

Significant Items (Supplement)

Item

Disease, Condition, or Topic List – In particular, the agreement continues to support NIH biomedical research activities in the following areas and requests an update for each listed disease, condition, or topic in the fiscal year 2016 budget request to describe the latest efforts ongoing and planned for the fiscal year 2016 request:

Action taken or to be taken

See consolidated items after the table of contents.

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Amyloidosis

The National Institutes of Health (NIH) continues to support research into amyloidosis – the phenomenon of abnormal protein deposits in tissues that result in disease. Coumarin derivatives have recently been shown to inhibit transthyretin (normally functions to transport thyroxine and vitamin A-retinol binding protein in the blood) amyloidosis, as well as to serve as probes to determine the extent of properly folded protein in cells (*Chem Commun* 49: 9188, 2013). Because decreased stability of transthyretin is linked to the tendency to form amyloid deposits, researchers have developed a method to assess stability of transthyretin in human blood (*Biochemistry* 53: 1993, 2014). Using mouse models of serum amyloid A amyloidosis, clodronate (an osteoporosis drug) treatment reduced amyloid load relative to controls during the early course of disease progression (*Amyloid* 21: 45, 2014). The protein, called ATF6, was shown to reduce the levels of amyloidogenic antibodies accumulated and secreted from human cells (*PNAS* 111: 13046, 2014). Further research on ATF6 has demonstrated that this protein also reduces the levels of disease-associated variants of transthyretin secreted from human cells and its accumulation (*Chem Biol* 21: 1564, 2014). The peptide p5 was shown to recognize and specifically attach to deposits in several tissues including kidney and liver in a mouse model of serum amyloid A amyloidosis (*Peptides* 60: 63, 2014). NIH remains committed to supporting innovative strategies for improving the health of patients with amyloidosis.

Amyotrophic Lateral Sclerosis (ALS)

ALS, sometimes called Lou Gehrig's disease or classical motor neuron disease, is a rapidly progressive, invariably fatal neurological disease that attacks the neurons responsible for controlling voluntary muscles. The National Institute of Neurological Disorders and Stroke (NINDS) supports a broad range of basic research, preclinical therapy development, and clinical trials in ALS. NINDS-funded research scientists are examining whether the familial and sporadic forms of ALS share common pathogenic mechanisms; investigating the molecular and cellular processes, such as the toxic accumulation of proteins, that contribute to the disease; developing animal and cellular models of ALS that can be used to study the disease and test new therapies; developing biomarkers to expedite diagnosis or monitor disease progression; and identifying genes involved in ALS and understanding the role they play in the disease process. One exciting discovery is that chromosome 9 open reading frame 72 (C9orf72) genetic mutations (the most common genetic cause of ALS) alter the three-dimensional shape of DNA and interfere with RNA transcription, resulting in short, misfolded RNA transcripts (PMID: 24598541).¹ Understanding the function of C9orf72 mutations may lead to new molecular targets for therapies for both ALS and frontotemporal degeneration (FTD), a form of dementia that is also caused by C9orf72 mutations. To facilitate communication among scientists conducting research in both of these diseases, NINDS convened the “Advances in ALS and FTD Genetics” Workshop, where scientists discussed strategies to improve clinical assessments, enable meta-analyses across genetic data sets, and validate candidate ALS and FTD-causing genes. NINDS is currently funding preclinical development of gene therapy for people with C9orf72-linked ALS; however, there are still many challenges to developing gene therapy for neuromuscular diseases. The Joint Muscular Dystrophy Association-NINDS Workshop on “Best Practices for Gene Therapy Programs” addressed core challenges and developed recommendations to help guide gene therapy efforts. NINDS is also funding the preclinical development of other forms of

¹ <http://www.ncbi.nlm.nih.gov/pubmed/2459841>

genetically targeted therapies, such as antisense oligonucleotides for mutant superoxide dismutase 1 (SOD1)-linked ALS, as well as broader therapeutic approaches, such as small molecules to induce clearance of toxic accumulations of proteins in both familial and sporadic forms of ALS. NINDS-funded researchers are also conducting an early-phase clinical trial to test whether human spinal cord-derived stem cells can be injected safely into the cervical spinal cord of patients with ALS.

Angelman Syndrome

Angelman Syndrome is a developmental disorder that is characterized by intellectual and motor deficits, and severe epilepsy, among other symptoms. The disorder results from a mutation or deletion of the gene Ube3a, which is located on the 15q11-13 chromosomal region that is inherited from the mother. The copy of the gene from the father is silenced in many cell types, resulting in expression of the mutated gene. NIH support of research on Angelman Syndrome has resulted in several advances in the last year. A group of researchers has mapped out when and where the maternal and paternal copies of Ube3a gene are expressed in the brain using an animal model. They found that, as neurons mature, the expression of the paternal copy decreases and is undetectable after the first week of life. However, in other types of brain cells (non-neurons), the paternal copy continues to be expressed. This study furthers our understanding of the development and the timing of Angelman Syndrome symptoms (PMID: 24254964).² In addition, researchers studying the role of Ube3a in neuronal activity found that, in an animal model with deficient Ube3a, there were decreased levels of a protein important for synaptic plasticity and memory formation. This may help to explain the causes of intellectual disability that is often seen in these patients (PMID: 24434871).³ NIH continues to support ongoing research to understand the mechanisms of the disease and discover new therapies. For example, researchers are examining how Ube3a affects the balance between excitatory and inhibitory signaling in neurons and the potential impact on seizure susceptibility, which is associated with hyperexcitability. Several research projects are testing novel ways to treat Angelman Syndrome, such as a gene therapy technique that introduces a normal copy of the Ube3a gene in an animal model with a mutated gene. Another project is testing drugs that could activate the paternal copy of the gene, which is usually silenced. If symptoms can be improved through these techniques in animal models, these studies will demonstrate the feasibility of treating Angelman Syndrome and will guide the development of future therapies.

ARV-Based Microbicides

A safe and effective microbicide will be an important asset to the HIV prevention tool kit. Microbicides are products, including antiretroviral (ARV) drugs and other agents, that could be applied topically or injected to prevent acquisition of HIV and other sexually transmitted infections. Microbicides could be used alone or in combination with other strategies. NIH supports a comprehensive and innovative microbicide research program that includes the screening, discovery, development, formulation, preclinical testing, and clinical evaluation of microbicide candidates. NIH supports basic science research aimed at understanding how HIV crosses mucosal membranes and infects cells. In addition, NIH supports behavioral and social science research on adherence to, and the acceptability and use of, microbicides among different

² <http://www.ncbi.nlm.nih.gov/pubmed/24254964>

³ <http://www.ncbi.nlm.nih.gov/pubmed/24434871>

populations. These projects include the safety of microbicide use during pregnancy and menopause; studies in adolescents, and in men who have sex with men; and implementation research to better understand how to integrate a potential product into community prevention practices. Basic science and clinical studies have shown promise for the use of ARV-based microbicides as HIV prevention strategies. Studies are under way and being developed to test different ARV- and non-ARV-based products; the safety of various microbicide formulations, including long-acting formulations; the safety and pharmacokinetics of microbicides combined with a contraceptive for multipurpose prevention; and microbicides combined with antimicrobial agents to simultaneously prevent HIV and other sexually transmitted infections. Microbicide formulations and new technologies that enhance adherence, such as injectable products, nanofibers and particles, ARV-containing films, and intravaginal rings also are being developed and studied.

Autism

NIH is committed to supporting innovative and high-impact biomedical research into the causes of autism spectrum disorder (ASD), and to improve detection, treatments, and services.⁴ ASD research activities are coordinated across NIH through the NIH Autism Coordinating Committee (ACC), which includes participation from seven Institutes and Centers (ICs).⁵ NIH efforts follow the roadmap provided by the Strategic Plan for ASD Research⁶ of the Interagency Autism Coordinating Committee (IACC),⁷ a Federal advisory committee established under the Children's Health Act of 2000 and reauthorized under the Combating Autism Act of 2006, the Combating Autism Reauthorization Act of 2011, and the Autism Collaboration, Accountability, Research, Education, and Support (CARES) Act of 2014, which reauthorized the IACC through September 30, 2019. All NIH-funded ASD investigators who are collecting data from human participants are expected to share those data via the NIH National Database for Autism Research.⁸

New ASD research initiatives include an enhanced emphasis on services, in line with the objectives of the 2013 IACC Strategic Plan and the Autism CARES Act. In September 2014, the National Institute of Mental Health (NIMH) awarded 12 research grants aimed at developing effective, real-world-ready approaches to providing early diagnosis, treatment, and supportive services for people with ASD. These grants are part of a broad NIMH research effort to provide models for the delivery of needed services to children, youth, and adults with ASD, across different communities and care settings, appropriate to each age and individual. The funded projects will evaluate the success of efforts to provide services to the broadest population of people with ASD, including those from ethnically diverse and low-income populations.

September 2014 also saw the release of an NIMH funding initiative to solicit a broad, multi-site research consortium to assess and validate a set of measures that can be used as stratification

⁴ NIH-funded research on ASD is administered primarily via five Institutes: *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 (NIEHS), National Institute of Mental Health (NIMH), and National Institute of Neurological Disorders and Stroke (NINDS).

⁵ The seven NIH ACC Institutes and Centers are: National Center for Complementary and Integrative Health (NCCIH), NICHD, NIDCD, NIEHS, NIMH, NINDS, and National Institute of Nursing Research (NINR).

⁶ <http://iacc.hhs.gov/strategic-plan/2013/index.shtml>

⁷ <http://iacc.hhs.gov/>

⁸ <http://ndar.nih.gov/>

biomarkers and/or as sensitive, reliable, and objective measures of social impairment in ASD clinical trials involving school-age children.

Autoimmune Diseases

In fiscal year (FY) 2016, funding will reflect the National Institute of Allergy and Infectious Diseases' (NIAID's) commitment and long-term interest in fundamental immunology and support research on autoimmune diseases, as well as organ transplantation, asthma, and other allergic diseases through initiatives such as the Asthma and Allergic Disease Cooperative Research Centers (AADCRC), the NIAID intramural research program's Primary Immune Deficiencies Clinic, and NIAID's Immune Tolerance Network.

NIAID funds several networks committed to research on autoimmune diseases. For example, the Hematopoietic Stem Cell Transplant Consortium (HSCTC) is conducting studies on multiple sclerosis and scleroderma. Three-year outcomes from an ongoing clinical trial conducted by the HSCTC in partnership with NIAID's Immune Tolerance Network suggest that high-dose immunosuppressive therapy followed by transplantation of a person's own blood-forming stem cells may induce sustained remission in some people with relapsing-remitting multiple sclerosis. NIAID will continue to investigate the applicability of this promising strategy to other autoimmune diseases, as well as support research on the underlying immunological mechanisms common to several autoimmune diseases.

Behavioral Research and Cancer

The National Cancer Institute (NCI) continues to support scientists across the country performing critical behavioral research in cancer prevention, detection, treatment, and survivorship care, among other areas. Examples of such support include:

- Funding Opportunities for transdisciplinary and translational research to identify specific biological or biobehavioral pathways through which physical activity and/or weight control may affect cancer prognosis and survival.⁹
- The Trans-NIH Collaborative Research on Addiction (CRAN) initiative and its recent funding opportunity to inspire and support research projects investigating the role of social media in risk behaviors associated with the use and abuse of alcohol, tobacco, and other drugs that contribute to the risk of cancer.¹⁰
- NCI-supported behavioral research continues to respond to the presence of medically underserved populations who face significant cancer health disparities. Recent funding opportunities include *Behavioral and Social Science Research on Understanding and Reducing Health Disparities* (R01¹¹, R21¹²) and *Interventions for Health Promotion and Disease Prevention in Native American Populations* (R01).¹³ The NCI Community Oncology Research Program's (NCORP's)¹⁴ cancer care delivery research (CCDR) portfolio includes multidisciplinary research focused on factors including individual

⁹ <http://grants.nih.gov/grants/guide/pa-files/PA-12-228.html>

¹⁰ <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-14-008.html>

¹¹ <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-14-008.html>

¹² <http://grants.nih.gov/grants/guide/pa-files/PA-13-288.html>

¹³ <http://grants.nih.gov/grants/guide/pa-files/PA-11-346.html>

¹⁴ <http://ncorp.cancer.gov/>

behaviors; financing systems; health care practices; organizational structures; and health technologies. Such research asks how these factors affect cancer outcomes, access to quality care, cancer care costs, and health and well-being of cancer patients and survivors.

Biomarkers

NIH supports a broad portfolio of research on identification and validation of biomarkers, which are valuable tools in many stages of research. Several examples of recent advances and current efforts are provided below.

- NIH-funded researchers provided preclinical support for the use of electrophysiological measures of muscle status as biomarkers for future clinical trials in spinal muscular atrophy (SMA) patients. NIH's NeuroNext clinical research network is currently evaluating electrophysiological and other biomarkers in SMA patients.¹⁵
- NIH-funded researchers identified a gene variant that may be able to predict which patients with a certain form of prostate cancer will have a more aggressive form of the cancer, and this may eventually inform treatment choices.
- NIH-funded researchers identified a signature of three RNA biomarkers in the urine of kidney transplant recipients that appear to both diagnose transplant rejection and predict future transplant rejection.
- The NIH-funded Parkinson's Disease Biomarkers Program supports a bio-repository, a data management resource, and discovery projects.¹⁶ The Data Management Resource was the 2014 Overall Winner of the Excellence.gov Awards.¹⁷
- FDA recently cleared a new screening test, the PLAC Test for Lp-PLA2 Activity, which predicts a patient's risk of future coronary heart disease events. Data from REGARDS, an NIH-funded longitudinal cohort study of geographic and racial differences in stroke and heart disease, were used for the clinical validation of the screening test.¹⁸
- NIH-funded researchers developed a programmable biochip assay system ("Bio-Nano-Chip") for analysis of biomarkers in saliva. Researchers used the system to identify promising biomarkers for cardiac events and are now evaluating those biomarkers for clinical diagnostic purposes. The same technology has been reprogrammed for use in monitoring patients with potentially cancerous lesions of the mouth.

Biomarker research also benefits from cross-sector collaboration. NIH is a member of the Biomarkers Consortium, a public-private partnership managed by the Foundation for the National Institutes of Health. Active and completed projects include the evaluation of adiponectin as a predictor of glycemic response in Type 2 diabetes.¹⁹ Another public-private partnership, the Accelerating Medicines Partnership, was launched in 2014 and is supporting biomarker analysis in several ongoing NIH-funded clinical trials designed to delay or prevent

¹⁵ <https://www.neuronext.org/>

¹⁶ <https://pdbp.ninds.nih.gov>

¹⁷ <https://actiac.org/custom-links/10055/65076/65298>

¹⁸ <http://www.regardsstudy.org/>

¹⁹ <http://www.biomarkersconsortium.org/>

onset of Alzheimer's disease.²⁰

Botanical Products to Treat Cancer

Natural products – such as botanicals (plants), marine organisms and microbes – continue to make an indispensable contribution to the discovery and development of effective drugs for the treatment of cancer. NCI's Natural Products Branch (NPB) plays an important role in facilitating this process by providing a unique resource of about 200,000 natural products extracts for use in testing for the presence of anti-cancer and anti-microbial activities. NPB bridges the distance between the collection of a unique plant (or other source organism) and the complex chemistry needed to isolate a pure natural product with promising anti-cancer properties. The resulting lead molecules can then be modified to enable the development of an effective drug.

Preclinical development of an agent requires close collaboration with medicinal chemists, pharmacologists and toxicologists in the determination of the optimal pharmacodynamic and toxicological parameters required for advancement of the agent into clinical trials with human patients. NCI currently supports both extramural and intramural research focused on collecting unique organisms, developing efficient screening systems (high-throughput screening) to identify lead molecules with anticancer activity, and the subsequent pre-clinical development of active natural products. This type of grant support, combined with NPB efforts, has facilitated new collaborations to support natural product chemistry and has enabled the identification of lead compounds now being studied in preclinical and clinical trials. In addition, NCI supports research and trials for alternative cancer therapies, including studies of assorted plant samples, crude extracts of natural substances, and un-fractionated extracts from marine organisms and microbes used for healing and the treatment of disease. Examples of currently ongoing clinical trials include Phase 2 studies of the therapeutic effect of green tree extract for low-risk prostate cancer patients and broccoli sprout extract for estrogen receptor-positive breast cancer, and Phase 1 studies of Chinese herbs in combination with FDA-approved chemotherapy agents for liver cancer, and the use of curcumin (a substance found in the spice turmeric) in combination with cholecalciferol (vitamin D₃) for certain types of leukemia and lymphomas.

Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative

A working group of the Advisory Committee to the NIH Director was established to inform planning for the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) InitiativeSM at NIH, and this group sought broad input from the scientific community, patient advocates, and the public. In June 2014, the group released a report entitled *BRAIN 2025: A Scientific Vision*,²¹ which articulates the Initiative's scientific goals, and charts a multi-year plan for achieving them, including timetables, milestones, and cost estimates. Additionally, a BRAIN Multi-Council Working Group²² of esteemed external experts assists NIH in ensuring a coordinated and focused effort across the agency.

In FY 2014, NIH issued 58 BRAIN initiative awards to develop new technologies and approaches to understand the brain. These projects include a systematic inventory of the brain's cell types, approaches for accessing specific cells and circuits, new capabilities for

²⁰ <http://www.nih.gov/science/amp/index.htm>

²¹ <http://www.braininitiative.nih.gov/2025/BRAIN2025.pdf>

²² <http://www.braininitiative.nih.gov/MCWG-Roster.pdf>

simultaneously recording activity across large groups of neurons, next generation methods for imaging human brains, and interdisciplinary approaches to understanding how brain circuits produce unique brain functions. As part of ongoing efforts to coordinate with other Federal agencies, in November 2014, NIH and the National Science Foundation co-hosted a first annual BRAIN investigators meeting²³ for agency staff and the recipients of the first BRAIN Initiative awards. A second meeting is planned for December 2015. NIH is also exploring ways to engage broader industry participation, such as via a Request for Information²⁴ issued in September 2014, seeking input to aid developing public/private partnerships with manufacturers of novel “significant risk” brain stimulating and/or recording devices.

For FY 2015 and beyond, NIH will issue new awards aiming to develop devices to record and modulate human nervous system activity, revolutionize human neuroimaging technologies to understand how individual cells and complex neural circuits interact in time and space, and model and analyze the complex data that scientists obtain in their quest to understand brain function. Together, these efforts aim to provide the critical knowledge base for researchers seeking new ways to treat, cure, and even prevent brain disorders. Informed by an NIH workshop on ethical issues in neuroscience research, NIH will also engage investigators to explore important neuro-ethical issues in modern brain science.

Breast Cancer Screening

NCI funds research to identify the most effective, risk-based breast cancer screening strategies, while taking into consideration their potential for harm, through programs such as:

- Population-Based Research Optimizing Screening through Personalized Regimens (PROSPR²⁵) is designed to improve the screening process for breast, colon and cervical cancer. Three sites are conducting research to compare the false positive rates of 3D vs. 2D digital mammography, evaluate the ability of an imaging biomarker to reduce false positive rates, and test strategies for communicating risk.
- The Breast Cancer Surveillance Consortium (BCSC²⁶) is a collaborative network of seven research registries that track outcomes of screening mammography in the community, including recall and biopsy rates and tumor stages at diagnosis. Its large standardized dataset is a research resource to assess the delivery and quality of breast cancer screening.
- The Cancer Intervention and Surveillance Modeling Network (CISNET²⁷) conducts modelling studies based on contributions on current screening practices and outcomes from the BCSC.
- The Early Detection Research Network (EDRN²⁸) has two overarching goals in breast cancer detection: risk assessment strategies to concentrate screening resources on women who are more likely to develop cancer and developing markers, and strategies that complement and improve current radiologic screening.

²³ <http://brainfeedback.nih.gov/collaborations-develop-among-first-brain-initiative-awardees-following-kickoff-meeting/>

²⁴ <http://grants.nih.gov/grants/guide/notice-files/NOT-NS-14-054.html>

²⁵ <http://appliedresearch.cancer.gov/prospr/introduction.html>

²⁶ <http://breastscreening.cancer.gov/about/>

²⁷ <http://cisnet.cancer.gov/>

²⁸ <http://edrn.nci.nih.gov/>

- The Digital Breast Tomosynthesis Guided Tomographic Optical Breast Imaging (TOBI) study²⁹ aims to determine the physiological state of the breast, which mammography cannot. The trial will evaluate TOBI as an inexpensive technique that is non-invasive and does not use ionizing radiation. TOBI is combined with digital breast tomosynthesis (DBT, a form of 3D mammography) to ask if such combined images can be used to diagnose breast cancer with significantly improved sensitivity and specificity compared to DBT alone.
- NCI is supporting 13 additional grants focused on new breast imaging technologies that have reached the early stages of clinical testing.

Chemical Risk Assessment

The National Institute of Environmental Health Sciences (NIEHS) Division of the National Toxicology Program (NTP) is working to understand the potential health risks of chemicals through Tox21, a dynamic, multi-agency collaborative effort involving the National Center for Advancing Translational Sciences (NCATS) at NIH, as well as FDA and the Environmental Protection Agency (EPA). Tox21 progress was substantial in FY 2014. Data from a 10,000 chemical set tested in 88 high throughput assays has been made publicly available.³⁰ To begin to evaluate population-level differences in responses to toxicants, data generated from 1,000 lymphoblastoid cell lines representing nine distinct ethnic groups on five continents were analyzed and used to launch the innovative NIEHS-NCATS-University of North Carolina (UNC) DREAM Toxicogenetics Challenge, a computational crowd sourcing initiative, with Sage Bionetworks.³¹ At the culmination of the challenge, two winners were selected based on how well their computational tools could predict toxicity in different populations.³²

To further define biological effects, NTP is developing physiologically relevant *in vitro* 2D and 3D cell systems and alternative animal models such as embryonic zebrafish and nematode assays. NTP continues efforts to develop a high throughput transcriptomics platform for human cells and tissues to better characterize toxicity and disease pathways. Once established, the same approach would be used to develop corresponding gene sets for animal species in order to improve the ability to extrapolate toxic effects to humans. NTP scientists have recently shown a mouse model, whose genetic variability mimics what might be observed in human populations, can accurately predict the range of response to chemical exposures expected in human populations.³³

In addition to in-house laboratory efforts, NTP provided libraries of compounds to 10 extramural investigators researching stem cell or alternative animal assays, and NIEHS awarded 11 Small Business Innovation Research Grants that focused on the use of stem cells for toxicology, allowing independent evaluation of Tox21-related methods. For FY 2015, NTP plans to provide

²⁹ <https://clinicaltrials.gov/ct2/show/NCT02033486>

³⁰ <https://www.ncbi.nlm.nih.gov/pcassay?term=Tox21>

³¹ <http://www.businesswire.com/news/home/20130610006627/en/NIEHS-NCATS-UNC-DREAM-Toxicogenetics-Challenge-Opens-Today#.VNyrNlb70yA>

³² http://www.niehs.nih.gov/funding/assets/docs/toxicogenetics_challenge_seminar_508.pdf

³³ French JE, Gatti DM, Morgan DL, Kissling GE, Shockley KR, Knudsen GA, Shepard KG, Price HC, King D, Witt KL, Pedersen LC, Munger SC, Svenson KL, Churchill GA. 2014. Diversity Outbred Mice Identify Population-Based Exposure Thresholds and Genetic Factors that Influence Benzene-Induced Genotoxicity. *Environ Health Perspect*; doi:10.1289/ehp.1408202

\$4 million in continued support to the NCATS high throughput screening (HTS) facility, and spend approximately \$1.5 million for staff and computer resources. The EPA is also contributing \$1 million to the NCATS HTS effort.

Chromosomal Abnormalities

In addition to intensive research efforts on Down Syndrome (trisomy 21), including DS-Connect™: The Down Syndrome Registry and a newly updated strategic research plan, the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) continues to support research regarding duplications and deletions of other chromosomes or specific segments of chromosomes. An NICHD-supported study showed that women with Turner Syndrome (lacking one of the two X chromosomes) have abnormalities in the aortic valves of the heart, and ongoing studies aim to allow clinicians to identify high-risk situations earlier than had previously been possible, allowing for prompt treatment. Angelman syndrome, characterized by intellectual disability, developmental delay, speech impairment, seizures, and ataxia, is caused by maternal deficiency of the imprinted gene UBE3A. NICHD-supported scientists have developed a potential therapeutic intervention for Angelman syndrome in a mouse model by reducing the levels of a specific transcript of UBE3a. Williams syndrome is a neurodevelopmental disorder caused by a deletion of genes on chromosome 7. An NICHD-supported scientist showed that the ability to perceive faces is present in very young children with Williams syndrome, which will allow for interventions that may help with communication skills. NICHD also is conducting research on chromosomal abnormalities through its intramural program. Recently, a duplication of a short stretch of the X chromosome and a highly likely gene candidate was discovered in some people with gigantism. Scientists from NICHD also recently showed that a gene called brain-derived neurotrophic factor (BDNF) may play an important role in neurocognitive development in people with WAGR syndrome (Wilms tumor). Collectively, these studies will allow new diagnostics and therapeutics to be developed for individuals with various chromosomal abnormalities.

Chronic Constipation

Research to improve understanding of chronic constipation continues to be a priority for NIH. Many factors can cause chronic constipation and its accompanying abdominal pain, but it is more common in women, older adults, and people with irritable bowel syndrome (IBS). In 2014, researchers participating in the NIH-supported Patient Reported Outcomes Measurement Information System (PROMIS) developed a standardized measurement scale for GI disorders, including constipation, to help health care providers and researchers understand symptoms from the patients' perspective (*Am J Gastroenterol* 109: 1804, 2014³⁴). Recently, NIH-supported researchers linked constipation in IBS patients to lower levels of fecal bile acids and slower movement of intestinal contents (*Clin Gastroenterol Hepatol* 11: 1270, 2013³⁵). The researchers also found that these changes could be due to variations in a particular gene called *GPBAR1* (*Am J Physiol Gastrointest Liver Physiol* 307: G508, 2014³⁶). Another group of researchers found sex-related differences in the activity of a certain part of the brain in individuals with IBS (*J Neurosci* 34: 14252, 2014)³⁷. These research advances not only expand our understanding of

³⁴ <http://www.ncbi.nlm.nih.gov/pubmed/25199473>

³⁵ <http://www.ncbi.nlm.nih.gov/pubmed/23639599>

³⁶ <http://www.ncbi.nlm.nih.gov/pubmed/25012842>

³⁷ <http://www.ncbi.nlm.nih.gov/pubmed/25339739>

gastrointestinal motility disorders such as chronic constipation and how they may affect people differently, but they also could provide potential avenues for treatment.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD), which includes emphysema and chronic bronchitis, is a major cause of disability and the third leading cause of death in the United States. The National Heart, Lung, and Blood Institute (NHLBI) supports research on the causes of COPD, its prevention, and treatment. Prevention of chronic lung diseases is a top priority because by the time symptoms appear, irreversible damage has already been done. Thus, it is critical to identify people at earlier stages of the disease. NHLBI's COPDGene³⁸ study is integrating genetics and imaging to identify who is at greatest risk of progression, the pathways involved, and ways to target treatments earlier and more effectively. In 2014, COPDGene researchers identified four clusters of subjects from data³⁹ on 10,192 smokers, suggesting that there are multiple sub-classes of COPD. COPDGene investigators also analyzed genome-wide association studies data⁴⁰ from smokers, with and without COPD, to identify gene variants associated with the disease. Their evaluation confirmed the association of COPD with three previously identified genetic locations and identified three new genetic locations. To further research in the prevention of chronic lung diseases, in 2014, NHLBI released two announcements for research to characterize pre-symptomatic stages of chronic lung disease(s)⁴¹ as well as resiliency factors that promote health⁴². Understanding susceptibility and progression to disease in pre-disposed versus "resistant" individuals is necessary in order to develop targeted prevention interventions. Finally, there is an urgent need for new treatments for chronic lung diseases. To facilitate the efficient conduct of studies in "real world" settings, the NHLBI is establishing the Pulmonary Trials Cooperative (PTC)⁴³ that will be enable studies across a wide range of lung diseases; encourage studies of patients with comorbid or intermediate conditions; and involve a wide range of institutions, from major medical centers to community-based providers, in the recruitment, retention and follow-up of research subjects.

Chronic Overlapping Pain Conditions

NIH continues to support a collaborative trans-NIH effort to better understand and identify effective treatments for overlapping chronic pain conditions. NIH funds large prospective population-based epidemiological studies on multiple pain conditions that commonly overlap. The National Institute of Dental and Craniofacial Research (NIDCR) funds a study to identify risk factors that predict whether temporomandibular joint disorders (TMD) will develop as a single condition or in conjunction with other chronic pain conditions, including headache, low back pain, irritable bowel syndrome, and widespread body pain. 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 and other co-occurring pain conditions. NINDS funds a multidisciplinary project to identify the risk factors that increase susceptibility to one or more complex persistent pain conditions, including episodic headache,

³⁸ <http://www.copdgene.org/>

³⁹ <http://www.ncbi.nlm.nih.gov/pubmed/24563194>

⁴⁰ <http://www.ncbi.nlm.nih.gov/pubmed/24621683>

⁴¹ <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-15-025.html>

⁴² <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-15-024.html>

⁴³ <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-15-015.html>

fibromyalgia, TMD, irritable bowel syndrome, and vulvar vestibulitis. To further expand understanding of chronic overlapping pain conditions, the NIH Pain Consortium released an FOIA on Chronic Overlapping Pain Conditions⁴⁴ developed to address several recommendations from a 2012 workshop on this topic, including leveraging existing patient cohorts, resources, and data repositories to optimize outcomes; conducting prospective population-based epidemiological studies to determine the natural history of, and risk factors for, onset and progression of disease; and studying central sensitization as a theme for discovery of common mechanisms of disease, diagnostics, and treatment. In September 2014, the NIH Pain Consortium held an Investigators' Meeting on Chronic Overlapping Pain Conditions⁴⁵ with the goal of developing approaches and models that leverage existing research resources and data repositories to better collect, analyze and integrate data that will enhance the research effort and ultimately serve to improve clinical management of people with pain. This meeting set the stage to initiate development of a case definition for overlapping conditions and a minimal set of common data elements to support clinical studies and practice guidelines. The NIH Office of Pain Policy is facilitating a set of future meetings with relevant investigators to develop these tools.

Chronic Pelvic Pain

Chronic pelvic pain reduces quality of life and productivity and incurs significant health care costs for millions of Americans. Associated conditions include irritable bowel syndrome (IBS), vulvodynia, uterine fibroids, endometriosis, and urologic pain conditions, such as interstitial cystitis/painful bladder syndrome (IC/PBS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). NIH-supported studies in this area are making strides toward better diagnosis, treatment, and prevention of conditions causing chronic pelvic pain. For example, findings emerging from the NIH-supported Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network⁴⁶ include new insights into the course, differing manifestations of, and possible biomarkers for urologic chronic pelvic pain conditions in people; in FY 2014, NIH renewed the Network for a second 5-year phase to continue studies that could provide a foundation for effective clinical interventions for IC/PBS and CP/CPPS. In IBS, two recent studies found that complex factors, such as fear of symptoms, stress, and anxiety, played a larger role in lowering patients' day-to-day quality of life or self-assessment of overall health than IBS symptom severity itself; greater awareness and attention to these factors may help improve overall health care and satisfaction for IBS patients. (*Am J Gastroenterol* 109: 1815, 2014⁴⁷; 109: 224, 2014⁴⁸) NIH also continues to support the Specialized Center of Research⁴⁹ (SCOR) for Neurovisceral Sciences and Women's Health, that is elucidating the interplay between gut and brain pathways in IC/PBS and IBS, focusing on sex differences in the development, clinical manifestation, and treatment response in these pain syndromes. NIH-supported researchers are also making progress in identifying non-surgical approaches to treating uterine fibroids (*Fertil Steril* 98: 1557, 2012⁵⁰; 102:272, 2014⁵¹). Researchers have learned more about the brain

⁴⁴ <http://grants.nih.gov/grants/guide/pa-files/PA-14-244.html>

⁴⁵ http://painconsortium.nih.gov/Conferences_and_Seminars/9-16-2014_Inv.MtgonCOPC.html

⁴⁶ http://rt5.cceb.upenn.edu/mapp_web/MAPP_About.html

⁴⁷ <http://www.ncbi.nlm.nih.gov/pubmed/25223577>

⁴⁸ <http://www.ncbi.nlm.nih.gov/pubmed/24419481>

⁴⁹ <http://uclacns.org/programs/center-for-neurovisceral-sciences-and-womens-health/>

⁵⁰ <http://www.ncbi.nlm.nih.gov/pubmed/22925684>

mechanisms underlying experience of vulvodynia pain, finding that they are similar to mechanisms activated in a more generalized pain disorder (*J Pain* 14:579, 2013⁵²). NIH continues to implement a research plan for vulvodynia, and is supporting a clinical trial⁵³ of gabapentin as a treatment for vulvar pain that is currently recruiting patients.

Congenital Heart Disease

NHLBI supports research on the causes of congenital heart disease (CHD); improved treatments, outcomes, and quality of life; and potential pathways towards prevention. For example, NHLBI supports programs such as the Bench to Bassinet Program (B2B)⁵⁴, which is identifying genetic and epigenetic causes of CHD to help personalize treatment for children and adults with CHD, and the Pediatric Heart Network (PHN)⁵⁵, which conducts research studies in children with CHD or acquired heart disease. In 2014, the PHN and the Marfan Foundation completed a clinical trial in 608 children and adults with Marfan syndrome and dilated aortas, showing the equivalence of losartan to atenolol (the most common current therapy). This finding suggests that losartan may be another effective treatment option for patients with Marfan syndrome. NHLBI also supports research to advance the field of adult congenital heart disease (ACHD) in partnership with the Adult Congenital Heart Association (ACHA) and the Alliance of Adult Research in Congenital Cardiology through The Health, Education, and Access Research Trial (HEART-ACHD)⁵⁶ and The Research Empowerment for Adult Congenital Hearts (REACH)⁵⁷ project. HEART-ACHD is a multi-center study to improve care delivery and long-term outcomes for adults with CHD; and REACH seeks to facilitate ACHD research by improving data-sharing. To further research in this area, in June 2014, a working group hosted by NHLBI and ACHA⁵⁸ assessed the current gaps in knowledge about ACHD and identified high-impact research topics for the field.

Contraception Research and Development

In the United States, approximately 50 percent of all pregnancies (three million annually) are unplanned. Unintended pregnancies can have serious and lifelong health and economic consequences for children and families. Despite the clear need for contraceptive options that are used consistently, the private sector has largely abandoned the field of contraceptive research, leaving the Federal Government, and NICHD in particular, the major source of funding in the United States. Findings from recent NICHD-supported studies buttress the need for further work in this area. For example, a study using data from the National Survey of Family Growth found that black women were substantially less likely than white women to use highly effective, reversible contraceptive methods. NICHD also is supporting research on proteins that are critical for sperm formation and function, which may lead to development of a safe, effective, and reversible form of male contraception. To help address ongoing challenges, in 2014, NICHD

⁵¹ <http://www.ncbi.nlm.nih.gov/pubmed/24825427>

⁵² <http://www.ncbi.nlm.nih.gov/pubmed/23578957>

⁵³ <https://clinicaltrials.gov/ct2/show/NCT01301001?term=Trials+of+Gabapentin+in+Vulvodynia%3A+Biological+Correlates+of+Response&rank=1>

⁵⁴ <http://www.benchtobassinet.org/>

⁵⁵ <http://www.pediatricheartnetwork.com/>

⁵⁶ <http://www.ncbi.nlm.nih.gov/pubmed/23651823>

⁵⁷ <http://www.ncbi.nlm.nih.gov/pubmed/24411207>

⁵⁸ <http://www.nhlbi.nih.gov/research/reports/2014-achd-emerging-research>

convened a panel of national experts representing a range of scientific disciplines to conduct an in-depth review of NICHD's entire contraceptive research program. The panel reported its findings in January 2015, strongly recommending that NICHD continue to support all facets of this research, including basic research leading to target discovery; product development; and behavioral research to assess user needs, preferences, and product acceptability. NICHD leadership is carefully evaluating the panel's findings for feasibility and prompt action.

Cures Related to Blindness-inducing Illnesses

Blindness and visual impairment can result from eye-specific diseases such as mutations in proteins that detect light in the eye, or they can be a complication of a complex disease, like diabetes. The National Eye Institute (NEI) funds clinical trials on therapeutics for diseases such as diabetic retinopathy, dry eye disease, and infectious eye diseases, but it also funds basic research on molecules and mechanisms of disease that may someday lead to the development of new therapeutics. In recent years, vision research has made remarkable progress developing therapies that prevent or even reverse vision impairment in common diseases such as age-related macular degeneration (AMD) and diabetic retinopathy. However, vision research is at the cutting edge of two fields of precision medicine that may someday cure certain diseases of vision: gene therapy and induced pluripotent stem (iPS) cell technology.

Gene therapy allows doctors to permanently replace disease causing genes with a healthy gene in patients' eyes. A key success in this promising field was restoration of vision to patients with Leber Congenital Amaurosis. NEI is now supporting gene therapy for retinitis pigmentosa, Stargardt disease, retinoschisis, and Leber hereditary optic neuropathy. In the burgeoning field of stem cell biology, NIH researchers achieved a breakthrough in converting iPS cells taken from AMD patients into retinal tissue. Creating patient-derived disease models in a dish enables scientists to explore causes of disease, to screen for drugs, and to develop cell-based therapies. NEI recently awarded a contract to Cellular Dynamics International to manufacture clinically compatible iPS cell derived human retinal tissue. Upon FDA-approval for use in humans, this will be used in the first U.S. clinical trial to treat patients using stem cells derived from their own tissue.

Cystic Fibrosis

Cystic fibrosis (CF) is an inherited disease of the mucus and sweat glands that affects the lungs, pancreas, liver, intestines, sinuses and sex organs. In 1962, few patients with CF survived into their teen years. In 1989, NIH researchers discovered that the underlying problem in patients with CF is a defect in the gene responsible for salt transport through cell membranes (CFTR). With the identification of the CFTR gene, the implementation of newborn screening, and dramatic improvements in treatments, the median life expectancy has increased to 37 years.

NIH is now funding research focused on eradicating CF through transformative strategies to prevent and treat this life-limiting disease. Clinical trials are under way to identify treatments that most effectively treat patients with various CF mutations. For example, NHLBI-funded investigators tested⁵⁹ the effect of two drugs, lumacaftor and ivacaftor, and found that a combination of the drugs improved lung function in CF patients who are homozygous for the most common CFTR mutation, present in almost 90 percent of patients with CF, suggesting this

⁵⁹ <http://www.ncbi.nlm.nih.gov/pubmed/2497328>

approach could be effective in treating CF. In 2014, NHLBI solicited small business grant applications to develop and validate novel in vitro human cell-based tools⁶⁰ for predicting the responses of individual patients to CFTR-directed therapeutics⁶¹. In addition, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is funding the Baby Observational and Nutrition Study of CF (BONUS⁶²) to investigate the appropriate diet for newborns with CF identified by newborn screening, and CF Research and Translation Centers⁶³, to promote translational research in promising areas including small molecule therapeutics, CFTR protein structure and function, CF-related diabetes, the CF microbiome, and neonatal nutrition.

Diabetes

Over 29 million Americans have diabetes, and over 90 percent of individuals with diabetes have Type 2 diabetes (T2D). Recent major research progress supported by NIH includes: 1) Research in various ethnic populations identified rare mutations in the gene SLC30A8 that appear to significantly reduce risk for T2D (*Nat Genet* 46: 357, 2014); 2) A rare mutation inactivating one copy of the *LIPE* gene was found to almost double the risk for T2D (*NEJM* 370: 2307, 2014); 3) Metformin, the first-line drug for T2D, may be limiting liver glucose production by inhibiting an enzyme that helps make it possible to convert energy stored in fat into glucose (*Nature* 510: 542, 2014); 4) Two small one-year trials found bariatric surgery more effective than non-surgical approaches for treating T2D in adults whose obesity is generally considered too mild to make them candidates for such procedures (*JAMA Surg* 149: 707, 2014; *JAMA Surg* 149: 716, 2014); 5) From 2001 to 2009, the proportion of youth with T2D rose by 30.5 percent. The increase in prevalence occurred in both sexes, and in White, Hispanic, and Black youth (*JAMA* 311:1778, 2014); 6) In people for whom the major diabetes complication diabetic macular edema had led to mild visual impairment, the drugs Lucentis®, Eylea®, and Avastin® were each found safe and effective for improving vision, on average by approximately a line and a half on an eye chart. In those with more significant vision impairment, an improvement of three or more lines occurred more often with Eylea® (67 percent) than Lucentis® (50 percent) or Avastin® (41 percent) (*NEJM February 18, 2015 [Epub ahead of print]*); 7) Eleven specific compounds applied in precise sequence over 4-5 weeks were found to coax large numbers of induced pluripotent stem cells to behave like naturally-occurring beta cells, responding to varying glucose levels by increasing or decreasing secretion of insulin (*Cell* 159: 428, 2014); and 8) Pancreatic delta cells in adult male mice induced to change into insulin-secreting beta cells (*Nature* 514: 503, 2014). Giving the hormone FGF1 was found to normalize blood glucose levels of insulin-resistant mice, but not to affect blood glucose levels in healthy mice. FGF1 appeared to act as an insulin sensitizer, but without some side-effects common in approved insulin-sensitizing drugs (*Nature* 513: 436, 2014). These advances contribute to understanding susceptibility to T2D, and ways to treat diabetes and its health complications.

Diabetes-related Kidney Disease

Diabetes-related kidney disease, also known as diabetic nephropathy, is the largest single cause

⁶⁰ <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-15-026.html>

⁶¹ <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-15-027.html>

⁶² http://projectreporter.nih.gov/project_info_details.cfm?aid=8661182&icde=22825947&ddparam=&ddvalue=&dds_ub=&cr=1&csb=default&cs=ASC

⁶³ <http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-13-007.html>

of kidney failure in the United States and accounts for nearly 44 percent of the nearly 115,000 newly affected individuals requiring dialysis each year. NIH supports numerous studies of diabetic kidney disease, ranging from investigator-initiated studies of this condition to large, long-term studies of large cohorts of patients such as the Chronic Renal Insufficiency Cohort (CRIC) study. The CRIC study is one of the largest and longest ongoing studies of Chronic Kidney Disease (CKD) epidemiology in the United States; it is following both white and African American people with CKD, about half of whom also have diabetes. Looking forward, studies such as this provide a rich source of material coupled with comprehensive information about their volunteers that will inform future studies. These studies could involve efforts to discover critical candidate genes for diabetic nephropathy, to identify regulatory pathways in the disease process, to generate novel models for preclinical work, and to develop biomarkers with clinical utility so that the lives of people with diabetic nephropathy can be improved. NIH is supporting the Preventing Early Renal Function Loss in Diabetes (PERL) trial, which seeks to prevent progression of early diabetic kidney disease in adults with Type 1 diabetes.⁶⁴ Additionally, NIH is supporting three studies – COMBINE, BASE, and TarGut⁶⁵ – as part of its chronic kidney disease pilot and feasibility studies. All three of these studies enroll people with diabetes.

NIH has recently completed the Kidney Research National Dialogue, a project that solicited the views of scientists, physicians, patients, and the public regarding the most critical issues in kidney disease research. More information about potential future directions in the field of diabetic nephropathy, as well as other areas of kidney disease research, is available on NIDDK's website.⁶⁶

DPCPSI Portfolio Analysis NIH-wide Policies

The NIH Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) serves as a portfolio analysis and research resource for ICs as well as the NIH Office of the Director. The Division is developing innovative methods to facilitate the content analysis of grant applications; developing and testing new computational tools to further information research portfolio analysis and management; and conducting bibliometric analyses to assess productivity, impact, and influence. The DPCPSI Office of Portfolio Analysis (OPA) focuses on the design and conduct of accurate quantitative analyses of the NIH portfolio. These analyses provide a precise, comprehensive characterization of how NIH resources are currently distributed across scientific areas. These analyses contribute to transparency and accountability for how NIH's funding is currently aligned with existing scientific objectives and goals.

DPCPSI has developed several new computational tools designed to provide information retrieval and database services to analyze information about NIH funding, collaborations, publication records, and commercialization, as well as data mining and knowledge discovery techniques to link researchers, funding, and research outputs across disparate data sets. The development and distribution of these tools NIH-wide permit the characterization of the impact of NIH-funded research and facilitate effective comparisons with cognate global investments. Specifically, these tools: 1) measure the dissemination of NIH-sponsored biomedical and behavioral and social science findings as new publications appear in the peer reviewed literature;

⁶⁴ <https://clinicaltrials.gov/ct2/show/NCT02017171?term=UC4DK101108-01&rank=1>

⁶⁵ <http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-12-016.html>

⁶⁶ <http://www.niddk.nih.gov/about-niddk/offices-divisions/division-kidney-urologic-hematologic-diseases/kidney-research-national-dialogue/Pages/kidney-research-national-dialogue.aspx>

2) track NIH-sponsored bench-to-bedside clinical advances; and 3) map NIH-catalyzed knowledge and technology transfer and economic impact through patents, patent applications, and start-up biotechnology entities. DPCPSI will continue to develop, validate, and apply new analytical techniques and conduct comprehensive evaluations of the research portfolio to guide agency policies to ensure that NIH-sponsored research continues to contribute to improving the public health of all Americans.

Drug Rescue and Repurposing

The length of time from target discovery to approval of a new drug currently averages about 14 years. The failure rate during this process exceeds 95 percent, and the cost per successful drug exceeds \$1 billion, after adjusting for all the failures. Alternatively, drugs can be repositioned for new indications, using drugs that have not been approved (sometimes known as drug rescue) or that are already approved (known as drug repurposing). Drug rescue and repurposing has been broadly accepted as an efficient and cost-effective means for drug development compared to de novo development. Industry holds many of the assets and data needed for efficient drug rescue and repurposing; however, the pharmaceutical industry may have insufficient incentive to pursue further development of these drugs due to either scientific or business reasons, which prevents potentially valuable therapies from reaching the public. NIH is working to provide opportunities and incentives to reposition and repurpose drugs for new indications.

- NCATS' Discovering New Therapeutic Uses (NTU) for Existing Molecules program⁶⁷ enables partnerships among academic investigators, small businesses, and the pharmaceutical industry to conduct research for finding new indications for existing, partially developed therapeutic candidates that are provided by industry. For FY 2014, NCATS issued four funding announcements for 26 agents, including several suitable for exploring pediatric indications.
- The NCATS Pharmaceutical Collection⁶⁸ is a valuable, publicly accessible resource of approved and investigational drugs that can be used for drug repurposing efforts. As an example, NCATS and NIDDK scientists screened a repurposed drug from the Collection, chlorcyclizine, for effectiveness against Hepatitis C and received IND approval in early 2014 for clinical trial testing.
- Nucleoside reverse transcriptase inhibitors possess intrinsic anti-inflammatory activity:⁶⁹ In a landmark study, NEI-supported investigators discovered that nucleoside reverse transcriptase inhibitors (NRTIs), which are used to treat HIV/AIDS, may also provide therapy in age-related macular degeneration (AMD). In animal models, NRTIs blocked NLRP3, a key component of inflammatory pathways involved in the innate immune response, and thereby prevented further damage to the retina. Various NRTIs, such as HIV/AIDS therapeutic AZT, are already FDA-approved for other indications, thus clinical trials in AMD could circumvent many regulatory hurdles.

Duchenne Muscular Dystrophy

The NIH muscular dystrophy portfolio includes a wide range of basic, translational, and clinical

⁶⁷ <http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/therapeutic-uses.html>

⁶⁸ <http://www.ncats.nih.gov/research/tools/preclinical/npc/pharmaceutical-collection.html>

⁶⁹ <http://www.sciencemag.org/content/346/6212/1000.full?sid=8526e7e6-5933-4b2a-bdb9-c8749562e423>

research focused on understanding and treating the many forms of muscular dystrophy, including Duchenne Muscular Dystrophy (DMD). Advances in the last several years include the identification of genetic modifiers of DMD, which may lead to new therapeutic avenues (PMID: 25338755⁷⁰), the development of non-invasive, quantitative biomarkers that could expedite clinical trials (PMID: 24798221⁷¹, 24929900⁷²), and the demonstration of genomic editing to treat DMD in a mouse model of the disease (PMID: 25123483⁷³). A number of translational projects have leveraged public-private funding to optimize therapy development efforts and, as a result, several therapies are at the point of clinical trial readiness and/or are going through appropriate FDA channels to move toward clinical trials.

The *Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (MDCRC)* are also an important component of the NIH DMD portfolio. Each center can conduct a mixture of basic research to understand the disease, translational research to turn basic research findings into interventions, and clinical research to understand how the disease affects patients and to test potential therapies. The six currently funded Wellstone MDCRCs also promote collaboration, develop and share research resources, and train new muscular dystrophy researchers.

Finally, the *Muscular Dystrophy Coordinating Committee (MDCC)*⁷⁴, coordinates activities related to the muscular dystrophies across the entire Federal Government. MDCC is currently drafting an update to the 2005 Action Plan to be released in 2015. In July 2014, NIH brought together researchers, scientists, and clinicians to discuss progress since the last Action Plan, as well as remaining and new opportunities to include in the updated version. The 2015 Action Plan has now been drafted and shared with MDCC members for input; it has also been posted for public comment through a Request for Information notice. The comments from MDCC and the public will then be discussed prior to voting on approval of the plan at the next MDCC on March 17, 2015.

Entrepreneurs-in-Residence Initiative (Office of Technology Transfer)

Currently there is one Entrepreneur-in-Residence (EIR) working with the Office of Technology Transfer (OTT) through BioHealth Innovation, Inc. (BHI), a Maryland public-private partnership focused on commercializing market-relevant bio-health innovations and increasing access to early-stage funding in Central Maryland. BHI will be renewing its Partnership Intermediary Agreement (PIA) with OTT for three more years and also just recently received an award from the National Heart, Lung, and Blood Institute. This will enable BHI to recruit five more EIRs this year that will work within several ICs. It is expected that BHI will have a total of seven EIRs at NIH in 2015.

Fiscal Management

NIH has an effective system of internal controls for its financial systems; that includes hard funds control at the extramural/intramural level, which NIH considers appropriate. NIH strives for continuous improvement in its fiscal management; for example, as part of the HHS Accounting Treatment Manual (ATM) initiative, the Office of Budget, Office of Financial

⁷⁰ <http://www.ncbi.nlm.nih.gov/pubmed/?term=25338755>

⁷¹ <http://www.ncbi.nlm.nih.gov/pubmed/?term=24798221>

⁷² <http://www.ncbi.nlm.nih.gov/pubmed/?term=24929900>

⁷³ <http://www.ncbi.nlm.nih.gov/pubmed/?term=25123483>

⁷⁴ http://www.ninds.nih.gov/about_ninds/groups/mdcc/

Management, and NIH Business System (NBS) examined budget execution with respect to Programs, Projects or Activities (PPAs). At NIH most PPAs are at the IC level, but there are some PPAs with direct budget authority that are below the IC level, such as the Institutional Development Award (IDeA) program, the Clinical and Translational Science Awards (CTSA) program, or the NIH Common Fund (all NIH PPAs are listed in the FY 2015 Operating Plan that is posted on the Office of Budget website.⁷⁵ Based on this review, NIH has ensured that each existing PPA has its own allotment in the financial system, and any new PPAs created by Congress would also receive a separate allotment. This will provide additional assurance of accurate budget execution and compliance with all applicable statutes and regulations.

Focal Gastric Cancer (Same Response as Gastrointestinal Cancer)

A group of researchers in the NIH Cancer Genome Atlas (TCGA) Network have discovered that gastric cancers fall into four distinct molecular subtypes. This discovery, published in July 2014, is changing the way researchers think about treatments for gastric cancers, informing the development of targeted therapies for defined sets of patients whose tumors have specific genomic abnormalities. This new genetically based classification system is an important complement to the current anatomical classification system, which consists of two categories: diffuse and intestinal.

NCI is supporting several trials specific to gastric cancer including a National Clinical Trials Network⁷⁶ (NCTN) study combining chemotherapy with an agent targeting alterations in the MET gene (associated with gastric cancer); in addition, candidate biomarkers will be tested as instruments to evaluate the effect of treatment. Other therapeutic studies include trials of trastuzumab, an FDA-approved antibody that targets the HER2 protein, expressed in many gastric as well as breast cancers. In addition, patients with gastric cancer will be included in NCI MATCH⁷⁷, a new type of clinical trial in which treatment is based on the molecular abnormalities of a tumor instead of its anatomic site.

Fragile X Research

Fragile X syndrome (FXS) is caused by mutations in the Fragile X FMR1 gene on the X chromosome, and is the most common form of inherited intellectual and developmental disability. Three related but distinct conditions can result from these changes, including FXS, Fragile X-associated tremor/ataxia syndrome, and Fragile X-associated primary ovarian insufficiency (FX-POI). NIH continues to maintain a substantial and diverse portfolio of Fragile X-related research, including translational research that could lead to potential treatments to improve the lives of individuals with FXS and related conditions. The trans-NIH Fragile X Research Coordinating Group of 11 ICs coordinates these efforts. A recent NIH-supported study showed that of the approximately 50 percent of children with FXS who were diagnosed with autism spectrum disorder (ASD) by the researchers, only half of that group had previously received a diagnosis of ASD. Other researchers found that providing hormone replacement therapy in young women with FX-POI restored bone mineral density to normal, which will prevent future osteoporosis and bone fractures for these women. In addition, NICHD, NINDS, and NIMH support the *Collaborative Centers for Research in Fragile X* program, originally

⁷⁵ <http://officeofbudget.od.nih.gov/pdfs/FY16/Op%20Plan%20for%20Web.pdf>

⁷⁶ <http://www.cancer.gov/clinicaltrials/netn>

⁷⁷ <http://www.cancer.gov/clinicaltrials/noteworthy-trials/match>

established in response to the Children’s Health Act of 2000. These ICs have produced many scientific advances in Fragile X research, such as identifying the risk of transmitting this gene mutation across generations. In September 2014, NIH announced \$35 million in funding over five years for three new centers.⁷⁸

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Global Health Technologies

The remarkable progress made in genomics, bioengineering, and other technology-related fields over the past decade has given rise to innovative, global health technologies that can help many different populations in diverse, low-resource settings. Point-of-care diagnostics provide compelling examples of such advances. For example, NIAID-sponsored investigators developed point-of-care testing for tuberculosis⁸¹, which has reduced the wait time of diagnosis from four months, using costly, traditional labs, to within two hours – allowing patients to start taking effective drugs on the same day they are tested. If deployed globally, this test would save an estimated 15 million lives by 2050. Because it understands the global health impact of diagnostic technologies, NIH funds additional research through *Developing a Point-of-Care Device for the Diagnosis of Sickle Cell Disease in Low Resource Settings* (NHLBI⁸²) and *Cancer Detection, Diagnosis, and Treatment Technologies for Global Health* (NCI⁸³ in collaboration with other ICs).

Research is vital to realizing the tremendous potential of mobile health (mHealth) technology to improve health in low-resource settings. National Institute of Biomedical Imaging and

⁷⁸ <http://www.nichd.nih.gov/news/releases/Pages/092214-collab-research-fragileX.aspx>

⁷⁹ <http://www.cancer.gov/clinicaltrials/nctn>

⁸⁰ <http://www.cancer.gov/clinicaltrials/noteworthy-trials/match>

⁸¹ <http://www.niaid.nih.gov/about/yearinreview/2010/advances/scientificFindings/Pages/RapidlyandEffectivelyDiagnosingTuberculosis.aspx>

⁸² <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-14-010.html>

⁸³ <http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-15-001.html>

Bioengineering (NIBIB) funded researchers developed a quarter-sized, lens-less microscope⁸⁴ that, when connected to a mobile phone, can beam high-quality images of cells and microbes halfway around the globe to computers that can automatically interpret the images. This device specifically addresses the challenge of quickly and accurately diagnosing malaria and other parasitic diseases in developing countries. NIH, through *Indo-US Collaborative Program on Affordable Medical Devices* (NIBIB⁸⁵ in collaboration with other ICs), *mHealth Tools for Individuals with Chronic Conditions to Promote Effective Patient-Provider Communication, Adherence to Treatment and Self-Management* (NINR⁸⁶ in collaboration with other ICs), and *Mobile Health: Technology and Outcomes in Low and Middle Income Countries* (FIC⁸⁷ in collaboration with other ICs) supports research to develop innovative mHealth technologies specifically suited for low-resource settings and to measure the health-related outcomes associated with their implementation.

Fulfilling the promise of global health technologies depends on strong partnerships, which can ensure the transfer of knowledge and the development of technology that is appropriate for low-resource settings. An NCI-sponsored study being conducted by researchers in the United States and Brazil is validating a high-resolution, micro-endoscope⁸⁸ used to diagnosis cervical cancer in real time. To ensure that results of this research lead to sustainable implementation and scale-up within and beyond Brazil, this multidisciplinary team is collaborating with an non-governmental organization that focuses on effective cervical cancer prevention and control in low-resource countries. Through FIC's⁸⁹ *eCapacity program*, FIC's⁹⁰ *Framework Programs for Global Health Innovation*, and the Office of Technology Transfer⁹¹ (OTT), NIH also invests in building research capacity in low-resource settings to ensure that cutting-edge global health technologies are understood, adopted, and brought to scale.

Health Disparities in Children and Adolescents

The National Institute on Minority Health and Health Disparities (NIMHD) funds health disparities research focused on children and adolescents through various mechanisms including the Investigator-Initiated Research on Health Disparities, Community-Based Participatory Research grants, and the Transdisciplinary Collaborative Centers (TCC) for Health Disparities Research programs. For example, in a newly awarded NIMHD grant, investigators are conducting a randomized clinical trial to evaluate the effectiveness of offering patient navigation to address unmet material needs (food security, employment, parental education, housing stability, household heating and cooling, and childcare) for low-income families to facilitate appropriate pediatric health care utilization for children from birth to age 3.

Another NIMHD-supported project used data from the Moving to Opportunity (MTO) study, in which low-income families were randomly assigned to remain in their communities or relocate to a low-poverty neighborhood. Investigators found that prior exposure to crime was associated

⁸⁴ <http://www.ncbi.nlm.nih.gov/pubmed/20445943>

⁸⁵ <http://grants.nih.gov/grants/guide/pa-files/PAR-13-390.html>

⁸⁶ <http://grants.nih.gov/grants/guide/pa-files/PA-14-180.html>

⁸⁷ <http://grants.nih.gov/grants/guide/pa-files/PAR-14-028.html>

⁸⁸ http://projectreporter.nih.gov/project_info_description.cfm?aid=8789574&icde=23506497&ddparam=&ddvalue=&ddsub=&cr=5&csb=AIC&cs=ASC

⁸⁹ <http://grants.nih.gov/grants/guide/pa-files/PAR-13-107.html>

⁹⁰ <http://grants.nih.gov/grants/guide/pa-files/PAR-12-003.html>

⁹¹ <http://www.ott.nih.gov/international-mentoring-opportunities>

with a lack of benefit of residential relocation. In contrast, the benefits of relocation were not predicted by other socioeconomic indicators, such as low parental education, receipt of public assistance, or parental unemployment, suggesting that tailoring residential mobility interventions by these characteristics is less important than addressing the consequences of violence and trauma in disadvantaged adolescents.^{92,93}

In addition, 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, NICHD can address ways to prevent health disparities, as well as identify therapeutic strategies for early intervention. One of NIMHD's new collaborations with NICHD is to participate in the Adolescent Trials Network to investigate behavioral interventions to reduce HIV/AIDS in adolescent and young adult populations, including those from racial and ethnic groups. Research in health disparities in children and adolescents is a priority for NIMHD. Through its programs and opportunities for collaboration, it will continue to be a focus of research.

Healthy Homes

NIEHS supports a range of research and outreach activities focused on potential health impact of exposures that occur in home environments. Studies reveal that high levels of pest allergens that act as asthma triggers in children are present in urban homes, and that levels of air pollutants such as particulate matter (PM) and nitrous oxide (NO_x), also associated with asthma, may be higher indoors than out.⁹⁴ A mouse allergen-targeted environmental intervention study in homes is being conducted to try to improve asthma outcomes in children.⁹⁵ Studies of tap water are looking at whether pesticides play a role in congenital heart defects, a birth defect that affects 1 percent of U.S. births, and for the role of inorganic arsenic in increasing risks of developing diabetes.^{96,97} Other studies are examining exposures to polybrominated diphenyl ether or PBDEs – flame retardants previously used widely in plastic components of TVs, computers, and furniture, and even pajamas – and long-term impacts on cognitive development and behavior in children.⁹⁸ An ongoing project in New York City will examine the variance in residential exposure to black carbon (BC) before and after implementation of a policy requiring residents to switch from oil heating to cleaner burning fuel sources, including lower sulfur No. 2 fuel, biodiesel, or natural gas.⁹⁹ More broadly, NIH continues to consider housing impacts on vulnerable populations; in November 2014, the NIEHS-supported environmental health sciences center at Columbia University, in partnership with West Harlem Environmental Action, Inc. (WE ACT), hosted the NYC Healthy Homes Summit, and a December 2014 research conference

⁹² <http://www.ncbi.nlm.nih.gov/pubmed/23792412?dopt=Citation>

⁹³ <http://www.ncbi.nlm.nih.gov/pubmed/22908105?dopt=Citation>

⁹⁴ Matsui, EC. Environmental exposures and asthma morbidity in children living in urban neighborhoods. *Allergy*, 2014, 69(5):553-8. [LINK](#)

⁹⁵ 5U01AI083238-05, Elizabeth Matsui, Mouse allergen and asthma intervention trial. [LINK](#)

⁹⁶ 1R21ES024895-01, A.J. Agopian, Pesticides in tap water and congenital heart defects, [LINK](#)

⁹⁷ 5R01ES021367-03, Ana Navas-Acien, Arsenic exposure, genetic determinants and diabetes risk in a family study. [LINK](#)

⁹⁸ 5R01ES021806-03, Julie Beth Herbstman, Pre- and postnatal PBDE exposure, thyroid hormones, and neurodevelopment. [LINK](#)

⁹⁹ 5R21ES024108-02, Diana Hernandez, Assessing the impact of clean heat policy intervention in New York City, [LINK](#)

brought together experts to explore the issue of farmworker housing quality and health in the United States.^{100,101}

Hepatitis B

Hepatitis B virus (HBV) infection continues to be an important public health concern. 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.

NIAID 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, along with NIDDK, also is partnering with small businesses to advance the development of diagnostics and treatments for hepatitis viruses, including HBV. NIAID offers a broad array of research resources and services to conduct *in vitro* screening of candidate drugs against HBV. In FY 2014, 203 compounds were screened for HBV antiviral activity by NIAID for industry and academic partners. NIAID also provides researchers with access to a transgenic mouse model and a woodchuck model that can be used to evaluate promising new antiviral drugs and agents to stimulate host immune responses to combat HBV infection.

In addition, NIAID researchers are partnering to characterize a promising vaccine candidate that targets three HBV antigens. The goal is to use this candidate 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.

In FY 2016, NIAID will sustain efforts to develop novel drugs, therapeutics, and vaccines to address chronic HBV infection.

Heterotaxy Research

Heterotaxy is a disorder that results in certain organs forming in abnormal positions within the body. For example, the heart may be on the right side of the chest, rather than on the left side. Heterotaxy occurs in approximately 1 in 10,000 live births and usually requires surgery and ongoing medication. Although the exact causes of heterotaxy are unknown, research points to genetic factors, because the damage occurs during fetal development, and the disorder may run in families. Scientists have identified some gene mutations, but these account for only a fraction of cases. NIH-supported scientists are working to understand the genetic causes of heterotaxy and to discover the mechanisms by which genetic variations cause structural anomalies. For example, in 2014, NICHD funded a study to assess the genetics of heterotaxy using a systems biology approach. Researchers identified 74 cases of classic heterotaxy from all live births in New York State from 1998 to 2005, extracted DNA from each infant's newborn dried blood spot, and genotyped the DNA using microarrays, successfully identifying 20 rare genetic variants that may be associated with heterotaxy. In 2011, researchers supported by NICHD learned that one specific gene is involved in the development of cilia and affects organ positioning during

¹⁰⁰ Papers from the Summit are published online in *Environmental Justice* at [LINK](#)

¹⁰¹ 1R13ES023709-01, Thomas Arcury, Farmworker Housing Quality and Health: A Transdisciplinary Conference, [LINK](#)

fetal development. Collaborating with German researchers, scientists identified a genetic link between heterotaxy and another rare condition, primary ciliary dyskinesia (PCD). Researchers supported by NICHD, NEI, NHLBI, and the National Institute of General Medical Sciences (NIGMS) are now exploring the genetic connections between PCD and heterotaxy, to develop knowledge that may ultimately lead to interventions for both conditions.

High-Risk, High-Reward

The NIH Common Fund's High-Risk, High-Reward Program¹⁰² includes four complementary initiatives that support exceptionally creative scientists proposing innovative and transformative research in any scientific area within the NIH mission. These initiatives include the Pioneer, New Innovator, Transformative Research, and Early Independence awards. Researchers supported through the High-Risk, High-Reward program have been extremely successful, publishing numerous high-impact research studies in many biomedical research disciplines. Recent examples include:

- A Transformative Research awardee has developed a new way to cultivate bacteria that live in the soil, and in the process has discovered a novel antibiotic with the potential to treat many dangerous drug-resistant bacteria including MRSA (methicillin-resistant *Staphylococcus aureus*) and *Mycobacterium tuberculosis*.¹⁰³
- A New Innovator awardee identified a single point of infection from an animal reservoir to a human in the current West African Ebola outbreak and traced how the genetic code of the virus is changing over time to adapt to human hosts.¹⁰⁴
- A Pioneer awardee has developed a device that uses electrical currents to drive chemotherapy drugs directly into tumors, potentially revolutionizing how doctors treat some of the most challenging types of cancer, including pancreatic and aggressive breast cancer.¹⁰⁵
- An Early Independence awardee has demonstrated that a defect in the generation of new neurons may cause intellectual disabilities seen in patients with Kabuki syndrome. Importantly, this defect could be treated after birth to restore memory function, suggesting that Kabuki syndrome may be a treatable cause of intellectual disability.¹⁰⁶

The Common Fund will continue to support these highly productive awards in FY 2016.¹⁰⁷ In addition to supporting awardees within the Common Fund's High-Risk High-Reward Program, several ICs now have implemented similar programs. These include the Avant-Garde Award Program for HIV/AIDS and the Avenir Award Program for Research on Substance Abuse and HIV/AIDS at the National Institute on Drug Abuse (NIDA), the Biobehavioral Research Awards

¹⁰² <http://commonfund.nih.gov/highrisk/index.aspx>

¹⁰³ Ling et al. (2014) [A new antibiotic kills pathogens without detectable resistance](#). Nature, doi:10.1038/nature14098.

¹⁰⁴ Gire et al. (2014) [Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak](#). Science, 345(6202), 1369-72.

¹⁰⁵ Byrne et al.(2015) [Local ionophoretic administration of cytotoxic therapies to solid tumors](#). Science Translational Medicine, 7(273).

¹⁰⁶ Bjornsson et al. (2014) [Histone deacetylase inhibition rescues structural and functional brain deficits in a mouse model of Kabuki syndrome](#). Science Translational Medicine, 6(256).

¹⁰⁷ Common Fund Congressional Justification: http://commonfund.nih.gov/sites/default/files/Common_Fund_FY2016_CJ.pdf.

for Innovative New Scientists (BRAINS) (NIMH), and the Outstanding New Environmental Scientist (ONES) award (NIEHS). While investigator-initiated (R01) awards are, and will continue to be, the primary component of NIH-funded research portfolio, the High-Risk, High-Reward Programs may be particularly useful in stimulating creativity and supporting researchers at all career stages, including early-career stage researchers, with transformative and innovative ideas.

Human Placenta Project

The Human Placenta Project (HPP) is a collaborative research effort, launched by NICHD in 2014, to understand the role of the placenta in health and disease. The placenta is the least understood human organ but arguably one of the most important, influencing not just the health of a woman and her fetus during pregnancy, but the lifelong health of both. Initial goals of the HPP are to improve current methods and develop new technologies for real-time assessment of placental structure and function across development. These technologies will be applied to understand and monitor placental development and function in normal and abnormal pregnancies, develop and evaluate non-invasive markers for prediction of adverse pregnancy outcomes, understand the contributions of placental development to long-term health and disease, and develop interventions to prevent abnormal placental development, thereby improving pregnancy outcomes. In early FY 2015, NICHD and NIBIB issued several funding announcements inviting grant applications for the development of new methods and tools to assess placental development and function. Building on the first HPP scientific conference in 2014, a second workshop in April 2015 will focus on developing the next steps for the research plan and an outline of interim goals. The goals of April's meeting are to bring together a group of broad thinkers, including technical subject matter experts, placental biologists, and clinicians, to discuss the value and limitations of various omics and imaging methods to achieve HPP goals, to explore technologies that have never been applied to placental assessment in hopes that novel solutions will emerge, and to leverage this breadth of expertise to inform the broader project roadmap and prioritize steps for moving forward.

Implementation of CTSA IOM Recommendations

In 2012, Congress requested that the Institute of Medicine (IOM) assess the Clinical and Translational Science Awards (CTSA) Program and its contributions to the acceleration and dissemination of advances in the prevention, diagnosis and treatment of human illness. The IOM Committee issued its June 2013 report¹⁰⁸ that concluded the CTSA Program had been successful in creating academic focal points for clinical and translational research at many medical research centers. The following were the main recommendations from the IOM Committee on the CTSA Program:

1. Strengthen NCATS leadership of the CTSA Program.
2. Reconfigure and streamline the CTSA Consortium.
3. Build on the strengths of individual CTSA's across the spectrum of clinical and translational research.

¹⁰⁸ <http://www.iom.edu/Reports/2013/The-CTSA-Program-at-NIH-Opportunities-for-Advancing-Clinical-and-Translational-Research.aspx>

4. Formalize and standardize evaluation processes for individual CTSA and the CTSA Network.
5. Advance innovation in education and training programs.
6. Ensure community engagement in all phases of research.
7. Strengthen clinical and translational research relevant to child health.

To provide guidance on the IOM's recommendations, an NCATS Advisory Council Working Group issued a report¹⁰⁹ in May 2014 that provided advice on changes to the CTSA program with a focus on establishing measurable goals and objectives.

NCATS leadership continues to evolve the CTSA program to respond to the IOM report, to meet the opportunities in translational science research, and to address the needs of clinical and translational investigators and the communities they serve. On September 12, 2014, NCATS released a new funding opportunity announcement¹¹⁰ for the CTSA program that begins to implement many of the recommendations of the IOM report and the NCATS Council working group. NCATS has informed the clinical and translational research community of its intent to issue additional funding opportunity announcements¹¹¹ for Clinical Trial Innovation Centers (TICs), Recruitment Innovation Centers (RICs), and Collaborative Innovation Awards to address system-wide challenges to the clinical and translational research process, which is in line with the IOM report recommendations.

Implementation of the Recalcitrant Cancer Research Act (RCRA)

NCI is meeting the requirements of the Recalcitrant Cancer Research Act (RCRA) and has already delivered to Congress "scientific framework" reports on both pancreatic ductal adenocarcinoma (PDAC) and small cell lung cancer (SCLC), two cancer types meeting the criteria for cancers as defined in the RCRA (cancers with 5-year survival of less than 20 percent that also cause 30,000 annual deaths in the United States). Reports to NCI's Clinical and Translational Research Advisory Committee (CTAC) at regular intervals will inform the public of progress on PDAC and SCLC. (This approach, it should be noted, is not unique to these cancer types: workshops to identify scientific opportunities relevant to many types of cancer occur as part of NCI's standard practices.)

The scientific framework¹¹² for PDAC was completed and delivered to Congress in February 2014. NCI is addressing the recommendations made in that report, including the relationship between PDAC and diabetes mellitus of recent onset; biomarker and imaging studies of pancreatic cysts to identify those at high risk of PDAC; and new immunotherapies. Coincidentally, NCI has begun the RAS Initiative to develop new ways to treat cancers, including PDAC, that are commonly driven by mutations in the RAS gene family. One of the three RAS genes is often mutated in pancreatic, lung, and colorectal cancers, as well as several other cancer types, yet methods for treating such tumors have been difficult to produce. NCI is also investing in the training of the next generation of RAS experts and has joined with the Pancreatic Cancer Action Network to support two training fellowships focused on a type of RAS

¹⁰⁹ <http://www.ncats.nih.gov/files/CTSA-IOM-WG-Draft-Report.pdf>

¹¹⁰ <http://grants.nih.gov/grants/guide/rfa-files/RFA-TR-14-009.html>

¹¹¹ <http://www.ncats.nih.gov/research/cts/ctsa/funding/funding.html>

¹¹² <http://deainfo.nci.nih.gov/advisory/ctac/workgroup/pc/PDACframework.pdf>

mutation relevant to pancreatic cancer.

The scientific framework¹¹³ for small cell lung cancer (SCLC) was completed and delivered to Congress in June 2014. NCI is currently pursuing several research efforts in support of the initiatives recommended in the framework. These include optimizing the collection of tumor tissue specimens representing distinct phases of SCLC (from initial diagnosis to disease recurrence following radio-chemotherapy); developing new tumor models (conditionally reprogrammed cell lines, patient-derived xenografts, and genetically engineered mouse models) that reflect the phases of SCLC found in the clinic; expanding comprehensive genomic profiling studies of SCLC specimens; investigating new diagnostic approaches for populations at high risk of developing SCLC; focusing therapeutic development efforts on specific molecular vulnerabilities of SCLC; and investigating the mechanisms underlying both the high initial rate of response to primary SCLC therapy and the rapid emergence of drug and radiation resistance following completion of treatment.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis (UC), is a complex genetic disease attributed to inappropriate immune responses to microbes that inhabit the human intestine, collectively known as the human microbiota or "microbiome." NIH supports a robust portfolio of basic and clinical research on understanding the causes, disease processes, treatment, and prevention of IBD, which has yielded important advances. For example, NIH supports the IBD Genetics Consortium, which in collaboration with international consortia has played a major role in identifying more than 160 genetic risk factors for IBD to date. Also, identifying bacterial communities that reside within the human intestine and understanding their roles in health and disease is crucial to developing treatments for IBD. The NIH Human Microbiome Project (HMP) and other efforts are contributing to advancing understanding of microbial influences in IBD. For example, a recent NIH-supported study found that children and adolescents with IBD have a particular microbial and genetic "signature" that could provide targets for improved diagnosis and therapy (*J Clin Invest* 124: 3617, 2014). Basic research on the intestinal stem cells that renew the intestine's inner lining, through such programs as the NIH's Intestinal Stem Cell Consortium, may lead to important applications based on these cells in treating intestinal injury caused by IBD. A recent advance in developing intestinal organoids made from stem cell-derived human tissue and grown in mice could enable patient-specific drug testing (*Nat Med* 20: 1310, 2014). NIH also supports clinical studies of new approaches to IBD therapy. One study is evaluating if a combination of clinical, genetic, and immunologic tests can predict response to standard medical therapy for children newly diagnosed with UC. A second study is investigating the therapeutic value of methotrexate, an inexpensive generic drug, in adults with UC in whom established therapies have failed.

Information Technology Related to Behavioral Risk Factors for Cancer

NCI continues to be at the forefront of funding innovative research into using telecommunications and IT to reduce risk factors. The rapidly expanding use of the internet, smartphones, and wearable technology is offering many new opportunities to produce new tools for research and systems for delivery of behavioral risk factor interventions. Examples include:

¹¹³ <http://deainfo.nci.nih.gov/advisory/ctac/workgroup/SCLC/SCLC%20Congressional%20Response.pdf>

- The award of NCI grants to researchers across the country investigating the use of telecommunications and new technologies in cancer prevention and control. Sample titles of such grants include: Addressing Prostate Cancer Information Disparities with Ehealth Technology¹¹⁴ (Tufts University Boston); Group Phone-Based Weight Control Among Rural Breast Cancer Survivors¹¹⁵ (University Of Kansas Medical Center); and QUIT4BABY: Reaching Pregnant Smokers with Health Information Via Text Messaging¹¹⁶ (George Washington University).
- NCI’s Health Information National Trends Survey (HINTS¹¹⁷), a biennial survey of the American public, provides foundational information on how Americans are using technology in relation to their health.
- An ongoing collaboration with the National Science Foundation to help computer scientists develop the digital technologies needed to improve support for healthy behaviors. Grants funded by the “Smart and Connected Health¹¹⁸” Funding Opportunity Announcement aim to improve the computational design of digital technologies so that these devices can intervene with behavioral reminders based on sophisticated computational models.
- The NCI Centers of Excellence in Cancer Communication Research¹¹⁹ initiative involves centers at the University of Pennsylvania, University of Michigan, University of Wisconsin, the Kaiser Health Research Institute in Colorado, and Washington University in St. Louis. These centers are working on social media interventions, smartphone-based behavioral modifications, the functionality of the use of pedometers and other wearable technology, and many other topics pertinent to understanding and reducing cancer risk factors.

Infusion Pumps

There has been major recent progress on the development of an “artificial pancreas,” or closed-loop technology, for managing Type 1 diabetes. Currently, patients must measure blood glucose levels with a finger stick or continuous glucose monitor and administer insulin through injections or an insulin infusion pump. An artificial pancreas would automate blood glucose sensing and insulin administration. NIH-supported researchers are now testing portable artificial pancreas devices in real-world settings and are seeing exciting results. In one study, adult and adolescent participants using a “bionic pancreas” for five days and nights had lower mean glucose levels and reduced episodes of dangerously low blood glucose levels (hypoglycemia); the device allowed nearly all participants to achieve recommended levels of blood glucose control (*NEJM* 371: 313, 2014). In another study, adolescents using a closed-loop system for 21 nights without supervision had improved glucose control during the day and night and reduced nighttime hypoglycemia (*Diabetes Care* 37:1204, 2014). NIH is also supporting research on next-

¹¹⁴ <http://maps.cancer.gov/overview/DCCPSGrants/abstract.jsp?appId=8568348&term=CA178296>

¹¹⁵ <http://maps.cancer.gov/overview/DCCPSGrants/abstract.jsp?appId=8676721&term=CA155014>

¹¹⁶ <https://gsspubssl.nci.nih.gov/nciportfolio/search/details.jsessionid=1222397A8323E4454B570C5A39BAE27B?action=abstract&grantNum=1R15CA167586-01A1&grantID=8436007&grtSCDC=FY%202013&absID=8436007&absSCDC=PUB2013>

¹¹⁷ <http://hints.cancer.gov/>

¹¹⁸ <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-13-041.html>

¹¹⁹ <http://cancercontrol.cancer.gov/brp/hcirb/ceccr/ceccr-index.html>

generation low-glucose suspend devices – an important component of artificial pancreas technologies. The first-generation device, approved by FDA in 2013, is an insulin infusion pump that temporarily stops insulin delivery once glucose levels fall below a predetermined threshold; the next-generation device predicts when this level will be reached and preemptively suspends insulin delivery. A study showed that nighttime hypoglycemia was reduced by over 70 percent when participants used a predictive device (*Diabetes Care* 37: 1885, 2014). These and other studies suggest that the artificial pancreas is a promising technology for managing Type 1 diabetes. It has the potential not only to reduce the burden associated with current treatment regimens, but also to help patients achieve recommended levels of blood glucose control known to reduce the risk of diabetes complications. NIH continues to work closely with the FDA to propel progress toward approval of these technologies.

Interstitial Cystitis

Interstitial cystitis/painful bladder syndrome (IC/PBS) affects millions of Americans and is characterized by pelvic pain strongly associated with the bladder and with urinary symptoms of frequency and urgency. Current NIH efforts in IC/PBS are focused on understanding the cause(s) of this condition, improving diagnosis, finding more effective treatments, and finding ways to prevent onset. The multi-site Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network is conducting innovative, collaborative studies of IC/PBS and another urologic pelvic pain condition, CP/chronic prostatitis/chronic pelvic pain syndrome (CPPS), to better understand and find the causes of these conditions. The Network is also studying the possible relationships between urologic pelvic pain and other chronic pain disorders, such as IBS and fibromyalgia. New findings emerging from Network studies include insights into the course of IC/PBS; potential biomarkers; differences in the “microbiome” between patients and healthy controls; different, potentially clinically relevant “sub-phenotypes” among people diagnosed with IC/PBS; and the importance of recognizing symptom flares in assessing IC/PBS. Network scientists recently reported for the first time the existence of regional brain differences between women with IC/PBS and healthy counterparts; future studies may help researchers understand the relationship between altered brain regions and pain sensitivity in IC/PBS patients (*J Urol* 193: 131, 2015). NIH renewed the Network for a second 5-year phase in FY 2014, in order to continue efforts that it is hoped will provide a foundation for effective clinical interventions. NIH has also been supporting additional, innovative research studies on IC/PBS and other urologic chronic pelvic pain syndromes, including a clinical treatment study for IC/PBS and a study to find urinary biomarkers that could help with IC/PBS diagnosis – a long-term challenge for patients and health care providers.

Jackson Heart Study

The Jackson Heart Study (JHS), initiated in 1998, has provided extensive information on the causes of diseases that disproportionately affect African Americans. New genetic studies involving JHS data and samples revealed the role of African-ancestry-specific mutations in heart disease and other conditions. For example, researchers¹²⁰ found that loss-of-function mutations in the Niemann-Pick C1-like 1 (NPC1L1) gene, including several mutations that are African ancestry specific, are associated with reduced LDL cholesterol levels and a 53 percent relative reduction in the risk of coronary heart disease (CHD). These findings show that life-long

¹²⁰ <http://www.nejm.org/doi/full/10.1056/NEJMoa1405386>

reduction of the function of the NPC1L1 protein results in reduced CHD risk. In another study¹²¹, investigators showed an association in African Americans between possessing the sickle cell trait (SCT) and developing chronic kidney disease (CKD). This finding adds to the evidence that SCT may be related to the higher risk of kidney disease in African Americans. NHLBI renewed funding for JHS in FY 2013, for another five years. Future investigations promise to yield similar insights into the health of African Americans.

Kennedy's Disease

Since the discovery that a gene defect in the androgen receptor, which enables cells to respond to testosterone related hormones, causes Kennedy's disease (also known as spinal bulbar muscular atrophy, or SBMA), researchers have made considerable progress in understanding step by step how the disease affects nerve and muscle cells and in developing candidate therapies in animal models of SBMA, but no treatment has yet proven effective in randomized, controlled clinical trials in people with SBMA. NINDS continues to support extramural and intramural research on SBMA across the full spectrum, from studies of disease mechanisms in animal and cell models of disease, through laboratory development of candidate drugs, and clinical testing in people with SBMA. Research has demonstrated that the protein that is abnormal in SBMA causes disease both by loss of its normal function and by gain of toxic properties. New findings this year suggest unexpectedly that muscle may be as important a contributor to the toxicity of the SBMA mutation as the motor neuron and provide further evidence in mouse models of SBMA that targeting therapy to muscle may be effective for treating the disorder.¹²² Muscle is more accessible to drugs and other interventions than the brain or spinal cord, and drugs that act outside the central nervous system are less likely to cause side effects. Research to pursue these promising leads is continuing. Complementing extramural research, the NINDS Intramural Research Program continues to be a leader in SBMA research. In addition to laboratory and clinical studies on the mechanisms of SBMA, intramural researchers conduct clinical trials at the NIH Clinical Center of drugs, exercise, and other interventions. This includes a new Phase 2 trial that is testing the safety, tolerability, and efficacy of a drug that activates growth factor pathways in partnership with a pharmaceutical company, which reflects how progress from NIH funded research is engaging biotech and pharmaceutical companies to develop treatments for SBMA.

Liver Cancer

NCI supports a comprehensive research portfolio on liver cancer. In addition to several grants to individual investigators, this research program includes the Early Detection Research Network's (EDRN) recently launched Hepatocellular Carcinoma Early Detection Strategy (HEDS),¹²³ which will collect blood samples at six-month intervals from cirrhotic patients who are being closely monitored for development of hepatocellular carcinoma (HCC), the most common type of liver cancer. A study is also under way to evaluate the effect of various medications in the prevention of liver cancer. The NCI-supported National Clinical Trials Network will launch a randomized Phase 3 study of focal radiation therapy for unresectable, localized intrahepatic cholangiocarcinoma (ICC), the second most common type of liver cancer.

¹²¹ <http://jama.jamanetwork.com/article.aspx?articleid=1935577>

¹²² <http://www.ncbi.nlm.nih.gov/pubmed/24742458>

¹²³ <http://edrn.nci.nih.gov/protocols/316-hepatocellular-carcinoma-early-detection-strategy>

NCI also supports the Hepatocellular Carcinoma Epidemiology Consortium,¹²⁴ an interdisciplinary translational research effort that links liver cancer investigators across the United States for the purpose of pooling their research tools and resources. NCI intramural investigators are leading a cohort study to examine risk factors for liver cancers in the United States. In addition, the NCI participates with other agencies in international efforts to study liver cancer in Thailand (Thailand Initiative for Genomics and Expression Research in Liver Cancer (TIGER-LC))¹²⁵ and in China, working with Chinese investigators. The NCI has also joined with several other ICs to participate in *Multidisciplinary Studies of HIV and Viral Hepatitis Co-Infection*¹²⁶ (to increase understanding of the relationship between these infections and liver cancer). In March 2014, NCI convened a workshop on liver cancer focused on the worldwide knowledge base opportunities for primary and secondary prevention, screening and early diagnosis, and treatment. Discussion topics included the molecular pathology and genomics of liver cancer, as well as the emergence of obesity and type II diabetes and their association with liver cancer. Research recommendations included focusing on infection and non-infectious risk factors, validation of biomarkers, development of clinically relevant animal models, identification of intervention strategies for prevention and treatment, incorporation of obesity research and resultant inflammation into animal models and human investigations, and exploration of health disparities related to HCC.

Lower Life Expectancy

In 2011, life expectancy in the United States was found to increase at a slower rate than in other high-income democracies.¹²⁷ A 2013 study from the National Research Council and the Institute of Medicine found that, on average, Americans die sooner and experience higher rates of disease and injury than people in 16 “peer countries.” The report highlighted infant mortality, homicides, teen pregnancy, drug-related deaths, obesity, and disabilities as health areas where the United States lags behind other wealthy countries.¹²⁸ This health disadvantage exists despite the fact that the United States spends more per capita on health care than any other nation, and is due to a number of factors, such as unhealthy behaviors.

Lower life expectancy is especially evident in people with serious mental illnesses (SMI), which result in functional impairment that substantially interferes with or limits one or more major life activity (such as schizophrenia, bipolar disorder, and major depression). Persons with SMIs experience chronic medical conditions, and the modifiable risk factors that contribute to them, more frequently and at earlier ages than the general population (see PMID: 21577183¹²⁹, PMID: 16884895¹³⁰). NIMH has implemented two initiatives to develop and test interventions to improve the health and longevity of people with SMI. First, NIMH has funded three projects to help States to build research capacity for rigorous testing of innovative approaches to reducing premature mortality in people with SMI. Second, NIMH has funded five large-scale trials to test the effectiveness of services interventions to reduce the prevalence and magnitude of common

¹²⁴ <http://www.hccec.org/>

¹²⁵ http://home.ccr.cancer.gov/connections/2010/vol4_no2/news_3.asp

¹²⁶ <http://grants.nih.gov/grants/guide/pa-files/PA-14-254.html>

¹²⁷ <http://www.nap.edu/catalog/13089/explaining-divergent-levels-of-longevity-in-high-income-countries>

¹²⁸ <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=13497>

¹²⁹ <http://www.ncbi.nlm.nih.gov/pubmed/21577183>

¹³⁰ <http://www.ncbi.nlm.nih.gov/pubmed/16884895>

modifiable health risk factors that contribute to premature mortality in people with SMI, using the most rigorous methods possible.

In terms of the latest advances, NIMH-funded researchers on the Recovery After an Initial Schizophrenia Episode¹³¹ (RAISE) Early Treatment Program recently reported that elevated risks of heart disease and metabolic issues such as high blood sugar in people with first-episode psychosis are due to an interaction of mental illness, unhealthy lifestyle behaviors, and antipsychotic medications that may accelerate these risks. Patients enter treatment for first-episode psychosis with significant health concerns – including excess weight, smoking, and metabolic issues – despite an average age of only 24 years. The study identifies key opportunities for health care systems to improve the treatment of such patients with first episode psychosis (PMID: 25321337¹³²).

Lupus

Recently, NIH-funded researchers reported progress toward developing biomarkers to help predict when people with lupus will experience a worsening of symptoms, commonly referred to as disease flares.¹³³ The results of this work may lead to earlier and more effective treatment or even prevention of flares. Other NIH-supported investigators have identified particular gene combinations that define subtypes of lupus, which hold great promise for improving treatment decisions.¹³⁴ Recent work by NIH intramural researchers sheds light on factors that contribute to the increased risk of cardiovascular disease seen in lupus patients, and suggested that antimalarial drugs that counteract those factors could potentially be used to treat or prevent early atherosclerosis in people with lupus.¹³⁵

NIH is partnering with FDA, industry, and non-profit organizations in the Accelerating Medicines Partnership (AMP) to speed the development of new therapeutics for lupus, rheumatoid arthritis, Type 2 diabetes, and Alzheimer’s disease.¹³⁶ In September 2014, NIH and several of its AMP partners awarded grants to 11 research groups across the United States to establish the AMP in Rheumatoid Arthritis and Lupus Network.¹³⁷ NIH also continues to support other initiatives relevant to lupus research, including the NIAID-funded Autoimmunity Centers of Excellence and the Immune Tolerance Network.¹³⁸ The NIH intramural program supports

¹³¹ <http://www.nimh.nih.gov/health/topics/schizophrenia/raise/index.shtml>

¹³² <http://www.ncbi.nlm.nih.gov/pubmed/25321337>

¹³³ [Proinflammatory Adaptive Cytokine and Shed Tumor Necrosis Factor Receptor Levels Are Elevated Preceding Systemic Lupus Erythematosus Flare](#). Munroe ME, Vista ES, Guthridge JM, Thompson LF, Merrill JT, James JA. *Arthritis & Rheumatology*. 2014 July; 66 (7): 1888-1399. doi 10.1002/art.38573. PMID: 24578190

¹³⁴ [Genetic analysis of the pathogenic molecular sub-phenotype interferon-alpha identifies multiple novel loci involved in systemic lupus erythematosus](#).

Kariuki SN, Ghodke-Puranik Y, Dorschner JM, Chrabot BS, Kelly JA, Tsao BP, Kimberly RP, Alarcón-Riquelme ME, Jacob CO, Criswell LA, Sivils KL, Langefeld CD, Harley JB, Skol AD, Niewold TB. *Genes Immun*. 2015 Jan;16(1):15-23. doi: 10.1038/gene.2014.57. Epub 2014 Oct 23. PMID: 25338677

¹³⁵ [Neutrophil extracellular trap-derived enzymes oxidize high-density lipoprotein: An additional proatherogenic mechanism in systemic lupus erythematosus](#). Smith CK, Vivekanandan-Giri A, Tang C, Knight JS, Mathew A, Padilla RL, Gillespie BW, Carmona-Rivera C, Liu X, Subramanian V, Hasni S, Thompson PR, Heinecke JW, Saran R, Pennathur S, Kaplan MJ. *Arthritis Rheumatol*. 2014 May 16. doi: 10.1002/art.38703. [Epub ahead of print]. PMID: 24838349

¹³⁶ <http://www.nih.gov/science/amp/index.htm>

¹³⁷ http://www.niams.nih.gov/News_and_Events/Press_Releases/2014/9_24.asp

¹³⁸ <http://www.niaid.nih.gov/topics/autoimmune/research/Pages/researchActivities.aspx>

clinical studies in lupus. For example, through its Systemic Autoimmunity Branch, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) intramural program has a major focus on lupus research.¹³⁹

NIH continues to lead the Lupus Federal Working Group (LFWG), which was established on behalf of the Secretary of Health and Human Services to facilitate collaboration among NIH components, other Federal agencies, voluntary and professional organizations, and industry groups with an interest in lupus.¹⁴⁰ At the request of the Congressional Lupus Caucus, NIAMS, as convener of the LFWG, is leading an NIH effort to evaluate progress in NIH-funded lupus research since 2007 and update the goals and priorities included in the 2007 report, *The Future Directions of Lupus Research*.¹⁴¹ The update is expected to be completed in fall 2015.

Lymphangioliomyomatosis

Lymphangioliomyomatosis (LAM) is a rare, slowly progressive, neoplastic disease that affects women almost exclusively and gradually destroys the lungs, often leading to death from respiratory failure. It is characterized by the proliferation of smooth muscle-like cells and cystic lesions in the lung. LAM may occur sporadically or it may be associated with tuberous sclerosis complex (TSC). Lung transplant is a treatment option for women whose lungs have been damaged by LAM. Recent research efforts have focused on finding effective multidrug therapies for LAM. NHLBI supports research to identify the causes and potential treatments of LAM. For example, a recent study¹⁴² in mice showed that a two drug regimen consisting of sirolimus (rapamycin) plus simvastatin prevents growth of the LAM-like lung lesions, prevents lung destruction, and can cause a dramatic regression of already established lesions. Another study¹⁴³ showed that a Src kinase inhibitor, saracatinib, was able to halt progression of LAM-like lesions in the lung. A pilot clinical trial based on the mouse study is ongoing. Other studies seek additional treatment targets, to identify molecular markers, and to determine the mechanisms of lung destruction. For example, a recently-approved clinical research protocol is characterizing the pathogenesis of primary and secondary lymphatic disorders to: a) define the natural history of lymphatic diseases; b) characterize the clinical phenotypes; and c) elucidate their pathogenesis at the physiological, cellular, and molecular levels. Finally, to promote LAM research, NHLBI co-funds LAM tissue collection, storage, and distribution by the National Disease Research Interchange¹⁴⁴ (NDRI). The program has distributed over 2,400 tissue specimens to 31 LAM and TSC investigators, and is open to U.S. and international investigators.

Malaria and Neglected Tropical Diseases

In the past year, NIAID reported significant progress in addressing major global killers including malaria and neglected tropical diseases. NIAID intramural researchers and grantees recently completed a Phase 1 clinical trial showing that PfSPZ, a novel malaria vaccine composed of weakened sporozoites (the infectious form of the parasite), was safe and protected against malaria. NIAID research is also a key contributor to the development of new diagnostics for

¹³⁹ http://www.niams.nih.gov/Research/Ongoing_Research/Branch_Lab/Systemic_Autoimmunity_Branch/

¹⁴⁰ http://www.niams.nih.gov/About_Us/Committees/lupus_fwg.asp

¹⁴¹ http://www.niams.nih.gov/about_us/Mission_and_Purpose/lupus_plan.asp

¹⁴² <http://stm.sciencemag.org/content/4/154/154ra134.full.pdf>

¹⁴³ <http://cancerres.aacrjournals.org/content/74/7/1996.long>

¹⁴⁴ http://www.ndriresource.org/NDRI_Initiatives/Rare_Disease/30/

malaria and neglected tropical diseases including lymphatic filariasis, onchocerciasis, and soil-transmitted helminths. A promising advance in the fight against malaria is the recent development of low-cost diagnostic tests that can rapidly detect resistance of malaria to artemisinin, a first-line antimalarial drug. Early detection of resistance allows clinicians to administer effective medications. In addition, the NIAID intramural research program is advancing high-priority research that includes the development of a new class of antimalarial compounds and the development of novel vaccine candidates for malaria. NIAID will continue to support all aspects of research on malaria and neglected tropical diseases, including the causative agent, vectors, and the human host of these diseases.

Marijuana Research

While marijuana (cannabis) has not been approved by FDA as a medicine, a growing number of States (23 States and the District of Columbia) have legalized marijuana or marijuana extracts for medicinal purposes, and the potential therapeutic properties of marijuana are the subject of increasing public debate. Several ICs (eight as of October, 2014) support a wide range of research on marijuana; its main psychoactive ingredient, delta-9-tetrahydrocannabinol (THC); and other constituent *cannabinoids* including cannabidiol (CBD). Ongoing NIH research is exploring the potential for marijuana and related compounds in the treatment of pain, nausea, obesity, wasting disease, addiction, autoimmune disorders, cancer, and other health problems. Smoked marijuana is unlikely to be an ideal medication due to effects on the lungs, risk for addiction, and difficulty in controlling the administered dose; therefore, most NIH-funded research projects are examining the medical benefits of cannabinoids derived from, or related to, those in the marijuana plant, not the plant itself, although a few use unprocessed plant material.

NIDA is also supporting research on the public health impacts of State medical marijuana policies on perceptions of marijuana's risks, related use, and health outcomes (RFA-DA-11-008¹⁴⁵). NIDA is currently funding three grants in response to this RFA to study how the availability of medical marijuana and dispensaries themselves affect access to marijuana, health, and community safety; social consequences of medical marijuana use; and medical marijuana use in patients with HIV.

NIDA also continues to provide marijuana for research purposes through a contract with the University of Mississippi – the only DEA-licensed entity for marijuana cultivation in the United States – and is working with Federal partners to identify ways of reducing the barriers to research utilizing marijuana.^{146 147}

Maternal Morbidity

NICHD is committed to improving the health and well-being of mothers and their families by supporting essential research on the challenges women face trying to achieve and maintain healthy pregnancies and childbirth. Critical to this effort is up-to-date information on the number of serious illnesses associated with childbirth. A new NICHD-funded study analyzed data from more than 100,000 new mothers, finding a range of predictors for severe complications, such as bleeding, high blood pressure, and heart or lung problems. This study,

¹⁴⁵ <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-11-008.html>

¹⁴⁶ <http://www.drugabuse.gov/drugs-abuse/marijuana/nida-research-therapeutic-benefits-cannabis-cannabinoids>

¹⁴⁷ <http://www.drugabuse.gov/drugs-abuse/marijuana/nidas-role-in-providing-marijuana-research>

requested by health care professionals, will help clinicians identify women likely to experience these serious illnesses and speed access to interventions. Another study supported by NICHD showed that maintaining a healthy exercise and diet regimen in the years after pregnancy can greatly reduce the development of Type 2 diabetes in women who had gestational diabetes, thereby improving health for the rest of their lives.¹⁴⁸

Perinatal mood and anxiety disorders are potentially devastating conditions that affect many women during and after pregnancy, and research in these areas also is supported by NICHD.

Finally, to address maternal morbidity more completely, research is needed to better understand normative pregnancies. In late 2014, NICHD awarded a contract for the development of a web-based data collection effort to learn more, in real time, about the range of physical and emotional experiences and alterations in behavior during and after pregnancy.

Medications in Pregnancy

Pharmaceutical companies rarely test the use of drugs in pregnant women. Yet, pregnant women commonly use prescription medications, whether for obstetric conditions (e.g., preeclampsia, infection) or for conditions independent of pregnancy, such as epilepsy or mental health conditions, and it is important to know whether such use in pregnancy is safe. For example, an NIMH-supported study found that post-traumatic stress disorder (PTSD), especially when coupled with a diagnosis of major depression, increased the risk of preterm birth four-fold, but that medications prescribed during pregnancy to treat the PTSD had no effect on whether the birth was premature. NICHD is addressing this issue through a variety of research mechanisms. Since 2004, the Institute has supported the Obstetric Pharmacology Research Units Network, which is currently conducting safety studies of medications in pregnancy, such as anti-depressants, oral hypoglycemics for treatment of gestational diabetes, and chemotherapy. An NICHD-funded study using a large insurance plan's database examined the frequency at which physicians prescribed opioids for pain during pregnancy (including back pain, migraine, and fibromyalgia), finding that more than 14 percent of pregnant women had been prescribed pain relievers, sometimes three or more times during their pregnancies. NICHD plans to continue to fill the gaps in knowledge about medication use during pregnancy through funding opportunities in translational research.

Metastasis Genetics

Understanding the process of metastasis is of great importance to the clinical management of cancer because most cancer deaths are attributable to disseminated disease rather than the primary tumor. NCI supports a broad portfolio of metastasis research specifically aimed at tracking the evolutionary changes associated with the metastatic process, often by performing genomic studies of multiple metastases in single patients through rapid autopsies performed within hours after a patient's death. 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. This approach has yielded valuable data for renal, lung, breast, prostate, and pancreatic cancers, informing new approaches for targeting and disruption of the process.

¹⁴⁸ <http://www.nichd.nih.gov/news/releases/Pages/052014-exercise-type2-diabetes.aspx>

NCI-supported research¹⁴⁹ using rapid autopsy specimens from pancreatic cancer patients has shown that cells within the primary tumor 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. Similar research using rapid autopsy specimens from prostate cancer patients have identified new insights¹⁵⁰ into the biology of prostate cancer and specific pathways active in the metastasis of prostate cancer to bone, and enabled the development¹⁵¹ of a patient-derived xenograft, a type of mouse model generated directly from a patient's tumor tissue that is better able to mimic the properties of a human cancer than a purely animal model.

In addition to rapid autopsy studies, NCI funds a variety of research examining the function of genes that may promote or suppress metastasis. Ongoing projects include the examination of genetic changes and metastasis in osteosarcoma, bladder cancer, melanoma, and medulloblastoma tumors. NCI's Provocative Questions Initiative is supporting several projects related to the metastatic processes. Research teams are creating and refining engineered tissue platforms that can mimic processes associated with metastasis and will enable researchers to experimentally manipulate and characterize these processes and the genetic and molecular signaling factors that control them. Other efforts are focusing on 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.

Minority Participation in Clinical Trials

Participants from racial and ethnic populations, as well as disabled, low SES, rural, and LGBT populations frequently are not recruited into clinical trials at levels that reflect the prevalence of the condition under study in those populations. This disparity in clinical trial recruitment can occur for many reasons, including: 1) referral bias by clinicians; 2) cost of, and access to, clinical trial care; and 3) medical mistrust. These obstacles, among others, can make recruitment of individuals from underserved and understudied populations more difficult. NIMHD will collaborate with the National Human Genome Research Institute (NHGRI) and the NIH intramural clinical trials network to examine obstacles and set forward new practices to foster inclusion of these population groups in clinical trials from the outset of the design, throughout recruitment, during analysis of data, and included in the final reporting. The initiative is designed to ensure that: 1) clinical trial studies demonstrate the inclusion of racial and ethnic population groups and other underserved populations; 2) clinical trial annual monitoring establishes accountability criteria for the progression of health disparity population groups' inclusion; 3) exclusion of racial and ethnic population groups and other underserved populations from research can only be done with strong biological justification; 4) protocols are developed that allow for co-morbidities and obesity; 5) a stronger pipeline between emerging basic science and clinical trials is facilitated; and 6) population-specific publications are expected as an outcome from clinical trials.

NIMHD will lead a trans-NIH collaborative effort to increase disparate population inclusion

¹⁴⁹ <http://www.ncbi.nlm.nih.gov/pubmed/20981102>

¹⁵⁰ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3869871>

¹⁵¹ <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3117947/>

within the NIH intramural and extramural clinical research programs. One initiative will employ recruitment and retention strategies to address issues such as mistrust, costs, transportation, and differences in cultural perspectives. A second initiative will be launched to improve the number of health disparity population specimens within biobanks and data registries in order to expand these research resources' capability and contribution to the development of precision medicine for all population groups.

Mitochondrial Disorders

Evidence is growing that genetic or acquired mitochondrial dysfunction contributes to many diseases. New approaches in imaging technologies and next generation sequencing are revolutionizing this field. NIH promotes a wide range of research on these diseases including the development of animal models for primary mitochondrial disorders, natural history and pathophysiology studies, and development of treatment interventions for mitochondrial diseases. NICHD supports research on mitochondria in reproductive function, neuroprotection in neonatal hypoxia and adult central nervous system injuries, and basic research on mitochondrial morphology and function. Recent NINDS-supported researchers have developed a new fruit fly model that mirrors the clinical features of complex I deficiency diseases, including neuronal loss and early death. NHLBI-funded research shows that sleep loss is a previously unrecognized cause of mitochondrial dysfunction and cell death. Other research has identified possible biomarkers for MELAS (mitochondrial encephalomyopathy), a serious brain condition. Still another recent study found that certain blood cells of children who are in septic shock showed dysfunctional mitochondria, which may lead to more effective treatments for these children. In addition, NICHD and NINDS have taken an active role in supporting the North American Mitochondrial Disease Consortium (NAMDC), partnering with the NAMDC investigators and the United Mitochondrial Disease foundation. The NAMDC recently established a mitochondrial disease registry and biorepository and initiated two natural history studies. NICHD has worked with Consortium investigators to develop an FDA application for a clinical trial to treat a mitochondrial condition, and additional research initiatives supported by NIH related to mitochondrial dysfunction include mitochondrial myopathies, tissue injury in alcohol abuse, HIV/AIDS, and cancer.

Multiple Sclerosis (MS)

NINDS funds a wide range of research focused on understanding the disease processes and on developing treatments for relapsing-remitting and progressive forms of multiple sclerosis (MS). NINDS-funded scientists are conducting studies to identify genetic and environmental risk factors for MS; to discover the mechanisms underlying gender differences in the incidence of MS, with emphasis on the role of sex hormones; to understand how myelin (the fatty sheath that insulates axons) forms and breaks down in MS; to investigate immune system function and dysfunction in the central nervous system; to understand blood-brain-barrier breakdown in MS; and to identify factors that repair or protect against neurodegeneration in MS. NINDS funds preclinical therapy development that is focused on finding treatments that stop or reverse the course of the disease by modulating immune system function, by repairing damaged myelin, or by protecting neurons from damage. NINDS intramural scientists are developing better methods and tools to diagnose MS and monitor disease progression and are conducting early-stage clinical trials to test treatments for both primary and secondary progressive MS. Researchers in the NINDS NeuroNEXT Phase 2 clinical trials network are testing a potential neuroprotective

drug for progressive MS. The NIAID Autoimmunity Centers of Excellence (ACEs) conduct collaborative research on MS and other autoimmune diseases, including clinical trials of immunomodulatory therapies and mechanistic studies, and the NIAID Immune Tolerance Network (ITN) evaluates novel, tolerance-inducing therapies for autoimmune diseases including multiple sclerosis, conducts integrated mechanistic studies, and develops and evaluates markers and assays to measure the induction, maintenance, and loss of tolerance in autoimmune disease.

National Pediatric Research Network Act

NIH is actively working to advance the goals of the National Pediatric Research Network Act (P.L. 113-55), enacted on November 27, 2013, and welcomes the opportunity to address specific obstacles as current funding expires for the more than 100 NIH-funded pediatric network and centers programs, and these programs are recompeted for additional funding. For example, in September 2014, NICHD, NINDS, and NIMH funded three new Fragile X centers of excellence, addressing and improving earlier iterations of the centers structure. Pediatric research continues to be a major NIH priority. NIH's strong basic research portfolio provides the foundation for pediatric research in a variety of scientific areas, including neurodevelopment, cardiology, cancer, a wide range of rare conditions, and behavioral and social sciences. In FY 2014, NIH funded nearly \$3.5 billion in research grants and projects directed specifically at pediatric research. Although NICHD funds the largest portion of pediatric research among the 27 ICs, it accounts for only 20 percent of the total NIH support for pediatric research. This reflects the breadth of the NIH research portfolio that is dedicated to improving the health of children. Ongoing discussions are assessing how to optimize the use of currently available resources.

Nephrotic Syndrome (Same Response as Segmental Glomerulosclerosis)

Nephrotic Syndrome is a kidney disease that is characterized by damage to the glomeruli, the filtering units of the kidney. In this condition, the kidneys' ability to remove waste and excess salts and fluid from the blood while retaining proteins, blood cells, and other components of the circulation is compromised. NIH is deeply concerned about people with glomerular diseases, including focal segmental glomerulosclerosis (FSGS), and promotes and supports studies of glomerular diseases in a number of ways. These include funding of research projects proposed by researchers; direct solicitation of research in a particular area; conducting cutting-edge research through the NIH Intramural Research Program; and support for scientific meetings where state-of-the-art science is discussed. Examples of NIH-initiated research includes the Nephrotic Syndrome Rare Diseases Clinical Research Network (NEPTUNE), a multi-site, multidisciplinary collaborative research and education network designed to foster innovative approaches to the understanding of glomerular disease. NIH is also supporting CureGN, a study that will help researchers better understand the causes of glomerular disease, patients' response to therapy, and disease progression, with the ultimate objective to find a cure. NIH supports a CKD Biomarkers Consortium (CKD BioCon) that promotes the discovery and validation of novel biomarkers for CKD initiation, progression, and development of complications. A more complete understanding of biomarkers could allow physicians to detect kidney disease earlier and perhaps identify people at greater risk of progression, allowing them to tailor treatments to a specific individual. Looking forward, NIH is planning a meeting to explore the role of mutations in the APOL1 gene in the increased risk of glomerular disease in African Americans.

NIH has recently completed the Kidney Research National Dialogue, a project that solicited the

views of scientists, physicians, patients, and the public regarding the most critical issues in kidney disease research.¹⁵²

Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT)

NINDS established the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT, www.neuronext.org¹⁵³) in 2011 to provide robust infrastructure and centralized resources for conducting efficient early-phase clinical trials in both pediatric and adult neurologic disorders. NeuroNEXT is currently conducting four clinical studies, each addressing a different disease. The first study is developing biomarkers for spinal muscular atrophy (SMA). Enrollment in this study finished ahead of schedule, and investigators are analyzing baseline data and following the cohort in order to develop important longitudinal data on SMA (ClinicalTrials.gov ID: NCT01736553).¹⁵⁴ Another study is testing the safety and efficacy of a potential neuroprotective therapy in patients with progressive multiple sclerosis (ClinicalTrials.gov ID: NCT01982942).¹⁵⁵ A third study is exploring whether the drug rituximab can reduce the need for steroid use, which can have intolerable side effects, in patients with myasthenia gravis (ClinicalTrials.gov ID: NCT02110706).¹⁵⁶ Finally, the most recent study to begin in the network is testing a new agent that has the potential to protect brain tissue in patients with moderate strokes who have been given the clot-busting drug tPA (ClinicalTrials.gov ID: NCT0222714).¹⁵⁷ Enrollment in the latter three trials is ongoing. The range of disorders and patient populations being addressed by the NeuroNEXT studies speaks to its expertise and ability to recruit across a broad range of neurology disciplines. The network has also successfully utilized public-private partnerships in each of these studies to engage communities and garner additional research support from private organizations. Innovative approaches utilized by the network to streamline clinical research, including use of a central Institutional Review Board or IRB, have been adopted by other networks at NINDS (e.g., StrokeNet) and across NIH. Lessons from NeuroNEXT's successful use of a central IRB are informing broader efforts to adopt this practice for all NIH-funded multi-site clinical trials.

Neurofibromatosis

Neurofibromatosis (NF) is 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. A number of ICs support research focused on neurofibromatosis types 1 and 2 (NF1, NF2), including NCI and NINDS. NINDS organizes biennial Trans-NIH NF Working Group meetings to coordinate efforts and includes representatives from eight ICs, the Department of Defense, and advocacy groups.

¹⁵² <http://www.niddk.nih.gov/about-niddk/offices-divisions/division-kidney-urollogic-hematologic-diseases/kidney-research-national-dialogue/Pages/kidney-research-national-dialogue.aspx>

¹⁵³ <http://www.neuronext.org/>

¹⁵⁴ <https://clinicaltrials.gov/ct2/show/NCT01736553?term=Spinal+Muscular+Atrophy+%28SMA%29+Biomarkers+in+the+Immediate+Postnatal+Period+of+Development&rank=1>

¹⁵⁵ <https://clinicaltrials.gov/ct2/show/NCT01982942?term=Randomized%2C+Double-Blind%2C+Placebo-Controlled+Study+to+Evaluate+the+Safety%2C+Tolerability+and+Activity+of+Ibutilast+%28MN-166%29+in+Subjects+with+Progressive+Multiple+Sclerosis&rank=1>

¹⁵⁶ <https://clinicaltrials.gov/ct2/show/NCT02110706?term=nowak&rank=5>

¹⁵⁷ <https://clinicaltrials.gov/ct2/show/NCT0222714?term=Safety+evaluation+of+3K3A-APC+in+ischemic+stroke&rank=1>

NCI's NF research portfolio includes ongoing investigation of the biology of NF1 and NF2 tumor suppressor genes and proteins. NCI also supports research to identify rare and under-recognized cancers that may be associated with NF1. NCI's intramural program is home to one of the largest clinical trial programs for children and adults with NF1, including treatment trials for plexiform neurofibromas (benign tumors arising from the outer layer of nerves) and for malignant peripheral nerve sheath tumors (aggressive cancers), and an NF1 natural history study¹⁵⁸ evaluating children and adults with NF1.

Additionally, NCI has developed a semi-automated method for volumetric (3D) MRI analysis of plexiform neurofibromas that allows researchers to sensitively and reproducibly monitor changes in tumor size over time. This provides for more rapid detection of tumor progression and decreases trial duration and exposure to potentially toxic inactive investigational agents. NCI is also leading a Phase 1 clinical trial¹⁵⁹ of the drug selumetinib to treat plexiform neurofibromas. Initial results have been promising with tumor shrinkage in 60 percent of the patients, and Phase 2 trials for children and for adults have been developed and are expected to open for enrollment by summer 2015.

Non-Small Cell Lung Cancer

NCI supports a comprehensive research portfolio on non-small cell lung cancer (NSCLC), which includes adenocarcinoma (the most common subtype of lung cancer), squamous cell carcinoma, and large cell carcinoma – three of the four main histologic subtypes of lung cancer that have been identified. The genomes of 178 cases of squamous cell carcinoma were extensively characterized by The Cancer Genome Atlas (TCGA¹⁶⁰) and published in 2012, identifying several promising therapeutic targets. In 2014, TCGA researchers published¹⁶¹ results that confirmed known mutations and identified novel mutations in a well-known cancer-causing pathway in lung adenocarcinoma. Knowledge of such genomic changes has already expanded the number of therapeutic targets, expanding the number of patients with treatable mutations since cancer drugs targeting some of those mutations already exist.

The NCI National Clinical Trials Network (NCTN¹⁶²) launched the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST¹⁶³) in 2014 to determine whether patients undergoing surgery for lung adenocarcinomas driven by two of the relatively common targetable mutations will benefit from the adjuvant use of approved drugs. The Squamous Lung Master Protocol (Lung-MAP¹⁶⁴), also launched by NCTN in 2014 in conjunction with pharmaceutical partners through the Foundation for the NIH, is a clinical trial for patients with advanced squamous cell lung cancer that no longer responds to routine therapies. In this trial, patients are assigned to therapy based on the molecular characteristics of their disease.

NCI also supports numerous grants to individual investigators studying NSCLC and early stage trials of several therapeutic strategies.

¹⁵⁸ <https://clinicaltrials.gov/ct2/show/NCT00924196>

¹⁵⁹ <https://www.clinicaltrials.gov/ct2/show/NCT01362803>

¹⁶⁰ <http://cancergenome.nih.gov/>

¹⁶¹ <http://www.cancer.gov/newscenter/newsfromnci/2014/TCGALungAdeno>

¹⁶² <http://www.cancer.gov/clinicaltrials/nctn>

¹⁶³ <http://www.cancer.gov/clinicaltrials/noteworthy-trials/alchemist>

¹⁶⁴ <http://www.cancer.gov/clinicaltrials/noteworthy-trials/lung-map>

Opioid Drug Abuse

According to current estimates, 1.9 million Americans are addicted to prescription opioid pain relievers, and 517,000 Americans are addicted to heroin. In 2013, 16,235 individuals died as a result of prescription opioid overdose, and another 8,257 died from heroin overdose, up from 16,007 and 5,925, respectively, in 2012. NIDA is working closely with Federal partners on several initiatives to reduce opioid-drug related overdose deaths. These include:

- The *NIDAMED* initiative¹⁶⁵: developing and disseminating two continuing medical education courses to educate health care professionals on prevention, identification, and treatment of substance use disorders (SUD) and on safe prescribing for pain. These courses have been completed by approximately 100,000 clinicians.
- Research on the implementation and dissemination of medication-assisted treatment (MAT) including the Prescription Opioid Addiction Treatment Study¹⁶⁶ (POATS), a large-scale effort at 10 treatment sites that studies patients receiving a combination of MAT and counseling sessions.
- Development of an intranasal formulation for naloxone, an opioid antagonist that, if administered in a timely fashion, rapidly restores normal breathing following an opiate overdose.

NIDA is currently funding 313 research projects related to opioid use and addiction including epidemiological studies of opioid use¹⁶⁷, studies of the effectiveness of prescription drug monitoring programs (PDMP¹⁶⁸), development of pain medications with diminished abuse potential¹⁶⁹, and development¹⁷⁰ and testing¹⁷¹ of prevention¹⁷² and treatment¹⁷³ interventions. Recent significant findings include evidence that ongoing buprenorphine¹⁷⁴ maintenance is more effective than tapering in the treatment of prescription opioid abuse; lower rates of prescription drug abuse in youth¹⁷⁵ participating in universal evidence-based prevention interventions; and characterization of the geographic variation in patients' use of multiple prescribers ("doctor shopping"¹⁷⁶).

¹⁶⁵ <http://www.drugabuse.gov/nidamed-medical-health-professionals>

¹⁶⁶ <http://www.drugabuse.gov/about-nida/organization/cctn/ctn/research-studies/prescription-opioid-addiction-treatment-study-poats>

¹⁶⁷ <http://www.monitoringthefuture.org/>

¹⁶⁸ http://projectreporter.nih.gov/project_info_description.cfm?aid=8610195&icde=23484383&ddparam=&ddvalue=&ddsub=&cr=2&csb=default&cs=ASC

¹⁶⁹ http://projectreporter.nih.gov/project_info_description.cfm?aid=8757208&icde=23484518&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC

¹⁷⁰ http://projectreporter.nih.gov/project_info_description.cfm?aid=8819197&icde=23484806&ddparam=&ddvalue=&ddsub=&cr=2&csb=default&cs=ASC

¹⁷¹ http://projectreporter.nih.gov/project_info_description.cfm?aid=8827581&icde=23484767&ddparam=&ddvalue=&ddsub=&cr=1&csb=default&cs=ASC

¹⁷² http://projectreporter.nih.gov/project_info_description.cfm?aid=8660676&icde=23484683&ddparam=&ddvalue=&ddsub=&cr=5&csb=default&cs=ASC

¹⁷³ <http://www.drugabuse.gov/about-nida/organization/cctn/ctn/research-studies/prescription-opioid-addiction-treatment-study-poats>

¹⁷⁴ <http://www.drugabuse.gov/news-events/news-releases/2014/11/buprenorphine-tapering-less-effective-than-ongoing-maintenance-prescription-opioid-abuse>

¹⁷⁵ <http://www.ncbi.nlm.nih.gov/pubmed/24521531>

¹⁷⁶ <http://www.ncbi.nlm.nih.gov/pubmed/25111716>

Ovarian Cancer

Ovarian cancer remains among the leading causes of cancer mortality in U.S. women, with approximately 22,000 women dying from the disease each year. This is partly because it remains difficult to detect ovarian cancers early, before they have spread beyond the primary site. For this reason, NCI supports research to develop better early detection and treatment methods for ovarian cancer through the Early Detection Research Network (EDRN). A few years ago, the TCGA reported the analysis of more than 500 serous ovarian adenocarcinomas, the most prevalent form of ovarian cancer. The analysis confirmed the high frequency of mutation in the p53 gene in ovarian cancer, but revealed few driver mutations in addition to p53. However, certain patterns of mutation were associated with the length of survival.

A randomized Phase 2 study¹⁷⁷ supported by NCI showed the combination of olaparib, a PARP-inhibitor, plus cediranib, an inhibitor of angiogenesis receptor kinases, was superior to treatment with olaparib alone, both in women with and without germline BRCA1/2 mutations. The NCTN is developing two trials to confirm the activity of this combination in women with platinum-sensitive recurrent ovarian cancer and to examine its role in women with platinum-resistant ovarian cancer.

A recent NCI-supported grantee is studying a new PARP-inhibitor drug, talazoparib, in the treatment of ovarian cancer in those with a BRCA mutation to see if the drug will shrink ovarian tumors that responded to initial treatment with another PARP-inhibitor, but then grew back. In addition, a new study is testing the ability of an agent that “unblocks” the immune system from attacking tumor cells to shrink tumors in women with certain breast and ovarian cancers.

Another ongoing Phase 1 treatment trial is aimed at determining the best sequence for administering chemotherapy and olaparib to women with recurrent gynecologic cancers, including ovarian cancer. Additionally, an observational study is evaluating the potential for monocytes, a type of white blood cell, to be used to treat ovarian cancer.

Palliative Care

As Americans live longer, they are increasingly likely to experience a life-limiting or serious illness. This means that individuals, families, and health care providers face difficult decisions regarding health care, relief of symptoms, and maintaining quality of life. Palliative care offers comprehensive treatment of the discomfort, symptoms, and stress of serious illness, and it is essential for addressing the needs of these individuals, as well as their caregivers and families, at all ages and stages of illness. To advance the science of palliative care, the National Institute of Nursing Research (NINR) created the Office of End-of-Life and Palliative Care Research that coordinates and supports research efforts in this area of science. For example, NINR supports the Palliative Care Research Cooperative¹⁷⁸ (PCRC), which includes a national infrastructure of more than 50 research sites designed to support high-quality, leading-edge research in end-of-life and palliative care. NINR also supports a variety of palliative care research efforts. One recent study found that clinician-patient discussions about preferences for life-sustaining treatments could reduce unwanted treatments at the end of life. Another study is currently investigating how geographic, demographic, and health characteristics of children influence use of hospice care services. In addition, NINR provides research-based information regarding palliative and

¹⁷⁷ <https://clinicaltrials.gov/ct2/show/NCT01116648>

¹⁷⁸ <http://palliativecareresearch.org/>

end-of-life care to the public. NINR recently launched the *Palliative Care: Conversations Matter*¹⁷⁹ campaign to raise awareness of pediatric palliative care and to facilitate conversations between health care providers and families. NINR also developed an End-of-Life module¹⁸⁰ for NIHSeniorHealthSeniorHealth.gov that provides clear, easy-to-read information for older adults and their caregivers regarding a range of end-of-life and palliative care issues, such as coping with pain and end-of-life care planning.

Pancreatic Cancer

NCI supports a comprehensive portfolio of pancreatic cancer research, as presented in the scientific framework for pancreatic ductal adenocarcinoma (PDAC) that was completed and delivered to Congress in February 2014. NCI is addressing the recommendations made in that report, including the relationship between PDAC and diabetes mellitus of recent onset; biomarker and imaging studies of pancreatic cysts to identify those at high risk of PDAC; and new immunotherapies. Coincidentally, NCI has begun the RAS Initiative to develop new ways to treat those cancers, such as PDAC, that are commonly driven by mutations in the RAS gene family. One of the three RAS genes is often mutated in pancreatic, lung, and colorectal cancers, as well as several other cancer types, yet methods for treating such tumors have been difficult to produce. NCI is also investing in the training of the next generation of RAS experts and has joined with the Pancreatic Cancer Action Network to support two training fellowships focused on a type of RAS mutation relevant to pancreatic cancer. NCI also supports research on islet cell tumors (also called pancreatic neuroendocrine tumors), including diagnostic¹⁸¹ and treatment clinical trials.¹⁸²

Pediatric Kidney Disease

NIH supports research to identify causes, understand and halt disease progression, develop and improve treatments, and ultimately prevent kidney diseases and kidney failure in children. Investigators recently reported that long-term use of a drug combination of antibiotics can reduce the risk of recurrent urinary tract infection by up to 80 percent in children with vesicoureteral reflux (*NEJM* 370: 2367, 2014). In children with chronic kidney disease, higher hepcidin (regulates both iron absorption and body distribution) levels were found to be associated with an increased risk of anemia and this association is most significant among children with less kidney function (*Pediatr Nephrol* 2014 Nov 8. [Epub ahead of print]). Urine was collected from healthy children and assayed for several biomarkers (e.g., NGAL, KIM-1) to establish a reference range with respect to age and gender; thereby providing a framework in which to use these biomarkers in studies of children suspected of having acute kidney injury (*Pediatr Nephrol* 2014 Oct 28. [Epub ahead of print]). In children with mild-to-moderate chronic kidney disease, the duration of disease rather than estimated kidney function was associated with neurocognitive deficit (*Kidney Int* 2014 Sep 24. doi: 10.1038/ki.2014.323. [Epub ahead of print]). Approximately 32 percent of severely obese adolescents undergoing weight-loss surgery have

¹⁷⁹ <http://www.ninr.nih.gov/newsandinformation/conversationsmatter>

¹⁸⁰ <http://nihseniorhealth.gov/endoflife/preparingfortheendoflife/01.html>

¹⁸¹ <http://www.cancer.gov/clinicaltrials/search/view?cdrid=754032&version=http://www.cancer.gov/clinicaltrials/search/view?cdrid=754032&version=HealthProfessional&protocolsearchid=13819353HealthProfessional&protocolsearchid=13819353>

¹⁸² <http://www.cancer.gov/clinicaltrials/search/view?cdrid=748567&version=HealthProfessional&protocolsearchid=13819353>

abnormal kidney function; future studies will determine whether these kidney abnormalities are reversible following the surgical procedure (*Obesity J* 22: 2319, 2014). In a small study, two APOL1 risk alleles in young African Americans with a family history of end-stage renal disease are associated with kidney disease (*Pediatr Nephrol* 2014 Dec 23 [Epub ahead of print]). Higher initial findings of protein in urine and systolic blood pressure are associated with faster declines in kidney function in children with kidney disease caused by cystinosis (an amino acid called cysteine inappropriately accumulates in the kidney), cystinuria (cysteine-based stones form in the kidney, ureter, and bladder), or hyperoxaluria (oxalate-based stones form in the kidney) (*CJASN* 10: 1, 2015). Mutations in the gene, EMP2 (encodes a protein found in the filtering unit of the kidney), were shown to cause childhood-onset nephrotic syndrome – a collection of symptoms that indicate kidney damage (*Am J Hum Genet* 94: 884, 2014).

Performance Measures for Each NCATS Program, Project, or Activity

Clinical and Translational Science Award (CTSA) Program: The CTSA program has been reviewed both by the IOM and an NCATS Advisory Council Working Group. The June 2013¹⁸³ IOM report included a recommendation to formalize and standardize the evaluation processes for individual CTSA and the CTSA Network, while the Working Group report¹⁸⁴ provided advice on changes to the CTSA program with a focus on establishing measurable goals and objectives. Both of these recommendations were taken into account when NCATS issued a new funding opportunity announcement¹⁸⁵ for the CTSA program on September 12, 2014. Throughout the announcement, which solicited applications for the establishment of CTSA hubs, applicants are asked to describe milestone goals for their CTSA hub, how they plan to collect metrics, and how leadership will monitor progress of the CTSA. NCATS will work with the grantees to develop specific operational plans to implement a set of common metrics across the hubs, building on existing efforts in the CTSA program. NCATS will evaluate the feasibility, burden and usefulness of these metrics and make adjustments as needed.

Cures Acceleration Network (CAN): At the May 2013 meeting (see pages 7-10 of the minutes¹⁸⁶) of the CAN Review Board, general principles were established for evaluating the work of CAN and for creating measurable outcomes to track the success of the program. Suggested metrics were organized into three groups: administrative outcomes, project outcomes, and transformative outcomes that would indicate if a project or program had advanced science or helped patients. Specific metrics should be designed prospectively and built into the programs supported by CAN to be used as a monitoring tool. The CAN Review Board also established several parameters for selecting potential CAN projects. Projects need to be: collaborative, have discrete and measurable outcomes, have a broad and significant impact, be focused on a compelling disease, and have a timeline for completion of less than five years.

Performance measures, as well as annual results and future annual targets, for CAN have been developed as part of the Agency's overall goals to advance basic biomedical and behavioral science, support translational research, and enhance the development of human capital and strengthen the scientific workforce. These can be found in the NIH Congressional Justification

¹⁸³ <http://www.iom.edu/Reports/2013/The-CTSA-Program-at-NIH-Opportunities-for-Advancing-Clinical-and-Translational-Research.aspx>

¹⁸⁴ <http://www.ncats.nih.gov/files/CTSA-IOM-WG-Draft-Report.pdf>

¹⁸⁵ <http://grants.nih.gov/grants/guide/rfa-files/RFA-TR-14-009.html>

¹⁸⁶ <http://www.ncats.nih.gov/files/council-can-minutes-05172013.pdf>

for FY 2016¹⁸⁷ (see SRO-3.11 on page 60). The overall expected outcome of the current program supported by CAN funds is to advance the discovery of high-need cures through innovations in the therapeutics discovery and development process, by developing 3-D human tissue chips that accurately model the structure and function of human organs.

Pediatric Low Grade Astrocytoma (PLGA)

NCI-supported research continues to build a greater understanding of PLGA. PLGA is the most common pediatric brain tumor, and the majority of PLGA cases have genomic alterations in the BRAF gene, which is also mutated in other cancer types that have been targeted for therapy with certain BRAF kinase inhibitors.

In 2011, the NCI Pediatric Preclinical Testing Program¹⁸⁸ developed a model for a subtype of PLGA with the BRAF mutation and identified a targeted therapy, selumetinib, for additional research. Building upon these findings, the NCI Pediatric Brain Tumor Consortium¹⁸⁹ conducted a Phase 1 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. In this trial¹⁹⁰ patients with BRAF-mutated PLGAs responded to treatment by showing tumor shrinkage. Based on these promising findings, the trial is now in a Phase 2 expansion. The trial is open at 14 sites across the country and is expected to enroll 135 children with PLGA.

Precision Medicine

Historically, medical practitioners have had to make recommendations about disease prevention and treatment based largely on the expected response of an average patient. However, recent advances in technology, along with decreasing costs of DNA sequencing, have developed a compelling and innovative approach to medicine by using individual variability. This emerging practice is known as precision medicine.

Precision medicine allows treatments to be tailored to the individual characteristics of each patient. To accomplish this, scientists and physicians must understand human variability and identify individuals who differ in the susceptibility to a particular disease, in the trajectory of a disease, or in response to a specific treatment. In this way, specific preventive or therapeutic interventions can be adapted for each patient – avoiding needless treatment and expense for those who will not benefit.

NIH understands the importance of treating disease at an individual level, and has made precision medicine a priority. In FY 2014, two cancer precision medicine clinical trials commenced, both capitalizing on the infrastructure of the National Clinical Trials Network supported by NCI. The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials, or ALCHEMIST, will identify early-stage lung cancer patients with tumors that have certain uncommon genetic changes. Patients will receive one of two supplemental treatments specifically targeted to these genetic alterations to determine if the drugs prevent cancer recurrence and prolong life. The Lung Cancer Master Protocol (Lung-MAP) trial for patients with advanced squamous cell lung cancer will test four experimental drugs. This trial is

¹⁸⁷ [http://officeofbudget.od.nih.gov/pdfs/FY16/Overview%20\(Volume%20I\).pdf](http://officeofbudget.od.nih.gov/pdfs/FY16/Overview%20(Volume%20I).pdf)

¹⁸⁸ http://ctep.cancer.gov/MajorInitiatives/Pediatric_Preclinical_Testing_Program.htm

¹⁸⁹ http://ctep.cancer.gov/MajorInitiatives/Pediatric_Brain_Tumor_Consortium.htm

¹⁹⁰ <https://clinicaltrials.gov/ct2/show/NCT01089101>

a unique public-private collaboration between NIH, non-profit organizations, and pharmaceutical companies. Patients are assigned to a particular drug (or “arm” of the trial) based on the results of a genetic screen for cancer-related genes. Unlike previous clinical trials, Lung-MAP tests patients for many biomarkers simultaneously to assess compatibility with several different treatment options. This innovative trial design could be pivotal as advances in precision medicine make this type of treatment possible.

As part of the President’s multi-agency Precision Medicine Initiative, the FY 2016 budget request includes \$200 million for NIH. The battle against cancer has been leading the way in precision medicine for many years. To capitalize on these successes, the FY 2016 request proposes \$70 million to expand current cancer genomics research to initiate new studies of how a tumor’s DNA can be used to predict and treat tumor cells that develop resistance to a therapy, apply new non-invasive methods to track response to therapy, and explore the efficacy of new combinations of cancer drugs targeted to specific tumor mutations. In addition, to harness the full potential of precision medicine across many diseases, NIH proposes \$130 million to launch a national research cohort of a million or more individuals, primarily those who have already participated in clinical research studies, who volunteer to share their genetic information in the context of other health data over time. This information will be linked to their electronic health records, while ensuring privacy protections are in place. A database of this scale will lay the foundation for a wealth of new research studies which promises to lead to new prevention strategies, and novel therapeutics and medical devices. It will also help improve how drugs are prescribed, allowing a more optimum choice of the right drug at the right dose for the right person.

Preterm Birth

Although the rate of preterm birth in the United States is declining, one out of every nine infants is still born preterm (before 37 weeks’ gestation) each year. Preterm birth is the Nation’s leading cause of infant death and long-term neurological disorders. NICHD, along with several other ICs, supports an extensive portfolio of investigator-initiated research and targeted clinical studies in preventing, managing, and treating preterm birth as well as improving the outcome of infants born preterm. NIH research has shown that carrying infants to term is essential; an NICHD-supported study concluded that infants born at 39-41 weeks had developmental advantages compared with those born at 37-38 weeks. NIH-supported research also focuses on improving neurologic neonatal outcomes. NICHD’s Maternal and Fetal Medicine Units network is conducting a trial testing interventions to improve outcome in late preterm infants and NICHD’s Neonatal Research Network has ongoing trials to improve the care of infants born extremely preterm, who face severe neurologic and respiratory risks. Preterm births account for approximately one-third of all neonatal deaths in the developing world. Although the evidence that a course of antenatal glucocorticoids improves preterm survival is very strong in developed countries, it was not clear whether antenatal glucocorticoids would be effective in the developing world, where specialized care is generally not available. NICHD’s Global Network for Women’s and Children’s Health Research enrolled 40,000 women in a randomized controlled trial, finding that the treatment could actually cause harm in low resource settings. This research was essential as numerous organizations were planning to implement this treatment in low-resource settings and waited for the trial results before launching their programs. In addition, NICHD’s National Child and Maternal Health Education Program launched a Continuing Medical Education program on raising awareness about late preterm birth to help inform health

care providers.

Psychosocial Distress Complications

NIH supports a portfolio of biomedical and behavioral and social science research on psychosocial distress complications. Psychosocial distress is defined as the “unpleasant experience of an emotional, psychological, social, or spiritual nature” that results from biomedical conditions and health experiences. Some of these experiences can be disabling, including depression, anxiety, and panic conditions.¹⁹¹ Several examples of the studies on this important topic include:

- NCI supports several initiatives related to psychosocial distress complications, including studies on the efficacy of psychosocial interventions in adult cancer patients and caregivers.^{192,193}
- The NIMH Psychiatric Consultation Liaison Service, provides critical psychiatric services on psychosocial functioning in NIH research subjects who often have complex medical and neuropsychiatric symptoms and complications.¹⁹⁴
- NIDA has recently funded research that examines links between psychosocial distress and drug use, including tobacco and marijuana.¹⁹⁵
- NIDDK supports several programs related to psychosocial distress, including research that examines caregiver responses to family members with diabetes.¹⁹⁶

The NIH Institutes and Centers will continue to support investigator-initiated grants and other funding mechanisms in the important area of research on psychosocial distress complications.

Psychotropic Medications in Children

Psychotropic medications are substances that affect brain chemicals related to mood and behavior. In recent years, research has been conducted to understand the benefits and risks of using psychotropics in children, but more needs to be learned about their effects, especially in children under six years of age. A number of psychotropic medications currently have FDA-approved pediatric indications. There are also a few clinical conditions for which the FDA has specifically approved the use of antipsychotic medications in children (i.e., schizophrenia, bipolar disorder, autism spectrum disorder). On the one hand, there is an assumption that psychotropic medications are over-prescribed to children, especially given the markedly increased use of antipsychotics in very young children (PMID: 22868273¹⁹⁷). On the other hand, it appears that many children who could benefit are not being treated (PMID: 23403911¹⁹⁸). The

¹⁹¹ Park, W. (1999) [NCCN practice guidelines for the management of psychosocial distress](#). *Oncology* 13(5A)

¹⁹² Yanez et al (2014) [The importance of perceived stress management skills for patients with prostate cancer in active surveillance](#). *Journal of Behavioral Medicine*, Sept. 19

¹⁹³ Peterson et al (2014) [Parent caregiver self-efficacy and child reactions to pediatric cancer](#). *Journal Pediatric Oncology and Nursing* 31(1).

¹⁹⁴ Horowitz et al (2014) [Screening youth for suicide risk in medical settings](#). *American Journal of Preventive Medicine* 47.

¹⁹⁵ Buckner et al (2014) [Direct and indirect associations between social anxiety and nicotine dependence](#). *Nicotine Tobacco Research* 16(6).

¹⁹⁶ Jaser et al (2014) [Coping and psychological distress in mothers of adolescents with type 1 diabetes](#). *Maternal and Child Health Journal* 18(1).

¹⁹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/22868273>

¹⁹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/23403911>

increased use of antipsychotics is of particular concern, because most antipsychotic use seems to be for non-psychotic conditions, such as aggressive behavior, and because antipsychotic use has been shown to increase the risk for adverse metabolic effects, such as obesity and diabetes (PMID: 23881713¹⁹⁹; PMID: 23965896²⁰⁰).

NIMH is funding research to develop and test alternatives to medication treatment for the management of depression, anxiety, and other behavioral problems (PMID: 24342385²⁰¹; PMID: 25151418²⁰²). Effectiveness trials have compared different interventions for the treatment of children and adolescents with anxiety, major depression, and autism spectrum disorders. Additionally, several studies in progress are seeking to identify ways of preventing, minimizing, or reversing common adverse effects of medications, such as weight gain, during antipsychotic treatment. NIMH also supports ongoing research that looks to understand the biological mechanisms through which medications work or cause adverse effects in children (see PMID: 23806775²⁰³; PMID: 23903242²⁰⁴).

The focus of future research will be on developing safer and more effective interventions (both behavioral and pharmacological) that are tailored to the individual needs and characteristics of the child. Another focus will be on preventing the onset of mental illness by intervening early among children who are at especially high risk or who have initial symptoms, before the full onset of the disorders.

Rare Bone Diseases

NIH supports a broad research portfolio that is relevant to understanding rare bone diseases and translating basic research findings into treatments. For example, NIH-funded investigators recently discovered a connection between the genetic cause of neurofibromatosis Type 1 (NF1) and low levels of an enzyme needed for bone mineralization. The finding suggested that simply increasing levels of the enzyme could ameliorate certain skeletal consequences of NF1, and mouse experiments using a synthetic form of the enzyme appeared promising.²⁰⁵ Because this treatment has been tested in children with the rare bone disease hypophosphatasia, assessing its effects on the bones of NF1 patients may be relatively straightforward.

Other NIH-supported scientists are designing clinical trials based on recent findings about the mechanisms underlying osteogenesis imperfecta (OI), a genetic disease characterized by fragile bones. After discovering that a key signaling molecule is overly active in two different forms of OI, investigators gave OI mice an antibody that blocks the molecule's communications. The antibody, which is being tested as a drug for other diseases, improved the animals' bones.²⁰⁶

¹⁹⁹ <http://www.ncbi.nlm.nih.gov/pubmed/23881713>

²⁰⁰ <http://www.ncbi.nlm.nih.gov/pubmed/23965896>

²⁰¹ <http://www.ncbi.nlm.nih.gov/pubmed/24342385>

²⁰² <http://www.ncbi.nlm.nih.gov/pubmed/25151418>

²⁰³ <http://www.ncbi.nlm.nih.gov/pubmed/23806775>

²⁰⁴ <http://www.ncbi.nlm.nih.gov/pubmed/23903242>

²⁰⁵ [Asfotase-α improves bone growth, mineralization and strength in mouse models of neurofibromatosis type-1](#), de la Croix Ndong J, Makowski AJ, Uppuganti S, Vignaux G, Ono K, Perrien DS, Joubert S, Baglio SR, Granchi D, Stevenson DA, Rios JJ, Nyman JS, Elefteriou F. *Nat Med*. 2014 Aug; 20(8):904-10. doi: 10.1038/nm.3583. Epub 2014 Jul 6. PMID: 24997609

²⁰⁶ [Excessive transforming growth factor-β signaling is a common mechanism in osteogenesis imperfecta](#). Grafe I, Yang T, Alexander S, Homan EP, Lietman C, Jiang MM, Bertin T, Munivez E, Chen Y, Dawson B, Ishikawa Y,

Now, the researchers are planning a Phase I clinical trial as part of the newly funded Brittle Bone Disorders Consortium of the Rare Diseases Clinical Research Network.²⁰⁷

Another group of investigators is harnessing knowledge about the complications of x-linked hypophosphatemia (XLH) to test interventions that might improve bone without damaging other organs. Their results suggest that combining an existing treatment strategy with paricalcitol (a form of vitamin D that is widely used to treat hyperparathyroidism in the context of chronic kidney disease) might mitigate some of the negative effects of the current therapy.²⁰⁸

Research Centers in Minority Institutions (RCMI)

The NIMHD Research Centers in Minority Institutions (RCMI) program supports activities that focus on the professional development of scientists, especially those that are underrepresented in the biomedical sciences. RCMI centers stress collaborations and 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. The RCMI program also provides access to scientific cores and technical support. There are opportunities for investigators to generate preliminary data required for successful investigator-initiated (R01) grant submissions, through peer-reviewed pilot project programs.

RCMI centers support research on a broad range of topics such as cancer, cardiovascular disease, diabetes, obesity, HIV/AIDS, neurological diseases, and many others. Research in these centers has led to advances such as:

- biomarkers for stroke in humans which help in identifying different stroke subtypes and serve as prognostic indicators for stroke outcomes.²⁰⁹
- the discovery of microRNA patterns in prostate cancer cells linked to progression to advanced prostate cancer and to the disproportionate mortality of African American men from the disease;²¹⁰ and
- links between mitochondrial DNA damage and lupus, setting the stage for strategies relevant to treatment of this disease.²¹¹

The RCMI program continues to play an important role in facilitating biomedical research thorough institutional resource development.

Research Focused on Drug Abuse in Veterans

Returning military personnel may face several challenges, including traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), suicidal behavior and thinking, and substance use

Weis MA, Sampath TK, Ambrose C, Eyre D, Bächinger HP, Lee B. Nat Med. 2014 May 4. doi: 10.1038/nm.3544. [Epub ahead of print] PMID: 2479323

²⁰⁷ <http://www.ncats.nih.gov/research/rare-diseases/rdcrn/projects/rdcrc-2014.html>

²⁰⁸ [Effect of paricalcitol on circulating parathyroid hormone in X-linked hypophosphatemia: a randomized, double-blind, placebo-controlled study.](#) Carpenter TO, Olear EA, Zhang JH, Ellis BK, Simpson CA, Cheng D, Gundberg CM, Insogna KL. *J Clin Endocrinol Metab.* 2014 Sep; 99(9):3103-11. PMID: 25029424

²⁰⁹ <http://www.ncbi.nlm.nih.gov/pubmed/24558093?dopt=Citation>

²¹⁰ [http://www.impactjournals.com/oncotarget/index.php?journal=oncotarget&page=article&op=view&path\[\]=1953](http://www.impactjournals.com/oncotarget/index.php?journal=oncotarget&page=article&op=view&path[]=1953)

²¹¹ <http://www.ncbi.nlm.nih.gov/pubmed/24899636>

disorders²¹² (SUDs). The rates of SUDs, tobacco use, and binge drinking²¹³ among service members, are all higher than in the civilian population. Of particular concern, prescription drug abuse increased dramatically among military personnel²¹⁴ – from 2 percent in 2002 to 11 percent in 2008. While the majority of NIDA’s SUD research portfolio (2,114 grants totaling more than \$763 million) is relevant to addressing SUD in military personnel, NIDA is currently funding 18 grants specifically addressing SUD in military populations, totaling more than \$5 million. In 2010, NIDA and Federal partners issued a joint call for research on Substance Use and Abuse among U.S. Military Personnel, Veterans and their Families (RFA-DA-10-001²¹⁵). This program has resulted in findings for new integrated treatment²¹⁶ for comorbid symptoms of PTSD and depression, better understanding of patterns of opioid use in chronic pain treatment²¹⁷ in the military, and identification of low intervention rates²¹⁸ for veterans positive for at-risk drinking.

NIDA research also informed the 2012 recommendations from the Institute of Medicine that pharmacological therapies for opioid addiction should be included in standards of care. This led the Department of Defense to authorize TRICARE²¹⁹ – the health care program for uniformed service members, retirees, and their families – to pay for these previously prohibited medications. NIDA is working with Federal partners on implementation of the National Research Action Plan²²⁰ (NRAP) to respond to the Executive Order, *Improving Access to Mental Health Services for Veterans, Service Members, and Military Families*. An ambitious plan has been outlined for research to be completed by the NRAP in the next 10 years, subject to available funding for these activities.

Scleroderma

NIH continues to support scleroderma research through investigator-initiated grants, as well as through Institute initiatives, such as the Center of Research Translation (CORT) in Pathogenic Mechanisms in Systemic Sclerosis.²²¹ The goal of the Center is to accelerate the understanding of systemic sclerosis by identifying the biomarkers of progression and complications associated with the disease, and to set the stage for developing more targeted therapies. Researchers funded by the CORT program recently published two studies that may help to identify patients who will progress to severe disease. One of the studies, conducted by CORT researchers collaborating with colleagues in Europe and the United States, identified a biomarker, CXCL4, that correlates with the presence and progression of serious complications such as pulmonary fibrosis and pulmonary arterial hypertension.²²² The other study showed that expression of certain genes

²¹² <http://www.drugabuse.gov/publications/topics-in-brief/substance-abuse-among-military-veterans-their-families>

²¹³ <http://www.tricare.mil/tma/dhcape/surveys/coresurveys/surveyhealthrelatedbehaviors/downloads/Final%202011%20HRB%20Active%20Duty%20Survey%20Exec%20Summary.pdf>

²¹⁴ <http://www.iom.edu/Reports/2012/Substance-Use-Disorders-in-the-US-Armed-Forces.aspx>

²¹⁵ <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-10-001.html>

²¹⁶ <http://www.ncbi.nlm.nih.gov/pubmed/22679240>

²¹⁷ <http://www.ncbi.nlm.nih.gov/pubmed/?term=%22Patterns+of+opioid+use+for+chronic+noncancer+pain+in+the+Veterans+Health+Administration+%22>

²¹⁸ <http://www.ncbi.nlm.nih.gov/pubmed/?term=%22Missed+opportunity+for+alcohol+problem+prevention+among+army+active+duty+service+members+%22>

²¹⁹ <http://www.gpo.gov/fdsys/pkg/FR-2013-10-22/pdf/2013-24232.pdf>

²²⁰ http://www.whitehouse.gov/sites/default/files/uploads/nrap_for_eo_on_mental_health_august_2013.pdf

²²¹ http://www.niams.nih.gov/News_and_events/Announcements/2011/4cort_awards.asp

²²² [Proteome-wide Analysis and CXCL4 as a Biomarker in Systemic Sclerosis](#). van Bon L, Affandi AJ, Broen J, Christmann RB, Marijnissen RJ, Stawski L, Farina GA, Stifano G, Mathes AL, Cossu M, York M, Collins C,

correlated with changes detected by pulmonary tests that are routinely used by clinicians to monitor lung disease.²²³ Another NIH-funded program, the Research Core Centers in Rheumatic Diseases, provides support for shared facilities and services to address scientific problems in rheumatic diseases, including scleroderma.²²⁴ Recently, researchers at one of the Core Centers reported that, in some patients, scleroderma may actually be triggered by an immune response to cancer.²²⁵ The findings reveal a possible new direction for developing therapies for this subset of patients, namely, strategies that focus on detecting, diagnosing, and treating the underlying cancer. They also suggest the need to explore the potential cancerous origins of other autoimmune diseases.

To facilitate the translation of research advances to benefit patients, NIH held a roundtable on February 27, 2015, titled *Scleroderma: Advancing Potential Drugs to Patient Care*. The meeting brought together representatives from academic institutions, regulatory and funding agencies, patient organizations, and industry to discuss the current status of scleroderma research leading to drug development, opportunities and barriers to advancing the evaluation of new therapeutic targets, and possible approaches to move potential drugs into clinical trials and, eventually, patient care.

Segmental Glomerulosclerosis (Same Response as Nephrotic Syndrome)

Nephrotic Syndrome is a kidney disease that is characterized by damage to the glomeruli, the filtering units of the kidney. In this condition, the kidneys' ability to remove waste and excess salts and fluid from the blood while retaining proteins, blood cells, and other components of the circulation is compromised. NIH is deeply concerned about people with glomerular diseases, including focal segmental glomerulosclerosis (FSGS), and promotes and supports studies of glomerular diseases in a number of ways. These include funding of research projects proposed by researchers; direct solicitation of research in a particular area; conducting cutting-edge research through the NIH Intramural Research Program; and support for scientific meetings where state-of-the-art science is discussed. Examples of NIH-initiated research includes the Nephrotic Syndrome Rare Diseases Clinical Research Network (NEPTUNE), a multi-site, multidisciplinary collaborative research and education network designed to foster innovative approaches to the understanding of glomerular disease. NIH is also supporting CureGN, a study that will help researchers better understand the causes of glomerular disease, patients' response to therapy, and disease progression, with the ultimate objective to find a cure. NIH supports a CKD Biomarkers Consortium (CKD BioCon) that promotes the discovery and validation of

Wenink M, Huijbens R, Hesselstrand R, Saxne T, Dimarzio M, Wuttge D, Agarwal SK, Reveille JD, Assassi S, Mayes M, Deng Y, Drenth JP, de Graaf J, den Heijer M, Kallenberg CG, Bijl M, Loof A, van den Berg WB, Joosten LA, Smith V, de Keyser F, Scorza R, Lunardi C, van Riel PL, Vonk M, van Heerde W, Meller S, Homey B, Beretta L, Roest M, Trojanowska M, Lafyatis R, Radstake TR. *N Engl J Med*. 2013 Dec 18. [Epub ahead of print]. PMID: 24350901

²²³ [Association of Interferon-and Transforming Growth Factor \$\beta\$ -Regulated Genes and Macrophage Activation with Systemic Sclerosis-Related Progressive Lung Fibrosis](#). Christmann RB, Sampaio-Barros P, Stifano G, Borges CL, de Carvalho CR, Kairalla R, Parra ER, Spira A, Simms R, Capellozzi VL, Lafyatis R. *Arthritis & Rheumatology*. 2014 March; 66 (3): 714-725. doi: 10.1002/art.38288. PMID: 24574232

²²⁴ http://www.niams.nih.gov/funding/Funded_Research/research_core.asp

²²⁵ [Association of the Autoimmune Disease Scleroderma with an Immunologic Response to Cancer](#). Joseph CG, Darrah E, Shah AA, Skora AD, Casciola-Rosen LA, Wigley FM, Boin F, Fava A, Thoburn C, Kinde I, Jiao Y, Papadopoulos N, Kinzler KW, Vogelstein B, Rosen A. *Science*. 2013 Dec 5. [Epub ahead of print]. PMID: 24310608

novel biomarkers for CKD initiation, progression, and development of complications. A more complete understanding of biomarkers could allow physicians to detect kidney disease earlier and perhaps identify people at greater risk of progression, allowing them to tailor treatments to a specific individual. Looking forward, NIH is planning a meeting to explore the role of mutations in the APOL1 gene in the increased risk of glomerular disease in African Americans.

NIH has recently completed the Kidney Research National Dialogue, a project that solicited the views of scientists, physicians, patients, and the public regarding the most critical issues in kidney disease research.²²⁶

Sickle Cell Disease

As recently as 1970, the average patient with sickle cell disease (SCD) died in childhood, often of overwhelming infection. The results of NIH-funded clinical trials led to the use of penicillin to prevent fatal infections, chronic blood transfusion to reduce stroke risk, and hydroxyurea to reduce pain – patients' lifespans have significantly increased. Nevertheless, the disease still has devastating and debilitating effects on many patients, and NIH is working to further improve patient outcomes by ensuring clinicians use existing treatments and by supporting the development of new treatment options, including interventions that could reverse SCD symptoms. To promote the use of existing therapies, in 2014 NHLBI released the first systematic evidence-informed report²²⁷ to guide clinicians in treating the many conditions affecting those living with SCD. Dissemination of this report is ongoing, and recent discoveries add to the available clinical guidance for physicians. For example, in 2014, researchers funded by NINDS found²²⁸ that regular blood transfusion therapy significantly reduced the incidence of cerebral infarct recurrence in children with SCD. And shortly before that published finding, investigators from the NHLBI and NIDDK reported new findings²²⁹ concerning a partial stem cell transplant: the transplant reversed SCD in 26 of the 30 patients, and half of the patients were able to stop immunosuppressant medication, which is an encouraging finding because immunosuppressant medication can endanger patients already weakened by years of organ damage from SCD. Even with these important advances, NIH continues to seek better treatments for SCD. For example, NHLBI is funding a number of promising studies²³⁰ through its Excellence in Hemoglobinopathies Research Award program, including studies seeking ways to increase levels of fetal hemoglobin, a form of hemoglobin that is normally silent in adults but if reactivated would enable normal red blood cell production.

Sleep Disorders

About 70 million Americans suffer from sleep problems. Sleep deficiency and disorders are associated with a 2-3 fold increased risk of cardiovascular disease, stroke, diabetes, certain cancers, and mortality. The National Center on Sleep Disorders Research (NCSDR), located within NHLBI, was established in 1993 to combat this serious public health concern by

²²⁶ <http://www.niddk.nih.gov/about-niddk/offices-divisions/division-kidney-urologic-hematologic-diseases/kidney-research-national-dialogue/Pages/kidney-research-national-dialogue.aspx>

²²⁷ <http://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines>

²²⁸ <http://www.nejm.org/doi/full/10.1056/NEJMoa1401731>

²²⁹ <http://www.ncbi.nlm.nih.gov/pubmed/25058217>

²³⁰ <http://www.nhlbi.nih.gov/news/spotlight/fact-sheet/nhlbi-funded-research-centers-target-hemoglobinopathies>

supporting research, training, technology transfer, and coordination. A recent study²³¹ supported by the NCSDR demonstrated that extended lack of sleep can lead to a loss of brain cells in mice. Specifically, investigators found that short-term sleep loss increases levels of the protein sirtuin type 3 (SirT3) in the locus coeruleus (LC), a brain region associated with alertness. This increase in SirT3 protects brain cells from metabolic injury. However, in extended sleep loss, SirT3 is reduced and leads to a loss of LC neurons, which are essential for optimal alertness and cognitive function. This discovery provides a direct link between sleep deficiency and loss of brain cells.

While sleep disorders and sleep deprivation are significant threats to public health and productivity, there are no practical tools for the objective measurement of sleepiness. Biomarkers of sleepiness could be invaluable in testing interventions to improve sleep and in developing policies to improve public safety. In 2014, NHLBI and the National Center for Complementary and Integrative Health (NCCIH) solicited small business applications²³² to develop biomarker panels for the point-of-care assessment of acute sleep deprivation, chronic sleep deficiency, sleep disorders, circadian rhythm abnormalities, risks to health or safety, or as intermediate markers of the efficacy achieved by sleep disorder interventions. Finally, in 2014, NHLBI launched a National Sleep Research Resource to leverage NIH's investments in the collection of sleep data in well-characterized cohort studies and clinical trials (approximately 50,000 sleep studies) to create a unique national resource of reliably-scored, well-annotated research polysomnographies. These data will provide the scientific community the opportunity to discover predictive bio-physiological signals for disease incidence and progression, and to address critical questions regarding disease susceptibility and subgroup differences not possible using data from single cohorts.

Spina Bifida

NICHD is committed to improving the outcome of children with spina bifida. In collaboration with NINDS, NICHD supports a follow-up study to the 2011 Management of Myelomeningocele Study (MOMS) clinical trial, which demonstrated that, compared to the standard postnatal surgery, prenatal repair of the defect before 26 weeks of pregnancy dramatically improved health outcomes for the baby. This follow-up study will determine whether children who received the surgery before birth have better health and cognitive outcomes longer term and can function more independently than those who received the surgery after birth. NICHD funds a range of other basic, translational, and clinical research on spina bifida and supports a national resource for mouse models for neural tube defect research. One recently completed study identified interactions between maternal genes involved in insulin resistance and fetal genes involved in glucose regulation that may increase the risk of neural tube defects such as spina bifida. In the near future, systems biology studies of embryonic development and structural birth defects are planned, and children with spina bifida also will be included in upcoming NICHD research efforts to improve health outcomes for children with physical disabilities. NIDDK supports a number of basic research studies of neurogenic bladder due to spina bifida, including how proper nerve connections are established, as well as bladder tissue regeneration. NINDS supports research into the causes of spina bifida and other neural tube defects, and on treatments for

²³¹http://www.jneurosci.org/content/34/12/4418.abstract?ijkey=7a1b526b9522f761ca78a9350c418f7921ca17fe&key_type=tf_ipsecsha

²³² <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-14-013.html>

associated secondary conditions, including hydrocephalus. NIH continues to support the Hydrocephalus Clinical Research Network, a multi-site network that is working to develop quality improvement measures, build a patient registry, and improve the diagnosis and treatment of pediatric hydrocephalus.

Spinal Muscular Atrophy (SMA)

Research has not yet developed a cure for spinal muscular atrophy, but there is encouraging progress. The identification of the gene defects that cause SMA led to improved diagnostics, animal and cell models to study the disease, and rational targets to develop therapies. The NINDS SMA Project, which ran from 2003 to 2012, did not ultimately yield a viable drug, but catalyzed industry interest in SMA. Now, several exciting drug, cell, and gene therapies for SMA are at various stages of development in the public and private sectors, including an industry-sponsored Phase 3 clinical trial launched this year. A gene therapy project in the milestone driven NINDS translational research program showed this year in SMA mice and non-human primates that a single injection of the gene vector into the cerebrospinal fluid effectively replaced the abnormal gene throughout the spinal cord at a dose 10 times lower than necessary with intravenous injection and improved survival and motor function.²³³ Interestingly, the dose required to affect motor neurons in non-human primates was lower than that in the mouse, and the gene vector was delivered via a “spinal tap” procedure which would be the preferred route for SMA patients. As laboratory research continues to improve understanding of SMA and develop therapies, NIH is also supporting clinical research to pave the way for more effective clinical testing of emerging treatments. A study published this year²³⁴ demonstrated that infants with the most severe form of SMA can be effectively enrolled and retained in a 12-month natural history study, providing useful outcome data for clinical trial design. The NINDS NeuroNext clinical network²³⁵ also completed enrollment ahead of schedule for an SMA biomarkers study, which will provide objective measures of disease progression that will greatly facilitate clinical trials. The NeuroNext network expedites early-phase clinical trials, including those for rare pediatric disorders like SMA, whether treatments arise from foundations, industry, or NIH research. Another key activity is an NICHD-supported five-year project that is exploring the ethical, regulatory, and policy issues regarding the use of State newborn screening programs to screen for SMA. Early detection and intervention will be crucial for successful treatment of the most serious infantile type of SMA. NIH is committed to supporting a full range of basic, translational, and clinical studies until an effective treatment for SMA is in hand.

Stroke

NIH investments in stroke research continue to be guided by the priorities identified in the 2011-2012 stroke research planning effort. The new stroke trials network, NIH StrokeNet²³⁶, has been established and is expected to start recruiting patients into ongoing NIH-funded stroke trials soon, including one that seeks to identify the best strategy for reducing stroke due to severely blocked carotid arteries, and another that is testing minimally invasive surgery in hemorrhagic stroke patients. NINDS and the National Center for Medical Rehabilitation Research (NCMR) are co-sponsoring a stroke recovery trial that will test a novel telemedicine intervention that

²³³ <http://www.ncbi.nlm.nih.gov/pubmed/25358252>

²³⁴ <http://www.ncbi.nlm.nih.gov/pubmed/25080519>

²³⁵ <https://www.neuronext.org/>

²³⁶ www.nihstrokenet.org

enables intensive, personalized, home-based rehabilitation of stroke patients who have lost arm function.

NINDS has spearheaded trans-NIH efforts to address the need for better understanding of basic biology and pathophysiology of the small blood vessels in the brain, another research area prioritized by the planning effort. A recent NIH workshop brought together scientists and clinicians from diverse areas of small blood vessel research to share their latest discoveries, identify common challenges, and foster collaborative research on small blood vessels in the brain as well as other organs including the heart, lung, kidney, and eye.

NINDS-supported research has led to exciting recent advances. The Silent Cerebral Infarct Multicenter Clinical Trial (SIT study) demonstrated that monthly blood transfusions safely and effectively prevented the recurrence of silent strokes in children with sickle cell disease (PMID: 25372094²³⁷). The Field Administration of Stroke Therapy–Magnesium (FAST MAG) trial tested a pre-hospital neuroprotection therapy for stroke, and successfully treated over 70 percent of patients within 60 minutes from stroke symptom onset. The drug that was tested did not improve outcomes, but the study demonstrated that pre-hospital treatment of stroke is feasible and laid the groundwork for future studies to use this approach (PMID: 25651247²³⁸). Finally, landmark findings from recent Dutch, Canadian, and Australian trials demonstrated that intra-arterial clot removal devices can improve outcomes in the most severe stroke patients (PMIDs: 25517348²³⁹, 25671798²⁴⁰, and 25671797²⁴¹). These studies were based on decades of NINDS investments and work with the community to develop this approach; the new results will revolutionize the way the most severe strokes are treated.

Telemedicine

The National Library of Medicine (NLM) continues to support research related to telemedicine and telehealth. Such work investigates the appropriateness, quality, and reliability of advanced communications technologies in different telemedicine and telehealth applications, including both static and mobile environments. In FY 2015, NLM completed data collection for a project with the Medical University of South Carolina to investigate the need for higher resolution images for accurately performing a tele-dermatology examination. In collaboration with faculty from the University of Missouri, NLM also made progress toward completion of the manuscript of a book that will review the evidence already collected on the efficacy of telemedicine. NLM also conducted experiments to test the available mobile bandwidth for speed and quality to gauge whether or not telemedicine could be performed using smartphone technology from a moving vehicle like an ambulance. New work was launched to assess the need and value of wireless bandwidth for telemedicine applications.

Temporomandibular Disorders

Thousands of Americans will be diagnosed this year with a painful and debilitating disorder of the jaw called temporomandibular joint and muscle disorder (TMD).²⁴² It is unclear why some of

²³⁷ <http://www.ncbi.nlm.nih.gov/pubmed/25372094>

²³⁸ <http://www.ncbi.nlm.nih.gov/pubmed/25651247>

²³⁹ <http://www.ncbi.nlm.nih.gov/pubmed/25517348>

²⁴⁰ <http://www.ncbi.nlm.nih.gov/pubmed/25671798>

²⁴¹ <http://www.ncbi.nlm.nih.gov/pubmed/25671797>

²⁴² Roda RP, et al. *Med Oral Patol Oral Cir Bucas.* 2007; 12:E292-8. PMID: 17664915

these individuals will recover after a single bout of TMD, while others will go on to develop chronic disease. NIDCR is supporting a large clinical study called Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA), which is providing key insights into the genetic, biological, and psychosocial factors that may contribute to the transition from acute to chronic TMD. Since a large number of those with chronic TMD also have other chronic pain conditions such as fibromyalgia, headache, and low back pain, NIDCR is supporting research in collaboration with other ICs to understand the overlap of these complex pain disorders. NIDCR also supports precision medicine research to understand the genetic and molecular differences between people that can affect the initiation, progression, and treatment of orofacial pain. NIDCR supports a clinical trial to test a common heart drug called propranolol to treat TMD in a subset of patients with a specific genetic variant. These findings can be translated into precision medicine approaches, utilizing individualized strategies for detecting, managing, and treating TMD. Building on this momentum, in 2016, NIDCR will launch a new initiative to better define the genetic variables that influence a person's response to pain management strategies, which will be critical to developing personalized treatment plans to effectively control pain and prevent adverse reactions.

Training and Career Development for Clinical Investigators (“K” And “T” Awards)

Clinical investigators are essential contributors to the advancement of biomedical research, and NIH is committed to maintaining and enhancing the training and career development programs (T and K awards) that allow clinicians to acquire and hone research skills to become independent investigators. In support of that commitment, NIH is currently working to implement a series of recommendations made in 2014 by the Physician Scientist Workforce Working Group of the Advisory Committee to the Director of NIH.

In recent years, much of NIH's support for clinical investigators has been concentrated in its Mentored Patient-Oriented Research Career Development Award program (K23) and the institutional research training (TL1) and career development (KL2) awards associated with the CTSA program. In FY 2014, NIH made a total of 922 new and continuing K23 awards, and provided training and career development support to more than 500 students and emerging investigators at over 60 CTSA sites.

In implementing the recommendations of the Physician Scientist Workforce Working Group, NIH is developing plans to expand and enhance the attractiveness of its existing training and career development programs for clinical investigators and is exploring possibilities for piloting programs that will reduce the length of research training for physician scientists and better ensure that they are able to successfully transition into research careers.

Translational Research Results and Expenditures since FY 2013

The National Center for Advancing Translational Sciences (NCATS) defines *translation* as the process of turning observations in the laboratory, clinic, and community into interventions that improve the health of individuals and the public – from diagnostics and therapeutics to medical procedures and behavioral changes. Translation is part of the mission of every NIH Institute and Center.

NCATS studies translational science, the field of investigation focused on understanding the

scientific and operational principles underlying each step of the translational process. Highlights of NCATS' translational science milestones, programs and initiatives are described in its first Annual Report²⁴³ covering 2012-2013. The 2014 Annual Report is in preparation and will be sent to the Congressional Appropriations Committees when it is available. The NCATS budget, which supports a broad range of translational research projects, was \$542.0 million in FY 2013, \$633.6 million in FY 2014, \$632.7 million in FY 2015, and is proposed to increase to \$660.1 million in the FY 2016 request.

Trans-NIH Basic Behavioral and Social Science Opportunity Network

In FY 2014, the NIH Basic Behavioral and Social Science Opportunity Network (OppNet) Program funded 17 new projects in the basic behavioral and social sciences including studies on: cognitive processing of multisensory stimuli and links to behavior basic individual and group psychosocial processes related to stigma; and epigenetics and behavior. Additional support was provided to coordinate studies using animal models with those involving human subjects within these topic areas. An additional 37 grants were funded in their respective out years. While FY 2014 represented the last year of pooled contributions from ICs to OppNET, this program will continue to be funded with voluntary contributions from NIH ICs.

In FY 2015, the NIH Office of Behavioral and Social Sciences Research (OBSSR) targeted \$1 million to OppNet for administrative supplements to existing grants that explore basic sociobehavioral mechanisms that facilitate or impede the self-management of chronic diseases. OBSSR and NIA are leading the effort to organize OppNet as a voluntary trans-NIH initiative. To date, 10 ICs have agreed to participate in this voluntary arrangement with several other ICs currently considering providing support for this restructured OppNet. OBSSR also is facilitating two concept-development workshops with the intent for new OppNet initiatives to be issued and funded through OppNet's voluntary structure. In FY 2015, OBSSR also initiated a two-year project to evaluate the OppNet program to determine its effectiveness in promoting trans-NIH activities in basic behavioral and social science research, and to inform future goals and directions for OppNet.

Type 1 Diabetes

NIH's landmark, long-term Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications Study (EDIC) continues to provide critical data about the importance of early intensive blood glucose control for people with Type 1 diabetes. Recently published DCCT/EDIC results showed that people who intensively control their blood glucose early in the course of their disease are likely to live longer than those who do not. (*JAMA* 313: 45, 2015) NIH supports research on new treatment approaches to help people with Type 1 diabetes achieve the intensive glucose control obtained in the DCCT, and tremendous progress has been made toward artificial pancreas technologies that link a continuous blood glucose sensor and an insulin delivery system. Two exciting studies reported reduced episodes of hypoglycemia (dangerously low blood glucose) and improved glucose control by adolescents in an unsupervised overnight home use study (*Diabetes Care* 37: 1204, 2014) and by adults and adolescents testing an automated, bihormonal (insulin and glucagon) "bionic pancreas." (*N Engl J Med* 371: 313, 2014) NIH also continues to vigorously support research toward cell-based therapies for type 1 diabetes; two research teams made major steps toward generating glucose-

²⁴³ http://www.ncats.nih.gov/files/NCATS_2012-2013_Report.pdf

responsive beta cells from other types of cells, including human induced pluripotent stem cells (iPSCs). (*Cell* 159: 428, 2014; *Nature* 415: 503, 2014) Research toward understanding the causes of Type 1 diabetes is also supported, and researchers recently learned more about the function of a gene linked to risk for type 1 diabetes. (*Cell* 157: 1577, 2014) Such insights could shed light on new prevention and treatment approaches.

Universal Flu Vaccine

The development of a universal flu vaccine that induces a potent immune response to common elements of the influenza virus is an important part of NIAID's research portfolio. Vaccines are proven tools for preventing infectious diseases, and NIAID is a world leader in vaccine design and development. Because seasonal influenza vaccines provide little or no protection against pandemic influenzas, a universal vaccine that would prompt the immune system to produce "broadly neutralizing" antibodies is an urgent research focus. A universal flu vaccine might protect against pandemic and seasonal influenza strains and could confer long-term protection, thereby reducing the need for annual vaccinations. NIAID, via its Vaccine Research Center and through support of intramural and extramural researchers, will support clinical development of the lead vaccine candidates to accelerate development of more effective influenza vaccines. The FY 2016 request proposes an increase of \$20 million to speed the development of these promising candidates.

Usher Syndrome

Usher Syndrome (USH) is a rare, inherited, genetic disorder affecting hearing, vision, and sometimes balance. There is no cure, but early diagnosis improves the success of rehabilitation by allowing educational programs to begin early. Several institutes and centers at NIH are conducting and supporting research on this debilitating disorder. The National Institute on Deafness and Other Communication Disorders (NIDCD) supports basic research to identify new USH genes and to develop USH animal models to test potential treatments; translational research to better diagnose children with USH, and to slow and/or prevent hearing loss; and clinical research to characterize variability in balance in USH.²⁴⁴ NIDCD and NEI clinical researchers are collaborating to understand neural mechanisms that underlie balance and vision in individuals with USH.²⁴⁵ NEI supports basic research to understand USH gene structure and function in relation to vision, and two clinical research studies to test the genes of USH individuals and their families, and monitoring disease progression over time.²⁴⁶ NICHD and NIGMS support basic research on protein structure, cell biology, and development involving USH genes. Further, NIDCD, NEI, and NCATS supported the International Symposium of Usher Syndrome. The two-day scientific meeting, held in July 2014, and organized by the Coalition for Usher Syndrome Research, explored current research challenges.

Vision Research Relating to "Regenerating Neurons and Neural Connections in the Eye and Visual System"

NEI launched the Audacious Goals Initiative²⁴⁷ (AGI) in 2012 as a prize competition that

²⁴⁴ <http://www.nidcd.nih.gov/health/hearing/pages/usher.aspx>

²⁴⁵ <http://www.ncbi.nlm.nih.gov/pubmed/25425308>

²⁴⁶ <https://www.nei.nih.gov/health/ushers>

²⁴⁷ <https://www.nei.nih.gov/audacious/>

challenged the vision research community and the broad public to imagine the greatest achievement for vision research during the next 10-15 years. The challenge attracted nearly 500 innovative proposals from around the world. NEI adopted the audacious goal to restore vision through the regeneration of neurons and neural connections in the eye and visual system, specifically targeting photoreceptors, the cells in the eye that detect light, and retinal ganglion cells, the nerve cells in the optic nerve, which conduct signals from the eye to the brain. To shepherd the initiative, NEI established an external steering committee of four preeminent vision researchers who will work with NEI scientific staff and the newly hired AGI program coordinator to identify knowledge gaps and strategies to bridge them.

As a critical first scientific step, NEI solicited research proposals in 2014 to develop new imaging and other enabling technologies that will enable monitoring of retinal structure and function with unprecedented temporal and spatial resolution and sensitivity. These tools will open a window through which scientists can observe regeneration as it happens and thereby measure the impact of new therapeutic interventions. To address other research gaps, NEI is hosting a series of scientific workshops. The first such workshop, in November 2014, explored the scientific challenges of optic nerve regeneration. When the optic nerve degenerates in diseases such as glaucoma, visual information cannot reach the brain, resulting in vision impairment. Successful regeneration involves not only regrowing nerve fibers, but ensuring they reach their proper targets in the brain. Future workshops planned for FY 2015 and FY 2016 will delineate the challenges around regenerating, integrating, and reconnecting neurons in the visual system and will focus on steps to transcend these barriers to restore meaningful vision.

Wilms Tumor

Wilms tumor (WT) is the most common type of childhood kidney cancer and usually occurs before the age of five years. NCI's Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative²⁴⁸ supports a kidney tumor project team that includes a specific research effort focused on understanding the genomic landscape of Wilms tumors. This research is taking a comprehensive genomic approach to identify new therapeutic targets for a subset of pediatric WT patients who have poor clinical outcomes. Investigators studied tumor samples from patients enrolled in the NCI-supported National Wilms Tumor Study²⁴⁹ clinical trial (a five-part trial originally established in 1969 that concluded in 2002). Through genome-wide characterization, TARGET investigators have identified novel mutations in genes previously unrecognized as associated with Wilms tumor. These discoveries will inform future efforts to identify treatments that appropriately match therapy to the biological and clinical characteristics of children with Wilms tumors.

NCI is also supporting the Children's Oncology Group (COG) Phase 3 clinical trial²⁵⁰ studying "Combination Chemotherapy and Surgery in Treating Young Patients With Wilms Tumor." The trial is for children with bilateral Wilms tumor and for children who are at increased risk for forming tumors in both kidneys. The trial expects to enroll 260 patients and is open at 148 COG sites. In FY 2015, the COG also plans to initiate a clinical trial of an antibody-drug conjugate that targets an antigen that is overexpressed on the cell surface of Wilms tumors and selected other childhood cancers.

²⁴⁸ <https://ocg.cancer.gov/programs/target/projects/kidney-tumors>

²⁴⁹ http://www.nwtsg.org/about/clinical_trials.html

²⁵⁰ <https://clinicaltrials.gov/ct2/show/NCT00945009>