

SIGNIFICANT ITEMS (SIs)

FY 2015 Senate Appropriations Committee Report
and
FY 2015 Conference Committee Report

Table of Contents

National Cancer Institute (NCI).....	1
National Heart, Lung, and Blood Institute (NHLBI).....	35
National Institute of Dental and Craniofacial Research (NIDCR).....	53
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).....	57
National Institute of Neurological Disorders and Stroke (NINDS).....	71
National Institute of Allergy and Infectious Diseases (NIAID).....	89
National Institute of General Medical Sciences (NIGMS).....	103
National Institute of Child Health and Human Development (NICHD).....	105
National Eye Institute (NEI).....	119
National Institute of Environmental Health Sciences (NIEHS).....	125
National Institute on Aging (NIA).....	129
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS).....	135
National Institute on Deafness and Other Communication Disorders (NIDCD).....	145
National Institute on Alcohol Abuse and Alcoholism (NIAAA).....	157
National Institute on Drug Abuse (NIDA).....	159
National Institute of Mental Health (NIMH).....	167
National Human Genome Research Institute (NHGRI).....	173
National Center for Complementary and Alternative Medicine (NCCAM).....	175
National Institute on Minority Health and Health Disparities (NIMHD).....	177
Fogarty International Center for Advanced Study in the Health Sciences (FIC).....	185
National Library of Medicine (NLM).....	187
National Center for Advancing Translational Sciences (NCATS).....	189
NIH Clinical Center (CC).....	199
Office of the Director (OD).....	201

A

Accelerating Commercialization of Therapies to Patients.....	194
Administrative Burden Reduction Workgroup.....	212
Alzheimer’s Disease	129, 130, 133
Amyloidosis	57
Angiogenesis.....	1
Antibiotic-Resistant Infections	89
Autism.....	167
Autism and Telehealth	168
Autoimmune Diseases	90

B

Basic Biomedical Research.....	213
Basic Research	201
Biomedical Research Workforce Diversity	202
BRAIN Initiative.....	71

C

Cancer Centers	2
Cardiovascular Disease.....	35
Career Development Awards for Clinical Researchers	204
Cell-Based Regenerative Treatments.....	36
Centers for Advanced Diagnostics and Experimental Therapeutics [CADET].....	37
Central Auditory Plasticity	145
Cerebral Cavernous Malformation [CCM].....	71
Chemical Risk Assessments	204
Childhood Lead Poisoning.....	125
Chimpanzees	206
Chromosome Abnormalities	105
Chronic Fatigue Syndrome (CFS)	207
Chronic Obstructive Pulmonary Disease [COPD].....	38
Clinical and Translational Science Awards [CTSA]	189, 195
Communication of Research Findings.....	187
Congenital Diaphragmatic Hernia [CDH]	106
Congenital Heart Defects	38
Consolidated Communications Activities.....	214
Critical Care	103
Cures Acceleration Network.....	189, 196
Cystic Fibrosis [CF].....	40

D

Demographic Research	107
Demographic, Economic, and Behavioral Research.....	131
Dental Materials Research	54
Diabetes.....	58
Diabetes in Minorities.....	177
Diabetic Retinopathy	119
Down Syndrome	108
Drug Abuse and HIV/AIDS.....	159
Drug Allergy.....	91
Drug Rescue and Repurposing.....	190
Duchenne Biomarkers.....	72

E

Environmental Exposures and Reproductive Health	126
Eosinophil-Associated Disorders.....	92
Epilepsy.....	73
Eustachian Tubes	145
Extramural and Intramural Research	216

F

Food Allergy	94
Fragile X-Associated Disorders [FXD]	110
Functional Gastrointestinal Disorders [FGIDs]	59
Functional Integration Initiative	157

G

Gastric Cancer.....	3
Gastrointestinal Stromal Tumor [GIST]	4
Genetic Causes of Communication Disorders	146
Gestational Diabetes	59
Global Health Research and Training.....	185
Guillain-Barré Syndrome [GBS]	191

H

Headache.....	75
Health Disparities in Children and Adolescents	178
Hearing Aids and Cochlear Implants	147
Hepatitis B	95
Hereditary Angioedema [HAE]	192

Heritable Connective Tissue Disorders	135
Human Microbiome Project.....	208
Human Tissue Supply	209

I

Inflammatory Bowel Disease.....	61
Inflammatory Nervous System Disorders.....	76
Influenza Antivirals	96
Information Technology	6
Inner Ear Hair Cell Regeneration	148
Interstitial Cystitis.....	62, 210

J

Jackson Heart Study.....	41
--------------------------	----

K

Kennedy’s Disease.....	86
------------------------	----

L

Liver Cancer.....	7
Lung Cancer.....	9
Lupus.....	136
Lymphangi leiomyomatosis [LAM]	42
Lymphatic Research and Lymphatic Disease	43

M

Marfan Syndrome	120
Marijuana	160
Melanoma	10
Mental Health Disparities	179
Metastasis.....	14
Metastasis to Bone	16
Microbicides	98
Mind-Body Interventions.....	45
Minority Population Cancer Rates.....	17
Mitochondrial Disease	111
Mucopolysaccharidosis [MPS]	77
Multifocal Motor Neuropathy [MMN]	192
Muscular Dystrophy Coordinating Committee [MDCC]	78

N

National Primate Research Centers [NPRCs].....	210
National Toxicology Program [NTP]	127
Network for Excellence in Neuroscience Clinical Trials	80
Neuroblastoma	19
Neurofibromatosis [NF].....	20
NIDAMed	161
NIH Third Party Collection Pilot.....	199
Noise-Induced Hearing Loss.....	149

O

Obesity	22, 63
Opioid Drug Abuse.....	164
OppNet.....	211
Osteogenesis Imperfecta [OI]	138
Otitis Media	151
Ovarian Cancer	23
Overlapping Chronic Pain Conditions	81
Oxalosis and Hyperoxaluria.....	70

P

Pain Medications.....	162
Pancreatic Cancer.....	25
Pancreatitis	64
Pediatric Brain Tumor.....	31
Pediatric Cancer	27
Pediatric Cancer Informatics Program	32
Pediatric Cardiomyopath	46
Pediatric Kidney Disease	65
Pelvic Pain	66
Polycystic Kidney Disease [PKD]	68
Pregnancy Health Status	113
Premature Mortality	169
Presbycusis.....	152
Preterm Birth.....	114
Prostatitis.....	69
Psoriasis	139
Psychotropic Medications and Children	171
Pulmonary Arterial Hypertension [PAH]	193
Pulmonary Fibrosis	47

R

Rehabilitation Research 116
Research Centers in Minority Institutions Program [RCMI]..... 181, 182
Robotic Biorepositories 28

S

Scleroderma 48, 141
Sleep Disorders 49, 50
Slow-Growing Children’s Brain Tumors..... 29
Spinal Muscular Atrophy [SMA] Carrier 173
STEM Programs..... 217
Stroke 82

T

Temporomandibular Disorders [TMD]..... 53, 142
Tinnitus 153
Tobacco Addiction..... 163
Traumatic Brain Injury [TBI] 83
Tuberculosis [TB] 99
Tuberous Sclerosis Complex [TSC] 85

U

Usher Syndrome..... 120, 121

V

Valley Fever 100
Vestibular Research 154
Vulvodynia..... 117

National Cancer Institute (NCI)

Senate Significant Items

Item

Angiogenesis - The Committee commends the research NIH is conducting on angiogenesis, specifically examining the need to address the lack of predictive markers for angiogenic therapies and the prospects for dietary modifications with anti-angiogenic properties to improve cancer prevention. The Committee urges NIH to further examine angiogenic predictive markers across NCI, NHLBI, NEI, NIDDK, and NICHD and to also consider focusing on angiogenic dietary modifications to reduce cancer risks.

Action taken or to be taken

Angiogenesis, the process of blood vessel formation, plays a role in cancer and in several diseases and conditions other than cancer, including blindness and diabetes, as well as arthritis and other inflammatory diseases. Institutes across NIH support angiogenesis research, and NCI collaborates with NIH colleagues to advance progress in this field.

Tumor angiogenesis is the growth of new blood vessels that tumors need to grow; therefore, angiogenesis inhibitors are sometimes used in cancer treatment to block signals that promote growth of blood vessels that supply tumors with needed nutrients and oxygen. These inhibitors have already been shown to have an important role in the treatment of some cancers when combined with additional therapies, especially chemotherapy. NCI supports a variety of angiogenesis research, and has sponsored clinical trials with antiangiogenic agents that have led to FDA approval for several cancer indications. NCI currently supports 55 clinical trials of the FDA-approved antiangiogenic agent bevacizumab (Avastin), including trials to evaluate the drug as a potential therapy for new cancer types. Other NCI-sponsored clinical trials include assessments of predictive biomarkers identified in basic lab research through support of imaging studies, specimen collection, and biomarker testing and analysis.

Biomarkers, biological molecules found in blood, other body fluids, or tissues, can sometimes be used for detection of disease, prediction of response to treatment, or monitoring of disease status. In general, there are significant challenges to clinical validation of biomarkers, and there are particular challenges to identifying biomarkers that may predict response to antiangiogenic therapies due to the inherent complexity of the process of angiogenesis and the multitude of growth factors that play key and sometimes interactive roles. Recent data suggest that a collection of predictive biomarkers, not just one, may need to be assessed to determine any sort of predictive value for anti-angiogenic therapies.

NCI's Division of Cancer Prevention plans, directs, and coordinates research in diet and nutrition to help establish a comprehensive understanding of the precise role of bioactive food

components in relation to cancer risk and tumor behavior. A variety of nutritional factors are assessed in this research, including micronutrients and angiogenic properties of food components. The ongoing development of both new animal models and imaging techniques elucidating diverse complex physiologic processes involved during *in vivo* blood vessel formation and its biologic interactions is part of the research program, including interactions with micronutrients and other food components.

NCI and NIDDK co-hosted a workshop in May 2013 to identify gaps and opportunities in integrating basic, translational, and clinical research in the prevention and treatment of angiogenesis-related diseases, and to stimulate critical collaborations and partnerships across stakeholders in the field. We anticipate that these discussions will spur interesting new research proposals in this area.

Item

Cancer Centers The Committee urges NCI to put a higher priority on linking its designated cancer centers with community health providers in order to better reach underserved and rural populations with state-of-the-art treatment and care. Strengthening these networks could help reduce disparities in cancer survival rates among racial, ethnic minority, and rural/non-rural groups.

Action taken or to be taken

NCI is committed to reducing cancer related disparities through a broad program focus that includes strong linkages between longstanding initiatives such as the NCI-designated cancer centers and the community research program. The new NCI Community Oncology Research Program (NCORP) combines three existing community based programs and incorporates focus on health disparities across the continuum of cancer research.

NCI-designated cancer centers are institutions dedicated to research in the development of more effective approaches to prevention, diagnosis, and treatment of cancer. They conduct cancer research and clinical trials, and training for health professionals in cancer related disciplines. Their missions also typically include public education and outreach about cancer prevention and screening, with special attention to the needs of underserved populations. The centers are integral parts of the local communities and many reach diverse and often underserved patient populations. The centers also link with community oncology sites by providing scientific and statistical leadership in the development of concepts for clinical trials and cancer care delivery research. This collaborative network of academics and community investigators provides a mechanism for research in the community setting that will contribute to improved patient outcomes and a reduction in cancer disparities.

NCORP is a new initiative that will bring state-of-the-art cancer prevention, control, screening/post-treatment surveillance, treatment and imaging clinical trials, cancer care delivery

research, and disparities studies to individuals in their own communities. It expands upon the clinical trials success of NCI's Community Clinical Oncology Program Network – including the network's Minority-Based program sites and Research Bases – and adds elements of the NCI Community Cancer Centers Program, creating a network for cancer care delivery research. NCORP consolidates these efforts and will continue to strengthen the network of cancer community practices and clinical trials research centers.

NCORP will include research bases with comprehensive expertise in cancer clinical trials, such as institutions that design, develop, and conduct cancer prevention, control, and screening/post-treatment surveillance clinical trials, as well as cancer care delivery research studies. These research bases will include cancer centers and community sites. The NCORP cancer disparities research agenda will be integrated into clinical trials and cancer care delivery research studies as appropriate. NCORP will also include community organizations or consortiums of community hospitals and minority/underserved sites that must have at least 30 percent of their cancer patients and accrual from racial/ethnic minority or rural populations. They must also have the potential to contribute data on disparities outcomes and care. Applications for NCORP are under review and it is anticipated that awards will be made in 2014.

Item

Gastric Cancer - The Committee continues to be concerned about gastric cancer, particularly among young people, and is pleased that gastric cancer has been selected for study under The Cancer Genome Atlas [TCGA]. Given that research on gastric cancer is less advanced than that of many other cancers, the Committee urges NCI to put a priority on helping investigators in this field make the best possible use of genomic data from the TCGA.

Action taken or to be taken

Approximately 21,600 Americans will be diagnosed with gastric cancer in 2013, with over 80 percent of these cases in individuals over 54 years of age. It is estimated that 12 percent of cases will be in the 45-54 age group, and just 6 percent of cases in the 20-44 age group. The annual death rate from gastric cancer is approximately 10,990. Gastric cancers are divided into two types: intestinal, which develops in the antrum and is usually well differentiated; and diffuse, which develops in the body of the stomach, is poorly differentiated, and usually has a poorer prognosis than the intestinal type. Gastric cancer does not appear to be hereditary, although, a few of the diffuse type do have a hereditary form, arising from an inherited mutation in the E-cadherin gene (*CDH1*). Most cases of gastric cancer are attributable to infection with the bacterium *Helicobacter pylori* (*H. pylori*), and progressively stronger evidence suggests that early antibiotic treatment of this common infection in high-risk patients can reduce the risk of developing this cancer. Recent data have also shown that some gastric cancers are associated with Epstein-Barr Virus (EBV).

Gastric cancer is being evaluated as part of The Cancer Genome Atlas (TCGA), a comprehensive analysis of the genomic changes of more than 20 types of cancer; currently over 300 gastric tumors, including a set of 50 cases of diffuse gastric cancer, are being analyzed. The first TCGA publication concerning gastric cancer should appear in fall 2014, and will include analysis of all major subtypes of gastric cancer. We anticipate that TCGA will provide new ways to define subtypes of gastric cancer by genomic analysis, and may elucidate important information about EBV-associated gastric cancers. Preliminary analysis suggests that the current definitions of gastric cancer subtypes by histology are imprecise and can be refined by analysis of the tumor genomes based on recurrent oncogenic abnormalities, some of which are restricted to particular gastric cancer subtypes. Importantly, some of these abnormalities may be amenable to testing candidate inhibitors for therapeutic intervention in the near future. Early data have identified genetic alterations to the cell surface receptor ERBB3/HER3 in 10-15 percent of gastric cancers, which suggests susceptibility to the drugs trastuzumab and lapatinib. Other research has showed that 20 percent of gastric cancers have mutations affecting cells that may be able to be targeted by kinase inhibitors.

A potential limitation is that most available gastric samples are from patients treated with chemotherapy and/or radiation prior to removal of the tumor, as is the standard of care in the U.S. Unfortunately, these treatments can induce mutations or otherwise alter the tumor, resulting in potentially misleading results. To address this, NCI has funded two major centers to collect biopsies from patients before exposure to therapy. These specimens will be subjected to comprehensive analysis by TCGA, and we anticipate this intensive focus on gastric cancer will elucidate valuable new information and provide a variety of scientific opportunities for the research community. In addition, NCI convened a workshop in August 2013 to explore development of new cell lines for several cancer types, including gastric cancer.

Data from TCGA gastric cancer samples are freely available to researchers and NCI has made access a priority by developing websites that allow researchers to search for genetic alterations in any cancer studied by TCGA. For example, researchers can use one cancer genomics portal to identify mutations in any particular gene of interest or determine the association between genetic abnormalities and clinical outcome. NCI plans to continue its support of such cancer genomics portals to promote the widest possible utilization of these data.

Item

Gastrointestinal Stromal Tumor [GIST] - Despite significant treatment advances over the past decade, metastatic GIST remains largely incurable. The Committee encourages NCI to intensify its research on GIST and explore with NCATS whether any drugs that have been approved for other uses could be repurposed to treat this disease.

Action taken or to be taken

Gastrointestinal stromal tumors (GIST) comprise less than 5 percent of all gastrointestinal (GI) tumors, with less than 6,000 new cases per year in the United States. The correct identification of GIST is critical because of the availability of specific, molecular-targeted therapy with tyrosine kinase inhibitors (TKI) such as imatinib and sunitinib.

Therapies using tyrosine kinase inhibitors (TKI) have revolutionized the management of GIST. Although complete responses are rare, a large majority of patients with metastatic or inoperable GIST can achieve either a partial response or disease stabilization with current therapy. Median survival rates have gone from less than 2 years to more than 5 years since the advent of imatinib therapy. Earlier this year, regorafenib (Stivarga®), a new TKI drug, was shown to be effective for patients with resistant GIST and subsequently approved for use in this disease. Regorafenib was reviewed under the U.S. Food and Drug Administration's priority review program, which provides an expedited six-month review for drugs that may provide safe and effective therapy when no satisfactory alternative therapy exists, or for drugs that offer substantial improvement compared with marketed products. The drug was also granted orphan product designation because it is intended to treat a rare disease. Despite these treatment advances for GIST, much work remains to be done for this disease, especially for children, and those whose disease has not improved with current treatments.

Pediatric GIST is extremely rare, representing only 1 to 2 percent of all GIST cases (approximately 60 cases per year in the United States). It is also very different from its adult counterpart. Whereas 85 percent of GISTs in adults harbor mutations in either the *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) genes, the opposite is true in children with GIST—85 percent have no detectable mutation in either gene. Thus, in children, the tumors do not respond to the drugs that have made such a difference for adults with GIST. NCI and the Eunice Kennedy Shriver National Institute of Child Health and Human Development have partnered with members of GIST advocacy groups to organize a consortium of pediatric GIST researchers to field a program aimed at designing innovative treatment protocols for children and youth who develop GIST. Within the past 4 years, 60 to 80 patients with pediatric GIST have been evaluated at NIH.

Currently, NCI is funding more than 70 clinical trials and 17 research projects on GIST at major institutions and cancer centers around the country, including Memorial Sloan-Kettering Cancer Center, Brigham and Women's Hospital, Fox Chase, Vanderbilt University Medical Center, and University of Kansas Medical Center. NCI and the National Center for Advancing Translational Sciences (NCATS) collaborate on a continual basis to explore a variety of translational opportunities stemming from The Cancer Genome Atlas and other advances in molecular characterization of cancer. NCI and NCATS have co-funded research at the University of Kansas Medical Center focusing specifically on drug repurposing opportunities for GIST – this work

screened 796 FDA-approved drugs and identified two compounds that inhibited GIST cell growth and viability.

Additionally, NCI is developing a clinical trial that will screen tumors for genetic abnormalities that may predict response to a targeted agent with a specific mechanism of action. The proposed study, NCI-MATCH (Molecular Analysis for Therapy Choice), will pursue this therapeutic approach for both common and rare tumors. Another relevant initiative is NCI's Experimental Therapeutics Program (NExT), designed to streamline development and testing of promising new anticancer drugs and to expedite delivery to patients. The program consolidates NCI's anticancer drug discovery and development resources to support a therapeutics pipeline from new target validation through Phase III clinical trial evaluation. Special consideration is given to addressing unmet needs for rare cancers as well as those with limited responses to treatment, with the goal of supporting the most promising new drug discovery and development projects.

Item

Information Technology - Certain health behaviors, including diet, exercise, and smoking, play a key role in cancer risk. As new technologies that may address behavioral risk factors are developed, the Committee urges NCI to expand research opportunities into how information technology and telecommunications can be leveraged to reduce these risks.

Action taken or to be taken

NCI supports research to study the efficacy of telecommunications/IT tools to address behavioral risk factors for cancer such as tobacco use, diet, and physical activity. The expanding use of the internet and telecommunications tools such as smartphones (mobile devices capable of performing many of the functions of a computer), is offering new opportunities for behavioral monitoring and engagement and intervention.

The NCI has funded a variety of projects including individualized, interactive web modules to assist in smoking cessation, diet, and exercise; a smartphone intervention project to help cancer survivors stay healthy following treatment; social media interventions that use connections between peers to encourage healthy behaviors; and the development of mobile applications to accompany feedback from digital pedometers.

NCI's Small Business Innovation Research (SBIR) portfolio supports various efforts to increase capacity for behavioral monitoring using health IT, including freely available web-based tools for adults and children that can be used to collect 24-hour food diaries in both English and Spanish. Other examples are the [Technology Assisted Dietary Assessment](#) program and the [Food Intake and Voice Recognizer](#) that combine technologies including camera, text, and video, to identify foods and portion sizes. These tools enable collection of real-time, behavioral and environmental data that are improving our understanding of health and disease, particularly when integrated with other data such as genomics, biomarkers, and electronic medical records.

Preventing and reducing tobacco use, especially among youth, continues to be one of the most effective ways to lower risk for cancer. NCI developed Smokefree.gov, which offers a variety of tools designed to help people quit smoking, including extensions of the site for specific populations such as women, Spanish-Speakers, and teenagers. Last year, over 3 million smokers accessed Smokefree.gov resources, with an estimate of 200,000-300,000 smokers succeeding in using the resources to quit smoking and stay smoke-free. Over 45,000 people signed up for a text-message program to help them quit smoking, and over 7,000 reported their success using the program.

The Smart and Connected Health Funding Initiative was established as a joint program of NCI, NIH, and the National Science Foundation to support cutting-edge IT research. Funded projects include the development of technologies for intervening, sensing, and modeling data from children at high risk for obesity. Additionally, NCI and the National Library of Medicine are leading an initiative to develop and disseminate evidence-based health information technologies to both healthcare systems and consumers, to prevent and reduce the risk of cancer.

NCI's Health Information National Trends Survey (HINTS) monitors how changes in the broad health information landscape may be contributing to, or detracting from, cancer risk reductive behaviors. HINTS is the only federally funded health survey to document a steady increase in the public's use of the Internet to look for information about their health and specifically about cancer; the use of email to communicate directly with health care providers; the use of personal health records to access personal data; the use of social media in the area of health behavior; and the use of online pharmaceutical ordering. The survey has also documented a general *increase in confusion* from a population inundated with online alternatives and conflicting recommendations. This cautionary finding suggests that more effort must be put into health IT that reduces confusion, promotes accountability, and ensures effectiveness.

Item

Liver Cancer - The Committee continues to urge NCI to put a higher priority on liver cancer research. In particular, the Committee urges the Institute to develop sustaining models of liver cancer for therapeutic drug development as well as to continue work in the area of biomarkers and drug discovery.

Action taken or to be taken

Although relatively uncommon in the U.S. with 30,640 cases in 2013, primary liver cancer (cancer that begins in the liver) is an increasing concern. The number of new cases of liver cancer is rising, with higher incidence in non-white populations. Asian Americans and Pacific Islanders have the highest incidence rates for liver cancer, and are twice as likely as Whites to die from liver cancer. The disease affects far more men than women across all groups. Most U.S. cases of liver cancer occur in people who first had cirrhosis, usually resulting from hepatitis B or C infection or from heavy alcohol use. Hepatocellular carcinoma (HCC) is the most

common form of liver cancer and one of the deadliest. Because HCC is often diagnosed at advanced stages of the disease, few patients are candidates for surgical resection. Therefore, improving the understanding of the biology of HCC is an important goal to enable the development of new targets for early diagnosis, prevention, and treatment.

Biomarkers, imaging studies, and clinical assessments are useful in distinguishing cirrhosis from liver cancer, improving clinical risk prediction, and guiding treatment decisions. NCI-supported investigators are evaluating the best uses for established and newly-identified serum protein markers, and looking to the growing base of genomic and molecular signaling information and the emerging field of metabolomics to understand the biology of liver malignancies and identify new candidate biomarkers. NCI's recently-launched Hepatocellular Carcinoma Early Detection Strategy (HEDS) study will feature a collection of blood samples collected from cirrhotic patients who are being closely monitored for development of HCC. This will provide a valuable reference set containing patient samples of serum and plasma collected prior to the development of HCC. This resource will be available for qualified researchers to use for validation of promising biomarkers. HEDS participants are currently working to optimize the use of alpha-fetoprotein (AFP) on its own and in concert with other tumor markers and ultrasound imaging to detect preclinical and early-stage HCC. Other NCI-supported investigators are exploring metabolic end products that can distinguish tumor from non-tumor tissue, and are studying certain proteins and nucleic acids circulating in the blood that may be biomarkers for early stage disease, response to therapy, or relapse.

NCI-funded research on HCC includes the study of HCC cells and their microenvironment (the normal cells and tissue around the tumor), with an emphasis on the immune response. Another group of researchers exploring HCC and cancer stem cells (cancers are composed of stem-like cancer cells and non-stem cancer cells) recently demonstrated that a certain type of cancer stem cell (label-retaining cancer cells, or LRCCs) are relatively resistant to the targeted agent sorafenib. They also showed that the number of LRCCs increases after treatment, which may explain recurrent HCC after treatment. This finding suggests that future therapies for HCC should also target this type of stem cell directly and focus on the mechanism of drug resistance.

Prior studies have identified aberrations in two signaling pathways that play roles in HCC development (the RAS/RAF/MAPK pathway and the PI3K/AKT/mTOR pathway), and investigators are now studying the therapeutic effects of two agents that target these pathways. Recent findings suggest that the combination of these two agents not only inhibits all the key enzymes in both pathways with an additive effect, but also has an inhibitory effect on liver cancer stem cells that is more profound than the effect of either of the drugs alone. In addition to these U.S. efforts, a collaborative effort is currently underway with Chinese investigators to expand the understanding of the etiology of HCC and for the identification of new biomarkers.

NCI supports extensive research into the development of model systems to inform all aspects of cancer research, including the development of genetically engineered mouse models to study the

molecular changes leading to the development and progression of HCC. Specific approaches include comprehensive analysis of genomic alteration in HBV-infected HCC patients to elucidate how integration of the HBV genome into the host (patient) genome increases opportunities for the development of HCC. Another NCI team is developing a mouse model to explore the functional role of the c-myc transcription factor, which regulates genes involved in the growth and proliferation of liver cells, and treating the mice with a special diet to observe the cascade of immunological events. These types of genetically engineered mouse models of cancer have potential as preclinical models for testing new treatment regimens and for studying mechanisms of acquired resistance to conventional chemotherapies or targeted therapies. The use of mouse models for studying HCC has enabled a better understanding of the development of HCC and has provided insight into possible biomarkers and treatments.

The NCI is committed to supporting high quality research on HCC and other liver cancers and stimulating interest in this field within the cancer research community. A range of initiatives are accepting applications for the study of primary liver cancers and we continue to encourage investigators in the field to pursue these funding opportunities. The Cancer Genome Atlas (TCGA), a comprehensive and coordinated effort to accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies, has collected data from 114 hepatocellular carcinoma cases. These data are available to qualified researchers through public databases designed to protect patient privacy. Currently, NCI is planning a workshop on liver cancer, to be held in FY 2014, which will focus on recent advances and research opportunities for prevention, screening, diagnosis, and treatment of liver cancer.

Item

Lung Cancer - The Committee urges NCI to collaborate closely with international lung cancer experts to continue to explore ways to translate the findings from the National Lung Cancer Screening Trial into public health recommendations that will reduce the mortality and morbidity of this deadly form of cancer.

Action taken or to be taken

In the second half of 2010, the NCI-sponsored National Lung Screening Trial (NLST) announced that there were 20 percent fewer lung cancer deaths among trial participants screened with low-dose helical CT (LDCT) (also known as spiral CT) than among those who received an ineffective screening procedure, chest X-ray. The NLST was a multi-year, randomized, national trial involving 53,454 current and former heavy smokers ages 55 to 74. Participants were required to have a smoking history of at least 30 pack-years and were either current or former smokers without signs, symptoms, or history of lung cancer. The NCI provided the scientific and financial resources required for this expansive study, because only trials such as this allow us to determine which methods of screening are effective, and how effective, in defined populations.

On December 30, 2013, the USPSTF released its updated lung cancer screening recommendation statement: “The USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in persons age 55 through 80 years with at least a 30 pack year history of smoking who are currently smoking or have quit within the past 15 years.” The recommendation is based largely on the findings of the NCI-supported NLST as well as modeling studies from the NCI’s Cancer Intervention and Surveillance Modeling Network (CISNET). The NLST found that screening with low-dose computed tomography (CT) results in about 16% fewer lung-cancer deaths among current and former heavy smokers compared with screening with chest X-ray. The CISNET studies provided additional information about potential ages to begin and end screening, screening intervals, and the benefits and harms of different screening strategies. The USPSTF commented that the benefit of screening depends on the accuracy of image interpretation being comparable to that found in the NLST, and the resolution of most false-positive results without invasive procedures. The USPSTF and the NCI have stressed the importance of learning to reduce false-positives by improving interpretation of images, to follow-up abnormalities with a high level of collaboration between imaging and surgery experts, and to continue to emphasize the primary importance of tobacco control.

The NCI continues to be committed to the translation of the findings from the NLST into public health benefit. For example, NLST investigators have begun discussions with nationally and internationally recognized experts in lung cancer screening and public health to develop a registry for analyzing the use of LDCT in various localities and healthcare settings. A meeting is being planned to discuss specific questions to be addressed and the common data elements needed to answer those questions. Coverage and reimbursement policies for LDCTs for this population are the purview of the Centers for Medicare and Medicaid Services (CMS) and of private insurers for their respective beneficiaries. Several representatives of the NCI have been meeting with counterparts at CMS to ensure that coverage guidelines are developed in accord with the latest reliable information about lung cancer screening methods.

NLST investigators supported by the NCI are also working with public health and lung cancer experts in other parts of the world, particularly in China. They are providing materials and operating procedures from the NLST that will help them set up a feasibility study of lung cancer screening with LDCT in several Chinese urban areas that have high lung cancer rates. Several meetings have already been held to discuss study design and implementation. The intent is to develop a lung cancer screening program that is culturally appropriate and practical within the Chinese healthcare system.

Item

Melanoma - The Committee continues to put a high priority on melanoma research. The Committee notes that increased translational work into wild-type BRAF melanomas, which represent 50 percent of tumors, is critical to spearhead drug development. The recent discoveries of unique mutations in uveal melanoma also warrant additional research. The Committee

continues to urge research into the mechanisms and early detection of drug resistance in BRAF mutant melanoma; further mapping of melanoma genetics and epigenetics; and clinical research into immune therapy checkpoint inhibitors, including biomarker research for response and lack of response, mechanistic analyses in patient-derived samples, and the testing of combination therapies that incorporate these inhibitors. The Committee continues to urge NCI to support research directed at the biology of tumor initiation and metastasis, risk reduction, and the relative utility of novel early detection strategies. The Committee requests an update in the fiscal year 2015 congressional budget justification on NCI's melanoma research portfolio.

Action taken or to be taken

Melanoma of the skin, or cutaneous melanoma, is one of the most common cancers in the United States and affects more Americans every year. The incidence of melanoma increased more than 600 percent between 1950 and 2000. Recent population-based data estimate that 76,690 men and women (45,060 men and 31,630 women) will be diagnosed with cutaneous melanoma in 2013, and 9,480 men and women will die of it. Based on the rates from 2008-2010, we can project that 1 in 49 people will be diagnosed with cutaneous melanoma during their lifetime. While cutaneous malignant melanoma represents less than 10 percent of all diagnosed skin cancers, it is responsible for greater than 75 percent of skin-cancer-related deaths.

As outlined in this response, the NCI supports a variety of research efforts addressing the multifaceted challenges of melanoma and the development of metastasis, and continues to refine its portfolio in response to scientific opportunities. Newly available therapeutic options like vemurafenib and ipilimumab demonstrate the power of understanding the genetic antecedents of disease and harnessing immune response mechanisms. Research is underway to maximize the potential of these treatments, and to learn more about the biology of melanocytic tumors and how the body responds to them with the goal of developing new treatment options, particularly for those patients with advanced disease. Deciphering the complex interplay of genetic and environmental factors involved in the development of melanoma will enhance our abilities to predict and reduce risk and to identify patient groups most likely to benefit from targeted therapies. Prevention is paramount in reducing mortality and morbidity associated with melanoma, and NCI is investing in behavioral research for the development, evaluation and dissemination of interventions to improve sun protection as a public health priority.

Melanoma is a highly heterogeneous disease. Precise molecular characterization of melanoma has taken a prominent role in our understanding of this collection of diseases and our recent progress in preventing, treating, and controlling them. Fifty percent of cutaneous melanomas have a well-characterized acquired genetic mutation known as BRAF^{V600E}. Mutant BRAF disrupts the proper functioning of a cell signaling pathway called RAS/MAPK – it maintains RAS/MAPK in a perpetually “on” state. Using therapeutic agents that inhibit this mutant BRAF function, or that simultaneously inhibit both mutant BRAF and other targets that affect the RAS/MAPK pathway, have conferred significant improvements in survival time for patients with

metastatic melanoma. Unfortunately, BRAF inhibitor-resistant melanomas invariably recur over time. Several NCI-supported teams have successfully identified resistance mechanisms, including alterations to the BRAF gene itself, as well as mutations in other genes, such as NRAS and other MAPK pathway members. Innate resistance to BRAF inhibitors has also been connected to secretion of hepatocyte growth factor (HGF) by the non-malignant tissues, or microenvironment, surrounding the tumor. NCI-supported investigators are studying other mechanisms by which the host and tumor microenvironments contribute to BRAF inhibitor resistance, helping to define novel microenvironment-directed strategies for delaying and abrogating melanoma drug resistance. Clinical and preclinical investigations are currently focused most intently on finding drug combinations that help ensure MAPK pathway inhibition. Researchers are also working to develop a new class of anti-cancer agents that selectively modify the metabolic characteristics of cancer cells to make them more susceptible to therapy.

The other 50 percent of cutaneous melanomas have a normal, or wildtype, BRAF gene. In 40 percent of these BRAF wildtype cancers, a mutation in the NRAS gene is responsible for disease development. NRAS has been elusive for direct targeting, forcing the employment of indirect targeting strategies toward other MAPK pathway components. Unfortunately, these have proven to be largely ineffective.

The NCI has recently initiated a major research effort at the Frederick National Laboratory for Cancer Research (FNLRCR) with the goal of identifying approaches that will directly and effectively target mutant NRAS and other mutations of the RAS gene family. Mutations in the RAS gene family are implicated in more than 25 percent of all human cancers and account for an even higher percentage of cancer mortality due to poor chemotherapeutic response. Progress in this initiative has the potential to reduce mortality in a broad spectrum of cancers, including melanoma.

Recent data have shown that the most abundant mutation in melanomas without BRAF or NRAS mutations is the loss of the tumor suppressor gene NF1, long associated with the disease neurofibromatosis type I. Loss of NF1 function has been shown to help confer resistance to BRAF inhibitors. Glutamate receptor genes, including GRIN2A and GRM3, are also frequently mutated in melanoma, and their encoded proteins represent targetable cell surface receptors. Specific epigenetic alterations (changes in gene activity not caused by changes in DNA sequence), such as formation of the nitrogen base 5-hydroxymethylcytosine, have also been associated with melanoma progression and may represent new therapeutic targets for subsets of melanoma patients.

Uveal melanoma is the most common intraocular cancer in adults and has a propensity to metastasize to the liver, which is almost always fatal. Inactivating mutations in the gene encoding BRCA1 associated protein-1 (BAP1) have been identified in nearly 50 percent of uveal melanomas, and have been associated with metastasis. Recent studies have identified two proteins that mediate signaling in the MAPK pathway in uveal melanoma. Researchers found a

50-percent mutation rate in the gene encoding GNAQ, a G-protein that when altered leads to changes in the MAPK pathway. An additional mutation in the gene for another G-protein, GNA11, was identified in 32 percent of primary uveal melanomas. NCI-supported researchers are evaluating GNAQ as a therapeutic target.

The melanoma research community has identified and continues to discover a multitude of genes altered in melanoma and has demonstrated a higher mutation load in melanoma tumors compared with those in other cancers. It is vital that we continue to build on this information. NCI continues to encourage strong collaborative research efforts. The Cancer Genome Atlas (TCGA) initiative has collected 543 biospecimens so far from multiple sites and NCI-supported teams are now performing next-generation sequencing on DNA extracted from these samples. In 2012, investigators from the NCI's four Specialized Program of Research Excellence (SPORE) centers devoted to skin/melanoma proposed to collaborate on a "Uveal Melanoma TCGA" as part of the TCGA Rare Tumors Project with the goal of providing tissues from 50 qualifying cases for a similar sequencing effort.

Immunotherapies that work by directly activating tumor-associated immune responses or by dampening suppression of those responses can be an effective treatment for advanced melanomas, including those with both cutaneous and uveal origins. Although they have thus far benefited only subsets of patients in clinical trials, NCI-supported laboratories are attempting to improve these promising new strategies by understanding the failure of T cell immune responses to promote melanoma regression, developing more effective immune-based strategies, and identifying critical biomarkers that would predict which patients are more likely to respond. An underlying problem is that melanomas can exploit the T cell's system of "checkpoint inhibitors," the body's way of preventing cytotoxic T cells from an autoimmune inflammatory attack against normal cells, to evade rejection by the immune system. Antibody-based drugs against key immune checkpoint inhibitors are now being used to block T cell inhibition and have demonstrated some durable clinical responses. Current clinical thinking is that the efficacy of these immune checkpoint inhibitors will be greatly enhanced when combined with targeted small molecule inhibitors of MAPK pathway members. For example, a CTLA-4 inhibitor (ipilimumab) is currently being combined with inhibitors of BRAF^{V600E} (vemurafenib, dabrafenib) and/or MEK1/2 (trametinib). Specific changes in certain categories of immune cells have been identified as biomarkers that might help predict efficacy of ipilimumab. An alternate strategy for anti-melanoma immunotherapy uses IL-15 cytokine to support T cell or NK effector cells. Several investigators are also attempting to develop more effective therapeutic anti-melanoma vaccines by overcoming immunological tolerance to tumor-associated antigens, or inducing tumor-reactive T cells with therapeutic efficacy. Investigators are attempting to develop improved preclinical animal models that will help uncover common underlying mechanisms and guide clinical choices.

Understanding the genetic and environmental initiators of melanomas is critical to the prevention and control of this disease. Melanoma is one of the few cancers in which a major etiological

agent is known – environmental exposure to ultraviolet (UV) radiation. However, surprisingly little is known about the underlying tumor-initiating mechanisms associated with UV radiation. Whole genome sequencing of melanomas has revealed thousands of mutations consistent with DNA damage caused by UV exposure. A continuing challenge is to distinguish true “driver” mutations – those that are causally implicated at some point in the cancer development process - from insignificant mutations called “passengers.” A gene called RAC1 is frequently mutated in melanocytic lesions associated with sun exposure, and a specific RAC1 mutation consistent with UV radiation damage (e.g., a cytosine to thymine transition) connects UV radiation exposure and resultant DNA damage with melanoma. It is now appreciated that tumor-initiating doses of UV radiation can also induce significant, long-term effects in inflammatory cells and other constituents of the tumor microenvironment, as well as in tumor cells.

Approximately 10 percent of all malignant melanomas occur in people with a familial predisposition. Three high-risk melanoma susceptibility genes have been identified: CDKN2A, CDK4, and BAP1, the third being predominantly associated with uveal melanoma. Lower risk susceptibility gene variants are currently being sought, predominantly using genome-wide association studies (GWAS). The emergence of whole-cancer genome sequencing by next-generation sequencing has transformed the field of melanoma genetics, enhancing the opportunities for germline and somatic gene discovery. Early detection could be improved by developing “genomic dosimeters” to identify genomic regions especially sensitive to UV radiation damage so high risk individuals can be identified and treated; NCI-supported investigators are developing this idea. Risk reduction strategies under evaluation include limitation of indoor tanning, particularly for young women, and studies of the effectiveness of UV-protective sunblock.

Metastasis is responsible for the death of the vast majority of the approximately 15 percent of melanoma patients who succumb to their disease. For this reason, the NCI devotes great efforts toward identifying factors responsible for metastatic spread and thus new candidate therapeutic targets. A new strategy is to learn more about metastatic melanoma cells by studying normal embryonic melanocytes, which also are inherently invasive, migratory and able to colonize distant sites, and are thus similar to metastatic cancer cells. A clinical priority is to attempt to eliminate all metastatic melanoma cells and avoid the survival of any small subpopulation of resistant cells that could recur and give rise to more aggressive and resistant tumors.

Item

Metastasis - Although 90 percent of cancer deaths are associated with metastasis, this phenomenon is not widely studied due to its complexity and corresponding requirement for the involvement of scientists representing multiple disciplines. The Committee encourages NCI to develop a consortium of institutions with expertise in cancer metastasis and metastasis genetics to leverage the unique strengths of each institution and facilitate progress toward controlling the most deadly attribute of cancer cells.

Action taken or to be taken

Metastasis, the process by which a cancer spreads from the place where it first started to another place in the body, is a complex, multi-step process of local invasion of normal tissue, entry into the bloodstream or lymphatic system, proliferation of cancer cells to form small tumors known as micrometastases, and ultimately the development of blood vessels to fuel tumor growth at the distant site.

NCI researchers are actively engaged in devising new ways to learn more about the cascade of events that guides the development of metastasis, and working together to find new options for cancer patients with metastatic disease. NCI supports a broad portfolio of melanoma research, and several projects described below include consortia that bring together, through meetings, working groups, and team projects, scientists viewing metastasis and other aspects of cancer biology from many perspectives. These consortia share expertise, data, and resources such as reagents and model systems to strengthen and leverage the entire community's contributions to the effort.

For instance, the NCI's Integrative Cancer Biology Program currently supports twelve centers that are bringing a systems biology approach to the study of cancer: they are using the tools of basic and clinical science, computational biology and bioinformatics, bioengineering, mathematics, and physical science to study the complex interplay of cancer cells within a tumor site with the surrounding tissues and with the entire harboring organism at all stages of cancer development and progression. The Tumor Microenvironment Network is a consortium focused on fundamental research into the composition of the supporting connective tissue of an organ, or stroma, in normal tissues and its roles in tumor initiation, progression, and metastasis. Animal models continue to be a useful tool for the study of metastasis. The Mouse Models of Human Cancers Consortium has delivered to the cancer research community improved mouse models that display the entire natural history and clinical course, including metastasis, of human cancers such as breast, prostate, and lung.

Other new approaches include rapid autopsy programs, a procedure in which tissue is collected within a few hours of a patient's death and preserved for analysis. Because DNA, RNA, and other molecules within cells begin to degrade shortly after death, rapid autopsy allows researchers to collect tissue samples that will yield clearer insights into the biological processes that contribute to the development and metastasis of cancer. NCI-supported research using rapid autopsy specimens from pancreatic cancer patients has shown that cells within the primary tumor, which all descended from a single cell, accumulate additional mutations over time, giving rise to sub-populations of cells, some of which leave the pancreas and settle in other parts of the body. The data also showed that metastasis is a late event in the evolution of pancreatic cancer, typically occurring a decade after the primary cancer, with an additional two to three years before those metastatic lesions disseminate and cause rapid clinical deterioration and death. Another group of NCI-supported researchers studying clear cell renal cell carcinoma (ccRCC)

found that although most ccRCC patients have a mutation in the VHL gene, this mutation is not correlated with clinical outcome. Instead, epigenetic alternations (changes in the expression of a gene or the activity of DNA and RNA activity that influence the performance of a gene) lead to the activation of metastasis-inducing genes. This discovery advances our understanding of how metastasis occurs for ccRCC and other cancer types.

Through NCI's Provocative Questions initiative, we are engaging the cancer research community in a collaborative process designed to define and attack potentially game-changing scientific questions. Since the inception of this program in 2011, NCI has challenged researchers to explore new ways of thinking about metastasis, and to develop their ideas for new approaches and tools to measure and study metastatic processes. In response, research teams are creating and refining engineered tissue platforms that reproduce the three-dimensional structures and biophysical and biochemical properties of human tumors, and can mimic processes associated with metastasis; these tools will enable researchers to experimentally manipulate and characterize these processes and the genetic and molecular signaling factors that control them. Sophisticated computational models are under development to complement the physical models and generate and rapidly test new - and potentially paradigm-shifting - hypotheses of how metastasis works. In addition, researchers are studying genetic changes that occur as indolent tumors progress and become invasive and metastatic, and characteristics of the microenvironment around disseminated tumor cells that may promote metastasis.

Item

Metastasis to Bone - The Committee urges additional research on how to repair bone defects caused by cancer cells. Basic research is needed to understand the impact of matrix properties on cell behavior. Translational research is also needed to understand the impact of metastasis on the biomechanical properties of bone and the mechanisms by which bone marrow- and tumor-derived cells can influence metastatic growth, survival, and therapeutic resistance.

Action taken or to be taken

NCI, as well as the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), are concerned about the effects of metastasis that occur in bones. NCI currently has several initiatives to pursue this challenge with the goal of preventing and reversing the effects of bone metastasis.

The Tumor Microenvironment Network (TMEN) initiative focuses on expanding our understanding of the role of the tumor microenvironment in cancer initiation, progression and metastases of all types. Through this initiative, the NCI's Division of Cancer Biology intends to generate a more comprehensive understanding of the composition of the stroma (the connective tissue framework of an organ, gland, or other structure) in normal tissues, with the goal of delineating the mechanisms of tumor-stromal interactions in human cancer. TMEN consists of eleven funded centers, an infrastructure intended to establish repositories of critical reagents,

resources and information as well as promote and facilitate interdisciplinary collaborations and progress in understanding the role of host stroma in tumorigenesis.

NCI supports three multi-institutional, multidisciplinary Program Project grants (P01s) on bone metastases: (1) Prostate Cancer Bone Metastasis: Biology and Targeting at Cedars-Sinai Medical Center, (2) The Biology of Prostate Cancer Skeletal Metastases at University of Michigan, and (3) Mechanisms and Markers of Prostate Cancer Metastases at University of Washington. In addition, NCI is supporting a study at the Vanderbilt University Center for Bone Biology, in which researchers found that stress can promote breast cancer cell colonization of bone. Their work in mouse models showed that activation of the sympathetic nervous system – the "fight-or-flight" response to stress – primes the bone environment for breast cancer cell metastasis, and that a cardiovascular drug, propranolol, an inhibitor of the sympathetic nervous system, substantially reduced bone lesions.

NIAMS also supports a robust portfolio on the interactions and communication between bone and other tissues and organ systems, the mechanisms of bone mineralization and mineral homeostasis, and the skeletal architecture and mechanical properties of bone. This includes the development of a tool that will help surgeons assess the impact of metastasis on the overall health of the bones of the spine. If successful, this strategy for analyzing computerized tomography images will improve the accuracy with which health care providers can advise patients, whose cancers have spread to their vertebrae, about their individual risks of fracture and paralysis if they choose not to have surgery. The investigators also are comparing the risks and benefits of a minimally invasive surgery with those of a more traumatic procedure, with the goal of reducing morbidity associated with both the cancer and the treatment. In many cases, surgical removal of a tumor and the surrounding bone leaves an empty space that must be filled with bone taken from elsewhere in the body, bone from donor tissue, or with an artificial scaffold that bone can grow into. As the lead institute for research on musculoskeletal tissue engineering, NIAMS supports several groups that are exploring use of natural and artificial matrices, cells and biomolecules, to promote bone formation and repair.

Item

Minority Population Cancer Rates - The Committee remains concerned by the disproportionately high cancer rates in minority populations. The Committee requests an update from NCI and NIMHD on efforts to address this disparity, including the possibility of establishing centers of excellence focused on research, treatment, prevention, and communication and outreach to minority communities for early intervention.

Action taken or to be taken

While major advances in cancer prevention and treatment have been made over the past few decades, some populations continue to experience a disproportionately higher burden of particular cancers than the general population. The occurrence of cancer, mortality rates, and

length of survival varies from group to group, and not all cancers are disproportionately represented in minority populations.

During the period from 2000 to 2009, incidence rates for all cancers combined declined among men in each racial and ethnic group, yet African American men had the highest overall cancer incidence rate of any racial and ethnic group, with prostate cancer incidence rates nearly 60 percent higher than whites. Additionally, more than twice as many African American men die from the disease each year, as compared with white men. On the other hand, compared to other racial and ethnic groups, Asian Americans and Pacific Islanders have the lowest overall incidence of cancer, nearly 34 percent lower than the average incidence across all races, and nearly 35 percent lower than in whites. The causes of these disparities are complex, often interrelated, and yet to be fully understood. NIH is pursuing research on many fronts to address these disparities.

The NIH Centers for Population Health and Health Disparities (CPHHD) program was established to address disparities and inequities in the prevalence and outcomes of several diseases, particularly cancer and heart disease. The ten CPHHD centers, five of which are supported by NCI, feature transdisciplinary research to improve knowledge of the causes of health disparities in the areas of prevention, diagnosis, treatment, and health promotion. The NCI also currently supports 67 NCI-Designated Cancer Centers, which aim to reduce the disproportionate burden of cancer in minority and other underserved populations. The NIMHD Center of Excellence (COE) Program supports academic institutions in conducting research and engaging in community outreach and dissemination related to health disparities, with 28 current COEs addressing cancer disparities.

The NCI Minority-Based Community Clinical Oncology Program (MB-CCOP) provides access to NCI-sponsored clinical trials in communities with at least 30 percent minority populations. Currently, 16 sites are funded in 11 states and Puerto Rico, and include public hospitals, Historically Black Colleges and Universities (HBCUs), and academic centers with a history of providing cancer care to large minority populations. Sixty to seventy percent of the enrollment from these institutions is comprised of racial and ethnic minorities and other underserved populations. MB-CCOPs select clinical trials that address the research needs of their communities and participate in community/academic partnerships that are essential for the development of research questions to help reduce cancer disparities. NCI is developing a new Community Oncology Research Program (NCORP), which will bring state-of-the-art cancer prevention, control, screening/post-treatment surveillance, treatment and imaging clinical trials, cancer care delivery research, and disparities studies to individuals in their own communities.

NCI is also expanding the participation of minority populations in genetics programs, such as The Cancer Genome Atlas (TCGA), to further our understanding of cancer biology and the molecular basis of cancer. Related research on the biological determinants of cancer health disparities includes projects examining genetic and epigenetic and metabolic factors for prostate

cancer disparities, identifying molecular signaling pathways in breast and prostate cancer, and identifying genetic variations for colorectal and leukemia related cancer disparities.

Item

Neuroblastoma - The Committee commends NCI for its leadership in convening a consensus panel to revise the international neuroblastoma response criteria. The Committee encourages NCI to expand its research portfolio on this devastating pediatric cancer with a focus on new treatment options for relapse patients.

Action taken or to be taken

NCI's research portfolio for neuroblastoma includes: (1) discovery research to identify candidate therapeutic targets, (2) preclinical testing to further validate candidate therapeutic targets and to prioritize specific drugs that modulate these targets, (3) early phase clinical trials to develop evidence for the safety and efficacy of new treatments, and (4) definitive clinical trials to provide convincing evidence for the effectiveness of new treatments. This comprehensive focus has been important in the development of new treatment options for both newly diagnosed patients and for those following relapse. These efforts include a variety of approaches aimed at preventing relapse as well as studies involving patients whose disease has progressed after an initial response to treatment.

NCI's Therapeutically Applicable Research to Generate Effective Treatments (TARGET) study recently completed extensive genomic analysis of neuroblastoma and, contrary to expectations, the scientists found relatively few recurrent gene mutations that would suggest new targets for neuroblastoma treatment. Instead, researchers are now focusing on how neuroblastoma tumors evolve in response to medicine and other factors, since neuroblastoma tumor cells often change rapidly over time. Given the few recurrent genetic mutations, this is likely due to factors including rare germline mutations, copy number variations, and epigenetic modifications during tumor evolution. Ongoing research includes studies of newly identified mutations that arise during the course of disease, particularly in patients who relapse after initial response to treatment. Extensive molecular characterization of the neuroblastoma genome, including RNA sequencing, is continuing to identify potential targets for treating these tumors, especially the most aggressive type of neuroblastoma, which shows amplification of the MYCN gene. Other research projects are focused on understanding how the tumors evolve in response to specific agents, and screening to identify genes regulating tumor growth, survival, and differentiation. NCI researchers are also examining cell surface proteins that are exclusively expressed in neuroblastoma tissues, which may be used as future therapeutic targets, and exploring newly identified mutations that arise during the course of disease, particularly in patients that relapse.

Extensive NCI-supported research over two decades, including a definitive Phase III clinical trial, has confirmed that another therapy, the antibody ch14.18, plus cytokines, significantly improves outcomes for neuroblastoma patients. NCI continues to support a clinical trial that

provides access to ch14.18 for children with neuroblastoma in the United States and collects additional toxicity and efficacy data for this agent. Two other ch14.18 trials have opened for patients with relapsed neuroblastoma to explore new ways of using this agent. In one clinical trial, ch14.18 is given with standard chemotherapy agents, and in the other, ch14.18 is given with the immune modulating agent lenalidomide. FDA approval of ch14.18 is pending. NCI is also supporting development of an immunotherapy approach using engineered T cells that target the same cellular marker as ch14.18 and may have clinical activity.

Preclinical testing also remains an important component of the strategy to develop more effective and less toxic therapies. NCI supports a testing program for anticancer agents against preclinical models of pediatric cancers and also is conducting drug screening in collaboration with NCATS to identify specific drugs for neuroblastoma therapy. NCI-supported research to validate candidate therapeutic targets has helped to identify pathways that mediate chemoresistance in preclinical models, which could lead to a better understanding of relapse. Additionally, NCI supports an initiative that brings together 15 university and children's hospitals to test promising new therapies and combination therapies for high-risk neuroblastoma in early-phase clinical trials with the goal of moving successful therapies into national testing through the Children's Oncology Group (COG). NCI's Pediatric Oncology Branch is collaborating with extramural and private sector partners on an individualized cancer therapy trial for high-risk neuroblastoma patients, utilizing genomic profiling to develop better treatment regimens.

Item

Neurofibromatosis [NF] - The Committee commends NIH for its continued support of NF research and again requests an update in the fiscal year 2015 congressional budget justification of relevant activities at NCI, NHLBI, NINDS, NICHD, NIMH, NIAMS, NIDCD, and NEI.

Action taken or to be taken

Many institutes within the NIH are engaged in research focused on neurofibromatosis (NF), a genetic disorder of the nervous system that manifests in ways such as skin and bone changes, vision and hearing problems, and the development of spinal, brain, and optical tumors. Neurofibromatosis Type 1 (NF1), one of the most common genetic disorders, affects one in every 3,500 individuals. NF1 is caused by mutations in the gene that contains the instructions for making a protein called neurofibromin, and symptoms include tumors (called neurofibromas) formed from nerve tissue. NF1 tumors are usually benign (non-cancerous) but they can be problematic based on their size and location. Neurofibromatosis type 2 (NF2) is less common, affecting about one in every 25,000 individuals. Typically, NF2 causes the development of tumors from the nerves important for hearing and balance.

NCI supports a comprehensive research program, which includes both intramural and extramural research, directed at NF and its related cancers. This work includes investigation of the biology of the NF1 and NF2 tumor suppressor genes and proteins. NCI also funds work focused on the

identification of rare and under-recognized cancers that may be associated with NF1, including development of a clinical setting to specifically evaluate these patients. To this end, NCI has established one of the largest clinical trial programs for children and adults with NF1, including more than 10 active clinical trials evaluating treatment approaches, and natural history trials that comprehensively evaluate NF1-related manifestations.

Another focus of NCI's intramural program is on the application of new molecularly targeted agents to treat NF1. This work includes the clinical development of drugs known as farnesyltransferase inhibitors (FTIs), which inhibit the activity of RAS, a protein that drives NF1. NCI's work in mouse models has demonstrated that a pathway known as RAS/ERK is critical for the growth of NF1 peripheral nerve tumors, providing a strong rationale for testing inhibitors of this pathway in NF1 clinical trials. NINDS-supported researchers are also investigating the cellular and molecular processes underlying the development of tumors in NF, and are conducting preclinical tests of potential therapies in mouse models of NF. To coordinate research across Institutes, NINDS organizes biennial Trans-NIH NF Working Group meetings, which include representatives from eight NIH Institutes, the Department of Defense, and advocacy groups.

Efforts to better monitor NF progression are also underway. The development at NCI of a semi-automated method for volumetric (3D) MRI analysis of plexiform neurofibromas (benign tumors arising from the outer layer of nerves) allows researchers to sensitively and reproducibly monitor changes in tumor size over time. Use of this method allows for more rapid detection of tumor progression compared to standard solid tumor response criteria, and decreases trial duration and exposure to potentially toxic inactive investigational agents. This method is now used in most national clinical trials for plexiform neurofibromas. NCI is utilizing this approach in collaboration with investigators from the NIH Clinical Center and the extramural community on a natural history study for children and adults with NF1. The study will longitudinally characterize NF1 manifestations, develop endpoints for clinical trials, perform genotype-phenotype correlations, and analyze potential biomarkers of disease and malignant degeneration.

In other efforts focused on NF-associated pediatric low-grade astrocytoma (PLGA), NCI researchers screened thousands of existing drugs and new compounds isolated from plants and marine life for potential therapeutic activity against PLGA. Also, certain PLGA, called optic pathway gliomas, occur in children with NF1 and are infrequently biopsied given their diagnostic appearance on initial imaging. In an effort to learn more about these tumors, the NCI intramural research program has initiated an imaging study that combines imaging techniques – newer MRI sequences in addition to a type of positron emission tomography scan known as FDG PET – for an enhanced approach to noninvasively evaluate the biology of pediatric brain tumors as well as their response to therapy. The NIDCD Otopathology Research Collaboration Network is also broadening our scientific understanding of NF by supporting laboratories that are studying human temporal bone specimens associated with the disorder. And, in collaboration with NCI, NIDCD continues to analyze how ear examination and brain imaging studies correlate with

cognitive problems associated with NF1. In addition to pursuing research that enhances scientific understanding of NF, NIDCD scientists are seeking ways to better detect and monitor NF2 tumors. NIDCD is also exploring how proteins associated with the NF2 gene can lead to the development of a wide range of new therapies (e.g., molecular and drug therapies). And, in pursuit of developing better treatment options for NF2 patients, NIDCD, NINDS, and NCI scientists are supporting a Phase II clinical trial to test the safety and efficacy of a potential therapeutic agent called bevacizumab.

Additionally, NIMH funds a wide portfolio of basic research on synaptic transmission—that is, the transmission of chemical or electrical signals across the tiny gaps between brain cells. NIMH-funded researchers are investigating the role of neurofibromin (the protein, which when mutated, underlies neurofibromatosis) in synaptic transmission. Emerging evidence from two ongoing NIMH-supported studies suggests that this protein may be a key contributor to the integrity of various facets of the synapse’s ability to respond and adapt to changes in the neural environment. This work may inform our understanding of the synaptic mechanisms that go awry in NF.

Item

Obesity - Excess body weight is linked to increased risk of primary diagnosis of colon, endometrium, kidney, esophageal, and postmenopausal breast cancers. Obesity is also linked to poor prognosis once cancer develops, especially in breast cancer and likely for prostate and colon cancer, the three most prevalent cancer types. Numerous underserved and minority groups have higher than average rates of obesity and as a result they suffer from higher obesity-related morbidity and mortality from cancer compared to other groups. Despite this statistic, these groups are typically underrepresented in obesity-related cancer prevention trials. In particular, nearly 20 percent of adults in the United States reside in a rural area, representing one of the largest medically underserved populations in the Nation and among the most understudied groups of cancer patients and survivors. The Committee urges NCI to focus research efforts on the effects of obesity on cancer outcomes in these underserved groups.

Action taken or to be taken

NIH supports research on obesity and cancer risk through a variety of activities, including basic research on mechanisms by which obesity may affect cancer risk, changes in hormonal or insulin levels, interaction with tumor growth regulators, or increases in inflammation or suppression of immune responses. NIH also supports web and data resources, such as those provided through the [National Collaborative on Childhood Obesity Research](#); extramural and intramural epidemiologic studies; and dissemination and implementation of obesity research findings. NCI also supports a variety of epidemiological studies, some of which have a particular focus on obesity in underserved groups such as rural or minority populations. example, NCI and NIMHD are studying linkages between race, obesity, and biomarkers of drug resistance in breast cancer

cells. NIMHD is supporting similar work to better understand the disproportionate mortality of African American men due to prostate cancer by examining the relationship between obesity and poor prostate cancer outcomes.

NCI supports a number of other important initiatives that include underserved populations in the study of obesity and cancer. For example, NCI's Transdisciplinary Research on Energetics and Cancer (TREC) Centers investigate how the combined effects of obesity, poor diet, and low levels of physical activity increase cancer risk, and Community Networks Program Centers (CNPC), several of which are conducting randomized controlled diet and physical activity interventions reaching African American, Hispanic, Native Hawaiian, and rural Appalachian communities, using culturally tailored strategies to raise awareness of healthy lifestyle behaviors and to ultimately reduce obesity. Another relevant initiative, the NCI National Outreach Network (NON) program, connects underserved communities, including rural populations, and NCI-funded cancer health disparities research institutions using materials and messages aimed at reducing obesity risk factors. These institutions include NCI-Designated Cancer Centers, as well as NCI Community Clinical Oncology Program (CCOP) sites, and Minority-Based CCOP sites. Additionally, a new program announcement from NCI entitled "Physical Activity and Weight Control Interventions Among Cancer Survivors: Effects on Biomarkers of Prognosis and Survival," will support research to identify specific biological or biobehavioral pathways through which physical activity and/or weight control may affect cancer prognosis and survival.

NCI has also issued a number of competitive funding opportunities related to obesity and cancer risk. For example, NCI's Provocative Questions initiative has resulted in a list of important questions to stimulate the NCI's research communities to use laboratory, clinical, and population sciences in especially effective and imaginative ways. The question, "How does obesity contribute to cancer risk?" is included in this funding opportunity. Research associated with this question has the potential to result in a deeper understanding of the mechanisms of the cancer risk posed by obesity and could suggest new strategies for countering these risks. Toward this end, NCI scientists recently identified a new mechanism, known as metabolic transduction, linking obesity with breast cancer. This understanding of how cellular metabolic status can influence epigenetic control of cellular function may help identify new drug targets and limit tumor-promoting effects in obese patients. A related area being explored is whether reversing obesity and inflammation may lower the risk of developing, or dying from breast cancer. These include lifestyle interventions as well as studies to explore the role of anti-inflammatory agents, two approaches that apply across all populations.

Item

Ovarian Cancer - The Committee urges NCI to integrate expertise in cancer biology, drug discovery and development, bioinformatics, and pharmacogenomics to advance treatment

options for patients with ovarian cancer. The Institute is also encouraged to collaborate with NCATS on drug repurposing efforts.

Action taken or to be taken

The incidence rate of ovarian cancer has been declining since the mid-1980s with 22,240 new cases expected in 2013. Yet, it is among the leading causes of cancer mortality in women. This is partly because it is difficult to detect early, before it has spread. Developing better early detection and treatment methods for ovarian cancer is an important area of NCI supported research.

The Cancer Genome Atlas (TCGA) project, sponsored by NCI and NHGRI, is systematically identifying the major genomic changes involved in more than 20 cancers, including ovarian cancer, using state-of-the-art genomic analysis technologies. TCGA reported the genomic analysis of more than 500 serous ovarian adenocarcinomas, the most prevalent form of ovarian cancer and which accounts for about 85 percent of all ovarian cancer deaths. TCGA results confirmed that mutations in gene *TP53*, a tumor suppressor gene, are present in more than 96 percent of ovarian adenocarcinomas.

TCGA researchers also established how sets of genes are expressed in a fashion that can predict patient survival. The researchers identified patterns for 108 genes associated with poor survival and 85 genes associated with better survival, affirmed the existence of four distinct subtypes of ovarian cancer, substantiated observations that patients with *BRCA1 and BRCA2* gene mutations have better survival rates than patients without those mutations, and identified therapeutic opportunities by searching for existing drugs that might correct a genomic error that causes a patient's ovarian cancer. The search yielded 68 genes that could be targeted by existing approved or experimental drugs that might inhibit amplified or over-expressed genes suggested to play a role in ovarian cancer. The investigators noted that one type of drug, a PARP (Poly ADP ribose polymerase) inhibitor, might be able to counteract the DNA repair gene observed in half of the ovarian tumors studied. While researchers have known that these drugs could be effective against the disease, this study revealed that 50 percent of tumors might be responsive to drugs that exploit the genetic instability of the tumors and induce the cancer cells to die.

In addition to the TCGA project, NCI is currently sponsoring over 350 clinical trials and 550 other research projects to expand our knowledge of and treatment options for ovarian cancer. Some notable examples include the Screening Methods for Finding Ovarian Cancer clinical trial that is studying new screening methods to identify women at increased risk of ovarian cancer. The study also is developing new prevention approaches and novel therapies. Another study is the large Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Trial that is determining whether specific cancer screening tests reduce deaths from these cancers. Researchers found that screening women for ovarian cancer with a blood test for the tumor marker CA 125 and transvaginal ultrasound in addition to standard medical care (physical exam and blood work) did

not reduce ovarian cancer mortality as compared to standard medical care alone. Such negative results provide clarity, are important contributions to the body of evidence surrounding ovarian cancer, and serve to move the entire cancer field forward.

An important ongoing treatment trial is aimed at determining the best sequence for administering chemotherapy and a drug called olaparib to women with recurrent gynecologic cancers, including ovarian cancer. Olaparib is in a relatively new class of medicines called “PARP inhibitors,” a type of drug that targets and blocks an enzyme involved in many cell functions, including the repair of DNA damage. Olaparib has shown activity against breast and ovarian cancers in women with BRCA1 or BRCA2 gene mutations, and ongoing research is exploring specifics about patients likely to respond and optimal therapeutic strategies using this drug. Another initiative, the Ovarian Cancer Epidemiology Consortia, includes four research consortia representing scientists from multiple institutions that conduct cooperative research efforts pooling information from numerous patient cohorts to identify genes related to the risk of ovarian cancer, and to evaluate new clinical treatments, prevention and risk reduction measures, and diagnostic tests to improve ovarian cancer outcomes.

NCI’s Early Detection Research Network (EDRN) is conducting a number of discovery and validation studies of a variety of biomarkers for risk assessment and early detection for ovarian cancers. More than 150 new candidate biomarkers identified through the EDRN are currently being validated for the early detection of ovarian cancer, and TCGA-guided discovery efforts in combination with gene expression data from genomic, proteomic and pathway studies are important new tools in the effort to identify promising candidate biomarkers for the early detection of ovarian cancer. NCI also supports five Specialized Programs of Research Excellence (SPORes) focused on early detection, screening, prevention, and therapeutic tools for ovarian cancer.

NCI and NCATS collaborate on a continual basis to explore a variety of translational opportunities stemming from The Cancer Genome Atlas and other advances in molecular characterization of cancer. Another important translational program is NCI’s Experimental Therapeutics Program (NExT), designed to streamline development and testing of promising new anticancer drugs and to expedite their delivery to the bedside. The program consolidates NCI’s anticancer drug discovery and development resources in support of a robust therapeutics pipeline from new target validation through Phase III clinical trial evaluation. Special consideration is given to addressing unmet needs for rare cancers as well as those with limited responses to treatment, with the goal of supporting the most promising new drug discovery and development projects.

Item

Pancreatic Cancer - The Committee strongly supports the goals of the Recalcitrant Cancer Research Act of 2012, a law that provides NCI with the tools to develop a scientific framework

for addressing the deadliest forms of cancer, including pancreatic cancer. While maintaining the integrity of the peer review system, the scientific framework will enable NCI to capitalize on the full range of its expertise, and that of extramural scientists, to assess scientific progress against the Nation's most lethal cancers, starting with pancreatic and lung cancer, and to develop a research agenda to reduce morbidity and mortality. The Committee urges the Institute to ensure that the final framework for pancreatic cancer fully addresses all aspects of the statute. The Committee also notes that the new law reinforces NCI's authority to award "exception funding" when relevant to a scientific framework.

Action taken or to be taken

NCI is continuing a strong focus on pancreatic cancer and is fully engaged in meeting the requirements of the Recalcitrant Cancers Research Act of 2012. In accordance with the Act, NCI identified two "recalcitrant cancers," pancreatic ductal adenocarcinoma (PDAC) and small cell lung cancer that each have less than 20 percent survival at 5 years after diagnosis and that cause at least 30,000 deaths in the U.S. per year. NCI then convened a group of experts and representatives of cancer advocacy groups for each cancer type and conducted "horizon scanning" workshops for these cancers in the second half of 2012 and the first half of 2013. These workshops were intended to identify new ideas and important, unsolved problems in the research and to identify approaches to solve those problems.

The PDAC workshop report, accepted by NCI's Clinical Trials and Translational Research Advisory Committee in early March 2013, recommended several areas for further investigation, including studying connections between PDAC and recent onset diabetes mellitus, evaluating biomarkers for populations at high risk for PDAC, and utilizing new chemical biology data to develop treatments to target genetic mutations associated with PDAC. This report was the first step in the process of developing the PDAC scientific framework as required by the Act. The full "scientific framework" will be completed over the next few months and submitted to Congress well in advance of the July 2014 deadline established in the Act.

Following up on the workshop recommendations, NCI is exploring associations between PDAC and recent onset diabetes mellitus; in June, NCI partnered with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to host a workshop to share data and to explore research opportunities about known and suspected mechanisms for the increased risk of PDAC associated with chronic pancreatitis and diabetes mellitus. NCI also funds a broad range of research into biomarkers to explore ways to identify PDAC at earlier and more treatable stages. NCI recently launched the RAS Project, an initiative to develop successful treatment of tumors that contain mutations in members of the RAS gene family, including K-RAS, which is mutated in more than 90 percent of pancreatic cancers, about 40 percent of colorectal cancers, and about 25 percent of lung adenocarcinomas. This group of tumors tends to respond poorly to conventional chemotherapy and to have a poor prognosis.

NCI makes every effort to both fund the most promising scientific ideas and to address public health needs. While expert peer review of grant applications by external peers and oversight of our scientific programs by outside advisory groups is the single biggest factor in evaluating funding potential, NCI has been giving special attention to grant applications that might in the past have been unfunded because they fell below what was once considered a “pay-line,” a percentile score below which applications were generally not funded. Since FY2011, NCI’s scientific program leaders have eliminated the traditional “pay-line” and instead have been performing additional evaluations of grant applications to ensure a balanced grant portfolio and to recognize the value of research proposals that are highly original or address important scientific priorities, such as those identified through recent meetings.

Item

Pediatric Cancer - The Committee encourages NCI to put a higher priority on pediatric cancer, as cancer remains the leading cause of disease-related death in children. More effective and less toxic treatments are needed, including materials-based strategies for localized drug delivery.

Action taken or to be taken

NCI supports a comprehensive research program for children with cancer, including basic molecular characterization projects, preclinical testing and clinical trials, and epidemiological studies. In addition to numerous projects focused solely on pediatric cancer, NCI also funds a wide range of research efforts that complement this investment and that contribute to progress in better understanding and treating pediatric cancers. Given that a number of treatments for adult tumors have been found to be effective in treating certain pediatric tumors, it is also critical to be aware of progress being made in treating adult tumors, and to continually assess whether this research may have implications for children.

Two promising examples include the drug crizotinib, the first FDA-approved to treat a subset of lung adenocarcinoma, and vismodegib, originally developed to treat basal cell carcinoma in adults. Clinical studies have shown crizotinib to be active against anaplastic large cell lymphoma, neuroblastoma, and myofibroblastic tumors in children; and vismodegib to be active against a subtype of medulloblastoma in children. With both crizotinib and vismodegib, the potential for the agents to be active against these childhood cancers was recognized prior to the drugs’ approval for use in adults, and research in children was underway in parallel to adult studies. NCI also leads a Phase I/II trial studying the drug mithramycin to prevent metastases in both children and adults with solid tumors or Ewing Sarcoma. This builds upon NCI-supported work identifying mithramycin as a small molecule inhibitor of EWS-FLI1, a fusion protein that drives the development of Ewing sarcoma. Pediatric cancers continue to be featured prominently in NCI’s most innovative and high-profile research efforts, particularly genomics research. This includes the TARGET (Therapeutically Applicable Research to Generate Effective Treatments) initiative, a program within NCI’s Center for Cancer Genomics (CCG). To date, the initiative

has led to two clinical trials for new drugs against childhood tumors and identified numerous new mutations and chromosomal abnormalities associated with pediatric tumors. TARGET is also collaborating with CCG's Cancer Genome Characterization Initiative as it leads genomic studies of various pediatric cancers that do not respond well to treatment: medulloblastoma, high-risk Acute Myeloid Leukemia, Burkitt Lymphoma, two types of rare kidney tumors, and gastrointestinal stromal tumor (GIST). Of note, 85 percent of pediatric GIST patients do not harbor the genetic mutations that are common and treatable in adults with GIST.

Other NCI-supported efforts include the Pediatric Preclinical Testing Program (PPTP), which develops preclinical models representing a wide range of childhood cancers and has tested more than 50 agents in the past five years with several agents moving into clinical testing. The Pediatric Brain Tumor Consortium (PBTC) conducts early phase clinical trials for experimental therapies for children with brain cancers. NCI also funds significant research efforts through the Children's Oncology Group (COG), a cooperative program that develops and coordinates pediatric cancer clinical trials at over 200 leading institutions, and includes a consortium dedicated to safely introducing novel agents. The COG is also able to manage international studies, allowing for more pediatric cancer patients to be enrolled into clinical trials. NCI's Pediatric Oncology Branch (POB) is also leading clinical research efforts in oncogenomics and the use of immunotherapies in pediatric patients. For example, based upon activity of T cell receptors targeting the protein CD19 in B-cell malignancies in adults, the POB has initiated a clinical trial of anti-CD19 T cell therapy for refractory B-cell malignancies in children – an approach designed to deliver the therapy directly to the cancer cells, with the goal of sparing healthy cells and therefore reducing toxicity.

The NCI also supports large cohort studies through the International Childhood Cancer Cohort Consortium, which allows researchers to follow 11 cohorts of more than 70,000 children to explore risk factors for cancer. Additionally, the Childhood Cancer Survivor Study (CCSS) is a collaboration of 27 institutions to learn more about the late effects of childhood cancer treatment. The CCSS began in 1994 and is composed of individuals who survived five or more years after diagnoses for cancer during childhood or adolescence. Recruitment is underway to expand the study to include approximately 15,000 survivors of childhood cancer diagnosed between 1986 and 1999 and an additional 4,000 siblings of survivors who serve as the comparison group.

Item

Robotic Biorepositories - To determine the genetic differences in the development, progression, and response to treatment of individuals with cancer, biospecimens must be collected and evaluated. As more are collected, NCI should consider the application of new technologies such as automated robotics to ensure an adequate supply of biospecimens and to promote better standardization of the collection process. The introduction of automated processes in biospecimen collection may also help to ensure an adequate supply of high-quality human biospecimens from multiethnic communities for research to understand and overcome cancer

health disparities. NCI has established networks for biospecimen collection that can be used to assess the application of robotic technology and determine if robotics can improve the functions of the biorepository network. The Committee encourages NCI to consider a pilot robotic biorepository project to determine if this technology can enhance the goals of NIH programs.

Action taken or to be taken

NCI agrees that standardized, high-quality biospecimens are an essential component of cancer research, and continues to support research efforts in this area. Over the past several years, NCI established a specific branch on Biorepositories and Biospecimen Research and undertook an intensive due diligence process to understand the state of its funded biospecimen resources and the quality of biospecimens used in cancer research. These efforts culminated in the development of NCI's Best Practices for Biospecimen Resources that outlines the operational, technical, ethical, legal, and policy best practices for NCI-supported biospecimen resources. The NCI Best Practices have become an important resource for biorepositories in the U.S. and internationally, including beyond the cancer research field.

Automation and robotic technologies have been used for many years to improve processes in biospecimen collection, processing, and storage. Examples of such technologies include the following: the use of bar codes for labeling biospecimens, which greatly reduce errors in specimen inventory systems; laboratory instruments that quickly divide large numbers of liquid samples into smaller portions or "aliquots," sometimes further processing such samples into nucleic acid derivatives; and robots which operate at low temperatures to automatically "pick" desired samples from their positions in freezers. Various robotic technologies are already in place in many NCI-funded programs. Automated technologies have improved NCI's ability to access the large numbers of biospecimens used for population-based and other studies.

NCI looks forward to additional advances in robotic technologies for biorepositories and the advances in biorepository science and improved operations that these technologies promise.

Item

Slow-Growing Children's Brain Tumors - The Committee urges NCI to address the shortage of tissue samples for slow-growing children's brain tumors by incentivizing researchers to centralize and share such samples, and to support the development of preclinical mouse models and other nonmammalian models for pediatric brain tumors. The Committee requests an update on these issues in the fiscal year 2015 congressional budget justification.

Action taken or to be taken

NCI supports a broad research portfolio relevant to pediatric low-grade astrocytoma (PLGA), the most common pediatric brain tumor and one that is characterized by slow growth and, in the majority of cases, mutations in the BRAF gene. NCI is involved in several projects focused on

obtaining high-quality biospecimens and sharing tissues for a variety of research purposes including analysis of slow-growing children's brain tumors. The NIH Cancer Genome Atlas (TCGA) and NCI's TARGET (Therapeutically Applicable Research to Generate Effective Treatments) initiative, focusing on adult and pediatric cancers respectively, are analyzing complete genomes of various cancer types. NCI is also participating in the International Cancer Genome Consortium (ICGC) and collaborating with German researchers in efforts to collect and analyze PLGA tumor tissue samples. NCI additionally monitors results from other large scale genomics projects, so that results from these projects can be quickly incorporated into ongoing preclinical and clinical research programs. A similar partnership exists between two NCI-designated cancer centers, the St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project. This group recently completed genomic sequencing of 151 PLGAs and low-grade glioneuronal tumors and identified novel genomic alterations in grade II diffuse PLGAs as well as confirmed the importance of BRAF genomic alterations for pilocytic astrocytomas.

NCI also supports a number of efforts to collect high-quality biospecimens for all cancer types, including pediatric cancers. The Pediatric Cooperative Human Tissue Network (pCHTN) works with investigators to acquire specimens to meet specific research project requirements, with a focus on basic and applied research studies. In addition, NCI supports the Children's Oncology Group (COG) Biopathology Center, the largest pediatric specimen bank in the country, and a centralized resource for the more than 200 COG member institutions. An example specific to PLGAs and other brain tumors is a COG protocol focusing on collecting and storing blood and brain tumor tissue samples from children with brain tumors treated at COG institutions. The study provides for long-term storage of specimens from these patients and makes these specimens available to qualified researchers to understand the biology of pediatric brain tumors. Pediatric patients treated at COG sites are eligible at time of diagnosis, second-look surgery, recurrence, or the development of a second cancer. This study is open at 160 sites, including more than 100 sites across the U.S., 13 in Canada, and one each in New Zealand and Switzerland.

The vast majority of PLGA cases have genomic alterations in the BRAF gene, which is mutated in other cancer types and can be targeted for therapy with certain RAF kinase inhibitors. NCI is supporting the development of preclinical models that will allow identification of promising candidate treatments for PLGAs with the BRAF alteration. The NCI-supported Pediatric Preclinical Testing Program developed a model for a subtype of PLGA with the BRAF mutation and identified a targeted therapy, selumetinib (AZD6244), for additional research. The Pediatric Brain Tumor Consortium, also supported by NCI, conducted a Phase I trial of selumetinib in children with PLGA who progressed after receiving chemotherapy and/or radiation therapy, to study the side effects and the best dose of selumetinib. This is the first clinical trial of a targeted agent directed against the BRAF genomic alterations that commonly occur in pediatric low-grade gliomas. The Phase I results will be presented at the Society for Neuro-Oncology (SNO) meeting

in November, 2013. Based on the promising results observed in the phase 1 component, the trial has been amended to include a phase II cohort focusing on patients whose tumors have BRAF mutations. The trial is open at 13 sites across the country, including at the NIH Clinical Research Center in NCI's Pediatric Oncology Branch, and is expected to enroll approximately 40 additional children with PLGA.

Additionally, NCI intramural scientists have developed a mouse model for astrocytoma/glioblastoma used to investigate key research questions. The investigators are developing methods to use the model for testing experimental therapeutics, which may lead to finding drugs with lower toxicity in children. These efforts have already identified promising candidate compounds, including the natural compound schweinfurthin, and NCI is collaborating with investigators at the University of Iowa to synthesize quantities for further research. Recent NCI-supported research conducted at the Dana-Farber/Harvard Cancer Center analyzed DNA from 44 tissue samples and identified an alteration in a gene called MYBL1 in approximately 30 percent of the patients who had grade II diffuse PLGAs. Mutated MYBL1 causes tumors in mice, and these findings may lead to development of diagnostic and prognostic tests for patients with this mutation.

Conference Significant Items

Item

Pediatric Brain Tumor – The National Cancer Institute (NCI) is encouraged to continue its focus on obtaining high-quality biospecimens for all cancer types and the sharing of tissues for research purposes, while exploring how genetic model and xenograft models can be used for biology studies and drug testing studies. In addition, NCI shall provide an update on the advantages and disadvantages of a time-limited special emphasis panel in the fiscal year 2015 budget request.

Action Taken or to be Taken

The availability of carefully collected and maintained, high-quality biospecimens is a pivotal element for the success of 21st century cancer research, and the National Cancer Institute is leading a national initiative to systematically improve the quality and consistency of human biospecimen collections. NCI is supporting research to learn more about best practices for collecting, handling, and processing biospecimens and leading the development and continuous improvement of policies and processes for proper management of these resources. NCI is cultivating partnerships within the research community, and working to harmonize national and international biospecimen and biobanking standards and exchange information about biospecimen-related issues. In addition, NCI is actively engaging the scientific community in the development of new and innovative technologies to measure and to maximize the quality and utility of biospecimens and has recently announced [new funding opportunities](#) in this area. NCI continues to support many research projects which feature high-quality biospecimen collections

resources with sustained value likely to extend long past their current purposes. For example, the Children's Oncology Group Biopathology Center located at the Research Institute of Nationwide Children's Hospital maintains the largest pediatric specimen bank in the nation, with a collection of tissues obtained from more than 32,000 children with cancer and other diseases. Tissues from approximately 90 percent of pediatric solid tumor cases and half of the leukemia cases found in the United States and Canada are sent to this facility. With regard to the sharing of tissues for research purposes, NCI is currently working to improve the online Specimen Resource Locator tool, which catalogs biospecimens collected under different studies, and is building an enhanced system for sharing biospecimens collected for clinical trials.

Model systems of cancer development and progression are vital tools for productive cancer research, particularly in the development of effective cancer therapies, and NCI is working to ensure that cancer researchers have access to reliable and informative tumor models. For example, NCI is collaborating with academia and industry to build a repository of pre-clinical model systems, including patient-derived xenograft models and genetically engineered mouse models, to be made available for use by the entire cancer research community for cancer discovery and therapeutics development. This [resource](#), maintained at NCI's Frederick National Laboratory for Cancer Research (FNL), has been designed to leverage existing FNL capabilities and NCI's designated cancer centers and extensive clinical trial networks to enhance the utility and predictive value of preclinical models in cancer research.

Special emphasis panels (SEPs) are among the tools on which the institutes and centers (ICs) comprising the National Institutes of Health rely to conduct rigorous peer review of applications for grant funding. Most of the external scientific review groups that provide the first tier of evaluation in our peer review system are managed by the NIH Center for Scientific Review. SEPs, however, are managed directly by the NIH ICs, and are generally utilized to review grant applications that are submitted in response to special solicitations such as Requests for Applications (RFAs) and other unique programs with features that require specialized review. For example, in early 2014, an NCI SEP will convene to review grant applications submitted in response to the active RFAs described above for projects focused on developing early-stage and validating emerging-stage technologies that assess cancer biospecimen quality.

Item

Pediatric Cancer Informatics Program - Efforts to establish a personalized medicine platform to improve treatment for pediatric cancer research patients in community hospitals may require the development of pediatric cancer informatics systems. The NIH shall provide an update in the fiscal year 2015 budget request on any such effort and how the effort could utilize cost-effective cloud or other types of technologies.

Action taken or to be taken

Biomedical informatics, which involves the management and analysis of enormous sets of molecular and clinical data, has emerged as a critical component of the National Cancer Institute's toolkit to study adult and pediatric cancer in all of its manifestations. In work that ranges from cancer genomics, to cell signaling, and to clinical trials, the proper collection, analysis, storage, retrieval, and distribution of "big data" are critical elements of the Institute's charge. NCI seeks to ensure that the entire cancer research community, including the newly forming National Cancer Trials Network (NCTN), comprised of adult and pediatric clinical trials groups, will have the necessary informatics capabilities to carry out its missions.

In January 2014 the NCI issued a request for proposals to sponsor the development of multiple Cancer Genomics Cloud pilots that will be available for use and testing by the scientific community as part of a competitive evaluation that will include technical benchmarking and cost analysis. If successful, the NCI, working in concert with the cancer research community and relevant oversight committees, will define and potentially construct a production version of one or more of the pilot clouds, or a successor design informed by the results of the pilot evaluations. The Cancer Genomics Cloud pilots will build upon the Cancer Genomics Data Commons initiative, which is designed to be an all-inclusive repository of genomic and relevant biological and clinical outcomes data, including but not limited to data from The Cancer Genome Atlas ([TCGA](#)), the Pediatric Cancer Genome Project (PCGP), and the Therapeutically Applicable Research to Generate Effective Treatments ([TARGET](#)). These projects are a major step toward the establishment of a full Cancer Knowledge Commons, similar to that called for in the National Academy report on Precision Medicine, and will be coordinated with NIH's Big Data to Knowledge (BD2K) initiative and other relevant efforts.

A major goal of the Pediatric Cancer Informatics Program is to develop capabilities that support precision medicine, that is, the ability to classify and treat a patient based on his/her detailed clinical presentation coupled with advanced imaging and the underlying molecular characteristics of the patient's tumor. The informatics capabilities developed through this project will be applicable to research across all cancer types, and available for clinical trials devoted to children and adolescents with cancer at both academic centers and community hospitals.

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National Heart, Lung, and Blood Institute (NHLBI)

Senate Significant Items

Item

Cardiovascular Disease - The costs of heart disease, stroke, and other forms of cardiovascular disease, in terms of lives lost and resources spent, remain the highest of any disease in the Nation. The Committee continues to believe that research against these devastating diseases should be a top NIH priority. The Committee recommends that NHLBI allocate resources for cardiovascular disease research according to the priority areas included in the Division of Cardiovascular Diseases Strategic Plan.

Action taken or to be taken

The NHLBI supports a robust portfolio of research to improve diagnosis, treatment, and prevention of cardiovascular disease (CVD) and has identified the following seven areas as top research priorities:

- Basic cardiovascular biology to identify candidate causal pathways for disease, including actions of small molecules called microRNAs; effects of epigenetic modifications; and use of new methods such as Mendelian randomization, an epidemiologic study design that incorporates genetic information into traditional epidemiologic models
- Innovative treatment approaches, including use of serial biomarker measurements to inform heart failure management, and use of genomic tests to guide dosage in patients receiving new prescriptions for anticoagulation
- Diagnostic imaging, including development of molecular imaging and conduct of trials of newer imaging technologies
- Device technologies, including renal artery stents for patients with severe hypertension and ventricular assist devices for patients with severe, but not end-stage, systolic heart failure
- Comparative effectiveness studies, including support for a trial to determine the effects of varying the aggressiveness of blood pressure reduction in patients with systolic hypertension
- Clinical outcomes, including assessment of clinical course in patients enrolled in integrated health plans who receive implantable defibrillators
- Project management, including development of innovative low-cost methods for conducting large-scale CVD trials and for transforming epidemiology studies in an era of “big data”— datasets so large and complex that they are difficult to analyze using standard statistical software.

Approximately 62 percent of the Institute's FY 2013 extramural investment addresses CVD directly. In addition, substantial research carried out through the Institute's blood diseases and resources program is highly relevant to CVD. The NHLBI continues to collaborate in some areas of CVD research with other NIH Institutes and HHS agencies. The Institute continues to support the Progenitor Cell Biology Consortium, the Pediatric Cardiac Genomics Consortium (PCGC), and the Pediatric Heart Network, and is renewing support for the Cardiovascular Cell Therapy Network and the Cardiothoracic Surgery Network. In 2013, researchers from the PCGC reported on a new molecular pathway that potentially links congenital heart disease and neurodevelopmental abnormalities and increases the number and kind of causal genes implicated in congenital heart disease.

Since the establishment of the Framingham Heart Study in 1948, the NHLBI has supported large cohort studies to understand CVD risk factors and suggest approaches for prevention. Newer cohort studies focus on minority populations, including African Americans (the Jackson Heart Study and the Coronary Artery Risk Development In Young Adults Study), Hispanic Americans (the Hispanic Community Health Study–Study of Latinos), multiracial populations (the Multi-Ethnic Study of Atherosclerosis), and geographically diverse communities (Atherosclerosis Risk in Communities Study). In fiscal year 2013, the Hispanic Community Health Study – Study of Latinos reported that American Latinos carry an unusually high burden of risk factors (like hypertension and diabetes) for CVD; 25 percent of people of Puerto Rican descent had at least three risk factors. The Study also reported associations between cardiovascular risk and characteristics like education level and immigration history.

Item

Cell-Based Regenerative Treatments - The Committee commends the Institute for its effort to harness the potential of cell-based regenerative treatments to address lung diseases and encourages additional work in this area.

Action taken or to be taken

Although scientific advances have greatly improved health outcomes, acute and chronic lung diseases remain leading causes of morbidity and mortality in the United States and the world. To make further progress in combating lung diseases, the NHLBI is investing in several initiatives to improve understanding of the basic biology of stem cells, an important prerequisite for the development of innovative cell-based therapies for lung diseases. Examples of NHLBI-supported research include:

- Establishing a consortium to characterize stem and progenitors cells and study the unique challenges presented by transplantation of those cells
- Developing new strategies for growing 3D tissues relevant to heart, lung, and blood diseases

- Understanding the basic biology of lung pluripotent cells and their potential use in cell therapy and lung regeneration
- Advancing modeling of lung regeneration, including recellularization of native lung bioscaffolds

These investments in basic research will position the scientific community to test stem cell populations in preclinical models and ultimately in first-in-human clinical trials.

Patients who suffer from chronic lung diseases are increasingly seeking stem cell therapies outside the United States due to the limited opportunities to participate in clinical studies of stem cells inside the country. Although conducting clinical studies of cell therapies for lung diseases is particularly challenging due to the structural and cellular complexity of the lung, the NHLBI recently funded, for the first time, a grant to test the safety and efficacy of cell-based therapy in adults with acute lung injury.

In FY 2013, the NHLBI convened a workshop of national experts in cell therapy to assess the pipeline of advanced preclinical models for chronic lung disease suitable for use in testing promising cell therapeutic approaches. A workshop report that outlines scientific needs and opportunities for research on cell-based therapies for acute and chronic lung diseases was published in 2013. Among other things, the workshop participants recommended the development of research models that closely reflect human lung disease for use in testing clinical grade cell products.

Item

Centers for Advanced Diagnostics and Experimental Therapeutics [CADET] - The Committee applauds the Institute's efforts to accelerate the translation of basic research findings into clinical advances in respiratory diseases through the CADET program.

Action taken or to be taken

Advances in understanding the biology of pulmonary diseases have enormous potential to improve patient care through the development of new diagnostic and therapeutic products, but translation of discovery to application is slow. The National Heart, Lung, and Blood Institute launched the Centers for Advanced Diagnostics and Experimental Therapeutics (CADET) program to shorten the time period between discovery of new scientific knowledge and its application to the development of clinically meaningful new products. During the first phase of the program, CADET I, which was completed in 2013, investigators identified potential therapeutic agents that can modulate the molecular processes underlying pulmonary diseases. The second phase of the program, CADET II, which will begin in FY 2014, will support further development of promising therapeutic agents, including candidate therapies in preparation for an Investigational New Drug application to the Food and Drug Administration. Investigators may

also develop diagnostic tests to assess the effects of therapies in different populations to minimize the risk to individuals who are most susceptible to toxicity or unlikely to benefit.

Item

Chronic Obstructive Pulmonary Disease [COPD] - The Committee applauds NHLBI for leading a cross-agency effort to respond to COPD, including collaborating with CDC in releasing the first-ever, State-by-State prevalence data on this disease. The Committee encourages the Institute to move forward with this important initiative.

Action taken or to be taken

The NHLBI continues to provide leadership for research and education to address the public health burden of COPD in collaboration with other components of the Federal government. In May 2013, the NHLBI hosted a forum of representatives from several Federal government agencies and National Institutes of Health institutes on COPD. The participants shared information about their current activities related to COPD and discussed opportunities to further cooperate and enhance the effectiveness of the federal response to this serious public health problem. Thematic areas included disease prevention, ascertainment, diagnosis, and treatment. In light of the severity and magnitude of the challenges associated with COPD, the participants saw merit in establishing a standing COPD federal action group. As a starting point, the federal representatives agreed to put their web pages on links to the web pages of the other agencies and institutes of the Federal government to provide interested individuals with a comprehensive picture of ongoing COPD federal activities. The NHLBI will coordinate this effort. The participants highlighted specific areas that would benefit from the development of collaborations to increase effectiveness and efficiency. The NHLBI will describe the areas in a meeting report that will be posted on the Institute's public website. The NHLBI will reassemble the federal representatives to report on progress and explore options for developing a national action plan to respond to the substantial burden of COPD; external, nonfederal stakeholders, including patients will also participate.

Item

Congenital Heart Defects - The Committee commends NHLBI for its increasing efforts to develop translational research activities related to congenital heart disease through programs such as Bench to Bassinet and participation in the Congenital Heart Public Health Consortium. The Committee urges NHLBI to continue its work with other Federal agencies, as well as professional and patient organizations, to expand collaborative research initiatives and other related activities targeted to the diverse life-long needs of individuals living with congenital heart disease.

Action taken or to be taken

The NHLBI-funded Bench to Bassinet Program is identifying genetic and epigenetic causes of congenital heart disease, with the ultimate goal of enabling clinicians to predict disease outcomes and personalize treatment based on genetic information. It comprises the Pediatric Cardiac Genomics Consortium (PCGC) and the Cardiovascular Development Consortium (CvDC). The consortia have achieved the following milestones:

- PCGC has recruited over 6,200 patients with congenital heart disease in less than 3 years, exceeding all of its recruitment targets
- PCGC investigators have identified a new molecular pathway that potentially links congenital heart disease and neurodevelopmental abnormalities and increases the number and kinds of causal genes implicated in congenital heart disease
- CvDC has published more than 30 articles and made numerous datasets available to the research community
- CvDC also has developed new methodologies and bioinformatics tools. One tool, Mutation Mapping Analysis Pipeline for Pooled RNA-seq (MMAPPR), has been downloaded by 67 research groups from around the world since January 2013
- One of the four centers that comprise the CvDC has identified a polygenic mouse model of hypoplastic left heart syndrome, the most severe of the congenital heart defects. The finding has led the CvDC to make a paradigm shift towards collaborative basic research whereby all four centers are sharing expertise and techniques to advance an integrated, systems-level understanding of this clinically important, complex abnormality.

NHLBI staff members have developed collaborations with other federal partners and advocacy organizations to address the needs of individuals with congenital heart disease across the lifespan. The NHLBI is working with the Centers for Disease Control and Prevention (CDC), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and other federal partners on a joint implementation plan for newborn screening for critical congenital heart diseases, which the Department of Health and Human Services added to the newborn screening panel in September 2011. The NHLBI also is collaborating with the CDC and the National Institute of Neurological Disorders and Stroke to develop effective screening and prevention strategies for sudden death in the young. The first part of the program will develop a surveillance system and registry for sudden cardiac death, sudden death in epilepsy, and sudden infant death. NIH and CDC have funded a Biorepository and Data Coordinating Center for Sudden Death in the Young Registry and will be releasing a funding opportunity announcement in the spring of 2014 for state public health agencies to apply to conduct surveillance and collect data for the Registry.

The NHLBI, along with the CDC, was one of the founding federal advisors for the Congenital Heart Public Health Consortium and is an active member of the group. The consortium has united several organizations with a strong interest in congenital heart disease. The Institute

participated in the planning of the Congenital Heart Disease Experts Meeting held in September 2012. NHLBI staff and other participants at the meeting discussed priority public health knowledge gaps regarding congenital heart defects across the lifespan and strategies to address them. NHLBI adult and pediatric cardiovascular staff members meet regularly with adult congenital heart disease experts and the Adult Congenital Heart Association to advise them about NIH research opportunities, discuss relevant NHLBI activities, and provide input on specific research proposals from the community.

Item

Cystic Fibrosis [CF] - The Committee encourages new personalized approaches to CF therapeutics, including new means to identify and characterize the efficacy of multidrug therapy that addresses the mutant protein which is the underlying cause of cystic fibrosis in the majority of those with the disease. The Committee supports research into nonsense mutations of CF, which impact about 10 percent of the CF population. In addition, the Committee urges further research into live imaging modalities that are able to characterize mucus and monitor mucociliary clearance, defense mechanisms at the heart of CF and many other respiratory diseases.

Action taken or to be taken

The National Institutes of Health (NIH) remains committed to identifying therapies to reduce the burden of illness and extend the life expectancy of cystic fibrosis (CF) patients. The recent success of the drug Kalydeco (approved by the FDA in 2012) has been a breakthrough in the treatment of CF. Kalydeco is a “potentiator” compound that acts on a protein called CFTR (CF transmembrane conductance regulator) that is defective in CF and improves its function in a small subset of CF patients. A second class of drugs being developed, called “correctors,” moves mutant CFTR present in most patients with CF to the cell surface where it can function. Recent experiments in tissue culture cells show that the most common CF mutation destabilizes the CFTR protein in three distinct ways; a multi-drug approach that addresses each of the three defects may be necessary to achieve healthy levels of CFTR function in patients with two copies of this mutation. Through a series of funding opportunity announcements released over the last few years, the NIH advanced the development of personalized therapies that potentially target the basic defects in protein structure and function that are most significant in each patient. In addition, the NIDDK supports research to discover candidate drugs that work as suppressors of CFTR nonsense mutations. Through initiatives released this year, the NIH supports translational research that moves basic research discoveries to clinical application and accelerates the development of new products for the treatment of lung diseases such as CF. Critical to achieving the goal of delivering molecular therapy to all individuals with CF is the development of useful preclinical surrogates of clinical efficacy and high-throughput methods to identify promising therapeutics. A new NHLBI program is focusing on early CF lung disease studies in humans and developing new biomarkers and imaging approaches to assess structural changes and

physiologic function, including targeting defects in mucociliary clearance at an early stage. The new knowledge that emerges from this program will be important for the design of clinical studies testing personalized approaches to prevent the onset and slow the progression of lung disease in infants and young children with CF.

Item

Jackson Heart Study - The Committee continues to recognize the efforts of the Jackson Heart Study to work with individuals and family members across generations in this longitudinal study of cardiovascular disease among African Americans. The Committee acknowledges the continued need for comprehensive research to address health disparities and the important implications for such research to all persons threatened by cardiovascular disease.

Action taken or to be taken

The Jackson Heart Study (JHS) was initiated in 1998 to characterize cardiovascular disease (CVD) and risk factors that influence its development and manifestations in African Americans, with the goal of identifying approaches for prevention. In FY 2013, the NHLBI renewed funding for the study for another five years. Results from the JHS are enriching our understanding of CVD and its risk factors in African Americans. An ancillary study is investigating the role of subclasses of high density lipoprotein cholesterol (HDL-c), —a substance in the blood often referred to as “good” cholesterol because it is associated with decreased risk of coronary heart disease (CHD). Preliminary findings suggest that only one of two HDL-c subclasses is associated with this decreased risk. If confirmed, the findings may lead to the development of more effective approaches for monitoring and managing risk of CHD among African Americans.

The JHS partners with 20 Vanguard Centers at academic institutions with whom it shares data and collaborates regularly to develop manuscripts and ancillary studies. This creates a large cadre of JHS-affiliated investigators with broad scientific expertise. The JHS participated in the 2013 NHLBI Population Studies Workshop to teach early-career investigators how to access and use JHS data and provide opportunities to collaborate. In FY 2013, the NHLBI funded three grants to support collaboration between external working groups and JHS investigators. A fourth grant was funded by the National Institute of Diabetes and Digestive and Kidney Diseases.

About 40 percent of African American adults have hypertension, a major contributor to high rates of stroke, heart failure, and kidney failure, and the NHLBI has focused significant research attention on the condition for many years. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, with 36 percent African American participants, was completed in 2003, but NHLBI continues to follow participants and analyze the data. The ongoing Systolic Blood Pressure Intervention Trial, with 30 percent African American participants, evaluates the benefits of maintaining systolic blood pressure at less than 120 mm Hg in adults at particular risk of heart or kidney disease.

The NHLBI is especially interested in supporting research to understand the genetic underpinnings of CVD. The Institute supports a group of family studies to identify rare genetic variants influencing heart, lung, and blood diseases and sleep disorders and their risk factors. Studies of dyslipidemia, sleep apnea, sarcoidosis, chronic obstructive pulmonary disease and components of metabolic syndrome are focused on African American families. The NHLBI also funds studies using induced pluripotent stem cells to understand how genetic variants influence cell function. Several of these studies are focusing on African American participants to understand the role of genetics in a variety of diseases and conditions, including thrombotic disease, sickle cell disease, and dyslipidemia.

The NHLBI funds five Centers for Population Health and Health Disparities that support trans-disciplinary collaborations to develop and evaluate interventions that reduce the impact of CVD on minority health in general and African Americans in particular. The Institute is committed to training and supporting the next generation of researchers who will focus on health disparities. The JHS Undergraduate Scholars Program training component continues to attract minorities to careers in public health, epidemiology, and biostatistics. The Programs to Increase Diversity among Individuals Engaged in Health-Related Research promotes scientific career development of young faculty and post-doctoral candidates from diverse backgrounds.

Item

Lymphangiomyomatosis [LAM] - The Committee continues to support both intramural and extramural means of expanding research on LAM and urges NHLBI to use all available mechanisms as appropriate to stimulate a broad range of clinical and basic research on this often fatal lung disease. The Committee commends NIH for supporting the MILES trial, which has shown that sirolimus suppresses disease activity in patients with moderate LAM. Additional controlled trials are needed to determine if the disease can be arrested in early stages. The Committee also applauds NHLBI for working with the LAM patient community to organize patient populations in a manner that facilitates clinical research.

Action taken or to be taken

The National Heart, Lung and Blood Institute (NHLBI) continues to support research to improve the outlook for patients with Lymphangiomyomatosis (LAM) using a variety of mechanisms and approaches. Current research includes collaborations between NIH intramural investigators and extramural colleagues in which human LAM cells are being introduced into mice to study the biological basis of lung damage in LAM, studies of LAM cell migration to the lymphatic system, and research on potential new therapies. NHLBI intramural investigators are using computed tomography imaging of the chest and histopathological analyses of lung tissue from LAM patients to improve detection of pulmonary abnormalities and inform prognosis.

Although the Multicenter International Lymphangiomyomatosis Efficacy of Sirolimus trial demonstrated that treatment with sirolimus can slow progression of pulmonary LAM,

deterioration in lung function resumed upon discontinuation of the treatment. Because sirolimus does not kill LAM cells and the drug has significant side effects (e.g., lung inflammation), other therapeutic options are being investigated. LAM's cancer-like behavior suggests that multi-drug therapy will be required. In this regard, the Safety Study of Sirolimus and Hydroxychloroquine in Women with Lymphangiomyomatosis trial, a collaborative effort between NHLBI intramural and extramural investigators, is examining sirolimus in combination with hydroxychloroquine, an antimalarial drug that is also used in the treatment of rheumatoid arthritis and other autoimmune diseases. Results from this study will inform efforts to suppress the disease.

Basic and translational studies are identifying new targets for multi-drug therapy that may prevent or stop tumor growth. Research continues on the pathways and mechanisms regulated by the tuberous sclerosis complex 2 gene, which malfunctions in LAM patients. Combination therapy with sirolimus and simvastatin, a cholesterol-lowering agent, has been tested in a new mouse model that mimics some features of human LAM. Results showed that simvastatin induces the death of LAM cells and shrinks the size of tumors, but other cholesterol-lowering drugs do not.

Other research is determining the role of hormones in the development and progression of LAM. Researchers are studying prolactin as a potential target for new drugs. The drug Faslodex has been shown to completely block estradiol-promoted lung metastasis and enhance survival of mice carrying tumors composed of LAM-like cells. Results of these and other basic studies should facilitate the design of future investigator-initiated controlled trials to determine if LAM can be arrested in early stages.

NHLBI continues to work with the LAM patient community to organize patient populations in a manner that facilitates clinical research. The Institute supports a LAM tissue repository; provides co-funding for the annual LAM scientific conference, now in its 13th year; participates in meetings of the trans-NIH Tuberous Sclerosis Coordinating Committee; and encourages investigators to submit applications to conduct clinical trials in LAM.

Item

Lymphatic Research and Lymphatic Disease - The Committee commends the trans-NIH Coordinating Committee for Lymphatic Research [CCLR] and, in particular, NHLBI, NIAID, and NIDDK for their efforts to advance research on the lymphatic system and medical care for lymphatic diseases. The Committee urges greater participation from other Institutes in the CCLR, particularly NIAMS, NHGRI, and NIBIB. The Committee encourages the reconvening of a trans-NIH Working Group to evaluate the implementation of the recommendations it made in 2007. Continued efforts within the ICs to create support for extramural interdisciplinary research training relevant to the lymphatic system in health and disease and within the Center for

Scientific Review to incorporate reviewer expertise in lymphatic biology/disease in the pertinent study sections are also requested.

Action taken or to be taken

The National Institutes of Health (NIH) supports research on the lymphatic system and disorders that affect it. The trans-NIH Coordinating Committee for Lymphatic Research (CCLR) serves as a resource for many activities in this area, including those highlighted below. It has current representation from several NIH components and in the future will include a representative from the National Human Genome Research Institute (NHGRI). The CCLR plans to propose for approval a trans-NIH workshop on lymphatic research, which could serve as a forum to obtain input on prior recommendations and their implementation in relation to emerging scientific opportunities. Through the following initiatives, the NIH is enhancing its support for extramural research and research training and ensuring appropriate expertise on peer-review committees:

- The Center for Scientific Review (CSR) convened a Special Emphasis Panel composed of experts in lymphatic research to review applications received for **National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)** and NHLBI companion funding opportunity announcements (FOAs) on lymphatics in health and disease in the digestive, urinary, cardiovascular, and pulmonary systems. Three applications have been funded.
- NIDDK issued an FOA to encourage small businesses to develop technologies to facilitate research on the lymphatic system. Applications have been received.
- The National Cancer Institute issued an FOA entitled “ Exploratory/Developmental Research Grant Award,” and will accept applications on lymphatic research.
- The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) encourages meritorious grant applications focusing on research related to lymphatic disease, including its role in inflammation, as it pertains to the Institute’s mission.
- The National Institute of Biomedical Imaging and Bioengineering (NIBIB) supports basic research to explore the use of various ultrasound methods and techniques to identify lymphatic malformations and monitor response to lymphatic disorder treatment in children.
- The NHLBI solicited proposals for a program to develop new treatments for vascular and lymphatic malformations.
- In November 2012, the National Institute of Allergy and Infectious Diseases (NIAID) sponsored a workshop on the relationship between lymphatic function and immune response to infection or vaccination and knowledge gaps within this area. The

proceedings of the workshop were published in a special issue of Lymphatic Research and Biology in September 2013.

- In December 2012, the NIAID issued an FOA to solicit applications for research that will improve understanding of the relationship between lymphatic function and the immune response to viral infection or vaccination. NIAID expects to make awards in fiscal year FY 2014.
- NIAID plans to sponsor a scientific symposium on the basic immunology of the lymphatic system at the annual meeting of the American Association of Immunologists in spring 2014. This symposium will provide training for extramural scientists entering lymphatic research.
- The CCLR held brainstorming sessions with lymphatic researchers to discuss ways to foster research training. Ideas discussed included staging a “road show” at academic centers to introduce a new generation of scientists to lymphatic biology and conducting training sessions in conjunction with major scientific conferences.
- The NHLBI engages in outreach activities with patient interest organizations dedicated to enabling research on lymphatic diseases. One specific interaction was credited with enabling the creation of a strategic and scientific plan for the Gorham-Stout Syndrome at the First International Conference on Generalized Lymphatic Anomaly and Gorham-Stout Syndrome held jointly in June 2013 by the Lymphangiomas and Gorham’s Disease Alliance and the Lymphatic Malformation Institute.

Item

Mind-Body Interventions - The Committee understands that mind-body interventions such as meditation have the potential to contribute to the prevention of cardiovascular disease. The Committee urges NHLBI to support multicenter, phase III randomized controlled trials, and pilot studies to prepare for such trials, of mind-body interventions that have shown promise in phase II trials to reduce cardiovascular risk factors, surrogate endpoints, and clinical events such as mortality, nonfatal myocardial infarction, and stroke.

Action taken or to be taken

The NHLBI supports research on mind-body interventions to reduce psychological risk factors in patients with cardiovascular disease. A phase III randomized controlled trial is examining the effects of a personalized mindfulness-based intervention on reducing inflammation, a significant predictor of future cardiovascular disease, via reductions in traditional risk factors, selected psychosocial attributes, and stress-reactivity. The outcome of treatment may include reducing risk for coronary heart disease, hypertension, and Type II diabetes. NHLBI has supported preliminary (phase II) trials of mind-body interventions such as meditation for the prevention of

cardiovascular disease. To identify promising candidate interventions and evaluate the infrastructure needed to advance clinical science in this area, NHLBI will continue to consult with other NIH Institutes and Centers to identify gaps in and opportunities for research examining the effect of mind-body interventions on cardiovascular risk factors and to consider future research on the topic. The NHLBI also welcomes meritorious investigator-initiated projects for pilot studies and clinical trials of mind-body interventions to prevent cardiovascular disease.

Item

Pediatric Cardiomyopathy - The Committee urges NHLBI to work with private and nonprofit stakeholders to develop and disseminate to the public a research agenda and 3-year strategic plan with specific activities to address gaps in research related to the causes, screening, diagnosis, and treatment of pediatric cardiomyopathy. Emphasis should be given on children who are at the highest risk for cardiomyopathy-related mortality.

Action taken or to be taken

The National Heart, Lung and Blood Institute (NHLBI) has taken steps to develop and disseminate to the public a research agenda to address gaps in research related to the causes, diagnosis, and treatment of pediatric cardiomyopathy. However, based on consultation with the community, the Institute does not believe that developing a strategic plan for cardiomyopathy would be the most fruitful approach to advancing science in this area at the present time because a broad approach to investigation of the basic biology in this area is still warranted. In fiscal year 2013, the NHLBI convened a working group entitled New Targets for Pediatric Heart Failure to assess the current state of science and identify new targets for research in pediatric heart failure, of which cardiomyopathy is a major cause. The working group included experts in pediatric and adult cardiology, heart failure, cardiomyopathy, cardiomyocyte proliferation, genomics, pediatric cardiac surgery, myocellular signaling, inherited myopathies, gene therapy, and cardiac imaging. The group outlined the following specific recommendations, all of which are relevant to pediatric cardiomyopathy:

- Create new paradigms for pediatric heart failure
- Focus research on molecular mechanisms relevant to pediatric heart failure
- Encourage collaboration in the pediatric heart failure community in order to bring together and augment existing resources
- Expand existing phenotype registries and databases with genomic data, increased granularity, and systematically-collected longitudinal data
- Develop surrogate systems and endpoints that are relevant to pediatric heart failure

- Create industry partnerships to advance research efforts in pediatric heart failure.

A detailed summary of the meeting will be published in a peer-reviewed journal. In addition, the NHLBI has been engaged in an ongoing dialogue with the Children's Cardiomyopathy Foundation to determine how collaborative activities can further mutual research goals and discuss scientific gaps and identify research opportunities.

The NHLBI participates actively with NIAMS, NINDS and NICHD in the Muscular Dystrophy Coordinating Committee, and provides co-funding for two of the Wellstone Centers. The MDCC is currently revising its Action Plan, and will have a three day meeting in April, 2014, to finalize the revised Action Plan. The NHLBI also supports nine investigator-initiated projects on cardiomyopathy in the muscular dystrophies, including a canine study of gene therapy for Duchenne muscular dystrophy cardiomyopathy.

The NHLBI continues to advance research on pediatric cardiomyopathy. Two successor projects to the Pediatric Cardiomyopathy Registry are currently being funded by NHLBI: The "Cardiac Biomarkers in Pediatric Cardiomyopathy" and the "Genotype-Phenotype Associations in Pediatric Cardiomyopathy." The former project aims to identify specific cardiac biomarkers and panels of biomarkers that will help determine the most appropriate evidence-based clinical care for pediatric cardiomyopathy patients, including when to consider heart transplantation as a therapeutic option. The latter project seeks to identify the genetic factors that determine the development and progression of cardiomyopathy to improve prevention, surveillance, early management, and prognosis. Both projects are in the early stages of participant recruitment. The Institute also supports investigator-initiated grants and the Pumps for Kids, Infants, and Neonates (PumpKIN) Program, which encourages the development of innovative ventricular assist devices for infants and young children with congenital or acquired heart disease, many of whom have cardiomyopathy.

Item

Pulmonary Fibrosis - The Committee applauds NHLBI for convening a workshop to develop a strategic plan for pulmonary fibrosis and supports efforts to enhance research on this disease.

Action taken or to be taken

In November 2012, the NHLBI convened a workshop to develop a strategic plan for pulmonary fibrosis research. Participants included pulmonary fibrosis experts, representatives from the NHLBI and the Food and Drug Administration, patient advocacy groups, and pharmaceutical companies. The working group participants identified several priority areas, opportunities for collaborations, and directions for future research in pulmonary fibrosis. They include the following:

- New tools to study abnormal lung cells in pulmonary fibrosis

- Standardization of methods to collect and distribute human lung cells for pulmonary fibrosis research
- Refinement of methods to investigate the role of extracellular matrix proteins in pulmonary fibrosis
- Collaborations among researchers studying different organs and systems to facilitate identification of common disease mechanisms and therapeutic targets across different fibrotic diseases
- Better preclinical models that closely mimic the effects of aging and relevant genetic characteristics
- Establishment of large, rigorously phenotyped patient cohorts and enhanced biorepositories with samples and data from well-phenotyped patients.

The consensus of the workshop is that transparent and coordinated efforts among all stakeholders will significantly enhance and accelerate progress in pulmonary fibrosis research. Since the workshop, the participants have had additional planning discussions to implement key aspects of the strategic plan such as establishing patient cohorts and enhancing of biorepositories for future NHLBI and pharmaceutical company-sponsored clinical trials.

Item

Scleroderma - The Committee recognizes that pulmonary fibrosis is a complication of scleroderma and the most common cause of death in a diagnosed patient. Therefore, the Committee encourages NHLBI to expand scleroderma research related to pulmonary complications and facilitate collaboration and data sharing among scleroderma investigators.

Action taken or to be taken

The National Heart, Lung, and Blood Institute (NHLBI) supports research to address pulmonary complications of scleroderma, such as pulmonary fibrosis and pulmonary arterial hypertension. An NHLBI-funded clinical trial, the Scleroderma Lung Study II, is comparing the effectiveness of two drugs in treating pulmonary fibrosis in scleroderma. The trial is being conducted at 12 academic medical centers; a data coordinating center facilitates data sharing among the study investigators. The NHLBI Pilot Clinical Trial Studies program provides an ongoing mechanism to support research on the pulmonary complications of scleroderma. The NHLBI-funded Centers for Advanced Diagnostics and Experimental Therapeutics in Lung Diseases Stage II program, which will begin in FY 2014, will provide a mechanism to accelerate the development of therapies for lung diseases, including pulmonary fibrosis and pulmonary arterial hypertension associated with scleroderma. The Institute has fostered scleroderma research by facilitating collaborations between pulmonary fibrosis researchers and those working on scleroderma. Clinicians involved with scleroderma research can in turn assist pulmonary fibrosis researchers with enrolling individuals in clinical studies of scleroderma-associated pulmonary fibrosis. The

NHLBI will continue to facilitate investigator-initiated collaborations among scleroderma researchers and researchers studying pulmonary diseases.

Item

Sleep Disorders - The Committee continues to support the implementation of the National Sleep Disorders Research Plan, including the emphasis on cross-Institute collaborations.

Action taken or to be taken

The National Center on Sleep Disorders Research monitors National Institutes of Health (NIH) progress toward achieving the scientific goals outlined in the NIH Sleep Disorders Research Plan and facilitates opportunities for cross-Institute coordination. Based on input from scientists and patient representatives to the Sleep Disorders Research Advisory Board, the NIH assesses its progress in sleep and circadian sciences with respect to basic scientific discovery, clinical research, sleep disorders medicine, research translation, and research training.

Recent basic scientific findings include the discovery of specific chemical abnormalities that link sleep problems to cardiometabolic and neurological diseases. For example, a genetic risk factor discovered in a study funded by the National Heart, Lung, and Blood Institute (NHLBI) on sleep was key to the discovery of a genetic risk factor for migraine by **National Institute of Mental Health**-funded researchers. Another study showed that abnormalities in the expression of the circadian gene *CRY2* are linked to mood disturbances and the risk of major depressive and bipolar disorders. The cross-disciplinary nature of recent basic research findings stimulates discussions of emerging opportunities for cross-Institute cooperation.

Cross-Institute collaborations also are accelerating clinical research. An ongoing collaboration between NHLBI and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is evaluating the contribution of sleep deprivation and sleep apnea to cardiometabolic disease during pregnancy and post-partum. In 2013, NHLBI and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) are working together to determine whether sleep deprivation contributes to difficulty losing weight during the post-partum period, and whether untreated sleep apnea complicates the medical management of type 2 diabetes. An ongoing collaboration between NHLBI and NIDDK is examining whether sleep apnea interferes with weight loss treatments in obese diabetics. A NHLBI-supported research resource launched in 2013 will increase the return on investment in clinical sleep research data collection using the internet to enhance data access and analysis.

Trans-NIH groups such as the Neuroscience Blueprint and the Basic Behavioral and Social Science Opportunity Network have fostered the development of translational sleep research activities, including testing new drug candidates for the treatment of narcolepsy and elucidating the basic behavioral mechanisms that link sleep problems to stress and cardiovascular disease risk. Translational studies supported by NHLBI in 2013 seek to develop new approaches to

diagnose sleep apnea and sleep deprivation and instruments to assess treatment efficacy. A 2013 joint initiative between NHLBI and NICHD has produced a new educational research project to develop community-based approaches for African-Americans with sleep apnea and sleep deprivation.

NIH supports cross-Institute workshops to identify new research directions and opportunities. In 2013, a cross-Institute workshop led by the NIH Office of Dietary Supplements addressed emerging needs for research on the relationships between caffeine and sleep deprivation. NIH also supports research training in sleep and circadian sciences at all stages of academic preparation.

Item

Sleep Disorders - The Committee urges NIH to initiate new training programs in sleep and circadian sciences in all relevant Institutes and Centers, consistent with the NIH Sleep Disorders Research Plan.

Action taken or to be taken

Many National Institutes of Health (NIH) Institutes and Centers offer funding opportunities for research training and career development in sleep and circadian sciences, including fellowships for researchers and health professionals working on doctorate degrees, career awards for post-doctoral training, and training grants for institutions supporting research training. In fiscal year 2013, NIH funded nine institutional awards to support sleep research training, the largest number of NIH training grants ever funded in a single year in sleep and circadian sciences and an important milestone for training in the area. One new institutional award funded by the NHLBI supports a research training project in genetic and genomic approaches to sleep disorders. The program seeks to expand the pool of researchers in the field by facilitating access to advanced training opportunities in sleep medicine research at several institutions across the nation. Another significant development is NHLBI support for a program that addresses the shortage of trained pediatric researchers specializing in pulmonary and sleep medicine. Research training in sleep sciences also is supported actively by the ongoing NHLBI Program to Increase Diversity among Individuals Engaged in Health Related Research, which provides under-represented junior scientists with mentoring and tools and opportunities for career advancement.

In addition to offering funding opportunities, NIH often sends staff from the trans-NIH Sleep Research Coordinating Committee to participate in research training and grantsmanship activities organized by the NIH in collaboration with professional societies. In fiscal year 2013, the National Institute of Nursing Research hosted a Sleep and Fatigue Research Boot Camp for young investigators. During the Boot Camp, several NIH program representatives provided information about sleep funding and training opportunities. NIH research experts also participated in the 2013 Young Investigator Forum organized by the American Academy of Sleep Medicine. The forum included mock proposal reviews and presentations on science and

funding opportunities. The 2013 Sleep Research Society Training Symposia Series featured small group activities with NIH staff who discussed funding opportunities and mentoring of early stage investigators. These activities together with an array of funding mechanisms supported NIH-wide advance progress toward achieving the training goals identified in the 2011 NIH Sleep Disorders Research Plan for both trainees and early-stage investigators.

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National Institute of Dental and Craniofacial Research (NIDCR)

Senate Significant Items

Item

Temporomandibular Disorders [TMD] - The Committee appreciates the advances that have been made as a result of NIDCR funding of research on TMD pain and urges the Institute to continue to lead this effort. Major findings that have emerged confirm that TMD is one of several chronic pain conditions co-occurring in some patients at odds greater than chance. The Committee strongly urges NIDCR to collaborate with other ICs to address these comorbid conditions. The Committee commends the Institute for working with NIAMS and NIBIB to organize the Temporomandibular Joint Working Group, which is charged with assessing the state of the science on the temporomandibular joint and identifying research gaps and future scientific opportunities.

Action taken or to be taken

Temporomandibular disorders (TMDs) are a group of conditions that cause pain and dysfunction in the jaw joint and the associated muscles and supporting tissues. TMD is often present in individuals with other chronic pain conditions, suggesting common mechanisms linking these conditions. The National Institute of Dental and Craniofacial Research (NIDCR) supports research on TMDs and other orofacial pain conditions with the goal of improving the prevention, diagnosis, and treatment of these disorders. NIDCR focuses on understanding the mechanisms underlying the development and maintenance of chronic orofacial pain and also the transition from acute to chronic pain. Additionally, NIDCR supports research on the development of new behavioral and pharmacological treatments for these conditions.

The National Institutes of Health (NIH) Pain Consortium is leading a trans-NIH effort to coordinate research on chronic overlapping pain conditions and bring researchers together to explore new areas of investigation. Several prospective studies addressing overlapping conditions are being conducted by member Institutes of the Pain Consortium, including NIDCR, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute of Neurological Disorders and Stroke (NINDS).

NIDCR funded a follow-up study, Orofacial Pain: Prospective Evaluation and Risk Assessment II (OPPERA-II), which will identify risk factors that predict whether acute TMD will transition to chronic TMD and whether TMD will develop as a single condition or in conjunction with other chronic pain conditions such as headache, low back pain, irritable bowel syndrome, and widespread body pain. The NIDDK Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network is exploring the underlying etiology, natural history, and risk factors for the urologic chronic pelvic pain syndromes (UCPPS) interstitial cystitis/painful bladder syndrome and chronic prostatitis/chronic pelvic pain syndrome, as well as the possible

relationships between UCPPS and several co-morbid chronic pain disorders, to develop a basis for future clinical studies and improved management of these conditions. NIDCR is working with NIDDK to determine other studies which will mutually complement the research of OPFERA II and the Network and lead to a better understanding of these conditions overlapping with TMD. NIDCR also supports NINDS' research effort to fund a multidisciplinary project which focuses on multiple complex persistent pain conditions (CPPCs), including episodic headache, fibromyalgia, temporomandibular joint disorders, irritable bowel syndrome, and vulvar vestibulitis.

In May of 2013, NIDCR co-sponsored a roundtable meeting with NIAMS and NIBIB on the "Temporomandibular Joint in Health and Disease". The meeting brought together scientists with expertise in areas related to the structures/tissues of the temporomandibular joint and along with patient advocates, applied their knowledge to explore new research approaches to advance understanding of temporomandibular joint function. A meeting summary and a comprehensive set of research recommendations are available

<http://www.nidcr.nih.gov/NewsAndFeatures/Announcements/TMJRoundtable.htm>).

As another example of collaborative efforts, NIDCR has recently approved the funding of a grant that will apply novel quantitative imaging technologies to assess changes in bone structure of the temporomandibular joint during the initiation and development of joint osteoarthritis. This project is being co-funded by NIBIB and takes advantage of the expertise available in their National Centers for Biomedical Computing program.

Conference Significant Items

Item

Dental Materials Research - The United Nations (UN) Environmental Programme, International Negotiating Committee completed deliberations in January 2013 on a global legally binding treaty on mercury. The UN agreement contains provisions for the reduction in the use of dental amalgam, as a mercury added product, and calls for increased dental research into alternative materials. Given the global commitment to reduce all uses of mercury, the NIH Director is expected to make the development of alternative dental restorative materials a high priority.

Action taken or to be taken

The National Institute of Dental and Craniofacial Research (NIDCR) has a long-standing commitment to improve the properties of materials used in dental restorations. Dental amalgam, a type of dental filling material, is a mixture of mercury, silver, tin and copper. The use of dental amalgam has been declining in developed countries for several decades in favor of tooth-colored dental materials called composite resins. About two-thirds of all restorations placed by dentists in the U.S. are composite resins. Although composite resins have improved esthetics, interactions

between oral bacteria and the composite resin may result in recurring tooth decay around the filling, thus shortening the restoration's life span.

A new, longer-lasting alternative dental restorative material could substantially benefit the public's oral health. In 2013, NIDCR awarded \$2.8 million to fund six research projects to design and develop novel dental composite restorative systems that double the current average service life of fillings. The five year studies will develop innovative new materials that are compatible with the oral environment, esthetically appropriate, structurally strong, and resistant to the degradation caused by exposure to saliva and bacteria. Given the complexity of the problem, each project will bring together materials scientists, polymer chemists, and microbiologists in a collaborative effort to address associated challenges; awardees will share research approaches, successes, roadblocks, and data. The diversity of NIDCR-funded dental materials research underscores the Institute's commitment to developing alternative dental restorative materials that substantially improve oral health.

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National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Senate Significant Items

Item

Amyloidosis - The Committee encourages NIH to continue its research efforts into amyloidosis, a group of rare diseases characterized by abnormally folded protein deposits in tissues. The Committee requests an update in the fiscal year 2015 congressional budget justification on the steps taken to understand the causes of amyloidosis and efforts to improve the diagnosis and treatment.

Action taken or to be taken

The NIH continues to support research into amyloidosis. In July 2013, NIDDK, along with the National Cancer Institute and the National Institute on Aging, released a Funding Opportunity Announcement entitled “Systemic Amyloidosis: Basic, Translational, and Clinical Research,” which seeks to encourage research to advance the understanding of pathogenic mechanisms underlying systemic amyloidosis, to develop improved techniques (in particular those that are non-invasive) for the clinical detection and diagnosis of systemic amyloid diseases, to develop novel cellular and in vivo models with which to identify candidate therapeutic agents, and to evaluate the clinical efficacy of novel therapies designed to prevent, arrest, and (when possible) reverse the morbid and lethal progression of these diseases. Recent NIDDK-supported research advances include the design and synthesis of a new potential drug for an inherited form of heart failure called familial amyloid cardiomyopathy. The drug, called AG10, stabilizes an aberrant form of the transthyretin protein that would otherwise form abnormal deposits. A second group of investigators has described the promising use of a potential reagent to detect and measure the amount of amyloid deposition in tissues. Called peptide p5, this reagent was shown to bind to multiple components of amyloid deposits in tissue samples from patients, enabling imaging of the amyloid.

The NHLBI supports both fundamental and clinical research addressing the effect of amyloidosis on the heart. Current basic studies include investigations of the toxic effects of human amyloidogenic light chain proteins on the heart, including how the proteins lead to increased cellular oxidant stress, altered calcium homeostasis, impaired cellular contractility, and ultimately cell death. Clinical studies include investigations of a new imaging technique, wideband multi-spectral late gadolinium enhancement magnetic resonance imaging, to diagnose cardiac amyloid in patients with implanted cardiac devices, and a project examining the relationship between preamyloid oligomer formation to post-operative and established atrial fibrillation.

Item

Diabetes - The Committee recognizes that diabetes is the leading cause of both kidney failure and adult-onset blindness. The Committee therefore urges NIDDK to fund basic research to better understand the causes of diabetic kidney and eye disease, as well as clinical studies to test potential therapies to prevent and treat these ailments.

Action taken or to be taken

Although diabetes rates continue to climb, there is now clear evidence that blood glucose control and rates of complications, including kidney failure and blindness, among those with diabetes are improving. These changes stem at least in part from NIH research that firmly established the link between poor blood glucose control and development of diabetes complications, and the tremendous long-term benefits of early, effective blood glucose control, particularly in recent onset diabetes. Indeed, new results show that 30 years after the landmark Diabetes Control and Complications Trial (DCCT) began and 20 years after the trial ended, those who received intensive therapy now have an impressive 50 percent lower rate of impaired kidney function and vision threatening diabetic eye disease or eye surgery. These findings underline that the rewards of effective treatment—although quite dramatic—are often reaped decades later. This also shows the critical importance of NIH’s commitment to long-term follow-up studies like the Epidemiology of Diabetes Interventions and Complications (EDIC) study, which has monitored long term outcomes of the DCCT participants. NIDDK is further leveraging these investments by funding ancillary studies utilizing biosamples from study participants for basic research to better understand the molecular underpinnings of complications, and more accurately forecast risk.

Other lines of basic research have already led to clinical trials that have revolutionized therapy. For example, the discovery and characterization of VEGF, a protein with a key role in triggering the growth of blood vessels, has led to a major improvement in care for diabetic eye disease: targeted use of VEGF inhibitors is now known to be a highly effective way to prevent excessive vascularization of the eye. Just as VEGF inhibitors improved on existing methods of preventing progression of diabetes complications in the eye, NIDDK is now investing in a study of the generic drug, allopurinol, to determine if it may improve on current methods of slowing the progression of diabetic kidney disease. In addition, because the DCCT and EDIC demonstrated the central importance of blood glucose control in reducing diabetes complications, the NIDDK continues its ongoing commitment to facilitate easier, more effective blood glucose control through research to develop an artificial pancreas, which could constantly and effectively monitor a patient’s blood glucose, and deliver accurate doses of insulin (and sometimes other hormones) to keep glucose levels at an optimal level. Promising clinical results from one such device were recently reported at the 2013 American Diabetes Association meeting.

Item

Functional Gastrointestinal Disorders [FGIDs] - The Committee continues to urge NIDDK to engage in multi-Institute collaborations to improve understanding of FGIDs.

Action taken or to be taken

Research to improve understanding of Functional Gastrointestinal Disorders (FGIDs), such as irritable bowel syndrome (IBS) and fecal incontinence, continues to be a priority for NIDDK. The NIDDK's multiple efforts in this area include collaborations with other NIH components, which complement other FGID research funded by the Institute. The NIDDK has collaborated with the NIH Office of Research on Women's Health (ORWH) and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to improve understanding of FGIDs.

As an example of a research collaboration on IBS, and because IBS is especially common in women, NIDDK collaborates with ORWH to fund a Specialized Center of Research at the University of California, Los Angeles, to examine sex and gender differences in the interaction of gut and brain pathways in the development of IBS and other abdominal pain disorders. Recently, researchers at the Center conducted a pilot study in women with IBS of a drug that targets a pathway implicated in the regulation of both pain and anxiety. The study results indicate that long-term treatment with this drug is associated with improved mood and pain ratings and with decreased activity of brain regions related to emotional agitation, suggesting that this pathway may be a good therapeutic target in IBS.

Fecal incontinence, or the unintentional loss of solid or liquid stool, is a condition that is slightly more prevalent in women, especially those who have experienced difficult childbirths. In August 2013, NIDDK collaborated with staff of the ORWH and NICHD to hold a workshop on "Developing a Clinical Research Agenda for Fecal Incontinence," which included a panel of experts in epidemiology, gastrointestinal physiology, gastroenterology, colorectal surgery, urogynecology, psychology, and behavioral medicine. The purpose of this workshop was to identify major issues in the diagnosis and treatment of fecal incontinence, examine the barriers encountered in addressing this condition, and develop research priorities in both basic and clinical research. Recommendations from this workshop will help guide future research on fecal incontinence.

Item

Gestational Diabetes - The Committee recognizes that women with gestational diabetes and their babies face long-term health consequences as a result of the disease, including an increased risk of developing type 2 diabetes. Therefore, the Committee urges NIDDK to explore additional opportunities for research on gestational diabetes, a disease affecting up to 18 percent of all pregnant women.

Action taken or to be taken

NIDDK supports a multi-faceted research program to understand and prevent gestational diabetes mellitus (GDM) and its long-term consequences in women and their offspring. Understanding GDM is also an active area of research for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the two institutes work to synergize GDM research efforts.

New and ongoing NIDDK-led clinical efforts highly germane to GDM include the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Follow-Up Study, which will leverage the completed NICHD-led HAPO clinical study to help determine whether elevated blood glucose during pregnancy less severe than GDM influences future levels of body fat in children and development of diabetes in mothers after giving birth. Also, the Lifestyle Interventions For Expectant Moms consortium, a trans-NIH effort spearheaded by NIDDK, is testing behavioral/lifestyle interventions in overweight and obese pregnant women to try to identify an effective intervention(s) that could reduce health risks for women and their babies during and after pregnancy, including those associated with GDM.

NIDDK also continues to support study of the long-term effects of the highly successful Diabetes Prevention Program (DPP) clinical trial interventions on development of diabetes and other outcomes in DPP participants, including women with a history of GDM. The robust number of DPP participants with a history of GDM was made possible by the generous co-support of the NIH Office of Research on Women's Health (ORWH), and ORWH continues to partner with NIDDK in the DPP Outcomes Study and other research important to GDM; for example, ORWH is co-funding with NIDDK a new study of genetic factors influencing maternal blood glucose levels during pregnancy. In another program, NIDDK continues to solicit research projects to translate to "real-world" settings those strategies shown in clinical trials to improve outcomes in diabetes and obesity. One study funded under this program is testing whether a DPP-like lifestyle intervention delivered in a health plan setting can help women with GDM achieve a healthy weight during and after pregnancy, thereby reducing risk for later type 2 diabetes. NIDDK will also welcome GDM research applications in response to recently issued funding opportunity announcements that encourage pragmatic trials in healthcare and evaluation of natural experiments in healthcare. NIDDK will continue to pursue research opportunities to improve outcomes for women with or at risk for GDM and their families.

To better understand optimal methods of diagnosing GDM, NICHD and the NIH Office of Disease Prevention, along with other NIH and U.S. Department of Health and Human Services components, including NIDDK and ORWH, co-sponsored a consensus development conference, "Diagnosing Gestational Diabetes Mellitus," in March 2013. A panel of invited experts examined available scientific evidence and came to consensus on how to diagnose GDM. The final statement for this conference is available at:

<http://prevention.nih.gov/cdp/conferences/2013/gdm/final-statement.aspx> . NICHD also

supports efforts to understand the symptoms and outcomes of GDM through its Maternal-Fetal Medicine Units Network, which studies various types of high-risk pregnancies and pregnancy outcomes, including GDM.

Item

Inflammatory Bowel Disease - The Committee commends NIDDK for its continued support of the Human Microbiome Project and urges the Institute to put a high priority on using the results to advance the understanding of inflammatory bowel disease and its impact on pediatric patients. The Committee requests an update on this program in the fiscal year 2015 congressional budget justification.

Action taken or to be taken

The NIDDK appreciates the Committee's commendation of the Institute's support for the NIH Human Microbiome Project (HMP). The HMP is managed by the National Human Genome Research Institute, in partnership with NIDDK and other NIH Institutes and Centers, to support research that continues to add to the understanding of microbial influences on human health and disease, including in inflammatory bowel disease (IBD) and its impact on pediatric and adult patients. NIDDK is supporting a new project through the HMP that will integrate many different types of measurements of gut microbes as they change within IBD patients over time. This project will profile the gut microbiome along with the genetics and activity of the human host to provide insight into how the microbiome interacts with the human body in patients with IBD, which may help advance understanding of how IBD develops and ultimately may be useful for informing new disease detection, prevention, and treatment strategies in children and adults.

Also, the NIDDK has recently co-supported HMP studies that add to the understanding of microbial influences on IBD, including a study where scientists explored the differences in gut microbes between healthy individuals and those with Crohn's disease, a form of IBD. The researchers found several genes and proteins that were different in people with Crohn's disease, which could lead to new ways to treat the disease in children and adults by using methods that alter the microbes in the gut, such as changes in diet. In a similar study, researchers studied intestinal tissue from teenagers and adults with either Crohn's disease or ulcerative colitis, another form of IBD, or from patients with no IBD. The scientists were able to correlate genetic mutations associated with IBD, and environmental factors such as smoking and medications, with changes in the gut microbes. This study showed that some of the factors known to cause or exacerbate IBD may do so by altering the composition of microbes in the gut.

Item

Interstitial Cystitis - The Committee commends NIDDK for its leadership in interstitial cystitis research and notes that researchers are making progress to dispel myths about this condition and identify potential therapeutic strategies. Recognizing that patients turn to a variety of treatments, from pharmaceutical to changes in diet and lifestyle, the Committee encourages NIDDK to continue its focus on interstitial cystitis research and to partner with NCCAM to study the impact of complementary therapies on this condition.

Action taken or to be taken

The NIDDK supports research on interstitial cystitis (IC), also referred to as IC/painful bladder syndrome (IC/PBS) or IC/bladder pain syndrome (BPS), in the hope that new discoveries can lead to improved, effective therapeutic strategies for people with this painful condition. A key, ongoing effort is the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, which is studying IC/PBS and other urologic chronic pelvic pain syndromes (UCPPS). This multi-center Network has successfully recruited over 1,000 participants at sites around the country. Its objective is to obtain insights into the fundamental causes, natural history, and risk factors for IC/PBS and other UCPPS that, in turn, can help inform future clinical intervention efforts and improve clinical management. To continue the Network's important efforts, the NIDDK recently issued multiple requests for applications (RFAs) to support renewal of and add additional sites to this multi-center Network for a second 5-year funding cycle beginning in FY 2014. Recently, the NIDDK also funded a group of 1-year projects relevant to IC/PBS in response to two RFAs issued in FY 2013. One RFA solicited projects to elucidate fundamental causes, pathology, natural history, and risk factors for UCPPS, including IC/PBS; the other RFA solicited projects focused on building a molecular "map" of cellular components and pathways involved in pain detection and processing in the urinary tract and pelvic region of a commonly used animal model, the mouse. Through these projects, the NIDDK seeks to foster emerging ideas and efforts in IC/PBS in a way that complements the ongoing efforts of the MAPP Research Network as well as investigator-initiated projects in IC/PBS.

The understanding of IC/PBS and other UCPPS sought by the MAPP Research Network and other research efforts could also help elucidate the efficacy of complementary therapies that can bring relief to some patients; NIDDK staff have been in contact with National Center for Complementary and Alternative Medicine (NCCAM) to provide detailed information on the MAPP Network's scientific organization, objectives, and scientific efforts to date. Research on the use of complementary health approaches for pain management is a high research priority for NCCAM. As a result, NCCAM, like NIDDK, is an active participant in the Trans-NIH Pain Consortium, which promotes collaboration across the many NIH Institutes and Centers that have programs and activities addressing pain. NCCAM program staff members have participated in meetings of the Urology Interagency Coordinating Committee (UICC) led by the NIDDK, and

NCCAM will explore collaborative opportunities with NIDDK for research on symptom management in chronic pain conditions, including chronic pelvic pain. In addition, NCCAM is investing in research on several promising non-pharmacological approaches, such as massage, spinal manipulation, yoga, mindfulness/meditative approaches, and acupuncture for pain management in other pain conditions. NIDDK-supported research has already demonstrated a beneficial effect of a specialized form of physical therapy, called myofascial physical therapy, for some women with IC/PBS; thus, synergy between the two ICs could lead to further understanding of the impact of complementary therapies on IC/PBS.

Item

Obesity - The Committee supports the NIH strategic plan for obesity research, which emphasizes a transdisciplinary approach to addressing the growing obesity problem in the United States. However, the Committee believes that additional efforts are needed to increase the involvement of high-risk communities in obesity studies and preventative research, particularly in rural areas, among low-income and racial minorities. The Committee urges NIH to prioritize its efforts on those areas of the country with the highest obesity rates by utilizing the existing resources of NIH-funded Nutrition Obesity Research Centers and academic schools of public health located in high-risk areas.

Action taken or to be taken

The NIH is pursuing several efforts to improve health of those disproportionately affected by obesity, including individuals in communities with high rates of obesity, racial/ethnic minorities, and those who are socioeconomically-disadvantaged. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funds Nutrition Obesity Research Centers (NORCs), which provide resources and services to advance and facilitate research at their local institutions and by the broader research community, to catalyze research collaborations, and to support training and pilot projects. A number of the Centers are in areas with high rates of obesity and substantial minority populations. The NORC at the University of Alabama, School of Public Health, has a strong emphasis on the study of health disparities; NORC researchers are also active in community outreach partnerships. The Pennington Biomedical Research Center NORC, located in a largely rural area of Louisiana, provides a wide range of research services and has catalyzed collaborations among institutions throughout Louisiana.

NIDDK also supports other efforts in areas and populations with high rates of obesity. The Look AHEAD study, which found health benefits from an intensive lifestyle intervention for obese people with type 2 diabetes, includes sites in Alabama, Louisiana, Texas, and other states. The Diabetes Prevention Program Outcomes Study (DPPOS), which demonstrated long-lasting health benefits from an intervention to prevent or delay type 2 diabetes through modest weight loss from diet and exercise, includes sites in Louisiana, Tennessee, and other areas; 45 percent of the study participants are from minority groups. The multi-site Lifestyle Interventions for Expectant

Moms (LIFE-Moms) consortium is testing lifestyle interventions for overweight/obese pregnant women, with the hope of achieving health benefits for the women and their children. The site in Missouri, for example, will test an intervention delivered by lay parent educators to underserved pregnant African American women in collaboration with a home visiting program. Led by NIDDK, with other NIH components collaborating, the DPPOS, Look AHEAD, and LIFE-Moms studies also include NIDDK's Southwest American Indian centers in Arizona with American Indian participants. Examples of other NIDDK-funded studies include research on healthy lifestyle interventions for children in rural areas delivered through Cooperative Extension Service offices, and a study to prevent further weight gain in overweight/obese African American women, particularly those socioeconomically disadvantaged, in primary care and community settings. NIDDK-funded Centers for Diabetes Translation Research aim to bring research findings to practice and community settings, including research to prevent type 2 diabetes through weight loss. The Centers emphasize research on health disparities, through partnership with minority serving institutions or other efforts focused on minority populations.

The National Heart, Lung, and Blood Institute (NHLBI) also supports studies in high risk communities. For example, the Healthy Communities Study, funded by NHLBI and others, aims to identify characteristics of community programs and policies associated with lower childhood obesity rates; it is oversampling low-income and high-proportion minority communities and ensuring representation of rural communities. Most of the children in the multi-component Childhood Obesity Prevention and Treatment Research trials are minorities from low income communities. Long-term observational studies are examining factors associated with obesity and its consequences; for example, the Jackson Heart Study in African Americans in Mississippi, and the Hispanic Community Health Study–Study of Latinos. With a recent initiative, NHLBI plans to fund new research to reduce cardiovascular disease risk factors, such as obesity, in rural areas. A NHLBI-led program “*We Can!*” (Ways to Enhance Children’s Activity & Nutrition) is a national public education outreach program to promote a healthy weight among children through efforts to improve food choices, increase physical activity, and reduce screen time. *We Can!* will continue to collaborate with the First Lady’s Let’s Move Faith and Community Initiative to provide guidance on curriculum implementation to faith and community health leaders around the country.

Item

Pancreatitis - The Committee encourages NIDDK to create a long-term scientific framework for pancreatitis including evaluating current efforts and making recommendations on ways to accelerate progress and improve outcomes. The Committee requests an update on this effort in the fiscal year 2015 congressional budget justification.

Action taken or to be taken

The NIDDK, together with partners at the NIH and in the scientific and patient advocacy communities, have worked toward developing a long-term scientific framework for pancreatitis research with two recent workshops on this topic.

In June 2012, the NIDDK convened a 2-day research workshop on “Advances in Acute and Chronic Pancreatitis: From Development to Inflammation and Repair,” which provided a state-of-the-art update on a wide range of research efforts addressing acute and chronic pancreatitis and charted a course for advancing future research in this area. The meeting was co-organized by NIDDK staff, extramural researchers, and representatives from the National Pancreas Foundation. A summary of this workshop was published in the January 2013 journal *Gastroenterology*.

In June 2013, the NIDDK and NCI co-sponsored a 2-day workshop on “Pancreatitis, Diabetes, and Pancreatic Cancer.” This workshop explored known and suspected mechanisms for the increased risk of pancreatic ductal adenocarcinoma (a form of pancreatic cancer) in individuals with chronic pancreatitis and diabetes, as well as population-level studies of prevalence and effects of anti-diabetic therapy. Participants contributed to developing a framework of opportunities and priorities for future research in this area sponsored by both Institutes. Recommendations from this workshop will be published in the scientific literature.

These scientific workshops will inform future research efforts on pancreatitis.

Item

Pediatric Kidney Disease - The Committee encourages NIDDK to assign a higher priority to research that explores pediatric renal disease. Because of the unique challenges of recruiting children into clinical trials, the Committee urges NIDDK to support research endeavors that include funding for infrastructure and the enhancement of collaborative and comparative multicenter, pediatric, prospective clinical/translational trials that improve patient outcomes.

Action taken or to be taken

NIDDK has taken several actions to address the important problem of kidney disease in children and adolescents. The Chronic Kidney Disease in Children (CKiD) multi-center study has produced 43 scientific papers as of September 2013 informing the community about newly defined risk factors for disease, as well as early manifestations of disease. The Institute has expanded its investment in this study by renewing funding for an additional five years; another 280 children are being enrolled. An ancillary study will investigate genetic factors associated with progression of kidney disease in this population, and to compare it with a European cohort

The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial, which compared prophylactic antimicrobial treatment with placebo for prevention of urinary tract

infections and kidney scarring in children with reflux, has been completed. Patient follow-up ended in May 2013, and the data are now being analyzed; the expectation is that the results will be published by the spring or early summer of 2014. NIDDK has funded two ancillary studies to the trial: one looking at genetic predisposition to infection and another looking at urinary tract infection in children without reflux. The results of these two studies are expected to be published shortly after the primary results of the RIVUR trial.

NIDDK, along with NIH Office of Rare Diseases Research and two patient advocacy groups, supports the Nephrotic Syndrome Rare Disease Clinical Research Network (NEPTUNE). It is a multi-site, multidisciplinary collaborative research and education network designed to foster innovative approaches to the understanding of three glomerular diseases: minimal change disease, FSGS, and membranous nephropathy.

To address the concern about acute kidney injury (AKI) in children, the NIDDK is co-funding a study with the National Institute of Neurological Disorders and Stroke (NINDS) to collect kidney data in a cohort of premature neonates who are part of a study to examine neurological developmental issues [Preterm Epo Neuroprotection Trial (PENUT Trial)]. This is of particular significance because there is evidence that AKI early in life can lead to increased risk of subsequent chronic kidney disease (CKD).

NIDDK is also concerned about kidney stone disease in pediatric patients. The Institute has funded the Rare Kidney Stone Consortium to study four diseases characterized by deposition of crystals in the kidneys that often lead to kidney stones and kidney failure. It focuses on the discovery of biomarkers of disease risk, disease activity, and response to therapy.

Finally, the Institute has conducted a “Kidney Research National Dialogue,” an effort to identify opportunities for future kidney disease research pediatric kidney disease. The pediatric research recommendations from this exercise are to be published in the Clinical Journal of the American Society of Nephrology and the journal Pediatric Nephrology.

Item

Pelvic Pain - The Committee is pleased that the Multidisciplinary Approach to the Study of Chronic Pelvic Pain [MAPP] Research Network has moved to its second phase. The Committee encourages NIDDK to continue these activities, including finding new treatment approaches, identifying risk factors, and helping to predict which patients may respond to various interventions for interstitial cystitis and other comorbid pelvic pain conditions.

Action taken or to be taken

The NIDDK is committed to continuing the efforts of the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. The multi-center MAPP Research Network has been conducting innovative, collaborative studies of the two most common urologic chronic pelvic pain syndromes (UCPPS)—interstitial cystitis/painful bladder syndrome (IC/PBS) (also known as interstitial cystitis/bladder pain syndrome (IC/BPS)) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). In the first phase of the Network, these studies have been carried out by six Discovery Sites across the United States that conduct research studies, and two Core Sites that coordinate data collection, analyze tissue samples, and provide technical support. With the cooperation of patient advocacy groups such as the Interstitial Cystitis Association and the Prostatitis Foundation, as well as the strong commitment of the patient community, over 1,000 participants have been recruited to the Network studies.

The NIDDK is pleased to report that it recently issued two requests for applications (RFAs) to continue and enhance the MAPP Research Network for an additional 5 years beginning in FY 2014. One is a “Limited Competition” RFA that solicits applications from the current MAPP Discovery and Core Sites for a second 5-year project period; this RFA is co-sponsored by the NIH Office of Research on Women’s Health. With the second RFA, the NIDDK seeks to enhance the MAPP Research Network by using a portion of the funds dedicated to this effort to add two to three new, smaller Discovery Sites, contingent upon the receipt of scientifically meritorious applications. The new Discovery Sites are expected to bring additional expertise to help address one or more high priority research areas within the second phase of the MAPP Research Network, such as detectable/measurable molecular factors associated with UCPPS, the contribution of microorganisms and infectious agents to symptoms and fundamental causes of UCPPS, and the involvement of the central nervous system and nerves elsewhere in the body in the characteristics, progression, and/or cause(s) of UCPPS.

Since its inception, the Network’s unique approach to UCPPS has entailed searching “beyond the bladder/prostate” to find the causes of these pain syndromes, including studying the possible relationships between UCPPS and other chronic pain disorders, such as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome. Groups of patients displaying these co-morbid disorders are being characterized within the major scientific efforts of the Network. It is anticipated that the second phase of the MAPP Research Network will enable investigators not only to continue analyses of the vast amounts of data and biological samples already generated, but also to collect additional data and establish new studies, all with the goal of understanding disease development, identifying risk factors, and finding clinically meaningful ways to differentiate between patients with UCPPS symptoms. It is hoped that such efforts will continue to elucidate both UCPPS and co-morbid conditions and provide a foundation for development of new therapeutic strategies for persons living with these pain syndromes.

In related efforts, NIDDK is a member of the Trans-NIH Pain Consortium, which promotes collaboration across the many NIH Institutes and Centers that have programs and activities addressing pain. Many Consortium efforts recognize the challenges posed by overlapping chronic pain conditions and will help to advance research strategies to address the causes, course, and diagnosis of pain conditions often found co-occurring in persons with IC/PBS.

Item

Polycystic Kidney Disease [PKD] - The Committee continues to urge NIH to put a high priority on PKD research.

Action taken or to be taken

NIH continues its significant investments in polycystic kidney disease (PKD) research. PKD is a genetic disorder characterized by the growth of numerous cysts in the kidneys. Slow, constrained cyst growth results from changes in cellular architecture, fluid secretion, and cell proliferation. Recent reports offer new insights into the basic mechanisms of cyst growth and introduced a promising new animal model for studying PKD. In addition, several genes involved in kidney cyst formation have been discovered in the past year, identifying a causative mutation in patients with rare cystic kidney diseases.

Two large NIDDK-funded clinical studies— Halt Progression of Polycystic Kidney Disease (HALT-PKD) and The Consortium for Radiologic Imaging Studies of PKD (CRISP)—are focused on identifying better monitoring and imaging approaches, as well as improvements in patient care for individuals with the most common form of PKD, autosomal dominant PKD. CRISP was established to develop innovative imaging techniques and analyses to follow disease progression or to evaluate treatments. The image analysis methods developed in CRISP are currently being implemented in HALT-PKD and have been used by industry-sponsored trials for patients with PKD. The HALT-PKD study has been extended to test the blockade of the renin-angiotensin system as a therapy for PKD, and to demonstrate the validity of total kidney volume and other biomarkers as surrogates for progression of disease. The NIH has funded further genetic research to identify genes that are associated with the severity of the disease.

The NIDDK has conducted a “Kidney Research National Dialogue,” an effort to identify opportunities for future kidney disease research, including PKD. This effort is designed to strengthen both the Institute’s kidney research programs as well as the broader nephrology research community. Several commentaries that address areas of interest to the kidney research community have been published in the Clinical Journal of the American Society of Nephrology in the fall of 2013.

The NHGRI is conducting a clinical trial at the NIH Clinical Center to provide diagnosis and care for patients, most of whom have the rarer form of PKD, autosomal recessive polycystic kidney disease (ARPKD), and other ciliopathies associated with polycystic kidneys. The goal of

the study is to better understand the medical complications of these disorders and identify characteristics that can help in the design of new treatments. This work was performed as part of “Clinical and Molecular Investigations into Ciliopathies” (clinical trial number NCT00068224).

Item

Prostatitis - The Committee urges NIDDK to continue the MAPP initiative’s support of research on the cause, cure, and prevention of prostatitis.

Action taken or to be taken

Researchers, patients, and health care providers alike face an enormous challenge when it comes to chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). To address the many long-standing questions regarding CP/CPPS and interstitial cystitis/painful bladder syndrome (IC/PBS), the NIDDK is continuing support for the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network. Begun in 2008, six Discovery Sites, along with two Core sites, across the United States comprise the Network. The Discovery Sites conduct research studies, while the Core Sites coordinate data collection, analyze tissue samples, and provide technical support. This innovative research program embraces a systemic, or whole-body, approach to understanding CP/CPPS and IC/PBS. Network investigators are conducting numerous complementary studies to investigate questions of significant clinical relevance to CP/CPPS. They pursue these studies with the view that that CP/CPPS may involve areas of the body beyond the prostate. One key objective of these studies is to advance understanding of underlying causes, symptom variation, and risk factors for CP/CPPS. Another key objective is to provide a comprehensive description of patient characteristics and, based on differing symptom profiles, identify potential patient sub-groupings, which may help in the future design of therapies for treatment and/or prevention. A third key objective is to address the relationships between CP/CPPS, IC/PBS, and other chronic pain syndromes commonly found in persons with urologic chronic pelvic pain conditions. The overarching goal of the MAPP Research Network is to provide findings useful for designing future, targeted clinical trials and ultimately to improve clinical management. Importantly, this effort is also generating a unique national resource of highly detailed clinical data associated with biological samples, which may be studied well beyond the lifetime of the Network.

With the cooperation of the Prostatitis Foundation and other patient advocacy groups, and the strong commitment of the patient community, the MAPP Research Network has met its recruitment goals, which are critical to completion of Network studies. This includes nearly 200 CP/CPPS patients, which exceeds the Network’s original recruitment goal. The NIDDK is pleased to report that it recently issued two requests for applications (RFAs) to continue and enhance the MAPP Research Network for an additional 5 years beginning in FY 2014. One is a “Limited Competition” RFA that solicits applications from the current MAPP Discovery and Core Sites for a second five year project period. With the second RFA, the NIDDK seeks to

enhance the MAPP Research Network by using a portion of the funds dedicated to this effort to add two to three new, smaller Discovery Sites, contingent upon the receipt of scientifically meritorious applications. The new Discovery Sites are expected to bring additional expertise to help address high priority research areas within the second phase of the MAPP Research Network. In the second phase, it is expected that the Network will design more focused studies to uncover the causes of CP/CPPS and other urologic chronic pelvic pain conditions and to pave the way to testing of potential treatments.

Conference Significant Items

Item

Oxalosis and Hyperoxaluria - Oxalate metabolism remains incompletely understood and elucidated in humans. The National Institute of Diabetes and Digestive and Kidney Diseases is encouraged to promote the study of additional aspects of oxalate metabolism in humans, especially the newly discovered type PH3, and to fund research into novel pathways with special attention to specific abnormalities in enzymes of the hydroxyproline pathway.

Action taken or to be taken

The NIDDK remains committed to maintaining a strong portfolio of hyperoxaluria-related research. In December 2012, the Institute re-issued Funding Opportunity Announcement PA-13-043 titled “Calcium Oxalate Stone Diseases” to encourage investigator interest in research into oxalate metabolism, transport and homeostasis, and oxalate stone diseases for the purpose of advancing basic, clinical, and epidemiologic studies that utilize new and innovative approaches to study the diagnosis, treatment, and prevention of these disorders. In response to this announcement, a grant was awarded in January 2014 to the University of Alabama at Birmingham to study mitochondrial metabolism in Primary Hyperoxaluria. Additional grant awards are contingent upon the receipt of scientifically meritorious applications. In September 2013, the NIDDK awarded a George M. O'Brien Urology Research Center to Mayo Clinic Rochester, which seeks to improve stone disease treatment by accurate phenotyping and risk assessment stratification. The Institute is also expanding the scope of basic research to develop new models in order to better understand calcium oxalate stone disease. NIDDK-supported research in mice has contributed to understanding stone disease including the first functional analysis of the key enzyme mutated in PH3, that progressive renal failure in oxalate nephropathy is caused by peripheral blood leukocyte-mediated inflammation, and that the “kidney injury molecule-1” may be a potential biomarker for oxalate-induced kidney injury. In addition, the Institute has supported the Rare Kidney Stone Center as part of the NIH Rare Disease Research Consortium, providing a resource for patients as well as carrying out a wide spectrum of clinical research studies on all forms of Primary Hyperoxaluria. The NIDDK will continue to pursue scientific opportunities to uncover knowledge and increase understanding in this area.

National Institute of Neurological Disorders and Stroke (NINDS)

Senate Significant Items

Item

BRAIN Initiative - The Committee strongly commends NIH for leading the Brain Research through Application of Innovative Neurotechnologies [BRAIN] Initiative, a multi-agency effort that also involves the National Science Foundation and the Defense Advanced Research Projects Agency as well as several private sector partners. Numerous researchers are already working to accelerate the development and application of new technologies that will help explain how the brain records, processes, uses, stores, and retrieves information. The BRAIN Initiative will help catalyze and integrate these efforts. The Committee understands that this work may take decades before it results in cures or treatments, but could eventually help unlock the secrets behind diseases such as Alzheimer's and epilepsy. The President's budget requests \$40,000,000 for this initiative in fiscal year 2014, to be pooled from several ICs and the OD. The Committee supports that amount as an initial investment but awaits more detailed budget projections for future years.

Action taken or to be taken

Developing new technologies that will enable scientists to explore how the brain records, processes, uses, stores, and retrieves vast quantities of information - and then applying these technologies to shed light on the complex links between brain function and behavior - will take time. For this reason, it is imperative that detailed budget projections be strongly informed by a rigorous scientific plan. NIH has charged a high-level, expert working group of the Advisory Committee to the Director, NIH (ACD), with developing a plan for the NIH commitment to the BRAIN Initiative, which is to include timetables, milestones, and cost estimates. As part of this process, members are consulting continuously with the scientific community, patient advocates, and the general public to ensure that this plan is informed by stakeholder input. As a first step, the working group issued an interim report on September 16, 2013 identifying nine high priority research areas for NIH funding in Fiscal Year (FY) 14 that are critical to supporting the mission of the BRAIN Initiative (http://www.nih.gov/science/brain/ACD_BRAIN_interimreport_executivesummary.htm). The ACD fully endorsed these findings and the NIH Director agreed that the ACD's recommendations would be used to guide NIH's future investments in the BRAIN Initiative. The working group will continue to work over the course of the next year to develop the longer term scientific plan, which is expected to be delivered to the ACD in June 2014.

Item

Cerebral Cavernous Malformation [CCM] - The Committee urges NINDS to put a higher priority on CCM by coordinating existing research and surveillance activities as well as

expanding clinical and research centers with the potential to manage a multisite clinical drug trial.

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) currently supports a portfolio of basic and translational research to understand the molecular, cellular and genetic processes involved in cerebral cavernous malformations (CCM). Active investigations are gaining a better understanding of the normal development of cerebral vessels and how genes associated with CCM cause abnormal vessel formation, while other studies are examining the role of specific CCM genes in vascular function that may give rise to clinical symptoms in patients impacted by CCM. Furthermore, several NINDS-supported studies are identifying small molecule compounds to disrupt development of vascular malformations by modifying CCM gene action or downstream effects.

NINDS sponsored a meeting held by the Angioma Alliance in Washington, DC on November 15 and 16, 2012, which brought together CCM basic and clinical research experts from academia, industry, the medical community and government agencies to discuss the recent research findings and identify promising future directions, and to encourage coordination and development of collaborative research strategies. The meeting was multi-disciplinary and incorporated expertise from proteomics, molecular biology, vascular biology, genetics, neurology, radiology, epidemiology, animal models, and neurosurgery. A stakeholder panel discussed important considerations for clinical trials in CCM, including the use of biomarkers, successful patient recruitment, FDA requirements and potential funding mechanisms. The group also discussed data and experiences from the NIH Rare Disease Clinical Research Network's Brain Vascular Malformations Consortium, which includes a prospective natural history and genome-wide association study investigating genetic, physiological and lifestyle factors which affect CCM clinical variability.

CCM is an important cause of hemorrhagic stroke, a severe type of stroke for which there is currently no effective treatment. NINDS is currently establishing a national Stroke Trials Network which will have the capacity and expertise to conduct small as well as large, multi-site clinical trials in stroke prevention, treatment and recovery research. This new network will be poised to answer clinical questions related to CCM, including testing promising treatments that may emerge from current preclinical work.

Item

Duchenne Biomarkers - The Committee recognizes the importance of biomarkers and related surrogate endpoints for application in clinical trials of potential therapies for Duchenne muscular dystrophy. Therefore, the Committee urges NINDS, in collaboration with the FDA, to develop a plan of action to support the development and qualification of Duchenne biomarkers and to support the regulatory science relevant to advancing new technologies to treat this disease.

Action taken or to be taken

The major barrier to qualification of Duchenne biomarkers by the FDA is the lack of necessary data. NIH-funded researchers are working to identify and evaluate biomarkers for the disease. Accordingly, NIH is supporting the efforts of a multi-site team to evaluate whether non-invasive imaging of leg muscles can provide information about muscle strength and disease progression that investigators can use as outcome measures in clinical trials. Putative biomarkers in blood are being evaluated in a large natural history study of Duchenne patients. The goal of this project is to identify biomarkers of disease severity, progression, and corticosteroid drug activity that can be used to monitor response to potential treatments during clinical trials. To help evaluate potential toxicity of certain drugs under development for Duchenne, an NIH-funded biomarker discovery program is assessing urine biomarkers for feasibility as kidney toxicity markers. Reliable markers will help speed the development of these drugs.

NIH staff has participated in meetings of the Duchenne Drug Development Roundtable, founded by the Muscular Dystrophy Association and Parent Project Muscular Dystrophy. One goal of this group, comprised of industry and academic scientists, advocacy, and NIH representatives, is to advance biomarkers and endpoints to help facilitate clinical trials and drug approval in Duchenne muscular dystrophy.

Biomarkers and related surrogate endpoints will be important components of the Action Plan for the Muscular Dystrophies, which is being revised and updated in 2013-2014. The topic will be the focus of one of the Action Plan working groups and recommendations in this area for the entire research and advocacy community will be included in the revised Action Plan. The revised plan will be developed in partnership with all MDCC member organizations, including the NIH and FDA, and is expected to be presented to the Muscular Dystrophy Coordinating Committee (MDCC) for approval by the end of 2014.

Item

Epilepsy - The Committee commends NINDS for its leadership in sponsoring the April 2013 conference “Curing the Epilepsies 2013: Pathways Forward” and for evaluating and guiding progress toward finding cures for the epilepsies through the community’s epilepsy research benchmarks. The Committee applauds the enhanced focus of the NINDS Anticonvulsant Screening Program on developing new compounds to better address the needs of the patients for whom current therapies are not effective and to focus on prevention and disease modification. The Committee encourages the continuation of the targeted Epilepsy Centers Without Walls grants to support multidisciplinary, collaborative research in targeted areas that can advance progress in the prevention, diagnosis, and treatment of epilepsy and related comorbidities, including mortality from epilepsy. The Committee also remains supportive of Exceptional Unconventional Research Enabling Knowledge Acceleration [EUREKA] grants and research in epileptogenesis, comorbidities, translational research on epilepsies, treatment resistant epilepsy,

and sudden unexplained death in epilepsy. Further, the Committee encourages the continuation of the Interagency Collaborative to Advance Research in Epilepsy [ICARE], led by NINDS, to coordinate the research efforts of Federal agencies and voluntary organizations and to identify areas for collaboration.

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) supports a broad range of basic, translational, and clinical research on the epilepsies. This research includes, among other topics, studies of epileptogenesis (the process by which epilepsy develops), treatment-resistant epilepsy, and sudden unexpected death in epilepsy (SUDEP), as well as conditions related to epilepsy or its treatment, such as depression, cognitive impairment, sleep disorders, and effects of anti-seizure treatment during pregnancy. Based on input received before and during the April 2013 Curing the Epilepsies conference, NINDS is revising the Benchmarks for Research on the Epilepsies. The 2014 Benchmarks will provide a framework for focusing efforts across the research community and benchmarking progress over the next several years.

New Anticonvulsant Screening Program (ASP) activities related to treatment-resistant epilepsy and disease prevention or modification include a subcontract to develop an animal model of mesial temporal lobe epilepsy, a common form of epilepsy for which existing therapies can be ineffective. The ASP is refining additional animal models for improved identification of novel drug candidates and is implementing assays to better detect potential adverse effects on cognitive function. NINDS supports other efforts to develop treatments for the epilepsies through a milestone-driven translational research program and investigator-initiated studies. Also, the NINDS epilepsies EUREKA program helped to foster innovative models and approaches in research to understand epilepsy and identify new strategies to prevent or control seizures. NINDS will continue to support a EUREKA program with an expanded scope across neuroscience and disorders of the nervous system, including the epilepsies.

The first awarded Center without Walls is in its third year of funding. The Epi4K project is analyzing the genomes of over 4,000 individuals with epilepsy and their families to improve understanding of the genetic basis of human epilepsies. Epi4K investigators recently identified new gene mutations associated with infantile spasms and Lennox-Gastaut syndrome, two severe forms of childhood onset epilepsy that are difficult to treat and associated with intellectual disability. Exploratory projects are building foundations for other potential Centers without Walls. Two of these focus on understanding causes and risk factors for SUDEP, which will inform strategies for prevention. NINDS will issue a funding opportunity announcement for a full SUDEP Center without Walls in FY2014. Three other exploratory grants support collaborative research on disease modification or prevention. These projects aim to identify biomarkers of epileptogenesis in tuberous sclerosis and after traumatic brain injury, prolonged febrile seizures, and other insults to the brain. Such biomarkers could help identify individuals at risk for epilepsy and facilitate research to develop preventive or disease-modifying interventions.

NINDS will convene the next meeting of ICARE in spring 2014. Beyond ICARE meetings, NINDS interacts regularly with several ICARE members through an HHS-wide working group and a collaborative group of non-governmental organizations. In addition, NINDS and the National Heart, Lung, and Blood Institute (NHLBI) are partnering with the Centers for Disease Control and Prevention (CDC) to improve surveillance of SUDEP and sudden cardiac death through a new Sudden Death in the Young registry. The registry will build on the CDC's Sudden Unexpected Infant Death (SUID) Case Registry to track all sudden unexpected deaths in individuals up to age 24 in as many as 10 states or major metropolitan areas. A panel of medical examiners and forensic pathologists will help develop and implement much-needed standards and definitions for autopsy protocols, and the program will also collect clinical information and biospecimens for broad research use.

Item

Headache - The Committee commends NIH for efforts to increase its focus on headache disorders over the past several years, especially in encouraging more junior investigators to enter the field. However, NIH's investment in this research is still not commensurate with the enormous disease burden of headache disorders. The Committee encourages intensified efforts to understand the causes, prevention, treatment, and eventual cure of headache disorders, including migraine, cluster headache, and chronic daily headache. In particular, the Committee urges NINDS to follow through on the recommendations from the May 2010 NIH Headache Research Planning Workshop by issuing requests for applications and program announcements for fundamental and translational research on headache disorders and providing career training and transition awards specifically devoted to the investigation of headache disorders.

Action taken or to be taken

The NIH and the National Institute of Neurological Disorders and Stroke (NINDS) recognize the tremendous burden of headache disorders and have worked to identify opportunities and encourage research to advance the field. NIH and NINDS are also responding to key recommendations from the May 2010 NIH Headache Research Planning Meeting. For example, one recommendation emphasized the need to facilitate development and sharing of consistent and harmonized clinical trial data, resources, and infrastructure among clinical researchers. To address this recommendation, NINDS recently released a set of Common Data Elements (CDEs; http://www.commondataelements.ninds.nih.gov/Headache.aspx#tab=Data_Standards) for headache studies. The headache CDEs, which are tools to facilitate the collection, analysis, and sharing of data through the use of common definitions and data sets, were developed in partnership with leaders in the headache research community, and NINDS is encouraging their adoption and use in clinical studies. Another recommendation from the meeting was to advance research on pediatric headaches. NINDS-funded researchers are now performing a pivotal clinical trial to determine the efficacy, tolerability, and safety of two medications for treating

migraines in children, which will eventually help determine the first-choice prevention medication for this condition.

To expand the portfolio of headache research and encourage relevant research proposals, NIH released Funding Opportunity Announcements (FOAs) in headache and migraine research, including the recently-renewed FOA, *Neurobiology of Migraine*. This FOA has supported 16 new grants since it was issued. In one project, NINDS-supported scientists are utilizing existing migraine animal models and developing new models to create standardized screening tests for potential migraine drugs. Another project funded through this FOA is investigating the mechanisms of sleep dysregulation in migraine, as sleep disturbance is a risk factor in the progression from episodic to chronic migraine. Projects funded through the FOA have led to a number of research advances, including a recent study demonstrating that activation of a particular receptor in the brain, TRPA1, may contribute to headache pain development. This finding may ultimately lead to new therapeutics targeting this particular receptor.

NINDS continues to uphold its commitment to training the next generation of scientists by funding training grants focused on headache disorders, including one that explores structural and functional changes in the cerebral cortex of people with migraines. NINDS also renewed funding for a grant to allow a mid-career investigator to mentor junior clinical investigators in the use of functional imaging to investigate how migraines alter brain structure, chemistry, and function in adults and children. Additionally, NIH funds Centers of Excellence in Pain Education (CoEPEs) to develop curriculum resources to improve training of clinicians in pain treatment and management. One of the 12 institutions designated as a CoEPE is focused solely on training in headache treatment. To inform the research community of funding opportunities and NIH activities in the area of headache research, NINDS program staff attends national headache meetings and regularly communicates with potential grantees. NINDS will continue to promote the expansion of fundamental basic and translational research on headache disorders, and is committed to reducing the burden of these conditions.

Item

Inflammatory Nervous System Disorders - The Committee urges NINDS to pursue expanded research focused on inflammatory disorders impacting the peripheral nervous system such as Guillain-Barre´ syndrome, chronic inflammatory demyelinating polyneuropathy, and related conditions.

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 the peripheral nerves, damaging myelin (the fatty covering that insulates and protects nerve fibers) and diminishing the ability of affected nerves to conduct electrical signals. NINDS-funded researchers are investigating the mechanisms by which the body's immune system stops recognizing peripheral nerves as "self" and starts attacking them. Some people with CIDP have mutations in the Autoimmune Regulator (AIRE) gene. Scientists are using animal models to study the mechanisms by which mutations in this gene lead to inflammation and nerve damage. GBS is usually preceded by a microbial infection, some as common as food poisoning or the flu. One hypothesis currently being investigated by NINDS-funded researchers is that antibodies generated by the immune system to attack certain molecules in bacteria also attack nervous system proteins. These researchers are also developing treatments that would block the antibodies from attacking nerve cell proteins.

The blood-nerve barrier normally prevents antibodies and immune cells from leaving the bloodstream and attacking nerves. NINDS-funded researchers are studying the mechanisms by which immune cells cross the blood-nerve barrier in inflammatory nervous system disorders and are developing strategies for reducing movement of immune cells from the blood into nerve tissue, which may reduce inflammation, demyelination, and nerve injury.

Currently there are no treatments to help repair nerve cells and myelin that have already been damaged. NINDS-funded researchers are investigating the molecular mechanisms of myelin formation, which may lead to novel therapeutic targets for promoting repair of demyelinated nerves and restoring nerve function.

Item

Mucopolysaccharidosis [MPS] - The Committee continues to urge NIH to put a high priority on better understanding and treating MPS and related 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 also commends NIDDK for funding gene therapy efforts. Continued funding of these grants is critical to understanding these diseases and evaluating the efficacy and safety of combination therapies. The Committee encourages NINDS, NIDDK, and ORDR to continue supporting the Lysosomal Disease Network.

Action taken or to be taken

The National Institutes of Health (NIH) are committed to investing in research to understand and develop treatments for MPS and related lysosomal storage disorders. The National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the Office of Rare Diseases Research (ORDR) within the National Center for Advancing Translational Sciences (NCATS) continue joint support for the Lysosomal Disease Network (LDN), a member of the Rare Disease Clinical Research Network (RDCRN) program led by ORDR. Studies on MPS disorders within the LDN include two

longitudinal studies in children with MPS disorders focusing on brain structure and function, and on bone disease and the effect of treatment with human growth hormone. MPS disorders are associated with an increased risk of cardiovascular disease, and LDN researchers are also comparing carotid artery structure and function in people with or without MPS.

In August 2013, NCATS and 10 other NIH components reissued the funding opportunity announcement (FOA) to support collaborative, multi-site clinical research consortia within the RDCRN. The program is intended to facilitate the identification of biomarkers for disease risk and severity and the development of new approaches to the diagnosis, prevention, and treatment of rare diseases, as well as outcomes measures for clinical trials. The LDN and other currently funded consortia are eligible for renewed support through this competitive FOA.

Beyond the LDN, NINDS supports research on MPS disorders to develop approaches for gene or enzyme replacement therapies, which must be able to cross the blood-brain barrier and be distributed widely throughout the brain to address impacts of these disorders on the nervous system. This research includes efforts by academic investigators and small businesses to develop and refine methods for effective gene delivery and to bioengineer novel fusion proteins for enzyme replacement. One small business project aims to develop the first small molecule drugs for treating MPS and has entered a collaborative agreement with a large pharmaceutical company for further development. The same small business is also developing biomarkers for diagnosing MPS types I, II, and VI, and for monitoring treatment responses.

NIDDK has also been supporting several grants to study gene therapy approaches for MPS, as well as two Molecular Therapy Centers that provide shared resources for researchers studying MPS and other genetic metabolic diseases. As another resource, the NIH Office of Research Infrastructure Programs (ORIP) funds a Referral Center for Animal Models of Human Genetic Disease, which serves to identify, characterize, preserve, and make available for research new and existing spontaneous canine and feline models with defects in the same genes as in human patients. In addition to basic genetic and pathophysiologic studies of the various Types of MPS, a variety of drugs, biologic, gene vector, enzyme replacement, and combination therapies are pursued in dog or cat models of MPS Types I, II, IIIA, IIIB, VI, and VII. Some of these treatments pioneered in animals have justified clinical trials in human subjects.

Item

Muscular Dystrophy Coordinating Committee [MDCC] - The Committee understands that the MDCC's next meeting is planned for August 2013—more than 2 years since the last meeting—and that the Action Plan for Muscular Dystrophy has not been updated in 5 years. The MDCC's charter stipulates that meetings of the full committee should be held not less than once each fiscal year; the Committee strongly urges MDCC to resume a more regular schedule. In addition, the Committee urges the MDCC to review and revise the action plan so that it is relevant to the full range of Duchenne patients, including adults and different racial and ethnic

populations affected by muscular dystrophy, and informed by Duchenne patient, caregiver, clinician, and research stakeholders.

Action taken or to be taken

The National Institutes of Health will resume a regular schedule of Muscular Dystrophy Coordinating Committee (MDCC) meetings, and NIH and the MDCC Chairperson have made a commitment to hold twice-yearly meetings of the committee. NIH and the MDCC Scientific Working Group are updating the “Action Plan for the Muscular Dystrophies”, and a revised plan will be brought to the MDCC by the end of 2014 for approval.

The most recent meeting of the MDCC took place on August 26, 2013. The meeting included an overview of NIH activities, updates from MDCC members, and an overview of the process for updating the Action Plan. The next meeting of the MDCC is already scheduled for April 7, 2014, and the planning workshop to update and revise the Action Plan will be held in 2014. This planning workshop will bring together MDCC member organizations, academic and corporate researchers, and clinical investigators to revisit the Action Plan, discuss accomplishments related to the original objectives, and develop new research objectives to help guide research in muscular dystrophy.

The revised Action Plan – like the original Plan – will include research objectives for the entire muscular dystrophy community to help advance the goal of timely detection, diagnosis, treatment, and prevention of all the muscular dystrophies. MDCC members will be given the opportunity to nominate individuals to serve on the scientific working groups, which will develop the revised Action Plan. The working groups will include members with appropriate expertise to address the full range of muscular dystrophy research and patient perspectives.

Given the important need to address care considerations for all populations of muscular dystrophy patients and the interest in this topic from the muscular dystrophy patient community, the revised Action Plan will include an expanded focus in this area. As a first step in discussing these issues, the August 2013 MDCC meeting included a presentation by the Muscular Dystrophy Association entitled “Living with Muscular Dystrophy: Life Transitions.” In addition, other agencies with an important role in these discussions will be invited to attend MDCC meetings.

Item

Network for Excellence in Neuroscience Clinical Trials - The Committee is pleased that NINDS plans to expand its support of the Network for Excellence in Neuroscience Clinical Trials [NeuroNEXT] program. The Committee urges NINDS to increase the efficiency of clinical trials conducted through NeuroNEXT, facilitate patient recruitment and retention, and increase the quality of the neuroscience trials.

Action taken or to be taken

The NINDS established the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT) in 2011 to provide robust infrastructure and centralized resources for conducting efficient early-phase clinical trials in both pediatric and adult neurologic disorders. Two clinical studies are being conducted within NeuroNEXT: the first is developing biomarkers for spinal muscular atrophy (SMA), and the other is testing the safety and efficacy of a potential neuroprotective therapy in patients with progressive multiple sclerosis. In addition, new proposed studies are being assessed currently for significance and for network feasibility, and, based on results from peer- and NINDS Council-review of the best proposals, at least one new trial will be implemented in the network during fiscal year 2014.

The NINDS is continuously assessing the success of the network to ensure that trials are of high quality, conducted efficiently, and that the network sites are able to recruit and retain study participants. The SMA biomarker study has exceeded patient recruitment and retention goals after a rapid start-up phase, and the multiple sclerosis began enrolling patients in early November 2013, also after a rapid start-up. Opportunities to continue improving the efficiency of the network and its ability to conduct efficient, high quality clinical trials have been identified. For example, the network's standard operating procedures will be posted on the NeuroNEXT public website to ensure uniformity and maximize safety and efficiency in research operations across its clinical sites. The NINDS has streamlined the internal review of study proposals, and will soon release a revised funding opportunity announcement that incorporates additional measures to improve efficiency in the network. Finally, efforts are underway to facilitate a dialogue between NeuroNEXT and two of NINDS's other major trials networks (Neurological Emergencies Treatment Trials, and the new Stroke Trials Network) so that key players can discuss lessons learned.

The NINDS is committed to improving the efficiency and quality of clinical trials in neurology and will continue to support the NeuroNEXT program and to identify opportunities for maximizing its impact.

Item

Overlapping Chronic Pain Conditions – The Committee continues to strongly support an expanded trans-NIH research effort to better understand and identify effective treatments for overlapping chronic pain conditions that disproportionately impact women, including chronic fatigue syndrome, endometriosis, fibromyalgia, interstitial cystitis, irritable bowel syndrome, chronic headache, temporomandibular disorders, and vulvodynia. The Committee urges NIH to promptly implement the recommendations from the August 2012 NIH scientific workshop on this topic. These include: developing a case definition and research diagnostic criteria for chronic overlapping pain conditions; leveraging existing patient cohorts, resources, and data repositories to achieve cost savings; conducting prospective population-based epidemiological studies to determine the natural history of and risk factors for onset and progression of disease; developing common data elements, standardized outcome measures, and methods to classify phenotypic subgroups; studying central sensitization as a theme for discovery of common mechanisms of disease, diagnostics, and treatment; and developing multidisciplinary training programs for scientists and clinicians. As no one Institute has the responsibility for addressing all overlapping chronic pain conditions, the Committee strongly urges multiple Institutes to combine their efforts through centers of excellence or other appropriate means of carrying out these recommendations.

Action taken or to be taken

The NIH recognizes the need to continue its collaborative efforts to better understand co-occurring chronic pain conditions. Several recommendations from the August 2012 workshop are being addressed by multiple NIH institutes and the trans-NIH Pain Consortium, which includes representatives from all NIH Institutes and Centers (ICs).

NIH funds three large prospective population-based epidemiological studies on multiple pain conditions. The National Institute of Dental and Craniofacial Research (NIDCR) funds the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study to identify causal determinants of Temporomandibular Disorder (TMD). NIDCR recently funded a follow-up study (OPPERA-II) to identify risk factors that predict whether TMD will develop as a single condition or in conjunction with other chronic pain conditions, including headache, low back pain, irritable bowel syndrome (IBS), and widespread body pain. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funds the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network, a multi-center study of two urologic chronic pelvic pain syndromes: interstitial cystitis/painful bladder syndrome and chronic prostatitis. The Network is investigating the relationships between these urological syndromes and other co-occurring pain conditions. The National Institute of Neurological Disorders and Stroke (NINDS) funds a multidisciplinary project on multiple complex persistent pain conditions (CPPCs), including episodic headache, fibromyalgia, temporomandibular joint disorders, irritable bowel syndrome, and vulvar vestibulitis. The goal of the project is to identify the risk factors that increase susceptibility to one or more CPPCs. The NIH Pain Consortium is

leading an effort to bring together investigators from these and other large studies of chronic pain conditions to coordinate approaches and discuss future research directions.

The NIH portfolio of pain research also includes studies on underlying pain pathways and mechanisms, many of which are relevant to recommendations from the August 2012 workshop. For example, NINDS funds a number of projects aimed at understanding central sensitization of the nervous system. These neural changes are thought to be involved in the transition from acute to chronic pain and are one avenue of research aimed at identifying shared mechanisms across multiple chronic pain conditions.

Several NIH Institutes are engaged in activities to develop common data elements (CDEs) for specific pain conditions. CDEs are common definitions and data sets that help insure that clinical information is consistently captured and recorded across studies, and will help investigators compare and integrate data across studies of overlapping conditions. NINDS has developed a set of common data elements to facilitate clinical headache research (http://www.commondataelements.ninds.nih.gov/Headache.aspx#tab=Data_Standards). Similarly, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is addressing recommendations from the NIH Research Plan on Vulvodynia and held a recent meeting to discuss research diagnostic criteria for vulvodynia. One outcome of this workshop will be to work toward developing CDEs on vulvodynia.

As part of the effort to enhance multidisciplinary training, the NIH Pain Consortium funds 12 Centers of Excellence in Pain Education (CoEPEs). These CoEPEs will act as hubs for the development, evaluation and distribution of pain management curriculum resources for health professional schools. Chronic and overlapping pain conditions will be highlighted through unique patient cases; for example, the UCSF Center of Excellence has already developed a case study of a patient with endometriosis, vulvodynia, and IBS.

Item

Stroke - The Committee continues to commend the effective leadership role of NINDS in stroke research planning and prioritization and congratulates the Institute for its efforts that have culminated in the identification of nine top areas in stroke prevention, treatment, and recovery research. The Committee urges NINDS to stimulate investment in each of these areas.

Action taken or to be taken

The NINDS Stroke Research Priorities Meeting, held in August of 2012, brought together leading stroke investigators who considered input from the broad community and used a structured consensus-development process to generate a set of nine high priority research areas that have the potential to produce significant advances for the field. The final report detailed three priority topics for stroke prevention, three for acute treatment, two for recovery research, and one that cuts across all domains. The NINDS has identified several important themes across

the nine priorities that will influence its investments so that the impact on prevention, treatment and recovery research is maximized.

One of the major opportunities cited by the planning panel was for development of infrastructure that would improve the efficiency and coordination of all stroke clinical trials. The NINDS is establishing a national Stroke Trials Network in fiscal year 2013 which will consist of 25 regional centers and two centralized coordinating centers that will have the expertise to plan, develop and execute high quality, innovative, multi-site clinical trials focused on key interventions and important scientific questions in stroke prevention, treatment and recovery. The network will facilitate patient recruitment and retention, support novel methodologies and streamline approaches to accelerate the development of promising stroke therapies.

The planning panel also identified research priorities related to basic vessel biology as well as vascular cognitive impairment (VCI), and their recommendations informed a session on this topic at the NIH Alzheimer's Disease-Related Dementias (ADRD) workshop, held in May of 2013. Draft recommendations from the ADRD meeting are synergistic with the priorities identified by the stroke panel, and address basic, translational and clinical research needs related to VCI and vascular biology. The NINDS is initiating trans-NIH discussions of how best to enhance investments in these areas which are shared among several different NIH Institutes.

Another theme that emerged throughout the planning effort and which was specifically addressed in the "cross-cutting" priority is the need to facilitate improved quality and translation of preclinical research in stroke. The NINDS has in recent years recognized this as a priority for all the diseases for which it is responsible and has been at the forefront of an NIH and community-wide effort to improve transparency and rigor of preclinical research. The Institute is currently considering innovative and more effective approaches for supporting the development and translation of promising new therapies along the research continuum, and these efforts will directly influence investments in preclinical stroke research. In addition, the NINDS has initiated discussion with European colleagues regarding a new European effort to support rigorous preclinical evaluation of new stroke therapies. NINDS will seek continued opportunities for dialogue and cooperation in these areas in order to leverage European efforts.

Item

Traumatic Brain Injury [TBI] - Traumatic Brain Injury [TBI].—The Committee understands that current brain imaging technology is inadequate to accurately characterize the various degrees of TBI. The Committee urges support for the development of new brain imaging technologies to address this challenge.

Action taken or to be taken

Advances in brain imaging have dramatically improved clinical care for civilians and military personnel with moderate and severe traumatic brain injuries (TBI). However, NIH recognizes

the need for further improvements in TBI imaging, especially for mild TBI, which is the most common TBI and is usually not detectable with current imaging methods. Thus, NIH supports extensive research through both extramural and intramural programs on the development of advanced imaging technologies and their application to TBI. Among ongoing research, more powerful magnetic resonance imaging devices are improving resolution and signal to noise of brain images for TBI, and techniques such as diffusion tensor imaging, susceptibility weighted imaging, and proton magnetic resonance spectroscopy are showing promise to detect injury in tissue that appears normal in conventional imaging, especially disruption of nerve fiber connections. Spectroscopic imaging methods and molecular probes are revealing biochemical changes in the brain following TBI and enabling researchers to study specific cell types, such as those that contribute to inflammation or may be transplanted therapeutically. Across all types of imaging, advanced computational methods are improving detection and measurement of changes in the brain, and investigators are working to make research techniques suitable for routine clinical use, e.g. by reducing the time required to image a patient using advanced methods. Researchers are applying the growing array of imaging methods to address key problems in TBI research. Among these issues are improving diagnosis of mild TBI that conventional imaging does not detect, clarifying how nerve connections within the brain are disrupted following TBI and change as recovery progresses, studying how mechanical forces displace and distort the brain during TBI, and measuring the effectiveness of therapies.

In addition to studies by individual investigators, imaging is an integral aspect of major NIH initiatives on TBI. The NINDS Common Data Elements (CDEs) for TBI, co-sponsored by other agencies including the Departments of Defense (DOD) and Veterans Affairs, engaged a broad range of experts from the scientific and clinical community to establish standards for the collection of TBI data. NINDS published the first version of TBI CDEs in 2010, and a second version in 2012 extended the relevance to all ages, severity of injury, and phases of recovery. These standards facilitate clinical and imaging comparisons across studies. NIH and DOD together led development of the Federal Interagency TBI informatics system (FITBIR) to facilitate collaboration and sharing among qualified investigators. FITBIR supports sharing of imaging data linked to relevant clinical information. Imaging is an important aspect of the new International Traumatic Brain Injury Research Initiative, a large observational study that is exploring diagnosis, classification, and effectiveness of current care practices to improve care and pave the way for future clinical trials. The development of diagnostic imaging for TBI is also a major research focus of the Center for Neuroscience and Regenerative Medicine, which is a collaboration between the NIH intramural research program and the DOD, including the Walter Reed National Military Medical Center. NIH is also collaborating with the Foundation for NIH Sports and Health Research Program, which was established with a major donation from the National Football League. Applying imaging to questions related to repetitive mild TBI in sports is a key component of this program.

Item

Tuberous Sclerosis Complex [TSC] - The Committee continues to encourage NIH to coordinate a multi-Institute approach to finding a cure for TSC. NINDS and NCATS should play leading roles, given the promising translational potential of new therapeutics for treating the neurological conditions of TSC, including autism and epilepsy. Other Institutes involved in this collaborative effort should include NCI, NIAMS, NHLBI, NIDDK, NINDS, NICHD, and NIBIB, as well as ORDR.

Action taken or to be taken

TSC1 and TSC2, the genes mutated in tuberous sclerosis complex (TSC), are part of the mTOR signaling pathway, which regulates cell growth and other processes throughout the body. Because TSC leads to tubers, or tumor-like growths, and other complications in multiple organ systems, including the nervous system, eyes, heart, kidney, skin, and lungs, several NIH Institutes and Centers support research to understand and develop treatments for the condition. To promote communication and coordination across NIH, NINDS leads a trans-NIH TSC working group with members from NCI, NHGRI, NHLBI, NIAMS, NICHD, NIDDK, NIGMS, NIMH, and ORDR within NCATS, as well as patient organizations and the Department of Defense Congressionally Directed Medical Research Program on TSC. The next working group meeting is planned for winter 2014. Collaboration across NIH has also included joint support for scientific conferences on TSC and participation in the fall 2013 funding opportunity for the Rare Diseases Clinical Research Network led by NCATS, which was open to all rare diseases.

NINDS and NICHD support research to understand disease mechanisms in TSC and develop treatments for associated neurological conditions. Researchers are using TSC animal models and patient-derived tissue and cells to study genetic and cellular factors involved in tuber growth and other disruptions in neural development that contribute to autism, epilepsy, and cognitive impairment. Another NICHD-funded study explores the neurological control of sleep, which is altered in 50-90 percent of children with TSC and affects cognition, daytime behavior, and seizure control. Toward treatments for TSC, NINDS funds preclinical research to assess gene therapy in TSC mouse models and to determine whether combining the diuretic bumetanide with antiseizure drugs may be an effective treatment for epilepsy in TSC. In clinical research, NINDS supports efforts to identify early brain imaging and electroencephalography (EEG) biomarkers of autism and epilepsy in infants and children with TSC, including studies within the NIH Autism Centers of Excellence program. Such markers could facilitate development and testing of early interventions for individuals at risk, and investigators are already establishing infrastructure for future clinical trials of treatments to prevent the development of epilepsy in TSC. An Intellectual and Developmental Disabilities Research Center funded by NICHD also provides core services for clinical and translational research, cellular imaging, and mouse behavior testing for NIH and non-NIH studies on TSC. These include NINDS-funded biomarker studies, a non-NIH project on autism and other neurobehavioral abnormalities in children and TSC mouse models, and a

clinical trial with nongovernmental and industry support to assess the safety and efficacy of mTOR pathway inhibitors for the treatment of cognitive deficits in children with TSC.

Beyond neurological aspects, better understanding how mutations in TSC1 and TSC2 lead to abnormalities in other organ systems will provide additional targets for intervention in TSC and related conditions. For example, NIDDK sponsored a workshop on “TSC, mTOR, and Chronic Kidney Disease” in June 2013. Leading experts on kidney disease in TSC highlighted challenges in developing a translational research program for treating kidney tumors and cysts that are a common feature of TSC. Priorities identified included better imaging modalities to monitor cyst growth, early intervention studies, the identification of biomarkers, and studies of the natural history of the disease. NHLBI supports research on lymphangioliomyomatosis (LAM), a progressive, rare lung disease caused by TSC gene dysfunction. Projects underway focus on improving LAM treatment, including basic research on key pathways and mechanisms regulated by the TSC2 gene. As another example, NIAMS supports research on how the loss of TSC2 promotes skin regeneration, which will inform strategies for treating severe skin wounds and yield insights into disease mechanisms in TSC, including those contributing to skin lesions.

Conference Significant Items

Item

Kennedy’s Disease - Continued research in this area is encouraged to better understand the causes of this disease, along with animal testing for possible avenues for treatment. The National Institute of Neurological Disorders and Stroke shall provide an update on the state of the science in the fiscal year 2015 budget justification.

Action taken or to be taken

Basic research has driven encouraging progress in understanding Kennedy’s disease (also known as spinal bulbar muscular atrophy, or SBMA) and in developing rational strategies for treatment. The discovery of the genetic error that causes SBMA implicated a defect in the androgen receptor, a protein that enables cells to respond to testosterone-related hormones. Since the discovery of the gene defect, researchers have made considerable progress in revealing step by step how the mutant protein damages nerve and muscle cells, leading to the progressively disabling, and even fatal, muscle weakness of the disease. Randomized, placebo-controlled clinical trials have not yet found a therapy that significantly slows the course of SBMA. However, trials, including those at the NIH Clinical Center, have provided key information on the disease course and manifestations that is guiding the design of future clinical trials.

NIH continues to support research to better understand SBMA and develop treatments through both extramural and intramural research programs. At the most basic level, scientists are studying how testosterone-related hormones affect the development and function of the nervous system. More directly focused on SBMA, several extramural grants are developing better animal

and cell models of the disease. These researchers are investigating specific molecular steps by which the gene defects in SBMA lead to the disease and testing whether these steps present targets for intervention to halt SBMA, with promising results in animal models.

Complementing the extramural program, the NINDS Intramural Research Program continues to be a leader in SBMA research. In addition to laboratory studies on the mechanisms of SBMA, intramural researchers are conducting clinical trials of interventions. Intramural researchers recently completed a clinical trial to test whether an exercise program can improve strength, function, or quality of life in people with SBMA. Intramural researchers will soon begin a phase II clinical trial to test the safety, tolerability, and efficacy of a drug under development by a pharmaceutical company, which reflects how progress from NIH-funded research is now engaging biotech and pharmaceutical companies to develop safe and effective treatments for SBMA.

As research advances, the relationships among diseases are becoming increasingly apparent, and research not focused on SBMA may also promote progress against this disease. SBMA was the first disease found with a type of gene defect called a triplet repeat expansion, that is, an abnormal repetition of a three letter sequence of the gene code. At least 9 diseases are now known to share the same repeat in different genes, and other triple repeat mutations cause at least 15 other diseases. More broadly, the gene defect in SBMA causes certain proteins to aggregate in an abnormal way, which contributes to the disease progress. Abnormal protein aggregation is similarly implicated in Alzheimer's, Parkinson's, Huntington's, ALS, and several other neurological disorders. These and other similarities among diseases illustrate how research on a single neurological disorder both informs and is informed by research on others. Similarly, research in cross-cutting areas including gene therapy, stem cells, natural nerve cell survival factors, and antisense therapies (which turn off specific genes) may drive progress against SBMA and many other diseases.

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National Institute of Allergy and Infectious Diseases (NIAID)

Senate Significant Items

Item

Antibiotic-Resistant Infections - The Committee remains concerned about the need to develop and approve new antibiotics. The Committee urges NIAID to facilitate, through its new antibiotic-resistant bacterial infections clinical research infrastructure, studies that lead to new endpoints for serious and life-threatening infections caused by multidrug-resistant pathogens, and in particular hospital-acquired and ventilator-associated bacterial pneumonias. NIAID also should support research leading to a better understanding of the natural history of pneumonia and other antibiotic-resistant infections.

Action taken or to be taken

The NIAID extramural and intramural research programs support and conduct a broad portfolio of research to combat antimicrobial resistance, including basic research on how microbes develop resistance, studies to translate laboratory findings into potential treatments, and clinical trials to evaluate vaccines and therapeutics against drug-resistant microbes. NIAID continues its efforts to shift the paradigm for antimicrobial drug development from a “one bug, one drug” model to focus on the discovery and testing of broad-spectrum therapies that could be applied against multiple pathogens including drug-resistant healthcare-associated bacterial strains.

With input from the global antimicrobial resistance research community, NIAID recently launched the Antibacterial Resistance Leadership Group (ARLG) to develop and implement a research agenda addressing key clinical questions in the origin, diagnosis, and treatment of antibacterial resistance. These research priorities will be investigated using existing clinical trials infrastructure, including NIAID’s Clinical Trials Units of the HIV/AIDS Clinical Trials Networks and the Vaccine and Treatment Evaluations Units. Studies conducted by the ARLG may include clinical testing of new drugs to treat multidrug-resistant Gram-negative bacteria and diagnostic devices for antimicrobial resistance, evaluation of antimicrobial stewardship programs to encourage better use of these drugs, and optimization of treatment regimens to reduce the emergence of resistance. Study findings may inform our understanding of appropriate clinical endpoints to assess new therapies to combat multidrug-resistant infections.

NIAID-funded studies are investigating novel drug classes, new members of existing drug classes, and innovative therapeutic approaches, such as vaccines to prevent drug-resistant infections, monoclonal antibodies, and compounds designed to make existing drugs more effective against resistant organisms. NIAID offers preclinical services including *in vitro* screening tools and animal models in order to foster drug development by academic and industry partners. NIAID also leads an integrated NIH intramural research effort to address antimicrobial resistance that includes the NIH Clinical Center, NHGRI, NCATS, NIDDK, NCI, and NIMHD,

with an initial focus on hospital-acquired bacteria, particularly carbapenem-resistant *Klebsiella pneumoniae*. The investigators aim to identify novel mechanisms and drug targets for resistant organisms; conduct epidemiologic and genomic characterization of drug-resistant pathogens; develop improved diagnostics, drugs, and vaccines; and investigate clinical interventions for serious and life-threatening drug-resistant infections. In addition, NIAID pursues efforts to prevent *Staphylococcus aureus* infections, including drug-resistant infections, using vaccines. Partnering with academic researchers and small businesses, NIAID offers preclinical services to support vaccine development and has held workshops in 2010 and 2013 to advance the field.

NIAID currently is supporting multiple clinical trials aimed at identifying ways to decrease the risk of antimicrobial resistance by reducing and/or optimizing the use of licensed antibacterial drugs. Strategies employed in this effort include shorter courses of drug treatment, combination drug therapies, the use of diagnostics to identify the most effective therapies, and the employment of non-antibiotic treatment strategies. Two trials are investigating the optimal treatment of ventilator-associated pneumonia caused by multidrug-resistant Gram-negative infections. These trials will contribute to greater understanding of multidrug-resistant pneumonia and may identify strategies applicable to other antibiotic-resistant infections. The clinical, microbiological, and pharmacodynamic endpoints in these studies are being evaluated and may inform future research on antimicrobial resistance.

Item

Autoimmune Diseases - The Committee urges NIAID and the Autoimmune Disease Coordinating Committee to establish programs to investigate common biological pathways of autoimmune diseases and potential therapies that can broadly prevent and treat them. The Committee requests an update on NIAID's current activities and plans for additional research in the fiscal year 2015 congressional budget justification.

Action taken or to be taken

NIAID has a longstanding commitment to basic, translational, and clinical research on autoimmune diseases, such as type 1 diabetes, rheumatoid arthritis, and inflammatory bowel disease. NIAID-supported research to understand the immune system and its role in the development of autoimmune diseases includes the identification of common biological pathways among these disorders that will be critical to development of therapies to prevent and treat them.

NIAID funds a diverse portfolio of extramural research initiatives and investigator-initiated research relevant to autoimmune disease pathogenesis. This includes development of animal models; identification of genes, biological pathways, and environmental factors contributing to autoimmune disease; and clinical testing of therapies that modulate the immune system and restore immune tolerance. NIAID research collaborations with other NIH Institutes and Centers (ICs) are central to this effort. The NIH Autoimmune Diseases Coordinating Committee, chaired

by NIAID, is a forum for discussion among the NIH ICs, other federal agencies, and private advocacy groups to identify common research gaps and opportunities.

The Immune Tolerance Network (ITN), which evaluates novel, tolerance-inducing therapies in autoimmune diseases, also conducts mechanistic research to understand the common biological pathways of immune-mediated diseases. In fiscal year (FY) 2013, an ITN clinical trial showed that rituximab is as effective as standard therapy for anti-neutrophil cytoplasmic antibody-associated vasculitis, a devastating blood vessel disease. Results from this trial informed Food and Drug Administration approval of rituximab, the first licensed therapy for this disease in 40 years. Recently, the ITN developed TrialShare, a public-access data-sharing portal to encourage testing of additional autoimmune disease research hypotheses by providing access to ITN study data and analyses. In FY 2014, the NIAID will re-compete the ITN.

NIAID and its partners, the NIH Office of Research on Women's Health and NIDDK, support the Autoimmunity Centers of Excellence (ACE). The Centers conduct collaborative basic and clinical research on autoimmune diseases, including clinical trials of immunomodulatory therapies for lupus, Sjögren's syndrome, and ulcerative colitis. NIAID will re-compete the ACE in FY 2014, soliciting separate applications on basic science and clinical trials. NIAID and NIDDK also fund the Cooperative Study Group for Autoimmune Disease Prevention, which is identifying common and disease-specific mechanisms of autoimmunity that will lead to novel pathways and methods to predict autoimmune disease and prevent its development.

The NIAID intramural research program is exploring the genetic, environmental, and immune factors that may influence how T cells become auto-reactive and lead to autoimmune disease. NIAID investigators are developing new treatments that will specifically target these auto-reactive T cells. Other NIAID scientists are studying the function of immune cells called T regulatory or Treg cells, which suppress auto-reactive T cells. Better understanding of Treg cells will help determine whether these cells, or therapies that regulate their function, can be used to treat autoimmune diseases.

Through support for basic, translational, and clinical research on immune-mediated diseases, NIAID is learning more about the underlying mechanisms of these diseases and is working to develop new treatments to prevent and reduce the burden of these illnesses. Public and private collaborations will be crucial to discovering paths toward autoimmune disease prevention and treatment.

Item

Drug Allergy - The Committee commends NIAID for leading a recent workshop to develop a research agenda on the diagnosis and management of patients with drug hypersensitivity. The Committee urges NCATS, NCI, NHLBI, NIAMS, and other relevant Institutes to collaborate with NIAID to support research in this area, as there is a critical need for better tools to predict patient drug allergies and for improved drug desensitization protocols. The Committee

encourages NIH to consider a multi-Institute, multidisciplinary collaborative effort in this area that might include support for centers of excellence as well as the development of a patient registry.

Action taken or to be taken

Drug allergy remains an important issue. NIAID has a longstanding commitment to basic, translational, and clinical research on allergic and immune-mediated diseases. These efforts have helped to inform our understanding of the mechanisms of allergic reactions, including those to medications, as well as the development of promising prevention and treatment strategies such as novel desensitization protocols.

Allergic reactions to drugs can vary from mild to severe. Severe and life-threatening drug reactions range from immunoglobulin E (IgE)-mediated anaphylaxis to blistering diseases such as toxic epidermal necrolysis. Drug allergy is caused by IgE- and non-IgE-mediated mechanisms. In some cases, genetics may play a pivotal role in development of drug allergy.

Desensitization to drugs can, in some cases, be achieved through administration of gradually increasing doses of the drug. Successful desensitization results in a reduced allergic reaction upon subsequent exposure to the drug. Desensitization has been studied extensively for other IgE-mediated allergies including reactions to pollen and to foods such as peanut, egg, and milk. Recent findings suggest that desensitization also is effective in certain cases of non-IgE-mediated drug allergy. Further research to better understand the mechanisms of desensitization for a variety of allergens is helping to inform the prevention and treatment of drug allergy.

Researchers are working to identify genetic susceptibilities that may contribute to certain drug allergies. With this genetic information, investigators are able to develop tools to predict allergies to specific medications, allowing at-risk patients to avoid these drugs. For example, screening for a particular genetically determined form of a highly variable protein can eliminate the risk of specific adverse reactions to the HIV drug abacavir.

In March 2013, NIAID sponsored the Drug Allergy Workshop. Participants from NIAID, NIAMS, NHLBI, NIGMS, NCI, and the Food and Drug Administration focused on the development of a prioritized research agenda for drug allergy. Following this successful workshop, NIAID plans to publish a manuscript outlining scientific gaps and recommended future directions for drug allergy research. NIAID will continue to explore with other NIH Institutes and Centers plans for moving forward on drug allergy research.

Item

Eosinophil-Associated Disorders - The Committee is pleased that NIAID recently convened the Task Force on Research Needs of Eosinophil-Associated Diseases [TREAD], which produced a research agenda to improve the diagnosis and treatment of these debilitating and often painful

diseases. The Committee urges NIDDK, NHLBI, NICHD, NIAMS, and NIMH to join NIAID's efforts to foster research in this area.

Action taken or to be taken

NIAID continues to conduct and support research to better understand, diagnose, and treat eosinophil-associated disorders. NIAID extramural researchers are exploring various aspects of eosinophilic gastrointestinal disorders (EGIDs) including eosinophilic esophagitis (EoE). As part of these efforts, NIAID, in conjunction with the American Partnership for Eosinophilic Disorders (APFED), coordinated the NIH Taskforce on the Research Needs of Eosinophil-Associated Diseases (TREAD). The TREAD is a working group of academic investigators and representatives from NIAID, NHLBI, NCI, NIDDK, and APFED. With sponsorship from NIAID and the NIH Office of Disease Prevention, the TREAD held a workshop in June 2012 and published a report outlining the basic and clinical research needs for eosinophilic disorders in the September 2012 issue of the *Journal of Allergy and Clinical Immunology*. In fiscal year 2014, NIAID will build upon this trans-NIH effort by releasing a Program Announcement to solicit basic and preclinical research to improve our understanding of eosinophilic-associated disorders, including EoE. NIAID program staff continue to communicate with other NIH Institutes to encourage their participation in this announcement.

NIAID and NIDDK continue to support the Consortium of Food Allergy Research (CoFAR) to develop new approaches to treat and prevent food allergy. A CoFAR project is examining the genetic mechanisms of food allergy-associated EoE. CoFAR also has established the Eosinophilic Esophagitis Databank that is recruiting patients with EoE to develop a research resource of clinical samples to help to identify and further characterize the genetic mechanisms underlying EoE. In addition, an NIAID-funded investigator has completed a pilot clinical trial to determine the efficacy of swallowed glucocorticoids for the treatment of EoE. Data for this trial are being analyzed, and publication of these research results is expected early next year.

NIAID intramural researchers are exploring novel treatments for eosinophilic disorders in clinical trials and collecting clinical samples from more than 350 patients with eosinophilic disorders. These samples are examined in trans-NIH collaborative research. Efforts include an NIAID-NIDDK partnership to characterize immune cells in patients with EGIDs; an NIAID-NCI effort to develop biomarkers for hypereosinophilic disorders; an NIAID-NHLBI collaboration to evaluate diagnostic imaging for heart problems in eosinophilic disorders; and an NIAID-NIAMS collaboration to study biomarkers and novel therapies for eosinophilic granulomatosis with polyangiitis, a systemic inflammation in blood vessel walls that can be life-threatening.

A number of other NIH Institutes and Centers also are pursuing research on eosinophil-associated disorders. NHLBI funds laboratory research on the role of eosinophils in the pathobiology of asthma and clinical trials comparing asthma treatments in patients with and without eosinophilic inflammation. In addition, NHLBI supports studies on eosinophilic

myocarditis, inflammation of the heart muscle. NIDDK supports basic, translational, and clinical studies on the causes and treatments of EGIDs. NIAMS-supported research examines the role of white blood cells called eosinophil leukocytes in immune-mediated blistering skin conditions, with the goal of developing treatments for these disorders.

Item

Food Allergy - The Committee is aware of the promising research on oral immunotherapy being funded by the Consortium of Food Allergy Research [CoFAR]. The Committee strongly urges NIAID to increase both the budget for and the number of institutions funded by CoFAR when the program is renewed. In addition, NIH should initiate other mechanisms of support for research and career development of investigators focused on food allergy research. The Committee also encourages NIAID to continue its public-private partnerships in support of complementary clinical immunological, immunomodulator, mechanistic, and genetic studies with private donors and foundations as components of ongoing food allergy clinical trials.

Action taken or to be taken

NIAID remains dedicated to supporting research to understand the causes of food allergy and to develop better treatments to address it. Between fiscal years (FY) 2003 and 2012, NIAID increased its investment in food allergy research from \$1.2 million to \$25.3 million. Through targeted initiatives, NIAID has encouraged new investigators to enter the field of food allergy research. NIAID support for extramural food allergy research includes investigator-initiated basic and translational research as well as clinical research networks that conduct accompanying mechanistic studies. NIAID intramural scientists also direct research on food allergy and its cellular and genetic mechanisms. Trans-NIH and public-private collaborations, including with the non-profit Food Allergy Research and Education (FARE), are an important component of NIAID's food allergy research program.

The Consortium of Food Allergy Research (CoFAR), sponsored by NIAID and NIDDK, is developing new immunotherapeutic approaches to prevent and treat immunoglobulin E (IgE)-mediated food allergy, including anaphylaxis caused by food allergy. In addition to a study on the natural history of food allergy, CoFAR investigators are conducting four clinical trials to determine the safety and efficacy of immunotherapy. These trials include two egg oral immunotherapy (OIT) studies in children with egg allergy, immunotherapy with peanut extract placed under the tongue in children and adults with peanut allergy, and peanut immunotherapy applied via skin patch in children and adults with peanut allergy. Previous CoFAR investigations have shown that egg OIT has a beneficial effect in children with egg allergy, and that peanut extract placed under the tongue induces modest, short-term therapeutic improvement in some teenagers and adults with peanut allergy. NIAID is in the early planning stages for the renewal of the CoFAR program, scheduled for FY 2015.

The NIAID Immune Tolerance Network (ITN), with support from FARE, is conducting a clinical trial to test if regular peanut consumption begun early in infants at risk of peanut allergy can prevent the development of this allergy by age 5. Another ITN trial is assessing whether peanut OIT can induce tolerance and desensitization in children with peanut allergy. Mechanistic studies are an integral component of ITN research. NIAID will re-compete the ITN in FY 2014. In addition, the NIAID Asthma and Allergic Diseases Cooperative Research Centers are supporting clinical trials of milk OIT and omalizumab (anti-IgE) for the treatment of milk allergy and peanut OIT in teens and adults with peanut allergy.

The NIAID intramural research program is working to identify the genetic components of food allergy and to characterize newly identified T cells that contribute to the development of eosinophilic gastrointestinal disease (EGID), a type of food allergy. Ongoing NIAID intramural clinical trials include a Phase I trial of the immunomodulator sirolimus in EGID.

In 2012, NIAID sponsored a workshop on allergen immunotherapy attended by experts in clinical research and basic and translational immunology. Participants underscored the importance of continuing to develop and test immunotherapeutic approaches to treat or prevent food allergy, but were unable to identify one approach that was superior to any other, indicating further research is necessary. NIAID and its CoFAR and ITN investigators are exploring partnerships to conduct immunological/mechanistic studies as components of privately supported clinical trials of food extracts and drugs to treat or prevent food allergy.

Item

Hepatitis B - While hepatitis B is preventable as a result of a safe and effective vaccine, this disease is not currently curable for those who are already infected. An estimated 800,000 to 1.4 million Americans are infected with hepatitis B and most do not know it. The Committee urges NIH to move aggressively to research a cure. In particular, the Committee urges more work in antiviral drug development and continued support and use of appropriate animal models to study the disease.

Action taken or to be taken

Hepatitis B virus (HBV) infection continues to be an important public health concern. In the United States, there are an estimated 38,000 new HBV infections each year, with chronic HBV-related cirrhosis and liver cancer leading to more than 3,000 deaths annually. NIH maintains significant investment in both basic and translational research on HBV, including efforts that could lead to improved therapeutics and inform research towards a cure.

NIDDK continues to support research efforts in HBV, including new studies through the Hepatitis B Research Network, which conducts clinical trials in both adults and children with HBV. The Network was established in 2008 to study the natural history and pathogenesis of chronic HBV and develop improved treatments with combinations of currently available

therapies. NIDDK, along with NIAID, also is partnering with small businesses to advance the development of diagnostics and treatments for hepatitis viruses, including HBV.

NIAID supports the scientific progress on HBV antiviral drugs and therapeutics through a variety of mechanisms. NIAID intramural investigators are collaborating with pharmaceutical companies to advance the development of improved HBV therapeutics. NIAID researchers are partnering to characterize a promising candidate HBV vaccine. The vaccine candidate, which targets three HBV antigens, could be used as a therapeutic vaccine to treat patients already infected with HBV. NIAID scientists also are assisting in ongoing industry efforts on improved treatments for chronic HBV. These include a multicenter study of the novel drug GS-9620 and clinical trials to test the safety, efficacy, and tolerability of the oral drug GS-7340.

NIAID extramural grant funding provides support for a number of approaches to HBV antiviral drugs, including novel classes of antiviral drugs that work by different mechanisms than currently licensed HBV polymerase inhibitors. NIAID also offers a broad array of preclinical and clinical research resources and services to academia and industry to bridge gaps in the product development pipeline. For example, NIAID supports contracts to conduct *in vitro* screening of candidate drugs against HBV. In fiscal year 2013, 215 compounds were screened for HBV antiviral activity. In addition, two NIAID HBV animal model contracts provide researchers with access to an HBV transgenic mouse model and a woodchuck HBV infection model. These animal model resources are used to evaluate promising new antiviral drugs, as well as agents to stimulate host immune responses to combat HBV infection.

NIAID will continue to support use of these animal models as important tools to study HBV. In addition, NIAID will pursue research to better understand the genetic, environmental, and immune influences on HBV infection, replication, and persistence in chronic carriers. In conjunction with industry partnerships for screening and preclinical development of HBV antiviral drugs, NIAID will sustain efforts to develop novel drugs, therapeutics, and vaccines to address chronic HBV infection.

Item

Influenza Antivirals - The Committee encourages NIAID to invest in research on new antiviral drugs that are easy to use and effective against emerging drug-resistant influenza variants, as well as influenza diagnostics. NIAID should give special consideration to treatment for the pediatric and obstetric populations.

Action taken or to be taken

Every year in the United States, more than 200,000 people are hospitalized and thousands die from influenza-related complications. Increasingly, circulating strains of seasonal influenza have become resistant to certain antiviral medications used to treat influenza. NIAID supports research to identify new influenza therapeutics that are safe, effective, easy to use, and targeted

to limit the emergence of resistance. This effort complements NIAID's work to develop better influenza vaccines, including universal influenza vaccines that could potentially target multiple strains over several years. All aspects of NIAID influenza research include consideration for the needs of high-risk populations such as the elderly, immunocompromised, children, and pregnant women.

NIAID also pursues the development of improved diagnostics that are critical to the rapid identification of both seasonal and pandemic influenza strains to facilitate use of strain-specific antiviral therapies. NIAID supports basic, preclinical, and early-stage clinical research to identify new influenza antiviral therapies. In fiscal year (FY) 2013, NIAID supported *in vitro* testing of 263 compounds for their efficacy against several influenza strains; 41 of these were selected for follow-up studies, including 25 that were evaluated in influenza animal models. Promising candidates will continue to move along the product development pipeline.

Through partnerships with industry, NIAID has supported preclinical investigation and early-stage clinical trials of several new antiviral drugs. A number of these employ novel strategies that could help to limit emergence of resistance, such as treatments designed to prevent influenza from attaching to host cells or producing infectious viral particles. Several treatments have been selected for additional development by federal partners including the Biomedical Advanced Research and Development Authority and the Department of Defense. Notably, NIAID extramural research support contributed to a recent success in treatment of influenza in children. Results from an NIAID-funded Phase I/II clinical trial of the antiviral drug Tamiflu® helped to define pediatric dosages and contributed to the December 2012 Food and Drug Administration approval of Tamiflu® for treating influenza in children as young as two weeks old.

NIAID intramural scientists leverage existing research networks to partner with influenza researchers on studies of innovative influenza treatments, including in pediatric and obstetric populations. For example, NIAID is exploring the use of hyperimmune plasma therapy in children and adults, including pregnant women. NIAID intramural investigators are using animal models to test a novel immune-based treatment that has shown promise against influenza strains resistant to the currently available antiviral drugs and to test an antiviral drug targeting both influenza replication and inflammation in order to limit severe disease. NIAID scientists also are conducting a Phase I clinical trial of a compound with activity against both sensitive and drug-resistant strains of influenza A.

NIAID is planning two initiatives in FY 2015 to target influenza through its collaborative, multidisciplinary *NIAID Partnerships Program*. One of the planned initiatives will support the development of new influenza diagnostics; the other will focus on the discovery and development of novel therapies for multiple strains of influenza A, including drug-resistant influenza. NIAID will continue to pursue promising approaches to improve the diagnosis and treatment of influenza. In conjunction with ongoing basic research and novel strategies in

influenza vaccination such as universal influenza vaccines, NIAID will sustain efforts to address the public health challenge of seasonal and pandemic influenza.

Item

Microbicides - The Committee encourages NIAID to continue coordination with USAID, the State Department, and others to advance the development of antiretroviral-based microbicides.

Action taken or to be taken

NIAID remains committed to the pursuit of safe and effective interventions, including microbicides, to prevent HIV infection. NIAID works collaboratively with the NIH Office of AIDS Research (OAR), other NIH Institutes and Centers (ICs), and external partners to advance the development of antiretroviral (ARV) and non-ARV-based microbicides. Key external partners in this effort include the U.S. Agency for International Development (USAID), the Department of State, the Centers for Disease Control and Prevention (CDC), and non-governmental entities, such as the International Partnership for Microbicides (IPM), the Centre for the AIDS Programme of Research in South Africa, CONRAD, and the Bill and Melinda Gates Foundation (BMGF).

NIAID supports preclinical and early clinical research to generate a sustainable pipeline of innovative microbicide products for clinical testing. NIAID's preclinical research program funds a broad range of academic and public-private partnerships and collaborative activities with multiple partners including USAID and the BMGF. Notable efforts include basic research to inform improved design of microbicide and other HIV prevention strategies, the development and early clinical evaluation of ARV-based microbicide gels that can be used by both men and women, and the development of alternative microbicide delivery methods including films, intravaginal rings, and suppositories.

NIAID, with NICHD and NIMH, collaborates with external partners to test promising microbicides for safety and effectiveness through the NIH-funded Microbicide Trials Network (MTN). The MTN is pursuing alternate approaches to address the results from the MTN Vaginal and Oral Interventions to Control the Epidemic (VOICE) study, which found that daily use of a vaginal microbicide gel or an oral ARV tablet was not a successful approach to HIV prevention for the women in the study. Since uptake of daily product use was low in VOICE, other strategies are being tested. MTN is currently conducting a Phase III trial to evaluate the safety and effectiveness of an intravaginal ring (IVR) containing the ARV dapivirine, an approach which does not require daily use of a product. MTN is working with IPM to harmonize data collection and safety parameters between this MTN study and a similar trial sponsored by IPM, the first trials to evaluate long-term sustained delivery of an ARV from an IVR. Coordination of these two trials will facilitate potential licensure of the dapivirine IVR should it prove safe and effective. Additional MTN trials are investigating the safety of tenofovir-based microbicides in men who have sex with men.

The OAR in the NIH Office of the Director facilitates collaboration among NIH ICs, including the development of the trans-NIH strategic plan for microbicides, as well as activities across the federal government. OAR established the Trans-Governmental Microbicides Coordinating Committee, consisting of representatives from NIH ICs, CDC, the Food and Drug Administration, the Departments of Defense and Veterans' Affairs, and USAID, to facilitate collaboration and coordination of microbicides research. In addition, OAR established the non-governmental Microbicides Research Working Group to advise NIH and other entities supporting microbicide research and development.

NIAID will continue to support and promote microbicides research to identify, develop, and evaluate new products, novel formulations and routes of administration, and promising approaches in diverse populations. NIAID and OAR will sustain successful collaborations within NIH and with USAID, the State Department, and a variety of non-governmental organizations in order to advance the development and evaluation of microbicides and other promising approaches to HIV prevention.

Item

Tuberculosis [TB] - The Committee continues to urge NIAID to expand its research into the development of new TB diagnostic tests, drugs, and vaccines to prevent, detect, and treat TB. In particular, the Committee encourages more research on developing shorter treatments for multidrug-resistant TB.

Action taken or to be taken

NIAID supports research in the United States and abroad on tools to prevent, diagnose, and treat tuberculosis (TB). These efforts are important to TB control in the face of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, as well as the challenge of TB/HIV co-infection.

In July 2013, the Food and Drug Administration (FDA) approved Cepheid's Gene Xpert MTB/RIF test to detect TB bacteria and resistance to the antibiotic rifampin. This rapid test developed with NIAID support is accelerating diagnosis of TB and drug-resistant TB worldwide. NIAID is working to expand use of the test to identify XDR TB within public health settings. In addition, the NIAID-supported TB Clinical Diagnostic Research Consortium is evaluating five early-stage diagnostic tests, including tests to identify drug-resistant TB and TB in children. Investigators funded by NIAID are collaborating with the Centers for Disease Control and Prevention (CDC) to improve tests to detect increasing resistance to pyrazinamide, a first-line TB drug. Researchers are evaluating new gene-based tests that could rapidly identify pyrazinamide resistance and inform design of regimens for MDR and XDR TB.

NIAID also funds research to discover new drugs and refine treatments for TB, including MDR and XDR TB. NIAID is supporting continued development of Sirturo, the first drug approved by

the FDA to treat MDR TB. New drug formulations, including those that can be inhaled, may help to expand treatments available for drug-resistant TB. For example, NIAID-funded research is evaluating pyrazinoic acid, the active form of pyrazinamide, for use as an inhaled drug. This formulation of the drug may be effective against pyrazinamide-resistant MDR and XDR TB. NIAID also is pursuing shorter courses of treatment for TB. NIAID is participating in a Phase III clinical trial sponsored by the Global Alliance for TB Drug Development to evaluate shortened TB treatment regimens containing moxifloxacin. Another NIAID-funded clinical trial is evaluating one-month courses of isoniazid and rifapentine to prevent re-activation of latent TB with HIV co-infection.

In addition to pursuit of new and improved TB therapies, NIAID is working to develop safe and effective vaccines to prevent TB. NIAID has supported the development of eight of the 13 TB vaccine candidates currently in clinical trials worldwide. In collaboration with Aeras and industry partners, NIAID is conducting a Phase I/II study to evaluate the safety and efficacy of a TB fusion protein vaccine given as a boost to the existing TB vaccine, BCG, in HIV-uninfected infants.

The NIAID intramural research program has an active research portfolio to address MDR and XDR TB. NIAID has developed collaborations in South Korea and China to pursue clinical studies of two new drugs for use against drug-resistant TB. With FDA approval of Sirturo for MDR TB, and NIAID's recent finding that linezolid is effective against XDR TB, NIAID also is investigating the possibility that combining these two therapies can lead to a six-month curative regimen for MDR TB. Working with Chinese and Korean officials, NIAID scientists plan to begin a clinical trial to explore shortening treatment duration in patients with MDR TB in 2014.

NIAID will continue to support TB research to increase basic understanding of the infection and to develop new diagnostic tests, drugs, and vaccines to prevent and treat TB. NIAID's efforts will lead to improved TB therapies, including shortened courses of treatment, and address the public health challenges of TB/HIV co-infection and drug-resistant TB.

Conference Significant Items

Item

Valley Fever - The upcoming joint NIH and CDC efforts to combat this disease are supported, which includes a field state of the science meeting and workshop. Specifically, the NIH and CDC are encouraged to work together to identify and intensify research into scientific gaps and to maximize public-private partnerships toward the development of a coccidioidomycosis vaccine and more effective treatments, which may include conducting a randomized controlled trial. The NIH shall provide an update in the fiscal year 2015 budget request that outlines the joint NIH and CDC recommendations, on-going efforts, and coordinated plans to further progress towards an effective Valley Fever treatment and vaccine.

Action taken or to be taken

Coccidioidomycosis (Valley Fever) is a fungal infection caused by airborne spores of two soil-dwelling *Coccidioides* species. The Centers for Disease Control and Prevention (CDC) reported over 22,000 Valley Fever cases in 2011, primarily in the southwestern United States. In most people, Valley Fever causes a mild, influenza-like illness. Many exposed to *Coccidioides* never develop disease. However, in some, the fungus disseminates throughout the body, causing serious illness, disability, or death. Clinicians may take a “watch and wait” approach to treating Valley Fever, and many people are never treated for Valley Fever or do not begin treatment until the disease worsens. Therapies for those with severe disease, while relatively effective, do not fully eradicate the fungus and the disease may return once the therapies are stopped. There is a need for better diagnostics to rapidly identify *Coccidioides* infection and determine when to initiate appropriate treatment, as well as a need for therapeutics to eliminate the fungus.

The National Institute of Allergy and Infectious Diseases (NIAID) of the NIH supports an array of research and outreach activities to improve the prevention and treatment of Valley Fever. NIAID intra- and extramural basic and clinical research is informing understanding of the disease, including why some populations are more likely to develop life-threatening illness. NIAID intramural researchers recently conducted an epidemiological study that identified African ancestry as an important risk factor for disseminated Valley Fever. Evidence also suggests that individuals of Filipino ancestry, the elderly, and those who work outdoors are more likely to be infected or more severely affected. NIAID scientists have discovered genetic mutations in some patients with disseminated disease that provide clues to Valley Fever susceptibility and severity, and insight into potential treatments.

NIAID continues to support the development of a promising new antifungal drug, Nikkomycin Z, for treatment of pneumonia caused by *Coccidioides*. The Institute also funds grants to develop diagnostics for *Coccidioides* infection to better guide treatment. NIAID encourages investigator-initiated research and industry partnerships aimed at the development of a vaccine to prevent Valley Fever.

NIAID is developing a randomized clinical trial to evaluate the antifungal drug fluconazole versus the current standard treatment for community-acquired pneumonia caused by *Coccidioides*. CDC is collaborating by identifying patient enrollment sites for the trial, which will be conducted in regions of California and Arizona where Valley Fever is highly endemic. Partnerships with local healthcare providers, patient participants, and Valley Fever scientific experts will contribute to the progress of this trial. Enrollment in the trial is expected to begin in 2015. In addition, this year NIAID intramural researchers will implement a clinical protocol at the NIH Clinical Center in Bethesda, Maryland, to study patients with severe disseminated Valley Fever.

NIH is committed to developing better diagnostics, therapeutics, and vaccines for Valley Fever. As part of this effort, NIH will engage its Federal partners and the scientific, public health, and affected communities to advance Valley Fever research.

National Institute of General Medical Sciences (NIGMS)

Senate Significant Items

Item

Critical Care - The Committee recognizes that the burden associated with the provision of care for critically ill patients is expected to increase significantly as the population ages. The Committee encourages NIGMS, through the new Office of Emergency Care Research, to heed the recommendations of the Critical Care Societies Collaborative in developing future research directions on critical care.

Action taken or to be taken

NIH appreciates the Committee's recognition of the importance of critical care research. Housed within NIGMS, the newly established Office of Emergency Care Research (OECR) is designed to improve the health outcomes of patients who require emergency care by serving as the focal point for basic, clinical, and translational emergency care research and training across NIH.

Because OECR's role cuts across the mission of all NIH Institutes and Centers, the office will foster innovation and improvement in emergency care and in the training of future researchers in this field by:

- coordinating and catalyzing the development of new funding opportunities that involve multiple NIH Institutes and Centers;
- working closely with the NIH Emergency Care Research Working Group, which includes representatives from most NIH Institutes and Centers;
- organizing scientific meetings to identify new research and training opportunities in the emergency setting;
- informing investigators about funding opportunities in their areas of interest;
- fostering career development for trainees in emergency care research; and
- representing NIH in government-wide efforts to improve the nation's emergency care system.

With the arrival of its first permanent Director in July 2013, OECR has begun developing an NIH strategic plan for research and research training within the emergency care setting. In developing this strategic plan, NIH will consider recommendations from the entire stakeholder community, including recommendations developed by the Critical Care Societies Collaborative. In addition, NIH will seek ongoing stakeholder input as it develops its plan to advance critical care research and thus improve patient care.

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National Institute of Child Health and Human Development (NICHD)

Senate Significant Items

Item

Chromosome Abnormalities - The Committee commends NIH's efforts to categorize genes, which are useful for the diagnosis of chromosome abnormalities. The path to treatment requires a greater understanding of gene function as it relates to abnormal gene copy number. The Committee again asks NICHD to hold a state of the science meeting focused on strategies for devising treatments for nonrecurring as well as recurring gene copy number changes. The Committee further urges new funding to support other investigators of chromosome abnormalities, particularly those involving chromosome 18.

Action taken or to be taken

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) recognizes the importance of identifying and understanding genes that are sensitive to copy number changes and may cause some of the clinical features that occur with chromosome abnormalities. Down syndrome research has advanced our understanding of several critical genes that contribute to intellectual disability, increased susceptibility to development of Alzheimer's disease, and heart defects in this condition. Less is known about the vast number of "copy number variants" (CNVs - deletions or duplications of a sequence of genes that reside on a chromosome) that can occur in humans. NICHD funds studies and conference grants that explore the critical genes within CNVs that are associated with birth defects such as congenital diaphragmatic hernia, foot deformities, Hirschsprung disease, omphalocele, fetal anomalies, and intellectual disability. Other studies are aimed at correlating genes with physical manifestations in specific syndromes such as Angelman syndrome, Prader-Willi syndrome, Williams syndrome, and 22q11 deletion syndrome (velocardiofacial syndrome), with the ultimate goal of developing specific treatments and therapies. In addition, through the University of Massachusetts Intellectual and Developmental Disabilities Research Center, NICHD supports studies to silence the extra copy of the chromosome seen in conditions such as trisomy 13, 18, and 21. Efforts to collect and associate CNVs with clinical features are now well underway through what was once the International Standards for Cytogenomic Arrays (ISCA) Consortium, which includes a catalog of over 35,000 clinical cases, many with intellectual disability, developmental delay, and/or autism. Given rapid advances in whole genome and whole exome sequencing and increasing understanding of the effects of genetic changes, the ISCA Consortium has now become the International Collaboration for Clinical Genomics (ICCG) comprising 190 institutions (mostly clinical laboratories) and 2800 individual members, with an expanded focus to include sequence-level variation.

The ISCA/ICCG Consortium held state-of-the-science meetings in 2012 and 2013 that have led to the development of a larger Consortium led by the National Human Genome Research

Institute, the National Cancer Institute, and NICHD. This Consortium will expand the ICCG activities to include increased informatics capabilities for collecting and storing data on CNV and other variants, standardizing phenotyping, curation of these variants, and making them available to clinicians and investigators through a NIH-funded public web portal, “ClinVar,” that allows seeing whether a particular variant is relevant to a disease or condition.

Thus, given the rapid pace of gene mutation discovery and the burgeoning availability of highly accurate, sensitive, and cost-effective technologies to sequence the human genome, genomic sequencing is supplanting cytogenomic arrays for detection of CNVs. This sea change in sequence generation and data processing and interpretation is establishing a paradigm for understanding the role of genetic and genomic changes in the spectrum of human disease, and is providing a knowledge base that will inform the development of new diagnostics and therapeutics for many individuals with rare diseases, including contiguous gene conditions.

Item

Congenital Diaphragmatic Hernia [CDH] - The Committee encourages NIH to put a higher priority on CDH research. In particular, the Committee urges NHLBI to investigate the pulmonary effects of this birth defect and requests NICHD to support additional research on whether the timing of surgical repair to the diaphragm can increase an infant’s chances of survival. Along with ORDR, these two Institutes are also encouraged to promote greater research interest in CDH by supporting a scientific meeting on this condition.

Action taken or to be taken

Infants with Congenital Diaphragmatic Hernia (CDH) are born facing life-threatening breathing problems and other difficulties related to organ position and development. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports research on the basic biological processes underlying both normal development and anatomical and functional birth defects such as CDH. For example, NICHD funded a unique collaboration between basic scientists who study CDH and clinicians who work with CDH patients and their families that offers a novel way to study this complex condition. Clinicians conduct interviews and study staff collect specific biological samples from infants and children with CDH and their families. Researchers then subject the samples to sequencing and other genetic investigations to identify the genes most likely related to diaphragmatic development.

NICHD also is supporting a study looking at how pulmonary blood flow in the developing mouse embryo affects lung development, as a way to shed light on defects in lung development, including CDH. Understanding the mechanisms that underlie the lung defects in CDH using animal models could lead to more effective treatment options directed at disrupting those mechanisms and improving outcomes for long-term CDH survivors.

NICHD has long supported a network of researchers who conduct studies on various structural birth defects, including several who conduct research on CDH. In April 2013, NICHD hosted the ninth scientific meeting for these grantees to allow them to present research findings and share new ideas.

The National Heart, Lung, and Blood Institute (NHLBI) supports research on the effects of CDH on lung structure and function. The major effects of CDH on the developing lung are underdevelopment of the lung air spaces (pulmonary hypoplasia) and pulmonary hypertension, which can lead to severe morbidity and mortality. NHLBI-supported investigators are studying the role of genetic factors as determinants of lung structure and function in CDH. A gene called *Fog2* has been found to cause a diaphragmatic defect as well as pulmonary hypoplasia. NHLBI also funds studies of pulmonary blood flow and pulmonary vessel maturation in CDH. In addition to investigations of genetic contributions to CDH and lung hypoplasia, NHLBI-supported investigators are developing predictive models of CDH outcomes using imaging studies. The insights gained from these studies hold promise for further enhancing the care of patients with CDH.

While efforts by the National Center for Advancing Translational Sciences (NCATS) do not focus on any single disease or area, research supported by NCATS enables advances across all therapeutics areas. In August 2013, the NCATS Office of Rare Diseases Research and 10 other NIH Institutes and Centers reissued a Funding Opportunity Announcement to support collaborative, multi-site clinical research in rare diseases (RFA-TR-13-002). The Rare Diseases Clinical Research Consortia facilitates the identification of biomarkers for disease risk and severity, measures clinical trial outcomes, and encourages the development of new approaches to the diagnosis, prevention and treatment of rare diseases. This initiative welcomes applications from all rare disease research communities, including the CDH research community.

Item

Demographic Research - The Committee is pleased that NICHD's recent reorganization and Scientific Vision initiative reflect the integral role that demographic, or population, research plays in the Institute's mission. As such, the Committee urges NICHD to include the Population Dynamics branch in all appropriate research mechanisms and programs. Further, the Committee encourages NICHD to sustain its support of large-scale, longitudinal surveys, particularly the National Longitudinal Survey of Adolescent Health and the Panel Study of Income Dynamics Child Supplement Survey.

Action taken or to be taken

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)'s "visioning" process reiterated the importance of demographic research strategies to assess biological, physical, and social processes in families, communities, and populations to determine interventions to improve public health at all of these levels. The newly renamed

Population Dynamics Branch reflects the breadth of the Institute's interests in these areas of research.

Over the last year, new findings have shed light on a myriad of issues that confront families in their daily lives. For example, recent NICHD-funded research showed increasing educational disparities in mortality and life expectancy in the United States. Currently, among people 25 years and older, those who graduate from college can expect to live about ten years longer than those who did not graduate from high school, a dramatically greater difference than was observed in 1960. An analysis of an NICHD-supported data set, the National Survey of Family Growth, showed that women in the United States are increasingly likely to cohabit with male partners before marriage (from 34 percent in 1995 to 48 percent in 2010), and that almost a fifth of these women became pregnant in the first year of their first non-marital cohabitation. Other NICHD-funded research has shed light on the impact of stress, such as a natural disaster.

Research also demonstrates that the effects of poverty may be more pervasive than formerly believed. New studies supported by NICHD show that low socioeconomic status during childhood increases the risk of depression, chronic pain, or both in adulthood. Another study showed that moving from a high-poverty to lower-poverty neighborhood leads to long-term improvements in adult physical and mental health, and subjective well-being, despite not affecting economic self-sufficiency.

NICHD remains committed to investing in longitudinal studies that provide insight into how a myriad of factors affect children's development and health and well-being throughout life. Using data from NICHD's National Longitudinal Survey of Adolescent Health (Add Health), researchers recently found that gays, lesbians, and bisexuals (LGB) are more likely than heterosexuals, to be exposed to child abuse or housing adversity. Greater exposure to these and other types of adversities provides a partial explanation of the higher levels of suicide, depression, tobacco use, and symptoms of alcohol and drug abuse among LGB youths compared to heterosexuals.

NICHD continues its longstanding support of its Population Infrastructure Research Program, and of longitudinal population studies that yield data widely used by the scientific community to inform understanding of human populations and health, demographic change, and behavioral and social science. Encouraging young investigators in these fields is also a high priority. In April 2014, the NICHD plans to expand eligibility for pre-doctoral fellowships (Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellows) to include all areas of science supported by the NICHD, including research areas within the mission of the Population Dynamics Branch.

Item

Down Syndrome - The Committee applauds NIH for the establishment of the Down Syndrome Patient Registry. The Committee urges continued investment and development of the registry to

fully realize its potential as a tool to stimulate meaningful clinical trials and research. The Committee recognizes that investing in Down syndrome-focused research has the potential to benefit many other diseases and conditions such as Alzheimer's disease. Therefore, the Committee urges NIH to seek public-private partnerships aimed at developing preventive therapies for the dementia associated with both Down syndrome and Alzheimer's disease. The Committee remains troubled by the stagnant number of investigator-driven research awards given in the area of Down syndrome and supports efforts to increase the Federal investment. The Committee requests a status update in the fiscal year 2015 congressional budget justification. The Committee urges the NIH to continue to utilize the Down Syndrome Consortium as it updates and implements the NIH Down Syndrome Research Plan.

Action taken or to be taken

Down syndrome comprises a set of developmental and physical symptoms resulting from having an extra copy of Chromosome 21. Current studies include research on the basic risk factors for this condition, interventions to ameliorate symptoms throughout the lifespan, and possible treatments. Since 2007, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) has funded new research projects, including behavioral and social science research, renewed its major animal and tissue repositories for use by researchers across the country, sponsored scientific workshops, increased its public outreach and information dissemination, and established *DS-Connect™: the Down Syndrome Registry*. Although Down syndrome is a relatively common chromosomal abnormality, little information regarding health outcomes of affected low birth weight infants has been available. The NICHD Neonatal Research Network conducted a study to evaluate morbidity and mortality in very low birth weight infants with Down syndrome, finding that these infants had increased risks of necrotizing enterocolitis, late onset sepsis, and bronchopulmonary problems compared to typically developing, but low birth weight, infants. This information is useful to guide medical care for infants with Down syndrome and to better inform parents. NICHD also issued a series of Funding Opportunity Announcements seeking research grant applications on understanding and treating co-morbid conditions in adolescents with Down syndrome, and other issues faced by adolescents and their families as they transition to adulthood.

Through the National Institutes of Health (NIH) Down Syndrome Working Group, NICHD partners with other NIH Institutes and Centers to support and conduct a wide range of research, such as determining which of the extra genes on Chromosome 21 are responsible for cognitive deficits in Down syndrome, and achieving a better understanding of the link between Down syndrome and Alzheimer's disease. In 2013, the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging, NICHD, and several Down syndrome organizations co-sponsored a workshop, "Advancing Treatment for Alzheimer's Disease in Individuals with Down Syndrome," to discuss how best to integrate current research activities, research resources, and future opportunities to inform development of therapies. In addition, NINDS supports basic research on Down syndrome to understand the mechanisms that lead to

developmental and cognitive impairment and, later in life, to Alzheimer's disease-related neurodegeneration. This includes studies using mouse models to determine the roles of specific genes in cognitive disability. Such research points to potential targets for treatment. For example, previous research in a Down syndrome mouse model showed that inhibitory signaling through the neurotransmitter GABA was increased in certain brain circuits and that decreasing this inhibition improved cognitive function in the mice. NINDS supports a translational research project that aims to move the drug PTZ, known to decrease GABA-mediated inhibition, into human clinical trials for the treatment of cognitive impairment in Down syndrome.

NICHD leads the public-private Down Syndrome Consortium, which includes the NIH Down Syndrome Working Group, national organizations whose missions focus on Down syndrome, individuals with Down syndrome, and family members, to foster exchange of information on Down syndrome biomedical and behavioral research, provide an avenue for outreach to the Down syndrome community through DS-Connect™, and update the NIH Research Plan on Down Syndrome, among other collaborative activities. NICHD posted a Request for Information (RFI) in August 2012 inviting Down syndrome researchers, health care providers, and patient advocates to comment on progress made since the 2007 Research Plan and remaining research gaps, and to provide input on research priorities for NIH. NIH received an excellent response to this RFI; the revised draft Research Plan will be posted for public comment in the coming year.

Item

Fragile X-Associated Disorders [FXD] - The Committee commends NICHD for leading the effort to map the molecular, physiological, biological, and genetic connections between Fragile X (and the Fragile X protein) and autism. The Committee urges all ICs with Fragile X and autism portfolios to explore these connections with the goals of better understanding both conditions and shortening the time it will take to bring effective treatments for both conditions to market. The Committee also commends NICHD and its NIH partners for leading the effort to update the NIH Research Plan on Fragile X Syndrome and Associated Disorders, and urges NIH to fully implement the updated recommendations.

Action taken or to be taken

The National Institutes of Health (NIH) continues to maintain a substantial and diverse portfolio of Fragile X syndrome (FXS)-related research, including translational research that could lead to treatments to improve the lives of individuals and families with FXS and related conditions. These studies may provide insights into specific aspects of the broad arena of autism spectrum disorder (ASD) research. An estimated 30 percent to 50 percent of people with FXS also meet the diagnostic criteria for ASD. For example, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports a wide array of research related to FXS, ranging from the development of outcome measures for clinical trials to targeted research

projects related to language development to understanding differences between FXS and ASD. NICHD currently is funding a study developing a genetic strategy to restore balanced synaptic protein synthesis, which has proven successful in correcting varied disease-related traits in mouse models of FXS. Further insight in animal models of FXS is likely to lead to new therapeutic approaches, not only for FXS in humans, but also for autism and other intellectual and developmental disabilities.

The National Institute of Neurological Disorders and Stroke (NINDS) supports basic studies in mouse models to determine whether cellular mechanisms implicated in FXS also contribute to autism-like features. Such mechanisms may represent therapeutic targets in FXS and other forms of ASD. In addition, NINDS supports research to understand the mechanisms that contribute to seizures and their consequences in FXS, which are common in both FXS and autism. In May 2012, NINDS, NICHD, and nongovernmental organizations co-sponsored a workshop on autism and epilepsy that included discussion of these conditions in FXS.

In addition to research projects supported by individual NIH Institutes and Centers, several multi-institute efforts at the NIH focus on FXS, such as the congressionally mandated Collaborative Centers for Research in Fragile X program. NICHD, along with NINDS and the National Institute of Mental Health, all members of the trans-NIH Working Group on Fragile X, have issued a Funding Opportunity Announcement to renew these Centers. In issuing the Request for Applications, NIH considered a wide range of input from the scientific community, including the 2008 NIH Research Plan on Fragile X and Associated Disorders, responses to a published Request for Information entitled, *Research Priorities in Fragile X syndrome, Fragile X Tremor Ataxia syndrome (FXTAS), Premature Ovarian Insufficiency (FXPOI) and Other Relevant Conditions Associated with FMR1 Gene Function* ([NOT-HD-08-003](#)), and the priorities and missions of the participating institutes. Once awarded, the Centers will be composed of transdisciplinary teams of investigators working together to stimulate specific areas of research in FXS, FXTAS and FXPOI. In another example of trans-NIH FXS-related research, the NIH Blueprint for Neuroscience's Neurotherapeutics Program includes a new drug development project for the treatment of social deficits and anxiety in FXS.

The trans-NIH Working Group on Fragile X has sought and received extensive helpful input from the FXS and related communities in revising the NIH Research Plan on Fragile X and Related Disorders, and plans to post a draft of the revised plan for public comment.

Item

Mitochondrial Disease - The Committee commends NIH for supporting a 2-day workshop on "Translational Research in Primary Mitochondrial Diseases," which led to the development of a white paper that identifies barriers to progress and makes recommendations for addressing those barriers. NIH has also created a working group on mitochondrial disease research with broad participation from various Institutes and Centers. The Committee urges NIH to expand its

mitochondrial research portfolio and fully implement the recommendations contained in the white paper.

Action taken or to be taken

The National Institutes of Health (NIH) continues to promote a wide range of research on mitochondrial diseases through support of extramural and intramural investigator-initiated research, training mechanisms, and conferences and workshops. Included are: basic research on mitochondrial morphology and function, animal models of primary mitochondrial disorders, studies of natural history and pathophysiology, and development of treatment interventions for mitochondrial diseases. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) also supports research on the role of mitochondria in reproductive function, neuroprotection in neonatal hypoxia, and adult central nervous system injuries.

NICHD and other NIH Institutes and Centers (ICs) are actively implementing the recommendations of the NIH-United Mitochondrial Disease Foundation (UMDF) workshop *Translational Research in Primary Mitochondrial Diseases: Challenges and Opportunities*, to identify priorities for primary mitochondrial disease research, translate basic science discoveries into better diagnostic and therapeutic measures for patients, and facilitate future collaborations.

Specifically, through the North American Mitochondrial Disease Consortium (NAMDC), a member of the NIH Rare Disease Clinical Research Network, the National Institute of Neurological Disorders and Stroke (NINDS), the National Center for Advancing Translational Sciences, NICHD, researchers, and the patient community are establishing the infrastructure and research resources needed to develop effective interventions for mitochondrial diseases, such as a patient registry and a biorepository of patient specimens. In addition, the group is supporting natural history studies of three mitochondrial disorders to better understand disease progression, develop biomarkers to define better end points for clinical trials, and conduct pilot studies assessing imaging and genetic screening approaches. NAMDC also has a fellowship trainee in primary mitochondrial disease to help grow the future research workforce in this area. NAMDC is also developing a platform for multicenter clinical trials and has initiated its first clinical trial. The private sector recognizes the Consortium as an excellent partner for multicenter clinical trials and NAMDC is working to stimulate these partnerships further.

The Mitochondrial Disease Sequence Data Resource Consortium (MSeqDR) has been established in partnership with NAMDC, NICHD and other NIH partners, mitochondrial disease researchers from around the world, and the United Mitochondrial Disease Foundation. MSeqDR is piloting a common data repository for genomic sequencing data for mitochondrial disorders that will build on and be integrated into ongoing national and international activities.

A trans-NIH Mitochondrial Disorders Working Group (WG) was established in March 2013, co-chaired by staff from NICHD, NINDS, and the National Institute of General Medical Sciences. Among other activities, the WG plans to increase trans-NIH communication and collaboration and to stimulate research by reaching out to other agencies as well as the mitochondrial research, clinician, and patient communities. With the WG's support, and to facilitate data sharing and aggregation in clinical research, NINDS recently initiated the development of standard data types and definitions for mitochondrial disease within the NINDS Common Data Elements project.

Item

Pregnancy Health Status - The Committee commends NIH for its work on the relationship between a woman's health status during pregnancy and her health post-pregnancy. The Committee urges NIH to prioritize the joint NICHD–NHLBI funding opportunity “Pregnancy as a Window to Future Cardiovascular Disease,” as potential life-threatening conditions such as heart disease can be prevented based on clues during a woman's pregnancy. The Committee also urges NICHD to ensure that short-term studies on lifestyle interventions and treatment for preeclampsia, as well as interventional studies that go beyond weight management to include gestational and type 2 diabetes, cardiovascular disease, and other chronic diseases, can be translated into longer-term trials that will ultimately lead to changes in obstetrical practice which result in a healthier population.

Action taken or to be taken

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) supports research using multiple approaches to understand the foundations of women's health during the reproductive process (from preconception through pregnancy and the postpartum period), the physiology of labor and delivery, and the pathophysiology of abnormal pregnancy outcomes. These efforts include supporting investigator-initiated research studies and developing cohort-specific networks. For instance, NICHD's Maternal and Fetal Medicine Units (MFMU) network is conducting clinical trials focused on a number of maternal health issues, such as the treatment of maternal subclinical hypothyroidism, prevention of congenital cytomegalovirus infection, and the effects of gestational diabetes mellitus (GDM) treatment during pregnancy on the later health of children.

More than half of U.S. women of childbearing age are now overweight or obese, with higher prevalence rates among some racial/ethnic minority populations and those of low socioeconomic status. Short-term adverse outcomes can include maternal and fetal mortality, pregnancy-induced hypertensive disorders, GDM, caesarean delivery, abnormally large fetuses, and congenital abnormalities. Longer-term adverse outcomes can include morbid obesity and related metabolic conditions, such as type 2 diabetes in both the mother and her offspring, creating a serious public health concern. NICHD recently funded investigators at the University of Puerto

Rico Medical Sciences Campus to conduct a study entitled “**Pregnancy and Early Lifestyle Improvement Study (PEARLS)**,” one of six funded projects in response to a Funding Opportunity Announcement (FOA) issued by the National Institute of Diabetes and Digestive and Kidney Diseases. PEARLS is a clinical trial in which obese pregnant women with high risk for complications will be randomized to different methods of interventions that involve diet, physical activity, metabolism, and behavioral modifications. NICHD anticipates that this study, along with the other five funded by other NIH Institutes and Centers under this FOA, will help to inform evidence-based guidelines for obese pregnant women who wish to reduce weight.

GDM increases the risk of complications during pregnancy and poses long-term health risks for both mother and baby. Understanding GDM is an active area of research for NICHD. To better understand optimal methods of diagnosing gestational diabetes, NICHD and the NIH Office of Disease Prevention co-sponsored a consensus development conference, Diagnosing Gestational Diabetes Mellitus (<http://prevention.nih.gov/cdp/conferences/2012/gdm/default.aspx>) in March 2013. A panel of invited experts examined available scientific evidence, and came to consensus on how to diagnose GDM. The final statement for this conference is available at: <http://prevention.nih.gov/cdp/conferences/2013/gdm/final-statement.aspx>. NICHD also supports efforts to understand the symptoms and outcomes of GDM through its (MFMU) Network.

Current medical practice assumes that women return to normal health following a pregnancy complicated by preeclampsia or other adverse pregnancy outcomes. NICHD joined with the National Heart, Lung, and Blood Institute to issue a new FOA in August 2012, “Pregnancy as a Window to Future Cardiovascular Health: Adverse Pregnancy Outcomes as Predictors of Increased Risk Factors for Cardiovascular Disease.” Several grants will be funded under this solicitation, which leverages the existing *Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be* cohort funded by NICHD, to assess cardiovascular risk at approximately two years postpartum in women with and without complications (e.g., preterm birth, preeclampsia, fetal growth restriction) during their first pregnancies.

Item

Preterm Birth - The Committee notes that the Institute’s new Scientific Vision highlights pregnancy and pregnancy outcomes as a priority for NICHD research. The Committee encourages NICHD to continue to emphasize its support of extramural preterm birth prevention research, the Maternal-Fetal Medicine Units Network, the Neonatal Research Network, and the intramural research program related to prematurity. The Committee also encourages NICHD to support transdisciplinary science as recommended in the Scientific Vision and to fund transdisciplinary research grants to study and identify the complex causes of prematurity.

Action taken or to be taken

As highlighted in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)’s Scientific Vision for the Next Decade, NICHD is placing a major focus

on research to study and identify the complex causes of, and supporting evidence-based attempts to prevent, preterm birth. For instance, to address the higher rates of preterm births in nulliparous women (first pregnancy), NICHD funded the *Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b)*. This is a prospective cohort study of a racially/ethnically/geographically diverse population of 10,000 nulliparous women carrying single fetuses during their first pregnancy. Participants undergo intensive research assessments during their pregnancies to study the possible mechanisms and predictors of preterm birth, preeclampsia, and other adverse pregnancy outcomes. Detailed ultrasound assessments of placental function and biomarker evaluation also will be performed throughout pregnancy. By determining the maternal characteristics, including genetic, clinical, environmental, and physiological factors, that may predict poor outcomes such as preterm births, *nuMoM2b* will be able to determine which women are at highest risk for poor pregnancy outcomes in their first pregnancies, which will assist in targeting future prevention efforts. Enrollment of the expected cohort of 10,000 women was completed during fall 2013; the last birth is expected during the spring of 2014.

Major, unexplained disparities in maternal health and perinatal outcomes (including preterm births) exist among ethnic and racial minority groups compared to white women in the United States. To explore possible reasons, NICHD funded the Community Child Health Research Network (CCHN) to conduct a community-based participatory research study. CCHN examined how community, family, and individual level stressors influence and interact with biological factors to affect maternal and child health, including health disparities in preterm birth and low birth weight rates. Researchers assessed allostatic load (the body's response to chronic or repeated episodes of stress) in new mothers and fathers for one year postpartum. CCHN recruited nearly 5,000 participants for this study, mostly from predominantly lower socioeconomic levels, living in African American, Latino, and Caucasian communities in five regions of the United States. Recruitment is complete, and analyses of the data are underway.

In another NICHD-funded study, researchers from Ohio State University studied a group of women who had recently given birth, examining whether stress-induced inflammation is the key biological pathway by which stress causes poor birth outcomes, such as preterm birth. Using a test for acute stress, the team examined the effects of race and pregnancy on inflammatory responses in pregnant African American and white women during the second trimester, comparing them to a group of women who were not pregnant. Psychosocial characteristics, health behaviors, and affective responses were assessed. The researchers also measured markers of inflammation in the blood. They found that stress led to significantly higher elevation in inflammatory markers in the African American participants; this effect was present both in pregnant and non-pregnant African American women. Moreover, pregnant white women in the study showed lower negative affective responses than did non-pregnant women of either race. These findings are novel in that they show that stress-induced inflammatory responses are more

robust among African American women versus whites during pregnancy, which may be used to develop interventions to reduce or prevent preterm births.

Item

Rehabilitation Research - The Committee recognizes the importance of rehabilitation research and commends the agency for its work to evaluate the performance of the National Center for Medical Rehabilitation Research. The Committee further recommends that NIH continue to implement the recommendations included in the final December 2012 report titled, “Blue Ribbon Panel on Medical Rehabilitation Research at the NIH.”

Action taken or to be taken

The Blue Ribbon Panel (BRP) on Medical Rehabilitation Research, empaneled by the National Institutes of Health (NIH) in 2011, was charged with focusing on the structure and function of the National Center for Medical Rehabilitation Research (NCMRR), while also assessing the state of rehabilitation research across the NIH and recommending how NCMRR and NIH can best catalyze and support rehabilitation research. The BRP made a number of recommendations to optimize rehabilitation research to meet the growing rehabilitation needs of Americans with physical disabilities. These included giving NCMRR independent status and budget within NIH, increasing NCMRR’s role in the coordination of rehabilitation research across NIH, and regularly updating the rehabilitation research strategic plan. It also recommended that NCMRR should collaborate with other NIH Institutes and Centers (ICs) on identifying and meeting rehabilitation research needs, including activities such as co-sponsoring Funding Opportunity Announcements and training opportunities, jointly planning and organizing conferences, and coordinating study groups.

While NCMRR will remain under the auspices of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), an innovative operating model for NCMRR has been developed that will help rehabilitation research not only function, but thrive within NIH. Previously, funding for research-related activities under NCMRR has been drawn from the overall NICHD budget. Under the new plan, NCMRR would have dedicated funding at approximately seven percent of NICHD’s extramural research funding, a modest increase from its share in recent years. NCMRR would support the majority of research project grants through leveraged co-funding with the various NIH ICs, coordinating this effort largely through a revitalized, trans-NIH Rehabilitation Research Coordinating Committee. A smaller portion of NCMRR funds would be used to allow NCMRR to make selected grants on its own, maximizing its ability to act strategically in furthering rehabilitation research and improving the lives of those in need of rehabilitation services. Research infrastructure grants, training and career development, research-related conferences, and Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) applications could also be funded either directly by NCMRR or through co-funding with other ICs. NCMRR’s congressionally

mandated National Advisory Board, which includes representatives from a range of rehabilitation stakeholder communities, would provide strategic thinking to NCMRR and NICHD to ensure that the needs of the rehabilitation community are being met.

NICHD is committed to updating the comprehensive Research Plan regularly, with substantial input from both the research and patient communities. The long-time director of the NCMRR has recently announced that he is stepping down from that post, and updating and implementing the Research Plan will be an important charge to the next NCMRR director, once he or she is selected. Another critical role for the new director will be continuing and possibly expanding NIH's efforts to coordinate our rehabilitation research efforts with those of the Departments of Defense and Veterans Affairs.

Without a change in law, NIH is unable to address two of the panel's other recommendations - to adopt the World Health Organization's definition of rehabilitation, and to delete "Medical" from NCMRR's name. Nonetheless, this new operating model achieves the major goals specified in the BRP report: a dedicated funding stream for NCMRR, increased coordination and less duplication of rehabilitation research at NIH, and a greater emphasis on strategic planning and priority setting.

Item

Vulvodynia - The Committee is pleased with the progress that NICHD has made to implement the major recommendations from the NIH Research Plan on Vulvodynia, particularly in convening the May 2013 workshop to develop research diagnostic criteria. The Committee urges NICHD to continue its work with the patient advocacy, medical, and scientific communities to develop these criteria, as well as common data elements to be collected across clinical studies to allow for the comparison of study populations and findings. The Committee also encourages the Institute to expand the cadre of basic and clinical investigators conducting vulvodynia research by helping interested researchers obtain greater expertise in pain research methodology and pelvic/urogenital neurobiology; encouraging NIH-funded investigators from various fields to expand their research to include vulvodynia; and reissuing a general funding opportunity with a special review panel that addresses foundational priority areas delineated in the vulvodynia research plan.

Action taken or to be taken

Clinicians and patients need stronger scientific evidence to address vulvodynia, a chronic, localized pain condition affecting millions of women. Without a fundamental understanding of vulvodynia – its mechanisms, its causes, and even its prevalence – developing effective treatments is difficult. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) held a workshop in May 2013 to begin the process of developing research diagnostic criteria for vulvodynia. The workshop responded directly to one of the key recommendations from the 2012 NIH Research Plan on Vulvodynia

(http://www.nichd.nih.gov/publications/pubs_details.cfm?from=&pubs_id=5781) and provided scientific direction for NICHD's new Gynecological Health and Disease Branch to help advance vulvodynia research. Over 30 leading experts in vulvodynia and chronic pain met to discuss vulvodynia phenotypes, inclusion/exclusion criteria, and common data elements. The researchers agreed that well-defined and consistent case definitions, phenotyping categories, and data elements could enable clearer interpretation of individual studies and greater ability to compare findings from related research efforts. Major studies on other chronic pain conditions were offered as potential models for developing research diagnostic criteria for vulvodynia.

Progress has been made recently in studying the basic science of vulvodynia, but further research is still required to describe better the underlying biological mechanisms. While the chance of finding a single gene for vulvodynia is unlikely, researchers are likely to find candidate genes that as a group may have an effect. The next steps in basic research are to determine whether it is possible to use imaging techniques to develop "vulvodynia pain signatures" for vulvodynia sub-phenotypes, refine the animal model to improve validity and reliability, determine the ideal stimulant to induce vulvodynia or discover an endogenous vulvodynia model, and refine the technique of evoking vulvar pain.

In clinical research, targeted randomized controlled trials on vulvodynia are needed to assess pain and pain-related outcomes, and categories of pain (intensity, quality, duration, and temporal aspects). NICHD-funded researchers found that the brains of women with vulvodynia had very similar responses to those of women with fibromyalgia (a generalized pain disorder), while women with no pain disorder showed a different pattern of brain response. Moreover, women with "provoked" vulvodynia - - who experienced the pain upon touch - - showed a different pattern of brain activation compared with women who experienced the pain even when not touched ("unprovoked" vulvodynia). The results of the study indicate that the same brain mechanisms may be at work in both localized and generalized pain disorders. Moreover, the difference in imaging findings for women with provoked and unprovoked vulvar pain may help to distinguish subtypes of vulvodynia. The next steps for clinical research include developing more specific terminology and classifications for the different phenotypic subgroups, and standardizing inclusion and exclusion criteria and outcome measures.

NICHD is making an ongoing investment in research related to vulvodynia. In 2012 and 2013, several new grants were funded in response to a specific Funding Opportunity Announcement (FOA) that encouraged research applications for basic, clinical, translational, epidemiological, or behavioral research on vulvodynia. This funding opportunity already has yielded valuable information; results from one recent study funded by NICHD found that women with vulvodynia are two to three times more likely than other women to suffer from other chronic pain conditions. NICHD is planning on reissuing this FOA.

National Eye Institute (NEI)

Senate Significant Items

Item

Diabetic Retinopathy - The Committee understands that diabetic eye disease is the leading cause of blindness in working age adults and urges NEI to continue its support of the Diabetic Retinopathy Clinical Research Network.

Action taken or to be taken

The Diabetic Retinopathy Clinical Research Network (DRCR.net) is a collaborative network of investigators and ophthalmologists dedicated to facilitating multicenter clinical research of diabetic retinopathy, diabetic macular edema, and associated conditions. DRCR.net was formed in September 2002 and currently includes 106 participating academic and community clinics with 344 physicians and 1,163 additional personnel spread over 41 states.

With its large network, DRCR.net enables NEI to implement rapidly protocols and recruit patients for large-scale clinical trials. In December 2013, the network concluded a landmark 5-year comparative effectiveness trial of therapies used to treat diabetic macular edema (DME). In this vision impairing complication of diabetes, damaged or abnormal blood vessels leak fluid into the retina. The preliminary results from this trial were reported in 2010 based on two years of data and demonstrated that Lucentis—a drug originally developed to block abnormal blood vessel growth in age-related macular degeneration (AMD)—was more effective than the standard-of-care laser treatment for DME and significantly improved vision in nearly 50 percent of patients. Following these results, the FDA approved Lucentis for DME in August 2012, making it the first new therapy for DME in 20 years. Building on these results, the network launched a clinical trial to evaluate Lucentis in proliferative diabetic retinopathy (PDR), a more advanced form of diabetic eye disease where fragile blood vessels grow into the retina. This trial has currently enrolled over 300 PDR patients.

In addition to Lucentis, two other drugs, Avastin and Eylea, are widely used for AMD and diabetic retinopathy. DRCR.net launched a trial in September 2012 to compare safety and efficacy of the three drugs in the treatment of DME. Enrollment of 660 patients was completed in 12 months due to highly efficient recruiting by the network investigators.

DRCR.net provides other unique capabilities. For example, the network is building a repository of blood samples from 2,000 consenting diabetic patients participating in various DRCR.net studies. These samples will form the basis of a genome-wide analysis that may uncover genes involved in development of diabetic eye disease, prognosis, and response to various interventions.

Item

Marfan Syndrome - The Committee understands the negative health effects that Marfan syndrome can have on the human eye and vision. The Committee encourages NEI to initiate research activities in this area.

Action taken or to be taken

Marfan syndrome is a connective tissue disorder that affects many organs and results from mutations in the gene *FBN-1*, which encodes the protein fibrillin-1. This protein helps maintain the extracellular matrix (ECM), which provides structural support for cells to form connective tissues in the body. For patients with Marfan syndrome, mutations in *FBN-1* lead to abnormal growth and development of the heart, lungs, and skeleton. In the eye, Marfan syndrome can lead to glaucoma, dislocation of the eye's lens, retinal detachment, nearsightedness and astigmatism. NEI currently supports Marfan syndrome research.

In the last decade, researchers have discovered that fibrillin-1 limits the activity of the protein transforming growth factor-beta (*TGF-β*), which also maintains the ECM. Mutations in *FBN-1* are thought to result in abnormally increased levels of the *TGF-β* protein, which degrades the ECM and leads to weakened tissues. These increased levels of *TGF-β* are thought to play a significant role in Marfan syndrome.

In the 1990s, NEI-supported investigators discovered elevated levels of *TGF-β* in the eyes of patients with glaucoma. The most common form of glaucoma, primary open angle glaucoma (POAG), results from increased intraocular pressure (IOP). Increased IOP damages retinal ganglion cells which transmit visual signals to the brain. Animal model and cell culture studies demonstrated that elevated *TGF-β* degrades the tissue that regulates eye pressure thereby increasing IOP. Recent NEI-sponsored studies of POAG have found risk variants in genes that interact with *TGF-β*. NEI is currently funding research to evaluate suppression of *TGF-β* in the Marfan syndrome mouse model. This work has direct bearing on our understanding of Marfan syndrome and its relationship to glaucoma.

Ectopia lentis, dislocation of the lens, occurs in up to 60 percent of patients with Marfan syndrome. The central positioning of the lens depends on the zonule of Zinn, a fibrous structure which has fibrillin-1 as a major component. NEI-supported investigators are studying the protein interactions of fibrillin-1 in health and disease in the zonule of Zinn to understand the disease mechanisms that cause ectopia lentis. It is hoped that this research will provide therapeutic insights to better treat this complication of Marfan syndrome.

Item

Usher Syndrome - The Committee urges NEI to put a higher priority on Usher syndrome, the leading cause of deaf-blindness.

Action taken or to be taken

NEI is committed to funding high-quality research to better understand and treat Usher syndrome. In 2007, NEI-supported investigators established proof-of-concept for gene therapy in a rodent model of Usher syndrome type 1B. Patients with this form of the disease are born profoundly deaf and begin to experience vision loss by age ten. The later onset of vision loss creates an opportunity to preemptively treat the ocular manifestations of the disease, which is caused by mutations in the *MYO7A* gene. The NEI study led to the 2012 launch of a phase 1 clinical trial, sponsored by Oxford Biomedica, evaluating the safety of the treatment in humans.

Although the 2007 preclinical study was successful, the vector—a modified non-pathogenic virus that transfers a therapeutic gene into cells—did not distribute the *MYO7A* gene uniformly in the retinal cell types that require *MYO7A*. NEI continues to support vector development. In 2013, investigators engineered a new vector, which improved the distribution of *MYO7A* in the Usher syndrome rodent model. NEI anticipates increased support for gene therapy for Usher syndrome as developments in the field warrant.

In 2013, NEI increased its commitment to Usher syndrome research by including a newly developed genetic screening panel as part of the NEI National Ophthalmic Genotyping and Phenotyping Network (eyeGENE®). Through the eyeGENE® Network, vision researchers are able to access high-quality DNA samples linked to clinical reports and genetic data. This information allows investigators to further our understanding of the mechanisms of eye diseases and develop potential treatments. By participating in eyeGENE®, patients, health care professionals, and researchers are able to join forces to further vision research. As of August 2013, 107 Usher syndrome patient samples were received for genetic screening and inclusion in eyeGENE®.

NEI will also increase its commitment to Usher Syndrome research in 2014 by providing financial support to the International Symposium on Usher Syndrome. This two-day scientific meeting, sponsored by the Coalition for Usher Syndrome Research, will explore current research challenges.

Conference Significant Items

Item

Usher Syndrome – The agreement supports research activities to prevent and correct the health related issues of Usher syndrome. An update is requested in the fiscal year 2015 congressional justification on the planned and ongoing activities related to Usher syndrome. The update should address the funding level and manner in which the various ICs coordinate on common goals and objectives.

Action taken or to be taken

NIH spends an estimated \$11 million on research projects directly related to Usher syndrome. Since Usher syndrome is a hereditary disease that affects hearing, balance, and vision, multiple institutes at NIH are studying the disease and coordinate on common research areas, such as disease genetics. The National Eye Institute (NEI) supports the majority of projects focused on blindness, while the National Institute on Deafness and Other Communication Disorders (NIDCD) funds deafness and balance projects. In addition, the National Institute of General Medical Sciences and the National Institute of Child Health and Human Development (NICHD) support research on Usher syndrome that involves protein structure, cell biology, and vertebrate development. In a trans-NIH supported research infrastructure project, investigators are developing animal models of the known genetic mutations that contribute to Usher syndrome. These genes encode a very diverse range of proteins, so this resource will provide tools to understand their roles in health and disease.

A collaboration between NIDCD and NEI investigators working at the NIH Clinical Center seeks to better understand the natural history and genetics of Usher syndrome. The collaboration is testing the genes of Usher syndrome patients and their family members and closely monitoring disease progression over time. This well-characterized cohort would make excellent candidates for clinical intervention trials. NEI and NIDCD scientists will continue to collaborate to develop possible therapeutic models for Usher syndrome.

In 2007, NEI-supported investigators established proof-of-concept for gene therapy in a rodent model of Usher syndrome type 1B. Patients with this form of the disease are born profoundly deaf and begin to experience vision loss by age ten. The NEI study led to the 2012 launch of a phase 1 clinical trial, sponsored by Oxford Biomedica, evaluating the safety of the treatment in humans. Although the 2007 preclinical study was successful, the vector—a modified non-pathogenic virus that transfers a therapeutic gene into cells—did not distribute the *MYO7A* gene uniformly in the retinal cell types that require *MYO7A*. In 2013, NEI-supported investigators engineered a new vector, which improved the distribution of *MYO7A* in the Usher syndrome rodent model.

NICHD is supporting a study on the genetics of Usher syndrome as part of a larger effort to better understand the relationship between disease symptoms and genetic variation. Patients with Usher syndrome exhibit significant variation in the onset, progression, and severity of symptoms. Some of this variation is due to different genetic mutations, yet even siblings with the same mutation exhibit variation. This study uses advanced imaging to test the hypothesis that differences in disease expression relate to developmental instability caused when Usher gene mutations disrupt cellular transport of a key protein complex.

NEI and NIDCD are also co-funding a conference grant to support the 2014 International Symposium on Usher Syndrome. This two-day scientific meeting, organized by the Coalition for Usher Syndrome Research, will explore current research challenges.

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National Institute of Environmental Health Sciences (NIEHS)

Senate Significant Items

Item

Childhood Lead Poisoning - The Committee understands that lead poisoning remains a serious health risk for children, with lifelong developmental consequences, and encourages NIEHS to prioritize research in this area.

Action taken or to be taken

NIEHS agrees that lead exposure continues to pose a critical health risk for children. Pregnant mothers who have been exposed to lead have a higher incidence of babies with low birth weights, suggesting lead disrupts the normal developmental processes that occur in pregnancy. Of significant concern is the increased susceptibility of children to low levels of lead and how this may permanently impact their cognitive function, delay puberty or increase their risk of developing cardiovascular disease, hypertension, diabetes, psychiatric disorder, or neurodegenerative disease later in life. Therefore, the National Toxicology Program (NTP) published a document in June 2012 that outlines the health effects of low-level lead exposure in children and adults. The NTP Monograph on Health Effects of Low-Level Lead was subjected to multiple types of review including feedback from the public and an expert panel of reviewers.

NIEHS-funded research continues to explore how lead impairs normal development. Recent work indicates pregnant mice exposed to lead give birth to mice that have significantly lower bone mass as a result of lead's action against the molecular building blocks of bone. With this knowledge, future research can target the bone development pathway, potentially reversing the lead-induced damage and preventing osteoporosis or fractures. NIEHS-funded research in pregnant mice exposed to lead also revealed genetic and sex-dependent susceptibilities to disruption in the brain reminiscent of schizophrenia. In addition, recent work has suggested developmental exposure to lead causes epigenetic changes in the brain that differ in males and females and by the window of exposure. Research on a population of elementary school-aged children in India identified a subset of children with a genetic susceptibility to the neurotoxic effects of lead exposure, indicating genetics may play a role in the effects of lead exposure. Finally, NIEHS-funded economic analysis of lead exposure in children of low-to middle-income countries estimates a total economic loss upwards of \$1,162.5 billion underlining the potential global impact of this work.

NIEHS has built a diverse portfolio of research on childhood lead exposure. Future work will focus on the effects of lead on human populations, epigenetics, neurodevelopment, obesity, puberty, osteoporosis, and global health. In addition, research has been funded to build accessible, cost-effective methods of lead detection to prevent exposure from occurring. Prevention research looking at the impact of nutrition and lead levels in children is ongoing. An

emerging area of research is the impact of electronic waste (e-waste) exposure on children's health. E-waste includes the growing volume of cell phones and computers that end up in unregulated recycling facilities throughout the world. NIEHS co-sponsored a World Health Organization working group meeting to discuss e-waste exposure in children and develop a strategic plan for addressing this issue with future research. Ongoing NIEHS-sponsored research is evaluating the cognitive and behavioral outcomes of children exposed to e-waste in early life.

Item

Environmental Exposures and Reproductive Health - Environmental exposures can have significant ramifications for reproductive health, such as infertility, sterility, and birth defects, in addition to causing other serious health conditions including osteoporosis, heart attack, and stroke. The Committee believes it is critical to examine these ramifications for both men and women. NIEHS is urged to place a greater priority on, and invest more funding in, environmental, sex-based, reproductive health research.

Action taken or to be taken

NIEHS funds critical research that explores the role of environmental exposures in adverse reproductive health outcomes for both sexes. NIEHS-funded researchers are using a multi-pronged approach to understand the effects of environmental exposures on reproductive and developing tissues. Not only has this work begun to shed light on the mechanisms that underlie exposure-related infertility, but it is also providing insight into the connection between developmental exposures and adverse health outcomes later in life, such as Alzheimer's disease, osteoporosis, heart attack, stroke, and cancer.

NIEHS uses diverse approaches to understand how environmental exposure can lead to adverse reproductive health outcomes affecting both men and women. Cell-based models, animal models, systems genetics, statistical models, and human population studies are all funded to address the role of exposures in adverse health effects. Adverse health outcomes such as endometriosis, ovarian cancer, breast cancer, early menopause, miscarriage, birth defects, infertility, testicular abnormalities, erectile dysfunction, testicular cancer, obesity, osteoporosis, and cardiovascular function are currently being evaluated using the aforementioned approaches.

NIEHS research using a genetic mouse model has identified the role of a protein in male fertility. The work showed the loss of this protein changed the permeability of the blood-testis barrier and prevented sperm from maturing, causing infertility. Environmental exposure of pregnant rats to bisphenol A has been shown to alter the gene expression of fetal female mammary glands. In addition, NIEHS-funded work has suggested exposure of pregnant mice to phthalate results in the disruption of testicular germ cells in males born to the exposed mother, as well as males in subsequent unexposed generations, suggesting exposure of the great-grandmother continues to have effects on her great-grandsons.

Item

National Toxicology Program [NTP] - The Committee urges NTP to be highly precise when describing the results of its studies on particular extracts of an herbal species to avoid any possible confusion about the relevance of such studies to other extracts of the species. The Committee also encourages NTP to reinstitute its practice of making available on its Web site a transcript and/or recording of its public meetings.

Action taken or to be taken

Since the inception of its herbals research program, the NTP has recognized that the evaluation of herbal supplements requires special chemical characterization considerations. In general, the NTP does not study specific commercial products but rather focuses on materials or constituents that are representative of many different specific commercial products. This can be a challenge because preparations can have very different composition and chemical constituent profiles due to variations in which part of the plant was used, growing conditions, harvesting conditions and processing conditions. As a result, extensive physicochemical characterization has always been a key aspect in the NTP research and testing program. A comprehensive characterization program is developed for each specific material to provide essential information for the selection of the test article, determination of test article stability during the study, and measurement of test article doses during the course of the study. A general approach that NTP uses includes initially evaluating the presence of known biologically active components, and use of chemical fingerprinting approaches that allow for the assessment of complex patterns for comparison across different formulations. Whenever possible NTP attempts to detect as many components as possible, so that “marker” constituents can be assessed during the study for dose certification. All of these details are routinely provided in NTP technical reports and publications, and specific publications or meeting abstracts have dealt with methods for characterization of ginseng, comfrey, ginkgo biloba extracts, goldenseal, grape seed and pine bark extracts.

The NTP routinely places summary meeting minutes from its public meetings on the NTP website, and will continue to follow this practice. The NTP has not placed full transcripts or recordings on its website in the past.

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National Institute on Aging (NIA)

Senate Significant Items

Item

Alzheimer's Disease - The Committee encourages NIA to continue addressing the research goals set forth in the National Plan to Address Alzheimer's Disease, as well as the recommendations from the Alzheimer's Disease Research Summit 2012. In addition, the Committee continues to urge NIH to take advantage of existing well-characterized, longitudinal, population-based cohort studies to provide new insights into risk factors and protective factors related to cognitive decline and dementia. The Committee also continues to encourage additional research in minority populations that are at particularly high risk for cognitive decline and dementia.

Action taken or to be taken

NIH, with the National Institute on Aging (NIA) taking the lead, supports a number of studies addressing the research goals set in the National Plan to Address Alzheimer's Disease and the expert recommendations from the 2012 AD Research Summit. Ongoing initiatives include:

Identification of risk and protective genes with support from the NIA Genetics of AD Data Storage Site, a unique web-based repository of genetic data. With the National Human Genome Research Institute, NIA co-funds the AD Sequencing Project to identify novel risk and protective alleles. NIA also supports studies to validate and quantify the impact of newly confirmed and/or identified genetic risk factors.

- Basic research, including the Dominantly Inherited Alzheimer's Network, in which investigators are studying the early-onset form of the disease to identify the sequence of brain changes in AD before symptoms appear. This may provide insight into the more common late-onset form of the disease.
- Refinement of brain imaging techniques to facilitate basic research, early diagnosis, and monitoring of therapies, through the Alzheimer's Disease Neuroimaging Initiative and similar ongoing studies.
- Translational research and drug development. For example, investigators are using new techniques to "reprogram" human skin cells into a special kind of stem cell which then becomes a neuron. This breakthrough work in cell-based modeling could make it possible to conduct rapid screens of tens of thousands of molecules as potential therapies for AD.
- Over 35 clinical trials for treating, preventing, or delaying onset of AD or mild cognitive impairment (MCI). The trials are aimed at a variety of targets and include the first primary prevention trial to focus on people who are cognitively normal but at extremely high risk of developing AD and a large study testing an insulin nasal spray for treating the disease.

- Research on AD-related dementias, with guidance from a May 2013 conference convened by the National Institute of Neurological Disorders and Stroke and NIA. Participants developed prioritized recommendations, including research on health disparities in AD-related dementias, to guide scientific research in this area for the next 5 to 10 years.

NIA also supports a number of large-scale cohort studies through which we can identify risk and protective factors related to cognitive decline and dementia. For example, the Baltimore Longitudinal Study of Aging, America's preeminent study of aging, continues to study potential risk and protective factors such as menopausal hormone therapy and treatment of hypertension. In addition, support from the American Reinvestment and Recovery Act enabled the Health and Retirement Study to conduct genotyping on approximately 20,000 participants and use these data to elucidate genetic influence on a number of parameters, including cognition. ARRA funds also facilitated the recruitment of additional minority participants.

Additional NIA-supported research aimed at elucidating risk and protective factors among vulnerable populations includes an ongoing study of genetic risk factors for AD in Hispanics of Caribbean descent and the Chicago Health and Aging project, which is exploring several genetic and other risk factors for cognitive decline and AD in African American and non-Hispanic white participants, including the intersection of markers of inflammation, blood pressure, and other vascular factors with cognitive function.

Item

Alzheimer's Disease - The Committee commends NIH for the recent use of its transfer authority and other means to direct additional funding to research on Alzheimer's disease within very tight budgets, with the goal of finding an effective prevention or treatment by 2025.

Action taken or to be taken

Identifying an effective prevention or treatment for Alzheimer's disease (AD) remains a high priority across the NIH. Alzheimer's disease research is funded across NIH and totaled over \$500 million in FY 2012. \$50 million of these funds were redirected from other programs or other potential uses within programs. An additional \$40 million was allocated for AD research from an increase to the Office of the Director appropriation in FY 2013. The additional funds have been used to support:

- Cutting-edge research to accelerate the identification of new risk and protective genes.
- Research to provide new cellular models of Alzheimer's disease to enable rapid screens of hundreds of thousands of molecules for potential as therapeutic agents.
- Research on the use of new induced pluripotent stem (iPS) cell methods to obtain insights into the cellular processes of Alzheimer's.

- Grants to small businesses to support translational and clinical research in developing and testing therapies.
- Studies to speed the testing of therapies in people at the highest risk of the disease.

Two major clinical trials supported by these efforts are:

- A \$7.9 million study testing an insulin nasal spray for treating Alzheimer’s disease. In a recent pilot clinical trial, investigators found that intranasal insulin treatment improved memory, cognition, and daily functioning with no side effects in participants with mild cognitive impairment (MCI) or mild to moderate Alzheimer’s disease. Now, a year-long study is testing the effects of intranasal insulin on cognition and function in a larger group of people with MCI or early Alzheimer’s.
- A prevention trial in people at the highest risk for the disease. NIH has committed \$16 million to this international effort, the first to focus on people who are cognitively normal but at extremely high risk of developing Alzheimer’s disease. The study participants are some 300 adult members of a Colombian clan with a family history of early-onset Alzheimer’s, as well as a smaller number of U.S. participants age 30 and older. This group includes both carriers and non-carriers of a genetic mutation known to cause observable signs of Alzheimer’s around age 45. The study will use brain scans, fluid biomarkers, and cognitive testing to track levels of disease-related protein, changes in brain structure and function, and cognitive performance in participants taking an experimental drug. The trial is co-funded by the non-profit Banner Alzheimer’s Foundation and by Genentech, a biotechnology company, which is also providing the drug being tested.

In addition, NIH is using these additional funds to support projects under four Funding Opportunity Announcements (FOAs) that were released by the National Institute on Aging early in FY 2013. These FOAs solicited research on drug discovery and development, identification of therapeutic targets, and prevention and treatment trials. Response to the FOAs has been robust, and several awards have been made.

Item

Demographic, Economic, and Behavioral Research - The Committee recognizes NIA for investing in large-scale longitudinal surveys, including the National Health and Aging Trends Study and the Health and Retirement Study. Further, the Committee applauds NIA for contributing to the recent National Academies report “Shorter Lives, Poorer Health,” which found that Americans live shorter lives and are in poorer health than people in other high-income countries and that behaviors and social circumstances are major contributing factors.

Action taken or to be taken

In FY 2012, NIH renewed funding for the Health and Retirement Study (HRS), which consists of a biennial collection of data from a nationally representative, population-based sample of over 26,000 Americans, aged 50+ and their spouses. Eleven waves of data have been collected since 1992, and a twelfth wave of data collection is planned for FY 2014. Recently, support from the American Reinvestment and Recovery Act facilitated doubling of the minority sample as well as genotyping of approximately 20,000 participants. HRS data are an important resource for researchers, students, and other government agencies: Over 2220 scientific publications have resulted from the HRS, and the number of registered users of HRS data continues to increase.

Importantly, the HRS is a model for similar studies around the world. The National Institute on Aging (NIA) has taken the lead in building the necessary infrastructure and harmonizing cross-national data resources to facilitate comparative studies and has funded the initial concept work and provided technical assistance for HRS-like studies in other countries. Today, similar national longitudinal cohort studies are ongoing in England, about 20 countries in the EU, China, South Korea, Mexico, Israel, India, and Japan. Other studies, notably the World Health Organization's Study on Global Health and Ageing and Adult Health (which includes sites in Asia, Russia, Mexico, and Africa), have adapted methods and/or instruments from the HRS for their own use. In addition, NIA has supported the development of an on-line resource that facilitates use and harmonization of data from the HRS and comparable studies.

NIA supports several large-scale longitudinal studies in addition to the HRS. For example, the National Health and Aging Trends Study (NHATS), which will assess national trends in disability as well as the determinants of disability and needs of the disabled, completed its baseline wave of data collection in October 2011, and the baseline data became publicly available to the research community in Spring 2012. The Baltimore Longitudinal Study of Aging, now in its fifty-fifth year, continues to produce important information on the physical consequences of aging. Other studies, including the Rancho Bernardo Study, which has tracked a variety of health measures among residents of a Southern California community since the early 1970s, and the Study of Women's Health across the Nation, which examines the health of a multicultural cohort of women throughout the menopausal transition and beyond, have provided a wealth of information about aging and age-related needs and concerns.

NIA sponsored the 2011 National Academies Report "Explaining Divergent Levels of Longevity in High-Income Countries" to explain why U.S. life expectancy has been overtaken by most other high income countries since 1980. The follow-on report "Shorter Lives, Poorer Health" was commissioned by NIA and the NIH Office of Behavioral and Social Sciences Research to provide an analysis of global mortality trends. The report provides strong and sobering evidence that Americans die sooner and experience greater rates of illness and injury than people in other high-income nations. This health disadvantage exists at all ages from birth to age 75, and even advantaged Americans -- those who have health insurance, college educations, higher incomes,

and healthy behaviors -- appear to be sicker than their peers internationally. The reasons for this disparity are complex and appear to involve an array of social, behavioral, and policy factors. Data from the HRS and comparable studies were used extensively in both NAS panels. Research is ongoing to identify and address the disparities in illness and death between the U.S. and other wealthy nations.

Conference Significant Items

Item

Alzheimer's Disease - The fiscal year 2014 budget request calls for a \$80,000,000 increase over the fiscal year 2012 funding level for Alzheimer's disease research at NIA. In keeping with longstanding practice, the House and Senate Appropriations Committees do not recommend a specific amount of NIH funding for this purpose or for any other individual disease. Doing so would establish a dangerous precedent that could politicize the NIH peer review system. Nevertheless, in recognition that Alzheimer's disease poses a serious threat to the Nation's long-term health and economic stability, the agreement expects that a significant portion of the recommended increase for NIA should be directed to research on Alzheimer's. The exact amount should be determined by the scientific opportunity of additional research on this disease and the quality of grant applications that are submitted for Alzheimer's relative to those submitted for other diseases. The NIA is encouraged to continue addressing the research goals set forth in the National Plan to Address Alzheimer's Disease, as well as the recommendations from the Alzheimer's Disease Research Summit in 2012. In addition, NIH is urged to take advantage of existing well-characterized, longitudinal, population-based cohort studies to provide new insights into risk factors and protective factors related to cognitive decline and dementia. The NIH is encouraged to support additional research in minority populations that are at particularly high risk for cognitive decline and dementia.

Action taken or to be taken

The National Institute on Aging (NIA) appreciates the significant budget increase over FY 2012 levels. Recognizing the toll that Alzheimer's disease (AD) continues to take upon the Nation at both the individual and societal levels, we anticipate that this new funding will allow support of additional high priority and high quality Alzheimer's-related research projects.

As we work toward the milestones established in the National Alzheimer's Project Act, NIH, with NIA taking the lead, supports a number of studies addressing the research goals set in the National Plan to Address Alzheimer's Disease and the expert recommendations from the 2012 AD Research Summit. For example, in response to the Summit recommendations, and with the support of additional funding allotted in FY 2013 for Alzheimer's research, NIA issued four Funding Opportunity Announcements for new projects aimed at speeding up drug development and testing new therapies. Seven projects have been funded, including basic and preclinical studies in which investigators are analyzing large datasets to identify, characterize, and validate

candidate genes and molecular networks that may influence susceptibility to disease and/or act as therapeutic targets, as well as clinical trials of potential interventions. Other activities include:

Identification and validation of risk and protective genes with support from the NIA Genetics of AD Data Storage Site, a unique web-based repository of genetic data.

- **Basic research** to facilitate our understanding of the genes, pathways, and networks involved in the disease.
- **Refinement of brain imaging techniques** to facilitate basic research, early diagnosis, and monitoring of therapies, through the Alzheimer’s Disease Neuroimaging Initiative and similar ongoing studies.
- **Translational research and drug development.** For example, investigators are using new techniques to “reprogram” human skin cells into a special kind of stem cell which then becomes a neuron. This breakthrough work in cell-based modeling could make it possible to conduct rapid screens of tens of thousands of molecules as potential therapies for AD.
- **Over 50 NIA-supported clinical trials** for treating, preventing, or delaying onset of AD or mild cognitive impairment, including the first primary prevention trial to focus on people who are cognitively normal but at extremely high risk of developing AD.
- **Research on AD-related dementias**, with guidance from a May 2013 conference convened by the National Institute of Neurological Disorders and Stroke and NIA. Participants developed prioritized recommendations, including research on health disparities in AD-related dementias, to guide scientific research in this area for the next 5 to 10 years.

NIA also supports a number of large cohort studies through which we can identify risk and protective factors related to cognitive decline and dementia. For example, the Baltimore Longitudinal Study of Aging continues to study potential risk and protective factors such as menopausal hormone therapy and treatment of hypertension. Other research includes an ongoing study of genetic risk factors for AD in Hispanics of Caribbean descent and the Chicago Health and Aging project, which explores genetic and other risk factors for cognitive decline and AD in African American and non-Hispanic white participants, including the intersection of markers of inflammation, blood pressure, and other vascular factors with cognitive function.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Senate Significant Items

Item

Heritable Connective Tissue Disorders - The Committee commends NIAMS for ongoing research efforts into heritable connective tissue disorders like Marfan syndrome.

Action taken or to be taken

Heritable disorders of connective tissue arise from mutations in the genes responsible for building tissues that hold the body together and provide a framework for growth and development (e.g., the extracellular matrix, or ECM). Mutations in the genes for ECM proteins are the basis of many rare, severe inherited diseases, including Marfan syndrome (MFS) and epidermolysis bullosa (EB). In MFS, the connective tissue found throughout the body is atypical, adversely affecting the skeleton, eyes, heart, nervous system, skin, and lungs, and can cause disruption of main arteries, leading to sudden death. In EB, a blistering skin disease, the damage can be widespread, affecting internal as well as external tissues, and in some cases, can be fatal.

A number of clinical trials are now being conducted around the world based on earlier NIAMS studies that identified therapeutic targets in MFS and pseudoxanthoma elasticum, another heritable connective tissue disorder. More recently, NIAMS-funded researchers have made several significant advances related to the mechanisms and potential treatments for heritable connective tissue disorders. Researchers supported by the NIAMS have developed a molecule that mimics and can bind to damaged collagen. Studied in a mouse model of MFS, this molecule made it possible to image areas where diseased tissue was being rapidly remodeled. This method can be a powerful tool for detecting both normal and disease processes in the connective tissue. Two additional studies funded by the NIAMS recently demonstrated the efficacy of intravenous and topical recombinant collagen VII (rC7) in treating recessive dystrophic EB (RDEB). Topical rC7 restored epidermal adherence when applied to existing RDEB wounds in mice, but was not able to prevent new blisters. However, intravenous rC7 showed a beneficial effect in preventing new wounds from forming. Taken together, these two discoveries provide potential treatments for existing wounds and prevention of new ones.

he NIAMS continues to support the Consortium for Translational Research in Marfan Syndrome, which is investigating the disease process in MFS. These studies, building on previous advances, are aimed at identifying new biological targets for therapy, as well as predictive biomarkers of vascular and skeletal manifestations, which are the major causes of mortality and morbidity in MFS.

To address the shortage of investigators researching skin diseases that involve connective tissue, NIAMS has awarded a training grant in molecular dermatology and cutaneous connective tissue

diseases. This program offers an opportunity for both M.D.s and Ph.Ds. to develop their clinical and basic research skills in this field. NIAMS has also issued a request for applications for Skin Diseases Research Core Centers. These centers will provide shared facilities and services to groups of established, currently funded investigators addressing scientific problems in skin biology and diseases, including connective tissue disorders, in order to improve efficiency, accelerate the pace of research, and ensure greater productivity.

Item

Lupus - The Committee urges the Director to promote collaboration among NIAMS, NIAID, NHLBI, NIDDK, NIEHS, NINDS, NICHD, and NIMHD on efforts to expand and intensify genetic, clinical, and basic research on lupus. Given the complexity and impact of lupus, the Committee urges a particular focus on understanding the underlying mechanisms of the disease, gene-gene and gene-environmental interactions, its relationship to kidney disease, biomarkers, pediatric research, and factors related to the health disparities and comorbidities associated with lupus.

Action taken or to be taken

Lupus is an autoimmune disease, one of several disorders of the immune system. Lupus can affect many parts of the body, including the joints, skin, kidneys, heart, lungs, blood vessels, and brain. Although people with the disease may have different symptoms, some of the most common ones include extreme fatigue, painful or swollen joints (arthritis), unexplained fever, skin rashes, and kidney problems.

The NIAMS-led Lupus Federal Working Group continues to facilitate collaboration among the NIH Institutes and Centers, other Federal agencies, voluntary and professional organizations, and industry with an interest in lupus. The most recent meeting focused on a discussion of the impact and utility of a prior report entitled, “The Future Directions of Lupus Research.”

NIH supports research to better understand the multiple aspects of lupus, across the spectrum of basic, translational, and clinical research. The NIH supports three Multidisciplinary Clinical Research Centers (MCRCs) that conduct research focused on lupus. These MCRCs address critical issues directly relevant to the prevention, assessment, and improvement of clinical outcomes for patients with lupus and other autoimmune diseases. Research conducted by the MCRCs is focusing on furthering understanding of the mechanisms underlying the development of pediatric neuropsychiatric lupus; determining the genetic and environmental influences in the development of lupus in African American women; and in the outcomes of treatment.

In the past few years, rapid advances have been made in our understanding of the genetic basis of lupus. Investigators have recently identified a genetic change in specialized immune cells, called B cells, which should aid in the diagnosis of at-risk individuals and provide important insights into the origins and development of the disease.

Current medications for lupus aim to suppress the errant immune responses in order to improve a patient's symptoms and their quality of life; and to prevent disease progression and damage. However, some medications can be highly toxic and cause serious short and long-term side effects, prompting patients or their providers to discontinue taking them. In an effort to determine if lupus therapies could be made more effective and tolerable, researchers supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and National Institute of Allergy and Infectious Diseases (NIAID) designed and tested a drug delivery mechanism called a nanogel to administer mycophenolic acid (MPA), an immunosuppressant sometimes used to treat lupus. Nanogel molecules are small enough to cross cell membranes and can be effectively programmed to seek specific cells. When these MPA-loaded nanogels were used to treat mice that had a genetic predisposition for lupus, the researchers found that the nanogel provided much longer survival benefits than a drug regimen without nanoparticles, and that the nanogel particles accumulated in the kidneys, protecting them from further damage. Nanogel delivery may allow for reduced amount and less frequent dosing, thus potentially alleviating toxic side effects and non-adherence rates observed with current therapies.

The NIAMS also supports other important avenues for treating lupus by re-purposing existing therapies already approved by the Food and Drug Administration for use in other diseases and by developing treatment strategies that target new mechanisms emerging from laboratory research.

NIAID supports investigators in the Immune Tolerance Network (ITN) who are evaluating novel, tolerance-inducing therapies for autoimmune diseases. The ITN is conducting a clinical trial in people with systemic lupus who have developed kidney complications to determine if adding the experimental medication abatacept to standard therapy with cyclophosphamide is more effective than the standard therapy alone.

The National Heart, Lung, and Blood Institute (NHLBI) funds research on lung, blood, and cardiovascular diseases in individuals with lupus. The NHLBI supports research on the relationship between abnormal vascular repair and premature atherosclerosis in lupus; the role of the immune system in atherosclerosis and hypertension; the genetics of asthma and hemolytic anemia in autoimmune diseases; biomarkers of cardiovascular disease in patients with lupus; and the effectiveness of statin therapy to decrease cardiovascular disease risk in pediatric and adult patients with lupus.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) investigators work closely with NIAMS and are involved collaboratively with projects that explore innovative strategies involving new disease-modifying drugs and new combinations of chemical and biological agents to optimize the balance of effectiveness and potential toxicities of standard immunosuppressive therapies.

The National Institute of Environmental Health Sciences (NIEHS) has partnered with other NIH Institutes to evaluate the role of genetics in disparately affected populations; perform basic research on the mechanisms underlying lupus; assess the developmental effects of children exposed to lupus medications in early life; and gain insight into the variability of drug efficacy in lupus patients affected with kidney disease. These partnerships have recently identified a distinct genetic component in African-derived populations and identified a link between developmental delays in children of lupus-affected mothers who took immunosuppressive medications during pregnancy.

Lupus continues to be a priority of the National Institute on Minority Health and Health Disparities' (NIMHD) research agenda. NIMHD-supported researchers at Tuskegee University examined the impact of thymic nurse cells (TNC) in the development of lupus. In studying mice with lupus, TNC numbers are significantly depleted with disease onset and progression, suggesting that loss of TNC function may contribute to the onset of the disease.

The National Institute of Neurological Disorders and Stroke (NINDS) is a member of the Lupus Federal Working Group and funds research to understand the molecular mechanisms underlying the neurological manifestations of lupus.

Item

Osteogenesis Imperfecta [OI] - The Committee continues to be concerned that the impact of OI on adults is not well understood and that very few primary care physicians or specialists possess training or experience in treating adults with OI. The Committee continues to encourage NIAMS to support natural history studies of OI and subsequent clinical research activities that will facilitate the development of clinical practice guidelines for adults with OI. The Committee also urges NIAMS to partner with the relevant professional societies, the OI advocacy community, and other stakeholders to develop opportunities for primary care physicians and specialists to receive education and training on providing care to adults with OI.

Action taken or to be taken

NIAMS supports a broad portfolio of bone biology and musculoskeletal research that is relevant to osteogenesis imperfecta (OI), a genetic disorder also known as “brittle bone disease.” Research in this field aims to improve patients’ quality of life and advances stemming from this research are helping to better inform researchers, clinicians, and patients. Ongoing NIAMS studies of potential OI treatments include a comparison of an experimental bone-building molecule and a bone preserving drug that has been approved for women who have osteoporosis. This mouse research should inform decisions about subsequent studies for OI patients. Other researchers are examining the effects of different drugs and dosing strategies on the long-term bone health of mice as their skeletons mature. Determining how best to treat children who have severe OI will likely improve their health when they reach adulthood. Because OI represents a range of conditions that are caused by different gene defects, NIAMS-funded researchers are

testing an experimental drug in multiple mouse models to predict who is more or less likely to benefit.

To raise awareness about OI research opportunities, NIAMS included OI in a fiscal year 2014 Funding Opportunity Announcement encouraging small businesses to conduct research that could lead to biomarkers or therapies for rare diseases. Other activities include partnering with the National Institute on Deafness and Other Communication Disorders (NIDCD) to provide grant support for a Gordon Research Conference focused on collagen – a protein that, in its defective forms, leads to different types of OI and other diseases. This meeting, like others in this series of biennial events, promoted interactions and collaborations among basic and clinical research groups, as well as pharmaceutical and biotechnology companies, interested in collagen biology and pathology.

NIAMS uses other strategies, in addition to conference grants, to work with stakeholders in order to encourage research that will improve the lives of people who have OI. The Institute leads the Federal Working Group on Bone Diseases, which offers a forum for Federal agencies and others who are interested in collaborative bone research activities—including research opportunities related to rare bone diseases such as OI—to exchange information and coordinate efforts. The Chief Executive Officer of the OI Foundation participated in a 2013 NIAMS roundtable on repairing bone, muscle, and connective tissue. Another member of the OI community serves on the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council.

NIAMS is participating in two Funding Opportunity Announcements, led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), to encourage studies that will establish an evidence base for health promotion strategies related to physical activity and diet for children who have physical disabilities. OI is one of the conditions noted in the solicitations.

Like NIAMS, NICHD supports a range of basic, translational, and clinical research on OI. Scientists working in NICHD-funded laboratories are examining mouse models of OI to better understand the mechanisms of the disease, and to identify new genes that cause recessive forms of OI. They are exploring the effects of a new antibody on the bones of the mouse model. The NICHD intramural program focuses on clinical studies for pediatric patients, including an ongoing study on the pulmonary, cardiac, auditory, and neurological complications of OI. Recently published data from this research demonstrated the decline of pulmonary function and early onset of cardiac valve problems in children with OI; the study will serve as the basis for the development of early interventions to prevent or delay these complications.

Item

Psoriasis - The Committee commends NIH for addressing the significant public health burden resulting from psoriasis and psoriatic arthritis, the Nation’s most common autoimmune disease. In order to address the connection between these diseases and other serious, life-threatening

comorbid conditions such as cardiovascular disease, diabetes, stroke, and cancer, the Committee urges NIH to further promote integrated, interdisciplinary research on the inflammatory nature of these diseases.

Action taken or to be taken

Psoriasis is a chronic skin disease with symptoms that include scaling and inflammation. Psoriasis occurs when skin cells quickly rise from their origin below the surface of the skin and pile up on the surface before they have a chance to mature. Usually this cell turnover takes about a month, but in psoriasis, it may occur in only a few days.

In typical form, psoriasis results in patches of thick, red, inflamed skin covered with silvery scales called plaques. These plaques usually itch or feel sore and most often occur on the elbows, knees, other parts of the legs, scalp, lower back, face, palms, and soles of the feet. However, they can occur on skin anywhere on the body. It is not unusual for the skin around the affected joints to crack and about 30 percent of those with psoriasis experience joint inflammation that produces symptoms of arthritis. This condition is called psoriatic arthritis.

Significant progress has been made in understanding the genetics of psoriasis and psoriatic arthritis. A number of genes involved in psoriasis and psoriatic arthritis are already known or suspected. Psoriasis and psoriatic arthritis are multi-factorial diseases, meaning that they can be caused by a combination of genetics, environmental triggers, and other factors. Genetic variation may result in a greater likelihood of developing the disease. NIH-supported researchers continue to study the genetic aspects of psoriasis and psoriatic arthritis, including how defined genes and their signaling pathways contribute to the onset and severity of this disease.

Since discovering that inflammation in psoriasis is triggered by a type of immune cell called T cells, including natural killer T (NK T) cells, researchers have been studying new treatments that reduce immune system reactions in the skin. Among these are treatments that block the activity of T cells or block their signaling molecules (cytokines) such as IL-23 and IL-17 – proteins that promote inflammation. In addition, novel pre-clinical studies are aimed at blocking NK T cells or their secreted factors that contribute to inflammation in psoriasis.

Recent research has suggested that psoriasis patients may be at greater risk of cardiovascular problems, especially if the psoriasis is severe. They may also be at increased risk of developing obesity, high blood pressure, and diabetes. NIH-supported researchers continue to examine the reasons for these associations and how best to treat individuals with psoriasis and other comorbid conditions. Scientists are also exploring how the nervous system within the skin may be connected to the pathology of psoriasis. These interactions and their role in psoriasis are currently under study.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is investigating the link between inflammation (seen in many disorders including psoriasis) and type 2 diabetes.

Inflammatory signals from adipose (fat) tissue and other sources promote insulin resistance. Inflammation may also contribute to loss of the insulin-producing beta cell. Given the potential contribution of inflammation to type 2 diabetes, NIDDK supported a multi-center clinical trial of the safe and well-tolerated anti-inflammatory drug salsalate as a therapy for type 2 diabetes. This research showed that reducing inflammation—through drugs like salsalate—can be an effective way to reduce blood glucose in type 2 diabetes.

The NIH continues to support research to investigate the molecular and genetic defects in skin underlying the development of psoriasis and psoriatic arthritis, and to improve the understanding of the role of autoimmunity in skin diseases like psoriasis and psoriatic arthritis. In addition, NIH will continue current research efforts in the basic science of chronic inflammation, especially as it relates to the development of cardiovascular disease. New research is underway to determine if the treatment of psoriasis will also lower the risk of major cardiovascular problems, which could lead to further understanding of how inflammation affects the development of atherosclerosis.

Item

Scleroderma - The Committee notes recent advances in scleroderma research, particularly in systemic scleroderma, and encourages NIAMS to provide sustained investments in this area.

Action taken or to be taken

Scleroderma is a group of autoimmune diseases involving abnormal growth of connective tissue. This is often manifested as hard, tight skin. However, in some individuals, this disease may also affect blood vessels and internal organs (e.g., heart, lungs, kidneys), leading to profound disability and premature death. This form of scleroderma, known as systemic sclerosis (SSc), is an important focus of current NIAMS funding. Understanding the genetic, environmental, and immune factors that lead to the development of SSc is a fundamental step toward effective treatments and potential cures.

The NIAMS is supporting several new SSc projects beginning in FY 2013. These include a research career award studying whether three gene expression signatures in skin can serve as accurate biomarkers predicting SSc progression and response to treatment. This may help to identify which patients need aggressive treatment, as well as those that have stable or regressive disease and can avoid potentially toxic treatments. New investigators are also being brought into SSc research through recent NIAMS funding. One of these early stage investigator's studies aims to clarify the complex interactions of T cells and interleukin-31 (IL-31) in producing inflammation and fibrosis, or scarring, in SSc. Information gained from this research may provide new therapeutic targets for the disease.

Research centers are also a vital component of the NIAMS' efforts in SSc research. The NIAMS continues to support the Center for Research Translation at Boston University, which is currently

studying potential biomarkers for pulmonary complications and disease activity in SSc. This center recently published results of a study that found skin gene expression signatures that indicated clinical improvement in SSc patients who received mycophenolate mofetil (MMF) treatment. Some patients improved with this treatment, while others did not. This finding may help clinicians target this treatment to those who will most benefit from it. The NIAMS is also supporting the Multidisciplinary Clinical Research Center for Rheumatic Diseases in African Americans (Medical University of South Carolina) and the Rheumatic Diseases Research Core Center (Boston University Medical Campus).

The NIAMS continues to seek new applications for funding in scleroderma research, including small business concerns to conduct preclinical studies for advancing the development of biomarkers or new treatments for rare diseases, including SSc. The NIAMS has issued a funding opportunity for small business innovation research on identifying biomarker candidate platforms for inflammatory diseases, an important step to early diagnosis and effective treatment before long-term damage occurs. Another funding opportunity announcement encourages applications for studies to follow up on genome-wide association studies (GWAS) that have identified certain genetic regions associated with various diseases, including scleroderma. A better understanding of how these genes contribute to disease may lead to more effective treatments.

In order to address the shortage of investigators trained to tackle the challenging research issues in this field and ensure that research progress will continue, the NIAMS is supporting the training of researchers and clinicians in SSc through grants to the Medical University of South Carolina and the University of Michigan.

Item

Temporomandibular Disorders [TMD] - Many people who have TMD suffer from conditions that routinely affect other joints in the body, such as trauma, arthritis, and fibromyalgia. However, researchers investigating other joints too often ignore TMD because they consider temporomandibular joints to be a subject for dental researchers only. The Committee notes that the Temporomandibular Joint Working Group has improved collaborations among ICs that should have a role in TMD research but believes that NIAMS, as well as NIBIB, should participate more fully, so that NIDCR is not expected to carry the workload alone.

Action taken or to be taken

Temporomandibular disorders (TMD) are a group of conditions that cause pain and dysfunction in the jaw joint and muscles that control jaw movement. NIAMS supports a robust research portfolio into joint physiology and mechanics and basic, translational, and clinical studies of chronic musculoskeletal pain—work which may help to inform studies that are focused primarily on understanding, treating, or preventing TMD. NIAMS also continues to fund a study of the molecular basis of TMD and inflammatory knee arthritis through the highly competitive Pathway

to Independence Award for promising early-stage scientists. This grant's principal investigator recently received a tenure-track faculty position and is establishing an independent research lab.

NIAMS-funded investigators also collaborate directly with researchers who are supported by the National Institute of Dental and Craniofacial Research (NIDCR). A recent example comes from a multidisciplinary team at Duke University which characterized the role that TRPV4, a protein on the surface of neurons, plays in transmitting the feeling of pain when biting or chewing. While the protein appears to be unrelated to the inflammation and structural changes that cause TMD, its unique role in the sensation of pain makes it a promising new target for therapy development. Other recent advances from teams supported by NIAMS and NIDCR include research describing the physical properties of the temporomandibular joint (TMJ) disc, the cartilage that provides a cushion between the upper and lower jaw bones, and a study demonstrating that standard methods of measuring pain sensitivity can be used in clinical trials for women who have TMD.

NIAMS continues to participate in the Temporomandibular Joint Disorders Interagency Working Group, as it has done since the working group's inception. Through this venue, staff provide updates on NIAMS-supported research projects that may impact future TMD research directions, contribute to the organization of scientific meetings on TMD and related conditions, and interact with relevant patient and health advocacy groups. The May 2013 workshop hosted by NIDCR, NIAMS, and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) is one example of activities that the working group facilitates. At the meeting, bioengineering and orthopaedic researchers, along with patient advocates, discussed scientific knowledge and opportunities related to the structure and function of the TMJ and its individual components (e.g., muscle, bone, cartilage) and the research tools available to advance the field.

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National Institute on Deafness and Other Communication Disorders (NIDCD)

Senate Significant Items

Item

Central Auditory Plasticity - The Committee continues to support research in animals and humans on changes in the functional organization of neural circuits along all of the pathways in the brain that process sound, following both temporary and permanent developmental and adult hearing loss.

Action taken or to be taken

The capacity of our nervous system to change its response properties is called plasticity. Developing a more complete understanding of changes in the brain caused by deafness is crucial to developing treatments for hearing disorders. To accomplish this goal, NIDCD extramural and intramural scientists are conducting research to better understand plasticity of the central auditory system by researching the molecular, cellular, and systems level components of the brain. For instance, scientists are seeking to understand how synaptic transmission is affected by hearing loss and whether there is a critical period in development, which requires auditory experience. NIDCD-supported scientists are also studying whether stimulation from a cochlear implant can prevent synaptic abnormalities in the deafened auditory system of cats.

Another NIDCD project has provided new insights about the relationship between auditory plasticity and continued performance of well-learned behavioral tasks by demonstrating how the nucleus basalis (a deep-brain structure which releases acetylcholine onto the neocortex during behaviorally important events) is involved with learned plastic changes in auditory memories of tones in rodents.

Lastly, NIDCD recently began two clinical trials, which capitalize on the brain's plasticity as a way to reduce tinnitus (ringing in the ear). One trial combines vagal nerve stimulation in the neck with sound stimulation in the ear to alleviate tinnitus. Another trial, deep brain stimulation, places an electrode directly into hearing and associated nerve pathways deep within the brain to block tinnitus-related brain activity.

Item

Eustachian Tubes - The Committee urges NIDCD to conduct additional studies on potential treatments for dysfunctional eustachian tubes.

Action taken or to be taken

The Eustachian tube is a small passageway located on both sides of the head that connects the upper part of the throat to the middle ear. It supplies fresh air, drains fluid, and keeps air pressure between the nose and the middle ear at a steady level. Studies of the Eustachian tubes have

provided new information on tubal mechanics, surfactant-like (fluid) substances, and middle ear pressure regulation.

NIDCD is supporting research to develop a more complete understanding of Eustachian tube dysfunction. For instance, NIDCD recently awarded a Clinical Research Center grant focused on characterizing middle ear pressure regulation. This grant will enable scientists to determine how Eustachian tube dysfunction is related to middle ear pressure malfunction and how such dysfunction contributes to ear infections. Another project in this Center is a study to understand if morphological changes in the Eustachian tubes during development contribute to improved Eustachian tube function and reduced risk for middle ear infection (otitis media).

Lastly, NIDCD is supporting several clinical trials involving the Eustachian tubes and otitis media to facilitate the development of treatments for dysfunctional Eustachian tubes. A Phase I clinical trial is determining the efficacy of using balloon dilation of the Eustachian tube to improve Eustachian tube function and cure chronic otitis media in adults. A Phase II clinical trial is studying the efficacy of a modification of cleft palate surgery to improve Eustachian tube function and reduce the prevalence of otitis media in children with cleft palate.

Item

Genetic Causes of Communication Disorders - The Committee recommends additional efforts by NIDCD to identify and understand the structure, function, and regulation of genes whose mutations are responsible for congenital and age-related deficits. Research to develop high-throughput platforms for testing of individuals is also encouraged.

Action taken or to be taken

NIDCD-supported scientists are actively working to understand how the structure, function, and regulation of genes results in deafness and other communication disorders. Current efforts include identification of genes whose mutation results in hereditary hearing loss and in stuttering. In addition, NIDCD is supporting both development of a database of medical data related to communication disorders, and more tests to screen for genetic causes of hearing loss.

NIDCD intramural scientists are using next-generation sequencing to identify novel genes for hereditary hearing loss. For example, NIDCD intramural scientists identified *TPRN* as a novel gene for nonsyndromic deafness, which is hearing loss or deafness not associated with other inherited clinical characteristics. Mutations of *TPRN* disrupt the encoding of taperin – a protein essential to the function of tiny hair-like projections found on hair cells in the inner ear that help transform sound energy into electrical energy. In addition, NIDCD intramural scientists discovered that mutations in the *GIPC3* gene cause one form of adult-onset hearing loss by encoding hair cell proteins that are less stable and break down quickly. A recent collaboration between NIDCD intramural and extramural scientists has resulted in the discovery that mutations of the *CLPP* gene cause hearing loss and pre-mature ovarian failure, a disorder referred to as

Perrault syndrome. NIDCD intramural scientists are working to describe the location and probable function of myosins, which are proteins within the sound-conducting structures of the ear. Their research is aimed at determining the cause of deafness and hearing loss when an individual inherits a gene that makes a mutant myosin protein, such as in late-onset hearing loss or in Usher syndrome, a disorder resulting in deafness and blindness.

NIDCD-supported scientists are working to understand the genetics of stuttering. A team of intramural scientists focused on families with many cases of stuttering that persist beyond childhood. They identified the locations of a number of causative genes on different chromosomes, and in some cases were able to identify the responsible gene. Although the genes identified thus far are responsible for a small fraction of stuttering, they provide new insights into the cellular and molecular causes of stuttering. The team is now actively working to identify additional genes to explain the causes of stuttering, and collectively account for a larger fraction of this communication disorder.

NIDCD is supporting the development of an integrated relational database of genetic, audiologic, otologic, and other medical data. The database will enable researchers and clinicians to study how underlying genetic and environmental factors influence the effectiveness and outcome of patient-directed therapies and interventions. It will also help healthcare professionals identify children at high risk for congenital or late onset hearing loss, assess the audiologic and otologic features of children with all forms of hearing loss, and characterize the genetic basis for hearing loss.

Lastly, NIDCD is supporting a greater number of research projects using genomic medicine to develop methods to screen for and diagnose genetic causes of hearing impairment. These projects translate basic research findings into clinical tools.

Item

Hearing Aids and Cochlear Implants - The Committee strongly urges NIDCD to support research grants that could lead to less expensive hearing aids, so such aids could become accessible and affordable to more people. The Committee also supports device research to improve users' understanding of speech through background noise. In addition, the Committee supports research that would enable users of cochlear implants to experience high-quality speech and music perception, as well as studies that would improve bilateral implants, short electrode implants, and hybrid cochlear implant/hearing aids.

Action taken or to be taken

For the 36 million American adults who report having some degree of hearing loss, the hearing aid is the primary device available for managing hearing loss. However, adoption is often slow. Even among those who use hearing aids, most people live with hearing loss that has progressed to moderate-to-severe levels. NIDCD has promoted research collaborations to improve the accessibility, affordability, and outcomes of hearing health care. In response to these initiatives,

NIDCD-supported scientists are examining several aspects of hearing aid outcomes, as well as service delivery, screening, and follow-up methods, with the goal of increasing access to effective, lower-cost, hearing health care for underserved older adults. Examples include researching: (1) in-home auditory training for older adults with hearing aids, (2) low-cost hearing aids and service-delivery models, (3) speech perception training for hearing-aid users, (4) developing and testing screening paradigms to better engage primary care physicians in the hearing screening process, and (5) conducting a randomized clinical trial of four community based hearing screening programs.

Despite advances in hearing technologies, hearing aid users frequently encounter difficulty understanding speech in noisy environments—limiting the user’s ability to communicate and interact in certain settings. Through its small business grant program, NIDCD supports several projects to foster the development of innovative technologies to lessen problems associated with background noise. For example, researchers are developing a hearing aid that can replay a short, recently received audio at the press of a button. Additionally, researchers are studying several types of microphone technology to mitigate background noise.

The cochlear implant is an important device for managing severe-to-profound hearing loss. NIDCD-supported scientists are examining a variety of combinations of electrical and acoustical stimulation in one or both (bilateral users) ears to determine optimal strategies to improve outcomes for both children and adults with various hearing loss profiles. In addition, there are a rapidly growing number of "bimodal" individuals who use a cochlear implant in one ear and a hearing aid in the other ear. Current research efforts are aimed at developing signal processing schemes, optimizing device selection, developing better fitting paradigms, ascertaining the benefits of various stimulation modes, and creating data-based tools to allow clinicians to maximize speech perception for these individuals.

Lastly, NIDCD supports several clinical trials related to hearing aids and cochlear implants. Examples include investigating the efficacy of (1) telemedicine versus traditional face-to-face post-implant aural rehabilitation in children, (2) cochlear implant(s) versus hearing aids in developmentally delayed children, and (3) robotic percutaneous cochlear implantation in children and adults.

Item

Inner Ear Hair Cell Regeneration - The Committee is aware of advances being made in the identification of cells in the inner ear that can be induced or reprogrammed to replace cells lost in deafness. Additional research to understand the processes of possible regeneration or transdifferentiation of inner ear hair cells to restore natural hearing is strongly encouraged. The Committee recommends funding to develop this therapeutic approach and move it into clinical applications.

Action taken or to be taken

NIDCD continues to place a high priority on research directed at regenerating the hair cells of the inner ear and understanding how inner ear cells can be induced to replace lost hair cells. In the past year, the laboratory mouse has served NIDCD-supported scientists as an invaluable model, providing insight into functional recovery following noise-induced hearing loss, enabling conditional hair cell deletion, and providing stem cells used in 3-D culture techniques to make cells that behave like hair cells.

In sensory portions of the normal ear, hair cells are surrounded by supporting cells. A group of NIDCD-supported scientists used their knowledge of cell signaling in the inner ear to regenerate a limited number of hair cells in an adult mouse. After exposing animals to noises loud enough to cause hair cell death and hearing loss, the team treated the mice with a drug that interferes with a cell signaling pathway that limits the number of hair cells that form during development of the ear. Since hair cell-limiting signals were removed, a small number of supporting cells were able to become new hair cells and the animals demonstrated some limited hearing recovery.

NIDCD-supported scientists recently overcame a roadblock to studying hair cell regeneration in whole animals. Methods of destroying hair cells to then study regeneration were inconsistent (i.e., many hair cells were killed in some animals, but very few in others). To overcome this barrier, NIDCD-supported scientists developed a mouse model in which only the hair cells are sensitive to human diphtheria toxin. By administering diphtheria toxin to the animal, the team was able to specifically and consistently destroy nearly all the hair cells in the utricle (balance organ) of the inner ear. Following this treatment, many supporting cells appeared to develop as new hair cells, a process called direct transdifferentiation.

Pluripotent stem cells have the potential to develop into any of the cells in the body. But scientists have had a difficult time coaxing pluripotent stem cells to become hair cells. Recently, however, a team of NIDCD-supported scientists found a way to reach that elusive goal. They carried mouse embryonic stem cells through the normal developmental pathway in a 3-dimensional environment. This technique enabled them to generate many hair cells from stem cells, and they were also able to show that these hair cells make contacts (synapses) with sensory neurons that also develop within the 3-D culture system. They will now use their new approach to test potential drugs, model diseases in culture, and work on cellular replacement therapy techniques.

The NIDCD continues to support hair cell regeneration research with the goal of translating basic science discoveries into hair cell replacement therapies for use in the clinic.

Item

Noise-Induced Hearing Loss - Hearing loss resulting from noise damage represents a major form of acquired deafness. The Committee therefore recommends studies to better understand

the pathogenesis of noise-induced hearing loss and encourages NIDCD to continue to promote public awareness of the importance of protecting hearing from noise, through public service announcements or other means.

Action taken or to be taken

Preventing and treating noise-induced hearing loss (NIHL) is a priority for NIDCD - especially given that people of all ages can suffer from NIHL. In fact, an estimated 26 million Americans between the ages of 20 and 69 have high frequency hearing loss that may have been caused by exposure to loud sounds or noise at work or in leisure activities.

To address this public health need, NIDCD continues to support research to better understand NIHL as well as to identify and develop treatments that can prevent or reduce NIHL. For example, recent animal studies suggest that moderate to mild noise exposure — once thought to have no long-term negative effects on hearing — may in fact result in the permanent loss of connections between sensory cells of the inner ear (auditory hair cells) and auditory neurons. As such, NIDCD-supported scientists are seeking to understand the cellular mechanisms that result in these lost connections and are exploring ways to preserve them.

NIDCD-supported scientists are also investigating the role of environmental factors, such as heavy metals, on susceptibility to NIHL. These animal studies will help scientists ascertain whether exposure to certain environmental factors can predispose individuals to NIHL. This information will help inform future NIHL prevention strategies.

In addition, NIDCD-supported scientists continue to research potential treatments that might prevent or reduce NIHL. One such study is exploring the effectiveness of certain pharmacological agents. In several NIDCD-supported clinical trials, scientists are exploring whether antioxidants administered with a vasodilator (a medication that widens blood vessels) following exposure to loud music can prevent or reduce NIHL. NIDCD-supported scientists are also comparing the impact of alternative NIHL prevention/intervention strategies on hearing protection device use and use-related attitudes/beliefs among farmers.

In addition to supporting NIHL research, NIDCD uses a variety of methods to increase public awareness of NIHL. For instance, NIDCD runs an educational campaign called *It's a Noisy Planet. Protect Their Hearing*[®] aimed at informing parents of tweens (ages 8 to 12 years) of the dangers of NIHL. Noisy Planet program materials are produced in both English and Spanish, and in 2013, the NIDCD distributed more than 73,000 informational items.

Outreach through partnerships with nonprofit organizations and professional societies and media help ensure broad distribution of the campaign's prevention messages. For example, in July 2012, Noisy Planet was featured as a category on the national television game show *Jeopardy!* in a special Kids' Week episode, with viewership of more than five million people.

NIDCD has released a series of English and Spanish radio and print public service announcements about NIHL. To further expand its reach and increase public engagement, the NIDCD launched a Facebook page focused on NIHL. In addition, the NIDCD Twitter handle is used to promote relevant research and public health messages.

In 2013, the NIDCD completed an evaluation of Noisy Planet using tools such as surveys, focus groups, and analyses of materials orders to measure how well the campaign reaches primary and secondary audiences, as well as how to better meet audience needs and improve outreach and dissemination strategies. The results will help guide the future direction of the campaign to ensure that activities remain relevant and effective for increasing awareness to improve public health.

It's a Noisy Planet. Protect Their Hearing[®] is a registered trademark of HHS.

Item

Otitis Media - The Committee encourages NIDCD to accelerate its research into susceptibility to and pathogenesis of otitis media and its consequences, and into new treatments for chronic and recurrent cases. In particular, the Committee urges studies related to genetic risk factors, bacterial biofilms, and the impact of vaccination on disease prevention.

Action taken or to be taken

Otitis media (OM), or middle ear infection, is one of the most common reasons for an infant to visit a doctor. Seventy-five percent of children experience at least one episode of OM by their third birthday, and almost half of these children will have three or more ear infections during their first three years. The medical costs and lost wages resulting from OM amount to billions of dollars in the U.S. each year. OM often begins when viral or bacterial infections that cause sore throats, colds, or other respiratory problems spread to the middle ear. NIDCD supports several projects on the cause of OM. For example, NIDCD recently funded a project that utilized whole genome sequencing to understand why one particular strain of the bacterium, nontypeable *Haemophilus influenzae* (*NTHi*), is more likely to cause disease. By sequencing the bacterial strain from children who are prone to acute OM, scientists will determine the subset of virulence genes responsible for OM.

NIDCD also supports a wide variety of studies to develop new treatments for chronic and recurrent OM. These studies examine the bacterial pathogenesis and human immune responses following infection, how genetic risk factors make individuals more or less susceptible to OM, and whether environmental factors could reduce OM risks in children with genetic predisposition. NIDCD also supports research on the delivery of drugs to the middle ear, including a project to develop an antibiotic gel that is applied once in the outer ear. Chemicals in the gel help antibiotics cross the eardrum, and the gel holds the medicine in place. This approach may help prevent antibiotic resistance and toxicity by keeping the medications localized.

NIDCD continues to fund studies that seek to develop vaccines against OM. NIDCD-supported scientists are evaluating how well two novel *Streptococcus pneumoniae* vaccines work to prevent OM and how they may be developed into an effective intranasal vaccine. In addition, NIDCD-supported scientists are developing non-invasive vaccines (e.g., transcutaneous or across the skin) to prevent middle ear infections aimed to target *NTHi* and the biofilms (sturdy bacterial structure that attacks respiratory tissue and is resistant to immune defenses) the bacteria produces.

Lastly, NIDCD is funding two clinical trials to prevent OM by improving Eustachian tube function. The Eustachian tube is a small passageway located on both sides of the head that connects the upper part of the throat to the middle ear. One clinical trial studies the efficacy of a modification of cleft palate surgery to improve Eustachian tube function and reduce the prevalence of middle ear infections in children with cleft palate. Another trial is examining the use of a balloon to open up the Eustachian tube to prevent middle ear fluid buildup and chronic OM in adults.

Item

Presbycusis - The Committee urges NIDCD to continue to delineate the multiple physiological and neurological processes resulting in presbycusis, or age-related hearing loss.

Action taken or to be taken

Presbycusis is gradual hearing loss that occurs in most individuals as they grow older. Approximately 40 percent of adults 65–74 years old and nearly 75 percent of people age 75 and older have hearing loss. NIDCD considers presbycusis an area of great importance and supports research on the complex interaction of inherited genes and environmental exposures that lead to presbycusis. NIDCD-funded research in the area of presbycusis includes both human and animal studies.

NIDCD continues to support the multidisciplinary Specialized Center on Experimental and Clinical Studies of Presbycusis, which aims to improve diagnostic, rehabilitative, and preventive measures for presbycusis. Scientists are using the Center’s extensive human subject database combined with information from presbycusis animal models to characterize the pathophysiology of human presbycusis. Such studies are expected to lead to improved diagnosis and treatment of presbycusis to enhance both the communication and the quality of life of older adults.

Animal model studies suggest that caloric restriction, which reduces oxidative stress to cellular components, may delay the onset of presbycusis. NIDCD is supporting a study examining the molecular basis for this effect in order to determine whether protecting the inner ear from oxidative stress may slow presbycusis. Additional NIDCD-supported studies are looking at the role of mitochondria in caloric restriction-mediated prevention of presbycusis and testing the

ability of two FDA-approved drugs to prevent presbycusis in animal models. Scientists hope to use these studies as the foundation for developing future preventative therapies.

However, damage and age-related changes to the inner ear are not the only causes of presbycusis. The nerve cells in parts of the brain that process sound (auditory neurons) are also affected by aging, and NIDCD-supported scientists are working to determine how these age-related changes in the brain cause changes in how an individual processes sound. NIDCD-supported scientists observed that in older mice, the brain sends fewer signals to tell the thalamus to pay less attention to some sounds. This likely makes it more difficult for the aging brain to focus attention on one sound in a noisy environment. Data from another NIDCD-supported study demonstrate that age-related changes in the rodent's auditory neurons make these cells less able to follow rapid changes in sound amplitude. Scientists hope to use this information to develop interventions that help deal with problems due to these changed neurons, to improve hearing processing in the aged brain.

The tissues of the human inner ear are difficult to study in living individuals, so scientists rely on postmortem study of human temporal bones to reveal the anatomy and pathology of presbycusis and other disorders, and cochlear implant placements. The NIDCD funds the National Temporal Bone, Hearing and Balance Pathology Resource Registry to disseminate information about temporal bone donation and to enroll donors. The NIDCD also funds the Otopathology Research Collaboration Network to coordinate temporal bone research laboratory studies on human ear disorders. The Network emphasizes modern imaging, biochemical, and molecular biological tools to study human presbycusis and other inner ear disorders. Two of the laboratories are analyzing how otosclerosis (overgrowth of bone in the inner ear) can lead to sensorineural hearing loss with age.

Item

Tinnitus - The Committee urges NIDCD to continue basic research on the specific neural dysfunction responsible for tinnitus as well as clinical trials to translate basic science into therapies.

Action taken or to be taken

Tinnitus is a symptom characterized as the sensation of sound when it is not physically present, and is likely to have more than one cause. It can range from intermittent and mildly annoying to chronic, severe, and debilitating. Tinnitus is commonly preceded by hearing loss, which can result from exposure to loud noises or as an unavoidable side effect of certain life-saving treatments (e.g., some antibiotics and/or chemotherapeutic agents). According to the American Tinnitus Association, up to 50 million people in the U.S suffer from tinnitus. There is no known cure.

NIDCD continues its commitment to basic research to identify the specific neural dysfunction responsible for tinnitus. For example, NIDCD-supported scientists are seeking to better understand the role of the dorsal cochlear nucleus (DCN) as it relates to tinnitus. During hearing loss, research has shown that other sensory signals entering the DCN are amplified, such as touch-sensing (somatosensory) signals. This overcompensation by the somatosensory neurons, which carry information about touch, vibration, skin temperature and pain, is believed to fuel tinnitus in many cases. Some tinnitus sufferers report the ability to change their perception of tinnitus by clenching their jaw and/or touching their ear. As a result, NIDCD is funding a study of how certain somatosensory inputs might play a role in suppressing tinnitus. In another research project, NIDCD-supported scientists are seeking to gain a detailed understanding of why some individuals with tinnitus report their tinnitus is briefly suppressed (typically less than a minute) following the offset of an appropriate masking stimulus (e.g., upon turning off a loud external sound). This phenomenon is known as residual inhibition (RI). Scientists anticipate that a detailed understanding of RI will enhance the knowledge of the central mechanism responsible for tinnitus and provide a foundation for the development of therapeutic drugs to treat tinnitus.

In addition to searching for the causes of tinnitus and detailing the mechanisms responsible for tinnitus, NIDCD is pursuing various experimental treatment modalities. In one clinical trial, NIDCD-supported scientists are using an integrated medicine approach to treat non-auditory emotional aspects of tinnitus. In another trial, NIDCD-supported scientists are exploring more traditional, sound-based masking therapy and special education techniques.

Also, upon receiving an Investigational Device Exemption from the Food and Drug Administration, NIDCD-supported clinicians plan to pursue the use of an investigational new device to stimulate the vagal nerve in the neck along with sound stimulation in the ear as a potential treatment. In a clinical trial that is expected to begin in 2014, NIDCD-supported clinicians plan to begin a deep brain stimulation trial to assess its ability to treat tinnitus.

Item

Vestibular Research - The danger of injury from falls is a health hazard, especially in the elderly. Therefore, the Committee urges NIDCD to conduct further basic vestibular-system studies to understand the cellular mechanisms involved in the coding of head movements necessary to assure an individual's ability to maintain balance.

Action taken or to be taken

The vestibular system of the inner ear provides the brain with sensory information needed for balance, eye stabilization, posture, and locomotion. Vestibular disorders cause dizziness and problems with balance, and affect an estimated 10 million adults in America. NIDCD's support of vestibular research includes basic research on the neural mechanisms of vestibular sensory function in animals and humans, and clinical research on human perceptions and disorders.

Turning the head stimulates the semicircular canal system in the inner ear. In response to this motion, an eye reflex called the vestibulo-ocular response (VOR) stabilizes the gaze. NIDCD-supported scientists are studying how nerve signals from the vestibular system work together with visual signals to help us navigate and maintain balance. This research shows how detection of motion direction can adapt to conflicting information from the vestibular and visual systems.

Scientists are developing a vestibular prosthesis to replace balance and positional information lost through disorders like Ménière's disease or head trauma. Using non-human primates as a translational model, NIDCD-supported scientists have developed and are testing implantable devices. Results indicate that the vestibular nerve can be safely, effectively, and specifically stimulated electrically to drive responses that mimic normal vestibular responses.

Another NIDCD-supported scientist has discovered that magnetic resonance imaging (MRI) brain-scanning machines with high magnetic fields stimulate the receptor cells of the inner ear, producing dizziness in many individuals. MRI-induced vertigo occurs when a strong magnetic field interacts with ionic currents in the inner ear endolymph fluid of the labyrinth, directly stimulating the sensory vestibular hair cells. The result is the perception of dizziness, which is measured by the drifting of the eyes (nystagmus). The potential clinical impact of this finding is great, because it affects interpretation of functional MRI scans of brain activity by introducing a previously unknown vestibular component, and because it provides a completely new potential diagnostic tool for quantitatively analyzing and perhaps diagnosing vestibular disorders.

Sensory hair cells in the portion of the inner ear that controls balance detect linear and angular movements of the head and convert them into electrical signals that are sent via the balance nerve to the brain. NIDCD intramural and extramural scientists are studying the genes, molecules, and cellular mechanisms underlying this process, known as mechanotransduction. This research may lead to therapies to prevent or treat balance disorders caused by disruptions of vestibular hair cell function and mechanotransduction.

In addition to vestibular information from the inner ear and the visual information from the eyes, the brain also processes touch information from bones, joints, and skin to maintain our sense of position and movement in space. NIDCD intramural scientists are studying the relative contributions of these three sensory systems in individuals with Usher syndrome, a disorder which causes a loss of inner ear function and progressive blindness, resulting in deprivation of two of the three senses required for balance. The results provide insight into the organization of these senses as well as a practical basis for physical rehabilitation and exercises to reduce the risk of falls.

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National Institute on Alcohol Abuse and Alcoholism (NIAAA)

Senate Significant Items

Item

Functional Integration Initiative - The Committee applauds the Trans-NIH Substance Use, Abuse, and Addiction Functional Integration initiative to help NIAAA, NIDA, NCI, and other ICs work more closely together on substance use, abuse, and addiction research. (p. 98)

Action taken or to be taken

The National Institutes of Health (NIH) appreciates the Committee's enthusiasm for the Trans-NIH Substance Use, Abuse, and Addiction Functional Integration initiative, now referred to as Collaborative Research on Addiction at NIH (CRAN). Enhanced collaboration between the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Drug Abuse (NIDA), and the National Cancer Institute (NCI) will bring new insights into the causes of substance use, abuse, and addiction, ultimately leading to improved prevention programs and enhanced treatment options. A recent example comes from a NIAAA-supported clinical trial demonstrating that the smoking cessation medicine varenicline (Chantix®) also reduces alcohol consumption and craving in both non-smokers and smokers, potentially expanding treatment options for alcohol dependence (addiction) in the future. This finding exemplifies how effective treatment for addiction to one substance can inform treatment for addiction to another and suggests that treatments can be developed that simultaneously address more than one substance use disorder.

CRAN was established this year and will begin to support studies that focus on comorbidity-related research in FY 2014. Two funding opportunity announcements have been issued soliciting administrative or competitive supplement proposals to augment existing research projects by targeting new and/or underrecognized opportunities and synergies addressing polysubstance use and comorbidity. Possible topics include: concurrent vs. sequential treatment of co-occurring substance use disorders; trajectories of polysubstance use; polysubstance screening for adolescents; services/systems research related to healthcare reform; extension of policy research to other substances; and secondary data analyses.

A Joint meeting of NIAAA's and NIDA's Advisory Councils with representation from NCI's Council has been scheduled for February 2014 to review grant proposals and explore other opportunities for advancing addiction science. CRAN also recently launched a [website](#) to inform the research community and other constituents about new funding opportunities, news and events, and other relevant resources. In addition, an integrated NIAAA/NIDA intramural clinical addictions research program was established for leveraging resources and expertise to investigate new avenues for understanding and treating substance use disorders.

In FY 2013, prior to the official launch of CRAN, NIAAA, NIDA, and other NIH Institutes, in partnership with the Department Of Defense, released a funding opportunity announcement focused on prevention and treatment of substance use, abuse, and addiction among veterans in support of the Executive Order – Improving Access to Mental Health Services for Veterans, Service Members, and Military Families. We look forward to sharing the results of the funded studies and helping to promote better health and greater well-being among our nation’s service members.

National Institute on Drug Abuse (NIDA)

Senate Significant Items

Item

Drug Abuse and HIV/AIDS - The Committee understands that drug abuse and addiction continue to fuel the spread of HIV/AIDS and that drug abuse prevention and treatment interventions can be very effective in reducing HIV risk. Research should continue to examine every aspect of this relationship. The Committee is also concerned about drug abuse and HIV/AIDS in criminal justice populations. Research efforts to empirically test and expand the “seek, test, treat, and retain” paradigm are encouraged.

Action taken or to be taken

Investment in HIV research over the past 30 years has transformed a deadly infection into a chronic illness that can be managed over decades while maintaining a productive lifestyle. Unfortunately approximately 50,000 new HIV infections occur each year in the United States, and nearly 1 in 5 people who are HIV positive are unaware they are infected. Furthermore, the burden of this disease is disproportionately borne by those with substance use disorders. Since the epidemic began, nearly 182,000 injection drug users diagnosed with AIDS have died, including over 4,000 in 2010. Risk of infection exists for all individuals under the influence of drugs, not just injection drug users, since intoxicated individuals are more likely to engage in risky behaviors that leave them vulnerable to contracting HIV.

For this reason, treatment for substance use disorders (SUDs) is HIV prevention in that it reduces risky behavior that may lead to HIV infection. Recent research has shown that treating HIV can also reduce HIV transmission as well as HIV incidence on a population level. However, eliminating HIV transmission can only be achieved if every person who is infected can be identified, tested, treated, and retained in care. NIDA has been encouraging research to learn how best to implement this Seek, Test, Treat, and Retain ([STTR](#)) [paradigm for those who suffer from SUDs](#), focused primarily on the criminal justice system and other vulnerable populations.

NIDA has recently expanded research efforts on vulnerable populations at the intersection of substance use and HIV. In June 2013, NIDA solicited grant applications targeting three such populations: 1) [older adults with chronic pain](#), 2) [African American women and young men who have sex with men \(MSM\)](#), and 3) [the unstably housed](#). Moreover, NIDA launched its newest initiative within the criminal justice system: Juvenile Justice Translation Research on Interventions for Adolescents in the Legal System ([JJ-TRIALS](#)) in July 2013. This research cooperative will determine how juvenile justice programs can effectively implement prevention and treatment services for SUDs and HIV to maximize the likelihood of sustained delivery of evidence-based practices to improve offender drug abuse and HIV outcomes.

While work continues to improve prevention, screening, and treatment for HIV, more research is focusing on implementation studies to identify how best to address the complete needs of the patient, including HIV, SUD, concurrent mental illnesses or infectious diseases (hepatitis). For example, NIDA is encouraging research to identify best practices for integrating SUD treatment and prevention in HIV/AIDS care settings. Integrating treatment services will not only expand the care available to patients who need it, but will also help retain these patients within the HIV care continuum – the top priority for the Administration’s HIV Care Continuum Initiative released in July 2013.

Item

Marijuana - NIDA is encouraged to continue to fund research on preventing and treating marijuana abuse and addiction, as well as the possible health and policy implications of proposals to implement “medical marijuana” or marijuana legalization programs.

Action taken or to be taken

Marijuana is the most-used illicit substance by all age groups in the U.S. NIDA is particularly concerned about the increasing use of marijuana by teenagers over the past several years. Nearly a quarter of 12th graders are current (past-month) marijuana users, and 6.5 percent use marijuana daily. Increased use parallels an increased perception among this age group that the drug is safe—a trend that may be linked to the intensifying public conversation about “medical marijuana” (and in some states legalization advocacy) over the past several years. This trend alarmingly contrasts with mounting scientific evidence that marijuana use during adolescence can permanently impair users’ intelligence as well as derail their lives in other ways.

NIDA supports a broad portfolio of research on prevention of marijuana use and treatment of marijuana use disorders. On the prevention side, NIDA-funded research testing a partnership-based intervention called PROSPER for grades 6–12 has shown significant reductions in marijuana use, particularly for higher-risk teens. NIDA also supports the development and testing of medications for cannabis use disorders. The nutritional supplement N-Acetylcysteine (NAC) has been shown to reduce use in cannabis-dependent adolescents, and a Phase 3 trial in NIDA’s Clinical Trials Network will study NAC for cannabis cessation, in combination with behavioral therapy. NIDA is also funding research on various compounds that target cannabinoid receptors as possible future treatments for cannabis and other substance use disorders.

The shifting policy landscape around medical marijuana is expected to have social, behavioral, and public health impacts. To better understand the effects of these policies, NIDA is funding grants to study the consequences of medical marijuana laws on nonmedical use, along with perceptions and attitudes; the effect of medical marijuana and dispensaries on access to marijuana, health, and community safety; and medical marijuana use in HIV positive patients. Initial findings from one study

<http://www.ncbi.nlm.nih.gov/pubmed?term=Kepple%20NJ%5BAuthor%20-%20First%5D> have

showed no association between marijuana dispensaries in Sacramento, CA neighborhoods and the number of violent or property crimes nearby. More recently NIDA has supplemented existing grantees (<http://grants.nih.gov/grants/guide/pa-files/PA-13-138.html>) to better understand the effects of marijuana legalization on norms, use, and parenting in Washington State.

Given the growing misperception of marijuana's safety by the public and especially young people, NIDA is using publications, social media, educational events such as National Drug Facts Week (<http://drugfactsweek.drugabuse.gov/>) (including the popular National Drug Facts Chat Day), and other avenues to educate the public, and especially youth, about the strong scientific evidence for the harmful consequences of marijuana use, as well as about the limited therapeutic suitability of smoked marijuana compared to safer medications derived from THC and other cannabinoids. NIDA recently released a newly updated version of its population publication *Marijuana: Facts for Teens* and soon will be releasing a newly updated version of *Marijuana: Facts Parents Need to Know*. In January 2014, NIDA published *Principles of Adolescent Substance Use Disorder Treatment: A Research-Based Guide*, that covers treatment approaches for all drug problems, including marijuana use disorder, which is the reason for nearly three fourths of adolescent substance abuse treatment admissions.

Item

NIDAMed - The Committee is pleased with NIDAMed, the Institute's physicians outreach initiative. The Committee urges NIDA to continue its focus on providing physicians and other medical professionals with the tools and skills they need to incorporate drug abuse screening and treatment into their clinical practices.

Action taken or to be taken

In April 2009, NIDA launched its first comprehensive Physician's Outreach Initiative, NIDAMED, to assist medical professionals as the first line of defense against substance abuse and addiction. At the heart of NIDAMED is the NIDA Drug Use Screening Tool, a web-based interactive tool that incorporates the NIDA Quick Screen, a single question substance abuse screener, and the NIDA-Modified NMASSIST, a more in depth screening tool based on the WHO Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST). This web-based interactive tool guides clinicians through a series of screening questions for tobacco, alcohol, and illicit and prescription drug abuse; and, based on the patient's responses, generates a substance involvement score that suggests the level of intervention needed. Between April 2011 and October 2013, the NIDA Quick Screen had been accessed over 25,000 times and the full screening tool had been completed about 5,000 times.

NIDA continues to develop resources to accompany the NIDA Drug Use Screening Tool. For example, in January 2012 NIDA released a new consumer-friendly treatment guide, "Seeking Drug Abuse Treatment: Know What to Ask," to help patients (and their physicians) identify appropriate treatment programs. More than 90,000 copies of the "Seeking Treatment" brochure

have been disseminated since its release. In 2012, with funding from the White House Office of National Drug Control Policy and in partnership with Medscape, NIDA developed and launched two new continuing medical education (CME/CE) courses—one focused on safe prescribing for pain, the other on managing patients who abuse prescription opioids. Both of these courses include video vignettes that demonstrate how to screen for substance abuse. To date, nearly 60,000 clinicians have completed these courses.

Finally, to help integrate substance abuse and addiction diagnosis, referral, and treatment into standard medical practice, NIDA launched its Centers of Excellence for Physician Information (CoEs) in 2006, specifically targeting physicians in training. Ten curriculum resources—educational materials to advance medical students’ and resident physicians’ understanding of drug abuse and addiction—have been released to date. NIDA is continuing to work with the CoEs to disseminate these curriculum resources, with two more anticipated in the coming year. NIDA has also taken the lead at NIH in the development of Centers of Excellence in Pain Education (CoEPEs). In May 2012, NIH designated 12 health professional schools as CoEPEs to develop pain management curriculum resources for medical, dental, nursing, and pharmacy schools to advance the safe and effective treatment of pain, while minimizing risks of addiction and diversion.

Item

Pain Medications - The Committee remains concerned about the continued crisis of prescription drug abuse. NIDA is strongly urged to continue its support of research on pain, including the development of pain medications with reduced abuse liability. In addition, NIDA should continue to fund research to better prevent and treat prescription drug abuse.

Action taken or to be taken

Commonly prescribed for treating severe and/or chronic pain, opioid pain medications are beneficial when used appropriately. Because they act on the same receptors as heroin, opioid pain medications are also prone to abuse. The consequences of abuse are potentially dire: CDC reports that since 1999, unintentional overdose deaths involving prescription opioid pain relievers have more than quadrupled in the United States.

NIDA takes a multipronged approach to its research on pain and prescription opioid abuse that includes (a) research to identify new pain relievers with reduced abuse, tolerance, and dependence risk; and (b) working with industry and government to devise alternative delivery systems and drug formulations that minimize diversion and prevent overdose deaths. For example, an exciting new strategy is based on the idea of developing a pro-drug opioid-based pain medication that would be inactive in the bloodstream until it reaches the digestive system where specific enzymes would cleave and activate it. This approach would ensure that the pro-drug could not be abused via non-oral routes (e.g., injection or inhalation). NIDA has recently partnered with the National Center for Advancing Translational Sciences (NCATS) at NIH to

assist Signature Therapeutics, a small biopharmaceutical company, in advancing the development of just such an abuse-deterrent pain medication, based on a novel, inactive pro-drug formulation of extended-release oxycodone. Our partnership with Signature Therapeutics and NCATS will support the studies necessary to file an investigational new drug application with the FDA.

NIDA also continues to support a diverse prescription drug abuse research portfolio including: epidemiological studies of the patterns, trends, and motivations underlying prescription drug abuse; research to better understand the factors that predispose someone to become addicted to prescription pain relievers and what can be done to prevent addiction among those at risk; studies of the effectiveness and impact of prescription drug monitoring programs; and the development and testing of prevention and treatment (both pharmacological and behavioral) interventions to reduce prescription drug abuse and prevent prescription drug overdoses. For example, NIDA recently entered into an agreement with Lightlake Therapeutics to conduct the dosing studies needed to obtain FDA approval for an intranasal formulation of the opioid antagonist naloxone to rapidly reverse opioid overdose and prevent lethality. Naloxone is currently available in an injectable form that is usually administered by health care professionals. If successful, an intranasal formulation could eventually be made widely available, including for over the counter distribution, expanding access to this lifesaving medication.

Item

Tobacco Addiction - The Committee applauds the recent progress of NIDA-supported researchers toward identifying genetic factors that contribute to nicotine dependence and affect the efficacy of smoking cessation treatments. NIDA is urged to continue developing evidence-based treatments, medications, and prevention strategies to combat nicotine addiction.

Action taken or to be taken

Responsible for more than 440,000 deaths in the United States each year, cigarette smoking (and exposure to cigarette smoke) remains the leading preventable cause of disease, disability and death. While public health interventions have prompted dramatic reductions in the initiation and prevalence of tobacco use and tobacco-related disease and death, more than 70 million Americans are still current smokers. NIDA therefore supports a comprehensive research portfolio aimed at understanding nicotine's effects on the brain and body, identifying effective prevention strategies and developing new medications to help addicted individuals quit for good.

There are currently seven FDA approved medications for smoking cessation; however, long-term abstinence rates are modest at best. NIDA is thus continuing to support the development of strategies to improve outcomes for smokers trying to quit.

- *Personalized Medicine:* Genetic studies are revealing individual differences in how people metabolize nicotine or respond to smoking cessation medications. For example, slow

metabolizers have been shown to have better outcomes when using the nicotine patch. Additionally, individuals carrying specific high risk genes related to heavy smoking and nicotine dependence are also more likely to quit when using cessation medications than those with lower genetic risk. Discoveries such as these will help to optimize medication approaches based on a person's genetic background or other characteristics.

- *Combined Treatments:* Existing medications work through differing biological mechanisms and may work synergistically in combination – a strategy that has been successful in the treatment of other diseases. Thus NIDA is employing a similar strategy to improve long-term smoking abstinence by simultaneously targeting multiple relapse symptoms like withdrawal, craving, and depression.
- *Anti-Nicotine Vaccines:* NIDA is continuing to make progress in the development of anti-nicotine vaccines, which induce the body to produce antibodies that can prevent nicotine from entering the brain. Safety and proof of concept for this approach have already been demonstrated in clinical trials. Previous vaccine candidates failed to sustain effective antibody levels, but newer candidates, with the addition of novel carriers and/or adjuvants, stimulate higher immune response and improved vaccine potency, and are thus showing great promise to combat nicotine addiction.
- *Behavioral Interventions:* Behavioral interventions play a pivotal role in smoking cessation, as they teach smokers how to recognize high-risk situations, develop alternative strategies and manage stress. For example, new research is demonstrating that mindfulness meditation can help smokers quit—even when they don't intend to do so—by reducing cigarette use, withdrawal symptoms and craving. NIDA also continues to support research on the development and testing of tailored interventions in vulnerable populations that have not benefited as much from existing interventions, including people with HIV, women who are pregnant or post-partum, youth, and smokers with psychiatric co-morbidities. Finally, using a multiplatform strategy that includes text, mobile, internet, and social media modalities, NIDA is harnessing technology to improve the availability, delivery and use of behavioral smoking cessation interventions, which may benefit hard-to-reach populations and increase access to treatment for millions of smokers.

Conference Significant Items

Item

Opioid Drug Abuse - Opioid narcotics are frequently abused through injection, inhalation, crushing, or oral overdose to create a highly addictive euphoria. According to some reports, more than 35 million Americans have abused prescription opioids at some point in their lifetimes. In addition, the June 2011 Institute of Medicine report on relieving pain indicates that such abuse and misuse resulted in an annual estimated cost to the nation of \$72.5 billion. The National Institute of Drug Abuse (NIDA) is expected to support meritorious scientific activities that

provide companies with the basic science to develop and implement innovative strategies to reduce opioid drug abuse. Such strategies may include new chemical molecule structures, coatings, agents, or other appropriate scientifically sound processes with a goal of providing barriers to abuse while still providing the pain relief necessary for appropriate patient care. The NIDA is strongly urged to continue its support of research on pain, including the development of pain medications with reduced abuse liability. In addition, NIDA should continue to fund research to better prevent and treat prescription drug abuse. The NIDA shall provide an update in the fiscal year 2015 budget request on activities related to addressing the opioid drug abuse problem.

Action taken or to be taken

NIDA takes a multipronged approach to this problem that includes (a) research to identify new pain relievers with reduced abuse, tolerance, and dependence risk; and (b) working with industry and government to devise alternative delivery systems and drug formulations that minimize diversion and prevent overdose deaths. For example, an exciting new strategy is based on the idea of developing an inactive opioid-based drug precursor (pro-drug) to treat pain that would be inactive in the bloodstream until it reaches the digestive system where specific enzymes would cleave the pro-drug, releasing the opioid therapy. This approach would ensure that the pro-drug could not be abused via non-oral routes (e.g., injection or inhalation). NIDA has recently partnered with the National Center for Advancing Translational Sciences (NCATS) at NIH to assist Signature Therapeutics, a small biopharmaceutical company, in advancing the development of just such an abuse-deterrent pain medication based on a novel, inactive pro-drug formulation of extended-release oxycodone. Additionally, through ARRA funding NIDA supported the development of Probuphine – a buprenorphine medication implanted under the skin that allows continuous medication delivery for 6 months to treat opioid addiction. Currently, Probuphine, developed by Titan Pharmaceuticals, is undergoing further clinical testing in preparation for a revised IND application with the FDA.

NIDA also continues to support a diverse prescription drug abuse research portfolio including epidemiological studies of the patterns, trends, and motivations underlying prescription drug abuse; research to better understand the factors that predispose someone to become addicted to prescription pain relievers and what can be done to prevent it among those at risk; studies of the effectiveness and impact of prescription drug monitoring programs; and the development and testing of treatments (both pharmacological and behavioral) and prevention approaches to reduce prescription drug abuse and prevent overdoses. For example, NIDA recently entered into an agreement with Lightlake Therapeutics to conduct the dosing studies needed to obtain FDA approval for an intranasal formulation of the opioid antagonist naloxone to rapidly reverse opioid overdose and prevent lethality. Naloxone is currently available in an injectable form that is usually administered by health care professionals. If successful, an intranasal formulation could eventually be made widely available, including for over the counter distribution, thereby expanding access to this lifesaving medication.

In an effort to raise awareness about the dangers of prescription drug abuse and further prevent abuse, NIDA, the Office of the Surgeon General and other agencies are working on the *Surgeon General's Call to Action to Prevent Prescription Drug Abuse among Youth* expected to be published in FY 2014. Additionally, NIDA has developed two online CME courses on safe prescribing for pain and managing patients who abuse prescription opioids (over 80,000 have completed the CMEs to date, combined). NIDA is also reaching out to teens with its [PEERx initiative](http://teens.drugabuse.gov/peerx) (<http://teens.drugabuse.gov/peerx>), providing factual information about the harmful effects of prescription drug abuse on the brain and body.

National Institute of Mental Health (NIMH)

Senate Significant Items

Item

Autism - The Committee continues to urge NIMH to focus on genetic as well as possible environmental causes of autism. (p.99)

Action taken or to be taken

ASD research activities are coordinated across NIH through the NIH Autism Coordinating Committee, which includes participation from seven Institutes and Centers (ICs).¹ All of these ICs continue their commitment to identify and support innovative and high-impact biomedical research into the genetic and environmental causes of autism spectrum disorder (ASD).

The NIH Autism Centers of Excellence (ACE) program, designed to conduct intensive and coordinated research programs into the causes of ASD and to develop and disseminate new interventions and treatments, provided new grants to nine institutions in 2012 and two in 2013. One of the new ACE awards will build on investigators' earlier work identifying genetic differences of ASD susceptibility with an important new emphasis: the ACE aims to recruit at least 600 African-American families with a child with an ASD.² The ACE will look for gene variants associated with ASD in Americans with self-reported African ancestry, and test genetic risk factors identified in White populations to see what role gene variants may play in the disorder in people of African descent. Another new ACE award will conduct a large-scale international study utilizing health records and biospecimens from 4.5 million births (20,000 cases) from seven countries (United States, Australia, Denmark, Finland, Israel, Norway and Sweden), to study genetic and environmental influences on autism.

The National Institute of Mental Health (NIMH) continues to support studies to advance our understanding of the potential genetic and environmental causes of ASD. NIMH-supported investigators analyzed data from a sample of 664 infants who had older siblings with ASD. They found that 18.7 percent of those infants had developed ASD themselves. Moreover, male infants with an older sibling with ASD had a higher risk of developing ASD than female infants did. This study provided a more accurate estimate of the risk for ASD among children with siblings who already have the disorder.³ A separate series of three studies conducted by the Autism

¹ The 7 NIH ACC Institutes and Centers are: National Center for Complementary and Alternative Medicine (NCCAM), Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD, National Institute on Deafness and Other Communication Disorders (NIDCD), National Institute of Environmental Health Sciences, National Institute of Mental Health, National Institute of Neurological Disorders and Stroke (NINDS), and National Institute of Nursing Research (NINR).

² <http://www.nimh.nih.gov/news/science-news/2013/new-nih-funding-for-two-autism-centers-of-excellence.shtml>

³ <http://www.ncbi.nlm.nih.gov/pubmed/21844053>

Sequencing Consortium found an increased risk of ASD associated with genetic mutations more commonly found among older fathers.^{4,5,6}

As part of the National Institute of Environmental Health Science's (NIEHS)-supported Childhood Autism Risk from Genes and Environment (CHARGE) study, researchers found a protective association in children and mothers who carried a common genetic variant linked to inefficient folate metabolism. This finding indicates that a sufficient amount of supplemental folic acid in the first month of pregnancy may reduce a child's risk for ASD.⁷ In addition, a population-based study in Norway, supported by the National Institute of Neurological Disorders and Stroke, is examining the potential role of a number of prenatal and perinatal risk factors and found evidence supporting a role for folic acid. Initial results demonstrate that prenatal folic acid supplementation is associated with a decreased risk for autism.⁸ Finally, NIEHS-supported studies identified several environmental factors, such as exposure to air pollution,⁹ agricultural pesticides,¹⁰ and antidepressants,¹¹ that were associated with an increased risk of ASD, mostly based on exposure during pregnancy. In the near future, additional studies that utilize prospective or longitudinal designs are necessary in order to isolate the specific causal mechanisms that link these various environmental factors to ASD.

Item

Autism and Telehealth. The Committee is aware of the increasing use of telehealth resources in the diagnosis and treatment of autism spectrum disorders (ASD). The NIMH has funded a small number of grants to examine whether such technologies can specifically be used to improve ASD diagnosis and treatment in underserved areas of rural states. Given the significant expansion in recent years of telehealth networks in rural states and the potential promise of such networks to significantly lower costs while expanding care, the Committee urges NIMH to expand its support of this research. (p.99)

Action taken or to be taken

The National Institute of Mental Health (NIMH) continues its commitment to encourage and support effective research studies on ASD treatment and services, and especially approaches designed to improve and increase access to underserved populations and communities through innovative telehealth technology.

⁴ <http://www.ncbi.nlm.nih.gov/pubmed/22495306>

⁵ <http://www.ncbi.nlm.nih.gov/pubmed/22495309>

⁶ <http://www.ncbi.nlm.nih.gov/pubmed/22495311>

⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22648721>

⁸ <http://www.ncbi.nlm.nih.gov/pubmed/23403681>

⁹ <http://www.ncbi.nlm.nih.gov/pubmed/23404082>

¹⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22534084>

¹¹ <http://www.ncbi.nlm.nih.gov/pubmed/21727247>

Research strongly indicates early intervention programs and services can help mitigate some of the behavioral and cognitive impairments that affect very young children who are at risk of developing, or who have been diagnosed with ASD. It is critical that such services are readily accessible to children who need them; and especially to families in underserved rural communities where specialists with ASD intervention training are scarce. NIMH has supported research using telehealth strategies in an effort to reach underserved populations. For example, one study is piloting a form of interactive television (ITV) that uses real-time video conferencing for clinical purposes. Families with a young child suspected of having ASD will be randomly assigned to interact with a lead psychologist via ITV or in person. During these interactions, one pair of clinicians will observe the child in-person with the family, while a second pair of clinicians will simultaneously observe via ITV. Each pair of clinicians will provide a determination on whether the child meets criteria for a diagnosis of ASD, and these determinations will be assessed for reliability. Identification of a reliable and valid protocol for ASD diagnosis via ITV would allow greater access to quality health care for individuals in rural and underserved areas, with greater access to early intervention and improved developmental outcomes.

Another study aims to develop a web-based screening tool for ASD that physicians can use as part of a routine well-child visit. The Child Health and Development Interactive system (CHADIS) has been developed as an ASD screening tool for school-age children. Researchers plan to extend this system to include a version for screening toddlers, which will include a touch screen kiosk that can be used in a doctor's office, to enable use by low-income families. The tool would involve interaction between parents and health providers, and provide risk scores and provisional diagnoses, as well as instant on-line access to individualized recommendations and resources that might not otherwise be available.

A third study has taken an existing commercial product, the Behavior Imaging Solutions® telehealth system, and improved upon it by adding unique video capture capabilities with smartphones, and web-based modules to enable clinicians and researchers to input important clinical notes and assessments when making ASD diagnoses. This innovative telehealth system of service delivery will allow parents and caregivers to capture and upload video of a child's developmental problems or conditions, which a clinician can then remotely review and analyze. Clinicians will also be able to make important diagnostic notes that can be interactively shared with families during remote or in-person consultations. When fully developed and implemented, this telehealth tool could help improve timely screening and diagnosis of ASD by clinicians; and help families receive critical information and consultation on how to improve their child's developmental outcomes and address problem behaviors.

Item

Premature Mortality - The Committee continues to be concerned about premature mortality and lower life expectancy experienced by adults living with serious mental illness as a result of

treatable medical conditions such as cardiovascular, pulmonary, endocrine, and infectious diseases. The Committee urges NIMH to collaborate with other Institutes, including NIDDK and NHLBI, on a focused research program into the causes and interventions needed to address this crisis. The Committee requests an update on this topic in the fiscal year 2015 budget justification. (p.99)

Action taken or to be taken

People with serious mental illness (SMI—those disorders resulting in significant functional impairment, illness, and death, such as schizophrenia, bipolar disorder, and major depression) die from the same causes as those in the general population, e.g., heart disease, diabetes, cancer, stroke, and pulmonary disease. However, these diseases are more common in people with SMI and lead to death 11-32 years earlier than the general population.^{12, 13} The modifiable health risk factors that contribute to these diseases—e.g., smoking, obesity, hypertension, metabolic disorder, substance use, poor fitness and diet—are also more common and have an earlier onset in people with SMI. The National Institute of Mental Health (NIMH) supports numerous studies addressing these factors in SMI, including co-sponsored research with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Heart, Lung, and Blood Institute (NHLBI), which aim to improve the general health of persons living with SMI.

In March 2013, NIMH-funded researchers reported that people with SMI such as schizophrenia, bipolar disorder and major depression can lose weight and keep it off through a modified lifestyle intervention program.¹⁴ The researchers attempted to address the issue of premature mortality by bringing the fitness instructors and nutritionists to places most of these patients frequent—psychiatric rehabilitation outpatient programs, under the trial name ACHIEVE.¹⁵ Participants in the specially tailored weight loss program lost seven pounds more than individuals receiving usual care, and continued to lose weight and did not regain it, despite the reduced frequency of classes and counseling sessions. In contrast, the general population tends to experience peak weight loss in the first six months and then rebound and gain part or all of their weight back. The researchers are now looking for ways to spread the program.

NIDDK is working to understand the causes of adverse chronic health outcomes for people with psychiatric disorders, supporting several projects funded under a recent initiative (co-sponsored with NIMH) on adverse metabolic side effects of second generation psychotropic medications leading to obesity and increased diabetes risk. In addition, major NIDDK-supported diabetes clinical trials, such as the Diabetes Prevention Program Outcomes Study and Action for Health in Diabetes, are following depression measures as secondary variables. NIDDK and NIMH held a joint conference on the biological effects that diabetes and depression have on each other, and

¹² <http://www.ncbi.nlm.nih.gov/pubmed/16539783>

¹³ <http://www.ncbi.nlm.nih.gov/pubmed/21577183>

¹⁴ <http://www.nimh.nih.gov/science-news/2013/nih-study-shows-people-with-serious-mental-illnesses-can-lose-weight.shtml>

¹⁵ <http://www.nimh.nih.gov/science-news/2008/new-grant-aims-to-overcome-obesity-in-people-with-serious-mental-illness.shtml>

on improved approaches to prevention and treatment.¹⁶ NIDDK also seeks to improve health care for those with chronic diseases, such as diabetes and obesity, by addressing the psychosocial factors that can adversely affect outcomes. In spring 2013, NIDDK sponsored a meeting on basic behavioral research in obesity, and has issued initiatives for research to develop, refine, and test strategies to improve diabetes management by limiting stress in patients of all ages, as well as their families.

Youth with mood disorders are at significantly increased risk for metabolic and cardiovascular disease (CVD). NHLBI is currently funding research to evaluate specific aspects of mood disorders that predict CVD risk and interventions to enhance CVD prevention.

In January 2013, NIMH released a new initiative to support grants to enable the subsequent testing of innovative services interventions that are already in the field and that aim to reduce the prevalence and magnitude of common modifiable health risk factors related to shortened lifespan in people with SMI.¹⁷ In March 2013, NIMH released another initiative to support rigorous effectiveness testing of innovative services interventions designed to reduce the prevalence and magnitude of common modifiable health risk factors related to shortened lifespan in adults with SMI, as well as in children and youth with serious emotional disturbances.¹⁸

Item

Psychotropic Medications and Children - The Committee understands that little is known about the short- and long-term effects of psychotropic medications on children's physical and mental development. The Committee encourages NICHD to undertake a concerted effort to determine the safety and efficacy of these medications in children, and to explore research into the effectiveness of evidence-based psychosocial therapies used instead of, or in combination with, psychotropic medications. (p.94)

Action taken or to be taken

Research on the effects of psychiatric medications during development and their implication for long-term treatment of children with attention deficit hyperactivity disorder (ADHD), depression, psychosis, and other disorders continues to be an active focus at the National Institute of Mental Health (NIMH) and the *Eunice Kennedy Shriver* National Institute of Child Health & Human Development (NICHD).

Recently completed NIH-funded studies have provided new information on the long-term effects of some of the most commonly used medications during development. A series of systematic assessments of children with ADHD treated for eight years found that long-term treatment with stimulant medications neither increased nor decreased the risk for substance abuse in

¹⁶ <http://www2.niddk.nih.gov/News/Calendar/DiabetesDepression12.htm>

¹⁷ <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-13-140.html>

¹⁸ <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-14-060.html>

adolescence.¹⁹ Another study conducted in adults with ADHD found that treatment with methylphenidate (Ritalin) for one year was associated with changes in the function of dopamine, a neurotransmitter involved in ADHD and in its treatment.²⁰ Though these data are from adults, they are relevant to the use of stimulants in children. Other researchers found no adverse effects of prolonged use of stimulants on growth, brain neurochemistry, or later susceptibility to stimulant abuse in animal models of the effects of pre-adolescent ADHD medication exposure.^{21,22}

NIMH funds studies aimed at optimizing pharmacological approaches to enhance efficacy and safety. For example, a recently funded study is investigating whether children taking stimulant medication for the treatment of ADHD develop physical tolerance to medication, and explores whether alternative dosing schedules can reduce the impact of this effect if and when it exists. Another ongoing NIMH-funded study is examining pharmacological strategies paired with a weight management program to optimize symptomatic relief, while minimizing weight gain and other treatment-emergent side effects among children treated with antipsychotic medications.

NIMH also continues to fund research aimed at developing and testing behavioral and other psychosocial interventions as alternatives to medication. Currently funded studies are examining the utility of school-based treatments for ADHD and anxiety disorders. Additional studies focus on preventive interventions delivered to children who are at risk because of family history, early adversity, or other factors, in an effort to forestall or prevent the development of behavioral and other psychosocial disorders.

The Best Pharmaceuticals for Children Act (BPCA) requires the NIH to identify off-patent drugs and therapeutic needs of high priority for study in pediatric populations. In 2012, NICHD, which leads implementation of the BPCA for the NIH, released an updated prioritization list of over 45 therapeutic areas in pediatric medicine, including antipsychotic medications. Data from two NIH-funded clinical trials on the dose, safety, and effectiveness of lithium in children with bipolar disorder are being analyzed for submission to the FDA for a labeling change.

Recently, NICHD, in partnership with the Health Resources and Services Administration and the American Academy of Pediatrics, co-funded research to evaluate the frequency of atypical antipsychotic medication use in pediatric practice, utilizing electronic health records. This work is ongoing.

¹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/23452682>

²⁰ <http://www.ncbi.nlm.nih.gov/pubmed/23696790>

²¹ <http://www.ncbi.nlm.nih.gov/pubmed/23806775>

²² <http://www.ncbi.nlm.nih.gov/pubmed/23903242>

National Human Genome Research Institute (NHGRI)

Senate Significant Items

Item

Spinal Muscular Atrophy [SMA] Carrier Screening - The Committee continues to support the development of a pan-ethnic carrier screening program for SMA. The Committee remains concerned that contradicting SMA carrier screening recommendations from professional societies persist and that this inconsistency creates confusion among health professionals and the public. The Committee encourages NHGRI, NICHD, and NINDS to collaborate with stakeholders from government, academia, professional societies, advocacy groups, and industry to resolve the discrepancy and develop unified and consistent recommendations, guidelines, and educational materials on SMA carrier screening for providers and patients.

Action taken or to be taken

NIH is aware that there is not a consensus among experts with regard to Spinal Muscular Atrophy (SMA) carrier screening. To initiate dialogue on this matter, NIH hosted a meeting in 2009 to examine the scientific basis for carrier screening and to consider the issues that accompany such screening²³. NIH continues to participate in stakeholder discussions on the science and public health issues intrinsic to carrier screening programs.

To inform these discussions, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) is currently funding a study that is examining the readiness of newborn screening for spinal muscular atrophy throughout the public health system. The project is exploring ethical, regulatory, and policy issues related to screening for SMA. It is also conducting a small pilot screening study to detect infants at risk for development of SMA. This project will add to the evidence base of information related to screening for SMA. In addition, NICHD has supported a contract to develop an accurate and cost-effective SMA screen that is amenable to a high throughput environment.

Where appropriate, NIH will continue to create opportunities to facilitate discussions to support the Federal role in assessing the evidence necessary to launch such screening programs. NIH supports research to generate evidence for creating healthcare practice guidelines and convenes the healthcare organizations responsible for development of clinical guidelines as and when necessary.

²³ Jonathan Max Gitlin et al., “Carrier Testing for Spinal Muscular Atrophy.,” vol. 12, 2010, 621–622, doi:10.1097/GIM.0b013e3181ef6079.

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National Center for Complementary and Alternative Medicine (NCCAM)

Senate Significant Items

Item

Natural Product Collections - The Committee continues to urge NIH to increase access to comprehensive and professionally organized natural product libraries.

Action taken or to be taken

Natural product libraries have the potential to serve as useful sources of pharmaceutical leads and therapeutic agents. As such collections provide valuable research resources, both the National Cancer Institute (NCI) and the National Center for Complementary and Alternative Medicine (NCCAM) are interested in advancing research on natural products by providing access to comprehensive natural product libraries.

For example, since 1986, the NCI's Developmental Therapeutics Program (DTP) has been collecting and storing natural product materials in a central repository. This collection contains approximately 210,000 extracts that are available for screening to researchers within the NIH as well as outside researchers. Also, DTP has acquired a collection of Traditional Chinese Medicinal plants that are being investigated in conjunction with the NCI's Office of Cancer Complementary and Alternative Medicine, as well as a collection of plant extracts collected by the New York Botanical Gardens.

Separately, NCCAM is funding two investigators to screen a natural product library created and donated by Merck to a non-profit institute, for compounds that may lead to the development of new drugs and/or advance our understanding of the mechanism of action of specific natural products. If the results from the initial studies are promising, NCCAM may fund additional research in this area.

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National Institute on Minority Health and Health Disparities (NIMHD)

Senate Significant Items

Item

Diabetes in Minorities - The Committee continues to urge NIMHD to support research and other activities with respect to pre-diabetes and diabetes, particularly type 2 diabetes, in minority populations.

Action taken or to be taken

The burden of diabetes and its associated costs fall disproportionately on racial and ethnic minorities. Diabetes research therefore continues to be a priority for NIMHD. Not only does NIMHD play an active role in related trans-NIH activities including the Diabetes Mellitus Interagency Coordinating Committee, the Institute supports new and ongoing research into the clinical, socioeconomic, geographical, cultural, and organizational factors that contribute to elevated diabetes rates in racial and ethnic minorities. A new project funded under the NIMHD Community Based Participatory Research (CBPR) initiative entitled, *Disseminating Effective Community-Led Programs to Eliminate Diabetes Disparities*, seeks to disseminate a low-cost, culturally appropriate, peer-led diabetes prevention program called Help Educate to Eliminate Diabetes (HEED) among the 34,000 adults living in East Harlem, New York, at heightened risk for diabetes, and among the 324 community organizations who serve them. This project will identify the best strategies to disseminate HEED broadly; translate HEED into real-world practice using principles of social marketing; develop an online portal for computers and smart phones to reach a wider audience; evaluate the impact of dissemination on health outcomes related to diabetes; and enhance community capacity to sustain the program. Another CBPR project, *Outcomes from a Diabetes Self-Management Intervention for Native Hawaiians and Pacific People: Partners in Care*, tested the feasibility and assessed the effects of a culturally-tailored, community-based diabetes self-management intervention on clinical, behavioral, and quality-of-life outcomes. Preliminary results show improvements in hemoglobin A1c levels, diabetes-related distress, and understanding and performance of self-care activities. Another study supported by the Research Centers in Minority Institutions (RCMI) Infrastructure for Clinical and Translational Research program entitled, *Association of Hand or Knee Osteoarthritis with Diabetes Mellitus in a Population of Hispanics from Puerto Rico*, is the first population-based study to estimate the prevalence of metabolic syndrome and its individual components in a population of 1,000 adults of both sexes in Puerto Rico. This study revealed that diabetic patients were more likely to have osteoarthritis (OA) of the hands or knees than were non-diabetic subjects, even after accounting for established OA risk factors. Moreover, among diabetic patients, females were at greater risk for OA. The findings also showed that a substantial proportion of adults with diabetes did not achieve American Diabetes Association recommendations on selected preventive practices and treatment goals.

The NIMHD Centers of Excellence (COE) conduct research exploring genetic risk factors in racial/ethnic minority populations, the impact of socioeconomic status, and life-style intervention programs in preventing diabetes and its complications. For example, a recent publication from investigators at Columbia University, *Adherence to diabetes self-care for white, African-American and Hispanic American telemedicine participants: 5 year results from the IDEATel project*, documented changes in adherence over time in response to a telemedicine intervention for elderly diabetes patients. Researchers found that a tailored telemedicine intervention was effective in achieving improved adherence in minority patients, demonstrating for the first time that better diabetes control using American Diabetes Association guidelines can lead to improved cognitive outcomes. In addition, The NIMHD Intramural Research Program (IRP) developed an integrative, multidisciplinary, and innovative research team that will provide opportunities to accelerate research progress in the determinants of prevention, diagnosis, and treatment of diabetes. Diabetes research is a priority health disparity disease for NIMHD. Through its programs, the Institute will continue to support diabetes research.

Item

Health Disparities in Children and Adolescents - The Committee urges NIH to put a high priority on improving the health status of children and adolescents, especially those living in poverty.

Action taken or to be taken

NIMHD funds health disparities research focused on children and adolescents through various mechanisms including the Investigator-Initiated Research on Health Disparities (R01), Community-Based Participatory research (R24) grant, and the Transdisciplinary Collaborative Centers (TCC) for Health Disparities Research programs. For example, a new research Investigator-Initiated Research (R01) project, *Families Preventing and Reducing Obesity Health Disparities in Hispanic Youth*, addresses a critical need to develop family-based obesity preventive interventions that target physical activity and diet among Hispanic youth. Preliminary data indicate that Familias Unidas, a family-based, culturally-specific intervention found to be efficacious in preventing or reducing negative health behaviors and conditions through improvements in family functioning, has positive effects on physical activity, mediated in part by parental involvement. Childhood obesity is one of our nation's most significant public health problems. Hispanic youth are particularly at risk, more likely to be overweight and obese than their non-Hispanic white counterparts partly because of their inadequate levels of physical activity and the poor quality of their dietary intake. This project will examine the efficacy of Familias Unidas, extended to target obesity, for increasing physical activity and improving the quality of dietary intake among overweight Hispanic youth. The project will also examine whether and to what extent family functioning mediates the observed effects.

Another NIMHD funded project, supports the Collaborative Research Center for American Indian Health. Established in September 2012, the Center is creating a platform for Tribal communities and health researchers to work together to develop cutting-edge research that will address significant health disparities experienced by American Indians in South Dakota, North Dakota, and Minnesota. Among the many disparities in health and health care facing American Indian children, one area that has received scant attention is the utilization and quality of care provided in hospital emergency departments (EDs). A new project supported by the Center, *Emergency Department Use and Care in American Indian Children*, aims to better understand patterns of ED usage and care. Investigators are partnering with several hospital EDs that serve different AI communities across the region to gather data on usage and care practices, and are working with parents, guardians, and elders to obtain their perspectives on ED usage and the care provided. This information will lay the basis for developing interventions to improve ED use and care for AI children across the region. Another project supported by the center, *Factors Influencing Pediatric Asthma*, involves collaboration with American Indians from the Cheyenne River Sioux Tribe in a cross-sectional study of factors ranging from genetics, immunity, environmental exposures, education, economic resources, access and utilization of medical care, to perceived quality of life. Children with asthma will also be recruited into a randomized trial of intensive education related to understanding, self-directed care and empowerment compared with usual care.

In addition, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) has dedicated its research to understanding the dynamic biological, behavioral, and social processes that dictate physical, emotional, and cognitive growth. By focusing and coordinating research on gestation, the early years of life, and the transitions into and out of adolescence and into young adulthood, the NICHD can address ways to prevent health disparities, as well as identify therapeutic strategies for early intervention. Research in health disparities in children and adolescents is priority for NIMHD. Through its programs and opportunities for collaboration that may be presented through the NIH Health Disparities Strategic Plan, it will continue to be a focus of research.

Item

Mental Health Disparities - The lack of access to mental health services in rural areas presents unique challenges in providing services to an especially vulnerable population. Greater poverty rates in rural areas, cultural attitudes toward mental illness, and limited transportation options all contribute to isolating individuals with mental health needs from access to care. In addition, individuals with mental health problems are at greater risk of poverty so the situation becomes part of a cycle of poverty and mental illness. The use of telemedicine in cooperation with community mental health programs in rural areas presents a new and effective way of providing for diagnosis and treatment of mental health problems. The Committee encourages NIMHD to fund research efforts to find innovative ways to address mental health disparities in underserved

populations, such as telepsychiatry programs, especially in designated Psychiatric Manpower Shortage Areas.

Action taken or to be taken

NIMHD fosters research on mental health disparities through various mechanisms including the Investigator-Initiated Research on Health Disparities, Community-Based Participatory research grant, and Disparities Research and Education Advancing our Mission (DREAM) Career Transition Award. For example, one project, *Epidemiology of Suicidal Behavior in Racially/Ethnically Diverse Older Americans* studies the prevalence and predictors of suicide and related behaviors over the lifetime of older racially and ethnically diverse adults. Another R01 project, *Preventing HIV/AIDS Among Teens in Juvenile Justice*, addresses the need for innovative prevention programs that address the intersecting health disparities of mental illness, HIV/AIDS, and sexually transmitted infections (STIs) among youth in juvenile justice. Juvenile offenders return to their communities with undiagnosed and untreated STIs. A new research project supported through a career development award, *Project LOVE: Preventing Adolescent Dating Violence among Rural African Americans*, will use community-based participatory research (CBPR) approaches to develop community-academic partnerships that include adolescent partners to develop a culturally and geographically appropriate and sustainable prevention intervention designed to significantly reduce the prevalence of dating violence among rural African American youth aged 10-14 in eastern North Carolina. In one CBPR project, *Substance Use & Mental Health Collaborative for Rural American Indian Adolescents*, investigators are partnering with the Spokane Tribe, a rural, federally recognized reservation community in a designated Health Provider Shortage Area in rural eastern Washington, to plan, implement, and evaluate culturally attuned interventions to reduce health disparities and promote health. Using digital storytelling, photo voice, and other culturally relevant methods, this project will provide a comprehensive community needs assessment, identify priority health concerns, and develop community-based interventions to be tested and evaluated. In another CBPR project, *Integrated Health Care for African Americans with Mental Illness Who Are Homeless*, researchers target the health care needs of African Americans who are homeless with serious mental illness in Chicago. As part of the integrated mental health care, they will use innovative mobile assessment technologies developed by investigators at the Illinois Institute of Technology. Another NIMHD grantee, *Use of Telemedicine to Overcome Barriers to Care Among Transwomen (TW) of Color*, will use telemedicine to provide a virtual medical home as a means to engage and retain TW of color in care. The study will assess the acceptability and feasibility of a novel telemedicine approach specific to TW to reduce barriers to care.

The National Institute of Mental Health (NIMH) continues to support innovative efforts to address mental health disparities in underserved populations, including rural populations, through research support and stakeholders engagement. NIMH-supported research has focused on the use of technologies to improve healthcare access in rural areas, through internet and telephone-based cognitive behavioral therapy for treatment of mental disorders; interactive

television to identify autism spectrum disorder in young children in rural areas; and, videoconferencing to provide treatment to children in rural areas. In 2012, to stimulate research on new ways to use existing technologies to improve access to and quality of mental health care, NIMH released a funding opportunity announcement, “Harnessing Advanced Health Technologies to Drive Mental Health Improvement (<http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-13-060.html>; <http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-13-061.html>).

NIMH also continues to participate in the initiative, “Interventions for Health Promotion and Disease Prevention in Native American Populations (<http://grants.nih.gov/grants/guide/pa-files/PA-11-346.html>).” The initiative encourages studies to develop, adapt, and test the effectiveness of health promotion and disease prevention interventions among Native Americans. In addition to NIMH’s funded research initiatives in this area, the Institute conducts activities to engage and educate stakeholders. The NIMH Office of Rural Mental Health Research participated in the National Association of Rural Mental Health Annual Meeting in 2012, and in the Mental Health Special Interest Group at the 2013 American Telemedicine Association Meeting. The NIMH Outreach Partnership works to increase the public’s access to science-based mental health information by partnering with national and state non-profit organizations, and emphasizing underserved populations. Fifty-five Outreach Partner organizations represent all States, the District of Columbia, and Puerto Rico.

NIMHD and NIMH will continue to focus on mental health disparities and opportunities for collaboration that may be presented through the NIH Health Disparities Strategic Plan.

Item

Research Centers in Minority Institutions Program [RCMI] - The Committee continues to recognize the critical role played by minority institutions, especially at the graduate level, in addressing the health research and training needs of minority populations. In particular, the RCMI program fosters the development of new generations of minority scientists for the Nation and provides support for crucial gaps in the biomedical workforce pipeline. The RCMI program has the capability to promote solutions to the significant gap in R01 grant funding among black and other minority researchers when compared to nonminority researchers. The Committee requests that NIH describe in the fiscal year 2015 congressional budget justification the extent to which the RCMI program is addressing R01 funding disparities.

Action taken or to be taken

The National Institute on Minority Health and Health Disparities (NIMHD) focuses on the health research and training needs of minority populations through programs such as the Research Centers in Minority Institutions (RCMI). The RCMI program supports activities that focus on the professional development of scientists, especially those that are underrepresented in the biomedical sciences. RCMI centers stress mentoring opportunities for junior investigators, pairing these investigators with experienced scientists with a successful track record of obtaining

extramural funding. The RCMI program also supports career development activities for investigators that include but are not limited to grant writing workshops, scientific seminars and technical workshops and access to scientific cores and technical support. There are also opportunities for investigators to generate preliminary data required for successful research project grant submissions, through peer-reviewed pilot project programs.

In order to broaden opportunities for collaborations, partnerships and mentoring, NIMHD supports the RCMI Translational Research Network (RTRN)-a consortium of investigators from RCMI-funded centers, other graduate schools and academic health centers; community health providers and other community stakeholders. While the focus of this network is on conducting collaborative clinical and translational research focused on reducing and eliminating health disparities, another major objective of RTRN is to provide expanded access to technical assistance, mentoring and training to minority investigators. RTRN has implemented a web-based platform to match investigators with mentors, collaborators and resources that are not resident at their home institution. In addition RTRN research clusters provide opportunities to discuss potential research projects, review best practices for responding to funding announcements and have pre-submission grant reviews by senior scientists.

NIMHD is also the lead institute for the Clinical Research Education and Career Development (CRECD) awards in minority institutions that develop and implement accredited degree programs in clinical research (or clinically-relevant areas), and provide mentored research opportunities for doctoral students, post-doctoral fellows and junior faculty.

Through these activities, the RCMI program plays a critical role in addressing gaps in the biomedical workforce pipeline, from the pre-doctoral to the junior faculty level, and has the capability to promote solutions to the gap in R01 grant funding among African American and other minority researchers.

Conference Significant Items

Item

Research Centers in Minority Institutions Program [RCMI] - Minority Institutions play a critical role, especially, at the graduate level in addressing the health research and training needs of the nation. The NIH is expected to continue in support of this program at no less than the fiscal year 2013 level.

Action taken or to be taken

The National Institute on Minority Health and Health Disparities (NIMHD) focuses on the health research and training needs of minority populations through programs such as the Research Centers in Minority Institutions (RCMI). The RCMI program supports activities that focus on the professional development of scientists, especially those that are underrepresented in the

biomedical sciences. RCMI centers stress mentoring opportunities for junior investigators, pairing these investigators with experienced scientists with a successful track record of obtaining extramural funding. The RCMI program also supports career development activities for investigators that include but are not limited to grant writing workshops, scientific seminars and technical workshops and access to scientific cores and technical support. There are also opportunities for investigators to generate preliminary data required for successful research project grant submissions, through peer-reviewed pilot project programs.

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Through these activities, the RCMI program plays a critical role in addressing gaps in the biomedical workforce pipeline, from the pre-doctoral to the junior faculty level, and has the capability to promote solutions to the gap in R01 grant funding among African American and other minority researchers. The FY 2014 RCMI budget will remain at the FY 2013 level.

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Fogarty International Center for Advanced Study in the Health Sciences (FIC)

Senate Significant Items

Item

Global Health Research and Training - The Committee recommendation includes \$72,380,000 for the Fogarty International Center. The Center plays an essential role in global health research and training that can both assist developing countries advance their own research and health solutions and help the United States form partnerships to fight malaria, neglected tropical diseases, and other infectious diseases that disproportionately impact the global poor. The Committee urges FIC to continue this important work. (pg 101)

Action taken or to be taken

The Center will also continue to support global health research and research training in partnership with U.S. Institutions to strengthen the ability of low- and middle-income countries to conduct research and generate solutions to critical health problems.

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National Library of Medicine (NLM)

Senate Significant Items

Item

Communication of Research Findings - The Committee is pleased that NLM has expanded the readership of NIH MedlinePlus magazine and the bilingual NIH MedlinePlus Salud magazine, which provide consumers and health professionals easy-to-read health information based on the latest NIH-supported research. The Committee urges NLM to continue exploring new avenues of online distribution that extends the publications' reach to the public.

Action taken or to be taken

Online distribution of *NIH MedlinePlus* and *NIH MedlinePlus Salud* (bilingual) magazines began several years ago, when the contents of each issue were included in NLM's MedlinePlus website, and a PDF replica of each issue was added to the website of the Friends of NLM. These were the first steps in what is planned as a major presence online for the magazines as multimedia interactive guides, digital magazines, e-newsletters, and apps for iPads and other tablet computers.

As complements to the print magazines, these electronic products will extend its reach and scope to the American public and to clinicians through extra editorial content and photos, links to other NIH resources, animations and videos, topical podcasts, and enhancements that take advantage of emerging technologies. The NLM will continue to partner with many healthcare membership organizations, such as the American Diabetes Association, American Heart Association, and American College of Physicians, among others, to provide electronic patient education solutions with the ability to reach millions of Americans. Organizations such as these are also able to work with NLM to provide electronic versions of the magazines to their members and constituencies.

Multimedia content in the online versions of the magazines makes it easier for the public to obtain health information in a learning style that best suits their needs: reading, listening, viewing, or any combination of the three. Having the magazines scaled to platforms—from computer to tablet to smartphone—means that more diverse populations can be reached, including those currently underserved. “Push” technology will allow the online versions to regularly reach populations who can opt in to receive links to the complete magazines, portions on specific topics, and automatic updates on topics of interest.

With the online versions of the magazines, NLM increases its ability to partner with other organizations, such as the National Network of Libraries of Medicine, the National Hispanic Medical Association, and other agencies within the U.S. Department of Health and Human Services, to reach the public in as many ways as possible. The ability to extend stories beyond the pages of the magazine and into people's lives in so many ways makes electronic editions of

both magazines much more of an engaging and helpful resource. They also help to increase the visibility of the NIH and public understanding of its vital medical research.

National Center for Advancing Translational Sciences (NCATS)

Senate Significant Items

Item

Clinical and Translational Science Awards [CTSA] - The Committee strongly endorses IOM's recommendations in its June 2013 report, "The CTSA Program at NIH: Opportunities for Advancing Clinical and Translational Research." In particular, the Committee agrees that NCATS should provide leadership to help the CTSA function more as a network than as a collection of discrete centers; only then will the full potential of the program be realized. In addition, the Committee agrees with the IOM that the CTSA program should address the full spectrum of clinical and translational research. This should include research on changing behaviors that impact the prevention and outcome of diseases and conditions such as obesity and type 2 diabetes.

Action taken or to be taken

In response to the FY 2012 appropriations Conference Report, NCATS commissioned the Institute of Medicine (IOM) to review the Clinical and Translational Science Award (CTSA) program and to recommend whether changes were needed to its mission. The IOM report, released on June 25, 2013, includes seven recommendations: 1) strengthen NCATS leadership of the CTSA program, 2) reconfigure and streamline the CTSA Consortium, 3) build on the strengths of individual CTSA across the spectrum of clinical and translational research, 4) formalize and standardize evaluation processes for individual CTSA and the CTSA program, 5) advance innovation in education and training programs, 6) ensure community engagement in all phases of research, and 7) strengthen clinical and translational research relevant to child health.

The IOM report was discussed with the NCATS Advisory Council during their meeting in September 2013, and a Working Group of the NCATS Advisory Council was established to advise the NCATS Director on implementation of the report, including designation of clear, measurable goals and objectives that address critical issues across the full spectrum of clinical and translational research. NCATS is committed to enhancing the ability of investigators to work efficiently and collaboratively across sites with CTSA awards.

Item

Cures Acceleration Network - The Committee encourages NCATS to look at existing successful public-private co-investment models and partnerships, particularly In-Q-Tel and SEMATECH, in establishing CAN's strategic focus, operating procedures, and processes.

Action taken or to be taken

Authorized to reduce significant barriers to successful translation and accelerate the development of high-need cures, the Cures Acceleration Network (CAN) provides NCATS with flexibility in how it funds projects. This authority is guided by the CAN Review Board, which meets four times a year, advising and providing recommendations to the NCATS Director on the policies, programs and procedures for carrying out the duties of the Office of the Director and identifying significant barriers to successful translation of basic science into clinical application.

NCATS believes that translation is a “team sport”, and the feedback from ongoing conversations with academia, government, industry and patient advocacy groups helps NCATS focus its priorities on the areas of greatest need and build the teams necessary to solve complex translational science problems that can prevent and delay the development of health-improving interventions. The CAN authority includes two mechanisms that will enhance NCATS’ ability to form unique and successful partnerships. The first mechanism includes the ability to award matching grants, which ensures that all partners have a vested and financial interest in the project. The second mechanism is the Other Transactions Authority, which allows NCATS to support partnerships in new and unique ways that don’t fit within the normal mechanisms utilized by NIH. NCATS will be open to various models of collaborations as it pursues various partnership opportunities, and the highly successful models of In-Q-Tel and SEMATECH will be among those models that are considered.

Item

Drug Rescue and Repurposing - NCATS’ drug rescue and repurposing initiatives have shown success since the Center’s establishment 2 years ago. Because rescue and repurposing builds upon previous research and development efforts, new candidate therapies could be ready for clinical trials quickly, advancing the timeframe for FDA approval and their integration into healthcare. The Committee notes with particular interest the success of The Learning Collaborative, which has had significant success employing drug repurposing strategies to rapidly advance new blood cancer therapies. The Committee encourages NCATS to pursue similar efforts for other rare diseases and unmet medical needs.

Action taken or to be taken

In 2012, NCATS launched its Discovering New Therapeutic Uses for Existing Molecules collaborative pilot program to “rescue” previously developed compounds that were abandoned after initial clinical testing, but before FDA approval, because of lack of effectiveness or business reasons. The program is catalyzing new strategies for drug rescue, pairing pharmaceutical companies with partially developed drugs with academic investigators with new ideas for disease indications in which the drugs could be tested. The program developed a “crowdsourcing” mechanism for obtaining the best ideas from the research community, and streamlined template collaboration agreements to speed negotiation time. Eight pharmaceutical

companies (AbbVie [formerly Abbott]; AstraZeneca; Bristol-Myers Squibb; Eli Lilly and Company; GlaxoSmithKline; Janssen Research & Development, LLC; Pfizer; and Sanofi) made available 58 molecules, which had undergone significant research and development, including safety testing in humans. Almost 160 different ideas were submitted by researchers for consideration, and in June 2013, nine projects were announced that matched academic research groups with companies to study compounds in eight disease areas, including two rare diseases (Duchenne Muscular Dystrophy and Lymphangiomyomatosis). After receiving their award, some projects were dosing patients within as few as two months. Through the program, NCATS is re-engineering how the public and private sectors collaborate, and creating new and rapid ways to test novel treatments for underserved diseases. Due to the extremely high level of enthusiasm of both pharmaceutical companies and the research community, NCATS plans to issue another funding opportunity announcement for projects to begin in FY 2015.

NCATS has been gratified by the success of The Learning Collaborative (TLC) in both identifying new potential therapies for blood cancers and developing new partnership models to make this critical work happen more efficiently. TLC's model has now been applied to two other types of cancers: Mantle Cell Lymphoma (MCL), which is a rare and difficult to treat lymphoma affecting 15,000 Americans, and Gastrointestinal Stromal Tumors (GIST), which afflicts approximately 4,000 Americans. Working through the TLC, investigators at the University of Kansas have demonstrated that auranofin is active in killing MCL cells and in treating GIST. Investigators submitted two new Investigational New Drug (IND) applications in March 2013 seeking to study auranofin treatment of these two diseases, and they received FDA approval in April 2013 to proceed with both of these trials.

Another example of NCATS' repurposing efforts is its collaboration with NICHD to explore the clinical utility of hydroxypropyl beta cyclodextrin (HPBCD) for Niemann-Pick disease type C1 (NPC1). NPC1 is a rare genetic disorder where cholesterol and other fats have trouble moving out of brain cells, which results in gradual loss of nervous system function. NCATS discovered HPBCD as part of its drug repurposing screening program and is testing the safety profile and efficacy of HPBCD for NPC1. HPBCD is currently approved for use as an "excipient", which is a non-active ingredient used to help solubilize other drugs.

Both auranofin and HPBCD were discovered in screens of the NCATS Pharmaceutical Collection (NPC), a comprehensive collection and database of approved and investigational drugs. NCATS will continue to collaborate with investigators worldwide to identify other drugs in the NPC that can be repurposed for unmet medical needs.

Item

Guillain-Barré Syndrome [GBS] - The Committee notes that the causes of GBS and related inflammatory disorders which impact the nervous system remain unknown. The Committee

encourages ORDR to initiate research activities in this area to improve our scientific understanding of these conditions.

Action taken or to be taken

The Office of Rare Diseases Research (ORDR), located within NCATS, supports and coordinates rare disease research and provides information on rare diseases to patients, their families, healthcare providers, researchers and the public. In collaboration with other NIH institutes, ORDR funds rare diseases research primarily through the Rare Diseases Clinical Research Network (RDCRN), which supports clinical studies, investigator training, pilot projects, and access to information on rare diseases. The most recent funding opportunity announcement, which was widely broadcast and open to all rare diseases, including GBS, was issued in the fall of 2013 and awards are expected to be made in the summer of 2014. All applications will be given appropriate consideration.

Item

Hereditary Angioedema [HAE] - The Committee continues to recognize that few treatment options are available for HAE and that they are not effective for all patients. The Committee continues to encourage the Center to convene a state of the science conference on this rare disease.

Action taken or to be taken

Staff of the NCATS Office of Rare Diseases Research met with representatives of the U.S. Hereditary Angioedema Association (HAE) and encouraged the association, together with research investigators, to develop a grant application for a scientific conference. The goals of the conference would be to identify new research opportunities and to develop a research agenda containing research priorities for HAE to help all patients with this disease. In April 2013, a principal investigator applied to NIAID for a conference grant titled *Hereditary Angioedema (HAE) Conference*. The application is under review.

Item

Multifocal Motor Neuropathy [MMN] - The Committee understands that ORDR will soon issue a new funding opportunity announcement for the Rare Disease Clinical Research Network. Given the importance of appropriate and early diagnosis of patients with MMN, the Committee encourages ORDR to give appropriate consideration to approving funding for a consortium for MMN that includes a registry for patients diagnosed with the disease.

Action taken or to be taken

The Office of Rare Diseases Research (ORDR), located within NCATS, supports and coordinates rare disease research and provides information on rare diseases to patients, their families, healthcare providers, researchers and the public. In collaboration with other NIH institutes, ORDR funds rare diseases research primarily through the Rare Diseases Clinical Research Network (RDCRN), which supports clinical studies, investigator training, pilot projects, and access to information on rare diseases. The most recent funding opportunity announcement, which was widely broadcast and open to all rare diseases, including MMN, was issued in the fall of 2013 and awards are expected to be made in the summer of 2014. All applications will be given appropriate consideration.

Item

Pulmonary Arterial Hypertension [PAH] - The Committee recognizes that pulmonary arterial hypertension is a rare and often fatal condition. The Committee encourages ORDR to expand research in this area by collaborating on research projects with the Pulmonary Hypertension Clinical Research Network, and the Committee encourages NCATS to consider pursuing indications for current drugs that have shown the potential to improve health outcomes for PAH patients.

Action taken or to be taken

The Office of Rare Diseases Research (ORDR), located within NCATS, supports and coordinates rare disease research and provides information on rare diseases to patients, their families, healthcare providers, researchers and the public. In collaboration with other NIH institutes, ORDR funds rare diseases research primarily through the Rare Diseases Clinical Research Network (RDCRN), which supports clinical studies, investigator training, pilot projects, and access to information on rare diseases. The most recent funding opportunity announcement, which was widely broadcast and open to all rare diseases, including PAH, was issued in the fall of 2013 and awards are expected to be made in the summer of 2014.

In addition to the efforts of the extramural RDCRN, there are dedicated NCATS intramural research efforts focused on supporting preclinical drug development for all diseases, including projects that seek to repurpose existing drugs for new indications. These efforts include the Therapeutics for Rare and Neglected Diseases (TRND) and Bridging Interventional Development Gaps (BrIDGs) programs. Similar to the RDCRN, TRND and BrIDGs broadcast the opportunity to submit collaborative research proposals widely, and are open to all rare disease drug development candidates.

Conference Significant Items

Item

Accelerating Commercialization of Therapies to Patients - The NIH shall provide an update in the fiscal year 2015 budget request on the models and next steps that resulted from the trans-NIH workshop with key research organizations, venture capitalists, pharmaceutical firms, Patent and Trademark Office, and Food and Drug Administration, which was held to examine ways to work together and foster private sector drug development. The update should identify how market risk and commercial viability criteria are factored into the NIH decisions to create or select projects within its drug repurposing and de-risking activity.

Action taken or to be taken

Accelerating the translation of biological insights into new medicines requires developing powerful new scientific knowledge, methodology and tools, as well as the thoughtful navigation of translational research policy issues.

Potential commercial viability is one of several factors NCATS considers in its programs. Applicants to the Discovering New Therapeutic Uses for Existing Molecules program (drug repurposing) are informed that NCATS is especially interested in projects that address areas of unmet medical need and are asked to “Describe the commercial potential of the Agent as a development candidate and potential challenges for commercialization of the Agent for the new disease indication” (<http://grants.nih.gov/grants/guide/rfa-files/RFA-TR-12-004.html>). Applications go through a peer review process using a Special Emphasis Panel that includes drug development experts. The panel’s review includes an assessment of each application’s ability to impact an unmet medical need and whether or not there is a commercial potential.

In addition, the likelihood of external adoption of the investigational compound is one of the metrics used by the Therapeutics for Rare and Neglected Diseases (TRND) program when evaluating applications (<http://www.ncats.nih.gov/research/rare-diseases/trnd/apply/scoring/scoring-matrix.html>).

However, it is important to note that other criteria such as medical need for a new therapeutic, or therapeutic validation, are also considered.

NCATS is partnering with multiple stakeholders in a variety of ways to prioritize the issues that need to be addressed to accomplish its mission. As an example, in December 2012, NCATS convened a workshop to discuss how policy research and analysis can inform translational research and to identify barriers in translation that could benefit from policy research and analysis. Participants included experts from academia, the non-profit sector, the pharmaceutical industry, other NIH ICs and the Office of the Director, the Food and Drug Administration, and the Patent and Trademark Office. The participants made recommendations in the areas of

informing regulatory science, navigating intellectual property challenges, streamlining clinical research, and forming efficient strategic alliances. Currently, NCATS is assessing the recommendations that resulted from the workshop and is planning the next steps.

Item

Clinical and Translational Science Awards [CTSA] - The agreement provides a specific funding level for the core CTSA program within the NCATS statutory language. This change removes the funding flexibility provided during the establishment Years of NCATS. The ICs are expected to continue to use and provide support to the CTSA infrastructure for clinical trials and other scientifically appropriate activity. In addition, NCATS should continue to collaborate with all ICs on the overall CTSA program. The 2013 Institute of Medicine (IOM) report recommends the development of a comprehensive strategic plan with measurable objectives. The NCATS is expected to move forward with implementing the IOM recommendations in consultation with the CTSA community. Any significant changes to the program should be done with transparent and ongoing consultation with the CTSA community and NIH ICs. NCATS shall provide an update in the fiscal year 2015 budget request of all planned and expected changes since the release of the IOM report through fiscal year 2015 to include a specific plan on how NCATS will communicate and coordinate with the CTSA community.

Action taken or to be taken

NCATS is committed to catalyzing the development and dissemination of new methods, technologies, and workforce to advance translation in the clinical space. In response to the IOM report, NCATS has launched a collaborative effort with its stakeholders to implement changes in the program. As a first step, NCATS is implementing increased programmatic and fiscal management of the grants that support this program. Improved transparency and accountability for the use of the funds for this program will ensure national priorities are addressed.

NCATS has streamlined the governance of the consortium by constituting a Steering Committee of a subset of CTSA Principal Investigators (PIs) and NIH IC members instead of the prior Steering Committee which had over 90 members. On the recommendation of the new Steering Committee, the CTSA Consortium committee structure will focus on targeted work groups. The many standing CTSA Consortium committees are being closed and the Steering Committee will form and oversee ad hoc work groups to address high priority activities. NCATS and the Steering Committee will provide and seek input from all CTSA PIs monthly.

Finally, a Working Group of the NCATS Advisory Council was established in December to provide advice on measurable objectives for the program, including metrics for the Steering Committee activities. The working group is addressing areas identified in the IOM CTSA Program Report, including systemic improvements in methods and processes for translation, translational workforce development, engagement and collaboration with patients and communities, and ensuring the program addresses translation across the lifespan, all types of

interventions and phases of translation. The Working Group Report is expected to release its report later in 2014.

Item

Cures Acceleration Network - The NIH shall provide additional details in the fiscal year 2015 and future budget requests. In particular, the request should breakout all CAN supported activity with funding details, performance measures, details on activities and partnerships, and criteria used to select projects. The request should describe the relationship of CAN activities with other NIH programs and projected termination dates.

Action taken or to be taken

CAN was authorized to advance the development of high need cures and reduce significant barriers between research discovery and clinical trials. At NCATS, CAN is intended to advance initiatives designed to address scientific and technical challenges that impede translational research.

Current Activities

The first program started under CAN is the Tissue Chip for Drug Screening program, which is working to streamline the therapeutic development pipeline by improving the process for predicting whether drugs will be safe in humans. This tissue-on-a-chip research program is supporting 19 cooperative agreement awards that will develop 3-D cellular microsystems that recreate the genomic diversity, disease complexity and pharmacological responses of approximately 10 different human organ systems that will significantly improve the predictability of a drug's effects in humans over currently used animal and cell based systems. For this program, NCATS is partnering with DARPA and FDA, as well as multiple NIH ICs.

For FY 2015, NCATS is requesting increased funding in order to support the next phase of the program, which involves integrating the different organ systems together. The program is expected to end in 2017.

Proposed New Activities

The CAN Review Board has established several parameters for selecting potential CAN projects. Projects need to be collaborative, have discrete and measurable outcomes, have a broad and significant impact, and be focused on a compelling disease. The timeline for completion of each project should be shorter than five years.

The CAN Review Board has discussed and identified several ideas for high priority projects. One of these is the use of the CAN matching authority to create foundation-academic-industry partnerships that support pilot studies to accelerate the development of cures. This could include projects aimed at developing biomarkers, disease models, patient-reported outcomes, processes,

and diagnostic tests. Another idea is the use of the CAN Other Transactions Authority (OTA) to accelerate ongoing programs and projects, such as trying to solve the “recruitment gap” in clinical trials, exploring drug development and regulatory innovation concepts, and using prize awards to solicit crowd sourcing ideas. Finally, the CAN Review Board discussed the idea of conducting regulatory science to develop standards for development, manufacturing, and clinical utilization of diagnostics, reagents, and devices.

CAN Performance Measures

The CAN Review Board is developing performance metrics by which to assess the progress and impact of the tissue chip program, as well as future initiatives supported through CAN. The proposed metrics would be organized into three groups: administrative outcomes, project outcomes, and transformative outcomes that would indicate a project or program advanced science or helped patients.

CAN Funding

Program	FY 2014 Est.	FY 2015 Request
Tissue Chip for Drug Screening*	\$9.8 M *	\$20.0 M
Proposed New Activities		\$ 9.8 M
Total	\$9.8 M	\$29.8 M

* The Tissue Chip for Drug Screening program also is receiving \$4.0 M from the NIH Common Fund in FY 2014. This amount is not included in the table.

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NIH Clinical Center (CC)
Conference Significant Items

Item

NIH Third Party Collection Pilot - The NIH is expected to implement the third party collection pilot in a manner that allows intramural clinical trial participants the opportunity to opt into this pilot.

Action taken or to be taken

In the FY2012 Statement of the Managers, accompanying the Consolidated Appropriations Act, 2012, Congress directed the NIH to conduct a 3-year pilot study to assess the viability of third party reimbursement at NIH by looking at one of the services commonly used by a significant number of outpatients at some point in the patient's protocol.

In 2012, the Clinical Center hired McKinsey and Company, a consultant with expertise in hospital billing in a clinical research setting, to identify a clinical area in which to conduct a robust pilot. McKinsey and Company also identified the high level requirements and resources necessary for implementing a billing pilot effort and developed an implementation plan and timeline. The NIH endorsed their recommendation to conduct the pilot in outpatient radiology and outpatient procedures (e.g., endoscopy, colonoscopy, etc.). On March 28, 2013, the NIH briefed the staff of the Committees on Appropriations on the proposed scope of the pilot. Subsequently, the scope was further refined to limit the pilot to patients enrolled in protocols that began on or after October 1, 2013 in order to avoid ethical concerns with patients in existing protocols. NIH briefed the staff of the Committees on Appropriations on this change on November 21, 2013. Additionally, patients will be given the opportunity to "opt in" or "opt-out" of participation in the pilot; there will be no penalty for opting out.

The NIH Clinical Center is preparing patients and staff for implementation of the pilot, which is expected to begin in March 2014.

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Office of the Director (OD)

Senate Significant Items

Item

Basic Research - The Committee urges the Director to maintain the NIH's current focus on the funding of basic biomedical research. The purpose of basic research is to discover the nature and mechanics of disease and identify potential therapeutic avenues likely to lead to the prevention and treatment of human disease. Without this early scientific investigation, future development of treatments and cures would be impossible.

Action taken or to be taken

NIH remains committed to its focus on funding basic biomedical research and appreciates the Committee's recognition of the importance of this fundamental investment in science for the Nation's health and well-being. By funding basic research, NIH provides the foundational knowledge of the mechanisms of biology and behavior that are necessary to understand the causes of disease onset and progression, identify risk factors and biological markers that allow for better diagnostics, and develop new cures and preventive treatments.

Studying the human microbiome—the normal bacteria that live in and on the human body—is a recent example of basic biomedical research that markedly expanded scientists' understanding of how bacterial communities affect human health and disease. NIH-supported researchers from more than 80 universities spent five years studying microbes in the human body, ultimately reporting in 2012 that more than 10,000 species occupy that space. These researchers estimated that the microbiome provides more genes that contribute to human survival than the human genome itself provides. Humans need these bacterial genes to aid in basic processes such as digestion.

Now that the normal, healthy human microbiome has been established, countless disease-specific studies are possible to determine how changes in the microbiome are associated with or cause illnesses. Variations in the microbiome could be early biomarkers of certain diseases, and introducing “good” bacteria or eliminating harmful bacteria could indicate new therapeutic avenues for disease amelioration. Without extensive basic science research as the foundation, none of these potential discoveries for the prevention and treatment of human disease would be possible.

Pushing the boundaries of basic science is vital to challenging the limits of current knowledge of human health and to discovering new information that can change the way we think about the function of the human body. Until recently, for example, scientists thought that only the protein-coding portion of human DNA—about 1.5 percent of the genome—was functional. However, new research from the NIH-funded Encyclopedia Of DNA Elements (ENCODE) project

indicates that as much as 80 percent of the genome has important biological functions. The regions that had previously been considered by some as “junk DNA” serve important roles in gene regulation and other activities. Further basic research in this area will help researchers understand the mechanics of disease genetics as well as identify novel targets for therapeutics development and disease prevention strategies that will aid future public health efforts.

While it is extremely difficult, if not impossible, to predict which scientific discoveries today will prove to be the most valuable in the future, NIH-funded research generates knowledge that other entities involved with public health can use down the road. For example, foundational knowledge about infectious diseases could enable the Centers for Disease Control and Prevention to act on NIH research findings in order to respond to a health emergency. And basic research on the immune system could help a private company develop a life-saving vaccine. NIH investments in basic research create invaluable “options” for this knowledge to be applied either immediately or at a later time and potentially in multiple ways. A single basic science finding can have widespread applicability. For example, understanding the fundamental basis of how genes work has altered not only our approach towards the diagnosis and treatment of a number of diseases and conditions but has also had implications for criminal justice efforts. The eventual ways in which basic research may be applied can be quite diverse, happen over a long period of time, and may be much different from the original purpose or vision for the research. Thus, NIH understands that one of its essential roles is to create a diverse portfolio of basic science research that will enable future endeavors to develop innovative treatments and cures.

Item

Biomedical Research Workforce Diversity - The Committee supports the Director’s efforts to increase racial and ethnic minority researchers in the biomedical research workforce through the Building Infrastructure Leading to Diversity [BUILD] and the National Research Mentoring Network programs. The Committee encourages NIH to promote partnerships with historically black colleges, universities, medical schools, and other graduate research institutions that have demonstrated a past commitment to this goal and proven achievement in recruiting, training, and mentoring racial and ethnic minority researchers. The Committee requests an update in the fiscal year 2015 congressional budget justification on this effort.

Action taken or to be taken

The NIH recognizes a unique and compelling need to promote diversity in the NIH-funded workforce. While efforts by NIH and others to attract and retain talent from all sectors of the population into the biomedical research pipeline have succeeded on an individual level, these efforts have had marginal effects for the biomedical research workforce as a whole. To address this need, the NIH Common Fund has established the "Enhancing the Diversity of the NIH-Funded Workforce" program to develop and test new and innovative ways of training and mentoring young scientists from diverse backgrounds. This program will support transformative

approaches to student engagement, research training, mentoring, faculty development, and infrastructure development with potential for a broad and sustainable impact on the diversity of the NIH-funded workforce through nationwide dissemination of successful approaches.

This program will consist of three integrated initiatives in which awardees will work together as the Diversity Program Consortium. (1) The Building Infrastructure Leading to Diversity (BUILD) initiative is a set of experimental training awards designed to learn how to attract students from diverse backgrounds into the training pipeline and to encourage their persistence to become future NIH-supported researchers. BUILD will support novel curricula, teaching laboratories, scholarships, faculty development, and administrative costs to enable awardee institutions to develop new training approaches that are designed to encourage persistence of all of their students in biomedical research pathways. (2) The National Research Mentoring Network (NRMN) initiative will develop a nationwide network of mentors linked with mentees from undergraduate to early career faculty level, with the goal of enriching training and career development through enhanced networking and mentorship experiences. The NRMN will also establish standards for good mentorship, provide training opportunities for mentors, and will provide networking and professional opportunities for mentees. (3) The Coordination and Evaluation Center (CEC) will work across all components of the consortium to determine what works and for whom. The CEC will work with BUILD and NRMN awardees to establish hallmarks of success at all career stages and develop methods to assess efficacy of approaches. It will also serve as a focal point for dissemination of information about successful approaches to the broader community, enabling transformative impact on a large scale.

Planning grant awards for BUILD and NRMN were announced in September 2013. Funding Opportunity Announcements for multi-year BUILD, NRMN, and CEC awards were published in December 2013, with award announcements anticipated in fall of 2014.

NIH anticipates that institutions with a history of recruiting, training, and mentoring researchers from diverse backgrounds will participate in this program. The BUILD Primary (applicant) Institution eligibility criteria are intended to target funds to relatively under-resourced institutions (less than \$7.5 million in annual NIH research project grant funding) with a demonstrated commitment to students from financially disadvantaged backgrounds (at least 25 percent of students must be Pell grant recipients). These institutions typically emphasize undergraduate training and may be ideally poised to encourage students from diverse backgrounds to enter research careers. BUILD Primary Institutions are encouraged to form partnerships to broaden the potential pool of participating students and maximize opportunities for research training and faculty and staff development. Potential partners include Graduate/Medical Partners (medical and graduate institutions that do not have undergraduate programs but do engage in research activities and that receive less than \$7.5 million annually in NIH research project grant funding), Pipeline Partners (two- or four-year undergraduate institutions that will expand the pool of students engaged in BUILD activities), and Research Partners (research-intensive institutions). Historically black institutions meeting the defined

criteria are welcome to apply to be Primary Institutions or participate in BUILD as Partner Institutions. Additionally, the nationwide network developed through NRMN will include

Item

Career Development Awards for Clinical Researchers - The Committee recommends continued support for “K” awards to ensure the next generation of clinical researchers is properly trained.

Action taken or to be taken

NIH considers clinical researchers to be essential contributors to the advancement of biomedical research, and remains committed to maintaining the career development activities (K awards) that allow clinicians to acquire and enhance their research skills and to become independent investigators. In support of that commitment, in late FY 2012 NIH Director Francis Collins established a working group of his Advisory Committee to consider further steps that NIH can take to foster a sustainable and diverse clinical research workforce.

In recent years, much of NIH’s career development support for patient-oriented clinical investigators has been concentrated in three activities: the Mentored Patient-Oriented Research Career Development Award (K23), Midcareer Investigator Award in Patient-Oriented Research (K24), and the institutional career development awards associated with the Clinical and Translational Science Awards program (CTSA). In FY 2012, NIH made a total of 997 new and continuing K23 awards, 242 K24 awards, and provided career development support to more than 500 individuals at just over 60 CTSA sites.

In their efforts to reduce the time it takes for laboratory discoveries to become treatments for patients, CTSA sites around the country provide a particularly rich environment for promoting multidisciplinary approaches to clinical studies and are an excellent setting for developing the careers of patient-oriented researchers.

A 2011 evaluation of NIH’s individual mentored career development award (http://grants.nih.gov/training/K_Awards_Evaluation_FinalReport_20110901.pdf) found that K23 awardees obtain NIH research grant support and publish research findings at significantly higher rates than individuals with similar research backgrounds who did not receive these awards. The success of these career awardees provides compelling reasons for NIH to continue supporting these programs.

Item

Chemical Risk Assessments - The Committee supports NIH’s leadership role in the creation of a new paradigm for chemical risk assessment based on the incorporation of advanced molecular biological and computational methods in lieu of animal toxicity tests. NIH has indicated that development of this science is critical to several of its priorities, from personalized medicine to

tackling specific diseases such as cancer and diabetes and including critical initiatives such as BRAIN. The Committee encourages NIH to continue to expand both its intramural and extramural support for the use of human biology-based experimental and computational approaches in health research to further define human biology, disease pathways, and toxicity and to develop tools for their integration into evaluation strategies. Extramural and intramural funding should be made available for the evaluation of the relevance and reliability of human biology-based and Tox21-related methods and prediction tools to assure readiness and utility for regulatory purposes, including pilot studies of pathway-based risk assessments. The Committee requests an update on current activities, a plan for future activities, and the fiscal year 2014 funding level for this area of research in the fiscal year 2015 congressional budget justification.

Action taken or to be taken

NIH continues its strong support of science in the area of Chemical Risk Assessments and is working aggressively to improve experimental and computational approaches for understanding human biology leading to a more individualized, or pathway-specific, approach to predicting toxicity. Accordingly, NIH is supporting this area both within its intramural program and through extramural initiatives and is working actively with other government agencies to ensure that new technologies and approaches are compatible with regulatory frameworks.

In 2008, in response to the National Academy of Sciences' report *Toxicity Testing in the 21st Century, a Vision and a Strategy* (NRC 2007), [Collins et al.](#) (2008) outlined an interagency intramural collaboration between the National Institute of Environmental Health Sciences (NIEHS)/National Toxicology Program (NTP), the U.S. Environmental Protection Agency's (EPA's) National Center for Computational Toxicology (NCCT), and the NIH Chemical Genomics Center (NCGC) (now located within the National Center for Advancing Translational Sciences) to shift chemical hazard assessments from reliance on traditional animal toxicology studies to target-specific, mechanism-based, biological observations largely obtained using *in vitro* assays. In mid-2010, the U.S. Food and Drug Administration (FDA) joined what is now known informally as Tox21.

In 2013, [Tice et al.](#) reported progress achieved from the inception of this program through 2010, and laid out current challenges. In brief, NIH has obtained reliable information from high throughput screening (HTS) technologies, which allows a researcher to assess the ability of tens of thousands of chemicals to interact with biological targets of toxicological and disease interest. NIH is now working to expand significantly the scientific community's understanding of the linkage between chemicals (and chemical mixtures), genes, pathways, and disease.

Another recent cutting-edge research initiative involves NIH, FDA, Defense Advanced Research Projects Agency (DARPA), and scientists receiving extramural support to develop new human tissue-based models for HTS (<http://www.nih.gov/news/health/jul2012/ncats-24.htm>). These microphysiological systems, more representative of human tissues and organs than current models, will reduce the time and costs of therapeutics development while providing better

efficacy and toxicity information for regulatory decisions. This high priority initiative continues through 2017. FY 2014 funding is estimated at \$14 million.

A major concern is that data generation is far outstripping our capabilities to analyze, store, share, and interpret these new data streams. Methods are needed to integrate HTS data with existing databases of chemical structures and biological pathways. The hurdles involve human resource constraints more than technological impediments. NIH is partnering with the EPA who is leading the effort to understand how and when this new information can be used to predict human risk. The NexGen program (<http://www.epa.gov/risk/nexgen/>) was created specifically to address this issue. Recently the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which represents essentially all of the government agencies that carry out chemical-health risk assessments, announced that this was a new priority area for its focus as well.

For FY 2014, NTP plans to provide \$4 million in continued support to the NCATS HTS facility, and spend approximately \$1.5 million for staff and computer resources. The EPA's contribution is part of a larger effort in computational toxicology collectively estimated at approximately \$21 million for FY 2014, with NCATS receiving \$1 million from the EPA.

Item

Chimpanzees - The Committee strongly commends NIH for its recent decision to substantially reduce the use of chimpanzees in NIH-funded biomedical research and designate for retirement most of the chimpanzees it currently owns or supports. However, technical changes in NIH's legal authority are needed to retire additional chimpanzees to the Federal Sanctuary System. Therefore, the Committee includes a new general provision that will allow NIH to achieve this goal. Specifically, the Chimpanzee Health Improvement, Maintenance and Protection [CHIMP] Act limits the amount of financial resources NIH may put toward retiring chimpanzees and caring for them in the Federal Sanctuary System. The CHIMP Act does not limit the amount of funding NIH may provide for chimpanzees who are not in the Federal Sanctuary System. The general provision modifies the CHIMP Act so that NIH funds that would otherwise be used to care only for non-Federal Sanctuary System chimpanzees can also be used for sanctuary chimpanzees.

Action taken or to be taken

On November 27, 2013, the President signed Public Law 113-55 that, among other things, lifted the \$30 million cap by providing NIH with authority to spend funds within the agency's annual appropriation on the care and maintenance of NIH-owned and -supported chimpanzees, including retired chimpanzees. The NIH will continue to fund the care, maintenance, and transportation of the agency's chimpanzees whether the animals are housed in a research facility, a research reserve or the federal sanctuary system according to the following schedule set in Public Law 113-5: for fiscal year 2014, up to \$12,400,000; for fiscal year 2015, up to

\$11,650,000; for fiscal year 2016, up to \$10,900,000; for fiscal year 2017, up to \$10,150,000; and for fiscal year 2018, up to \$9,400,000.

As of October 2013, the NIH owned 555* chimpanzees, which are housed in five locations around the United States. Approximately 149 of the agency's chimpanzees are already retired in the federal sanctuary with another 59 scheduled to move there in spring 2014, at which time the federal sanctuary system reaches capacity. In addition, the agency plans to retire up to 300 more chimpanzees as federal sanctuary space becomes available. These chimpanzees currently reside in research facilities or a reserve facility where no research occurs. The funds used to support the chimpanzees in these facilities can support the same chimpanzees as they relocate to the federal sanctuary system.

Public Law 113-55 also requires the NIH Director to submit to Congress a report regarding the care, maintenance, and transportation of the chimpanzees under the ownership or control of the NIH; costs related to such care, maintenance, and transportation, and any other related costs; and the research status of such chimpanzees. The first report will be due May 27, 2014 and will be updated biennially. In addition, the Comptroller General of the United States will conduct an independent evaluation and submit to Congress a report regarding chimpanzees under the ownership or control the NIH within two years after the date of enactment of this Act.

*Data are collected at the end of each fiscal year.

Item

Chronic Fatigue Syndrome (CFS) - The Committee commends the Office of Disease Prevention for agreeing to review the case definition for CFS, also known as ME/CFS, as part of an evidence-based methodology workshop. NIH is urged to include experienced professionals in the ME/CFS research and clinical fields as well as patients and their advocates in this process. Further, the Committee encourages NIH to issue a special funding opportunity to spur research into ME/CFS using the clinical specimens collected under an NIAID-funded study. This resource could help speed diagnostics and better understanding of the pathophysiology of this severely disabling condition.

Action taken or to be taken

The NIH Office of Disease Prevention (ODP) is managing the development of an evidence-based methodology workshop in collaboration with the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research Working Group. The process combines an evidence review (by the Agency for Healthcare Research and Quality [AHRQ]) and an independent, un-biased panel to assess the evidence and make recommendations for the future research on ME/CFS. The workshop process takes into account the interests of the advocacy community while also addressing the needs of the research

community by engaging individuals deeply committed to ME/CFS in their roles of researcher, clinician, advocate, and patient.

The National Institute of Allergy and Infectious Diseases released a Notice in the Guide to Grants and Contracts (NOT-AI-13-005; <http://grants.nih.gov/grants/guide/notice-files/NOT-AI-13-005.html>), which encouraged the submission of applications proposing a plan of research to accelerate the discovery of biomarkers and improve the understanding of the pathophysiology of ME/CFS using the well-characterized samples from ME/CFS patients and healthy controls. Research proposals to use the samples continue to be received by NIH and are reviewed within the NIH peer review system.

Item

Human Microbiome Project - The Committee commends NIH for establishing the Common Fund Human Microbiome Project, which has great potential to advance scientific understanding of many important areas of human health, including the immune system, and urges NIH to continue to work to understand the basis of healthy microbiome-induced immunoregulation and how it is altered in disease.

Action taken or to be taken

The Common Fund's Human Microbiome Project (HMP) is examining the immense collection of bacteria, viruses, and fungi that live on and in the human body. For each person, bacterial cells alone outnumber human cells ten to one, and it is estimated that microbial genes outnumber human genes approximately 300 to one. While many microbes support human health in various ways, such as helping to digest food and supporting a healthy immune system, others are implicated in conditions such as inflammatory bowel syndrome, autoimmune diseases, cancer, and obesity. However, we understand very little about how these microbes influence human health and disease, or how scientists could harness the power of the microbiome to treat diseases and improve health.

One promising area of research being explored by the HMP is the complex interaction between the microbiome and the immune system. Researchers supported by the HMP discovered specific microbial-host interactions that promote proper immune system development and reduce susceptibility to inflammation and allergic disease. Other HMP supported research has demonstrated that microbiomes associated with diseased tissues can stimulate inflammation, potentially contributing to disease occurrence, severity, and duration. Intriguingly, several studies have demonstrated a connection between Western-type diets rich in animal products, alterations in the gut microbiome, and diseases linked to inflammation. One study demonstrated that saturated fats found in milk promote changes in the microbiome that can perturb the immune system, leading to inflammatory bowel disease, while another study showed that consumption of red meat promotes the growth of intestinal microbes that produce by-products known to accelerate heart disease. Since 70-80 percent of the immune system resides in the gut,

understanding how the food we eat influences the gut microbiome is critical to understanding how diet, microbes, and the immune system interact to influence health and disease.

Human microbiome research is also taking place in many NIH Institutes and Centers, catalyzed in part by the foundational resources, tools, and technologies made available by the HMP. The National Human Genome Research Institute (NHGRI) supports intramural research projects classifying and sequencing DNA from fungal components of the microbiome, and examining bacterial communities that affect pediatric atopic dermatitis, a skin condition involving chronic inflammation. The National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) supports research through the HMP to understand how the microbiome is altered in diabetes and inflammatory bowel disease (IBD). Ongoing research is analyzing correlations between microbiome activity and changes in blood glucose levels and diabetes onset, and examining changes in gut microbes within IBD patients over time. The National Institute of Dental and Craniofacial Research (NIDCR) supports research on the relationship between the oral microbiome and the health and disease of the oral cavity, including the role of the microbiome in conditions such as periodontitis, caries, inflammation and infection, endodontic and restoration failures, and secondary oral manifestations of microbial origin due to conditions such as cancer, HIV infection, and immunosuppressive states. The National Institute of Allergy and Infectious Disease (NIAID) supports studies on microbiome-immune system interactions, including interactions between environmental exposures, the microbiome, and the development of allergies and respiratory diseases. The NIAID intramural research program is exploring the role of the microbiome in the regulation of immunity during infection, inflammatory diseases, and vaccine responses, as well as immune system discrimination between beneficial microbes and pathogens. NIAID and NHGRI have collaborated to develop the NIH Microbiome Cloud Project, which will pilot the use of cloud computing with biomedical big data, such as data generated by the HMP.

Item

Human Tissue Supply - The Committee continues to urge NIH to support its nationwide human tissue and organ procurement program.

Action taken or to be taken

The Office of Research Infrastructure Programs (ORIP) in the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) supports the Human Tissues and Organs Resource for Research (HTOR) Cooperative Agreement. HTOR is a procurement network within the National Disease Research Interchange. This resource supports the procurement, preservation, and distribution of human tissues and organs for basic and clinical research at research centers, academic institutions, NIH, and other federal agencies. An overarching purpose of the research funded by DPCPSI/ORIP is to reduce the burden on society of morbidity and mortality of diverse conditions and diseases and to understand normal human tissue and organ function. With the participation of NEI, NHLBI, NIAID, NIAMS, NIDDK, and

the Office of Rare Diseases Research within NCATS, DPCPSI/ORIP continues to support the HTOR program in FY2014. The resource for human organs and tissues will continue to provide a wide variety of human tissues and organs, both diseased and normal, to biomedical researchers. Such samples will include tissues from the nervous system, pulmonary system, cardiovascular system, endocrine system, eyes, skin, bone, and cartilage.

Item

Interstitial Cystitis - The Committee commends ORWH for its continued collaborations with NIDDK to support research on interstitial cystitis, which disproportionately affects women.

Action taken or to be taken

The Office of Research on Women's Health (ORWH) continues to partner with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to support meritorious interstitial cystitis research. New grant awards, part of an NIDDK and ORWH issued Request for Applications (RFA), focus on the causes, pathology, natural history, and risk factors for interstitial cystitis. ORWH continues its long-term support, with NIDDK, of a large Specialized Center of Research on Sex Differences (SCOR) that focuses on visceral pain conditions, including interstitial cystitis. ORWH remains committed to advancing research in this area, in partnership with NIDDK.

Item

National Primate Research Centers [NPRCs] - The Committee continues to support NPRCs, which are essential to ensuring the availability of nonhuman primate models and the expertise needed to help researchers pursue new drugs, treatments, and vaccines.

Action taken or to be taken

In FY 2014, the Office of Research Infrastructure Programs (ORIP) plans to increase non-construction related support for the National Primate Research Centers (NPRCs) on average, 2% over FY 13 levels. This level of support is consistent with the overall FY14 budget allocation to ORIP. In addition, ORIP will support the transfer of breeding colonies, archived samples and informational resources such as pathology records from the New England National Primate Research Center (which is in the process of being closed by Harvard Medical School) to recipient National Primate Research Centers. Therefore, these animals, samples and information will remain accessible to the research community. ORIP program staff will continue to work closely with the NPRCs to enhance consortium-based activities aimed at improving efficiency of operations, creating cost savings across the Centers and making detailed information regarding the capabilities of the NPRCs available to the research community. In FY14 the NPRC consortium will launch a web site with information regarding functional capabilities to support studies of specific human disease using nonhuman primates as animal models.

Item

OppNet - The Committee commends NIH for its commitment to the Basic Behavioral and Social Science Opportunity Network [OppNet] initiative launched in 2009. Basic behavioral science research helps improve human health by contributing to our understanding of the complex factors that influence individuals. As fiscal year 2014 is the fifth year of this initiative, the Committee requests an update in the fiscal year 2015 congressional budget justification on the contributions made by the initiative along with recommendations on how best to continue the program and the OppNet mission.

Action taken or to be taken

Between October 2010 and September 2013, the Basic Behavioral and Social Science Opportunity Network (OppNet) provided \$63,967,326 to fund 150 extramural research projects. OppNet lists all its grants by original year of funding under the Resources tab at <http://www.oppnet.nih.gov/>. One OppNet priority is *Mechanistic Pathways Linking Psychosocial Stress and Behavior*. Among the mechanistic and measurement grants funded is one conducted by early stage investigator (ESI/New PI) Dr. Santosh Kumar titled *Predicting Smoking Abstinence via Mobile Monitoring of Stress and Social Context*. The study broke important new ground by demonstrating how modern sensor technology can be used to obtain a much more detailed and accurate representation of personal and environmental influences on smoking than was previously possible. Based partially on this work, Dr. Kumar was named one of the 10 most brilliant young scientists by *Popular Science* magazine. Another priority is *Basic Mechanisms Influencing Behavioral Maintenance*; one project, Neural Mechanisms of Habit Formation and Maintenance, analyzes behaviors, as well as cellular, molecular, and circuit mechanisms to understand how people develop and maintain behaviors so they become “automatic” regardless of outside influences. The investigators found that stimulating mouse neurons to generate dopamine can foster the adoption of healthy behaviors and reduce unhealthy behaviors—all without providing incentives (e.g., food rewards). These findings, already appearing in at least five peer-reviewed publications, suggest exciting possibilities for future studies with important clinical implications.

NIH founded OppNet in response to comments that the agency’s basic sociobehavioral research portfolio was incomplete, that NIH did not welcome applications from all basic sociobehavioral researchers, and that the most appropriate way to resolve these issues would be to create or designate one Institute or Center (IC) to be the home for this scientific field. NIH officials thought OppNet to be a more appropriate, strategic response because basic sociobehavioral research is relevant to prevention and to a wide range of diseases and health conditions. One objective of OppNet was to engage more quality investigators in NIH research. An objective evaluation found that OppNet expanded the perspective of researchers and NIH program directors, respectively. Nineteen of OppNet’s 28 new investigators (68 percent) had received non-Federal funding prior to applying, compared with 21 percent of basic behavioral and social

sciences research (BSSR) and 39 percent of BSSR—an example of the initiative’s success at expanding NIH’s scope of basic-BSSR and the scientists who receive NIH’s OppNet funding. NIH program directors report that OppNet has increased their knowledge of other NIH Institutes and Centers (IC)’ missions and research interests and that OppNet has allowed them to solicit and fund projects that likely could not have occurred without OppNet’s infrastructure. Perhaps the best example to date among OppNet’s 19 funding opportunities is titled *Basic Behavioral Research on Multisensory Processing* (<http://grants.nih.gov/grants/guide/rfa-files/RFA-EY-13-001.html>). This funding opportunity is for projects that increase understanding of how multisensory (visual, auditory, olfactory, gustatory, non-pain somatosensory, vestibular) input influences basic perceptual and behavioral processes. This initiative stimulated new collaborations between ICs that were supporting research on sensory processing, but from the perspective of single sensory systems, such as vision or audition. OppNet funded nine of the successful applications.

OppNet’s infrastructure facilitates basic sociobehavioral research projects that likely would not be solicited or submitted for lack of a clear “home” for these types of grants and has enhanced overall coordination of basic and applied BSSR across NIH to allow the agency to fund basic-BSSR that ICs would not necessarily solicit and fund individually. Indeed, OppNet has generated so many innovative applications that some ICs have funded all or part of 23 projects in addition to those that OppNet’s main budget had allowed. The current memorandum of understanding expires at the end of Fiscal Year (FY) 2014. The ICs will have the option to continue their support in FY 2015.

Conference Significant Items

Item

Administrative Burden Reduction Workgroup - The Director of NIH should establish a workgroup that includes coordination and participation of universities, not-for-profits, and institutes receiving support from the NIH to develop a methods to track and measure the administrative burden on entities participating in NIH supported activities with the goal of developing a plan to reduce such administrative burden as practicable.

Action taken or to be taken

NIH is committed to implementing oversight processes that minimize the administrative burden on grantees while maintaining high standards for accountability and management. NIH welcomes the opportunity to partner with universities, not-for-profits, and research institutes that receive federal grant support to develop methods to track and measure the administrative burden on entities. The Federal Demonstration Partnership (FDP) is an association of federal agencies; academic research institutions with administrative, faculty, and technical representation; and research policy organizations that work to streamline the administration of federally sponsored research. The FDP sponsored a [Faculty Burden Survey](#) in 2007 and again in 2012 to assess the

nature and magnitude of administrative burden among its member organizations. NIH leadership will invite the FDP to partner with NIH to identify ways to reduce burden using the results of the recent FDP survey, and to plan future assessments for ongoing tracking and measurement of administrative burden.

Item

Basic Biomedical Research - The NIH is expected to maintain funding support for basic biomedical research. Basic biomedical research is an important investment in the future health, wealth, and international competitiveness of our Nation and plays a critical role in the Nation's economy. The purpose of basic research is to discover the nature and mechanics of disease and identify potential therapeutic avenues likely to lead to the prevention and treatment of human disease. Without this early scientific investigation, future development of treatments and cures would be impossible. Basic biomedical research must remain a key component of both the intramural and extramural research portfolio at NIH.

Action taken or to be taken

NIH remains committed to its focus on funding basic biomedical research and appreciates Congress's recognition of the importance of this fundamental investment in science for the Nation's health, economic well-being, and international competitiveness. Approximately 54% of NIH's budget is devoted to basic research. By funding basic research, NIH provides the foundational knowledge of the mechanisms of biology and behavior that are necessary to understand the causes of disease onset and progression, identify risk factors and biological markers that allow for better diagnostics, and develop new cures and preventive treatments.

NIH investment in basic research also benefits local economies by supporting the biomedical workforce and fueling biotechnology and other industries. For example, last year, roughly 300,000 researchers at more than 2,500 universities, medical schools, and other research institutions in every state benefited from NIH support. This investment and the ensuing research results are making possible advances in the sciences of human health and disease; innovations in diagnosis, treatment, and prevention; and significant economic benefits to the Nation. At a time when U.S. leadership in science is at risk from increased global competitiveness, a strong basic research backbone is vital to remain at the forefront of scientific innovation and discovery.

Because of its fundamental importance, basic biomedical research is an integral part of both intramural and extramural research at NIH. For example, intramural NIH scientists in the National Cancer Institute (NCI) are combining basic science knowledge of bacterial function and protein structure to specifically target cancer cells for destruction. Other intramural scientists in the National Institute of Allergy and Infectious Diseases (NIAID) are making progress toward a universal influenza vaccine by identifying targets on surface proteins that are shared by all influenza viruses. And researchers at NCI and NIAID are using novel three-dimensional imaging along with computational and cell biological tools to develop a vaccine for HIV.

Extramural researchers supported by NIH are also discovering disease mechanisms that can lead to the treatment and prevention of human diseases and disorders. Studying the human microbiome—the normal bacteria that live in and on the human body—is a recent example of basic biomedical research that markedly expanded scientists’ understanding of how bacterial communities affect human health and disease. NIH-supported researchers from more than 80 universities spent five years studying microbes in the human body, ultimately reporting in 2012 that more than 10,000 species occupy that space. Now that the normal, healthy human microbiome has been established, countless disease-specific studies are possible to determine how changes in the microbiome are associated with or cause illnesses.

Pushing the boundaries of basic science is also vital to challenging the limits of current knowledge of human health and to discovering new information that can change the way we think about the function of the human body. Until recently, for example, scientists thought that only the protein-coding portion of human DNA—about 1.5 percent of the genome—was functional. However, new research from the NIH-funded ENCyclopedia Of DNA Elements (ENCODE) project indicates that as much as 80 percent of the genome has important biological functions. The regions that had previously been considered by some as “junk DNA” serve important roles in gene regulation and other activities. Further basic research in this area will help researchers understand the mechanics of disease genetics as well as identify novel targets for therapeutics development and disease prevention strategies that will aid future public health efforts.

It is extremely difficult, if not impossible, to predict which scientific discoveries today will prove to be the most valuable in the future. Thus, fostering a broad basic biomedical research portfolio is critical for NIH’s mission to seek fundamental knowledge about the nature and behavior of living systems and to apply that knowledge to enhance health, lengthen life, and reduce illness and disability.

Item

Consolidated Communications Activities - The NIH has an important role in communications activities. The NIH Director is expected to develop an NIH wide process to reduce duplication of effort, consolidate, improve efficiencies, improve coordination of messages and generally reduce costs in this area.

Action taken or to be taken

The NIH communications community, led by the OD-Office of Communications and Public Liaison (OD-OCPL), meets bi-weekly to share information, coordinate efforts, and look at best practices and opportunities to make cost-effective community decisions.

Over the past two years, there has been an increasing effort to collaborate, cost-share, and rethink practices agency-wide. Among the action items were the completion of a cost-controlling and

unifying communications plan and logo control effort; a trans-NIH treatment of exhibiting opportunities; and, development of manual chapters regarding social and public-facing resources in order to set and maintain standards and share resources.

The effort to clarify NIH identity and reduce the art and graphics costs of a proliferation of logos across the agency was completed at the end of calendar year 2013. Not only was the cost of production reduced, but there was an agreement made with NIH contracting for the use of special circumstances clearance for the creation of any new logos or campaigns through individual contracts.

Underway is the second phase of the development of a trans-NIH effort with NIH human resources recruitment to consolidate exhibiting at meetings, to unify the NIH presence, to reduce costs of individualized booths with individualized contracts, and to have the science and health exhibits work in collaboration with NIH recruitment efforts for scientists, trainees, and employees.

OD OCPL took the lead and shared responsibility with the Privacy Act and Information Technology and Security office in an effort that led to the development of manual chapter policies on the *NIH Social and New Media Policy* and the *NIH Public-Facing Web Management Policy*. This offers guidance and reduces the duplication of effort and costs by articulating standard guidelines. Collaborative listserves that are highly active in sharing solutions have been established.

In the past several months, NIH communications, led by OD-OCPL, has been working on policies to help guide print versus digital decisions that are within the control of the communications community and their contractors and clearinghouses. Subcommittees looked at: (a) review of an internal survey of current printing practice for general trends; (2) categorizing, meta-tagging, and archiving publications for easy access; (3) current and planned digital and mobile health standard operating procedures (SOPs); (4) opportunities to share resources; and (5) identifying key audiences that need print information because of specific disabilities or without regular access to the web. These working groups provided information to create a decision-making checklist tool so that NIH is consistent across the agency about the SOP for printing decisions. To further inform these efforts, OD-OCPL conducted an evaluation study that sought to better understand the communications needs of NIH stakeholders and to find the most effective and efficient ways to meet those needs. This study sought input from members of the general public, extramural researchers and administrative staff, and advocacy and professional organizations, among others. The results helped to provide a guide to improve collaboration and coordination throughout the NIH, allowing for a more efficient utilization of NIH information and communications resources.

On a parallel track, the HHS Office of the Assistant Secretary for Public Affairs has been introducing a centralized plan for publications approval to save time and effort and to ensure all

the Institutes and Centers and the HHS Operating Divisions are aware of communications program planning across the agency. NIH has a significant role in this effort. In addition, OD-OCPL is convening the Institute and Center Communications Directors to take a fresh look at appropriate and effective ways to consolidate activities, reduce duplication of effort, improve efficiencies, coordinate messages, and reduce costs in this area.

Item

Extramural and Intramural Research - The NIH has announced plans to impose an additional level of scrutiny on extramural principal investigators with grants of \$1,500,000 or more. The NIH is directed to ensure that this policy, and any other new measures which are intended to improve oversight and accountability for extramural researchers, should apply equally to intramural researchers as well. The NIH shall include an update on this topic in the fiscal year 2015 budget justifications. In addition, peer reviewers for extramural research would benefit from knowing the scope of intramural activities that are related to the subjects under consideration to reduce the possibility of duplication. Therefore, NIH is directed to make such information available to extramural peer review study sections. The NIH shall include an update in the fiscal year 2015 budget request on this action.

Action taken or to be taken

In 2012, the NIH instituted a policy of Special Council Review for extramural grant applications from well-funded investigators. Applications recommended for funding that were submitted by Principal Investigator(s) who have active NIH research project grant (RPG) support of more than \$1 million in direct costs are subject to additional consideration. The National Advisory Council/Board is asked to recommend funding for such applications if they afford a unique opportunity to advance research that is both highly promising and distinct from the Principal Investigator(s)' other funded projects. The policy does not represent a cap on NIH funding; rather, the policy is intended to further contribute to responsible stewardship of public funds and to support meritorious and innovative research.

It is important to note that, although the trigger for invoking Special Council Review is a financial threshold, the National Advisory Council/Boards (NACs) are directed to provide advice on the unique and promising nature of the science proposed, and not the research budgets. Similarly, peer review study sections are directed to assess the scientific and technical merit, and potential impact, of the work proposed. NIH program officers monitor ongoing research activities in their field, including those of intramural research laboratories, to identify new research opportunities as well as areas of scientific overlap, and advise their Institutes and Centers about the best ways to invest in their research portfolios. Responsibility for the assessment of scientific and budgetary overlap, including overlap with intramural projects, is not the responsibility of peer review. Rather it is the responsibility of the Institute and Center Directors with assistance and counsel from their Program Directors. These assessments by the

Institute and Center Directors and Program Directors prevent duplication between intramural and extramural funded research projects.

The review processes for oversight and accountability of intramural scientists differ from those for the extramural program. Annual reviews of budgets and scientific progress are carried out by the Scientific Directors of each Institute and Center. NIH's intramural laboratories also are examined by external peer review panels (Boards of Scientific Counselors [BSCs]) chartered under the Federal Advisory Committee Act. BSCs are overseen by the Office of Intramural Research, Office of the NIH Director. BSCs review each intramural research program and PI at least every 4 years. Reviewers comment on methodology, budget, timeliness, and originality of the research, and these reviews are used to increase or decrease resources or to close non-productive laboratories. BSC reviews are presented annually to the NACs.

A process similar to the Special Council Review will be introduced for NIH's intramural laboratories by presenting to the NACs for further review and comment a listing of intramural principal investigators with attributed budgets of >\$1.5 million. Intramural attributed budgets represent the entire cost of NIH intramural research divided by the number of Principal Investigator(s) and weighted by the size of the laboratory or clinical program. Thus, although attributed budgets are not fully comparable to the budgets of extramural grants, the Special Council Review process for intramural researchers will impose a level of scrutiny comparable to the practice followed for well-funded extramural investigators.

Item

STEM Programs - The President's fiscal year 2014 budget recommends eliminating the Science Education and Partnership Awards (SEPA) programs within the Office of the Director (OD) and consolidating it within the Education Department as part of a government wide reorganization of Science, Technology, Engineering and Mathematics (STEM) education activities. The STEM proposed consolidation would also affect the Office Science Education within OD and several other smaller STEM programs throughout NIH. The NIH is directed to continue funding these programs in fiscal year 2014 and sufficient funding is provided within OD to include the Office of Science Education. The NIH shall continue these programs based on the same policies that existed at the start of fiscal year 2013. The agreement does not support NIH's proposed new educational programs.

Action taken or to be taken

In FY 2014 NIH will maintain support to the Science Education Partnership Award (SEPA) Program as part of the NIH Office of Science Education (OSE). The goals of the OSE and SEPA program are to 1) implement an innovative science education program of educational grants aimed at increasing the pipeline of future scientists and clinicians, especially from minority, underserved, and rural pre-kindergarten to grade 12 (preK-12) students; 2) provide professional development resources for preK-12 teachers; and 3) through informal science

education (ISE) projects engage and educate the general public on the health-related advances made possible by NIH-funded research. In FY 2013, NIH funded 64 SEPA grants, and plans to award a similar number of projects in FY 2014. The program continues its emphasis on rural and underserved populations with SEPA awards to states (and Puerto Rico) eligible for the Institutional Development Award Program. Additionally, NIH will continue distribution of the *NIH Curriculum Supplements* through OSE.