to regimen, monitoring adherence, and supporting clinician engagement with patients. In addition, the NICHD is currently funding a STTR application that is developing assistive software to help developmentally disabled youth, including those with SB, provide valid healthcare assessment self-reports. The institute also supports the Gait and Clinical Movement Analysis Society annual meeting, which is aimed at bringing scientists together who are working on improving ambulation and quality of life for children and adults with neuromuscular disorders, including those with SB.

In addition to NICHD, several other NIH Institutes and Centers fund research on SB. For example, the National Institute of Nursing Research (together with the Office of the NIH Director) is funding a study whose goal is to identify targets for effective self-management, adherence and health care interventions for youth with SB. Focusing on self-management in late adolescence and young adulthood will allow for an examination of the transition from pediatric to adult health care. The National Institute of Diabetes and Digestive and Kidney Diseases has long supported research efforts on congenital genitourinary conditions, recently holding a meeting in February 2018, entitled “Individualizing Treatment for Urinary Incontinence—Evolving Research Questions into Research Plans.” The focus of the meeting was to develop an interdisciplinary research plan for individualizing treatment for urinary incontinence.

NINDS also funds research projects aimed at the understanding and improving treatments for hydrocephalus, which often affects people with SB. Shunts to divert excess cerebrospinal fluid are the primary treatment for hydrocephalus, but complications due to shunt malfunction, obstruction, or infection are common. Investigators are working to understand and prevent such complications, to develop less invasive ways to monitor hydrocephalus and shunt function, and to develop and test potential alternatives to shunt treatment. NINDS also supports research relevant to understanding and treating neurogenic bladder in SB, including efforts to develop a drug to induce urine voiding as an alternative to catheterization, a low oxygen breathing therapy to improve urinary tract function and a surgical method to restore neural connectivity to the bladder and urethral sphincter.
Stroke Research
The Committee continues its concern that stroke inflicts a vast burden, including topping per capita spending for all chronic conditions in the Medicare fee-for-service program. The Committee encourages NINDS to prioritize and implement robust investment to spur, strengthen, accelerate, and coordinate stroke research. This investment should focus on expediting novel basic, clinical and translational research by all available and appropriate mechanisms. The Committee encourages NINDS to intensify enactment of top stroke priorities, including prevention, endovascular therapy, early stroke recovery, and tele-rehabilitation.

Action taken or to be taken:

NINDS shares the Committee’s concern about the vast burden of stroke and continues its robust investments to advance research. The NIH StrokeNet, which recently began its second phase of funding, has contributed to the completion of four NINDS-funded clinical trials since its launch in 2013 and results from these trials are influencing patient care. The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE)-3 trial showed that brain imaging can be used to identify patients who can be treated with clot-retrieval devices up to 16 hours after stroke onset, broadening the reach of this intervention that can save patients with severe strokes from major disability.

In StrokeNet’s first recovery trial, investigators found that home-based tele-rehabilitation may offer a solution to access barriers that prevent some stroke patients from receiving adequate rehabilitation services. Two trials that recently completed enrollment assessed novel and less invasive interventions for hemorrhagic stroke, a severe type of stroke for which effective treatments are lacking. Other NIH StrokeNet studies that are underway or in development include assessment of the best way to prevent strokes due to asymptomatic carotid stenosis; testing combination therapies to enhance the effectiveness of tissue plasminogen activator (tPA); determining whether early recovery can be enhanced with transcranial stimulation; testing whether treatment of obstructive sleep apnea after a recent stroke improves recovery and prevents future strokes; and determining whether statin treatment should be continued after intracerebral hemorrhage. NIH StrokeNet is also a platform for collaboration with other Federal partners, industry stakeholders, and the international research community.

Leveraging lessons from the European Multi-Part collaborative study, recommendations from the 2016 NINDS-sponsored workshop on translational stroke research, and the recent advances extending the time window for endovascular therapy (i.e., DEFUSE-3), NINDS is developing a stroke preclinical network that will use innovative study designs and rigorous methodologies to test potential neuroprotective agents in animal models and identify robust candidates for subsequent clinical evaluation. NINDS is also planning a workshop that will take place in November, 2018 to bring together basic and clinical experts in recovery and rehabilitation research to discuss research challenges, opportunities, and priorities in the field. NINDS maintains a robust portfolio of basic investigator-initiated research that explores the basic cerebrovascular biology and mechanisms that underlie stroke and recovery processes, including studies of intrauterine and neonatal stroke.

Silent stroke and diffuse white matter disease are common and contribute to the risk of an Alzheimer’s disease diagnosis. As part of the National Plan to Address Alzheimer’s, NINDS launched a consortium to identify biomarkers related to the vascular contribution to cognitive
impairment and dementia to inform prevention trials. Preliminary results from the NIH-funded Systolic Blood Pressure Intervention-Memory and Cognition in Decreased Hypertension (SPRINT-MIND) trial suggest that lower blood pressure targets reduce risk of cognitive impairment, adding to the accumulating evidence that midlife blood pressure affects brain health later in life. The NINDS Mind Your Risks public messaging campaign aims to raise public awareness of this link and encourage individuals to keep their blood pressure under control.

Collectively, these efforts represent scientific priorities and opportunities identified from the 2012 planning effort and subsequent scientific workshops. Discussions are underway for an NINDS-led effort to assess how the science has changed, identify new or unaddressed challenges and gaps, and ultimately to identify a new set of focused priorities for the field.
Stroke

The Committee continues its concern that stroke inflicts a vast burden, including topping per capita spending for all chronic conditions in the Medicare fee-for-service program, yet NIH spends only one percent of its budget on stroke research. This funding level is not commensurate with its burden on U.S. long-term health outcomes, financial stability, and novel scientific opportunities. The Committee strongly encourages NINDS to prioritize and implement robust investment to drastically spur, strengthen, accelerate, and coordinate stroke research. This investment shall focus on expediting novel basic, clinical, and translational research by all available and appropriate mechanisms. The Committee expects NINDS to intensify enactment of top stroke priorities, including prevention, endovascular therapy, and early stroke recovery.

Action taken or to be taken:

NINDS shares the Committee’s concern about the vast burden of stroke and continues its robust investments to advance research. The NIH StrokeNet, which recently began its second phase of funding, has contributed to the completion of four NINDS-funded clinical trials since its launch in 2013 and results from these trials are influencing patient care. The Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke (DEFUSE)-3 trial showed that brain imaging can be used to identify patients who can be treated with clot-retrieval devices up to 16 hours after stroke onset, broadening the reach of this intervention that can save patients with severe strokes from major disability.

In StrokeNet’s first recovery trial, investigators found that home-based tele-rehabilitation may offer a solution to access barriers that prevent some stroke patients from receiving adequate rehabilitation services. Two trials that recently completed enrollment assessed novel and less invasive interventions for hemorrhagic stroke, a severe type of stroke for which effective treatments are lacking. Other NIH StrokeNet studies that are underway or in development include assessment of the best way to prevent strokes due to asymptomatic carotid stenosis; testing combination therapies to enhance the effectiveness of tissue plasminogen activator (tPA); determining whether early recovery can be enhanced with transcranial stimulation; testing whether treatment of obstructive sleep apnea after a recent stroke improves recovery and prevents future strokes; and determining whether statin treatment should be continued after intracerebral hemorrhage. NIH StrokeNet is also a platform for collaboration with other Federal partners, industry stakeholders, and the international research community.

Leveraging lessons from the European Multi-Part collaborative study, recommendations from the 2016 NINDS-sponsored workshop on translational stroke research, and the recent advances extending the time window for endovascular therapy (i.e., DEFUSE-3), NINDS is developing a stroke preclinical network that will use innovative study designs and rigorous methodologies to test potential neuroprotective agents in animal models and identify robust candidates for subsequent clinical evaluation. NINDS is also planning a workshop that will take place in November, 2018 to bring together basic and clinical experts in recovery and rehabilitation research to discuss research challenges, opportunities, and priorities in the field. NINDS maintains a robust portfolio of basic investigator-initiated research that explores the basic cerebrovascular biology and mechanisms that underlie stroke and recovery processes, including studies of intrauterine and neonatal stroke.
Silent stroke and diffuse white matter disease are common and contribute to the risk of an Alzheimer’s disease diagnosis. As part of the National Plan to Address Alzheimer’s, NINDS launched a consortium to identify biomarkers related to the vascular contribution to cognitive impairment and dementia to inform prevention trials. Preliminary results from the NIH-funded Systolic Blood Pressure Intervention-Memory and Cognition in Decreased Hypertension (SPRINT-MIND) trial suggest that lower blood pressure targets reduce risk of cognitive impairment, adding to the accumulating evidence that midlife blood pressure affects brain health later in life. The NINDS Mind Your Risks public messaging campaign aims to raise public awareness of this link and encourage individuals to keep their blood pressure under control.

Collectively, these efforts represent scientific priorities and opportunities identified from the 2012 planning effort and subsequent scientific workshops. Discussions are underway for an NINDS-led effort to assess how the science has changed, identify new or unaddressed challenges and gaps, and ultimately to identify a new set of focused priorities for the field.
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 had some encouraging breakthroughs in research on risk detection algorithms, and these tools can be made increasingly sophisticated now with the power of big data tools. The Committee urges NIMH to prioritize its suicide prevention research efforts to produce models that are interpretable, scalable, and practical for clinical implementation, including mental and behavioral health care interventions, to combat suicide in the United States. The Committee directs NIH to provide an update on these efforts, including its work with CDC, SAMHSA, and the Department of Education, in the fiscal year 2020 CJ.

Action taken or to be taken:

Suicide prevention research is a top priority for the National Institute on Mental Health (NIMH). NIMH-funded research has produced suicide screening tools and risk detection algorithms to improve the identification of individuals at risk for suicide. As NIMH continues to support these efforts, NIMH-funded researchers are also examining ways to effectively implement these evidence-based practices into healthcare systems and communities, target populations at higher risk for suicide, and leverage partnerships to save lives.

NIMH uses surveillance information from its federal partners (e.g., Centers for Disease Control and Prevention (CDC) and, Substance Abuse and Mental Health Services Administration (SAMHSA), Bureau of Justice Statistics) to discern which settings (e.g., health care systems, jails) are accessed by individuals who have attempted suicide, to determine where to prioritize research efforts. Approaches to suicide risk detection and effective treatments are then modeled and tested in these settings to efficiently build evidence-based practices for vulnerable populations. For example, NIMH staff collaborated with researchers from the Department of Veteran’s Affairs (VA) to develop the Recovery Engagement and Coordination for Health – Veterans Enhanced Treatment (REACH VET) algorithm, which identifies veterans with the highest risk for suicide. NIMH also recently partnered with the National Institute of Justice to support a suicide prevention study focused on high-risk individuals who are transitioning from jail to community settings. Additionally, NIMH-funded collaborative research hubs are exploring the factors underlying the high suicide rates among American Indian and Alaska Native youth and designing and testing community-based strategies for suicide prevention.

Because most suicide decedents have accessed health care services in the 12 months preceding death, healthcare systems can play a vital role in identifying individuals at risk and preventing suicide attempts. NIMH has focused on emergency departments (EDs) as a starting point. One such NIMH-funded study demonstrated that a brief screening tool improved providers’ ability to identify individuals at risk for suicidal behavior. If instituted nationally, the

295 https://projectreporter.nih.gov/project_info_description.cfm?aid=9523227
296 https://www.nimh.nih.gov/about/organization/gmh/ai-an/index.shtml
298 https://www.sprc.org/micro-learnings/patientsafety screener
investigators estimated that this tool could identify and refer to care more than three million additional at-risk adults each year.\textsuperscript{299} To assess youth suicide risk, NIMH-funded researchers created a two-minute, personally tailored, computerized screening tool.\textsuperscript{300} NIMH intramural researchers also developed the Ask Suicide-Screening Questions (ASQ) screening tool to help nurses or physicians identify youth at risk for suicide.\textsuperscript{301} The ASQ is now being used in EDs, inpatient units, and outpatient primary care clinics around the country. In addition, NIMH researchers modeled the benefits of caring contact after an ED visit and found that simple interventions, such as post-discharge postcards or caring letters, could save lives and save money for healthcare systems.\textsuperscript{302}

NIMH is also supporting suicide prevention research looking more broadly across health care systems. The Mental Health Research Network is a collaborative effort of private sector HMOs, the NIH Common Fund, and NIMH, which is examining integrated electronic health records for nearly 13 million individuals with mental illness across 13 health system research centers. Activities in this network include fielding the largest trial of adult suicide prevention; evaluating multiple health care system efforts for the Zero Suicide quality improvement initiative; and, developing and validating a risk algorithm that can inform providers about patient risk status for a suicide attempt following an outpatient visit.\textsuperscript{303, 304}

NIH hosted a workshop and federal partners meeting, which included representatives from the CDC, SAMHSA, and Department of Education, to identify strategies to leverage existing studies to learn more about risk factors, intervention benefits, and linkage to surveillance of youth suicidal behaviors.\textsuperscript{305} In response, NIMH, in collaboration with National Institute on Drug Abuse (NIDA), National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institute on Minority Health and Health Disparities (NIMHD), and National Center for Complementary and Integrative Health (NCCIH), requested research proposals to link data sets and develop tools to validate, harmonize, and analyze the data to address suicide research gaps.\textsuperscript{306} Funded studies are examining suicide risk and behaviors in a variety of populations and settings, including sexual minority youth.

Translating research findings into evidence-based practice requires strong collaboration. NIMH’s past partnerships with the Army and the VA have produced suicide screening tools and risk prediction algorithms.\textsuperscript{307, 308} NIMH continues to work with the Department of Defense, the VA, and other agencies to improve suicide prevention in the military and develop tools that can

\textsuperscript{299} https://www.ncbi.nlm.nih.gov/pubmed/26654691
\textsuperscript{300} https://projectreporter.nih.gov/project_info_description.cfm?aid=8755416&icde=40647785
\textsuperscript{301} See www.nimh.nih.gov/ASQ
\textsuperscript{302} https://www.ncbi.nlm.nih.gov/pubmed/28945181
\textsuperscript{303} https://projectreporter.nih.gov/project_info_description.cfm?aid=9538844&icde=40649106l
\textsuperscript{304} https://www.ncbi.nlm.nih.gov/pubmed/29792051
\textsuperscript{305} https://prevention.nih.gov/research-priorities/research-needs-and-gaps/pathways-prevention/advancing-research-prevent-youth-suicide
\textsuperscript{306} See RFA-MH-18-400 and RFA-MH-18-410
\textsuperscript{308} https://www.ncbi.nlm.nih.gov/pubmed/26066914
be applied to civilian populations as well. NIMH also works with SAMHSA through the Interdepartmental Serious Mental Illness Coordinating Committee to identify opportunities to implement risk identification tools and evidence-based suicide prevention practices. Furthermore, as a member of the National Action Alliance for Suicide Prevention, NIMH works with federal and private sector partners to continue to advance an evidence base for suicide prevention.
Task Force on Research Specific to Pregnant Women and Lactating Women

The Committee looks forward to the Task Force’s report to the Secretary and Congress in September 2018, and continues to encourage and support the important work of the Task Force to ensure that pregnant and lactating women are included in research, and that consumers and health care professionals have up-to-date and accurate information on the safety and efficacy of drugs that women are taking while pregnant or breastfeeding.

Action Taken or to be Taken

The Task Force on Research Specific to Pregnant Women and Lactating Women (“Task Force” or “PRGLAC”) was established by the 21st Century Cures Act (P.L. 114-255), and charged with providing advice and guidance to the Secretary of Health and Human Services (HHS) on activities related to identifying and addressing gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women, including the development of such therapies and the collaboration on and coordination of such activities. The Task Force was charged with preparing and submitting to the Secretary and Congress a report on its findings and recommendations by September 2018. In May 2018, the Task Force developed and voted upon 15 recommendations based on information gleaned during four open meetings and a public comment period. Throughout these discussions resonated the theme that cultural assumptions about use of medications by pregnant and lactating women need to be altered, which have significantly limited scientific knowledge of therapeutic product safety, effectiveness, and dosing for these groups of women.

Over six million women are pregnant in the United States each year. Of these women, more than 90 percent take at least one medication during pregnancy and lactation. However, pregnant women and lactating women are often excluded from clinical research that could ultimately help these populations. A comprehensive review of research in recent years conducted for the Task Force clearly showed the extremely limited information available on medication use in pregnancy and lactation. More evidence is needed so that women and their clinicians can make fully informed choices based on the risks and benefits of medicating or not medicating conditions during pregnancy and lactation. The provision of clinical data is essential to increasing the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant women and lactating women. Including pregnant and lactating women in clinical research – except when exclusion is scientifically justified – may require regulatory changes, targeted communications efforts with professional societies and the research community, and creative approaches to building a database of information about therapeutics that are already being used by pregnant and lactating women.

Per the 21st Century Cures Act, the charter of the Task Force will expire in March 2019. The work of the Task Force augments and extends prior efforts that recommended the inclusion of pregnant women and lactating women in research. Without research and the establishment of an evidence base, practitioners care for pregnant women and lactating
women without adequate data on the safety, efficacy, or appropriate dosing of therapeutic products. Pregnant women and lactating women and their health care providers are left with undesirable options—either taking a therapeutic product without high-quality dosing or safety information or not treating a condition adequately. While NICHD/NIH currently supports research on medication use among pregnant women and lactating women with various medical conditions, including asthma, seizure disorders, mental health disorders, diabetes, and bacterial and viral infections, far more needs to be done to encourage inclusion of these populations in clinical studies.
Technology and Ophthalmic Disorders
The Committee notes that the specific use of technology, such as web-based telemicine software, centralized reading centers, hand-held fundus cameras, photography training programs, and internet-based storage and transmission of images can efficiently detect early signs of diabetic retinopathy and glaucoma in rural and underserved populations.

**Action taken or to be taken:**

NIH supports a growing portfolio of projects developing telemedicine and automated technologies for detecting disease outside the clinic. Eye doctors often rely on imaging to diagnose disease: the fundus photograph captures the back of the eye to detect abnormalities in the retina or optic disc; optical coherence tomography (OCT) uses light and special mirrors to take high-resolution cross-section images of the retina and optic nerve to help doctors detect diabetic retinopathy (DR), age-related macular degeneration (AMD), and glaucoma. NIH has spurred new hand-held imaging tools for use in settings without a traditional vision clinic. NEI scientists recently developed a hand-held OCT-angiography system that can detect changes in blood capillaries in the eye to diagnose and track abnormal vessel growth in DR and AMD.309 Another NEI ophthalmologist is pioneering a telemedicine glaucoma detection and management program using a comprehensive remote optic nerve assessment tool at community clinics (Walmart Vision Centers) in predominantly at-risk African American communities from underserved areas of Alabama. The goal is to treat glaucoma at lower costs while improving patient adherence in filling glaucoma prescriptions.

The NIH Small Business Innovation Research (SBIR) program funds preclinical and Phase I trials to bring translational products to market. For example, NEI SBIR supported VisionQuest Biomedical LLC to develop its EyeStar™ automated diabetic retinopathy screening system.310 EyeStar software performs real-time image quality assessment and disease detection for disease referral to ophthalmologists. It has been tested in rural Hispanic communities in Texas and received an NIH Commercialization Readiness Pilot grant for clinical trials to obtain FDA approval. NEI SBIR grants also support RetiVue, LLC, a company that produces low-cost retinal imagers that integrate with off-the-shelf digital cameras to detect DR, AMD, and glaucoma. They are developing a wide-field imager for detecting retinopathy-of-prematurity, a serious blinding disease affecting severely premature infants, which can usually be treated if detected promptly. NEI SBIR support for Aeon Imaging, LLC, led to the development of a low-cost retinal imaging device designed to screen patients for early AMD at their primary care clinic.311 NIDDK SBIR supported the next generation of retinal imaging technology to improve detail, resolution, and accuracy in diagnosing and monitoring DR. The research seeks to bring to market imaging technology that employs adaptive optics (AO), a technique used heretofore primarily in the laboratory to compensate for the eye's aberrations and provide cellular level detail of the

---

retina. NEI scientists have also developed a hand-held AO imager that can image individual light-sensitive cone photoreceptor cells in infant eyes. \textsuperscript{312}

The latest technology trend is applying artificial intelligence to detect eye disease. Machine learning computer algorithms train on a reference set of retinal images of diseases, classified by experts. \textsuperscript{313} The iterative algorithms then develop their own rules for sophisticated pattern recognition analyses to predict disease in new images. For example, Google LLC used 128,000 retinal images to train a computer network to automatically grade diabetic retinopathy. The algorithm determined which image features were critical for detecting disease, and which features to ignore. Statistics suggest these algorithms have already surpassed the ability of doctors to predict AMD, DR, and glaucoma.

\textsuperscript{312} DuBose et al. Handheld adaptive optics scanning later ophthalmoscope. \textit{Optica}. 2018. 5(9) 1027-36 doi: 10.1364/OPTICA.5.001027  
\textsuperscript{313} Lee, Aaron, Taylor, Paul, Kalpathy-Cramer, Jayashree, Tufail, Adnan et al. Ophthalmology , Volume 124 , Issue 12 , 1726 - 1728
Temporomandibular Disorders
The Committee is 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 multi-system disorder with overlapping conditions influenced by multiple biological and environmental factors rather than solely an orofacial pain condition. Therefore, the Committee urges NIDCR to support multidisciplinary research and attract scientists across other disciplines to this research. At the same time, the Committee is encouraged by the scientific meetings between NIDCR, several Institutes and Centers as well as Temporomandibular Joint [TMJ] patient groups on an integrated systems approach of precision medicine related to cellular-molecular-genetic-epigenetic mechanisms related to diagnosis and treatment of TMD and its comorbid conditions. The Committee requests an update on initiatives that resulted from the recommendations that came forth from these meetings. Further, it applauds NIDCR's involvement in the TMJ Patient RoundTable to advance collaboration to work toward the common end of providing safe and effective treatments that improve patient's quality of life. The Committee encourages continued collaboration with governmental agencies and other stakeholders in the project.

Action taken or to be taken:

To encourage multidisciplinary research and attract scientists across other disciplines to temporomandibular disorder (TMD) research, the National Institute of Dental and Craniofacial Research (NIDCR) supports research training and career development programs designed to enhance research capacity in dental, oral, and craniofacial health, including TMD and orofacial pain. These programs span career levels and bring together scientists from a variety of basic, translational, and clinical research fields, including neuroscience, genetics, imaging, pharmacology, physiology, biomaterials, and bioengineering to tackle the problem of TMD and orofacial pain. Many of the scientists from these programs go on to obtain academic faculty and training positions and achieve subsequent individual research awards to continue to study TMD. As a member of the collaborative NIH Blueprint for Neuroscience Research program, NIDCR supports research training programs to help students pursue interdisciplinary areas of neuroscience, and to bring students from underrepresented groups into the neurosciences, including TMD and orofacial pain. In addition, NIDCR is supporting TMD research through a collaboration with the NCATS Clinical and Translational Science Awards (CTSA) Program, providing translational research training opportunities to scientists early in their careers. Through supplemental funding to the CTSA Mentored Career Development Awards, NIDCR is supporting a scholar studying the interactions between cells and their extracellular environment (matrix) in temporomandibular health and disease.

NIDCR agrees that involvement in the TMJ Patient RoundTable advances collaboration to work toward the common goal of providing safe and effective treatments that improve patient's quality of life. NIDCR recognizes the importance of these interactions and will continue to work with our Federal partners as well as TMJ patient groups on these efforts. Scientific meetings between NIDCR, several other Institutes and Centers as well as Temporomandibular Joint (TMJ) patient groups have provided recommendations to advance the diagnosis, treatment, and prevention of
TMD and associated overlapping pain conditions, using precision medicine approaches. Stemming from these recommendations, in 2018 NIDCR announced a new initiative to catalyze multidisciplinary research on TMD, including the evaluation of TMD animal models and analysis of the underlying biological mechanisms of how chronic TMD develops and how it can be resolved. As part of the NIH HEAL (Helping to End Addiction Long-term) Initiative and in collaboration with many other NIH Institutes and Offices, NIDCR is supporting efforts to promote discovery of strong candidate biomarkers and endpoints for pain conditions, including TMD, that can be used to facilitate development of non-opioid therapeutics.

Looking ahead, NIDCR and the NIH Office of the Director plan to support a National Academy of Sciences consensus study on temporomandibular disorders (TMD), from research discoveries to clinical treatment. The estimated start date of this project is fall 2018. The study will bring together an expert committee in an objective and independent environment that assures rigorous analysis to 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 TMD. The committee will identify approaches to advance basic, translational, and clinical research in the field and inform development of policies related to evidence-based treatment and clinical management of TMD patients.
Tick-Borne Diseases

The Committee encourages NIAID to intensify research on Lyme and other tick-borne diseases, including research that will increase understanding of the full range of processes that cause Lyme disease infection, including any possible mechanisms of persistent infection as well as potential treatments for Lyme disease. This should include research on the pathophysiology of infection with Borrelia burgdorferi and Borrelia mayonii, as well as the development of more sensitive and accurate diagnostic tests for Lyme and other tick-borne diseases, including next-generation polymerase chain reaction and new testing methodologies such as proteomics and metabolomics.

Lyme Disease

With an estimated 300,000 new cases of Lyme disease each year, especially in rural States across 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, prevention, and treatments for those conditions. The Committee notes that in patients who suffer from long-term complications associated with Lyme disease, clear treatment pathways are often missed as a result of inaccurate and incomplete testing. The Committee urges NIAID, in coordination with CDC, to study the long-term effects on patients suffering from post-treatment Lyme disease syndrome, or "chronic Lyme disease." Specifically, the Committee urges NIAID to evaluate the effectiveness of laboratory tests associated with the detection of Borrelia burgdorferi to diagnose the disease early, which can improve the treatment of patients suffering from Lyme disease. 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 chronic Lyme disease.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) supports a robust portfolio of basic, translational, and clinical research on tick-borne diseases, including Lyme disease. NIAID-supported research in this area focuses on the development of improved diagnostics, vaccines, and therapeutics, as well as studies to better understand mechanisms of pathogenesis and factors that may contribute to post-treatment Lyme disease syndrome (PTLDS).

A major focus of NIAID research into tick-borne diseases is the development of improved and innovative diagnostics to enable earlier clinical intervention. These include the identification of biomarkers and biosignatures that could form the basis of rapid point-of-care tests; direct visualization of Borrelia bacteria in patients with early Lyme disease; a cytokine-based immunoassay; and a serological assay to measure treatment efficacy. NIAID-supported scientists also have developed a multiplex platform, the TBD-Serochip, which can test for exposure to Lyme-causing Borrelia bacteria and seven other tick-borne pathogens.

NIAID encourages investigator-initiated research into tick-borne diseases and has an active funding opportunity targeting diverse scientific areas of Lyme disease and co-infections.
transmitted by ticks. NIAID is supporting research into the persistence of *Borrelia* bacteria and potential implications for PTLDS. This includes a comprehensive assessment of Lyme-infected patients post-treatment to determine if viable *Borrelia* bacteria can be detected, and another study tracking patients with Lyme disease before, during, and following treatment to understand any long-term effects of Lyme disease and treatment. NIAID researchers are conducting Phase 2 clinical trials on an approach, known as xenodiagnosis, that uses disease-free, laboratory-bred ticks to detect the presence of *Borrelia* bacteria following Lyme disease treatment. This trial is investigating whether positive xenodiagnostic results for *B. burgdorferi* can be linked to ongoing symptoms in patients who have completed treatment. These studies may contribute to a better understanding of PTLDS and improved diagnostic criteria for Lyme disease.

NIAID collaborates with the Centers for Disease Control and Prevention (CDC) and other Federal partners as a member of the Tick-Borne Diseases Working Group. The Working Group, established by the 21st Century Cures Act, brings together Federal partners, Lyme disease experts, and patient advocates to examine research priorities and ensure inter-agency coordination in tick-borne disease research. NIAID also is an active member of the long-standing HHS Lyme and Other Tick-Borne Diseases Working Group (separate from the Cures Act-established Working Group), consisting of representatives from HHS agencies that share information on advances and initiatives, and host public webinars on tick-borne diseases.

NIAID will continue to conduct and support intra- and extramural research on the development of diagnostics, vaccines, and therapeutics for Lyme and other tick-borne diseases. NIAID also will continue to work with the National Library of Medicine to ensure that terminology accurately reflects the current state of scientific knowledge about Lyme disease and its effects. NIAID remains committed to collaborative research efforts in the tick-borne diseases field.
Transformative High-Resolution Cryo-Electron Microscopy

The Committee commends NIH on its initial investment in the Transformative High Resolution Cryo-Electron Microscopy (Cryo-EM) program. The recent Nobel Prize for chemistry was awarded for the development of Cryo-EM research funded by NIH. The Committee urges the NIH to expand the number of national service centers and training opportunities to further refine and advance Cryo-EM research. The Committee directs NIH to provide an update of these efforts in the fiscal year 2020 Congressional Justification.

Action taken or to be taken:

The NIH Common Fund addresses emerging scientific opportunities and pressing challenges by providing a space to support high-risk endeavors with the potential for extraordinary impact. NIH leadership recognizes the importance of cryo-electron microscopy (cryo-EM) in the production and analysis of high resolution data that provide detailed information about viruses, proteins, and other medically important biomolecules, and enthusiastically supports the Transformative High Resolution Cryo-Electron Microscopy program. During summer 2018, NIH made awards through the Common Fund to the New York Structural Biology Center, Oregon Health & Science University in partnership with the Pacific Northwest National Laboratory, and the SLAC National Accelerator Laboratory at Stanford University for the creation of national service and training centers for cryo-EM sample preparation, collection of high-resolution data, and computational analysis. The centers will be equipped with state-of-the-art equipment with cross-training capabilities. In addition to the national service centers, the program made four awards for the development of training materials to build a skilled and technically savvy cryo-EM workforce. The Common Fund spent $26 million on the program in FY 2018, plans to spend $15 million in FY 2019, and plans to continue funding the program in FY 2020.

Looking to the future, the NIH is exploring Common Fund support of cryo-electron tomography (cryo-ET), which allows high-resolution imaging of larger cellular structures in near natural conditions. NIH will consider expanding the Transformative High Resolution Cryo-Electron Microscopy program to include a cryo-ET center or supporting cryo-ET technology development for FY 2020.
Translational Research Program

The Committee notes the Specialized Programs of Research Excellence [SPORE] program is one of NCI’s cornerstone efforts to promote collaborative, interdisciplinary translational cancer research. The Committee continues robust support for SPORE grant programs as it works to bring basic research into practical treatments. The Committee commends NCI’s investment in this area and notes that over 60 percent of the NCI SPOREs are multicenter, and that 37 percent of those multicenter sites involve more than two institutions. Likewise, the Committee notes that several of the existing SPOREs focus on related organ site diseases (such as the GI, Neuroendocrine, and Sarcoma SPOREs), and another SPORE focuses on a specific pathway called hyperactive RAS in the context of mutations in the NFI gene. The Committee requests an update in the fiscal year 2020 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 22 states, housed at 36 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 54 SPOREs focusing on 18 organ sites, groups of related cancers, or diseases that share a common pathway or molecular characteristic. Specifically, these organ sites/diseases include brain, breast, cervical, endometrial, gastrointestinal, head and neck, hepatobiliary, kidney, leukemia, lung, lymphoma, myeloma, neuroendocrine, ovarian, pancreatic, prostate, skin, and thyroid cancers, as well as hyperactive RAS tumors.

The newest SPORE, funded in September 2018, is the Mayo Clinic Hepatobiliary SPORE.314 This is the first SPORE focused on liver cancer. It is based at the Mayo Clinic–Rochester (MN); other performance sites include the Mayo Clinic–Scottsdale (AZ), the Mayo Clinic–Jacksonville (FL), Rockefeller University (NY), and the University of Pittsburgh (PA). One goal of this SPORE is to develop diagnostic tests for the early detection of fibrolamellar hepatocellular carcinoma (FLHCC), a rare lethal liver disease that primarily affects children and young adults; FLHCC is usually not diagnosed until it has reached an advanced stage due to the lack of effective early detection methods. Another focus in FLHCC will be on inhibiting the activity of an oncogenic fusion protein315 thought to be a major driver of FLHCC in most patients. Other goals of the SPORE are to develop ways to inhibit a key protein316 as a treatment for cholangiocarcinoma (bile duct cancer), and to develop novel treatment strategies for hepatocellular carcinoma.

NCI issued a funding opportunity announcement in 2017 to invite applications for planning grants to develop SPOREs that focus on research in cancer health disparities.317 The aim is to improve the prevention, early detection, diagnosis, and treatment of cancers that

314 https://projectreporter.nih.gov/project_info_description.cfm?aid=9418217
315 DNAJB1-protein kinase A
316 Fibroblast growth factor receptor 2

264
disproportionately affect specific racial and ethnic minority populations. Four awards were made in 2018 for projects focused on breast cancer, prostate cancer, and colon cancers.318

Examples of recent advances made by SPORE investigators include:

- The hyperactive RAS tumor SPORE (Indiana University–Purdue University at Indianapolis) demonstrated that childhood cancer survivors without a history of a familial cancer predisposition syndrome who develop a second cancer frequently have germline mutations in the tumor suppressor gene \(TP53\). This finding suggests that identifying germline \(TP53\) mutations at the time of the initial cancer diagnosis may identify patients at high risk of developing a second cancer who might benefit from modified treatment approaches and/or intensive posttreatment monitoring.319

- The University of Colorado–Denver Lung SPORE demonstrated that the drug larotrectinib exhibited marked and durable anticancer activity in adults and pediatric patients whose tumors had \(TRK\) gene fusions, regardless of the age of the patient or the tumor type.320 Larotrectinib was issued an orphan drug status and was granted Priority Review by the FDA this year.

- The Dana-Farber Cancer Institute Gastrointestinal SPORE showed that, in cancers driven by amplification of the \(KRAS\) gene, which are resistant to treatment with inhibitors that target the protein MEK, pharmacologic inactivation of a protein called SHP2 restores tumor sensitivity to MEK inhibition.321


Translational Research
The Committee encourages the NIBIB to conduct state of the art translational research in the diagnosis, prognosis, and treatment of neurotrauma. Neurotrauma is the umbrella term for two primary pathologies, spinal cord injuries and traumatic brain injuries. These injuries are unique in that they affect how and who a person is, with incredible variation between patients. The sizable incidence of injury and prevalence of disability resulting from neurotrauma results in significant human and economic burden. As befits the complexity of the challenges from neurotrauma, multiple NIH Institutes and Centers coordinate research, which ranges across a wide spectrum, from understanding the cellular mechanisms of immediate and delayed damage, though development of better prevention, treatment, and rehabilitation, and engages scientists, engineers, and clinicians from a broad range of disciplines. The Committee recognizes the need for cross-disciplinary collaboration to meet these challenges and strongly encourages NIH to support such research through all appropriate support mechanisms.

Action taken or to be taken:

Neurotrauma is a medical challenge that encompasses mild to severe traumatic brain injury and spinal cord injury and can impact mobility, cognitive function, sensation, and emotion. These complex disorders can occur in an instant and result in lifelong disability. Building on research and knowledge gained over the last decade, early intervention can help to limit the impact of neurotrauma and manage its effect on a person’s health and quality of life. NIH supports a multi-pronged approach to the challenges of neurotrauma and effective interventions including: research on the normal functions of the brain and spinal cord and mechanisms of damage from trauma, stem cell biology, medical imaging, development of devices to restore function, tissue engineering, small molecule drugs and biologics, behavioral rehabilitation, research to develop prosthetics and brain computer interfaces, and clinical studies on a wide range of interventions.

The Institutes at NIH collaborate and coordinate research in this area within NIH and with other federal agencies. The National Institute of Neurological Disorders and Stroke (NINDS) leads NIH research in this area and has a broad portfolio of basic, pre-clinical translational, and clinical research on neurotrauma. The National Institute of Biomedical Imaging and Bioengineering (NIBIB) continues to focus on early stage technology development such as supporting research during the technical and clinical feasibility phases of the development pipeline. The coordination of rehabilitation research related to spinal cord injuries (SCI) and traumatic brain injuries (TBI) is managed through the Medical Rehabilitation Research Coordinating Committee, which is led by National Center for Medical Rehabilitation Research in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD).

A few examples of ongoing research and collaboration include:

- NINDS-funded consortium to support development and validation of outcome measures in preclinical TBI to improve translation between basic and clinical research.
- Strategies to Innovate EmeRgENcy Care Clinic Trials network (SIREN) is a joint program of NINDS and the National Heart, Lung, and Blood Institute (NHLBI); one study is working to optimize the treatment schedule in preparation for the next phase of the study.
• **Transforming Research and Clinical Knowledge in TBI** is an observational study at 11 sites of more than 3,000 adults and children with TBI across the spectrum of injury severity with the goal to better characterize and stratify patients, allowing meaningful comparisons of treatments and outcomes to improve patient care and the next generation of clinical trials.

• **The Epilepsy Bioinformatics Study for Antiepileptogenic Therapy (EpiBioS4Rx)** is a large, international, multicenter study to develop techniques and patient populations necessary to carry out future cost-effective trials to prevent post-traumatic epilepsy.

• **The Evaluation of Longitudinal Outcomes in Mild TBI active-duty military and veterans study** is investigating long-term advanced magnetic resonance imaging measures and clinical outcomes of concussive TBI sustained by military personnel during deployment.

• **Center for Neurosciences and Regenerative Medicine** is a multi-agency effort focused on understanding and developing better treatments for traumatic brain injury.

• Pre-clinical studies of an implantable systems in patients with SCI and paralysis to help restore function.

• Machine learning and imaging to help pinpoint diagnosis.

• Research to identify effective prevention, screening, and treatment of neurotrauma in children from abusive head trauma, falls, and accidents.

NIH investment in understanding the mechanisms of neurotrauma is incrementally being translated to the private sector for further development of diagnostic capability and interventions such as a collaboration between NIH and the Department of Defense (DoD), which led to a Food and Drug Administration (FDA) approved blood test to aid in the evaluation of concussion in adults. NIH is committed to using the full spectrum of research approaches and expertise to address the scientific challenges posed by neurotrauma.
Translational Vaccine Research

The Committee notes a very promising area in the field of vaccine and immunology is translational vaccinology, in which researchers use innovative principles of vaccine design and enhancement to generate novel, experimental vaccines suitable for assessment and development through pre-clinical studies and clinical trials. The Committee strongly encourages NIAID to continue to support universal flu vaccine research and to continue to support a robust portfolio of extramural, highly meritorious translational vaccine research that focuses on an interdisciplinary approach to this research. The Committee requests NIAID provide an update in the fiscal year 2020 CJ on expansion opportunities for interdisciplinary translational vaccinology research.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) is implementing collaborative programs that enable a translational vaccinology approach toward development of novel vaccine candidates, platforms, and technologies, including those that can be adapted to quickly address specific emerging and re-emerging infectious disease threats. For example, the NIAID Partnerships Program for Translational Research fosters collaboration among extramural scientists to advance development of vaccines and other products to address biological threats. In 2018, NIAID released solicitations for proposals to establish consortia comprising multidisciplinary teams of investigators to conduct iterative research projects to inform development of vaccines against tuberculosis and influenza. The NIAID Vaccine Research Center (VRC) also brings together experts in diverse scientific fields including structural biology, immunology, and vaccine production to advance innovative vaccine designs and strategies. NIAID intramural and extramural efforts exemplify the transformational, interdisciplinary approach required to accelerate the development of novel vaccines, platforms, and technologies.

NIAID continues to support innovative vaccine approaches that build on basic research advances. NIAID is exploring novel vaccine platforms including non-infectious virus-like particles (VLPs), structurally engineered proteins, nanoparticles, viral vectors, and RNA- and DNA-based vaccines. The NIAID VRC used a DNA-based platform to develop a vaccine candidate for the Zika virus that went from concept to first-in-human clinical trials in less than four months. The vaccine is currently being tested in Phase 2/2b clinical trials in Zika-endemic areas in the Americas. NIAID researchers also have developed a nanoparticle-based universal influenza vaccine currently in a Phase 1 clinical trial, as well as an experimental VLP-based vaccine that offered broad protection in mice from a variety of influenza viruses. An initial clinical study is planned for the VLP-based vaccine candidate. A more complete overview of NIAID efforts to develop a universal influenza vaccine may be found in the FY 2020 Significant Item “Universal Influenza Vaccine.” NIAID investigators also are conducting clinical trials to evaluate novel candidate vaccines against malaria and respiratory syncytial virus as well as an experimental chimeric Zika/dengue vaccine.

NIAID also provides access to essential vaccine development resources – including animal models, safety and toxicity testing, and preparation of pilot lots for testing – to assist scientists in industry and academia in the development of novel vaccine candidates and platforms. These resources are particularly valuable to extramural researchers pioneering groundbreaking
technologies that may require extensive preclinical data to enable their advancement along the regulatory pathway.

NIAID is dedicated to growing the field of translational vaccinology, including through the encouragement of investigator-initiated research that is needed to facilitate the entry of new, promising vaccine technologies into the development pipeline. NIAID will continue to support groundbreaking interdisciplinary research for the development of vaccines and vaccine platforms designed to address emerging and re-emerging infectious diseases.
Traumatic Brain Injury
The Committee understands that regenerative medicine research, including the use of adult stem cells, tissue engineered scaffolds, and means to promote neuroplasticity, may play an important role in the treatment of traumatic brain injury (TBI) and stroke. The Committee strongly encourages NINDS to work with the National Institute on Aging and other relevant ICs to ensure a robust and coordinated portfolio of research on how to leverage regenerative medicine research in the treatment of TBI and stroke. The Committee requests an update in the fiscal year 2020 Congressional Justification on efforts in these specific areas of research.

Action taken or to be taken:

Basic research has led to remarkable advances in our understanding of neuroplasticity, the brain’s capacity to adapt, which is important in recovery from stroke or TBI. Extensive research on the underlying mechanisms of neuroplasticity, on what stimulates and limits brain plasticity following injury, and on stem cell biology more generally have led to several promising regenerative medicine strategies for treatment of stroke and TBI that are at various stages of investigation, mostly in laboratory animals.

To a variable extent, the brain may repair itself or compensate following stroke or TBI, although that self-repair is often far from adequate. Neurogenesis, the generation of new nerve cells, may contribute to that self-repair. Neuroplasticity also contributes to recovery via new or altered connections that rewire remaining brain circuits to take on new functions. Researchers are intensively investigating the mechanisms that control neurogenesis and rewiring and using that knowledge to develop a variety of different approaches to enhance brain self-repair following TBI or stroke. Among the interventions currently under investigation are small molecule drugs and biologics that target the control systems underlying these processes, as well as electrical stimulation and behavioral methods to enhance plasticity.

Other studies are investigating cell transplantation, using stem cells themselves or specific types of cells derived from stem cells in cell culture, such as cells that restore white matter or the balance of inhibition and excitation. Many cell-based strategies use biomaterials such as tissue engineered scaffolds and hydrogels to provide an environment that enhances survival and integration of transplanted cells into the surviving brain tissue. Researchers are also using drugs targeting the signaling pathways that control cells to enhance cell survival. Transplanted cells may foster recovery in a variety of ways other than directly replacing lost cells, such as by providing beneficial chemical signals that enhance recovery of surviving brain tissue. There is ongoing research on these mechanisms as well.

Rehabilitation interventions for stroke and TBI also rely on brain plasticity. Rehabilitation training and environmental enrichment are designed to optimize the plasticity that underlies recovery, and research is exploring drugs and electrical stimulation that may enhance the effects of training. Neuroplasticity research has become integral to many areas of neuroscience. As befits the breadth of basic plasticity research and its potential applications, NINDS works closely with NIA, as with all parts of NIH whose missions intersect the various aspects of neuroplasticity, via the BRAIN Initiative, the NIH Neuroscience Blueprint, and many other trans-NIH groups, as well as the myriad daily interactions among Institute directors and scientific program staff. Research on regenerative medicine is also boosted by the NIH-wide Regenerative
Medicine Innovation Project, which is supported by funds allocated by Congress via the 21st Century Cures Act.
Trisomy 21
The Committee applauds the NIH for prioritizing its investment in the current pipeline of Down syndrome research and the NIH Director's leadership in advancing the trans-NIH initiative recommended by the Committee in the fiscal year 2018 Omnibus bill. Through the trans-NIH Initiative and other NIH supported research efforts that involve cohorts of individuals with Down syndrome, the Committee urges NIH to continue to expand such cohorts and build its current pipeline of early-stage investigators focused on Down syndrome. NIH should prioritize funding for research to improve the health and neurodevelopment of individuals with Down syndrome and of typical individuals at risk for immune system dysregulation, Alzheimer's disease, cancer, cardiovascular disease, and autism.

Action Taken or to be Taken

Down syndrome is the most common genetic cause of intellectual disability and one of the most visible and universally recognized genetic syndromes. Each year there are approximately 5,300 babies born in the United States with Down syndrome. Within the past 25 years, the average lifespan for a person with Down syndrome has doubled, but despite this promising increase, individuals with Down syndrome and their families still face significant health challenges. In 2014, the National Institutes of Health (NIH) published *Down Syndrome Directions: The NIH Research Plan on Down Syndrome*, which pointed out the need for greater understanding of commonly co-occurring conditions in individuals with Down syndrome that are also seen in the general population, such as Alzheimer’s disease/dementia, autism, cataracts, celiac disease, congenital heart disease and diabetes, to improve the health of those with Down syndrome and all individuals who share these conditions. The plan also recommended additional study of common complications of aging, such as coronary heart disease and solid cancers, which are rarely seen in individuals with Down syndrome.

Building on its ongoing research efforts, following collaborative discussions with 18 NIH institutes and centers, in 2018 NIH launched a major new project focused on improving the health and well-being of individuals with Down syndrome, and on learning more about risk and resilience factors for common diseases that they share with individuals who do not have Down syndrome. Known as the INvestigating Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) project, INCLUDE is a comprehensive, trans-NIH strategy that addresses critical health and quality-of-life needs to bring results rapidly to individuals with Down syndrome and their families. The main goals are to accelerate the development of new therapies, informed by critical basic science discoveries and studies of large cohorts of individuals with Down syndrome, while simultaneously bringing promising agents already in development to individuals with Down syndrome as quickly as possible. At the same time, full inclusion of individuals with Down syndrome into ongoing clinical studies will ensure that they will reap the benefits of agents already in development. A clinical trials network will be developed to engage individuals with Down syndrome where they may already receive health care or developmental services, to help them manage multiple health needs. Such a resource will also ensure that new therapies can be brought to trial as they emerge in the future.

In FY 2018, NIH published two notices to the research community to announce supplements for the most promising existing basic science awards and contracts, cohort studies, or clinical trial networks, to jumpstart this effort while setting the stage for FY2019 and beyond. These notices
have generated a great deal of interest from the research community, from early-stage as well as established investigators and those who study Down syndrome as well as those who are new to the field. Awards were made in late FY 2018. Engagement efforts with key stakeholders and a series of scientific workshops are planned for FY2019 and FY2020 to ensure that the scientific goals of INCLUDE are continually informed by the research and constituency communities to produce meaningful results for individuals with Down syndrome and their families.
Tuberous Sclerosis Complex
The Committee is encouraged by NIH's updated TSC Research Plan published in 2016. Building on this Research Plan, the Committee encourages the Director to coordinate the participation of multiple Institutes and Centers on a research strategy aimed at addressing the numerous medical and neuropsychological burdens associated with TSC while deciphering the biology underlying phenotypic heterogeneity. This effort should apply recommendations from NIH's Neurodevelopmental Disorders Biomarkers Workshop held in December 2017 involving TSC and related neurodevelopmental dis-orders, to take advantage of biomarker expertise and lessons learned across disease groups. Manifestations of TSC are highly variable among affected individuals, and TSC can be a model condition for developing precision medicine approaches to treat each individual's symptoms to maximize the benefit-risk ratio. NIH should encourage research opportunities in the five key areas prioritized by workshop participants: understanding phenotypic heterogeneity in TSC, gaining a deeper knowledge of TSC signaling pathways and the cellular consequences of TSC deficiency, improving TSC disease models, developing clinical biomarkers of TSC, and facilitating therapeutics and clinical trials research.

Action taken or to be taken:

NINDS supports research projects focused on understanding the roles of the tuberous sclerosis complex (TSC) 1 and 2 genes (TSC1 and TSC2) in typical nervous system development, and how mutations in these genes give rise to common features of TSC such as autism, cognitive impairment, and epilepsy. NINDS-funded research on TSC covers all five of the themes that emerged from the 2015 NINDS-sponsored workshop on TSC as recommended areas of emphasis.

Because TSC manifests differently among individuals, NINDS supports basic research to better understand the heterogeneity of TSC, as well as translational research to personalize treatment of TSC. A recent NINDS-supported study shed light on the rate and predictive factors of epilepsy co-occurring with TSC. Another project is using stem cells derived from patients with TSC to study how individual TSC gene mutations differentially affect nervous system development and could potentially pave the way for personalized treatments.

NINDS also supports research focused on characterizing cell signaling pathways that are abnormal in TSC, with the hope of identifying novel therapeutic targets in these pathways. For example, research projects are studying how the TSC1 gene interacts with the cellular pathways that regulate energy production, play important roles in tumor formation, and control production of myelin, an insulating substance critical for healthy nerve cell function.

Because the development of effective new treatments depends on the availability and validity of disease models, NINDS supports projects focused on modeling specific aspects of TSC in animal models. Two such projects are developing novel mouse models to study how TSC gene mutations cause seizures to arise in the disease.

---

Early diagnosis is also critical for the successful treatment of TSC: to this end, NINDS supports research efforts to discover and rigorously test clinical biomarkers for TSC. NINDS-funded projects recently validated diagnostic biomarkers that can identify those infants with TSC who will develop seizures or autism. NINDS also led a workshop in December 2017 on biomarker development for neurodevelopmental disorders including TSC. The workshop brought together leading researchers, government agencies, and advocacy groups, culminating in recommendations for the research community which are currently being finalized for publication.

NINDS also supports therapeutic development studies and clinical trials. A new project supported by NINDS, the National Heart, Lung, and Blood Institute, and the National Center for Advancing Translational Sciences will use cutting-edge technology known as “organ-on-chip” models to test the effects of TSC mutations on the health of heart tissue, with the goal of rapidly identifying new biomarkers and drug candidates. In the ongoing Preventing Epilepsy Using Vigabatrin in Infants with Tuberous Sclerosis Complex (PREvENT) clinical trial, NINDS-supported researchers are testing the anticonvulsant drug vigabatrin’s capacity to prevent seizures and improve cognitive function in infants diagnosed with TSC.

NINDS continues to embrace the multifaceted research recommendations from the TSC Research Plan, and will continue to support meritorious research on the basic understanding and improved treatment of TSC.
Undiagnosed Diseases
The Committee supports the efforts of the Undiagnosed Diseases Network [UDN], funded through the Common Fund, to enhance access to patients, caregivers, and other stakeholders as well as make information obtained through the UDN available to Federal agencies and health-related agencies. To that end, the Committee urges the Director to ensure that information on diagnoses and patient populations identified by UDN is coordinated with the NCATS' Office of Rare Disease Research and its Genetic and Rare Diseases Information Center. The Committee is pleased with the work of the UDN to advance patient care and treatment options. The Committee is particularly focused on ensuring that as research (produced at UDN or any of the Institutes) provides more information on treatments for rare, undiagnosed, and underdiagnosed diseases that this information is transitioned to become more readily accessible. This work is one example of the success of NIH and illustrates how the UDN program's successes must be built upon. The Director is encouraged to identify successful work completed by UDN and disseminate it to the medical community, and continue to engage with patient advocacy organizations.

Action taken or to be taken:

In Fall 2018, the Undiagnosed Diseases Network [UDN] will fund a second phase of awards supported by the NIH Common Fund. During Phase II, the UDN will continue accepting participants with undiagnosed medical cases and anticipates increasing the number of clinical sites to enhance the diversity of the UDN as a national network both geographically and ethnically. Since Common Fund projects are typically only supported for two phases, the second phase of the UDN also aims to study the components required for long-term sustainability of the network once Common Fund support ends.

The UDN regularly shares data and findings throughout the research community and will continue to identify new and better ways to disseminate information and connect participants to outside research studies in Phase II. In an effort to circulate findings, this research consortium has published 34 manuscripts describing novel diagnoses and innovative approaches to diagnosing rare diseases since 2015. The UDN has also submitted 164 reports to ClinVar, an NIH-funded, freely accessible and public archive of reports describing the relationships among human genetic variations and phenotypes, or observable characteristics. Data in ClinVar helps build evidence for the clinical significance of certain genetic variants. Additionally, the UDN has submitted the data of 150 participants plus 312 of their family members to the Database of Genotypes and Phenotypes [dbGaP], an NIH archive of research data and results from studies that look at the interaction of genotype, the genomic profile, and phenotype in humans. Through dbGaP, researchers around the world can request access to the UDN’s dataset to pursue new scientific inquiries. Finally, the UDN collaborates and shares data with clinicians and researchers around the world through Matchmaker Exchange. The Matchmaker Exchange project is an international endeavor launched in 2013 that connects multiple databases of patient information to match individuals with similar phenotypic and genotypic profiles. This matching process may help improve understanding of a genetic disorder and maximizes opportunities for

diagnosis and treatment of patients. All of the efforts described here are making data collected by
the UDN accessible to stakeholders invested in rare disease research not only in the United
States, but also around the world.

Recently, there has been interest within the network to increase engagement with the US
Department of Veterans Affairs [VA]. VA representatives have attended the UDN’s in-person
Steering Committee Meetings and VA patients have been referred to the UDN. Additionally, the
UDN is collaborating with the National Center for Advancing Translational Sciences’ [NCATS]
Office of Rare Diseases Research on a regular basis to coordinate efforts. Staff from the Office
of Rare Diseases Research are on the UDN program team that meets weekly to discuss program
management, including opportunities to leverage collaborations between other research programs
at the NIH. The UDN also shares new diagnoses to ensure that they are available through the
NCATS-supported Genetic and Rare Diseases Information Center [GARD].

The UDN is continually working to find new ways to engage the patient community and make
patients partners in research. Furthermore, in January 2017, the UDN researchers and study
participants created the Participant Engagement and Empowerment Resource group. This group
consists of parents, patients, genetic counselors, and other medical support staff to provide
support for the UDN families, improve the participant experience, connect families with each
other, and share the UDN with others.

---

325 https://ncats.nih.gov/gard
Universal Influenza Vaccine

The Committee appreciates the investments that NIAID has made and intends to make to improve our response to the seasonal influenza virus. In response to the severity of the 2017-2018 flu season, Congress encourages NIAID to continue to prioritize investment in the basic and clinical scientific research necessary to develop a universal influenza vaccine. The Committee directs NIAID to allocate not less than $100,000,000 in fiscal year 2019 to advance basic, translational, and clinical research necessary to develop a universal influenza vaccine. In response to the severity of the 2017-2018 influenza season, the agreement encourages NIAID to continue to prioritize investment in the basic and clinical scientific research necessary to develop a universal influenza vaccine. The Committee encourages the continued support of the long-standing NIAID Vaccine and Treatment Evaluation Units [VTEUs] program. The NIAID VTEUs continue to play a critical role in NIAID's effort to respond to emerging and reemerging infectious disease threats to the public health through their ability to rapidly test new and improved vaccine and therapeutic candidates. The Committee encourages NIAID to develop universal influenza vaccine candidates by utilizing the research capacity of the VTEUs, including extended stay research units with experience in studying human lung responses, multi-platform 'omic analyses, and the development of t-cell targeting universal influenza vaccines.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) maintains a comprehensive portfolio of basic, translational, and clinical research on seasonal and pandemic influenza. The severity of the most recent influenza season, the consistently changing nature of seasonal influenza viruses, and the ever-present threat of pandemic influenza underscore the importance of developing a universal influenza vaccine that would provide lasting protection against multiple influenza viruses. NIAID recently published a strategic plan for universal influenza vaccine development that focuses on three key areas: improving knowledge of the transmission and pathogenesis of influenza infection; characterizing influenza immunity and immune factors that correlate with protection; and supporting the design of universal influenza vaccines.

NIAID will use funding included in the 2018 Consolidated Appropriations Act to accelerate discoveries toward the development of universal influenza vaccine candidates. Among other purposes, these funds will support the NIAID-funded Centers of Excellence for Influenza Research and Surveillance (CEIRS) network. The CEIRS network has developed a strategy to predict the viral mutations that might affect human immune responses to influenza viruses so they can be incorporated into innovative influenza vaccine strategies. NIAID scientists also have established a human influenza challenge model that will be critical in testing new universal influenza vaccine candidates. In addition, NIAID recently released new funding announcements to encourage influenza vaccine development and research into how initial and repeated exposures to influenza viruses shape immunity to future exposures.

NIAID is actively investigating candidate universal influenza vaccines to assess their ability to protect against diverse influenza strains. The NIAID Vaccine Research Center has developed a ferritin nanoparticle-based vaccine candidate currently being tested in a Phase 1 trial alone and in prime-boost regimens with a DNA vaccine candidate. NIAID investigators also are planning
Phase 1 clinical trials to evaluate experimental vaccines using non-infectious virus-like particles that protected mice and ferrets from diverse influenza viruses.

NIAID continues to support the Vaccine and Treatment Evaluation Units (VTEUs), which are currently conducting multiple clinical trials evaluating candidate universal influenza vaccines. In 2018, NIAID launched a Phase 2 VTEU clinical trial to evaluate the M-001 vaccine candidate. M-001 contains several influenza fragments that are recognized by the human immune system and are common among multiple influenza virus strains. In addition, NIAID is sponsoring a Phase 1 VTEU clinical trial to evaluate the safety and immunogenicity of a regimen using an investigational live attenuated intranasal influenza vaccine candidate followed by a boost with a licensed, quadrivalent inactivated seasonal influenza vaccine. NIAID also is expanding capacity of the VTEUs to conduct human influenza challenge studies using extended stay research units that provide a unique environment to examine the durability and efficacy of candidate vaccines.

NIAID remains committed to investing in influenza virus research to accelerate the development of universal influenza vaccine candidates. The NIAID-supported CEIRS network and VTEUs are vital for developing promising countermeasures against influenza, including a universal influenza vaccine, and supporting this valuable research infrastructure is a high priority.
Vaccination Acceleration
The Committee encourages NIH to promote vaccination acceleration through controlled human experimental infection models, particularly enteric challenge models. These models may enable vaccination testing to move more rapidly, and involve fewer subjects (smaller sample sizes), launching vaccinations in the public faster. Supporting these challenge models will support critical research that is advancing responses to such diseases as salmonellosis and cholera.

Action taken or to be taken:

The National Institute of Allergy and Infectious Diseases (NIAID) supports a comprehensive portfolio of research covering basic, translational, and clinical studies to inform the development of diagnostics, therapeutics, and vaccines for infectious diseases of public health concern, including those caused by enteric (intestinal) pathogens. To support these efforts, NIAID provides access to comprehensive vaccine development resources in addition to supporting the development of human challenge models of infectious diseases. Human challenge models are research tools that allow for human volunteers to be infected with pathogens under carefully controlled conditions monitored for safety. Challenge models can reveal important details about how pathogens cause disease as well as offer opportunities to test candidate countermeasures including vaccines.

NIAID supports the development and implementation of human challenge studies for several enteric diseases. NIAID currently is supporting two Phase 1 studies to evaluate the safety, reactogenicity, and optimal dose of norovirus for challenge studies. The results of these studies will inform the development of robust human challenge models for norovirus, a major cause of gastroenteritis. NIAID also is supporting a Phase 2b human challenge study to evaluate the immunogenicity and efficacy of a live, attenuated oral Shigella vaccine candidate. NIAID is supporting additional efforts to advance the development of a candidate vaccine for Shigella, a highly infectious foodborne illness that causes diarrhea and can lead to severe complications. NIAID is funding Phase 1 studies of two experimental Shigella vaccines; development of functional assays to predict vaccine efficacy; investigation of protective maternal antibodies to inform the development of a preventive vaccine for children; development of a stable needleless vaccine; and early stage development of a three-dimensional (3D) human tissue model of the colon to overcome inadequacies of Shigella animal models.

NIAID also supports human challenge models of non-enteric infectious diseases and is expanding the capacity of its Vaccine and Treatment Evaluation Units to conduct human challenge studies with influenza and other pathogens. The NIAID dengue controlled human infection models have been used to assess the efficacy of an experimental vaccine that has moved into Phase 3 evaluation in dengue-endemic Brazil. NIAID researchers also recently developed and implemented the first human influenza challenge study in healthy volunteers in the United States in over a decade, resulting in new insights into the human immune response to influenza virus infection. NIAID scientists are actively exploring the use of this model to evaluate novel vaccine and therapeutic candidates in partnership with industry and academic collaborators. In addition, NIAID scientists are establishing a human challenge model of respiratory syncytial virus (RSV) for the evaluation of RSV vaccine and antiviral candidates.
NIAID is committed to encouraging and supporting creative and robust approaches to accelerating the design and development of vaccine candidates for enteric and non-enteric infectious diseases. NIAID recognizes the importance of human challenge models in these efforts and will continue to support their development.